

NOVEL CXCR4-TARGETING COMPOUNDS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 63/094,839, filed October 21, 2020, the disclosures of which are hereby incorporated by reference in their entireties for all purposes.

FIELD OF INVENTION

[0002] The present invention relates to novel peptidic compounds, particularly compounds that target CXCR4 for purposes such as imaging and/or therapeutics.

BACKGROUND OF THE INVENTION

[0003] C-X-C chemokine receptor type 4 (CXCR4) is a G protein-coupled transmembrane receptor that is expressed in hematological and immune tissues and systems.^{1,2} CXCR4 has only one chemokine as a substrate named stromal-derived-factor-1 (SDF-1), also known as CXCL12.³ CXCR4 is aberrantly expressed in a number of important pathologies that involve inflammation and immune cell trafficking, including atherosclerosis,⁴ systemic erythematous lupus^{5,6}, cancer and others. Importantly, CXCR4 has been found to play key roles in tumorigenesis, chemoresistance and metastasis and its expression has been detected in more than twenty different subtypes of cancers with an accompanying negative prognosis.^{7–}

¹² As such, there is a need for non-invasive *in vivo* molecular probes to image CXCR4-expressing tumours for better detection, staging and monitoring of aggressive cancers.^{13–16} Such imaging agents enable the rapid assessment of patients for expression of specific biomarkers without the need for invasive biopsy procedures that may not always properly capture the heterogeneity of a patient's disease. Furthermore, with the largely poor efficacy of CXCR4 inhibitors in clinical trials, an alternative strategy is to couple the inhibitor with a radiotherapeutic isotope to deliver ionizing β , α , or auger electrons to the sites of the disease.

[0004] LY2510924 (cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2-Nal-Gly-D-Glu]-Lys(iPr)-NH₂) is a cyclic peptide that is reported to block SDF-1 α binding to CXCR4 with an IC₅₀ value of 79 pM¹⁷. It was reported that LY2510924 was able to inhibit growth of non-Hodgkin lymphoma, renal cell carcinoma, lung cancer, colorectal cancer, and breast cancer xenograft models. LY2510924 failed to improve treatment efficacy of carboplatin/etoposide chemotherapy for small cell lung cancer patients¹⁸.

[0005] Many CXCR4 peptide-based inhibitors rely on key amino acid residues that include 1) one or more cationic charged side chain residues to make contact with several anionic residues present on the CXCR4 pocket, 2) a tyrosine residue and 3) a naphthalene-based

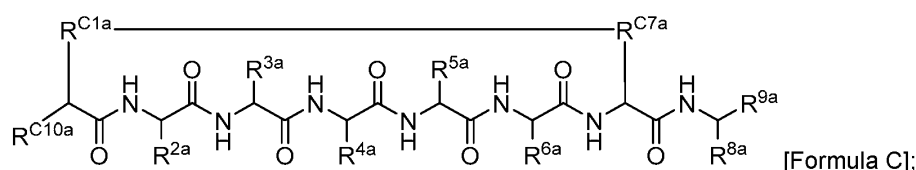
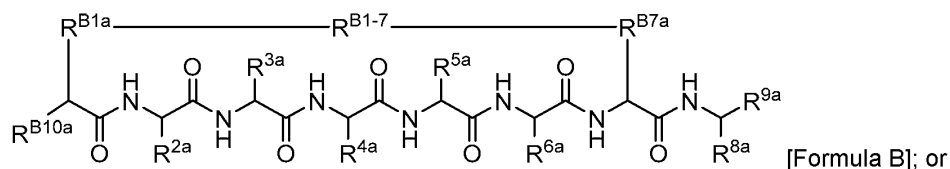
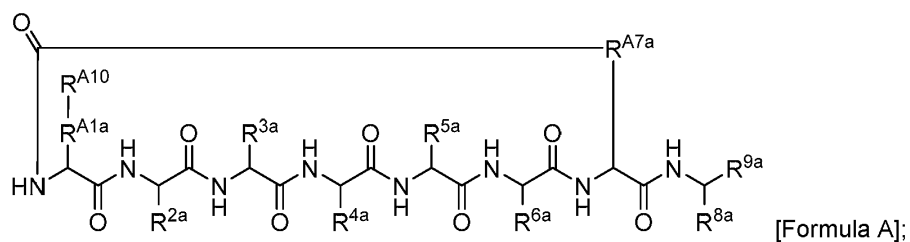
unnatural amino acid in order to maintain good binding affinity with CXCR4.¹⁹ This is exemplified in the development of T140, which systematically substituted out each amino acid of a prototype peptide (T22) based on a natural peptide with HIV inhibitory activity via CXCR4 antagonism.¹⁹ This has resulted in a number of strong antagonists to CXCR4, including FC131 (which was later repurposed as Pentixafor and Pentixather for imaging and radionuclide therapeutic purposes, respectively) and LY2510924 for radiotheranostic purposes.²⁰

[0006] There is therefore an unmet need in the field for improved CXCR4-targeting compounds, e.g. imaging and therapeutic agents for *in-vivo* diagnosis and treatment, respectively, of diseases/disorders characterized by expression of CXCR4.

[0007] No admission is necessarily intended, nor should it be construed, that any of the preceding information constitutes prior art against the present invention.

SUMMARY OF THE DISCLOSURE

[0008] The present disclosure relates to compounds useful as imaging agents and/or therapeutic agents. In some embodiments, the compound of the present disclosure relates to a compound of Formula A, Formula B, or Formula C, or a salt or solvate thereof:



[0009] wherein:

[0010] R^{2a} is $-(CH_2)-(R^{2b})-(phenyl)$, wherein R^{2b} is absent, $-CH_2-$, $-NH-$, $-S-$ or $-O-$, wherein the phenyl is optionally 4-substituted with $-NH_2$, $-NO_2$, $-OH$, $-OR^{2c}$, $-SH$, $-SR^{2c}$, or $-O-phenyl$, wherein the phenyl is optionally 3-substituted with halogen or $-OH$, wherein the phenyl is optionally 5-substituted with halogen or $-OH$, wherein the $-O-phenyl$ ring is optionally 4-substituted with $-NH_2$, $-NO_2$, $-OH$, $-OR^{2c}$, $-SH$, or $-SR^{2c}$, wherein the $-O-$

phenyl ring is optionally 3-substituted with halogen or -OH, wherein the -O-phenyl ring is optionally 5-substituted with halogen or -OH, wherein each R^{2c} is independently a C_1 - C_3 linear or branched alkyl group;

[0011] R^{3a} is $R^{3b}R^{3c}$ wherein R^{3b} is a linear C_1 - C_5 alkynyl, C_2 - C_5 alkenyl, or C_2 - C_5 alkynyl, wherein 0-2 carbons in C_2 - C_5 are independently replaced with one or more N, S, and/or O heteroatoms, wherein R^{3c} is $-N(R^{3d})_{2-3}$ or guanidino, wherein each R^{3d} is independently -H or a linear or branched C_1 - C_3 alkyl;

[0012] R^{4a} is $R^{4b}R^{4c}$ wherein R^{4b} is a linear C_1 - C_5 alkynyl, C_2 - C_5 alkenyl, or C_2 - C_5 alkynyl, in which 0-2 carbons in C_2 - C_5 are independently replaced with one or more N, S, and/or O heteroatoms, wherein R^{4c} is $-N(R^{4d})_{2-3}$ or guanidino, wherein each R^{4d} is independently -H or a linear or branched C_1 - C_3 alkyl;

[0013] R^{5a} is $-(CH_2)_{1-3}-R^{5b}$, wherein 1 carbon in $-(CH_2)_{2-3}-$ is optionally replaced with a N, S, or O heteroatom, wherein R^{5b} is:

[0014] phenyl optionally substituted with one or a combination of the following: 4-substituted with $-NH_2$, $-NO_2$, $-OH$, $-OR^{5c}$, $-SH$, $-SR^{5c}$, or $-O$ -phenyl; 3-substituted with halogen or $-OH$; and/or 5-substituted with halogen or $-OH$; wherein the $-O$ -phenyl ring is optionally 4-substituted with $-NH_2$, $-NO_2$, $-OH$, $-OR^{5c}$, $-SH$, or $-SR^{5c}$, wherein the $-O$ -phenyl ring is optionally 3-substituted with halogen or $-OH$, wherein the $-O$ -phenyl ring is optionally 5-substituted with halogen or $-OH$; or

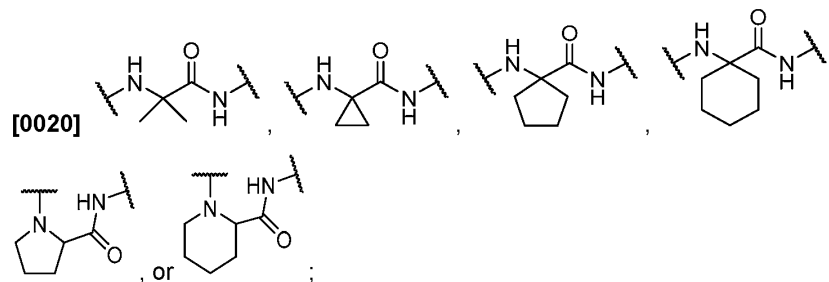
[0015] a fused bicyclic or fused tricyclic aryl or heteroaryl ring, each optionally substituted with one or more of halogen, $-OH$, $-OR^{5c}$, amino, $-NHR^{5c}$, and/or $N(R^{5c})_2$;

[0016] wherein each R^{5c} is independently a C_1 - C_3 linear or branched alkyl group;

[0017] either R^{6a} is H, methyl, ethyl, $-C\equiv CH$, $-CH=CH_2$, $-C\equiv C-(CH_2)_{1-3}-OH$, $-C\equiv C-(CH_2)_{1-3}-SH$, $-C\equiv C-(CH_2)_{1-3}-NH_2$, $-C\equiv C-(CH_2)_{1-3}-COOH$, $-C\equiv C-(CH_2)_{1-3}-CONH$, $-C\equiv C-(CH_2)_{1-3}-R^{6b}R^{6c}$, $-CH=CH-(CH_2)_{1-3}-OH$, $-CH=CH-(CH_2)_{1-3}-SH$, $-CH=CH-(CH_2)_{1-3}-NH_2$, $-CH=CH-(CH_2)_{1-3}-COOH$, $-CH=CH-(CH_2)_{1-3}-CONH$, $-CH=CH-(CH_2)_{1-3}-R^{6b}R^{6c}$, $-CH_2-R^{6b}-OH$, $-CH_2-R^{6b}-COOH$, $-CH_2-(R^{6b})_{1-3}-NH_2$, $-CH_2-R^{6b}-CONH$, or $-CH_2-R^{6b}R^{6c}$, wherein each R^{6b} is independently absent, $-CH_2-$, $-NH-$, $-S-$ or $-O-$, and wherein R^{6c} is:

[0018] a 5 or 6 membered aromatic ring wherein one or more carbons are optionally independently replaced by N, S, and/or O heteroatoms, and optionally substituted with one or more groups independently selected from oxo, hydroxyl, sulfhydryl, nitro, amino, and/or halogen;

[0019] or $-NH-CH(R^{6a})-C(O)-NH-$ is replaced with:



[0021] R^{A7a} is a linear C_1 - C_5 alkynyl wherein 0-2 carbons in C_2 - C_5 are independently replaced with one or more N, S, and/or O heteroatoms;

[0022] R^{8a} is $R^{8b}R^{8c}$ wherein R^{8b} is a linear C_1 - C_5 alkynyl, C_2 - C_5 alkenyl, or C_2 - C_5 alkynyl, in which 0-2 carbons in C_2 - C_5 alkynyl, alkenyl, or alkynyl are independently replaced with one or more N, S, and/or O heteroatoms, wherein R^{8c} is $-N(R^{8d})_{2-3}$ or guanidino, wherein each R^{8d} is independently $-H$ or a linear or branched C_1 - C_3 alkyl;

[0023] R^{9a} is $-C(O)NH_2$, $-C(O)-OH$, $-CH_2-C(O)NH_2$, $-CH_2-C(O)-OH$, $-CH_2-NH_2$, $-CH_2-OH$, $-CH_2-CH_2-NH_2$, $-R^{9b}-R^{9c}$, or $-R^{9b}-[linker]-R^{X_{n1}}$, wherein:

[0024] R^{9b} is $-CH_2-NH-C(O)-$, $-CH_2-C(O)-$, $-CH_2-O-$, $-C(O)NH-$, $-C(O)-N(CH_3)-$, $-CH_2-NHC(S)-$, $-C(S)NH-$, $-CH_2-N(CH_3)C(S)-$, $-C(O)N(CH_3)-$, $-CH_2-N(CH_3)C(O)-$, $-C(S)N(CH_3)-$, $-CH_2-NHC(S)NH-$, $-CH_2-NHC(O)NH-$, $-CH_2-S-$, $-CH_2-S(O)-$, $-CH_2-S(O)_2-$, $-CH_2-S(O)_2-NH-$, $-CH_2-S(O)-NH-$, $-CH_2-Se-$, $-CH_2-Se(O)-$, $-CH_2-Se(O)_2-$, $-CH_2-NHNHC(O)-$, $-C(O)NHNH-$, $-CH_2-OP(O)(O^-)O-$, $-CH_2$ -phosphamide-, $-CH_2$ -thiophosphodiester-, $-CH_2-S-$

tetrafluorophenyl-S-,

polyethylene glycol; and

[0025] R^{9c} is hydrogen or a linear, branched, and/or cyclic C_1 - C_{20} alkyl, C_2 - C_{20} alkenyl or C_2 - C_{20} alkynyl, wherein 0-6 carbons in C_2 - C_{20} alkyl, alkenyl or alkynyl are independently replaced by N, S, and/or O heteroatoms, and substituted with 0-3 groups independently selected from one or a combination of oxo, hydroxyl, sulfhydryl, halogen, guanidino, carboxylic acid, sulfonic acid, sulfinic acid, and/or phosphoric acid;

[0026] R^{A10} is absent or $-[linker]-R^{X_{n1}}$;

[0027] when R^{A10} is absent, then R^{A1a} is:

[0028] a linear C_1 - C_5 alkyl, C_2 - C_5 alkenyl, or C_2 - C_5 alkynyl, wherein 0-2 carbons in C_2 - C_5 alkyl, alkenyl, or alkynyl, are independently replaced by one or more N, S, and/or O heteroatoms, optionally C-substituted with a single substituent selected from: $-SH$, $-OH$, amino, carboxy, guanidino, $-NH-C(O)-CH_3$, $-S-C(O)-CH_3$, $-O-C(O)-$

CH₃, -NH-C(O)-(phenyl), -S-C(O)-(phenyl), -O-C(O)-(phenyl), -NH-(CH₃)₁₋₂, -NH₂-CH₃, -N(CH₃)₂₋₃, -S-CH₃, or -O-CH₃;

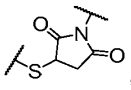
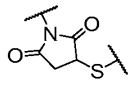
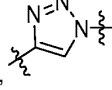
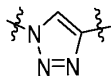
[0029] a branched C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, or C₂-C₁₀ alkynyl, wherein 0-3 carbons in C₂-C₁₀ alkyl, alkenyl, or alkynyl, are independently replaced by one or more N, S, and/or O heteroatoms; or

[0030] R^{A1b}R^{A1c}, wherein R^{A1b} is a linear C₁-C₃ alkylenyl, wherein C₂ alkylenyl or C₃ alkylenyl is optionally replaced with a N, S, or O heteroatom, wherein R^{A1c} is:

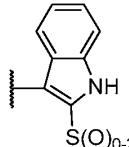
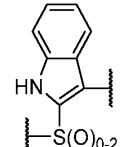
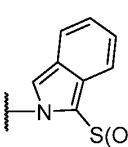
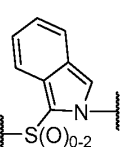
[0031] a 5 or 6 membered aromatic ring wherein one or more carbons are optionally independently replaced by N, S, and/or O heteroatoms, and optionally substituted with one or more groups independently selected from oxo, hydroxyl, sulfhydryl, nitro, amino, and/or halogen; or

[0032] a fused bicyclic or fused tricyclic aryl group wherein one or more carbons are optionally independently replaced by N, S, and/or O heteroatoms, and optionally substituted with one or more groups independently selected from halogen, -OH, -OR^{A1d}, amino, -NHR^{A1d}, and/or N(R^{A1d})₂, wherein each R^{A1d} is independently a C₁-C₃ linear or branched alkyl group;

[0033] when R^{A10} is -[linker]-R^X_{n1}, then R^{A1a} is R^{A1e}R^{A1f}, wherein R^{A1e} is a linear C₁-C₅ alkylenyl, C₂-C₅ alkenylenyl, or C₂-C₅ alkynylenyl, in which 0-2 carbons in C₂-C₅ alkylenyl, alkenylenyl, or alkynylenyl are independently replaced with N, S, and/or O heteroatoms, and R^{A1f} is -NH-C(O)-, -C(O)-, -O-, -C(O)NH-, -C(O)-N(CH₃)-, -NHC(S)-, -C(S)NH-, -N(CH₃)C(S)-, -C(O)N(CH₃)-, -N(CH₃)C(O)-, -C(S)N(CH₃)-, -NHC(S)NH-, -NHC(O)NH-, -S-, -S(O)-, -S(O)-O-, -S(O)₂-, -S(O)₂-O-, -S(O)₂-NH-, -S(O)-NH-, -Se-, -Se(O)-, -Se(O)₂-, -NHNHC(O)-, -C(O)NHNH-, -OP(O)(O-)O-, -phosphamide-, -

thiophosphodiester-, -S-tetrafluorophenyl-S-, , , , , or polyethylene glycol;

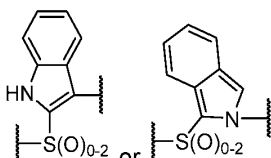
[0034] R^{B1a} is a linear, branched, and/or cyclic C₁-C₁₀ alkylenyl, C₂-C₁₀ alkenylenyl, or C₂-C₁₀ alkynylenyl, wherein one or more carbons in C₂-C₁₀ alkylenyl, alkenylenyl, or alkynylenyl are optionally independently replaced with N, S, and/or O heteroatoms;

[0035] R^{B1-7} is: , , , or ,

wherein the indole ring and the isoindole ring are each optionally substituted with one or

more of -F, -Br, -Cl, -I, -OH, -O-R^{B1-7b}, -CO-, -COOH, -CONH₂, -CN, -O-aryl, -NH₂, -NHR^{B1-7b}, N₃, -NH, -CHO, and/or -R^{B1-7b}, wherein each R^{B1-7b} is a linear or branched C₁-C₃ alkyl, alkenyl, or alkynyl;

[0036] R^{B7a} is a linear C₁-C₅ alkynyl wherein 0-2 carbons in C₂-C₅ are independently replaced with one or more N, S, and/or O heteroatoms;

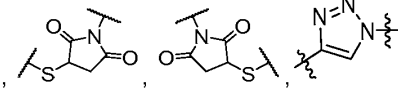
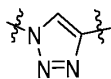
[0037] R^{C1a} is: , wherein the indole ring and the isoindole ring are each optionally substituted with one or more of -F, -Br, -Cl, -I, -OH, -O-R^{C1b}, -CO-, -COOH, -CONH₂, -CN, -O-aryl, -NH₂, -NHR^{C1b}, N₃, -NH, -CHO, and/or -R^{C1b}, wherein each R^{C1b} is a linear or branched C₁-C₃ alkyl, C₂-C₃ alkenyl, or C₂-C₃ alkynyl;

[0038] R^{C7a} is a linear C₁-C₅ alkynyl wherein optionally 0-2 carbons in C₂-C₅ are independently replaced with one or more N, S, and/or O heteroatoms;

[0039] R^{C10a} is R^{C10b}-R^{C10c}-[linker]-R^X_{n1} or R^{C10d}, wherein:

[0040] R^{C10b} is a linear C₁-C₅ alkynyl, C₂-C₅ alkenyl, or C₂-C₅ alkynyl, in which 0-2 carbons in C₂-C₅ alkynyl, alkenyl, or alkynyl are independently replaced with N, S, and/or O heteroatoms;

[0041] R^{C10c} is -NH-C(O)-, -C(O)-, -O-, -C(O)NH-, -C(O)-N(CH₃)-, -NHC(S)-, -C(S)NH-, -N(CH₃)C(S)-, -C(O)N(CH₃)-, -N(CH₃)C(O)-, -C(S)N(CH₃)-, -NHC(S)NH-, -NHC(O)NH-, -S-, -S(O)-, -S(O)-O-, -S(O)₂-, -S(O)₂-O-, -S(O)₂-NH-, -S(O)-NH-, -Se-, -Se(O)-, -Se(O)₂-, -NHNHC(O)-, -C(O)NHNH-, -OP(O)(O-)O-, -phosphamide-, -

thiophosphodiester-, -S-tetrafluorophenyl-S-, , , or polyethylene glycol; and

[0042] R^{C10d} is:

[0043] a linear C₁-C₅ alkyl, C₂-C₅ alkenyl, or C₂-C₅ alkynyl, wherein 0-2 carbons in C₂-C₅ are independently replaced by N, S, and/or O heteroatoms, optionally C-substituted with a single substituent selected from: -SH, -OH, amino, carboxy, guanidino, -NH-C(O)-CH₃, -S-C(O)-CH₃, -O-C(O)-CH₃, -NH-C(O)-(phenyl), -S-C(O)-(phenyl), -O-C(O)-(phenyl), -NH-(CH₃)₁₋₂, -NH₂-CH₃, -N(CH₃)₂₋₃, -S-CH₃, or -O-CH₃;

[0044] a branched C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, or C₂-C₁₀ alkynyl, wherein 0-3 carbons in C₂-C₁₀ are independently replaced by N, S, and/or O heteroatoms; or

[0045] $R^{C10e}R^{C10f}$, wherein R^{C10e} is a linear C_1 - C_3 alkyl, wherein C_2 alkyl or C_3 alkyl is optionally replaced with N, S, or O heteroatom, wherein R^{C10f} is:

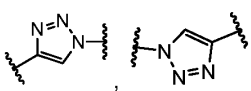
[0046] a 5 or 6 membered aromatic ring wherein one or more carbons are optionally independently replaced by N, S, and/or O heteroatoms, and optionally substituted with one or more groups independently selected from oxo, hydroxyl, sulfhydryl, nitro, amino, and/or halogen;

[0047] a fused bicyclic or fused tricyclic aryl group wherein one or more carbons are optionally independently replaced by N, S, and/or O heteroatoms, and optionally substituted with one or more groups independently selected from halogen, -OH, -OR^{C10g}, amino, -NHR^{C10g}, and/or N(R^{C10g})₂, wherein R^{C10g} is C_1 - C_3 linear or branched alkyl;

[0048] each n_1 is independently 0, 1 or 2;

[0049] each R^x is a therapeutic moiety, a fluorescent label, a radiolabeled group, or a group capable of being radiolabelled;

[0050] wherein 0-3 peptide backbone amides are independently replaced with

[0051] , or thioamide;

[0052] wherein 0-3 peptide backbone amides are N-methylated;

[0053] with the proviso that Formula A excludes the following combination:

[0054] -NH-CH(R^{2a})-C(O)- forms a Tyr residue;

[0055] -NH-CH(R^{4a})-C(O)- forms a D-Arg residue;

[0056] -NH-CH(R^{5a})-C(O)- forms a 2Nal residue; and

[0057] R^{6a} is H.

[0058] The present disclosure also relates to one or more compounds of Table A.

[0059] In some embodiments, one or more of the compounds of Table A are bound to a radiolabeled group or a group capable of being radiolabelled, optionally through a linker.

[0060] In some embodiments of the compounds of the present disclosure, the compound is complexed with a radioisotope.

[0061] The present disclosure also relates to use of any one of the compounds disclosed herein for imaging a CXCR4-expressing tissue in a subject.

[0062] The present disclosure also relates to use of any one of the compounds disclosed herein for imaging an inflammatory condition or disease.

[0063] The present disclosure also relates to a method of treating a disease or a condition characterized by expression of CXCR4 in a subject, comprising administering an effective amount of the compound to a subject in need thereof. In some embodiments, the disease or condition is a CXCR4-expressing cancer.

[0064] The present disclosure also relates to a method of imaging a CXCR4-expressing tissue in a subject, comprising administering an effective amount of the compound to the subject in need of such imaging.

BRIEF DESCRIPTION OF THE DRAWINGS

[0065] FIGURE 1 shows PET/CT images of [⁶⁸Ga]Ga-BL34 in mice bearing Z-138-cell tumors acquired at 1 or 2 hrs post-injection.

[0066] FIGURE 2 shows SPECT/CT images of [¹⁷⁷Lu]Lu-BL34 in mice bearing Z-138-cell tumors acquired at 1, 4, 24 or 72 hrs post-injection.

[0067] FIGURE 3 shows PET/CT images of [¹⁸F]BL40 in mice bearing Z-138-cell tumors acquired at 1 or 2 hrs post-injection or 1 hrs post-injection after pre-injection by 15 minutes of 7.5 µg of LY2510924 for blocking.

[0068] FIGURE 4 shows PET/CT images of [¹⁸F]BL41 in mice bearing Z-138-cell tumors acquired at 1 or 2 hrs post-injection or 1 hrs post-injection after pre-injection by 15 minutes of 7.5 µg of LY2510924 for blocking.

[0069] FIGURE 5 shows PET/CT images of [⁶⁸Ga]Ga-BL42 in mice bearing Z-138-cell tumors acquired at 1 post-injection

[0070] FIGURE 6 shows PET/CT images of [⁶⁸Ga]Ga-BL43 in mice bearing Z-138-cell tumors acquired at 1 post-injection

[0071] FIGURE 7 shows PET/CT images of [⁶⁸Ga]Ga-BL44 in mice bearing Z-138-cell tumors acquired at 1 post-injection

[0072] FIGURE 8 shows PET/CT images of [⁶⁸Ga]Ga-BL45 in mice bearing Z-138-cell tumors acquired at 1 post-injection

[0073] FIGURES 9A-9B shows the Therapeutic efficacy of [¹⁷⁷Lu]Lu-BL34 in Z138 xenograft-bearing mice. The mean tumor volumes are shown for the treated mice that received either 30 or 60 MBq (Fig. 9A) as compared to PBS (Fig. 9B).

DETAILED DESCRIPTION

[0074] All publications, patents and patent applications, including any drawings and appendices therein are incorporated by reference in their entirety for all purposes to the same extent as if each individual publication, patent or patent application, drawing, or appendix was specifically and individually indicated to be incorporated by reference in its entirety for all purposes.

[0075] As used herein, the terms “comprising,” “having,” “including” and “containing,” and grammatical variations thereof, are inclusive or open-ended and do not exclude additional, unrecited elements and/or method steps. The term “consisting essentially of” if used herein

in connection with a composition, use or method, denotes that additional elements and/or method steps may be present, but that these additions do not materially affect the manner in which the recited composition, method or use functions. The term “consisting of” if used herein in connection with a composition, use or method, excludes the presence of additional elements and/or method steps. A composition, use or method described herein as comprising certain elements and/or steps may also, in certain embodiments consist essentially of those elements and/or steps, and in other embodiments consist of those elements and/or steps, whether or not these embodiments are specifically referred to. A use or method described herein as comprising certain elements and/or steps may also, in certain embodiments consist essentially of those elements and/or steps, and in other embodiments consist of those elements and/or steps, whether or not these embodiments are specifically referred to.

[0076] A reference to an element by the indefinite article “a” does not exclude the possibility that more than one of the elements is present, unless the context clearly requires that there be one and only one of the elements. The singular forms “a”, “an”, and “the” include plural referents unless the content clearly dictates otherwise. The use of the word “a” or “an” when used herein in conjunction with the term “comprising” may mean “one,” but it is also consistent with the meaning of “one or more,” “at least one” and “one or more than one.”

[0077] Unless otherwise specified, “certain embodiments”, “various embodiments”, “an embodiment” and similar terms includes the particular feature(s) described for that embodiment either alone or in combination with any other embodiment or embodiments described herein, whether or not the other embodiments are directly or indirectly referenced and regardless of whether the feature or embodiment is described in the context of a method, product, use, composition, compound, *et cetera*.

[0078] As used herein, the terms “treat”, “treatment”, “therapeutic” and the like includes ameliorating symptoms, reducing disease progression, improving prognosis and reducing recurrence (e.g. reducing cancer recurrence).

[0079] As used herein, the term “diagnostic agent” includes an “imaging agent”. As such, a “diagnostic radiometal” includes radiometals that are suitable for use in imaging agents and “diagnostic radioisotope” includes radioisotopes that are suitable for use in imaging agents. Without limitation, diagnostic and imaging agents include compounds comprising at least one fluorescent moiety and/or at least one radioisotope that is suitable for imaging.

[0080] The term “subject” refers to an animal (e.g. a mammal or a non-mammal animal). The subject may be a human or a non-human primate. The subject may be a laboratory mammal (e.g., mouse, rat, rabbit, hamster and the like). The subject may be an agricultural animal (e.g., equine, ovine, bovine, porcine, camelid and the like) or a domestic animal (e.g., canine, feline and the like). In some embodiments, the subject is a human.

[0081] The compounds disclosed herein may also include free-base forms, salts or pharmaceutically acceptable salts thereof. Unless otherwise specified, the compounds claimed and described herein are meant to include all racemic mixtures and all individual enantiomers or combinations thereof, whether or not they are explicitly represented herein.

[0082] The compounds disclosed herein may be shown as having one or more charged groups, may be shown with ionizable groups in an uncharged (e.g. protonated) state or may be shown without specifying formal charges. As will be appreciated by the person of skill in the art, the ionization state of certain groups within a compound (e.g. without limitation, carboxylic acid, sulfonic acid, sulfinic acid, phosphoric acid and the like) is dependent, *inter alia*, on the pKa of that group and the pH at that location. For example, but without limitation, a carboxylic acid group (i.e. COOH) would be understood to usually be deprotonated (and negatively charged) at neutral pH and at most physiological pH values, unless the protonated state is stabilized. Likewise, sulfonic acid groups, sulfinic acid groups, and phosphoric acid groups would generally be deprotonated (and negatively charged) at neutral and physiological pH values.

[0083] As used herein, the terms "salt" and "solvate" have their usual meaning in chemistry. As such, when the compound is a salt or solvate, it is associated with a suitable counter-ion. It is well known in the art how to prepare salts or to exchange counter-ions. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of a suitable base (e.g. without limitation, Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate, or the like), or by reacting free base forms of these compounds with a stoichiometric amount of a suitable acid. Such reactions are generally carried out in water or in an organic solvent, or in a mixture of the two. Counter-ions may be changed, for example, by ion-exchange techniques such as ion-exchange chromatography. Solvates may be made any methodology known in the art, e.g. by dissolving the compound in hot solvent (e.g. water or another solvent) followed by cooling and/or evaporation. All zwitterions, salts, solvates and counter-ions are intended, unless a particular form is specifically indicated.

[0084] In certain embodiments, the salt or counter-ion may be pharmaceutically acceptable, for administration to a subject. More generally, with respect to any pharmaceutical composition disclosed herein, non-limiting examples of suitable excipients include any suitable buffers, stabilizing agents, salts, antioxidants, complexing agents, tonicity agents, cryoprotectants, lyoprotectants, suspending agents, emulsifying agents, antimicrobial agents, preservatives, chelating agents, binding agents, surfactants, wetting agents, non-aqueous vehicles such as fixed oils, or polymers for sustained or controlled release. See, for example, Berge et al. 1977. (*J. Pharm Sci.* 66:1-19), or Remington— The Science and Practice of Pharmacy, 21st edition (Gennaro et al editors. Lippincott Williams & Wilkins Philadelphia), each of which is incorporated by reference in its entirety.

[0085] As used herein, the expression “Cy-Cz”, where y and z are integers (e.g. C₁-C₁₅, C₁-C₅, and the like), refers to the number of carbons in a compound, R-group or substituent, or refers to the number of carbons plus heteroatoms when a certain number of carbons are specified as being replaced (or optionally replaced) by heteroatoms. Heteroatoms may include any, some or all possible heteroatoms. For example, in some embodiments, the heteroatoms are selected from N, O, S, P and Se. In some embodiments, the heteroatoms are selected from N, S and O. Unless otherwise specified, such embodiments are non-limiting. When replacing a carbon with a heteroatom, it will be understood that the replacements only include those that would be reasonably made by the person of skill in the art. For example, -O-O- linkages are explicitly excluded. The expression “C₁-C₅ ... wherein one or more carbons in C₂-C₅ are optionally independently replaced with N, S, and or O heteroatoms” and similar expressions are intended to specify that the C₁ carbon (i.e. the first carbon in the defined group and therefore the carbon directly bonded to the remainder of the compound) is not replaced. Such expressions are also intended to include replacement of one carbon, and replacement of multiple carbons, either with the same heteroatom (e.g. one of N, S, or O) or with a combination of different heteroatoms (e.g. combinations of N, S, and/or O in suitable configurations).

[0086] Unless explicitly stated otherwise, the term “alkyl” includes any reasonable combination of the following: (1) linear or branched; (2) acyclic or cyclic, the latter of which may include multi-cyclic (fused rings, multiple non-fused rings or a combination thereof; and (3) unsubstituted or substituted. In the context of the expression “alkyl, alkenyl or alkynyl” and similar expressions, the “alkyl” would be understood to be a saturated alkyl. As used herein, the term “linear” may be used as it is normally understood to a person of skill in the art and generally refers to a chemical entity that comprises a skeleton or main chain that does not split off into more than one contiguous chain. Non-limiting examples of linear alkyls include methyl, ethyl, n-propyl, and n-butyl. As used herein, the term “branched” may be used as it is normally understood to a person of skill in the art and generally refers to a chemical entity that comprises a skeleton or main chain that splits off into more than one contiguous chain. The portions of the skeleton or main chain that split off in more than one direction may be linear, cyclic or any combination thereof. Non-limiting examples of a branched alkyl group include tert-butyl and isopropyl.

[0087] The term “alkylenyl” refers to a divalent analog of an alkyl group. In the context of the expression “alkylenyl, alkenylenyl or alkynylenyl”, and similar expressions, the “alkylenyl” would be understood to be a saturated alkylenyl.

[0088] As used herein, the term “saturated” when referring to a chemical entity may be used as it is normally understood to a person of skill in the art and generally refers to a chemical entity that comprises only single bonds, and may include linear, branched, and/or cyclic

groups. Non-limiting examples of a saturated C₁-C₂₀ alkyl group may include methyl, ethyl, n-propyl, i-propyl, sec-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, n-pentyl, i-pentyl, sec-pentyl, t-pentyl, n-hexyl, i-hexyl, 1,2-dimethylpropyl, 2-ethylpropyl, 1-methyl-2-ethylpropyl, 1-ethyl-2-methylpropyl, 1,1,2-trimethylpropyl, 1,1,2-triethylpropyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 2-ethylbutyl, 1,3-dimethylbutyl, 2-methylpentyl, 3-methylpentyl, sec-hexyl, t-hexyl, n-heptyl, i-heptyl, sec-heptyl, t-heptyl, n-octyl, i-octyl, sec-octyl, t-octyl, n-nonyl, i-nonyl, sec-nonyl, t-nonyl, n-decyl, i-decyl, sec-decyl, t-decyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, and the like. Unless otherwise specified, a C₁-C₂₀ alkyl group therefore encompasses, without limitation, all divalent analogs of the above-listed saturated alkyl groups.

[0089] As used herein, an expression such as “C₃-C₅ alkenyl, alkenyl or alkynyl” is understood to mean C₃-C₅ alkenyl, C₃-C₅ alkenyl, or C₃-C₅ alkynyl and expression such as “C₁-C₅ alkenyl, alkenyl or alkynyl” is understood to mean C₁-C₅ alkenyl, C₂-C₅ alkenyl, or C₂-C₅ alkynyl. Similarly, as used herein, an expression such as “C₅-C₂₀ alkyl, alkyl or alkynyl” is understood to mean C₅-C₂₀ alkyl, C₅-C₂₀ alkyl or C₅-C₂₀ alkynyl and expression such as “C₁-C₂₀ alkyl, alkyl or alkynyl” is understood to mean C₁-C₂₀ alkyl, C₂-C₂₀ alkyl or C₂-C₂₀ alkynyl.

[0090] As used herein, the term “unsaturated” when referring to a chemical entity may be used as it is normally understood to a person of skill in the art and generally refers to a chemical entity that comprises at least one double or triple bond, and may include linear, branched, and/or cyclic groups. Non-limiting examples of a C₂-C₂₀ alkenyl group may include vinyl, allyl, isopropenyl, 1-propene-2-yl, 1-butene-1-yl, 1-butene-2-yl, 1-butene-3-yl, 2-butene-1-yl, 2-butene-2-yl, octenyl, decenyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclononanenyl, cyclodecanenyl, and the like. Unless otherwise specified, a C₁-C₂₀ alkenyl group therefore encompasses, without limitation, all divalent analogs of the above-listed alkenyl groups. Non-limiting examples of a C₂-C₂₀ alkynyl group may include ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, and the like. Unless otherwise specified, a C₁-C₂₀ alkynyl group therefore encompasses, without limitation, all divalent analogs of the above-listed alkynyl groups.

[0091] Where it is specified that 1 or more carbons in an alkyl, alkenyl, alkynyl, alkenyl, alkenyl, alkynyl, etc., are independently replaced by a heteroatom, the person of skill in the art would understand that various combinations of different heteroatoms may be used. Non-limiting examples of non-aromatic heterocyclic groups include aziridinyl, azetidyl, diazetidinyl, pyrrolidinyl, pyrrolinyl, piperidinyl, piperazinyl, imidazolyl, pyrazolidinyl, imidazolidinyl, phthalimidyl, succinimidyl, oxiranyl, tetrahydropyranyl, oxetanyl, dioxanyl, thietanyl, thiepinyl, morpholinyl, oxathiolanyl, and the like. The expression “a linear, branched, and/or cyclic ... alkyl, alkenyl or alkynyl” includes, *inter alia*, aryl groups. Unless further

specified, an “aryl” group includes both single aromatic rings as well as fused rings containing at least one aromatic ring. Non-limiting examples of C₃-C₂₀ aryl groups include phenyl (Ph), pentalenyl, indenyl, naphthyl and azulenyl. Non-limiting examples of C₃-C₂₀ aromatic rings with one or more carbons replaced with heteroatoms include pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pirazinyl, quinolinyl, isoquinolinyl, acridinyl, indolyl, isoindolyl, indoliziny, purinyl, carbazolyl, indazolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, phenanthridinyl, phenazinyl, phenanthrolinyl, perimidinyl, furyl, dibenzofuryl, xanthenyl, benzofuryl, thiophenyl, thianthrenyl, benzothiophenyl, phosphorinyl, phosphinolyl, phosphindolyl, thiazolyl, oxazolyl, isoxazolyl, and the like. Likewise, the expression “a linear, branched, and/or cyclic ... alkylenyl, alkenylenyl or alkynylenyl” includes, *inter alia*, divalent analogs of the above-defined linear, branched, and/or cyclic alkyl, alkenyl or alkynyl groups, including all aryl groups encompassed therein.

[0092] As used herein, the term “substituted” is used as it would normally be understood to a person of skill in the art and generally refers to a compound or chemical entity that has one chemical group replaced with a different chemical group. Unless otherwise specified, a substituted alkyl is an alkyl in which one or more hydrogen atom(s) are independently each replaced with an atom that is not hydrogen. For example, chloromethyl is a non-limiting example of a substituted alkyl, more particularly an example of a substituted methyl. Aminoethyl is another non-limiting example of a substituted alkyl, more particularly an example of a substituted ethyl. Unless otherwise specified, a substituted compound or group (e.g. alkyl, alkylenyl, aryl, and the like) may be substituted with any chemical group reasonable to the person of skill in the art. For example, but without limitation, a hydrogen bonded to a carbon or heteroatom (e.g. N) may be substituted with halide (e.g. F, I, Br, Cl), amine, amide, oxo, hydroxyl, thiol (sulfhydryl), phosphate (or phosphoric acid), phosphonate, sulfate, SO₂H (sulfinic acid), SO₃H (sulfonic acid), alkyls, aryl, ketones, carboxaldehyde, carboxylic acid, carboxamides, nitriles, guanidino, monohalomethyl, dihalomethyl or trihalomethyl.

[0093] As used herein, the term “guanidino” refers to the group —NHC(=NH)NH₂ or —NHC(=NR)NR₂, wherein each R is independently H or alkyl.

[0094] As used herein, the term “unsubstituted” is used as it would normally be understood to a person of skill in the art. Non-limiting examples of unsubstituted alkyls include methyl, ethyl, tert-butyl, pentyl and the like. The expression “optionally ... substituted” is used interchangeably with the expression “unsubstituted or substituted”.

[0095] In the structures provided herein, hydrogen may or may not be shown. In some embodiments, hydrogens (whether shown or implicit) may be protium (i.e. ¹H), deuterium (i.e. ²H) or combinations of ¹H and ²H. Methods for exchanging ¹H with ²H are well known in the art. For solvent-exchangeable hydrogens, the exchange of ¹H with ²H occurs readily in the presence of a suitable deuterium source, without any catalyst. The use of acid, base or metal

catalysts, coupled with conditions of increased temperature and pressure, can facilitate the exchange of non-exchangeable hydrogen atoms, generally resulting in the exchange of all ^1H to ^2H in a molecule.

[0096] The compounds disclosed herein incorporate amino acids, e.g. as residues in a peptide chain (linear or branched) or as amino acids that are otherwise part of a compound. Amino acids have both an amino group and a carboxylic acid group, either or both of which can be used for covalent attachment. In attaching to the remainder of the compound, the amino group and/or the carboxylic acid group may be converted to an amide or other structure; e.g. a carboxylic acid group of a first amino acid is converted to an amide (e.g. a peptide bond) when bonded to the amino group of a second amino acid. As such, amino acid residues may have the formula $-\text{N}(\text{R}^a)\text{R}^b\text{C}(\text{O})-$, where R^a and R^b are R-groups. R^a will typically be hydrogen or methyl. The amino acid residues of a peptide may comprise typical peptide (amide) bonds and may further comprise bonds between side chain functional groups and the side chain or main chain functional group of another amino acid. For example, the side chain carboxylate of one amino acid residue in the peptide (e.g. Asp, Glu, etc.) may be bonded to and the amine of another amino acid residue in the peptide (e.g. Dap, Dab, Orn, Lys). Further details are provided below. The term "amino acid" includes proteinogenic and nonproteinogenic amino acids. Non-limiting examples of nonproteinogenic amino acids are shown in Table 1 and include: D-amino acids (including without limitation any D-form of the following amino acids), ornithine (Orn), 3-(1-naphtyl)alanine (Nal), 3-(2-naphtyl)alanine (2-Nal), α -aminobutyric acid, norvaline, norleucine (Nle), homonorleucine, beta-(1,2,3-triazol-4-yl)-L-alanine, 1,2,4-triazole-3-alanine, Phe(4-F), Phe(4-Cl), Phe(4-Br), Phe(4-I), Phe(4-NH₂), Phe(4-NO₂), N $^{\epsilon}$, N $^{\epsilon}$, N $^{\epsilon}$ -trimethyl-lysine, homoarginine (hArg), 2-amino-4-guanidinobutyric acid (Agb), 2-amino-3-guanidinopropionic acid (Agp), B-alanine, 4-aminobutyric acid, 5-aminovaleric acid, 6-aminohexanoic acid, 7-aminoheptanoic acid, 8-aminooctanoic acid, 9-aminononanoic acid, 10-aminodecanoic acid, 2-amino-octanoic acid, 2-amino-3-(anthracen-2-yl)propanoic acid, 2-amino-3-(anthracen-9-yl)propanoic acid, 2-amino-3-(pyren-1-yl)propanoic acid, Trp(5-Br), Trp(5-OCH₃), Trp(6-F), Trp(5-OH) or Trp(CHO), 2-amino-adipic acid (2-Aad), 3-amino-adipic acid (3-Aad), propargylglycine (Pra), homopropargylglycine (Hpg), beta-homopropargylglycine (Bpg), 2,3-diaminopropionic acid (Dap), 2,4-diaminobutyric acid (Dab), azidolysine (Lys(N₃)), azido-ornithine (Orn(N₃)), 2-amino-4-azidobutanoic acid Dab(N₃), Dap(N₃), 2-(5'-azidopentyl)alanine, 2-(6'-azidohexyl)alanine, 4-amino-1-carboxymethyl-piperidine (Pip), 4-(2-aminoethyl)-1-carboxymethyl-piperazine (Acp), and tranexamic acid. If not specified as an L- or D-amino acid, an amino acid shall be understood to be an L-amino acid.

[0097] TABLE 1. List of non-limiting examples of non-proteinogenic amino acids.

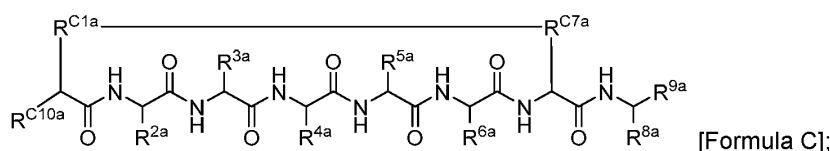
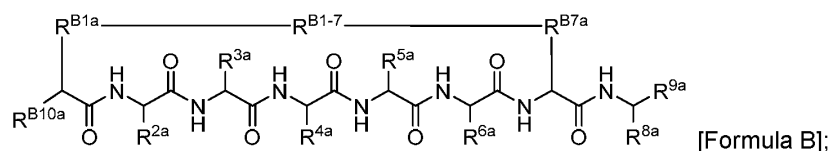
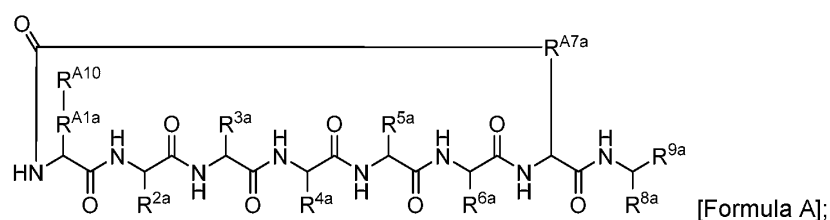
Any D-amino acid of a proteinogenic amino acid	10-aminodecanoic acid
ornithine (Orn)	2-aminooctanoic acid
3-(1-naphtyl)alanine (Nal)	2-amino-3-(anthracen-2-yl)propanoic acid
3-(2-naphtyl)alanine (2-Nal)	2-amino-3-(anthracen-9-yl)propanoic acid
α -aminobutyric acid	2-amino-3-(pyren-1-yl)propanoic acid
norvaline	Trp(5-Br)
norleucine (Nle)	Trp(5-OCH ₃)
homonorleucine	Trp(6-F)
beta-(1,2,3-triazol-4-yl)-L-alanine	Trp(5-OH)
1,2,4-triazole-3-alanine	Trp(CHO)
Phe(4-F) or (4-F)Phe	2-aminoadipic acid (2-Aad)
Phe(4-Cl) or (4-Cl)Phe	3-aminoadipic acid (3-Aad)
Phe(4-Br) or (4-Br)Phe	propargylglycine (Pra)
Phe(4-I) or (4-I)Phe	homopropargylglycine (Hpg)
Phe(4-NH ₂) or (4-NH ₂)Phe	beta-homopropargylglycine (Bpg)
Phe(4-NO ₂) or (4-NO ₂)Phe	2,3-diaminopropionic acid (Dap)
(3-I)Tyr	2,4-diaminobutyric acid (Dab)
homoarginine (hArg)	Cysteic acid (CysAcid)
homotyrosine (hTyr)	N ϵ -isopropyl-lysine (Lys(iPr))
3-(2-phenanthryl)-L-alanine (2-(Ant)Ala)	Arg(Me)
3-(9-phenanthryl)-L-alanine (9-(Ant)Ala)	Arg(Me) ₂ (symmetrical or asymmetrical)
4-(2-aminoethyl)-1-carboxymethyl-piperazine (Acp)	azidolysine (Lys(N ₃))
2-(5'-azidopentyl)alanine	azido-ornithine (Orn(N ₃))
2-(6'-azidohexyl)alanine	amino-4-azidobutanoic acid Dab(N ₃)
2-amino-4-guanidinobutyric acid (Agb)	tranexamic acid
2-amino-3-guanidinopropionic acid (Agp)	4-amino-1-carboxymethyl-piperidine (Pip)
β -alanine	NH ₂ (CH ₂) ₂ O(CH ₂) ₂ C(O)OH
4-aminobutyric acid	NH ₂ (CH ₂) ₂ [O(CH ₂) ₂] ₂ C(O)OH
5-aminovaleric acid	NH ₂ (CH ₂) ₂ [O(CH ₂) ₂] ₃ C(O)OH
6-aminohexanoic acid	NH ₂ (CH ₂) ₂ [O(CH ₂) ₂] ₄ C(O)OH
7-aminoheptanoic acid	NH ₂ (CH ₂) ₂ [O(CH ₂) ₂] ₅ C(O)OH
8-aminooctanoic acid	NH ₂ (CH ₂) ₂ [O(CH ₂) ₂] ₆ C(O)OH
9-aminononanoic acid	N ϵ -acetyl-lysine (Lys(Ac))

[0098] As used herein, "peptide backbone amides" refers to the amides (-C(O)-NH-) drawn in the structures of Formula A-I, A-II, A-III, B, or C, for example, including the amide bond between carbon atoms bonded to R^{2a} and R^{3a}. One or more peptide backbone amides can be

methylated or N-methylated, unless otherwise discussed herein. For example, the amide bond between carbon atoms bonded to R^{2a} and R^{3a} can be methylated ($-C(O)-NCH_3-$).

[0099] The wavy line “~” symbol shown through or at the end of a bond in a chemical formula (e.g. in the definition L^1) is intended to define the R group on one side of the wavy line, without modifying the definition of the structure on the opposite side of the wavy line. Where an R group is bonded on two or more sides (e.g. certain definitions of X^1), any atoms shown outside the wavy lines are intended to clarify orientation of the R group. As such, only the atoms between the two wavy lines constitute the definition of the R group. When atoms are not shown outside the wavy lines, or for a chemical group shown without wavy lines but does have bonds on multiple sides (e.g. $-C(O)NH-$, and the like.), the chemical group should be read from left to right matching the orientation in the formula that the group relates to (e.g. for formula $-R^a-R^b-R^c-$, the definition of R^b as $-C(O)NH-$ would be incorporated into the formula as $-R^a-C(O)NH-R^c-$ not as $-R^a-NHC(O)-R^c-$).

[00100] In various aspects, there is disclosed a compound of Formula A, B, or C, or a salt or solvate of Formula A, B, or C:

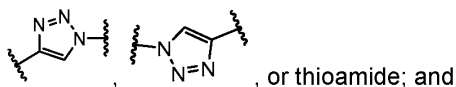


R-groups are defined below;

with the proviso that Formula A excludes the following combination:

- NH-CH(R^{2a})-C(O)- forms a Tyr residue;
- NH-CH(R^{4a})-C(O)- forms a D-Arg residue;
- NH-CH(R^{5a})-C(O)- forms a 2-Nal residue; and
- R^{6a} is H;

wherein 0-3 peptide backbone amides are independently replaced with



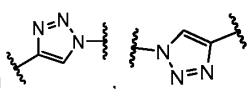
wherein 0-3 peptide backbone amides are N-methylated.

[00101] In some embodiments, the compound has the structure of Formula A. In some embodiments, the compound is a salt of Formula A. In some embodiments, the compound is a solvate of Formula A.

[00102] In some embodiments, the compound has the structure of Formula B. In some embodiments, the compound is a salt of Formula B. In some embodiments, the compound is a solvate of Formula B.

[00103] In some embodiments, the compound has the structure of Formula C. In some embodiments, the compound is a salt of Formula C. In some embodiments, the compound is a solvate of Formula C.

[00104] In some embodiments of the compounds of Formula A, B, and/or C, 1 peptide

backbone amide is replaced with , or thioamide. In some embodiments, two peptide backbone amides are replaced. In some embodiments, three peptide backbone amides are replaced. In some embodiments, zero peptide backbone amides are replaced.

[00105] In some embodiments of the compounds of Formula A, B, and/or C, 1 peptide backbone amide is N-methylated. In some embodiments, two peptide backbone amides are N-methylated. In some embodiments, three peptide backbone amides are N-methylated. In some embodiments, zero peptide backbone amides are N-methylated.

[00106] In some embodiments of the compounds of Formula A, B, and/or C, R^{2a} is $-(CH_2)-(R^{2b})-(phenyl)$, wherein R^{2b} is absent, $-CH_2-$, $-NH-$, $-S-$ or $-O-$, wherein the phenyl is 4-substituted with $-NH_2$, $-NO_2$, $-OH$, $-OR^{2c}$, $-SH$, $-SR^{2c}$, or $-O-phenyl$, wherein the phenyl is optionally 3-substituted with halogen or $-OH$, wherein the phenyl is optionally 5-substituted with halogen or $-OH$, wherein the $-O-phenyl$ ring is optionally 4-substituted with $-NH_2$, $-NO_2$, $-OH$, $-OR^{2c}$, $-SH$, or $-SR^{2c}$, wherein the $-O-phenyl$ ring is optionally 3-substituted with halogen or $-OH$, wherein the $-O-phenyl$ ring is optionally 5-substituted with halogen or $-OH$, wherein each R^{2c} is independently a C_1 - C_3 linear or branched alkyl group.

[00107] In some embodiments of the compounds of Formula A, B, and/or C, R^{2b} is absent. In some embodiments, R^{2b} is $-CH_2-$. In some embodiments, R^{2b} is $-NH-$. In some embodiments, R^{2b} is $-S-$. In some embodiments, R^{2b} is $-O-$.

[00108] In some embodiments of the compounds of Formula A, B, and/or C, R^{2a} is $-(CH_2)-(R^{2b})-(phenyl)$, wherein R^{2b} is absent or $-CH_2-$, wherein the phenyl is 4-substituted with $-NH_2$, $-NO_2$, $-OH$, $-OR^{2c}$, $-SH$, $-SR^{2c}$, or $-O-phenyl$. In some embodiments, the phenyl is 4-

substituted with -NH_2 . In some embodiments, the phenyl is 4-substituted with -NO_2 . In some embodiments, the phenyl is 4-substituted with -OH . In some embodiments, the phenyl is 4-substituted with -SH . In some embodiments, the phenyl is 4-substituted with -O-phenyl . In some embodiments, the phenyl is 3,5-unsubstituted. In some embodiments, the phenyl is 3-substituted. In some embodiments, phenyl is 5-substituted. In some embodiments, the phenyl is 3,5-substituted. In some embodiments, the halogen substituent is iodine. The 3,5-substituents may be the same or different (e.g. different halogens, or a mix of halogen and -OH).

[00109] In some embodiments of the compounds of Formula A, B, and/or C, $\text{-NH-CH(R}^{2a}\text{)-C(O)-}$ forms an L-amino acid residue. In some embodiments, $\text{-NH-CH(R}^{2a}\text{)-C(O)-}$ forms a D-amino acid residue. In some embodiments, $\text{-NH-CH(R}^{2a}\text{)-C(O)-}$ forms a Tyr residue. In some embodiments, $\text{-NH-CH(R}^{2a}\text{)-C(O)-}$ forms a Phe residue. In some embodiments, $\text{-NH-CH(R}^{2a}\text{)-C(O)-}$ forms a (4- NO_2)-Phe residue. In some embodiments, $\text{-NH-CH(R}^{2a}\text{)-C(O)-}$ forms a (4- NH_2)-Phe residue. In some embodiments, $\text{-NH-CH(R}^{2a}\text{)-C(O)-}$ forms a hTyr residue. In some embodiments, $\text{-NH-CH(R}^{2a}\text{)-C(O)-}$ forms a (3-I)Tyr residue. In some embodiments, $\text{-NH-CH(R}^{2a}\text{)-C(O)-}$ forms a Glu residue. In some embodiments, $\text{-NH-CH(R}^{2a}\text{)-C(O)-}$ forms a Gln residue. In some embodiments, $\text{-NH-CH(R}^{2a}\text{)-C(O)-}$ forms a D-Tyr residue.

[00110] In some embodiments, of the compounds of Formula A, B, and/or C, R^{3a} is $\text{R}^{3b}\text{R}^{3c}$ wherein R^{3b} is a linear $\text{C}_1\text{-C}_5$ alkylenyl, alkenylenyl, or alkynylenyl, wherein 0-2 carbons in $\text{C}_2\text{-C}_5$ alkylenyl, alkenylenyl, or alkynylenyl are independently replaced with one or more N, S, and/or O heteroatoms, wherein R^{3c} is $\text{-N(R}^{3d}\text{)}_{2-3}$ or guanidino, wherein each R^{3d} is independently -H or a linear or branched $\text{C}_1\text{-C}_3$ alkyl.

[00111] In some embodiments of the compounds of Formula A, B, and/or C, R^{3b} is a linear $\text{C}_1\text{-C}_5$ alkylenyl, alkenylenyl, or alkynylenyl (i.e. no heteroatoms). In some embodiments, R^{3b} comprises a single heteroatom (N, S or O) in any one of $\text{C}_2\text{-C}_5$ alkylenyl, alkenylenyl, or alkynylenyl. In some embodiments, R^{3b} is a linear $\text{C}_1\text{-C}_5$ alkylenyl.

[00112] In some embodiments of the compounds of Formula A, B, and/or C, R^{3c} is guanidino. In some embodiments, R^{3c} is $\text{-N(R}^{3d}\text{)}_{2-3}$. In some embodiments, R^{3c} is $\text{-N(R}^{3d}\text{)}_{2-3}$ wherein each R^{3d} is a linear or branched $\text{C}_1\text{-C}_3$ alkyl. In some embodiments, R^{3c} is $\text{-N(R}^{3d}\text{)}_{2-3}$ wherein each R^{3d} is methyl. In some embodiments, R^{3c} is $\text{-N(R}^{3d}\text{)}_{2-3}$ wherein each R^{3d} is independently -H or methyl. In some embodiments, R^{3c} is -NH_2 or -NH_3 .

[00113] In some embodiments of the compounds of Formula A, B, and/or C, $\text{-NH-CH(R}^{3a}\text{)-C(O)-}$ forms an L-amino acid residue. In some embodiments, $\text{-NH-CH(R}^{3a}\text{)-C(O)-}$ forms a D-amino acid residue. In some embodiments, $\text{-NH-CH(R}^{3a}\text{)-C(O)-}$ forms a Lys(iPr) residue. In some embodiments, $\text{-NH-CH(R}^{3a}\text{)-C(O)-}$ forms an Arg(Me)₂ (asymmetrical) residue. In some embodiments, $\text{-NH-CH(R}^{3a}\text{)-C(O)-}$ forms an Arg(Me) residue.

[00114] In some embodiments of the compounds of Formula A, B, and/or C, R^{4a} is $R^{4b}R^{4c}$ wherein R^{4b} is a linear C_1 - C_5 alkylenyl, alkenylenyl, or alkynylenyl, in which 0-2 carbons in C_2 - C_5 are independently replaced with one or more N, S, and/or O heteroatoms, wherein R^{4c} is $-N(R^{4d})_{2-3}$ or guanidino, wherein each R^{4d} is independently -H or a linear or branched C_1 - C_3 alkyl.

[00115] In some embodiments of the compounds of Formula A, B, and/or C, R^{4b} is a linear C_1 - C_5 alkylenyl, alkenylenyl, or alkynylenyl (i.e. no heteroatoms). In some embodiments, R^{4b} comprises a single heteroatom (N, S or O) in any one of C_2 - C_5 . In some embodiments, R^{4b} is a linear C_1 - C_5 alkylenyl.

[00116] In some embodiments of the compounds of Formula A, B, and/or C, R^{4c} is guanidino. In some embodiments, R^{4c} is $-N(R^{4d})_{2-3}$. In some embodiments, R^{4c} is $-N(R^{4d})_{2-3}$ wherein each R^{4d} is a linear or branched C_1 - C_3 alkyl. In some embodiments, R^{4c} is $-N(R^{4d})_{2-3}$ wherein each R^{4d} is methyl. In some embodiments, R^{4c} is $-N(R^{4d})_{2-3}$ wherein each R^{4d} is independently -H or methyl. In some embodiments, R^{4c} is $-NH_2$ or $-NH_3$.

[00117] In some embodiments of the compounds of Formula A, B, and/or C, $-NH-CH(R^{4a})-C(O)-$ forms a D-amino acid residue. In some embodiments, $-NH-CH(R^{4a})-C(O)-$ forms an L-amino acid residue. In some embodiments, $-NH-CH(R^{4a})-C(O)-$ forms a D-Arg residue. In some embodiments, $-NH-CH(R^{4a})-C(O)-$ forms a D-hArg residue.

[00118] In some embodiments of the compounds of Formula A, B, and/or C, R^{5a} is $-(CH_2)_{1-3}-R^{5b}$, wherein 1 carbon in $-(CH_2)_{2-3}-$ is optionally replaced with a N, S, or O heteroatom, wherein R^{5b} is:

phenyl optionally substituted with one or a combination of the following: 4-substituted with $-NH_2$, $-NO_2$, $-OH$, $-OR^{5c}$, $-SH$, $-SR^{5c}$, or $-O$ -phenyl; 3-substituted with halogen or $-OH$; and/or 5-substituted with halogen or $-OH$; wherein the $-O$ -phenyl ring is optionally 4-substituted with $-NH_2$, $-NO_2$, $-OH$, $-OR^{5c}$, $-SH$, or $-SR^{5c}$, wherein the $-O$ -phenyl ring is optionally 3-substituted with halogen or $-OH$, wherein the $-O$ -phenyl ring is optionally 5-substituted with halogen or $-OH$; or

a fused bicyclic or fused tricyclic aryl group wherein one or more carbons are optionally independently replaced by N, S, and/or O heteroatoms, and independently optionally substituted with one or a combination of halogen, $-OH$, $-OR^{5c}$, amino, $-NHR^{5c}$, and/or $N(R^{5c})_2$;

wherein each R^{5c} is independently a C_1 - C_3 linear or branched alkyl group.

[00119] In some embodiments of the compounds of Formula A, B, and/or C, R^{5a} is $-CH_2-R^{5b}$. In some embodiments, R^{5a} is $-CH_2-CH_2-R^{5b}$. In some embodiments, R^{5a} is $-CH_2-CH_2-CH_2-R^{5b}$.

[00120] In some embodiments of the compounds of Formula A, B, and/or C, R^{5b} is phenyl optionally substituted with one or a combination of the following: 4-substituted with -

NH₂, -NO₂, -OH, -OR^{5c}, -SH, -SR^{5c}, or -O-phenyl; 3-substituted with halogen or -OH; and/or 5-substituted with halogen or -OH; wherein the -O-phenyl ring is optionally 4-substituted with -NH₂, -NO₂, -OH, -OR^{5c}, -SH, or -SR^{5c}, wherein the -O-phenyl ring is optionally 3-substituted with halogen or -OH, wherein the -O-phenyl ring is optionally 5-substituted with halogen or -OH. In some embodiments, R^{5b} is phenyl optionally substituted with one or a combination of the following: 4-substituted with -NH₂, -NO₂, -OH, -SH, or -O-phenyl; 3-substituted with halogen or -OH; and/or 5-substituted with halogen or -OH. In some embodiments, the phenyl is 4-unsubstituted. In some embodiments, the phenyl is 4-substituted with -NH₂. In some embodiments, the phenyl is 4-substituted with -NO₂. In some embodiments, the phenyl is 4-substituted with -OH. In some embodiments, the phenyl is 4-substituted with -OR^{5c}. In some embodiments, the phenyl is 4-substituted with -SH. In some embodiments, the phenyl is 4-substituted with -SR^{5c}. In some embodiments, the phenyl is 4-substituted with -O-phenyl. In some embodiments, each R^{5c} is independently a C₁-C₃ linear or branched alkyl group. In some embodiments, each R^{5c} is methyl. In some embodiments, the phenyl is 3-unsubstituted. In some embodiments, the phenyl is 3-substituted with halogen. In some embodiments, the phenyl is 3-substituted with -OH. In some embodiments, the phenyl is 5-substituted with halogen. In some embodiments, the phenyl is 5-substituted with -OH. In some embodiments, the halogen is iodine. In some embodiments, the -O-phenyl ring is unsubstituted. In some embodiments, the -O-phenyl ring is 4-substituted. In some embodiments, the -O-phenyl ring is 3-substituted. In some embodiments, the -O-phenyl ring is 5-substituted.

