(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
02 June 2022 (02.06.2022)

WIPO | PCT

(10) International Publication Number
WO 2022/115799 A1

(51) International Patent Classification:
A61K 51/04 (2006.01) *A61K 49/00* (2006.01)
A61K 38/10 (2006.01) *C07K 16/30* (2006.01)
A61K 38/17 (2006.01) *A61P 35/00* (2006.01)
C07K 7/08 (2006.01) *G01N 30/02* (2006.01)

(21) International Application Number:
PCT/US2021/061252

(22) International Filing Date:
30 November 2021 (30.11.2021)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/119,557 30 November 2020 (30.11.2020) US

(71) Applicant: **RAYZEBIO, INC.** [US/US]; 5505 Morehouse Dr., Suite 300, San Diego, CA 92121 (US).

(72) Inventors: **SONG, Ken**; 5505 Morehouse Dr., Suite 300, San Diego, CA 92121 (US). **CHARYCH, Deborah**; 5505 Morehouse Dr., Suite 300, San Diego, CA 92121 (US). **LIU, Junjie**; 5505 Morehouse Dr., Suite 300, San Diego, CA 92121 (US). **NONCOVICH, Alain**; 5505 Morehouse Dr., Suite 300, San Diego, CA 92121 (US). **JIANG, Guangcheng**; 5505 Morehouse Dr., Suite 300, San Diego, CA 92121 (US). **COLE, Derek**; 5505 Morehouse Dr., Suite 300, San Diego, CA 92121 (US).

(74) Agent: **CHEN, Ying**; Wilson Sonsini, 650 Page Mill Road, Palo Alto, CA 94304 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW,

(54) Title: RADIOPHARMACEUTICAL CONJUGATES TARGETING GUANYLYL CYCLASE C, AND COMPOSITIONS AND USES THEREOF

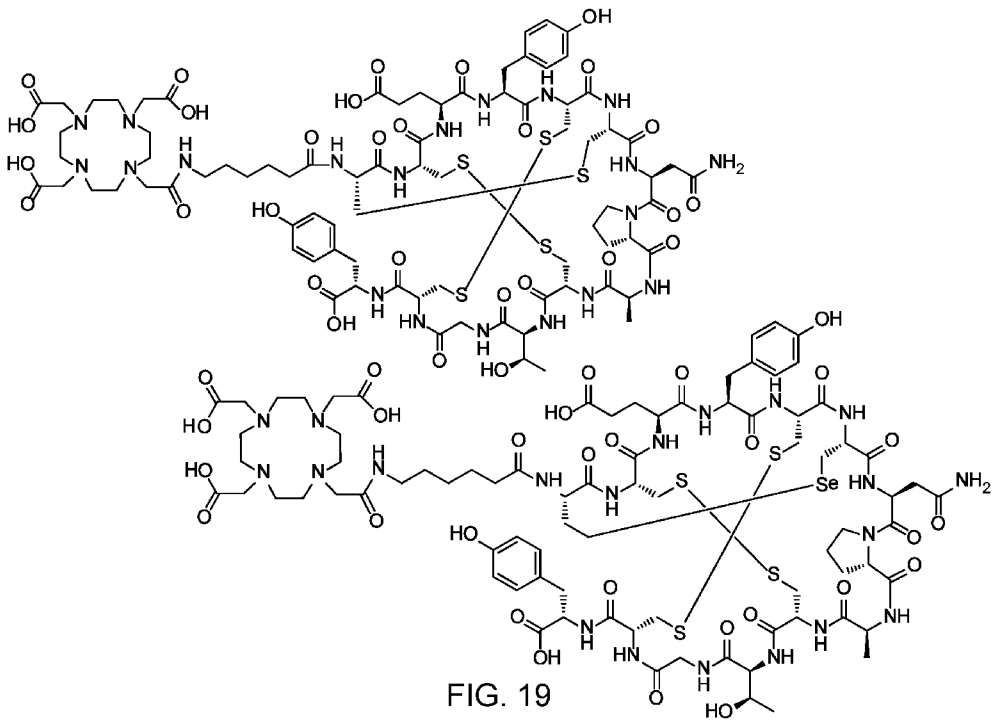


FIG. 19

(57) Abstract: Provided herein are radiopharmaceutical conjugate compositions and uses thereof. In one aspect, provided herein are conjugates that comprise a GCC binding peptide, a metal chelator configured to bind with a radionuclide, a linker that attaches the GCC binding peptide with the metal chelator, and optionally a radionuclide. Also provided herein are conjugates that have improved elimination profile and plasma stability that are suitable for radiopharmaceutical applications and methods of using the same in treating and/or diagnosing diseases such as cancer.

WO 2022/115799 A1

[Continued on next page]

SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*
— *with sequence listing part of description (Rule 5.2(a))*

RADIOPHARMACEUTICAL CONJUGATES TARGETING GUANYLYL CYCLASE C, AND COMPOSITIONS AND USES THEREOF

CROSS-REFFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 63/119,557, filed on November 30, 2020, which is incorporated herein by reference in its entirety.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on November 24, 2021, is named 59541-708_601_SL.txt and is 27,279 bytes in size.

BACKGROUND

[0003] Cancers of the gastrointestinal tract such as colorectal cancer remain one of the leading cause of death in the United States. Despite process in early detection and treatment, a portion of the diagnosed patients still suffer late stage disease. Although many promising agents for metastatic disease have become clinically available (e.g., tyrosine kinase inhibitors, anti-angiogenesis agents, etc.), the five-year survival rate for this population remains low. Therefore, a need exists in the medicinal arts for compounds, formulations, and methods for treating these cancers.

SUMMARY

[0004] Provided herein are radiopharmaceutical conjugates and pharmaceutical compositions comprising said conjugates. In some embodiments, the subject radiopharmaceutical conjugates are useful for the treatment of diseases, e.g., cancer. In one aspect, the present disclosure provides conjugates having improved elimination profile and metabolic, chemical and/or physical stabilities that are suitable for radiopharmaceutical applications while maintaining the protein binding affinity. It is surprisingly discovered that, for some conjugates, the target binding affinity, plasma stability and serum half-live can be adjusted by modifying the hydrophobicity and length of the linker connecting a guanylyl cyclase C (GCC) binding peptide with a metal chelator. Accordingly, in one aspect, disclosed herein are GCC binding conjugates with optimized linkers and configurations.

[0005] In one aspect, the present disclosure provides a conjugate comprising a guanylyl cyclase C (GCC) binding peptide, wherein the GCC binding peptide comprises an amino acid sequence that has at least 85% identity to any one of SEQ ID NOs: 1-42; a metal chelator configured to bind

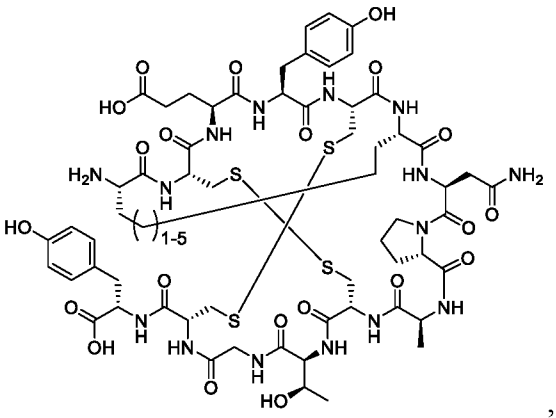
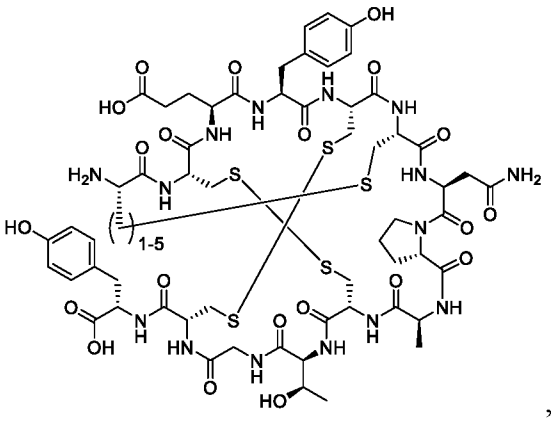
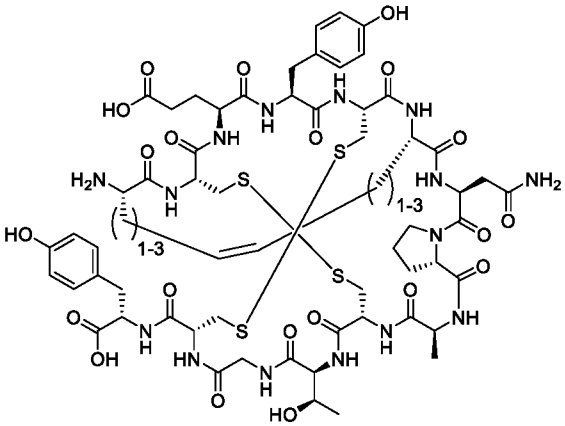
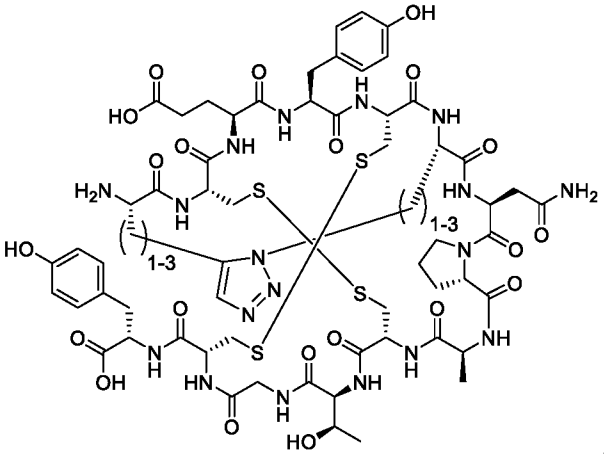
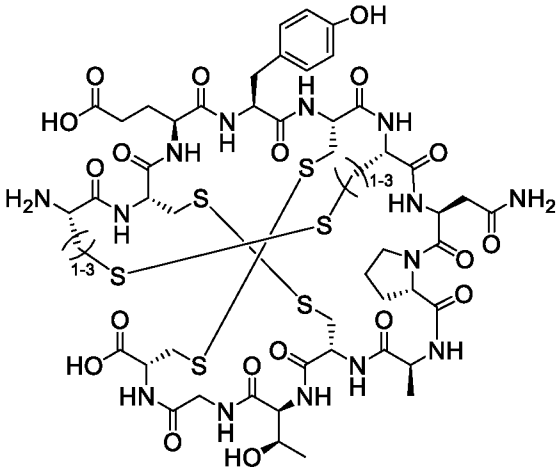
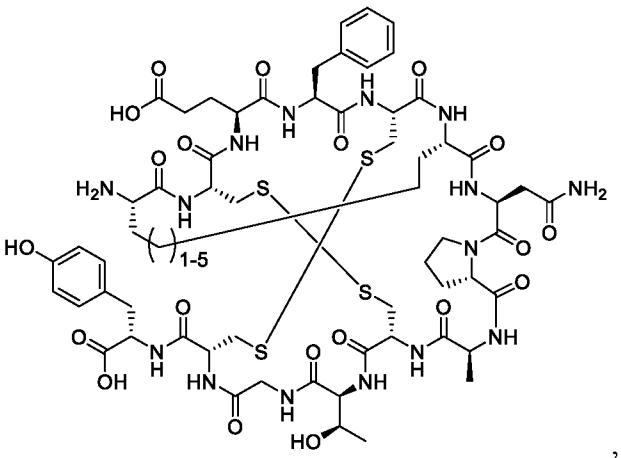
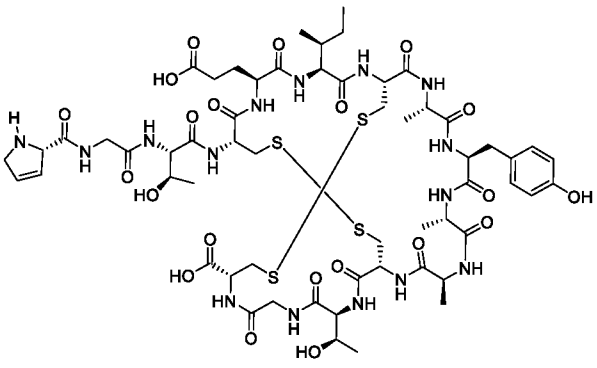
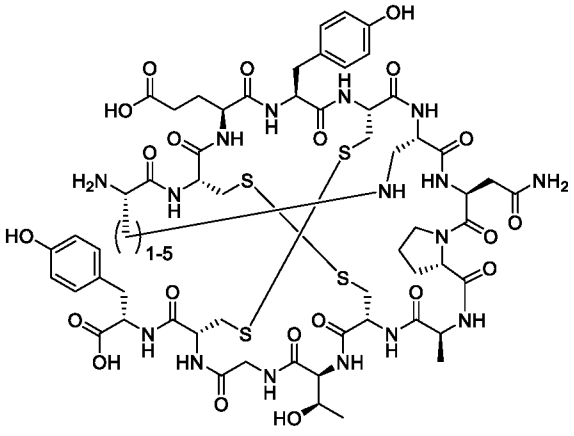
with a radionuclide, wherein the metal chelator is selected from FIGs. 3-17; one or more linkers; and optionally a radionuclide, e.g., a radionuclide of Table 5A or Table 5B.

[0006] In one aspect, the present disclosure provides a conjugate comprising a guanylyl cyclase C (GCC) binding peptide, wherein the GCC binding peptide comprises an amino acid sequence that has at least 85% identity to any one of SEQ ID NOs: 1-42, a metal chelator configured to bind with a radionuclide; a linker that covalently attaches the GCC binding peptide with the metal chelator; and an alpha particle-emitting radionuclide.

[0007] In one aspect, the present disclosure provides a conjugate comprising a guanylyl cyclase C (GCC) binding peptide; a metal chelator configured to bind with a radionuclide; and a linker that covalently attaches the GCC binding peptide with the metal chelator, wherein a dissociation constant (Kd) between the linker and human serum albumin is at most 100 μM, as determined at room temperature in human serum condition.

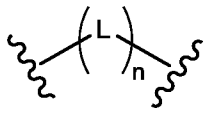
[0008] In one aspect, the present disclosure provides a conjugate comprising (i) a guanylyl cyclase C (GCC) binding peptide, wherein the GCC binding peptide comprises an amino acid sequence that has at least 85% identity to any one of SEQ ID NOs: 1-42; (ii) a metal chelator configured to bind with a radionuclide; (iii) a linker that covalently attaches the GCC binding peptide with the metal chelator; and (iv) an alpha-particle emitting radionuclide bound to the metal chelator. In one aspect, the present disclosure provides a conjugate comprising (i) a guanylyl cyclase C (GCC) binding peptide; (ii) a metal chelator configured to bind with a radionuclide; and (iii) a linker that covalently attaches the GCC binding peptide with the metal chelator, wherein 5% to 99% of the conjugate binds to Human Serum Albumin (HSA) in vitro as determined by HSA-HPLC method. In some embodiments, the GCC binding peptide comprises an amino acid sequence that has at least 85% identity to any one of SEQ ID NOs: 1-42. In some embodiments, the GCC binding peptide consists of an amino acid sequence of any one of SEQ ID NOs: 1-19. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 1. In some embodiments, the binding peptide further comprises 1, 2 or 3 intramolecular disulfide bonds. In some embodiments, the binding peptide further comprises one or more of alkylene, alkenylene,

heteroalkylene, and heteroaryl. In some embodiments, the binding peptide is selected from:


,

,

,

,

,

,

and

.

In some embodiments, the binding peptide further comprises one intramolecular heteroalkylene, alkylene or alkenylene bond. In some embodiments, the heteroalkylene, alkylene or alkenylene is optionally substituted with one or more R^{10}, wherein each R^{10} is independently halogen, amino, -OH, -SH, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; or two R^{10} on the same atoms are taken together to form a cycloalkyl or heterocycloalkyl; or two R^{10} on different atoms are taken together to form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl. In some embodiments, the binding peptide comprises an unnatural amino acid at the N-terminus, the C-terminus, or both. In some embodiments, the binding peptide comprises a modified tyrosine at the C-terminus. In some embodiments, the modified tyrosine is a D-tyrosine, N-methyl-L-tyrosine, α-methyl-L-tyrosine, or L-tyrosinamide. In some embodiments, the metal chelator is selected from DOTA, DOTP, DOTMA, DOTAM, DTPA, NTA, EDTA, DO3A, DO2A, NOC, NOTA, TETA, DiAmSar, CB-Cyclam, CB-TE2A, DOTA-4AMP, and NOTP. In some embodiments, the metal chelator is DOTA. In some embodiments, the linker is a bond.

[0009] In some embodiments, the linker has a structure of Formula (II-1)



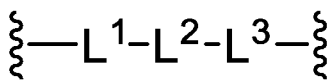
Formula (II-1)

wherein each L is independently -O-, $-NR^L$-, $-N(R^L)_2$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, =CH-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LC(=S)NR^L$-, $-CR^L=N$-, $-N=CR^L$, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, $-S(=O)_2NR^LC(=O)$-, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{30} alkylene, substituted or unsubstituted C_2-C_{30} alkenylene, substituted or unsubstituted C_2-C_{30} alkynylene, substituted or unsubstituted C_1-C_{30} heteroalkylene, -(C_1-C_{30} alkylene)-O-, -O-(C_1-C_{30} alkylene)-, -(C_1-C_{30} alkylene)-NR^L-, $-NR^L$-(C_1-C_{30} alkylene)-, -(C_1-C_{30} alkylene)-$N(R^L)_2$-, or $-N(R^L)_2$-(C_1-C_{30} alkylene)-; and

each R^L is independently hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

n is 1 to 20.

[0010] In some embodiments, the linker comprises a structure of Formula (II-1a),

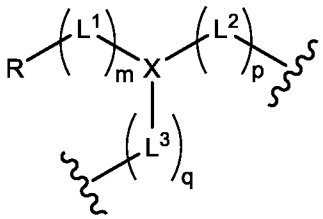


Formula (II-1a)

wherein each of L^1 and L^3 is independently -O-, $-NR^L$-, $-N(R^L)_2$-, -OP(=O)(OR^L)O-, -S-, -S(=O)-, $-S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, or $-S(=O)_2NR^LC(=O)$-; and

L^2 is absent, substituted or unsubstituted C_1-C_{30} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene.

[0011] In some embodiments, the linker has a structure of Formula (II-2)



Formula (II-2),

wherein each L^1, L^2, and L^3 is independently -O-, $-NR^L$-, $-N(R^L)_2$-, -OP(=O)(OR^L)O-, -S-, -S(=O)-, $-S(=O)_2$-, =CH-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LC(=S)NR^L$-, $-CR^L=N$-, $-N=CR^L$, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, $-S(=O)_2NR^LC(=O)$-, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{30} alkylene, substituted or unsubstituted C_2-C_{30} alkenylene, substituted or unsubstituted C_2-C_{30} alkynylene, substituted or unsubstituted C_1-C_{30} heteroalkylene, -(C_1-C_{30} alkylene)-O-, -O-(C_1-C_{30} alkylene)-, -(C_1-C_{30} alkylene)-NR^L-, $-NR^L$-(C_1-C_{30} alkylene)-, -(C_1-C_{30} alkylene)-$N(R^L)_2$-, or $-N(R^L)_2$-(C_1-C_{30} alkylene)-; and

R is hydrogen, azide, substituted or unsubstituted C_1-C_{30} alkyl, substituted or unsubstituted C_1-C_{30} heteroalkyl, substituted or unsubstituted C_2-C_{30} alkenyl, substituted or unsubstituted C_2-C_{30} alkynyl, substituted or unsubstituted C_3-C_{30} cycloalkyl, substituted or unsubstituted C_2-C_{30} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R^L is independently hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted

or unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted C_3-C_{30} cycloalkyl, substituted or unsubstituted C_2-C_{30} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^X is independently hydrogen, halo, -CN, -NO_2, -OH, -SH, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted C_3-C_8 cycloalkyl, or substituted or unsubstituted C_2-C_7 heterocycloalkyl,

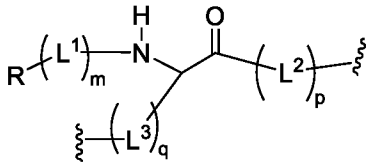
X is N or CR^X;

m is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

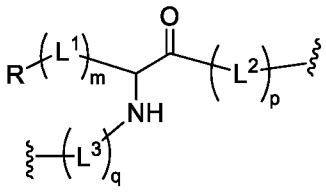
p is 0, 1, 2, 3, 4, 5, or 6; and

q is 0, 1, 2, 3, 4, 5, and 6.

[0012] In some embodiments, the linker has a structure of Formula (II-2a) or Formula (II-2b)



Formula (II-2a) or



Formula (II-2b),

wherein

each L^1, L^2, and L^3 is independently -O-, –NR^L-, –$N(R^L)_2$-, -OP(=O)(OR^L)O-, -S-, -S(=O)-, -$S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, -C(=O)NR^L-, -NR^LC(=O)-, -OC(=O)NR^L-, -NR^LC(=O)O-, -NR^LC(=O)NR^L-, -$NR^L$$S(=O)_2$-, -$S(=O)_2NR^L$-, -C(=O)$NR^L$$S(=O)_2$-, -$S(=O)_2NR^L$C(=O)-, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{20} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene;

R^L is hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted C_3-C_8 cycloalkyl, or substituted or unsubstituted C_2-C_7 heterocycloalkyl;

R is hydrogen, azide, substituted or unsubstituted C_1-C_{30} alkyl, substituted or unsubstituted C_1-C_{30} heteroalkyl, substituted or unsubstituted C_2-C_{30} alkenyl, substituted or unsubstituted C_2-C_{30} alkynyl, substituted or unsubstituted C_3-C_{30} cycloalkyl, substituted or unsubstituted C_2-C_{30} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

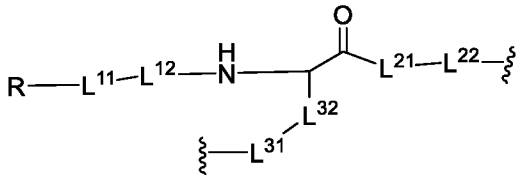
m is 0, 1, 2, 3, 4, 5, 6, 7, 8, or 9;

p is 0, 1, 2, 3, 4, or 5; and

q is 0, 1, 2, 3, 4, or 5.

[0013] In some embodiments, the linker connects to the metal chelator through L^3 and to the peptide through L^2. In some embodiments, the linker has a structure of Formula (II-2a).

[0014] In some embodiments, the linker of Formula (II-2a) has a structure of Formula (II-2aa),



Formula (II-2aa)

wherein,

L^{11} is absent, -O-, $-NR^L$-, $-N(R^L)_2$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, or $-S(=O)_2NR^LC(=O)$-;

L^{12} is absent, -O-, $-NR^L$-, $-N(R^L)_2$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, $-S(=O)_2NR^LC(=O)$-, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{20} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene;

L^{21} is absent, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{20} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene;

L^{22} is absent, -O-, $-NR^L$-, $-N(R^L)_2$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, or $-S(=O)_2NR^LC(=O)$-;

L^{31} is absent, -O-, $-NR^L$-, $-N(R^L)_2$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, or $-S(=O)_2NR^LC(=O)$-;

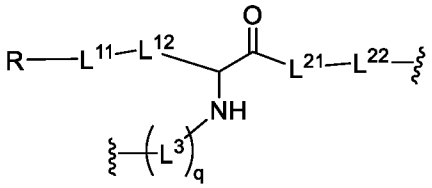
L^{32} is absent, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{20} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene;

R^L is hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted C_3-C_8 cycloalkyl, or substituted or unsubstituted C_2-C_7 heterocycloalkyl;

R is hydrogen, substituted or unsubstituted C_1-C_{30} alkyl, substituted or unsubstituted C_1-C_{30} heteroalkyl, substituted or unsubstituted C_2-C_{30} alkenyl, substituted or unsubstituted C_3-C_{30} cycloalkyl, substituted or unsubstituted C_2-C_{30} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

q is 0, 1, 2, 3, 4, or 5.

[0015] In some embodiments, the linker has a structure of Formula (II-2b). In some embodiments, the linker of Formula (II-2b) has a structure of Formula (II-2ba),



Formula (II-2ba)

wherein,

L^{11} is absent, -O-, $-NR^L$-, $-N(R^L)_2$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, or $-S(=O)_2NR^LC(=O)$-;

L^{12} is absent, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{20} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene;

L^{21} is absent, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{20} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene;

L^{22} is absent, -O-, $-NR^L$-, $-N(R^L)_2$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, -

$OC(=O)NR^L$-, -$NR^LC(=O)O$-, -$NR^LC(=O)NR^L$-, -$NR^LS(=O)_2$-, -$S(=O)_2NR^L$-, -$C(=O)NR^LS(=O)_2$-, or -$S(=O)_2NR^LC(=O)$-;

L^3 is -O-, –NR^L-, –$N(R^L)_2$-, -$OP(=O)(OR^L)O$-, -S-, -S(=O)-, -$S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, -$C(=O)NR^L$-, -$NR^LC(=O)$-, -$OC(=O)NR^L$-, -$NR^LC(=O)O$-, -$NR^LC(=O)NR^L$-, -$NR^LS(=O)_2$-, -$S(=O)_2NR^L$-, -$C(=O)NR^LS(=O)_2$-, -$S(=O)_2NR^LC(=O)$-, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{20} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene;

R^L is hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted C_3-C_8 cycloalkyl, or substituted or unsubstituted C_2-C_7 heterocycloalkyl;

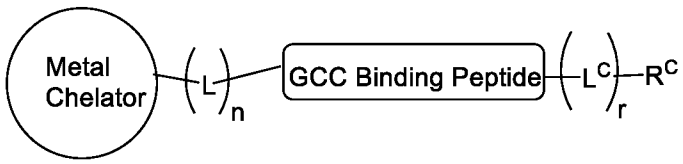
R is hydrogen, substituted or unsubstituted C_1-C_{30} alkyl, substituted or unsubstituted C_1-C_{30} heteroalkyl, substituted or unsubstituted C_2-C_{30} alkenyl, substituted or unsubstituted C_3-C_{30} cycloalkyl, substituted or unsubstituted C_2-C_{30} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

q is 0, 1, 2, 3, 4, or 5.

[0016] In some embodiments, the linker comprises a click chemistry residue. In some embodiments, the linker comprises one or more of substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and one or more amino acids. In some embodiments, the linker comprises one or more of a substituted or unsubstituted C_6-C_{10} aryl, substituted or unsubstituted C_5-C_9 heteroaryl, a sterol, sulfonamide, phosphate ester, polyethylene glycol, C_3-C_{20} alkylene, or amino acid residues. In some embodiments, the linker comprises one or more lysine residues. In some embodiments, the linker comprises one or more glutamate residues. In some embodiments, the linker comprises phenyl iodide or carboxylic acid. In some embodiments, the linker comprises 3 to 30 intervening atoms between the metal chelator and the binding peptide. In some embodiments, the linker comprises 6 to 18 intervening atoms between the metal chelator and the binding peptide. In some embodiments, a dissociation constant (Kd) between the linker and human serum albumin is at most 25 μM, as determined in vitro at room temperature in human serum condition. In some embodiments, about 40%-60% of the conjugate binds to HSA in vitro as determined by HSA-HPLC method. In some embodiments, about 60%-80% of the conjugate binds to HSA in vitro as

determined by HSA-HPLC method. In some embodiments, the linker is attached to the binding peptide via the N terminus of the binding peptide. In some embodiments, the conjugate comprises a second linker attached to the C terminus of the binding peptide. In some embodiments, the conjugate comprises an alpha particle-emitting radionuclide bound to the metal chelator. In some embodiments, the alpha particle-emitting radionuclide is actinium-225, astatine-211, radium-223, or thorium-227. n some embodiments, the alpha particle-emitting radionuclide is actinium-225. In some embodiments, the conjugate comprises two or more metal chelators. In some embodiments, the conjugate has an elimination half-life in rats of about 1 to 120 hours. In some embodiments, the conjugate has an elimination half-life in rats of about 2 to 24 hours. In some embodiments, a half-life of the conjugate in human serum condition is about 2 to 20 hours, 5 to 20 hours, 8 to 15 hours, or 10 to 14 hours at 37 °C.

[0017] In one aspect, the present disclosure provides a conjugate comprising (i) a guanylyl cyclase C (GCC) binding peptide; (ii) a metal chelator configured to bind with a radionuclide; and (iii) a linker that covalently attaches the GCC binding peptide with the metal chelator, wherein the conjugate has a structure of Formula (I)



Formula (I)

wherein,

the linker $-(L)_n-$ comprises 2 to 50 intervening atoms between the metal chelator and the binding peptide;

each L is independently -O-, $-NR^L-$, $-OP(=O)(OR^L)O-$, -S-, -S(=O)-, $-S(=O)_2-$, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L-$, $-NR^LC(=O)-$, $-OC(=O)NR^L-$, $-NR^LC(=O)O-$, $-NR^LC(=O)NR^L-$, $-NR^LC(=S)NR^L-$, $-CR^L=N-$, $-N=CR^L$, $-NR^LS(=O)_2-$, $-S(=O)_2NR^L-$, $-C(=O)NR^LS(=O)_2-$, $-S(=O)_2NR^LC(=O)-$, substituted or unsubstituted C_1-C_{30} alkylene, substituted or unsubstituted C_2-C_{30} alkenylene, substituted or unsubstituted C_2-C_{30} alkynylene, substituted or unsubstituted C_1-C_{30} heteroalkylene, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

L^C is absent, -O-, $-NR^L-$, $-OP(=O)(OR^L)O-$, -S-, -S(=O)-, $-S(=O)_2-$, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L-$, $-NR^LC(=O)-$, $-OC(=O)NR^L-$, $-NR^LC(=O)O-$, $-NR^LC(=O)NR^L-$, $-NR^LC(=S)NR^L-$, $-CR^L=N-$, $-N=CR^L$, $-NR^LS(=O)_2-$, $-S(=O)_2NR^L-$, $-C(=O)NR^LS(=O)_2-$, $-S(=O)_2NR^LC(=O)-$, substituted or unsubstituted C_1-C_{30} alkylene, substituted or unsubstituted C_2-C_{30} alkenylene, substituted or unsubstituted C_2-C_{30}

alkynylene, substituted or unsubstituted C_1-C_{30} heteroalkylene, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or an amino acid;

each R^L is independently hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

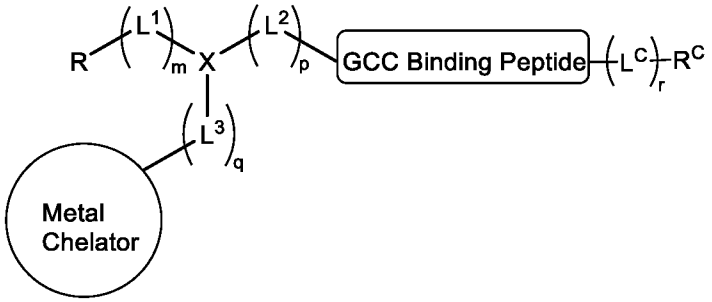
R^C is hydrogen, halogen, -CN, -NO_2, -SR^a, -OR^a, -$N(R^a)_2$, -$C(=O)R^a$, -$C(=O)OR^a$, -$C(=O)NR^aR^a$, azide, substituted or unsubstituted C_1-C_{30} alkyl, substituted or unsubstituted C_1-C_{30} heteroalkyl, substituted or unsubstituted C_2-C_{30} alkenyl, substituted or unsubstituted C_2-C_{30} alkynyl, substituted or unsubstituted C_3-C_{30} cycloalkyl, substituted or unsubstituted C_2-C_{30} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl,

wherein each R^a is independently H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl);

n is 0 or an integer from 1 to 20; and

r is 0 or an integer from 1 to 5.

[0018] In some embodiments, the linker –$(L)_n$- comprises 3 to 20 intervening atoms between the metal chelator and the binding peptide. In some embodiments, –$(L)_n$- is bound to the N-terminus of the GCC binding peptide and L^C is bound to the C-terminus of the GCC binding peptide. In some embodiments, the linker –$(L)_n$- comprises a hydrophobic group selected from a C_8-C_{30} fatty acid, C_8-C_{30} fatty alcohol, C_8-C_{30} alkyl, aryl, heteroaryl, one or more amino acid residues, or a combination thereof. In some embodiments, –$(L)_n$- comprises one or more lysine residues. In some embodiments, –$(L)_n$- comprises one or more glutamate residues. In some embodiments, the conjugate has a structure of Formula (Ia),



Formula (Ia)

wherein,

each L^1, L^2, and L^3 is independently -O-, $-NR^L$-, -OP(=O)(OR^L)O-, -S-, -S(=O)-, $-S(=O)_2$-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LC(=S)NR^L$-, $-CR^L=N$-, $-N=CR^L$, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, $-S(=O)_2NR^LC(=O)$-, substituted or unsubstituted C_1-C_{30} alkylene, substituted or unsubstituted C_2-C_{30} alkenylene, substituted or unsubstituted C_2-C_{30} alkynylene, substituted or unsubstituted C_1-C_{30} heteroalkylene, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R and R^C are each independently hydrogen, halogen, -CN, $-NO_2$, $-SR^a$, $-OR^a$, $-N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, azide, substituted or unsubstituted C_1-C_{30} alkyl, substituted or unsubstituted C_1-C_{30} heteroalkyl, substituted or unsubstituted C_2-C_{30} alkenyl, substituted or unsubstituted C_2-C_{30} alkynyl, substituted or unsubstituted C_3-C_{30} cycloalkyl, substituted or unsubstituted C_2-C_{30} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl,

wherein each R^a is independently H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl);

R^L is hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted C_3-C_{30} cycloalkyl, substituted or unsubstituted C_2-C_{30} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^X is independently hydrogen, halo, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted C_3-C_8 cycloalkyl, or substituted or unsubstituted C_2-C_7 heterocycloalkyl,

X is N or CR^X;

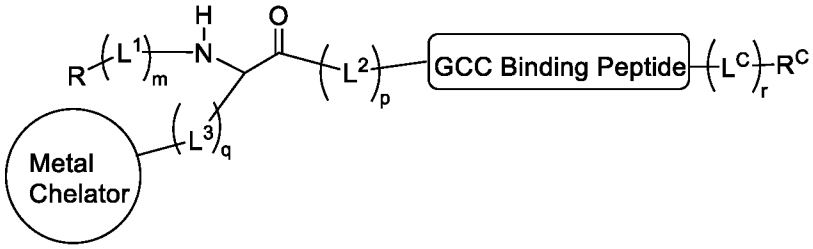
m is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

p is 0, 1, 2, 3, 4, 5, or 6;

q is 0, 1, 2, 3, 4, 5, or 6; and

r is 0, 1, 2, 3, 4, or 5.

[0019] In some embodiments, the conjugate has a structure of Formula (Iaa),



Formula (Iaa)

wherein

each L^1, L^2, and L^3 is independently -O-, $–NR^L$-, $–N(R^L)_2$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, $-S(=O)_2NR^LC(=O)$-, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{20} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene;

R^L is hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted C_3-C_8 cycloalkyl, or substituted or unsubstituted C_2-C_7 heterocycloalkyl;

R is hydrogen, azide, substituted or unsubstituted C_1-C_{30} alkyl, substituted or unsubstituted C_1-C_{30} heteroalkyl, substituted or unsubstituted C_2-C_{30} alkenyl, substituted or unsubstituted C_2-C_{30} alkynyl, substituted or unsubstituted C_3-C_{30} cycloalkyl, substituted or unsubstituted C_2-C_{30} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

L^C is absent, -O-, $–NR^L$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LC(=S)NR^L$-, $-CR^L=N$-, $-N=CR^L$, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, $-S(=O)_2NR^LC(=O)$-, substituted or unsubstituted C_1-C_{30} alkylene, substituted or unsubstituted C_2-C_{30} alkenylene, substituted or unsubstituted C_2-C_{30} alkynylene, substituted or unsubstituted C_1-C_{30} heteroalkylene, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or an amino acid;

R^C is hydrogen, halogen, -CN, $-NO_2$, $-SR^a$, $-OR^a$, $-N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, azide, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_1-C_{12} heteroalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl,

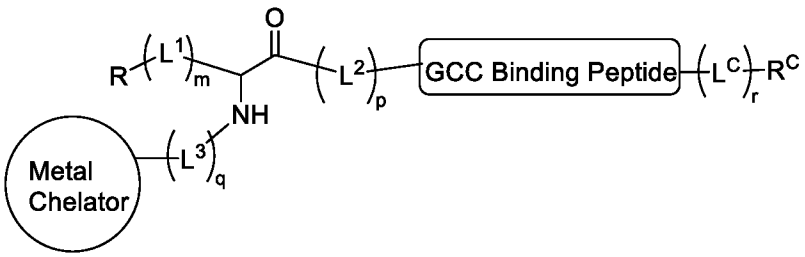
wherein each R^a is independently H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl);

m is 0, 1, 2, 3, 4, 5, 6, 7, 8, or 9;

p is 0, 1, 2, 3, 4, or 5; and

q is 0, 1, 2, 3, 4, or 5.

[0020] In some embodiments, the conjugate has a structure of Formula (Iab),



Formula (Iab)

wherein

each L^1, L^2, and L^3 is independently -O-, $-NR^L$-, $-N(R^L)_2$-, -OP(=O)(OR^L)O-, -S-, -S(=O)-, -$S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, -C(=O)NR^L-, -NR^LC(=O)-, -OC(=O)NR^L-, -NR^LC(=O)O-, -NR^LC(=O)NR^L-, -$NR^L S(=O)_2$-, -$S(=O)_2NR^L$-, -C(=O)$NR^L S(=O)_2$-, -$S(=O)_2NR^L$C(=O)-, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{20} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene;

R^L is hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted C_3-C_8 cycloalkyl, or substituted or unsubstituted C_2-C_7 heterocycloalkyl;

R is hydrogen, azide, substituted or unsubstituted C_1-C_{30} alkyl, substituted or unsubstituted C_1-C_{30} heteroalkyl, substituted or unsubstituted C_2-C_{30} alkenyl, substituted or unsubstituted C_2-C_{30} alkynyl, substituted or unsubstituted C_3-C_{30} cycloalkyl, substituted or unsubstituted C_2-C_{30} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

L^C is absent, -O-, $-NR^L$-, -OP(=O)(OR^L)O-, -S-, -S(=O)-, -$S(=O)_2$-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, -C(=O)NR^L-, -NR^LC(=O)-, -OC(=O)NR^L-, -NR^LC(=O)O-, -NR^LC(=O)NR^L-, -NR^LC(=S)NR^L-, -CR^L=N-, -N=CR^L, -$NR^L S(=O)_2$-, -$S(=O)_2NR^L$-, -

$C(=O)NR^LS(=O)_2$-, -$S(=O)_2NR^LC(=O)$-, substituted or unsubstituted C_1-C_{30} alkylene, substituted or unsubstituted C_2-C_{30} alkenylene, substituted or unsubstituted C_2-C_{30} alkynylene, substituted or unsubstituted C_1-C_{30} heteroalkylene, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or an amino acid;

R^C is hydrogen, halogen, -CN, -NO_2, -SR^a, -OR^a, -$N(R^a)_2$, -$C(=O)R^a$, -$C(=O)OR^a$, -$C(=O)NR^aR^a$, azide, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_1-C_{12} heteroalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl,

wherein each R^a is independently H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl);

m is 0, 1, 2, 3, 4, 5, 6, 7, 8, or 9;

p is 0, 1, 2, 3, 4, or 5; and

q is 0, 1, 2, 3, 4, or 5.

[0021] In some embodiments, the binding peptide comprises an unnatural amino acid, e.g., at the C-terminus. In some embodiments, the binding peptide comprises a modified tyrosine at the C-terminus. In some embodiments, the GCC binding peptide comprises an amino acid sequence that has at least 85% identity to any one of SEQ ID NOs: 1-42. In some embodiments, the GCC binding peptide comprises an amino acid sequence selected from SEQ ID NOs: 1-42. In some embodiments, the GCC binding peptide further comprises 1 to 3 intramolecular bonds selected from heteroalkylene, alkylene and alkenylene bonds. In some embodiments, the metal chelator is selected from DOTA, DOTP, DOTMA, DOTAM, DTPA, NTA, EDTA, DO3A, DO2A, NOC, NOTA, TETA, DiAmSar, CB-Cyclam, CB-TE2A, DOTA-4AMP, or NOTP. In some embodiments, the metal chelator is DOTA. In some embodiments, the conjugate comprises a radionuclide bound to the metal chelator. In some embodiments, the radionuclide is an alpha particle-emitting radionuclide selected from actinium-225, astatine-211, radium-223, and thorium-227. In some embodiments, the radionuclide is lutetium-177 or actinium-225.

[0022] In one aspect, the present disclosure provides a conjugate selected from a structure of Table 1.

[0023] In one aspect, the present disclosure provides a conjugate comprising: a structure selected from Table 1 and a radionuclide bound to a metal chelator of the structure.

[0024] In one aspect, the present disclosure provides a conjugate, wherein the conjugate is a salt or solvate of a conjugate of described herein.

[0025] In one aspect, the present disclosure provides a pharmaceutical composition comprising a herein-described conjugate and a pharmaceutically acceptable excipient or carrier.

[0026] In one aspect, the present disclosure provides a method of treating a gastrointestinal tract cancer in a subject in need thereof, comprising administering to the subject a conjugate described herein, or a pharmaceutical composition described herein. In some embodiments, the cancer is colorectal cancer. In some embodiments, the method comprises administering a second therapeutic agent that is a GCC receptor agonist. In some embodiments, the method comprises administering (i) a first conjugate comprising a radionuclide configured for companion diagnostic and (ii) a second conjugate comprising a radionuclide selected from an alpha or beta-particle emitter, wherein the first and the second conjugate have the same structure except for the radionuclide. In some embodiments, the radionuclide of the first conjugate is selected from Lu-177, Technetium-99m, In-111, Ga-68, Cu-64, and Zr-89.

[0027] In one aspect, the present disclosure provides a method of treating a gastrointestinal tract cancer in a subject in need thereof, comprising administering to the subject a herein-described conjugate or a pharmaceutical composition comprising the conjugate. In some embodiments, the cancer is colorectal cancer. In some embodiments, the method comprises administering a second agent that binds to a GCC receptor. In some embodiments, the method comprises administering a second agent that is a GCC receptor agonist. In some embodiments, the method comprises administering a second agent that is a GCC receptor antagonist.

INCORPORATION BY REFERENCE

[0028] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference for the specific purposes identified herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0029] Various aspects of the disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the disclosure are utilized, and the accompanying drawings of which:

[0030] FIGs. 1A-1J illustrate amino acid sequences of exemplary GCC binding peptides, including disulfide bridges. FIG. 1A illustrates amino acid sequence for linaclotide; FIG. 1B illustrates amino acid sequence for plecanatide; FIG. 1C illustrates amino acid sequence for F^{19}-STh (1-19), an analogue of a wild-type *Escherichia coli* heat-stable peptide (STh) moiety with a Tyr to Phe alteration at position 19; FIG. 1D illustrates amino acid sequence for $R^{1,4}$, F^{19}-STh(1-19), an analogue of a wild-type STh moiety with a Tyr to Phe alteration at position 19 and having

arginine residues at positions 1 and 4; FIG. 1E illustrates amino acid sequence for F^9-STh(6-19), an analogue of a wild-type STh moiety; FIG. 1F illustrates amino acid sequence for F^{19}-STh (2-19), an analogue of a wild-type STh moiety; FIG. 1G illustrates amino acid sequence for uroguanylin; FIG. 1H illustrates amino acid sequence for guanylin; FIG. 1I illustrates amino acid sequence for lymphoguanylin; and FIG. 1J illustrates amino acid sequence for E. coli ST.

[0031] FIGs.2A-2D illustrate conjugates comprising exemplary linker structures that contain one or more motifs. FIG. 2A illustrates a conjugate comprising a metal chelator, a linker and a cyclized GCC binding peptide; FIG. 2B and FIG.2C illustrate conjugates comprising a metal chelator, a cyclized GCC binding peptide, and a linker that comprises two or more motifs; FIG. 2D illustrates a conjugate comprising a metal chelator, two cyclized GCC binding peptides, and a linker that comprises two or more motifs.

[0032] FIG.3 illustrates the structures of representative metal chelators.

[0033] FIG.4 illustrates the structures of representative metal chelators.

[0034] FIG.5 illustrates the structures of representative metal chelators.

[0035] FIG.6 illustrates the structures of representative metal chelators.

[0036] FIG.7 illustrates the structures of representative metal chelators.

[0037] FIG.8 illustrates the structures of representative metal chelators.

[0038] FIG.9 illustrates the structures of representative metal chelators.

[0039] FIG.10 illustrates the structures of representative metal chelators.

[0040] FIG.11 illustrates the structures of representative metal chelators.

[0041] FIG.12 illustrates the structures of representative metal chelators.

[0042] FIG.13 illustrates the structures of representative metal chelators.

[0043] FIG.14 illustrates the structures of representative metal chelators.

[0044] FIG.15 illustrates the structures of representative metal chelators.

[0045] FIG.16 illustrates the structures of representative metal chelators.

[0046] FIG.17 illustrates the structures of representative metal chelators.

[0047] FIG.18A illustrates plasma stability of linaclotide; FIG.18B illustrates plasma stability of La-C-02.

[0048] FIG.19 illustrates the structures of representative conjugates of the present disclosure.

[0049] FIG.20 illustrates the structures of representative conjugates of the present disclosure.

[0050] FIG.21 illustrates the structures of representative conjugates of the present disclosure.

[0051] FIG.22 illustrates the structures of representative conjugates of the present disclosure.

DETAILED DESCRIPTION

[0052] The present disclosure relates to radiopharmaceutical conjugate compositions and their use.

[0053] The following description and examples illustrate embodiments of the present disclosure in detail. It is to be understood that this present disclosure is not limited to the particular embodiments described herein and as such can vary. Those of skill in the art will recognize that there are numerous variations and modifications of this present disclosure, which are encompassed within its scope.

[0054] Although various features of the present disclosure may be described in the context of a single embodiment, the features may also be provided separately or in any suitable combination. Conversely, although the present disclosure may be described herein in the context of separate embodiments for clarity, the present disclosure may also be implemented in a single embodiment.

[0055] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[0056] All terms are intended to be understood as they would be understood by a person skilled in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the disclosure pertains.

[0057] The following definitions supplement those in the art and are directed to the current application and are not to be imputed to any related or unrelated case, *e.g.*, to any commonly owned patent or application. Although any methods and materials similar or equivalent to those described herein can be used in the practice for testing of the present disclosure, the preferred materials and methods are described herein. Accordingly, the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

I. Definitions

[0058] As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated below.

[0059] As used herein and in the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an agent" includes a plurality of such agents, and reference to "the cell" includes reference to one or more cells (or to a plurality of cells) and equivalents thereof known to those skilled in the art, and so forth. When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and subcombinations of ranges and specific embodiments therein are intended to be included.

[0060] The term "about" or "approximately" can mean within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, *i.e.*, the limitations of the measurement system. For example, "about" can mean within 1 or more than 1 standard deviation, per the practice in the art. Alternatively, "about" can mean a range of up to 20%, up to 15%, up to 10%, up to 5%, or up to 1% of a given value. Alternatively, particularly with respect to biological systems or processes, the term can mean within an order of magnitude, within 5-fold, or within 2-fold, of a value.

[0061] The term "comprising" (and related terms such as "comprise" or "comprises" or "having" or "including") is not intended to exclude that in other certain embodiments, for example, an embodiment of any composition of matter, composition, method, or process, or the like, described herein, "consist of" or "consist essentially of" the described features.

[0062] "Amino" refers to the $-NH_2$ radical.

[0063] "Cyano" refers to the -CN radical.

[0064] "Nitro" refers to the $-NO_2$ radical.

[0065] "Oxo" refers to the =O radical.

[0066] "Imino" refers to the =N-H radical.

[0067] "Oximo" refers to the =N-OH radical.

[0068] "Hydroxy" or "hydroxyl" refers to the -OH radical.

[0069] "Hydroxyamino" refers to the -NH-OH radical.

[0070] "Acyl" refers to a substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkenylcarbonyl, substituted or unsubstituted alkynylcarbonyl, substituted or unsubstituted cycloalkylcarbonyl, substituted or unsubstituted heterocycloalkylcarbonyl, substituted or unsubstituted arylcarbonyl, substituted or unsubstituted heteroarylcarbonyl, amide, or ester, wherein the carbonyl atom of the carbonyl group is the point of attachment. Unless stated otherwise specifically in the specification, an alkylcarbonyl group, alkenylcarbonyl group, alkynylcarbonyl group, cycloalkylcarbonyl group, amide group, or ester group is optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like.

[0071] "Alkyl" refers to an optionally substituted straight-chain, or optionally substituted branched-chain saturated hydrocarbon monoradical. An alkyl group can have from one to about twenty carbon atoms, from one to about ten carbon atoms, or from one to six carbon atoms. Examples include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl,

4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, tert-amyl, and hexyl, and longer alkyl groups, such as heptyl, octyl, and the like. Whenever it appears herein, a numerical range such as "C_1-C_6 alkyl" means that the alkyl group consists of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated. In some embodiments, the alkyl is a C_1-C_{10} alkyl, a C_1-C_9 alkyl, a C_1-C_8 alkyl, a C_1-C_7 alkyl, a C_1-C_6 alkyl, a C_1-C_5 alkyl, a C_1-C_4 alkyl, a C_1-C_3 alkyl, a C_1-C_2 alkyl, or a C_1 alkyl. Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkyl is optionally substituted with oxo, halogen, -CN, -CF_3, -OH, -OMe, -NH_2, -NO_2, or -C≡CH. In some embodiments, the alkyl is optionally substituted with oxo, halogen, -CN, -CF_3, -OH, or -OMe. In some embodiments, the alkyl is optionally substituted with halogen.

[0072] "Alkylene" refers to a straight or branched divalent hydrocarbon chain. Unless stated otherwise specifically in the specification, an alkylene group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, an alkylene is optionally substituted with oxo, halogen, -CN, -CF_3, -OH, -OMe, -NH_2, or -NO_2. In some embodiments, an alkylene is optionally substituted with oxo, halogen, -CN, -CF_3, -OH, or -OMe. In some embodiments, the alkylene is optionally substituted with halogen. In some embodiments, the alkylene is -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, or -$CH_2CH(CH_3)CH_2$-. In some embodiments, the alkylene is -CH_2-. In some embodiments, the alkylene is -CH_2CH_2-. In some embodiments, the alkylene is -$CH_2CH_2CH_2$-.

[0073] "Alkenyl" refers to an optionally substituted straight-chain, or optionally substituted branched-chain hydrocarbon monoradical having one or more carbon-carbon double-bonds. In some embodiments, an alkenyl group has from two to about ten carbon atoms, or two to about six carbon atoms. The group may be in either the *cis* or *trans* configuration about the double bond(s), and should be understood to include both isomers. Examples include, but are not limited to, ethenyl (-CH=CH_2), 1-propenyl (-CH_2CH=CH_2), isopropenyl [-C(CH_3)=CH_2], butenyl, 1,3-butadienyl, and the like. Whenever it appears herein, a numerical range such as "C_2-C_6 alkenyl" means that the alkenyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms, or 6 carbon atoms, although the present definition also covers the occurrence of the term "alkenyl" where no numerical range is designated. In some embodiments, the alkenyl is a C_2-C_{10} alkenyl, a C_2-C_9 alkenyl, a C_2-C_8 alkenyl, a C_2-C_7 alkenyl, a C_2-C_6 alkenyl, a C_2-C_5 alkenyl,

a C_2-C_4 alkenyl, a C_2-C_3 alkenyl, or a C_2 alkenyl. Unless stated otherwise specifically in the specification, an alkenyl group is optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, an alkenyl is optionally substituted with oxo, halogen, -CN, -CF_3, -OH, -OMe, -NH_2, or -NO_2. In some embodiments, an alkenyl is optionally substituted with oxo, halogen, -CN, -CF_3, -OH, or -OMe. In some embodiments, the alkenyl is optionally substituted with halogen.

[0074] The term "alkenylene" or "alkenylene chain" refers to an optionally substituted straight or branched divalent hydrocarbon chain in which at least one carbon-carbon double bond is present linking the rest of the molecule to a radical group. In some embodiments, the alkenylene is –CH=CH-, -CH_2CH=CH-, or –CH=CHCH_2-. In some embodiments, the alkenylene is –CH=CH-. In some embodiments, the alkenylene is –CH_2CH=CH-. In some embodiments, the alkenylene is –CH=CHCH_2-.

[0075] "Alkynyl" refers to an optionally substituted straight-chain or optionally substituted branched-chain hydrocarbon monoradical having one or more carbon-carbon triple-bonds. In some embodiments, an alkynyl group has from two to about ten carbon atoms, more preferably from two to about six carbon atoms. Examples include, but are not limited to, ethynyl, 2-propynyl, 2-butynyl, 1,3-butadiynyl, and the like. Whenever it appears herein, a numerical range such as "C_2-C_6 alkynyl" means that the alkynyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms, or 6 carbon atoms, although the present definition also covers the occurrence of the term "alkynyl" where no numerical range is designated. In some embodiments, the alkynyl is a C_2-C_{10} alkynyl, a C_2-C_9 alkynyl, a C_2-C_8 alkynyl, a C_2-C_7 alkynyl, a C_2-C_6 alkynyl, a C_2-C_5 alkynyl, a C_2-C_4 alkynyl, a C_2-C_3 alkynyl, or a C_2 alkynyl. Unless stated otherwise specifically in the specification, an alkynyl group is optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, an alkynyl is optionally substituted with oxo, halogen, -CN, -CF_3, -OH, -OMe, -NH_2, or -NO_2. In some embodiments, an alkynyl is optionally substituted with oxo, halogen, -CN, -CF_3, -OH, or -OMe. In some embodiments, the alkynyl is optionally substituted with halogen. The term "alkynylene" refers to an optionally substituted straight-chain or optionally substituted branched-chain divalent hydrocarbon having one or more carbon-carbon triple-bonds.