[00121] In some embodiments of the compounds of Formula A, B, and/or C, R^{5b} is a fused bicyclic or fused tricyclic aryl group wherein one or more carbons are optionally independently replaced by N, S, and/or O heteroatoms, and optionally independently substituted with one or a combination of halogen, -OH, -OR^{5c}, amino, -NHR^{5c}, and/or N(R^{5c})₂. In some embodiments, each R^{5c} is independently a C₁-C₃ linear or branched alkyl group. In some embodiments, each R^{5c} is methyl. In some embodiments, R^{5b} is a fused bicyclic or fused tricyclic aryl group wherein 0-3 carbons are independently replaced by N, S, and/or O heteroatoms, and optionally independently substituted with one or a combination of halogen, -OH, and/or amino. In some embodiments, R^{5b} is a fused bicyclic or fused tricyclic aryl group optionally independently substituted with one or a combination of halogen, -OH, and/or amino. In some embodiments, R^{5b} is a fused bicyclic or fused tricyclic aryl group optionally independently substituted with 0-3 groups selected from halogen, -OH, and/or amino. In some embodiments, R^{5b} is a fused bicyclic or fused tricyclic aryl group. In some embodiments, R^{5b} excludes 9-linked anthracenyl. In some embodiments, each ring in the fused bicyclic or fused tricyclic aryl group independently has 4, 5 or 6 ring carbons, wherein 0-3 carbons are independently replaced by N, S, and/or O heteroatoms; such embodiments may be substituted or unsubstituted as defined above.

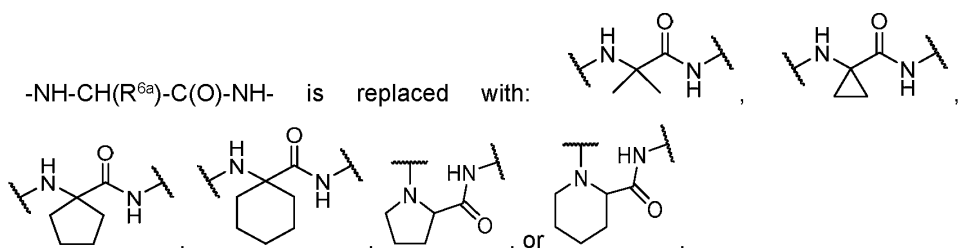
[00122] In some embodiments of the compounds of Formula A, B, and/or C, $\text{-NH-CH(R}^{5a}\text{)-C(O)-}$ forms an L-amino acid residue. In some embodiments, $\text{-NH-CH(R}^{5a}\text{)-C(O)-}$ forms a D-amino acid residue. In some embodiments, $\text{-NH-CH(R}^{5a}\text{)-C(O)-}$ forms a 2-(Ant)Ala residue. In some embodiments, $\text{-NH-CH(R}^{5a}\text{)-C(O)-}$ forms a 2-Nal residue. In some embodiments, $\text{-NH-CH(R}^{5a}\text{)-C(O)-}$ forms a Trp residue. In some embodiments, $\text{-NH-CH(R}^{5a}\text{)-C(O)-}$ forms a (4-NH₂)Phe residue. In some embodiments, $\text{-NH-CH(R}^{5a}\text{)-C(O)-}$ forms a hTyr residue. In some embodiments, $\text{-NH-CH(R}^{5a}\text{)-C(O)-}$ forms a Tyr residue.

[00123] In some embodiments of the compounds of Formula A, B, and/or C, either:

(a) R^{6a} is H, methyl, ethyl, $\text{-C}\equiv\text{CH}$, -CH=CH_2 , $\text{-C}\equiv\text{C-(CH}_2\text{)}_{1-3}\text{-OH}$, $\text{-C}\equiv\text{C-(CH}_2\text{)}_{1-3}\text{-SH}$, $\text{-C}\equiv\text{C-(CH}_2\text{)}_{1-3}\text{-NH}_2$, $\text{-C}\equiv\text{C-(CH}_2\text{)}_{1-3}\text{-COOH}$, $\text{-C}\equiv\text{C-(CH}_2\text{)}_{1-3}\text{-CONH}$, $\text{-C}\equiv\text{C-(CH}_2\text{)}_{1-3}\text{R}^{6b}\text{R}^{6c}$, $\text{-CH=CH-(CH}_2\text{)}_{1-3}\text{-OH}$, $\text{-CH=CH-(CH}_2\text{)}_{1-3}\text{-SH}$, $\text{-CH=CH-(CH}_2\text{)}_{1-3}\text{-NH}_2$, $\text{-CH=CH-(CH}_2\text{)}_{1-3}\text{-COOH}$, $\text{-CH=CH-(CH}_2\text{)}_{1-3}\text{-CONH}$, $\text{-CH=CH-(CH}_2\text{)}_{1-3}\text{R}^{6b}\text{R}^{6c}$, $\text{-CH}_2\text{-R}^{6b}\text{-OH}$, $\text{-CH}_2\text{-R}^{6b}\text{-COOH}$, $\text{-CH}_2\text{-(R}^{6b}\text{)}_{1-3}\text{-NH}_2$, $\text{-CH}_2\text{-R}^{6b}\text{-CONH}$, or $\text{-CH}_2\text{-R}^{6b}\text{R}^{6c}$, wherein each R^{6b} is independently absent, $\text{-CH}_2\text{-}$, -NH- , -S- or -O- , and wherein R^{6c} is:

a 5 or 6 membered aromatic ring wherein one or more carbons are optionally independently replaced by N, S, and/or O heteroatoms, and optionally substituted with one or more groups independently selected from oxo, hydroxyl, sulfhydryl, nitro, amino, and/or halogen; or

(b) $\text{-NH-CH(R}^{6a}\text{)-C(O)-NH-}$ is replaced with:

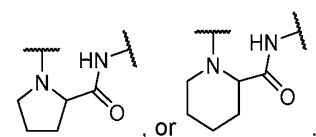
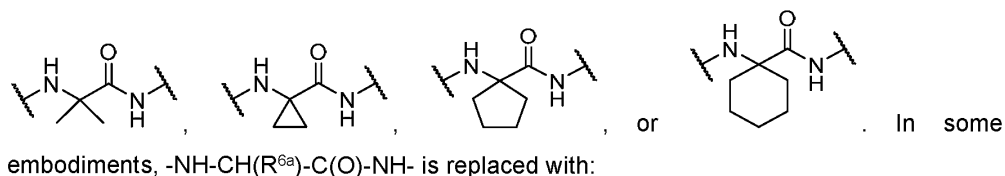


[00124] In some embodiments of the compounds of Formula A, B, and/or C, R^{6a} is H. In some embodiments, R^{6a} is methyl. In some embodiments, R^{6a} is ethyl. In some embodiments, R^{6a} is $\text{-C}\equiv\text{CH}$. In some embodiments, R^{6a} is -CH=CH_2 . In some embodiments, R^{6a} is $\text{-CH}_2\text{-R}^{6b}\text{-OH}$. In some embodiments, R^{6a} is $\text{-CH}_2\text{-R}^{6b}\text{-COOH}$. In some embodiments, R^{6a} is $\text{-CH}_2\text{-(R}^{6b}\text{)}_{1-3}\text{-NH}_2$. In some embodiments, R^{6a} is $\text{-CH}_2\text{-R}^{6b}\text{-CONH}$. In some embodiments, R^{6a} is $\text{-C}\equiv\text{C-(CH}_2\text{)}_{1-3}\text{-OH}$. In some embodiments, R^{6a} is $\text{-C}\equiv\text{C-(CH}_2\text{)}_{1-3}\text{-SH}$. In some embodiments, R^{6a} is $\text{-C}\equiv\text{C-(CH}_2\text{)}_{1-3}\text{-NH}_2$. In some embodiments, R^{6a} is $\text{-C}\equiv\text{C-(CH}_2\text{)}_{1-3}\text{-COOH}$. In some embodiments, R^{6a} is $\text{-C}\equiv\text{C-(CH}_2\text{)}_{1-3}\text{-CONH}$. In some embodiments, R^{6a} is $\text{-C}\equiv\text{C-(CH}_2\text{)}_{1-3}\text{R}^{6b}\text{R}^{6c}$. In some embodiments, R^{6a} is $\text{-CH=CH-(CH}_2\text{)}_{1-3}\text{-OH}$. In some embodiments, R^{6a} is $\text{-CH=CH-(CH}_2\text{)}_{1-3}\text{-SH}$. In some embodiments, R^{6a} is $\text{-CH=CH-(CH}_2\text{)}_{1-3}\text{-NH}_2$. In some embodiments, R^{6a} is $\text{-CH=CH-(CH}_2\text{)}_{1-3}\text{-COOH}$. In some embodiments, R^{6a} is $\text{-CH=CH-(CH}_2\text{)}_{1-3}\text{-CONH}$. In some embodiments, R^{6a} is $\text{-CH=CH-(CH}_2\text{)}_{1-3}\text{R}^{6b}\text{R}^{6c}$. Each R^{6b} is

independently absent, $-\text{CH}_2-$, $-\text{NH}-$, $-\text{S}-$ or $-\text{O}-$. In some embodiments, R^{6b} is absent. In some embodiments, R^{6b} is $-\text{CH}_2-$.

[00125] In some embodiments of the compounds of Formula A, B, and/or C, R^{6a} is H, methyl, ethyl, $-\text{C}\equiv\text{CH}$, $-\text{CH}=\text{CH}_2$, $-\text{CH}_2-\text{R}^{6b}-\text{OH}$, $-\text{CH}_2-\text{R}^{6b}-\text{COOH}$, $-\text{CH}_2-(\text{R}^{6b})_{1-3}-\text{NH}_2$, $-\text{CH}_2-\text{R}^{6b}-\text{CONH}$, or $-\text{CH}_2-\text{R}^{6b}\text{R}^{6c}$. In some embodiments, R^{6a} is $-\text{CH}_2-\text{R}^{6b}\text{R}^{6c}$. Each R^{6b} is independently absent, $-\text{CH}_2-$, $-\text{NH}-$, $-\text{S}-$ or $-\text{O}-$. In some embodiments, R^{6b} is absent. In some embodiments, R^{6b} is $-\text{CH}_2-$. In some embodiments, R^{6c} is a 5 or 6 membered aromatic ring wherein 0-3 carbons are independently replaced by N, S, and/or O heteroatoms, and optionally substituted with 0-3 groups independently selected from oxo, hydroxyl, sulfhydryl, nitro, amino, and/or halogen; in some embodiments, the ring is unsubstituted. In some embodiments, R^{6c} is a 5 or 6 membered aryl, optionally substituted with 0-3 groups independently selected from oxo, hydroxyl, sulfhydryl, nitro, amino, and/or halogen; in some embodiments, the aryl is unsubstituted.

[00126] In some embodiments of the compounds of Formula A, B, and/or C, $-\text{NH}-\text{CH}(\text{R}^{6a})-\text{C}(\text{O})-\text{NH}-$ is replaced with:



[00127] In some embodiments of the compounds of Formula A, B, and/or C, $-\text{NH}-\text{CH}(\text{R}^{6a})-\text{C}(\text{O})-$ forms a D-amino acid residue. In some embodiments, $-\text{NH}-\text{CH}(\text{R}^{6a})-\text{C}(\text{O})-$ forms an L-amino acid residue. In some embodiments, $-\text{NH}-\text{CH}(\text{R}^{6a})-\text{C}(\text{O})-$ forms a His residue. In some embodiments, $-\text{NH}-\text{CH}(\text{R}^{6a})-\text{C}(\text{O})-$ forms a D-His residue. In some embodiments, $-\text{NH}-\text{CH}(\text{R}^{6a})-\text{C}(\text{O})-$ forms a D-Glu residue. In some embodiments, $-\text{NH}-\text{CH}(\text{R}^{6a})-\text{C}(\text{O})-$ forms a D-Gln residue. In some embodiments, $-\text{NH}-\text{CH}(\text{R}^{6a})-\text{C}(\text{O})-$ forms a D-Ala residue. In some embodiments, $-\text{NH}-\text{CH}(\text{R}^{6a})-\text{C}(\text{O})-$ forms a D-Phe residue. In some embodiments, $-\text{NH}-\text{CH}(\text{R}^{6a})-\text{C}(\text{O})-$ forms a D-Ser residue. In some embodiments, $-\text{NH}-\text{CH}(\text{R}^{6a})-\text{C}(\text{O})-$ forms a D-Dab residue. In some embodiments, $-\text{NH}-\text{CH}(\text{R}^{6a})-\text{C}(\text{O})-$ forms a D-Dap residue.

[00128] In some embodiments of the compounds of Formula A, B, and/or C, R^{8a} is $\text{R}^{8b}\text{R}^{8c}$ wherein R^{8b} is a linear C_1-C_5 alkylenyl, alkenylenyl, or alkynylenyl, in which 0-2 carbons in C_2-C_5 are independently replaced with one or more N, S, and/or O heteroatoms, wherein

R^{8c} is $-N(R^{8d})_{2-3}$ or guanidino, wherein each R^{8d} is independently -H or a linear or branched C_1-C_3 alkyl.

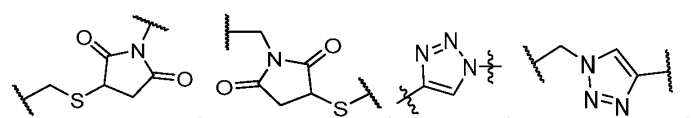
[00129] In some embodiments of the compounds of Formula A, B, and/or C, R^{8b} is a linear C_1-C_5 alkynyl, alkenyl, or alkynyl (i.e. no heteroatoms). In some embodiments, R^{8b} comprises a single heteroatom (N, S or O) in any one of C_2-C_5 . In some embodiments, R^{8b} is a linear C_1-C_5 alkynyl.

[00130] In some embodiments of the compounds of Formula A, B, and/or C, R^{8c} is guanidino. In some embodiments, R^{8c} is $-N(R^{8d})_{2-3}$. In some embodiments, R^{8c} is $-N(R^{8d})_{2-3}$ wherein each R^{8d} is a linear or branched C_1-C_3 alkyl. In some embodiments, R^{8c} is $-N(R^{8d})_{2-3}$ wherein each R^{8d} is methyl. In some embodiments, R^{8c} is $-N(R^{8d})_{2-3}$ wherein each R^{8d} is independently -H or methyl. In some embodiments, R^{8c} is $-NH_2$ or $-NH_3$.

[00131] In some embodiments of the compounds of Formula A, B, and/or C, $-NH-CH(R^{8a})-C(O)-$ forms an L-amino acid residue. In some embodiments, $-NH-CH(R^{8a})-C(O)-$ forms a D-amino acid residue. In some embodiments, $-NH-CH(R^{8a})-C(O)-$ forms a Lys(iPr) residue. As used herein, in the expression “ $-NH-CH(R^{8a})-C(O)-$ ” made about Formula A, A-I, A-II, B, and/or C, it is understood that the $-C(O)-$ portion is part of R^{9a} definition.

[00132] In some embodiments of the compounds of Formula A, B, and/or C, R^{9a} is: $-C(O)NH_2$, $-C(O)-OH$, $-CH_2-C(O)NH_2$, $-CH_2-C(O)-OH$, $-CH_2-NH_2$, $-CH_2-OH$, $-CH_2-CH_2-NH_2$, $-R^{9b}-R^{9c}$, or $-R^{9b}-[linker]-R^{X_{n1}}$, wherein:

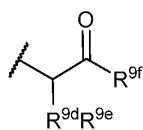
R^{9b} is $-CH_2-NH-C(O)-$, $-CH_2-C(O)-$, $-CH_2-O-$, $-C(O)NH-$, $-C(O)-N(CH_3)-$, $-CH_2-NHC(S)-$, $-C(S)NH-$, $-CH_2-N(CH_3)C(S)-$, $-C(O)N(CH_3)-$, $-CH_2-N(CH_3)C(O)-$, $-C(S)N(CH_3)-$, $-CH_2-NHC(S)NH-$, $-CH_2-NHC(O)NH-$, $-CH_2-S-$, $-CH_2-S(O)-$, $-CH_2-S(O)_2-$, $-CH_2-S(O)_2-NH-$, $-CH_2-S(O)-NH-$, $-CH_2-Se-$, $-CH_2-Se(O)-$, $-CH_2-Se(O)_2-$, $-CH_2-NHNHC(O)-$, $-C(O)NHNH-$, $-CH_2-OP(O)(O)O-$, $-CH_2-phosphamide-$, $-CH_2-thiophosphodiester-$, $-CH_2-S-$

tetrafluorophenyl-S-, , or polyethylene glycol; and

R^{9c} is hydrogen or a linear, branched, and/or cyclic C_1-C_{20} alkyl, alkenyl or alkynyl, wherein 0-6 carbons in C_2-C_{20} are independently replaced by N, S, and/or O heteroatoms, and substituted with 0-3 groups independently selected from one or a combination of oxo, hydroxyl, sulfhydryl, halogen, guanidino, carboxylic acid, sulfonic acid, sulfinic acid, and/or phosphoric acid;

[00133] In some embodiments of the compounds of Formula A, B, and/or C, R^{9a} is: $-C(O)NH_2$, $-C(O)-OH$, $-CH_2-C(O)NH_2$, $-CH_2-C(O)-OH$. In some embodiments, R^{9a} is $-R^{9b}-R^{9c}$ wherein R^{9b} is $-C(O)NH-$.

[00134] In some embodiments of the compounds of Formula A, B, and/or C, R^{9c} is



, wherein R^{9d} is a linear or branched C_1 - C_5 alkyl, alkenyl, or alkynyl, in which 0-2 carbons in C_2 - C_5 are independently replaced with N, S, and/or O heteroatoms, wherein R^{9e} is carboxylic acid, sulfonic acid, sulfinic acid, phosphoric acid, amino, guanidino, -SH, -OH, -NH-C(O)-CH₃, -S-C(O)-CH₃, -O-C(O)-CH₃, -NH-C(O)-(phenyl), -S-C(O)-(phenyl), -O-C(O)-(phenyl), -NH-CH₃, -N(CH₃)₂, -S-CH₃, -O-CH₃, and phenyl, and wherein R^{9f} is amino or -OH. In some embodiments, R^{9d} is a linear or branched C_1 - C_5 alkyl, alkenyl, or alkynyl (i.e. no heteroatoms). In some embodiments, R^{9d} is a linear or branched C_1 - C_5 alkyl.

[00135] In some embodiments of the compounds of Formula A, B, and/or C, R^{9a} is - R^{9b} -[linker]- $R^{X_{n1}}$. In some of these embodiments, R^{9b} is -C(O)NH-.

[00136] In some embodiments of the compounds of Formula A, B, and/or C: R^{9a} is -C(O)NH₂, -C(O)-OH, - R^{9b} - R^{9c} , or - R^{9b} -[linker]- $R^{X_{n1}}$; and R^{9b} is -C(O)NH-, -C(O)-N(CH₃)-, -C(O)N(CH₃)₂-, or -C(O)NHNH-.

[00137] In some embodiments of the compounds of Formula A, R^{A7a} is a linear C_1 - C_5 alkyl wherein 0-2 carbons in C_2 - C_5 are independently replaced with one or more N, S, and/or O heteroatoms. In some embodiments, R^{A7a} is a linear C_1 - C_5 alkyl (i.e. no heteroatoms). In some embodiments, R^{A7a} is a linear C_1 - C_5 alkyl in which one carbon in C_2 - C_5 is a heteroatom selected from N, S or O. In some embodiments, R^{A7a} is -CH₂-. In some embodiments, R^{A7a} is -CH₂-CH₂-. In some embodiments, -NH-CH(R^{A7a})-C(O)- forms a D-amino acid residue. In some embodiments, -NH-CH(R^{A7a})-C(O)- forms an L-amino acid residue.

[00138] In some embodiments of the compounds of Formula A, R^{A10} is absent or -[linker]- $R^{X_{n1}}$.

[00139] In some embodiments of the compounds of Formula A, when R^{A10} is absent, then R^{A1a} is:

a linear C_1 - C_5 alkyl, alkenyl, or alkynyl, wherein 0-2 carbons in C_2 - C_5 are independently replaced by one or more N, S, and/or O heteroatoms, optionally C-substituted with a single substituent selected from: -SH, -OH, amino, carboxy, guanidino, -NH-C(O)-CH₃, -S-C(O)-CH₃, -O-C(O)-CH₃, -NH-C(O)-(phenyl), -S-C(O)-(phenyl), -O-C(O)-(phenyl), -NH-(CH₃)₁₋₂, -NH₂-CH₃, -N(CH₃)₂₋₃, -S-CH₃, or -O-CH₃;

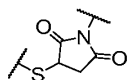
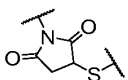
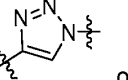
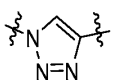
a branched C_1 - C_{10} alkyl, alkenyl, or alkynyl, wherein 0-3 carbons in C_2 - C_{10} are independently replaced by one or more N, S, and/or O heteroatoms; or

$R^{A1b}R^{A1c}$, wherein R^{A1b} is a linear C_1 - C_3 alkylenyl, wherein C_2 alkylenyl or C_3 alkylenyl is optionally replaced with a N, S, or O heteroatom, wherein R^{A1c} is:

a 5 or 6 membered aromatic ring wherein one or more carbons are optionally independently replaced by N, S, and/or O heteroatoms, and optionally substituted with one or more groups independently selected from oxo, hydroxyl, sulfhydryl, nitro, amino, and/or halogen; or

a fused bicyclic or fused tricyclic aryl group wherein one or more carbons are optionally independently replaced by N, S, and/or O heteroatoms, and optionally substituted with one or more groups independently selected from halogen, -OH, -OR^{A1d}, amino, -NHR^{A1d}, and/or N(R^{A1d})₂, wherein each R^{A1d} is independently a C_1 - C_3 linear or branched alkyl group.

[00140] In some embodiments of the compounds of Formula A, when R^{A10} is -[linker]-R^{X_{n1}}, then R^{A1a} is R^{A1e}R^{A1f}, wherein R^{A1e} is a linear C_1 - C_5 alkylenyl, alkenylenyl, or alkynylenyl, in which 0-2 carbons in C_2 - C_5 are independently replaced with N, S, and/or O heteroatoms, and R^{A1f} is -NH-C(O)-, -C(O)-, -O-, -C(O)NH-, -C(O)-N(CH₃)-, -NHC(S)-, -C(S)NH-, -N(CH₃)C(S)-, -C(O)N(CH₃)-, -N(CH₃)C(O)-, -C(S)N(CH₃)-, -NHC(S)NH-, -NHC(O)NH-, -S-, -S(O)-, -S(O)-O-, -S(O)₂-, -S(O)₂-O-, -S(O)₂-NH-, -S(O)-NH-, -Se-, -Se(O)-, -Se(O)₂-, -NHNHC(O)-, -C(O)NHNH-, -OP(O)(O)-O-, -phosphamide-, -thiophosphodiester-, -S-

tetrafluorophenyl-S-, polyethylene glycol, , , , or .

[00141] In some embodiments of the compounds of Formula A, -NH-CH(R^{A1a})-C(O)- forms an L-amino acid residue. In some embodiments, -NH-CH(R^{A1a})-C(O)- forms a D-amino acid residue.

[00142] In some embodiments of the compounds of Formula A, R^{A10} is absent.

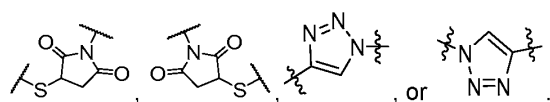
[00143] In some of embodiments of the compounds of Formula A, where R^{A10} is absent, R^{A1a} is a linear C_1 - C_5 alkyl, alkenyl, or alkynyl, optionally substituted with a single substituent selected from: -SH, -OH, amino, carboxy, guanidino, -NH-C(O)-CH₃, -S-C(O)-CH₃, -O-C(O)-CH₃, -NH-C(O)-(phenyl), -S-C(O)-(phenyl), -O-C(O)-(phenyl), -NH-(CH₃)₁₋₂, -NH₂-CH₃, -N(CH₃)₂₋₃, -S-CH₃, or -O-CH₃. In some of embodiments where R^{A10} is absent, R^{A1a} is a linear C_1 - C_5 alkyl optionally substituted with a single substituent selected from: -SH, -OH, amino, carboxy, guanidino, -NH-C(O)-CH₃, -S-C(O)-CH₃, -O-C(O)-CH₃, -NH-C(O)-(phenyl), -S-C(O)-(phenyl), -O-C(O)-(phenyl), -NH-(CH₃)₁₋₂, -NH₂-CH₃, -N(CH₃)₂₋₃, -S-CH₃, or -O-CH₃.

[00144] In some of embodiments of the compounds of Formula A, where R^{A10} is absent, R^{A1a} is a branched C_1 - C_{10} alkyl, alkenyl, or alkynyl. In some of embodiments where R^{A10} is absent, R^{A1a} is a branched C_1 - C_{10} alkyl.

[00145] In some embodiments of the compounds of Formula A, where R^{A10} is absent, R^{A1a} is $R^{A1b}R^{A1c}$. In some embodiments, R^{A1b} is a linear C_1 - C_3 alkylenyl. In some embodiments, R^{A1c} is a 5 or 6 membered aromatic ring wherein 0-4 carbons are independently replaced by N, S, and/or O heteroatoms, and substituted with 0-4 groups independently selected from oxo, hydroxyl, sulfhydryl, nitro, amino, and/or halogen. In some embodiments, R^{A1c} is a fused bicyclic or fused tricyclic aryl group wherein 0-6 carbons are independently replaced by N, S, and/or O heteroatoms, and optionally substituted with 0-6 groups independently selected from halogen, -OH, -OR^{A1d}, amino, -NHR^{A1d}, and/or N(R^{A1d})₂. In some embodiments, R^{A1d} is methyl. In some embodiments, each ring in the fused bicyclic or fused tricyclic aryl group independently has 4, 5 or 6 ring carbons, wherein 0-3 carbons are independently replaced by N, S, and/or O heteroatoms; such embodiments may be substituted or unsubstituted as defined above.

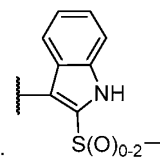
[00146] In some embodiments of the compounds of Formula A, -NH-CH(R^{A1a})-C(O)- forms a Phe residue, a 1-Nal residue, a 2-Nal residue, a Tyr residue, a Trp residue, a Lys residue, a hLys residue, a Lys(Ac) residue, a Dap residue, a Dab residue, or an Orn residue. In some embodiments of the compounds of Formula A, -NH-CH(R^{A1a})-C(O)- forms an L-Phe residue, an L-1-Nal residue, an L-2-Nal residue, an L-Tyr residue, an L-Trp residue, an L-Lys residue, an L-hLys residue, an L-Lys(Ac) residue, an L-Dap residue, an L-Dab residue, or an L-Orn residue. In some embodiments of the compounds of Formula A, -NH-CH(R^{A1a})-C(O)- forms a Phe residue. In some embodiments, -NH-CH(R^{A1a})-C(O)- forms a 1-Nal residue. In some embodiments, -NH-CH(R^{A1a})-C(O)- forms a 2-Nal residue. In some embodiments, -NH-CH(R^{A1a})-C(O)- forms a Tyr residue. In some embodiments, -NH-CH(R^{A1a})-C(O)- forms a Trp residue. In some embodiments, -NH-CH(R^{A1a})-C(O)- forms a Lys residue. In some embodiments, -NH-CH(R^{A1a})-C(O)- forms a hLys residue. In some embodiments, -NH-CH(R^{A1a})-C(O)- forms a Lys(Ac) residue. In some embodiments, -NH-CH(R^{A1a})-C(O)- forms a Dap residue. In some embodiments, -NH-CH(R^{A1a})-C(O)- forms a Dab residue. In some embodiments, -NH-CH(R^{A1a})-C(O)- forms an Orn residue.

[00147] In some embodiments of the compounds of Formula A, R^{A10} is -[linker]-R^X_{n1} and R^{A1a} is $R^{A1e}R^{A1f}$. In some embodiments, R^{A1e} is a linear C_1 - C_5 alkylenyl, alkenylenyl, or alkynylenyl. In some embodiments, R^{A1e} is a linear C_1 - C_5 alkylenyl. In some embodiments, R^{A1f} is -NH-C(O)-, -C(O)-, -O-, -C(O)NH-, -C(O)-N(CH₃)-, -NHC(S)-, -C(S)NH-, -N(CH₃)C(S)-, -C(O)N(CH₃)-, -N(CH₃)C(O)-, -C(S)N(CH₃)-, -NHC(S)NH-, -NHC(O)NH-, -S-, -S(O)-, -S(O)-O-, -S(O)₂-, -S(O)₂-NH-, -S(O)-NH-, -NHNHC(O)-, -C(O)NHNH-, polyethylene glycol,

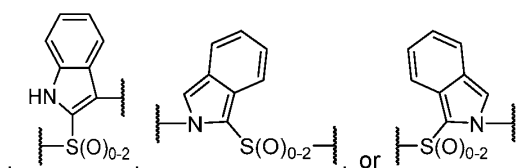


[00148] All embodiments described herein for Formula A can be embodiments for Formula A-I and/or Formula A-II to the extent the definitions are encompassed by Formula A-I and/or Formula A-II.

[00149] In some embodiments of the compounds of Formula B, R^{B1a} is a linear, branched, and/or cyclic C_1 - C_{10} alkylenyl, alkenylenyl, or alkynylenyl, wherein one or more carbons in C_2 - C_{10} are optionally independently replaced with N, S, and/or O heteroatoms.

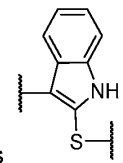


[00150] In some embodiments of the compounds of Formula B, R^{B1-7} is:

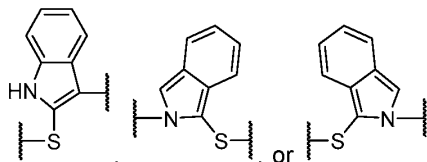


, wherein the indole and the isoindole are optionally substituted with one or more of -F, -Br, -Cl, -I, -OH, -O- R^{B1-7b} , -CO-, -COOH, -CONH₂, -CN, -O-aryl, -NH₂, -NHR^{B1-7b}, N₃, -NH-, -CHO, and/or - R^{B1-7b} , wherein each R^{B1-7b} is a linear or branched C_1 - C_3 alkyl, alkenyl, or alkynyl. In some embodiments, the indole and the isoindole are not substituted. In some embodiments, the indole and the isoindole are substituted with 1-3 groups selected from -F, -Br, -Cl, -I, -OH, -O- R^{C1b} , -CO-, -COOH, -CONH₂, -CN, -O-aryl, -NH₂, -NHR^{C1b}, N₃, -NH-, -CHO, and/or - R^{C1b} . In some embodiments, each R^{C1b} is methyl. In some embodiments, the aryl is a 5 or 6 membered aromatic ring.

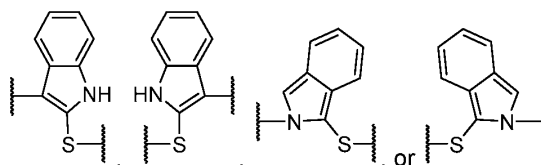
[00151] In some embodiments of the compounds of Formula B, R^{B7a} is a linear C_1 - C_5 alkylenyl wherein optionally 0-2 carbons in C_2 - C_5 are independently replaced with one or more N, S, and/or O heteroatoms. In some embodiments, R^{B7a} is a linear C_1 - C_5 alkylenyl (i.e. no heteroatoms). In some embodiments, R^{B7a} is a linear C_1 - C_5 alkylenyl in which one carbon in C_2 - C_5 is a heteroatom selected from N, S or O. In some embodiments, R^{B7a} is -CH₂-. In some embodiments, R^{B7a} is -CH₂-CH₂-. In some embodiments, -NH-CH(R^{C7a})-C(O)- forms a D-amino acid residue. In some embodiments, -NH-CH(R^{C7a})-C(O)- forms an L-amino acid residue.



[00152] In some embodiments of the compounds of Formula B, R^{B1-7} is

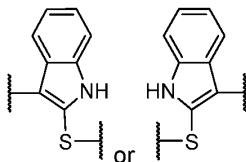


, wherein the indole and the isoindole are optionally substituted with one or more of -F, -Br, -Cl, -I, -OH, -O- R^{B1-7b} , -CO-, -COOH, -CONH₂, -CN, -O-aryl, -NH₂, -NHR^{B1-7b}, N₃, -NH-, -CHO, and/or - R^{B1-7b} , wherein each R^{B1-7b} is a linear or branched C₁-C₃ alkyl, alkenyl, or alkynyl. In some embodiments, the indole and the isoindole are substituted with 1-3 groups selected from -F, -Br, -Cl, -I, -OH, -O- R^{C1b} , -CO-, -COOH, -CONH₂, -CN, -O-aryl, -NH₂, -NHR^{C1b}, N₃, -NH-, -CHO, and/or - R^{C1b} . In some embodiments, each R^{C1b} is methyl. In some embodiments, the aryl is a 5 or 6 membered aromatic ring. In



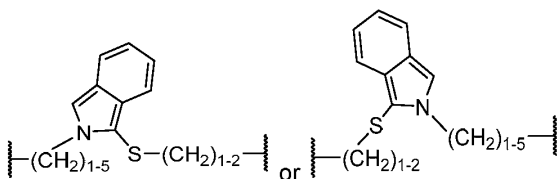
some embodiments, R^{B1-7} is

[00153] In some embodiments of the compounds of Formula B, R^{B1a} is $-(CH_2)_{1-2}$, R^{B1-7} is



, and R^{B7a} is $-(CH_2)_{1-2}$.

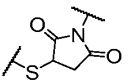
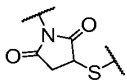
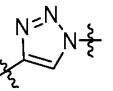
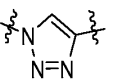
[00154] In some embodiments of the compounds of Formula B, R^{B1a} - R^{B1-7} - R^{B7a} is



[00155] In some embodiments of the compounds of Formula B, -NH-CH(R^{B7a})-C(O)- forms a D-amino acid residue. In some embodiments, -NH-CH(R^{B7a})-C(O)- forms an L-amino acid residue.

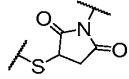
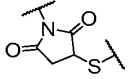
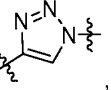
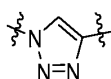
[00156] In some embodiments of the compounds of Formula B, R^{B10a} is: amine, -NH-(CH₃)₁₋₂, -N(CH₃)₂₋₃, -NH-C(O)-CH₃, -NH-C(O)-(phenyl), or - R^{B10b} -[linker]- $R^{X_{n1}}$ wherein R^{B10b} is:

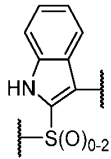
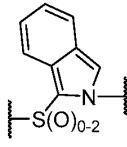
-NH-C(O)-, -C(O)-, -O-, -C(O)NH-, -C(O)-N(CH₃)-, -NHC(S)-, -C(S)NH-, -N(CH₃)C(S)-, -C(O)N(CH₃)-, -N(CH₃)C(O)-, -C(S)N(CH₃)-, -NHC(S)NH-, -NHC(O)NH-, -S-, -S(O)-, -S(O)-O-, -S(O)₂-, -S(O)₂-O-, -S(O)₂-NH-, -S(O)-NH-, -Se-, -Se(O)-, -Se(O)₂-, -NHNHC(O)-, -C(O)NHNH-, -OP(O)(O)O-, -phosphamide-, -thiophosphodiester-, -S-

tetrafluorophenyl-S-, , , , , or polyethylene glycol.

[00157] In some embodiments of the compounds of Formula B, R^{B10a} is: amine, -NH-(CH₃)₁₋₂, -N(CH₃)₂₋₃, -NH-C(O)-CH₃, or -NH-C(O)-(phenyl).

[00158] In some embodiments of the compounds of Formula B, R^{B10a} is -R^{B10b}-[linker]-R^{X_{n1}}. In some of these embodiments R^{B10b} is: -NH-C(O)-, -C(O)-, -O-, -C(O)NH-, -C(O)-N(CH₃)-, -NHC(S)-, -C(S)NH-, -N(CH₃)C(S)-, -C(O)N(CH₃)-, -N(CH₃)C(O)-, -C(S)N(CH₃)-, -

NHC(S)NH-, -NHC(O)NH-, -NHNHC(O)-, -C(O)NHNH-, , , , , or polyethylene glycol. In some embodiments, R^{B10a} is -NHC(O)-[linker]-R^{X_{n1}} or -N(CH₃)C(O)-[linker]-R^{X_{n1}}.

[00159] In some embodiments of the compounds of Formula C, R^{C1a} is:  or , wherein the indole and the isoindole are optionally substituted with one or more

of -F, -Br, -Cl, -I, -OH, -O-R^{C1b}, -CO-, -COOH, -CONH₂, -CN, -O-aryl, -NH₂, -NHR^{C1b}, N₃, -NH, -CHO, and/or -R^{C1b}, wherein each R^{C1b} is a linear or branched C₁-C₃ alkyl, alkenyl, or alkynyl. In some embodiments, the indole and the isoindole are not substituted. In some embodiments, the indole and the isoindole are substituted with 1-3 groups selected from -F, -Br, -Cl, -I, -OH, -O-R^{C1b}, -CO-, -COOH, -CONH₂, -CN, -O-aryl, -NH₂, -NHR^{C1b}, N₃, -NH, -CHO, and/or -R^{C1b}. In some embodiments, each R^{C1b} is methyl. In some embodiments, the aryl is a 5 or 6 membered aromatic ring.

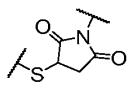
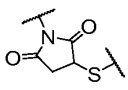
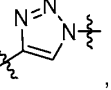
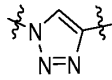
[00160] In some embodiments of the compounds of Formula C, R^{C7a} is a linear C₁-C₅ alkylenyl wherein optionally 0-2 carbons in C₂-C₅ are independently replaced with one or more N, S, and/or O heteroatoms. In some embodiments, R^{C7a} is a linear C₁-C₅ alkylenyl (i.e. no

heteroatoms). In some embodiments, R^{C7a} is a linear C_1 - C_5 alkylenyl in which one carbon in C_2 - C_5 is a heteroatom selected from N, S or O. In some embodiments, R^{C7a} is $-(CH_2)_{1-2}-$. In some embodiments, $-NH-CH(R^{C7a})-C(O)-$ forms a D-amino acid residue. In some embodiments, $-NH-CH(R^{C7a})-C(O)-$ forms an L-amino acid residue.

[00161] In some embodiments of the compounds of Formula C, R^{C10a} is R^{C10b} - R^{C10c} -[linker]- $R^{X_{n1}}$ or R^{C10d} , wherein:

R^{C10b} is a linear C_1 - C_5 alkylenyl, alkenylenyl, or alkynylenyl, in which 0-2 carbons in C_2 - C_5 are independently replaced with N, S, and/or O heteroatoms;

R^{C10c} is $-NH-C(O)-$, $-C(O)-$, $-O-$, $-C(O)NH-$, $-C(O)-N(CH_3)-$, $-NHC(S)-$, $-C(S)NH-$, $-N(CH_3)C(S)-$, $-C(O)N(CH_3)-$, $-N(CH_3)C(O)-$, $-C(S)N(CH_3)-$, $-NHC(S)NH-$, $-NHC(O)NH-$, $-S-$, $-S(O)-$, $-S(O)-O-$, $-S(O)_2-$, $-S(O)_2-O-$, $-S(O)_2-NH-$, $-S(O)-NH-$, $-Se-$, $-Se(O)-$, $-Se(O)_2-$, $-NHNHC(O)-$, $-C(O)NHNH-$, $-OP(O)(O)O-$, $-phosphamide-$, $-$

thiophosphodiester-, $-S$ -tetrafluorophenyl- S -, , , , , or polyethylene glycol; and

R^{C10d} is:

a linear C_1 - C_5 alkyl, alkenyl, or alkynyl, wherein 0-2 carbons in C_2 - C_5 are independently replaced by N, S, and/or O heteroatoms, optionally C-substituted with a single substituent selected from: $-SH$, $-OH$, amino, carboxy, guanidino, $-NH-C(O)-CH_3$, $-S-C(O)-CH_3$, $-O-C(O)-CH_3$, $-NH-C(O)-(phenyl)$, $-S-C(O)-(phenyl)$, $-O-C(O)-(phenyl)$, $-NH-(CH_3)_{1-2}$, $-NH_2-CH_3$, $-N(CH_3)_{2-3}$, $-S-CH_3$, or $-O-CH_3$;

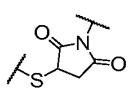
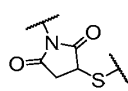
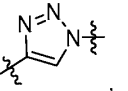
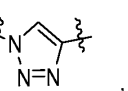
a branched C_1 - C_{10} alkyl, alkenyl, or alkynyl, wherein 0-3 carbons in C_2 - C_{10} are independently replaced by N, S, and/or O heteroatoms; or

$R^{C10e}R^{C10f}$, wherein R^{C10e} is a linear C_1 - C_3 alkyl, wherein C_2 alkyl or C_3 alkyl is optionally replaced with N, S, or O heteroatom, wherein R^{C10f} is:

a 5 or 6 membered aromatic ring wherein one or more carbons are optionally independently replaced by N, S, and/or O heteroatoms, and optionally substituted with one or more groups independently selected from oxo, hydroxyl, sulfhydryl, nitro, amino, and/or halogen; or

a fused bicyclic or fused tricyclic aryl group wherein one or more carbons are optionally independently replaced by N, S, and/or O heteroatoms, and optionally substituted with one or more groups independently selected from halogen, $-OH$, $-OR^{C10g}$, amino, $-NHR^{C10g}$, and/or $N(R^{C10g})_2$, wherein R^{C10g} is C_1 - C_3 linear or branched alkyl.

[00162] In some embodiments of the compounds of Formula C, R^{C10a} is $R^{C10b}-R^{C10c}$ -[linker]- $R^{X_{n1}}$. In some embodiments, R^{C10b} is a linear C_1 - C_5 alkylenyl, alkenylenyl, or alkynylenyl. In some embodiments, R^{C10b} is a linear C_1 - C_5 alkylenyl. In some embodiments, R^{C10c} is: -NH-C(O)-, -C(O)-, -O-, -C(O)NH-, -C(O)-N(CH₃)-, -NHC(S)-, -C(S)NH-, -N(CH₃)C(S)-, -C(O)N(CH₃)-, -N(CH₃)C(O)-, -C(S)N(CH₃)-, -NHC(S)NH-, -NHC(O)NH-, -NHNHC(O)-, -

C(O)NHNH-, , , , , or polyethylene glycol. In some embodiments, R^{C10c} is -NHC(O)- or -N(CH₃)C(O)-.

[00163] In some embodiments of the compounds of Formula C, R^{C10a} is R^{C10d} .

[00164] In some embodiments of the compounds of Formula C, R^{C10d} is a linear C_1 - C_5 alkyl, alkenyl, or alkynyl, wherein 0-2 carbons in C_2 - C_5 are independently replaced by N, S, and/or O heteroatoms, optionally C-substituted with a single substituent selected from the group consisting of: -SH, -OH, amino, carboxy, guanidino, -NH-C(O)-CH₃, -S-C(O)-CH₃, -O-C(O)-CH₃, -NH-C(O)-(phenyl), -S-C(O)-(phenyl), -O-C(O)-(phenyl), -NH-(CH₃)₁₋₂, -NH₂-CH₃, -N(CH₃)₂₋₃, -S-CH₃, and -O-CH₃.

[00165] In some embodiments of the compounds of Formula C, R^{C10d} is a linear C_1 - C_5 alkyl, alkenyl, or alkynyl, optionally C-substituted with a single substituent selected from the group consisting of: -SH, -OH, amino, carboxy, guanidino, -NH-C(O)-CH₃, -S-C(O)-CH₃, -O-C(O)-CH₃, -NH-C(O)-(phenyl), -S-C(O)-(phenyl), -O-C(O)-(phenyl), -NH-(CH₃)₁₋₂, -NH₂-CH₃, -N(CH₃)₂₋₃, -S-CH₃, and -O-CH₃. In some embodiments, R^{C10d} is a linear C_1 - C_5 alkyl optionally C-substituted with a single substituent selected from the group consisting of: -SH, -OH, amino, carboxy, guanidino, -NH-C(O)-CH₃, -S-C(O)-CH₃, -O-C(O)-CH₃, -NH-C(O)-(phenyl), -S-C(O)-(phenyl), -O-C(O)-(phenyl), -NH-(CH₃)₁₋₂, -NH₂-CH₃, -N(CH₃)₂₋₃, -S-CH₃, and -O-CH₃.

[00166] In some embodiments of the compounds of Formula C, R^{C10d} is a branched C_1 - C_{10} alkyl, alkenyl, or alkynyl, wherein 0-3 carbons in C_2 - C_{10} are independently replaced by N, S, and/or O heteroatoms. In some embodiments, R^{C10d} is a branched C_1 - C_{10} alkyl, alkenyl, or alkynyl. In some embodiments, R^{C10d} is a branched C_1 - C_{10} alkyl.

[00167] In some embodiments of the compounds of Formula C, R^{C10d} is $R^{C10e}R^{C10f}$. In some embodiments, R^{C10e} is a linear C_1 - C_3 alkyl. In some embodiments, R^{C10f} is a 5 or 6 membered aromatic ring wherein 0-4 carbons are independently replaced by N, S, and/or O heteroatoms, and substituted with 0-4 groups independently selected from oxo, hydroxyl, sulfhydryl, nitro, amino, and/or halogen. In some embodiments, R^{C10f} is a fused bicyclic or fused tricyclic aryl group wherein 0-6 carbons are independently replaced by N, S, and/or O heteroatoms, and substituted with 0-6 groups independently selected from halogen, -OH, -OR^{C10g}, amino, -NHR^{C10g}, and/or N(R^{C10g})₂, wherein R^{C10g} is C_1 - C_3 linear or branched alkyl. In some embodiments, R^{C10g} is methyl. In some embodiments, each ring in the fused bicyclic or

fused tricyclic aryl group independently has 4, 5 or 6 ring carbons, wherein 0-3 carbons are independently replaced by N, S, and/or O heteroatoms; such embodiments may be substituted or unsubstituted as defined above.

[00168] In some embodiments of the compounds of Formula A: -NH-CH(R^{1a})-C(O)- forms a Phe residue; -NH-CH(R^{2a})-C(O)- forms a (3-I)Tyr residue; -NH-CH(R^{3a})-C(O)- forms a Lys(iPr) residue; -NH-CH(R^{4a})-C(O)- forms a D-Arg residue; -NH-CH(R^{5a})-C(O)- forms a 2-Nal or a (4-NH₂)Phe residue; -NH-CH(R^{6a})-C(O)- forms a Gly residue; -NH-CH(R^{A7a})-C(O)- forms a D-amino acid, wherein R^{A7a} is C₁-C₃ alkyenyl; and -NH-CH(R^{8a})-C(O)- forms a Lys(iPr) residue. In some of these embodiments, -NH-CH(R^{5a})-C(O)- forms a 2-Nal residue. In some of these embodiments, -NH-CH(R^{5a})-C(O)- forms a (4-NH₂)Phe residue.

[00169] In some embodiments of the compounds of Formula A: -NH-CH(R^{1a})-C(O)- forms a Phe residue; -NH-CH(R^{2a})-C(O)- forms a Tyr residue; -NH-CH(R^{3a})-C(O)- forms a Lys(iPr) residue; -NH-CH(R^{4a})-C(O)- forms a D-Arg residue; -NH-CH(R^{5a})-C(O)- forms a 2-Nal residue or a (4-NH₂)Phe residue; -NH-CH(R^{6a})-C(O)- forms a D-Ala residue; -NH-CH(R^{A7a})-C(O)- forms a D-amino acid residue, wherein R^{A7a} is C₁-C₃ alkyenyl; and -NH-CH(R^{8a})-C(O)- forms a Lys(iPr) residue. In some of these embodiments, -NH-CH(R^{5a})-C(O)- forms a 2-Nal residue. In some of these embodiments, -NH-CH(R^{5a})-C(O)- forms a (4-NH₂)Phe residue.

[00170] In some embodiments of the compounds of Formula A: -NH-CH(R^{1a})-C(O)- forms a Phe residue; -NH-CH(R^{2a})-C(O)- forms a (4-NH₂)Phe residue; -NH-CH(R^{3a})-C(O)- forms a Lys(iPr) residue; -NH-CH(R^{4a})-C(O)- forms a D-Arg residue; -NH-CH(R^{5a})-C(O)- forms a 2-Nal residue or a (4-NH₂)Phe residue; -NH-CH(R^{6a})-C(O)- forms a Gly residue; -NH-CH(R^{A7a})-C(O)- forms a D-amino acid residue, wherein R^{A7a} is C₁-C₃ alkyenyl; and -NH-CH(R^{8a})-C(O)- forms a Lys(iPr) residue. In some of these embodiments, -NH-CH(R^{5a})-C(O)- forms a 2-Nal residue. In some of these embodiments, -NH-CH(R^{5a})-C(O)- forms a (4-NH₂)Phe residue.

[00171] In some embodiments of the compounds of Formula A: -NH-CH(R^{1a})-C(O)- forms a Phe residue; -NH-CH(R^{2a})-C(O)- forms a (4-NO₂)Phe residue; -NH-CH(R^{3a})-C(O)- forms a Lys(iPr) residue; -NH-CH(R^{4a})-C(O)- forms a D-Arg residue; -NH-CH(R^{5a})-C(O)- forms a 2-Nal residue or a (4-NH₂)Phe residue; -NH-CH(R^{6a})-C(O)- forms a Gly residue; -NH-CH(R^{A7a})-C(O)- forms a D-amino acid residue, wherein R^{A7a} is C₁-C₃ alkyenyl; and -NH-CH(R^{8a})-C(O)- forms a Lys(iPr) residue. In some of these embodiments, -NH-CH(R^{5a})-C(O)- forms a 2-Nal residue. In some of these embodiments, -NH-CH(R^{5a})-C(O)- forms a (4-NH₂)Phe residue.

[00172] In some embodiments of the compounds of Formula A: -NH-CH(R^{1a})-C(O)- forms a Phe residue; -NH-CH(R^{2a})-C(O)- forms a hTyr residue; -NH-CH(R^{3a})-C(O)- forms a Lys(iPr) residue; -NH-CH(R^{4a})-C(O)- forms a D-Arg residue; -NH-CH(R^{5a})-C(O)- forms a 2-Nal residue or a (4-NH₂)Phe residue; -NH-CH(R^{6a})-C(O)- forms a Gly residue; -NH-CH(R^{A7a})-C(O)-

forms a D-amino acid residue, wherein R^{A7a} is C_1 - C_3 alkyenyl; and $-NH-CH(R^{8a})-C(O)-$ forms a Lys(iPr) residue. In some of these embodiments, $-NH-CH(R^{5a})-C(O)-$ forms a 2-Nal residue. In some of these embodiments, $-NH-CH(R^{5a})-C(O)-$ forms a (4- NH_2)Phe residue.

[00173] In some embodiments of the compounds of Formula A: $-NH-CH(R^{1a})-C(O)-$ forms a Phe residue; $-NH-CH(R^{2a})-C(O)-$ forms a Tyr residue; $-NH-CH(R^{3a})-C(O)-$ forms a Lys(iPr) residue; $-NH-CH(R^{4a})-C(O)-$ forms a D-Arg residue; $-NH-CH(R^{5a})-C(O)-$ forms a 2-Nal residue or (4- NH_2)Phe residue; $-NH-CH(R^{6a})-C(O)-$ forms a D-His residue; $-NH-CH(R^{A7a})-C(O)-$ forms a D-amino acid residue, wherein R^{A7a} is C_1 - C_3 alkyenyl; and $-NH-CH(R^{8a})-C(O)-$ forms a Lys(iPr) residue. In some of these embodiments, $-NH-CH(R^{5a})-C(O)-$ forms a 2-Nal residue. In some of these embodiments, $-NH-CH(R^{5a})-C(O)-$ forms a (4- NH_2)Phe residue.

[00174] In some embodiments of the compounds of Formula A: $-NH-CH(R^{1a})-C(O)-$ forms a Phe residue; $-NH-CH(R^{2a})-C(O)-$ forms a Tyr residue; $-NH-CH(R^{3a})-C(O)-$ forms a Lys(iPr) residue; $-NH-CH(R^{4a})-C(O)-$ forms a D-Arg residue; $-NH-CH(R^{5a})-C(O)-$ forms a 2-Nal residue or a (4- NH_2)Phe residue; $-NH-CH(R^{6a})-C(O)-$ forms a His residue; $-NH-CH(R^{A7a})-C(O)-$ forms a D-amino acid residue, wherein R^{A7a} is C_1 - C_3 alkyenyl; and $-NH-CH(R^{8a})-C(O)-$ forms a Lys(iPr) residue. In some of these embodiments, $-NH-CH(R^{5a})-C(O)-$ forms a 2-Nal residue. In some of these embodiments, $-NH-CH(R^{5a})-C(O)-$ forms a (4- NH_2)Phe residue.

[00175] In some embodiments of the compounds of Formula A: $-NH-CH(R^{1a})-C(O)-$ forms a Phe residue; $-NH-CH(R^{2a})-C(O)-$ forms a Tyr residue; $-NH-CH(R^{3a})-C(O)-$ forms a Lys(iPr) residue; $-NH-CH(R^{4a})-C(O)-$ forms a D-Arg residue; $-NH-CH(R^{5a})-C(O)-$ forms a 2-Nal residue or a (4- NH_2)Phe residue; $-NH-CH(R^{6a})-C(O)-$ forms a D-Ser residue; $-NH-CH(R^{A7a})-C(O)-$ forms a D-amino acid residue, wherein R^{A7a} is C_1 - C_3 alkyenyl; and $-NH-CH(R^{8a})-C(O)-$ forms a Lys(iPr) residue. In some of these embodiments, $-NH-CH(R^{5a})-C(O)-$ forms a 2-Nal residue. In some of these embodiments, $-NH-CH(R^{5a})-C(O)-$ forms a (4- NH_2)Phe residue.

[00176] In some embodiments of the compounds of Formula A: $-NH-CH(R^{1a})-C(O)-$ forms a Phe residue; $-NH-CH(R^{2a})-C(O)-$ forms a Tyr residue; $-NH-CH(R^{3a})-C(O)-$ forms a Lys(iPr) residue; $-NH-CH(R^{4a})-C(O)-$ forms a D-Arg residue; $-NH-CH(R^{5a})-C(O)-$ forms a 2-Nal residue or a (4- NH_2)Phe residue; $-NH-CH(R^{6a})-C(O)-$ forms a D-Glu residue; $-NH-CH(R^{A7a})-C(O)-$ forms a D-amino acid residue, wherein R^{A7a} is C_1 - C_3 alkyenyl; and $-NH-CH(R^{8a})-C(O)-$ forms a Lys(iPr) residue. In some of these embodiments, $-NH-CH(R^{5a})-C(O)-$ forms a 2-Nal residue. In some of these embodiments, $-NH-CH(R^{5a})-C(O)-$ forms a (4- NH_2)Phe residue.

[00177] In some embodiments of the compounds of Formula A: $-NH-CH(R^{1a})-C(O)-$ forms a Phe residue; $-NH-CH(R^{2a})-C(O)-$ forms a Tyr residue; $-NH-CH(R^{3a})-C(O)-$ forms a Lys(iPr) residue; $-NH-CH(R^{4a})-C(O)-$ forms a D-Arg residue; $-NH-CH(R^{5a})-C(O)-$ forms a 2-Nal residue or a (4- NH_2)Phe residue; $-NH-CH(R^{6a})-C(O)-$ forms a D-His residue; $-NH-CH(R^{A7a})-C(O)-$ forms a D-amino acid residue, wherein R^{A7a} is C_1 - C_3 alkyenyl; and $-NH-CH(R^{8a})-C(O)-$

forms a Lys(iPr) residue. In some of these embodiments, -NH-CH(R^{5a})-C(O)- forms a 2-Nal residue. In some of these embodiments, -NH-CH(R^{5a})-C(O)- forms a (4-NH₂)Phe residue.

[00178] In some embodiments of the compounds of Formula A: -NH-CH(R^{1a})-C(O)- forms a Phe residue; -NH-CH(R^{2a})-C(O)- forms a Tyr residue; -NH-CH(R^{3a})-C(O)- forms a Lys(iPr) residue; -NH-CH(R^{4a})-C(O)- forms a D-Arg residue; -NH-CH(R^{5a})-C(O)- forms a (2-Ant)Ala residue; -NH-CH(R^{6a})-C(O)- forms a Gly residue; -NH-CH(R^{A7a})-C(O)- forms a D-amino acid residue, wherein R^{A7a} is C₁-C₃ alkyenyl; and -NH-CH(R^{8a})-C(O)- forms a Lys(iPr) residue. In some of these embodiments, -NH-CH(R^{5a})-C(O)- forms a 2-Nal residue. In some of these embodiments, -NH-CH(R^{5a})-C(O)- forms a (4-NH₂)Phe residue.

[00179] In some embodiments of the compounds of Formula A: -NH-CH(R^{1a})-C(O)- forms a Lys(Ac) residue; -NH-CH(R^{2a})-C(O)- forms a Tyr residue; -NH-CH(R^{3a})-C(O)- forms a Lys(iPr) residue; -NH-CH(R^{4a})-C(O)- forms a D-Arg residue; -NH-CH(R^{5a})-C(O)- forms a 2-Nal residue or a (4-NH₂)Phe residue; -NH-CH(R^{6a})-C(O)- forms a D-Ala residue; -NH-CH(R^{A7a})-C(O)- forms a D-amino acid residue, wherein R^{A7a} is C₁-C₃ alkyenyl; and -NH-CH(R^{8a})-C(O)- forms a Lys(iPr) residue. In some of these embodiments, -NH-CH(R^{5a})-C(O)- forms a 2-Nal residue. In some of these embodiments, -NH-CH(R^{5a})-C(O)- forms a (4-NH₂)Phe residue.

[00180] In some embodiments of the compounds of Formula A: -NH-CH(R^{2a})-C(O)- forms a Tyr residue; -NH-CH(R^{3a})-C(O)- forms a Lys(iPr) residue; -NH-CH(R^{4a})-C(O)- forms a D-Arg residue; -NH-CH(R^{A7a})-C(O)- forms a D-amino acid residue, wherein R^{A7a} is C₁-C₃ alkyenyl; and -NH-CH(R^{8a})-C(O)- forms a Lys(iPr) residue. In some of these embodiments, -NH-CH(R^{6a})-C(O)- forms a Gly residue. In some of these embodiments, -NH-CH(R^{6a})-C(O)- forms a D-Ala residue. In some of these embodiments, -NH-CH(R^{5a})-C(O)- forms a 2-Nal residue. In some of these embodiments, -NH-CH(R^{5a})-C(O)- forms a (4-NH₂)Phe residue. In some of these embodiments, -NH-CH(R^{1a})-C(O)- forms a Phe residue and R^{10a} is absent. In some of these embodiments, R^{A10} is -[linker]-R^{X_{n1}}, R^{A1e} is linear C₁-C₅ alkyenyl, and R^{A1f} is -NH-C(O)-.

[00181] In some embodiments of the compounds of Formula A, one or more of the following conditions are met:

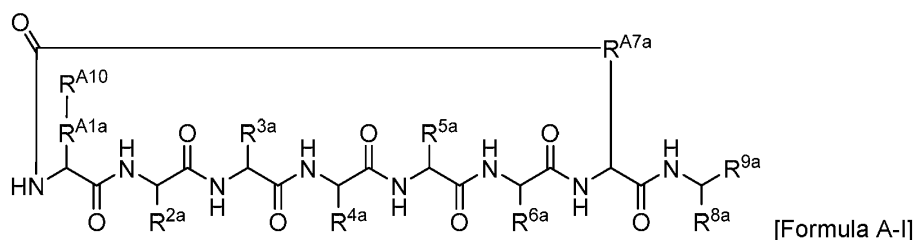
- a) -NH-CH(R^{2a})-C(O)- forms a Tyr residue;
- b) -NH-CH(R^{3a})-C(O)- forms a Lys(iPr) residue;
- c) -NH-CH(R^{4a})-C(O)- forms a D-Arg residue;
- d) -NH-CH(R^{5a})-C(O)- forms a 2-Nal residue; and/or
- e) -NH-CH(R^{6a})-C(O)- forms a D-Ala residue.

[00182] In some embodiments of the compounds of Formula A, -NH-CH(R^{2a})-C(O)- forms a Tyr residue; -NH-CH(R^{3a})-C(O)- forms a Lys(iPr) residue; -NH-CH(R^{4a})-C(O)- forms a D-Arg residue; -NH-CH(R^{5a})-C(O)- forms a 2-Nal residue; and -NH-CH(R^{6a})-C(O)- forms a D-Ala residue.

[00183] In some embodiments of the compounds of Formula A, $-\text{NH}-\text{CH}(\text{R}^{2a})-\text{C}(\text{O})-$ forms a Tyr residue; $-\text{NH}-\text{CH}(\text{R}^{3a})-\text{C}(\text{O})-$ forms a Lys(iPr) residue; $-\text{NH}-\text{CH}(\text{R}^{4a})-\text{C}(\text{O})-$ forms a D-Arg residue; $-\text{NH}-\text{CH}(\text{R}^{7a})-\text{C}(\text{O})-$ forms a D-amino acid residue, wherein R^{A7a} is C_1 - C_3 alkenyl; and $-\text{NH}-\text{CH}(\text{R}^{8a})-$ together with $-\text{C}(\text{O})-$ from R^{9a} forms a Lys(iPr) residue. In some embodiments, $-\text{NH}-\text{CH}(\text{R}^{6a})-\text{C}(\text{O})-$ forms a Gly residue, a D-Ala residue, a D-Gln residue, or a D-Asn residue. In some embodiments, $-\text{NH}-\text{CH}(\text{R}^{1a})-\text{C}(\text{O})-$ forms a Phe residue and R^{10a} is absent. In some embodiments, R^{A10} is $-\text{[linker]}-\text{R}^{X_{n1}}$, R^{A1e} is linear C_1 - C_5 alkenyl, and R^{A1f} is $-\text{NH}-\text{C}(\text{O})-$.

[00184] In some embodiments of the compounds of Formula B: $-\text{NH}-\text{CH}(\text{R}^{2a})-\text{C}(\text{O})-$ forms a Tyr residue; $-\text{NH}-\text{CH}(\text{R}^{3a})-\text{C}(\text{O})-$ forms a Lys(iPr) residue; $-\text{NH}-\text{CH}(\text{R}^{4a})-\text{C}(\text{O})-$ forms a D-Arg residue; and $-\text{NH}-\text{CH}(\text{R}^{8a})-\text{C}(\text{O})-$ forms a Lys(iPr) residue. In some of these embodiments, $-\text{NH}-\text{CH}(\text{R}^{6a})-\text{C}(\text{O})-$ forms a Gly residue, a D-Ala residue, a D-Gln residue, or a D-Asn residue; and $-\text{NH}-\text{CH}(\text{R}^{5a})-\text{C}(\text{O})-$ forms a 2-Nal residue, a (2-Ant)Ala residue or a (4- NH_2)Phe residue.