[0076] "Alkylamino" refers to a radical of the formula -$N(R_a)_2$ where R_a is an alkyl radical as defined, or two R_a, taken together with the nitrogen atom, can form a substituted or unsubstituted C_2-C_7 heterocyloalkyl ring. Unless stated otherwise specifically in the specification, an alkylamino group may be optionally substituted, for example, with oxo, halogen, amino, nitrile,

nitro, hydroxyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, an alkylamino is optionally substituted with oxo, halogen, -CN, -CF_3, -OH, -OMe, -NH_2, or -NO_2. In some embodiments, an alkylamino is optionally substituted with oxo, halogen, -CN, -CF_3, -OH, or -OMe. In some embodiments, the alkylamino is optionally substituted with halogen.

[0077] "Alkoxy" refers to a radical of the formula -OR_a where R_a is an alkyl radical as defined. Unless stated otherwise specifically in the specification, an alkoxy group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, an alkoxy is optionally substituted with oxo, halogen, -CN, -CF_3, -OH, -OMe, -NH_2, or -NO_2. In some embodiments, an alkoxy is optionally substituted with oxo, halogen, -CN, -CF_3, -OH, or -OMe. In some embodiments, the alkoxy is optionally substituted with halogen.

[0078] "Aminoalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more amines. In some embodiments, the alkyl is substituted with one amine. In some embodiments, the alkyl is substituted with one, two, or three amines. Hydroxyalkyl include, for example, aminomethyl, aminoethyl, aminopropyl, aminobutyl, or aminopentyl. In some embodiments, the hydroxyalkyl is aminomethyl.

[0079] "Hydroxyalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more hydroxyls. In some embodiments, the alkyl is substituted with one hydroxyl. In some embodiments, the alkyl is substituted with one, two, or three hydroxyls. Hydroxyalkyl include, for example, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, or hydroxypentyl. In some embodiments, the hydroxyalkyl is hydroxymethyl.

[0080] The term "aryl" refers to a radical comprising at least one aromatic ring wherein each of the atoms forming the ring is a carbon atom. Aryl groups can be optionally substituted. Examples of aryl groups include, but are not limited to phenyl, and naphthyl. In some embodiments, the aryl is phenyl. Depending on the structure, an aryl group can be a monoradical or a diradical (i.e., an arylene group). Unless stated otherwise specifically in the specification, the term "aryl" or the prefix "ar-"(such as in "aralkyl") is meant to include aryl radicals that are optionally substituted. In some embodiments, an aryl group comprises a partially reduced cycloalkyl group defined herein (e.g., 1,2-dihydronaphthalene). In some embodiments, an aryl group comprises a fully reduced cycloalkyl group defined herein (e.g., 1,2,3,4-tetrahydronaphthalene). When aryl comprises a cycloalkyl group, the aryl is bonded to the rest of the molecule through an aromatic ring carbon atom. An aryl radical can be a monocyclic or polycyclic (e.g., bicyclic, tricyclic, or tetracyclic) ring system, which may include fused, spiro or bridged ring systems. Unless stated otherwise specifically in the specification, an aryl may be optionally substituted, for example, with

halogen, amino, alkylamino, aminoalkyl, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-S(O)_2NH-C_1-C_6$alkyl, and the like. In some embodiments, an aryl is optionally substituted with halogen, methyl, ethyl, -CN, $-CF_3$, -OH, -OMe, $-NH_2$, $-NO_2$, $-S(O)_2NH_2$, $-S(O)_2NHCH_3$, $-S(O)_2NHCH_2CH_3$, $-S(O)_2NHCH(CH_3)_2$, $-S(O)_2N(CH_3)_2$, or $-S(O)_2NHC(CH_3)_3$. In some embodiments, an aryl is optionally substituted with halogen, methyl, ethyl, -CN, $-CF_3$, -OH, or -OMe. In some embodiments, the aryl is optionally substituted with halogen. In some embodiments, the aryl is substituted with alkyl, alkenyl, alkynyl, haloalkyl, or heteroalkyl, wherein each alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl is independently unsubstituted, or substituted with halogen, methyl, ethyl, -CN, $-CF_3$, -OH, -OMe, $-NH_2$, or $-NO_2$.

[0081] The term "cycloalkyl" refers to a monocyclic or polycyclic non-aromatic radical, wherein each of the atoms forming the ring (i.e. skeletal atoms) is a carbon atom. In some embodiments, cycloalkyls are saturated or partially unsaturated. In some embodiments, cycloalkyls are spirocyclic or bridged compounds. In some embodiments, cycloalkyls are fused with an aromatic ring (in which case the cycloalkyl is bonded through a non-aromatic ring carbon atom). Cycloalkyl groups include groups having from 3 to 10 ring atoms. Representative cycloalkyls include, but are not limited to, cycloalkyls having from three to ten carbon atoms, from three to eight carbon atoms, from three to six carbon atoms, or from three to five carbon atoms. Monocyclic cycloalkyl radicals include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. In some embodiments, the monocyclic cycloalkyl is cyclopentyl. In some embodiments, the monocyclic cycloalkyl is cyclopentenyl or cyclohexenyl. In some embodiments, the monocyclic cycloalkyl is cyclopentenyl. Polycyclic radicals include, for example, adamantyl, 1,2-dihydronaphthalenyl, 1,4-dihydronaphthalenyl, tetrainyl, decalinyl, 3,4-dihydronaphthalenyl-1(2H)-one, spiro[2.2]pentyl, norbornyl and bicycle[1.1.1]pentyl. Unless otherwise stated specifically in the specification, a cycloalkyl group may be optionally substituted. Representative cycloalkyls include, but are not limited to, cycloalkyls having from three to fifteen carbon atoms (C_3-C_{15} cycloalkyl), from three to ten carbon atoms (C_3-C_{10} cycloalkyl), from three to eight carbon atoms (C_3-C_8 cycloalkyl), from three to six carbon atoms (C_3-C_6 cycloalkyl), from three to five carbon atoms (C_3-C_5 cycloalkyl), or three to four carbon atoms (C_3-C_4 cycloalkyl). In some embodiments, the cycloalkyl is a 3- to 6-membered cycloalkyl. In some embodiments, the cycloalkyl is a 5- to 6-membered cycloalkyl. Monocyclic cycloalkyls include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyls or carbocycles include, for example, adamantyl, norbornyl, decalinyl, bicyclo[3.3.0]octane, bicyclo[4.3.0]nonane, cis-decalin, trans-decalin, bicyclo[2.1.1]hexane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, and bicyclo[3.3.2]decane, and

7,7-dimethyl-bicyclo[2.2.1]heptanyl. Partially saturated cycloalkyls include, for example, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. Unless stated otherwise specifically in the specification, a cycloalkyl is optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a cycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, $-CF_3$, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, a cycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, $-CF_3$, -OH, or -OMe. In some embodiments, the cycloalkyl is optionally substituted with halogen.

[0082] "Halo" or "halogen" refers to bromo, chloro, fluoro, or iodo. In some embodiments, halogen is fluoro or chloro. In some embodiments, halogen is fluoro.

[0083] "Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halogens. In some embodiments, the alkyl is substituted with one, two, or three halogens. In some embodiments, the alkyl is substituted with one, two, three, four, five, or six halogens. Haloalkyl can include, for example, iodoalkyl, bromoalkyl, chloroalkyl, and fluoroalkyl. For example, "fluoroalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more fluoro radicals, as defined above, for example, trifluoromethyl, difluoromethyl, fluoromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like. In some embodiments, the alkyl part of the fluoroalkyl radical is optionally substituted as defined above for an alkyl group.

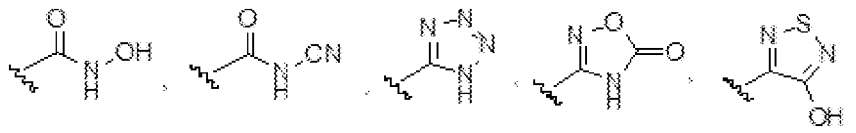
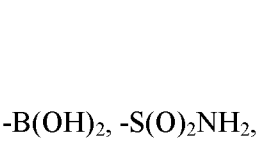
[0084] "Heteroalkyl" refers to an alkyl group in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, e.g., oxygen, nitrogen (e.g., -NH-, -N(alkyl)-), sulfur, or combinations thereof. A heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. In one aspect, a heteroalkyl is a C_1-C_6 heteroalkyl wherein the heteroalkyl is comprised of 1 to 6 carbon atoms and one or more atoms other than carbon, e.g., oxygen, nitrogen (e.g. -NH-, -N(alkyl)-), sulfur, or combinations thereof wherein the heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. Examples of such heteroalkyl are, for example, $–CH_2$-O-CH_2-, $–CH_2$-N(alkyl)-CH_2-, $–CH_2$-N(aryl)-CH_2-, $-OCH_2CH_2O-$, $–OCH_2CH_2OCH_2CH_2O-$, or $–OCH_2CH_2OCH_2CH_2OCH_2CH_2O-$. Unless stated otherwise specifically in the specification, a heteroalkyl is optionally substituted for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a heteroalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, $-CF_3$, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, a heteroalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, $-CF_3$, -OH, or -OMe. In some embodiments, the heteroalkyl is optionally substituted with halogen. As used herein, a "heteroalkylene" refers to divalent heteroalkyl group.

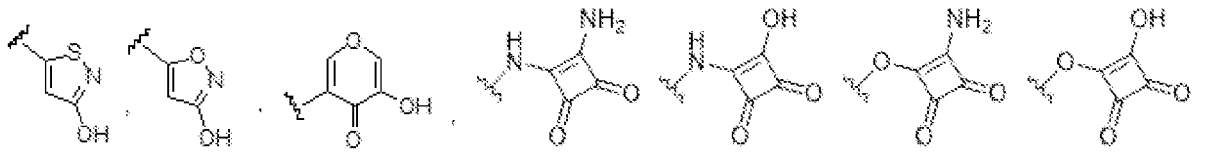
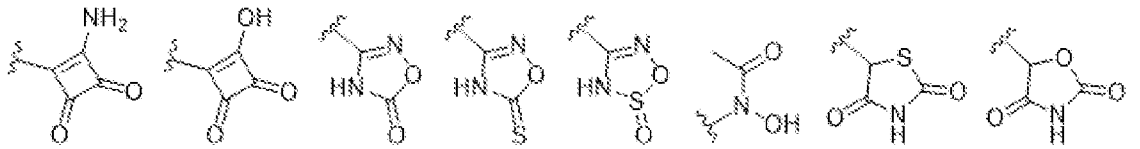
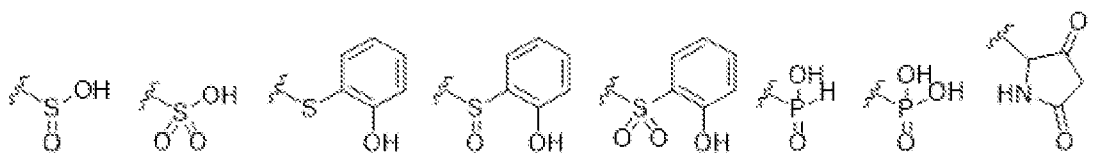
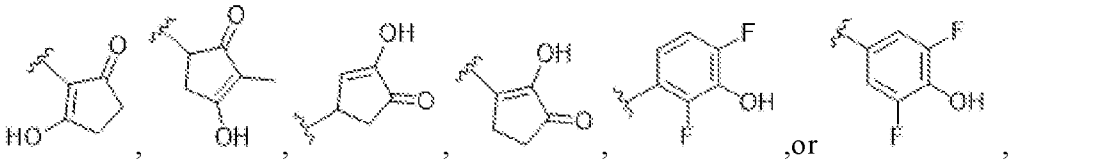
[0085] The term "heterocycloalkyl" refers to a cycloalkyl group that includes at least one hetero ring atom, e.g., a heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiment, heterocycloalkyl are saturated. In some embodiment, heterocycloalkyl are partially unsaturated. Unless stated otherwise specifically in the specification, the heterocycloalkyl radical may be a monocyclic, or bicyclic ring system, which may include fused (when fused with an aryl or a heteroaryl ring, the heterocycloalkyl is bonded through a non-aromatic ring atom) or bridged ring systems. The nitrogen, carbon or sulfur atoms in the heterocyclyl radical may be optionally oxidized. The nitrogen atom may be optionally quaternized. The heterocycloalkyl radical is partially or fully saturated. Examples of heterocycloalkyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, tetrahydroquinolyl, tetrahydroisoquinolyl, decahydroquinolyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, 1,1-dioxo-thiomorpholinyl. The term heterocycloalkyl also includes all ring forms of carbohydrates, including but not limited to monosaccharides, disaccharides and oligosaccharides. Unless otherwise noted, heterocycloalkyls have from 2 to 12 carbons in the ring. In some embodiments, heterocycloalkyls have from 2 to 10 carbons in the ring. In some embodiments, heterocycloalkyls have from 2 to 10 carbons in the ring and 1 or 2 N atoms. In some embodiments, heterocycloalkyls have from 2 to 10 carbons in the ring and 3 or 4 N atoms. In some embodiments, heterocycloalkyls have from 2 to 12 carbons, 0-2 N atoms, 0-2 O atoms, 0-2 P atoms, and 0-1 S atoms in the ring. In some embodiments, heterocycloalkyls have from 2 to 12 carbons, 1-3 N atoms, 0-1 O atoms, and 0-1 S atoms in the ring. It is understood that when referring to the number of carbon atoms in a heterocycloalkyl, the number of carbon atoms in the heterocycloalkyl is not the same as the total number of atoms (including the heteroatoms) that make up the heterocycloalkyl (i.e. skeletal atoms of the heterocycloalkyl ring). Unless stated otherwise specifically in the specification, a heterocycloalkyl is optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a heterocycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, $-CF_3$, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, a heterocycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, $-CF_3$, -OH, or -OMe. In some embodiments, the heterocycloalkyl is optionally substituted with halogen.

[0086] "Heteroaryl" refers to a ring system radical comprising carbon atom(s) and one or more ring heteroatoms selected from the group consisting of nitrogen, oxygen, phosphorous, and sulfur,

and at least one aromatic ring. In some embodiments, heteroaryl is monocyclic, bicyclic or polycyclic. Illustrative examples of monocyclic heteroaryls include pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, pyridazinyl, triazinyl, oxadiazolyl, thiadiazolyl, furazanyl, indolizine, indole, benzofuran, benzothiophene, indazole, benzimidazole, purine, quinolizine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8-naphthyridine, and pteridine. Illustrative examples of monocyclic heteroaryls include pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, pyridazinyl, triazinyl, oxadiazolyl, thiadiazolyl, and furazanyl. Illustrative examples of bicyclic heteroaryls include indolizine, indole, benzofuran, benzothiophene, indazole, benzimidazole, purine, quinolizine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8-naphthyridine, and pteridine. In some embodiments, heteroaryl is pyridinyl, pyrazinyl, pyrimidinyl, thiazolyl, thienyl, thiadiazolyl or furyl. In some embodiments, a heteroaryl contains 0-6 N atoms in the ring. In some embodiments, a heteroaryl contains 1-4 N atoms in the ring. In some embodiments, a heteroaryl contains 4-6 N atoms in the ring. In some embodiments, a heteroaryl contains 0-4 N atoms, 0-1 O atoms, 0-1 P atoms, and 0-1 S atoms in the ring. In some embodiments, a heteroaryl contains 1-4 N atoms, 0-1 O atoms, and 0-1 S atoms in the ring. In some embodiments, heteroaryl is a C_1-C_9 heteroaryl. In some embodiments, monocyclic heteroaryl is a C_1-C_5 heteroaryl. In some embodiments, monocyclic heteroaryl is a 5-membered or 6-membered heteroaryl. In some embodiments, a bicyclic heteroaryl is a C_6-C_9 heteroaryl. In some embodiments, a heteroaryl group comprises a partially reduced cycloalkyl or heterocycloalkyl group defined herein (e.g., 7,8-dihydroquinoline). In some embodiments, a heteroaryl group comprises a fully reduced cycloalkyl or heterocycloalkyl group defined herein (e.g., 5,6,7,8-tetrahydroquinoline). When heteroaryl comprises a cycloalkyl or heterocycloalkyl group, the heteroaryl is bonded to the rest of the molecule through a heteroaromatic ring carbon or hetero atom. A heteroaryl radical can be a monocyclic or polycyclic (e.g., bicyclic, tricyclic, or tetracyclic) ring system, which may include fused, spiro or bridged ring systems. Unless stated otherwise specifically in the specification, a heteroaryl is optionally substituted, for example, with halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a heteroaryl is optionally substituted with halogen, methyl, ethyl, -CN, $-CF_3$, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, a heteroaryl is optionally substituted with halogen, methyl, ethyl, -CN, $-CF_3$, -OH, or -OMe. In some embodiments, the heteroaryl is optionally substituted with halogen.

[0087] As used herein, "carboxylic acid or an isostere thereof" refers to a carboxylic acid moiety, or a functional group or moiety that exhibits similar physical, biological and/or chemical properties as a carboxylic acid moiety. Examples of carboxylic acid isosteres include, but are not limited to, hydroxamic acids, hydroxamic esters, sulfinic acids, sulfonic acids, sulfonamides, acyl-sulfonamides, sulfonylureas, acylureas, tetrazole, thiazolidine diones, oxozolidine diones, oxadiazol-5(4*H*)-one, oxothiadiazole-2-oxide, oxadiazol-5(4*H*)-thione, isoxazole, tetramic acid, cyclopentane 1,3-diones, cyclopentane 1,2-diones, squaryl groups, phosphoric acids, phosphinic acids, and halogenated phenols. For example, a carboxylic acid isostere can be:



-$B(OH)_2$, -$S(O)_2NH_2$,

wherein each hydrogen bound to a carbon atom is optionally replaced with methyl, ethyl, -CN, -CF_3, -OH, -OMe, -NH_2, or -NO_2, or a different halogen.

[0088] The term "moiety" refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[0089] The terms "treat," "prevent," "ameliorate," and "inhibit," as well as words stemming therefrom, as used herein, do not necessarily imply 100% or complete treatment, prevention, amelioration, or inhibition. Rather, there are varying degrees of treatment, prevention, amelioration, and inhibition of which one of ordinary skill in the art recognizes as having a potential benefit or therapeutic effect. In this respect, the disclosed methods can provide any amount of any level of treatment, prevention, amelioration, or inhibition of the disorder in a

mammal. For example, a disorder, including symptoms or conditions thereof, may be reduced by, for example, about 100%, about 90%, about 80%, about 70%, about 60%, about 50%, about 40%, about 30%, about 20%, or about 10%. Furthermore, the treatment, prevention, amelioration, or inhibition provided by the methods disclosed herein can include treatment, prevention, amelioration, or inhibition of one or more conditions or symptoms of the disorder, e.g., cancer or an inflammatory disease. As used herein, "treating" includes the concepts of "alleviating", which refers to lessening the frequency of occurrence or recurrence, or the severity, of any symptoms or other ill effects related to a disorder and/or the associated side effects. The term "treating" also encompasses the concept of "managing" which refers to reducing the severity of a particular disease or disorder in a patient or delaying its recurrence, e.g., lengthening the period of remission in a patient who had suffered from the disease.

[0090] In certain embodiments, the term "prevent" or "preventing" as related to a disease or disorder may refer to a compound that, in a statistical sample, reduces the occurrence of the disorder or condition in the treated sample relative to an untreated control sample, or delays the onset or reduces the severity of one or more symptoms of the disorder or condition relative to the untreated control sample.

[0091] The term "therapeutically effective amount" as used herein to refer to an amount effective at the dosage and duration necessary to achieve the desired therapeutic result. A therapeutically effective amount of the composition may vary depending on factors such as the individual's condition, age, sex, and weight, and the ability of the protein to elicit the desired response of the individual. A therapeutically effective amount can also be an amount that exceeds any toxic or deleterious effect of the composition that would have a beneficial effect on the treatment.

[0092] The term "optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted alkyl" means either "alkyl" or "substituted alkyl" as defined above. Further, an optionally substituted group may be un-substituted (e.g., $-CH_2CH_3$), fully substituted (e.g., $-CF_2CF_3$), mono-substituted (e.g., $-CH_2CH_2F$) or substituted at a level anywhere in-between fully substituted and mono-substituted (e.g., $-CH_2CHF_2$, $-CH_2CF_3$, $-CF_2CH_3$, $-CFHCHF_2$, etc.).

[0093] As used herein, the term "substituent" means positional variables on the atoms of a core molecule that are substituted at a designated atom position, replacing one or more hydrogens on the designated atom, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. A person of ordinary skill in the art should note that any carbon as well as heteroatom with valences that appear to be

unsatisfied as described or shown herein is assumed to have a sufficient number of hydrogen atom(s) to satisfy the valences described or shown. In certain instances one or more substituents having a double bond (e.g., "oxo" or "=O") as the point of attachment may be described, shown or listed herein within a substituent group, wherein the structure may only show a single bond as the point of attachment to the core structure. A person of ordinary skill in the art would understand that, while only a single bond is shown, a double bond is intended for those substituents.

[0094] The term "optionally substituted" or "substituted" means that the referenced group is optionally substituted with one or more additional group(s) individually and independently selected from D, halogen, -CN, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, -OH, $-CO_2H$, $-CO_2$alkyl, $-C(=O)NH_2$, -C(=O)NH(alkyl), $-C(=O)N(alkyl)_2$, $-S(=O)_2NH_2$, $-S(=O)_2$NH(alkyl), $-S(=O)_2N(alkyl)_2$, alkyl, cycloalkyl, fluoroalkyl, heteroalkyl, alkoxy, fluoroalkoxy, heterocycloalkyl, aryl, heteroaryl, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, and arylsulfone. In some other embodiments, optional substituents are independently selected from D, halogen, -CN, $-NH_2$, $-NH(CH_3)$, $-N(CH_3)_2$, -OH, $-CO_2H$, $-CO_2(C_1$-C_4alkyl), $-C(=O)NH_2$, $-C(=O)NH(C_1$-C_4alkyl), $-C(=O)N(C_1$-C_4alkyl$)_2$, $-S(=O)_2NH_2$, $-S(=O)_2NH(C_1$-C_4alkyl), $-S(=O)_2N(C_1$-C_4alkyl$)_2$, C_1-C_4alkyl, C_3-C_6cycloalkyl, C_1-C_4fluoroalkyl, C_1-C_4heteroalkyl, C_1-C_4alkoxy, C_1-C_4fluoroalkoxy, $-SC_1$-C_4alkyl, $-S(=O)C_1$-C_4alkyl, and $-S(=O)_2C_1$-C_4alkyl. In some embodiments, optional substituents are independently selected from D, halogen, -CN, $-NH_2$, -OH, $-NH(CH_3)$, $-N(CH_3)_2$, -NH(cyclopropyl), $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-OCH_3$, and $-OCF_3$. In some embodiments, substituted groups are substituted with one or two of the preceding groups. In some embodiments, an optional substituent on an aliphatic carbon atom (acyclic or cyclic) includes oxo (=O). When indicating the number of substituents, the term "one or more" means from one substituent to the highest possible number of substitutions, i.e. replacement of one hydrogen up to replacement of all hydrogens by substituents.

[0095] The term "unsubstituted" means that the specified group bears no substituents.

[0096] Certain compounds described herein may exist in tautomeric forms, and all such tautomeric forms of the compounds being within the scope of the disclosure. Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the disclosure.

[0097] The term "peptide" as used herein refers to a compound that includes two or more amino acids. A peptide described herein can comprise one or more unnatural amino acids. The term "peptide" also encompasses peptide mimetics. In the present disclosure, the term "amino acid" is used in its broadest meaning and it embraces not only natural amino acids but also derivatives

thereof and artificial amino acids. For example, the term "amino acid" encompasses unnatural amino acids.

[0098] As used herein, the term "unnatural amino acid" refers to an amino acid other than the 20 amino acids that occur naturally in protein.

[0099] The term "protein" as used herein refers to a polypeptide (i.e., a string of at least 3 amino acids linked to one another by peptide bonds). Proteins can include moieties other than amino acids (e.g., may be glycoproteins, proteoglycans, etc.) and/or can be otherwise processed or modified. A protein can be a complete polypeptide as produced by and/or active in a cell (with or without a signal sequence). In some embodiments, a protein is or comprises a characteristic portion such as a polypeptide as produced by and/or active in a cell. A protein can include more than one polypeptide chain. For example, polypeptide chains can be linked by one or more disulfide bonds or associated by other means.

[0100] The term "peptide mimetic" or "mimetic" refers to biologically active compounds that mimic the biological activity of a peptide or a protein but are no longer entirely peptidic in chemical nature, e.g.,, they can contain non-peptide bonds (that are, bonds other than amide bonds between amino acids). As used herein, the term peptide mimetic is used in a broader sense to include molecules that are no longer completely peptidic in nature, such as pseudo-peptides, semi-peptides and peptoids. Whether completely or partially non-peptide, peptide mimetics described herein can provide a spatial arrangement of reactive chemical moieties that closely resemble the three-dimensional arrangement of active groups in the subject amino acid sequence or subject molecule on which the peptide mimetic is based. As a result of this similar active-site geometry, the peptide mimetic can have effects on biological systems that are similar to the biological activity of the subject entity.

[0101] In some embodiments, the peptide mimetics are substantially similar in both three-dimensional shape and biological activity to the subject amino acid sequence or subject molecule on which the peptide mimetic is based. Examples of methods of structurally modifying a peptide to create a peptide mimetic include the inversion of backbone chiral centers leading to D-amino acid residue structures that may, particularly at the N-terminus, lead to enhanced stability for proteolytical degradation without adversely affecting activity. An example is described in the paper "Tritiated D-ala1-Peptide T Binding", Smith C. S. et al., Drug Development Res., 15, pp. 371-379 (1988). A second method is altering cyclic structure for stability, such as N to C interchain imides and lactams (Ede et al. in Smith and Rivier (Eds.) "Peptides: Chemistry and Biology", Escom, Leiden (1991), pp. 268-270). An example of this is provided in conformationally restricted thymopentin-like compounds, such as those disclosed in US4457489.

A third method is to substitute peptide bonds in the subject entity by pseudopeptide bonds that confer resistance to proteolysis.

[0102] As used herein, "guanylyl cyclase C, " also known as "GCC," "STAR," "GUC2C, "GUCY2C or "ST receptor" refers to mammalian GCC, preferably human GCC protein. Human GCC refers to the protein shown in SEQ ID NO: **43** and naturally occurring allelic protein variants thereof (e.g., natural variants of SEQ ID NO: 43 as provided in UniProtKB Accession No. P25092). Natural variants of SEQ ID NO: 43 as provided in UniProtKB Accession No. P25092 include VAR_067724, VAR_068174, VAR_042221, VAR_042222, VAR_042223, VAR_049253, VAR_068174, VAR_042224, VAR_042225, VAR_067724, VAR_042226, VAR_042227, VAR_042228, etc. Other variants are known in the art. See, e.g., accession number Ensp0000261170, Ensembl Database, European Bioinformatics Institute and Wellcome Trust Sanger Institute, which has a leucine at residue 281; SEQ ID NO: 14 of published US patent application number 20060035852; or GenBank accession number AAB 19934. Typically, a naturally occur ring allelic variant has an amino acid sequence at least 95%, 97% or 99% identical to the GCC sequence of SEQ ID NO: **43**. The transcript encodes a protein product of 1073 amino acids, and is described in GenBank accession no.: NM 004963. GCC protein is characterized as a transmembrane cell surface receptor protein, and is believed to play a critical role in the maintenance of intestinal fluid, electrolyte homeostasis and cell proliferation.

[0103] Amino acid sequence for human GCC protein (UniProtKB Accession No. P25092; SEQ ID NO: **43**):

```
        10          20          30          40          50
MKTLLLDLAL WSLLFQPGWL SFSSQVSQNC HNGSYEISVL MMGNSAFAEP
        60          70          80          90         100
LKNLEDAVNE GLEIVRGRLQ NAGLNVTVNA TFMYSDGLIH NSGDCRSSTC
       110         120         130         140         150
EGLDLLRKIS NAQRMGCVLI GPSCTYSTFQ MYLDTELSYP MISAGSFGLS
       160         170         180         190         200
CDYKETLTRL MSPARKLMYF LVNFWKTNDL PFKTYSWSTS YVYKNGTETE
       210         220         230         240         250
DCFWYLNALE ASVSYFSHEL GFKVVLRQDK EFQDILMDHN RKSNVIIMCG
       260         270         280         290         300
GPEFLYKLKG DRAVAEDIVI ILVDLFNDQY FEDNVTAPDY MKNVLVLTLS
       310         320         330         340         350
PGNSLLNSSF SRNLSPTKRD FALAYLNGIL LFGHMLKIFL ENGENITTPK
       360         370         380         390         400
FAHAFRNLTF EGYDGPVTLD DWGDVDSTMV LLYTSVDTKK YKVLLTYDTH
       410         420         430         440         450
VNKTYPVDMS PTFTWKNSKL PNDITGRGPQ ILMIAVFTLT GAVVLLLLVA
       460         470         480         490         500
LLMLRKYRKD YELRQKKWSH IPPENIFPLE TNETNHVSLK IDDDKRRDTI
       510         520         530         540         550
QRLRQCKYDK KRVILKDLKH NDGNFTEKQK IELNKLLQID YYNLTKFYGT
       560         570         580         590         600
VKLDTMIFGV IEYCERGSLR EVLNDTISYP DGTFMDWEFK ISVLYDIAKG
```

```
       610         620         630         640         650
MSYLHSSKTE VHGRLKSTNC VVDSRMVVKI TDFGCNSILP PKKDLWTAPE
       660         670         680         690         700
HLRQANISQK GDVYSYGIIA QEIILRKETF YTLSCRDRNE KIFRVENSNG
       710         720         730         740         750
MKPFRPDLFL ETAEEKELEV YLLVKNCWEE DPEKRPDFKK IETTLAKIFG
       760         770         780         790         800
LFHDQKNESY MDTLIRRLQL YSRNLEHLVE ERTQLYKAER DRADRLNFML
       810         820         830         840         850
LPRLVVKSLK EKGFVEPELY EEVTIYFSDI VGFTTICKYS TPMEVVDMLN
       860         870         880         890         900
DIYKSFDHIV DHHDVYKVET IGDAYMVASG LPKRNGNRHA IDIAKMALEI
       910         920         930         940         950
LSFMGTFELE HLPGLPIWIR IGVHSGPCAA GVVGIKMPRY CLFGDTVNTA
       960         970         980         990        1000
SRMESTGLPL RIHVSGSTIA ILKRTECQFL YEVRGETYLK GRGNETTYWL
      1010        1020        1030        1040        1050
TGMKDQKFNL PTPPTVENQQ RLQAEFSDMI ANSLQKRQAA GIRSQKPRRV
      1060        1070
ASYKKGTLEY LQLNTTDKES TYF
```

[0104] As used herein, the term "guanylyl cyclase C (GCC) binding peptide" or "guanylate cyclase C (GCC) binding peptide" refers to peptides that bind to the class of guanylate cyclase C receptor proteins on any cell type. The term "GCC binding peptide" also includes all peptides that have amino acid sequences substantially equivalent to at least a portion of any one of SEQ ID NOs: 1-42 and derivatives thereof. This term also covers fragments and pro-peptides that bind to guanylate cyclase receptor. The term "substantially equivalent" refers to a peptide that has an amino acid sequence equivalent to that of the binding domain where certain residues may be deleted or replaced with other amino acids without impairing the peptide's ability to bind to a guanylate cyclase receptor.

[0105] As used herein, the term "GCC binding peptide" encompasses "GCC receptor agonists," which refer to peptides and/or other compounds that bind to a guanylate cyclase C receptor and stimulate cGMP production. The term "GCC binding peptide" also encompasses "GCC receptor antagonist."

[0106] Ranges provided herein are understood to be shorthand for all of the values within the range. For example, a range of 1 to 50 is understood to include any number, combination of numbers, or sub-range from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50, as well as all intervening decimal values between the aforementioned integers such as, for example, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, and 1.9. With respect to sub-ranges, "nested sub-ranges" that extend from either end point of the range are specifically contemplated. For example, a nested sub-range of an exemplary range of 1 to 50 may comprise 1 to 10, 1 to 20, 1 to 30, and 1 to 40 in one direction, or 50 to 40, 50 to 30, 50 to 20, and 50 to 10 in the other direction.

[0107] As used herein, C_1-C_x (or C_{1-x}) includes C_1-C_2, C_1-C_3... C_1-C_x. By way of example only, a group designated as "C_1-C_4" indicates that there are one to four carbon atoms in the moiety, i.e. groups containing 1 carbon atom, 2 carbon atoms, 3 carbon atoms or 4 carbon atoms. Thus, by way of example only, "C_1-C_4 alkyl" indicates that there are one to four carbon atoms in the alkyl group, *i.e.*, the alkyl group is selected from among methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, and *t*-butyl. Also, by way of example, C_0-C_2 alkylene includes a direct bond, -CH_2-, and -CH_2CH_2- linkages.

[0108] The term "cyclized" or "cyclization" as used herein means that two amino acids apart from each other by at least one amino acid bind directly or bind indirectly to each other in one peptide to form a cyclic structure in the molecule. In some cases, the two amino acids bind via a linker or the like.

[0109] The term "subject" or "patient" encompasses mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. In one aspect, the mammal is a human.

[0110] The term "therapeutically effective amount" as used herein to refer to an amount effective at the dosage to achieve the desired therapeutic result. A therapeutically effective amount of a composition may vary depending on factors such as the individual's condition (e.g., age, sex, and weight), the radiopharmaceutical conjugate, and the method of administration (e.g., oral or parenteral).

II. Radiopharmaceutical Conjugates

[0111] Provided herein are radiopharmaceutical conjugates and pharmaceutical compositions comprising the conjugates. The conjugates and compositions are useful for treating guanylyl cyclase C (GCC) associated diseases or conditions. The conjugates and compositions can also be useful in disease diagnosis.

[0112] In one aspect, described herein is a conjugate that comprises a GCC binding peptide, a metal chelator that is configured to bind with a radionuclide, a linker that covalently attaches the GCC binding peptide with the metal chelator, and optionally a radionuclide. In one aspect, described herein is a conjugate that comprises a GCC binding peptide, a metal chelator that is configured to bind with a radionuclide, optionally a linker that covalently attaches the GCC binding peptide with the metal chelator, and optionally a radionuclide. In some embodiments, described herein is a conjugate comprising: a GCC binding peptide, wherein the GCC binding peptide comprises an amino acid sequence that has at least 85% identity to any one of SEQ ID

NOs: 1-42; a metal chelator configured to bind with a radionuclide; a linker that covalently attaches the GCC binding peptide with the metal chelator; and optionally an alpha particle-emitting radionuclide.

[0113] In some embodiments, described herein is a conjugate comprising: a GCC binding peptide; a metal chelator configured to bind with a radionuclide; and a linker that covalently attaches the GCC binding peptide with the metal chelator, wherein a dissociation constant (Kd) between the linker and human serum albumin is at most 500 μM, as determined at room temperature in human serum condition. In some embodiments, the Kd is at most 100 μM. In some embodiments, the Kd is at most 15 μM.

[0114] In some embodiments, the GCC binding peptide comprises 7 to 40 amino acid residues. In some embodiments, the alpha particle-emitting radionuclide is ^{225}Ac bound to the metal chelator.

[0115] In some embodiments, the radiopharmaceutical conjugate comprises two or more GCC binding peptides. In some embodiments, the radiopharmaceutical conjugate comprises two GCC binding peptides. In some embodiments, the radiopharmaceutical conjugate comprises three GCC binding peptides. In some embodiments, the two or more GCC binding peptides are the same (e.g., both comprising SEQ ID NO: 1). In some embodiments, the two or more GCC binding peptides are different.

[0116] In some embodiments, a conjugate described herein is designed to have a prescribed elimination profile. The elimination profile can be designed by adjusting the sequence and length of the peptide, the property of the linker, the type of radionuclide, etc. In some embodiments, the conjugate has an elimination half-life of about 0.1 to 200 hours. In some embodiments, the conjugate has an elimination half-life of about 0.5 to 150 hours. In some embodiments, the conjugate has an elimination half-life of about 1 to 120 hours. In some embodiments, the conjugate has an elimination half-life of at least 0.1 hour, 0.5 hour, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 7 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, or 24 hours. In some embodiments, the conjugate has an elimination half-life of at most 120 hour, 80 hours, 70 hours, 60 hours, 50 hours, 40 hours, 30 hours, 24 hours, 12 hours, 10 hours, 5 hours, or 1 hour. In some embodiments, the conjugate has an elimination half-life of about 0.5 to 48 hours. In some embodiments, the conjugate has an elimination half-life of about 1 to 36 hours. In some embodiments, the conjugate has an elimination half-life of about 2 to 24 hours. In some embodiments, the conjugate has an elimination half-life of about 3 to 9 hours. In some embodiments, the conjugate has an elimination half-life of about 2 to 12 hours. In some embodiments, the conjugate has an elimination half-life of about 2 to 8 hours. In some

embodiments, the conjugate has an elimination half-life of about 2 to 5 hours. In some embodiments, the conjugate has an elimination half-life of about 3 to 4 hours. In some embodiments, the blood elimination half-life is determined in rats. In some embodiments, the blood elimination half-life is determined in humans.

[0117] A herein described conjugate can have an elimination half-life in a tumor and non-tumor tissue of the subject. The elimination half-life in a tumor can be the same as or different from (either longer or shorter than) the elimination half-life in a non-tumor issue. In some embodiments, the elimination half-life of the conjugate in a tumor is about 3 hours to 14 days, about 2 to 10 days, about 7 to 10 days, or about 4 to 7 days. In some embodiments, the elimination half-life of the conjugate in a tumor is more than 14 days. In some embodiments, the elimination half-life of the conjugate in a non-tumor tissue is about 1 hour to 14 days, about 12 hours to 2 days, about 1 day to 3 days, about 2 to 10 days, about 7 to 10 days, or about 4 to 7 days. In some embodiments, the elimination half-life of the conjugate in a tumor is at least 1.1, 1.2, 1.3, 1.4, 1.5, 2.0, 2.5, 3.0, 4.0, or 5.0 fold of the elimination half-life of the conjugate in a non-tumor tissue of the subject.

[0118] As used herein, the "elimination half-life" can refer to the time it takes from the maximum concentration after administration to half maximum concentration. In some embodiments, the elimination half-life is determined after intravenous administration. In some embodiments, the elimination half-life is measured as biological half-life, which is the half-life of the cold pharmaceutical in the living system. In some embodiments, the elimination half-life is measured as effective half-life, which is the half-life of a radiopharmaceutical in a living system taking into account the half-life of the radionuclide.

[0119] A conjugate described herein can have a described time-integrated activity coefficient (i.e., ã) in a tumor or non-tumor tissues of a subject. As used herein, ã represents the cumulative number of nuclear transformations occurring in a source tissue over a dose-integration period per unit administered activity. The ã value of a conjugate can be tuned by modifications of the peptide in the conjugate, e.g., modifying the amino acid sequences and length of the peptide. The ã value can be determined using a method known in the art. In some embodiments, the ã value of the conjugate in a tumor is from about 6 hours to 14 days. In some embodiments, the ã value in a tumor is about 2 to 10 days. In some embodiments, the ã value in a tumor is about 4 to 7 days. In some embodiments, the ã value in a tumor is about 7 to 10 days. In some embodiments, the ã value in a tumor is from about 1 day, 2 days, 3 days, or 4 days to about 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, or 12 days. In some embodiments, the ã value in a tumor is about 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, or 12 days. In some embodiments, the ã value of the conjugate in a non-tumor tissue is from

about 6 hours to 14 days. In some embodiments, the ã value in a non-tumor tissue is about 2 to 10 days. In some embodiments, the ã value in a non-tumor tissue is about 4 to 7 days. In some embodiments, the ã value in a non-tumor tissue is about 7 to 10 days. In some embodiments, the ã value in a non-tumor tissue is from about 1 day, 2 days, 3 days, or 4 days to about 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, or 12 days. In some embodiments, the ã value in a non-tumor tissue is about 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, or 12 days. The ã value of the conjugate in a tumor can be the same as the ã value of the conjugate in a non-tumor tissue of the subject. The ã value of the conjugate in a tumor can be longer or shorter than the ã value of the conjugate in a non-tumor tissue of the subject. In some embodiments, the ã value of the conjugate in a tumor is at least 1.1, 1.2, 1.3, 1.4, 1.5, 2.0, 2.5, 3.0, 4.0, or 5.0 fold of the ã value of the conjugate in a non-tumor tissue of the subject.

[0120] A conjugate described herein can have an ã value in an organ of a subject. In some embodiments, the conjugate has an ã value in a kidney of the subject of at most 24 hours. In some embodiments, the ã value of the conjugate in a kidney of the subject is at most 18 hours, 15 hours, 12 hours, 10 hours, 8 hours, 6 hours, or 5 hours. In some embodiments, the ã value of the conjugate in a kidney of the subject is about 30 minutes to about 24 hours. In some embodiments, the ã value of the conjugate in a kidney of the subject is about 2 to 24 hours. In some embodiments, the ã value of the conjugate in a kidney of the subject is more than 24 hours. In some embodiments, the ã value of the conjugate in a liver of the subject is at most 24 hours. In some embodiments, the ã value of the conjugate in a liver of the subject is at most 18 hours, 15 hours, 12 hours, 10 hours, 8 hours, 6 hours, or 5 hours. In some embodiments, the ã value of the conjugate in a liver of the subject is about 30 minutes to about 24 hours. In some embodiments, the ã value of the conjugate in a liver of the subject is about 2 to 24 hours. In some embodiments, the ã value of the conjugate in a liver of the subject is more than 24 hours.

[0121] In some cases, the elimination profile of the conjugate can be adjusted by a reversible binding between the conjugate and a plasma protein such as albumin. A suitable affinity between the conjugate and the plasma protein can utilize the plasma protein as a reservoir for the conjugates, attaching and preserving the conjugates at high concentration and releasing the conjugates at a lower concentration, thereby improving elimination profile. In some embodiments, a dissociation constant (Kd) between the conjugate and human serum albumin is at most 500 μM, as determined at room temperature in human serum condition. In some embodiments, the Kd is at most 100 μM. In some embodiments, the Kd is at most 15 μM. In some embodiments, the Kd is from about 0.1 nM to about 10 μM. In some embodiments, the Kd is from about 10 nM to about 10 μM. In some embodiments, the Kd is from about 50 nM to about 1 μM. In some embodiments,

the Kd is from about 100 nM to about 10 μM. In some embodiments, the Kd is from about 500 nM to about 5 μM.

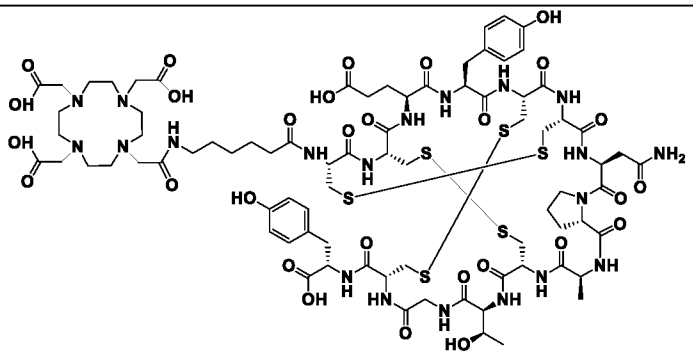
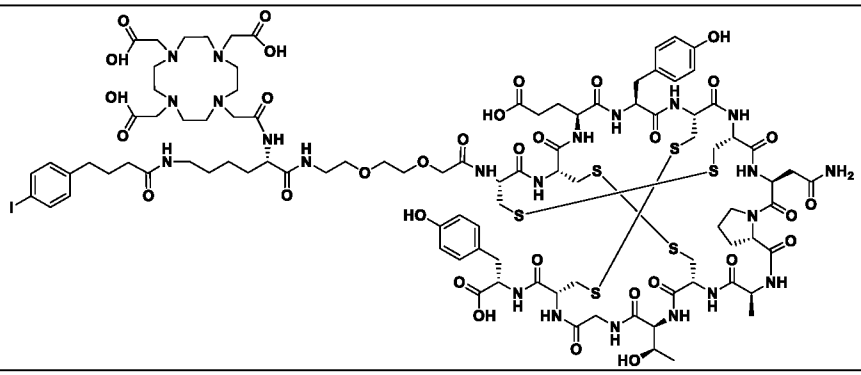
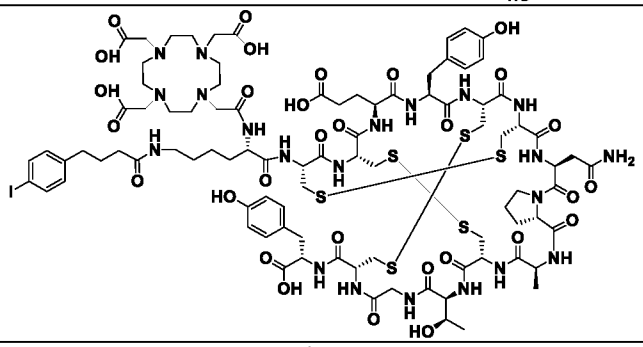
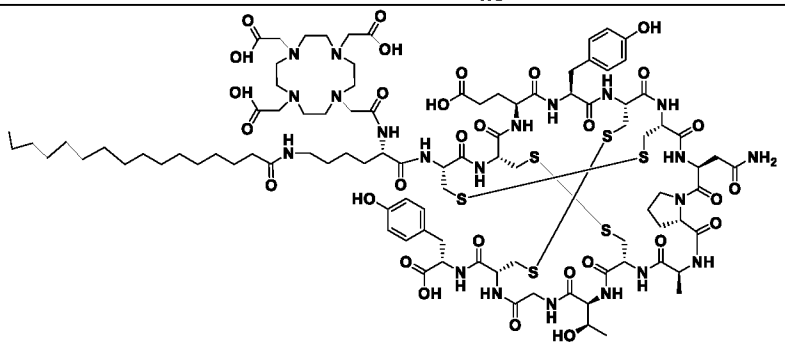
[0122] In some embodiments, a conjugate described herein is bound is bound to plasma proteins. In some embodiments, a conjugate described herein is bound to albumin. In some embodiments, a conjugate described herein has a plasma protein binding percentage of between 40% to 100%. In some embodiments, a conjugate described herein has a plasma protein binding percentage of 40% to 80%. In some embodiments, a conjugate described herein has a plasma protein binding percentage of 40% to 60%. In some embodiments, a conjugate described herein has a plasma protein binding percentage of 60% to 80%. In some embodiments, the conjugate described herein has a plasma protein binding percentage of about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%. In some embodiments, a conjugate described herein has a plasma protein binding percentage of between 40% to 45%, between 45% to 50%, between 50% to 55%, between 55% to 60%, between 60% to 65%, between 70% to 75%, between 75% to 80%, or between 80% to 85%.

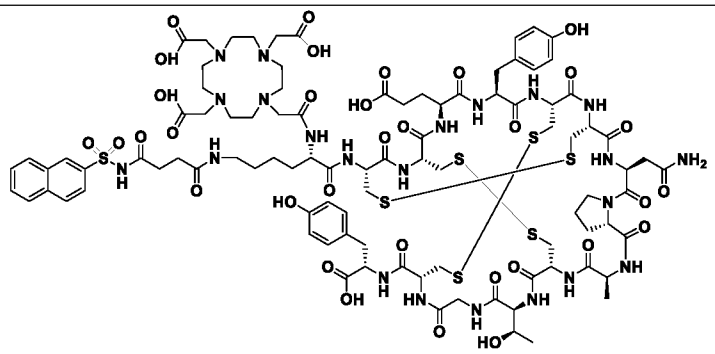
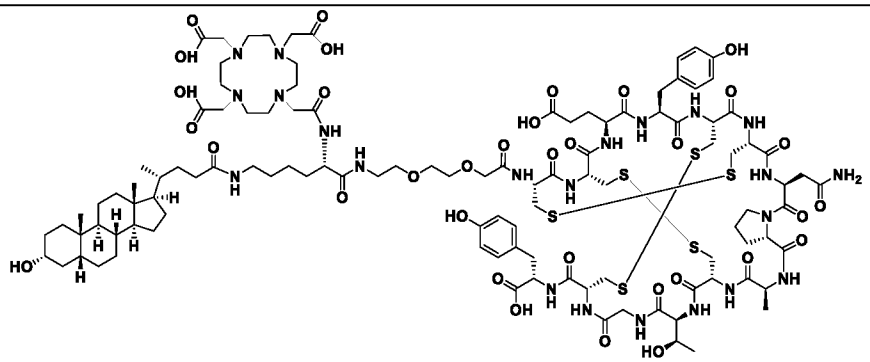
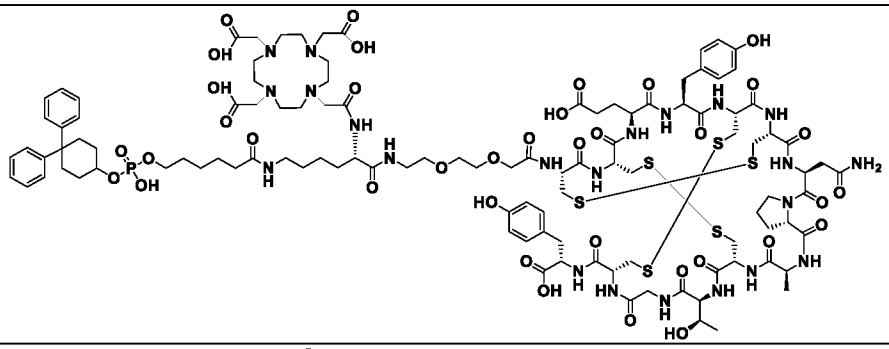
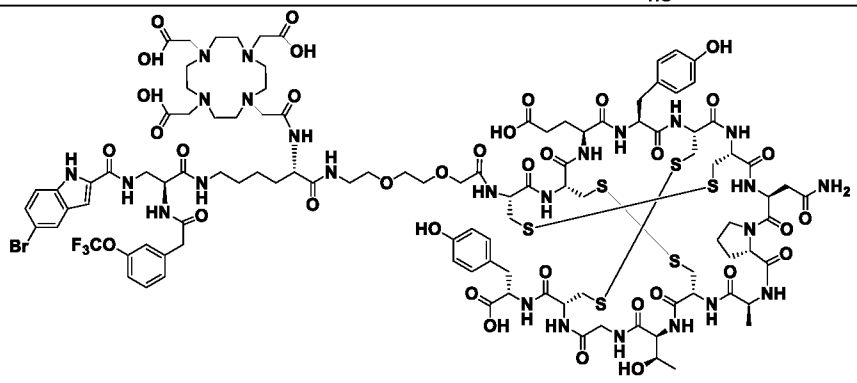
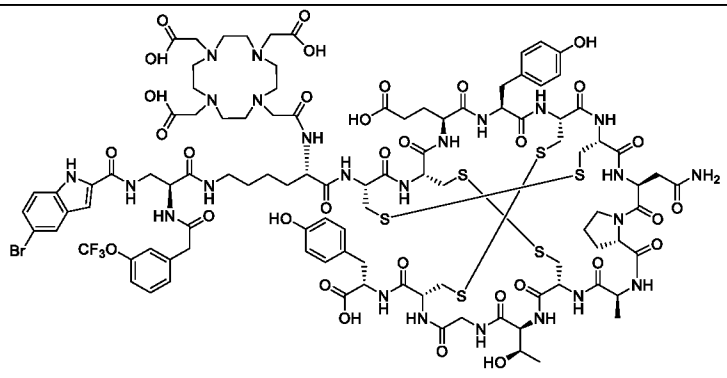
[0123] In one aspect, provided herein are conjugates having a prescribed serum stability. In some embodiments, the human serum half-life of the conjugate is at least 0.1 hour, 0.5 hour, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, or 16 hours at 37 °C. In some embodiments, the human serum half-life of the conjugate is at most 48 hours, 36 hours, 24 hours, 23 hours, 22 hours, 21 hours, 20 hours, 19 hours, 18 hours, 17 hours, 16 hours, 15 hours, 14 hours, 13 hours, 12 hours, 11 hours, 10 hours, 9 hours, 8 hours, 7 hours, 6 hours, 5 hours, or 1 hour at 37 °C. In some embodiments, the human serum half-life of the conjugate is about 2 to 20 hours, 5 to 20 hours, 8 to 15 hours, or 10 to 14 hours at 37 °C.

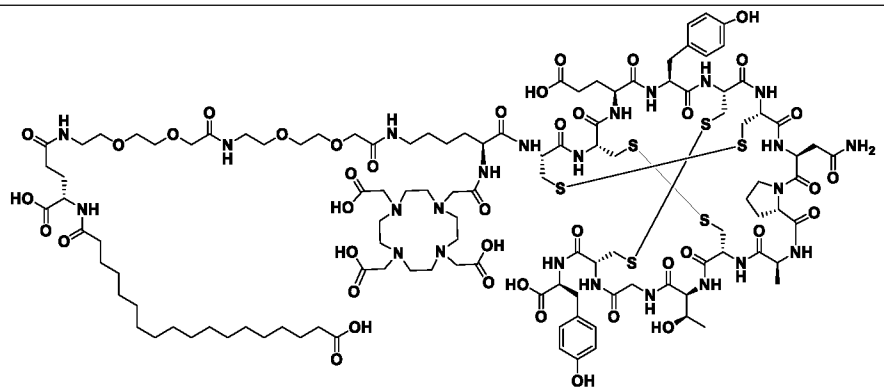
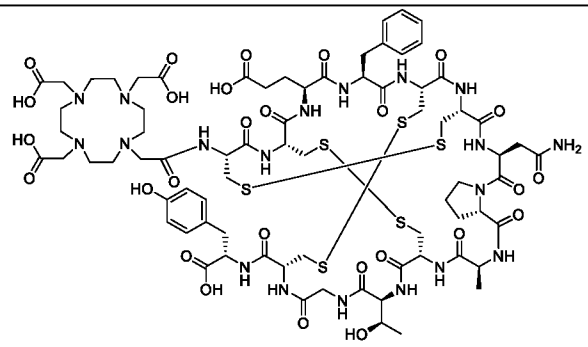
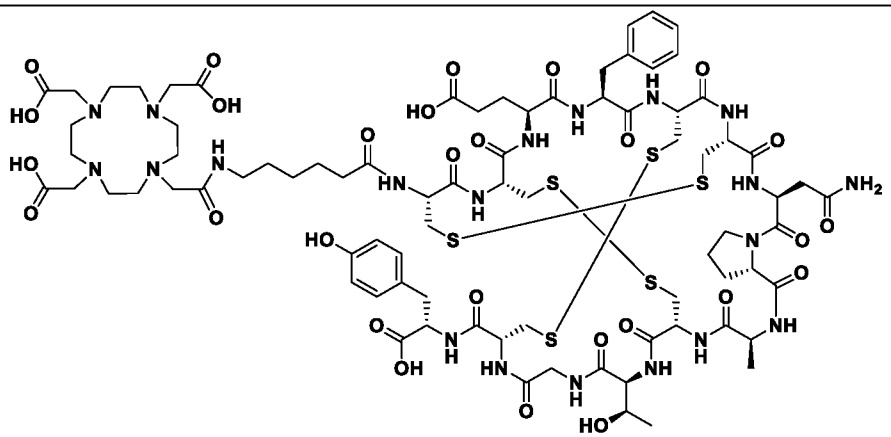
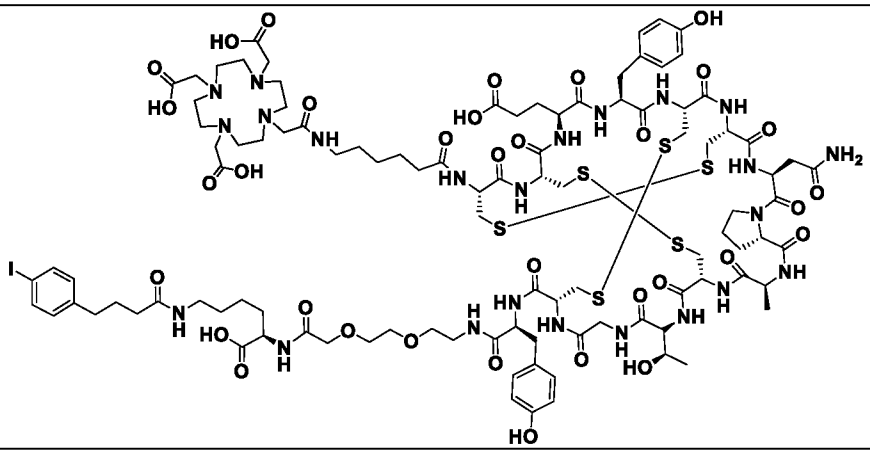
[0124] In some embodiments, a herein described conjugate is a conjugate of FIG. 19. In some embodiments, a herein described conjugate is a conjugate of FIG.20. In some embodiments, a herein described conjugate is a conjugate of FIG. 21. In some embodiments, a herein described conjugate is a conjugate of FIG. 22. In some embodiments, a herein described conjugate is a conjugate of Table 1 or Table 2. In some embodiments, the conjugate further comprises a radionuclide such as Ac-225 or Lutetium-177. In some embodiments, described herein is a conjugate that comprises a conjugate of FIGs 9-22 and a radionuclide of Table 5A or 5B. In some embodiments, described herein is a conjugate that comprises a conjugate of Table 1 and a radionuclide of Table 5A or 5B. In some embodiments, described herein is a conjugate that comprises a conjugate of Table 2 and a radionuclide of Table 5A or 5B. In some embodiments, a herein described conjugate is a conjugate of Table 6. In some embodiments, a herein described

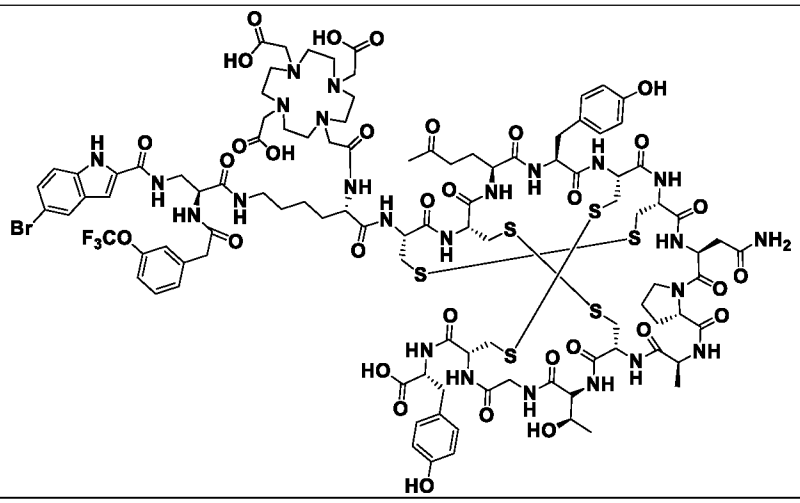
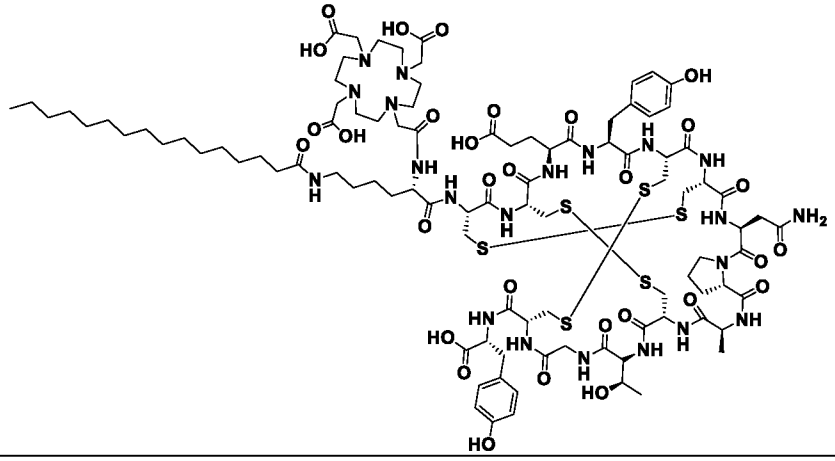
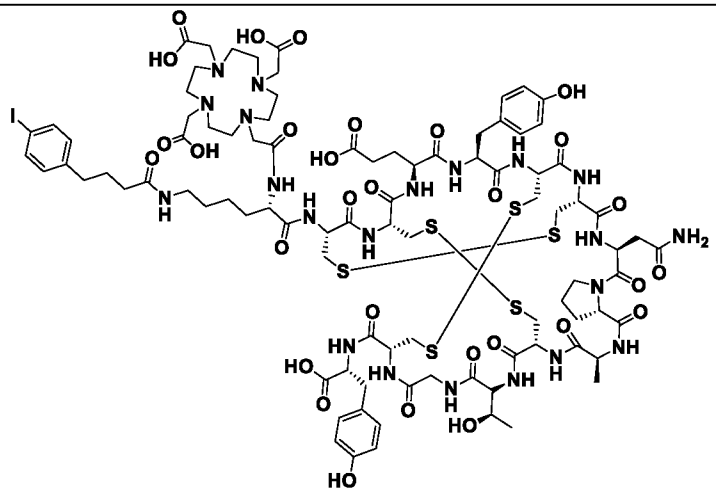
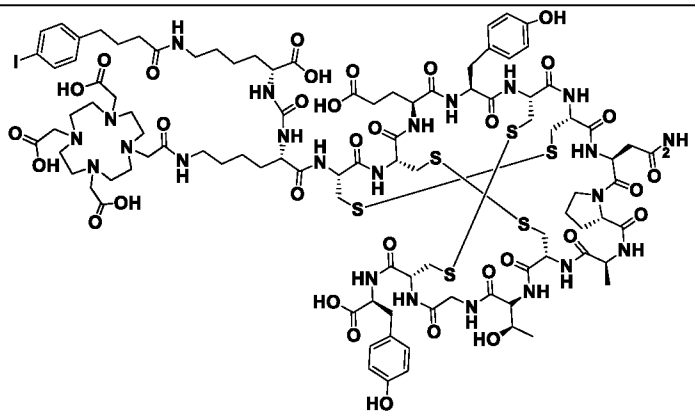
conjugate is a conjugate of Table 7. In some embodiments, a herein described conjugate is a conjugate of Table 8. In some embodiments, a herein described conjugate is a conjugate of Table 9.

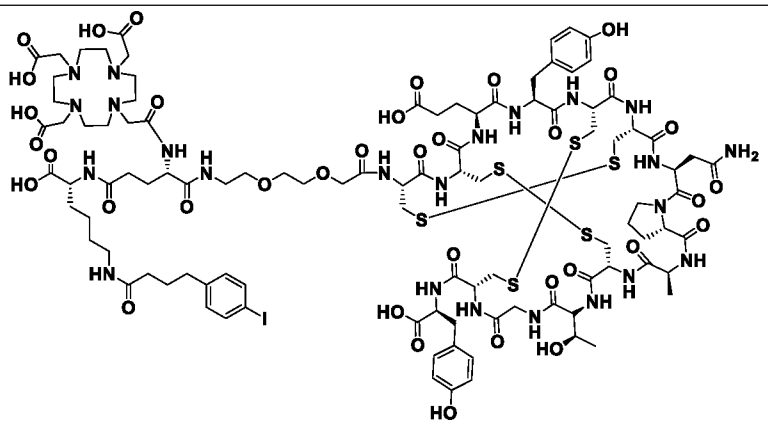
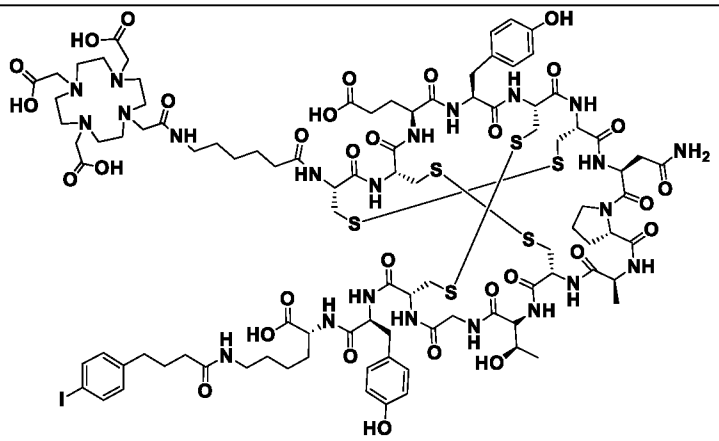
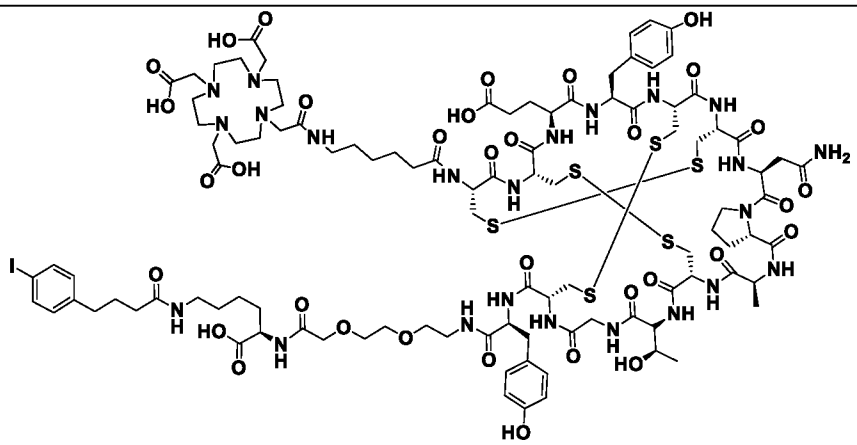
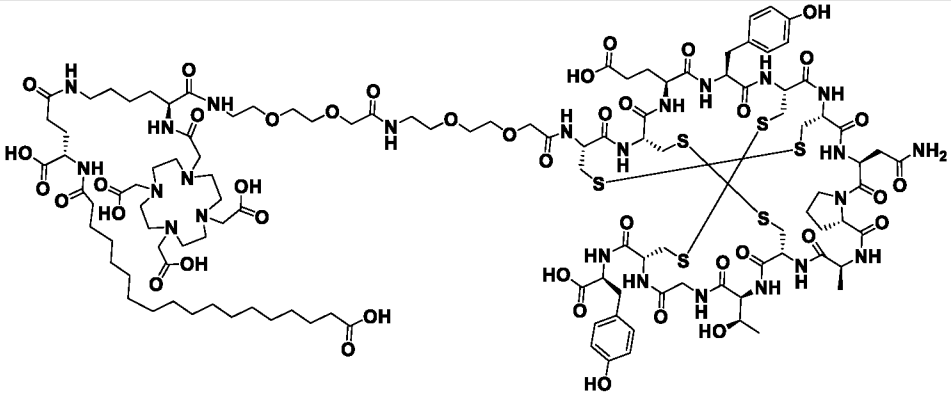
Table 1. Exemplary Conjugates

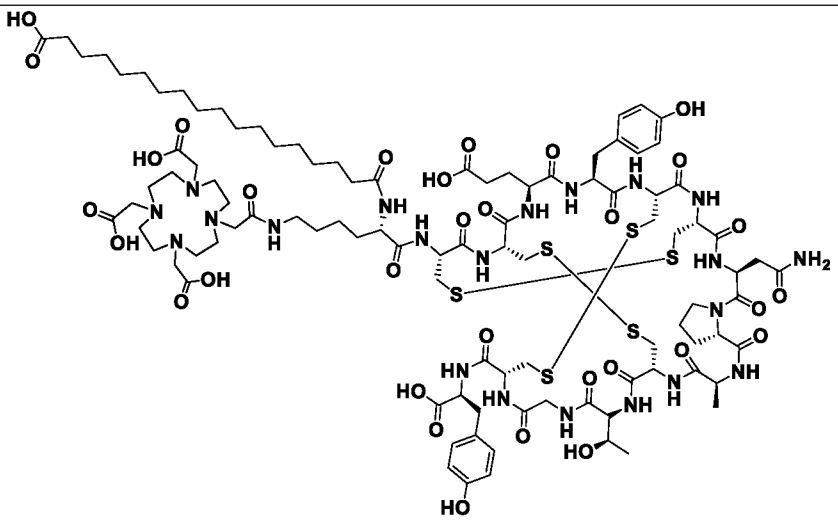
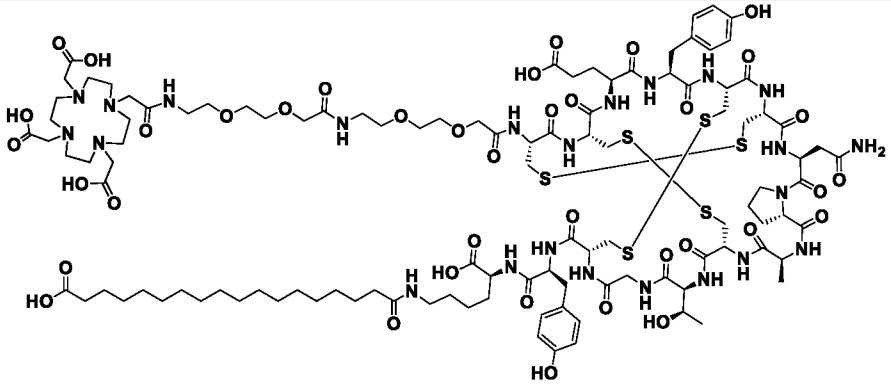
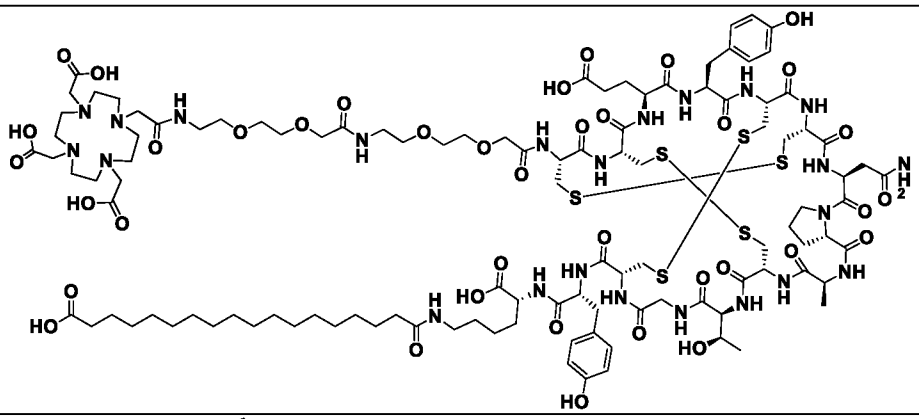
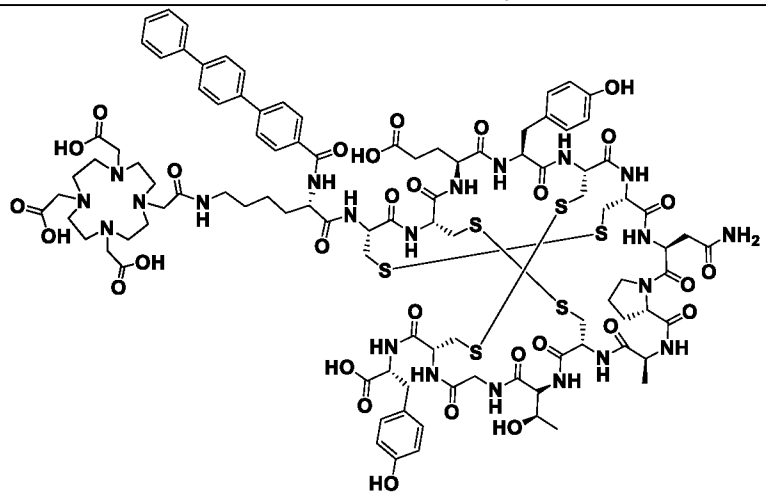
Compound	Chemical structure
C-01	
C-02	
C-03	
C-04	

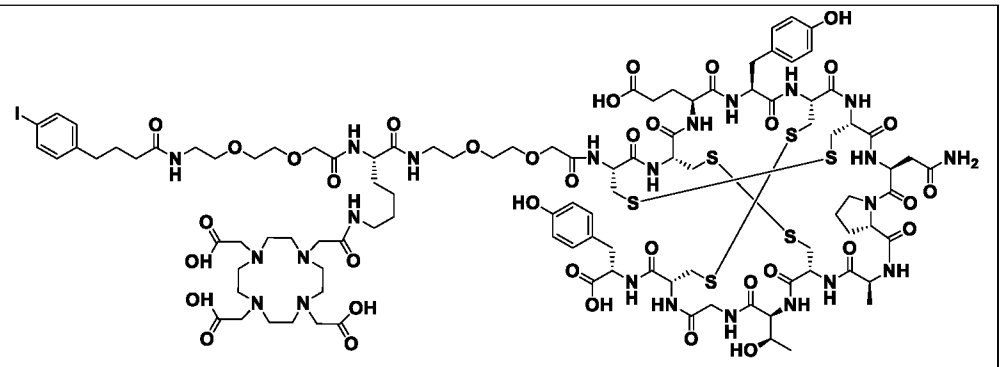
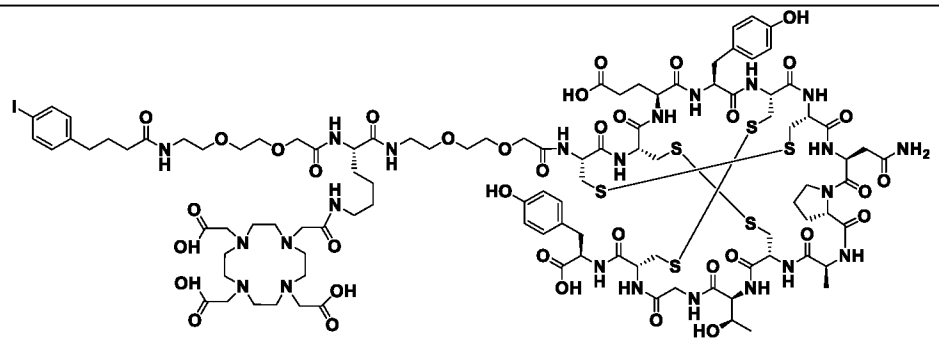
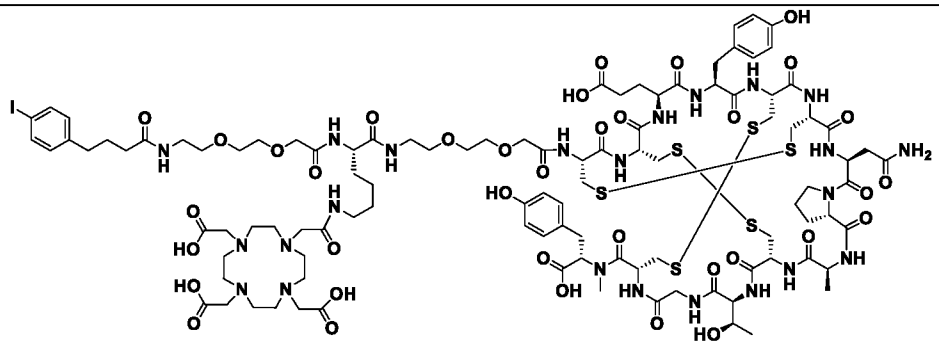
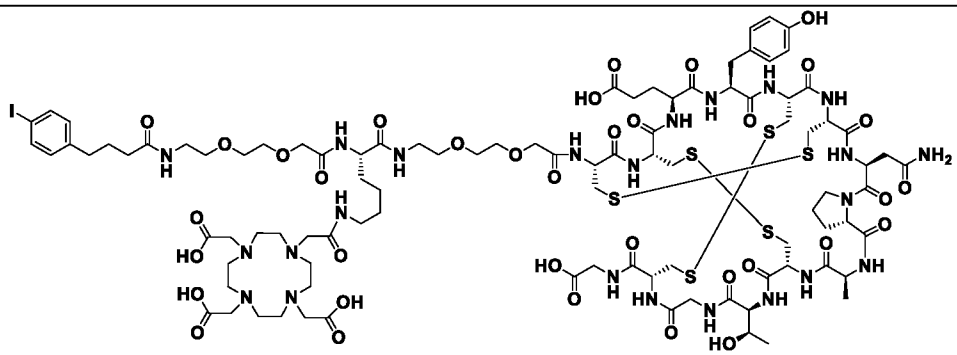
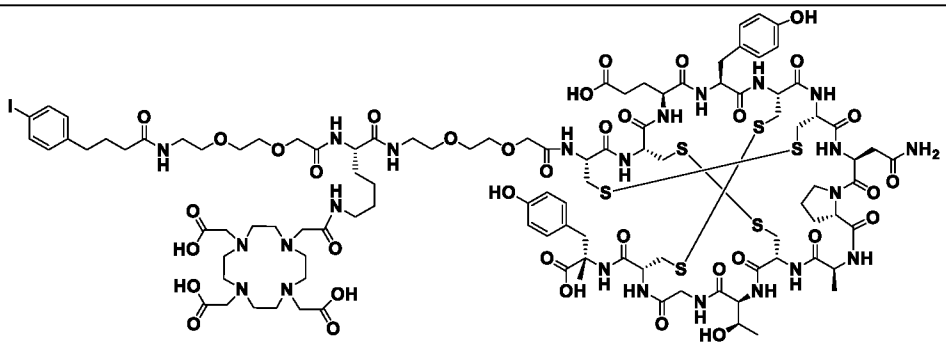
C-05	
C-06	
C-07	
C-08	
C-09	

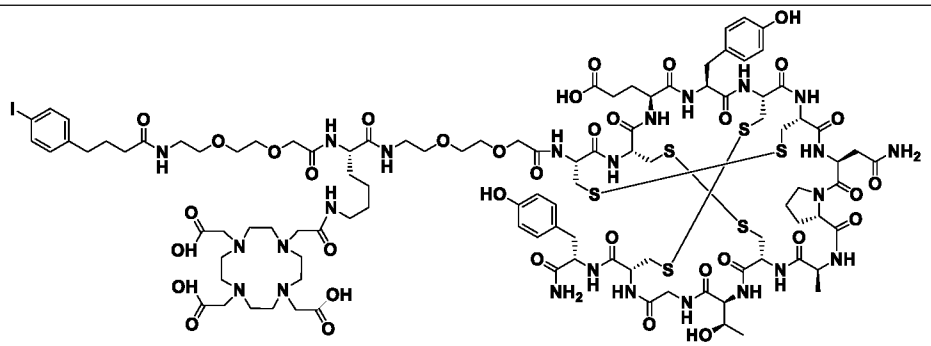
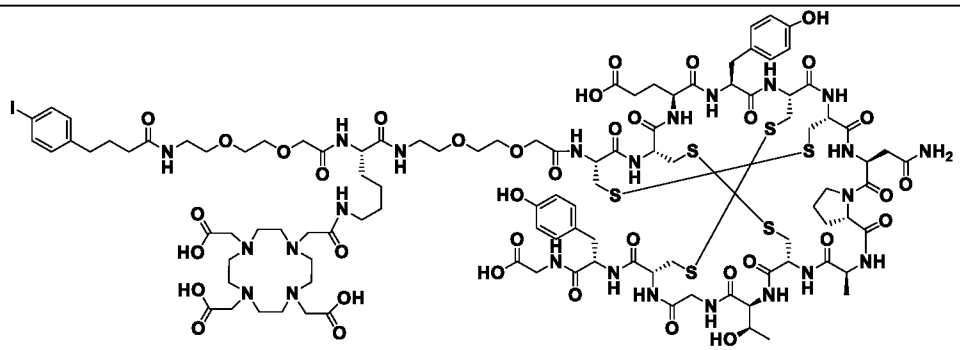
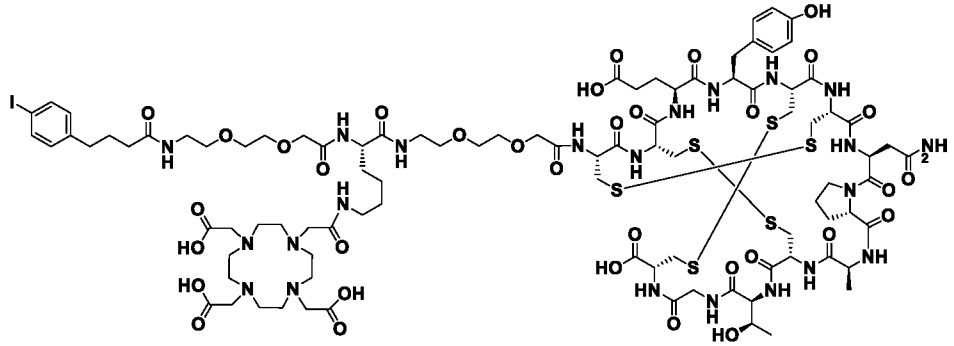
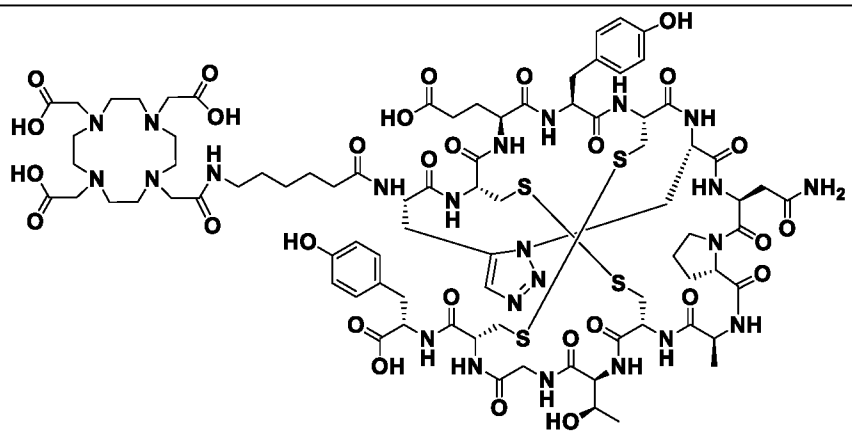
C-10	
C-13	
C-14	
C-15	

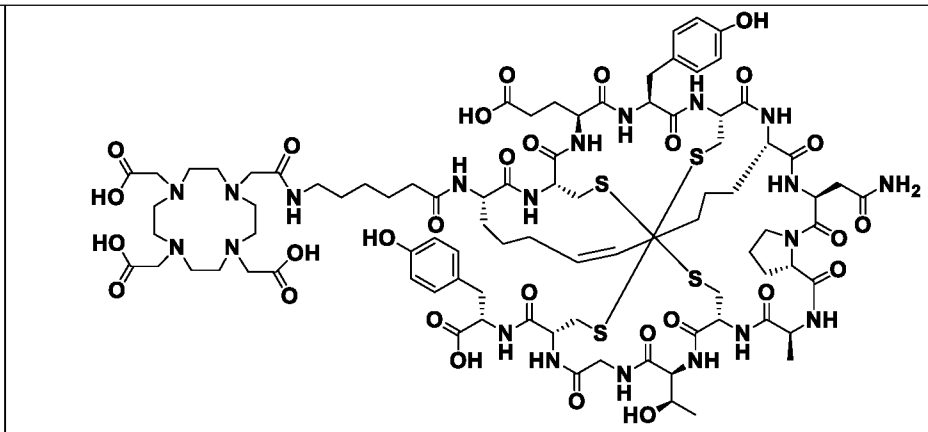
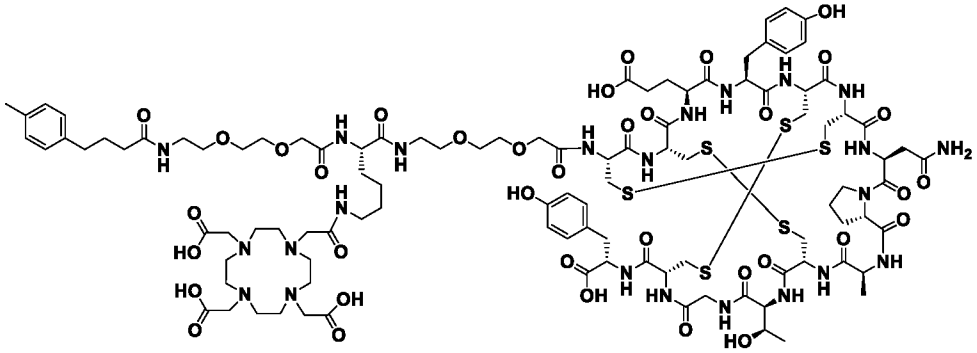
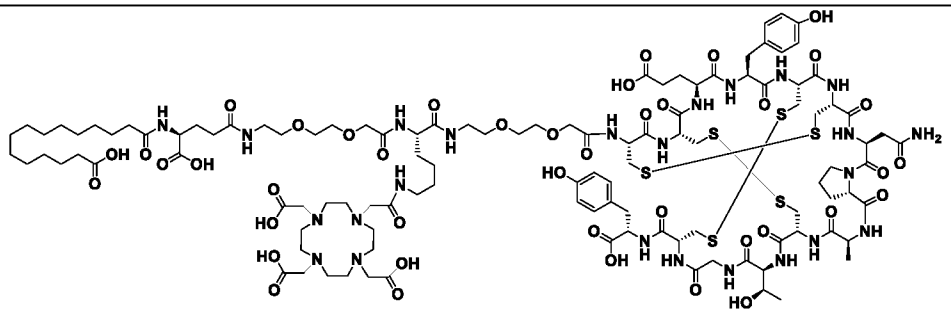
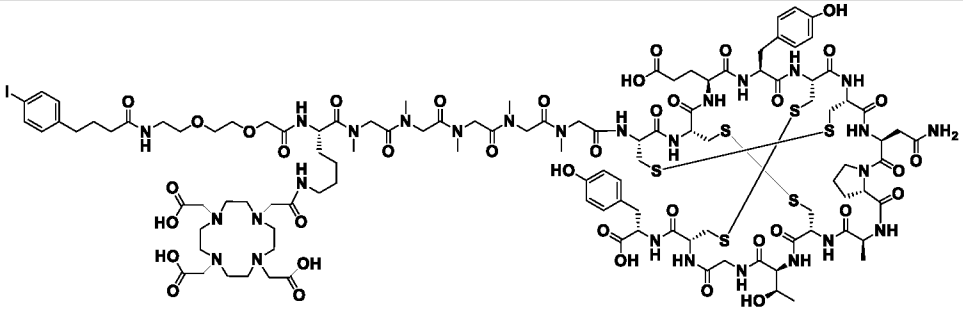
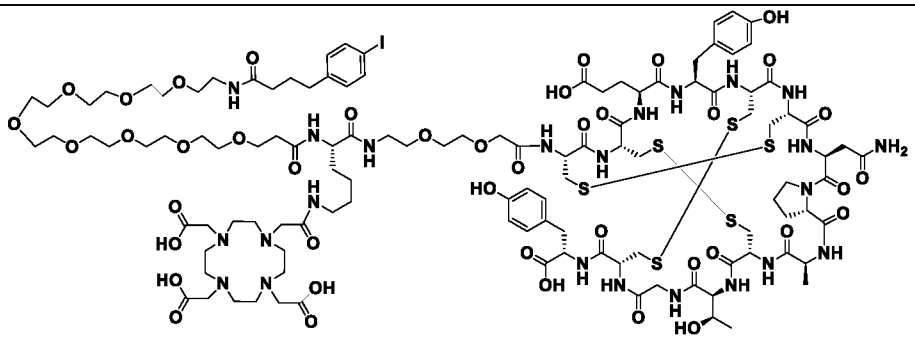
C-16	
C-17	
C-18	
C-19	

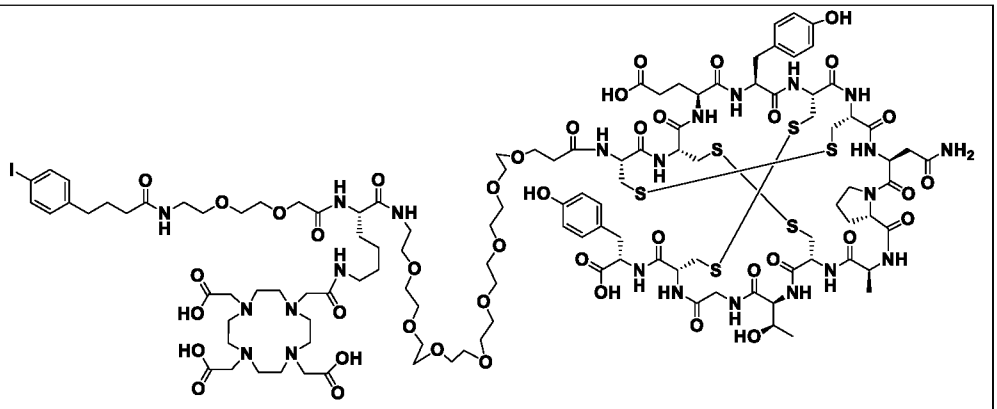
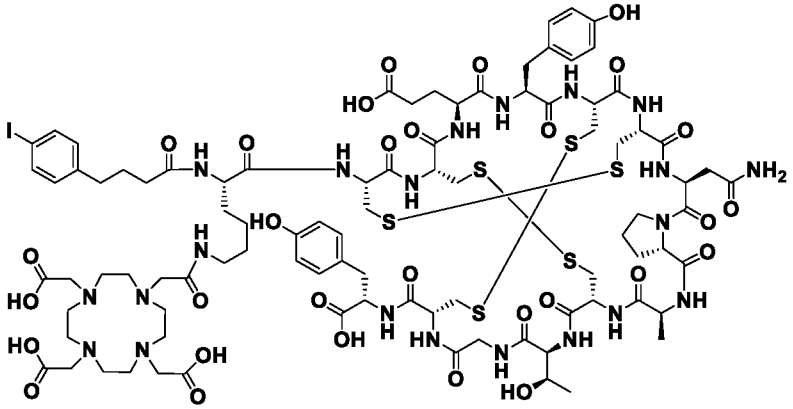
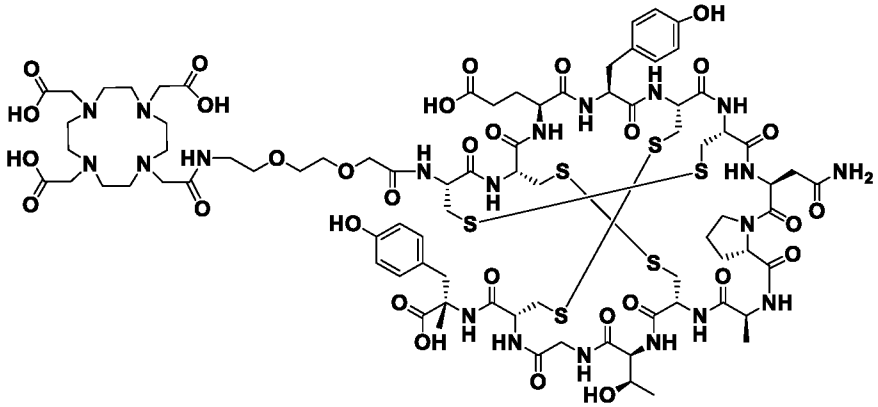
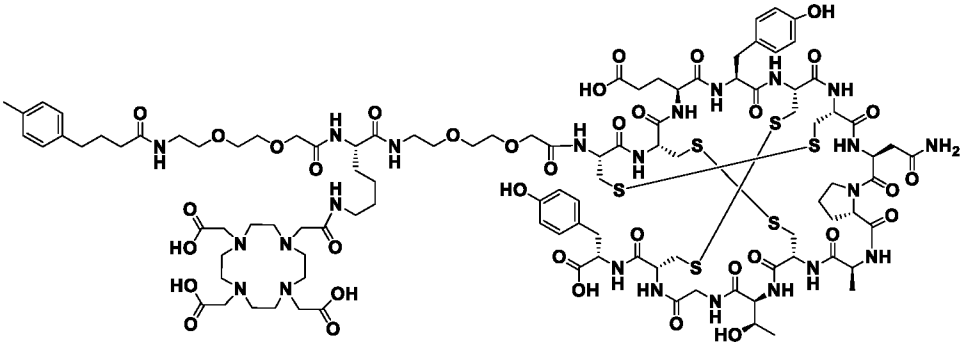
C-20	
C-21	
C-22	
C-23	

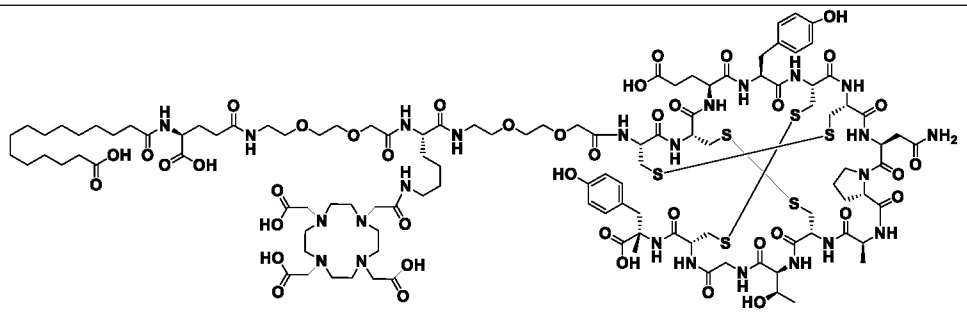
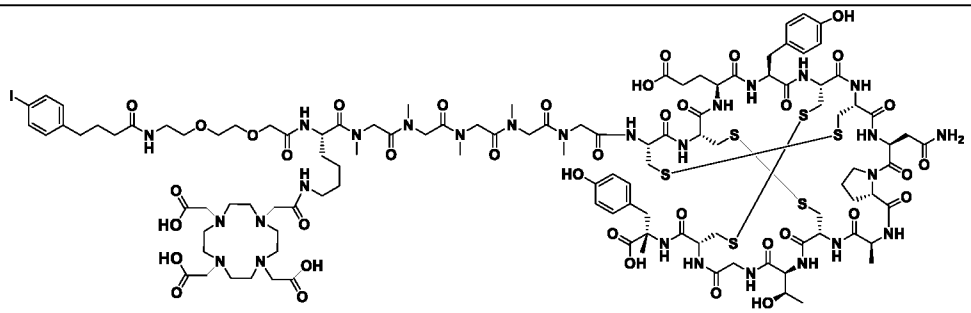
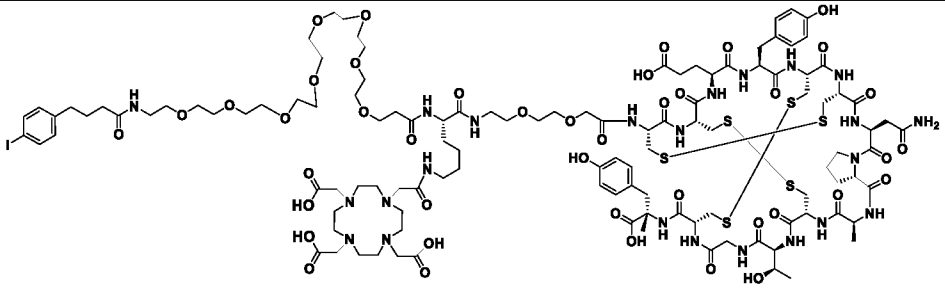
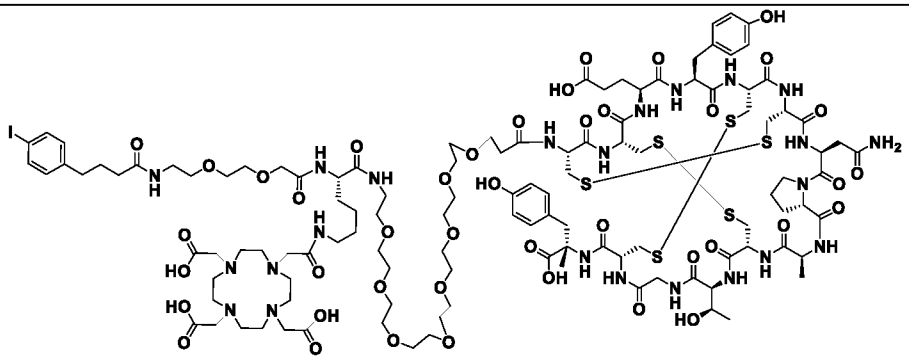
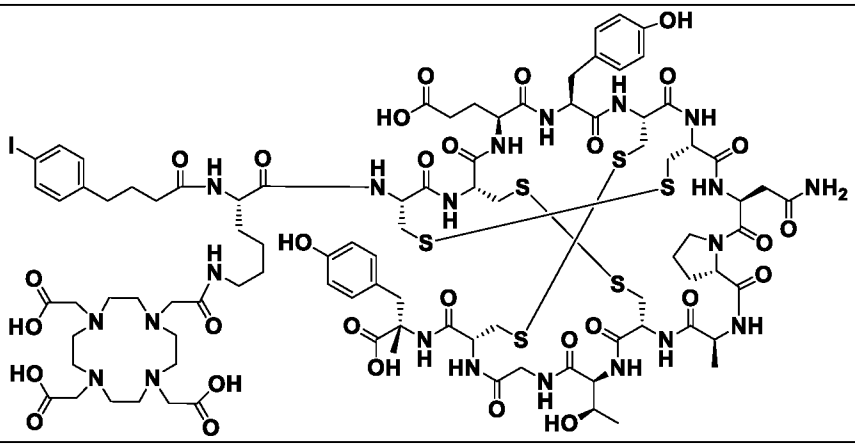
C-24	
C-25	
C-26	
C-27	

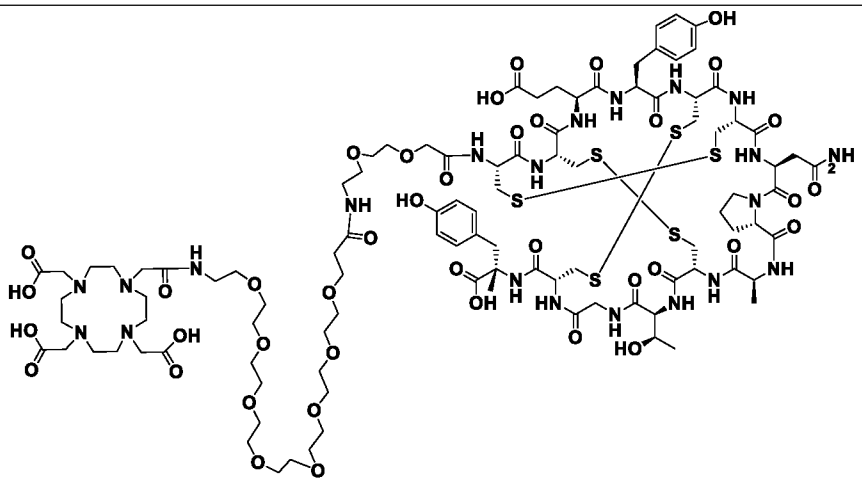
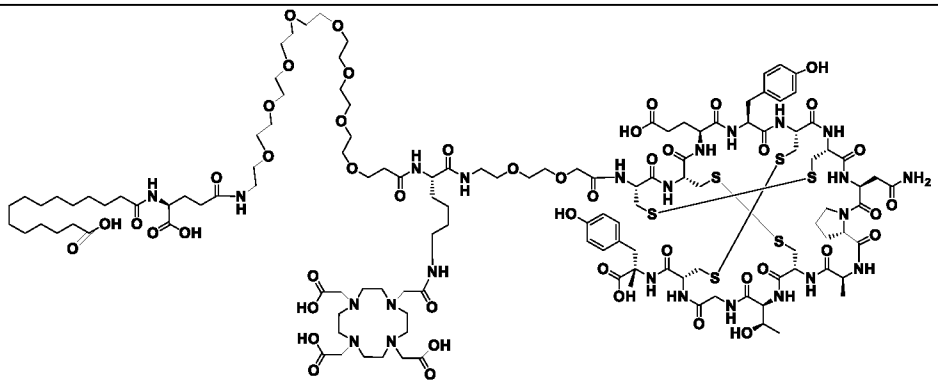
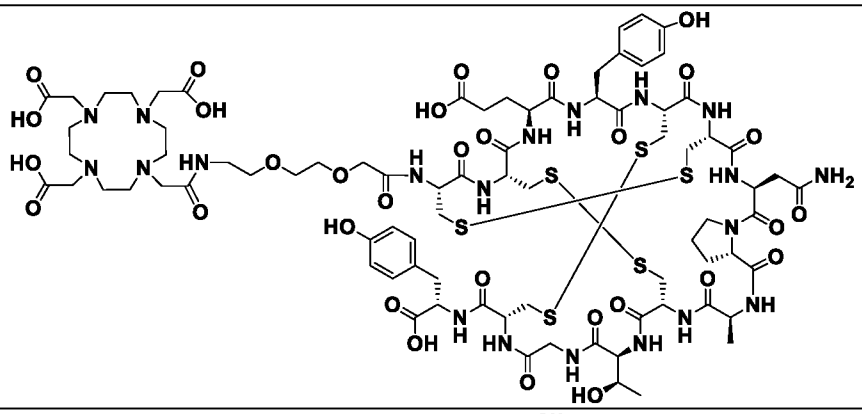
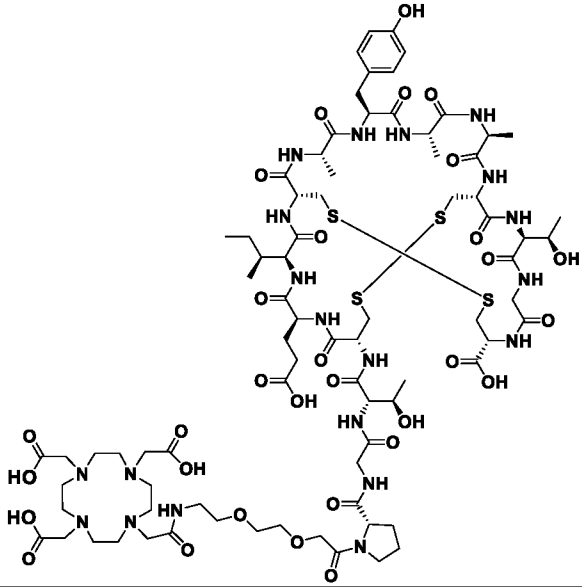
C-30	
C-31	
C-32	
C-33	
C-34	

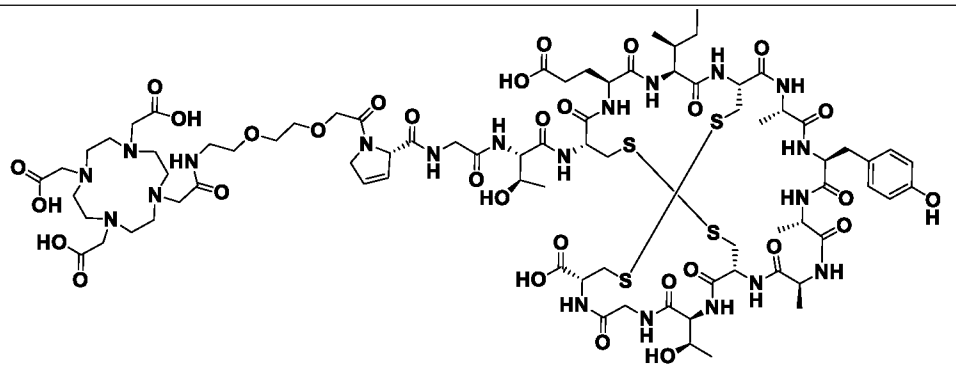
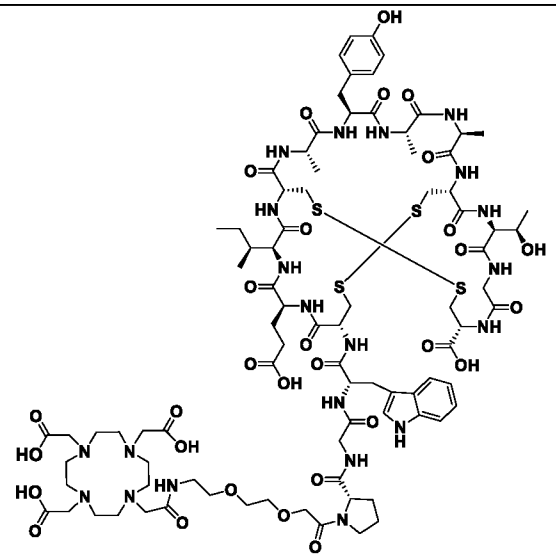
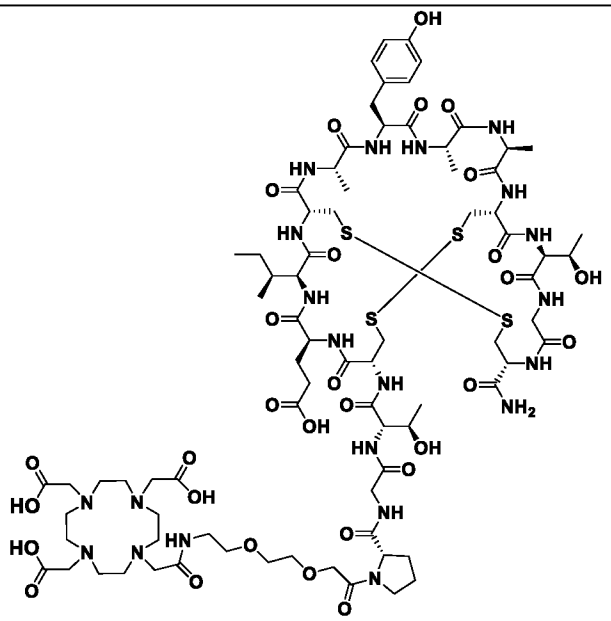
C-35	
C-36	
C-37	
C-40	

C-41	
C-48	
C-49	
C-50	
C-51	

C-52	
C-53	
C-54	
C-55	

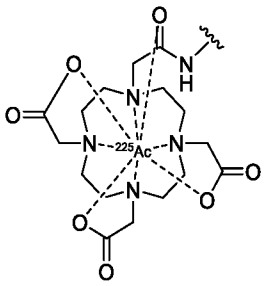
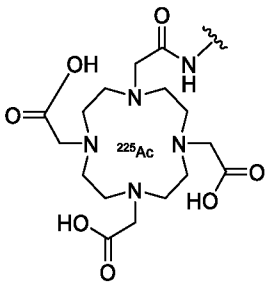
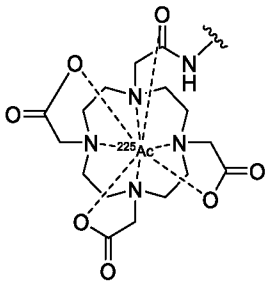
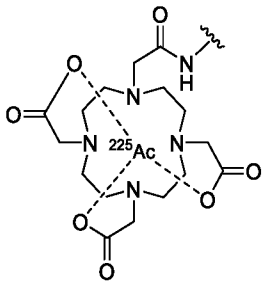
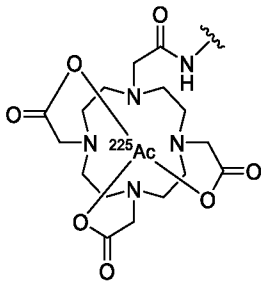
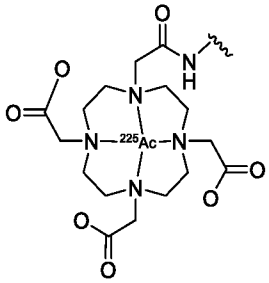
C-56	
C-57	
C-58	
C-59	
C-60	

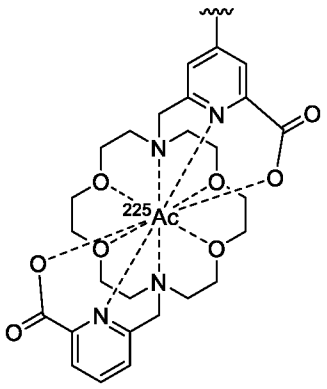
C-67	
C-68	
C-70	
C-87	

C-88	
C-89	
C-96	

[0125] It is understood that the structures of conjugates in Tables 6-7 are shown for illustration purposes. A person skilled in the art would appreciate that the bonding between the metal or radionuclide (La3+, ^{177}Lu or ^{225}Ac) and the metal chelator in the conjugates is for illustration purpose.