[00185] In some embodiments of the compound of Formula A, the compound has the structure of Formula A-I or salt or solvate thereof:



[00186] wherein:

[00187] R^{2a} is $-(\text{CH}_2)-(\text{R}^{2b})-(\text{phenyl})$, wherein R^{2b} is absent, $-\text{CH}_2-$, $-\text{NH}-$, $-\text{S}-$ or $-\text{O}-$, wherein the phenyl is optionally 4-substituted with $-\text{NH}_2$, $-\text{NO}_2$, $-\text{OH}$, $-\text{OR}^{2c}$, $-\text{SH}$, $-\text{SR}^{2c}$, or $-\text{O-phenyl}$ or optionally 3-substituted with halogen or $-\text{OH}$, wherein each R^{2c} is independently a C_1 - C_3 linear or branched alkyl group;

[00188] R^{3a} is $\text{R}^{3b}\text{R}^{3c}$ wherein R^{3b} is a linear C_1 - C_5 alkenyl, C_2 - C_5 alkenyl, or C_2 - C_5 alkynyl, wherein R^{3c} is $-\text{N}(\text{R}^{3d})_{2-3}$ or guanidino, wherein each R^{3d} is independently $-\text{H}$ or a linear or branched C_1 - C_3 alkyl;

[00189] R^{4a} is $\text{R}^{4b}\text{R}^{4c}$ wherein R^{4b} is a linear C_1 - C_5 alkenyl, C_2 - C_5 alkenyl, or C_2 - C_5 alkynyl, wherein R^{4c} is $-\text{N}(\text{R}^{4d})_{2-3}$ or guanidino, wherein each R^{4d} is independently $-\text{H}$ or a linear or branched C_1 - C_3 alkyl;

[00190] R^{5a} is $-(\text{CH}_2)_{1-3}-\text{R}^{5b}$, wherein R^{5b} is:

[00191] phenyl optionally substituted with one or a more of the following: 4-substituted with $-\text{NH}_2$, $-\text{NO}_2$, $-\text{OH}$, $-\text{SH}$, or $-\text{O-phenyl}$; 3-substituted with halogen or $-\text{OH}$; and/or 5-substituted with halogen or $-\text{OH}$;

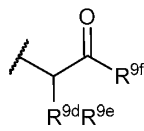
[00192] a fused bicyclic or fused tricyclic aryl or heteroaryl ring which is optionally substituted with one or more of halogen, -OH, -OR^{5c}, amino, -NHR^{5c}, and/or N(R^{5c})₂; and

[00193] wherein R^{5c} is each independently a C₁-C₃ linear or branched alkyl group;

[00194] R^{6a} is methyl, ethyl, -C≡CH, -CH=CH₂, -CH₂-R^{6b}-OH, -CH₂-R^{6b}-COOH, -CH₂-(R^{6b})₁₋₃-NH₂, -CH₂-R^{6b}-CONH, or -CH₂-R^{6b}R^{6c}, wherein each R^{6b} is independently absent, -CH₂-, -NH-, -S- or -O-; and wherein R^{6c} is a 5 or 6 membered aromatic ring wherein 0-3 carbons are independently replaced by N, S, and/or O heteroatoms, and optionally substituted with 0-3 groups independently selected from oxo, hydroxyl, sulfhydryl, nitro, amino, and/or halogen;

[00195] R^{8a} is R^{8b}R^{8c}, wherein R^{8b} is a linear C₁-C₅ alkylenyl, C₂-C₅ alkenylenyl, or C₂-C₅ alkynylenyl, wherein R^{8c} is -N(R^{8d})₂₋₃ or guanidino, wherein each R^{8d} is independently -H or a linear or branched C₁-C₃ alkyl;

[00196] R^{9a} is: -C(O)NH₂, -C(O)-OH, -CH₂-C(O)NH₂, -CH₂-C(O)-OH, -R^{9b}-R^{9c} or -R^{9b}-



[linker]-R^X_{n1}; wherein R^{9b} is -C(O)NH-; and R^{9c} is R^{9d}R^{9e}, wherein R^{9d} is a linear or branched C₁-C₅ alkylenyl, R^{9e} is carboxylic acid, sulfonic acid, sulfinic acid, phosphoric acid, amino, guanidino, -SH, -OH, -NH-C(O)-CH₃, -S-C(O)-CH₃, -O-C(O)-CH₃, -NH-C(O)-(phenyl), -S-C(O)-(phenyl), -O-C(O)-(phenyl), -NH-CH₃, -N(CH₃)₂, -S-CH₃, -O-CH₃, or phenyl, and R^{9f} is amino or -OH;

[00197] R^{A7a} is C₁-C₃ alkylenyl;

[00198] R^{A10} is absent or -[linker]-R^X_{n1};

[00199] when R^{A10} is absent, then R^{A1a} is:

[00200] a linear C₁-C₅ alkyl, alkenyl, or alkynyl, wherein 0-2 carbons in C₂-C₅ are independently replaced by one or more N, S, and/or O heteroatoms, optionally C-substituted with a single substituent selected from: -SH, -OH, amino, carboxy, guanidino, -NH-C(O)-CH₃, -S-C(O)-CH₃, -O-C(O)-CH₃, -NH-C(O)-(phenyl), -S-C(O)-(phenyl), -O-C(O)-(phenyl), -NH-(CH₃)₁₋₂, -NH₂-CH₃, -N(CH₃)₂₋₃, -S-CH₃, or -O-CH₃;

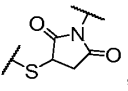
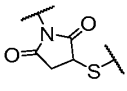
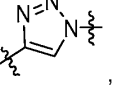
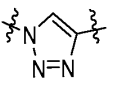
[00201] a branched C₁-C₁₀ alkyl, alkenyl, or alkynyl, wherein 0-3 carbons in C₂-C₁₀ are independently replaced by one or more N, S, and/or O heteroatoms; or

[00202] R^{A1b}R^{A1c}, wherein R^{A1b} is a linear C₁-C₃ alkylenyl, wherein C₂ alkylenyl or C₃ alkylenyl is optionally replaced with a N, S, or O heteroatom, wherein R^{A1c} is:

[00203] a 5 or 6 membered aromatic ring wherein one or more carbons are optionally independently replaced by N, S, and/or O heteroatoms, and optionally substituted with one or more groups independently selected from oxo, hydroxyl, sulfhydryl, nitro, amino, and/or halogen; or

[00204] a fused bicyclic or fused tricyclic aryl group wherein one or more carbons are optionally independently replaced by N, S, and/or O heteroatoms, and optionally substituted with one or more groups independently selected from halogen, -OH, -OR^{A1d}, amino, -NHR^{A1d}, and/or N(R^{A1d})₂, wherein each R^{A1d} is independently a C₁-C₃ linear or branched alkyl group;

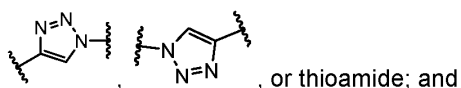
[00205] when R^{A10} is -[linker]-R^X_{n1}, then R^{A1a} is R^{A1e}R^{A1f}, wherein R^{A1e} is a linear C₁-C₅ alkynyl, alkenyl, or alkynyl, in which 0-2 carbons in C₂-C₅ are independently replaced with N, S, and/or O heteroatoms, and R^{A1f} is -NH-C(O)-, -C(O)-, -O-, -C(O)NH-, -C(O)-N(CH₃)-, -NHC(S)-, -C(S)NH-, -N(CH₃)C(S)-, -C(O)N(CH₃)-, -N(CH₃)C(O)-, -C(S)N(CH₃)-, -NHC(S)NH-, -NHC(O)NH-, -S-, -S(O)-, -S(O)-O-, -S(O)₂-, -S(O)₂-O-, -S(O)₂-NH-, -S(O)-NH-, -Se-, -Se(O)-, -Se(O)₂-, -NHNHC(O)-, -C(O)NHNH-, -OP(O)(O-)O-, -phosphamide-, -thiophosphodiester-, -S-

tetrafluorophenyl-S-, , , , , or polyethylene glycol;

[00206] each n₁ is independently 0, 1 or 2;

[00207] each R^X is a therapeutic moiety, a fluorescent label, a radiolabeled group, or a group capable of being radiolabelled;

[00208] wherein 0-3 peptide backbone amides are independently replaced with



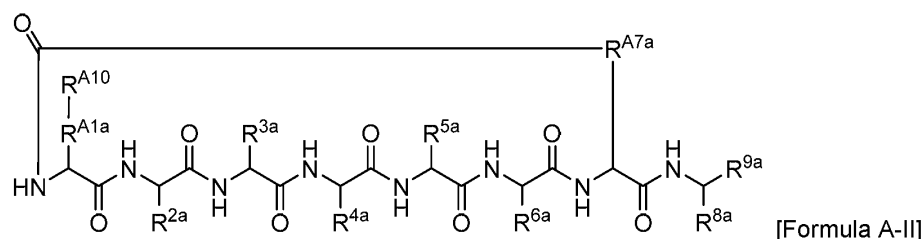
[00209] wherein 0-3 peptide backbone amides are N-methylated.

[00210] In some embodiments of the compounds of Formula A or A-I, -NH-CH(R^{A1a})-C(O)- forms an L amino acid residue.

[00211] In some embodiments of the compounds of Formula A or A-I, -NH-CH(R^{A1a})-C(O)- forms a Phe residue, a 1-Nal residue, a 2-Nal residue, a Tyr residue, a Trp residue, a Lys residue, a hLys residue, a Lys(Ac) residue, a Dap residue, a Dab residue, or an Orn residue. In some embodiments of the compounds of Formula A, -NH-CH(R^{A1a})-C(O)- forms an L-Phe residue, an L-1-Nal residue, an L-2-Nal residue, an L-Tyr residue, an L-Trp residue, an L-Lys residue, an L-hLys residue, an L-Lys(Ac) residue, an L-Dap residue, an L-Dab residue, or an L-Orn residue.

[00212] In some embodiments of the compounds of Formula A or A-I, R^{A10} is -[linker]- $R^{X_{n1}}$ and R^{9a} is -C(O)NH₂, -C(O)-OH, -CH₂-C(O)NH₂, or -CH₂-C(O)-OH.

[00213] In some embodiments of the compound of Formula A, the compound has the structure of Formula A-II or salt or solvate thereof:



[00214] wherein:

[00215] -NH-CH(R^{2a})-C(O)- in Formula A-II forms a Tyr residue, a Phe residue, a (4-NO₂)-Phe residue, a (4-NH₂)-Phe residue, a hTyr residue, a (3-I)Tyr residue, a Glu residue, a Gln residue, or a D-Tyr residue;

[00216] -NH-CH(R^{3a})-C(O)- in Formula A-II forms a Lys(iPr) residue, a Arg(Me)₂ (asymmetrical) residue, or a Arg(Me) residue;

[00217] -NH-CH(R^{4a})-C(O)- in Formula A-II forms a D-Arg residue or a D-hArg residue;

[00218] -NH-CH(R^{5a})-C(O)- in Formula A-II forms a 2-(Ant)Ala residue, a 2-Nal residue, a Trp residue, a (4-NH₂)Phe residue, a hTyr residue, or a Tyr residue;

[00219] -NH-CH(R^{6a})-C(O)- in Formula A-II forms a His residue, a D-His residue, a D-Glu residue, a D-Gln residue, a D-Ala residue, a D-Phe residue, a D-Ser residue, a D-Dab residue, a D-Dap residue;

[00220] R^{9a} is $R^{8b}R^{8c}$, wherein R^{8b} is a linear C₁-C₅ alkylenyl, C₂-C₅ alkenylenyl, or C₂-C₅ alkynylenyl, wherein R^{8c} is -N(R^{8d})₂₋₃ or guanidino, wherein each R^{8d} is independently -H or a linear or branched C₁-C₃ alkyl;

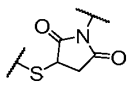
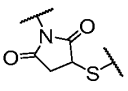
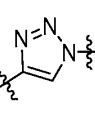
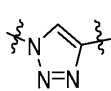
[00221] R^{9a} is -C(O)NH₂, -C(O)-OH, -CH₂-C(O)NH₂, -CH₂-C(O)-OH, or - R^{9b} -[linker]- $R^{X_{n1}}$;

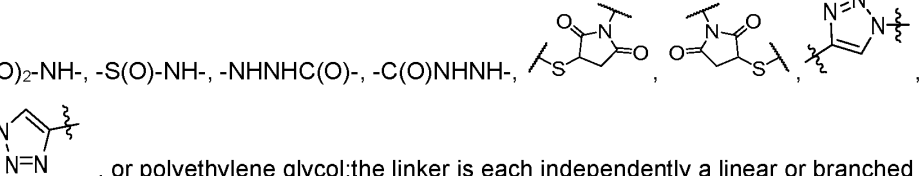
[00222] R^{9b} is -C(O)NH-;

[00223] R^{A7a} is C₁-C₃ alkylenyl;

[00224] R^{A10} is absent or -[linker]- $R^{X_{n1}}$;

[00225] when R^{A10} is absent, then R^{A1a} is a linear C₁-C₅ alkyl optionally substituted with a single substituent selected from: -SH, -OH, amino, carboxy, guanidino, -NH-C(O)-CH₃, -S-C(O)-CH₃, -O-C(O)-CH₃, -NH-C(O)-(phenyl), -S-C(O)-(phenyl), -O-C(O)-(phenyl), -NH-(CH₃)₁₋₂, -NH₂-CH₃, -N(CH₃)₂₋₃, -S-CH₃, or -O-CH₃, or a branched C₁-C₁₀ alkyl, alkenyl, or alkynyl;

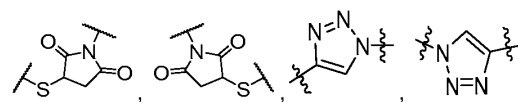
[00226] when R^{A10} is $[\text{linker}]-R^X_{n1}$, then R^{A1a} is $R^{A1e}R^{A1f}$, wherein R^{A1e} is a linear C_1 - C_5 alkenyl, C_2 - C_5 alkenyl, or C_2 - C_5 alkynyl, and R^{A1f} is $-\text{NH}-\text{C}(\text{O})-$, $-\text{C}(\text{O})-$, $-\text{O}-$, $-\text{C}(\text{O})\text{NH}-$, $-\text{C}(\text{O})-\text{N}(\text{CH}_3)-$, $-\text{NHC}(\text{S})-$, $-\text{C}(\text{S})\text{NH}-$, $-\text{N}(\text{CH}_3)\text{C}(\text{S})-$, $-\text{C}(\text{O})\text{N}(\text{CH}_3)-$, $-\text{N}(\text{CH}_3)\text{C}(\text{O})-$, $-\text{C}(\text{S})\text{N}(\text{CH}_3)-$, $-\text{NHC}(\text{S})\text{NH}-$, $-\text{NHC}(\text{O})\text{NH}-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{S}(\text{O})-\text{O}-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{NH}-$, $-\text{S}(\text{O})-\text{NH}-$, $-\text{NHNHC}(\text{O})-$, $-\text{C}(\text{O})\text{NHNH}-$, , , , , or polyethylene glycol; the linker is each independently a linear or branched chain of 1-10 units of X^1L^1 and/or $X^1(L^1)_2$, wherein:



chain of 1-10 units of X^1L^1 and/or $X^1(L^1)_2$, wherein:

[00227] each X^1 is, independently, a linear, branched, and/or cyclic C_1 - C_{15} alkenyl, C_2 - C_{15} alkenyl or C_2 - C_{15} alkynyl wherein 0-6 carbons are independently replaced by N, S, and/or O heteroatoms, and substituted with 0-3 groups independently selected from one or a combination of oxo, hydroxyl, sulfhydryl, halogen, guanidino, carboxylic acid, sulfonic acid, sulfinic acid, and/or phosphoric acid;

[00228] each L^1 is independently $-\text{NH}-\text{C}(\text{O})-$, $-\text{NH}-$, $-\text{C}(\text{O})-$, $-\text{O}-$, $-\text{C}(\text{O})\text{NH}-$, $-\text{C}(\text{O})-\text{N}(\text{CH}_3)-$, $-\text{NHC}(\text{S})-$, $-\text{C}(\text{S})\text{NH}-$, $-\text{N}(\text{CH}_3)\text{C}(\text{S})-$, $-\text{C}(\text{O})\text{N}(\text{CH}_3)-$, $-\text{N}(\text{CH}_3)\text{C}(\text{O})-$, $-\text{C}(\text{S})\text{N}(\text{CH}_3)-$, $-\text{NHC}(\text{S})\text{NH}-$, $-\text{NHC}(\text{O})\text{NH}-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{S}(\text{O})-\text{O}-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})_2-\text{O}-$, $-\text{S}(\text{O})_2\text{NH}-$, $-\text{S}(\text{O})-\text{NH}-$, $-\text{Se}-$, $-\text{Se}(\text{O})-$, $-\text{Se}(\text{O})_2-$, $-\text{NHNHC}(\text{O})-$, $-\text{C}(\text{O})\text{NHNH}-$, $-\text{OP}(\text{O})(\text{O})\text{O}-$, $-\text{phosphamide}-$, $-\text{thiophosphodiester}-$, $-\text{S-tetrafluorophenyl-S}-$,

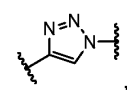
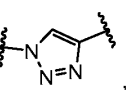


[00229] alternatively, the linker together with R^{A1f} forms a linear or branched peptide linker $(\text{Xaa})_{1-5}$, wherein each Xaa is independently selected from a proteinogenic amino acid residue or a nonproteinogenic amino acid residue; and wherein an amino group in each Xaa is optionally methylated;

[00230] each $n1$ is independently 0, 1 or 2;

[00231] each R^X is a therapeutic moiety, a fluorescent label, a radiolabeled group, or a group capable of being radiolabelled;

[00232] wherein 0-3 peptide backbone amides are independently replaced with

[00233] , , or thioamide; and

[00234] wherein 0-3 peptide backbone amides are N-methylated.

[00235] In some embodiments of the compounds of Formula A, A-I, A-II, B, or C, -NH-CH(R^{6a})-C(O)- forms a Gly residue, a D-Ala residue, a D-Gln residue, or a D-Asn residue. In some embodiments of the compounds of Formula A, A-I, A-II, B, or C, -NH-CH(R^{1a})-C(O)- forms a Phe residue and R^{10a} is absent. In some embodiments, R^{A10} is -[linker]-R^X_{n1}, R^{A1e} is linear C₁-C₅ alkylenyl, and R^{A1f} is -NH-C(O)-.

[00236] The term "[linker]" represents a linker, which may be any linker. Non-limiting examples include peptide and polyethylene glycol-based linkers.

[00237] In some embodiments of the compounds of Formula A, A-I, A-II, B, or C, each n1 in R^X_{n1} is independently 0, 1 or 2. In some embodiments, each n1 is 0. In some embodiments, each n1 is 1. In some embodiments, each n1 is 2. In some embodiments, each n1 is the same. In some embodiments, each n1 is different.

[00238] In some embodiments of the compounds of Formula A, A-I, A-II, B, or C, each R^X is an albumin binder, a therapeutic moiety, a fluorescent label, a radiolabeled group, or a group capable of being radiolabelled. In some embodiments, each R^X is a therapeutic moiety, a fluorescent label, a radiolabeled group, or a group capable of being radiolabelled.

[00239] The present disclosure also relates to one or more of compounds selected from Table A, or a salt or solvate thereof; wherein the compound is optionally bound to a radiolabeled group or a group capable of being radiolabelled, optionally through a linker

[00240] Table A

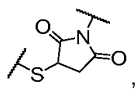
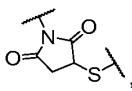
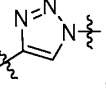
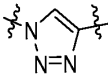
cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-D-Gln-D-Glu]-Lys(iPr);
cyclo[Phe-(3-I)Tyr-Lys(iPr)-D-Arg-2-Nal-Gly-D-Glu]-Lys(iPr);
cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr);
cyclo[Phe-(4-NH ₂)Phe-Lys(iPr)-D-Arg-2-Nal-Gly-D-Glu]-Lys(iPr);
cyclo[Phe-(4-NO ₂)Phe-Lys(iPr)-D-Arg-2-Nal-Gly-D-Glu]-Lys(iPr);
cyclo[Phe-hTyr-Lys(iPr)-D-Arg-2-Nal-Gly-D-Glu]-Lys(iPr);
cyclo[Phe-hTyr-Lys(iPr)-D-Arg-2-Nal-D-Ala-D-Glu]-Lys(iPr);
cyclo[Phe-(4-NH ₂)Phe-Lys(iPr)-D-Arg-2-Nal-D-Ala-D-Glu]-Lys(iPr);
cyclo[Lys(Ac)-Tyr-Lys(iPr)-D-Arg-Trp-D-Ala-D-Glu]-Lys(iPr);
cyclo[Phe-Tyr-Lys(iPr)-D-Arg-(4-NH ₂)Phe-D-Ala-D-Glu]-Lys(iPr);
cyclo[Lys(Ac)-Glu-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr);
cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-D-His-D-Glu]-Lys(iPr);
cyclo[Lys(Ac)-Gln-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr);
cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-His-D-Glu]-Lys(iPr);
cyclo[Phe-D-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr);

cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ser-D-Glu]-Lys(iPr);
 cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-D-Leu-D-Glu]-Lys(iPr);
 cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-D-Asn-D-Glu]-Lys(iPr);
 cyclo[Phe-Tyr-Arg(Me)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr);
 cyclo[Phe-Tyr-Arg(Me)₂](asym)-D-Arg-2Nal-Gly-D-Glu]-Lys(iPr);
 cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-D-Glu-D-Glu]-Lys(iPr);
 cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-D-Dab-D-Glu]-Lys(iPr);
 cyclo[Phe-Tyr-Lys(iPr)-D-Arg-(2-Ant)Ala-Gly-D-Glu]-Lys(iPr);
 cyclo(isoindole)[Phe-Tyr-Lys(iPr)-D-Arg-(2-Ant)Ala-Gly-D-Cys]-Lys(iPr);
 cyclo(isoindole)[Phe-Tyr-Lys(iPr)-D-Arg-(2-Ant)Ala-Gly-Cys]-Lys(iPr);
 cyclo[Lys(Ac)-Tyr-Lys(iPr)-D-Arg-2Nal-Gly-D-Glu]-Lys(iPr);
 cyclo[Lys(CysAcid)-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr);
 cyclo[Orn(CysAcid)-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr);
 cyclo[Dap(CysAcid)-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr);
 cyclo[Lys(CysAcid)-(3-I)Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr);
 cyclo[Lys(D-Arg)-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr); or
 cyclo(tryptathionine)[Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Cys]-Lys(iPr)

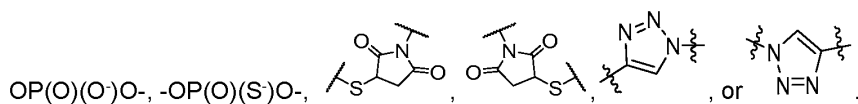
[00241] In some embodiments of the compounds of Formula A, A-I, B, or C, or Table A, each linker, if present, is independently a linear or branched chain of 1-10 units of X¹L¹ and/or X¹(L¹)₂, wherein:

each X¹ is, independently, a linear, branched, and/or cyclic C₁-C₁₅ alkylenyl, alkenylenyl or alkynylenyl wherein 0-6 carbons are independently replaced by N, S, and/or O heteroatoms, and substituted with 0-3 groups independently selected from one or a combination of oxo, hydroxyl, sulfhydryl, halogen, guanidino, carboxylic acid, sulfonic acid, sulfinic acid, and/or phosphoric acid;

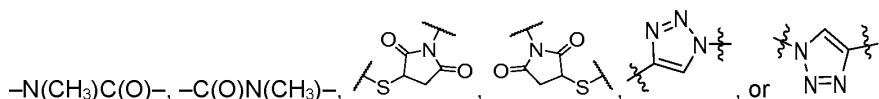
each L¹ is independently -NH-C(O)-, -C(O)-, -O-, -C(O)NH-, -C(O)-N(CH₃)-, -NHC(S)-, -C(S)NH-, -N(CH₃)C(S)-, -C(O)N(CH₃)-, -N(CH₃)C(O)-, -C(S)N(CH₃)-, -NHC(S)NH-, -NHC(O)NH-, -S-, -S(O)-, -S(O)-O-, -S(O)₂-, -S(O)₂-O-, -S(O)₂-NH-, -S(O)-NH-, -Se-, -Se(O)-, -Se(O)₂-, -NHNHC(O)-, -C(O)NHNH-, -OP(O)(O)O-, -phosphamide-, -

thiophosphodiester-, -S-tetrafluorophenyl-S-, , , , , or polyethylene glycol.

[00242] In some embodiments, each L^1 is independently $-S-$, $-NHC(O)-$, $-C(O)NH-$, $-N(CH_3)C(O)-$, $-C(O)N(CH_3)-$, $-NHC(S)-$, $-C(S)NH-$, $-N(CH_3)C(S)-$, $-C(S)N(CH_3)-$, $NHC(S)NH-$, $-S-$, $-O-$, $-S(O)-$, $-S(O)_2-$, $-Se-$, $-Se(O)-$, $-Se(O)_2-$, $-NHNHC(O)-$, $-C(O)NHNH-$, $-$



[00243] In some embodiments, each L^1 is independently $-S-$, $-NHC(O)-$, $-C(O)NH-$,

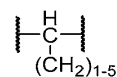


[00244] In some embodiments of the compounds of Formula A, A-I, A-II, B, or C or Table A, at least one linker comprises at least one carboxylic acid, sulfonic acid, sulfinic acid, or phosphoric acid, and has a net negative charge at physiological pH.

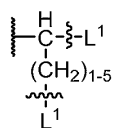
[00245] In some embodiments of the compounds of Formula A, A-I, A-II, B, or C, or Table A, at least one linker comprises at least one chemical group such as a guanidino or an amino group that has a net positive charge at physiological pH.

[00246] In some embodiments of the compounds of Formula A, A-I, A-II, B, or C, or Table A, at least one linker consists of 1-8 units of X^1L^1 and 0-2 units of $X^1(L^1)_2$.

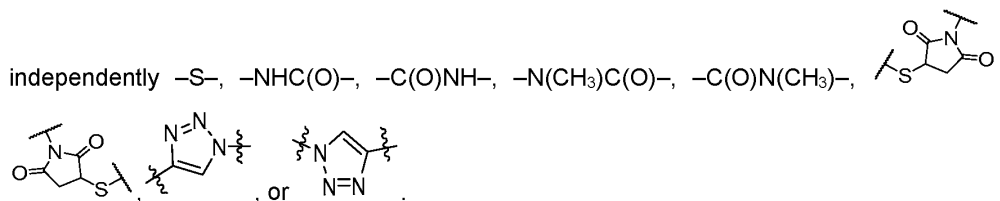
[00247] In some embodiments, each X^1 is independently a linear, branched, and/or cyclic C_1 - C_{15} alkylenyl.



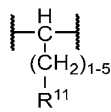
[00248] In some embodiments, each X^1 is independently: $-CH-$;  wherein each R^{11} is independently carboxylic acid, sulfonic acid, sulfinic acid, or phosphoric acid; or



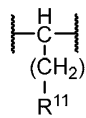
[00249] In some embodiments, each L^1 between two X^1 groups is independently $-NHC(O)-$, $-C(O)NH-$, $-N(CH_3)C(O)-$, or $-C(O)N(CH_3)-$, and each L^1 linking an R^x is



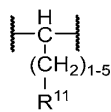
[00250] In some embodiments of the compounds of Formula A, A-I, A-II, B, or C, or Table A, the linker is X^1L^1 , $X^1L^1X^1L^1$, or $X^1L^1X^1L^1X^1L^1$, wherein each X^1 is same or different, and each L^1 is same or different.



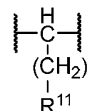
[00251] In one embodiment, X¹ is $\begin{array}{c} \text{H} \\ | \\ \text{---C---} \\ | \\ (\text{CH}_2)_{1-5} \\ | \\ \text{R}^{11} \end{array}$, wherein each R¹¹ is independently a carboxylic acid, a sulfonic acid, a sulfinic acid, or a phosphoric acid. In one embodiment, X¹ is



, wherein each R¹¹ is independently a carboxylic acid, a sulfonic acid, a sulfinic acid, or a phosphoric acid.



[00252] In one embodiment, X¹ is $\begin{array}{c} \text{H} \\ | \\ \text{---C---} \\ | \\ (\text{CH}_2)_{1-5} \\ | \\ \text{R}^{11} \end{array}$, wherein each R¹¹ is independently a



guanidino or an amino group. In one embodiment, X¹ is $\begin{array}{c} \text{H} \\ | \\ \text{---C---} \\ | \\ (\text{CH}_2) \\ | \\ \text{R}^{11} \end{array}$, wherein each R¹¹ is independently a guanidino or an amino group.

[00253] In some embodiments of the compounds of Formula A, A-I, A-II, B, or C, or Table A, the linker together with R^{A1f} forms a linear or branched peptide linker (Xaa)₁₋₅, wherein each Xaa is independently selected from a proteinogenic amino acid residue or a nonproteinogenic amino acid residue; and wherein an amino group in each Xaa is optionally methylated. In one embodiment, the amino group in each Xaa is optionally N-methylated.

[00254] In some embodiments of the compounds of Formula A, A-I, A-II, B, or C, or Table A, the linker together with R^{A1f} forms a linear or branched peptide linker (Xaa)₁₋₅, wherein at least one Xaa is selected from cysteic acid, Glu, Asp, or 2-aminoadipic acid (2-Aad); and wherein an amino group in each Xaa is optionally methylated. In one embodiment, the amino group in each Xaa is optionally N-methylated.

[00255] In some embodiments of the compounds of Formula A, A-I, A-II, B, or C, or Table A, the linker together with R^{A1f} forms a single amino acid residue selected from cysteic acid, Glu, Asp, or 2-aminoadipic acid (2-Aad); and wherein an amino group in Xaa is optionally methylated. In one embodiment, the amino group in each Xaa is optionally N-methylated.

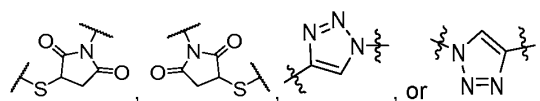
[00256] In some embodiments of the compounds of Formula A, A-I, A-II, B, or C, or Table A, the linker together with R^{A1f} forms a linear or branched peptide linker (Xaa)₁₋₅, wherein at least one Xaa is selected from Dap, Dab, Orn, Arg, hArg, Agb, Agp, Acp, Pip, or N^ε, N^ε, N^ε-trimethyl-lysine; and wherein an amino group in each Xaa is optionally methylated. In one embodiment, the amino group in each Xaa is optionally N-methylated.

[00257] In some embodiments of the compounds of Formula A, A-I, A-II, B, or C, or Table A, the linker together with R^{A1f} forms a single amino acid residue selected from D-Arg,

L-Arg, D-hArg, L-hArg, or Pip; and wherein an amino group in Xaa is optionally methylated. In one embodiment, the amino group in each Xaa is optionally N-methylated.

[00258] In some embodiments of the compounds of Formula A, A-I, A-II, B, or C, or Table A, at least one linker is a linear or branched peptide of amino acid residues selected from proteinogenic amino acid residues and/or nonproteinogenic amino acid residues listed in Table 1.

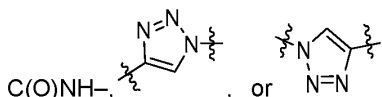
[00259] In some embodiments of the compounds of Formula A, A-I, A-II, B, or C, each L^1 between two X^1 groups in the linker is methylated or unmethylated, and wherein each L^1 linking an R^X is independently $-S-$, $-NHC(O)-$, $-C(O)NH-$, $-N(CH_3)C(O)-$, $-C(O)N(CH_3)-$,



[00260] In some embodiments, each L^1 between two X^1 groups is an unmethylated amide.

[00261] In some embodiments of the compounds of Formula A, A-I, A-II, B, or C, or Table A, the linker forms a peptide linker of 1 to 3 amino acids selected from one or a combination of: cysteic acid, Glu, Asp, and/or 2-aminoadipic acid (2-Aad) connected via amide bonds. In some embodiments, the linker forms a single amino acid residue selected from cysteic acid, Glu, Asp, or 2-aminoadipic acid (2-Aad). In some embodiments, the linker is a cysteic acid residue.

[00262] In some embodiments, each L^1 linking an R^X is independently $-NHC(O)-$, $-$



$C(O)NH-$, $-NHC(O)-$, or $-C(O)NH-$. In some embodiments, each L^1 linking an R^X is independently $-NHC(O)-$ or $-C(O)NH-$.

[00263] In some embodiments of the compounds of Formula A, A-I, A-II, B, or C, at least one R^X is an albumin binder. In some embodiments, the albumin binder is bonded to an L^1 of the linker, wherein the albumin binder is: $-(CH_2)_{n2}-CH_3$ wherein $n2$ is 8-20; $-(CH_2)_{n3}-$

$C(O)OH$ wherein $n3$ is 8-20, or $-(CH_2)_{n4}-C_6H_4-R^{12}$ wherein $n4 = 1-4$ and R^{12} is I, Br, F, Cl, H, OH, OCH_3 , NH_2 , NO_2 or CH_3 ;

[00264] In some embodiments of the compounds of Formula A, A-I, A-II, B, or C, at least one R^X is a radiolabeled group or a group capable of being radiolabelled (e.g. through conjugation of a radiometal or radiolabeled prosthetic group, or through an isotope-radioisotope exchange reaction).

[00265] In some embodiments of the compounds of Formula A, A-I, A-II, B, or C, or Table A, the compound comprises a first linker bonded to a radiolabeled group or to a group

capable of being radiolabelled, and further comprises a second linker bonded to an albumin binder.

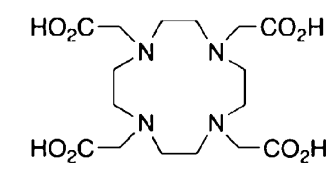
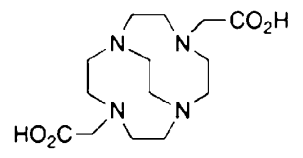
[00266] In some embodiments of the compounds of Formula A, A-I, A-II, B, or C, or Table A, the compound comprises a first linker bonded to a first radiolabeled group or to a first group capable of being radiolabelled, and further comprises a second linker bonded to a second radiolabeled group or to a second group capable of being radiolabelled, wherein the compound optionally further comprises an albumin binder attached to either or both of the first linker and the second linker.

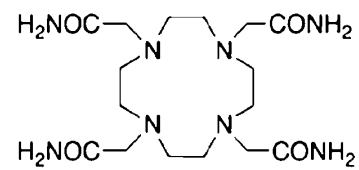
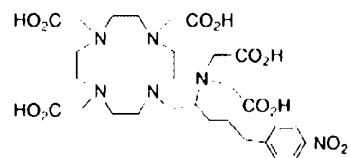
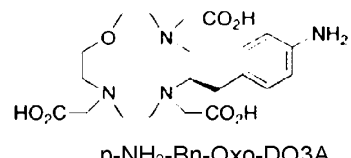
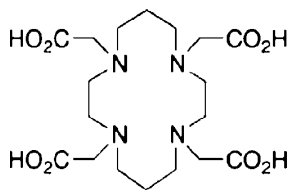
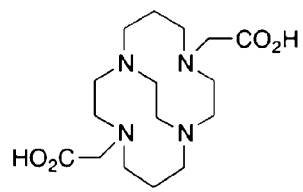
[00267] In some embodiments of the compounds of Formula A, A-I, A-II, B, or C, or Table A, the compound comprises only a single linker bonded to 1-2 groups consisting of radiolabeled groups and/or group capable of being radiolabelled, the linker optionally further bonded to an albumin binder.

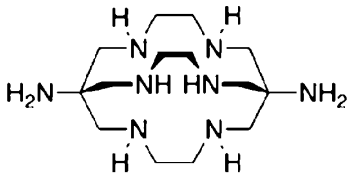
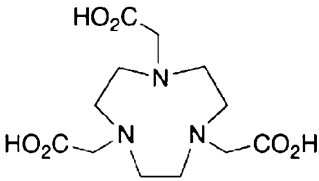
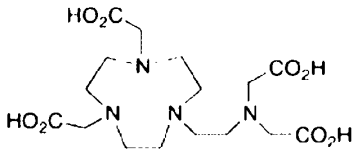
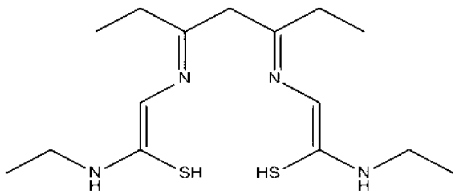
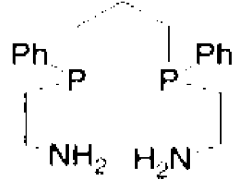
[00268] In some embodiments of the compounds of Formula A, A-I, A-II, B, or C, or Table A, each group capable of being radiolabelled is independently selected from: a metal chelator optionally in complex with a radiometal or radioisotope-bound metal; a prosthetic group containing trifluoroborate (BF_3); or a prosthetic group containing a silicon-fluorine-acceptor moiety, a sulphonyl fluoride, or a phosphoryl fluoride.

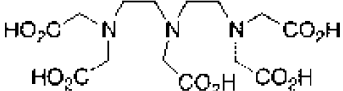
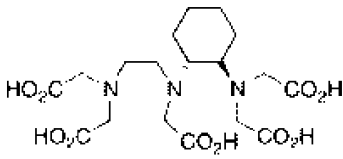
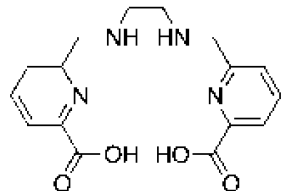
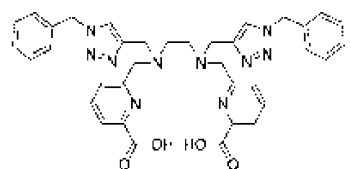
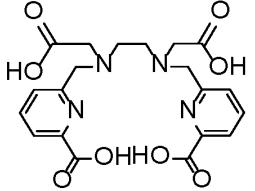
[00269] In some embodiments of the compounds of Formula A, A-I, A-II, B, or C, or Table A, an R^x comprises a metal chelator optionally in complex with a radiometal (e.g. ^{68}Ga or ^{177}Lu) or in complex with a radioisotope-bound metal (e.g. Al^{18}F). The chelator may be any metal chelator suitable for binding to the radiometal or to the metal-containing prosthetic group bonded to the radioisotope (e.g. polyaminocarboxylates and the like). Many suitable chelators are known, e.g. as summarized in Price and Orvig, *Chem. Soc. Rev.*, 2014, 43, 260-290, which is incorporated by reference in its entirety. Non-limiting examples of suitable chelators include those selected from the group consisting of: DOTA and derivatives; DOTAGA; NOTA; NODAGA; NODASA; CB-DO2A; 3p-C-DEPA; TCMC; DO3A; DTPA and DTPA analogues optionally selected from CHX-A"-DTPA and 1B4M-DTPA; TETA; NOPO; Me-3,2-HOPO; CB-TE1A1P; CB-TE2P; MM-TE2A; DM-TE2A; sarcophagine and sarcophagine derivatives optionally selected from SarAr, SarAr-NCS, diamSar, AmBaSar, and BaBaSar; TRAP; AAZTA; DATA and DATA derivatives; H₂-macropa or a derivative thereof; H₂dedpa, H₄octapa, H₄py4pa, H₄Pypa, H₂azapa, H₅decapa, and other picolinic acid derivatives; CP256; PCTA; C-NETA; C-NE3TA; HBED; SHBED; BCPA; CP256; YM103; desferrioxamine (DFO) and DFO derivatives; and H₆phospa. Exemplary non-limiting examples of suitable chelators and example radioisotopes (radiometals) chelated by these chelators are shown in Table 2. In alternative embodiments, an R^x comprises a chelator selected from those listed above or in Table 2, or is any other suitable chelator. One skilled in the art could replace any of the chelators listed herein with another chelator.

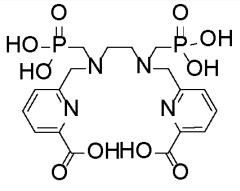
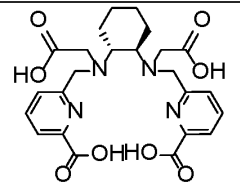
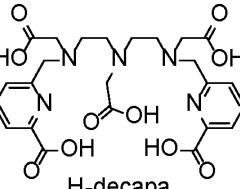
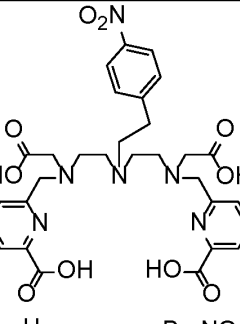
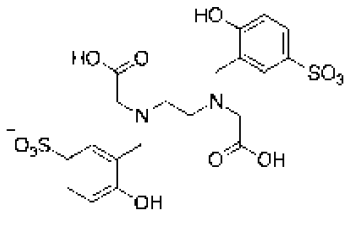
[00270] **TABLE 2:** Exemplary chelators and exemplary isotopes which bind said chelators.

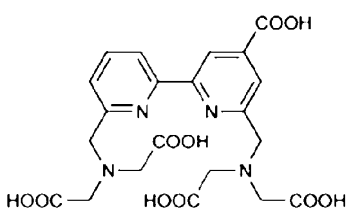
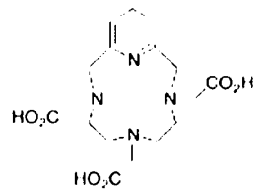
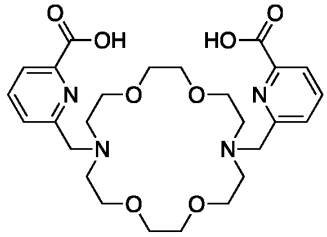
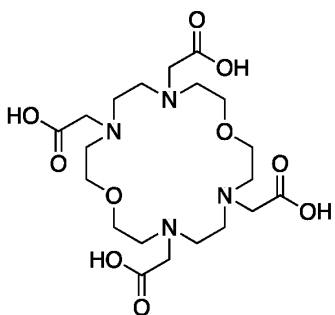
Chelator	Isotopes
 DOTA, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid	Cu-64/67 Ga-67/68 In-111 Lu-177 Y-86/90 Bi-203/212/213 Pb-212 Ac-225 Gd-159 Yb-175 Ho-166 As-211 Sc-44/47 Pm-149 Pr-142 Sn-117m Sm-153 Tb-149/161 Er-165 Ra-223/224 Th-227
 CB-DO2A, 4,10-bis(carboxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane	Cu-64/67

 TCMC, 1,4,7,10-tetrakis(carbamoylmethyl)- 1,4,7,10-tetraazacyclododecane	Pb-212
 3p-C-DEPA	Bi-212/213
 p-NH₂-Bn-Oxo-DO3A	Cu-64/67
 TETA, 1,4,8,11-tetraazacyclotetradecane- 1,4,8,11-tetraacetic acid	Cu-64/67
 CB-TE2A, 4,11-bis-(carboxymethyl)-1,4,8,11- tetraazabicyclo[6.6.2]-hexadecane	Cu-64/67

 Diamsar	Cu-64/67
 NOTA, 1,4,7-triazacyclononane-1,4,7-triacetic acid	Cu-64/67 Ga-68 In-111 Sc-44/47
 NETA, {4-[2-(bis-carboxymethylamino)-ethyl]-7-carboxymethyl-[1,4,7]triazonan-1-yl}-acetic acid	Cu-64/67 Ga-68 Lu-177 Y-86/90 Bi-213 Pb-212
 HxTSE	Au-198/199
 P₂N₂Ph₂	Rh-105

 DTPA, diethylenetriaminepentaacetic acid	In-111 Sc-44/47 Lu-177 Y-86/90 Sn-117m Pd-109
 CHX-A00-DTPA, 2-(p-isothiocyanatobenzyl)- Cyclohexyldiethylenetriaminepentaacetic acid	In-111 Lu-177 Y-86/90 Bi-212/213
 H₂dedpa, 1,2-[[6-(carboxy)-pyridin-2-yl]- methylamino]ethane	Cu-64/67
 H₂azapa, N,N'-[1-benzyl-1,2,3-triazole-4-yl]methyl- N,N'-[6-(carboxy)pyridin-2-yl]-1,2-diaminoethane	Cu-64/67
 H₄octapa	In-111 Lu-177 Y-86/90 Ac-225

 H₆phospa	Ac-225
 H₄CHXoctapa	In-111 Ac-225
 H₅decapa	In-111 Lu-177 Ac-225
 H₄neunpa-p-Bn-NO₂	In-111 Lu-177 Ac-225
 SHBED, N,N'-bis(2-hydroxy-5-sulfobenzyl)- ethylenediamine-N,N'-diacetic acid	In-111 Ga-68

 BPCA	In-111
 PCTA, 3,6,9,15-tetraazabicyclo[9.3.1]-pentadeca-1(15),11,13-triene-3,6,9-triacetic acid	Cu-64/67
 H2-MACROPA (N,N'-bis[(6-carboxy-2-pyridil)methyl]-4,13-diaza-18-crown-6)	Ac-225
 CROWN, 2,2',2'',2'''-(1,10-dioxa-4,7,13,16-tetraazacyclooctadecane-4,7,13,16-tetrayl)tetraacetic acid	Bis-213 Lu-177 Ac-225

[00271] It would be understood by one skilled in the art how the metal chelators, such as those listed in Table 2, can be connected to a linker or the peptide of the present disclosure by replacing one or more atoms or chemical groups of the metal chelators to form the connection. For example, one of the carboxylic acids present in the metal chelator structure can form an amide or an ester bond with the linker or the peptide. In one embodiment, the link formed between the linker and the metal chelator can be covered by the definition of the linker, such as L¹ (e.g., if an amide bond connects to the metal chelator to the linker, even if the carbonyl group could be coming from the metal chelator as drawn in Table 2, the definition of L¹ (-NH-C(O)-) can encompass the amide under Formula A, A-I, A-II, B, or C).

[00272] In some embodiments of the compounds of Table A, the compound is one or more compound selected from Table B, or a salt or solvate thereof.

[00273] Table B

cyclo[Lys(CysAcid-DOTA)-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr);
 cyclo[Lys(CysAcid-amido-N,N-dimethyl-ammoniomethyl-trifluoroborate)-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr); or
 cyclo[Lys(CysAcid-triazole-N,N-dimethyl-ammoniomethyl-trifluoroborate)-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr)

[00274] In some embodiments, cyclo[Lys(CysAcid-DOTA)-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr) is in complex with a radioisotope. In one embodiment, the radioisotope is ⁶⁴Cu, ⁶⁷Cu, ⁹⁰Y, ¹⁵³Sm, ¹⁴⁹Tb, ¹⁶¹Tb, ¹⁷⁷Lu, ²²⁵Ac, ²¹³Bi, ²²⁴Ra, ²¹²Bi, ²¹²Pb, ²²⁷Th, ²²³Ra, ⁴⁷Sc, ¹⁸⁶Re, ¹⁸⁸Re, ^{94m}Tc, ⁶⁸Ga, ⁶¹Cu, ⁶⁷Ga, ^{99m}Tc, ¹¹¹In, ⁴⁴Sc, ⁸⁶Y, ⁸⁹Zr, ⁹⁰Nb, ^{117m}Sn, ¹⁶⁵Er, ²¹¹As, ²⁰³Pb, ²¹²Pb, ⁴⁷Sc, ¹⁶⁶Ho, ¹⁴⁹Pm, ¹⁵⁹Gd, ¹⁰⁵Rh, ¹⁰⁹Pd, ¹⁹⁸Au, ¹⁹⁹Au, ¹⁷⁵Yb, ¹⁴²Pr, or ^{114m}In. In one embodiment, the radioisotope is ¹⁷⁷Lu, ¹¹¹In, ²¹³Bi, ⁶⁸Ga, ⁶⁷Ga, ²⁰³Pb, ²¹²Pb, ⁴⁴Sc, ⁴⁷Sc, ⁹⁰Y, ⁸⁶Y, ²²⁵Ac, ^{117m}Sn, ¹⁵³Sm, ¹⁴⁹Tb, ¹⁶¹Tb, ¹⁶⁵Er, ²²⁴Ra, ²¹²Bi, ²²⁷Th, ²²³Ra, ⁶⁴Cu, or ⁶⁷Cu.

[00275] In some embodiments of the compounds of Formula A, A-I, A-II, B, or C, an R^x of the compound is a polyaminocarboxylate chelator. In some such embodiments, the chelator is attached through an amide bond. In some embodiments, R^x is: DOTA or a derivative thereof; TETA or a derivative thereof; SarAr or a derivative thereof; NOTA or a derivative thereof; TRAP or a derivative thereof; HBED or a derivative thereof; 2,3-HOPO or a derivative thereof; PCTA (3,6,9,15-tetraazabicyclo[9.3.1]-pentadeca-1(15),11,13-triene-3,6,9,-triacetic acid) or a derivative thereof; DFO or a derivative thereof; DTPA or a derivative thereof; OCTAPA (N,N'-bis(6-carboxy-2-pyridylmethyl)-ethylenediamine-N,N'-diacetic acid) or a derivative thereof; or H2-MACROPA or a derivative thereof. In some embodiments, an R^x is DOTA. In some embodiments, an R^x is a chelator moiety in complex with radioisotope X wherein X is ⁶⁴Cu, ⁶⁷Cu, ⁹⁰Y, ¹¹¹In, ^{114m}In, ^{117m}Sn, ¹⁵³Sm, ¹⁴⁹Tb, ¹⁶¹Tb, ¹⁷⁷Lu, ²²⁵Ac, ²¹³Bi, ²²⁴Ra, ²¹²Bi, ²¹²Pb, ²²⁷Th,

^{223}Ra , ^{47}Sc , ^{186}Re or ^{188}Re . In some embodiments, X is ^{177}Lu . In some embodiments, an R^{X} is a chelator moiety in complex with radioisotope X wherein X is ^{64}Cu , ^{68}Ga , ^{86}Y , ^{111}In , $^{94\text{m}}\text{Tc}$, ^{44}Sc , ^{89}Zr , or $^{99\text{m}}\text{Tc}$. In some embodiments, X is ^{68}Ga .

[00276] In some embodiments, the chelator is conjugated with a radioisotope. The conjugated radioisotope may be, without limitation, ^{68}Ga , ^{61}Cu , ^{64}Cu , ^{67}Ga , $^{99\text{m}}\text{Tc}$, ^{111}In , ^{44}Sc , ^{86}Y , ^{89}Zr , ^{90}Nb , ^{177}Lu , $^{117\text{m}}\text{Sn}$, ^{165}Er , ^{90}Y , ^{227}Th , ^{225}Ac , ^{213}Bi , ^{212}Bi , ^{211}As , ^{203}Pb , ^{212}Pb , ^{47}Sc , ^{166}Ho , ^{188}Re , ^{186}Re , ^{149}Pm , ^{159}Gd , ^{105}Rh , ^{109}Pd , ^{198}Au , ^{199}Au , ^{175}Yb , ^{142}Pr , $^{114\text{m}}\text{In}$, and the like. In some embodiments, the chelator is a chelator from Table 2 and the conjugated radioisotope is a radioisotope indicated in Table 2 as a binder of the chelator.

[00277] In some embodiments, the chelator is not conjugated to a radioisotope.

[00278] In some embodiments, the chelator is: DOTA or a derivative thereof, conjugated with ^{177}Lu , ^{111}In , ^{213}Bi , ^{68}Ga , ^{67}Ga , ^{203}Pb , ^{212}Pb , ^{44}Sc , ^{47}Sc , ^{90}Y , ^{86}Y , ^{225}Ac , $^{117\text{m}}\text{Sn}$, ^{153}Sm , ^{149}Tb , ^{161}Tb , ^{165}Er , ^{224}Ra , ^{212}Bi , ^{227}Th , ^{223}Ra , ^{64}Cu or ^{67}Cu ; H₂-MACROPA conjugated with ^{225}Ac ; Me-3,2-HOPO conjugated with ^{227}Th ; H₄py4pa conjugated with ^{225}Ac , ^{227}Th or ^{177}Lu ; H₄pypa conjugated with ^{177}Lu ; NODAGA conjugated with ^{68}Ga ; DTPA conjugated with ^{111}In ; or DFO conjugated with ^{89}Zr .

[00279] In some embodiments, the chelator is TETA, SarAr, NOTA, TRAP, HBED, 2,3-HOPO, PCTA, DFO, DTPA, OCTAPA or another picolinic acid derivative.

[00280] In some embodiments of the compounds of Formula A, A-I, A-II, B, or C, an R^{X} is a chelator for radiolabelling with $^{99\text{m}}\text{Tc}$, $^{94\text{m}}\text{Tc}$, ^{186}Re , or ^{188}Re , such as mercaptoacetyl, hydrazinonicotinamide, dimercaptosuccinic acid, 1,2-ethylenediylbis-L-cysteine diethyl ester, methylenediphosphonate, hexamethylpropyleneamineoxime and hexakis(methoxy isobutyl isonitrile), and the like. In some embodiments, an R^{X} is a chelator, wherein the chelator is mercaptoacetyl, hydrazinonicotinamide, dimercaptosuccinic acid, 1,2-ethylenediylbis-L-cysteine diethyl ester, methylenediphosphonate, hexamethylpropyleneamineoxime or hexakis(methoxy isobutyl isonitrile). In some of these embodiments, the chelator is bound by a radioisotope. In some such embodiments, the radioisotope is $^{99\text{m}}\text{Tc}$, $^{94\text{m}}\text{Tc}$, ^{186}Re , or ^{188}Re .

[00281] In one embodiment of the compounds of Formula A, A-I, A-II, B, or C, Table A or derivatives thereof (e.g., where compounds of Table A is bound to a radiolabeled group or a group capable of being radiolabelled, optionally through a linker), or Table B, the radioisotope is ^{64}Cu , ^{67}Cu , ^{90}Y , ^{153}Sm , ^{149}Tb , ^{161}Tb , ^{177}Lu , ^{225}Ac , ^{213}Bi , ^{224}Ra , ^{212}Bi , ^{212}Pb , ^{227}Th , ^{223}Ra , ^{47}Sc , ^{186}Re , ^{188}Re , $^{94\text{m}}\text{Tc}$, ^{68}Ga , ^{61}Cu , ^{67}Ga , $^{99\text{m}}\text{Tc}$, ^{111}In , ^{44}Sc , ^{86}Y , ^{89}Zr , ^{90}Nb , $^{117\text{m}}\text{Sn}$, ^{165}Er , ^{211}As , ^{203}Pb , ^{212}Pb , ^{47}Sc , ^{166}Ho , ^{149}Pm , ^{159}Gd , ^{105}Rh , ^{109}Pd , ^{198}Au , ^{199}Au , ^{175}Yb , ^{142}Pr , or $^{114\text{m}}\text{In}$. In one embodiment, the radioisotope is ^{177}Lu , ^{111}In , ^{213}Bi , ^{68}Ga , ^{67}Ga , ^{203}Pb , ^{212}Pb , ^{44}Sc , ^{47}Sc , ^{90}Y , ^{86}Y , ^{225}Ac , $^{117\text{m}}\text{Sn}$, ^{153}Sm , ^{149}Tb , ^{161}Tb , ^{165}Er , ^{224}Ra , ^{212}Bi , ^{227}Th , ^{223}Ra , ^{64}Cu , or ^{67}Cu .

[00282] In one embodiment of the compounds of Formula A, A-I, A-II, B, or C, or Table A or derivatives thereof, or Table B, at least one R^{X} comprises an imaging radioisotope or is

complexed with an imaging radioisotope, the compound is bound to a metal chelator complexed with an imaging radioisotope, or the compound is bound to a prosthetic group containing BF_3 comprising an imaging radioisotope.

[00283] In one embodiment of the compounds of Formula A, A-I, A-II, B, or C, or Table A or derivatives thereof, or Table B, the imaging radioisotope is ^{68}Ga , ^{67}Ga , ^{61}Cu , ^{64}Cu , $^{99\text{m}}\text{Tc}$, $^{114\text{m}}\text{In}$, ^{111}In , ^{44}Sc , ^{86}Y , ^{89}Zr , ^{90}Nb , ^{18}F , ^{131}I , ^{123}I , ^{124}I or ^{72}As . In one embodiment, the imaging radioisotope is ^{68}Ga , ^{67}Ga , ^{61}Cu , ^{64}Cu , $^{99\text{m}}\text{Tc}$, $^{114\text{m}}\text{In}$, ^{111}In , ^{44}Sc , ^{86}Y , ^{89}Zr , ^{90}Nb , ^{131}I , ^{123}I , ^{124}I or ^{72}As .

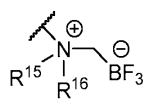
[00284] In one embodiment of the compounds of Formula A, A-I, A-II, B, or C, or Table A or derivatives thereof, or Table B, at least one R^{X} comprises an imaging radioisotope or is complexed with a therapeutic radioisotope, or the compound is bound to a metal chelator complexed with a therapeutic radioisotope.

[00285] In one embodiment of the compounds of Formula A, A-I, A-II, B, or C, or Table A or derivatives thereof, or Table B, the therapeutic radioisotope is ^{165}Er , ^{212}Bi , ^{211}At , ^{166}Ho , ^{149}Pm , ^{159}Gd , ^{105}Rh , ^{109}Pd , ^{198}Au , ^{199}Au , ^{175}Yb , ^{142}Pr , ^{177}Lu , ^{111}In , ^{213}Bi , ^{203}Pb , ^{212}Pb , ^{47}Sc , ^{90}Y , $^{117\text{m}}\text{Sn}$, ^{153}Sm , ^{149}Tb , ^{161}Tb , ^{224}Ra , ^{225}Ac , ^{227}Th , ^{223}Ra , ^{77}As , ^{131}I , ^{64}Cu or ^{67}Cu .

[00286] In some embodiments of the compounds of Formula A, A-I, A-II, B, or C, an R^{X} is a chelator that can bind ^{18}F -aluminum fluoride (^{18}F -AlF), such as 1,4,7-triazacyclononane-1,4-diacetate (NODA) and the like. In some embodiments, the chelator is NODA. In some embodiments, the chelator is bound by ^{18}F -AlF.

[00287] In some embodiments of the compounds of Formula A, A-I, A-II, B, or C, an R^{X} is a chelator that can bind ^{72}As or ^{77}As , such as a trithiol chelate and the like. In some embodiments, the chelator is a trithiol chelate. In some embodiments, the chelator is conjugated to ^{72}As . In some embodiments, the chelator is conjugated to ^{77}As .

[00288] In some embodiments of the compounds of Formula A, A-I, A-II, B, or C, an R^{X} is a prosthetic group containing a trifluoroborate (BF_3), capable of $^{18}\text{F}/^{19}\text{F}$ exchange radiolabeling. Such an R^{X} group may be the only R^{X} ($n1 = 1$), or may be in addition to additional R^{X} groups, which may be the same as or different than the first R^{X} . The prosthetic group may be $-\text{R}^{13}\text{R}^{14}\text{BF}_3$, wherein R^{13} is independently $-(\text{CH}_2)_{1-5}-$ and the group $-\text{R}^{14}\text{BF}_3$ may independently be selected from one or a combination of those listed in Table 3 (below), Table

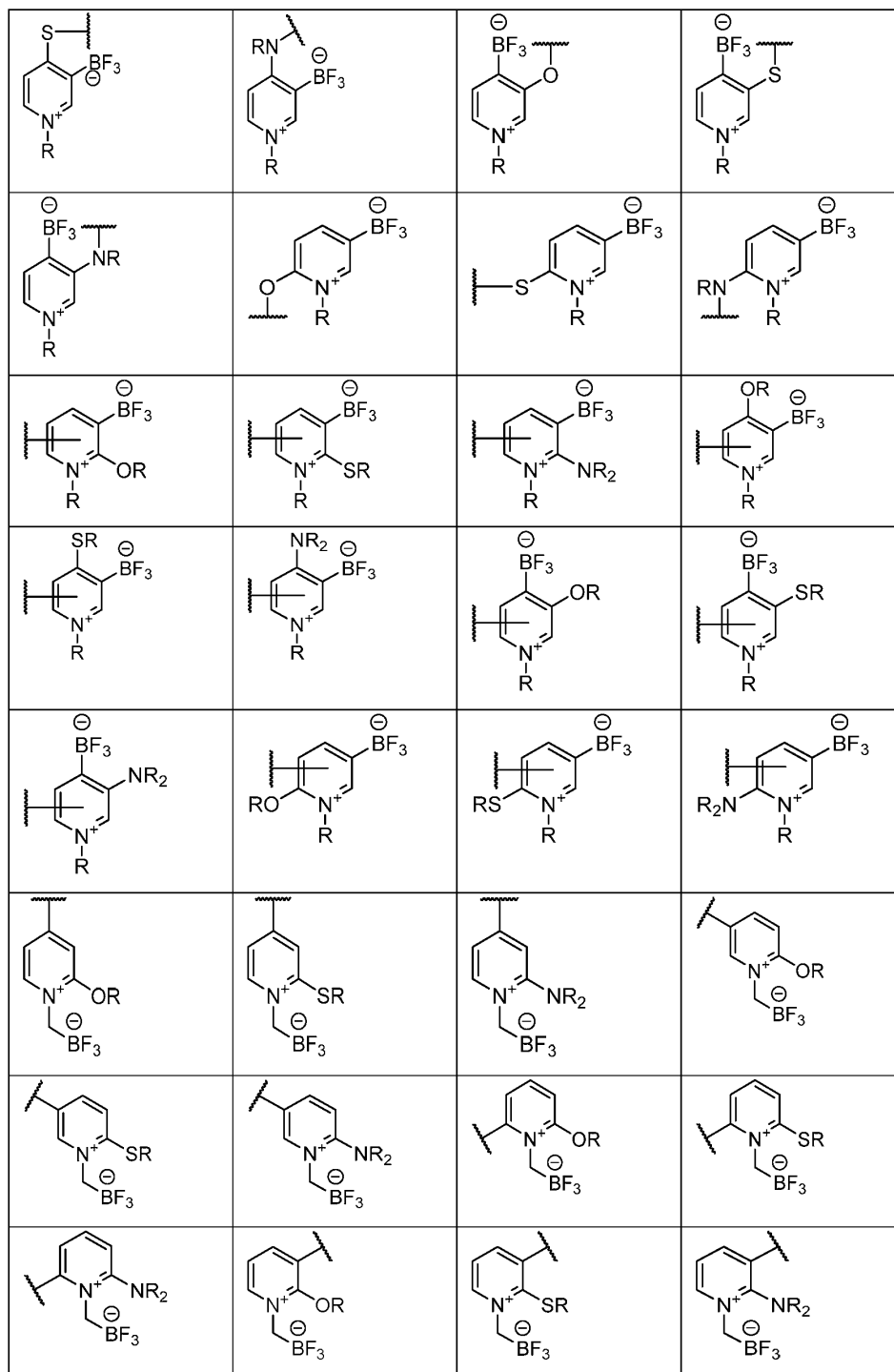
4 (below), or  wherein each R^{15} and each R^{16} are independently C_1 - C_5 linear or branched alkyl groups. For Tables 3 and 4, the R in the pyridine substituted with $-\text{OR}$, $-\text{SR}$, $-\text{NR}-$, $-\text{NHR}$ or $-\text{NR}_2$ groups is C_1 - C_5 branched or linear alkyl.

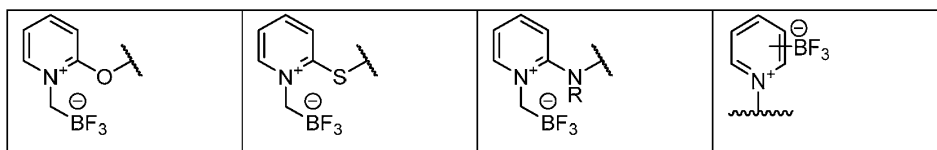
[00289] In some embodiments of the compounds of Formula A, A-I, A-II, B, or C, or Table A or derivatives thereof, or Table B, $-\text{R}^{14}\text{BF}_3$ is selected from those listed in Table 3. In

some embodiments, $-R^{14}BF_3$ is independently selected from one or a combination of those listed in Table 4. In some embodiments, at least one fluorine is ^{18}F . In some embodiments, all three fluorines are ^{19}F .

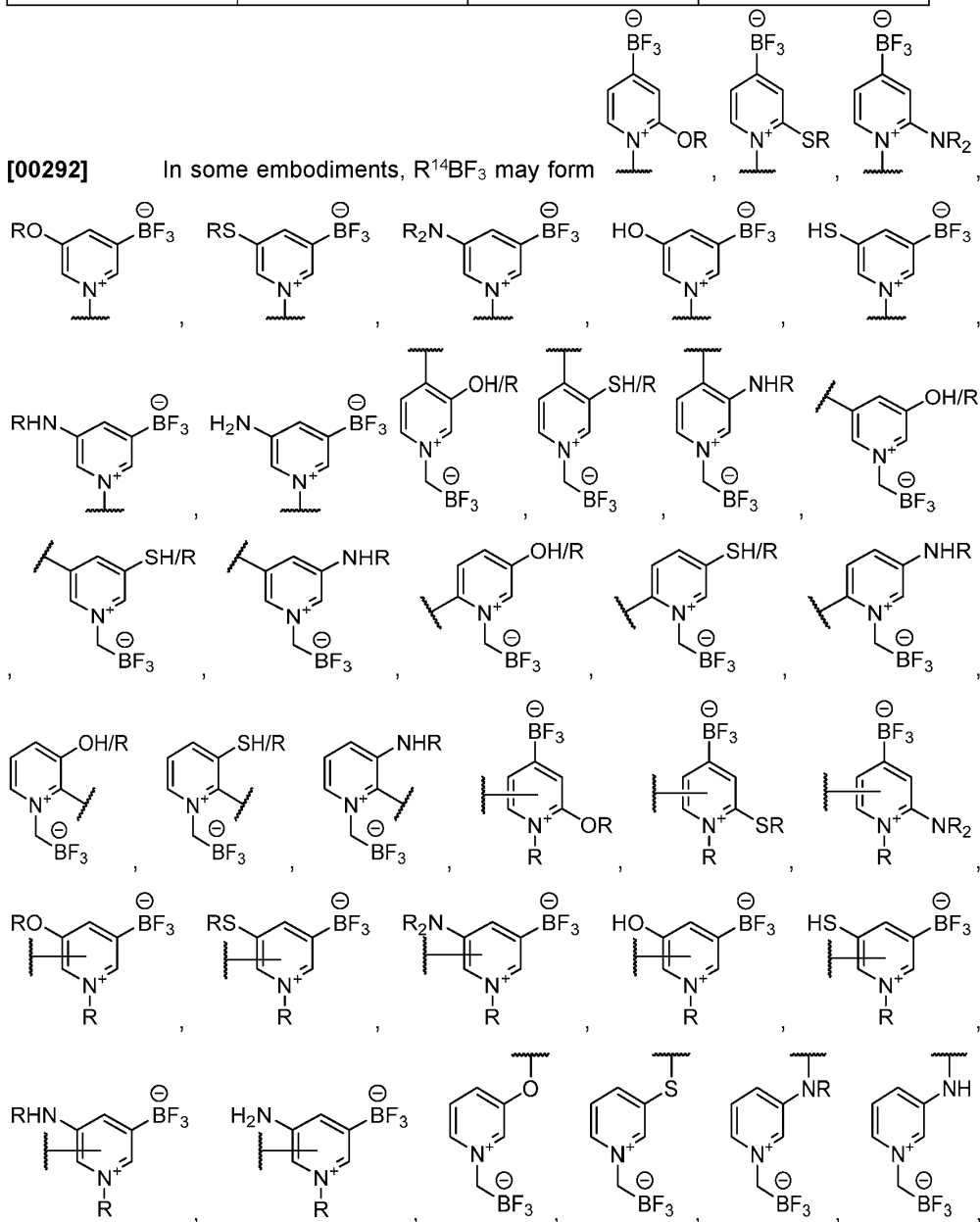
[00290] TABLE 3: Exemplary $R^{14}BF_3$ groups.

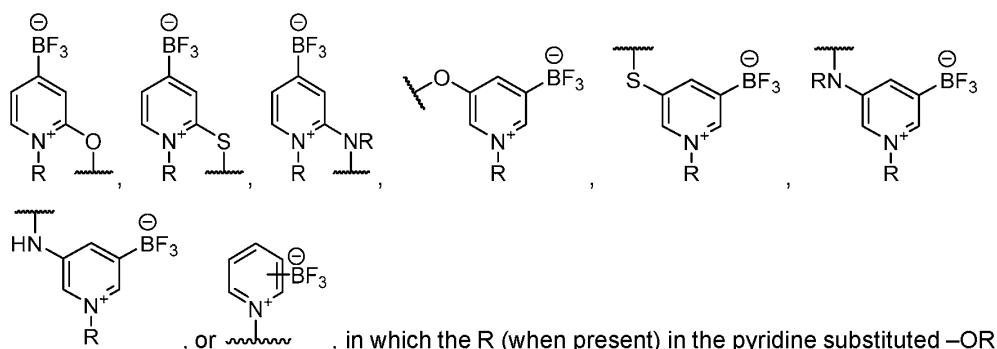
[00291] TABLE 4: Exemplary R¹⁴BF₃ groups.



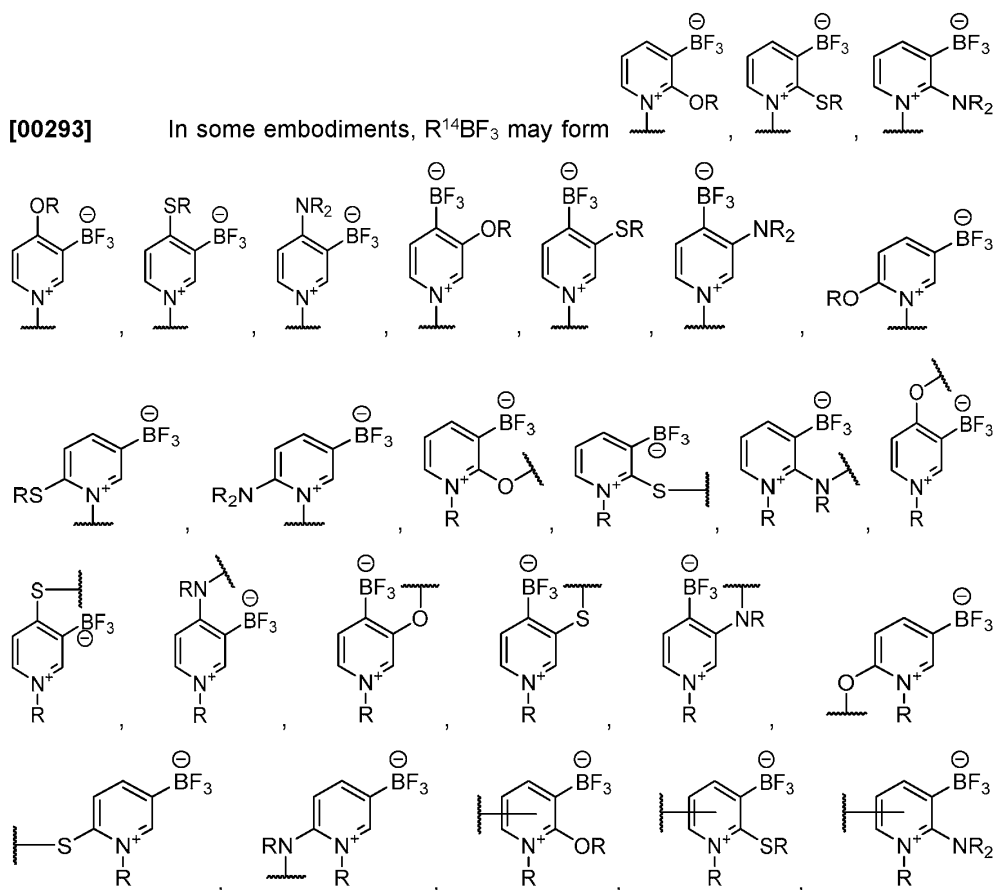


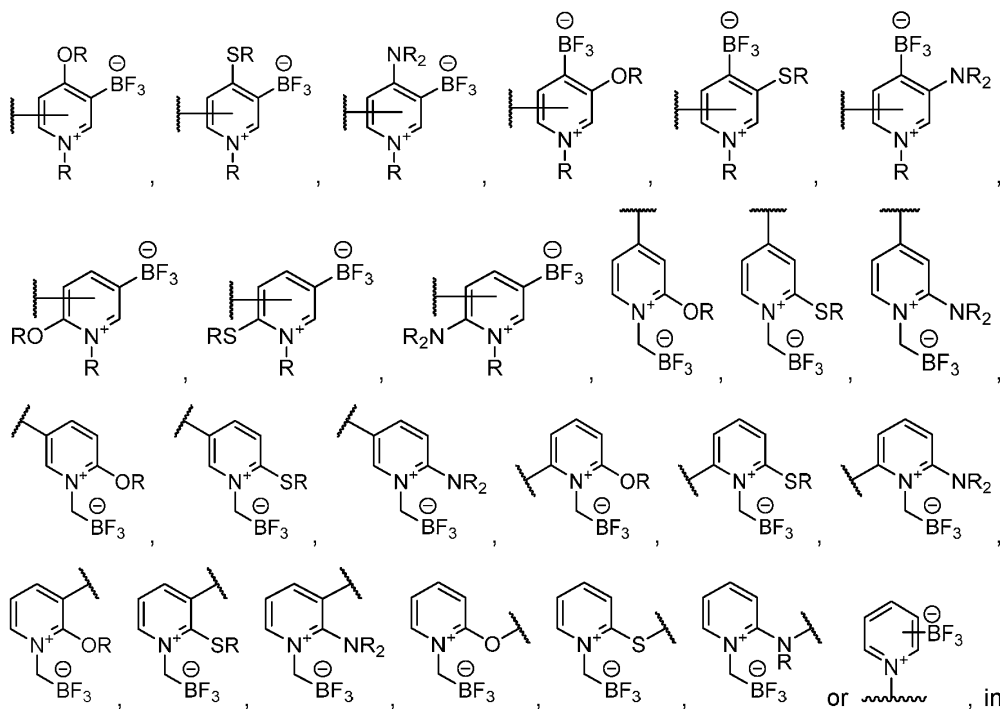
[00292]

In some embodiments, R¹⁴BF₃ may form

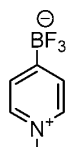


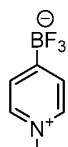
—SR, —NR—, —NHR or —NR₂ is a branched or linear C₁-C₅ alkyl. In some embodiments, R is a branched or linear C₁-C₅ saturated alkyl. In some embodiments, R is methyl. In some embodiments, R is ethyl. In some embodiments, R is propyl. In some embodiments, R is isopropyl. In some embodiments, R is n-butyl. In some embodiments, one fluorine is ¹⁸F. In some embodiments, all three fluorines are ¹⁹F.

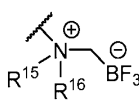




which the R (when present) in the pyridine substituted $-OR$, $-SR$, $-NR$ or $-NR_2$ is branched or linear C_1 - C_5 alkyl. In some embodiments, R is a branched or linear C_1 - C_5 saturated alkyl. In some embodiments, R is methyl. In some embodiments, R is ethyl. In some embodiments, R is propyl. In some embodiments, R is isopropyl. In some embodiments, R is n-butyl. In some

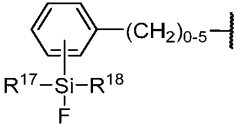


embodiments, $-R^{14}BF_3$ is . In some embodiments, one fluorine is ^{18}F . In some embodiments, all three fluorines are ^{19}F .

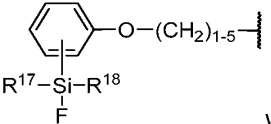
[00294] In some embodiments, $-R^{14}BF_3$ is . In some embodiments, R^{15} is methyl. In some embodiments, R^{15} is ethyl. In some embodiments, R^{15} is propyl. In some embodiments, R^{15} is isopropyl. In some embodiments, R^{15} is butyl. In some embodiments, R^{15} is n-butyl. In some embodiments, R^{15} is pentyl. In some embodiments, R^{16} is methyl. In some embodiments, R^{16} is ethyl. In some embodiments, R^{16} is propyl. In some embodiments, R^{16} is isopropyl. In some embodiments, R^{16} is butyl. In some embodiments, R^{16} is n-butyl. In some embodiments, R^{16} is pentyl. In some embodiments, R^{15} and R^{16} are both methyl. In some embodiments, at least one fluorine is ^{18}F . In some embodiments, all three fluorines are ^{19}F .

[00295] In some embodiments of the compounds of Formula A, A-I, A-II, B, or C, an R^X is a prosthetic group containing a silicon-fluorine-acceptor moiety. In some embodiments, the fluorine of the silicon-fluorine acceptor moiety is ^{18}F . The prosthetic groups containing a silicon-fluorine-acceptor moiety may be independently selected from one or a combination of the

following:

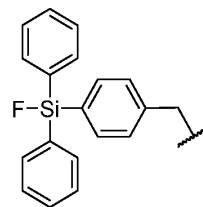


or

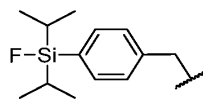


wherein R^{17} and R^{18} are independently a linear or branched, cyclic or acyclic, and/or aromatic or non-aromatic $\text{C}_1\text{-C}_{10}$ alkyl, alkenyl or alkynyl group. In some embodiments, R^{17} and R^{18} are independently selected from the group consisting of phenyl, tert-butyl, sec-propyl, isopropyl, methyl, pyridyl, 2-indolyl,

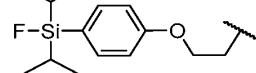
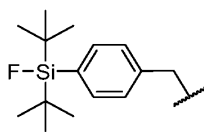
and 3-indolyl. In some embodiments, the prosthetic group is



embodiments, the prosthetic group is



prosthetic group is



[00296] In some embodiments of the compounds of Formula A, A-I, A-II, B, or C, an R^X is a therapeutic moiety, including any chemical moiety capable of producing a therapeutic effect, e.g. small molecule drugs.

[00297] In some embodiments of the compounds of Formula A, A-I, A-II, B, or C, R^X is fluorescent label.

[00298] The present disclosure also relates to a composition comprising any one of the compounds of Formula A, A-I, A-II, B, or C, or Table A or derivatives thereof, or Table B as described herein.

[00299] The present disclosure also relates to any one of the compounds of Formula A, A-I, A-II, B, or C, or Table A or derivatives thereof, or Table B as described herein, for use in imaging a CXCR4-expressing tissue in a subject or for imaging an inflammatory condition or disease. In one embodiment, the compound comprises at least one R^X comprises an

imaging radioisotope or is complexed with an imaging radioisotope, the compound is bound to a metal chelator complexed with an imaging radioisotope, or the compound is bound to a prosthetic group containing BF₃ comprising an imaging radioisotope. In one embodiment, the imaging radioisotope is ⁶⁸Ga, ⁶⁷Ga, ⁶¹Cu, ⁶⁴Cu, ^{99m}Tc, ^{114m}In, ¹¹¹In, ⁴⁴Sc, ⁸⁶Y, ⁸⁹Zr, ⁹⁰Nb, ¹⁸F, ¹³¹I, ¹²³I, ¹²⁴I or ⁷²As. In one embodiment, the imaging radioisotope is ⁶⁸Ga, ⁶⁷Ga, ⁶¹Cu, ⁶⁴Cu, ^{99m}Tc, ^{114m}In, ¹¹¹In, ⁴⁴Sc, ⁸⁶Y, ⁸⁹Zr, ⁹⁰Nb, ¹³¹I, ¹²³I, ¹²⁴I or ⁷²As.

[00300] The present disclosure also relates to a method of imaging a CXCR4-expressing tissue, comprising administering an effective amount of any one of the compounds of Formula A, A-I, A-II, B, or C, or Table A or derivatives thereof, or Table B as described herein, to a subject in need of such imaging. In one embodiment, the compound comprises at least one R^x comprises an imaging radioisotope or is complexed with an imaging radioisotope, the compound is bound to a metal chelator complexed with an imaging radioisotope, or the compound is bound to a prosthetic group containing BF₃ comprising an imaging radioisotope. In one embodiment, the imaging radioisotope is ⁶⁸Ga, ⁶⁷Ga, ⁶¹Cu, ⁶⁴Cu, ^{99m}Tc, ^{114m}In, ¹¹¹In, ⁴⁴Sc, ⁸⁶Y, ⁸⁹Zr, ⁹⁰Nb, ¹⁸F, ¹³¹I, ¹²³I, ¹²⁴I or ⁷²As. In one embodiment, the imaging radioisotope is ⁶⁸Ga, ⁶⁷Ga, ⁶¹Cu, ⁶⁴Cu, ^{99m}Tc, ^{114m}In, ¹¹¹In, ⁴⁴Sc, ⁸⁶Y, ⁸⁹Zr, ⁹⁰Nb, ¹³¹I, ¹²³I, ¹²⁴I or ⁷²As.

[00301] The present disclosure also relates to any one of the compounds of Formula A, A-I, A-II, B, or C, or Table A or derivatives thereof, or Table B as described herein, for use in treating a disease or condition characterized by expression of CXCR4 in a subject. In one embodiment, the disease or condition is a CXCR4-expressing cancer. In one embodiment, the compound comprises at least one R^x comprises an imaging radioisotope or the compound is complexed with a therapeutic radioisotope, or the compound is bound to a metal chelator complexed with a therapeutic radioisotope. In one embodiment, the therapeutic radioisotope is ¹⁶⁵Er, ²¹²Bi, ²¹¹At, ¹⁶⁶Ho, ¹⁴⁹Pm, ¹⁵⁹Gd, ¹⁰⁵Rh, ¹⁰⁹Pd, ¹⁹⁸Au, ¹⁹⁹Au, ¹⁷⁵Yb, ¹⁴²Pr, ¹⁷⁷Lu, ¹¹¹In, ²¹³Bi, ²⁰³Pb, ²¹²Pb, ⁴⁷Sc, ⁹⁰Y, ^{117m}Sn, ¹⁵³Sm, ¹⁴⁹Tb, ¹⁶¹Tb, ²²⁴Ra, ²²⁵Ac, ²²⁷Th, ²²³Ra, ⁷⁷As, ¹³¹I, ⁶⁴Cu or ⁶⁷Cu.

[00302] The present disclosure also relates to a method of treating a disease or condition characterized by expression of CXCR4, comprising administering an effective amount of any one of the compounds of Formula A, A-I, A-II, B, or C, or Table A or derivatives thereof, or Table B as described herein, to a subject in need thereof. In one embodiment, the disease or condition is a CXCR4-expressing cancer. In one embodiment, the compound comprises at least one R^x comprises an imaging radioisotope or the compound is complexed with a therapeutic radioisotope, or the compound is bound to a metal chelator complexed with a therapeutic radioisotope. In one embodiment, the therapeutic radioisotope is ¹⁶⁵Er, ²¹²Bi, ²¹¹At, ¹⁶⁶Ho, ¹⁴⁹Pm, ¹⁵⁹Gd, ¹⁰⁵Rh, ¹⁰⁹Pd, ¹⁹⁸Au, ¹⁹⁹Au, ¹⁷⁵Yb, ¹⁴²Pr, ¹⁷⁷Lu, ¹¹¹In, ²¹³Bi, ²⁰³Pb, ²¹²Pb, ⁴⁷Sc, ⁹⁰Y, ^{117m}Sn, ¹⁵³Sm, ¹⁴⁹Tb, ¹⁶¹Tb, ²²⁴Ra, ²²⁵Ac, ²²⁷Th, ²²³Ra, ⁷⁷As, ¹³¹I, ⁶⁴Cu or ⁶⁷Cu.

[00303] In some embodiments, the compounds of Formula A, A-I, A-II, B, or C, or Table A or derivatives thereof, or Table B, inhibit SDF-1 α binding to CXCR4 *in vitro* with an IC₅₀ of 50 nM or lower. In some embodiments, the compounds inhibit SDF-1 α binding to CXCR4 *in vitro* with an IC₅₀ of 25 nM or lower. In some embodiments, the compounds inhibit SDF-1 α binding to CXCR4 *in vitro* with an IC₅₀ of 10 nM or lower.

[00304] The overexpression of CXCR4 has been observed in over 23 types of malignancies, including brain, breast, and prostate cancers. Moreover, leukemia, lymphoma and myeloma have significant CXCR4 expression. Retrospective studies have shown that CXCR4 expression is correlated with lowered survival for prostate and melanoma patients. Furthermore, CXCR4 expression is a prognostic factor of disease relapse for acute and chronic myeloid leukemia, acute myelogenous leukemia and multiple myeloma. The SDF-1/CXCR4 axis mediates cancer growth, potentiates metastasis, recruits stromal and immune cells to support malignant growth, and confers chemotherapeutic resistance. Radiolabeled CXCR4 probes could be used in the early diagnosis of solid and hematological malignancies that express CXCR4. Such imaging agents could be used to confirm the diagnostic of malignancy, or guide focal ablative treatment if the disease is localized. Such ligands could also be used to monitor response to therapy, by providing an independent assessment of the residual cellular content of a tumour known to overexpress CXCR4. [⁶⁸Ga]Ga-Pentixafor has been used by the Wester group for cancer imaging and to identify potential responders to endoradiotherapy.

[00305] Dysregulation of the SDF-1/CXCR4 axis also mediates a number of inflammatory conditions. In rheumatoid arthritis (RA), SDF-1/CXCR4 signaling is responsible for the pro-inflammatory migration of activated T-cells into the site of inflammation; specifically, the synovium of patients with RA showed that the presence of T-cells with increased expression of CXCR4. Given the burden of RA on the population with respect to morbidity and mortality, there is a significant amount of research into developing therapeutics to mediate the inflammatory response, especially with novel biologics being approved by the FDA in the past few years. Radiolabeled CXCR4 probes for positron emission tomography imaging would enable diagnosis and prognosis of the rheumatoid arthritis and also be used to monitor therapy of emerging disease-modifying antirheumatic drugs in clinical trials. CXCR4 expression has been detected with PET imaging using [⁶⁸Ga]Ga-Pentixafor in diseases with an inflammatory component, including infectious bone diseases, urinary tract infections as a complication after kidney transplantation, myocardial infarctions, and ischemic strokes. CXCR4 imaging may have a significant role in diagnosing and monitoring other inflammatory diseases in the future.

[00306] In the setting of cardiac pathology, inflammatory diseases of the cardiac vessel walls are mediated in part by the dysregulation of the SDF-1/CXCR4 axis. In the early stages of atherosclerosis, the SDF-1/CXCR4 axis recruits endothelial progenitor cells towards sites

of peripheral vascular damage, thereby initiating plaque formation, though there is some evidence towards an atheroprotective effect. Atherosclerotic plaques are characterized by the presence of hypoxia, which has been shown to upregulate the expression of CXCR4 and influence cell trafficking. Finally, in a rabbit model of atherosclerosis, [⁶⁸Ga]Ga-Pentixafor enabled visualization of atherosclerotic plaques by PET. In the same study, atherosclerotic plaques were identified in patients with a history of atherosclerosis using [⁶⁸Ga]Ga-Pentixafor. As such, PET diagnostic agents targeting CXCR4 are potentially viable as an alternative method of diagnosing and obtaining prognostic information about atherosclerosis.

[00307] In some embodiments, the disease or condition characterized by expression of CXCR4 is leukemia, lymphoma and myeloma. In some embodiments, the disease or condition characterized by expression of CXCR4 is a hematological malignancy. In some embodiments, the disease or condition characterized by expression of CXCR4 is an inflammatory disease.

[00308] In some embodiments, the disease or condition characterized by expression of CXCR4 is a disease or condition characterized by an overexpression of CXCR4 or an abnormal expression of CXCR4.

[00309] In some embodiment, the CXCR4-expressing cancer is a hematologic malignancy. In some embodiment, the CXCR4-expressing cancer is leukemia, lymphoma and myeloma.

[00310] In certain embodiments, the compound of Formula A, A-I, A-II, B, or C is conjugated with a radioisotope for positron emission tomography (PET) or single photon emission computed tomography (SPECT) imaging of a CXCR4-expressing tissue or for imaging an inflammatory condition or disease (e.g. rheumatoid arthritis or cardiovascular disease), wherein the compound is conjugated with a radioisotope that is a positron emitter or a gamma emitter. Without limitation, the positron or gamma emitting radioisotope may be ⁶⁸Ga, ⁶⁷Ga, ⁶¹Cu, ⁶⁴Cu, ^{99m}Tc, ^{110m}In, ¹¹¹In, ⁴⁴Sc, ⁸⁶Y, ⁸⁹Zr, ⁹⁰Nb, ¹⁸F, ¹³¹I, ¹²³I, ¹²⁴I or ⁷²As.

[00311] When the radioisotope (e.g. X) is a diagnostic radioisotope, there is disclosed use of certain embodiments of the compound for preparation of a radiolabelled tracer for imaging. There is also disclosed a method of imaging CXCR4-expressing tissues or an inflammatory condition or disease in a subject, in which the method comprises: administering to the subject a composition comprising certain embodiments of the compound and a pharmaceutically acceptable excipient; and imaging the subject, e.g. using positron emission tomography (PET). When the tissue is a diseased tissue (e.g. a CXCR4-expressing cancer), CXCR4-targeted treatment may then be selected for treating the subject. There is therefore disclosed the use of certain compounds of the invention in imaging a CXCR4-expressing cancer in a subject, wherein R^x comprises or is complexed with a diagnostic or imaging radioisotope. In some embodiments, the subject is human.

[00312] Given the broad expression of CXCR4 in cancers, there has been a significant push to develop CXCR4-targeting therapeutics. While CXCR4 inhibitors have demonstrated efficacy in tumor models in mice, in both treating tumors and preventing metastasis, very few pharmaceutical agents have demonstrated efficacy in clinical trials. Plerixafor, also known as AMD3100, developed originally for HIV treatment, is the lone CXCR4 antagonist to receive FDA approval to date. AMD3100 is given to lymphoma and multiple myeloma patients to mobilize hematopoietic stem cells into peripheral blood for collection and autologous transplantation, and not as a method of direct treatment. There is an unmet clinical need for treating CXCR4-expressing cancers, many of which are resistant to the standard of care available today.

[00313] Cancers that are CXCR4 positive could be susceptible to endoradiotherapy. In this application, a peptide targeting CXCR4 is radiolabeled with a radioisotope, usually a β - or α -particle emitter, to deliver a high local dose of radiation to lesions. These radioactive emissions usually inflict DNA damage, thereby inducing cellular death. This method of therapy has been exploited in oncology, with the somatostatin receptor (for neuroendocrine tumors) and prostate-specific membrane antigen (for metastatic castration-resistant prostate cancer) being two examples. Unlike external beam radiation therapy, this systemic treatment can be effective even in the metastatic setting. Therapeutic radioisotopes include but are not restricted to ^{177}Lu , ^{90}Y , ^{225}Ac and ^{64}Cu .

[00314] With respect to cardiac pathologies, a small retrospective study with endoradiotherapy by [^{90}Y]Y- or [^{177}Lu]Lu-Pentixather demonstrated regression of CXCR4 expression and activity in patients with previously identified atherosclerotic plaques. Therefore, radionuclide therapy may present a novel route of therapy for inflammatory diseases such as atherosclerosis.

[00315] In certain embodiments the compound of Formula A, A-I, A-II, B, or C is conjugated with a radioisotope that is used for therapy (e.g. cancer therapy). This includes radioisotopes such as ^{165}Er , ^{212}Bi , ^{211}At , ^{166}Ho , ^{149}Pm , ^{159}Gd , ^{105}Rh , ^{109}Pd , ^{198}Au , ^{199}Au , ^{175}Yb , ^{142}Pr , ^{177}Lu (β -emitter, $t_{2/1} = 6.65$ d), ^{111}In , ^{213}Bi , ^{203}Pb , ^{212}Pb , ^{47}Sc , ^{90}Y (β -emitter, $t_{2/1} = 2.66$ d), $^{117\text{m}}\text{Sn}$, ^{153}Sm , ^{149}Tb , ^{161}Tb , ^{224}Ra , ^{225}Ac (α -emitter, $t_{2/1} = 9.95$ d), ^{227}Th , ^{223}Ra , ^{77}As , ^{131}I , ^{64}Cu or ^{67}Cu .

[00316] When the radioisotope (e.g. X) is a therapeutic radioisotope, there is disclosed use of certain embodiments of the compound (or a pharmaceutical composition thereof) for the treatment of a disease or condition characterized by expression of CXCR4 in a subject. Accordingly, there is provided use of the compound in preparation of a medicament for treating a disease or condition characterized by expression of CXCR4 in a subject. There is also provided a method of treating a disease or condition characterized by expression of CXCR4 in a subject, in which the method comprises: administering to the subject a composition

comprising the compound of Formula A, A-I, A-II, B, or C, or a salt or solvate thereof and a pharmaceutically acceptable excipient. For example, but without limitation, the disease may be a CXCR4-expressing cancer (e.g. non-Hodgkin lymphoma, lymphoma, multiple myeloma, leukemia, adrenocortical cancer, lung cancer, breast cancer, renal cell cancer, colorectal cancer). There is therefore disclosed the use of certain compounds of the invention for treating a CXCR4-expressing cancer in a subject, wherein R^x comprises or is complexed with a therapeutic radioisotope. In some embodiments, the subject is human.

[00317] The compounds presented herein incorporate peptides, which may be synthesized by any of a variety of methods established in the art. This includes but is not limited to liquid-phase as well as solid-phase peptide synthesis using methods employing 9-fluorenylmethoxycarbonyl (Fmoc) and/or t-butyloxycarbonyl (Boc) chemistries, and/or other synthetic approaches.

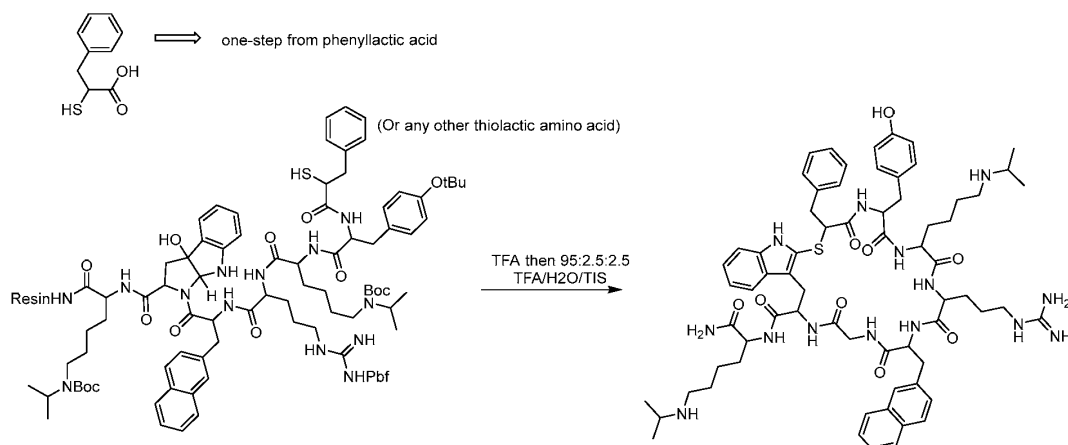
[00318] Solid-phase peptide synthesis methods and technology are well-established in the art. For example, peptides may be synthesized by sequential incorporation of the amino acid residues of interest one at a time. In such methods, peptide synthesis is typically initiated by attaching the C-terminal amino acid of the peptide of interest to a suitable resin. Prior to this, reactive side chain and alpha amino groups of the amino acids are protected from reaction by suitable protecting groups, allowing only the alpha carboxyl group to react with a functional group such as an amine group, a hydroxyl group, or an alkyl halide group on the solid support. Following coupling of the C-terminal amino acid to the support, the protecting group on the side chain and/or the alpha amino group of the amino acid is selectively removed, allowing the coupling of the next amino acid of interest. This process is repeated until the desired peptide is fully synthesized, at which point the peptide can be deprotected and cleaved from the support, and purified. A non-limiting example of an instrument for solid-phase peptide synthesis is the Aapptec Endeavor 90 peptide synthesizer.

[00319] To allow coupling of additional amino acids, Fmoc protecting groups may be removed from the amino acid on the solid support, e.g. under mild basic conditions, such as piperidine (20-50% v/v) in DMF. The amino acid to be added must also have been activated for coupling (e.g. at the alpha carboxylate). Non-limiting examples of activating reagents include without limitation 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), 2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), benzotriazole-1-yl-oxy-tris(dimethylamino)phosphoniumhexafluorophosphate (BOP), benzotriazole-1-yl-oxy-tris(pyrrolidino)phosphoniumhexafluorophosphate (PyBOP). Racemization is minimized by using triazoles, such as 1-hydroxy-benzotriazole (HOBt) and 1-hydroxy-7-aza-benzotriazole (HOAt). Coupling may be performed in the presence of a suitable base, such as N,N-

diisopropylethylamine (DIPEA/DIEA) and the like. For long peptides or if desired, peptide synthesis and ligation may be used.

[00320] Apart from forming typical peptide bonds to elongate a peptide, peptides may be elongated in a branched fashion by attaching to side chain functional groups (e.g. carboxylic acid groups or amino groups), either: side chain to side chain; or side chain to backbone amino or carboxylate. Coupling to amino acid side chains may be performed by any known method, and may be performed on-resin or off-resin. Non-limiting examples include: forming an amide between an amino acid side chain containing a carboxyl group (e.g. Asp, D-Asp, Glu, D-Glu, Aad, and the like) and an amino acid side chain containing an amino group (e.g. Lys, D-Lys, Orn, D-Orn, Dab, D-Dab, Dap, D-Dap, and the like) or the peptide N-terminus; forming an amide between an amino acid side chain containing an amino group (e.g. Lys, D-Lys, Orn, D-Orn, Dab, D-Dab, Dap, D-Dap, and the like) and either an amino acid side chain containing a carboxyl group (e.g. Asp, D-Asp, Glu, D-Glu, and the like) or the peptide C-terminus; and forming a 1, 2, 3-triazole via click chemistry between an amino acid side chain containing an azide group (e.g. Lys(N₃), D-Lys(N₃), and the like) and an alkyne group (e.g. Pra, D-Pra, and the like). The protecting groups on the appropriate functional groups must be selectively removed before amide bond formation, whereas the reaction between an alkyne and an azido groups via the click reaction to form an 1,2,3-triazole does not require selective deprotection. Non-limiting examples of selectively removable protecting groups include 2-phenylisopropyl esters (O-2-PhiPr) (e.g. on Asp/Glu) as well as 4-methyltrityl (Mtt), allyloxycarbonyl (alloc), 1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl (Dde), and 1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-3-methylbutyl (ivDde) (e.g. on Lys/Orn/Dab/Dap). O-2-PhiPr and Mtt protecting groups can be selectively deprotected under mild acidic conditions, such as 2.5% trifluoroacetic acid (TFA) in DCM. Alloc protecting groups can be selectively deprotected using tetrakis(triphenylphosphine)palladium(0) and phenylsilane in DCM. Dde and ivDde protecting groups can be selectively deprotected using 2-5% of hydrazine in DMF. Deprotected side chains of Asp/Glu (L- or D-forms) and Lys/Orn/Dab/Dap (L- or D-forms) can then be coupled, e.g. by using the coupling reaction conditions described above.

[00321] Formula A, A-I, and A-II compounds may be cyclized by linking the peptide N-terminus to a side chain carboxylate (at residue 7 in the peptide) using the technologies discussed above (exemplary reaction conditions are described in the Examples). Formula B compounds may be cyclized using an intra-annular tryptathionine stapling reaction or an isoindole stapling reaction, called FIICK²¹, to link the side chains of residues 1 and 7 in the peptide (exemplary reaction conditions are described in the Examples); the resulting isoindoles have intrinsic fluorescent properties imaging. Formula C compounds may be similarly cyclized using a thiolactic amino acid at residue 1 in the peptide, e.g. as shown in the following scheme:



[00322] Peptide backbone amides may be N-methylated (i.e. alpha amino methylated). This may be achieved by directly using Fmoc-N-methylated amino acids during peptide synthesis. Alternatively, N-methylation under Mitsunobu conditions may be performed. First, a free primary amine group is protected using a solution of 4-nitrobenzenesulfonyl chloride (Ns-Cl) and 2,4,6-trimethylpyridine (collidine) in NMP. N-methylation may then be achieved in the presence of triphenylphosphine, diisopropyl azodicarboxylate (DIAD) and methanol. Subsequently, N-deprotection may be performed using mercaptoethanol and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in NMP. For coupling protected amino acids to N-methylated alpha amino groups, HATU, HOAt and DIEA may be used.

[00323] The formation of the thioether (-S-) linkages (e.g. for L¹) can be achieved either on solid phase or in solution phase. For example, the formation of thioether (-S-) linkage can be achieved by coupling between a thiol-containing compound (such as the thiol group on cysteine side chain) and an alkyl halide (such as 3-(Fmoc-amino)propyl bromide and the like) in an appropriate solvent (such as N,N-dimethylformamide and the like) in the presence of base (such as N,N-diisopropylethylamine and the like). If the reactions are carried out in solution phase, the reactants used are preferably in equivalent molar ratio (1 to 1), and the desired products can be purified by flash column chromatography or high performance liquid chromatography (HPLC). If the reactions are carried out on solid phase, meaning one reactant has been attached to a solid phase, then the other reactant is normally used in excess amount (≥ 3 equivalents of the reactant attached to the solid phase). After the reactions, the excess unreacted reactant and reagents can be removed by sequentially washing the solid phase (resin) using a combination of solvents, such as N,N-dimethylformamide, methanol and dichloromethane, for example.

[00324] The formation of the linkage (e.g. for L¹) between a thiol group and a maleimide group can be performed using the conditions described above for the formation of the thioether group.

(-S-) linkage simply by replacing the alkyl halide with a maleimide-containing compounds. Similarly, this reaction can be conducted in solid phase or solution phase. If the reactions are carried out in solution phase, the reactants used are preferably in equivalent molar ratio (1 to 1), and the desired products can be purified by flash column chromatography or high performance liquid chromatography (HPLC). If the reactions are carried out on solid phase, meaning one reactant has been attached to a solid phase, then the other reactant is normally used in excess amount (≥ 3 equivalents of the reactant attached to the solid phase). After the reactions, the excess unreacted reactant and reagents can be removed by sequentially washing the solid phase (resin) using a combination of solvents, such as N,N-dimethylformamide, methanol and dichloromethane, for example.

[00325] Non-peptide moieties (e.g. radiolabeling groups, albumin-binding groups and/or linkers) may be coupled to the peptide N-terminus while the peptide is attached to the solid support. This is facile when the non-peptide moiety comprises an activated carboxylate (and protected groups if necessary) so that coupling can be performed on resin. For example, but without limitation, a bifunctional chelator, such as 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) tris(tert-butyl ester) may be activated in the presence of N-hydroxysuccinimide (NHS) and N,N'-dicyclohexylcarbodiimide (DCC) for coupling to a peptide. Alternatively, a non-peptide moiety may be incorporated into the compound via a copper-catalyzed click reaction under either liquid or solid phase conditions. Copper-catalyzed click reactions are well established in the art. For example, 2-azidoacetic acid is first activated by NHS and DCC and coupled to a peptide. Then, an alkyne-containing non-peptide moiety may be clicked to the azide-containing peptide in the presence of Cu^{2+} and sodium ascorbate in water and organic solvent, such as acetonitrile (ACN) and DMF and the like. Non-peptide moieties may also be added in solution phase, which is routinely performed.

[00326] The synthesis of chelators is well-known and many chelators are commercially available (e.g. from Sigma-Aldrich™/Milipore Sigma™ and others). Protocols for conjugation of radiometals to the chelators are also well known (e.g. see Example 1, below). The synthesis of the silicon-fluorine-acceptor moieties can be achieved following previously reported procedures (e.g. Bernard-Gauthier et al. *Biomed Res Int.* 2014 2014:454503; Kostikov et al. *Nature Protocols* 2012 7:1956–1963; Kostikov et al. *Bioconjug Chem.* 2012 18:23:106-114; each of which is incorporated by reference in its entirety). The synthesis or acquisition of radioisotope-substituted aryl groups is likewise facile.

[00327] The synthesis of the $\text{R}^{13}\text{R}^{14}\text{BF}_3$ component on the compounds can be achieved following previously reported procedures (e.g.: Liu et al. *Angew Chem Int Ed* 2014 53:11876-11880; Liu et al. *J Nucl Med* 2015 55:1499-1505; Liu et al. *Nat Protoc* 2015 10:1423-1432; Kuo et al., *J Nucl Med* 2019 60:1160-1166; each of which is incorporated by reference in its entirety). Generally, the BF_3 -containing motif can be coupled to the linker via click chemistry

by forming a 1,2,3-triazole ring between a BF_3 -containing azido (or alkynyl) group and an alkynyl (or azido) group on the linker, or by forming an amide linkage between a BF_3 -containing carboxylate and an amino group on the linker. To make the BF_3 -containing azide, alkyne or carboxylate, a boronic acid ester-containing azide, alkyne or carboxylate is first prepared following by the conversion of the boronic acid ester to BF_3 in a mixture of HCl , DMF and KHF_2 . For alkyl BF_3 , the boronic acid ester-containing azide, alkyne or carboxylate can be prepared by coupling boronic acid ester-containing alkyl halide (such as iodomethylboronic acid pinacol ester) with an amine-containing azide, alkyne or carboxylate (such as N,N -dimethylpropargylamine). For aryl BF_3 , the boronic acid ester can be prepared via Suzuki coupling using aryl halide (iodine or bromide) and bis(pinacolato)diboron.

[00328] ^{18}F -Fluorination of the BF_3 -containing compounds via ^{18}F - ^{19}F isotope exchange reaction can be achieved following previously published procedures (Liu *et al. Nat Protoc* 2015 10:1423-1432, incorporated by reference in its entirety). Generally, ~ 100 nmol of the BF_3 -containing compound is dissolved in a mixture of 15 μl of pyridazine- HCl buffer ($\text{pH} = 2.0$ – 2.5 , 1 M), 15 μl of DMF and 1 μl of a 7.5 mM KHF_2 aqueous solution. ^{18}F -Fluoride solution (in saline, 60 μl) is added to the reaction mixture, and the resulting solution is heated at 80°C for 20 min. At the end of the reaction, the desired product can be purified by solid phase extraction or by reversed high performance liquid chromatography (HPLC) using a mixture of water and acetonitrile as the mobile phase.

[00329] When the peptide has been fully synthesized on the solid support, the desired peptide may be cleaved from the solid support using suitable reagents, such as TFA, triisopropylsilane (TIS) and water. Side chain protecting groups, such as Boc, pentamethyldihydrobenzofuran-5-sulfonyl (Pbf), trityl (Trt) and tert-butyl (tBu) are simultaneously removed (i.e. deprotection). The crude peptide may be precipitated and collected from the solution by adding cold ether followed by centrifugation. Purification and characterization of the peptides may be performed by standard separation techniques, such as high performance liquid chromatography (HPLC) based on the size, charge and polarity of the peptides. The identity of the purified peptides may be confirmed by mass spectrometry or other similar approaches.

[00330] The present invention will be further illustrated in the following examples for the synthesis and evaluation of specific compounds.

[00331] EXAMPLES

[00332] Chemical Synthesis

[00333] Reagents and solvents were purchased from commercial sources and used without further purification, unless otherwise stated. Peptides were synthesized on a Liberty Blue automated microwave peptide synthesis (CEM Corporations). High performance liquid

chromatography (HPLC) was performed on 1) an Agilent 1260 infinity system equipped with a model 1200 quaternary pump, a model 1200 UV absorbance detector and a Bioscan NaI scintillation detector, 2) an Agilent 1100 HPLC system or 3) an Agilent 1260 Infinity II Preparative System equipped with a model 1260 Infinity II preparative binary pump, a model 1260 Infinity variable wavelength detector (set at 220 nm), and a 1290 Infinity II preparative open-bed fraction collector. The HPLC column used for synthesis was a semi-preparative column (Agilent Eclipse XDB-C18, 5 μ m, 9.4x250mm) or a preparative column (Gemini, NX-C18, 5 μ m, 110 Å, 50x30 mm) purchased from Phenomenex. Mass analyses were performed using an AB SCIEX 4000 QTRAP mass spectrometer system with an ESI ion source or a Waters 2695 Separation module and Waters-Micromass ZQ mass spectrometer system.

[00334] All Fmoc-amino acids are coupled using a 4/8/4 equiv. of Fmoc-AA-OH/DIC/Oxyma in DMF for 4 min at 90°C using microwave heating, unless stated otherwise. All Fmoc groups are removed with 20% v/v piperidine in DMF for 1 min at 90°C unless stated otherwise. Coupled twice implies two cycles of the activated Fmoc amino acid solution. After the coupling of the first Fmoc-protected amino acid to the resin, the free amines on the resin polymer are capped with a solution of 5% 1-acetylimidazole in DMF.

[00335] Peptides are C-terminally amidated.

[00336] The term “cyclo” in the peptide nomenclature used herein refers to the cyclization shown in Formula A, i.e. an amide linkage formed by the N-terminal amino group of the first amino acid residue and the side chain carboxy group of the seventh amino acid residue. The terms “cyclo(isoindole)” and “cyclo(tryptathionine)” in the peptide nomenclature used herein refers to the cyclization shown in Formula B, i.e. an isoindole linkage or tryptathionine linkage formed by linking the side chain functional groups of the first and seventh side chain amino acid residues using FliCk or a similar reaction.

[00337] *Synthesis of cyclo[Phe-(4-NH₂)Phe-Lys(iPr)-D-Arg-2-Nal-Gly-D-Glu]-Lys(iPr) (1)*

[00338] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-Gly-OH (coupled twice), Fmoc-2Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Phe(4-NH(Boc))-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 μ L) in DCM (6 mL) (2 $\times$ 6 min at 35°C). The N^F-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 $\times$ 10 min at 90°C).

Following cyclization, the peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 14-34% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **1** was 7.88 min with the preparative column. ESI-MS: calculated [M+2H]²⁺ for **1** C₆₂H₉₁N₁₅O₉ 594.86; found [M+2H]²⁺ 595.12.

[00339] *Synthesis of cyclo[Phe-(4-NO₂)Phe-Lys(iPr)-D-Arg-2-Nal-Gly-D-Glu]-Lys(iPr) (2)*

[00340] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-Gly-OH (coupled twice), Fmoc-2Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Phe(4-NO₂)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*^ε-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 18-38% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **2** was 12.04 min with the preparative column. ESI-MS: calculated [M+2H]²⁺ for **2** C₆₂H₈₉N₁₅O₁₁ 609.84; found [M+2H]²⁺ 609.95.

[00341] *Synthesis of cyclo[Phe-hTyr-Lys(iPr)-D-Arg-2-Nal-Gly-D-Glu]-Lys(iPr) (3)*

[00342] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-Gly-OH (coupled twice), Fmoc-2Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-hTyr-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20

mg)/Phenylsilane (300 μ L) in DCM (6 mL) (2 $\times$ 6 min at 35°C). The *N*^F-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 $\times$ 10 min at 90°C). Following cyclization, the peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 16-36% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **3** was 10.86 min with the preparative column. ESI-MS: calculated $[M+2H]^{2+}$ for **3** C₆₃H₉₂N₁₄O₁₀ 602.36; found $[M+2H]^{2+}$ 602.12.

[00343] *Synthesis of cyclo[Phe-(3-I) Tyr-Lys(iPr)-D-Arg-2-Nal-Gly-D-Glu]-Lys(iPr) (4)*

[00344] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-Gly-OH (coupled twice), Fmoc-2Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-(3-I)Tyr-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 μ L) in DCM (6 mL) (2 $\times$ 6 min at 35°C). The *N*^F-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 $\times$ 10 min at 90°C). Following cyclization, the peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 14-34% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **4** was 14.66 min with the preparative column. ESI-MS: calculated $[M+2H]^{2+}$ for **4** C₆₂H₈₉N₁₄O₁₀ 658.30; found $[M+2H]^{2+}$ 658.40.

[00345] *Synthesis of cyclo[Phe-Tyr-Arg(Me)₂(asym)-D-Arg-2-Nal-Gly-D-Glu]-Lys(iPr) (5)*

[00346] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-Gly-OH (coupled twice), Fmoc-2Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Arg(Me)₂(asym)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-

OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAllyl protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*^t-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 13-33% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **5** was 11.55 min with the preparative column. ESI-MS: calculated [M+2H]²⁺ for **5** C₆₁H₈₈N₁₆O₁₀ 602.34; found [M+2H]²⁺ 602.46.

[00347] *Synthesis of cyclo[Phe-Tyr-Lys(iPr)-D-Arg-(2-Ant)Ala-Gly-D-Glu]-Lys(iPr) (6)*

[00348] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAllyl)-OH, Fmoc-Gly-OH (coupled twice), Fmoc-(2-Ant)Ala-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAllyl protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*^t-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 15-35% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **6** was 11.22 min with the preparative column. ESI-MS: calculated [M+3H]³⁺ for **6** C₆₆H₉₃N₁₄O₁₀ 413.91; found [M+3H]³⁺ 414.40.

[00349] *Synthesis of cyclo[Phe-Tyr-Lys(iPr)-D-Arg-(9-Ant)Ala-Gly-D-Glu]-Lys(iPr) (7)*

[00350] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAllyl)-OH, Fmoc-Gly-OH (coupled twice), Fmoc-(9-Ant)Ala-OH (coupled twice), Fmoc-D-

Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAllyl protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*^t-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 15-35% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **7** was 10.70 min with the preparative column. ESI-MS: calculated [M+3H]³⁺ for **7** C₆₆H₉₃N₁₄O₁₀ 413.91; found [M+3H]³⁺ 413.60.

[00351] *Synthesis of cyclo[Phe-Tyr-Lys(iPr)-D-Arg-(Adamantyl)Ala-Gly-D-Glu]-Lys(iPr) (8)*

[00352] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAllyl)-OH, Fmoc-Gly-OH (coupled twice), Fmoc-(Adamantyl)Ala-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAllyl protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*^t-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column.

[00353] *Synthesis of cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr) (9)*

[00354] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAllyl)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-

OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAllyl protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*^t-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 16-36% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **9** was 10.74 min with the preparative column. ESI-MS: calculated [M+3H]³⁺ for **9** C₆₃H₉₃N₁₄O₁₀ 401.91; found [M+3H]³⁺ 401.40.

[00355] *Synthesis of cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-D-His-D-Glu]-Lys(iPr) (10)*

[00356] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAllyl)-OH, Fmoc-D-His(Trt)-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures, except Fmoc-D-His(Trt)-OH, which was coupled for 10 min at 50°C. The -OAllyl protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*^t-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 16-36% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **10** was 7.86 min with the preparative column. ESI-MS: calculated [M+3H]³⁺ for **10** C₆₆H₉₅N₁₆O₁₀ 423.91; found [M+3H]³⁺ 424.01.

[00357] *Synthesis of cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-His-D-Glu]-Lys(iPr) (11)*

[00358] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-

Glu(OAll)-OH, Fmoc-His(Trt)-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures, except Fmoc-His(Trt)-OH, which was coupled for 10 min at 50°C. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*^ε-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 16-36% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **11** was 8.33 min with the preparative column. ESI-MS: calculated [M+3H]³⁺ for **11** C₆₆H₉₅N₁₆O₁₀ 423.91; found [M+3H]³⁺ 423.70.

[00359] *Synthesis of cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-D-Phe-D-Glu]-Lys(iPr) (12)*

[00360] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-D-Phe-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*^ε-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 13-33% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **12** was 14.45 min with the preparative column. ESI-MS: calculated [M+3H]³⁺ for **12** C₆₉H₉₇N₁₄O₁₀ 427.25; found [M+3H]³⁺ 427.39.

[00361] *Synthesis of cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-D-Leu-D-Glu]-Lys(iPr) (13)*

[00362] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink

Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-D-Leu-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*^F-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 17-37% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **13** was 13.44 min with the preparative column. ESI-MS: calculated [M+3H]³⁺ for **13** C₆₆H₉₈N₁₄O₁₀ 415.59; found [M+3H]³⁺ 414.98.

[00363] *Synthesis of cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-D-Glu-D-Glu]-Lys(iPr) (14)*

[00364] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-D-Glu(tBu)-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*^F-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 17-37% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **14** was 8.71 min with the preparative column. ESI-MS: calculated [M+3H]³⁺ for **14** C₆₅H₉₄N₁₄O₁₂ 420.90; found [M+3H]³⁺ 421.21.

[00365] *Synthesis of cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-D-Dab-D-Glu]-Lys(iPr) (15)*

[00366] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of

DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-D-Dab(Boc)-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*^F-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 13-33% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **15** was 11.0 min with the preparative column. ESI-MS: calculated [M+3H]³⁺ for **15** C₆₄H₉₅N₁₅O₁₀ 411.25; found [M+3H]³⁺ 411.53.

[00367] *Synthesis of cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-D-Dap-D-Glu]-Lys(iPr) (16)*

[00368] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-D-Dap(Boc)-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*^F-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 13-33% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **16** was 11.3 min with the preparative column. ESI-MS: calculated [M+2H]²⁺ for **16** C₆₃H₉₃N₁₅O₁₀ 609.86; found [M+3H]³⁺ 610.10.

[00369]

[00370] *Synthesis of cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ser-D-Glu]-Lys(iPr) (17)*

[00371] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-D-Ser(tBu)-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*^F-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 15-35% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **17** was 10.7 min with the preparative column. ESI-MS: calculated [M+3H]³⁺ for **17** C₆₃H₉₃N₁₄O₁₁ 407.24; found [M+3H]³⁺ 406.52.

[00372] *Synthesis of cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-D-Gln-D-Glu]-Lys(iPr) (18)*

[00373] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-D-Gln(Trt)-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*^F-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 17-37% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **18** was 7.78 min with the preparative column. ESI-MS: calculated [M+3H]³⁺ for **18** C₆₅H₉₆N₁₅O₁₀ 420.91; found [M+3H]³⁺ 420.35.

[00374] *Synthesis of cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-D-Asn-D-Glu]-Lys(iPr) (19)*

[00375] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-D-Asn(Trt)-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in CH₂Cl₂ (6 mL) (2 × 6 min at 35°C). The *N*^ε-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 15-35% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **19** was 10.19 min with the preparative column. ESI-MS: calculated [M+3H]³⁺ for **19** C₆₄H₉₄N₁₅O₁₁ 416.24; found [M+3H]³⁺ 415.75.

[00376] *Synthesis of cyclo[1Nal-Tyr-Lys(iPr)-D-Arg-2Nal-Gly-D-Glu]-Lys(iPr) (20)*

[00377] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-Gly-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-1-Nal-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*^ε-Fmoc on 1Nal was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 14-34% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30

mL/min. The retention time of **20** was 14.9 min with the preparative column. ESI-MS: calculated $[M+2H]^{2+}$ for **20** $C_{66}H_{92}N_{14}O_{10}$ 620.36; found $[M+2H]^{2+}$ 620.77.

[00378] *Synthesis of cyclo[Tyr-Tyr-Lys(iPr)-D-Arg-2Nal-Gly-D-Glu]-Lys(iPr) (21)*

[00379] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-Gly-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Tyr(tBu)-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using $Pd(PPh_3)_4$ (20 mg)/Phenylsilane (300 μ L) in DCM (6 mL) (2 $\times$ 6 min at 35°C). The *N*^ε-Fmoc on Tyr was then removed, and cyclization was performed using DIC/HOBt in DMF (3 $\times$ 10 min at 90°C). Following cyclization, the peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 15-35% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) at a flow rate of 30 mL/min. The retention time of **21** was 15.1 min with the preparative column. ESI-MS: calculated $[M+2H]^{2+}$ for **21** $C_{62}H_{90}N_{14}O_{11}$ 603.35; found $[M+2H]^{2+}$ 603.99.

[00380] *Synthesis of cyclo[Trp-Tyr-Lys(iPr)-D-Arg-2Nal-Gly-D-Glu]-Lys(iPr) (22)*

[00381] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-Gly-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Trp(Boc)-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using $Pd(PPh_3)_4$ (20 mg)/Phenylsilane (300 μ L) in DCM (6 mL) (2 $\times$ 6 min at 35°C). The *N*^ε-Fmoc on Trp was then removed, and cyclization was performed using DIC/HOBt in DMF (3 $\times$ 10 min at 90°C). Following cyclization, the peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column

eluted with 16-36% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **22** was 10.46 min with the preparative column. ESI-MS: calculated [M+2H]²⁺ for **22** C₆₂H₉₀N₁₄O₁₁ 614.85; found [M+2H]²⁺ 615.17.

[00382] *Synthesis of cyclo(isoindole)[Phe-Tyr-Lys(iPr)-D-Arg-2-Nal-Gly-D-Cys]-Lys(iPr) (23)*

[00383] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. At a 0.05 mmol scale, Fmoc-D-Cys(Trt)-OH, Fmoc-Gly-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAllyl protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The N^F-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). The peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The linear crude peptide (~0.5mg) as a lyophilized powder in a 15mL falcon tube was dissolved in 80 µL borate Buffer (pH~9-9.5) and 20 µL ortho-*phthalaldehyde* in EtOH (5x10-2M) was added. After 20 minutes, 0.5 µL of Formic Acid was added to the reaction mixture. The crude peptide was purified by HPLC using the semi-preparative column. ESI-MS: calculated [M+H]⁺ for **23** C₆₈H₉₁N₁₄O₉S 1279.7; found [M+H]⁺ 1279.9.

[00384] *Synthesis of cyclo(isoindole)[Phe-Tyr-Lys(iPr)-D-Arg-2-Nal-Gly-Cys]-Lys(iPr) (24)*

[00385] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. At a 0.05 mmol scale, Fmoc-Cys(Trt)-OH, Fmoc-Gly-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAllyl protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The N^F-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). The

peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The linear crude peptide (~0.5mg) as a lyophilized powder in a 15mL falcon tube was dissolved in 80 µL Borate Buffer (pH~9-9.5) and 20 µL ortho-*phthalaldehyde* in EtOH (5x10⁻²M) was added. After 20 minutes, 0.5 µL of Formic Acid was added to the reaction mixture. ESI-MS: calculated [M+H]⁺ for **24** C₆₈H₉₁N₁₄O₉S 1279.7; found [M+H]⁺ 1279.9.

[00386] *Synthesis of cyclo[Phe-Tyr-Lys(iPr)-D-Arg-(carboxy-m-carborane)Dap-Gly-D-Glu]-Lys(iPr) (25)*

[00387] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-Gly-OH (coupled twice), and Fmoc-Dap(Mtt)-OH were sequentially coupled to the peptidyl resin following similar procedures. The Mtt group was removed by three washes with DCM, followed by incubation with 2/1/97 TFA/TIS/DCM five times, then washed three times with DCM and then washed three times with DMF. The *m*-Carborane-1-carboxylic acid was coupled to the free amine group using a 3/3/6 equiv. of *m*-Carborane-1-carboxylic acid/HATU/DIEA in 2 mL DMF for 10 mins at 90°C using microwave heating. After Fmoc deprotection, Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*^ε-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 17-3% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **25** was 14.35 min with the preparative column. ESI-MS: calculated [M+2H]²⁺ for **25** C₅₅H₉₄B₁₀N₁₅O₁₁ 624.41; found [M+2H]²⁺ 625.50.

[00388] *Synthesis of cyclo[Lys(Ac)-Tyr-Lys(iPr)-D-Arg-2NaI-Gly-D-Glu]-Lys(iPr) (26)*

[00389] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min

at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-Gly-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Lys(ivDde)-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*³-Fmoc on Lys(ivDde) was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the ivDde group was removed *via* adding 3 mL of 2% N₂H₄ in DMF for 5 minutes, with 5 cycles. The terminal amine was then acetylated using 0.1 w/v of 1-acetylimidazole in DMF for 30 minutes at room temperature. The peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 15-35% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **26** was 8.1 min with the preparative column.

[00390] *Synthesis of cyclo[Phe-D-Tyr-Lys(iPr)-DArg-2Nal-D-Ala-D-Glu]-Lys(iPr) (27)*

[00391] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-D-Tyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*³-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 14-34% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **27** was 14.04 min with the preparative column. ESI-MS: calculated [M+2H]²⁺ for **27** C₆₃H₉₁N₁₄O₁₀ 601.85; found [M+2H]²⁺ 602.01.

[00392] *Synthesis of cyclo[Phe-Tyr-Lys(iPr)-DArg-(4-NH₂)Phe-D-Ala-D-Glu]-Lys(iPr) (28)*

[00393] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-(4-NHBoc)Phe-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*^t-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 14-34% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **28** was 9.04 min with the preparative column. ESI-MS: calculated [M+2H]²⁺ for **28** C₅₉H₉₁N₁₅O₁₀ 584.85; found [M+2H]²⁺ 585.36.

[00394] *Synthesis of cyclo[Phe-Tyr-Lys(iPr)-DArg-hTyr-D-Ala-D-Glu]-Lys(iPr) (29)*

[00395] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-hTyr-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*^t-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 14-34% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **29** was 8.64 min with the preparative column. ESI-MS: calculated [M+2H]²⁺ for **29** C₆₀H₉₂N₁₄O₁₁ 592.35; found [M+2H]²⁺ 592.92.

[00396] *Synthesis of cyclo[Phe-Tyr-Lys(iPr)-DArg-(COOH)Phe-D-Ala-D-Glu]-Lys(iPr) (30)*

[00397] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-p-carboxy-Phe(OtBu)-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*^t-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 12-32% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **30** was 10.31 min with the preparative column. ESI-MS: calculated [M+2H]²⁺ for **30** C₆₀H₉₀N₁₄O₁₂ 599.34; found [M+2H]²⁺ 599.85.

[00398] *Synthesis of cyclo[Phe-Tyr-Lys(iPr)-DArg-Thyronine-D-Ala-D-Glu]-Lys(iPr) (31)*

[00399] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-Thyronine-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*^t-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column

eluted with 12-32% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **31** was 10.31 min with the preparative column. ESI-MS: calculated $[M+2H]^{2+}$ for **31** C₆₀H₉₀N₁₄O₁₂ 631.36; found $[M+2H]^{2+}$ 632.11.

[00400] *Synthesis of cyclo[Phe-Tyr-Arg(Me)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr) (32)*

[00401] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Arg(Me,Pbf)-OH (coupled twice), Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The N^t-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 14-34% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **32** was 12.55 min with the preparative column. ESI-MS: calculated $[M+2H]^{2+}$ for **32** C₆₁H₈₈N₁₆O₁₀ 602.35; found $[M+2H]^{2+}$ 602.98.

[00402] *Synthesis of cyclo[Lys(Ac)-Gln-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr) (33)*

[00403] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Gln(Trt)-OH, and Fmoc-Lys(ivDde)-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The N^t-Fmoc on Lys(ivDde) was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the ivDde group was removed *via* adding 3 mL of 2% N₂H₄ in DMF for 5 minutes, with 5 cycles. The terminal amine was then acetylated using 0.1 w/v of 1-acetylimidazole in DMF for 30 minutes at room temperature. The peptide was deprotected and

simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 13-33% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **33** was 7.61 min with the preparative column. ESI-MS: calculated [M+2H]²⁺ for **33** C₅₈H₉₅N₁₆O₁₁ 595.87 found [M+2H]²⁺ 595.54.

[00404] *Synthesis of cyclo[Lys(Ac)-Glu-Lys(iPr)-D-Arg-2-Nal-D-Ala-D-Glu]-Lys(iPr) (34)*

[00405] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Glu(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*^ε-Fmoc on Lys(ivDde) was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the ivDde group was removed *via* adding 3 mL of 2% N₂H₄ in DMF for 5 minutes, with 5 cycles. The terminal amine was then acetylated using 0.1 w/v of 1-acetylimidazole in DMF for 30 minutes at room temperature. The peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified using preparative HPLC. ESI-MS: calculated [M+2H]²⁺ for **34** C₅₈H₉₄N₁₅O₁₂ 596.36; found [M+2H]²⁺ 596.74.

[00406] *Synthesis of cyclo[Phe-(4-NH₂)Phe-Lys(iPr)-D-Arg-2-Nal-D-Ala-D-Glu]-Lys(iPr) (35)*

[00407] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-4-NHBocPhe-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar

procedures. The -OAllyl protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in CH₂Cl₂ (6 mL) (2 × 6 min at 35°C). The *N*^ε-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 11-31% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **35** was 7.87 min with the preparative column. ESI-MS: calculated [M+2H]²⁺ for **35** C₆₃H₉₃N₁₅O₉ 601.86; found [M+2H]²⁺ 602.36.

[00408] *Synthesis of cyclo[Lys(Ac)-Tyr-Lys(iPr)-D-Arg-Trp-D-Ala-D-Glu]-Lys(iPr) (36)*

[00409] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAllyl)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-Trp(Boc)-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAllyl protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*^ε-Fmoc on Lys(ivDde) was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the ivDde group was removed *via* adding 3 mL of 2% N₂H₄ in DMF for 5 minutes, with 5 cycles. The terminal amine was then acetylated using 0.1 w/v of 1-acetylimidazole in DMF for 30 minutes at room temperature. The peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. ESI-MS: calculated [M+2H]²⁺ for **36** C₆₂H₉₇N₁₅O₁₁ 613.87; found [M+2H]²⁺ 613.81.