[0126] A metal chelator such as DOTA can interact with a radionuclide (e.g., ^{177}Lu or ^{225}Ac) via one or more functional groups and/or atoms. For example, a metal chelator can interact with a

radionuclide via nitrogen and/or oxygen atoms. As another example, a metal chelator can interact with a radionuclide via carbonyl, carboxylic acid, amino, and/or amide groups of the metal chelator. In some embodiments, the interaction of a metal chelator and a radionuclide of the conjugates disclosed herein can be illustrated as  . In some embodiments, the interaction of a metal chelator and a radionuclide of the conjugates disclosed herein can be illustrated as  . In some embodiments, the interaction of a metal chelator and a radionuclide of the conjugates disclosed herein can be illustrated as  . In some embodiments, the interaction of a metal chelator and a radionuclide of the conjugates disclosed herein can be illustrated as  or  . In some embodiments, the interaction of a metal chelator and a radionuclide of the conjugates disclosed herein can be illustrated as  . In some embodiments, the interaction of a metal chelator and a radionuclide of the conjugates disclosed herein can be illustrated as



. In some embodiments, the radionuclide exists in a positive oxidation state e.g., $^{225}Ac^{3+}$, $^{177}Lu^{3+}$. In some embodiments, for example in certain aqueous conditions, the radionuclide exists in a salt form, e.g., as $^{225}Ac^{3+}$, $^{177}Lu^{3+}$. In some embodiments, for example in certain acidic aqueous conditions, the radionuclide exists in a salt form, e.g., as $^{225}Ac^{3+}$, $^{177}Lu^{3+}$. In some embodiments, the conjugate is in a salt form. In some embodiments, one or more of the carboxylic acid groups of the conjugate may exist as carboxylate anions. In some embodiments, one or more of the carboxylate anions of the conjugate may coordinate to the radionuclide. A person of ordinary skill would appreciate that the dissociation of an acid can depend on the pH value of the environment and its pK value. Accordingly, in some embodiments, a conjugate described herein can exist in a completely ionized, partially ionized or non-ionized form.

Table 2. Design of Exemplary Conjugates

Compound	Compound Structure	Chelator	Linker	Peptide Sequence	SEQ ID NO:	C-Terminal
C-01	(DOTA)-Ahx-linaclotide	DOTA-	-Ahx-*	*-CCEYCCNPACTGCY	1	-OH
C-02	(DOTA)-K(IPhBu)-Aeea-linaclotide	DOTA-	-Aeea-*	*-CCEYCCNPACTGCY	1	-OH
C-03	(DOTA)-K(IPhBu)-linaclotide	DOTA-	-K(IPhBu)-*	*-CCEYCCNPACTGCY	1	-OH
C-04	(DOTA)-K(Palmitoyl)-linaclotide	DOTA-	- K(Palmitoyl)-*	*-CCEYCCNPACTGCY	1	-OH
C-05	(DOTA)-K (NaphSulfonamide)-linaclotide	DOTA-	-K (NaphSulfonamide)-*	*-CCEYCCNPACTGCY	1	-OH
C-06	(DOTA)-K(Cholyl)-Aeea-linaclotide	DOTA-	-K(Cholyl)-Aeea-*	*-CCEYCCNPACTGCY	1	-OH
C-07	(DOTA)-K(Ph2-cHex-Phospho-Hexanoyl)-Aeea-linaclotide	DOTA-	-K(Ph2-cHex-Phospho-Hexanoyl)-Aeea-*	*-CCEYCCNPACTGCY	1	-OH
C-08	(DOTA)-K(Het-Alb-tag)-Aeea-linaclotide	DOTA-	-K(Het-Alb-tag)-Aeea-*	*-CCEYCCNPACTGCY	1	-OH
C-09	(DOTA)-K(Het-Alb-tag)-linaclotide	DOTA-	-K(Het-Alb-tag)-*	*-CCEYCCNPACTGCY	1	-OH
C-10	(DOTA)-K[C18-diacid-γE-$(Aeea)_2$]-linaclotide	DOTA-	-K[C18-diacid-γE-$(Aeea)_2$]-*	*-CCEYCCNPACTGCY	1	-OH
C-13	(DOTA)-[F4]-STh(6-19)	DOTA-*	-	*-CCEFCCNPACTGCY	17	-OH

C-14	(DOTA)-Ahx-[F4]-STh(6-19)	DOTA-	-Ahx-*	*-CCEFCCNPACTGCY	17	-OH
C-15	(DOTA)-K(C18-diacid-γE-Aeea$_2$)-linaclotide-(dY)	DOTA-	-K[C18-diacid-γE-(Aeea)$_2$]-*	*-CCEYCCNPACTGC**dY**	39	-OH
C-16	(DOTA)-K(Het-Alb-tag)-linaclotide-(dY)	DOTA-	-K(Het-Alb-tag)-*	*-CCEYCCNPACTGC**dY**	39	-OH
C-17	(DOTA)-K(Palmitoyl)-linaclotide-(dY)	DOTA-	- K(Palmitoyl)-*	*-CCEYCCNPACTGC**dY**	39	-OH
C-18	(DOTA)-K(IPhBu)-linaclotide-(dY)	DOTA-	-K(IPhBu)-*	*-CCEYCCNPACTGC**dY**	39	-OH
C-19	[-CO-dK(IPhBu)-OH]-K(DOTA)-linaclotide	DOTA-	-K[-CO-dK(IPhBu)-OH]-*	*-CCEYCCNPACTGCY	1	-OH
C-20	(DOTA)-E[dK(IPhBu)-OH]-Aeea-linaclotide	DOTA-	-E[dK(IPhBu)-OH]-Aeea-*	*-CCEYCCNPACTGCY	1	-OH
C-21	(DOTA)-Ahx-linaclotide-dK(IPhBu)	DOTA-	-Ahx-*	*-CCEYCCNPACTGC-**	33	**-dK(IPhBu)
C-22	(DOTA)-Ahx-linaclotide-Aeea-dK(IPhBu)	DOTA-	-Ahx-*	*-CCEYCCNPACTGC-**	33	**-Aeea-dK(IPhBu)
C-23	(DOTA)-K(C18-diacid-γE)-(Aeea)$_2$-linclotide	DOTA-	-K(C18-diacid-γE-(Aeea)$_2$)-*	*-CCEYCCNPACTGCY	1	-OH
C-24	C18-diacid-K(DOTA)-linaclotide	DOTA-	-K(C18-diacid)-*	*-CCEYCCNPACTGCY	1	-OH
C-25	(DOTA)-(Aeea)$_2$-linaclotide-K(C18-diacid)	DOTA-	-(Aeea)$_2$-*	*-CCEYCCNPACTGCY-**	1	**-K(C18-diacid)-OH
C-26	(DOTA)-(Aeea)$_2$-linaclotide-dY-dK(C18-diacid)	DOTA-	-(Aeea)$_2$-*	*-CCEYCCNPACTGC**dY**-**	39	**-dK(C18-diacid)-OH
C-27	TerPhCO-K(DOTA)-linaclotide	DOTA-	-K(TerPhCO)-*	*-CCEYCCNPACTGCY	1	-OH
C-28	Linaclotide-dY	H	-	CCEYCCNPACTGC**dY**	39	-OH
C-29	Linaclotide-desY	H	-	CCEYCCNPACTGC	33	-OH
C-30	IPhBu-Aeea-K(DOTA)-Aeea-linaclotide	DOTA-	-K(IPhBu-Aeea)-Aeea-*	*-CCEYCCNPACTGCY	1	-OH
C-31	IPhBu-Aeea-K(DOTA)-Aeea-linaclotide-dY	DOTA-	-K(IPhBu-Aeea)-Aeea-*	*-CCEYCCNPACTGC**dY**	39	-OH
C-32	IPhBu-Aeea-K(DOTA)-Aeea-linaclotide-NMeY	DOTA-	-K(IPhBu-Aeea)-Aeea-*	*-CCEYCCNPACTGC**NMeY**	35	-OH
C-33	IPhBu-Aeea-K(DOTA)-Aeea-linaclotide-(desY)-Gly	DOTA-	-K(IPhBu-Aeea)-Aeea-*	*-CCEYCCNPACTGCG	40	-OH
C-34	IPhBu-Aeea-K(DOTA)-Aeea-linaclotide-αMeY	DOTA-	-K(IPhBu-Aeea)-Aeea-*	*-CCEYCCNPACTGC**αMeY**	38	-OH
C-35	IPhBu-Aeea-K(DOTA)-Aeea-linaclotide-NH2	DOTA-	-K(IPhBu-Aeea)-Aeea-*	*-CCEYCCNPACTGC**Y**-	36	-NH2
C-36	IPhBu-Aeea-K(DOTA)-Aeea-linaclotide-Gly	DOTA-	-K(IPhBu-Aeea)-Aeea-*	*-CCEYCCNPACTGCY	1	G-OH
C-37	IPhBu-Aeea-K(DOTA)-Aeea-linaclotide-desY	DOTA-	-K(IPhBu-Aeea)-Aeea-*	*-CCEYCCNPACTGC	33	-OH

C-48	MePhBu-Aeea-K(DOTA)-Aeea-linaclotide	DOTA-	-K(MePhBu-Aeea)-Aeea-*	*-CCEYCCNPACTGCY	1	-OH
C-49	C15-diacid-γE-Aeea-K(DOTA)-Aeea-linaclotide	DOTA-	-K(C15-diacid-γE-Aeea)-Aeea-*	*-CCEYCCNPACTGCY	1	-OH
C-50	IPhBu-Aeea-K(DOTA)-Sar5-linaclotide	DOTA-	-K(IPhBu-Aeea)-Sar5-*	*-CCEYCCNPACTGCY	1	-OH
C-51	IPhBu-PEG8-K(DOTA)-linaclotide	DOTA-	-K(IPhBu-PEG8)-*	*-CCEYCCNPACTGCY	1	-OH
C-52	IPhBu-Aeea-K(DOTA)-PEG8-linaclotide	DOTA-	-K(IPhBu-Aeea)-PEG8-*	*-CCEYCCNPACTGCY	1	-OH
C-53	IPhBu-K(DOTA)-linaclotide	DOTA-	-K(IPhBu)-*	*-CCEYCCNPACTGCY	1	-OH
C-54	(DOTA)-Aeea-linaclotide-(αMeY)	DOTA-	-Aeea-*	*-CCEYCCNPACTGC**αMeY**	38	-OH
C-55	MePhBu-Aeea-K(DOTA)-Aeea-linaclotide-(αMeY)	DOTA-	-K(MePhBu-Aeea)-Aeea-*	*-CCEYCCNPACTGC**αMeY**	38	-OH
C-56	C15-diacid-γE-Aeea-K(DOTA)-Aeea-linaclotide-(αMeY)	DOTA-	-K(C15-diacid-γE-Aeea)-Aeea-*	*-CCEYCCNPACTGC**αMeY**	38	-OH
C-57	IPhBu-Aeea-K(DOTA)-Sar5-linaclotide-(αMeY)	DOTA-	-K(IPhBu-Aeea)-Sar5-*	*-CCEYCCNPACTGC**αMeY**	38	-OH
C-58	IPhBu-PEG8-K(DOTA)-Aeea-linaclotide-(αMeY)	DOTA-	-K(IPhBu-PEG8)-Aeea-*	*-CCEYCCNPACTGC**αMeY**	38	-OH
C-59	IPhBu-Aeea-K(DOTA)-PEG8-linaclotide-(αMeY)	DOTA-	-K(IPhBu-Aeea)-PEG8-*	*-CCEYCCNPACTGC**αMeY**	38	-OH
C-60	IPhBu-K(DOTA)-linaclotide-(αMeY)	DOTA-	-K(IPhBu)-*	*-CCEYCCNPACTGC**αMeY**	38	-OH
C-66	Guanylin (human)	-	-	PGTCEICAYAACTGC	13	-OH
C-67	(DOTA)-PEG8-Aeea-linaclotide-(αMeY)	DOTA-	-PEG8-Aeea-*	*-CCEYCCNPACTGC**αMeY**	38	-OH
C-68	C15-diacid-γE-PEG8-K(DOTA)-Aeea-linaclotide-(αMeY)	DOTA-	-K(C15-diacid-γE-PEG8)-Aeea-*	*-CCEYCCNPACTGC**αMeY**	38	-OH
C-69	Uroguanylin Topoisomer A	-	-	NDDCELCVNVACTGCL	14	-OH
C-70	(DOTA)-Aeea-linaclotide	DOTA-	-Aeea-*	*-CCEYCCNPACTGCY	1	-OH
C-84	Linaclotide-(αMeY)	H	-	CCEYCCNPACTGC**αMeY**	38	-OH
C-85	Enterotoxin STp	H	-	NTFYCCELCCNPACAGCY	44	-OH
C-86	Uroguanylin Topoisomer B	H	-	NDDCELCVNVACTGCL	14	-OH
C-87	(DOTA)-Aeea-Guanylin	DOTA-	-Aeea-*	*-PGTCEICAYAACTGC	13	-OH
C-88	(DOTA)-Aeea-[Dhp1]-Guanylin	DOTA-	-Aeea-*	*- **Dhp**GTCEICAYAACTGC	41	-OH
C-89	(DOTA)-Aeea-[Trp3]-Guanylin	DOTA-	-Aeea-*	*-PGWCEICAYAACTGC	42	-OH
C-96	(DOTA)-Aeea-Guanylin-NH2	DOTA-	-Aeea-*	*-PGTCEICAYAACTGC	13	-NH2
C-182	[Dhp8]-STp(5-18); CMP-101	H	-	*-CCELCCN**Dhp**ACAGCY	31	-OH

[0127] In Table 2, * denotes the side of a linker being connected to the N-terminus of the peptide sequence (also marked by *), while ** denotes the side of a linker being connected to the C-terminus of the peptide sequence (also marked by **).

[0128] Definitions for abbreviated compounds in Table 2 above are listed in Table 3.

Table 3. Definitions of abbreviated compounds in Table 2.

Abbreviation	Definition
*	N-terminal linker attachment point
**	C-terminal linker attachment point
Ahx	6-aminohexanoic acid
NaphSulfonamide	4-(naphthalene-2-sulfonamido)-4-oxobutanoic acid
γE	Gamma glutamate
Aeea	8-amino-3,6-dioxaoctanoic acid
Het-Alb-tag	(S)-3-(5-bromo-1H-indole-2-carboxamido)-2-(2-(3-(trifluoromethoxy)phenyl)acetamido)propanoic acid
IPhBu	4-(4-iodophenyl)butanoyl/4-(4-iodophenyl)butanoic acid
MePhBu	4-(4-methylphenyl)butanoyl/4-(4-methylphenyl)butanoic acid
dK, dY	D-lysine, D-tyrosine
TerPhCO	p-Terphenyl-4-carboxylic acid
NMeY	N-methyltyrosine
αMeY	α-methyl tyrosine
Y-NH2	Tyrosinamide
Pra	Propargylglycine
Dap(N3)	3-Azidoalanine
PentenylG	Pentenylglycine
Sar5	5,8,11,14-tetramethyl-4,7,10,13-tetraoxo-2,5,8,11,14-pentaazahexadecan-16-oic acid
Dhp	3,4-dehydro-proline
desY	Tyrosine deleted

[0129] In one aspect, a conjugate described herein has a structure of Formula (I), (Ia), (Iaa) or (Iab), or a salt or solvate thereof, which is further described below.

Peptide Ligands

[0130] In one aspect, a conjugate described herein comprises a GCC binding peptide. The GCC binding peptide can be linear or cyclic (e.g., cyclized by disulfide bond or other bonds). The cyclization can occur between the N- and C-terminus, or it can occur between a terminal amino acid and a non-terminal amino acid. In some embodiments, the cyclization occurs between two non-terminal amino acids. In some embodiments, the peptide is monocyclic. In some

embodiments, the peptide is bicyclic or polycyclic. The peptide can comprise any suitable number of amino acid residues. In some embodiments, the peptide comprises from 5 to 50, 6 to 40, 7 to 30, 8 to 25, 12 to 25, or 9 to 20 amino acid residues. In some embodiments, the peptide comprises from 10 to 15 amino acid residues. In some embodiments, the peptide comprises from 12 to 15 amino acid residues. In some embodiments, the peptide comprises from 13 to 16 amino acid residues. In some embodiments, the peptide comprises 9 amino acid residues. In some embodiments, the peptide comprises 10 amino acid residues. In some embodiments, the peptide comprises 11 amino acid residues. In some embodiments, the peptide comprises 12 amino acid residues. In some embodiments, the peptide comprises 13 amino acid residues. In some embodiments, the peptide comprises 14 amino acid residues. In some embodiments, the peptide comprises 15 amino acid residues. In some embodiments, the peptide comprises 16 amino acid residues. In some embodiments, the peptide comprises 17 amino acid residues. In some embodiments, the peptide comprises 18 amino acid residues. In some embodiments, the peptide comprises 16 to 25 amino acid residues. In some embodiments, the peptide comprises 9 amino acid residues. In some embodiments, the peptide consists of 10 amino acid residues. In some embodiments, the peptide consists of 11 amino acid residues. In some embodiments, the peptide consists of 12 amino acid residues. In some embodiments, the peptide consists of 13 amino acid residues. In some embodiments, the peptide consists of 14 amino acid residues. In some embodiments, the peptide consists of 15 amino acid residues. In some embodiments, the peptide consists of 16 amino acid residues. In some embodiments, the peptide consists of 17 amino acid residues.

[0131] In some embodiments, the GCC binding peptide is an endogenous GCC ligand, e.g., guanylin and uroguanylin. In some embodiments, the GCC binding peptide is an enterotoxin, e.g., enterotoxigenic *E. coli, K. pneumonia, V. cholera, and Y. enterocolitica*. In some embodiments, the GCC binding peptide is a synthetic peptide, e.g., linaclotide, plecanatide and dolcantide. Exemplary GCC binding peptides include, but are not limited to linaclotide, plecantide, dolcantide, E. coli ST, guanylin, Uroguanylin, limphoguanylin, E.coli STp, E.coli EAST1, V. cholerae STh, V. mimicus ST, Y. enterocolitica ST, and guanylin. GCC binding peptides are further provided in Lin et al., Toxins 2010, 2, 2028-2054 and Aka et al., Expert Rev Clin Pharmacol. 2017 May ; 10(5): 549–557, each of which is hereby incorporated by reference in its entirety. In some embodiments, the GCC binding peptide is linaclotide or a derivative thereof.

[0132] In some embodiments, a GCC binding peptide comprises an amino acid sequence that has at least 50% identity to any one of SEQ ID NOs: 1-42. In some embodiments, a GCC binding peptide comprises an amino acid sequence that has at least 60% identity to any one of SEQ ID NOs: 1-42. In some embodiments, a GCC binding peptide comprises an amino acid sequence that

has at least 70% identity to any one of SEQ ID NOs: 1-42. In some embodiments, a GCC binding peptide comprises an amino acid sequence that has at least 80% identity to any one of SEQ ID NOs: 1-42. In some embodiments, a GCC binding peptide comprises an amino acid sequence that has at least 85% identity to any one of SEQ ID NOs: 1-42. In some embodiments, a GCC binding peptide comprises an amino acid sequence that has at least 90% identity to any one of SEQ ID NOs: 1-42. In some embodiments, a GCC binding peptide comprises an amino acid sequence that has at least 95% identity to any one of SEQ ID NOs: 1-42. In some embodiments, a GCC binding peptide comprises an amino acid sequence of any one of SEQ ID NOs: 1-42, or a binding fragment thereof. In some embodiments, a GCC binding peptide comprises an amino acid sequence that has at least 70% identity to any one of SEQ ID NOs: 1-19. In some embodiments, a GCC binding peptide comprises an amino acid sequence that has at least 80% identity to any one of SEQ ID NOs: 1-19. In some embodiments, a GCC binding peptide comprises an amino acid sequence that has at least 85% identity to any one of SEQ ID NOs: 1-19. In some embodiments, a GCC binding peptide comprises an amino acid sequence that has at least 90% identity to any one of SEQ ID NOs: 1-19. In some embodiments, a GCC binding peptide comprises an amino acid sequence that has at least 95% identity to any one of SEQ ID NOs: 1-19. In some embodiments, a GCC binding peptide comprises an amino acid sequence of any one of SEQ ID NOs: 1-19, or a binding fragment thereof. In some embodiments, the GCC binding peptide comprises any one of sequences in FIGs. 1A-1J, or a binding fragment thereof. In some embodiments, the GCC binding peptide comprises any one of sequences in Table 2.

Table 4. Amino acid sequences for exemplary GCC binding peptides

SEQ ID NO: 1	CCEYCCNPACTGCY
SEQ ID NO: 2	CCELCCNPACTGCY
SEQ ID NO: 3	NSSNYCCELCCNPACTGCY
SEQ ID NO: 4	SHTCEICAFAACAGC
SEQ ID NO: 5	QEDCELCINVACTGC
SEQ ID NO: 6	QEECELCINMACTGY
SEQ ID NO: 7	SSNYCCELCCNPACTGCF
SEQ ID NO: 8	NTFYCCELCCNPACTGCY
SEQ ID NO: 9	ASSYASCIWCTTACASCHG
SEQ ID NO: 10	GNLIDCCEICCNPACFGCLN
SEQ ID NO: 11	GNLIDRCEICCNPACFGCLN
SEQ ID NO: 12	SSDWDCCDVCCNPACAGC
SEQ ID NO: 13	PGTCEICAYAACTGC
SEQ ID NO: 14	NDDCELCVNVACTGCL

SEQ ID NO: 15	NSSNYCCELCCNPACTGCF
SEQ ID NO: 16	RSSRYCCELCCNPACTGCF
SEQ ID NO: 17	CCEFCCNPACTGCY
SEQ ID NO: 18	NDECELCVNVACTGCL
SEQ ID NO: 19	*NDECELCVNVACTGC*L, (one or both of *designated amino acids are be D-amino acids)
SEQ ID NO: 20	CCELCCNPACTGCY
SEQ ID NO: 21	CEICAFAACAGC
SEQ ID NO: 22	CELCINVACTGC
SEQ ID NO: 23	CELCINMACTGY
SEQ ID NO: 24	CCELCCNPACTGCF
SEQ ID NO: 25	SCIWCTTACASCHG
SEQ ID NO: 26	CCEICCNPACFGCLN
SEQ ID NO: 27	RCEICCNPACFGCLN
SEQ ID NO: 28	CCDVCCNPACAGC
SEQ ID NO: 29	CEICAYAACTGC
SEQ ID NO: 30	CELCVNVACTGCL
SEQ ID NO: 31	CCELCCNDhpACAGCY, (Dhp is 3,4-dehydro-proline)
SEQ ID NO: 32	CCELCVNVACTGCL
SEQ ID NO: 33	CCEYCCNPACTGC
SEQ ID NO: 34	CCEYCCNPACTGC*K, (*designated amino acids can be D-amino acids)
SEQ ID NO: 35	CCEYCCNPACTGC*Y (*Y is NMeY)
SEQ ID NO: 36	CCEYCCNPACTGC*Y (*Y is Y-NH_2)
SEQ ID NO: 37	CCEYCCNPACTGC*Y*K, (one or both of *designated amino acids can be D-amino acids)
SEQ ID NO: 38	CCEYCCNPACTGC*Y, (*Y is αMeY)
SEQ ID NO: 39	CCEYCCNPACTGC*Y, (*designated amino acids can be D-amino acids)
SEQ ID NO: 40	CCEYCCNPACTGCG
SEQ ID NO: 41	DhpGTCEICAYAACTGC (Dhp is 3,4-dehydro-proline)
SEQ ID NO: 42	PGWCEICAYAACTGC

[0133] In some embodiments, the GCC binding peptide comprises SEQ ID NO: 1. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 2. In some embodiments, the

GCC binding peptide comprises SEQ ID NO: 3. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 4. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 5. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 6. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 7. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 8. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 9. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 10. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 11. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 12. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 13. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 14. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 15. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 16. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 17. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 18. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 19. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 20. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 21. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 22. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 23. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 24. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 25. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 26. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 27. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 28. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 29. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 30. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 31. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 32. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 33. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 34. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 35. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 36. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 37. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 38. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 39. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 40. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 41. In some embodiments, the GCC binding peptide comprises SEQ ID NO: 42. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 1. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 2. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 3. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 4. In some

embodiments, the GCC binding peptide consists of SEQ ID NO: 5. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 6. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 7. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 8. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 9. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 10. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 11. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 12. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 13. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 14. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 15. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 16. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 17. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 18. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 19. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 20. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 21. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 22. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 23. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 24. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 25. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 26. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 27. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 28. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 29. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 30. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 31. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 32. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 33. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 34. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 35. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 36. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 37. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 38. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 39. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 40. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 41. In some embodiments, the GCC binding peptide consists of SEQ ID NO: 42. In some embodiments, one or more amino acids in any one of the SEQ ID NOs: 1-42 are derivatized, modified, and/or replaced with an unnatural amino acid.

[0134] Percent sequence identity can be calculated using computer programs or direct sequence comparison. Preferred computer program methods to determine identity between two sequences include, but are not limited to, the GCG program package, FASTA, BLASTP, and TBLASTN (see,

e.g., D. W. Mount, 2001, Bioinformatics: Sequence and Genome Analysis, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.). The BLASTP and TBLASTN programs are publicly available from NCBI and other sources. The Smith Waterman algorithm can also be used to determine percent identity. Exemplary parameters for amino acid sequence comparison include the following: 1) algorithm from Needleman and Wunsch (J. Mol. Biol., 48:443-453 (1970)); 2) BLOSSUM62 comparison matrix from Hentikoff and Hentikoff (Proc. Nat. Acad. Sci. USA., 89:10915-10919 (1992)) 3) gap penalty=12; and 4) gap length penalty=4. A program useful with these parameters can be publicly available as the "gap" program (Genetics Computer Group, Madison, Wis.). The aforementioned parameters are the default parameters for polypeptide comparisons (with no penalty for end gaps). Alternatively, polypeptide sequence identity can be calculated using the following equation: % identity—(the number of identical residues)/(alignment length in amino acid residues)*100. For this calculation, alignment length includes internal gaps but does not include terminal gaps.

[0135] In some embodiments, the GCC binding peptide described herein is a GCC receptor agonist. Exemplary GCC receptor agonists are described in U.S. Pat. Nos. 7,041,786, 7,799,897, and U.S. Patent Application Publication Nos. US2009/0048175, US 2010/0069306, US 2010/0120694, US 2010/0093635, and US 2010/0221329.

[0136] A peptide described herein can be a peptide mimetic. For example, the peptide can comprise non-peptide bonds and it can comprise one or more unnatural amino acids. Unless stated otherwise, each of the amino acid in a peptide described herein (except the natural amino acid glycine) can independently be in its D or L form. Both D and L forms are encompassed by the present disclosure.

[0137] In the present disclosure, the term amino acid embraces derivatives of amino acids. The derivatives include, for example, amino acids obtained by modifying a natural amino acid constituting a protein produced by cellular DNA-encoded biological matter. Examples of such non-natural amino acids include hydroxyproline and hydroxylysine, which are amino acids having a hydroxyl group introduced therein, and diaminopropionic acid, which is an amino acid having an amino group introduced therein. Examples of the derivatives also include derivatives having an amide, ester, or carboxyl group as the C-terminus and/or N-terminus thereof. Additional examples of the derivatives of the peptide include those obtained by modification such as phosphorylation, methylation, acetylation, adenylylation, ADP-ribosylation, or glycosylation and fused protein obtained by fusion with another peptide or protein. These derivatives can be prepared by those skilled in the art in a known manner or a method based thereon.

[0138] Examples of the amino acids include natural protein L-amino acids, unnatural amino acids, and chemically synthesized compounds having properties known in the art as characteristics

of an amino acid. Examples of the unnatural amino acids include, but not limited to, α,α-disubstituted amino acids (such as α-methylalanine), N-alkyl-α-amino acids, D-amino acids, β-amino acids, and α-hydroxy acids, each having a backbone structure different from that of natural amino acids; amino acids (such as norleucine and homohistidine) having a side-chain structure different from that of natural amino acids; amino acids (such as "homo" amino acids, homophenylalanine, and homohistidine) having extra methylene in the side chain thereof; and amino acids (such as cysteic acid) obtained by substituting a carboxylic acid functional amino group in the side chain thereof by a sulfonic acid group.

[0139] Accordingly, each amino acid residue of the GCC binding peptide can be independently derivatized. For example, the N- and/or C-terminus of the residue of any of the sequences in Table 4 can be replaced with a derivatized and/or unnatural amino acid. Modifications of the amino acid residues can improve the properties of the peptide (e.g., stability) and the conjugate comprising the peptide. In some embodiments, the GCC binding peptide comprises one or more D-amino acids. In some embodiments, the GCC binding peptide comprises one or more β-amino acids. In some embodiments, the GCC binding peptide comprises N-alkylation (such as N-methylation). In some embodiments, the GCC binding peptide comprises one or more polyethylene glycol chains. In some embodiments, the GCC binding peptide is cyclized. In some embodiments, the GCC binding peptide comprises an amide to sulfonamide substitution. In some embodiments, the GCC binding peptide comprises terminal modification.

[0140] A binding peptide (e.g., GCC binding peptide) described herein can be modified internally, and/or at N-terminus, C-terminus or both. In some embodiments, the GCC binding peptide comprises N-terminal methylation, N-terminal acetylation, N-terminal propionylation, N-terminal myristoylation, or N-terminal palmitoylation. In some embodiments, the GCC binding peptide comprises C-terminal methylation, C-terminal acetylation, C-terminal propionylation, C-terminal myristoylation, or C-terminal palmitoylation. In some embodiments, the GCC binding peptide comprises N-terminal modification such as amidation. In some embodiments, the GCC binding peptide comprises C-terminal modification such as amidation. In some embodiments, the GCC binding peptide comprises internal modification such as cyclization, carbamidomethylation, phosphorylation, or PEGylation. In some embodiments, the modification can function to increase the bulkiness of the terminal amino acid thereby improving metabolic stability. In some embodiments, the modification increases half-life and/or proteolysis stability. Exemplary C-terminal modification on a tyrosine residue (e.g., peptide having SEQ ID NO: 1) includes D-tyrosine, N-methyl-L-tyrosine, α-methyl-L-tyrosine, L-tyrosinamide, O-methyl-L-tyrosine, O-4-allyl-L-tyrosine, 4-propyl-L-tyrosine, O-propargyltyrosine, etc. In some embodiments, the C-terminal modification on a tyrosine residue is D-tyrosine. In some embodiments, the C-terminal

modification on a tyrosine residue is N-methyl-L-tyrosine. In some embodiments, the C-terminal modification on a tyrosine residue is α-methyl-L-tyrosine.

[0141] A GCC binding peptide described herein can be modified by cyclization. In some embodiments, the cyclization occurs between the N- and C-terminus. In some embodiments, the cyclization occurs between a terminal amino acid and a non-terminal amino acid. In some embodiments, the cyclization occurs between two non-terminal amino acids. In some embodiments, a GCC binding peptide described herein comprises 1, 2 or 3 intramolecular disulfide bonds. In some embodiments, a GCC binding peptide comprises 2 or 3 intramolecular disulfide bonds. In some embodiments, a GCC binding peptide comprises 2 intramolecular disulfide bonds. In some embodiments, a GCC binding peptide comprises 3 intramolecular disulfide bonds. In some embodiments, a GCC binding peptide comprises one intramolecular alkylene or alkenylene bond. In some embodiments, a GCC binding peptide comprises an intramolecular alkylene bond. In some embodiments, a GCC binding peptide comprises an intramolecular heteroalkylene bond. In some embodiments, a GCC binding peptide comprises an intramolecular alkenylene bond. In some embodiments, a GCC binding peptide comprises an intramolecular bond that is bridged by a triazole. In some embodiments, a GCC binding peptide described herein comprises two intramolecular disulfide bonds and one intramolecular heteroalkene, alkylene or alkenylene bond. In some embodiments, the intramolecular bond comprises a triazole bridge. In some embodiments, a GCC binding peptide comprises intramolecular alkylene bridge. In some embodiments, a GCC binding peptide comprises intramolecular heteroalkylene bridge. In some embodiments, the alkylene bridge is C_2-C_{10} alkylene. In some embodiments, the alkylene bridge is C_3-C_8 alkylene. In some embodiments, the alkylene bridge is C_3-C_6 alkylene. In some embodiments, the bridge is C_2-C_{10} heteroalkylene. In some embodiments, the bridge is C_3-C_8 heteroalkylene. In some embodiments, the bridge is C_3-C_6 heteroalkylene. In some embodiments, the alkylene bridge is C_3 alkylene. In some embodiments, the alkylene bridge is C_4 alkylene. In some embodiments, a GCC binding peptide comprises intramolecular heteroalkylene bridge. In some embodiments, the heteroalkylene bridge is C_2-C_{10} heteroalkylene. In some embodiments, the heteroalkylene bridge is C_2-C_8 heteroalkylene. In some embodiments, the heteroalkylene bridge is C_2-C_4 heteroalkylene. In some embodiments, the heteroalkylene bridge is C_3 heteroalkylene. In some embodiments, the heteroalkylene bridge is C_4 heteroalkylene. In some embodiments, the heteroalkylene bridge comprises 1, 2, or 3 atoms each independently selected from O, N, P, S, and Se. In some embodiments, the heteroalkylene bridge comprises S. In some embodiments, the heteroalkylene bridge comprises Se.

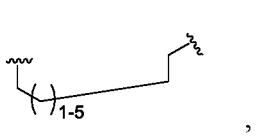
[0142] In some embodiments, the heteroalkylene, alkylene or alkenylene is optionally substituted with one or more R^{10}, wherein

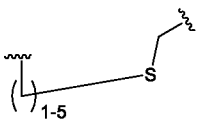
each R^{10} is independently halogen, amino, -OH, -SH, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

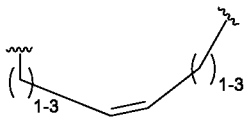
or two R^{10} on the same atoms are taken together to form a cycloalkyl or heterocycloalkyl;

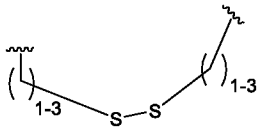
or two R^{10} on different atoms are taken together to form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

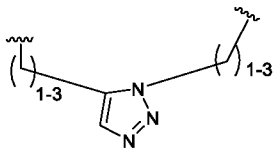
[0143] In some embodiments, two R^{10} adjacent atoms are taken together to form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl. In some embodiments, two R^{10} adjacent atoms are taken together to form a heteroaryl such as triazole. In some embodiments, the intramolecular bridge is



,


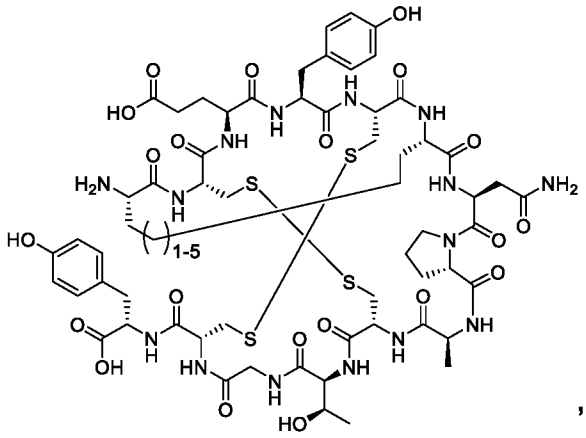
,


,


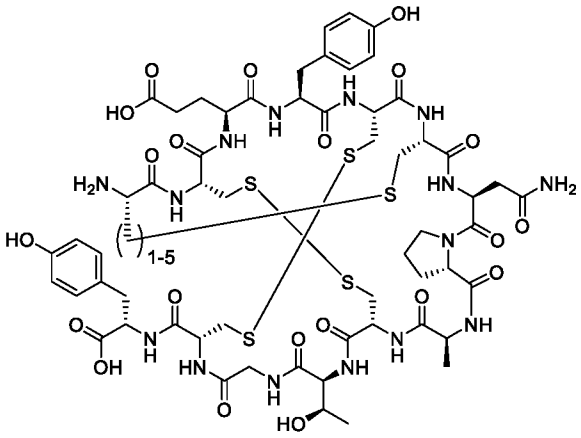
or


.

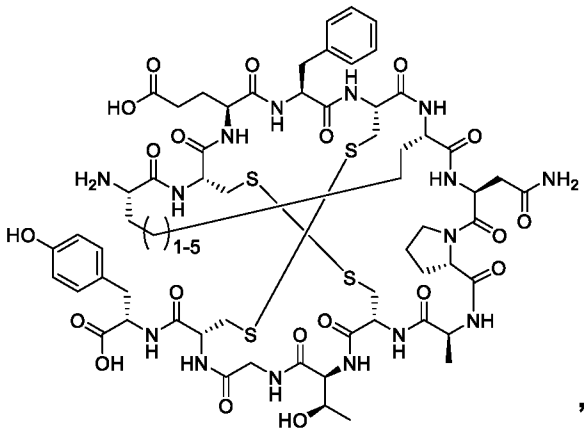
[0144] In some embodiments, a cyclized GCC binding peptide comprises a structure selected from:



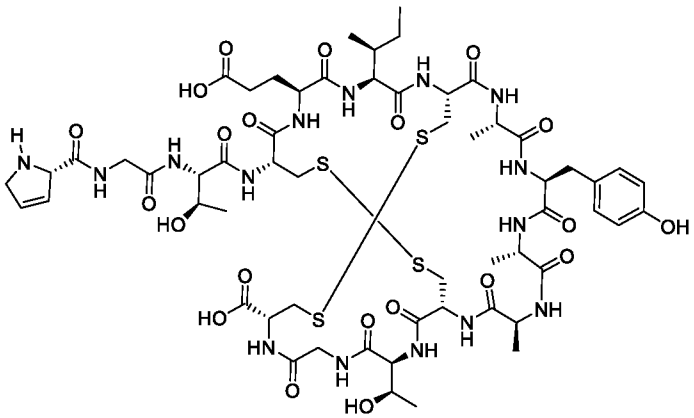
,

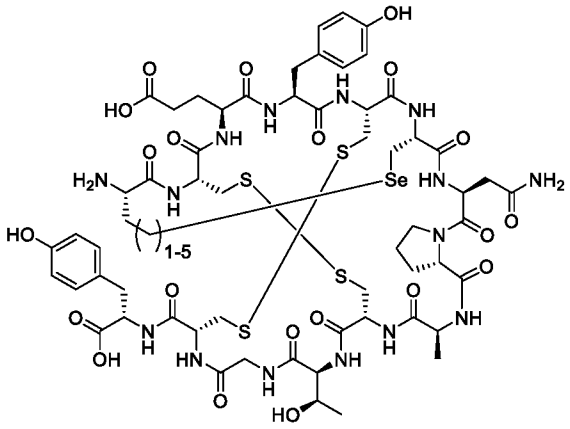


,

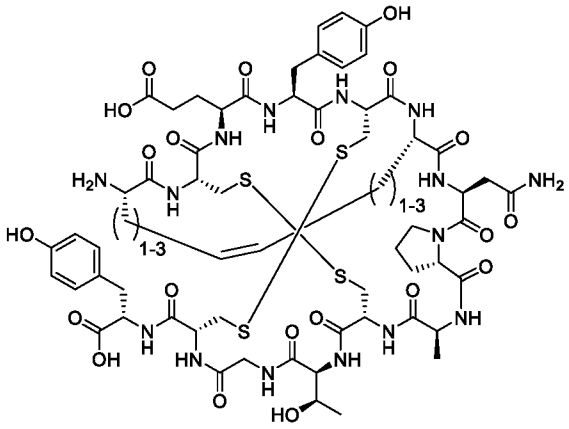


,

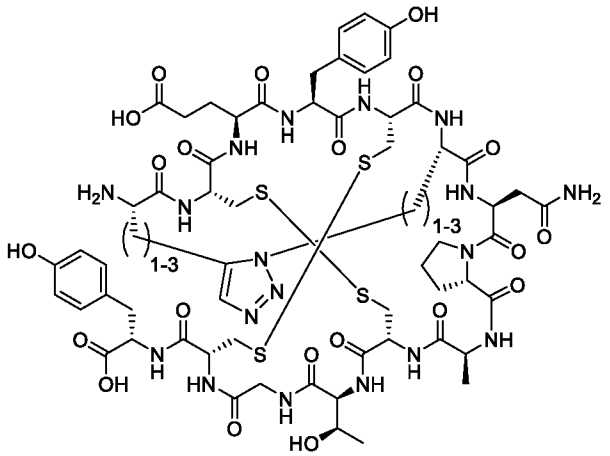




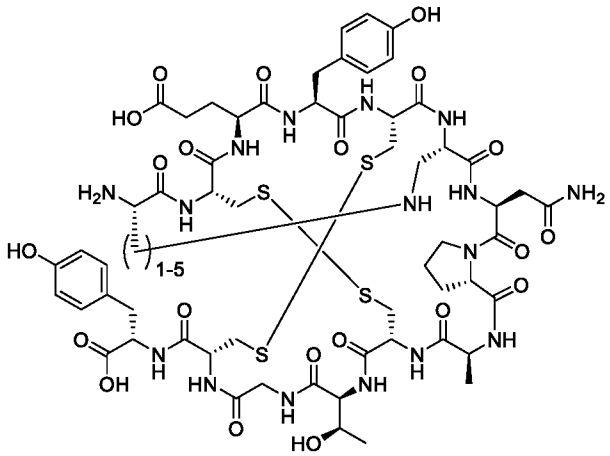
,



,

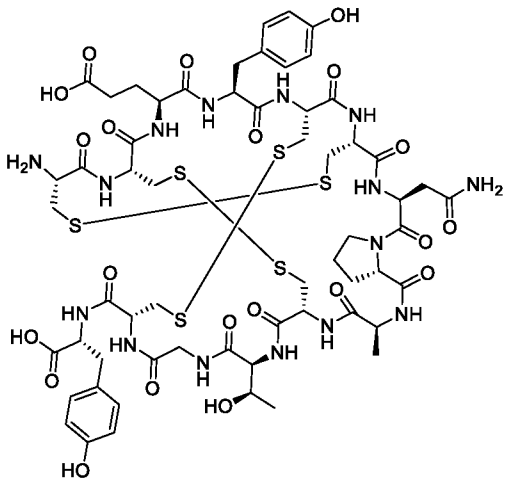


, and

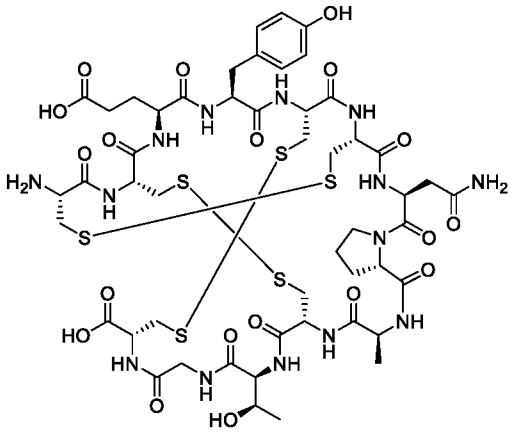


.

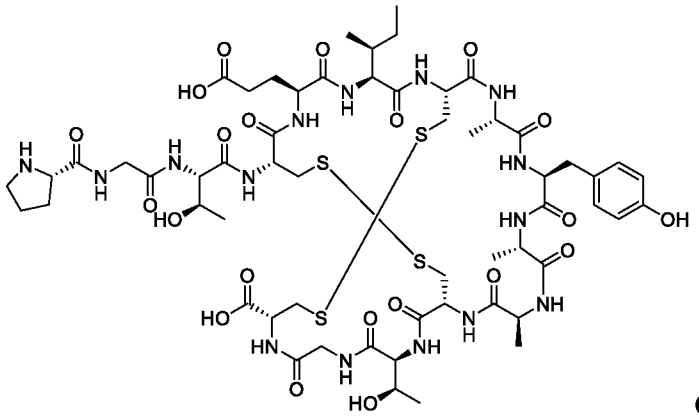
[0145] In some embodiments, a cyclized GCC binding peptide comprises a structure of



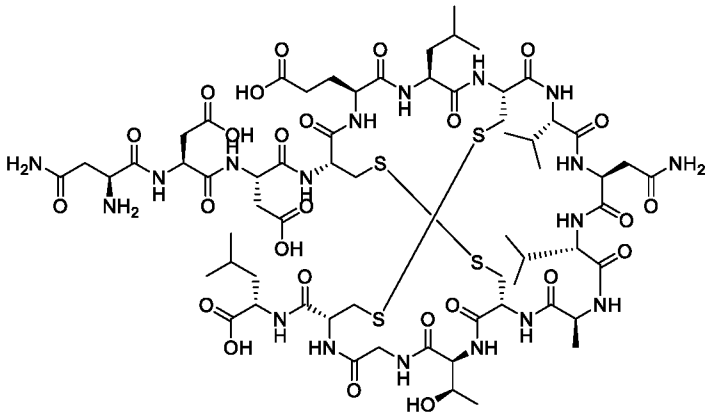
C-28. In some embodiments, a cyclized GCC binding



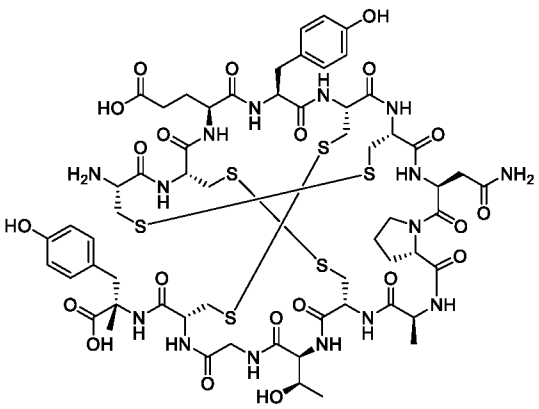
peptide comprises a structure of **C-29.** In some embodiments, a cyclized GCC binding peptide comprises a structure of



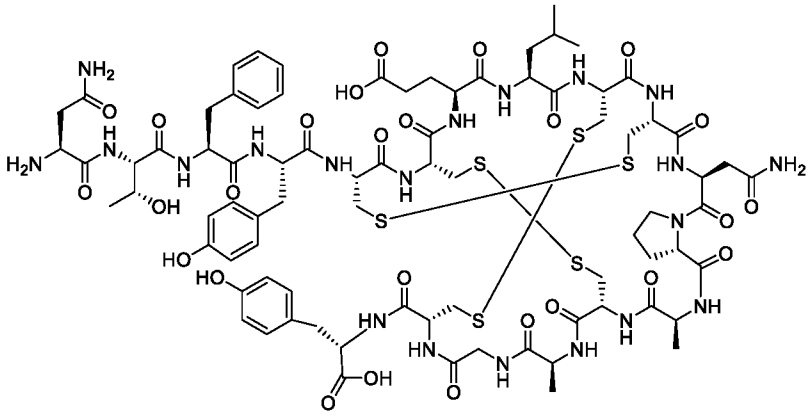
C-66. In some embodiments, a cyclized GCC binding peptide comprises a structure of



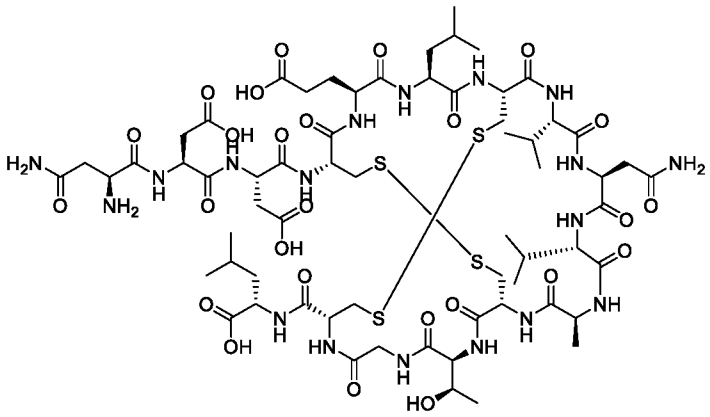
C-69. In some embodiments, a cyclized GCC binding peptide comprises a structure of



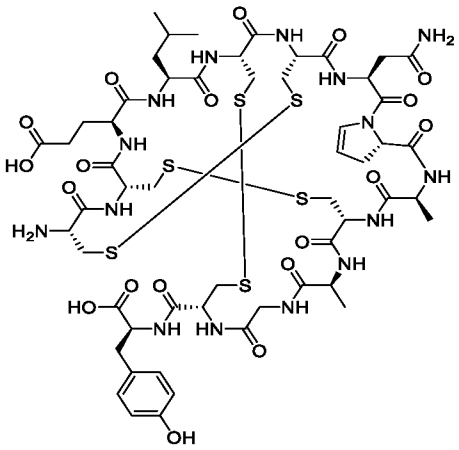
C-84. In some embodiments, a cyclized GCC binding peptide comprises a structure of



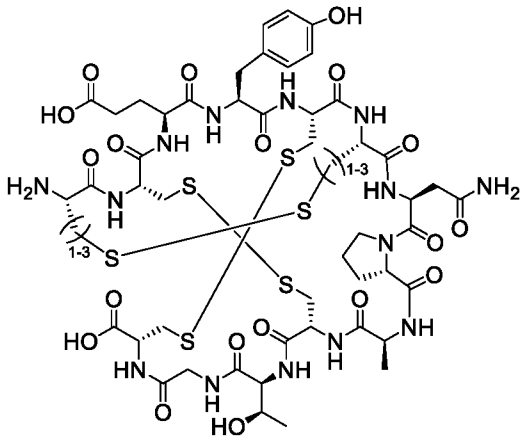
C-85. In some embodiments, a cyclized GCC binding peptide comprises a structure of



C-86. In some embodiments, a cyclized GCC binding peptide comprises a structure of



C-182. In some embodiments, a cyclized GCC binding peptide comprises a structure of



[0146] A peptide having SEQ ID NO: 1 or a fragment thereof can contain one or more intramolecular bonds. A peptide having SEQ ID NO: 1-42 or a fragment thereof can contain one or more intramolecular bonds. Similarly, a peptide of Tables 2 and 4 can contain one or more intramolecular bonds. For example, the peptide can comprise one or more of Cys^1 - Cys^6 disulfide bond, Cys^2 -Cys^{10} disulfide bond, and Cys^5 - Cys^{13} disulfide bonds. In some embodiments, the peptide comprises Cys^1 -Cys^6 alkylene, heteroalkylene, or alkenylene bond. In some embodiments, the peptide comprises Cys^2 - Cys^{10} alkylene, heteroalkylene or alkenylene bond. In some embodiments, the peptide comprises Cys^5 - Cys^{13} alkylene, heteroalkylene, or alkenylene bond. In some embodiments, the intramolecular bond comprises a triazole bridge.

[0147] Peptide ligands disclosed herein can contain two or more cysteine residues. For example, a peptide sequence of Table 2 or 4 can contain two or more cysteine residues, e.g., 2, 3, 4, 5, or 6 cysteine residues. In some embodiments, the first cysteine residue in the sequence forms a disulfide bond with the 4^{th} cysteine residue in the same sequence. In some embodiments, the second cysteine residue in the sequence forms a disulfide bond with the 5^{th} cysteine residue in the same sequence. In some embodiments, the third cysteine residue in the sequence forms a disulfide bond with the 6^{th} cysteine residue in the same sequence.

[0148] In one aspect, provided herein are GCC binding peptides that have improved metabolic, chemical and/or physical stability against a variety of degradation mechanisms. In some embodiments, the GCC binding peptide is more resistant to carboxypeptidase hydrolysis than linaclotide. In some embodiments, the GCC binding peptide is more resistant to protease degradation than linaclotide. In some embodiments, the human serum half-life of a GCC binding peptide described herein is at least 100%, 120%, 150%, 200%, or 300% compared to the human serum half-life of linaclotide at 37 °C. In some embodiments, the human serum half-life of a GCC binding peptide described herein is at least 1.1, 1.2, 1.5, 2.0, 3.0, 5.0 or 10 fold compared to the human serum half-life of linaclotide at 37 °C.