[00410] *Synthesis of cyclo[Lys(D-Glu-Ac)-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr) (37)*

[00411] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-

Glu(OAll)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*^t-Fmoc on Lys(ivDde) was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the ivDde group was removed *via* adding 3 mL of 2% N₂H₄ in DMF for 5 minutes, with 5 cycles. Fmoc-D-Glu(tBu)-OH was then coupled and the Fmoc group removed. The terminal amine was then acetylated using 0.1 w/v of 1-acetylimidazole in DMF for 30 minutes at room temperature. The peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 13-33% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **37** was 9.76 min with the preparative column.

[00412] *Synthesis of cyclo[Lys(Ac-D-Arg)-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr) (38)*

[00413] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*^t-Fmoc on Lys(ivDde) was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the ivDde group was removed *via* adding 3 mL of 2% N₂H₄ in DMF for 5 minutes, with 5 cycles. Fmoc-D-Arg(Pbf)-OH was then coupled and the Fmoc group removed. The terminal amine was then acetylated using 0.1 w/v of 1-acetylimidazole in DMF for 30 minutes at room temperature. The peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 12-32% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 25 mL/min. The retention time of **38** was 10.02 min with the preparative

column. ESI-MS: calculated $[M+2H]^{2+}$ for **38** $C_{68}H_{109}N_{19}O_{12}$ 691.92; found $[M+2H]^{2+}$ 691.70. The term "Ac-D-Arg" refers to D-Arg that is N(alpha)-acetylated and C-terminally amide-bonded to the sidechain of Lys in position 1.

[00414] *Synthesis of cyclo[Lys(Ac-D-Arg)-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr) (39)*

[00415] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using $Pd(PPh_3)_4$ (20 mg)/Phenylsilane (300 μ L) in DCM (6 mL) (2 $\times$ 6 min at 35°C). The N^t -Fmoc on Lys(ivDde) was then removed, and cyclization was performed using DIC/HOBt in DMF (3 $\times$ 10 min at 90°C). Following cyclization, the ivDde group was removed via adding 3 mL of 2% N_2H_4 in DMF for 5 minutes, with 5 cycles. Fmoc-D-Ala-OH was then coupled and the Fmoc group removed. The terminal amine was then acetylated using 0.1 w/v of 1-acetylimidazole in DMF for 30 minutes at room temperature. The peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/ H_2O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 15-35% acetonitrile (0.1% TFA) in H_2O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **39** was 8.46 min with the preparative column. ESI-MS: calculated $[M+2H]^{2+}$ for **39** $C_{65}H_{102}N_{16}O_{12}$ 649.39; found $[M+2H]^{2+}$ 649.98.

[00416] *Synthesis of cyclo[Lys(Ac-D-Phe)-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr) (40)*

At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using $Pd(PPh_3)_4$ (20 mg)/Phenylsilane (300 μ L) in

DCM (6 mL) (2 × 6 min at 35°C). The *N*^ε-Fmoc on Lys(ivDde) was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the ivDde group was removed *via* adding 3 mL of 2% N₂H₄ in DMF for 5 minutes, with 5 cycles. Fmoc-D-Phe-OH was then coupled and the Fmoc group removed. The terminal amine was then acetylated using 0.1 w/v of 1-acetylimidazole in DMF for 30 minutes at room temperature. The peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 14-34% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **40** was 12.51 min with the preparative column. ESI-MS: calculated [M+2H]²⁺ for **40** C₇₁H₁₀₆N₁₆O₁₂ 687.41; found [M+2H]²⁺ 687.01. Note that “*Ac-D-Phe*” refers to *D-Phe* that is *N*-acetylated and *C*-terminally amide-bonded to the side chain of Lys in position 1.

[00417] *Synthesis of cyclo[Lys(CysAcid-CysAcid-CysAcid-DOTA-Ga)-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr) (41)*

[00418] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 μL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*^ε-Fmoc on Lys was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the ivDde group was removed *via* adding 3 mL of 2% N₂H₄ in DMF for 5 minutes, with 5 cycles. Fmoc-CysAcid-OH was then coupled in succession three times. DOTA(tBu)₃ was then coupled at room temperature using HATU and DIEA in DMF using 4/4/8 equivalents. The peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The lyophilized powder was dissolved in 0.1 NaOAc buffer (4.2 pH) and to it was added 5 eq of GaCl₃. The solution was heated to 80°C for 20 minutes and the crude peptide was directly purified by preparative HPLC using the preparative column eluted with 12.5-32.5%

acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **41** was 9.33 min with the preparative column.

[00419] *Synthesis of cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr)-Lys(Glu-Ac) (42)*

[00420] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(ivDde)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-Lys(iPr, Boc)-OH, Fmoc-D-Glu(OAll)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*³-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the ivDde group was removed *via* adding 3 mL of 2% N₂H₄ in DMF for 5 minutes, with 5 cycles. Fmoc-Glu(tBu)-OH was then coupled. The terminal amine was then acetylated using 0.1 w/v of 1-acetylimidazole in DMF for 30 minutes at room temperature. The peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 16-36% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **42** was 13.32 min with the preparative column.

[00421] *Synthesis of cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr)-Lys(Ac) (43)*

[00422] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(ivDde)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-Lys(iPr, Boc)-OH, Fmoc-D-Glu(OAll)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*³-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min

at 90°C). Following cyclization, the ivDde group was removed via adding 3 mL of 2% N₂H₄ in DMF for 5 minutes, with 5 cycles. The terminal amine was then acetylated using 0.1 w/v of 1-acetylimidazole in DMF for 30 minutes at room temperature. The peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 16-36% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **43** was 13.69 min with the preparative column.

[00423] *Synthesis of cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr)-Lys(Glu-Glu-Ac) (44)*

[00424] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(ivDde)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-Lys(iPr, Boc)-OH, Fmoc-D-Glu(OAll)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The N^α-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the ivDde group was removed via adding 3 mL of 2% N₂H₄ in DMF for 5 minutes, with 5 cycles. Two instances of Fmoc-Glu(tBu)-OH was then coupled. The terminal amine was then acetylated using 0.1 w/v of 1-acetylimidazole in DMF for 30 minutes at room temperature. The peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 13-33% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **44** was 14.00 min with the preparative column.

[00425] *Synthesis of cyclo[Phe-(4NH₂)Phe-Lys(iPr)-D-Arg-2Nal-Gly-D-Glu]-Lys(iPr)-Lys(Glu-Glu-Glu-DOTA-Ga) (45)*

[00426] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(ivDde)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min

at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-Lys(iPr, Boc)-OH, Fmoc-D-Glu(OAll)-OH, Fmoc-Gly-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-(4-NHBoc)Phe-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*³-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the ivDde group was removed *via* adding 3 mL of 2% N₂H₄ in DMF for 5 minutes, with 5 cycles. Three instances of Fmoc-Glu(tBu)-OH was then coupled. DOTA(tBu)₃ was then coupled at room temperature using HATU and DIEA in DMF using 4/4/8 equivalents. The peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The lyophilized powder was dissolved in 0.1 NaOAc buffer (4.2 pH) and to it was added 5 eq of GaCl₃. The solution was heated to 80°C for 20 minutes and the crude peptide was directly purified by preparative HPLC using the preparative column eluted with 13-33% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **45** was 8.11 min with the preparative column. ESI-MS: calculated [M+2H]²⁺ for **45** C₉₉H₁₄₈GaN₂₄O₂₆ 1079.51; found [M+2H]²⁺ 1080.21.

[00427] Synthesis of cyclo[Phe-(4-NH₂)Phe-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr)-Lys(Glu-Glu-Glu-DOTA-Ga) (**46**)

[00428] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(ivDde)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-Lys(iPr,Boc)-OH, Fmoc-D-Glu(OAll)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-(4-NHBoc)Phe-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in CH₂Cl₂ (6 mL) (2 × 6 min at 35°C). The *N*³-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the ivDde group was removed *via* adding 3 mL of 2% N₂H₄ in DMF for 5 minutes, with 5 cycles. Three instances of Fmoc-Glu(tBu)-OH was then coupled. DOTA(tBu)₃ was then coupled at room temperature using HATU and DIEA in DMF using 4/4/8 equivalents. The peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5

TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The lyophilized powder was dissolved in 0.1 NaOAc buffer (4.2 pH) and to it was added 20 µL of a solution of 0.2 M GaCl₃. The solution was heated to 80°C for 20 minutes and the crude peptide was directly purified by preparative HPLC using the preparative column eluted with 11-31% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **46** was 10.91 min with the preparative column. ESI-MS: calculated [M+2H]²⁺ for **46**

C₁₀₀H₁₅₀GaN₂₄O₂₆ 1086.52; found [M+2H]²⁺ 1086.94.

[00429] *Synthesis of cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr)-Lys(Glu-Glu-Glu-DOTA-Ga) (47)*

[00430] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(ivDde)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-Lys(iPr, Boc)-OH, Fmoc-D-Glu(OAll)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The N³-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the ivDde group was removed *via* adding 3 mL of 2% N₂H₄ in DMF for 5 minutes, with 5 cycles. Three instances of Fmoc-Glu(tBu)-OH was then coupled. DOTA(tBu)₃ was then coupled at room temperature using HATU and DIEA in DMF using 4/4/8 equivalents. The peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The lyophilized powder was dissolved in 0.1 NaOAc buffer (4.2 pH) and to it was added 5 eq of GaCl₃. The solution was heated to 80°C for 20 minutes and the crude peptide was directly purified by preparative HPLC using the preparative column eluted with 13-33% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **47** was 12.00 min with the preparative column. ESI-MS: calculated [M+2H]²⁺ for **47** C₁₀₀H₁₄₉GaN₂₃O₂₇ 1087.01; found [M+2H]²⁺ 1086.97.

[00431] *Synthesis of cyclo[Phe-hTyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr)-Lys(Glu-Glu-Glu-DOTA-Ga) (48)*

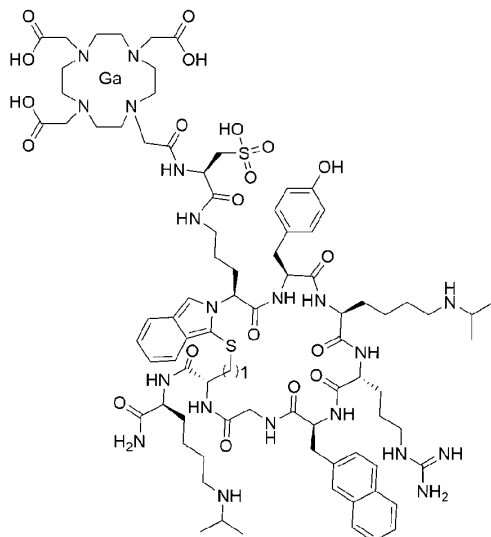
[00432] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of

DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(ivDde)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-Lys(iPr, Boc)-OH, Fmoc-D-Glu(OAll)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-hTyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*³-Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the ivDde group was removed via adding 3 mL of 2% N₂H₄ in DMF for 5 minutes, with 5 cycles. Three instances of Fmoc-Glu(tBu)-OH was then coupled. DOTA(tBu)₃ was then coupled at room temperature using HATU and DIEA in DMF using 4/4/8 equivalents. The peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The lyophilized powder was dissolved in 0.1 NaOAc buffer (4.2 pH) and to it was added 5 eq of GaCl₃. The solution was heated to 80°C for 20 minutes and the crude peptide was directly purified by preparative HPLC using the preparative column eluted with 13-33% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **48** was 12.55 min with the preparative column.

[00433] *Synthesis of cyclo(tryptathionine)[Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Cys]-Lys(iPr) (49)*

[00434] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Cys(Trt)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, were sequentially coupled to the peptidyl resin following similar procedures. Next, the resin was suspended in a solution of Fmoc-Hpi-OH, HCTU, and NMM using 10/10/20 equivalents. The resin was then resuspended in TFA, agitated lightly with N₂ for 90 min. The TFA was then collected and enough TIS and H₂O were added to make the final solution 95:2.5:2.5 TFA/TIS/H₂O and the reaction was allowed to proceed for another 30 minutes. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. After being allowed to dry in air, the precipitated peptide was dissolved in 0.1% Formic Acid H₂O/MeCN and purified by preparative HPLC.

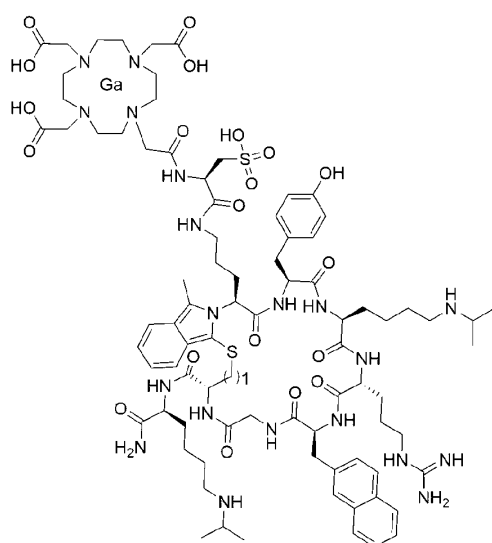
[00435] *Cyclo(isoindole N³-S)[Lys(Cys(Acid)-DOTA-Ga)-Tyr-Lys(iPr)-D-Arg-2-Nal-D-Ala-D-Cys]-Lys(iPr) (50)*



[00436] The linear peptide was synthesized using Liberty Blue automated microwave peptide synthesizer from CEM. At a 0.25 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C and washed with DMF (3 mL x 3). At a 1 mmol scale, Fmoc-Lys(iPr, Boc)-OH was conjugated to the Rink Amide MBHA resin using OxymaPure in DMF (1 M) and DIC in DMF (1 M) at 90°C for 4 min. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with DMF (3 mL) after deprotection. Fmoc-Cys(Trt)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH were sequentially coupled to the peptidyl resin following similar procedures. After standard Fmoc-deprotection, Boc-Lys(Fmoc)-OH was coupled with HATU/HOAt/DIPEA using 4/4/8 equivalents in DMF for 4 min at 75°C. After removal of the Fmoc group, Fmoc-Cys(Acid)-OH was coupled to the side chain amine, followed by DOTA(tBu)₃ coupling at 75°C using HATU/HOAt/DIPEA using 4/4/8 equivalents in DMF (2 mL). The peptide was deprotected and cleaved simultaneously from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIPS/H₂O for 3 h at 35°C. After filtering off the resin, the crude peptide was precipitated by adding the crude solution to cold diethyl ether (10x vol. of the cleavage solution) dropwise. The crude peptide was washed twice with diethyl ether, vortexed and centrifuged. The washed crude peptide pellet was re-dissolved in 30% ACN in H₂O (0.1% TFA) and lyophilized. crude peptide (~2 μmol, lyophilized, in a 15mL falcon tube) was dissolved in HEPES (2 M, pH = 5, 560 μL) and Ga(NO₂)₃ in 1 M HCl (0.0282 M, 400 μL). The solution was transferred to a scintillation vial and heated in a

commercial food microwave for 1 min at 20% power. $\text{NaOH}_{(\text{aq})}$ (5M) was added to the solution until pH ~ 8 . Ortho-*phthalaldehyde* in EtOH (0.05M, 60 μL) was then added. The solution was vortexed and allowed to reaction at room temperature for 15 minutes. Reaction mixture then adjusted to pH $\sim 3-4$ with Formic Acid and then directly purified using preparative HPLC eluted with 5-35% acetonitrile (0.1% FA) in H_2O (0.1% FA) from 0 to 7.5 mins, then 35-100% acetonitrile (0.1% FA) in H_2O (0.1% FA) in 7.5 to 8.0 mins. The retention time was 27.0 min. ESI-MS: calculated $[\text{M}+2\text{H}]^{2+}$ for **50** $\text{C}_{85}\text{H}_{123}\text{GaN}_{20}\text{O}_{20}\text{S}_2$ 939.9; found $[\text{M}+2\text{H}]^{2+}$ 940.6.

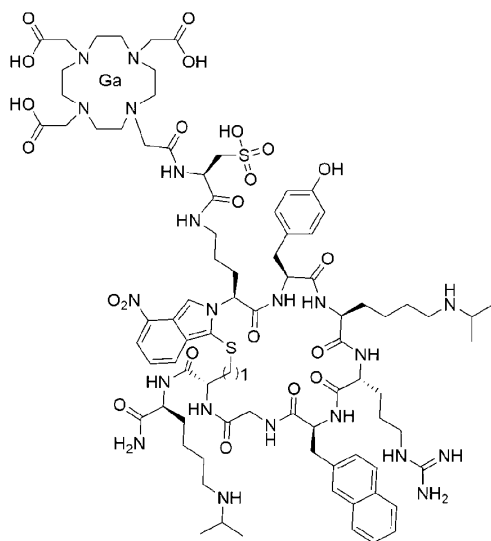
[00437] *Cyclo(Me-isoindole N^B-S)[Lys(Cys(Acid)-DOTA-Ga)-Tyr-Lys(iPr)-D-Arg-2-Nal-D-Ala-D-Cys]-Lys(iPr) (51)*



[00438] The linear peptide was synthesized using Liberty Blue automated microwave peptide synthesizer from CEM. At a 0.25 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C and washed with DMF (3 mL x 3). At a 1 mmol scale, Fmoc-Lys(iPr, Boc)-OH was conjugated to the Rink Amide MBHA resin using OxymaPure in DMF (1 M) and DIC in DMF (1 M) at 90°C for 4 min. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with DMF (3 mL) after deprotection. Fmoc-Cys(Trt)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH were sequentially coupled to the peptidyl resin following similar procedures. After standard Fmoc-deprotection, Boc-Lys(Fmoc)-OH was coupled with HATU/HOAt/DIPEA using 4/4/8 equivalents in DMF for 4 min at 75°C. After removal of the Fmoc group, Fmoc-Cys(Acid)-OH was coupled to the side chain amine, followed by DOTA(tBu)₃ coupling at 75°C using HATU/HOAt/DIPEA using 4/4/8 equivalents

in DMF (2 mL). The peptide was deprotected and cleaved simultaneously from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIPS/H₂O for 3 h at 35°C. After filtering off the resin, the crude peptide was precipitated by adding the crude solution to cold diethyl ether (10x vol. of the cleavage solution) dropwise. The crude peptide was washed twice with diethyl ether, vortexed and centrifuged. The washed crude peptide pellet was re-dissolved in 30% ACN in H₂O (0.1% TFA) and lyophilized. crude peptide (~2 µmol, lyophilized, in a 15mL falcon tube) was dissolved in HEPES (2 M, pH = 5, 560 µL) and Ga(NO₂)₃ in 1 M HCl (0.0282 M, 400µL). The solution was transferred to a scintillation vial and heated in a commercial food microwave for 1 min at 20% power. NaOH_(aq) (5M) was added to the solution until pH ~ 8. Me-ortho-*phthalaldehyde* in EtOH (0.05M, 60µL) was then added. The solution was vortexed and allowed to reaction at room temperature for 15 minutes. Reaction mixture then adjusted to pH ~ 3-4 with Formic Acid and then directly purified using preparative HPLC eluted with 5-35% acetonitrile (0.1% FA) in H₂O (0.1% FA) from 0 to 7.5 mins, then 35-100% acetonitrile (0.1% FA) in H₂O (0.1% FA) in 7.5 to 8.0 mins. The retention time was 25.9 min. ESI-MS: calculated [M+2H]²⁺ for **51** C₈₆H₁₂₅GaN₂₀O₂₀S₂ 946.9; found [M+2H]²⁺ 947.4.

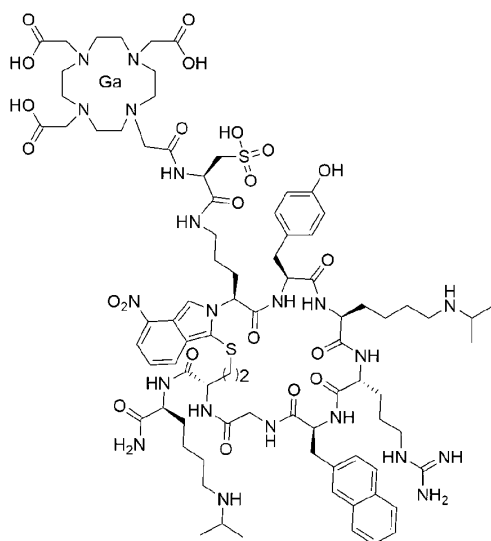
[00439] *Cyclo(NO₂-isoindole N³-S)[Lys(Cys(Acid)-DOTA-Ga)-Tyr-Lys(iPr)-D-Arg-2-Nal-D-Ala-D-Cys]-Lys(iPr) (52)*



[00440] The linear peptide was synthesized using Liberty Blue automated microwave peptide synthesizer from CEM. At a 0.25 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C and washed with DMF (3 mL x 3). At a 1 mmol scale, Fmoc-Lys(iPr, Boc)-OH was conjugated to the Rink Amide MBHA resin using OxymaPure in DMF (1 M) and DIC in DMF (1 M) at 90°C for 4 min.

The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with DMF (3 mL) after deprotection. Fmoc-Cys(Trt)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH were sequentially coupled to the peptidyl resin following similar procedures. After standard Fmoc-deprotection, Boc-Lys(Fmoc)-OH was coupled with HATU/HOAt/DIPEA using 4/4/8 equivalents in DMF for 4 min at 75°C. After removal of the Fmoc group, Fmoc-Cys(Acid)-OH was coupled to the side chain amine, followed by DOTA(tBu)₃ coupling at 75°C using HATU/HOAt/DIPEA using 4/4/8 equivalents in DMF (2 mL). The peptide was deprotected and cleaved simultaneously from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIPS/H₂O for 3 h at 35°C. After filtering off the resin, the crude peptide was precipitated by adding the crude solution to cold diethyl ether (10x vol. of the cleavage solution) dropwise. The crude peptide was washed twice with diethyl ether, vortexed and centrifuged. The washed crude peptide pellet was re-dissolved in 30% ACN in H₂O (0.1% TFA) and lyophilized. crude peptide (~2 µmol, lyophilized, in a 15mL falcon tube) was dissolved in HEPES (2 M, pH = 9, 400 µL), to which 3-nitro-ortho-phthalaldehyde in EtOH Solution (0.05M, 80 µL) was added. The solution was allowed to react overnight. The reaction mixture was then acidified with 1 M HCl(aq) to pH ~ 4, Ga(NO₂)₃ in 1 M HCl (0.0282M, 300 µL) added (pH ~ 3) and then transferred to a scintillation vial and heated in a commercial food microwave for 1 min at 20% power. The reaction mixture was then directly purified using preparative HPLC eluted with 5-35% acetonitrile (0.1% FA) in H₂O (0.1% FA) from 0 to 7.5 mins, then 35-100% acetonitrile (0.1% FA) in H₂O (0.1% FA) in 7.5 to 8.0 mins. The retention time was 27.2 min. ESI-MS: calculated [M+2H]²⁺ for **52** C₈₅H₁₂₂GaN₂₁O₂₂S₂ 962.4; found [M+2H]²⁺ 963.1.

[00441] *Cyclo(NO₂-isoindole N³-S)[Lys(Cys(Acid)-DOTA-Ga)-Tyr-Lys(iPr)-D-Arg-2-Nal-D-Ala-D-hCys]-Lys(iPr) (53)*



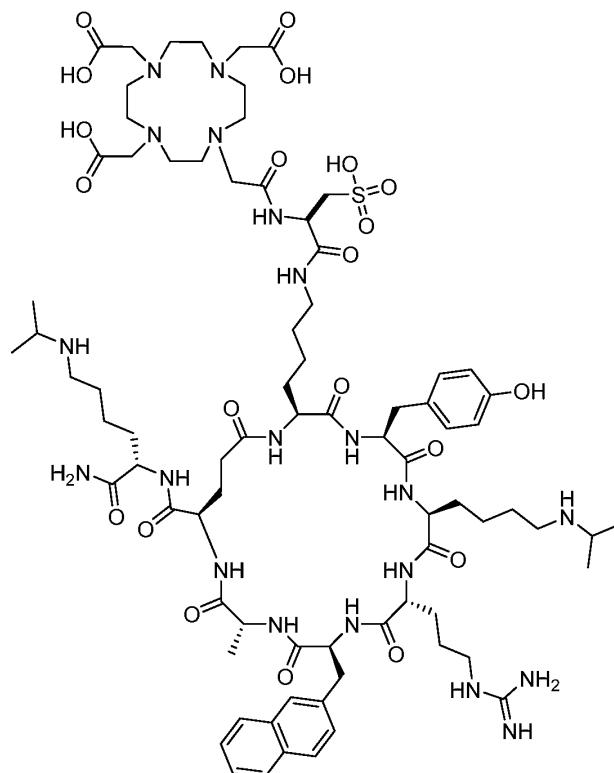
[00442] The linear peptide was synthesized using Liberty Blue automated microwave peptide synthesizer from CEM. At a 0.25 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C and washed with DMF (3 mL x 3). At a 1 mmol scale, Fmoc-Lys(iPr, Boc)-OH was conjugated to the Rink Amide MBHA resin using OxymaPure in DMF (1 M) and DIC in DMF (1 M) at 90°C for 4 min. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with DMF (3 mL) after deprotection. Fmoc-hCys(Trt)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH were sequentially coupled to the peptidyl resin following similar procedures. After standard Fmoc-deprotection, Boc-Lys(Fmoc)-OH was coupled with HATU/HOAt/DIPEA using 4/4/8 equivalents in DMF for 4 min at 75°C. After removal of the Fmoc group, Fmoc-Cys(Acid)-OH was coupled to the side chain amine, followed by DOTA(tBu)₃ coupling at 75°C using HATU/HOAt/DIPEA using 4/4/8 equivalents in DMF (2 mL). The peptide was deprotected and cleaved simultaneously from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIPS/H₂O for 3 h at 35°C. After filtering off the resin, the crude peptide was precipitated by adding the crude solution to cold diethyl ether (10x vol. of the cleavage solution) dropwise. The crude peptide was washed twice with diethyl ether, vortexed and centrifuged. The washed crude peptide pellet was re-dissolved in 30% ACN in H₂O (0.1% TFA) and lyophilized. crude peptide (~2 µmol, lyophilized, in a 15mL falcon tube) was dissolved in HEPES (2 M, pH = 9, 400 µL), to which 3-nitro-ortho-phthalaldehyde in EtOH Solution (0.05M, 80 µL) was added. The solution was allowed to react overnight. The reaction mixture was then acidified with 1 M HCl(aq) to pH ~ 4, Ga(NO₂)₃ in 1 M HCl (0.0282M, 300 µL) added (pH ~ 3) and then transferred to a scintillation

vial and heated in a commercial food microwave for 1 min at 20% power. The reaction mixture was then directly purified using preparative HPLC eluted with 5-35% acetonitrile (0.1% FA) in H₂O (0.1% FA) from 0 to 7.5 mins, then 35-100% acetonitrile (0.1% FA) in H₂O (0.1% FA) in 7.5 to 8.0 mins. The retention time was 27.6 min. ESI-MS: calculated $[M+2H]^{2+}$ for **53** C₈₆H₁₂₄GaN₂₁O₂₂S₂ 969.4; found $[M+2H]^{2+}$ 969.8.

[00443] *Synthesis of cyclo[Lys(CysAcid₂-DOTA-Ga)-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr) (BL33) (55)*

[00444] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Lys(ivDde)-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in CH₂Cl₂ (6 mL) (2 × 6 min at 35°C). The N^F-Fmoc on Lys(ivDde) was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the ivDde group was removed *via* adding 3 mL of 2% N₂H₄ in DMF for 5 minutes, with 5 cycles. Fmoc-cysteic acid-OH was coupled (coupled twice) in two instances and the Fmoc group removed. DOTA(tBu)₃ was then coupled at room temperature using HATU and DIEA in DMF using 4/4/8 equivalents. The peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The lyophilized powder was dissolved in 0.1 NaOAc buffer (4.2 pH) and to it was added 20 µL of a solution of 0.2 M GaCl₃. The solution was heated to 80°C for 20 minutes and the crude peptide was directly purified by preparative HPLC using the preparative column eluted with 14-34% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **Ga-BL33** was 7.71 min with the preparative column. ESI-MS: calculated $[M+2H]^{2+}$ for **Ga-BL33** C₈₂H₁₂₉GaN₂₁O₂₅S₂ 970.40; found $[M+2H]^{2+}$ 970.97.

[00445] *Synthesis of cyclo[Lys(CysAcid-DOTA)-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr) (BL34) (56)*



At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Lys(ivDde)-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*^ε-Fmoc on Lys(ivDde) was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the ivDde group was removed *via* adding 3 mL of 2% N₂H₄ in DMF for 5 minutes, with 5 cycles. Fmoc-CysAcid-OH was then coupled (coupled twice) to the terminal amine and the Fmoc group removed. DOTA(tBu)₃ was then coupled at room temperature using HATU and DIEA in DMF using 4/4/8 equivalents. The peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified

by preparative HPLC using the preparative column eluted with 12-32% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **BL34** was 9.19 min with the preparative column. ESI-MS: calculated $[M+2H]^{2+}$ for **BL34** C₇₉H₁₂₃N₂₀O₂₁S 861.46; found $[M+2H]^{2+}$ 861.98.

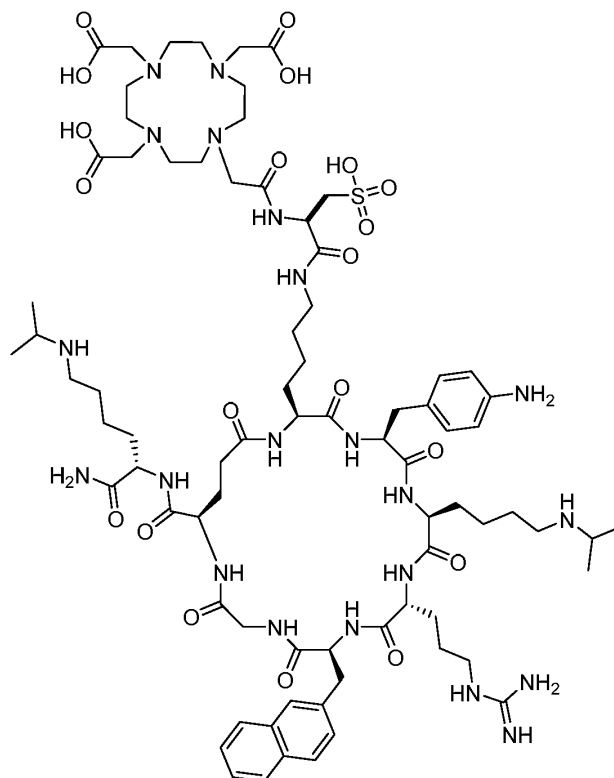
[00446] *Synthesis of cyclo[Lys(CysAcid-DOTA-Ga)-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr) (Ga-BL34) (57)*

[00447] 1.1 mg of **BL34** (0.59 μmol) was dissolved in 0.1 NaOAc buffer (4.2 pH) and to it was added 5 eq of GaCl₃ (14.7 μL, 0.2 M, 2.93 μmol). The solution was heated to 80°C for 20 minutes and the peptide was directly purified by preparative HPLC using the preparative column eluted with 12-32% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of Ga-BL34 was 9.64 min with the preparative column and produced 0.79 mg of Ga-BL34 (71% yield). ESI-MS: calculated $[M+2H]^{2+}$ for Ga-BL34 C₇₉H₁₂₄GaN₂₀O₂₁S 894.91; found $[M+2H]^{2+}$ 891.33.

[00448] *Synthesis of cyclo[Lys(CysAcid-DOTA-Lu)-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr) (Lu-BL34) (58)*

[00449] 1.2 mg of **BL34** (0.70 μmol) was dissolved in 0.1 NaOAc buffer (4.2 pH) and to it was added 5 eq of LuCl₃ (17.4 μL, 0.2 M, 3.48 μmol). The solution was heated to 80°C for 20 minutes and the peptide was directly purified by preparative HPLC using the preparative column eluted with 12-32% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **Lu-BL34** was 9.71 min with the preparative column. ESI-MS: calculated $[M+2H]^{2+}$ for **Lu-BL34** C₇₉H₁₂₃LuN₂₀O₂₁S 947.41; found $[M+2H]^{2+}$ 947.91.

[00450] *Synthesis of cyclo[Lys(CysAcid-DOTA)-(4-NH₂)Phe-Lys(iPr)-D-Arg-2Nal-Gly-D-Glu]-Lys(iPr) (BL36) (59)*



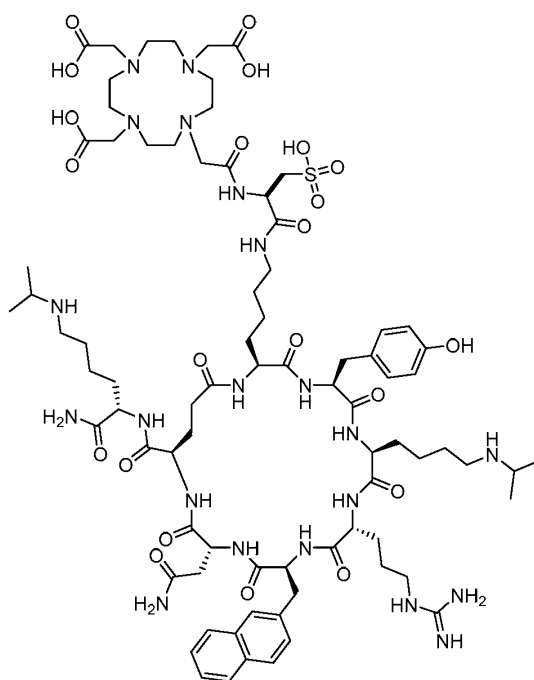
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overnight. The crude peptide was purified by preparative HPLC using the preparative column eluted with 11-31% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **BL36** was 7.55 min with the preparative column. ESI-MS: calculated $[M+2H]^{2+}$ for **BL36** C₇₈H₁₂₅N₂₁O₂₀S 853.96; found $[M+2H]^{2+}$ 853.34

[00452] *Synthesis of cyclo[Lys(CysAcid-DOTA)-(4-NH₂)Phe-Lys(iPr)-D-Arg-2Nal-Gly-D-Glu]-Lys(iPr) (**Ga-BL36**) (60)*

[00453] 1.5 mg of **BL36** (0.87 μ mol) was dissolved in 0.1 NaOAc buffer (4.2 pH) and to it was added 5 eq of GaCl₃ (21.8 μ L, 0.2 M, 4.35 μ mol). The solution was heated to 80°C for 20 minutes and the peptide was directly purified by preparative HPLC using the preparative column eluted with 10-30% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **Ga-BL36** was 8.85 min with the preparative column and produced 1.21 mg of **Ga-BL36** (77% yield). ESI-MS: calculated $[M+2H]^{2+}$ for **Ga-BL36** C₇₈H₁₂₃GaN₂₁O₂₀S 887.41; found $[M+2H]^{2+}$ 887.12.

[00454] *Synthesis of cyclo[Lys(CysAcid-DOTA)-Tyr-Lys(iPr)-D-Arg-2Nal-D-Asn-D-Glu]-Lys(iPr) (**BL37**) (61)*



[00455] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-

Glu(OAll)-OH, Fmoc-D-Asn(Trt)-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Lys(ivDde)-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in CH₂Cl₂ (6 mL) (2 × 6 min at 35°C). The *N*^α-Fmoc on Lys(ivDde) was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the ivDde group was removed *via* adding 3 mL of 2% N₂H₄ in DMF for 5 minutes, with 5 cycles. Fmoc-CysAcid-OH was coupled (coupled twice) and the Fmoc group removed. DOTA(tBu)₃ was coupled at room temperature using HATU and DIEA in DMF using 4/4/8 equivalents. The peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude was dissolved in water, frozen, and lyophilized overnight. The crude peptide was purified by preparative HPLC using the preparative column eluted with 11-31% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **BL37** was 8.70 min with the preparative column. ESI-MS: calculated [M+2H]²⁺ for **BL37** C₈₀H₁₂₇N₂₁O₂₂S 882.96; found [M+2H]²⁺ 882.12.

[00456] *Synthesis of cyclo[Lys(CysAcid-DOTA)-Tyr-Lys(iPr)-D-Arg-2Nal-D-Asn-D-Glu]-Lys(iPr) (Ga-BL37) (62)*

[00457] 1.1 mg of **BL37** (0.62 µmol) was dissolved in 0.1 NaOAc buffer (4.2 pH) and to it was added 5 eq of GaCl₃ (15.6 µL, 0.2 M, 3.1 µmol). The solution was heated to 80°C for 20 minutes and the peptide was directly purified by preparative HPLC using the preparative column eluted with 11-31% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of Ga-BL36 was 7.11 min with the preparative column and produced 0.91 mg of **Ga-BL37** (80% yield). ESI-MS: calculated [M+2H]²⁺ for **Ga-BL37** C₈₀H₁₂₅GaN₂₁O₂₂S 916.41; found [M+2H]²⁺ 916.32.

[00458] *Synthesis of cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-D-Asn-D-Glu]-Lys(iPr)-Lys(CysAcid-DOTA) (BL38) (63)*

[00459] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(ivDde)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-Lys(iPr, Boc)-OH, Fmoc-D-Glu(OAll)-OH, Fmoc-D-Asn(Trt)-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using

$\text{Pd}(\text{PPh}_3)_4$ (20 mg)/Phenylsilane (300 μL) in DCM (6 mL) (2×6 min at 35°C). The N^{α} -Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3×10 min at 90°C). Following cyclization, the ivDde group was removed *via* adding 3 mL of 2% N_2H_4 in DMF for 5 minutes, with 5 cycles. Fmoc-CysAcid-OH was then coupled (coupled twice) and the Fmoc group removed. DOTA(tBu)₃ was then coupled at room temperature using HATU and DIEA in DMF using 4/4/8 equivalents. The peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/ H_2O for 3 h at 35°C . After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 12-32% acetonitrile (0.1% TFA) in H_2O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **BL38** was 11.66 min with the preparative column.

[00460] *Synthesis of cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-D-Asn-D-Glu]-Lys(iPr)-Lys(CysAcid-DOTA) (Ga-BL38) (64)*

[00461] 1.2 mg of **BL38** (0.63 μmol) was dissolved in 0.1 NaOAc buffer (4.2 pH) and to it was added 5 eq of GaCl_3 (21.8 μL , 0.2 M, 4.35 μmol). The solution was heated to 80°C for 20 minutes and the peptide was directly purified by preparative HPLC using the preparative column eluted with 10-30% acetonitrile (0.1% TFA) in H_2O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **Ga-BL38** was 12.31 min with the preparative column and produced 0.9 mg of **Ga-BL38** (74% yield). ESI-MS: calculated $[\text{M}+2\text{H}]^{2+}$ for **Ga-BL38** $\text{C}_{89}\text{H}_{134}\text{GaN}_{22}\text{O}_{23}\text{S}$ 989.95; found $[\text{M}+2\text{H}]^{2+}$ 989.32.

[00462] *Synthesis of cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-D-Asn-D-Glu]-Lys(iPr)-Lys(CysAcid₂-DOTA) (BL39) (65)*

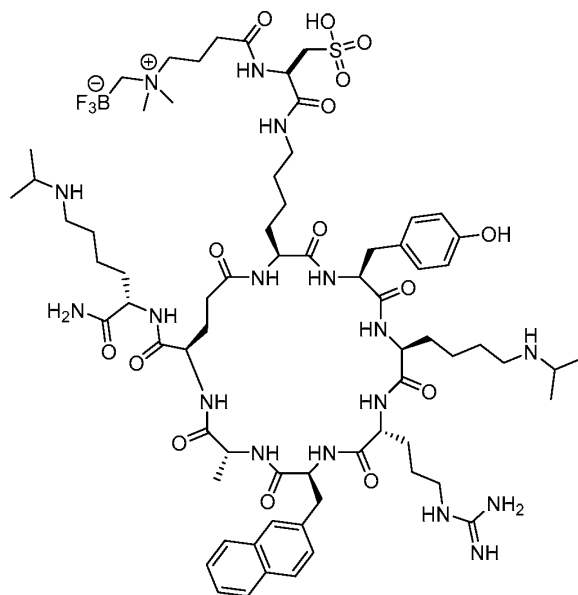
[00463] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(ivDde)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C . The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-Lys(iPr, Boc)-OH, Fmoc-D-Glu(OAll)-OH, Fmoc-D-Asn(Trt)-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Phe-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using $\text{Pd}(\text{PPh}_3)_4$ (20 mg)/Phenylsilane (300 μL) in DCM (6 mL) (2×6 min at 35°C). The N^{α} -Fmoc on Phe was then removed, and cyclization was performed using DIC/HOBt in DMF (3×10 min at 90°C). Following cyclization, the ivDde group was removed *via* adding 3 mL of 2% N_2H_4 in DMF for 5 minutes, with 5 cycles. Fmoc-CysAcid-OH was then coupled (coupled twice) in two instances and the Fmoc group removed. DOTA(tBu)₃ was then coupled at room temperature

using HATU and DIEA in DMF using 4/4/8 equivalents. The peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 12-32% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **BL39** was 12.18 min with the preparative column.

[00464] Synthesis of *cyclo*[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-D-Asn-D-Glu]-Lys(iPr)-Lys(CysAcid₂-DOTA-Ga) (**Ga-BL39**) (**66**)

[00465] 1.4 mg of **BL39** (0.79 μmol) was dissolved in 0.1 NaOAc buffer (4.2 pH) and to it was added 5 eq of GaCl₃ (21.8 μL, 0.2 M, 4.35 μmol). The solution was heated to 80°C for 20 minutes and the peptide was directly purified by preparative HPLC using the preparative column eluted with 10-30% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of Ga-BL36 was 12.57 min with the preparative column and produced 1.2 mg of **Ga-BL39** (86% yield). ESI-MS: calculated [M+2H]²⁺ for **Ga-BL39** C₉₂H₁₃₉GaN₂₃O₂₇S₂ 1065.44; found [M+2H]²⁺ 1065.98.

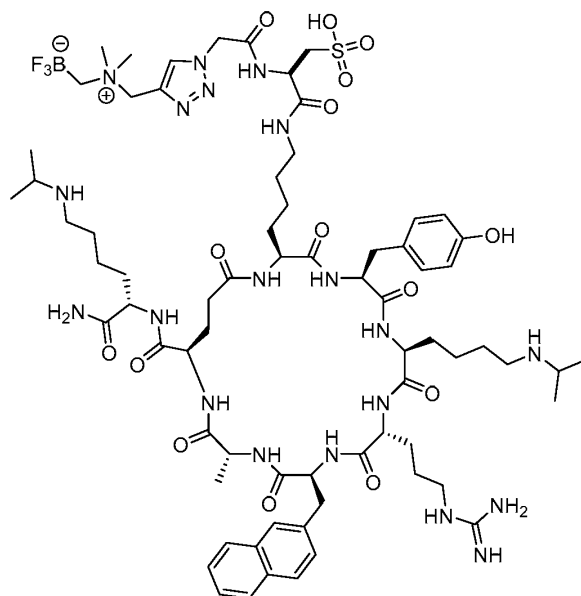
[00466] Synthesis of *cyclo*[Lys(CysAcid-amido-N,N-dimethyl-ammoniomethyl-trifluoroborate)-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr) (**PepBF₃-BL40**) (**67**)



[00467] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min

at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Lys(ivDde)-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*³-Fmoc on Lys(ivDde) was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the ivDde group was removed *via* adding 3 mL of 2% N₂H₄ in DMF for 5 minutes, with 5 cycles. Fmoc-CysAcid-OH was then coupled (coupled twice) and the Fmoc group removed. The resin was placed into a spin column and was swelled using degassed and freshly distilled DMF (10 mL) for 30 mins. The solution was then drained and rinsed with DCM. At a 0.025 mmol scale, (3-Carboxy-propyl)-*N,N*-dimethylammoniummethyl-trifluoroborate (32 mg, 149 µmol) was dissolved in DMF (5 mL) and was transferred to the spin column. HBTU (54.5 mg, 144 µmol) was directly added to the bead solution followed by DIPEA (52 µL, 609 µmol). The mixture was mixed for 4 hours using a tube rotator. The solution was drained and rinsed with DCM, DMF, and DCM three times in 10 mL portions each followed by a rinse of Et₂O and dried *in vacuo* for 30 minutes. The beads were transferred into a falcon tube and were suspended in 500 µL DCM and added with 50 µL TIPS, 10 µL H₂O, and a stir bar. KHF₂ (200 mg) was placed into a separate falcon tube. TFA (1 mL) was added to the falcon tube of KHF₂ using a hypodermic needle and 1 mL syringe. The tube was then sealed and sonicated until all the solids were observed to completely dissolve. After complete dissolution, the mixture was added to the falcon tube containing the beads. The mixture was stirred uncapped for 1 hour. Afterwards, the mixture was cooled then diluted with H₂O (1 mL) in an ice bath followed by the slow addition of excess NH₄OH until basic. ACN was then added to the mixture and the solution was filtered into a falcon tube and concentrated at low heat to remove the organic solvents. The resulting mixture was further diluted into water, frozen, and lyophilized to yield a white powder. This was then triturated with ACN and centrifuged, and was purified by preparative HPLC eluted with **8-18%** acetonitrile (0.1% FA) in H₂O (0.1% FA) in 15 mins at a flow rate of 30 mL/min. The retention time of **PepBF₃-BL40** was 9.57 min with the preparative column. ESI-MS: calculated [M+2H]²⁺ for C₇₀H₁₁₅BF₃N₁₇O₁₅S 765.9; found [M+2H]²⁺ 766.3.

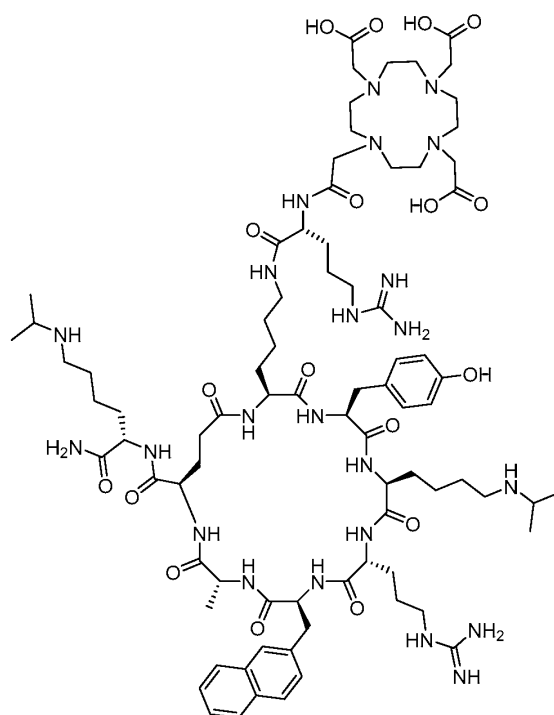
[00468] Synthesis of cyclo[Lys(CysAcid-triazole-*N,N*-dimethyl-ammoniomethyl-trifluoroborate)-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr) (**AMBF₃-BL41**) (**68**)



[00469] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Lys(ivDde)-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*^ε-Fmoc on Lys(ivDde) was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the ivDde group was removed *via* adding 3 mL of 2% N₂H₄ in DMF for 5 minutes, with 5 cycles. Fmoc-CysAcid-OH was then coupled (coupled twice) and the Fmoc group removed. 2-Azidoacetic acid was then coupled at 50°C using HATU and DIEA in DMF using 4/4/8 equivalents. The azido-peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the azido-peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 13-33% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time was 10.98 min with the preparative column. ESI-MS: calculated [M+2H]²⁺ for the azido-peptide C₆₅H₁₀₁N₁₉O₁₅S 709.87; found [M+2H]²⁺ 710.58. The fractions containing the pure azido-peptide were collected and

lyophilized and dissolved in 1 mL of H₂O. 5 μ L of 1 M CuSO₄, 5 μ L of 1 M *N*-propargyl-*N,N*-dimethylammoniomethyl-trifluoroborate, 500 μ L of 0.1 M NH₄OH solution, and 6 μ L of 1 M sodium ascorbate were added sequentially and heated to 45°C until the reaction mixture turned clear and starting material was consumed based on HPLC. The reaction mixture was purified again by HPLC using the preparative column eluted with 10-20% acetonitrile (0.1% FA) in H₂O (0.1% FA) in 15 mins at a flow rate of 30 mL/min. The retention time was 6.22 min. ESI-MS: calculated [M+2H]²⁺ for **AMBF₃-BL41** C₇₁H₁₁₂BF₃N₂₀O₁₅S 792.42; found [M+2H]²⁺ 792.62.

[00470] Synthesis of cyclo[Lys(D-Arg-DOTA)-Tyr-Lys(*i*Pr)-D-Arg-2-Nal-D-Ala-D-Glu]-Lys(*i*Pr) (**BL42**) (**69**)



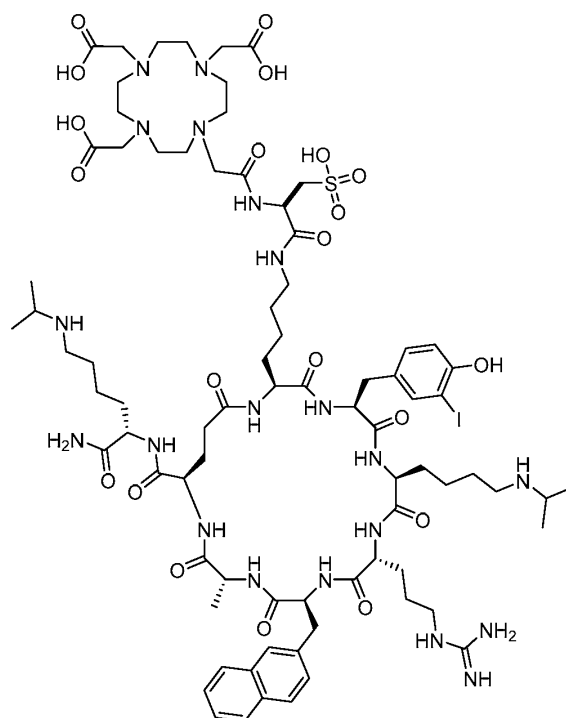
[00471] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(*i*Pr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(*i*Pr, Boc)-OH, Fmoc-Tyr(*t*Bu)-OH, and Fmoc-Lys(*iv*Dde)-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20

mg)/Phenylsilane (300 μ L) in DCM (6 mL) (2×6 min at 35°C). The N^{α} -Fmoc on Lys(ivDde) was then removed, and cyclization was performed using DIC/HOBt in DMF (3×10 min at 90°C). Following cyclization, the ivDde group was removed *via* adding 3 mL of 2% N_2H_4 in DMF for 5 minutes, with 5 cycles. Fmoc-D-Arg(Pbf)-OH was then coupled (coupled twice) and the Fmoc group removed. DOTA(tBu)₃ was then coupled at room temperature using HATU and DIEA in DMF using 4/4/8 equivalents. The peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/ H_2O for 3 h at 35°C . After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 11-31% acetonitrile (0.1% TFA) in H_2O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **BL42** was 10.08 min with the preparative column.

[00472] *Synthesis of cyclo[Lys(D-Arg-DOTA-Ga)-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr) (Ga-BL42) (70)*

[00473] 1.2 mg of **BL42** (0.69 μ mol) was dissolved in 0.1 NaOAc buffer (4.2 pH) and to it was added 5 eq of GaCl_3 (17.4 μ L, 0.2 M, 3.47 μ mol). The solution was heated to 80°C for 20 minutes and the peptide was directly purified by preparative HPLC using the preparative column eluted with 11-31% acetonitrile (0.1% TFA) in H_2O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **Ga-BL42** was 10.18 min with the preparative column and produced 0.9 mg of **Ga-BL42** (73% yield). ESI-MS: calculated $[\text{M}+2\text{H}]^{2+}$ for **Ga-BL42** $\text{C}_{82}\text{H}_{131}\text{GaN}_{23}\text{O}_{18}$ 897.5; found $[\text{M}+2\text{H}]^{2+}$ 897.3.

[00474] *Synthesis of cyclo[Lys(CysAcid-DOTA)-(3-I) Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr) (BL43) (71)*



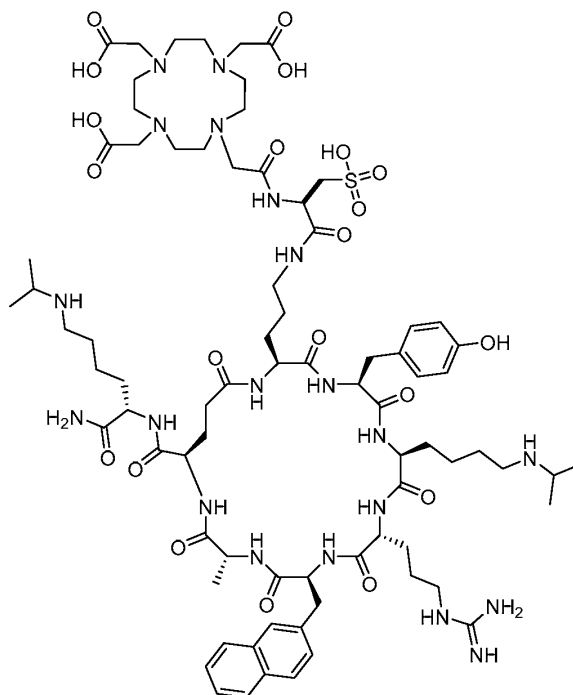
[00475] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(3-I)-OH (coupled twice), and Fmoc-Lys(ivDde)-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*^ε-Fmoc on Lys(ivDde) was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the ivDde group was removed *via* adding 3 mL of 2% N₂H₄ in DMF for 5 minutes, with 5 cycles. Fmoc-CysAcid-OH was then coupled (coupled twice) and the Fmoc group removed. DOTA(tBu)₃ was then coupled at room temperature using HATU and DIEA in DMF using 4/4/8 equivalents. The peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 12-32% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins

at a flow rate of 30 mL/min. The retention time of **BL43** was 11.63 min with the preparative column.

[00476] Synthesis of *cyclo[Lys(CysAcid-DOTA-Ga)-(3-I)Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr) (Ga-BL43) (72)*

[00477] 0.8 mg of **BL43** (0.43 μ mol) was dissolved in 0.1 NaOAc buffer (4.2 pH) and to it was added 5 eq of GaCl₃ (10.8 μ L, 0.2 M, 2.17 μ mol). The solution was heated to 80°C for 20 minutes and the peptide was directly purified by preparative HPLC using the preparative column eluted with 13-33% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **Ga-BL34** was 10.98 min with the preparative column and produced 0.8 mg of **Ga-BL43** (97% yield). ESI-MS: calculated [M+2H]²⁺ for **Ga-BL43** C₇₉H₁₂₃GaN₂₀O₂₁S 957.9; found [M+2H]²⁺ 957.8.

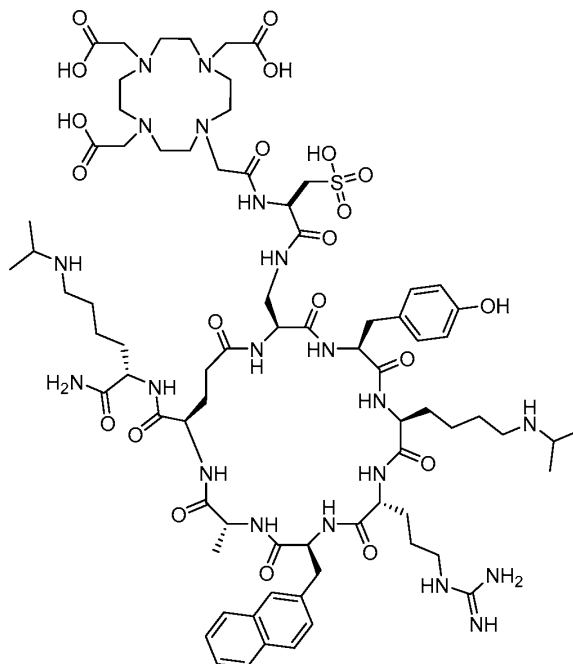
[00478] Synthesis of *cyclo[Orn(CysAcid-DOTA)-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr) (BL44) (73)*



[00479] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-

Orn(ivDde)-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAllyl protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 μ L) in DCM (6 mL) (2 $\times$ 6 min at 35°C). The *N*^ε-Fmoc on Lys(ivDde) was then removed, and cyclization was performed using DIC/HOBt in DMF (3 $\times$ 10 min at 90°C). Following cyclization, the ivDde group was removed *via* adding 3 mL of 2% N₂H₄ in DMF for 5 minutes, with 5 cycles. Fmoc-CysAcid-OH was then coupled (coupled twice) and the Fmoc group removed. DOTA(tBu)₃ was then coupled at room temperature using HATU and DIEA in DMF using 4/4/8 equivalents. The peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 12-32% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **BL44** was 9.24 min with the preparative column. ESI-MS: calculated [M+2H]²⁺ for C₇₈H₁₂₄N₂₀O₂₁S 854.45; found [M+2H]²⁺ 854.98.

[00480] *Synthesis of cyclo[Dap(CysAcid-DOTA)-Tyr-Lys(iPr)-D-Arg-2NaI-D-Ala-D-Glu]-Lys(iPr) (BL45) (74)*



[00481] At a 0.1 mmol scale, Fmoc-Rink Amide MBHA resin (CEM, 0.56 mmol/g) was deprotected with 20% v/v piperidine in DMF for 1 min at 90°C twice and washed with 3 mL of DMF 5 times. At a 0.02 mmol scale, Fmoc-Lys(iPr, Boc)-OH was then conjugated to the Rink Amide MBHA resin. The Fmoc group was removed with 20% v/v piperidine in DMF for 1 min

at 90°C. The resin was washed three times with 3 mL DMF after each deprotection. Fmoc-D-Glu(OAll)-OH, Fmoc-D-Ala-OH (coupled twice), Fmoc-2-Nal-OH (coupled twice), Fmoc-D-Arg(Pbf)-OH (coupled twice), Fmoc-Lys(iPr, Boc)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Dap(Mtt)-OH (coupled twice) were sequentially coupled to the peptidyl resin following similar procedures. The -OAll protecting group on D-Glu was removed using Pd(PPh₃)₄ (20 mg)/Phenylsilane (300 µL) in DCM (6 mL) (2 × 6 min at 35°C). The *N*^ε-Fmoc on Dap(Mtt) was then removed, and cyclization was performed using DIC/HOBt in DMF (3 × 10 min at 90°C). Following cyclization, the Mtt group was removed *via* adding 3 mL of 2/5/93 TFA/TIS/DCM for 5 minutes, with 5 cycles. Fmoc-CysAcid-OH was then coupled (coupled twice) and the Fmoc group removed. DOTA(tBu)₃ was then coupled at room temperature using HATU and DIEA in DMF using 4/4/8 equivalents. The peptide was deprotected and simultaneously cleaved from the resin by treating with a cocktail solution of 92.5/5/2.5 TFA/TIS/H₂O for 3 h at 35°C. After filtration, the TFA was removed *in vacuo* and the peptide was precipitated by the addition of cold diethyl ether. The crude peptide was purified by preparative HPLC using the preparative column eluted with 12-32% acetonitrile (0.1% TFA) in H₂O (0.1% TFA) in 20 mins at a flow rate of 30 mL/min. The retention time of **BL45** was 9.85 min with the preparative column. ESI-MS: calculated [M+2H]²⁺ for C₇₆H₁₂₀N₂₀O₂₁S 840.43; found [M+2H]²⁺ 840.49.

[00482] *Cell Culture*

[00483] The Z138 mantle cell lymphoma cell line was given by Dr. Christian Steidl (BC Cancer) as a gift. The CHO: CXCR4 cell line was given by Drs. David McDermott and Xiaoyuan Chen (National Institutes of Health) as a gift. The cell line was cultured in a 5% CO₂ atmosphere at 37°C in a humidified incubator. The Z138 cells were incubated with IMDM medium (Life Technologies Corporations) and the CHO: CXCR4 cells were incubated with F12K medium (Life Technologies Corporations), both of which were supplemented with 10% fetal bovine serum (Sigma-Aldrich), 100 I.U./mL penicillin, and 100 µg/mL streptomycin (Penicillin-Streptomycin Solution).

[00484] *Competitive Binding Assay*

[00485] CHO: CXCR4 cells were seeded at a density of 1 × 10⁵ cells/well in 24-well poly-D-lysine coated plates (Corning BioCoat) and incubated with [¹²⁵I]SDF-1α (0.01 nM, PerkinElmer) and competing nonradioactive ligands (1 µM to 0.1 pM). The cells, radioligand, and competing peptides were incubated for 1 h at 27 °C with moderate shaking. Following the incubation period, the supernatant was aspirated, followed by three washes with 1 mL of ice-cold PBS. Cells were harvested with 200 µL of trypsin and counted on a γ counter. Data were plotted in GraphPad Prism 7 to determine IC₅₀ values (GraphPad Software, Inc., La Jolla, CA). The values are reported as mean ± standard deviation. Results for a subset of compounds are shown in Table 5.

[00486] *Radiolabeling*

[00487] ⁶⁸Ga-Labeling: [⁶⁸Ga]GaCl₃ was eluted from an iThemba Labs generator with a total of 4 mL of 0.1 M HCl. The eluted [⁶⁸Ga]GaCl₃ solution was added to 2 mL of concentrated HCl. This radioactive mixture was then added to a DGA resin column and washed with 3 mL of 5 M HCl. The column was then dried with air and the [⁶⁸Ga]GaCl₃ (0.10 – 0.50 GBq) was eluted with 0.5 mL of water into a vial containing a solution of the unlabeled precursor (25 µg) in 0.7 mL HEPES buffer (2 M, pH 5.3). The reaction mixture was heated in a microwave oven (Danby; DMW7700WDB) for 1 min at power setting 2. The mixture was purified by semi-prep HPLC and quality control was performed via analytical HPLC with the co-injection of the unlabeled standard with a one-twelfth of the radiotracer. Radiochemical yields (decay-corrected) were >50% and radiochemical purities were >95%.

[00488] ¹⁷⁷Lu-Labeling:

[00489] [¹⁷⁷Lu]LuCl₃ was purchased from ITM Isotopen Technologien Munchen AG. [¹⁷⁷Lu]LuCl₃ (0.1–3.0 GBq) in 0.04 M HCl (10–300 µL) was added to a solution of the unlabeled precursor (25 µg) in 0.5 mL of NaOAc buffer (0.1 M, pH 4.5). The reaction mixture was incubated at 100 °C for 15 min. The mixture was purified by semi-prep HPLC and quality control was performed via analytical HPLC with the co-injection of the unlabeled standard with a one-twelfth of the radiotracer. Radiochemical yields (decay-corrected) were >50% and radiochemical purities were >95%.

[00490] *Animal Model*

Animal experiments were performed in accordance with guidelines established by the Canadian Council on Animal Care, under a research protocol approved by the Animal Ethics Committee of the University of British Columbia. For all studies, male NOD.Cg-Rag1tm1Mom1l2rgtm1Wjl/SzJ (NRG) mice were used and cells injected in a 100 µL solution of 1:1 ratio of PBS/Matrigel. For preclinical imaging and biodistribution studies, 5 × 10⁶ cells of Z138, cells were subcutaneously inoculated on the left or right flank and tumors were grown to a size of 200-300 mm³. For radionuclide therapy studies, 4 × 10⁶ Z138 cells (p.n. 5-10) were subcutaneously inoculated on the left flank and grown for 19 days.

[00491] *PET/CT Imaging*

[00492] PET and CT scans were performed on a Siemens Inveon microPET/CT. Tumor-bearing mice were briefly sedated with isoflurane (2-2.5% isoflurane in 2 L/min O₂) for i.v. injection of 4-7 MBq of [⁶⁸Ga]Ga-BL34. The animals were allowed to roam freely during the uptake period (50 or 110 minutes), after which they were sedated and scanned. The CT scan was obtained for attenuation correction and anatomical localization (80 kV; 500 µA; 3 bed positions; 34% overlap; 220° continuous rotation) followed by a 10 min PET acquisition at 1 or 2 h p.i. of the radiotracer. PET data were acquired in list mode, reconstructed using 3-dimensional ordered-subsets expectation maximization (2 iterations) followed by a fast maximum a priori algorithm (18 iterations) with CT-based attenuation correction. Images were

analyzed using the Inveon Research Workplace software (Siemens Healthineers). Results for compound BL34 is shown in Figure 1.