[0149] In some embodiments, a peptide described herein has a molecular weight from 500 Da to 10,000 Da. In some embodiments, a peptide described herein has a molecular weight from 500 Da to 5,000 Da. In some embodiments, a peptide described herein has a molecular weight from 500 Da to 3,000 Da. In some embodiments, the peptide has a molecular weight from 1,000 Da to 1,500 Da. In some embodiments, the peptide has a molecular weight from 1,500 Da to 2,000 Da. In some embodiments, the peptide has a molecular weight from 2,000 Da to 2,500 Da. In some embodiments, the peptide has a molecular weight from 2,500 Da to 3,000 Da. In some embodiments, the peptide has a molecular weight from 3,000 Da to 3.500 Da. In some embodiments, the peptide has a molecular weight from 3.500 Da to 4,000 Da. In some embodiments, the peptide has a molecular weight from 4,000 Da to 4,500 Da. In some

embodiments, the peptide has a molecular weight from 4,500 Da to 5,000 Da. In some embodiments, the peptide has a molecular weight from 5,000 Da to 5,500 Da. In some embodiments, the peptide has a molecular weight from 5,500 Da to 6,000 Da. In some embodiments, the peptide has a molecular weight from 6,000 Da to 6,500 Da. In some embodiments, the peptide has a molecular weight from 6,500 Da to 7,000 Da. In some embodiments, the peptide has a molecular weight of at least 500 Da, 800 Da, 1,000 Da, 1,200 Da, 1,400 Da, 1,600 Da, 1,800 Da, 2,000 Da, 2,200 Da, 2,400 Da, 2,600 Da, 2,800 Da, 3,000 Da, 3,200 Da, 3,400 Da, 3,600 Da, 3,800 Da, 4,000 Da, 4,200 Da, 4,400 Da, 4,600 Da, 4,800 Da, 5,000 Da, 5,200 Da, 5,400 Da, 5,600 Da, 5,800 Da, 6,000 Da, 6,200 Da, 6,400 Da, 6,600 Da, 6,800 Da, or 7,000 Da. In some embodiments, the peptide has a molecular weight of at most 600 Da, 800 Da, 1,000 Da, 1,200 Da, 1,400 Da, 1,600 Da, 1,800 Da, 2,000 Da, 2,200 Da, 2,400 Da, 2,600 Da, 2,800 Da, 3,000 Da, 3,200 Da, 3,400 Da, 3,600 Da, 3,800 Da, 4,000 Da, 4,200 Da, 4,400 Da, 4,600 Da, 4,800 Da, 5,000 Da, 5,200 Da, 5,400 Da, 5,600 Da, 5,800 Da, 6,000 Da, 6,200 Da, 6,400 Da, 6,600 Da, 6,800 Da, 7,000 Da, or 7,500 Da.

[0150] In some embodiments, a cyclic GCC binding peptide described herein has a net charge of -3 to +1. In some embodiments, the cyclic peptide has a net charge of -3. In some embodiments, the cyclic peptide has a net charge of -2. In some embodiments, the cyclic peptide has a net charge of -1. In some embodiments, the cyclic peptide has a net charge of 0. In some embodiments, the cyclic peptide has a net charge of +1. The net charge can be determined by aggregating the charge of each of the amino acids in the peptide. For example, aspartic acid (D) and glutamic acid (E) each has a charge of -1, lysine (K), arginine (R) and histidine (H) each has a charge of +1, and the rest of the canonical amino acids each has a charge of 0.

[0151] In some embodiments, a cyclic GCC binding peptide described herein has a net charge of at most -4. In some embodiments, the cyclic peptide has a net charge of -4. In some embodiments, a cyclic GCC binding peptide described herein has a net charge of at least +2. In some embodiments, the cyclic peptide has a net charge of +2. In some embodiments, the cyclic peptide has a net charge of +3.

[0152] In some embodiments, a GCC binding peptide comprises unnatural amino acid. In some embodiments, a GCC binding peptide comprises an amino acid sequence of any one of SEQ ID NOs: 1-42, wherein the amino acid sequence of any one of SEQ ID NOs: 1-30 comprises unnatural amino acid. In some embodiments, C-terminus of a GCC binding peptide comprises unnatural amino acid. In some embodiments, a GCC binding peptide comprises an amino acid sequence of any one of SEQ ID NOs: 1-42, wherein C-terminus of the amino acid sequence of any one of SEQ ID NOs: 1-42 comprises unnatural amino acid.

[0153] The peptides described herein can comprise one or more unnatural amino acids. Non-limiting examples of unnatural amino acids include: p-acetyl-L-phenylalanine, p-iodo-L-phenylalanine, p-methoxyphenylalanine, O-methyl-L-tyrosine, p-propargyloxyphenylalanine, p-propargyl-phenylalanine, L-3-(2-naphthyl)alanine, 3-methyl-phenylalanine, O-4-allyl-L-tyrosine, 4-propyl-L-tyrosine, tri-O-acetyl-GlcNAcp-serine, L-Dopa, fluorinated phenylalanine, isopropyl-L-phenylalanine, p-azido-L-phenylalanine, p-acyl-L-phenylalanine, p-benzoyl-L-phenylalanine, Boronophenylalanine, O-propargyltyrosine, L-phosphoserine, phosphonoserine, phosphonotyrosine, p-bromophenylalanine, selenocysteine, p-amino-L- phenylalanine, isopropyl-L-phenylalanine, 3,4-dehydro-proline, and azido-lysine (AzK). In some embodiments, the unnatural amino acid is an unnatural analogue of a tyrosine amino acid; an unnatural analogue of a glutamine amino acid; an unnatural analogue of a phenylalanine amino acid; an unnatural analogue of an alanine amino acid; an unnatural analogue of a serine amino acid; an unnatural analogue of a threonine amino acid; an alkyl, aryl, acyl, azido, cyano, halo, hydrazine, hydrazide, hydroxyl, alkenyl, alkynl, ether, thiol, sulfonyl, seleno, ester, thioacid, borate, boronate, phospho, phosphono, phosphine, heterocyclic, enone, imine, aldehyde, hydroxylamine, keto, or amino substituted amino acid; or a combination thereof. In some embodiments, the unnatural amino acid is an amino acid with a photoactivatable cross-linker; a spin-labeled amino acid; a fluorescent amino acid; a metal binding amino acid; a metal-containing amino acid; a radioactive amino acid; a photocaged and/or photoisomerizable amino acid; a biotin or biotin-analogue containing amino acid; a keto containing amino acid; an amino acid comprising polyethylene glycol or polyether; a heavy atom substituted amino acid; a chemically cleavable or photocleavable amino acid; an amino acid with an elongated side chain; an amino acid containing a toxic group; a sugar substituted amino acid; a carbon-linked sugar-containing amino acid; a redox-active amino acid; an a-hydroxy containing acid; an amino thio acid; an α, α-disubstituted amino acid; a β-amino acid; a cyclic amino acid other than proline or histidine, or an aromatic amino acid other than phenylalanine, tyrosine or tryptophan.

[0154] In some embodiments, the unnatural amino acids incorporated into the peptides include one or more of: 1) a ketone functional group (as found in para or meta acetyl-phenylalanine) that can be specifically reacted with hydrazines, hydroxylamines and their derivatives (Addition of the keto functional group to the genetic code of Escherichia coli. Wang L, Zhang Z, Brock A, Schultz P G. Proc Natl Acad Sci USA. 2003 Jan. 7; 100(1):56-61; Bioorg Med Chem Lett. 2006 Oct. 15; 16(20):5356-9. Genetic introduction of a diketone-containing amino acid into proteins. Zeng H, Xie J, Schultz P G), 2) azides (as found in p-azido-phenylalanine) that can be reacted with alkynes via copper catalyzed "click chemistry" or strain promoted (3+2) cycloadditions to form the corresponding triazoles (Addition of p-azido-L-phenylalanine to the genetic code of Escherichia

coli. Chin J W, Santoro S W, Martin A B, King D S, Wang L, Schultz P G. J Am Chem Soc. 2002 Aug. 7; 124(31):9026-7; Adding amino acids with novel reactivity to the genetic code of Saccharomyces cerevisiae. Deiters A, Cropp T A, Mukherji M, Chin J W, Anderson J C, Schultz P G. J Am Chem Soc. 2003 Oct. 1; 125(39):11782-3), or azides that can be reacted with aryl phosphines, via a Staudinger ligation (Selective Staudinger modification of proteins containing p-azidophenylalanine. Tsao M L, Tian F, Schultz P G. Chembiochem. 2005 December; 6(12):2147-9), to form the corresponding amides, 3) alkynes that can be reacted with azides to form the corresponding triazole (In vivo incorporation of an alkyne into proteins in Escherichia coli. Deiters A, Schultz P G. Bioorg Med Chem Lett. 2005 Mar. 1; 15(5):1521-4), 4) boronic acids (boronates) than can be specifically reacted with compounds containing more than one appropriately spaced hydroxyl group or undergo palladium mediated coupling with halogenated compounds (Angew Chem Int Ed Engl. 2008; 47(43):8220-3. A genetically encoded boronate-containing amino acid., Brustad E, Bushey M L, Lee J W, Groff D, Liu W, Schultz P G), and 5) metal chelating amino acids, including those bearing bipyridyls, that can specifically co-ordinate a metal ion (Angew Chem Int Ed Engl. 2007; 46(48):9239-42. A genetically encoded bidentate, metal-binding amino acid. Xie J, Liu W, Schultz P G).

[0155] The peptide of the present disclosure embraces various derivatives thereof. Examples of the derivatives include derivatives having an amide, ester, or carboxyl group as the C-terminus and/or N-terminus thereof. Additional examples of the derivatives of the peptide include those obtained by modification such as phosphorylation, methylation, acetylation, adenylylation, ADP-ribosylation, or glycosylation and fused protein obtained by fusion with another peptide or protein. These derivatives can be prepared by those skilled in the art in a known manner or a method based thereon.

[0156] In some embodiments, the binding peptide is bicyclic or polycyclic. In some embodiments, a conjugate described herein comprises a bicyclic peptide. Exemplary bicyclic peptides include the bicyclic targeting peptides of BT5528, BT1718, and BT8009. Exemplary bicyclic peptides are described in US20180200378, US10441663, US8680022B2, US20180280525, and US20200215199, each of which is hereby incorporated by reference in its entirety.

[0157] In some embodiments, the binding peptide is a lasso peptide. Lasso peptides can be synthetic or naturally produced by bacteria, and they possess a distinctive threaded lariat fold that offers a 3D array of functionality for engaging biological targets. This lasso structure can enable beneficial properties such as affinity, stability and potent biological activities. Suitable lasso structure can be designed by algorithms. Exemplary lasso peptides are provided in Hegemann, J.D., et al., Lasso Peptides: An Intriguing Class of Bacterial Natural Products, Acc. Chem. Res.,

2015, 48, 1909−1919; Tietz, J.I., et al., A new genome-mining tool redefines the lasso peptide biosynthetic landscape, Nature Chem Bio, 2017, 13, 470-478; DiCaprio, A.J., et al., Enzymatic Reconstitution and Biosynthetic Investigation of the Lasso Peptide Fusilassin, J. Am. Chem. Soc., 2019, 141, 290−297; Al Toma, R.S., et al., Site-Directed and Global Incorporation of Orthogonal and Isostructural Noncanonical Amino Acids into the Ribosomal Lasso Peptide Capistruin, ChemBioChem, 2015, 16, 503–509.

[0158] In some embodiments, a cyclic peptide described herein is configured to bind to a plasma protein with a prescribed affinity, for example, measured as Plasma Protein Albumin Binding (PPB) percentage. The % bound can be determined by HSA-HPLC method (measurement of drug protein binding by immobilized human serum albumin-HPLC). PPB can be determined in vitro by HPLC (e.g., Example B4) or by other suitable means known in the art. In some embodiments, 1% to 99% of the cyclic peptide binds to Human Serum Albumin (HSA) in vitro as determined by HPLC, according to the conditions described in Example B3. In some embodiments, about 2% to about 99%, about 5% to about 99%, about 10% to about 99%, about 20% to about 99%, about 30% to about 99%, about 40% to about 99%, about 50% to about 99%, about 60% to about 99%, about 70% to about 99%, or about 80% to about 99% of the cyclic peptide binds to HSA in vitro as determined by HPLC. In some embodiments, about 10% to about 95% of the cyclic peptide binds to HSA in vitro (i.e., PPB of about 10% to about 95%). In some embodiments, about 20% to about 90% of the cyclic peptide binds to HSA in vitro. In some embodiments, about 20% to about 60% of the cyclic peptide binds to HSA in vitro. In some embodiments, about 40% to about 95% of the cyclic peptide binds to HSA in vitro. In some embodiments, about 40% to about 80% of the cyclic peptide binds to HSA in vitro. In some embodiments, about 40% to about 60% of the cyclic peptide binds to HSA in vitro. In some embodiments, about 60% to about 99% of the cyclic peptide binds to HSA in vitro. In some embodiments, about 60% to about 95% of the cyclic peptide binds to HSA in vitro. In some embodiments, about 60% to about 80% of the cyclic peptide binds to HSA in vitro. In some embodiments, about 60% to about 70% of the cyclic peptide binds to HSA in vitro. In some embodiments, about 40% to about 50% of the cyclic peptide binds to HSA in vitro. In some embodiments, about 50% to about 60% of the cyclic peptide binds to HSA in vitro. In some embodiments, about 70% to about 80% of the cyclic peptide binds to HSA in vitro. In some embodiments, about 80% to about 99% of the cyclic peptide binds to HSA in vitro. In some embodiments, about 80% to about 85% of the cyclic peptide binds to HSA in vitro.

[0159] In some embodiments, a conjugate described herein (e.g., a conjugate of Table 1 or Table 2) is configured to bind to a plasma protein with a prescribed affinity, for example, measured as Plasma Protein Albumin Binding (PPB) percentage. The % bound can be determined by HSA-

HPLC method (measurement of drug protein binding by immobilized human serum albumin-HPLC). PPB can be determined in vitro by HPLC (e.g., Example B4) or by other suitable means known in the art. In some embodiments, 1% to 99% of the conjugate binds to Human Serum Albumin (HSA) in vitro as determined by HPLC, according to the conditions described in Example B3. In some embodiments, about 2% to about 99%, about 5% to about 99%, about 10% to about 99%, about 20% to about 99%, about 30% to about 99%, about 40% to about 99%, about 50% to about 99%, about 60% to about 99%, about 70% to about 99%, or about 80% to about 99% of the conjugate binds to HSA in vitro as determined by HPLC. In some embodiments, about 10% to about 95% of the conjugate binds to HSA in vitro (i.e., PPB of about 10% to about 95%). In some embodiments, about 20% to about 90% of the conjugate binds to HSA in vitro. In some embodiments, about 20% to about 60% of the conjugate binds to HSA in vitro. In some embodiments, about 40% to about 95% of the conjugate binds to HSA in vitro. In some embodiments, about 40% to about 80% of the conjugate binds to HSA in vitro. In some embodiments, about 40% to about 60% of the conjugate binds to HSA in vitro. In some embodiments, about 60% to about 99% of the conjugate binds to HSA in vitro. In some embodiments, about 60% to about 95% of the conjugate binds to HSA in vitro. In some embodiments, about 60% to about 80% of the conjugate binds to HSA in vitro. In some embodiments, about 60% to about 70% of the conjugate binds to HSA in vitro. In some embodiments, about 40% to about 50% of the conjugate binds to HSA in vitro. In some embodiments, about 50% to about 60% of the conjugate binds to HSA in vitro. In some embodiments, about 70% to about 80% of the conjugate binds to HSA in vitro. In some embodiments, about 80% to about 99% of the conjugate binds to HSA in vitro. In some embodiments, about 80% to about 85% of the conjugate binds to HSA in vitro.

Target

[0160] Guanylate cyclase C (GCC) is a transmembrane form of guanylate cyclase that is expressed on various cells, including gastrointestinal epithelial. It was originally discovered as the intestinal receptor for the heat-stable toxin (ST) peptides secreted by enteric bacteria and which cause diarrhea. The ST peptides share a similar primary amino acid structure with two peptides isolated from intestinal mucosa and urine, guanylin and uroguanylin.

[0161] In the intestines, guanylin and uroguanylin act as regulators of fluid and electrolyte balance. In response to high oral salt intake, these peptides are released into the intestinal lumen where they bind to guanylate cyclase C localized on the luminal membrane of enterocytes (simple columnar epithelial cells of the small intestines and colon). The binding of the guanylin peptides to guanylate cyclase C induces electrolyte and water excretion into the intestinal lumen via a

complex intracellular signaling cascade that is initiated by an increase in cyclic guanosine monophosphate (cGMP). The cGMP-mediated signaling that is initiated by the guanylin peptides can be important for the normal functioning of the gut. Any abnormality in this process could lead to gastrointestinal disorders. In addition to a role for uroguanylin and guanylin as modulators of intestinal fluid and ion secretion, these peptides may also be involved in the continual renewal of gastrointestinal mucosa by maintaining the balance between proliferation and apoptosis. For example, uroguanylin and guanylin peptides can promote apoptosis by controlling cellular ion flux. Given the prevalence of inflammatory conditions in Western societies a need exists to improve the treatment options for inflammatory conditions, particularly of the gastrointestinal tract.

[0162] Further, GCC as a tumor suppressor expressed by the intestinal epithelium, can be a target for the treatment of certain cancers. GCC is densely expressed throughout the intestine, and overexpressed by tumor tissue, which can enable GCC as a suitable target for diagnostic and therapeutic goals.

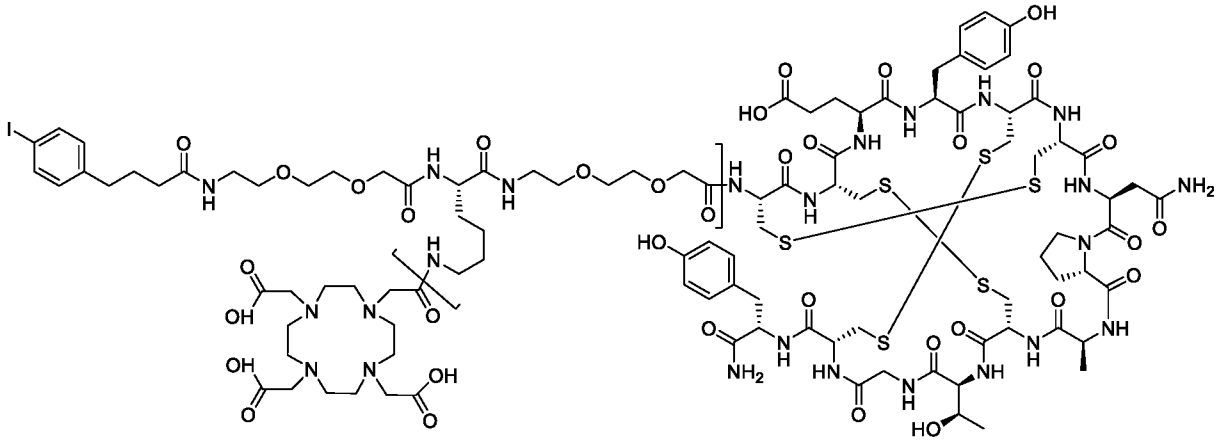
Linkers

[0163] A conjugate described herein can comprise one or more linkers. In some embodiments, the linker covalently attaches the GCC binding peptide with the metal chelator. In some embodiments, the GCC binding peptide attaches directly to the metal chelator without a linker.

[0164] In some embodiments, the present disclosure describes linkers that function as a spacer. A linker can comprise a number of intervening atoms (on a linear chain, excluding pendant groups or substituents) between the metal chelator and the binding peptide thereby creating a distance between the metal chelator and the binding peptide. In some embodiments, a linker comprises 10-100 intervening atoms between the metal chelator and the binding peptide. In some embodiments, a linker comprises 2-60 intervening atoms between the metal chelator and the binding peptide. In some embodiments, a linker comprises 2 to 20, 2 to 50, 5 to 15, 5 to 25, 10 to 40, 30 to 60, or 10 to 20 intervening atoms between the metal chelator and the binding peptide. In some embodiments, a linker comprises 3 to 30 intervening atoms between the metal chelator and the binding peptide. In some embodiments, a linker comprises 5 to 25 intervening atoms between the metal chelator and the binding peptide. In some embodiments, a linker comprises 6 to 18 intervening atoms between the metal chelator and the binding peptide. In some embodiments, a linker comprises 10 to 20 intervening atoms between the metal chelator and the binding peptide. The intervening atoms can comprise 1 or more carbons, and optionally one or more heteroatoms such as O and N. In some embodiments, the intervening atoms comprise 2 to 20, 2 to 50, 5 to 15, 5 to 25, 10 to 40, 30 to 60, or 10 to 20 carbons. In some embodiments, the intervening atoms

comprise 0, 1, 2, 3, 4, 5, or 6 nitrogen. In some embodiments, the intervening atoms comprise 0, 1, 2, 3, 4, 5, 6, 7 or 8 oxygen.

[0165] As an example, the intervening atoms between the metal chelator and the binding peptide of conjugate C-035 are illustrated in brackets below and there are 16 intervening atoms.



[0166] A linker can comprise one or more amino acid residues. In some embodiments, the linker comprises 1 to 3, 1 to 5, 1 to 10, 5 to 10, or 5 to 20 amino acid residues. In some embodiments, the linker comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid residues. In some embodiments, the linker comprises 1 to 5 amino acid residues. For example, the linker can comprise one or more lysine (K) residues such as K, KK, or KKK sequences. In some embodiments, one or more amino acids of the linker are unnatural amino acids.

[0167] A herein-described linker can attach to the N-terminus of the peptide, the C-terminus of the peptide, or a non-terminal amino acid of the peptide, or it can attach to the peptide through a combination of the above. In some embodiments, a linker is attached to the GCC binding peptide via its N-terminus. In some embodiments, a linker is attached to the GCC binding peptide via its C-terminus. In some embodiments, a linker is attached to the GCC binding peptide via its N-terminus and via its C-terminus. In some embodiments, a linker is attached to the peptide via a non-terminal amino acid. A conjugate described herein can comprise 2, 3, 4, 5 or more linkers. In some embodiments, the conjugate comprises two linkers, one attached to the N-terminus of the peptide and the other attached to the C-terminus of the peptide. In some embodiments, the conjugate comprises two linkers, one attached to the N or C-terminus of the peptide and the other attached to a non-terminal amino acid of the peptide.

[0168] The linker can be bonded to the peptide, the metal chelator, or both, for example, through a chemically reactive group. Exemplary chemically reactive groups include, but are not limited to, a free amino, imino, hydroxyl, thiol or carboxyl group (e.g., to the N- or C-terminus, to the epsilon amino group of one or more lysine residues, the free carboxylic acid group of one or more glutamic acid or aspartic acid residues, or to the sulfhydryl group of one or more cysteinyl

residues). The site to which the linker is bound to the peptide can be a natural or unnatural amino acid of the peptide and/or it can be introduced into the peptide, e.g., by DNA recombinant technology (e.g., by introducing a cysteine or protease cleavage site in the amino acid sequence) or by protein biochemistry (e.g., reduction, pH adjustment or proteolysis). Exemplary methods for attaching the linker includes carbodiimide reaction, reactions using bifunctional agents such as dialdehydes or imidoesters, Schiff base reaction, Suzuki-Miyaura cross-coupling reactions, Isothiocyanates as coupling agents, and click chemistry.

[0169] The linker can have a prescribed length thereby linking the metal chelator (and optionally radionuclide) and the peptide while allowing an appropriate distance therebetween. In some embodiments, the linker has 1 to 100 atoms, 1 to 60 atoms, 1 to 30 atoms, 1 to 15 atoms, 1 to 10 atoms, 1 to 5, or 2 to 20 atoms in length. In some embodiments, the linker has 1 to 10 atoms in length.

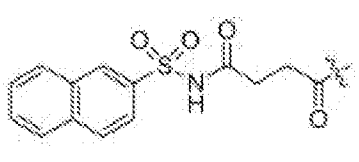
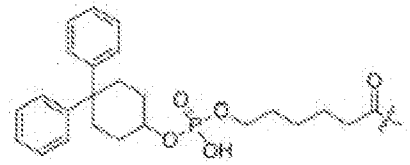
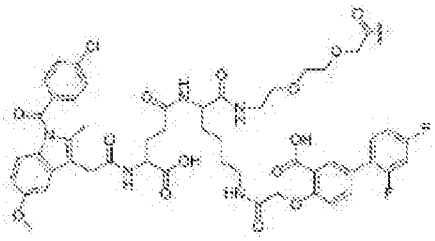
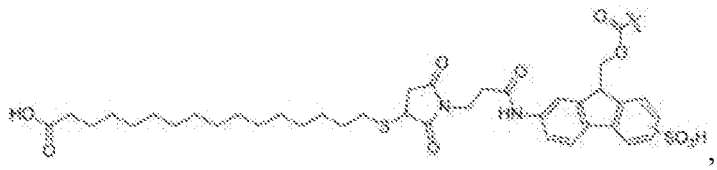
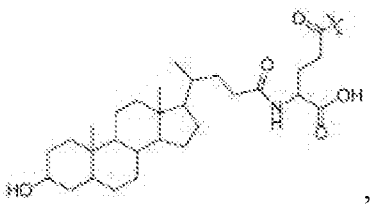
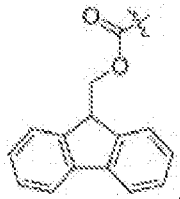
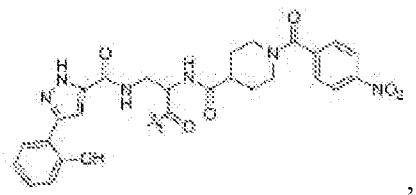
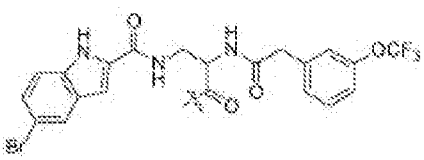
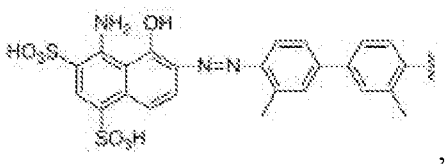
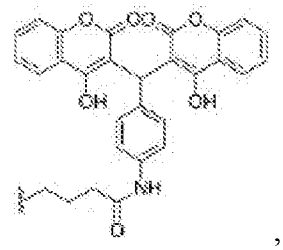
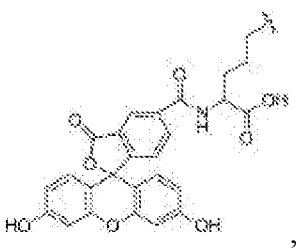
[0170] The linker can function as a "spacer" between the GCC binding peptide and the radionuclide. In some embodiments, the linker is configured to provide a distance between the GCC binding peptide and the metal chelator of at least 3 atoms, 4 atoms, 5 atoms, 6 atoms, 7 atoms, 8 atoms, 9 atoms, 10 atoms, 15 atoms, 20 atoms, or 25 atoms in length. In some embodiments, the linker comprises an alkylene or heteroalkylene bond moiety between the GCC binding peptide and the metal chelator. In some embodiments, the alkylene or heteroalkylene comprises at least 3 atoms, 4 atoms, 5 atoms, 6 atoms, 7 atoms, 8 atoms, 9 atoms, 10 atoms or 20 atoms in length. In some embodiments, the linker comprises one or more polyethylene glycol units between the GCC binding peptide and the metal chelator. In some embodiments, the linker comprises at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, or at least 10 – (CH_2-CH_2-O)- units between the GCC binding peptide and the metal chelator, wherein the units can be contiguous or noncontiguous.

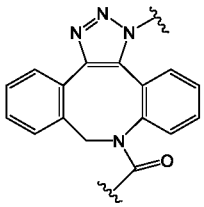
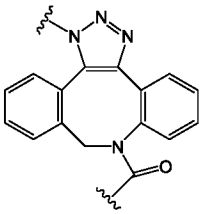
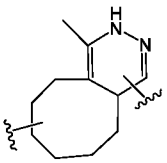
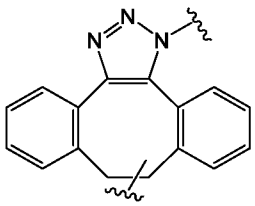
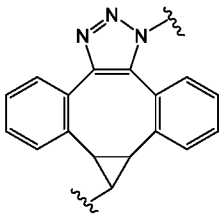
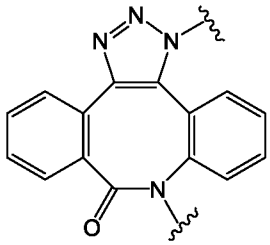
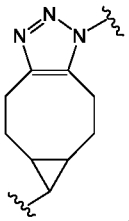
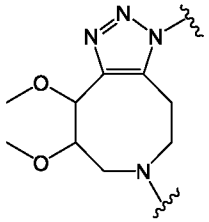
[0171] The linker can comprise flexible and/or rigid regions. Exemplary flexible linker regions include those comprising Gly and Ser residues ("GS" linker), glycine residues, alkylene chain, PEG chain, etc. Exemplary rigid linker regions include those comprising alpha helix-forming sequences (e.g., EAAAK (SEQ ID NO: 45)), proline-rich sequences, and regions rich in double and/or triple bonds.

[0172] The linker can be cleavable, e.g., under physiological conditions, e.g., under intracellular conditions, such that cleavage of the linker releases the chelator and radionuclide in the intracellular environment. The linker can be, e.g., a peptidyl linker that is cleaved by an intracellular peptidase or protease enzyme, including, but not limited to, a lysosomal or endosomal protease. In some embodiments, the peptidyl linker is at least two amino acids long or at least three amino acids long. Cleaving agents can include cathepsins B and D and plasmin. In other

embodiments, the linker is not cleavable. In some embodiments, the linker is pH-sensitive, i.e., sensitive to hydrolysis at certain pH values. For example, the pH-sensitive linker can be hydrolyzable under acidic conditions. For example, a linker can be an acid-labile linker that is hydrolyzable in the lysosome (e.g., a hydrazone, semicarbazone, thiosemicarbazone, cis-aconitic amide, orthoester, acetal, ketal, or the like). Such linkers can be relatively stable under neutral pH conditions, such as those in the blood, but are unstable at below pH 5.5 or 5.0, the approximate pH of the lysosome. In some embodiments, the hydrolyzable linker is a thioether linker.

[0173] In some embodiments, the linker comprises one or more of substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. In some embodiments, the linker comprises substituted or unsubstituted C_1-C_{30} alkylene. In some embodiments, the linker comprises polyethylene glycol such as $(-CH_2-CH_2-O-)_{1-10}$. In some embodiments, the linker comprises a structure selected from:

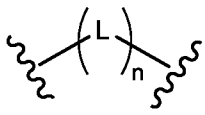

,

,

,

,

,

,

,

,

,

,

, and structures derived from any one thereof.

[0174] In some embodiments, the linker comprises a click chemistry residue. In some embodiments, the linker is attached to the peptide, to the metal chelator, or both via click chemistry, thereby forming a click chemistry residue. For example, the peptide can comprise an azide group (at N- or C-terminus or at a non-terminal amino acid) that reacts with an alkyne moiety of the linker. For another example, the peptide can comprise an alkyne group (at N- or C-terminus or at a non-terminal amino acid) that reacts with an azide of the linker. The metal chelator and the linker can be attached similarly. In some embodiments, the linker comprises an azide moiety, an alkyne moiety, or both. In some embodiments, the linker comprises a triazole. In some embodiments, the click chemistry residue is  (DBCO-azide residue),  ,  ,  ,  ,  ,   , or . In some embodiments, the click chemistry residue is a DIBO-azide residue, BARAC-azide residue, DBCO-azide residue, DIFO-azide residue, COMBO-azide residue, BCN-azide residue, or DIMAC-azide residue. In some embodiments, the linker comprises a residue of nitrone dipole cycloaddition. In some embodiments, the linker comprises a residue of tetrazine ligation. In some embodiments, the linker comprises a residue of quadricyclane ligation. Exemplary groups of click chemistry residue are shown in Hein at al., "Click Chemistry, A Powerful Tool for Pharmaceutical Sciences," Pharmaceutical Research volume 25, pages2216–2230 (2008); Thirumurugan et al, "Click Chemistry for Drug Development and Diverse Chemical–Biology Applications," Chem. Rev. 2013, 113, 7, 4905–4979; US20160107999A1; US10266502B2; and US20190204330A1, each of which is incorporated by reference in its entirety.

[0175] In some embodiments, a linker described herein comprises two or more motifs (see FIGs. 2A-2D). The motifs can be connected by any suitable covalent bond. In some embodiments, one or more of the motifs are connected via click chemistry such that they can be clicked in/out of the

linker. Each of the motifs in a linker can have independent functions. For example, a linker can comprise a motif that functions to adjust plasma half-life and/or a motif that functions as a spacer between the peptide and metal chelator. In some embodiments, each of the motifs independently comprises one or more of substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. In some embodiments, the linker comprises substituted or unsubstituted C_1-C_{30} alkylene. In some embodiments, the linker comprises polyethylene glycol such as $(-CH_2-CH_2-O-)_{1-10}$.

[0176] In some embodiments, the linker has a structure of



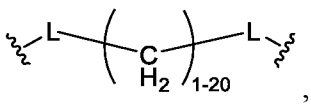
Formula (II-1),

wherein each L is independently -O-, $-NR^L-$, $-N(R^L)_2-$, $-OP(=O)(OR^L)O-$, -S-, -S(=O)-, $-S(=O)_2-$, =CH-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L-$, $-NR^LC(=O)-$, $-OC(=O)NR^L-$, $-NR^LC(=O)O-$, $-NR^LC(=O)NR^L-$, $-NR^LC(=S)NR^L-$, $-CR^L=N-$, $-N=CR^L$, $-NR^LS(=O)_2-$, $-S(=O)_2NR^L-$, $-C(=O)NR^LS(=O)_2-$, $-S(=O)_2NR^LC(=O)-$, substituted or unsubstituted C_1-C_{30} alkylene, substituted or unsubstituted C_2-C_{30} alkenylene, substituted or unsubstituted C_2-C_{30} alkynylene, substituted or unsubstituted C_1-C_{30} heteroalkylene, -(C_1-C_{30} alkylene)-O-, -O-(C_1-C_{30} alkylene)-, -(C_1-C_{30} alkylene)-NR^L-, $-NR^L$-(C_1-C_{30} alkylene)-, -(C_1-C_{30} alkylene)-$N(R^L)_2$-, or $-N(R^L)_2$-(C_1-C_{30} alkylene)-; and

each R^L is independently hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

n is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15.

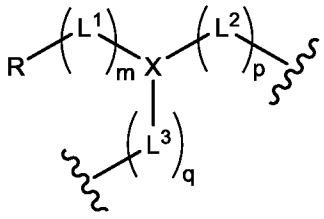
[0177] In some embodiments, the linker has a structure of



,

wherein each L is independently -O-, $-NR^L-$, $-N(R^L)_2-$, $-OP(=O)(OR^L)O-$, -S-, -S(=O)-, $-S(=O)_2-$, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L-$, $-NR^LC(=O)-$, $-OC(=O)NR^L-$, $-NR^LC(=O)O-$, $-NR^LC(=O)NR^L-$, $-NR^LS(=O)_2-$, $-S(=O)_2NR^L-$, $-C(=O)NR^LS(=O)_2-$, or $-S(=O)_2NR^LC(=O)-$.

[0178] In some embodiments, the linker has a structure of



Formula (II-2)

wherein each L^1, L^2, and L^3 is independently -O-, $-NR^L-$, $-N(R^L)_2-$, $-OP(=O)(OR^L)O-$, -S-, -S(=O)-, $-S(=O)_2-$, =CH-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L-$, $-NR^LC(=O)-$, $-OC(=O)NR^L-$, $-NR^LC(=O)O-$, $-NR^LC(=O)NR^L-$, $-NR^LC(=S)NR^L-$, $-CR^L=N-$, $-N=CR^L$, $-NR^LS(=O)_2-$, $-S(=O)_2NR^L-$, $-C(=O)NR^LS(=O)_2-$, $-S(=O)_2NR^LC(=O)-$, substituted or unsubstituted C_1-C_{30} alkylene, substituted or unsubstituted C_2-C_{30} alkenylene, substituted or unsubstituted C_2-C_{30} alkynylene, substituted or unsubstituted C_1-C_{30} heteroalkylene, substituted or unsubstituted C_1-C_{15} arylene, -(C_1-C_{30} alkylene)-O-, -O-(C_1-C_{30} alkylene)-, -(C_1-C_{30} alkylene)-NR^L-, $-NR^L$-(C_1-C_{30} alkylene)-, -(C_1-C_{30} alkylene)-$N(R^L)_2$-, or $-N(R^L)_2$-(C_1-C_{30} alkylene)-; and

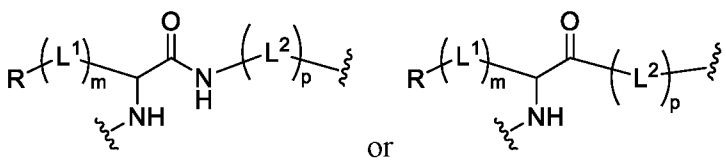
R is hydrogen, azide, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted C_3-C_{30} cycloalkyl, substituted or unsubstituted C_2-C_{30} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^L is hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted C_3-C_{30} cycloalkyl, substituted or unsubstituted C_2-C_{30} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

X is N or CR^L; and

each of m, p, and q is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15.

[0179] In some embodiments, the linker has a structure of



or , wherein

each L^1 and L^2 is independently -O-, $-NR^L-$, $-N(R^L)_2-$, $-OP(=O)(OR^L)O-$, -S-, -S(=O)-, $-S(=O)_2-$, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L-$, $-NR^LC(=O)-$, $-OC(=O)NR^L-$, $-NR^LC(=O)O-$, $-NR^LC(=O)NR^L-$, $-NR^LS(=O)_2-$, $-S(=O)_2NR^L-$, $-C(=O)NR^LS(=O)_2-$, $-S(=O)_2NR^LC(=O)-$, substituted or unsubstituted C_1-C_{20} alkylene, or $-(CHR^L-CHR^L-O)_{1\text{-}10}-$;

R^L is hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted C_3-C_8 cycloalkyl, or substituted or unsubstituted C_2-C_7 heterocycloalkyl;

R is hydrogen, azide, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

m is 1 to 10; and p is 0 to 3.

[0180] In some embodiments,

L^2 is -O-, $-NR^L$-, $-N(R^L)_2$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, $-S(=O)_2NR^LC(=O)$-, substituted or unsubstituted C_1-C_6 alkylene, or $-(CH_2-CH_2-O)_{1-6}$-;

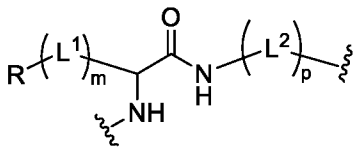
L^1 is -O-, $-NR^L$-, $-N(R^L)_2$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, $-S(=O)_2NR^LC(=O)$-, substituted or unsubstituted C_1-C_{20} alkylene, or $-(CH_2-CH_2-O)_{1-6}$-;

R^L is hydrogen or substituted or unsubstituted C_1-C_4 alkyl;

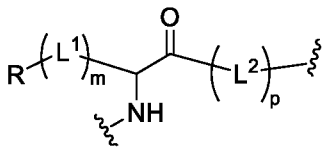
R is hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_3-C_{30} cycloalkyl, substituted or unsubstituted C_2-C_{30} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

m is 1 to 10; and p is 0 to 3.

[0181] In some embodiments, the linker has a structure of



or



, wherein

L^2 is -O-, $-NR^L$-, $-N(R^L)_2$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, $-S(=O)_2NR^LC(=O)$-, substituted or unsubstituted C_1-C_6 alkylene, or $-(CH_2-CH_2-O)_{1-6}$-;

L^1 is -O-, $-NR^L$-, $-N(R^L)_2$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, $-S(=O)_2NR^LC(=O)$-, substituted or unsubstituted C_1-C_{20} alkylene, or $-(CH_2-CH_2-O)_{1-6}$-;

R^L is hydrogen or substituted or unsubstituted C_1-C_4 alkyl;

R is hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_3-C_{30} cycloalkyl, substituted or unsubstituted C_2-C_{30} heterocycloalkyl, substituted or unsubstituted C_6-C_{10} aryl, or substituted or unsubstituted C_5-C_9 heteroaryl;

m is 1 to 4; and p is 0 to 3.

[0182] In some embodiments, R is hydrogen, substituted or unsubstituted C_6-C_{10} aryl, substituted or unsubstituted C_5-C_9 heteroaryl, or a sterol.

[0183] In some embodiments, at least one L^1 is unsubstituted C_3-C_{20} alkylene. In some embodiments, the linker comprises a click chemistry residue. In some embodiments, the linker comprises one or more lysine residues.

[0184] In some embodiments, the linker comprises one or more of a substituted or unsubstituted C_6-C_{10} aryl, substituted or unsubstituted C_5-C_9 heteroaryl, a sterol, sulfonamide, phosphate ester, polyethylene glycol, or C_3-C_{20} alkylene, or amino acid residues.

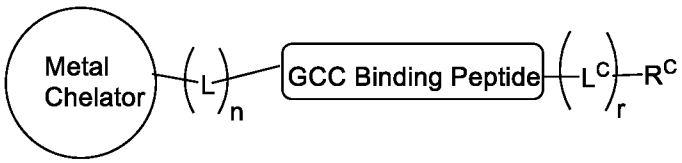
[0185] In one aspect, disclosed herein is a conjugate comprising

a guanylyl cyclase C (GCC) binding peptide;

a metal chelator configured to bind with a radionuclide; and

a linker that covalently attaches the GCC binding peptide with the metal chelator,

wherein the conjugate has a structure of Formula (I)



Formula (I)

wherein,

the linker $-(L)_n$- comprises 2 to 100 (e.g., 2 to 50 or 2 to 25) intervening atoms between the metal chelator and the binding peptide;

each L is independently -O-, $-NR^L$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LC(=S)NR^L$-, $-CR^L=N$-, $-N=CR^L$, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, $-S(=O)_2NR^LC(=O)$-, substituted or unsubstituted C_1-C_{30} alkylene, substituted or unsubstituted C_2-C_{30} alkenylene, substituted or unsubstituted

C_2-C_{30} alkynylene, substituted or unsubstituted C_1-C_{30} heteroalkylene, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

L^C is absent, -O-, $-NR^L$-, -OP(=O)(OR^L)O-, -S-, -S(=O)-, -S($=O)_2$-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, -C(=O)NR^L-, -NR^LC(=O)-, -OC(=O)NR^L-, -NR^LC(=O)O-, -NR^LC(=O)NR^L-, -NR^LC(=S)NR^L-, -CR^L=N-, -N=CR^L, -NR^LS($=O)_2$-, -S($=O)_2NR^L$-, -C(=O)NR^LS($=O)_2$-, -S($=O)_2NR^L$C(=O)-, substituted or unsubstituted C_1-C_{30} alkylene, substituted or unsubstituted C_2-C_{30} alkenylene, substituted or unsubstituted C_2-C_{30} alkynylene, substituted or unsubstituted C_1-C_{30} heteroalkylene, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or an amino acid;

each R^L is independently hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^C is hydrogen, halogen, -CN, -NO_2, -SR^a, -OR^a, -$N(R^a)_2$, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^aR^a, azide, substituted or unsubstituted C_1-C_{30} alkyl, substituted or unsubstituted C_1-C_{30} heteroalkyl, substituted or unsubstituted C_2-C_{30} alkenyl, substituted or unsubstituted C_2-C_{30} alkynyl, substituted or unsubstituted C_3-C_{30} cycloalkyl, substituted or unsubstituted C_2-C_{30} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl,

wherein each R^a is independently H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl);

n is 0 or an integer from 1 to 20; and

r is 0 or an integer from 1 to 5.

[0186] In some embodiments, the linker $-(L)_n$- comprises 3 to 20 intervening atoms between the metal chelator and the binding peptide. In some embodiments, the linker $-(L)_n$- comprises 3 to 50, 2 to 25, 2 to 75, 15 to 25, 10 to 30, or 15 to 40 intervening atoms between the metal chelator and the binding peptide.

[0187] In some embodiments, $-(L)_n$- is bound to the N-terminus of the GCC binding peptide and L^C is bound to the C-terminus of the GCC binding peptide. In some embodiments, $-(L)_n$- is

bound to the C-terminus of the GCC binding peptide and L^C is bound to the N-terminus of the GCC binding peptide. In some embodiments, $-(L)_n-$ is bound to the N-terminus of the GCC binding peptide. In some embodiments, $-(L)_n-$ is bound to the C-terminus of the GCC binding peptide. In some embodiments, $-(L)_n-$ is bound to a non-terminus amino acid of the GCC binding peptide. In some embodiments, L^C is bound to the N-terminus of the GCC binding peptide. In some embodiments, L^C is bound to the C-terminus of the GCC binding peptide. In some embodiments, L^C is bound to a non-terminus amino acid of the GCC binding peptide.

[0188] In some embodiments, the linker $-(L)_n-$ comprises a hydrophobic group selected from a C_8-C_{30} fatty acid, C_8-C_{30} fatty alcohol, C_8-C_{30} alkyl, aryl, heteroaryl, one or more amino acid residues, or a combination thereof. In some embodiments, the fatty acid contains 1, 2, 3 or more carboxylic acid groups. In some embodiments, the one or more amino acids contain a hydrophobic group such as an alkyl chain or a phenyl or heteroaryl group.

[0189] In some embodiments, each of -L- and - L^C- is independently, optionally substituted with one or more R^{12},

each R^{12} is independently halogen, -CN, -NO_2, -OH, -OR^a, -$OC(=O)R^a$, -$OC(=O)OR^b$, -$OC(=O)NR^cR^d$, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -NR^cR^d, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, -$Si(R^a)_3$, -$P(=O)(R^b)_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{12a};

or two R^{12} on the same atom are taken together to form an oxo;

each R^{12a} is independently halogen, -CN, -NO_2, -OH, -OR^a, -NR^cR^d, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{12a} on the same atom are taken together to form an oxo;

each R^a is independently C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl), wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^f;

or two R^a are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more R^f;

each R^b is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl), wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^f;

or two R^b are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more R^f;

R^c and R^d are each independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl), wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^f;

or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more R^f; and

each R^f is independently halogen, -CN, -OH, -OCH_3, -$S(=O)CH_3$, -$S(=O)_2CH_3$, -$S(=O)_2NH_2$, -$S(=O)_2NHCH_3$, -$S(=O)_2N(CH_3)_2$, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -$C(=O)CH_3$, -C(=O)OH, -$C(=O)OCH_3$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, and C_1-C_6heteroalkyl,

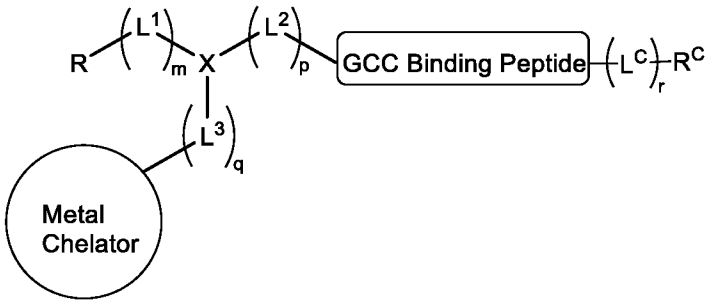
or two R^f on the same atom form an oxo.

[0190] In some embodiments, $-(L)_n-$ comprises one or more lysine residues. In some embodiments, $-(L)_n-$ comprises one or more glutamate residues. In some embodiments, $-(L)_n-$ comprises one or more tyrosine residues. In some embodiments, $-(L)_n-$ comprises one or more lysine residues. In some embodiments, $-(L)_n-$ comprises one or more amino acid residues selected from glycine (Gly), alanine (Ala), valine (Val), leucine (Leu), isoleucine (Ile), proline (Pro), phenylalanine (Phe), methionine (Met), and tryptophan (Trp).

[0191] In some embodiments of Formula (I), n is 0. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4. In some embodiments, n is 5. In some embodiments, n is 6. In some embodiments, n is 7. In some embodiments, n is 8. In some embodiments, n is 9. In some embodiments, n is 10. In some embodiments, n is 11. In some embodiments, n is 12. In some embodiments, n is 13. In some embodiments, n is 14. In some embodiments, n is 15. In some embodiments, n is 16. In some embodiments, n is 17. In some embodiments, n is 18. In some embodiments, n is 19. In some embodiments, n is 20.

[0192] In some embodiments of Formula (I), (Ia), (Iaa) or (Iab), r is 0. In some embodiments, r is 1. In some embodiments of Formula (I), r is 2. In some embodiments of Formula (I), r is 3. In some embodiments of Formula (I), r is 4. In some embodiments of Formula (I), r is 5.

[0193] In some embodiments, the conjugate has a structure of Formula (Ia),



Formula (Ia)

wherein,

each L^1, L^2, and L^3 is independently -O-, $-NR^L$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LC(=S)NR^L$-, $-CR^L=N$-, $-N=CR^L$, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, $-S(=O)_2NR^LC(=O)$-, substituted or unsubstituted C_1-C_{30} alkylene, substituted or unsubstituted C_2-C_{30} alkenylene, substituted or unsubstituted C_2-C_{30} alkynylene, substituted or unsubstituted C_1-C_{30} heteroalkylene, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R and R^C are each independently hydrogen, halogen, -CN, $-NO_2$, $-SR^a$, $-OR^a$, $-N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, azide, substituted or unsubstituted C_1-C_{30} alkyl, substituted or unsubstituted C_1-C_{30} heteroalkyl, substituted or unsubstituted C_2-C_{30} alkenyl, substituted or unsubstituted C_2-C_{30} alkynyl, substituted or unsubstituted C_3-C_{30} cycloalkyl, substituted or unsubstituted C_2-C_{30} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl,

wherein each R^a is independently H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl);

R^L is hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted C_3-C_{30} cycloalkyl, substituted or unsubstituted C_2-C_{30} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^X is independently hydrogen, halo, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or

unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted C_3-C_8 cycloalkyl, or substituted or unsubstituted C_2-C_7 heterocycloalkyl,

X is N or CR^X;

m is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

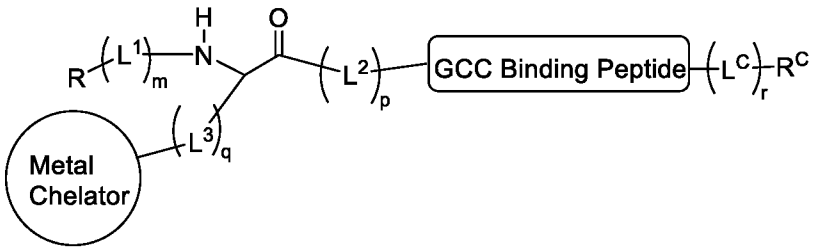
p is 0, 1, 2, 3, 4, 5, or 6;

q is 0, 1, 2, 3, 4, 5, or 6; and

r is 0, 1, 2, 3, 4, or 5.

[0194] In some embodiments, at least one of L^1, L^2, and L^3 comprises a hydrophobic group selected from a C_8-C_{30} fatty acid, C_8-C_{30} fatty alcohol, C_4-C_{12} alkylene chain, heteroaryl, or aryl group, each of which is optionally substituted.

[0195] In some embodiments, the conjugate has a structure of Formula (Iaa),



Formula (Iaa)

wherein

each L^1, L^2, and L^3 is independently -O-, $-NR^L$-, $-N(R^L)_2$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, $-S(=O)_2NR^LC(=O)$-, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{20} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene;

R^L is hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted C_3-C_8 cycloalkyl, or substituted or unsubstituted C_2-C_7 heterocycloalkyl;

R is hydrogen, azide, substituted or unsubstituted C_1-C_{30} alkyl, substituted or unsubstituted C_1-C_{30} heteroalkyl, substituted or unsubstituted C_2-C_{30} alkenyl, substituted or unsubstituted C_2-C_{30} alkynyl, substituted or unsubstituted C_3-C_{30} cycloalkyl, substituted or unsubstituted C_2-C_{30} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

L^C is absent, -O-, $-NR^L$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LC(=S)NR^L$-, $-CR^L=N$-, $-N=CR^L$, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, $-S(=O)_2NR^LC(=O)$-, substituted or unsubstituted C_1-C_{30} alkylene, substituted or unsubstituted C_2-C_{30} alkenylene, substituted or unsubstituted C_2-C_{30} alkynylene, substituted or unsubstituted C_1-C_{30} heteroalkylene, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or an amino acid;

R^C is hydrogen, halogen, -CN, $-NO_2$, $-SR^a$, $-OR^a$, $-N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, azide, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_1-C_{12} heteroalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl,

wherein each R^a is independently H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl);

m is 0, 1, 2, 3, 4, 5, 6, 7, 8, or 9;

r is 0, 1, 2, 3, 4, or 5;

p is 0, 1, 2, 3, 4, or 5; and

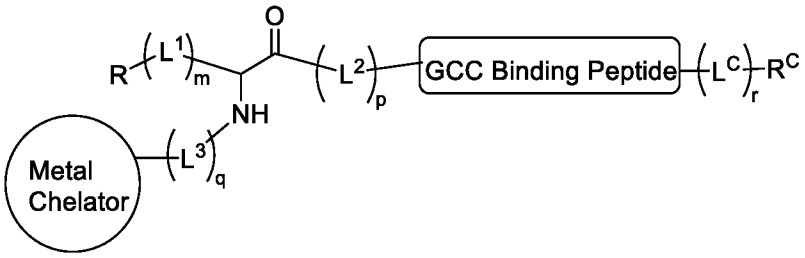
q is 0, 1, 2, 3, 4, or 5.