[00493] SPECT/CT Imaging

[00494] The CT scan was performed first, at 60 kV and 615 μ A. The SPECT scan was performed via a 60 min static emission scan acquired in list mode using the U-SPECT II scanner (MILabs), equipped with an extra ultra-high sensitivity big mouse (2mm pinhole size) collimator. The imaging dataset was reconstructed via the U-SPECT II software with a 20% window width on three energy windows. The photopeak window was centered at 208 keV, with the lower and upper scatter windows at 187.2 and 228.8 keV, respectively. The images were reconstructed using the ordered subset expectation maximization algorithm (4 iterations, 32 subsets) and a 1 mm post-processing Gaussian filter (collimator dependent calibration factor = 10012.659). Images were decay corrected to the injection time in PMOD (PMOD Technologies) and then converted to DICOM for qualitative visualization in the Inveon Research Workplace software (Siemens Medical Solutions US).

[00495] Biodistribution Studies

[00496] Under brief isoflurane sedation (2-2.5% isoflurane in 2 L/min O₂) for the injection only, the mice were injected intravenously with 0.8-3.0 MBq of the radiotracer, allowed to roam freely afterwards in their cage, and euthanized at the selected timepoints. Additional groups of mice received 7.5 μ g (0.25-0.3 mg/kg) LY2510924 as a blocking control i.p. 15 min before radiotracer injection and euthanized 1 h p.i.

[00497] Radioligand Therapy Studies

[00498] When the Z138 xenografts had grown to a volume of 500 $\pm$ 180 mm³, the mice were randomized into two groups (n=8 each). Z138 xenograft mice were briefly sedated (2-2.5% isoflurane in 2 L/min O₂) and injected with either [¹⁷⁷Lu]Lu-BL34 or PBS (100 μ L). Both treatment groups were longitudinally monitored for tumor volume, body weight, and behaviour every other day until 60 days or until mice reached the volume endpoint (>1500 mm³), loss of body weight (>15%) or unwell behavioural signs (e.g. lethargy, loss of appetite). Tumors were measured using a Bioptron Imager 2.

[00499] TABLE 5. Binding Affinity of Select Peptides to CXCR4

Peptide	IC ₅₀ (nM)
cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2-Nal-D-Gln-D-Glu]-Lys(iPr)	1-10
cyclo[Phe-(3-I)Tyr-Lys(iPr)-D-Arg-2-Nal-Gly-D-Glu]-Lys(iPr)	10-50
cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2-Nal-D-Ala-D-Glu]-Lys(iPr)	1-10
cyclo[Phe-(4-NH ₂)Phe-Lys(iPr)-D-Arg-2-Nal-Gly-D-Glu]-Lys(iPr)	1-10
cyclo[Phe-(4-NO ₂)Phe-Lys(iPr)-D-Arg-2-Nal-Gly-D-Glu]-Lys(iPr)	10-50
cyclo[Phe-hTyr-Lys(iPr)-D-Arg-2-Nal-Gly-D-Glu]-Lys(iPr)	1-10

Peptide	IC ₅₀ (nM)
cyclo[Phe-hTyr-Lys(iPr)-D-Arg-2-Nal-D-Ala-D-Glu]-Lys(iPr)	50-100
cyclo[Phe-(4-NH ₂)Phe-Lys(iPr)-D-Arg-2-Nal-D-Ala-D-Glu]-Lys(iPr)	10-50
cyclo[Lys(Ac)-Tyr-Lys(iPr)-D-Arg-Trp-D-Ala-D-Glu]-Lys(iPr)	10-50
cyclo[Phe-Tyr-Lys(iPr)-D-Arg-(4-NH ₂)Phe-D-Ala-D-Glu]-Lys(iPr)	10-50
cyclo[Lys(Ac)-Glu-Lys(iPr)-D-Arg-2-Nal-D-Ala-D-Glu]-Lys(iPr)	50-100
cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2-Nal-D-His-D-Glu]-Lys(iPr)	1-10
cyclo[Lys(Ac)-Gln-Lys(iPr)-D-Arg-2-Nal-D-Ala-D-Glu]-Lys(iPr)	10-50
cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2-Nal-D-His-D-Glu]-Lys(iPr)	10-50
cyclo[Phe-D-Tyr-Lys(iPr)-D-Arg-2-Nal-D-Ala-D-Glu]-Lys(iPr)	50-100
cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2-Nal-D-Ser-D-Glu]-Lys(iPr)	1-10
cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2-Nal-D-Leu-D-Glu]-Lys(iPr)	50-100
cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2-Nal-D-Asn-D-Glu]-Lys(iPr)	1-10
cyclo[Phe-Tyr-Arg(Me)-D-Arg-2-Nal-D-Ala-D-Glu]-Lys(iPr)	1-10
cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2-Nal-D-Glu-D-Glu]-Lys(iPr)	10-50
cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2-Nal-D-Dab-D-Glu]-Lys(iPr)	1-10
cyclo[Phe-Tyr-Lys(iPr)-D-Arg-(2-Ant)Ala-Gly-D-Glu]-Lys(iPr)	1-10
cyclo(isoindole)[Phe-Tyr-Lys(iPr)-D-Arg-(2-Ant)Ala-Gly-D-Cys]-Lys(iPr)	10-50
cyclo(isoindole)[Phe-Tyr-Lys(iPr)-D-Arg-(2-Ant)Ala-Gly-Cys]-Lys(iPr)	10-50
cyclo[Lys(Ac)-Tyr-Lys(iPr)-D-Arg-2-Nal-Gly-D-Glu]-Lys(iPr)	1-10
cyclo[Lys(CysAcid-DOTA(Ga))-Tyr-Lys(iPr)-D-Arg-2-Nal-D-Ala-D-Glu]-Lys(iPr) (Ga-BL34)	1-10
cyclo[Lys(CysAcid-amido-N,N-dimethyl-ammoniomethyl-trifluoroborate)-Tyr-Lys(iPr)-D-Arg-2-Nal-D-Ala-D-Glu]-Lys(iPr) (PepBF₃-BL40)	10-50
cyclo[Lys(CysAcid-triazole-N,N-dimethyl-ammoniomethyl-trifluoroborate)-Tyr-Lys(iPr)-D-Arg-2-Nal-D-Ala-D-Glu]-Lys(iPr) (AMBF₃-BL41)	10-50

[00500] **Table 6.** Biodistribution data (%ID/g) of [⁶⁸Ga]Ga-BL34 in Z138 tumor-bearing mice at selected time points. Mice in the 1 h blocked group received an injection of 7.5 µg of LY2510924 (i.p.) 15 min before tracer administration.

<u>[⁶⁸Ga]Ga-BL34</u>	1 h			1 h blocked			2 h		
	Mean	SD	n	Mean	SD	n	Mean	SD	n
Blood	0.37	0.16	2	0.61	NA	1	0.10	0.04	3
Fat	0.03	0.01	2	0.10	NA	1	0.02	0.01	3
Testes	0.16	0.07	2	0.28	NA	1	0.06	0.01	3
Intestine	0.28	0.06	2	0.43	NA	1	0.12	0.04	3
Stomach	0.06	0.01	2	0.12	NA	1	0.02	0.12	3
Spleen	0.41	0.09	2	0.38	NA	1	0.25	0.05	3
Liver	0.75	0.06	2	0.69	NA	1	0.73	0.10	3
Pancreas	0.09	0.04	2	0.18	NA	1	0.04	0.01	3
Adrenals	0.15	0.06	2	0.12	NA	1	0.04	0.09	3
Kidney	2.95	0.33	2	4.30	NA	1	2.32	0.21	3
Lung	0.64	0.08	2	0.79	NA	1	0.20	0.05	3
Heart	0.13	0.03	2	0.25	NA	1	0.06	0.01	3
Muscle	0.07	0.03	2	0.15	NA	1	0.03	0.01	3
Bone	0.20	0.07	2	0.11	NA	1	0.07	0.04	3
Brain	0.03	0.02	2	0.03	NA	1	0.01	0.01	3
Tumor	18.99	5.12	2	3.18	NA	1	18.66	3.95	3
Ratios									
Tumor:Blood	59.41	38.85	2	5.22	NA	1	192.96	49.97	3
Tumor:Liver	25.85	8.99	2	4.58	NA	1	25.38	2.68	3
Tumor:Spleen	48.87	23.40	2	8.29	NA	1	80.31	22.99	3
Tumor:Muscle	318.49	211.64	2	21.26	NA	1	752.72	273.87	3
Tumor:Bone	106.23	63.90	2	28.89	NA	1	284.15	92.30	3
Tumor:Lung	30.36	11.86	2	4.04	NA	1	99.84	31.31	3
Tumor:Kidney	6.57	2.47	2	0.74	NA	1	8.06	0.69	3

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[00501] **Table 7.** Biodistribution data (%ID/g) of [¹⁷⁷Lu]Lu-BL34 in Z138 tumor-bearing mice at selected time points. Mice in the 1 h blocked group received an injection of 7.5 µg of LY2510924 (i.p.) 15 min before tracer administration.

<u>[¹⁷⁷Lu]Lu-BL34</u>	1 h			1 h blocked			4 h			24 h			72 h		
	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n
Blood	0.45	0.14	6	1.20	0.86	6	0.04	0.02	6	0.01	0.01	6	0.01	0.00	5
Testes	0.21	0.06	6	0.32	0.13	6	0.04	0.01	6	0.03	0.00	6	0.02	0.00	5
Intestines	0.37	0.13	6	0.60	0.16	6	0.06	0.01	6	0.06	0.02	6	0.07	0.07	5
Spleen	0.37	0.13	6	0.71	0.22	5	0.28	0.06	6	0.23	0.01	5	0.34	0.15	5
Liver	0.70	0.13	6	0.86	0.22	6	0.73	0.09	6	0.53	0.08	6	0.39	0.09	5
Pancreas	0.11	0.02	6	0.69	0.65	6	0.04	0.01	6	0.02	0.00	6	0.01	0.00	5
Adrenal glands	0.15	0.03	6	0.75	0.33	6	0.10	0.08	6	0.04	0.02	6	0.04	0.01	4
Kidney	2.73	0.50	6	5.57	3.13	6	2.43	0.36	6	0.88	0.02	5	0.48	0.14	5
Lungs	0.77	0.41	6	1.39	0.87	6	0.22	0.04	6	0.08	0.01	6	0.05	0.02	5
Heart	0.17	0.04	6	0.43	0.25	6	0.05	0.01	6	0.02	0.00	6	0.02	0.00	5
Tumor	14.30	2.51	6	5.86	2.89	6	15.20	1.34	6	9.39	1.80	6	4.00	1.26	5
Muscle	0.12	0.06	5	0.31	0.13	6	0.02	0.00	5	0.01	0.01	6	0.01	0.00	5
Bone	0.21	0.08	6	0.67	0.37	6	0.06	0.05	6	0.03	0.01	6	0.03	0.01	5
Brain	0.01	0.00	5	0.05	0.02	6	0.01	0.00	5	0.00	0.00	5	0.00	0.00	5
Stomach	0.18	0.12	6	0.24	0.08	6	0.03	0.00	6	0.10	0.08	6	0.16	0.26	4

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<u>[¹⁷⁷Lu]Lu-BL34</u>	1 h			1 h blocked			4 h			24 h			72 h		
	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n
Ratios															
Tumour:Blood	33.10	7.42	6	8.74	7.47	6	476.00	181.00	6	988.00	490.00	6	993.00	927.00	5
Tumour:Liver	20.50	3.69	6	7.77	5.22	6	21.10	3.40	6	17.70	1.43	6	10.40	3.24	5
Tumour:Spleen	41.40	13.40	6	9.13	8.20	5	56.10	12.90	6	42.40	6.04	5	12.70	4.01	5
Tumour:Muscle	155.00	81.80	5	24.02	16.12	6	861.00	134.00	5	814.00	325.00	6	776.00	457.00	5
Tumour:Bone	78.50	33.10	6	13.02	11.82	6	340.00	200.00	6	353.00	145.00	6	149.00	40.30	5
Tumour:Lung	21.20	7.70	6	6.87	6.16	6	72.30	15.40	6	122.30	22.60	6	90.60	23.00	5

[00502] Table 8. Biodistribution data (%ID/g) of [⁶⁸Ga]Ga-BL36 in Z138 tumor-bearing mice at selected time points.

<u>[⁶⁸Ga]Ga-BL36</u>	1 h			2 h		
	Mean	SD	n	Mean	SD	n
Blood	0.39	0.02	2	0.16	0.02	2
Fat	0.03	0.00	2	0.01	0.00	2
Testes	0.28	0.07	2	0.08	0.01	2
Intestine	0.34	0.01	2	0.20	0.00	2
Stomach	0.05	0.01	2	0.02	0.01	2
Spleen	0.35	0.06	2	0.25	0.02	2
Liver	0.68	0.07	2	0.71	0.03	2
Pancreas	0.08	0.01	2	0.04	0.00	2
Adrenals	0.14	0.06	2	0.03	0.01	2
Kidney	2.98	0.28	2	2.66	0.49	2
Lung	0.68	0.09	2	0.39	0.00	2
Heart	0.14	0.01	2	0.07	0.02	2
Muscle	0.10	0.00	2	0.03	0.00	2
Bone	0.20	0.14	2	0.07	0.00	2
Brain	0.01	0.00	2	0.01	0.00	2
Tumor	12.19	0.78	2	10.35	1.09	2
Ratios						
Tumor:Blood	31.30	0.52	2	64.40	2.19	2
Tumor:Liver	18.07	0.77	2	16.17	2.22	2
Tumor:Spleen	35.06	3.83	2	46.93	8.01	2
Tumor:Muscle	119.04	11.24	2	337.03	13.67	2
Tumor:Bone	77.38	48.78	2	143.14	6.81	2
Tumor:Lung	18.00	1.15	2	28.69	2.97	2
Tumor:Kidney	4.10	0.12	2	4.82	1.15	2

[00503] Table 9. Biodistribution data (%ID/g) of [⁶⁸Ga]Ga-BL37 in Z138 tumor-bearing mice at selected time points. Mice in the 1 h blocked group received an injection of 7.5 µg of LY2510924 (i.p.) 15 min before tracer administration.

<u>[⁶⁸Ga]Ga-BL37</u>	1 h			1 h blocked			2 h		
	Mean	SD	n	Mean	SD	n	Mean	SD	n
Blood	0.50	0.13	3	1.10	NA	1	0.18	0.02	4
Fat	0.05	0.02	3	0.11	NA	1	0.05	0.01	4
Testes	0.15	0.03	3	0.30	NA	1	0.07	0.01	4
Intestine	0.27	0.13	3	0.51	NA	1	0.15	0.04	4
Stomach	0.07	0.03	3	0.09	NA	1	0.04	0.02	4
Spleen	0.26	0.05	3	0.33	NA	1	0.26	0.06	4
Liver	0.65	0.05	3	0.65	NA	1	0.69	0.09	4
Pancreas	0.11	0.03	3	0.23	NA	1	0.07	0.02	4
Adrenals	0.42	0.48	3	0.59	NA	1	0.13	0.06	4
Kidney	3.20	0.34	3	4.79	NA	1	2.83	0.18	4
Lung	0.57	0.08	3	1.06	NA	1	0.29	0.04	4
Heart	0.17	0.05	3	0.33	NA	1	0.08	0.02	4
Muscle	0.09	0.02	3	0.19	NA	1	0.08	0.04	4
Bone	0.16	0.04	3	0.19	NA	1	0.16	0.08	4
Brain	0.04	0.03	3	0.03	NA	1	0.01	0.00	4
Tumor	6.15	0.56	3	0.75	NA	1	4.51	0.74	4
Ratios									
Tumor:Blood	12.73	2.57	3	1.46	NA	1	25.35	1.23	4
Tumor:Liver	9.43	0.53	3	2.46	NA	1	6.51	0.27	4
Tumor:Spleen	24.31	4.01	3	4.81	NA	1	18.13	5.65	4
Tumor:Muscle	68.67	12.44	3	8.66	NA	1	62.92	16.27	4
Tumor:Bone	38.59	5.76	3	8.51	NA	1	39.30	34.86	4
Tumor:Lung	10.76	0.71	3	1.51	NA	1	15.76	1.35	4
Tumor:Kidney	1.93	0.24	3	0.34	NA	1	1.59	0.23	4

[00504] **Table 10.** Biodistribution data (%ID/g) of [^{18}F]BL40 in Z138 tumor-bearing mice at selected time points. Mice in the 1 h blocked group received an injection of 7.5 μg of LY2510924 (i.p.) 15 min before tracer administration.

<u>[^{18}F]BL40</u>	1 h			1 h blocked			2 h		
	Mean	SD	n	Mean	SD	n	Mean	SD	n
Blood	0.42	0.14	5	1.36	0.62	4	0.07	0.01	6
Fat	0.08	0.06	5	0.23	0.11	4	0.03	0.01	6
Testes	0.18	0.07	5	0.37	0.17	4	0.06	0.01	6
Intestines	0.31	0.09	5	0.42	0.18	4	0.14	0.05	6
Spleen	0.49	0.14	5	0.75	0.27	4	0.30	0.02	6
Liver	0.97	0.05	5	0.86	0.23	4	0.96	0.19	6
Pancreas	0.15	0.07	5	1.32	0.36	4	0.10	0.08	6
Adrenal glands	0.27	0.11	5	0.41	0.18	4	0.21	0.11	6
Kidney	3.14	0.35	5	0.76	0.56	4	2.76	0.28	6
Lungs	0.64	0.18	5	13.62	7.48	4	0.27	0.02	6
Heart	0.16	0.03	5	1.60	0.64	4	0.06	0.01	6
Z138	21.13	2.09	5	0.48	0.17	4	20.72	1.92	6
Muscle	0.11	0.05	5	5.75	1.79	4	0.06	0.02	6
Bone	0.31	0.15	5	0.31	0.14	4	0.31	0.16	6
Brain	0.02	0.01	5	0.70	0.32	4	0.03	0.04	6
Stomach	0.19	0.15	5	0.05	0.01	4	0.06	0.01	6
Ratios									
Tumor:Blood	54.28	12.76	5	5.06	2.85	4	298.10	57.49	6
Tumor:Liver	21.86	2.15	5	4.47	1.39	4	22.16	3.81	6
Tumor:Spleen	45.03	10.08	5	7.63	2.94	4	69.73	8.27	6
Tumor:Muscle	207.70	73.53	5	21.49	11.85	4	381.50	90.28	6
Tumor:Bone	80.68	34.58	5	10.08	5.92	4	76.47	26.76	6
Tumor:Lung	34.94	8.74	5	4.18	2.31	4	76.59	9.20	6
Tumor:Kidney	6.76	0.66	5	0.60	0.47	4	7.55	0.92	6

[00505] Table 11. Biodistribution data (%ID/g) of [^{18}F]BL41 in Z138 tumor-bearing mice at selected time points. Mice in the 1 h blocked group received an injection of 7.5 μg of LY2510924 (i.p.) 15 min before tracer administration.

<u>[^{18}F]BL41</u>	1 h			1 h blocked			2 h		
	Mean	SD	n	Mean	SD	n	Mean	SD	n
Blood	0.37	0.06	3	1.20	0.86	4	0.09	0.01	7
Fat	0.05	0.01	3	0.18	0.11	4	0.03	0.02	7
Testes	0.15	0.04	3	0.32	0.13	4	0.05	0.01	7
Intestines	0.26	0.04	3	0.60	0.16	4	0.17	0.06	7
Spleen	0.46	0.08	3	0.71	0.22	4	0.36	0.06	7
Liver	0.73	0.14	3	0.86	0.22	4	0.73	0.11	7
Pancreas	0.11	0.02	3	0.69	0.65	4	0.07	0.02	7
Adrenal glands	0.18	0.07	3	0.75	0.33	4	0.12	0.04	7
Kidney	2.83	0.43	3	5.57	3.13	4	2.25	0.24	7
Lungs	0.77	0.18	3	1.39	0.87	4	0.35	0.13	7
Heart	0.16	0.04	3	0.43	0.25	4	0.06	0.01	7
Z138	16.90	3.25	3	5.86	2.89	4	17.62	1.85	6
Muscle	0.12	0.03	3	0.31	0.13	4	0.13	0.03	7
Bone	0.25	0.02	3	0.67	0.37	4	0.21	0.05	7
Brain	0.03	0.01	3	0.05	0.02	4	0.05	0.04	7
Stomach	0.09	0.03	3	0.24	0.08	4	0.07	0.03	7
Ratios									
Tumor:Blood	46.01	7.45	3	8.74	7.47	4	198.30	18.88	7
Tumor:Liver	23.15	1.88	3	7.77	5.22	4	24.50	3.29	7
Tumor:Spleen	37.16	7.35	3	9.13	8.20	4	49.39	8.94	7
Tumor:Muscle	147.30	46.31	3	24.02	16.12	4	146.80	41.09	7
Tumor:Bone	67.49	8.07	3	13.02	11.82	4	88.06	19.37	7
Tumor:Lung	23.18	8.03	3	6.87	6.16	4	53.31	11.47	7
Tumor:Kidney	5.94	0.40	3	1.63	1.40	4	7.87	0.63	7

[00506] Table 12. Biodistribution data (%ID/g) of [⁶⁸Ga]Ga-BL42 in Z138 tumor-bearing mice at selected time points.

<u>[⁶⁸Ga]Ga-BL42</u>	1 h		
	Mean	SD	n
Blood	0.43	0.05	3
Fat	0.08	0.02	3
Testes	0.18	0.04	3
Intestines	0.36	0.03	3
Spleen	4.67	1.22	3
Liver	15.50	2.29	3
Pancreas	0.16	0.02	3
Adrenal glands	0.96	0.18	3
Kidney	6.11	1.39	3
Lungs	2.80	2.04	3
Heart	0.24	0.01	3
Z138	16.26	1.34	3
Muscle	0.18	0.03	3
Bone	2.51	1.55	3
Brain	0.03	0.02	3
Stomach	0.16	0.02	3
Ratios			
Tumor:Blood	37.93	6.98	3
Tumor:Liver	1.06	0.18	3
Tumor:Spleen	3.61	0.82	3
Tumor:Muscle	91.81	23.29	3
Tumor:Bone	9.83	8.54	3
Tumor:Lung	8.00	4.99	3
Tumor:Kidney	2.75	0.68	3

[00507] **Table 13.** Biodistribution data (%ID/g) of [⁶⁸Ga]Ga-BL43 in Z138 tumor-bearing mice at selected time points.

<u>[⁶⁸Ga]Ga-BL43</u>	<u>1 h</u>		
	Mean	SD	n
Blood	0.63	0.27	5
Fat	0.15	0.08	5
Testes	0.29	0.12	5
Intestines	0.48	0.11	5
Spleen	0.45	0.16	5
Liver	1.92	0.40	5
Pancreas	0.20	0.13	5
Adrenal glands	0.25	0.14	5
Kidney	4.48	1.46	5
Lungs	0.89	0.27	5
Heart	0.28	0.12	5
Z138	11.81	2.42	5
Muscle	0.23	0.18	5
Bone	0.34	0.16	5
Brain	0.02	0.01	5
Stomach	0.16	0.07	5
Ratios			
Tumor:Blood	20.60	6.85	5
Tumor:Liver	6.25	1.17	5
Tumor:Spleen	28.27	9.20	5
Tumor:Muscle	79.03	48.29	5
Tumor:Bone	39.49	15.03	5
Tumor:Lung	13.94	3.60	5
Tumor:Kidney	2.78	0.80	5

[00508] **Table 14.** Biodistribution data (%ID/g) of [⁶⁸Ga]Ga-BL44 in Z138 tumor-bearing mice at selected time points.

[00509]

<u>[⁶⁸Ga]Ga-BL44</u>	1 h		
	Mean	SD	n
Blood	0.26	0.08	3
Fat	0.09	0.03	3
Testes	0.16	0.07	3
Intestines	0.19	0.04	3
Spleen	0.20	0.03	3
Liver	0.50	0.07	3
Pancreas	0.07	0.02	3
Adrenal glands	0.16	0.06	3
Kidney	2.47	0.21	3
Lungs	0.41	0.10	3
Heart	0.10	0.02	3
Z138	18.35	1.76	3
Muscle	0.16	0.17	3
Bone	0.23	0.11	3
Brain	0.02	0.00	3
Stomach	0.05	0.01	3
Ratios			
Tumor:Blood	73.09	15.89	3
Tumor:Liver	36.78	3.31	3
Tumor:Spleen	92.14	19.84	3
Tumor:Muscle	221.68	171.40	3
Tumor:Bone	91.52	34.62	3
Tumor:Lung	46.07	9.46	3
Tumor:Kidney	7.45	0.51	3

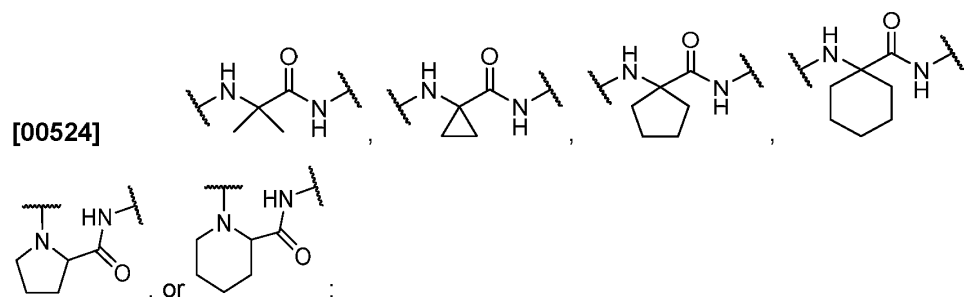
[00510] Table 15. Biodistribution data (%ID/g) of [⁶⁸Ga]Ga-BL45 in Z138 tumor-bearing mice at selected time points.

<u>[⁶⁸Ga]Ga-BL45</u>	<u>1 h</u>		
	<u>Mean</u>	<u>SD</u>	<u>n</u>
Blood	0.46	0.11	3
Fat	0.04	0.01	2
Testes	0.39	0.20	3
Intestines	0.31	0.08	3
Spleen	0.22	0.05	3
Liver	0.40	0.02	3
Pancreas	0.14	0.04	3
Adrenal glands	0.23	0.17	3
Kidney	2.84	0.14	3
Lungs	0.48	0.06	3
Heart	0.15	0.04	3
Z138	14.39	5.01	3
Muscle	0.35	0.25	3
Bone	0.19	0.09	3
Brain	0.02	0.00	3
Stomach	0.06	0.01	3
Ratios			
Tumor:Blood	31.04	4.36	3
Tumor:Liver	36.07	10.76	3
Tumor:Spleen	64.39	16.76	3
Tumor:Muscle	51.16	24.92	3
Tumor:Bone	87.49	39.63	3
Tumor:Lung	30.41	12.13	3
Tumor:Kidney	5.12	2.02	3

[00521] either R^{6a} is absent, methyl, ethyl, -C≡CH, -CH=CH₂, -C≡C-(CH₂)₁₋₃-OH, -C≡C-(CH₂)₁₋₃-SH, -C≡C-(CH₂)₁₋₃-NH₂, -C≡C-(CH₂)₁₋₃-COOH, -C≡C-(CH₂)₁₋₃-CONH-, -C≡C-(CH₂)₁₋₃R^{6b}R^{6c}, -CH=CH-(CH₂)₁₋₃-OH, -CH=CH-(CH₂)₁₋₃-SH, -CH=CH-(CH₂)₁₋₃-NH₂, -CH=CH-(CH₂)₁₋₃-COOH, -CH=CH-(CH₂)₁₋₃-CONH-, -CH=CH-(CH₂)₁₋₃R^{6b}R^{6c}, -CH₂-R^{6b}-OH, -CH₂-R^{6b}-COOH, -CH₂-(R^{6b})₁₋₃-NH₂, -CH₂-R^{6b}-CONH-, or -CH₂-R^{6b}R^{6c}, wherein each R^{6b} is independently absent, -CH₂-, -NH-, -S- or -O-, and wherein R^{6c} is:

[00522] a 5 or 6 membered aromatic ring wherein one or more carbons are optionally independently replaced by N, S, and/or O heteroatoms, and optionally substituted with one or more groups independently selected from oxo, hydroxyl, sulfhydryl, nitro, amino, and/or halogen;

[00523] or -NH-CH(R^{6a})-C(O)-NH- is replaced with:

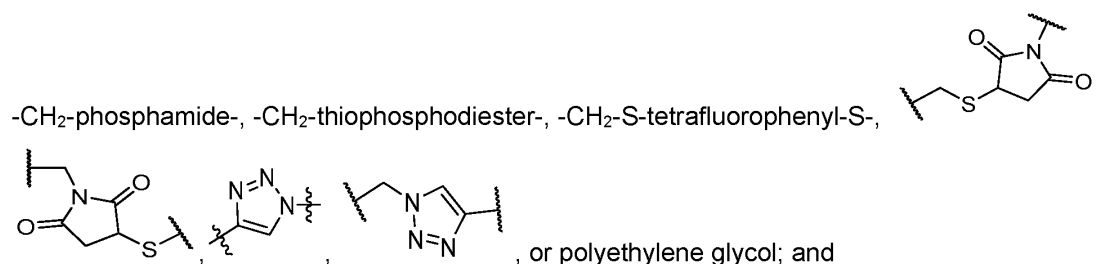


[00525] R^{A7a} is a linear C₁-C₅ alkylenyl wherein 0-2 carbons in C₂-C₅ are independently replaced with one or more N, S, and/or O heteroatoms;

[00526] R^{8a} is R^{8b}R^{8c} wherein R^{8b} is a linear C₁-C₅ alkylenyl, alkenylenyl, or alkynylenyl, in which 0-2 carbons in C₂-C₅ are independently replaced with one or more N, S, and/or O heteroatoms, wherein R^{8c} is -N(R^{8d})₂₋₃ or guanidino, wherein each R^{8d} is independently -H or a linear or branched C₁-C₃ alkyl;

[00527] R^{9a} is: -C(O)NH₂, -C(O)-OH, -CH₂-C(O)NH₂, -CH₂-C(O)-OH, -CH₂-NH₂, -CH₂-OH, -CH₂-CH₂-NH₂, -R^{9b}-R^{9c}, or -R^{9b}-[linker]-R^X_{n1}, wherein:

[00528] R^{9b} is -CH₂-NH-C(O)-, -CH₂-C(O)-, -CH₂-O-, -C(O)NH-, -C(O)-N(CH₃)-, -CH₂-NHC(S)-, -C(S)NH-, -CH₂-N(CH₃)C(S)-, -C(O)N(CH₃)-, -CH₂-N(CH₃)C(O)-, -C(S)N(CH₃)-, -CH₂-NHC(S)NH-, -CH₂-NHC(O)NH-, -CH₂-S-, -CH₂-S(O)-, -CH₂-S(O)₂-, -CH₂-S(O)₂-NH-, -CH₂-S(O)-NH-, -CH₂-Se-, -CH₂-Se(O)-, -CH₂-Se(O)₂-, -CH₂-NHNHC(O)-, -C(O)NHNH-, -CH₂-OP(O)(O')O-,



[00529] R^{9c} is hydrogen or a linear, branched, and/or cyclic C₁-C₂₀ alkyl, alkenyl or alkynyl, wherein 0-6 carbons in C₂-C₂₀ are independently replaced by N, S, and/or O heteroatoms, and substituted with 0-3 groups independently selected from one or a combination of oxo, hydroxyl, sulfhydryl, halogen, guanidino, carboxylic acid, sulfonic acid, sulfinic acid, and/or phosphoric acid;

[00530] R^{A10} is absent or -[linker]-R^X_{n1};

[00531] when R^{A10} is absent, then R^{A1a} is:

[00532] a linear C₁-C₅ alkyl, alkenyl, or alkynyl, wherein 0-2 carbons in C₂-C₅ are independently replaced by one or more N, S, and/or O heteroatoms, optionally C-substituted with a single substituent selected from: -SH, -OH, amino, carboxy, guanidino, -NH-C(O)-CH₃, -S-C(O)-CH₃, -O-C(O)-CH₃, -NH-C(O)-(phenyl), -S-C(O)-(phenyl), -O-C(O)-(phenyl), -NH-(CH₃)₁₋₂, -NH₂-CH₃, -N(CH₃)₂₋₃, -S-CH₃, or -O-CH₃;

[00533] a branched C₁-C₁₀ alkyl, alkenyl, or alkynyl, wherein 0-3 carbons in C₂-C₁₀ are independently replaced by one or more N, S, and/or O heteroatoms; or

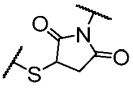
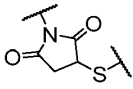
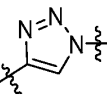
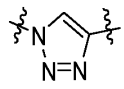
[00534] R^{A1b}R^{A1c}, wherein R^{A1b} is a linear C₁-C₃ alkyl, wherein C₂ alkyl or C₃ alkyl is optionally replaced with a N, S, or O heteroatom, wherein R^{A1c} is:

[00535] a 5 or 6 membered aromatic ring wherein one or more carbons are optionally independently replaced by N, S, and/or O heteroatoms, and optionally substituted with one or more groups independently selected from oxo, hydroxyl, sulfhydryl, nitro, amino, and/or halogen; or

[00536] a fused bicyclic or fused tricyclic aryl group wherein one or more carbons are optionally independently replaced by N, S, and/or O heteroatoms, and optionally substituted with one or more groups independently selected from halogen, -OH, -OR^{A1d}, amino, -NHR^{A1d}, and/or N(R^{A1d})₂, wherein each R^{A1d} is independently a C₁-C₃ linear or branched alkyl group;

[00537] when R^{A10} is -[linker]-R^X_{n1}, then R^{A1a} is R^{A1e}R^{A1f}, wherein R^{A1e} is a linear C₁-C₅ alkyl, alkenyl, or alkynyl, in which 0-2 carbons in C₂-C₅ are independently replaced with N, S, and/or O heteroatoms, and R^{A1f} is -NH-C(O)-, -C(O)-, -O-, -C(O)NH-, -C(O)-N(CH₃)-, -NHC(S)-, -C(S)NH-, -N(CH₃)C(S)-, -C(O)N(CH₃)-, -N(CH₃)C(O)-, -C(S)N(CH₃)-, -NHC(S)NH-, -

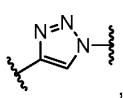
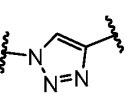
NHC(O)NH-, -S-, -S(O)-, -S(O)-O-, -S(O)₂-, -S(O)₂-O-, -S(O)₂-NH-, -S(O)-NH-, -Se-, -Se(O)-, -Se(O)₂-, -NHNHC(O)-, -C(O)NHNH-, -OP(O)(O-)O-, -phosphamide-, -thiophosphodiester-, -S-

tetrafluorophenyl-S-, , , , , or polyethylene glycol;

[00538] each n1 is independently 0, 1 or 2;

[00539] each R^x is an albumin binder, a therapeutic moiety, a fluorescent label, a radiolabeled group, or a group capable of being radiolabelled;

[00540] wherein 0-3 peptide backbone amides are independently replaced with

[00541] , , or thioamide;

[00542] wherein 0-3 peptide backbone amides are N-methylated;

[00543] with the proviso that Formula A excludes the following combination:

[00544] -NH-CH(R^{2a})-C(O)- forms a Tyr residue;

[00545] -NH-CH(R^{4a})-C(O)- forms a D-Arg residue;

[00546] -NH-CH(R^{5a})-C(O)- forms a 2Nal residue; and

[00547] R^{6a} is absent.

[00548] 2. The compound of Embodiment 1, wherein -NH-CH(R^{A1a})-C(O)- forms an L-amino acid residue.

[00549] 3. The compound of Embodiment 1 or 2, wherein R^{A10} is absent.

[00550] 4. The compound of Embodiment 3, wherein R^{A1a} is a linear C₁-C₅ alkyl, alkenyl, or alkynyl, optionally substituted with a single substituent selected from: -SH, -OH, amino, carboxy, guanidino, -NH-C(O)-CH₃, -S-C(O)-CH₃, -O-C(O)-CH₃, -NH-C(O)-(phenyl), -S-C(O)-(phenyl), -O-C(O)-(phenyl), -NH-(CH₃)₁₋₂, -NH₂-CH₃, -N(CH₃)₂₋₃, -S-CH₃, or -O-CH₃.

[00551] 5. The compound of Embodiment 3, wherein R^{A1a} is a linear C₁-C₅ alkyl optionally substituted with a single substituent selected from: -SH, -OH, amino, carboxy, guanidino, -NH-C(O)-CH₃, -S-C(O)-CH₃, -O-C(O)-CH₃, -NH-C(O)-(phenyl), -S-C(O)-(phenyl), -O-C(O)-(phenyl), -NH-(CH₃)₁₋₂, -NH₂-CH₃, -N(CH₃)₂₋₃, -S-CH₃, or -O-CH₃.

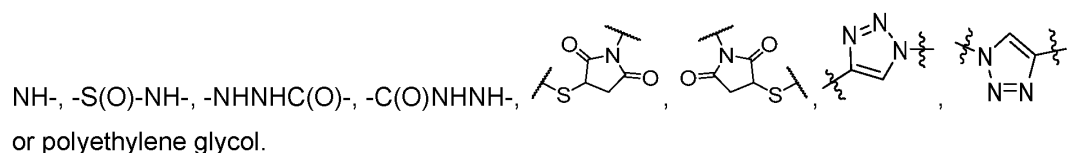
[00552] 6. The compound of Embodiment 3, wherein R^{A1a} is a branched C₁-C₁₀ alkyl, alkenyl, or alkynyl.

[00553] 7. The compound of Embodiment 3, wherein R^{A1a} is a branched C₁-C₁₀ alkyl.

[00554] 8. The compound of Embodiment 3, wherein R^{A1a} is R^{A1b}R^{A1c}.

[00555] 9. The compound of Embodiment 8, wherein R^{A1b} is a linear C₁-C₃ alkyl.

- [00556] 10. The compound of Embodiment 8 or 9, wherein R^{A1c} is a 5 or 6 membered aromatic ring wherein 0-4 carbons are independently replaced by N, S, and/or O heteroatoms, and substituted with 0-4 groups independently selected from oxo, hydroxyl, sulfhydryl, nitro, amino, and/or halogen.
- [00557] 11. The compound of Embodiment 8 or 9, wherein R^{A1c} is a fused bicyclic or fused tricyclic aryl group wherein 0-6 carbons are independently replaced by N, S, and/or O heteroatoms, and optionally substituted with 0-6 groups independently selected from halogen, -OH, $-OR^{A1d}$, amino, $-NHR^{A1d}$, and/or $N(R^{A1d})_2$.
- [00558] 12. The compound of any one of Embodiments 1 to 3, wherein $-NH-CH(R^{A1a})-C(O)-$ forms a Phe residue.
- [00559] 13. The compound of any one of Embodiments 1 to 3, wherein $-NH-CH(R^{A1a})-C(O)-$ forms a 1-Nal residue.
- [00560] 14. The compound of any one of Embodiments 1 to 3, wherein $-NH-CH(R^{A1a})-C(O)-$ forms a 2-Nal residue.
- [00561] 15. The compound of any one of Embodiments 1 to 3, wherein $-NH-CH(R^{A1a})-C(O)-$ forms a Tyr residue.
- [00562] 16. The compound of any one of Embodiments 1 to 3, wherein $-NH-CH(R^{A1a})-C(O)-$ forms a Trp residue.
- [00563] 17. The compound of any one of Embodiments 1 to 3, wherein $-NH-CH(R^{A1a})-C(O)-$ forms a Lys(Ac) residue.
- [00564] 18. The compound of Embodiment 1 or 2, wherein R^{A10} is $-[linker]-R^{X_{n1}}$.
- [00565] 19. The compound of Embodiment 18, wherein R^{A1e} is a linear C_1-C_5 alkylenyl, alkenylenyl, or alkynylenyl
- [00566] 20. The compound of Embodiment 18, wherein R^{A1e} is a linear C_1-C_5 alkylenyl.
- [00567] 21. The compound of any one of Embodiments 18 to 20, wherein R^{A1f} is $-NH-C(O)-$, $-C(O)-$, $-O-$, $-C(O)NH-$, $-C(O)-N(CH_3)-$, $-NHC(S)-$, $-C(S)NH-$, $-N(CH_3)C(S)-$, $-C(O)N(CH_3)-$, $-N(CH_3)C(O)-$, $-C(S)N(CH_3)-$, $-NHC(S)NH-$, $-NHC(O)NH-$, $-S-$, $-S(O)-$, $-S(O)-O-$, $-S(O)_2-$, $-S(O)_2-$

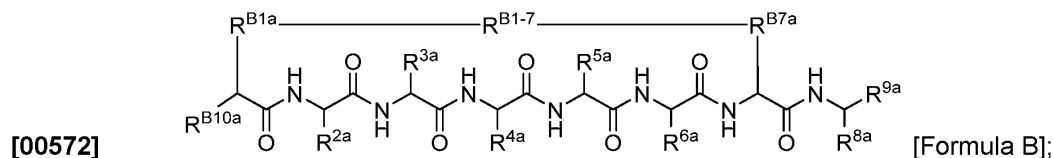


- [00568] 22. The compound of any one of Embodiments 1 to 21, wherein $-NH-CH(R^{A7a})-C(O)-$ forms a D-amino acid residue.

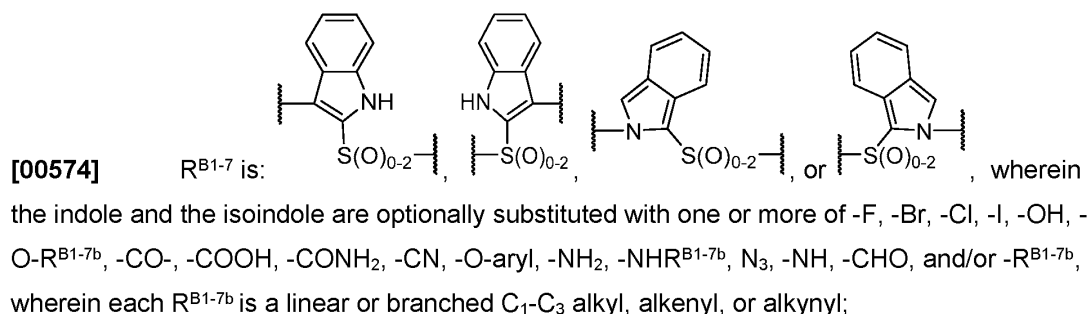
[00569] 23. The compound of any one of Embodiments 1 to 22, wherein R^{A7a} is C_1 - C_3 alkenyl.

[00570] 24. The compound of Embodiment 23, wherein R^{A7a} is $-\text{CH}_2\text{CH}_2-$.

[00571] 25. A compound of Formula B or a salt or solvate of Formula B:



[00573] R^{B1a} is a linear, branched, and/or cyclic C_1 - C_{10} alkenyl, alkenyl, or alkynyl, wherein one or more carbons in C_2 - C_{10} are optionally independently replaced with N, S, and/or O heteroatoms;



[00575] R^{B7a} is a linear C_1 - C_5 alkenyl wherein 0-2 carbons in C_2 - C_5 are independently replaced with one or more N, S, and/or O heteroatoms;

[00576] R^{2a} is $-(\text{CH}_2)-(\text{R}^{2b})-(\text{phenyl})$, wherein R^{2b} is absent, $-\text{CH}_2-$, $-\text{NH}-$, $-\text{S}-$ or $-\text{O}-$, wherein the phenyl is 4-substituted with $-\text{NH}_2$, $-\text{NO}_2$, $-\text{OH}$, $-\text{OR}^{2c}$, $-\text{SH}$, $-\text{SR}^{2c}$, or $-\text{O-phenyl}$, wherein the phenyl is optionally 3-substituted with halogen or $-\text{OH}$, wherein the phenyl is optionally 5-substituted with halogen or $-\text{OH}$, wherein the $-\text{O-phenyl}$ ring is optionally 4-substituted with $-\text{NH}_2$, $-\text{NO}_2$, $-\text{OH}$, $-\text{OR}^{2c}$, $-\text{SH}$, or $-\text{SR}^{2c}$, wherein the $-\text{O-phenyl}$ ring is optionally 3-substituted with halogen or $-\text{OH}$, wherein the $-\text{O-phenyl}$ ring is optionally 5-substituted with halogen or $-\text{OH}$, wherein each R^{2c} is independently a C_1 - C_3 linear or branched alkyl group;

[00577] R^{3a} is $R^{3b}R^{3c}$ wherein R^{3b} is a linear C_1 - C_5 alkenyl, alkenyl, or alkynyl, wherein 0-2 carbons in C_2 - C_5 are independently replaced with one or more N, S, and/or O heteroatoms, wherein R^{3c} is $-\text{N}(\text{R}^{3d})_{2-3}$ or guanidino, wherein each R^{3d} is independently $-\text{H}$ or a linear or branched C_1 - C_3 alkyl;

[00578] R^{4a} is $R^{4b}R^{4c}$ wherein R^{4b} is a linear C_1 - C_5 alkenyl, alkenyl, or alkynyl, in which 0-2 carbons in C_2 - C_5 are independently replaced with one or more N, S, and/or O

heteroatoms, wherein R^{4c} is $-N(R^{4d})_{2-3}$ or guanidino, wherein each R^{4d} is independently -H or a linear or branched C_{1-3} alkyl;

[00579] R^{5a} is $-(CH_2)_{1-3}-R^{5b}$, wherein 1 carbon in $-(CH_2)_{2-3}-$ is optionally replaced with a N, S, or O heteroatom, wherein R^{5b} is:

[00580] phenyl optionally substituted with one or a combination of the following: 4-substituted with $-NH_2$, $-NO_2$, $-OH$, $-OR^{5c}$, $-SH$, $-SR^{5c}$, or $-O$ -phenyl; 3-substituted with halogen or $-OH$; and/or 5-substituted with halogen or $-OH$; wherein the $-O$ -phenyl ring is optionally 4-substituted with $-NH_2$, $-NO_2$, $-OH$, $-OR^{5c}$, $-SH$, or $-SR^{5c}$, wherein the $-O$ -phenyl ring is optionally 3-substituted with halogen or $-OH$, wherein the $-O$ -phenyl ring is optionally 5-substituted with halogen or $-OH$; or

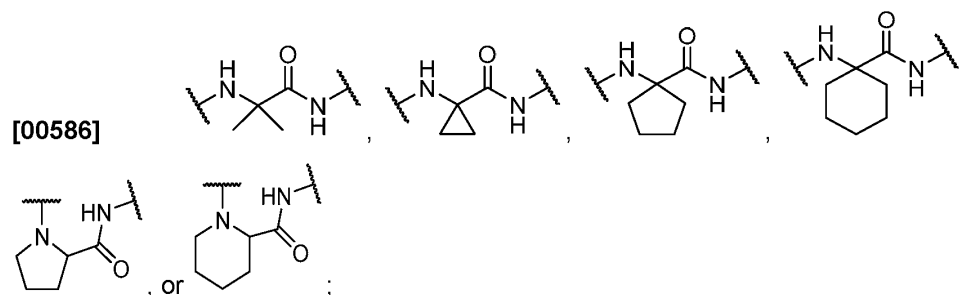
[00581] a fused bicyclic or fused tricyclic aryl group wherein one or more carbons are optionally independently replaced by N, S, and/or O heteroatoms, and optionally independently substituted with one or a combination of halogen, $-OH$, $-OR^{5c}$, amino, $-NHR^{5c}$, and/or $N(R^{5c})_2$;

[00582] wherein each R^{5c} is independently a C_{1-3} linear or branched alkyl group;

[00583] either R^{6a} is absent, methyl, ethyl, $-C\equiv CH$, $-CH=CH_2$, $-C\equiv C-(CH_2)_{1-3}-OH$, $-C\equiv C-(CH_2)_{1-3}-SH$, $-C\equiv C-(CH_2)_{1-3}-NH_2$, $-C\equiv C-(CH_2)_{1-3}-COOH$, $-C\equiv C-(CH_2)_{1-3}-CONH$, $-C\equiv C-(CH_2)_{1-3}-R^{6b}R^{6c}$, $-CH=CH-(CH_2)_{1-3}-OH$, $-CH=CH-(CH_2)_{1-3}-SH$, $-CH=CH-(CH_2)_{1-3}-NH_2$, $-CH=CH-(CH_2)_{1-3}-COOH$, $-CH=CH-(CH_2)_{1-3}-CONH$, $-CH=CH-(CH_2)_{1-3}-R^{6b}R^{6c}$, $-CH_2-R^{6b}-OH$, $-CH_2-R^{6b}-COOH$, $-CH_2-(R^{6b})_{1-3}-NH_2$, $-CH_2-R^{6b}-CONH$, or $-CH_2-R^{6b}-R^{6c}$, wherein each R^{6b} is independently absent, $-CH_2-$, $-NH-$, $-S-$ or $-O-$, and wherein R^{6c} is:

[00584] a 5 or 6 membered aromatic ring wherein one or more carbons are optionally independently replaced by N, S, and/or O heteroatoms, and optionally substituted with one or more groups independently selected from oxo, hydroxyl, sulfhydryl, nitro, amino, and/or halogen;

[00585] or $-NH-CH(R^{6a})-C(O)-NH-$ is replaced with:



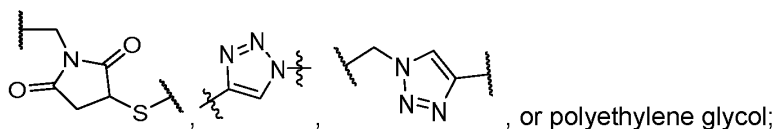
[00587] R^{8a} is $R^{8b}R^{8c}$ wherein R^{8b} is a linear C_{1-5} alkylenyl, alkenylenyl, or alkynylenyl, in which 0-2 carbons in C_{2-5} are independently replaced with one or more N, S, and/or O

heteroatoms, wherein R^{8c} is $-N(R^{8d})_{2-3}$ or guanidino, wherein each R^{8d} is independently -H or a linear or branched C_1 - C_3 alkyl;

[00588] R^{9a} is: $-C(O)NH_2$, $-C(O)-OH$, $-CH_2-C(O)NH_2$, $-CH_2-C(O)-OH$, $-CH_2-NH_2$, $-CH_2-OH$, $-CH_2-CH_2-NH_2$, $-R^{9b}-R^{9c}$, or $-R^{9b}-[linker]-R^{X_{n1}}$, wherein:

[00589] R^{9b} is $-CH_2-NH-C(O)-$, $-CH_2-C(O)-$, $-CH_2-O-$, $-C(O)NH-$, $-C(O)-N(CH_3)-$, $-CH_2-NHC(S)-$, $-C(S)NH-$, $-CH_2-N(CH_3)C(S)-$, $-C(O)N(CH_3)-$, $-CH_2-N(CH_3)C(O)-$, $-C(S)N(CH_3)-$, $-CH_2-NHC(S)NH-$, $-CH_2-NHC(O)NH-$, $-CH_2-S-$, $-CH_2-S(O)-$, $-CH_2-S(O)_2-$, $-CH_2-S(O)_2-NH-$, $-CH_2-S(O)-NH-$, $-CH_2-Se-$, $-CH_2-Se(O)-$, $-CH_2-Se(O)_2-$, $-CH_2-NHNHC(O)-$, $-C(O)NHNH-$, $-CH_2-OP(O)(O)O-$,

$-CH_2$ -phosphamide-, $-CH_2$ -thiophosphodiester-, $-CH_2$ -S-tetrafluorophenyl-S-,



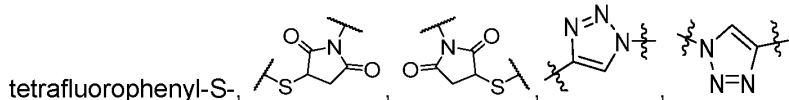
, or polyethylene glycol;

[00590] R^{9c} is hydrogen or a linear, branched, and/or cyclic C_1 - C_{20} alkyl, alkenyl or alkynyl, wherein 0-6 carbons in C_2 - C_{20} are independently replaced by N, S, and/or O heteroatoms, and substituted with 0-3 groups independently selected from one or a combination of oxo, hydroxyl, sulfhydryl, halogen, guanidino, carboxylic acid, sulfonic acid, sulfinic acid, and/or phosphoric acid;

[00591] R^{B10a} is: amine, $-NH-(CH_3)_{1-2}$, $-N(CH_3)_{2-3}$, $-NH-C(O)-CH_3$, $-NH-C(O)-(phenyl)$, or $-R^{B10b}-[linker]-R^{X_{n1}}$ wherein R^{B10b} is:

[00592] $-NH-C(O)-$, $-C(O)-$, $-O-$, $-C(O)NH-$, $-C(O)-N(CH_3)-$, $-NHC(S)-$, $-C(S)NH-$, $-N(CH_3)C(S)-$, $-C(O)N(CH_3)-$, $-N(CH_3)C(O)-$, $-C(S)N(CH_3)-$, $-NHC(S)NH-$, $-NHC(O)NH-$, $-S-$, $-S(O)-$, $-S(O)-O-$, $-S(O)_2-$, $-S(O)_2-O-$, $-S(O)_2-NH-$, $-S(O)-NH-$, $-Se-$, $-Se(O)-$, $-Se(O)_2-$, $-NHNHC(O)-$, $-C(O)NHNH-$, $-OP(O)(O)O-$, $-phosphamide-$, $-thiophosphodiester-$, $-S-$

tetrafluorophenyl-S-,

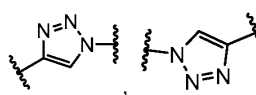


, or polyethylene glycol;

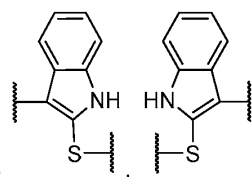
[00593] each $n1$ is independently 0, 1 or 2;

[00594] each R^X is an albumin binder, a therapeutic moiety, a fluorescent label, a radiolabeled group, or a group capable of being radiolabeled;

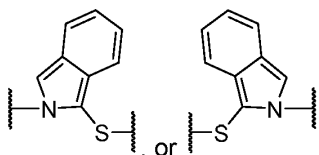
[00595] wherein 0-3 peptide backbone amides are independently replaced with

[00596] , or thioamide; and

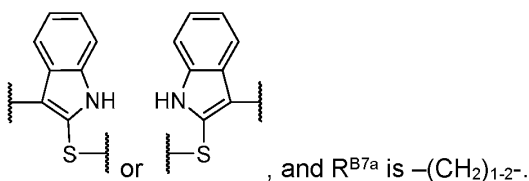
[00597] wherein 0-3 peptide backbone amides are N-methylated.



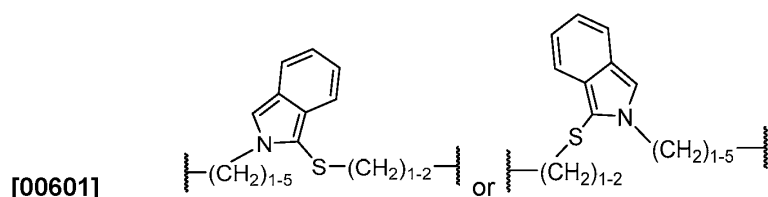
[00598] 26. The compound of Embodiment 25, wherein R^{B1-7} is



[00599] 27. The compound of Embodiment 25, wherein R^{B1a} is $-(CH_2)_{1-2}$, R^{B1-7} is



[00600] 28. The compound of Embodiment 25, wherein R^{B1a} - R^{B1-7} - R^{B7a} is



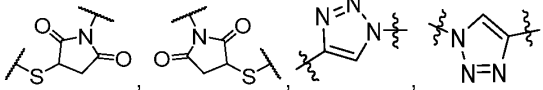
[00601] 29. The compound of any one of Embodiments 25 to 28, wherein $-NH-CH(R^{B7a})-C(O)-$ forms a D-amino acid residue.

[00603] 30. The compound of any one of Embodiments 25 to 29, wherein R^{B10a} is: amine, $-NH-(CH_3)_{1-2}$, $-N(CH_3)_{2-3}$, $-NH-C(O)-CH_3$, or $-NH-C(O)-(phenyl)$.

[00604] 31. The compound of any one of Embodiments 25 to 29, wherein R^{B10a} is $-R^{B10b}-[linker]-R^{X_{n1}}$.

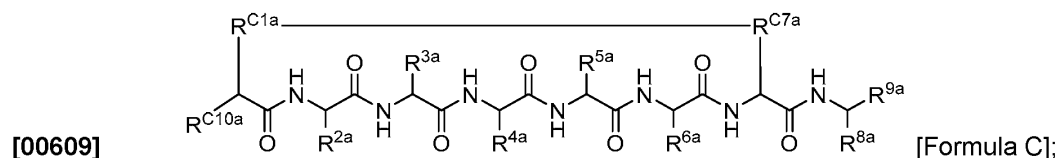
[00605] 32. The compound of Embodiment 31, wherein R^{B10b} is:

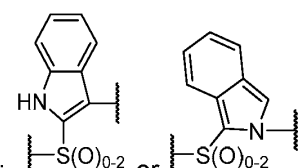
[00606] $-NH-C(O)-$, $-C(O)-$, $-O-$, $-C(O)NH-$, $-C(O)-N(CH_3)-$, $-NHC(S)-$, $-C(S)NH-$, $-N(CH_3)C(S)-$, $-C(O)N(CH_3)-$, $-N(CH_3)C(O)-$, $-C(S)N(CH_3)-$, $-NHC(S)NH-$, $-NHC(O)NH-$, $-$

$NHNHC(O)-$, $-C(O)NHNH-$, , or polyethylene glycol.

[00607] 33. The compound of Embodiment 31, wherein R^{B10a} is $-NHC(O)-[linker]-R^{X_{n1}}$ or $-N(CH_3)C(O)-[linker]-R^{X_{n1}}$.

[00608] 34. A compound of Formula C or a salt or solvate of Formula C:



[00610] R^{C1a} is: , wherein the indole and the isoindole are optionally substituted with one or more of -F, -Br, -Cl, -I, -OH, -O- R^{C1b} , -CO-, -COOH, -CONH₂, -CN, -O-aryl, -NH₂, -NHR^{C1b}, N₃, -NH-, -CHO, and/or - R^{C1b} , wherein each R^{C1b} is a linear or branched C₁-C₃ alkyl, alkenyl, or alkynyl;

[00611] R^{2a} is $-(CH_2)-(R^{2b})-(phenyl)$, wherein R^{2b} is absent, -CH₂-, -NH-, -S- or -O-, wherein the phenyl is 4-substituted with -NH₂, -NO₂, -OH, -OR^{2c}, -SH, -SR^{2c}, or -O-phenyl, wherein the phenyl is optionally 3-substituted with halogen or -OH, wherein the phenyl is optionally 5-substituted with halogen or -OH, wherein the -O-phenyl ring is optionally 4-substituted with -NH₂, -NO₂, -OH, -OR^{2c}, -SH, or -SR^{2c}, wherein the -O-phenyl ring is optionally 3-substituted with halogen or -OH, wherein the -O-phenyl ring is optionally 5-substituted with halogen or -OH, wherein each R^{2c} is independently a C₁-C₃ linear or branched alkyl group;

[00612] R^{3a} is $R^{3b}R^{3c}$ wherein R^{3b} is a linear C₁-C₅ alkynyl, alkenyl, or alkynyl, wherein 0-2 carbons in C₂-C₅ are independently replaced with one or more N, S, and/or O heteroatoms, wherein R^{3c} is $-N(R^{3d})_{2-3}$ or guanidino, wherein each R^{3d} is independently -H or a linear or branched C₁-C₃ alkyl;

[00613] R^{4a} is $R^{4b}R^{4c}$ wherein R^{4b} is a linear C₁-C₅ alkynyl, alkenyl, or alkynyl, in which 0-2 carbons in C₂-C₅ are independently replaced with one or more N, S, and/or O heteroatoms, wherein R^{4c} is $-N(R^{4d})_{2-3}$ or guanidino, wherein each R^{4d} is independently -H or a linear or branched C₁-C₃ alkyl;

[00614] R^{5a} is $-(CH_2)_{1-3}-R^{5b}$, wherein 1 carbon in $-(CH_2)_{2-3}-$ is optionally replaced with a N, S, or O heteroatom, wherein R^{5b} is:

[00615] phenyl optionally substituted with one or a combination of the following: 4-substituted with -NH₂, -NO₂, -OH, -OR^{5c}, -SH, -SR^{5c}, or -O-phenyl; 3-substituted with halogen or -OH; and/or 5-substituted with halogen or -OH; wherein the -O-phenyl ring is optionally 4-

substituted with $-\text{NH}_2$, $-\text{NO}_2$, $-\text{OH}$, $-\text{OR}^{5c}$, $-\text{SH}$, or $-\text{SR}^{5c}$, wherein the -O-phenyl ring is optionally 3-substituted with halogen or $-\text{OH}$, wherein the -O-phenyl ring is optionally 5-substituted with halogen or $-\text{OH}$; or

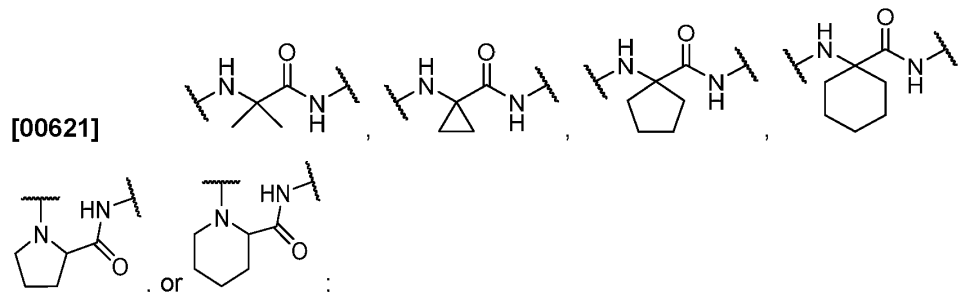
[00616] a fused bicyclic or fused tricyclic aryl group wherein one or more carbons are optionally independently replaced by N, S, and/or O heteroatoms, and optionally independently substituted with one or a combination of halogen, $-\text{OH}$, $-\text{OR}^{5c}$, amino, $-\text{NHR}^{5c}$, and/or $\text{N}(\text{R}^{5c})_2$;

[00617] wherein each R^{5c} is independently a C_1 - C_3 linear or branched alkyl group;

[00618] either R^{6a} is H, methyl, ethyl, $-\text{C}\equiv\text{CH}$, $-\text{CH}=\text{CH}_2$, $-\text{C}\equiv\text{C}-(\text{CH}_2)_{1-3}-\text{OH}$, $-\text{C}\equiv\text{C}-(\text{CH}_2)_{1-3}-\text{SH}$, $-\text{C}\equiv\text{C}-(\text{CH}_2)_{1-3}-\text{NH}_2$, $-\text{C}\equiv\text{C}-(\text{CH}_2)_{1-3}-\text{COOH}$, $-\text{C}\equiv\text{C}-(\text{CH}_2)_{1-3}-\text{CONH}$, $-\text{C}\equiv\text{C}-(\text{CH}_2)_{1-3}-\text{R}^{6b}\text{R}^{6c}$, $-\text{CH}=\text{CH}-(\text{CH}_2)_{1-3}-\text{OH}$, $-\text{CH}=\text{CH}-(\text{CH}_2)_{1-3}-\text{SH}$, $-\text{CH}=\text{CH}-(\text{CH}_2)_{1-3}-\text{NH}_2$, $-\text{CH}=\text{CH}-(\text{CH}_2)_{1-3}-\text{COOH}$, $-\text{CH}=\text{CH}-(\text{CH}_2)_{1-3}-\text{CONH}$, $-\text{CH}=\text{CH}-(\text{CH}_2)_{1-3}-\text{R}^{6b}\text{R}^{6c}$, $-\text{CH}_2-\text{R}^{6b}-\text{OH}$, $-\text{CH}_2-\text{R}^{6b}-\text{COOH}$, $-\text{CH}_2-(\text{R}^{6b})_{1-3}-\text{NH}_2$, $-\text{CH}_2-\text{R}^{6b}-\text{CONH}$, or $-\text{CH}_2-\text{R}^{6b}\text{R}^{6c}$, wherein each R^{6b} is independently absent, $-\text{CH}_2-$, $-\text{NH}-$, $-\text{S}-$ or $-\text{O}-$, and wherein R^{6c} is:

[00619] a 5 or 6 membered aromatic ring wherein one or more carbons are optionally independently replaced by N, S, and/or O heteroatoms, and optionally substituted with one or more groups independently selected from oxo, hydroxyl, sulfhydryl, nitro, amino, and/or halogen;

[00620] or $-\text{NH}-\text{CH}(\text{R}^{6a})-\text{C}(\text{O})-\text{NH}-$ is replaced with:

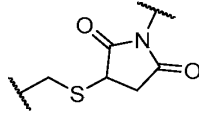


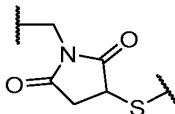
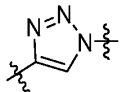
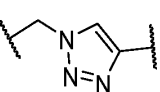
[00622] R^{C7a} is a linear C_1 - C_5 alkylenyl wherein optionally 0-2 carbons in C_2 - C_5 are independently replaced with one or more N, S, and/or O heteroatoms;

[00623] R^{8a} is $\text{R}^{8b}\text{R}^{8c}$ wherein R^{8b} is a linear C_1 - C_5 alkylenyl, alkenylenyl, or alkynylenyl, in which 0-2 carbons in C_2 - C_5 are independently replaced with one or more N, S, and/or O heteroatoms, wherein R^{8c} is $-\text{N}(\text{R}^{8d})_{2-3}$ or guanidino, wherein each R^{8d} is independently $-\text{H}$ or a linear or branched C_1 - C_3 alkyl;

[00624] R^{9a} is: $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})-\text{OH}$, $-\text{CH}_2-\text{C}(\text{O})\text{NH}_2$, $-\text{CH}_2-\text{C}(\text{O})-\text{OH}$, $-\text{CH}_2-\text{NH}_2$, $-\text{CH}_2-\text{OH}$, $-\text{CH}_2-\text{CH}_2-\text{NH}_2$, $-\text{R}^{9b}-\text{R}^{9c}$, or $-\text{R}^{9b}-[\text{linker}]-\text{R}^{9c}$, wherein:

[00625] R^{9b} is $-\text{CH}_2\text{-NH-C(O)-}$, $-\text{CH}_2\text{-C(O)-}$, $-\text{CH}_2\text{-O-}$, $-\text{C(O)NH-}$, $-\text{C(O)-N(CH}_3\text{)-}$, $-\text{CH}_2\text{-NHC(S)-}$, $-\text{C(S)NH-}$, $-\text{CH}_2\text{-N(CH}_3\text{)C(S)-}$, $-\text{C(O)N(CH}_3\text{)-}$, $-\text{CH}_2\text{-N(CH}_3\text{)C(O)-}$, $-\text{C(S)N(CH}_3\text{)-}$, $-\text{CH}_2\text{-NHC(S)NH-}$, $-\text{CH}_2\text{-NHC(O)NH-}$, $-\text{CH}_2\text{-S-}$, $-\text{CH}_2\text{-S(O)-}$, $-\text{CH}_2\text{-S(O)}_2\text{-}$, $-\text{CH}_2\text{-S(O)}_2\text{-NH-}$, $-\text{CH}_2\text{-S(O)-NH-}$, $-\text{CH}_2\text{-Se-}$, $-\text{CH}_2\text{-Se(O)-}$, $-\text{CH}_2\text{-Se(O)}_2\text{-}$, $-\text{CH}_2\text{-NHNHC(O)-}$, $-\text{C(O)NHNH-}$, $-\text{CH}_2\text{-OP(O)(O-)O-}$,

$-\text{CH}_2\text{-phosphamide-}$, $-\text{CH}_2\text{-thiophosphodiester-}$, $-\text{CH}_2\text{-S-tetrafluorophenyl-S-}$, ,

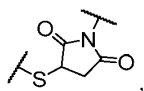
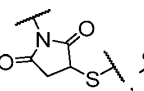
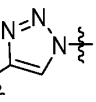
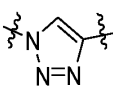
, , , or polyethylene glycol; and

[00626] R^{9c} is hydrogen or a linear, branched, and/or cyclic $\text{C}_1\text{-C}_{20}$ alkyl, alkenyl or alkynyl, wherein 0-6 carbons in $\text{C}_2\text{-C}_{20}$ are independently replaced by N, S, and/or O heteroatoms, and substituted with 0-3 groups independently selected from one or a combination of oxo, hydroxyl, sulfhydryl, halogen, guanidino, carboxylic acid, sulfonic acid, sulfinic acid, and/or phosphoric acid;

[00627] $\text{R}^{\text{C}10a}$ is $\text{R}^{\text{C}10b}\text{-R}^{\text{C}10c}\text{-[linker]-R}^{\text{X}}_{n1}$ or $\text{R}^{\text{C}10d}$, wherein:

[00628] $\text{R}^{\text{C}10b}$ is a linear $\text{C}_1\text{-C}_5$ alkynyl, alkenyl, or alkynyl, in which 0-2 carbons in $\text{C}_2\text{-C}_5$ are independently replaced with N, S, and/or O heteroatoms;

[00629] $\text{R}^{\text{C}10c}$ is $-\text{NH-C(O)-}$, $-\text{C(O)-}$, $-\text{O-}$, $-\text{C(O)NH-}$, $-\text{C(O)-N(CH}_3\text{)-}$, $-\text{NHC(S)-}$, $-\text{C(S)NH-}$, $-\text{N(CH}_3\text{)C(S)-}$, $-\text{C(O)N(CH}_3\text{)-}$, $-\text{N(CH}_3\text{)C(O)-}$, $-\text{C(S)N(CH}_3\text{)-}$, $-\text{NHC(S)NH-}$, $-\text{NHC(O)NH-}$, $-\text{S-}$, $-\text{S(O)-}$, $-\text{S(O)-O-}$, $-\text{S(O)}_2\text{-}$, $-\text{S(O)}_2\text{-O-}$, $-\text{S(O)}_2\text{-NH-}$, $-\text{S(O)-NH-}$, $-\text{Se-}$, $-\text{Se(O)-}$, $-\text{Se(O)}_2\text{-}$, $-\text{NHNHC(O)-}$, $-\text{C(O)NHNH-}$, $-\text{OP(O)(O-)O-}$, $-\text{phosphamide-}$, $-\text{thiophosphodiester-}$, $-\text{S-}$

, , , , or polyethylene glycol; and

[00630] $\text{R}^{\text{C}10d}$ is:

[00631] a linear $\text{C}_1\text{-C}_5$ alkyl, alkenyl, or alkynyl, wherein 0-2 carbons in $\text{C}_2\text{-C}_5$ are independently replaced by N, S, and/or O heteroatoms, optionally C-substituted with a single substituent selected from: $-\text{SH}$, $-\text{OH}$, amino, carboxy, guanidino, $-\text{NH-C(O)-CH}_3$, $-\text{S-C(O)-CH}_3$, $-\text{O-C(O)-CH}_3$, $-\text{NH-C(O)-(phenyl)}$, $-\text{S-C(O)-(phenyl)}$, $-\text{O-C(O)-(phenyl)}$, $-\text{NH-(CH}_3\text{)}_{1-2}$, $-\text{NH}_2\text{-CH}_3$, $-\text{N(CH}_3\text{)}_{2-3}$, $-\text{S-CH}_3$, or $-\text{O-CH}_3$;

[00632] a branched $\text{C}_1\text{-C}_{10}$ alkyl, alkenyl, or alkynyl, wherein 0-3 carbons in $\text{C}_2\text{-C}_{10}$ are independently replaced by N, S, and/or O heteroatoms; or

[00633] $R^{C10e}R^{C10f}$, wherein R^{C10e} is a linear C_1 - C_3 alkyl, wherein C_2 alkyl or C_3 alkyl is optionally replaced with N, S, or O heteroatom, wherein R^{C10f} is:

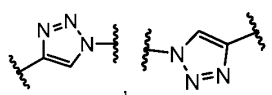
[00634] a 5 or 6 membered aromatic ring wherein one or more carbons are optionally independently replaced by N, S, and/or O heteroatoms, and optionally substituted with one or more groups independently selected from oxo, hydroxyl, sulfhydryl, nitro, amino, and/or halogen;

[00635] a fused bicyclic or fused tricyclic aryl group wherein one or more carbons are optionally independently replaced by N, S, and/or O heteroatoms, and optionally substituted with one or more groups independently selected from halogen, -OH, -OR^{C10g}, amino, -NHR^{C10g}, and/or N(R^{C10g})₂, wherein R^{C10g} is C_1 - C_3 linear or branched alkyl;

[00636] each n_1 is independently 0, 1 or 2;

[00637] each R^X is an albumin binder, a therapeutic moiety, a fluorescent label, a radiolabeled group, or a group capable of being radiolabelled;

[00638] wherein 0-3 peptide backbone amides are independently replaced with

[00639] , or thioamide; and

[00640] wherein 0-3 peptide backbone amides are N-methylated.

[00641] 35. The compound of Embodiment 34, wherein -NH-CH(R^{C7a})-C(O)- forms a D-amino acid residue.

[00642] 36. The compound of Embodiment 34 or 35, wherein R^{C7a} is a linear C_1 - C_5 alkylenyl.

[00643] 37. The compound of Embodiment 34 or 35, wherein R^{C7a} is -(CH₂)₁₋₂-.

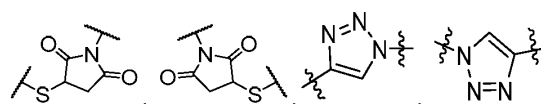
[00644] 38. The compound of any one of Embodiments 34 to 37, wherein R^{C10a} is R^{C10b} - R^{C10c} -[linker]- R^X .

[00645] 39. The compound of Embodiment 38, wherein R^{C10b} is a linear C_1 - C_5 alkylenyl, alkenylenyl, or alkynylenyl.

[00646] 40. The compound of Embodiment 38, wherein R^{C10b} is a linear C_1 - C_5 alkylenyl.

[00647] 41. The compound of any one of Embodiment 38 to 40, wherein R^{C10c} is:

[00648] -NH-C(O)-, -C(O)-, -O-, -C(O)NH-, -C(O)-N(CH₃)-, -NHC(S)-, -C(S)NH-, -N(CH₃)C(S)-, -C(O)N(CH₃)-, -N(CH₃)C(O)-, -C(S)N(CH₃)-, -NHC(S)NH-, -NHC(O)NH-, -

NHNHC(O)-, -C(O)NHNH-, , or polyethylene glycol.

- [00649] 42. The compound of any one of Embodiments 38 to 40, wherein R^{C10c} is –NHC(O)- or -N(CH₃)C(O)-.
- [00650] 43. The compound of any one of Embodiments 34 to 37, wherein R^{C10a} is R^{C10d} .
- [00651] 44. The compound of Embodiment 43, wherein R^{C10d} is a linear C₁-C₅ alkyl, alkenyl, or alkynyl, wherein 0-2 carbons in C₂-C₅ are independently replaced by N, S, and/or O heteroatoms, optionally C-substituted with a single substituent selected from: -SH, -OH, amino, carboxy, guanidino, -NH-C(O)-CH₃, -S-C(O)-CH₃, -O-C(O)-CH₃, -NH-C(O)-(phenyl), -S-C(O)-(phenyl), -O-C(O)-(phenyl), -NH-(CH₃)₁₋₂, -NH₂-CH₃, -N(CH₃)₂₋₃, -S-CH₃, or -O-CH₃.
- [00652] 45. The compound of Embodiment 43, wherein R^{C10d} is a linear C₁-C₅ alkyl, alkenyl, or alkynyl, optionally C-substituted with a single substituent selected from: -SH, -OH, amino, carboxy, guanidino, -NH-C(O)-CH₃, -S-C(O)-CH₃, -O-C(O)-CH₃, -NH-C(O)-(phenyl), -S-C(O)-(phenyl), -O-C(O)-(phenyl), -NH-(CH₃)₁₋₂, -NH₂-CH₃, -N(CH₃)₂₋₃, -S-CH₃, or -O-CH₃.
- [00653] 46. The compound of Embodiment 43, wherein R^{C10d} is a linear C₁-C₅ alkyl optionally C-substituted with a single substituent selected from: -SH, -OH, amino, carboxy, guanidino, -NH-C(O)-CH₃, -S-C(O)-CH₃, -O-C(O)-CH₃, -NH-C(O)-(phenyl), -S-C(O)-(phenyl), -O-C(O)-(phenyl), -NH-(CH₃)₁₋₂, -NH₂-CH₃, -N(CH₃)₂₋₃, -S-CH₃, or -O-CH₃.
- [00654] 47. The compound of Embodiment 43, wherein R^{C10d} is a branched C₁-C₁₀ alkyl, alkenyl, or alkynyl, wherein 0-3 carbons in C₂-C₁₀ are independently replaced by N, S, and/or O heteroatoms.
- [00655] 48. The compound of Embodiment 43, wherein R^{C10d} is a branched C₁-C₁₀ alkyl, alkenyl, or alkynyl.
- [00656] 49. The compound of Embodiment 43, wherein R^{C10d} is a branched C₁-C₁₀ alkyl.
- [00657] 50. The compound of Embodiment 43, wherein R^{C10d} is $R^{C10e}R^{C10f}$.
- [00658] 51. The compound of Embodiment 50, wherein R^{C10e} is a linear C₁-C₃ alkyl.
- [00659] 52. The compound of Embodiment 50 or 51, wherein R^{C10f} is a 5 or 6 membered aromatic ring wherein 0-4 carbons are independently replaced by N, S, and/or O heteroatoms, and substituted with 0-4 groups independently selected from oxo, hydroxyl, sulfhydryl, nitro, amino, and/or halogen.
- [00660] 53. The compound of Embodiment 50 or 51, wherein R^{C10f} is a fused bicyclic or fused tricyclic aryl group wherein 0-6 carbons are independently replaced by N, S, and/or O heteroatoms, and substituted with 0-6 groups independently selected from halogen, -OH, -OR^{C10g}, amino, -NHR^{C10g}, and/or N(R^{C10g})₂, wherein R^{C10g} is C₁-C₃ linear or branched alkyl.
- [00661] 54. The compound of Embodiment 53, wherein R^{C10g} is methyl.

- [00662]** 55. The compound of any one of Embodiments 1 to 54, wherein zero peptide backbone amides are replaced.
- [00663]** 56. The compound of any one of Embodiments 1 to 55, wherein zero peptide backbone amides are N-methylated.
- [00664]** 57. The compound of any one of Embodiments 1 to 56, wherein R^{2b} is absent or $-CH_2-$.
- [00665]** 58. The compound of any one of Embodiments 1 to 56 wherein R^{2a} is $-(CH_2)-(R^{2b})-(phenyl)$, wherein R^{2b} is absent or $-CH_2-$, wherein the phenyl is 4-substituted with $-NH_2$, $-NO_2$, $-OH$, $-SH$, or $-O-phenyl$.
- [00666]** 59. The compound of any one of Embodiments 1 to 58, wherein $-NH-CH(R^{2a})-C(O)-$ forms an L-amino acid residue.
- [00667]** 60. The compound of any one of Embodiments 1 to 58, wherein $-NH-CH(R^{2a})-C(O)-$ forms a Tyr residue.
- [00668]** 61. The compound of any one of Embodiments 1 to 58, wherein $-NH-CH(R^{2a})-C(O)-$ forms a Phe residue.
- [00669]** 62. The compound of any one of Embodiments 1 to 58, wherein $-NH-CH(R^{2a})-C(O)-$ forms a (4- NO_2)-Phe residue.
- [00670]** 63. The compound of any one of Embodiments 1 to 58, wherein $-NH-CH(R^{2a})-C(O)-$ forms a (4- NH_2)-Phe residue.
- [00671]** 64. The compound of any one of Embodiments 1 to 58, wherein $-NH-CH(R^{2a})-C(O)-$ forms a hTyr residue.
- [00672]** 65. The compound of any one of Embodiments 1 to 58, wherein $-NH-CH(R^{2a})-C(O)-$ forms a (3-I)Tyr residue.
- [00673]** 66. The compound of any one of Embodiments 1 to 58, wherein $-NH-CH(R^{2a})-C(O)-$ forms a Glu residue.
- [00674]** 67. The compound of any one of Embodiments 1 to 58, wherein $-NH-CH(R^{2a})-C(O)-$ forms a Gln residue.
- [00675]** 68. The compound of any one of Embodiments 1 to 58, wherein $-NH-CH(R^{2a})-C(O)-$ forms a D-Tyr residue.
- [00676]** 69. The compound of any one of Embodiments 1 to 68, wherein R^{3a} is $R^{3b}R^{3c}$, wherein R^{3b} is a linear C_1-C_5 alkylenyl, alkenylenyl, or alkynylenyl, wherein R^{3c} is $-N(R^{3d})_{2-3}$ or guanidino, wherein each R^{3d} is independently $-H$ or a linear or branched C_1-C_3 alkyl.
- [00677]** 70. The compound of any one of Embodiments 1 to 69, wherein R^{3b} is a linear C_1-C_5 alkylenyl, alkenylenyl, or alkynylenyl.

- [00678] 71. The compound of any one of Embodiments 1 to 69, wherein R^{3b} is a linear C_1 - C_5 alkylenyl.
- [00679] 72. The compound of any one of Embodiments 1 to 71, wherein each R^{3d} is independently -H or methyl.
- [00680] 73. The compound of any one of Embodiments 1 to 71, wherein R^{3c} is $-NH_2$ or $-NH_3$.
- [00681] 74. The compound of any one of Embodiments 1 to 71, wherein R^{3c} is guanidino.
- [00682] 75. The compound of any one of Embodiments 1 to 74, wherein $-NH-CH(R^{3a})-C(O)-$ forms an L-amino acid residue.
- [00683] 76. The compound of any one of Embodiments 1 to 74, wherein $-NH-CH(R^{3a})-C(O)-$ forms a Lys(iPr) residue.
- [00684] 77. The compound of any one of Embodiments 1 to 74, wherein $-NH-CH(R^{3a})-C(O)-$ forms a Arg(Me)₂ (asymmetrical) residue.
- [00685] 78. The compound of any one of Embodiments 1 to 74, wherein $-NH-CH(R^{3a})-C(O)-$ forms a Arg(Me) residue.
- [00686] 79. The compound of any one of Embodiments 1 to 78, wherein R^{4a} is $R^{4b}R^{4c}$, wherein R^{4b} is a linear C_1 - C_5 alkylenyl, alkenylenyl, or alkynylenyl, wherein R^{4c} is $-N(R^{4d})_{2-3}$ or guanidino, wherein each R^{4d} is independently -H or a linear or branched C_1 - C_3 alkyl.
- [00687] 80. The compound of any one of Embodiments 1 to 79, wherein R^{4b} is a linear C_1 - C_5 alkylenyl, alkenylenyl, or alkynylenyl.
- [00688] 81. The compound of any one of Embodiments 1 to 79, wherein R^{4b} is a linear C_1 - C_5 alkylenyl.
- [00689] 82. The compound of any one of Embodiments 1 to 81, wherein each R^{4d} is independently -H or methyl.
- [00690] 83. The compound of any one of Embodiments 1 to 81, wherein R^{4c} is $-NH_2$ or $-NH_3$.
- [00691] 84. The compound of any one of Embodiments 1 to 81, wherein R^{4c} is guanidino.
- [00692] 85. The compound of any one of Embodiments 1 to 78, wherein $-NH-CH(R^{4a})-C(O)-$ forms a D-amino acid residue.
- [00693] 86. The compound of any one of Embodiments 1 to 78, wherein $-NH-CH(R^{4a})-C(O)-$ forms a D-Arg residue.
- [00694] 87. The compound of any one of Embodiments 1 to 78, wherein $-NH-CH(R^{4a})-C(O)-$ forms a D-hArg residue.

[00695] 88. The compound of any one of Embodiments 1 to 87, wherein R^{5a} is $-\text{CH}_2\text{-R}^{5b}$, $-\text{CH}_2\text{-CH}_2\text{-R}^{5b}$, or $-\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-R}^{5b}$.

[00696] 89. The compound of any one of Embodiments 1 to 88, wherein R^{5b} is phenyl optionally substituted with one or a combination of the following: 4-substituted with $-\text{NH}_2$, $-\text{NO}_2$, $-\text{OH}$, $-\text{OR}^{5c}$, $-\text{SH}$, $-\text{SR}^{5c}$, or $-\text{O-phenyl}$; 3-substituted with halogen or $-\text{OH}$; and/or 5-substituted with halogen or $-\text{OH}$; wherein the $-\text{O-phenyl}$ ring is optionally 4-substituted with $-\text{NH}_2$, $-\text{NO}_2$, $-\text{OH}$, $-\text{OR}^{5c}$, $-\text{SH}$, or $-\text{SR}^{5c}$, wherein the $-\text{O-phenyl}$ ring is optionally 3-substituted with halogen or $-\text{OH}$, wherein the $-\text{O-phenyl}$ ring is optionally 5-substituted with halogen or $-\text{OH}$.

[00697] 90. The compound of any one of Embodiments 1 to 88, wherein R^{5b} is phenyl optionally substituted with one or a combination of the following: 4-substituted with $-\text{NH}_2$, $-\text{NO}_2$, $-\text{OH}$, $-\text{SH}$, or $-\text{O-phenyl}$; 3-substituted with halogen or $-\text{OH}$; and/or 5-substituted with halogen or $-\text{OH}$.

[00698] 91. The compound of any one of Embodiments 1 to 88, wherein R^{5b} is a fused bicyclic or fused tricyclic aryl group wherein one or more carbons are optionally independently replaced by N, S, and/or O heteroatoms, and optionally independently substituted with one or a combination of halogen, $-\text{OH}$, $-\text{OR}^{5c}$, amino, $-\text{NHR}^{5c}$, and/or $\text{N}(\text{R}^{5c})_2$.

[00699] 92. The compound of any one of Embodiments 1 to 88, wherein R^{5b} is a fused bicyclic or fused tricyclic aryl group wherein 0-3 carbons are independently replaced by N, S, and/or O heteroatoms, and optionally independently substituted with one or a combination of halogen, $-\text{OH}$, and/or amino.

[00700] 93. The compound of any one of Embodiments 1 to 88, wherein R^{5b} excludes 9-linked anthracenyl.

[00701] 94. The compound of any one of Embodiments 1 to 87, wherein $-\text{NH-CH}(\text{R}^{5a})\text{-C}(\text{O})\text{-}$ forms an L-amino acid residue.

[00702] 95. The compound of any one of Embodiments 1 to 87, wherein $-\text{NH-CH}(\text{R}^{5a})\text{-C}(\text{O})\text{-}$ forms a 2-(Ant)Ala residue.

[00703] 96. The compound of any one of Embodiments 1 to 87, wherein $-\text{NH-CH}(\text{R}^{5a})\text{-C}(\text{O})\text{-}$ forms a 2-Nal residue.

[00704] 97. The compound of any one of Embodiments 1 to 87, wherein $-\text{NH-CH}(\text{R}^{5a})\text{-C}(\text{O})\text{-}$ forms a Trp residue.

[00705] 98. The compound of any one of Embodiments 1 to 87, wherein $-\text{NH-CH}(\text{R}^{5a})\text{-C}(\text{O})\text{-}$ forms a (4- NH_2)Phe residue.

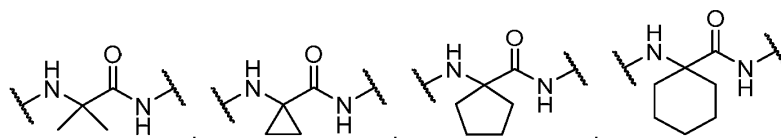
[00706] 99. The compound of any one of Embodiments 1 to 87, wherein $-\text{NH-CH}(\text{R}^{5a})\text{-C}(\text{O})\text{-}$ forms a hTyr residue.

[00707] 100. The compound of any one of Embodiments 1 to 87, wherein -NH-CH(R^{5a})-C(O)- forms a Tyr residue.

[00708] 101. The compound of any one of Embodiments 1 to 100, wherein R^{6a} is absent or methyl, ethyl, -C≡CH, -CH=CH₂, -CH₂-R^{6b}-OH, -CH₂-R^{6b}-COOH, -CH₂-(R^{6b})₁₋₃-NH₂, -CH₂-R^{6b}-CONH, or -CH₂-R^{6b}R^{6c}, wherein each R^{6b} is independently absent, -CH₂-, -NH-, -S- or -O-.

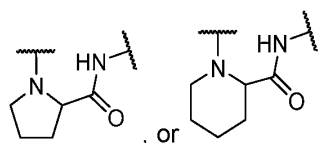
[00709] 102. The compound of any one of Embodiments 1 to 101, wherein R^{6c} is a 5 or 6 membered aromatic ring wherein 0-3 carbons are independently replaced by N, S, and/or O heteroatoms, and optionally substituted with 0-3 groups independently selected from oxo, hydroxyl, sulfhydryl, nitro, amino, and/or halogen.

[00710] 103. The compound of any one of Embodiments 1 to 101, wherein -NH-CH(R^{6a})-C(O)-NH- is replaced with:



[00711]

[00712] 104. The compound of any one of Embodiments 1 to 101, wherein -NH-CH(R^{6a})-C(O)-NH- is replaced with:



[00713]

[00714] 105. The compound of any one of Embodiments 1 to 101, wherein R^{6a} is absent.

[00715] 106. The compound of any one of Embodiments 1 to 102, wherein -NH-CH(R^{6a})-C(O)- forms a D-amino acid residue.

[00716] 107. The compound of any one of Embodiments 1 to 102, wherein -NH-CH(R^{6a})-C(O)- forms a His residue.

[00717] 108. The compound of any one of Embodiments 1 to 102, wherein -NH-CH(R^{6a})-C(O)- forms a D-His residue.

[00718] 109. The compound of any one of Embodiments 1 to 102, wherein -NH-CH(R^{6a})-C(O)- forms a D-Glu residue.

[00719] 110. The compound of any one of Embodiments 1 to 102, wherein -NH-CH(R^{6a})-C(O)- forms a D-Gln residue.

[00720] 111. The compound of any one of Embodiments 1 to 102, wherein -NH-CH(R^{6a})-C(O)- forms a D-Ala residue.

[00721] 112. The compound of any one of Embodiments 1 to 102, wherein -NH-CH(R^{6a})-C(O)- forms a D-Phe residue.

[00722] 113. The compound of any one of Embodiments 1 to 102, wherein -NH-CH(R^{6a})-C(O)- forms a D-Ser residue.

[00723] 114. The compound of any one of Embodiments 1 to 102, wherein -NH-CH(R^{6a})-C(O)- forms a D-Dab residue.

[00724] 115. The compound of any one of Embodiments 1 to 102, wherein -NH-CH(R^{6a})-C(O)- forms a D-Dap residue.

[00725] 116. The compound of any one of Embodiments 1 to 115, wherein R^{8a} is R^{8b}R^{8c}, wherein R^{8b} is a linear C₁-C₅ alkylenyl, alkenylenyl, or alkynylenyl, wherein R^{8c} is -N(R^{8d})₂₋₃ or guanidino, wherein each R^{8d} is independently -H or a linear or branched C₁-C₃ alkyl.

[00726] 117. The compound of any one of Embodiments 1 to 116, wherein R^{8b} is a linear C₁-C₅ alkylenyl, alkenylenyl, or alkynylenyl.

[00727] 118. The compound of any one of Embodiments 1 to 116, wherein R^{8b} is a linear C₁-C₅ alkylenyl.

[00728] 119. The compound of any one of Embodiments 1 to 118, wherein each R^{8d} is independently -H or methyl.

[00729] 120. The compound of any one of Embodiments 1 to 118, wherein R^{8c} is -NH₂ or -NH₃.

[00730] 121. The compound of any one of Embodiments 1 to 118, wherein R^{8c} is guanidino.

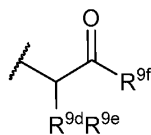
[00731] 122. The compound of any one of Embodiments 1 to 121, wherein -NH-CH(R^{8a})-C(O)- forms an L-amino acid residue.

[00732] 123. The compound of any one of Embodiments 1 to 115, wherein -NH-CH(R^{8a})-C(O)- forms a Lys(iPr) residue.

[00733] residue.

[00734] 124. The compound of any one of Embodiments 1 to 141, wherein R^{9a} is: -C(O)NH₂, -C(O)-OH, -CH₂-C(O)NH₂, -CH₂-C(O)-OH, or -R^{9b}-R^{9c}, wherein R^{9b} is -C(O)NH-.

[00735] 125. The compound of any one of Embodiments 1 to 124, wherein R^{9c} is



, wherein R^{9d} is a linear or branched C₁-C₅ alkylenyl, alkenylenyl, or alkynylenyl, in which 0-2 carbons in C₂-C₅ are independently replaced with N, S, and/or O heteroatoms,

wherein R^{9e} is carboxylic acid, sulfonic acid, sulfinic acid, phosphoric acid, amino, guanidino, -SH, -OH, -NH-C(O)-CH₃, -S-C(O)-CH₃, -O-C(O)-CH₃, -NH-C(O)-(phenyl), -S-C(O)-(phenyl), -O-C(O)-(phenyl), -NH-CH₃, -N(CH₃)₂, -S-CH₃, -O-CH₃, and phenyl, and wherein R^{9f} is amino or -OH.

[00736] 126. The compound of Embodiment 125, wherein R^{9d} is a linear or branched C₁-C₅ alkylenyl, alkenylenyl, or alkynylenyl.

[00737] 127. The compound of Embodiment 125, wherein R^{9d} is a linear or branched C₁-C₅ alkylenyl.

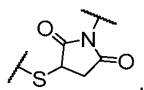
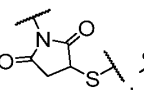
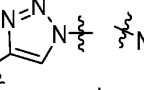
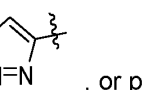
[00738] 128. The compound of any one of Embodiments 1 to 124, wherein R^{9a} is -R^{9b}-[linker]-R^X_{n1}.

[00739] 129. The compound of Embodiment 128, wherein R^{9b} is -C(O)NH-.

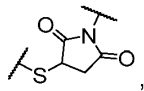
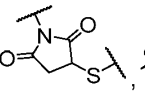
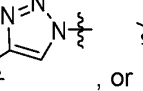
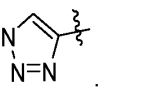
[00740] 130. The compound of any one of Embodiments 1 to 129, wherein each linker, if present, is independently a linear or branched chain of 1-10 units of X¹L¹ and/or X¹(L¹)₂, wherein:

[00741] each X¹ is, independently, a linear, branched, and/or cyclic C₁-C₁₅ alkylenyl, alkenylenyl or alkynylenyl wherein 0-6 carbons are independently replaced by N, S, and/or O heteroatoms, and substituted with 0-3 groups independently selected from one or a combination of oxo, hydroxyl, sulfhydryl, halogen, guanidino, carboxylic acid, sulfonic acid, sulfinic acid, and/or phosphoric acid;

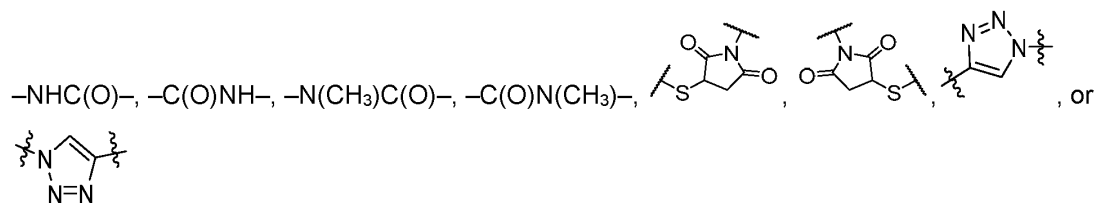
[00742] each L¹ is independently -NH-C(O)-, -C(O)-, -O-, -C(O)NH-, -C(O)-N(CH₃)-, -NHC(S)-, -C(S)NH-, -N(CH₃)C(S)-, -C(O)N(CH₃)-, -N(CH₃)C(O)-, -C(S)N(CH₃)-, -NHC(S)NH-, -NHC(O)NH-, -S-, -S(O)-, -S(O)-O-, -S(O)₂-, -S(O)₂-O-, -S(O)₂-NH-, -S(O)-NH-, -Se-, -Se(O)-, -Se(O)₂-, -NHNHC(O)-, -C(O)NHNH-, -OP(O)(O)O-, -phosphamide-, -thiophosphodiester-, -S-

tetrafluorophenyl-S-, , , , , or polyethylene glycol.

[00743] 131. The compound of Embodiment 130, wherein each L¹ is independently -S-, -NHC(O)-, -C(O)NH-, -N(CH₃)C(O)-, -C(O)N(CH₃)-, -NHC(S)-, -C(S)NH-, -N(CH₃)C(S)-, -C(S)N(CH₃)-, NHC(S)NH-, -S-, -O-, -S(O)-, -S(O)₂-, -Se-, -Se(O)-, -Se(O)₂-, -NHNHC(O)-, -

C(O)NHNH-, -OP(O)(O)O-, -OP(O)(S)O-, , , , or .

[00744] 131. The compound of Embodiment 130, wherein each L^1 is independently $-S-$,

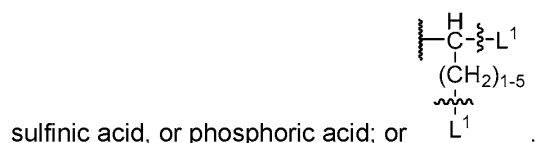
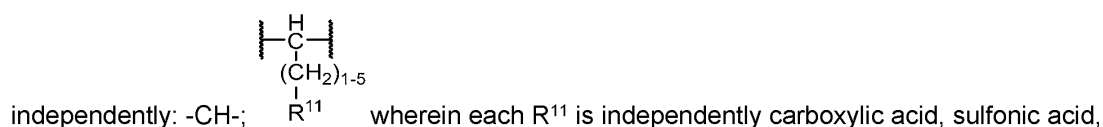


[00745] 132. The compound of 130, wherein at least one linker comprises at least one carboxylic acid, sulfonic acid, sulfinic acid, or phosphoric acid, and has a net negative charge at physiological pH.

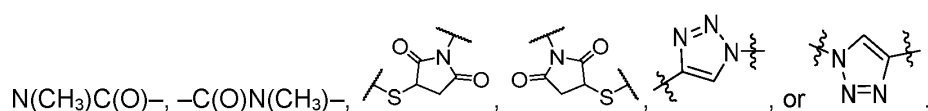
[00746] 133. The compound of any one of Embodiments 130 to 132, wherein at least one linker consists of 1-8 units of X^1L^1 and 0-2 units of $X^1(L^1)_2$.

[00747] 134. The compound of any one of Embodiments 130 to 133, wherein each X^1 is independently a linear, branched, and/or cyclic C_1 - C_{15} alkylenyl.

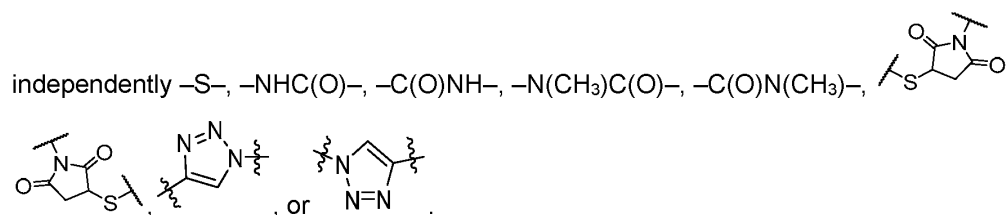
[00748] 135. The compound of any one of Embodiments 130 to 133, wherein each X^1 is



[00749] 136. The compound of any one of Embodiments 130 to 135, wherein each L^1 between two X^1 groups is independently $-NHC(O)-$, $-C(O)NH-$, $-N(CH_3)C(O)-$, or $-C(O)N(CH_3)-$, and each L^1 linking an R^X is independently $-S-$, $-NHC(O)-$, $-C(O)NH-$, $-$



[00750] 137. The compound of any one of Embodiments 130 to 133, wherein at least one linker is a linear or branched peptide of amino acid residues selected from proteinogenic amino acid residues and/or nonproteinogenic amino acid residues listed in Table 1, wherein each L^1 between two X^1 groups is methylated or unmethylated, and wherein each L^1 linking an R^X is

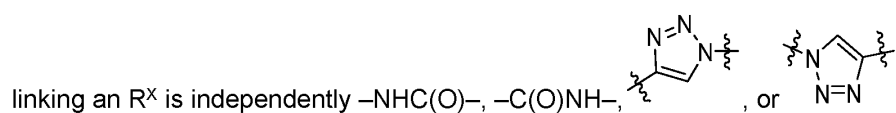


[00751] 138. The compound of Embodiment 136 or 137, wherein each L^1 between two X^1 groups is an unmethylated amide.

[00752] 139. The compound of any one of Embodiments 130 to 138, wherein the linker forms a peptide linker of 1 to 3 amino acids selected from one or a combination of: cysteic acid, Glu, Asp, and/or 2-aminoadipic acid (2-Aad).

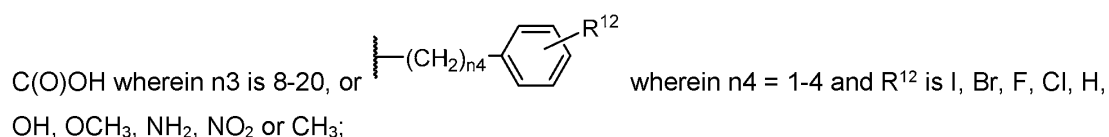
[00753] 140. The compound of Embodiment 139, wherein the linker forms a single amino acid residue selected from cysteic acid, Glu, Asp, or 2-aminoadipic acid (2-Aad).

[00754] 141. The compound of any one of Embodiments 130 to 140, wherein each L^1



[00755] 142. The compound of any one of Embodiments 1 to 141, wherein at least one R^x is an albumin binder.

[00756] 143. The compound of Embodiment 142, wherein the albumin binder is bonded to an L^1 of the linker, wherein the albumin binder is: $-(CH_2)_{n2}-CH_3$ wherein $n2$ is 8-20; $-(CH_2)_{n3}-$



[00757]

[00758] 144. The compound of any one of v 1 Embodiments 143, wherein at least one R^x is a radiolabeled group or a group capable of being radiolabelled.

[00759] 145. The compound of any one of Embodiments 1 to 144, comprising a first linker bonded to a radiolabeled group, or a group capable of being radiolabelled, and a second linker bonded to an albumin binder.

[00760] 146. The compound of any one of Embodiments 1 to 144, comprising a first linker bonded to a first radiolabeled group, or a first group capable of being radiolabelled, and a second linker bonded to a second radiolabeled group, or a second group capable of being radiolabelled, optionally further comprising an albumin binder attached to either or both of the first linker and the second linker.

[00761] 147. The compound of any one of Embodiments 1 to 144, comprising only a single linker bonded to 1-2 groups consisting of radiolabeled groups and/or group capable of being radiolabelled, and optionally further bonded to an albumin binder.

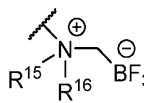
[00762] 148. The compound of any one of Embodiments 1 to 147, wherein each group capable of being radiolabelled is independently selected from: a metal chelator optionally in complex with a radiometal or radioisotope-bound metal; a prosthetic group containing trifluoroborate (BF_3); or a prosthetic group containing a silicon-fluorine-acceptor moiety, a sulphonyl fluoride, or a phosphoryl fluoride.

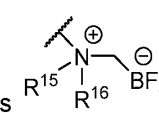
[00763] 149. The compound of Embodiment 148, wherein the metal chelator is in complex with the radioisotope.

[00764] 150. The compound of Embodiment 148 or 149, wherein the metal chelator is a polyaminocarboxylate chelator.

[00765] 151. The compound of Embodiment 150, wherein the metal chelator is DOTA or a DOTA derivative.

[00766] 152. The compound of any one of Embodiments 148 to 151, wherein a prosthetic group containing BF_3 is $-\text{R}^{13}\text{R}^{14}\text{BF}_3$ wherein R^{13} is $-(\text{CH}_2)_{1-5}-$ and $-\text{R}^{14}\text{BF}_3$ is selected from

Table 3 or 4 or is  wherein each R^{15} and each R^{16} are independently a branched or linear C_1 - C_5 alkyl.

[00767] 153. The compound of Embodiment 152, wherein $-\text{R}^{14}\text{BF}_3$ is .

[00768] 154. The compound of Embodiment 153, wherein R^{15} and R^{16} are each methyl.

[00769] 155. The compound of any one of Embodiments 148 to 154, wherein the prosthetic group containing BF_3 comprises ^{18}F .

[00770] 156. The compound of any one of Embodiments 1 to 155, wherein at least R^x is a therapeutic moiety.

[00771] 157. The compound of any one of Embodiments 1 to 156, wherein at least one R^x is fluorescent label.

[00772] 158. The compound of any one of Embodiments 1 to 157, for use in imaging a CXCR4-expressing tissue in a subject or for imaging an inflammatory condition or disease, wherein at least one R^x comprises or is complexed with an imaging radioisotope.

[00773] 159. The compound of any one of Embodiments 1 to 158, for use in treating a disease or condition characterized by expression of CXCR4 in a subject, wherein at least one

R^x comprises or is complexed with a therapeutic radioisotope or at least one R^x comprises a therapeutic moiety.

[00774] 160. The compound of Embodiment 159, wherein the disease or condition is a CXCR4-expressing cancer.

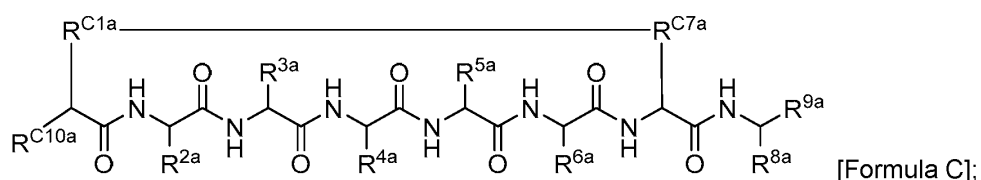
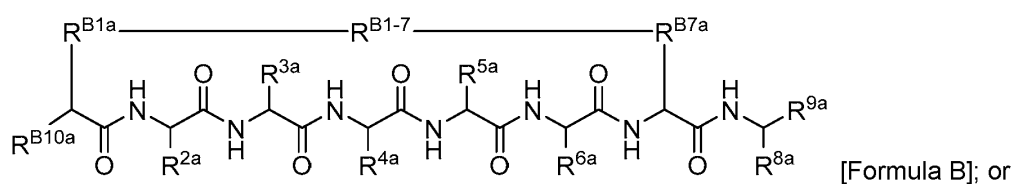
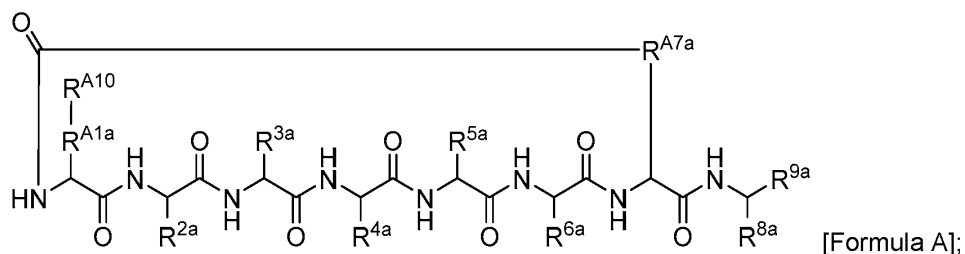
[00775] REFERENCES

1. Murdoch, C. CXCR4: chemokine receptor extraordinaire. *Immunol. Rev.* **177**, 175–184 (2000).
2. Griffith, J. W., Sokol, C. L. & Luster, A. D. Chemokines and Chemokine Receptors: Positioning Cells for Host Defense and Immunity. *Annu. Rev. Immunol.* **32**, 659–702 (2014).
3. Ratajczak, M. Z. *et al.* The pleiotropic effects of the SDF-1–CXCR4 axis in organogenesis, regeneration and tumorigenesis. *Leukemia* **20**, 1915–1924 (2006).
4. George, J. *et al.* Transfer of Endothelial Progenitor and Bone Marrow Cells Influences Atherosclerotic Plaque Size and Composition in Apolipoprotein E Knockout Mice. *Arterioscler. Thromb. Vasc. Biol.* **25**, 2636–2641 (2005).
5. Wang, A. *et al.* CXCR4/CXCL12 Hyperexpression Plays a Pivotal Role in the Pathogenesis of Lupus. *J. Immunol.* **182**, 4448–4458 (2009).
6. Wang, A. *et al.* Dysregulated expression of CXCR4/CXCL12 in subsets of patients with systemic lupus erythematosus. *Arthritis Rheum.* **62**, 3436–3446 (2010).
7. Guo, F. *et al.* CXCL12/CXCR4: a symbiotic bridge linking cancer cells and their stromal neighbors in oncogenic communication networks. *Oncogene* **35**, 816–26 (2016).
8. Jacobson, O. & Weiss, I. D. CXCR4 chemokine receptor overview: biology, pathology and applications in imaging and therapy. *Theranostics* **3**, 1–2 (2013).
9. Balkwill, F. Cancer and the chemokine network. *Nat. Rev. Cancer* **4**, 540–550 (2004).
10. Zlotnik, A., Burkhardt, A. M. & Homey, B. Homeostatic chemokine receptors and organ-specific metastasis. *Nat. Rev. Immunol.* **11**, 597–606 (2011).
11. Domanska, U. M. *et al.* A review on CXCR4/CXCL12 axis in oncology: No place to hide. *Eur. J. Cancer* **49**, 219–230 (2013).
12. Zhao, H. *et al.* CXCR4 over-expression and survival in cancer: a system review and meta-analysis. *Oncotarget* **6**, 5022–40 (2015).
13. Woodard, L. E. & Nimmagadda, S. CXCR4-Based Imaging Agents. *J. Nucl. Med.* **52**, 1665–1669 (2011).
14. Kuil, J., Buckle, T. & van Leeuwen, F. W. B. Imaging agents for the chemokine receptor 4 (CXCR4). *Chem. Soc. Rev.* **41**, 5239 (2012).
15. Weiss, I. D. & Jacobson, O. Molecular Imaging of Chemokine Receptor CXCR4. *Theranostics* **3**, 76–84 (2013).
16. George, G. P. C., Pisaneschi, F., Nguyen, Q.-D. & Aboagye, E. O. Positron Emission Tomographic

- Imaging of CXCR4 in Cancer: Challenges and Promises. *Mol. Imaging* **14**, 7290.2014.00041 (2015).
17. Peng, S. *et al.* Identification of LY2510924 , a Novel Cyclic Peptide CXCR4 Antagonist That Exhibits Antitumor Activities in Solid Tumor and Breast Cancer Metastatic Models. *Mol. Cancer Ther.* **14**, 480–491 (2015).
 18. Salgia, R. *et al.* A randomized phase II study of LY2510924 and carboplatin / etoposide versus carboplatin / etoposide in extensive-disease small cell lung cancer. *Lung Cancer* **105**, 7–13 (2017).
 19. Tamamura, H. *et al.* A Low-Molecular-Weight Inhibitor against the Chemokine Receptor CXCR4: A Strong Anti-HIV Peptide T140. *Biochem. Biophys. Res. Commun.* **253**, 877–882 (1998).
 20. Fujii, N. *et al.* Molecular-Size Reduction of a Potent CXCR4-Chemokine Antagonist Using Orthogonal Combination of Conformation- and Sequence-Based Libraries. *Angew. Chemie Int. Ed.* **42**, 3251–3253 (2003).
 21. Todorovic, M. *et al.* Fluorescent Isoindole Crosslink (FIICk) Chemistry: A Rapid, User-friendly Stapling Reaction. *Angew. Chemie Int. Ed.* **58**, 14120–14124 (2019).

What is Claimed is:

1. A compound of Formula A, Formula B, or Formula C, or a salt or solvate thereof:



wherein:

R^{2a} is $-(CH_2)-(R^{2b})-(phenyl)$, wherein R^{2b} is absent, $-CH_2-$, $-NH-$, $-S-$ or $-O-$, wherein the phenyl is optionally 4-substituted with $-NH_2$, $-NO_2$, $-OH$, $-OR^{2c}$, $-SH$, $-SR^{2c}$, or $-O-phenyl$, wherein the phenyl is optionally 3-substituted with halogen or $-OH$, wherein the phenyl is optionally 5-substituted with halogen or $-OH$, wherein the $-O-phenyl$ ring is optionally 4-substituted with $-NH_2$, $-NO_2$, $-OH$, $-OR^{2c}$, $-SH$, or $-SR^{2c}$, wherein the $-O-phenyl$ ring is optionally 3-substituted with halogen or $-OH$, wherein the $-O-phenyl$ ring is optionally 5-substituted with halogen or $-OH$, wherein each R^{2c} is independently a C_1 - C_3 linear or branched alkyl group;

R^{3a} is $R^{3b}R^{3c}$ wherein R^{3b} is a linear C_1 - C_5 alkylenyl, C_2 - C_5 alkenylenyl, or C_2 - C_5 alkynylenyl, wherein 0-2 carbons in C_2 - C_5 are independently replaced with one or more N, S, and/or O heteroatoms, wherein R^{3c} is $-N(R^{3d})_{2-3}$ or guanidino, wherein each R^{3d} is independently $-H$ or a linear or branched C_1 - C_3 alkyl;

R^{4a} is $R^{4b}R^{4c}$ wherein R^{4b} is a linear C_1 - C_5 alkylenyl, C_2 - C_5 alkenylenyl, or C_2 - C_5 alkynylenyl, in which 0-2 carbons in C_2 - C_5 are independently replaced with one or more N, S, and/or O heteroatoms, wherein R^{4c} is $-N(R^{4d})_{2-3}$ or guanidino, wherein each R^{4d} is independently $-H$ or a linear or branched C_1 - C_3 alkyl;

R^{5a} is $-(CH_2)_{1-3}-R^{5b}$, wherein 1 carbon in $-(CH_2)_{2-3}-$ is optionally replaced with a N, S, or O heteroatom, wherein R^{5b} is:

phenyl optionally substituted with one or a combination of the following:

4-substituted with $-NH_2$, $-NO_2$, $-OH$, $-OR^{5c}$, $-SH$, $-SR^{5c}$, or $-O$ -phenyl; 3-substituted with halogen or $-OH$; and/or 5-substituted with halogen or $-OH$; wherein the $-O$ -phenyl ring is optionally 4-substituted with $-NH_2$, $-NO_2$, $-OH$, $-OR^{5c}$, $-SH$, or $-SR^{5c}$, wherein the $-O$ -phenyl ring is optionally 3-substituted with halogen or $-OH$, wherein the $-O$ -phenyl ring is optionally 5-substituted with halogen or $-OH$; or

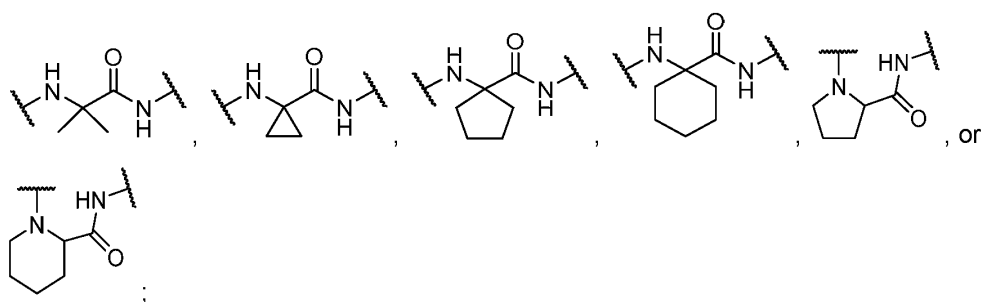
a fused bicyclic or fused tricyclic aryl or heteroaryl ring, each optionally substituted with one or more of halogen, $-OH$, $-OR^{5c}$, amino, $-NHR^{5c}$, and/or $N(R^{5c})_2$;

wherein each R^{5c} is independently a C_1 - C_3 linear or branched alkyl group;

either R^{6a} is H, methyl, ethyl, $-C\equiv CH$, $-CH=CH_2$, $-C\equiv C-(CH_2)_{1-3}-OH$, $-C\equiv C-(CH_2)_{1-3}-SH$, $-C\equiv C-(CH_2)_{1-3}-NH_2$, $-C\equiv C-(CH_2)_{1-3}-COOH$, $-C\equiv C-(CH_2)_{1-3}-CONH$, $-C\equiv C-(CH_2)_{1-3}-R^{6b}R^{6c}$, $-CH=CH-(CH_2)_{1-3}-OH$, $-CH=CH-(CH_2)_{1-3}-SH$, $-CH=CH-(CH_2)_{1-3}-NH_2$, $-CH=CH-(CH_2)_{1-3}-COOH$, $-CH=CH-(CH_2)_{1-3}-CONH$, $-CH=CH-(CH_2)_{1-3}-R^{6b}R^{6c}$, $-CH_2-R^{6b}-OH$, $-CH_2-R^{6b}-COOH$, $-CH_2-(R^{6b})_{1-3}-NH_2$, $-CH_2-R^{6b}-CONH$, or $-CH_2-R^{6b}-R^{6c}$, wherein each R^{6b} is independently absent, $-CH_2-$, $-NH-$, $-S-$ or $-O-$, and wherein R^{6c} is:

a 5 or 6 membered aromatic ring wherein one or more carbons are optionally independently replaced by N, S, and/or O heteroatoms, and optionally substituted with one or more groups independently selected from oxo, hydroxyl, sulfhydryl, nitro, amino, and/or halogen;

or $-NH-CH(R^{6a})-C(O)-NH-$ is replaced with:



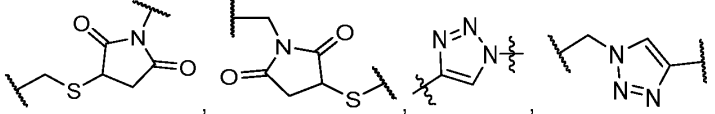
R^{A7a} is a linear C_1 - C_5 alkylenyl wherein 0-2 carbons in C_2 - C_5 are independently replaced with one or more N, S, and/or O heteroatoms;

R^{8a} is $R^{8b}R^{8c}$ wherein R^{8b} is a linear C_1 - C_5 alkylenyl, C_2 - C_5 alkenylenyl, or C_2 - C_5 alkynylenyl, in which 0-2 carbons in C_2 - C_5 alkylenyl, alkenylenyl, or alkynylenyl are independently replaced

with one or more N, S, and/or O heteroatoms, wherein R^{8c} is $-N(R^{8d})_{2-3}$ or guanidino, wherein each R^{8d} is independently -H or a linear or branched C_1 - C_3 alkyl;

R^{9a} is $-C(O)NH_2$, $-C(O)-OH$, $-CH_2-C(O)NH_2$, $-CH_2-C(O)-OH$, $-CH_2-NH_2$, $-CH_2-OH$, $-CH_2-CH_2-NH_2$, $-R^{9b}-R^{9c}$, or $-R^{9b}$ -[linker]- $R^{X_{n1}}$, wherein:

R^{9b} is $-CH_2-NH-C(O)-$, $-CH_2-C(O)-$, $-CH_2-O-$, $-C(O)NH-$, $-C(O)-N(CH_3)-$, $-CH_2-NHC(S)-$, $-C(S)NH-$, $-CH_2-N(CH_3)C(S)-$, $-C(O)N(CH_3)-$, $-CH_2-N(CH_3)C(O)-$, $-C(S)N(CH_3)-$, $-CH_2-NHC(S)NH-$, $-CH_2-NHC(O)NH-$, $-CH_2-S-$, $-CH_2-S(O)-$, $-CH_2-S(O)_2-$, $-CH_2-S(O)_2-NH-$, $-CH_2-S(O)-NH-$, $-CH_2-Se-$, $-CH_2-Se(O)-$, $-CH_2-Se(O)_2-$, $-CH_2-NHNHC(O)-$, $-C(O)NHNH-$, $-CH_2-OP(O)(O)O-$, $-CH_2$ -phosphamide-, $-CH_2$ -thiophosphodiester-, $-CH_2-S-$

tetrafluorophenyl-S-, , or polyethylene glycol; and

R^{9c} is hydrogen or a linear, branched, and/or cyclic C_1 - C_{20} alkyl, alkenyl or alkynyl, wherein 0-6 carbons in C_2 - C_{20} are independently replaced by N, S, and/or O heteroatoms, and substituted with 0-3 groups independently selected from one or a combination of oxo, hydroxyl, sulfhydryl, halogen, guanidino, carboxylic acid, sulfonic acid, sulfinic acid, and/or phosphoric acid;

R^{A10} is absent or $-[linker]-R^{X_{n1}}$;

when R^{A10} is absent, then R^{A1a} is:

a linear C_1 - C_5 alkyl, C_2 - C_5 alkenyl, or C_2 - C_5 alkynyl, wherein 0-2 carbons in C_2 - C_5 alkyl, alkenyl, or alkynyl are independently replaced by one or more N, S, and/or O heteroatoms, optionally C-substituted with a single substituent selected from: -SH, -OH, amino, carboxy, guanidino, $-NH-C(O)-CH_3$, $-S-C(O)-CH_3$, $-O-C(O)-CH_3$, $-NH-C(O)-$ (phenyl), $-S-C(O)-$ (phenyl), $-O-C(O)-$ (phenyl), $-NH-(CH_3)_{1-2}$, $-NH_2-CH_3$, $-N(CH_3)_{2-3}$, $-S-CH_3$, or $-O-CH_3$;

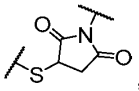
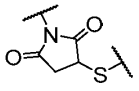
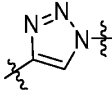
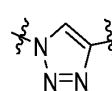
a branched C_1 - C_{10} alkyl, alkenyl, or alkynyl, wherein 0-3 carbons in C_2 - C_{10} are independently replaced by one or more N, S, and/or O heteroatoms; or

$R^{A1b}R^{A1c}$, wherein R^{A1b} is a linear C_1 - C_3 alkylenyl, wherein C_2 alkylenyl or C_3 alkylenyl is optionally replaced with a N, S, or O heteroatom, wherein R^{A1c} is:

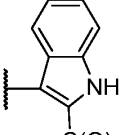
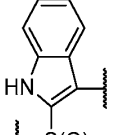
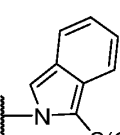
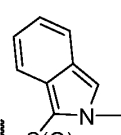
a 5 or 6 membered aromatic ring wherein one or more carbons are optionally independently replaced by N, S, and/or O heteroatoms, and optionally substituted with one or more groups independently selected from oxo, hydroxyl, sulfhydryl, nitro, amino, and/or halogen; or

a fused bicyclic or fused tricyclic aryl group wherein one or more carbons are optionally independently replaced by N, S, and/or O heteroatoms, and optionally substituted with one or more groups independently selected from halogen, -OH, -OR^{A1d}, amino, -NHR^{A1d}, and/or N(R^{A1d})₂, wherein each R^{A1d} is independently a C₁-C₃ linear or branched alkyl group;

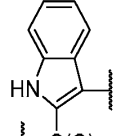
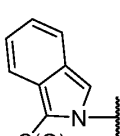
when R^{A10} is -[linker]-R^X_{n1}, then R^{A1a} is R^{A1e}R^{A1f}, wherein R^{A1e} is a linear C₁-C₅ alkenyl, C₂-C₅ alkenyl, or C₂-C₅ alkynyl, in which 0-2 carbons in C₂-C₅ alkenyl, alkenyl, alkynyl are independently replaced with N, S, and/or O heteroatoms, and R^{A1f} is -NH-C(O)-, -C(O)-, -O-, -C(O)NH-, -C(O)-N(CH₃)-, -NHC(S)-, -C(S)NH-, -N(CH₃)C(S)-, -C(O)N(CH₃)-, -N(CH₃)C(O)-, -C(S)N(CH₃)-, -NHC(S)NH-, -NHC(O)NH-, -S-, -S(O)-, -S(O)-O-, -S(O)₂-, -S(O)₂-O-, -S(O)₂-NH-, -S(O)-NH-, -Se-, -Se(O)-, -Se(O)₂-, -NHNHC(O)-, -C(O)NHNH-, -OP(O)(O)O-, -

phosphamide-, -thiophosphodiester-, -S-tetrafluorophenyl-S-, , , , , or polyethylene glycol;

R^{B1a} is a linear, branched, and/or cyclic C₁-C₁₀ alkenyl, C₂-C₁₀ alkenyl, or C₂-C₁₀ alkynyl, wherein one or more carbons in C₂-C₁₀ alkenyl, alkenyl, alkynyl are optionally independently replaced with N, S, and/or O heteroatoms;

R^{B1-7} is , , , or , wherein the indole ring and the isoindole ring are each optionally substituted with one or more of -F, -Br, -Cl, -I, -OH, -O-R^{B1-7b}, -CO-, -COOH, -CONH₂, -CN, -O-aryl, -NH₂, -NHR^{B1-7b}, N₃, -NH-, -CHO, and/or -R^{B1-7b}, wherein each R^{B1-7b} is a linear or branched C₁-C₃ alkyl, C₂-C₃ alkenyl, or C₂-C₃ alkynyl;

R^{B7a} is a linear C₁-C₅ alkenyl wherein 0-2 carbons in C₂-C₅ alkenyl are independently replaced with one or more N, S, and/or O heteroatoms;

R^{C1a} is , or , wherein the indole ring and the isoindole ring are each optionally substituted with one or more of -F, -Br, -Cl, -I, -OH, -O-R^{C1b}, -CO-, -COOH, -CONH₂, -

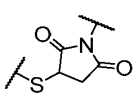
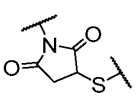
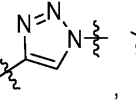
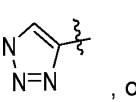
CN, -O-aryl, -NH₂, -NHR^{C1b}, N₃, -NH-, -CHO, and/or -R^{C1b}, wherein each R^{C1b} is a linear or branched C₁-C₃ alkyl, C₂-C₃ alkenyl, or C₂-C₃ alkynyl;

R^{C7a} is a linear C₁-C₅ alkylenyl, wherein optionally 0-2 carbons in C₂-C₅ alkylenyl are independently replaced with one or more N, S, and/or O heteroatoms;

R^{C10a} is R^{C10b}-R^{C10c}-[linker]-R^X_{n1} or R^{C10d}, wherein:

R^{C10b} is a linear C₁-C₅ alkylenyl, C₂-C₅ alkenylenyl, or C₂-C₅ alkynylenyl, in which 0-2 carbons in C₂-C₅ alkylenyl, alkenylenyl, alkynylenyl are independently replaced with N, S, and/or O heteroatoms;

R^{C10c} is -NH-C(O)-, -C(O)-, -O-, -C(O)NH-, -C(O)-N(CH₃)-, -NHC(S)-, -C(S)NH-, -N(CH₃)C(S)-, -C(O)N(CH₃)-, -N(CH₃)C(O)-, -C(S)N(CH₃)-, -NHC(S)NH-, -NHC(O)NH-, -S-, -S(O)-, -S(O)-O-, -S(O)₂-, -S(O)₂-O-, -S(O)₂-NH-, -S(O)-NH-, -Se-, -Se(O)-, -Se(O)₂-, -NHNHC(O)-, -C(O)NHNH-, -OP(O)(O-)O-, -phosphamide-, -thiophosphodiester-, -S-

tetrafluorophenyl-S-, , , , , or polyethylene glycol; and

R^{C10d} is:

a linear C₁-C₅ alkyl, C₂-C₅ alkenyl, or C₂-C₅ alkynyl, wherein 0-2 carbons in C₂-C₅ alkyl, alkenyl, or alkynyl are independently replaced by N, S, and/or O heteroatoms, optionally C-substituted with a single substituent selected from: -SH, -OH, amino, carboxy, guanidino, -NH-C(O)-CH₃, -S-C(O)-CH₃, -O-C(O)-CH₃, -NH-C(O)-(phenyl), -S-C(O)-(phenyl), -O-C(O)-(phenyl), -NH-(CH₃)₁₋₂, -NH₂-CH₃, -N(CH₃)₂₋₃, -S-CH₃, or -O-CH₃;

a branched C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, or C₂-C₁₀ alkynyl, wherein 0-3 carbons in C₂-C₁₀ alkyl, alkenyl, or alkynyl are independently replaced by N, S, and/or O heteroatoms; or

R^{C10e}R^{C10f}, wherein R^{C10e} is a linear C₁-C₃ alkyl, wherein C₂ alkyl or C₃ alkyl is optionally replaced with N, S, or O heteroatom, wherein R^{C10f} is:

a 5 or 6 membered aromatic ring wherein one or more carbons are optionally independently replaced by N, S, and/or O heteroatoms, and optionally substituted with one or more groups independently selected from oxo, hydroxyl, sulfhydryl, nitro, amino, and/or halogen;

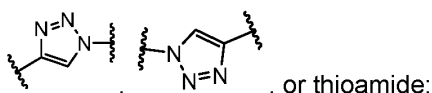
a fused bicyclic or fused tricyclic aryl group wherein one or more carbons are optionally independently replaced by N, S, and/or O heteroatoms, and

optionally substituted with one or more groups independently selected from halogen, -OH, -OR^{C10g}, amino, -NHR^{C10g}, and/or N(R^{C10g})₂, wherein R^{C10g} is C₁-C₃ linear or branched alkyl;

each n₁ is independently 0, 1 or 2;

each R^x is a therapeutic moiety, a fluorescent label, a radiolabeled group, or a group capable of being radiolabelled;

wherein 0-3 peptide backbone amides are independently replaced with



wherein 0-3 peptide backbone amides are N-methylated;

with the proviso that Formula A excludes the following combination:

- NH-CH(R^{2a})-C(O)- forms a Tyr residue;
- NH-CH(R^{4a})-C(O)- forms a D-Arg residue;
- NH-CH(R^{5a})-C(O)- forms a 2Nal residue; and
- R^{6a} is H.