[0196] In some embodiments of Formula (Ia), (Iaa) or (Iab), m is 0 or 1-9. In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, m is 3. In some embodiments, m is 4. In some embodiments, m is 5. In some embodiments, m is 6. In some embodiments, m is 7. In some embodiments, m is 8. In some embodiments, m is 9. In some embodiments of Formula (Ia), m is 10.

[0197] In some embodiments of Formula (Ia), (Iaa) or (Iab), p is 0 or 1-5. In some embodiments, p is 0. In some embodiments, p is 1. In some embodiments, p is 2. In some embodiments, p is 3. In some embodiments, p is 4. In some embodiments, p is 5. In some embodiments of Formula (Ia), p is 6.

[0198] In some embodiments of Formula (Ia), (Iaa) or (Iab), q is 0 or 1-5. In some embodiments, q is 0. In some embodiments, q is 1. In some embodiments, q is 2. In some embodiments, q is 3. In some embodiments, q is 4. In some embodiments, q is 5. In some embodiments of Formula (Ia), q is 6.

[0199] In some embodiments, the conjugate has a structure of Formula (Iab),



Formula (Iab)

wherein

each L^1, L^2, and L^3 is independently -O-, $-NR^L$-, $-N(R^L)_2$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, $-S(=O)_2NR^LC(=O)$-, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{20} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene;

R^L is hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted C_3-C_8 cycloalkyl, or substituted or unsubstituted C_2-C_7 heterocycloalkyl;

R is hydrogen, azide, substituted or unsubstituted C_1-C_{30} alkyl, substituted or unsubstituted C_1-C_{30} heteroalkyl, substituted or unsubstituted C_2-C_{30} alkenyl, substituted or unsubstituted C_2-C_{30} alkynyl, substituted or unsubstituted C_3-C_{30} cycloalkyl, substituted or unsubstituted C_2-C_{30} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

L^C is absent, -O-, $-NR^L$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LC(=S)NR^L$-, $-CR^L=N$-, $-N=CR^L$, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, $-S(=O)_2NR^LC(=O)$-, substituted or unsubstituted C_1-C_{30} alkylene, substituted or unsubstituted C_2-C_{30} alkenylene, substituted or unsubstituted C_2-C_{30} alkynylene, substituted or unsubstituted C_1-C_{30} heteroalkylene, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or an amino acid;

R^C is hydrogen, halogen, -CN, $-NO_2$, $-SR^a$, $-OR^a$, $-N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, azide, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_1-C_{12} heteroalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl,

wherein each R^a is independently H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl);

m is 0, 1, 2, 3, 4, 5, 6, 7, 8, or 9;

r is 0, 1, 2, 3, 4, or 5;

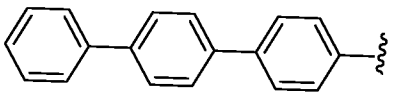
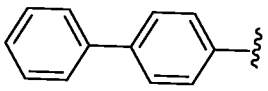
p is 0, 1, 2, 3, 4, or 5; and

q is 0, 1, 2, 3, 4, or 5.

[0200] In some embodiments of Formula (Ia), (Iaa), (Iab), (II-2), (II-2a), (II-2b), (II-2aa), or (II-2ba), R is a hydrophobic group.

[0201] In some embodiments of Formula (Ia), (Iaa), (Iab), (II-2), (II-2a), (II-2b), (II-2aa), or (II-2ba), R is phenyl, naphthyl, monocyclic heteroaryl, or bicyclic heteroaryl, each of which is optionally substituted with one or more substituents selected from halogen, -CN, $-NO_2$, $-OR^a$, $-N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl, wherein each R^a is independently H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl). In some embodiments, R is optionally substituted naphthyl. In some embodiments, R is optionally substituted monocyclic heteroaryl. In some embodiments, R is optionally substituted bicyclic heteroaryl. In some embodiments, R is optionally substituted monocyclic cycloalkyl. In some embodiments, R is optionally substituted bicyclic cycloalkyl. In some embodiments, R is optionally substituted monocyclic heterocycloalkyl. In some embodiments, R is optionally substituted bicyclic heterocycloalkyl. In some embodiments of Formula (Ia), (Iaa), (Iab), (II-2), (II-2a), (II-2b), (II-2aa), or (II-2ba), R is hydrogen, substituted or unsubstituted C_6-C_{10} aryl, substituted or unsubstituted C_5-C_9 heteroaryl, or a sterol. In some embodiments, R is H. In some embodiments, R is a sterol or a derivative thereof. In some embodiments, R is phenyl. In some embodiments, R is phenyl substituted with one or more substituents selected from halogen, -CN, $-NO_2$, $-OR^a$, $-N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl. In some embodiments, is phenyl substituted with one or more halogen. In some embodiments, R is phenyl substituted with one or more substituents selected from halogen, -CN, $-NO_2$, -OH, $-NH_2$,

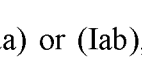
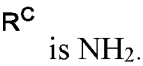
-C(=O)H, -C(=O)OH, -C(=O)NH_2, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, and C_1-C_6heteroalkyl.

[0202] In some embodiments of Formula (Ia), (Iaa), (Iab), (II-2), (II-2a), (II-2b), (II-2aa), or (II-2ba), R is iodophenyl. In some embodiments, R is  . In some embodiments, R is  .

[0203] In some embodiments of Formula (Ia), (Iaa), (Iab), (II-2), (II-2a), (II-2b), (II-2aa), or (II-2ba), R is C_6-C_{30} fatty acid, C_6-C_{30} fatty alcohol or C_6-C_{30} alkyl. In some embodiments, R is C_6-C_{12} fatty acid. In some embodiments, R is C_{12}-C_{24} fatty acid. In some embodiments, R is C_6-C_{12} fatty alcohol. In some embodiments, R is C_{12}-C_{24} fatty alcohol. In some embodiments, R is C_6-C_{12} alkyl. In some embodiments, R is C_{12}-C_{24} alkyl. In some embodiments, R is C_6-C_{12} alkenyl. In some embodiments, R is C_{12}-C_{24} alkenyl.

[0204] In some embodiments of Formula (Ia), (Iaa), (Iab), (II-2), (II-2a), (II-2b), (II-2aa), or (II-2ba), R is optionally substituted with one or more substituents selected from halogen, -CN, -NO_2, -OR^a, -$N(R^a)_2$, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^aR^a, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl, wherein each R^a is independently H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl).

[0205] In some embodiments of Formula (I), (Ia), (Iaa) or (Iab), R^C is a C_6-C_{30} fatty acid, C_6-C_{30} fatty alcohol or C_6-C_{30} alkyl. In some embodiments, R^C is C_6-C_{12} fatty acid. In some embodiments, R^C is C_{12}-C_{24} fatty acid. In some embodiments, R^C is C_6-C_{12} fatty alcohol. In some embodiments, R^C is C_{12}-C_{24} fatty alcohol. In some embodiments, R^C is C_6-C_{12} alkyl. In some embodiments, R^C is C_{12}-C_{24} alkyl. In some embodiments, R^C is C_6-C_{12} alkenyl. In some embodiments, R^C is C_{12}-C_{24} alkenyl.

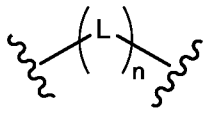
[0206] In some embodiments of Formula (I), (Ia), (Iaa) or (Iab),  is -OH. In some embodiments of Formula (I), (Ia), (Iaa) or (Iab),  is NH_2.

[0207] In some embodiments of Formula (I), (Ia), (Iaa) or (Iab), R^C is optionally substituted with one or more substituents selected from halogen, -CN, -NO_2, -OR^a, -$N(R^a)_2$, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^aR^a, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl,

C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl, wherein each R^a is independently H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl).

[0208] In some embodiments, a conjugate of Formula (I) has a linker of Formula (II-1).

[0209] In some embodiments, described herein is a linker that has a structure of Formula (II-1)



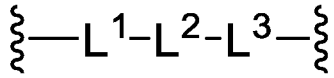
Formula (II-1)

wherein each L is independently -O-, $-NR^L$-, $-N(R^L)_2$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, =CH-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LC(=S)NR^L$-, $-CR^L=N$-, $-N=CR^L$, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, $-S(=O)_2NR^LC(=O)$-, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{30} alkylene, substituted or unsubstituted C_2-C_{30} alkenylene, substituted or unsubstituted C_2-C_{30} alkynylene, substituted or unsubstituted C_1-C_{30} heteroalkylene, -(C_1-C_{30} alkylene)-O-, -O-(C_1-C_{30} alkylene)-, -(C_1-C_{30} alkylene)-NR^L-, $-NR^L$-(C_1-C_{30} alkylene)-, -(C_1-C_{30} alkylene)-$N(R^L)_2$-, or $-N(R^L)_2$-(C_1-C_{30} alkylene)-; and

each R^L is independently hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

n is 1 to 20.

[0210] In some embodiments, the linker comprises a structure of Formula (II-1a),



Formula (II-1a)

wherein each of L^1 and L^3 is independently -O-, $-NR^L$-, $-N(R^L)_2$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-,

-C(=O)NR^L-, -NR^{L}C(=O)-, -OC(=O)NR^L-, -NR^{L}C(=O)O-, -NR^{L}C(=O)NR^L-, -NR^{L}S(=O)$_2$-, -S(=O)$_2$NR^L-, -C(=O)NR^{L}S(=O)$_2$-, or -S(=O)$_2$NR^{L}C(=O)-; and

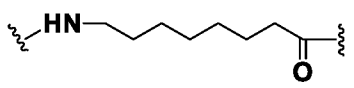
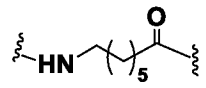
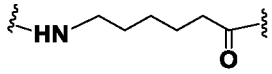
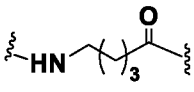
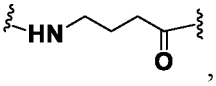
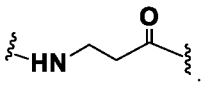
L^2 is absent, substituted or unsubstituted C_1-C_{30} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene.

[0211] In some embodiments for Formula (II-1a), L^1 is -NH-;

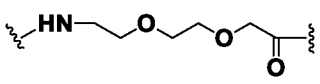
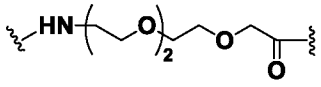
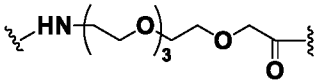
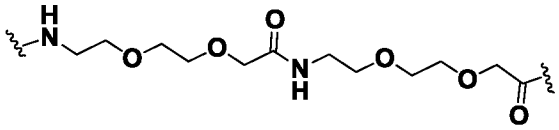
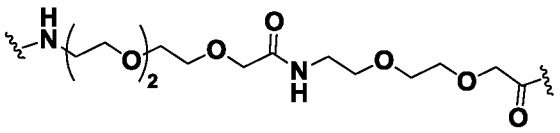
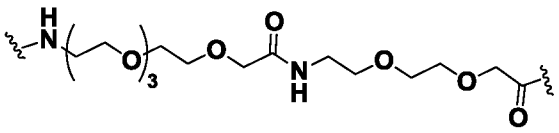
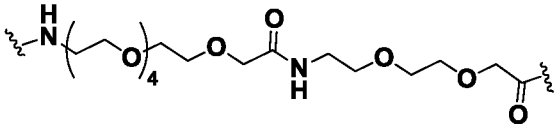
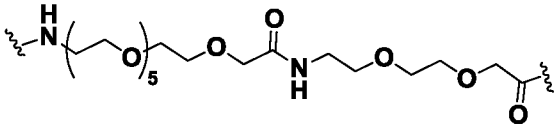
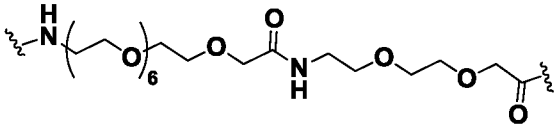
L^3 is -C(=O)-;

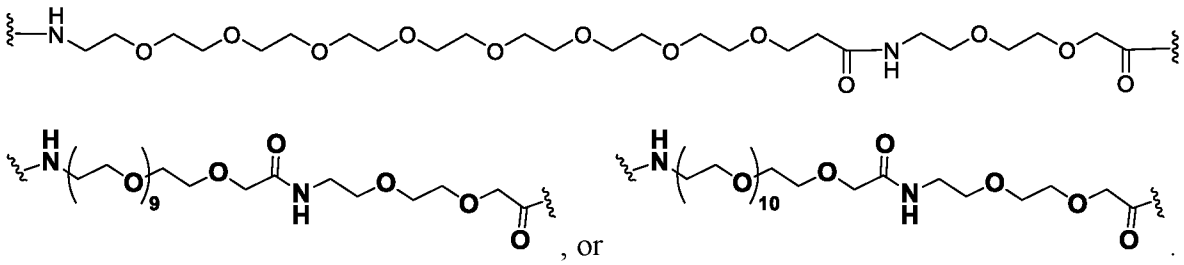
L^2 is unsubstituted C_1-C_{12} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene, wherein the heteroalkylene is optionally substituted with one or more substituents selected from -OH, -SH, oxo, amino, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, and C_1-C_6 aminoalkyl.

[0212] In some embodiments for Formula (II-1a), L^2 is unsubstituted C_1-C_{12} alkylene.

[0213] In some embodiments, a linker of the present disclosure (e.g., a linker of Formula (II-1a)) has a structure of  ,  ,  ,  , or  ,  .

[0214] In some embodiments for Formula (II-1a), L^2 is C_1-C_{30} heteroalkylene that is optionally substituted with one or more substituents selected from -OH, -SH, oxo, amino, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, and C_1-C_6 aminoalkyl.

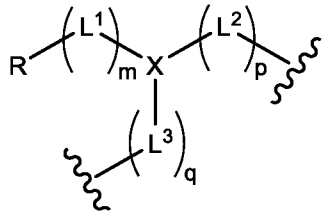
[0215] In some embodiments, a linker of the present disclosure (e.g., a linker of Formula (II-1a)) has a structure of  ,  ,  ,  ,  ,  ,  ,  ,  .



, or .

[0216] In some embodiments, a conjugate of Formula (Ia) has a linker of Formula (II-2).

[0217] In some embodiments, a linker of the present disclosure has a structure of Formula (II-2)



Formula (II-2),

wherein each L^1, L^2, and L^3 is independently -O-, $-NR^L$-, $-N(R^L)_2$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, =CH-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LC(=S)NR^L$-, $-CR^L=N$-, $-N=CR^L$, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, $-S(=O)_2NR^LC(=O)$-, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{30} alkylene, substituted or unsubstituted C_2-C_{30} alkenylene, substituted or unsubstituted C_2-C_{30} alkynylene, substituted or unsubstituted C_1-C_{30} heteroalkylene, -(C_1-C_{30} alkylene)-O-, -O-(C_1-C_{30} alkylene)-, -(C_1-C_{30} alkylene)-NR^L-, $-NR^L$-(C_1-C_{30} alkylene)-, -(C_1-C_{30} alkylene)-$N(R^L)_2$-, or $-N(R^L)_2$-(C_1-C_{30} alkylene)-; and

R is hydrogen, azide, substituted or unsubstituted C_1-C_{30} alkyl, substituted or unsubstituted C_1-C_{30} heteroalkyl, substituted or unsubstituted C_2-C_{30} alkenyl, substituted or unsubstituted C_2-C_{30} alkynyl, substituted or unsubstituted C_3-C_{30} cycloalkyl, substituted or unsubstituted C_2-C_{30} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R^L is independently hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted C_3-C_{30} cycloalkyl, substituted or unsubstituted C_2-C_{30} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^X is independently hydrogen, halo, -CN, -NO_2, -OH, -SH, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted C_3-C_8 cycloalkyl, or substituted or unsubstituted C_2-C_7 heterocycloalkyl,

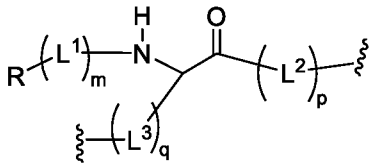
X is N or CR^X;

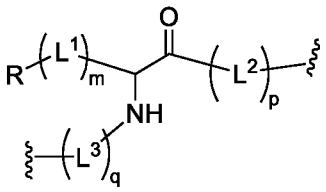
m is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

p is 0, 1, 2, 3, 4, 5, or 6; and

q is 0, 1, 2, 3, 4, 5, and 6.

[0218] In some embodiments, the linker has a structure of Formula (II-2a) or Formula (II-2b)



Formula (II-2a) or  Formula (II-2b),

wherein

each L^1, L^2, and L^3 is independently -O-, –NR^L-, –$N(R^L)_2$-, -OP(=O)(OR^L)O-, -S-, -S(=O)-, -$S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, -C(=O)NR^L-, -NR^LC(=O)-, -OC(=O)NR^L-, -NR^LC(=O)O-, -NR^LC(=O)NR^L-, -NR^LS(=O)$_2$-, -S(=O)$_2$$NR^L$-, -C(=O)$NR^L$S(=O)$_2$-, -S(=O)$_2$$NR^L$C(=O)-, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{20} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene;

R^L is hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted C_3-C_8 cycloalkyl, or substituted or unsubstituted C_2-C_7 heterocycloalkyl;

R is hydrogen, azide, substituted or unsubstituted C_1-C_{30} alkyl, substituted or unsubstituted C_1-C_{30} heteroalkyl, substituted or unsubstituted C_2-C_{30} alkenyl, substituted or unsubstituted C_2-C_{30} alkynyl, substituted or unsubstituted C_3-C_{30} cycloalkyl, substituted or unsubstituted C_2-C_{30} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

m is 0, 1, 2, 3, 4, 5, 6, 7, 8, or 9;

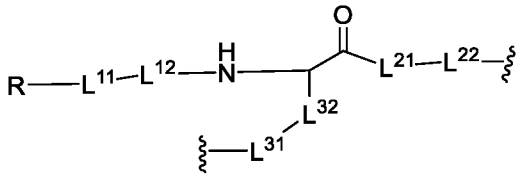
p is 0, 1, 2, 3, 4, or 5; and

q is 0, 1, 2, 3, 4, or 5.

[0219] In some embodiments, the linker of Formula (II-2a) or Formula (II-2b) connects to the metal chelator through L^3 and to the peptide through L^2.

[0220] In some embodiments, the linker has a structure of Formula (II-2a). In some embodiments, a conjugate of Formula (Ia) or (Iaa) has a linker of Formula (II-2aa).

[0221] In some embodiments, the linker of Formula (II-2a) has a structure of Formula (II-2aa),



Formula (II-2aa)

wherein,

L^{11} is absent, -O-, $-NR^L$-, $-N(R^L)_2$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, or $-S(=O)_2NR^LC(=O)$-;

L^{12} is absent, -O-, $-NR^L$-, $-N(R^L)_2$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, $-S(=O)_2NR^LC(=O)$-, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{20} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene;

L^{21} is absent, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{20} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene;

L^{22} is absent, -O-, $-NR^L$-, $-N(R^L)_2$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, or $-S(=O)_2NR^LC(=O)$-;

L^{31} is absent, -O-, $-NR^L$-, $-N(R^L)_2$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, or $-S(=O)_2NR^LC(=O)$-;

L^{32} is absent, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{20} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene;

R^L is hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted C_3-C_8 cycloalkyl, or substituted or unsubstituted C_2-C_7 heterocycloalkyl;

R is hydrogen, substituted or unsubstituted C_1-C_{30} alkyl, substituted or unsubstituted C_1-C_{30} heteroalkyl, substituted or unsubstituted C_2-C_{30} alkenyl, substituted or unsubstituted C_3-C_{30} cycloalkyl, substituted or unsubstituted C_2-C_{30} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

q is 0, 1, 2, 3, 4, or 5.

[0222] In some embodiments of a structure of Formula (II-2aa), L^{31} is -NH- and L^{32} is substituted or unsubstituted C_1-C_{12} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene.

[0223] In some embodiments, L^{31} is -NH- and L^{32} is $-(CH_2)_4-$.

[0224] In some embodiments of a structure of Formula (II-2aa), L^{31} is absent, -O-, $-NR^L-$, $-N(R^L)_2-$, $-OP(=O)(OR^L)O-$, -S-, $-S(=O)-$, $-S(=O)_2-$, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L-$, $-NR^LC(=O)-$, $-OC(=O)NR^L-$, $-NR^LC(=O)O-$, $-NR^LC(=O)NR^L-$, $-NR^LS(=O)_2-$, $-S(=O)_2NR^L-$, $-C(=O)NR^LS(=O)_2-$, or $-S(=O)_2NR^LC(=O)-$. In some embodiments, L^{31} is absent, $-OP(=O)(OH)O-$, -NHC(=O)-, -C(=O)NH-, or $-S(=O)_2NH-$. In some embodiments, L^{31} is $OP(=O)(OR^L)O-$. In some embodiments, L^{31} is $OP(=O)(OH)O-$. In some embodiments, L^{31} is $-C(=O)NR^L-$. In some embodiments, L^{31} is -C(=O)NH-. In some embodiments, L^{31} is- $S(=O)_2NR^L-$. In some embodiments, L^{31} is- $S(=O)_2NH-$. In some embodiments, L^{31} is absent.

[0225] In some embodiments of a structure of Formula (II-2aa), L^{32} is absent, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{20} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene. In some embodiments, L^{32} is substituted or unsubstituted C_1-C_{12} alkylene. In some embodiments, L^{32} is C_1-C_{30} heteroalkylene. In some embodiments, L^{32} is C_{10}-C_{20} heteroalkylene. In some embodiments, L^{32} is C_1-C_{12} alkenyl. In some embodiments, L^{32} is absent.

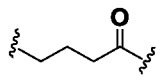
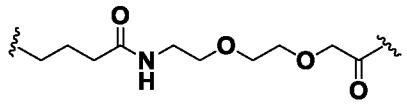
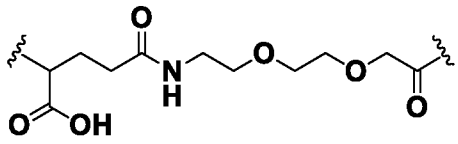
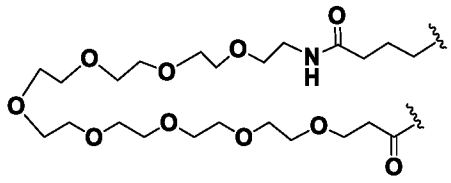
[0226] In some embodiments of a structure of Formula (II-2aa) or (II-2ba), wherein L^{11} is absent, -O-, $-OP(=O)(OR^L)O-$, -S-, $-S(=O)_2-$, $-C(=O)-$, $-C(=O)O-$, $-OC(=O)-$, $-OC(=O)O-$, $-C(=O)NR^L-$,

-$NR^LC(=O)$-, -$OC(=O)NR^L$-, -$NR^LC(=O)O$-, -$NR^LC(=O)NR^L$-, -$NR^LS(=O)_2$-, -$S(=O)_2NR^L$-, -$C(=O)NR^LS(=O)_2$-, or -$S(=O)_2NR^LC(=O)$-. In some embodiments, L^{11} is absent, -OP(=O)(OH)O-, -NHC(=O)-, -C(=O)NH-, or -$S(=O)_2NH$-. In some embodiments, L^{11} is $OP(=O)(OR^L)O$-. In some embodiments, L^{11} is OP(=O)(OH)O-. In some embodiments, L^{11} is -$C(=O)NR^L$-. In some embodiments, L^{11} is -C(=O)NH-. In some embodiments, L^{11} is- $S(=O)_2NR^L$-. In some embodiments, L^{11} is- $S(=O)_2NH$-. In some embodiments, L^{11} is absent.

[0227] In some embodiments of a structure of Formula (II-2aa) or (II-2ba), L^{12} is absent, -O-, -$OP(=O)(OR^L)O$-, -S-, -$S(=O)_2$-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, -$C(=O)NR^L$-, -$NR^LC(=O)$-, -$OC(=O)NR^L$-, -$NR^LC(=O)O$-, -$NR^LC(=O)NR^L$-, -$NR^LS(=O)_2$-, -$S(=O)_2NR^L$-, -$C(=O)NR^LS(=O)_2$-, or -$S(=O)_2NR^LC(=O)$-, substituted or unsubstituted C_1-C_{12} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene. In some embodiments, L^{12} is substituted or unsubstituted C_1-C_{12} alkylene. In some embodiments, L^{12} is C_1-C_{30} heteroalkylene. In some embodiments, L^{12} is C_{10}-C_{20} heteroalkylene. In some embodiments, L^{12} is C_1-C_{12} alkenyl. In some embodiments, L^{12} is absent.

[0228] In some embodiments of a structure of Formula (II-2aa) or (II-2ba), L^{21} is absent, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{20} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene. In some embodiments, L^{21} is substituted or unsubstituted C_1-C_{12} alkylene. In some embodiments, L^{21} is C_1-C_{30} heteroalkylene. In some embodiments, L^{21} is C_{10}-C_{20} heteroalkylene. In some embodiments, $L^{21v}$is C_1-C_{12} alkenyl. In some embodiments, L^{21} is absent.

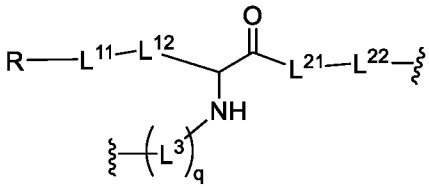
[0229] In some embodiments of a structure of Formula (II-2aa) or (II-2ba), L^{22} is -O-, –NR^L-, –$N(R^L)_2$-, -$OP(=O)(OR^L)O$-, -S-, -S(=O)-, -$S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, -$C(=O)NR^L$-, -$NR^LC(=O)$-, -$OC(=O)NR^L$-, -$NR^LC(=O)O$-, -$NR^LC(=O)NR^L$-, -$NR^LS(=O)_2$-, -$S(=O)_2NR^L$-, -$C(=O)NR^LS(=O)_2$-, or -$S(=O)_2NR^LC(=O)$-. In some embodiments, L^{22} is absent, -OP(=O)(OH)O-, -NHC(=O)-, -C(=O)NH-, or -$S(=O)_2NH$-. In some embodiments, L^{22} is $OP(=O)(OR^L)O$-. In some embodiments, L^{22} is OP(=O)(OH)O-. In some embodiments, L^{22} is -$C(=O)NR^L$-. In some embodiments, L^{22} is -C(=O)NH-. In some embodiments, L^{22} is- $S(=O)_2NR^L$-. In some embodiments, L^{22} is- $S(=O)_2NH$-. In some embodiments, L^{22} is absent.

[0230] In some embodiments, L^{12} is  ,  ,  , or  .

[0231] In some embodiments of a structure of Formula (II-2aa) or (II-2ba), L^{12} is -C(=O)- and L^{11} is absent.

[0232] In some embodiments, the linker has a structure of Formula (II-2b). In some embodiments, a conjugate of Formula (Ia) or (Iab) has a linker of Formula (II-2ba).

[0233] In some embodiments, a linker of Formula (II-2b) has a structure of Formula (II-2ba),



Formula (II-2ba)

wherein,

L^{11} is absent, -O-, $-NR^L$-, $-N(R^L)_2$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, or $-S(=O)_2NR^LC(=O)$-;

L^{12} is absent, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{20} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene;

L^{21} is absent, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{20} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene;

L^{22} is absent, -O-, $-NR^L$-, $-N(R^L)_2$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, or $-S(=O)_2NR^LC(=O)$-;

L^3 is -O-, $-NR^L$-, $-N(R^L)_2$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, -

$OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, $-S(=O)_2NR^LC(=O)$-, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{20} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene;

R^L is hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted C_3-C_8 cycloalkyl, or substituted or unsubstituted C_2-C_7 heterocycloalkyl;

R is hydrogen, substituted or unsubstituted C_1-C_{30} alkyl, substituted or unsubstituted C_1-C_{30} heteroalkyl, substituted or unsubstituted C_2-C_{30} alkenyl, substituted or unsubstituted C_3-C_{30} cycloalkyl, substituted or unsubstituted C_2-C_{30} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

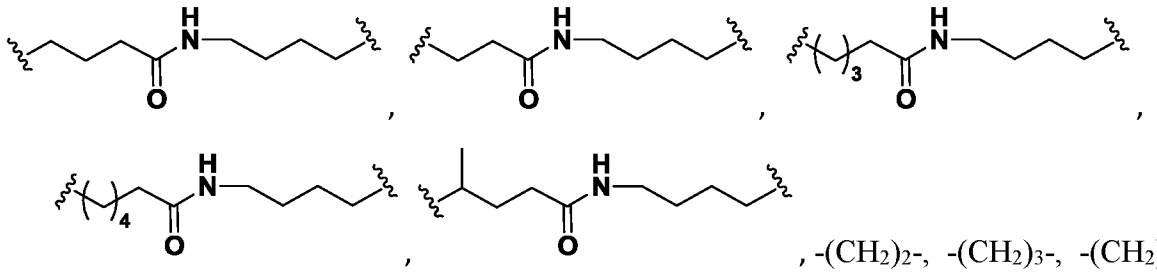
q is 0, 1, 2, 3, 4, or 5.

[0234] I some embodiments of Formula (II-2ba), q is 0. In some embodiments, q is 1. In some embodiments, q is 2. In some embodiments, q is 3. In some embodiments, q is 4. In some embodiments, q is 5.

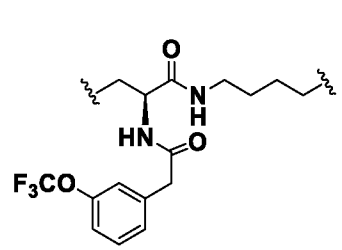
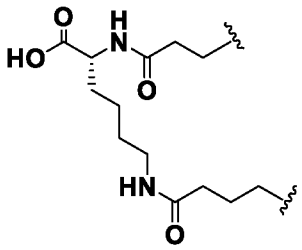
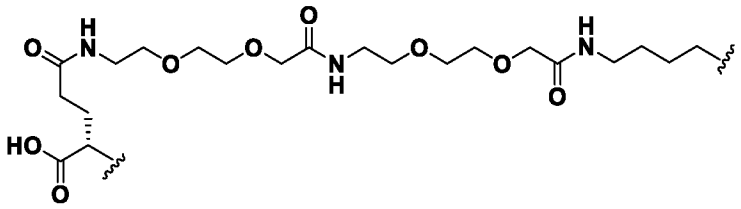
[0235] In some embodiments of a structure of Formula (II-2aa) or (II-2ba), L^{11} is absent, -O-, $-OP(=O)(OR^L)O$-, -S-, $-S(=O)_2$-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, or $-S(=O)_2NR^LC(=O)$-. In some embodiments, L^{11} is absent, $-OP(=O)(OH)O$-, -NHC(=O)-, -C(=O)NH-, or $-S(=O)_2NH$-.

[0236] In some embodiments of a structure of Formula (II-2aa) or (II-2ba), L^{12} is substituted or unsubstituted C_1-C_{12} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene.

[0237] In some embodiments, L^{12} is

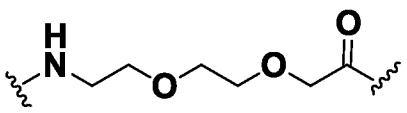
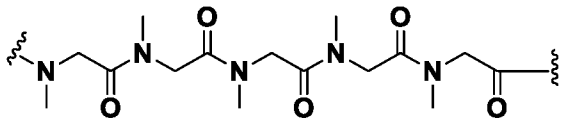


, $-(CH_2)_2$-, $-(CH_2)_3$-, $-(CH_2)_4$-,

-$(CH_2)_5$-, -$(CH_2)_6$-,  ,  , or  .

[0238] In some embodiments of a structure of Formula (II-2aa) or (II-2ba), L^{22} and L^{21} are both absent.

[0239] In some embodiments of a structure of Formula (II-2aa) or (II-2ba), L^{22} is -C(=O)- and L^{21} is substituted or unsubstituted C_1-C_{12} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene.

[0240] In some embodiments of a structure of Formula (II-2aa) or (II-2ba), -L^{21}-L^{22}- is  or  .

[0241] In some embodiments of a structure of Formula (Ia), (Iaa), (Iab), (II-2), (II-2a), or (II-2b), each of L^1 is independently -O-, –NR^L-, –$N(R^L)_2$-, -OP(=O)(OR^L)O-, -S-, -S(=O)-, -$S(=O)_2$-, =CH-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, -C(=O)NR^L-, -NR^LC(=O)-, -OC(=O)NR^L-, -NR^LC(=O)O-, -NR^LC(=O)NR^L-, -NR^LC(=S)NR^L-, -CR^L=N-, -N=CR^L, -NR^LS(=O)$_2$-, -$S(=O)_2NR^L$-, -C(=O)NR^LS(=O)$_2$-, -$S(=O)_2NR^L$C(=O)-, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{30} alkylene, substituted or unsubstituted C_2-C_{30} alkenylene, substituted or unsubstituted C_2-C_{30} alkynylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene, In some embodiments, L^1 is -O-, –NR^L-, -OP(=O)(OR^L)O-, -S-, -S(=O)-, -$S(=O)_2$-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, -C(=O)NR^L-, -NR^LC(=O)-, -OC(=O)NR^L-, -NR^LC(=O)O-, -NR^LC(=O)NR^L-, -NR^LC(=S)NR^L-, -NR^LS(=O)$_2$-, -$S(=O)_2NR^L$-, -C(=O)NR^LS(=O)$_2$-, or -$S(=O)_2NR^L$C(=O)-. In some embodiments, L^1 is -O-, –NH-, -S(=O)-, -$S(=O)_2$-, or -C(=O)-. In some embodiments, L^1 is -C(=O)NH- or -NHC(=O)-. In some embodiments, L^1 is substituted or unsubstituted C_3-C_{15} cycloalkyl, or substituted or unsubstituted C_1-C_{12} heterocycloalkyl. In some embodiments, L^1 is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl. In some embodiments, L^1 is

substituted or unsubstituted C_1-C_{30} alkylene. In some embodiments, L^1 is substituted or unsubstituted C_2-C_{30} alkenylene. In some embodiments, L^1 is substituted or unsubstituted C_1-C_{30} heteroalkylene. In some embodiments, L^1 is substituted or unsubstituted C_5-C_{25} heteroalkylene. In some embodiments, L^1 is substituted or unsubstituted C_5-C_{12} heteroalkylene.

[0242] In some embodiments of a structure of Formula (Ia), (Iaa), (Iab), (II-2), (II-2a), or (II-2b), each of L^2 is independently -O-, $-NR^L$-, $-N(R^L)_2$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, =CH-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LC(=S)NR^L$-, $-CR^L=N$-, $-N=CR^L$, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, $-S(=O)_2NR^LC(=O)$-, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{30} alkylene, substituted or unsubstituted C_2-C_{30} alkenylene, substituted or unsubstituted C_2-C_{30} alkynylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene, In some embodiments, L^2 is -O-, $-NR^L$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LC(=S)NR^L$-, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, or $-S(=O)_2NR^LC(=O)$-. In some embodiments, L^2 is -O-, –NH-, -S(=O)-, $-S(=O)_2$-, or -C(=O)-. In some embodiments, L^2 is -C(=O)NH- or -NHC(=O)-. In some embodiments, L^2 is substituted or unsubstituted C_3-C_{15} cycloalkyl, or substituted or unsubstituted C_1-C_{12} heterocycloalkyl. In some embodiments, L^2 is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl. In some embodiments, L^2 is substituted or unsubstituted C_1-C_{30} alkylene. In some embodiments, L^2 is substituted or unsubstituted C_2-C_{30} alkenylene. In some embodiments, L^2 is substituted or unsubstituted C_1-C_{30} heteroalkylene. In some embodiments, L^2 is substituted or unsubstituted C_5-C_{25} heteroalkylene. In some embodiments, L^2 is substituted or unsubstituted C_5-C_{12} heteroalkylene.

[0243] In some embodiments of a structure of Formula (Ia), (Iaa), (Iab), (II-2), (II-2a), (II-2b), or (II-2ba), each of L^3 is independently -O-, $-NR^L$-, $-N(R^L)_2$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, =CH-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LC(=S)NR^L$-, $-CR^L=N$-, $-N=CR^L$, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, $-S(=O)_2NR^LC(=O)$-, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{30} alkylene, substituted or unsubstituted C_2-C_{30} alkenylene, substituted or unsubstituted C_2-C_{30} alkynylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene, In some embodiments, L^3 is -O-, $-NR^L$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, -

$NR^LC(=S)NR^L$-, -$NR^LS(=O)_2$-, -$S(=O)_2NR^L$-, -$C(=O)NR^LS(=O)_2$-, or -$S(=O)_2NR^LC(=O)$-. In some embodiments, L^3 is -O-, –NH-, -S(=O)-, -$S(=O)_2$-, or -C(=O)-. In some embodiments, L^3 is -C(=O)NH- or -NHC(=O)-. In some embodiments, L^3 is substituted or unsubstituted C_3-C_{15} cycloalkyl, or substituted or unsubstituted C_1-C_{12} heterocycloalkyl. In some embodiments, L^3 is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl. In some embodiments, L^3 is substituted or unsubstituted C_1-C_{30} alkylene. In some embodiments, L^3 is substituted or unsubstituted C_2-C_{30} alkenylene. In some embodiments, L^3 is substituted or unsubstituted C_1-C_{30} heteroalkylene. In some embodiments, L^3 is substituted or unsubstituted C_5-C_{25} heteroalkylene. In some embodiments, L^3 is substituted or unsubstituted C_5-C_{12} heteroalkylene.

[0244] In some embodiments of Formula (Ia), (Iaa), (Iab), (II-2), (II-2a) or (II-2b), each of L^1, L^2, L^3, and L^C is independently optionally substituted with one or more R^{12},

each R^{12} is independently halogen, -CN, -NO_2, -OH, -OR^a, -$OC(=O)R^a$, -$OC(=O)OR^b$, -$OC(=O)NR^cR^d$, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -NR^cR^d, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, -$Si(R^a)_3$, -$P(=O)(R^b)_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{12a};

or two R^{12} on the same atom are taken together to form an oxo;

each R^{12a} is independently halogen, -CN, -NO_2, -OH, -OR^a, -NR^cR^d, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{12a} on the same atom are taken together to form an oxo;

each R^a is independently C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl), wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^f;

or two R^a are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more R^f;

each R^b is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl),

C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl), wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^f;

or two R^b are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more R^f;

R^c and R^d are each independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl), wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^f;

or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more R^f; and

each R^f is independently halogen, -CN, -OH, $-OCH_3$, $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-S(=O)_2NH_2$, $-S(=O)_2NHCH_3$, $-S(=O)_2N(CH_3)_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-C(=O)CH_3$, -C(=O)OH, $-C(=O)OCH_3$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, and C_1-C_6heteroalkyl,

or two R^f on the same atom form an oxo.

[0245] In some embodiments of Formula (II-2aa) or (II-2ba), L^{11}, L^{12}, L^{21}, L^{22}, L^{31}, and L^{32} are each independently, optionally substituted with one or more substituents selected from halogen, -CN, $-NO_2$, $-OR^a$, $-N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl, wherein each R^a is independently H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl).

[0246] In some embodiments, a linker comprises a click chemistry residue.

[0247] In some embodiments, a linker comprises one or more of substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and one or more amino acids.

[0248] In some embodiments, a linker comprises one or more of a substituted or unsubstituted C_6-C_{10} aryl, substituted or unsubstituted C_5-C_9 heteroaryl, a sterol, sulfonamide, phosphate ester, polyethylene glycol, C_3-C_{20} alkylene, or amino acid residues.

[0249] In some embodiments, a linker comprises one or more lysine residues.

[0250] In some embodiments, a linker comprises one or more glutamate residues.

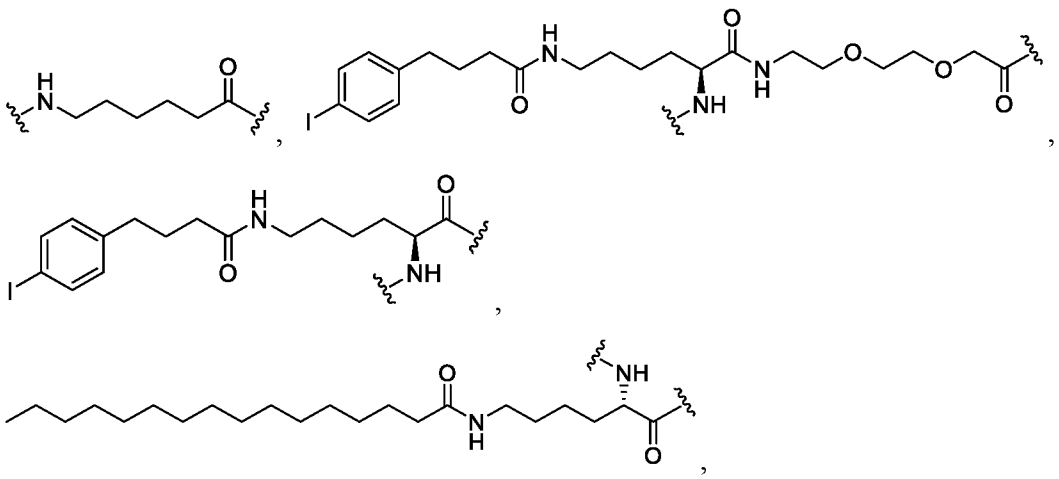
[0251] In some embodiments, the linker comprises phenyl iodide or carboxylic acid.

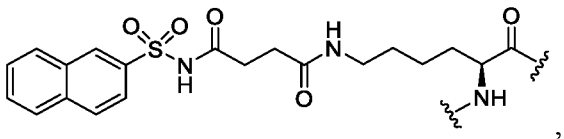
[0252] A linker described herein can reversibly bind to human serum albumin. In some embodiments, the linker binds to Sudlow Site I of the human serum albumin. In some embodiments, the linker binds to Sudlow Site II of the human serum albumin. In some embodiments, the linker binds to Sudlow Site I and site II of the human serum albumin. In some embodiments, the linker comprises one or more negatively charged groups such as a carboxylic acid and aromatic carboxylic acid.

[0253] In some embodiments, the linker comprises a halo substituted aryl group. In some embodiments, the linker comprises phenyl iodide. In some embodiments, the linker comprises phenyl bromide. In some embodiments, the linker comprises an unsubstituted or halo substituted 1,1'-biphenyl. In some embodiments, the linker comprises an unsubstituted or halo substituted 1,1':4',1''-terphenyl. In some embodiments, the linker comprises an unsubstituted or halo substituted naphthyl. In some embodiments, the linker comprises a carboxylic acid or an isostere thereof. In some embodiments, the linker comprises a carboxylic acid. The halo substituted aryl group and the carboxylic acid group can be located in the same linker or in two different linkers. It is revealed by the present disclosure that the presence of a halo substituted aryl group (e.g., phenyl iodide), the presence of a carboxylic acid or an isostere thereof, or both in the conjugate can improve elimination half-life of the conjugate.

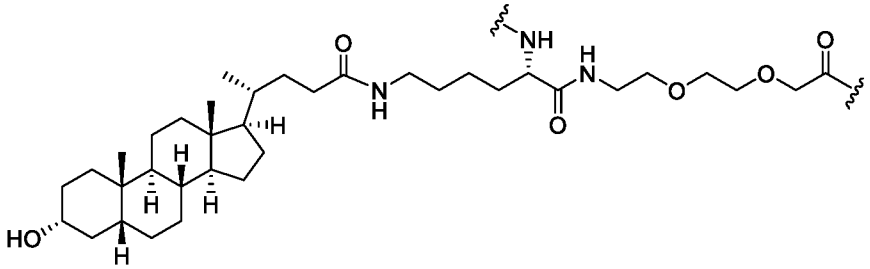
[0254] In some embodiments, the linker comprises a lysine residue. In some embodiments, the lysine residue is D-lysine.

[0255] In some embodiments, a linker described herein comprises one or more structures selected from:

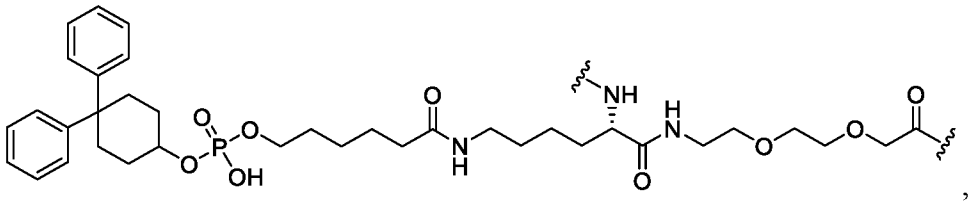




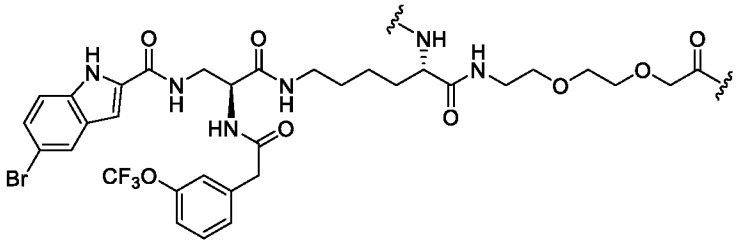
,



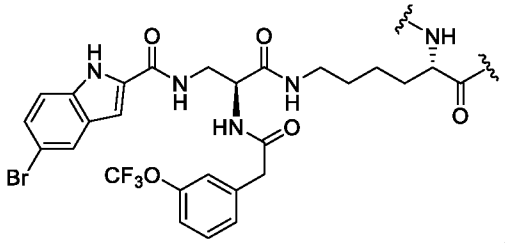
,



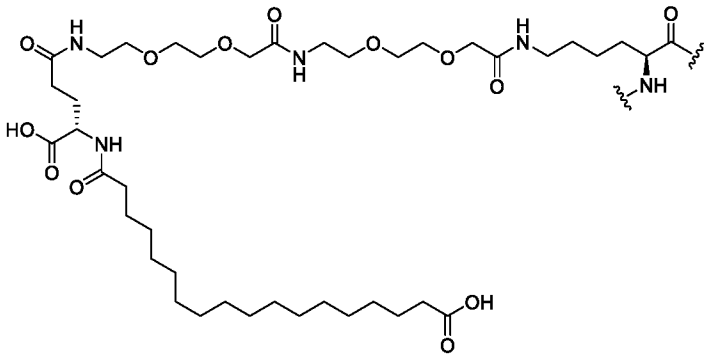
,



,

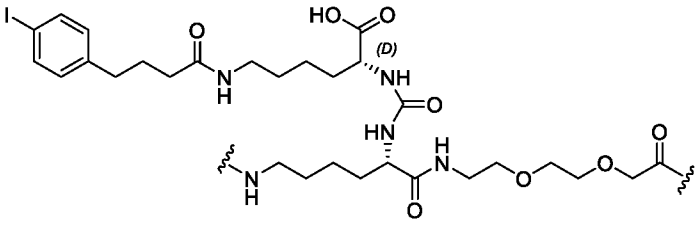


, and

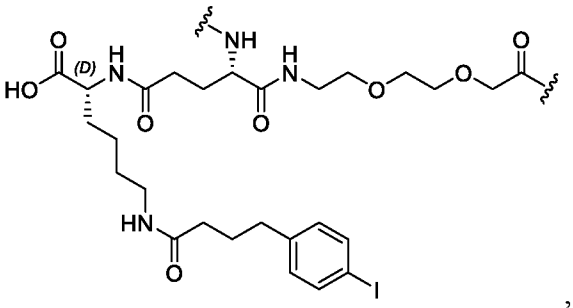


.

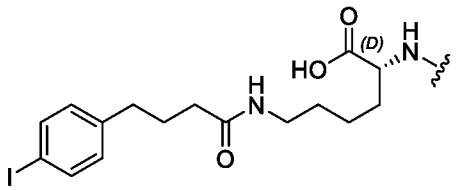
[0256] In some embodiments, the linker comprises:



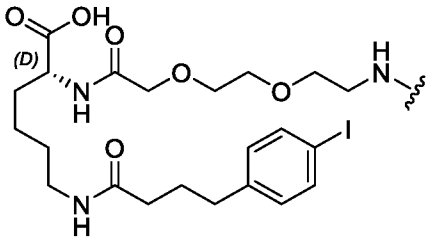
,



,

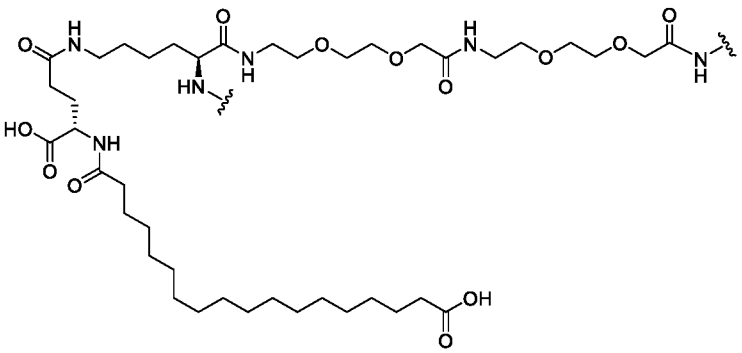


, or

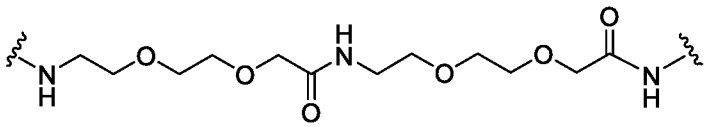


.

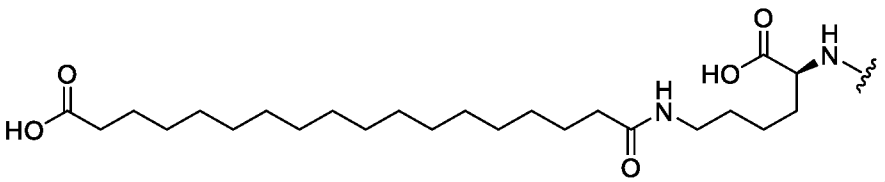
[0257] In some embodiments, the linker comprises:



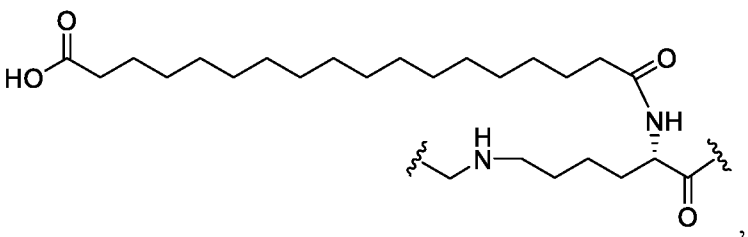
,



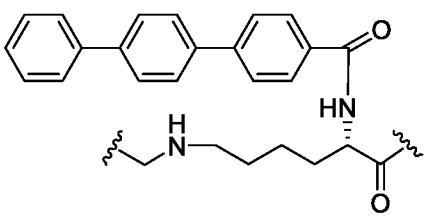
,



,



, or



.

[0258] In some embodiments, a dissociation constant (Kd) between the linker and human serum albumin is at most 500 μM, as determined at room temperature in human serum condition. In some embodiments, the Kd is at most 100 μM. In some embodiments, the Kd is at most 15 μM. In some embodiments, the Kd is from about 0.1 nM to about 10 μM. In some embodiments, the Kd is from about 10 nM to about 10 μM.

Metal Chelators

[0259] In one aspect, described herein are conjugates that comprise a metal chelator that is configured to bind with a radionuclide. The metal chelator can refer to a moiety of the conjugate that is configured to bind with a radionuclide. In some embodiments, a conjugate described herein comprises two or more independent metal chelators, e.g., 2, 3, 4, 5, or more metal chelators. In some embodiments, a conjugate described herein comprises two metal chelators, which can be the same or different. In some embodiments, a conjugate described herein comprises two or more metal chelators. In some embodiments, the conjugate comprises two radionuclides bound to the metal chelators. The metal chelator can be attached to the linker or the peptide through any suitable group/atom of the chelator.

[0260] In some embodiments, the metal chelator is capable of binding a radioactive atom. The binding can be direct, e.g., the metal chelator can make hydrogen bonds or electrostatic interactions with the radioactive atom. The binding can also be indirect, e.g., the metal chelator binds to a molecule that comprises a radioactive atom. In some embodiments, the metal chelator comprises, or is, a macrocycle. In some embodiments, the metal chelator comprises, or is, 2,2′,2″,2‴-(1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetrayl)tetraacetic acid (DOTA) or 1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA). In some embodiments, the metal chelator comprises a macrocycle, e.g., a macrocycle comprising an O and/or a N, DOTA, NOTA, one or more amines, one or more ethers, one or more carboxylic acids, EDTA, DTPA, TETA, DO3A, PCTA, or desferrioxamine.

[0261] In some embodiments, the metal chelator comprises a plurality of amines. In some embodiments, the metal chelator includes 4 or more N, 4 or more carboxylic acid groups, or a combination thereof. In some embodiments, the metal chelator does not comprise S. In some embodiments, the metal chelator comprises a ring. In some embodiments, the ring comprises an O and/or an N. In some embodiments, the metal chelator is a ring that includes 3 or more N, 3 or more carboxylic acid groups, or a combination thereof. In some embodiments, the metal chelator is poly polydentate.