2. The compound of claim 1, wherein R^{2a} is -(CH₂)-(R^{2b})-(phenyl), wherein R^{2b} is absent, -CH₂-, -NH-, -S- or -O-, wherein the phenyl is optionally 4-substituted with -NH₂, -NO₂, -OH, -OR^{2c}, -SH, -SR^{2c}, or -O-phenyl, or optionally 3-substituted with halogen or -OH, wherein each R^{2c} is independently a C₁-C₃ linear or branched alkyl group.

3. The compound of claim 1 or 2, wherein -NH-CH(R^{2a})-C(O)- of Formula A, Formula B, or Formula C forms an L-amino acid residue.

4. The compound of any one of claims 1-3, wherein -NH-CH(R^{2a})-C(O)- of Formula A, Formula B, or Formula C forms a Tyr residue, a Phe residue, a (4-NO₂)-Phe residue, a (4-NH₂)-Phe residue, a hTyr residue, a (3-I)Tyr residue, a Glu residue, a Gln residue, or a D-Tyr residue.

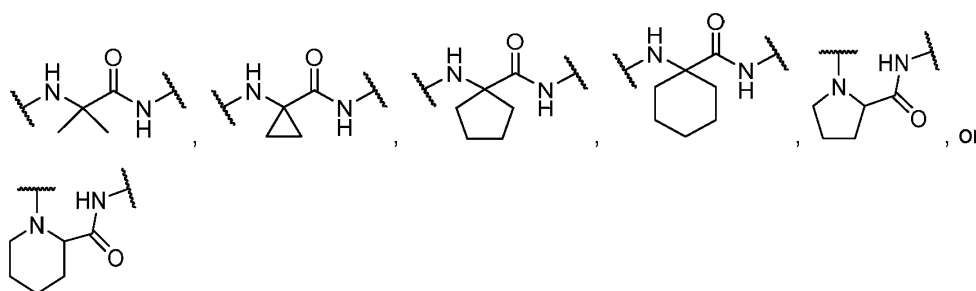
5. The compound of any one of claims 1-4, wherein R^{3a} is R^{3b}R^{3c} wherein R^{3b} is a linear C₁-C₅ alkynyl, C₂-C₅ alkenyl, or C₂-C₅ alkynyl, wherein R^{3c} is -N(R^{3d})₂₋₃ or guanidino, wherein each R^{3d} is independently -H or a linear or branched C₁-C₃ alkyl.

6. The compound of any one of claims 1-5 wherein -NH-CH(R^{3a})-C(O)- of Formula A, Formula B, or Formula C forms an L-amino acid residue.

7. The compound of any one of claims 1-5 wherein -NH-CH(R^{3a})-C(O)- of Formula A, Formula B, or Formula C forms a Lys(iPr) residue, a Arg(Me)₂ (asymmetrical) residue, or a Arg(Me) residue.
8. The compound of any one of claims 1-7, wherein R^{4a} is R^{4b}R^{4c} wherein R^{4b} is a linear C₁-C₅ alkylenyl, C₂-C₅ alkenylenyl, or C₂-C₅ alkynylenyl, wherein R^{4c} is -N(R^{4d})₂₋₃ or guanidino, wherein each R^{4d} is independently -H or a linear or branched C₁-C₃ alkyl.
9. The compound of any one of claims 1-8, wherein -NH-CH(R^{4a})-C(O)- of Formula A, Formula B, or Formula C forms a D-amino acid residue.
10. The compound of any one of claims 1-9, wherein -NH-CH(R^{4a})-C(O)- forms a D-Arg residue or a D-hArg residue.
11. The compound of any one of claims 1-10, wherein R^{5a} is -(CH₂)₁₋₃-R^{5b}, wherein R^{5b} is: phenyl optionally substituted with one or a more of the following: 4-substituted with -NH₂, -NO₂, -OH, -SH, or -O-phenyl; 3-substituted with halogen or -OH; and/or 5-substituted with halogen or -OH; or a fused bicyclic or fused tricyclic aryl or heteroaryl ring which is optionally substituted with one or more of halogen, -OH, -OR^{5c}, amino, -NHR^{5c}, and/or N(R^{5c})₂; and wherein R^{5c} is each independently a C₁-C₃ linear or branched alkyl group.
12. The compound of any one of claims 1-11, wherein -NH-CH(R^{5a})-C(O)- of Formula A, Formula B, or Formula C forms an L-amino acid residue.
13. The compound of any one of claims 1-12, wherein -NH-CH(R^{5a})-C(O)- of Formula A, Formula B, or Formula C forms a 2-(Ant)Ala residue, a 2-Nal residue, a Trp residue, a (4-NH₂)Phe residue, a hTyr residue, or a Tyr residue.
14. The compound of any one of claims 1-13, wherein R^{6a} is H, methyl, ethyl, -C≡CH, -CH=CH₂, -CH₂-R^{6b}-OH, -CH₂-R^{6b}-COOH, -CH₂-(R^{6b})₁₋₃-NH₂, -CH₂-R^{6b}-CONH, or -CH₂-R^{6b}R^{6c}, wherein each R^{6b} is independently absent, -CH₂-, -NH-, -S- or -O-; and wherein R^{6c} is a 5 or 6 membered aromatic ring wherein 0-3 carbons are independently replaced by N, S, and/or O

heteroatoms, and optionally substituted with 0-3 groups independently selected from oxo, hydroxyl, sulfhydryl, nitro, amino, and/or halogen.

15. The compound of any one of claims 1-13, wherein -NH-CH(R^{6a})-C(O)-NH- of Formula A, Formula B, or Formula C is replaced with:



16. The compound of any one of claims 1-15, wherein -NH-CH(R^{6a})-C(O)- of Formula A, Formula B, or Formula C forms a D-amino acid residue.

17. The compound of any one of claims 1-16, wherein -NH-CH(R^{6a})-C(O)- of Formula A, Formula B, or Formula C forms a His residue, a D-His residue, a D-Glu residue, a D-Gln residue, a D-Ala residue, a D-Phe residue, a D-Ser residue, a D-Dab residue, a D-Dap residue.

18. The compound of any one of claims 1-17, wherein R^{8a} is R^{8b}R^{8c}, wherein R^{8b} is a linear C₁-C₅ alkylenyl, C₂-C₅ alkenylenyl, or C₂-C₅ alkynylenyl, wherein R^{8c} is -N(R^{8d})₂₋₃ or guanidino, wherein each R^{8d} is independently -H or a linear or branched C₁-C₃ alkyl.

19. The compound of any one of claims 1-18, wherein:

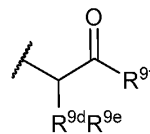
R^{9a} is -C(O)NH₂, -C(O)-OH, -R^{9b}-R^{9c}, or -R^{9b}-[linker]-R^{X_{n1}}; and

R^{9b} is -C(O)NH-, -C(O)-N(CH₃)-, -C(O)N(CH₃)-, or -C(O)NHNH-.

20. The compound of any one of claims 1-19, wherein -NH-CH(R^{8a})- together with -C(O)- from R^{9a} in Formula A, Formula B, or Formula C forms an L-amino acid residue.

21. The compound of any one of claims 1-20, wherein -NH-CH(R^{8a})- together with -C(O)- from R^{9a} in Formula A, Formula B, or Formula C forms a Lys(iPr) residue.

22. The compound of any one of claims 1-21, wherein R^{9a} is $-C(O)NH_2$, $-C(O)-OH$, $-CH_2-$



$C(O)NH_2$, $-CH_2-C(O)-OH$, or $-R^{9b}-R^{9c}$; R^{9b} is $-C(O)NH-$; and R^{9c} is $R^{9d}R^{9e}$, wherein R^{9d} is a linear or branched C_1-C_5 alkylenyl, R^{9e} is carboxylic acid, sulfonic acid, sulfinic acid, phosphoric acid, amino, guanidino, $-SH$, $-OH$, $-NH-C(O)-CH_3$, $-S-C(O)-CH_3$, $-O-C(O)-CH_3$, $-NH-C(O)-(phenyl)$, $-S-C(O)-(phenyl)$, $-O-C(O)-(phenyl)$, $-NH-CH_3$, $-N(CH_3)_2$, $-S-CH_3$, $-O-CH_3$, or phenyl, and R^{9f} is amino or $-OH$.

23. The compound of any one of claims 1-21, wherein R^{9a} is $-R^{9b}-[linker]-R^{X_{n1}}$.

24. The compound of any one of claims 1-23, wherein R^{9b} is $-C(O)NH-$.

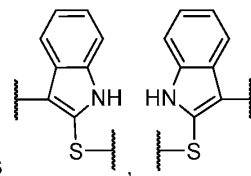
25. The compound of any one of claims 1-24, wherein $-NH-CH(R^{A1a})-C(O)-$ of Formula A forms an L-amino acid residue.

26. The compound of any one of claims 1-25, wherein $-NH-CH(R^{A1a})-C(O)-$ of Formula A, forms a Phe residue, a 1-Nal residue, a 2-Nal residue, a Tyr residue, a Trp residue, Lys residue, a hLys residue, a Lys(Ac) residue, a Dap residue, a Dab residue, or an Orn residue.

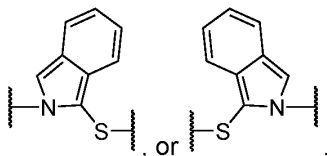
27. The compound of any one of claims 1-26, wherein R^{A10} is $-[linker]-R^{X_{n1}}$.

28. The compound of any one of claims 1-7, wherein $-NH-CH(R^{A7a})-C(O)-$ of Formula A forms a D-amino acid residue.

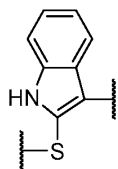
29. The compound of any one of claims 1-28, wherein R^{A7a} is C_1-C_3 alkylenyl.



30. The compound of any one of claims 1-24, wherein R^{B1-7} is

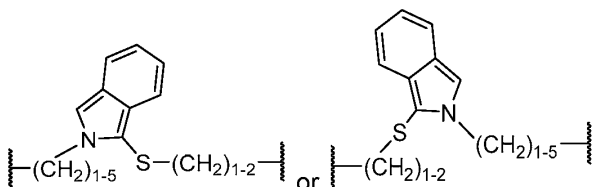


31. The compound of any one of claims 1-24, wherein R^{B1a} is $-(CH_2)_{1-2}-$, R^{B1-7} is



, and R^{B7a} is $-(CH_2)_{1-2}-$.

32. The compound of any one of claims 1-24, wherein $R^{B1a}-R^{B1-7}-R^{B7a}$ is



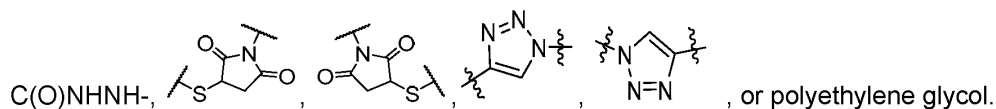
33. The compound of any one of claims 1-24 and 30-32, wherein $-NH-CH(R^{B7a})-C(O)-$ of Formula B forms a D-amino acid residue.

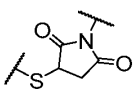
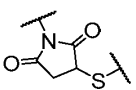
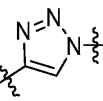
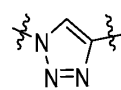
34. The compound of any one of claims 1-24 and 30-33, wherein R^{B10a} is: amine, $-NH-(CH_3)_{1-2}$, $-N(CH_3)_{2-3}$, $-NH-C(O)-CH_3$, or $-NH-C(O)-(phenyl)$.

35. The compound of any one of claims 1-24 and 30-34, wherein R^{B10a} is $-R^{B10b}-[linker]-R^X_{n1}$.

36. The compound of claim 35, wherein R^{B10b} is:

-NH-C(O)-, -C(O)-, -O-, -C(O)NH-, -C(O)-N(CH₃)-, -NHC(S)-, -C(S)NH-, -N(CH₃)C(S)-, -C(O)N(CH₃)-, -N(CH₃)C(O)-, -C(S)N(CH₃)-, -NHC(S)NH-, -NHC(O)NH-, -NHNHC(O)-, -



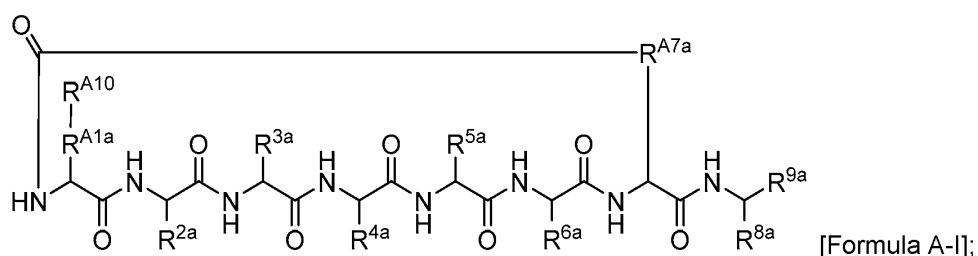
37. The compound of claim 35, wherein R^{B10a} is -NHC(O)-[linker]-R^{X_{n1}} or -N(CH₃)C(O)-[linker]-R^{X_{n1}}.
38. The compound of any one of claims 1-24, wherein -NH-CH(R^{C7a})-C(O)- of Formula C forms a D-amino acid residue.
39. The compound of any one of claims 1-24 and 38, wherein R^{C7a} is a linear C₁-C₅ alkylenyl.
40. The compound of any one of claims 1-24 and 38-39, wherein R^{C10a} is R^{C10b}-R^{C10c}-[linker]-R^{X_{n1}}.
41. The compound of claim 40, wherein R^{C10b} is a linear C₁-C₅ alkylenyl; and R^{C10c} is:
- NH-C(O)-, -C(O)-, -O-, -C(O)NH-, -C(O)-N(CH₃)-, -NHC(S)-, -C(S)NH-, -N(CH₃)C(S)-, -C(O)N(CH₃)-, -N(CH₃)C(O)-, -C(S)N(CH₃)-, -NHC(S)NH-, -NHC(O)NH-, -NHNHC(O)-, -
- C(O)NHNH-, , , , , or polyethylene glycol.
42. The compound of any one of claims 1-24 and 38-39, wherein R^{C10a} is R^{C10d}, wherein R^{C10d} is:
- a linear C₁-C₅ alkyl, C₂-C₅ alkenyl, or C₂-C₅ alkynyl, optionally C-substituted with a single substituent selected from: -SH, -OH, amino, carboxy, guanidino, -NH-C(O)-CH₃, -S-C(O)-CH₃, -O-C(O)-CH₃, -NH-C(O)-(phenyl), -S-C(O)-(phenyl), -O-C(O)-(phenyl), -NH-(CH₃)₁₋₂, -NH₂-CH₃, -N(CH₃)₂₋₃, -S-CH₃, -O-CH₃;
 - a branched C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, or C₂-C₁₀ alkynyl; or
 - R^{C10e}R^{C10f};

wherein R^{C10e} is a linear C₁-C₃ alkyl; and R^{C10f} is

(i) a 5 or 6 membered aromatic ring wherein 0-4 carbons are independently replaced by N, S, and/or O heteroatoms, and substituted with 0-4 groups independently selected from oxo, hydroxyl, sulfhydryl, nitro, amino, and/or halogen; or

(ii) a fused bicyclic or fused tricyclic aryl group wherein 0-6 carbons are independently replaced by N, S, and/or O heteroatoms, and substituted with 0-6 groups independently selected from halogen, -OH, -OR^{C10g}, amino, -NHR^{C10g}, and/or N(R^{C10g})₂, wherein R^{C10g} is C₁-C₃ linear or branched alkyl.

43. The compound of claim 1, wherein the compound has the structure of Formula A-I or salt or solvate thereof:



wherein:

R^{2a} is -(CH₂)-(R^{2b})-(phenyl), wherein R^{2b} is absent, -CH₂-, -NH-, -S- or -O-, wherein the phenyl is optionally 4-substituted with -NH₂, -NO₂, -OH, -OR^{2c}, -SH, -SR^{2c}, or -O-phenyl or optionally 3-substituted with halogen or -OH, wherein each R^{2c} is independently a C₁-C₃ linear or branched alkyl group;

R^{3a} is R^{3b}R^{3c} wherein R^{3b} is a linear C₁-C₅ alkylenyl, C₂-C₅ alkenylenyl, or C₂-C₅ alkynylenyl, wherein R^{3c} is -N(R^{3d})₂₋₃ or guanidino, wherein each R^{3d} is independently -H or a linear or branched C₁-C₃ alkyl;

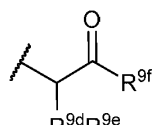
R^{4a} is R^{4b}R^{4c} wherein R^{4b} is a linear C₁-C₅ alkylenyl, C₂-C₅ alkenylenyl, or C₂-C₅ alkynylenyl, wherein R^{4c} is -N(R^{4d})₂₋₃ or guanidino, wherein each R^{4d} is independently -H or a linear or branched C₁-C₃ alkyl;

R^{5a} is -(CH₂)₁₋₃-R^{5b}, wherein R^{5b} is:

phenyl optionally substituted with one or a more of the following: 4-substituted with -NH₂, -NO₂, -OH, -SH, or -O-phenyl; 3-substituted with halogen or -OH; and/or 5-substituted with halogen or -OH;

a fused bicyclic or fused tricyclic aryl or heteroaryl ring which is optionally substituted with one or more of halogen, -OH, -OR^{5c}, amino, -NHR^{5c}, and/or N(R^{5c})₂; and

wherein R^{5c} is each independently a C_1 - C_3 linear or branched alkyl group;
 R^{6a} is H, methyl, ethyl, $-C\equiv CH$, $-CH=CH_2$, $-CH_2-R^{6b}-OH$, $-CH_2-R^{6b}-COOH$, $-CH_2-(R^{6b})_{1-3}-NH_2$, $-CH_2-R^{6b}-CONH$, or $-CH_2-R^{6b}-R^{6c}$, wherein each R^{6b} is independently absent, $-CH_2-$, $-NH-$, $-S-$ or $-O-$; and wherein R^{6c} is a 5 or 6 membered aromatic ring wherein 0-3 carbons are independently replaced by N, S, and/or O heteroatoms, and optionally substituted with 0-3 groups independently selected from oxo, hydroxyl, sulfhydryl, nitro, amino, and/or halogen;
 R^{8a} is $R^{8b}R^{8c}$, wherein R^{8b} is a linear C_1 - C_5 alkylenyl, C_2 - C_5 alkenylenyl, or C_2 - C_5 alkynylenyl, wherein R^{8c} is $-N(R^{8d})_{2-3}$ or guanidino, wherein each R^{8d} is independently $-H$ or a linear or branched C_1 - C_3 alkyl;
 R^{9a} is $-C(O)NH_2$, $-C(O)-OH$, $-CH_2-C(O)NH_2$, $-CH_2-C(O)-OH$, $-R^{9b}-R^{9c}$ or $-R^{9b}-[linker]-R^{9c}$;



wherein R^{9b} is $-C(O)NH-$; and R^{9c} is $R^{9d}R^{9e}$, wherein R^{9d} is a linear or branched C_1 - C_5 alkylenyl, R^{9e} is carboxylic acid, sulfonic acid, sulfinic acid, phosphoric acid, amino, guanidino, $-SH$, $-OH$, $-NH-C(O)-CH_3$, $-S-C(O)-CH_3$, $-O-C(O)-CH_3$, $-NH-C(O)-(phenyl)$, $-S-C(O)-(phenyl)$, $-O-C(O)-(phenyl)$, $-NH-CH_3$, $-N(CH_3)_2$, $-S-CH_3$, $-O-CH_3$, or phenyl, and R^{9f} is amino or $-OH$;
 R^{A7a} is C_1 - C_3 alkylenyl;
 R^{A10} is absent or $-[linker]-R^{A11}$;
 when R^{A10} is absent, then R^{A1a} is:

a linear C_1 - C_5 alkyl, C_2 - C_5 alkenyl, or C_2 - C_5 alkynyl, wherein 0-2 carbons in C_2 - C_5 alkyl, alkenyl, or alkynyl are independently replaced by one or more N, S, and/or O heteroatoms, optionally C-substituted with a single substituent selected from: $-SH$, $-OH$, amino, carboxy, guanidino, $-NH-C(O)-CH_3$, $-S-C(O)-CH_3$, $-O-C(O)-CH_3$, $-NH-C(O)-(phenyl)$, $-S-C(O)-(phenyl)$, $-O-C(O)-(phenyl)$, $-NH-(CH_3)_{1-2}$, $-NH_2-CH_3$, $-N(CH_3)_{2-3}$, $-S-CH_3$, or $-O-CH_3$;

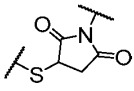
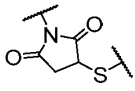
a branched C_1 - C_{10} alkyl, alkenyl, or alkynyl, wherein 0-3 carbons in C_2 - C_{10} are independently replaced by one or more N, S, and/or O heteroatoms; or

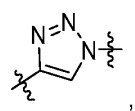
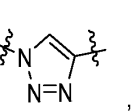
$R^{A1b}R^{A1c}$, wherein R^{A1b} is a linear C_1 - C_3 alkylenyl, wherein C_2 alkylenyl or C_3 alkylenyl is optionally replaced with a N, S, or O heteroatom, wherein R^{A1c} is:

a 5 or 6 membered aromatic ring wherein one or more carbons are optionally independently replaced by N, S, and/or O heteroatoms, and optionally substituted with one or more groups independently selected from oxo, hydroxyl, sulfhydryl, nitro, amino, and/or halogen; or

a fused bicyclic or fused tricyclic aryl group wherein one or more carbons are optionally independently replaced by N, S, and/or O heteroatoms, and optionally substituted with one or more groups independently selected from halogen, -OH, -OR^{A1d}, amino, -NHR^{A1d}, and/or N(R^{A1d})₂, wherein each R^{A1d} is independently a C₁-C₃ linear or branched alkyl group;

when R^{A10} is -[linker]-R^X_{n1}, then R^{A1a} is R^{A1e}R^{A1f}, wherein R^{A1e} is a linear C₁-C₅ alkenyl, C₂-C₅ alkenyl, or C₂-C₅ alkynyl, in which 0-2 carbons in C₂-C₅ alkenyl, alkenyl, or alkynyl are independently replaced with N, S, and/or O heteroatoms, and R^{A1f} is -NH-C(O)-, -C(O)-, -O-, -C(O)NH-, -C(O)-N(CH₃)-, -NHC(S)-, -C(S)NH-, -N(CH₃)C(S)-, -C(O)N(CH₃)-, -N(CH₃)C(O)-, -C(S)N(CH₃)-, -NHC(S)NH-, -NHC(O)NH-, -S-, -S(O)-, -S(O)-O-, -S(O)₂-, -S(O)₂-O-, -S(O)₂-NH-, -S(O)-NH-, -Se-, -Se(O)-, -Se(O)₂-, -NHNHC(O)-, -C(O)NHNH-, -OP(O)(O)O-, -

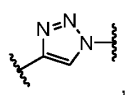
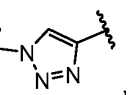
phosphamide-, -thiophosphodiester-, -S-tetrafluorophenyl-S-, , ,

, , or polyethylene glycol;

each n₁ is independently 0, 1 or 2;

each R^X is a therapeutic moiety, a fluorescent label, a radiolabeled group, or a group capable of being radiolabeled;

wherein 0-3 peptide backbone amides are independently replaced with

, , or thioamide; and

wherein 0-3 peptide backbone amides are N-methylated.

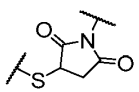
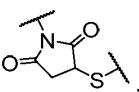
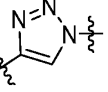
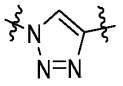
44. The compound of claim 43, wherein -NH-CH(R^{A1a})-C(O)- of Formula A-I forms a Phe residue, a 1-Nal residue, a 2-Nal residue, a Tyr residue, a Trp residue, a Lys residue, a hLys residue, a Lys(Ac) residue, a Dap residue, a Dab residue, or an Orn residue.

45. The compound of claim 43 or 44, wherein R^{A10} is -[linker]-R^X_{n1} and R^{9a} is -C(O)NH₂, -C(O)-OH, -CH₂-C(O)NH₂, or -CH₂-C(O)-OH.

46. The compound of any one of claims 1-45, wherein the linker is each independently a linear or branched chain of 1-10 units of X¹L¹ and/or X¹(L¹)₂, wherein:

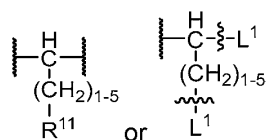
each X^1 is, independently, a linear, branched, and/or cyclic C_1 - C_{15} alkylenyl, C_2 - C_{15} alkenylenyl or C_2 - C_{15} alkynylenyl wherein 0-6 carbons are independently replaced by N, S, and/or O heteroatoms, and substituted with 0-3 groups independently selected from one or a combination of oxo, hydroxyl, sulfhydryl, halogen, guanidino, carboxylic acid, sulfonic acid, sulfinic acid, and/or phosphoric acid; and

each L^1 is independently -NH-C(O)-, -NH-, -C(O)-, -O-, -C(O)NH-, -C(O)-N(CH₃)-, -NHC(S)-, -C(S)NH-, -N(CH₃)C(S)-, -C(O)N(CH₃)-, -N(CH₃)C(O)-, -C(S)N(CH₃)-, -NHC(S)NH-, -NHC(O)NH-, -S-, -S(O)-, -S(O)-O-, -S(O)₂-, -S(O)₂-O-, -S(O)₂-NH-, -S(O)-NH-, -Se-, -Se(O)-, -Se(O)₂-, -NHNHC(O)-, -C(O)NHNH-, -OP(O)(O)O-, -phosphamide-,

-thiophosphodiester-, -S-tetrafluorophenyl-S-, , , , , or polyethylene glycol.

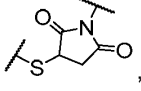
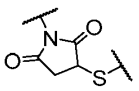
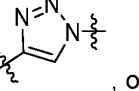
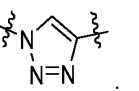
47. The compound of claim 46, wherein at least one linker comprises at least one carboxylic acid, sulfonic acid, sulfinic acid, or phosphoric acid, and has a net negative charge at physiological pH.

48. The compound of claim 46 or 47, wherein each X^1 is each independently: -CH-,



; wherein each R^{11} is independently a carboxylic acid, a sulfonic acid, a sulfinic acid, or a phosphoric acid.

49. The compound of any one of claims 46-48, wherein each L^1 between two X^1 groups is independently -NHC(O)-, -C(O)NH-, -N(CH₃)C(O)-, or -C(O)N(CH₃)-, and each L^1 linking an

R^X is independently -S-, -NHC(O)-, -C(O)NH-, -N(CH₃)C(O)-, -C(O)N(CH₃)-, , , , or .

R^{8a} is $R^{8b}R^{8c}$, wherein R^{8b} is a linear C_1 - C_5 alkynyl, C_2 - C_5 alkenyl, or C_2 - C_5 alkynyl, wherein R^{8c} is $-N(R^{8d})_{2-3}$ or guanidino, wherein each R^{8d} is independently -H or a linear or branched C_1 - C_3 alkyl;

R^{9a} is $-C(O)NH_2$, $-C(O)-OH$, $-CH_2-C(O)NH_2$, $-CH_2-C(O)-OH$, or $-R^{9b}-[linker]-R^{X_{n1}}$;

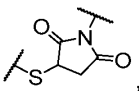
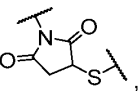
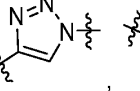
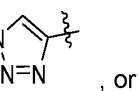
R^{9b} is $-C(O)NH-$;

R^{A7a} is C_1 - C_3 alkynyl;

R^{A10} is absent or $-[linker]-R^{X_{n1}}$;

when R^{A10} is absent, then R^{A1a} is a linear C_1 - C_5 alkyl optionally substituted with a single substituent selected from: -SH, -OH, amino, carboxy, guanidino, $-NH-C(O)-CH_3$, $-S-C(O)-CH_3$, $-O-C(O)-CH_3$, $-NH-C(O)-(phenyl)$, $-S-C(O)-(phenyl)$, $-O-C(O)-(phenyl)$, $-NH-(CH_3)_{1-2}$, $-NH_2-CH_3$, $-N(CH_3)_{2-3}$, $-S-CH_3$, $-O-CH_3$, or a branched C_1 - C_{10} alkyl, alkenyl, or alkynyl;

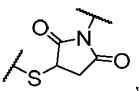
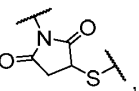
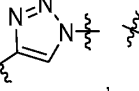
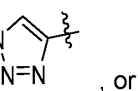
when R^{A10} is $-[linker]-R^{X_{n1}}$, then R^{A1a} is $R^{A1e}R^{A1f}$, wherein R^{A1e} is a linear C_1 - C_5 alkynyl, C_2 - C_5 alkenyl, or C_2 - C_5 alkynyl, and R^{A1f} is $-NH-C(O)-$, $-C(O)-$, $-O-$, $-C(O)NH-$, $-C(O)-N(CH_3)-$, $-NHC(S)-$, $-C(S)NH-$, $-N(CH_3)C(S)-$, $-C(O)N(CH_3)-$, $-N(CH_3)C(O)-$, $-C(S)N(CH_3)-$, $-NHC(S)NH-$, $-NHC(O)NH-$, $-S-$, $-S(O)-$, $-S(O)-O-$, $-S(O)_2-$, $-S(O)_2-NH-$, $-S(O)-NH-$, $-NHNHC(O)-$,

$-C(O)NHNH-$, , , , , or polyethylene glycol;

the linker is each independently a linear or branched chain of 1-10 units of X^1L^1 and/or $X^1(L^1)_2$, wherein:

each X^1 is, independently, a linear, branched, and/or cyclic C_1 - C_{15} alkyl, C_2 - C_{15} alkenyl or C_2 - C_{15} alkynyl wherein 0-6 carbons are independently replaced by N, S, and/or O heteroatoms, and substituted with 0-3 groups independently selected from one or a combination of oxo, hydroxyl, sulfhydryl, halogen, guanidino, carboxylic acid, sulfonic acid, sulfinic acid, and/or phosphoric acid;

each L^1 is independently $-NH-C(O)-$, $-NH-$, $-C(O)-$, $-O-$, $-C(O)NH-$, $-C(O)-N(CH_3)-$, $-NHC(S)-$, $-C(S)NH-$, $-N(CH_3)C(S)-$, $-C(O)N(CH_3)-$, $-N(CH_3)C(O)-$, $-C(S)N(CH_3)-$, $-NHC(S)NH-$, $-NHC(O)NH-$, $-S-$, $-S(O)-$, $-S(O)-O-$, $-S(O)_2-$, $-S(O)_2-O-$, $-S(O)_2-NH-$, $-S(O)-NH-$, $-Se-$, $-Se(O)-$, $-Se(O)_2-$, $-NHNHC(O)-$, $-C(O)NHNH-$, $-OP(O)(O)O-$, -phosphamide-, -thiophosphodiester-, -S-

tetrafluorophenyl-S-, , , , , or polyethylene glycol;

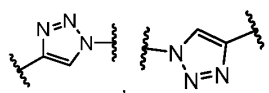
or

alternatively, the linker together with R^{A1f} forms a linear or branched peptide linker (Xaa)₁₋₅, wherein each Xaa is independently selected from a proteinogenic amino acid residue or a nonproteinogenic amino acid residue; and wherein an amino group in each Xaa is optionally methylated;

each n₁ is independently 0, 1 or 2;

each R^x is a therapeutic moiety, a fluorescent label, a radiolabeled group, or a group capable of being radiolabelled;

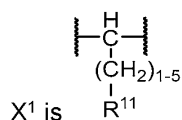
wherein 0-3 peptide backbone amides are independently replaced with

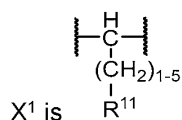


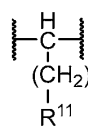
wherein 0-3 peptide backbone amides are N-methylated.

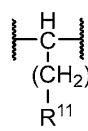
54. The compound of any one of claims 1-53, wherein R^{A10} is -[linker]-R^x_{n1}.

55. The compound of claim 53 or 54, wherein the linker is X¹L¹, X¹L¹X¹L¹, or X¹L¹X¹L¹X¹L¹, wherein each X¹ is same or different and each L¹ is same or different; and



X¹ is , wherein each R¹¹ is independently a carboxylic acid, a sulfonic acid, a sulfinic acid, or a phosphoric acid.



56. The compound of claim 55, wherein each X¹ is , wherein each R¹¹ is independently a carboxylic acid, a sulfonic acid, a sulfinic acid, or a phosphoric acid.

57. The compound of claim 53 or 54, wherein the linker together with R^{A1f} forms a linear or branched peptide linker (Xaa)₁₋₅, wherein at least one Xaa is selected from cysteic acid, Glu, Asp, or 2-amino adipic acid (2-Aad); and wherein an amino group in each Xaa is optionally methylated.

58. The compound of claim 53 or 54, wherein the linker together with R^{A1f} forms a single amino acid residue selected from cysteic acid, Glu, Asp, or 2-aminoadipic acid (2-Aad); and wherein an amino group in Xaa is optionally methylated.

59. The compound of claim 53 or 54, wherein the linker together with R^{A1f} forms a linear or branched peptide linker (Xaa)₁₋₅, wherein at least one Xaa is selected from Dap, Dab, Orn, Arg, hArg, Agb, Agp, Acp, Pip, or N^ε, N^ε, N^ε-trimethyl-lysine; and wherein an amino group in each Xaa is optionally methylated.

60. The compound of claim 53 or 54, wherein the linker together with R^{A1f} forms a single amino acid residue selected from D-Arg, L-Arg, D-hArg, L-hArg, or Pip; and wherein an amino group in Xaa is optionally methylated.

61. The compound of any one of claims 1-60, wherein zero peptide backbone amides are replaced.

62. The compound of any one of claims 1-61, wherein zero peptide backbone amides are N-methylated.

63. The compound of any one of claims 1-62, wherein:
R^{9a} is -C(O)NH₂, -C(O)-OH, -R^{9b}-R^{9c}, or -R^{9b}-[linker]-R^{X_{n1}}; and
R^{9b} is -C(O)NH-, -C(O)-N(CH₃)-, -C(O)N(CH₃)-, or -C(O)NHNH-.

64. The compound of claim 63, wherein the compound of Formula A, Formula A-I, or Formula A-II, or a salt or solvate thereof have the following combinations:

- (1) -NH-CH(R^{1a})-C(O)- forms a Phe residue;
- NH-CH(R^{2a})-C(O)- forms a (3-I)Tyr residue;
- NH-CH(R^{3a})-C(O)- forms a Lys(iPr) residue;
- NH-CH(R^{4a})-C(O)- forms a D-Arg residue;
- NH-CH(R^{5a})-C(O)- forms a 2-Nal or a (4-NH₂)Phe residue;
- NH-CH(R^{6a})-C(O)- forms a Gly residue;
- NH-CH(R^{A7a})-C(O)- forms a D-amino acid residue, wherein R^{A7a} is C₁-C₃ alkyenyl;
- and
- NH-CH(R^{8a})- together with -C(O)- from R^{9a} forms a Lys(iPr) residue;

- (2) -NH-CH(R^{1a})-C(O)- forms a Phe residue;
 -NH-CH(R^{2a})-C(O)- forms a Tyr residue;
 -NH-CH(R^{3a})-C(O)- forms a Lys(iPr) residue;
 -NH-CH(R^{4a})-C(O)- forms a D-Arg residue;
 -NH-CH(R^{5a})-C(O)- forms a 2-Nal residue or (4-NH₂)Phe residue;
 -NH-CH(R^{6a})-C(O)- forms a D-Ala;
 -NH-CH(R^{A7a})-C(O)- forms a D-amino acid residue, wherein R^{A7a} is C₁-C₃ alkyenyl;
 and
 -NH-CH(R^{8a})- together with -C(O)- from R^{9a} forms a Lys(iPr) residue;
- (3) -NH-CH(R^{1a})-C(O)- forms a Phe residue;
 -NH-CH(R^{2a})-C(O)- forms a (4-NH₂)Phe residue;
 -NH-CH(R^{3a})-C(O)- forms a Lys(iPr) residue;
 -NH-CH(R^{4a})-C(O)- forms a D-Arg residue;
 -NH-CH(R^{5a})-C(O)- forms a 2-Nal residue or a (4-NH₂)Phe residue;
 -NH-CH(R^{6a})-C(O)- forms a Gly residue;
 -NH-CH(R^{A7a})-C(O)- forms a D-amino acid residue, wherein R^{A7a} is C₁-C₃ alkyenyl;
 and
 -NH-CH(R^{8a})- together with -C(O)- from R^{9a} forms a Lys(iPr) residue;
- (4) -NH-CH(R^{1a})-C(O)- forms a Phe residue;
 -NH-CH(R^{2a})-C(O)- forms a (4-NO₂)Phe residue;
 -NH-CH(R^{3a})-C(O)- forms a Lys(iPr) residue;
 -NH-CH(R^{4a})-C(O)- forms a D-Arg residue;
 -NH-CH(R^{5a})-C(O)- forms a 2-Nal residue or a (4-NH₂)Phe residue; and
 -NH-CH(R^{6a})-C(O)- forms a Gly residue;
 -NH-CH(R^{A7a})-C(O)- forms a D-amino acid residue, wherein R^{A7a} is C₁-C₃ alkyenyl;
 and
 -NH-CH(R^{8a})- together with -C(O)- from R^{9a} forms Lys(iPr) residue;
- (5) -NH-CH(R^{1a})-C(O)- forms a Phe residue;
 -NH-CH(R^{2a})-C(O)- forms a hTyr residue;
 -NH-CH(R^{3a})-C(O)- forms a Lys(iPr) residue;

- NH-CH(R^{4a})-C(O)- forms a D-Arg residue;
 - NH-CH(R^{5a})-C(O)- forms a 2-Nal residue or a (4-NH₂)Phe residue;
 - NH-CH(R^{6a})-C(O)- forms a Gly residue;
 - NH-CH(R^{A7a})-C(O)- forms a D-amino acid residue, wherein R^{A7a} is C₁-C₃ alkyenyl;
 - and
 - NH-CH(R^{8a})- together with -C(O)- from R^{9a} forms Lys(iPr) residue;
- (6)
- NH-CH(R^{1a})-C(O)- forms a Phe residue;
 - NH-CH(R^{2a})-C(O)- forms a Tyr residue;
 - NH-CH(R^{3a})-C(O)- forms a Lys(iPr) residue;
 - NH-CH(R^{4a})-C(O)- forms a D-Arg residue;
 - NH-CH(R^{5a})-C(O)- forms a 2-Nal residue or a (4-NH₂)Phe residue;
 - NH-CH(R^{6a})-C(O)- forms a D-His residue;
 - NH-CH(R^{A7a})-C(O)- forms a D-amino acid residue, wherein R^{A7a} is C₁-C₃ alkyenyl;
 - and
 - NH-CH(R^{8a})- together with -C(O)- from R^{9a} forms a Lys(iPr) residue;
- (7)
- NH-CH(R^{1a})-C(O)- forms a Phe residue;
 - NH-CH(R^{2a})-C(O)- forms a Tyr residue;
 - NH-CH(R^{3a})-C(O)- forms a Lys(iPr) residue;
 - NH-CH(R^{4a})-C(O)- forms a D-Arg residue;
 - NH-CH(R^{5a})-C(O)- forms a 2-Nal residue or a (4-NH₂)Phe residue;
 - NH-CH(R^{6a})-C(O)- forms a His residue;
 - NH-CH(R^{A7a})-C(O)- forms a D-amino acid residue, wherein R^{A7a} is C₁-C₃ alkyenyl;
 - and
 - NH-CH(R^{8a})- together with -C(O)- from R^{9a} forms a Lys(iPr) residue;
- (8)
- NH-CH(R^{1a})-C(O)- forms a Phe residue;
 - NH-CH(R^{2a})-C(O)- forms a Tyr residue;
 - NH-CH(R^{3a})-C(O)- forms a Lys(iPr) residue;
 - NH-CH(R^{4a})-C(O)- forms a D-Arg residue;
 - NH-CH(R^{5a})-C(O)- forms a 2-Nal residue or a (4-NH₂)Phe residue;
 - NH-CH(R^{6a})-C(O)- forms a D-Ser residue;

- NH-CH(R^{A7a})-C(O)- forms a D-amino acid residue, wherein R^{A7a} is C₁-C₃ alkyenyl;
and
-NH-CH(R^{8a})- together with -C(O)- from R^{9a} forms a Lys(iPr) residue;
- (9) -NH-CH(R^{1a})-C(O)- forms a Phe residue;
-NH-CH(R^{2a})-C(O)- forms a Tyr residue;
-NH-CH(R^{3a})-C(O)- forms a Lys(iPr) residue;
-NH-CH(R^{4a})-C(O)- forms a D-Arg residue;
-NH-CH(R^{5a})-C(O)- forms a 2-Nal residue or a (4-NH₂)Phe residue;
-NH-CH(R^{6a})-C(O)- forms a D-Glu residue;
-NH-CH(R^{A7a})-C(O)- forms a D-amino acid residue, wherein R^{A7a} is C₁-C₃ alkyenyl;
and
-NH-CH(R^{8a})- together with -C(O)- from R^{9a} forms a Lys(iPr) residue;
- (10) -NH-CH(R^{1a})-C(O)- forms a Phe residue;
-NH-CH(R^{2a})-C(O)- forms a Tyr residue;
-NH-CH(R^{3a})-C(O)- forms a Lys(iPr) residue;
-NH-CH(R^{4a})-C(O)- forms a D-Arg residue;
-NH-CH(R^{5a})-C(O)- forms a 2-Nal residue or a (4-NH₂)Phe residue;
-NH-CH(R^{6a})-C(O)- forms a D-His residue;
-NH-CH(R^{A7a})-C(O)- forms a D-amino acid residue, wherein R^{A7a} is C₁-C₃ alkyenyl;
and
-NH-CH(R^{8a})- together with -C(O)- from R^{9a} forms a Lys(iPr) residue;
- (11) -NH-CH(R^{1a})-C(O)- forms a Phe residue;
-NH-CH(R^{2a})-C(O)- forms a Tyr residue;
-NH-CH(R^{3a})-C(O)- forms a Lys(iPr) residue;
-NH-CH(R^{4a})-C(O)- forms a D-Arg residue;
-NH-CH(R^{5a})-C(O)- forms a (2-Ant)Ala residue;
-NH-CH(R^{6a})-C(O)- forms a Gly residue;
-NH-CH(R^{A7a})-C(O)- forms a D-amino acid residue, wherein R^{A7a} is C₁-C₃ alkyenyl;
and
-NH-CH(R^{8a})- together with -C(O)- from R^{9a} forms a Lys(iPr) residue;

- (12) -NH-CH(R^{1a})-C(O)- forms a Lys(Ac) residue;
 -NH-CH(R^{2a})-C(O)- forms a Tyr residue;
 -NH-CH(R^{3a})-C(O)- forms a Lys(iPr) residue;
 -NH-CH(R^{4a})-C(O)- forms a D-Arg residue;
 -NH-CH(R^{5a})-C(O)- forms a 2-Nal residue or a (4-NH₂)Phe residue;
 -NH-CH(R^{6a})-C(O)- forms a D-Ala residue;
 -NH-CH(R^{A7a})-C(O)- forms a D-amino acid residue, wherein R^{A7a} is C₁-C₃ alkyenyl;
 and
 -NH-CH(R^{8a})- together with -C(O)- from R^{9a} forms a Lys(iPr) residue.
65. The compound of claim 63, wherein the compound of Formula A, Formula A-I, or Formula A-II, or a salt or solvate thereof have the following combinations:
 -NH-CH(R^{2a})-C(O)- forms a Tyr residue;
 -NH-CH(R^{3a})-C(O)- forms a Lys(iPr) residue;
 -NH-CH(R^{4a})-C(O)- forms a D-Arg residue;
 -NH-CH(R^{A7a})-C(O)- forms a D-amino acid residue, wherein R^{A7a} is C₁-C₃ alkyenyl; and
 -NH-CH(R^{8a})- together with -C(O)- from R^{9a} forms a Lys(iPr) residue.
66. The compound of claim 65, wherein -NH-CH(R^{6a})-C(O)- forms a Gly residue, a D-Ala residue, a D-Gln residue, or a D-Asn residue.
67. The compound of claim 65 or 66, wherein -NH-CH(R^{1a})-C(O)- forms a Phe residue and R^{10a} is absent.
68. The compound of any one of claims 65-67, wherein R^{A10} is -[linker]-R^{X_{n1}}, R^{A1e} is linear C₁-C₅ alkylenyl, and R^{A1f} is -NH-C(O)-.
69. The compound of claim 63, wherein the compound of Formula B, or a salt or solvate thereof have the following combinations:
 -NH-CH(R^{2a})-C(O)- forms a Tyr residue;
 -NH-CH(R^{3a})-C(O)- forms a Lys(iPr) residue;
 -NH-CH(R^{4a})-C(O)- forms a D-Arg residue; and
 -NH-CH(R^{8a})- together with -C(O)- from R^{9a} forms a Lys(iPr) residue.

70. The compound of claim 69, wherein:

-NH-CH(R^{6a})-C(O)- forms a Gly residue, a D-Ala residue, a D-Gln residue, or a D-Asn residue; and

-NH-CH(R^{5a})-C(O)- forms a 2-Nal residue, a (4-NH₂)Phe residue or a (2-Ant)Ala residue.

71. The compound of any one of claims 1 to 70, wherein at least one R^x is a radiolabeled group or a group capable of being radiolabelled.

72. The compound of any one of claims 1 to 71, wherein each group capable of being radiolabelled is independently selected from: a metal chelator optionally in complex with a radiometal or radioisotope-bound metal; a prosthetic group containing trifluoroborate (BF₃); or a prosthetic group containing a silicon-fluorine-acceptor moiety, a sulphonyl fluoride, or a phosphoryl fluoride.

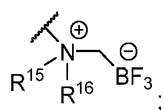
73. The compound of claim 72, wherein the metal chelator is in complex with the radioisotope.

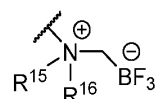
74. The compound of claim 72 or 73, wherein the metal chelator is a polyaminocarboxylate chelator.

75. The compound of claim 712 or 73, wherein the metal chelator is DOTA, MACROPA, or a derivative thereof.

76. The compound of claim 72 or 73, wherein the metal chelator is selected from Table 2.

77. The compound of claim 72, wherein the prosthetic group containing BF₃ is -R¹³R¹⁴BF₃

wherein R¹³ is -(CH₂)₁₋₅- and -R¹⁴BF₃ is selected from Table 3 or Table 4 or is ; wherein each R¹⁵ and each R¹⁶ are independently a branched or linear C₁-C₅ alkyl.

78. The compound of claim 77, wherein -R¹⁴BF₃ is .

79. The compound of claim 78, wherein R¹⁵ and R¹⁶ are each methyl.
80. The compound of any one of claims 72 and 77-79, wherein the prosthetic group containing BF₃ comprises at least one ¹⁸F.
81. The compound of any one of claims 1 to 80, wherein at least one R^x is a therapeutic moiety.
82. The compound of any one of claims 1 to 81, wherein at least one R^x is fluorescent label.
83. A compound selected from one or more of:
- cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-D-Gln-D-Glu]-Lys(iPr);
 - cyclo[Phe-(3-I)Tyr-Lys(iPr)-D-Arg-2-Nal-Gly-D-Glu]-Lys(iPr);
 - cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr);
 - cyclo[Phe-(4-NH₂)Phe-Lys(iPr)-D-Arg-2-Nal-Gly-D-Glu]-Lys(iPr);
 - cyclo[Phe-(4-NO₂)Phe-Lys(iPr)-D-Arg-2-Nal-Gly-D-Glu]-Lys(iPr);
 - cyclo[Phe-hTyr-Lys(iPr)-D-Arg-2-Nal-Gly-D-Glu]-Lys(iPr);
 - cyclo[Phe-hTyr-Lys(iPr)-D-Arg-2-Nal-D-Ala-D-Glu]-Lys(iPr);
 - cyclo[Phe-(4-NH₂)Phe-Lys(iPr)-D-Arg-2-Nal-D-Ala-D-Glu]-Lys(iPr);
 - cyclo[Lys(Ac)-Tyr-Lys(iPr)-D-Arg-Trp-D-Ala-D-Glu]-Lys(iPr);
 - cyclo[Phe-Tyr-Lys(iPr)-D-Arg-(4-NH₂)Phe-D-Ala-D-Glu]-Lys(iPr);
 - cyclo[Lys(Ac)-Glu-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr);
 - cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-D-His-D-Glu]-Lys(iPr);
 - cyclo[Lys(Ac)-Gln-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr);
 - cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-His-D-Glu]-Lys(iPr);
 - cyclo[Phe-D-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr);
 - cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ser-D-Glu]-Lys(iPr);
 - cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-D-Leu-D-Glu]-Lys(iPr);
 - cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-D-Asn-D-Glu]-Lys(iPr);
 - cyclo[Phe-Tyr-Arg(Me)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr);

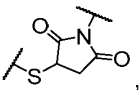
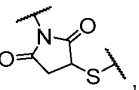
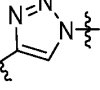
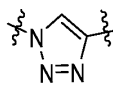
cyclo[Phe-Tyr-Arg(Me₂)(asym)-D-Arg-2Nal-Gly-D-Glu]-Lys(iPr);
 cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-D-Glu-D-Glu]-Lys(iPr);
 cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2Nal-D-Dab-D-Glu]-Lys(iPr);
 cyclo[Phe-Tyr-Lys(iPr)-D-Arg-(2-Ant)Ala-Gly-D-Glu]-Lys(iPr);
 cyclo(isoindole)[Phe-Tyr-Lys(iPr)-D-Arg-(2-Ant)Ala-Gly-D-Cys]-Lys(iPr);
 cyclo(isoindole)[Phe-Tyr-Lys(iPr)-D-Arg-(2-Ant)Ala-Gly-Cys]-Lys(iPr);
 cyclo[Lys(Ac)-Tyr-Lys(iPr)-D-Arg-2Nal-Gly-D-Glu]-Lys(iPr);
 cyclo[Lys(CysAcid)-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr);
 cyclo[Orn(CysAcid)-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr);
 cyclo[Dap(CysAcid)-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr);
 cyclo[Lys(CysAcid)-(3-I)Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr);
 cyclo[Lys(D-Arg)-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr); or
 cyclo(tryptathionine)[Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Cys]-Lys(iPr);
 or a salt or solvate thereof;

wherein the compound is optionally bound to a radiolabeled group or a group capable of being radiolabelled, optionally through a linker.

84. The compound of claim 83, wherein the linker is each independently a linear or branched chain of 1-10 units of X¹L¹ and/or X¹(L¹)₂, wherein:

each X¹ is, independently, a linear, branched, and/or cyclic C₁-C₁₅ alkylenyl, C₂-C₁₅ alkenenyl or C₂-C₁₅ alkynenyl wherein 0-6 carbons are independently replaced by N, S, and/or O heteroatoms, and substituted with 0-3 groups independently selected from one or a combination of oxo, hydroxyl, sulfhydryl, halogen, guanidino, carboxylic acid, sulfonic acid, sulfinic acid, and/or phosphoric acid; and

each L¹ is independently -NH-C(O)-, -NH-, -C(O)-, -O-, -C(O)NH-, -C(O)-N(CH₃)-, -NHC(S)-, -C(S)NH-, -N(CH₃)C(S)-, -C(O)N(CH₃)-, -N(CH₃)C(O)-, -C(S)N(CH₃)-, -NHC(S)NH-, -NHC(O)NH-, -S-, -S(O)-, -S(O)-O-, -S(O)₂-, -S(O)₂-O-, -S(O)₂-NH-, -S(O)-NH-, -Se-, -Se(O)-, -Se(O)₂-, -NHNHC(O)-, -C(O)NHNH-, -OP(O)(O)O-, -phosphamide-, -thiophosphodiester-, -S-

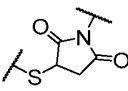
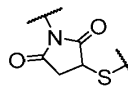
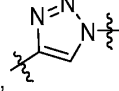
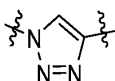
tetrafluorophenyl-S-, , , , , or polyethylene glycol;
 or

alternatively, the linker is a linear or branched peptide linker (Xaa)₁₋₅, wherein each Xaa is independently selected from a proteinogenic amino acid residue or a nonproteinogenic amino acid residue; and wherein an amino group in each Xaa is optionally methylated.

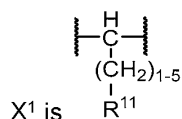
85. The compound of claim 83 or 84, wherein the linker is X¹L¹, X¹L¹X¹L¹, or X¹L¹X¹L¹X¹L¹, wherein each X¹ is same or different and each L¹ is same or different; wherein:

each X¹ is, independently, a linear, branched, and/or cyclic C₁-C₁₅ alkylenyl, C₂-C₁₅ alkenylenyl or C₂-C₁₅ alkynylenyl wherein 0-6 carbons are independently replaced by N, S, and/or O heteroatoms, and substituted with 0-3 groups independently selected from one or a combination of oxo, hydroxyl, sulfhydryl, halogen, guanidino, carboxylic acid, sulfonic acid, sulfinic acid, and/or phosphoric acid; and

each L¹ is independently -NH-C(O)-, -C(O)-, -O-, -C(O)NH-, -C(O)-N(CH₃)-, -NHC(S)-, -C(S)NH-, -N(CH₃)C(S)-, -C(O)N(CH₃)-, -N(CH₃)C(O)-, -C(S)N(CH₃)-, -NHC(S)NH-, -NHC(O)NH-, -S-, -S(O)-, -S(O)-O-, -S(O)₂-, -S(O)₂-O-, -S(O)₂-NH-, -S(O)-NH-, -Se-, -Se(O)-, -Se(O)₂-, -NHNHC(O)-, -C(O)NHNH-, -OP(O)(O-)O-, -phosphamide-, -

thiophosphodiester-, -S-tetrafluorophenyl-S-, , , , , or polyethylene glycol.

86. The compound of claim 84 or 85, wherein the linker is X¹L¹, X¹L¹X¹L¹, or X¹L¹X¹L¹X¹L¹, wherein each X¹ is same or different and each L¹ is same or different; and



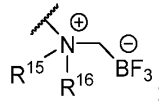
X¹ is $\begin{array}{c} \text{H} \\ | \\ \text{---C---} \\ | \\ (\text{CH}_2)_{1-5} \\ | \\ \text{R}^{11} \end{array}$, wherein each R¹¹ is independently a carboxylic acid, a sulfonic acid, a sulfinic acid, or a phosphoric acid.

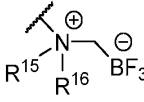


87. The compound of claim 84 or 85, wherein each X¹ is $\begin{array}{c} \text{H} \\ | \\ \text{---C---} \\ | \\ (\text{CH}_2) \\ | \\ \text{R}^{11} \end{array}$, wherein each R¹¹ is independently a carboxylic acid, a sulfonic acid, a sulfinic acid, or a phosphoric acid.

88. The compound of claim 84, wherein the linker is a linear or branched peptide linker (Xaa)₁₋₅, wherein at least one Xaa is selected from cysteic acid, Glu, Asp, or 2-aminoadipic acid (2-Aad); and wherein an amino group in each Xaa is optionally methylated.
89. The compound of claim 84, wherein the linker is a single amino acid residue selected from cysteic acid, Glu, Asp, or 2-aminoadipic acid (2-Aad); and wherein an amino group the single amino acid residue is optionally methylated.
90. The compound of claim 84, wherein the linker is a linear or branched peptide linker (Xaa)₁₋₅, wherein at least one Xaa is selected from Dap, Dab, Orn, Arg, hArg, Agb, Agp, Acp, Pip, or N^ε, N^ε, N^ε-trimethyl-lysine; and wherein an amino group in each Xaa is optionally methylated.
91. The compound of claim 84, wherein the linker is a single amino acid residue selected from D-Arg, L-Arg, D-hArg, L-hArg, or Pip; and wherein an amino group in the single amino acid residue is optionally methylated.
92. The compound of any one of claims 83-91, wherein the group capable of being radiolabelled is independently selected from: a metal chelator optionally in complex with a radiometal or radioisotope-bound metal; a prosthetic group containing trifluoroborate (BF₃); or a prosthetic group containing a silicon-fluorine-acceptor moiety, a sulphonyl fluoride, or a phosphoryl fluoride.
93. The compound of claim 92, wherein the metal chelator is in complex with the radioisotope.
94. The compound of claim 92 or 93, wherein the metal chelator is DOTA, H2-MACROPA, or a derivative thereof.
95. The compound of claim 92 or 93, wherein the metal chelator is selected from Table 2.

96. The compound of claim 92, wherein the prosthetic group containing BF_3 is $-\text{R}^{13}\text{R}^{14}\text{BF}_3$

wherein R^{13} is $-(\text{CH}_2)_{1-5}-$ and $-\text{R}^{14}\text{BF}_3$ is selected from Table 3 or Table 4 or is ; wherein each R^{15} and each R^{16} are independently a branched or linear $\text{C}_1\text{-C}_5$ alkyl.

97. The compound of claim 96, wherein $-\text{R}^{14}\text{BF}_3$ is , wherein R^{15} and R^{16} are each methyl.

98. The compound of any one of claims 92, 96, and 97, wherein the prosthetic group containing BF_3 comprises at least one ^{18}F .

99. The compound of claim 83, selected from
 cyclo[Lys(CysAcid-DOTA)-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr);
 cyclo[Lys(CysAcid-amido-N,N-dimethyl-ammoniomethyl-trifluoroborate)-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr); or
 cyclo[Lys(CysAcid-triazole-N,N-dimethyl-ammoniomethyl-trifluoroborate)-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr);
 or a salt or solvate thereof.

100. The compound of 99, wherein cyclo[Lys(CysAcid-DOTA)-Tyr-Lys(iPr)-D-Arg-2Nal-D-Ala-D-Glu]-Lys(iPr) is in complex with the radioisotope.

101. The compound of any one of claims 72-76, 92-95 and 100, wherein the radioisotope is ^{64}Cu , ^{67}Cu , ^{90}Y , ^{153}Sm , ^{149}Tb , ^{161}Tb , ^{177}Lu , ^{225}Ac , ^{213}Bi , ^{224}Ra , ^{212}Bi , ^{212}Pb , ^{227}Th , ^{223}Ra , ^{47}Sc , ^{186}Re , ^{188}Re , $^{94\text{m}}\text{Tc}$, ^{68}Ga , ^{61}Cu , ^{67}Ga , $^{99\text{m}}\text{Tc}$, ^{111}In , ^{44}Sc , ^{86}Y , ^{89}Zr , ^{90}Nb , $^{117\text{m}}\text{Sn}$, ^{165}Er , ^{211}As , ^{203}Pb , ^{212}Pb , ^{47}Sc , ^{166}Ho , ^{149}Pm , ^{159}Gd , ^{105}Rh , ^{109}Pd , ^{198}Au , ^{199}Au , ^{175}Yb , ^{142}Pr , or $^{114\text{m}}\text{In}$.

102. The compound of any one of claims 101, wherein the radioisotope is ^{177}Lu , ^{111}In , ^{213}Bi , ^{68}Ga , ^{67}Ga , ^{203}Pb , ^{212}Pb , ^{44}Sc , ^{47}Sc , ^{90}Y , ^{86}Y , ^{225}Ac , $^{117\text{m}}\text{Sn}$, ^{153}Sm , ^{149}Tb , ^{161}Tb , ^{165}Er , ^{224}Ra , ^{212}Bi , ^{227}Th , ^{223}Ra , ^{64}Cu , or ^{67}Cu .

103. The compound of any one of claims 1-82, for use in imaging a CXCR4-expressing tissue in a subject or for imaging an inflammatory condition or disease, wherein at least one R^x comprises an imaging radioisotope or is complexed with an imaging radioisotope.

104. The compound of claim 103, wherein the imaging radioisotope is ⁶⁸Ga, ⁶⁷Ga, ⁶¹Cu, ⁶⁴Cu, ^{99m}Tc, ^{114m}In, ¹¹¹In, ⁴⁴Sc, ⁸⁶Y, ⁸⁹Zr, ⁹⁰Nb, ¹⁸F, ¹³¹I, ¹²³I, ¹²⁴I or ⁷²As.

105. The compound of any one of claims 83-102, for use in imaging a CXCR4-expressing tissue in a subject or for imaging an inflammatory condition or disease, wherein the compound is bound to a metal chelator complexed with an imaging radioisotope, optionally through a linker; or the compound is bound to a prosthetic group containing BF₃ comprising at least one ¹⁸F, optionally through a linker.

106. The compound of claim 105, wherein the imaging radioisotope is ⁶⁸Ga, ⁶⁷Ga, ⁶¹Cu, ⁶⁴Cu, ^{99m}Tc, ^{114m}In, ¹¹¹In, ⁴⁴Sc, ⁸⁶Y, ⁸⁹Zr, ⁹⁰Nb, ¹³¹I, ¹²³I, ¹²⁴I or ⁷²As.

107. The compound of claim 101 for use in imaging a CXCR4-expressing tissue in a subject or for imaging an inflammatory condition or disease.

108. The compound of any one of claims 1-82, for use in treating a disease or condition characterized by expression of CXCR4 in a subject, wherein at least one R^x comprises a therapeutic radioisotope or is complexed with a therapeutic radioisotope, or at least one R^x comprises a therapeutic moiety.

109. The compound of any one of claims 83-102, for use in treating a disease or condition characterized by expression of CXCR4 in a subject, wherein the compound is bound to a metal chelator complexed with a therapeutic radioisotope, optionally through a linker.

110. The compound of claim 108 or 109, wherein the therapeutic radioisotope is ¹⁶⁵Er, ²¹²Bi, ²¹¹At, ¹⁶⁶Ho, ¹⁴⁹Pm, ¹⁵⁹Gd, ¹⁰⁵Rh, ¹⁰⁹Pd, ¹⁹⁸Au, ¹⁹⁹Au, ¹⁷⁵Yb, ¹⁴²Pr, ¹⁷⁷Lu, ¹¹¹In, ²¹³Bi, ²⁰³Pb, ²¹²Pb, ⁴⁷Sc, ⁹⁰Y, ^{117m}Sn, ¹⁵³Sm, ¹⁴⁹Tb, ¹⁶¹Tb, ²²⁴Ra, ²²⁵Ac, ²²⁷Th, ²²³Ra, ⁷⁷As, ¹³¹I, ⁶⁴Cu or ⁶⁷Cu.

111. The compound of any one of claims 108-110, wherein the disease or condition is a CXCR4-expressing cancer.

112. A method of imaging a CXCR4-expressing tissue, comprising administering an effective amount of the compound of any one of claims 103-107 to a subject in need of such imaging.

113. A method of treating a disease or condition characterized by expression of CXCR4 in a subject, comprising administering an effective amount of the compound of any one of claims 108-111 to a subject in need thereof.

114. The method of claim 113, wherein the disease or condition is a CXCR4-expressing cancer.