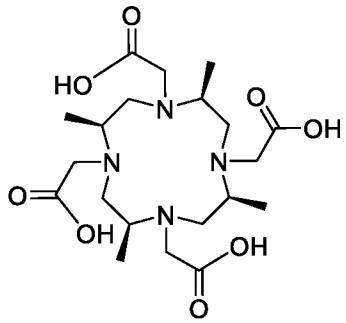
[0262] In some embodiments, a metal chelator described herein comprises a cyclic chelating agent. Exemplary cyclic chelating agents include, but are not limited to, AAZTA, BAT, BAT-

TM, Crown, Cyclen, DO2A, CB-DO2A, DO3A, H3HP-DO3A, Oxo-DO3A, p-NH_2-Bn-Oxo-DO3A, DOTA, DOTA-3py, DOTA-PA, DOTA-GA, DOTA-4AMP, DOTA-2py, DOTA-1py, p-SCN-Bn-DOTA, CHX-A″-EDTA, MeO-DOTA-NCS EDTA, DOTAMAP, DOTAGA, DOTAGA-anhydride, DOTMA, DOTASA, DOTAM, DOTP, CB-Cyclam, TE2A, CB-TE2A, CB-TE2P, DM-TE2A, MM-TE2A, NOTA, NOTP, HEHA, HEHA-NCS, p-SCN-Bn-HEHA, DTPA, CHX-A″-DTPA, p-NH_2-Bn-CHX-A″-DTPA, p-SCN-DTPA, p-SCN-Bz-Mx-DTPA, 1B4M-DTPA, p-SCN-Bn1B-DTPA, p-SCN-Bn-1B4M-DTPA, p-SCN-Bn-CHX-A″-DTPA, PEPA, p-SCN-Bn-PEPA, TETPA, DOTPA, DOTMP, DOTPM, t-Bu-calix[4]arene-tetracarboxylic acid, macropa, macropa-NCS, macropid, H_3L^1, H_3L^4, H_2azapa, H_5decapa, bispa^2, H_4pypa, H_4octapa, H_4CHXoctapa, p-SCN-Bn-H_4octapa, p-SCN-Bn-H_4octapa, TTHA, p-NO_2-Bn-neunpa, H_4octox, H_2macropa, H_2bispa^2, H_4phospa, H_6phospa, p-SCN-Bn-H_6phospa, TETA, p-NO_2-Bn-TETA, TRAP, TPA, HBED, SHBED, HBED-CC, (HBED-CC)TFP, DMSA, DMPS, DHLA, lipoic acid, TGA, BAL, Bis-thioseminarabazones, p-SCN-NOTA, nNOTA, NODAGA, CB-TE1A1P, 3P-C-NETA-NCS, 3p-C-DEPA, 3P-C-DEPA-NCS, TCMC, PCTA, NODIA-Me, TACN, pycup1A1B, pycup2A, THP, DEDPA, H_2DEDPA, p-SCN-Bn-H_2DEDPA, p-SCN-Bn-TCMC, motexafin, NTA, NOC, 3p-C-NETA, p-NH_2-Bn-TE3A, SarAr, DiAmSar, SarAr-NCS, AmBaSar, BaBaSar, TACN-TM, CP256, C-NE3TA, C-NE3TA-NCS, NODASA, NETA-monoamide, C-NETA, NOPO, BPCA, p-SCN-Bn-DFO, DFO-ChX-Mal, DFO, DFO-IAC, DFO-BAC, DiP-LICAM, EC, SBAD, BAPEN, TACHPYR, NEC-SP, L^{py}, L1, L2, L3, and EuK-106. In some embodiments, the metal chelator is DOTA, TRITA, TETA, DOTA-MA, DO3A-HP, DOTMA, DOTA-pNB, DOTP, DOTMP, DOTEP, DOTMPE, F-DOTPME, DOTPP, DOTBzP, DOTA-monoamide, p-NCS-DOTA, p-NCS-PADOTA, BAT, DO3TMP-Monoamide, p-NCS-TRITA, NOTA, and CHX-A″-DTPA. In some embodiments, a metal chelator described herein comprises an acyclic chelating agent. Exemplary acyclic chelating agents include, but are not limited to, DTA, CyEDTA, EDTMP, DTPMP, DTPA, CyDTPA, Cy2DTPA, DTPA-MA, DTPA-BA, and BOPA. In some embodiments, a metal chelator described herein comprises DOTA, DOTP, DOTMA, DOTAM, DTPA, NTA, EDTA, DO3A, DO2A, NOC, NOTA, TETA, TACN, DiAmSar, CB-Cyclam, CB-TE2A, DOTA-4AMP, or NOTP. In some embodiments, a metal chelator described herein comprises H_4pypa, H_4octox, H_4octapa, p-NO_2-Bn-neunpa, p-SCN–Bn–H_4neunpa, TTHA, ^{t}Bu$_4$pypa-C7-NHS, H_4neunpa, H_2macropa, HP-DO3A, BT-DO3A, DO3A-Nprop, DO3AP, DO2A2P, DOA3P, DOTP, DOTPMB, DOTAMAE, DOTAMAP, DO3AM^{Bu}, DOTMA, TCE-DOTA, DEPA, PCTA, p-NO_2-Bn-PCTA, p-NO_2-Bn-DOTA, symPC2APA, symPCA2PA, asymPC2APA, asymPCA2PA, TRAP, AAZTA, DATA^m, THP, HEHA, or HBED.

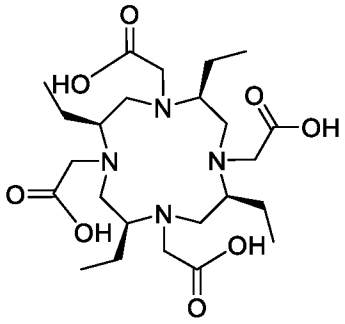
[0263] In some embodiments, the metal chelator is DO3A. In some embodiments, the metal chelator is PEPA. In some embodiments, the metal chelator is EDTA. In some embodiments, the

metal chelator is CHX-A″-DTPA. In some embodiments, the metal chelator is HEHA. In some embodiments, the metal chelator is DOTMP. In some embodiments, the metal chelator is t-Bu-calix[4]arene-tetracarboxylic acid. In some embodiments, the metal chelator is macropa. In some embodiments, the metal chelator is macropa-NCS. In some embodiments, the metal chelator is H_4pypa. In some embodiments, the metal chelator is H_4octapa. In some embodiments, the metal chelator is H_4CHXoctapa. In some embodiments, the metal chelator is DOTP. In some embodiments, the metal chelator is crown.

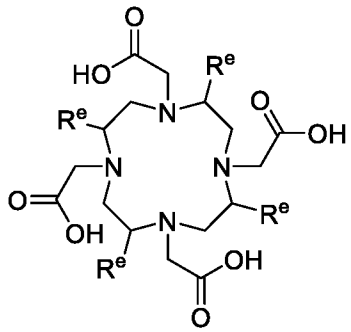
[0264] In some embodiments, the metal chelator is DOTA. In some embodiments, the metal chelator is a chiral derivative of DOTA. Exemplary chiral DOTA chelators are described in Dai et al., Nature Communications (2018) 9:857. In some embodiments, the metal chelator is 2,2',2",2'"-((2S,5S,8S,11S)-2,5,8,11-tetramethyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrayl)tetraacetic acid. In some embodiments, the metal chelator has a structure of



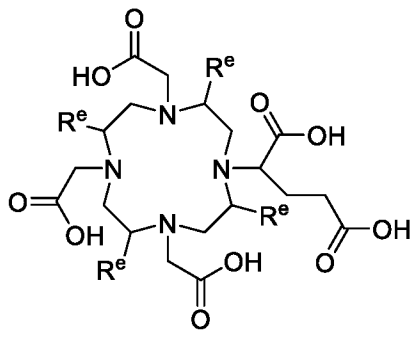
. In some embodiments, the metal chelator is 2,2',2",2'"-((2S,5S,8S,11S)-2,5,8,11-tetraethyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrayl)tetraacetic acid. In some embodiments, the metal chelator has a structure of



.



[0265] In some embodiments, the metal chelator has a structure of , wherein each R^e is independently selected from hydrogen, alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkylcycloalkyl, alkylheterocycloalkyl, alkylaryl, alkylheteroaryl, or an amino acid side chain. In

some embodiments, the metal chelator has a structure of  wherein each R^e is independently selected from hydrogen, alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkylcycloalkyl, alkylheterocycloalkyl, alkylaryl, alkylheteroaryl, or an amino acid side chain.

[0266] In some embodiments, the conjugate comprises DOTA. In some embodiments, the conjugate comprises a DOTA derivative such as p-SCN-Bn-DOTA and MeO-DOTA-NCS. In some embodiments, the conjugate comprises two independent metal chelators, and at least one or both are DOTA. The structures of some exemplary metal chelators are illustrated in FIGs. 3-17 (without showing the attachment points). Exemplary metal chelators are further described in WO2012/174136; US20130183235A1; US20120219495A1; Ramogidaand et al., EJNMMI radiopharm. chem. 4, 21 (2019); Thiele et al., Cancer Biotherapy and Radiopharmaceuticals 2018; Li et al., Bioconjugate Chem. 2019, 30, 5, 1539–1553; and Baranyai et al., Eur. J. Inorg. Chem. 36–56 (2020), each of which is incorporated by reference in its entirety.

Radionuclides

[0267] In one aspect, described herein are conjugates that comprise a radionuclide. Generally, the type of radionuclide used in a therapeutic radiopharmaceutical can be tailored to the specific type of cancer, the type of targeting moiety (e.g., binding peptide), etc. Radionuclides that undergo α-decay produce particles composed of two neutrons and two protons, and radionuclides that undergo β-decay emit energetic electrons from their nuclei. Some radionuclides can also emit Auger. In some embodiments, the conjugate comprises an alpha particle-emitting radionuclide. Alpha radiation can cause direct, irreparable double-strand DNA breaks compared with gamma and beta radiation, which can cause single-stranded breaks via indirect DNA damage. The range of these particles in tissue and the half-life of the radionuclide can also be considered in designing the radiopharmaceutical conjugate. Tables 5A and 5B below illustrate some properties of exemplary radionuclides.

Table 5A. Exemplary radionuclides

Nuclide	Emission	Half-life (days)
Actinium-225 (Ac-225)	α	about 10.0

Lutetium (Lu-177)	β	about 6.7
Radium-223	α	about 11.4
Radium-224	α	about 3.63
Astatine-211	α	about 0.3
Yttrium-90	β	about 2.7
Samarium-153	β	about 1.9
Lead-212	β	about 0.4
Bismuth-212	α	about 0.04
Thorium-227	α	about 18.7
Terbium-149	α	about 0.17

Table 5B. Exemplary radionuclides

Nuclide	Half-life
Lutetium-177 (Lu-177)	about 6.7 days
Indium-111 (In-111)	about 2.8 days
Gallium-68 (Ga-68)	about 68 minutes
Copper-64 (Cu-64)	about 12.7 hours
Zirconium-89 (Zr-89)	about 78.4 hours
Cerium-134 (Ce-134)	about 3.2 days

[0268] In some embodiments, a conjugate described herein comprises one or more independent radionuclides. In some embodiments, the conjugate comprises two radionuclides. In some embodiments, each of the one or more radionuclides is bound to a metal chelator of the conjugate. In some embodiments, two radionuclides of a conjugate are bound to the same metal chelator. In some embodiments, two radionuclides of a conjugate are bound to two independent metal chelators. In some embodiments, each of the one or more radionuclides is an alpha particle-emitting radionuclide.

[0269] In some embodiments, a conjugate described herein comprises an alpha particle-emitting radionuclide. In some embodiments, the alpha particle-emitting radionuclide is actinium-225 (^{225}Ac), astatine-211 (^{211}At), radium-223 (^{223}Ra), radium-224 (^{224}Ra), bismuth-213 (^{213}Bi), Terbium-149 (^{149}Tb), or thorium-227 (^{227}Th). In some embodiments, the alpha particle-emitting radionuclide is ^{225}Ac. In some embodiments, the alpha particle-emitting radionuclide is ^{213}Bi. In some embodiments, the alpha particle-emitting radionuclide is ^{212}Bi. In some embodiments, the

alpha particle-emitting radionuclide is ^{212}Pb. In some embodiments, the alpha particle-emitting radionuclide is ^{224}Ra. In some embodiments, the alpha particle-emitting radionuclide is ^{223}Ra. In some embodiments, the alpha particle-emitting radionuclide is ^{227}Th. In some embodiments, the alpha particle-emitting radionuclide is ^{211}At. In some embodiments, the alpha particle-emitting radionuclide is ^{149}Tb. In some embodiments, the radionuclide is Zirconium-89 (^{89}Zr). In some embodiments, a conjugate described herein comprises a radionuclide selected from ^{67}Cu, ^{64}Cu, ^{90}Y, ^{109}Pd, ^{111}Ag, ^{149}Pm, ^{153}Sm, ^{166}Ho, ^{99m}Tc, ^{67}Ga, ^{68}Ga, ^{111}In, ^{90}Y, ^{177}Lu, ^{186}Re, ^{188}Re, ^{197}Au, ^{198}Au, ^{199}Au, ^{105}Rh, ^{165}Ho, ^{161}Tb, ^{149}Pm, ^{44}Sc, ^{47}Sc, ^{70}As, ^{71}As, ^{72}As, ^{73}As, ^{74}As, ^{76}As, ^{77}As, ^{212}Pb, ^{212}Bi, ^{213}Bi, ^{225}Ac, ^{117m}Sn, ^{67}Ga, ^{201}Tl, ^{123}I, ^{131}I, ^{160}Gd, ^{148}Nd, ^{89}Sr, ^{89}Zr, and ^{211}At. In some embodiments, the radionuclide is ^{225}Ac. In some embodiments, the radionuclide is a decay daughter of ^{225}Ac such as ^{221}Fr, ^{217}At, ^{213}Bi, ^{213}Po, ^{209}Tl, ^{209}Pb, or ^{209}Bi. In some embodiments, the conjugate comprises two ^{225}Ac radionuclides. In some embodiments, the radionuclide is ^{177}Lu. In some embodiments, the conjugate comprises two ^{177}Lu radionuclides.

[0270] In some embodiments, the conjugate comprises an alpha particle-emitting radionuclide bound to the metal chelator. In some embodiments, the alpha particle-emitting radionuclide is actinium-225, astatine-211, thorium-227, or radium-223. In some embodiments, the alpha particle-emitting radionuclide is actinium-225.

[0271] In some embodiments, the conjugate comprises a beta particle-emitting radionuclide bound to the metal chelator. In some embodiments, the beta particle emitting radionuclide is zircronium-89, yttrium-90, samarium-153, lutetium-177, or lead-212.

[0272] In some embodiments, the conjugate comprises a gamma particle emitting radionuclide. In some embodiments, the gamma particle emitting radionuclide is indium-111.

[0273] In some embodiments, conjugates described herein do not contain any radionuclide, i.e., a cold conjugate. For example, in some cases, a radionuclide can be replaced with a surrogate (e.g., ^{225}Ac replaced with lanthanum) for testing and experimental purposes.

Conjugates Comprising non-radioactive Drugs

[0274] In one aspect, described herein is a conjugate that comprises a GCC binding peptide, a non-radioactive drug, and optionally a linker. In some embodiments, the conjugate further comprises a metal chelator and optionally a radionuclide bound to the metal chelator. The non-radioactive drug can be a toxin. In some embodiments, the toxin is selected from *pseudomonas* exotoxin (PE), deBouganin, Bouganin, diphtheria toxin (DT) and ricin. The non-radioactive drug can be a chemotherapy agent.

[0275] The non-radioactive drug can be a cytotoxic drug. Exemplary cytotoxic drugs include aplidin, azaribine, anastrozole, azacytidine, bleomycin, bortezomib, bryostatin-1, busulfan,

calicheamycin, camptothecin, 10-hydroxycamptothecin, carmustine, celebrex, chlorambucil, cisplatin, irinotecan (CPT-11), SN-38, carboplatin, cladribine, cyclophosphamide, cytarabine, dacarbazine, docetaxel, dactinomycin, daunomycin glucuronide, daunorubicin, dexamethasone, diethylstilbestrol, doxorubicin, 2-pyrrolinodoxorubicin (2P-DOX), cyano-morpholino doxorubicin, doxorubicin glucuronide, epirubicin glucuronide, ethinyl estradiol, estramustine, etoposide, etoposide glucuronide, etoposide phosphate, floxuridine (FUdR), 3′,5′-O-dioleoyl-FudR (FUdR-dO), fludarabine, flutamide, fluorouracil, fluoxymesterone, gemcitabine, hydroxyprogesterone caproate, hydroxyurea, idarubicin, ifosfamide, L-asparaginase, leucovorin, lomustine, mechlorethamine, medroprogesterone acetate, megestrol acetate, melphalan, mercaptopurine, 6-mercaptopurine, methotrexate, mitoxantrone, mithramycin, mitomycin, mitotane, phenyl butyrate, prednisone, procarbazine, paclitaxel, pentostatin, PSI-341, semustine streptozocin, tamoxifen, taxanes, taxol, testosterone propionate, thalidomide, thioguanine, thiotepa, teniposide, topotecan, uracil mustard, velcade, vinblastine, vinorelbine, vincristine, ricin, abrin, ribonuclease, onconase, rapLR1, DNase I, Staphylococcal enterotoxin-A, pokeweed antiviral protein, gelonin, diphtheria toxin, *Pseudomonas* exotoxin, *Pseudomona* endotoxin, or combinations of these.

[0276] In some embodiments, the non-radioactive drug is selected from duocarmycin and its analogues, dolastatins, combretastatin, calicheamicin, N-acetyl-□-calicheamycin (CMC), a calicheamycin derivative, maytansine and analogues thereof, DM-I, auristatin E, auristatin EB (AEB), auristatin EFP (AEFP), monomethyl auristatin E (MMAE), monomethyl auristatin F (MMAF), tubulysin, disorazole, the epothilones, Paclitaxel, docetaxel, Topotecan, echinomycin, estramustine, cemadotine, eleutherobin, methopterin, actinomycin, daunorubicin, the daunorubicin conjugates, mitomycin C, mitomycin A, vincristine, retinoic acid, camptothecin, a camptothecin derivative, SN38, maytansine, a derivative of the maytansinoid type, DM1, DM4, TK1, amanitin, a pyrrolobenzodiazepine, a pyrrolobenzodiazepine dimer, methotrexate, ilomedine, aspirin, an IMIDs, lenalidomide, pomalidomide.

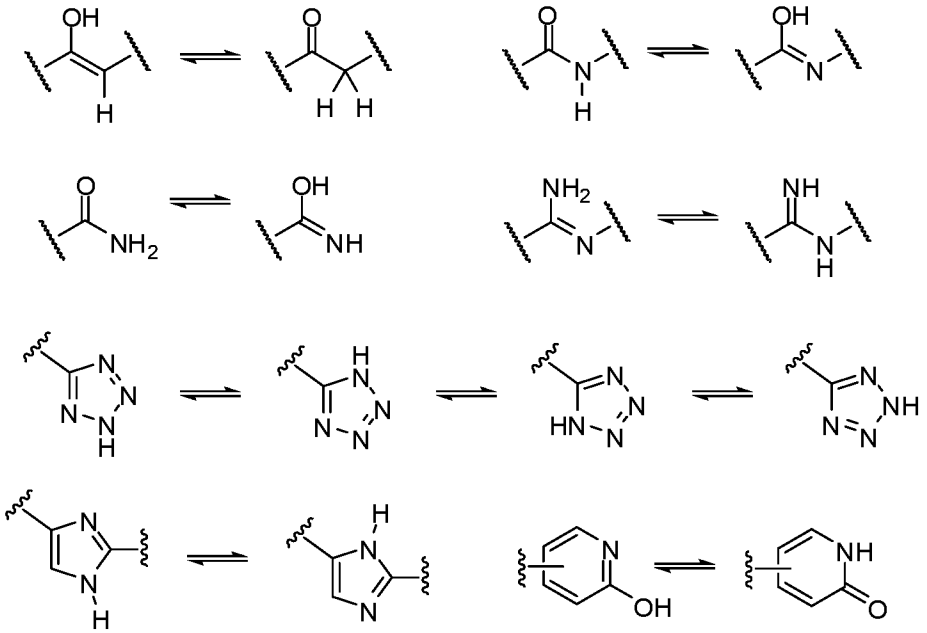
Isomers/Stereoisomers

[0277] In some embodiments, the compounds described herein exist as geometric isomers. In some embodiments, the compounds described herein possess one or more double bonds. The compounds presented herein include cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the corresponding mixtures thereof. In some situations, the compounds described herein possess one or more chiral centers and each center exists in the R configuration or S configuration. The compounds described herein include diastereomeric, enantiomeric, and epimeric forms as well as the corresponding mixtures thereof. In additional embodiments of the

compounds and methods provided herein, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion are useful for the applications described herein. In some embodiments, the compounds described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers, and recovering the optically pure enantiomers. In some embodiments, dissociable complexes are preferred. In some embodiments, the diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and are separated by taking advantage of these dissimilarities. In some embodiments, the diastereomers are separated by chiral chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. In some embodiments, the optically pure enantiomer is then recovered, along with the resolving agent.

Tautomers

[0278] A "tautomer" refers to a molecule wherein a proton shift from one atom of a molecule to another atom of the same molecule is possible. The compounds presented herein, in certain embodiments, exist as tautomers. In circumstances where tautomerization is possible, a chemical equilibrium of the tautomers will exist. The exact ratio of the tautomers depends on several factors, including physical state, temperature, solvent, and pH. Some examples of tautomeric equilibrium include:



[0279] In some instances, the compounds disclosed herein exist in tautomeric forms. The structures of said compounds are illustrated in the one tautomeric form for clarity. The alternative tautomeric forms are expressly included in this disclosure.

Labeled compounds

[0280] In some embodiments, the compounds described herein exist in their isotopically-labeled forms. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds as pharmaceutical compositions. Thus, in some embodiments, the compounds disclosed herein include isotopically-labeled compounds, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds described herein, or a solvate, or stereoisomer thereof, include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, and chloride, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Compounds described herein, and the pharmaceutically acceptable salts, solvates, or stereoisomers thereof which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this disclosure. Certain isotopically-labeled compounds, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H and carbon-14, i.e., ^{14}C, isotopes are notable for their ease of preparation and detectability. Further, substitution with heavy isotopes such as deuterium, *i.e.*, ^{2}H, produces certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements. In some embodiments, the isotopically labeled compound or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof is prepared by any suitable method.

[0281] In some embodiments, the compounds described herein are labeled by other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

Pharmaceutically acceptable salts

[0282] In some embodiments, the compounds described herein exist as their pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts as pharmaceutical compositions. As used herein, a “pharmaceutically acceptable salt” refers to any salt of a compound that is be useful for therapeutic purposes of a subject.

[0283] In some embodiments, the compounds described herein possess acidic or basic groups and therefore react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. In some embodiments, these salts are prepared *in situ* during the final isolation and purification of the compounds disclosed herein, or by separately reacting a purified compound in its free form with a suitable acid or base, and isolating the salt thus formed.

[0284] Examples of pharmaceutically acceptable salts include those salts prepared by reaction of the compounds described herein with a mineral acid, organic acid, or inorganic base, such salts including acetate, acrylate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, bisulfite, bromide, butyrate, butyn-1,4-dioate, camphorate, camphorsulfonate, caproate, caprylate, chlorobenzoate, chloride, citrate, cyclopentanepropionate, decanoate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hexyne-1,6-dioate, hydroxybenzoate, γ-hydroxybutyrate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isobutyrate, lactate, maleate, malonate, methanesulfonate, mandelate, metaphosphate, methanesulfonate, methoxybenzoate, methylbenzoate, monohydrogenphosphate, 1-napthalenesulfonate, 2-napthalenesulfonate, nicotinate, nitrate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, pyrosulfate, pyrophosphate, propiolate, phthalate, phenylacetate, phenylbutyrate, propanesulfonate, salicylate, succinate, sulfate, sulfite, succinate, suberate, sebacate, sulfonate, tartrate, thiocyanate, tosylate, undeconate, and xylenesulfonate.

[0285] Further, the compounds described herein can be prepared as pharmaceutically acceptable salts formed by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid, including, but not limited to, inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, metaphosphoric acid, and the like; and organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, p-toluenesulfonic acid, tartaric acid, trifluoroacetic acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, arylsulfonic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, and muconic acid.

[0286] In some embodiments, those compounds described herein which comprise a free acid group react with a suitable base, such as the hydroxide, carbonate, bicarbonate, or sulfate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary, tertiary, or quaternary amine. Representative salts include the alkali or alkaline earth salts, like lithium, sodium, potassium, calcium, and magnesium, and aluminum salts, and the like. Illustrative examples of bases include sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate, $N^+(C_{1-4}$ alkyl$)_4$, and the like.

[0287] Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, and the like. It should be understood that the compounds described herein also include the quaternization of any basic nitrogen-containing groups they contain. In some embodiments, water or oil-soluble or dispersible products are obtained by such quaternization.

Solvates

[0288] In some embodiments, the compounds described herein exist as solvates. This disclosure provides for methods of treating diseases by administering such solvates. This disclosure further provides for methods of treating diseases by administering such solvates as pharmaceutical compositions.

[0289] Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and, in some embodiments, are formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of the compounds described herein can be conveniently prepared or formed during the processes described herein. In addition, the compounds provided herein can exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein. Accordingly, one aspect of the present disclosure pertains to hydrates and solvates of compounds of the present disclosure and/or their pharmaceutical acceptable salts, as described herein, that can be isolated and characterized by methods known in the art, such as, thermogravimetric analysis (TGA), TGA-mass spectroscopy, TGA-Infrared spectroscopy, powder X-ray diffraction (PXRD), Karl Fisher titration, high resolution X-ray diffraction, and the like.

Preparation of the Compounds

[0290] The compounds used in the reactions described herein are made according to organic synthesis techniques known to those skilled in this art, starting from commercially available

chemicals and/or from compounds described in the chemical literature. "Commercially available chemicals" are obtained from standard commercial sources including Acros Organics (Pittsburgh, PA), Aldrich Chemical (Milwaukee, WI, including Sigma Chemical and Fluka), Apin Chemicals Ltd. (Milton Park, UK), Avocado Research (Lancashire, U.K.), BDH, Inc. (Toronto, Canada), Bionet (Cornwall, U.K.), Chem Service Inc. (West Chester, PA), Crescent Chemical Co. (Hauppauge, NY), Eastman Organic Chemicals, Eastman Kodak Company (Rochester, NY), Fisher Scientific Co. (Pittsburgh, PA), Fisons Chemicals (Leicestershire, UK), Frontier Scientific (Logan, UT), ICN Biomedicals, Inc. (Costa Mesa, CA), Key Organics (Cornwall, U.K.), Lancaster Synthesis (Windham, NH), Maybridge Chemical Co. Ltd. (Cornwall, U.K.), Parish Chemical Co. (Orem, UT), Pfaltz & Bauer, Inc. (Waterbury, CN), Polyorganix (Houston, TX), Pierce Chemical Co. (Rockford, IL), Riedel de Haen AG (Hanover, Germany), Spectrum Quality Product, Inc. (New Brunswick, NJ), TCI America (Portland, OR), Trans World Chemicals, Inc. (Rockville, MD), and Wako Chemicals USA, Inc. (Richmond, VA).

[0291] Suitable reference books and treatises that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, "Synthetic Organic Chemistry", John Wiley & Sons, Inc., New York; S. R. Sandler et al., "Organic Functional Group Preparations," 2nd Ed., Academic Press, New York, 1983; H. O. House, "Modern Synthetic Reactions", 2nd Ed., W. A. Benjamin, Inc. Menlo Park, Calif. 1972; T. L. Gilchrist, "Heterocyclic Chemistry", 2nd Ed., John Wiley & Sons, New York, 1992; J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", 4th Ed., Wiley-Interscience, New York, 1992. Additional suitable reference books and treatises that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, Fuhrhop, J. and Penzlin G. "Organic Synthesis: Concepts, Methods, Starting Materials", Second, Revised and Enlarged Edition (1994) John Wiley & Sons ISBN: 3-527-29074-5; Hoffman, R.V. "Organic Chemistry, An Intermediate Text" (1996) Oxford University Press, ISBN 0-19-509618-5; Larock, R. C. "Comprehensive Organic Transformations: A Guide to Functional Group Preparations" 2nd Edition (1999) Wiley-VCH, ISBN: 0-471-19031-4; March, J. "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure" 4th Edition (1992) John Wiley & Sons, ISBN: 0-471-60180-2; Otera, J. (editor) "Modern Carbonyl Chemistry" (2000) Wiley-VCH, ISBN: 3-527-29871-1; Patai, S. "Patai's 1992 Guide to the Chemistry of Functional Groups" (1992) Interscience ISBN: 0-471-93022-9; Solomons, T. W. G. "Organic Chemistry" 7th Edition (2000) John Wiley & Sons, ISBN: 0-471-19095-0; Stowell, J.C., "Intermediate Organic Chemistry" 2nd Edition (1993) Wiley-Interscience, ISBN: 0-471-57456-2; "Industrial Organic Chemicals: Starting Materials and Intermediates: An Ullmann's Encyclopedia" (1999)

John Wiley & Sons, ISBN: 3-527-29645-X, in 8 volumes; "Organic Reactions" (1942-2000) John Wiley & Sons, in over 55 volumes; and "Chemistry of Functional Groups" John Wiley & Sons, in 73 volumes.

[0292] Specific and analogous reactants are optionally identified through the indices of known chemicals prepared by the Chemical Abstract Service of the American Chemical Society, which are available in most public and university libraries, as well as on-line. Chemicals that are known but not commercially available in catalogs are optionally prepared by custom chemical synthesis houses, where many of the standard chemical supply houses (*e.g.*, those listed above) provide custom synthesis services. A reference for the preparation and selection of pharmaceutical salts of the compounds described herein is P. H. Stahl & C. G. Wermuth "Handbook of Pharmaceutical Salts", Verlag Helvetica Chimica Acta, Zurich, 2002.

III. Pharmaceutical Compositions

[0293] The radiopharmaceutical conjugate described herein, including e.g., pharmaceutically acceptable salt or solvate thereof, can be administered per se as a pure chemical or as a component of a pharmaceutically acceptable formulation. In some embodiments, a conjugate described herein is combined with a pharmaceutically suitable or acceptable carrier selected on the basis of a chosen route of administration and standard pharmaceutical practice as described, for example, in *Remington: The Science and Practice of Pharmacy* (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)). Provided herein is a pharmaceutical composition comprising at least one conjugate described herein, or a stereoisomer, pharmaceutically acceptable salt, amide, ester, solvate, or N-oxide thereof, together with one or more pharmaceutically acceptable carriers. The carrier(s) (or excipient(s)) is acceptable or suitable if the carrier is compatible with the other ingredients of the composition and not deleterious to the recipient (*i.e.*, the subject or patient) of the composition.

[0294] In one aspect, the disclosure provides a pharmaceutical composition comprising a herein described conjugate, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient or carrier. In certain embodiments, the conjugate as described is substantially pure, in that it contains less than about 10%, less than about 5%, or less than about 1%, or less than about 0.1%, of other organic small molecules, such as unreacted intermediates or synthesis by-products that are created, for example, in one or more of the steps of a synthesis method.

[0295] Pharmaceutical compositions can include pharmaceutically acceptable carriers, diluents or excipients. Exemplary pharmaceutically acceptable carriers include solvents (aqueous or non-aqueous), solutions, emulsions, dispersion media, coatings, isotonic and absorption promoting or

delaying agents, compatible with pharmaceutical administration. Such formulations can be contained in a liquid; emulsion, suspension, syrup or elixir, or solid form; tablet (coated or uncoated), capsule (hard or soft), powder, granule, crystal, or microbead. Supplementary components (e.g., preservatives, antibacterial, antiviral and antifungal agents) can also be incorporated into the compositions. Pharmaceutical compositions can be formulated to be compatible with a particular local or systemic route of administration. Thus, pharmaceutical compositions include carriers, diluents, or excipients suitable for administration by particular routes.

[0296] The compounds and pharmaceutical compositions of the current disclosure can be administered by any suitable means, including oral, topical (including buccal and sublingual), rectal, vaginal, transdermal, parenteral, subcutaneous, intraperitoneal, intrapulmonary, intradermal, intrathecal and epidural and intranasal, and, if desired for local treatment, intralesional administration. The term parenteral as used herein includes e.g., subcutaneous, intravenous, intramuscular, intrasternal, intraperitoneal, and infusion techniques. The term parenteral also includes injections, into the eye or ocular, intravitreal, intrabuccal, transdermal, intranasal, into the brain, including intracranial and intradural, into the joints, including ankles, knees, hips, shoulders, elbows, wrists, and the like, and in suppository form. In certain embodiments, the compounds and/or formulations are administered orally. In certain embodiments, the compounds and/or formulations are administered by systemic administration. In certain embodiments, the compounds and/or formulations are administered parenterally. In certain embodiments, the compounds and/or formulations are administered locally at a targeted site.

[0297] In some embodiments, conjugates, or pharmaceutically acceptable salts or solvates thereof, and pharmaceutical compositions described herein are administered via parenteral injection as liquid solution, which can include other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, preservatives, or excipients. Parenteral injections can be formulated for bolus injection or continuous infusion. The pharmaceutical compositions can be in a form suitable for parenteral injection as a sterile suspension, solution or emulsion in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing or dispersing agents. Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water soluble form. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerin, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid, gentisic acid, or sodium bisulfite; surfactants such

as polysorbate 80; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. In some embodiments, the pharmaceutical composition comprises a reductant. The presence of a reductant can help minimize potential radiolysis. In some embodiments, the reductant is ascorbic acid, gentisic acid, sodium thiosulfate, citric acid, tartaric acid, or a combination thereof.

[0298] Pharmaceutical compositions comprising the conjugates or pharmaceutically acceptable salts or solvates thereof described herein can be prepared according to standard techniques and further comprise a pharmaceutically acceptable carrier. In some embodiments, normal saline can be employed as the pharmaceutically acceptable carrier. Other suitable carriers include, e.g., water, buffered water, 0.9% isotonic saline, 0.4% saline, 0.3% glycine, and the like, including glycoproteins for enhanced stability, such as albumin, lipoprotein, globulin, etc. These compositions can be sterilized by conventional sterilization techniques. The resulting aqueous solutions may be packaged for use or filtered under aseptic conditions and lyophilized. In some embodiments, the lyophilized preparation is combined with a sterile aqueous solution prior to administration. The compositions can contain pharmaceutically acceptable auxiliary substances as appropriate to approximate physiological conditions, such as pH adjusting and buffering agents, tonicity adjusting agents and the like, for example, sodium acetate, sodium lactate, sodium chloride, potassium chloride, calcium chloride, sodium lactate, sorbitan monolaurate, triethanolamine oleate, etc. Pharmaceutical compositions can be selected according to their physical characteristic, including, but not limited to fluid volumes, viscosities and other parameters in accordance with the particular mode of administration selected. The amount of conjugates administered can depend upon the particular targeting moiety used, the disease state being treated, the therapeutic agent being delivered, and the judgment of the clinician.

[0299] The concentration of the conjugates or pharmaceutically acceptable salts or solvates thereof described herein in the pharmaceutical formulations can vary. In some embodiments, the conjugate is present in the pharmaceutical composition from about 0.05% to about 1% by weight, about 1% to about 2% by weight, about 2% to about 5% by weight, about 5% to about 10% by weight, about 10% to about 30% by weight, about 30% to about 50% by weight, about 50% to about 75% by weight, or about 75% to about 99% by weight.

[0300] Pharmaceutical compositions are administered in a manner appropriate to the disease to be treated. An appropriate dose and a suitable duration and frequency of administration will be determined by such factors as the condition of the subject, the type and severity of the subject's disease, the particular form of the active ingredient, and the method of administration. In some

embodiments, an appropriate dose and treatment regimen provides the composition(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit (*e.g.*, an improved clinical outcome), or a lessening of symptom severity. Optimal doses are generally determined using experimental models and/or clinical trials. The optimal dose depends upon the body mass, weight, or blood volume of the subject.

[0301] The amount of conjugates or pharmaceutically acceptable salts or solvates thereof and/or pharmaceutical compositions administered can be sufficient to deliver a therapeutically effective dose of the particular subject. In some embodiments, conjugate dosages can be between about 0.1 pg and about 50 mg per kilogram of body weight, 1 μg and about 50 mg per kilogram of body weight, or between about 0.1 and about 10 mg/kg of body weight. Therapeutically effective dosages can also be determined at the discretion of a physician. By way of example only, the dose of the conjugate or a pharmaceutically acceptable salt or solvate thereof described herein for methods of treating a disease as described herein is about 0.001 mg/kg to about 1 mg/kg body weight of the subject per dose. In some embodiments, the dose of conjugate or a pharmaceutically acceptable salt or solvate thereof described herein for the described methods is about 0.001 mg to about 1000 mg per dose for the subject being treated. In some embodiments, a conjugate or a pharmaceutically acceptable salt or solvate thereof described herein is administered to a subject at a dosage of from about 0.01 mg to about 500 mg, from about 0.01 mg to about 100 mg, or from about 0.01mg to about 50 mg. In some embodiments, a conjugate or a pharmaceutically acceptable salt or solvate thereof described herein is administered to a subject at a dosage of about 0.01 picomole to about 1 mole, about 0.1 picomole to about 0.1 mole, about 1 nanomole to about 0.1 mole, or about 0.01 micromole to about 0.1 millimole. In some embodiments, a conjugate or a pharmaceutically acceptable salt or solvate thereof described herein is administered to a subject at a dosage of about 0.01 Gbq to about 1000 Gbq, about 0.5 Gbq to about 100 Gbq, or about 1 Gbq to about 50 Gbq. In some embodiments, the dose is administered once a day, 1 to 3 times a week, 1 to 4 times a month, or 1 to 12 times a year.

[0302] The pharmaceutical formulations can be packaged in unit dosage form for ease of administration and uniformity of dosage. A unit dosage form can refer to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the pharmaceutical carrier or excipient.

IV. Method of Treatment.

[0303] In one aspect, the disclosure provides methods of treating a disease or condition in a subject in need thereof. In some embodiments, the methods comprise administering a conjugate

or a pharmaceutically acceptable salt or solvate thereof described herein, or a pharmaceutical composition comprising the same to the subject in need thereof. In some embodiments, provided herein is a method of providing a therapeutic and/or prophylactic benefit to a subject in need thereof comprising administering a compound or pharmaceutical composition described herein.

[0304] In some embodiments, the methods comprise administering to a subject a therapeutically effective amount of a conjugate or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the conjugate or pharmaceutically acceptable salt or solvate thereof is administered in a pharmaceutical composition. In some embodiments, the subject has cancer. In some embodiments, the cancer is a solid tumor or hematological cancer.

[0305] In embodiments, the treatment is sufficient to reduce or inhibit the growth of the subject's tumor, reduce the number or size of metastatic lesions, reduce tumor load, reduce primary tumor load, reduce invasiveness, prolong survival time, or maintain or improve the quality of life.

[0306] In some embodiments, provided herein are methods for killing a cell comprising contacting the cell with a conjugate or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the cell expresses a guanylate cyclase C (GCC) receptor. In some embodiments, the conjugate or pharmaceutically acceptable salt or solvate thereof binds to a structure on the cell, e.g., GCC. In some embodiments, the conjugate or pharmaceutically acceptable salt or solvate thereof releases a number of alpha particles by natural radioactive decay. In some embodiments, the conjugate or pharmaceutically acceptable salt or solvate thereof releases a number of beta particles, gamma rays, and/or Auger electrons by natural radioactive decay. The conjugate described herein can kill a cell by radiation. In some embodiments, the conjugate kills the cell directly by radiation. In some embodiments, the radiation creates, in the cell, oxidized bases, abasic sites, single-stranded breaks, double-stranded breaks, DNA crosslink, chromosomal rearrangement, or a combination thereof. In some embodiments, the conjugate kills the cell by inducing double-stranded DNA breaks. In some embodiments, the released alpha particles are sufficient to kill the cell. In some embodiments, the released alpha particles are sufficient to stop cell growth. In some embodiments, the conjugate kills the cell indirectly via the production of reactive oxygen species (ROS) such as free hydroxyl radicals. In some embodiments, the conjugate kills the cell indirectly by releasing tumor antigens from one or more different cells, which can have vaccine effect. In some embodiments, the conjugate kills the cell by abscopal effect. In some embodiments, the cell is a cancer cell. In some embodiments, the method comprises killing a cell with an alpha-particle emitting radionuclide.

[0307] After contacting a cell, the described conjugate can be internalized by the cell. The internalization can be mediated by cell receptors, cell membrane endocytosis, etc. In some

embodiments, rapid internalization rate into cancer cells accompanied by a slow externalization rate can offer therapeutic benefit.

[0308] In one aspect, the disclosed conjugate or a pharmaceutically acceptable salt or solvate thereof is configured to treat cancer by ablating tumor cells. In some embodiments, the conjugate or a pharmaceutically acceptable salt or solvate thereof does not modulate the biology of the tumor cell and/or the surrounding stroma. In some embodiments, the conjugate or a pharmaceutically acceptable salt or solvate thereof does not modulate immune cells. In some embodiments, the ablating of tumor cells can lead to a downstream immunological cascade.

[0309] In one aspect, provided herein are methods and compositions for treating cancers. Cancer includes tissue and organ carcinogenesis including metastases such as for example gastrointestinal cancer, (e.g., gastric cancer, esophageal cancer, pancreatic cancer colorectal cancer, intestinal cancer, anal cancer, liver cancer, gallbladder cancer, or colon cancer; lung cancer; thyroid cancer; skin cancer (e.g., melanoma); oral cancer; urinary tract cancer (e.g. bladder cancer or kidney cancer); blood cancer (e.g. myeloma or leukemia) or prostate cancer. In some embodiments, the present disclosure provides methods and compositions for treating gastrointestinal cancer in a subject in need thereof by administering an effective amount of a GCC binding peptide conjugate to the subject. Non-limiting examples of gastrointestinal cancers that can be treated according to the methods of the present disclosure include gastric cancer, esophageal cancer, pancreatic cancer, lung cancer (small cell lung cancer and/or non small-cell lung cancer), colorectal cancer, intestinal cancer, anal cancer, liver cancer, gallbladder cancer, or colon cancer.

[0310] In one aspect, provided herein are methods and compositions for treating a GCC-expressing cancer. In some embodiments, the GCC-expressing cancer to be treated is a primary or metastatic cancer of gastrointestinal origin, such as colorectal cancer, stomach cancer, small intestine cancer, or esophageal cancer. In some embodiments, the GCC-expressing cancer to be treated is primary or metastatic pancreatic cancer. In some embodiments, the GCC-expressing cancer to be treated is primary or metastatic lung cancer, such as squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma. In some embodiments, the GCC-expressing cancer to be treated is a sarcoma, such as leiomyosarcoma or rhabdomyosarcoma. In some embodiments, the GCC-expressing cancer to be treated is a primary or metastasized neuroectodermal tumor, such as aphaechromotcytoma or a paraganglioma. In some embodiments, the GCC-expressing cancer is a primary or a metastasized bronchopulmonary or a gastrointestinal neuroendocrine tumor. In some embodiments, the cancer is colorectal cancer.

[0311] The method can be useful in treating a relevant disorder at any stage or subclassification. For example, method can be used to treat early or late stage colon cancer, or colon cancer of any of stages 0, I, IIA, IIB, IIIA, IIIB, IIIC, and IV.

Disease to be Imaged

[0312] In addition to the methods of treatment described above, the compounds and compositions described herein can be used to image, and/or as part of a treatment for, any disease in which GCC is expressed, and in which a doctor wants to deliver a therapeutic to the GCC expressing tissue. An example of this type of disease is cancer (e.g., a cancer described above). GCC is expressed, for example, in colorectal cancer, gastric cancer, pancreatic cancer, esophageal cancer, cancer of the gastroesophageal junction, small intestine cancer, lung cancer, soft tissue sarcomas such as leiomyosarcomas and rhabdomyosarcomas, gastrointestinal and bronchopulmonary neuroendocrine tumors, and neuroectodermal tumors, and metastases derived from GCC-expressing primary tumors. An example of the last category is a liver metastasis derived from a primary colorectal tumor. Conjugates for imaging applications, e.g., single-photon emission computed tomography (SPECT) and positron emission tomography (PET), can comprise a radionuclide suitable for use as imaging isotopes such as the isotopes in Table 5B.

[0313] Further provided herein are methods and compositions that distinguish between GCC-expressing tumors and non-GCC-expressing tumors. In some embodiments, the compounds can identify patients likely to respond to a GCC-targeted therapy, e.g., an anti-GCC antibody, e.g., an immunoconjugate comprising an anti-GCC antibody. Accordingly, the conjugate can be administered as a companion diagnostic for GCC-targeted therapy thereby informing whether a patient suffering from a proliferative disease such as cancer, or a gastrointestinal disorder such as inflammatory bowel syndrome, Crohn's Disease or constipation, or should be treated or not with a GCC-targeted therapy, based on the presence or absence, respectively, of GCC expression on the surface of or within the patient's cells or tissue. A patient having one more cells that express GCC on the cell surface or within the cell can be candidate for treatment with a GCC-targeted therapy.

[0314] In one aspect, described herein is a method of treatments that comprises administering a first conjugate and a second conjugate. The first conjugate can be used as companion diagnostics and the second conjugate can be used for therapeutics. In some embodiments, the first conjugate and the second conjugate have the same structure except for the radionuclide. In some embodiments, the first conjugate comprises a gamma particle emitting radionuclide. In some embodiments, the first conjugate comprises a radionuclide of Table 5B. In some embodiments, the first conjugate comprises a radionuclide selected from Lu-177, In-111, Ga-68, Cu-64, and Zr-

89. In some embodiments, the second conjugate comprises an alpha or beta-particle emitting radionuclide. In some embodiments, the second conjugate comprises a radionuclide of Table 5A. In some embodiments, the second conjugate comprises Ac-225.

Combination Therapy

[0315] In some embodiments, a GCC binding peptide conjugate described herein can be administered alone or in combination with one or more additional therapeutic agents. In some embodiments, the conjugate and a second therapeutic agent are administered in combination to prevent or treat inflammation, cancer and other disorders, particularly of the gastrointestinal tract.

[0316] For example, the combination therapy can include a composition comprising a conjugate described herein co-formulated with, and/or co-administered with, one or more additional therapeutic agents, e.g., one or more anti-cancer agents, e.g., cytotoxic or cytostatic agents, immune checkpoint inhibitors, hormone treatment, vaccines, and/or other immunotherapies. In some embodiments, the conjugate is administered in combination with other therapeutic treatment modalities, including surgery, radiation, cryosurgery, and/or chemotherapy. Such combination therapies may advantageously utilize lower dosages of the administered therapeutic agents, thus avoiding possible toxicities or complications associated with the various monotherapies.

[0317] When administered in combination, two (or more) different treatments can be delivered to the subject during the course of the subject's affliction with the disorder, e.g., the two or more treatments are delivered after the subject has been diagnosed with the disorder and before the disorder has been cured or eliminated. In some embodiments, the delivery of one treatment is still occurring when the delivery of the second begins, so that there is overlap. This is sometimes referred to herein as "simultaneous" or "concurrent delivery." In some embodiments, the delivery of one treatment ends before the delivery of the other treatment begins. In some embodiments of either case, the treatment is more effective because of combined administration. For example, the second treatment is more effective, e.g., an equivalent effect is seen with less of the second treatment, or the second treatment reduces symptoms to a greater extent, than would be seen if the second treatment were administered in the absence of the first treatment, or the analogous situation is seen with the first treatment. In some embodiments, delivery is such that the reduction in a symptom, or other parameter related to the disorder is greater than what would be observed with one treatment delivered in the absence of the other. The effect of the two treatments can be partially additive, wholly additive, or greater than additive. The delivery can be such that an effect of the first treatment delivered is still detectable when the second is delivered.

[0318] In some embodiments, the herein-described conjugate is used in combination with a chemotherapeutic agent, e.g., a DNA damaging chemotherapeutic agent. Non-limiting examples

of DNA damaging chemotherapeutic agents include topoisomerase I inhibitors (e.g., irinotecan, topotecan, camptothecin and analogs or metabolites thereof, and doxorubicin); topoisomerase II inhibitors (e.g., etoposide, teniposide, and daunorubicin); alkylating agents (e.g., melphalan, chlorambucil, busulfan, thiotepa, ifosfamide, carmustine, lomustine, semustine, streptozocin, decarbazine, methotrexate, mitomycin C, and cyclophosphamide); DNA intercalators (e.g., cisplatin, oxaliplatin, and carboplatin); DNA intercalators and free radical generators such as bleomycin; and nucleoside mimetics (e.g., 5-fluorouracil, capecitibine, gemcitabine, fludarabine, cytarabine, mercaptopurine, thioguanine, pentostatin, and hydroxyurea). In some embodiments, the herein-described conjugate is used in combination with a radiation sensitizer, which makes tumor cells more sensitive to radiation therapy. In some embodiments, the herein-described conjugate is used in combination with a DNA damage repair inhibitor (or DNA damage response (DDR) inhibitor).

[0319] In some embodiments, the method comprises administering a second agent that binds to a GCC receptor. In some embodiments, the method comprises administering a second agent that is a GCC receptor agonist. In some embodiments, the method comprises administering a second agent that is a GCC receptor antagonist. In some embodiments, a GCC binding peptide conjugate described herein is administered in combination with one or more of GCC binding peptides such as a GCC receptor agonist. In some embodiments, the GCC binding peptide conjugate is administered in combination with one or more of GCC binding peptides, wherein the one or more of GCC binding peptides comprises an amino acid sequence that has at least 85% identity to any one of SEQ ID NOs: 1-42. In some embodiments, the GCC binding peptide conjugate is administered in combination with one or more of GCC binding peptides, wherein the one or more of GCC binding peptides comprises an amino acid sequence that has at least 85% identity to any one of SEQ ID NOs: 1-19. In some embodiments, the GCC binding peptide conjugate is administered in combination with one or more of GCC binding peptides, wherein the one or more of GCC binding peptides consists of an amino acid sequence of any one of SEQ ID NOs: 1-42. In some embodiments, the GCC binding peptide conjugate is administered in combination with one or more of GCC binding peptides, wherein the one or more of GCC binding peptides consists of an amino acid sequence of any one of SEQ ID NOs: 1-19.

[0320] In some embodiments, a GCC binding peptide is co-administered in conjunction with the radiopharmaceutical. In some embodiments, a GCC binding peptide comprises an amino acid sequence that has at least 85% identity to any one of SEQ ID NOs: 1-42. In some embodiments, a GCC binding peptide consists of an amino acid sequence of any one of SEQ ID NOs: 1-42. In some embodiments, a GCC binding peptide comprises an amino acid sequence

that has at least 85% identity to any one of SEQ ID NOs: 1-19. In some embodiments, a GCC binding peptide consists of an amino acid sequence of any one of SEQ ID NOs: 1-19.

[0321] In some embodiments, a GCC binding peptide conjugate described herein is administered in combination with one or more of GCC binding peptides. In some embodiments, a GCC binding peptide conjugate described herein is administered with one or more of linaclotide, plecanatide and dolcantide. In some embodiments, the conjugate is administered in combination with linaclotide.

[0322] In some embodiment, the GCC binding peptide conjugate is administered in combination with one or more additional therapeutic agents selected from the group consisting of phosphodiesterase inhibitors, cyclic nucleotides (such as cGMP and cAMP), a laxative (such as SENNA, METAMUCIL, MIRALAX, PEG, or calcium polycarbophil), a stool softener, an anti-tumor necrosis factor alpha therapy for IBD (such as REMICADE, ENBREL, or HUMAIRA), anti-inflammatory drugs (such as COX-2 inhibitors, sulfasalazine, 5-ASA derivatives and NSAIDS), anti-GCC antibody molecules, and GCC receptor agonists. In certain embodiments, the GCC binding peptide conjugate is administered in combination with an effective dose of an inhibitor of cGMP-specific phosphodiesterase (cGMP-PDE). cGMP-PDE inhibitors include, for example, suldinac sulfone, zaprinast, motapizone, vardenifil, and sildenafil. When administered with a second therapeutic agent, the herein-described conjugate can be administered simultaneously or sequentially with the second agent, and they can be administered via the same or different routes.

[0323] In some embodiments, the conjugate is administered in combination with a treatment that increases urinary excretion. In one embodiment, the agent which increases urinary excretion, is administered prior to, concurrently with and/or after administration with the radiolabeled peptide. In one embodiment, the agent which ameliorates bladder toxicity associated with therapy is saline, e.g., intravenous saline, D5 half normal saline or D5 water.

[0324] In some embodiments, the subject is 4 to 100 years old. In some embodiments, the subject is 5 to 10, 5 to 15, 5 to 18, 5 to 25, 5 to 35, 5 to 45, 5 to 55, 5 to 65, 5 to 75, 10 to 15, 10 to 18, 10 to 25, 10 to 35, 10 to 45, 10 to 55, 10 to 65, 10 to 75, 15 to 18, 15 to 25, 15 to 35, 15 to 45, 15 to 55, 15 to 65, 15 to 75, 18 to 25, 18 to 35, 18 to 45, 18 to 55, 18 to 65, 18 to 75, 25 to 35, 25 to 45, 25 to 55, 25 to 65, 25 to 75, 35 to 45, 35 to 55, 35 to 65, 35 to 75, 45 to 55, 45 to 65, 45 to 75, 55 to 65, 55 to 75, or 65 to 75 years old. In some embodiments, the subject is at least 5, 10, 15, 18, 25, 35, 45, 55, or 65 years old. In some embodiments, the subject is at most 10, 15, 18, 25, 35, 45, 55, 65, or 75 years old.

[0325] Although the present disclosure and its advantages have been described in detail, it should be understood that various changes, substitutions and alterations can be made herein without departing from the spirit and scope of the disclosure as defined in the appended claims.

[0326] The present disclosure is further illustrated in the following Examples which are given for illustration purposes only and are not intended to limit the disclosure in any way.

EXAMPLES

A: Synthesis of the Compounds

[0327] Example A1: Experimental procedures

[0328] Solid phase peptide synthesis (SPPS) was performed in a standard manual reaction vessel under nitrogen. 2-CTC resin was purchased from Sunresin New Materials Co. (China). Fmoc protected amino acids were purchased from GL Biochem (China). HBTU and HATU were purchased from Highfine Biotech Co. (China). Piperidine was purchased from Damao Chemical Reagent Factory (China). The peptides and their derivatives were purified on a Gilson GX-281 preparative HPLC system using reverse-phase C18 columns (Gemini, 5 μm, 110 Å + luna, 10 μm, 100 Å) at 30 °C. HPLC solvents consisted of H_2O containing 0.075% trifluoroacetic acid (mobile phase A) and acetonitrile (mobile phase B).

[0329] High performance liquid chromatography (HPLC) analyses were performed on an Agilent 1260 series equipped with a binary pump G7112A, micro vacuum degasser, standard autosampler ALS G7129A, thermostatted column compartment TCC G7116A, variable wavelength detector VWD G7114A, and data were analyzed by OpenLab CDS 2.2 network workstation software from Agilent Technologies. HPLC solvents consisted of H_2O containing 0.1% trifluoroacetic acid (mobile phase A) and acetonitrile containing 0.075% trifluoroacetic acid (mobile phase B). Conditions: a Phenomenex Gemini-NX C-18 (5 μm, 110 Å, 4.6 × 250 mm) column was used with a flow rate of 1.0 mL/min.

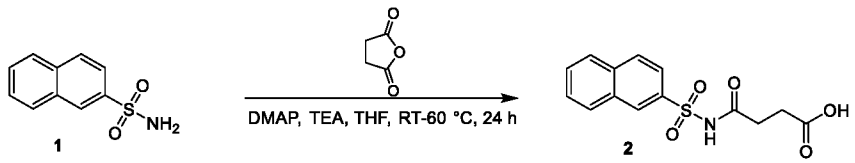
[0330] LC-MS analyses were carried out on an Agilent 1200 series coupled to an Agilent MSD G6125C, equipped with a binary pump G7112A, micro vacuum degasser, standard autosampler ALS G7129A, thermostatted column compartment TCC G7116A, variable wavelength detector VWD G7114A, and data were analyzed by OpenLab CDS 2.3 standalone workstation software from Agilent Technologies. HPLC solvents consisted of H_2O containing 0.1% trifluoroacetic acid (mobile phase A) and acetonitrile containing 0.075% trifluoroacetic acid (mobile phase B).

LC-MS conditions are as follows:

Method	Column	%B	Time (min)	Temp (°C)	Flow rate (mL/min)
A	Waters Xbridge C-18 (3.5 μm, 3.1× 30mm)	0-60	1	room temperature	1.2
B	Phenomenex Gemini C-18 110A (5 μm, 4.6× 150mm)	25-55	20	50	1.0
C	Phenomenex Gemini C-18 110A (5 μm, 4.6× 150mm)	10-80	20	70	1.0
D	Phenomenex Gemini C-18 110A (5 μm, 4.6× 150mm)	30-60	20	50	1.0
E	Phenomenex Gemini C-18 110A (5 μm, 4.6× 150mm)	15-45	20	50	1.0
F	Phenomenex Gemini C-18 110A (5 μm, 4.6× 150mm)	20-50	20	50	1.0
G	Phenomenex Gemini C-18 110A (5 μm, 4.6× 150mm)	10-40	20	70	1.0
H	Phenomenex Gemini C-18 110A (5 μm, 4.6× 150mm)	15-45	20	70	1.0
I	Agilent AdvancedBio Peptide Plus (2.7 μm, 2.1× 150mm)	5-95*	15	40	0.7

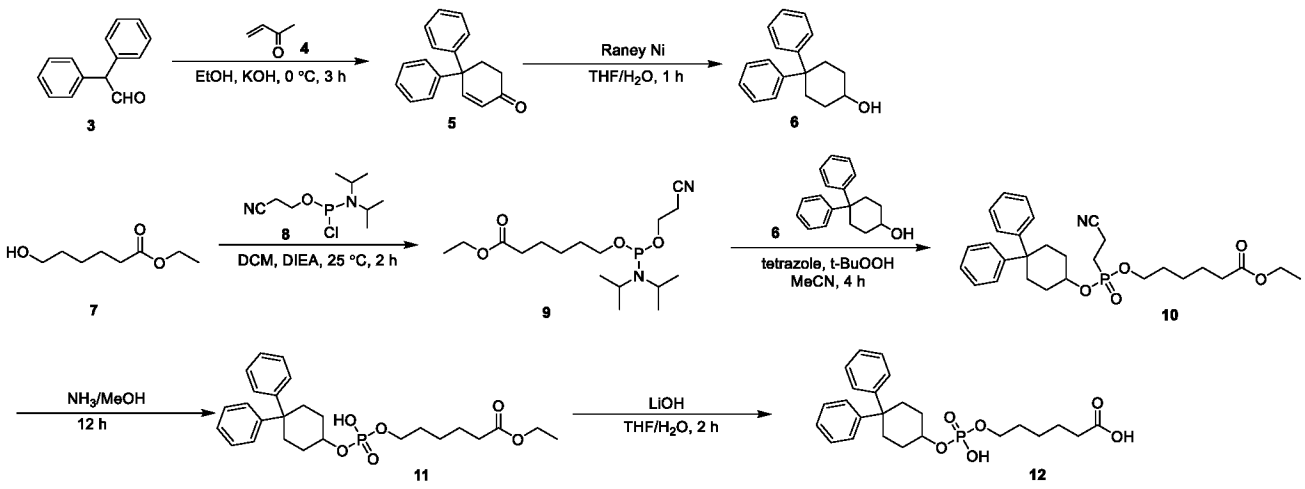
* Method I uses acetonitrile containing 0.0375% trifluoroacetic acid for mobile phase B.

*Example A-1: Synthesis of 4-(naphthalene-2-sulfonamido)-4-oxobutanoic acid (**2**)*



[0331] To a solution of sulfonamide **1** (10.0 g, 48.3 mmol) in THF (20.0 mL) under N_2 atmosphere were added DMAP (7.07 g, 57.9 mmol), TEA (5.86 g, 57.9 mmol) and succinic anhydride (5.79 g, 57.9 mmol). The reaction mixture was stirred for 18 h at room temperature and then refluxed for 6 h. The solvent was concentrated *in vacuo*, and the resulting residue was partitioned between ethyl acetate and hydrochloric acid (1.0 N). The layers were separated, and the organic layer was washed with brine and saturated aqueous $NaHCO_3$ solution. The basic aqueous layer was acidified with hydrochloric acid (1.0 N). The precipitate was collected through filtration and dried to give compound **2** (10.3 g, 27.6 mmol, 57.1%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.23 (s, 1H), 8.58 (s, 1 H), 8.22-8.15 (m, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 8.6 Hz, 1H), 7.74-7.72 (m, 1H), 7.70-7.69 (m, 2H), 2.46 (br d, J = 6.9 Hz, 2H), 2.38-2.31 (m, 2H); MS(ESI): *m/e* 308.0 $[M + H]^+$.

*Example A-2: Synthesis of 6-((((4,4-diphenylcyclohexyl)oxy)(hydroxy)phosphoryl)oxy)hexanoic acid (**12**)*



[0332] To a solution of aldehyde **3** (5.00 g, 25.5 mmol) and alkene **4** (3.34 g, 47.7 mmol) in EtOH (20.0 mL) at 0 °C was slowly added a pre-cooled solution of KOH (715 mg, 12.7 mmol) in EtOH (10.0 mL) over 10 min. The reaction mixture was stirred at 0 °C for 3 h. After the solvent was removed *in vacuo*, the residue was partitioned between H_2O (30.0 mL) and EtOAc (50.0 mL). The mixture was acidified to pH 3 with 2.0 M aqueous HCl. The layers were separated, and the organic fraction was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 5/1, R_f = 0.60). to afford ketone **5** (4.00 g, 16.1 mmol, 63.2%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 - 7.38 (m, 5 H), 7.23 - 7.29 (m, 6 H), 6.23 (d, J = 10.2 Hz, 1 H), 2.65 - 2.78 (m, 2 H), 2.44 (dd, J = 7.2, 5.6 Hz, 2 H).

[0333] An aqueous Raney-Ni (138 mg, 1.61 mmol) suspension, washed free of salt in advance, was added to ketone **5** (4.00 g, 16.1 mmol) in THF (50.0 mL). The resulting mixture was stirred vigorously at room temperature under hydrogen (50 psi) for 1 h. The mixture was filtered, and the filtrate was concentrated *in vacuo* to give alcohol **6** (4.00 g, 15.9 mmol, 98.4%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 - 7.41 (m, 2 H), 7.19 - 7.33 (m, 6 H), 7.06 - 7.17 (m, 2 H), 4.44 (d, J = 4.4 Hz, 1 H), 3.52 - 3.64 (m, 1 H), 2.56 - 2.69 (m, 2 H), 1.97 (br t, J = 11.2 Hz, 2 H), 1.69 (br dd, J = 10.0, 3.8 Hz, 2 H), 1.24 - 1.41 (m, 2 H).

[0334] The mixture of alcohol **7** (6.00 g, 37.5 mmol), 2-cyanoethyl *N*,*N*-diisopropylchlorophosphor-amidite **8** (9.31 g, 39.32 mmol) and DIEA (19.4 g, 150 mmol) in DCM (250 mL) was stirred at room temperature for 2 h. The mixture was washed with saturated aqueous $NaHCO_3$ solution (50.0 mL × 2). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 10/1, with 0.1 % TEA, Rf = 0.80) to afford Compound **9** (5.70 g, 15.8 mmol, 42.2%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.14 - 4.18 (m, 2 H), 3.84 - 3.63

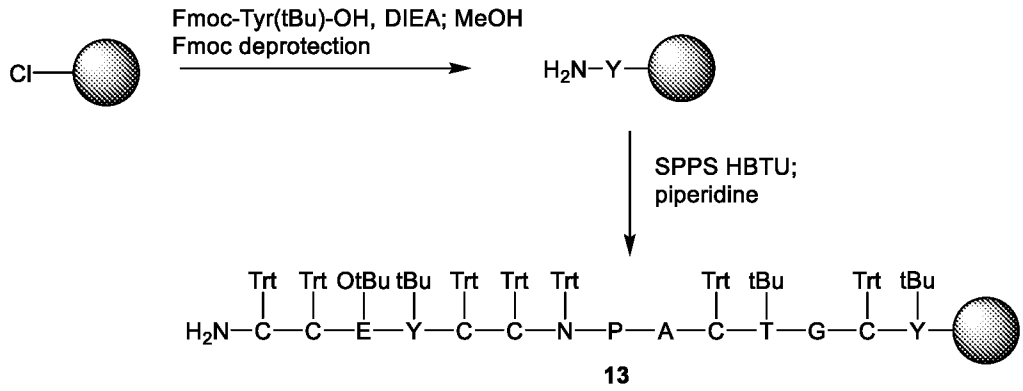
(m, 2 H), 3.61 - 3.55 (m, 4 H), 2.65 - 2.62 (m, 2 H), 2.31 - 2.27 (m, 2 H), 1.64 - 1.62 (m, 4 H), 1.39 - 1.26 (m, 2 H), 1.24 - 1.22 (m, 3 H), 1.18 - 1.01 (m, 12 H).

[0335] To a solution of Compound **9** (2.00 g, 5.55 mmol) and alcohol **6** (1.47 g, 5.83 mmol) in acetonitrile (30.0 mL) was added tetrazole (0.45 M, 13.0 mL). The resulting mixture was stirred under N_2 for 3 h. *t*-Butyl hydroperoxide (5.64 g, 43.8 mmol, 70% purity) was added, and the reaction was stirred at 25 °C for an additional 1 h. The mixture was quenched with saturated $Na_2S_2O_6$ solution (50.0 mL) and extracted with EtOAc (50.0 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 1/1 with 0.1% TEA, R_f = 0.10) to afford Compound **10** (1.50 g, 2.93 mmol, 52.8%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 - 7.32 (m, 7 H), 7.26 (br d, J = 7.4 Hz, 1 H), 7.11 - 7.20 (m, 2 H), 4.52 - 4.62 (m, 1 H), 4.20 (dt, J = 8.0, 6.2 Hz, 2 H), 4.14 (br s, 1 H), 4.05 - 4.16 (m, 3 H), 2.74 (t, J = 6.2 Hz, 2 H), 2.52 - 2.59 (m, 2 H), 2.19 - 2.34 (m, 4 H), 1.90 - 2.00 (m, 2 H), 1.77 - 1.88 (m, 2 H), 1.59 - 1.76 (m, 5 H), 1.39 - 1.46 (m, 2 H), 1.22 - 1.26 (m, 2 H), 1.21 - 1.26 (m, 1 H).

[0336] Compound **10** (1.50 g, 2.93 mmol) was dissolved in ammonia (50.0 mL, 2.00 M in MeOH). The mixture was stirred at 25 °C for 12 h under N_2 and concentrated *in vacuo* to afford **11** (1.39 g, 2.93 mmol, 100%) as a colorless oil. The crude product was used directly in the next step. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 - 7.33 (m, 8 H), 7.09 - 7.20 (m, 2 H), 4.25 (dt, J = 7.8, 3.8 Hz, 1 H), 4.04 - 4.15 (m, 2 H), 3.76 - 3.84 (m, 2 H), 2.52 - 2.60 (m, 2 H), 2.23 - 2.32 (m, 2 H), 2.14 (br t, J = 10.6 Hz, 2 H), 1.82 - 1.94 (m, 2 H), 1.68 (br d, J = 8.4 Hz, 2 H), 1.64 (br s, 4 H), 1.33 - 1.42 (m, 2 H), 1.27 - 1.32 (m, 1 H), 1.21 - 1.27 (m, 3 H).

[0337] To a solution of Compound **11** (1.39 g, 2.93 mmol) in THF (20.0 mL) and H_2O (2.00 mL) was added $LiOH \cdot H_2O$ (246 mg, 5.86 mmol). The mixture was stirred at 25 °C for 2 h. The volatiles were removed *in vacuo* and water (20.0 mL) was added. The mixture was washed with EtOAc (20 mL × 3), acidified with HCl (1.0 N) until pH < 7 and extracted with EtOAc (20.0 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give acid **12** (1.20 g, 2.60 mmol, 88.8%, 96.8% purity) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 - 7.29 (m, 8 H), 7.08 - 7.19 (m, 2 H), 4.47 (dt, J = 6.8, 3.6 Hz, 1 H), 4.00 (q, J = 6.6 Hz, 2 H), 2.49 - 2.60 (m, 2 H), 2.33 (t, J = 7.2 Hz, 2 H), 2.15 - 2.26 (m, 2 H), 1.79 - 1.95 (m, 4 H), 1.61 - 1.71 (m, 4 H), 1.38 - 1.47 (m, 2 H); MS (ESI): *m/e* 447.4 $[M + H]^+$.

*Example A-3: Synthesis of peptidyl-resin **13**. Example discloses SEQ ID NO: 46*

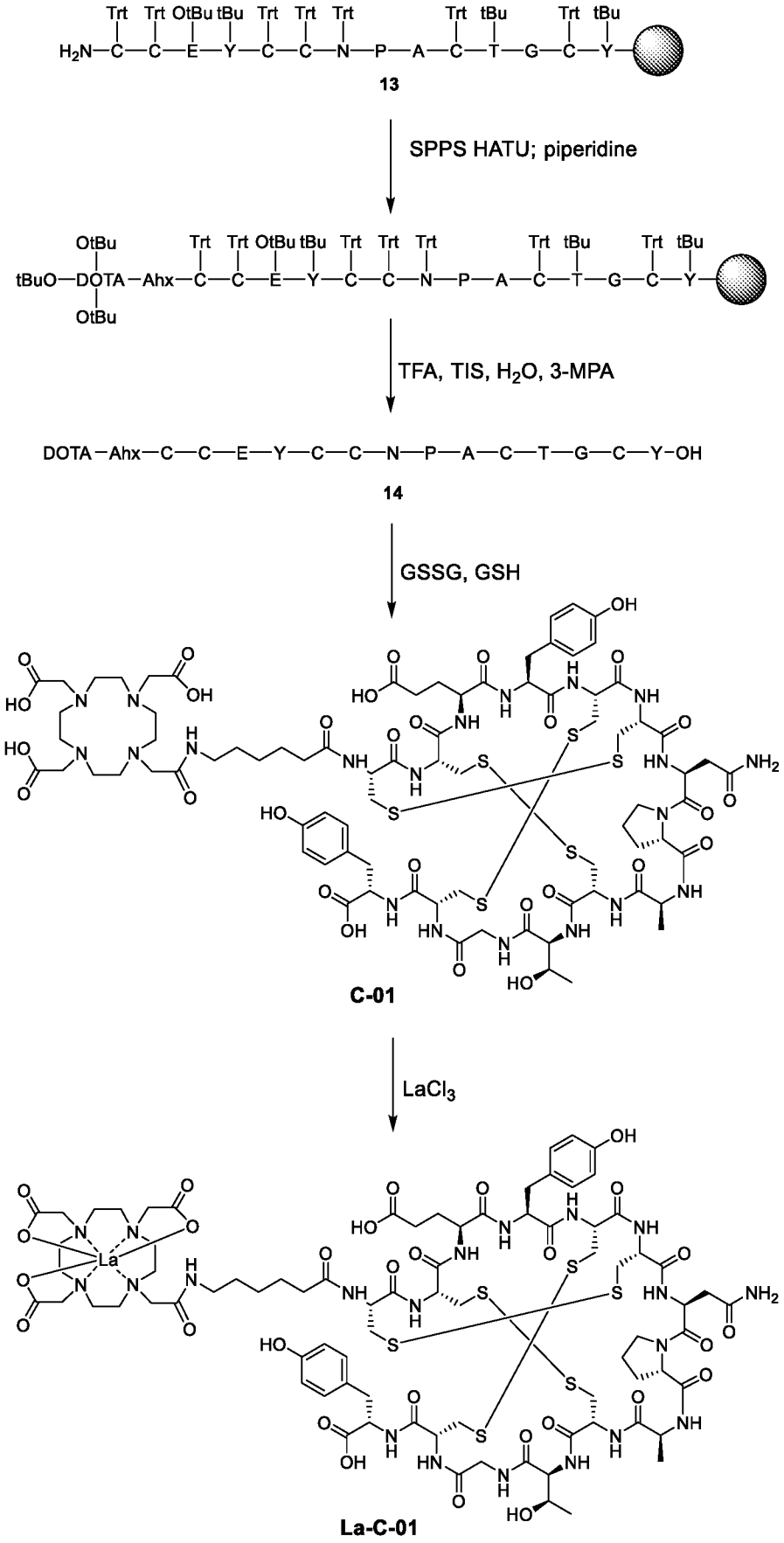


13

[0338] To the swollen 2-CTC resin (0.50 mmol, 1.10 mmol/g, 1.00 equiv) were added Fmoc-Tyr(tBu)-OH (0.23 g, 0.50 mmol) and DIEA (0.35 mL, 2.00 mmol) in DCM (4.00 mL). The mixture was agitated for 2 h under nitrogen. MeOH (0.50 mL) was then added. The resulting mixture was agitated for 30 min. After the reaction solution was removed through filtration, the resin was washed three times with DMF (10 mL). The Fmoc protecting group was removed via 30 min agitation with 20% piperidine in DMF followed by filtration and washing.

[0339] Subsequent amino acids were coupled using Fmoc-protected amino acid (3.00 equiv), HBTU (2.85 equiv) and DIEA (6.00 equiv) in dry DMF, shaking for 30 min. Pre-activation of any amino acid was not performed prior to coupling. Between amino acid couplings, the Fmoc protecting group was removed via 30 min agitation with 20% piperidine in DMF followed by filtration and washing. Success of Fmoc removal steps and amino acid couplings were monitored qualitatively using a ninhydrin test.

[0340] **Example A2: Synthesis of C-01 and La-C-01**. Example discloses SEQ ID NOS 46-48, respectively, in order of appearance.



[0341] Fmoc-Ahx-OH (2.00 equiv), HATU (1.90 equiv) and DIEA (4.00 equiv) were dissolved in dry DMF. The solution was mixed with the resin-bound peptide and then agitated for 30 min

under nitrogen. The resin was then washed three times with DMF. Fmoc removal was carried out while the peptide was on resin using 20% piperidine in DMF followed by filtration and washing.

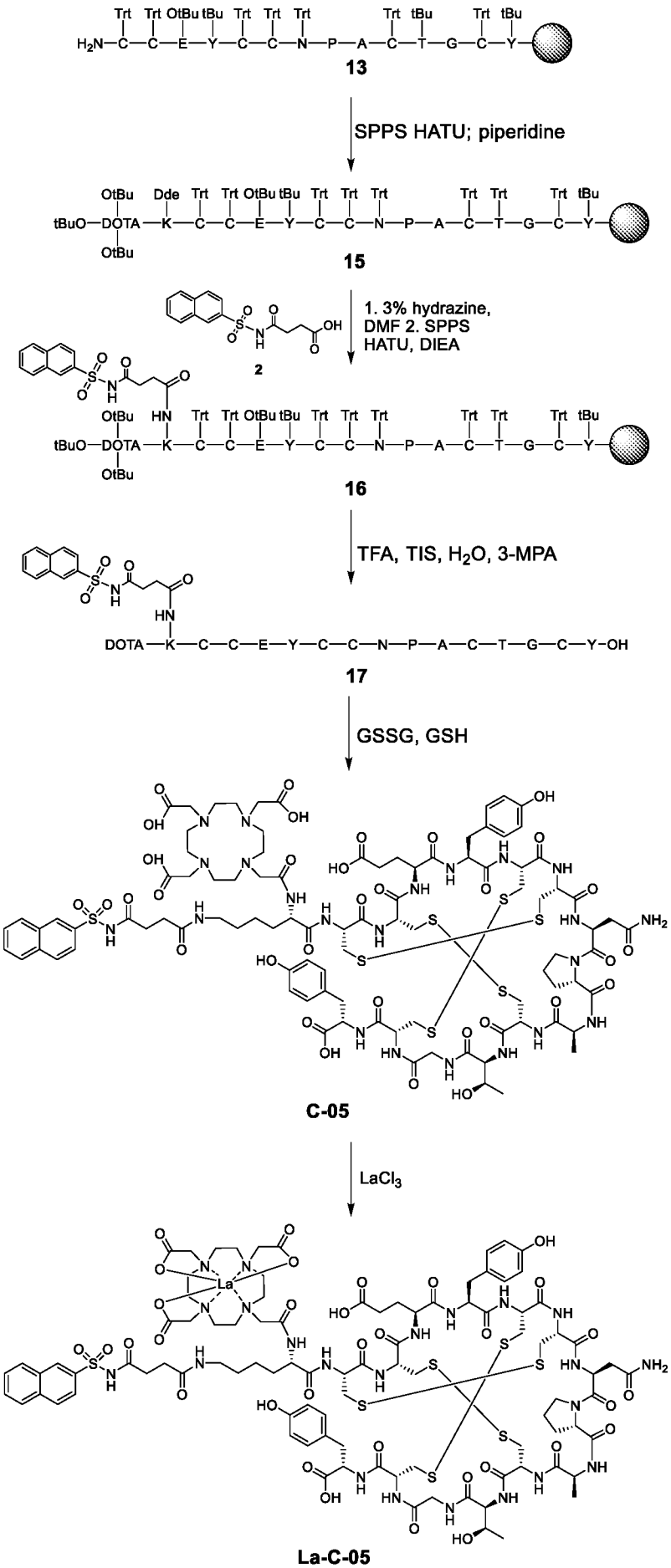
[0342] 2-(4,7,10-Tris(2-(tert-butoxy)-2-oxoethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid (DOTA-(OtBu)$_3$-OH, 1.50 equiv), HATU (1.90 equiv) and DIEA (4.00 equiv) were dissolved in dry DMF. The solution was mixed with the resin-bound peptide-Ahx and then agitated for 30 min under nitrogen. The resin was then washed three times with DMF.

[0343] After the resin was washed three times with MeOH and dried under vacuum, a cocktail of trifluoroacetic acid/H_2O/triisopropylsilane/3-mercaptopropionic acid (90:2.5:2.5:5.0) was added. The resulting mixture was stirred for 2 h at room temperature. Cold isopropyl ether was added. The precipitated crude linear peptide-DOTA **14** was collected through filtration and dried under vacuum.

[0344] *Oxidative folding of DOTA-linker-peptide **14***: To a solution of crude **14** (0.88 g) in water (330 mL) and MeCN (100 mL) were added GSSG (798 mg) and GSH (798 mg). The pH of the solution was adjusted to 8.0 using saturated NH_4HCO_3 solution. The resulting mixture was stirred at room temperature for 12 h. The pH of the solution was then adjusted to 5.0 using 1.0 N HCl. After lyophilization, the crude was purified by preparative HPLC to afford **C-01** (91.2 mg, 7.3% yield, 80.8% purity) as a white solid.

[0345] *La^{3+} complexation*: To a solution of **C-01** (45.3 mg, 80.8% purity, 14.5 μmol) in H_2O (2.50 mL) and MeCN (0.5 mL) was added $LaCl_3$ (4.43 mg, 18.0 μmol) and Na_2CO_3 (0.19 mg, 1.8 μmol). The resulting mixture was stirred at 70 °C for 1 h. After filtration, the crude product was purified by preparative HPLC to afford **La-C-01** (7.9 mg, 19.2% yield, 95.0% purity) as a white solid.

[0346] **Example A3: Synthesis of C-05 and La-C-05**. Example discloses SEQ ID NOS 46, and 49-51, respectively, in order of appearance.


13
SPPS HATU; piperidine
15
1. 3% hydrazine, DMF 2. SPPS HATU, DIEA
2
16
TFA, TIS, H2O, 3-MPA
17
GSSG, GSH
C-05
LaCl3
La-C-05

[0347] Fmoc-Lys(Dde)-OH (1.50 equiv), HATU (1.42 equiv) and DIEA (3.00 equiv) were dissolved in dry DMF. The solution was mixed with the resin-bound peptide **13** and agitated for 30 min under nitrogen. The resin was then washed three times with DMF. Fmoc removal was carried out while the peptide was on resin using 20% piperidine in DMF followed by filtration and washing.

[0348] 2-(4,7,10-Tris(2-(tert-butoxy)-2-oxoethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid (DOTA-$(OtBu)_3$-OH, 1.50 equiv), HATU (1.42 equiv) and DIEA (3.00 equiv) were dissolved in dry DMF. The solution was mixed with the resin-bound peptide-Lys(Dde) and agitated for 30 min under nitrogen. The resin was then washed three times with DMF and agitated in 3% hydrazine in DMF for 10 min. After the solvent was removed through filtration, the peptidyl-resin **15** was washed five times with DMF.

[0349] 4-(Naphthalene-2-sulfonamido)-4-oxobutanoic acid **2** (2.00 equiv), HATU (1.90 equiv) and DIEA (4.00 equiv) were dissolved in dry DMF. The solution was mixed with the resin-bound peptide **15** and then agitated for 30 min under nitrogen. The resin-bound peptide **16** was washed three times with DMF.

[0350] After the resin was washed three times with MeOH and dried under vacuum, a cocktail of trifluoroacetic acid/H_2O/triisopropylsilane/3-mercaptopropionic acid (90:2.5:2.5:5.0) was added. The resulting mixture was stirred for 2 h at room temperature. Cold isopropyl ether was used to precipitate the cleaved peptide-linker-DOTA. The crude linear peptide-DOTA **17** (0.95 g) was collected through filtration and dried under vacuum.

[0351] *Oxidative folding of DOTA-linker-peptide **17***: To a solution of crude **17** (0.95 g) in water (330 mL) and MeCN (100 mL) was added GSSG (666 mg) and GSH (666 mg). The pH of the solution was adjusted to 8.0 using saturated NH_4HCO_3 solution. The resulting mixture was stirred at room temperature for 12 h. The pH of the solution was then adjusted to 5.0 using 1.0 N HCl. After lyophilization, the crude was purified by preparative HPLC to afford compound **C-05** (63.4 mg, 3.6% yield, 67.0% purity) as a white solid.

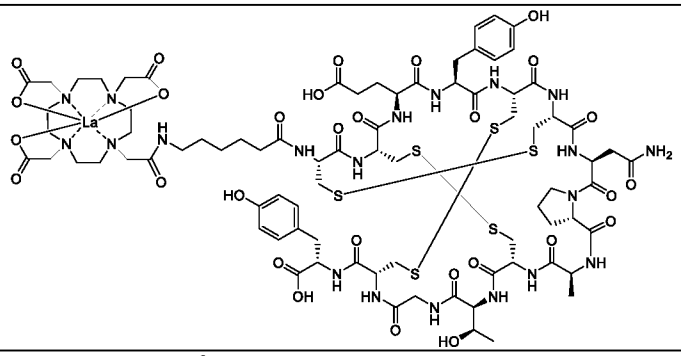
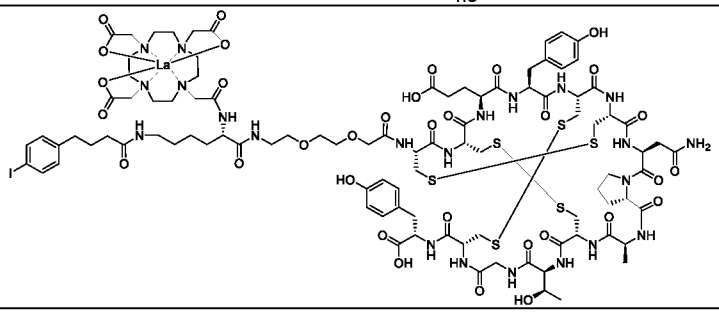
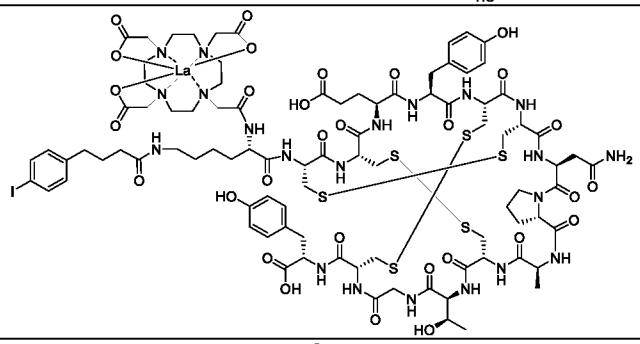
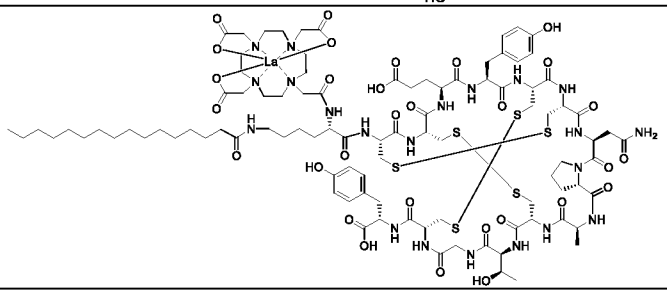
[0352] *La^{3+} complexation*: To a solution of **C-05** (45.1 mg, 67.0% purity, 13.0 μmol) in H_2O (2.00 mL) and MeCN (1.00 mL) was added $LaCl_3$ (3.82 mg, 15.6 μmol) and Na_2CO_3 (1.37 mg, 13.0 μmol). The resulting mixture was stirred at 70 °C for 1 h. After filtration, the crude product was purified by preparative HPLC to afford **La-C-05** (12.7 mg, 37.7% yield, 95.1% purity) as a white solid.

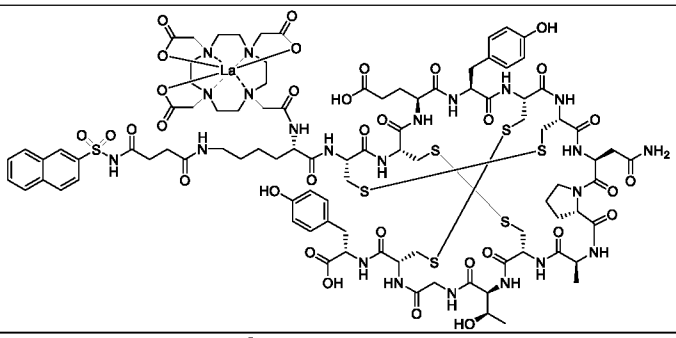
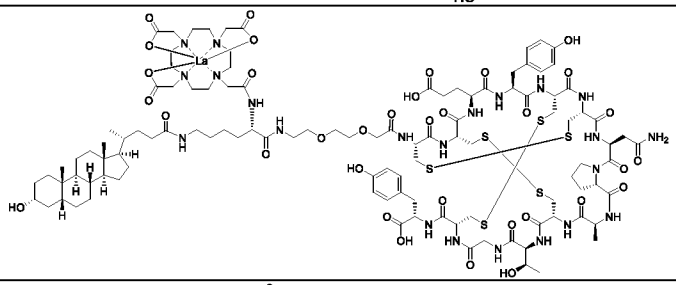
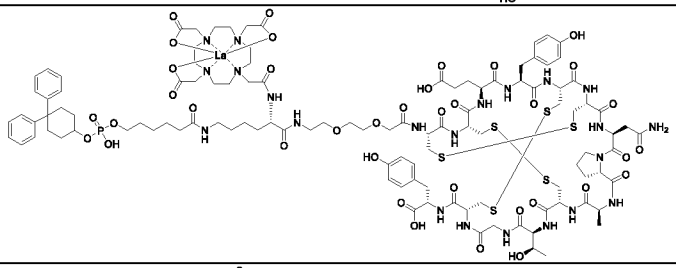
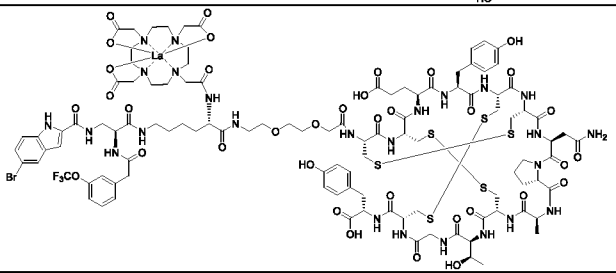
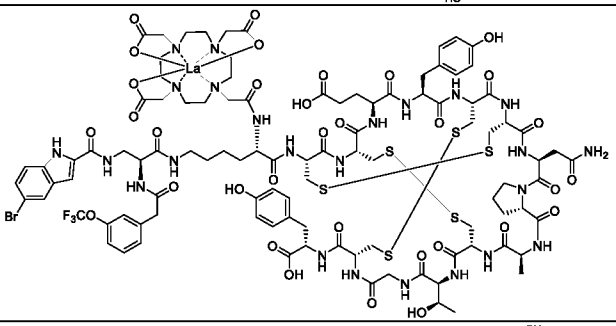
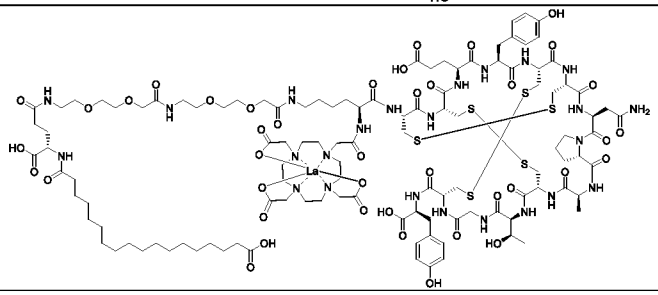
[0353] Conjugates in Table 1 and their corresponding La^{3+} complexed conjugates of Table 6 were synthesized similarly according to the methods described above.

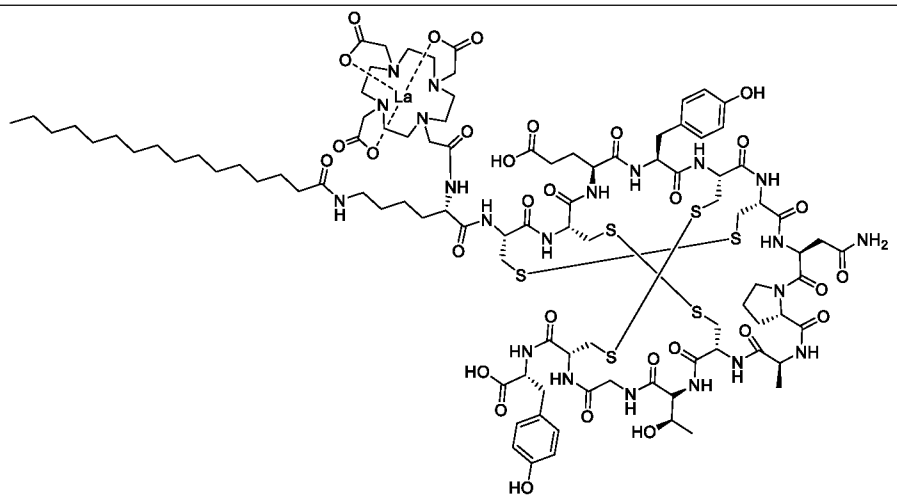
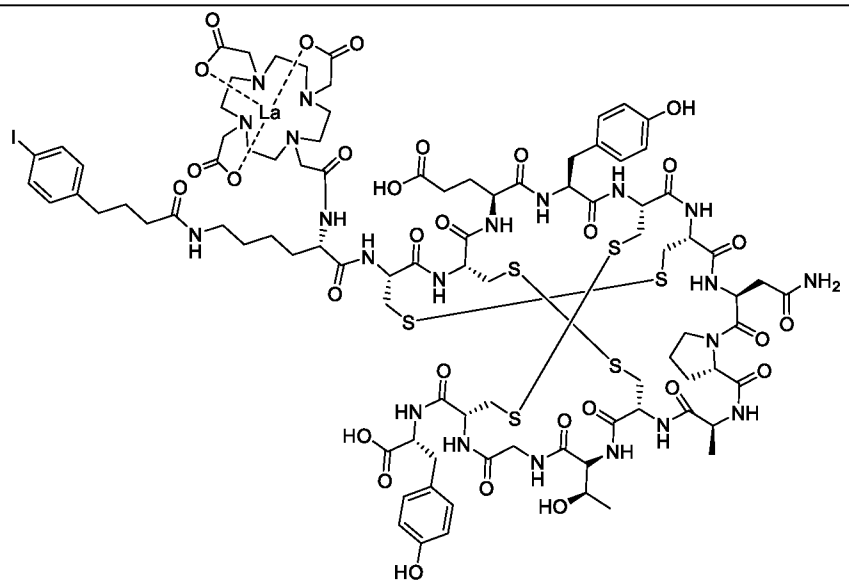
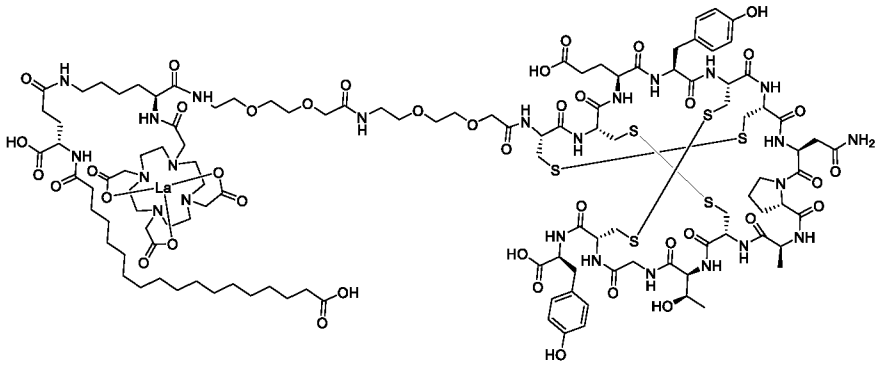
[0354] Example A4: Synthesis of conjugate of Table 1

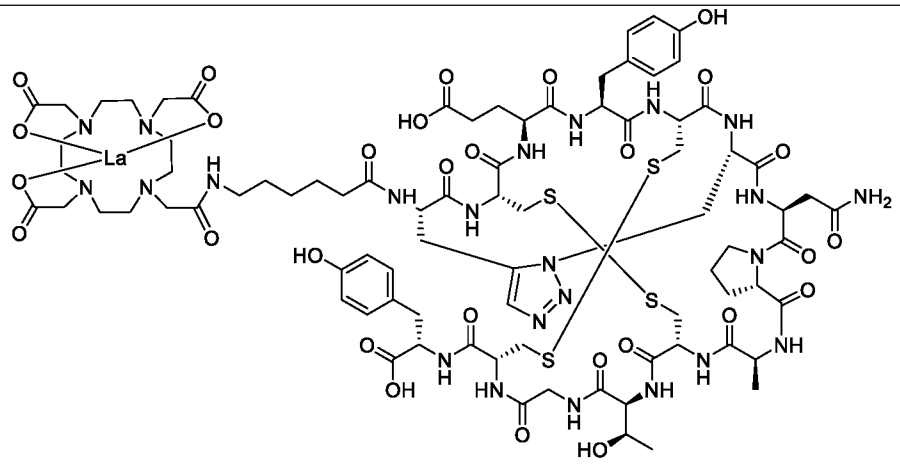
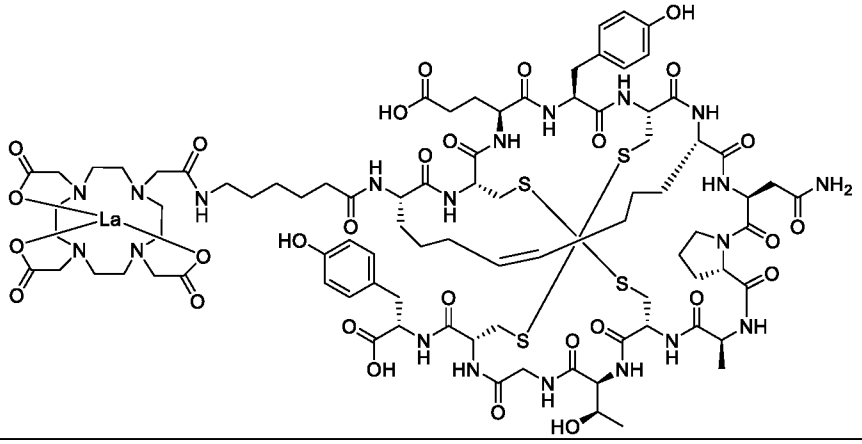
[0355] Conjugates of Table 1 and corresponding conjugates containing chelated lutetium or lanthanum were synthesized according to the same methods described in Examples A1-A3. See Table 6 and Table 7 below.

Table 6. Exemplary La^{3+}-labelled conjugates

Compound	Chemical structure	LC-MS method	MS (ESI) *m/e*
La-C-01		A	1081.7 $[M + 2H]^{2+}$
La-C-02		A	1297.8 $[M + 2H]^{2+}$
La-C-03		A	1225.2 $[M + 2H]^{2+}$
La-C-04		A	1208.3 $[M + 2H]^{2+}$

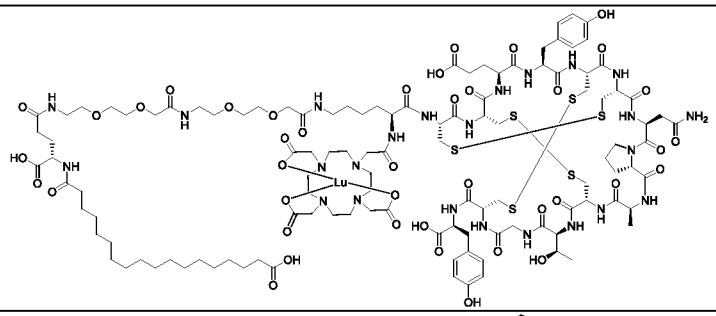
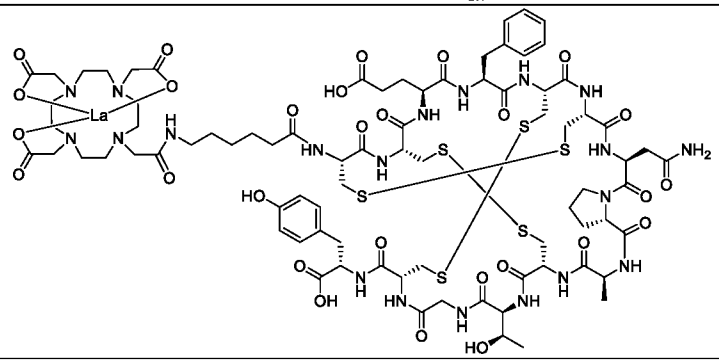
La-C-05		A	1234.2 [M + 2H]$^{2+}$
La-C-06		A	1341.4 [M + 2H]$^{2+}$
La-C-07		A	1376.3 [M + 2H]$^{2+}$
La-C-08		A	1417.2 [M + 2H]$^{2+}$
La-C-09		A	1344.7 [M + 2H]$^{2+}$
La-C-10		A	1447.4 [M + 2H]$^{2+}$
La-C-17			

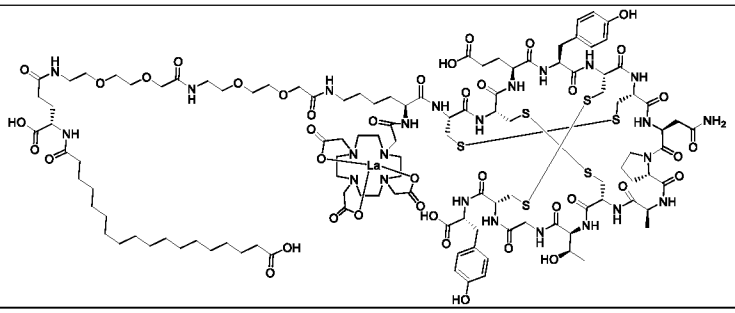
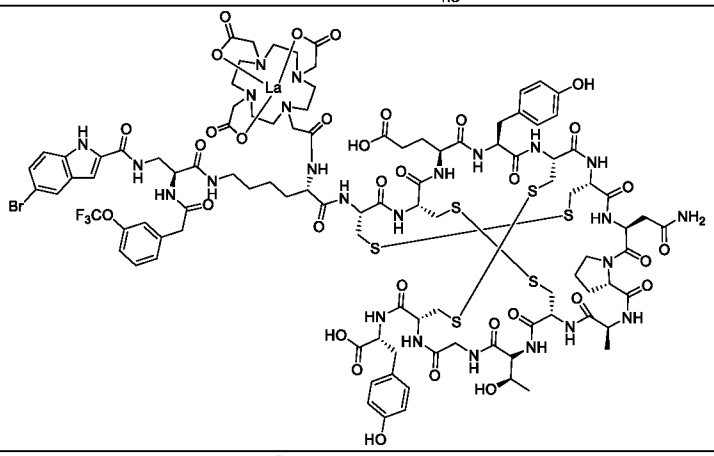
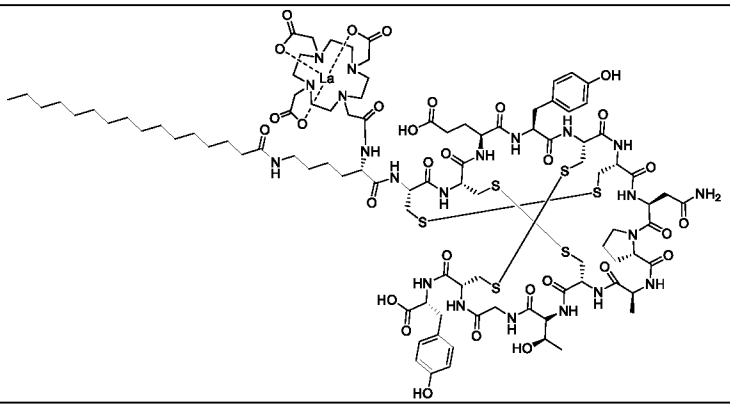
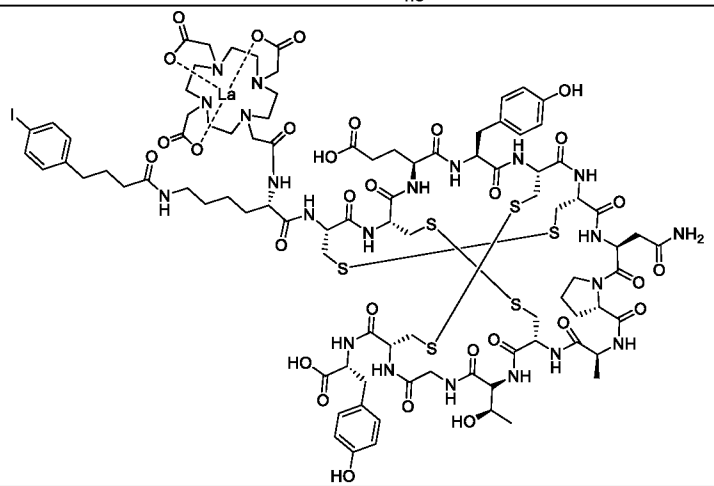
			
La-C-18			
La-C-23			

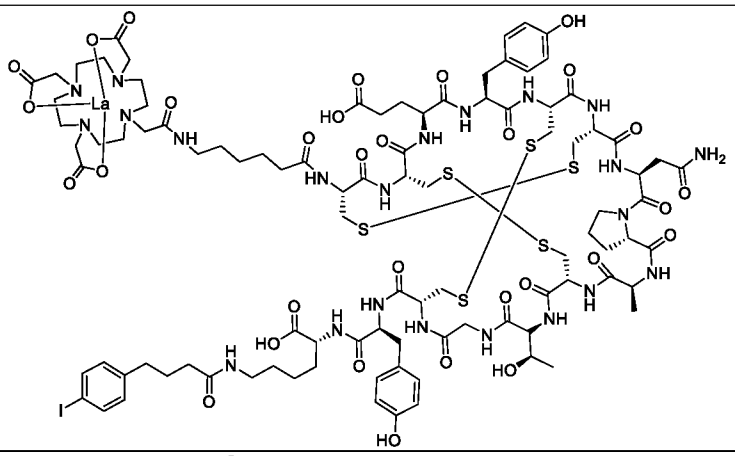
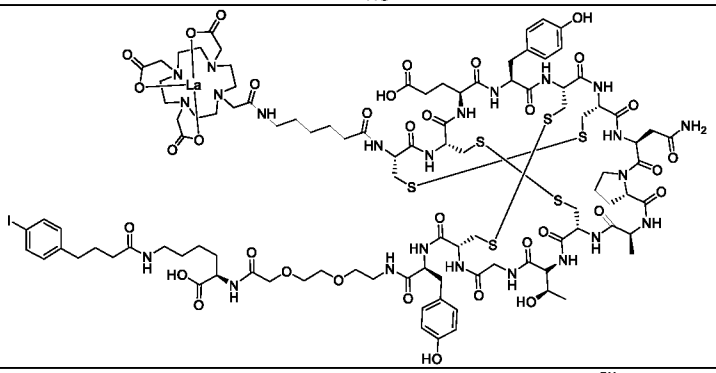
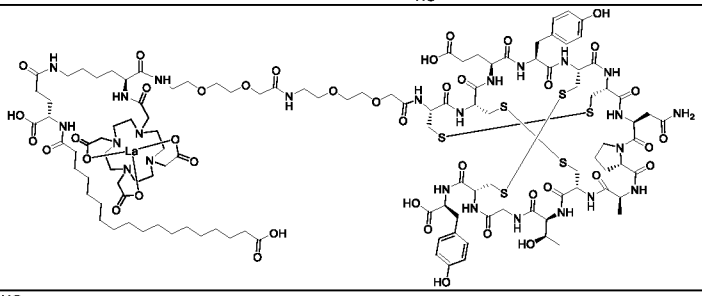
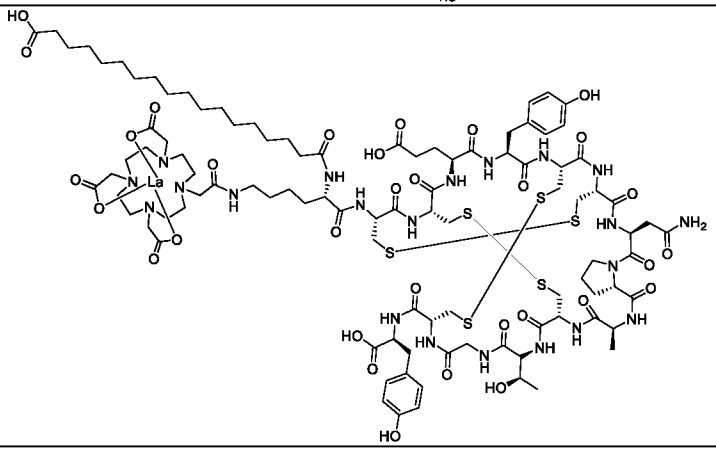
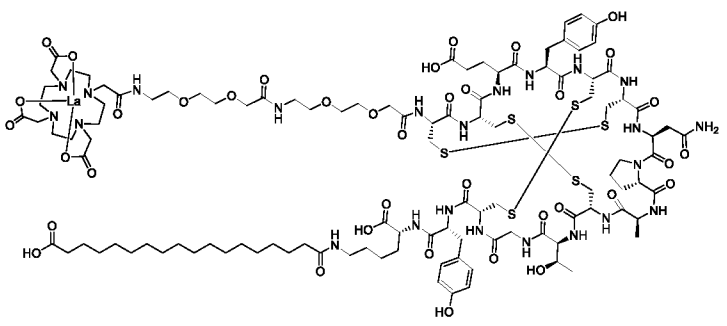
La-C-40			
La-C-41			

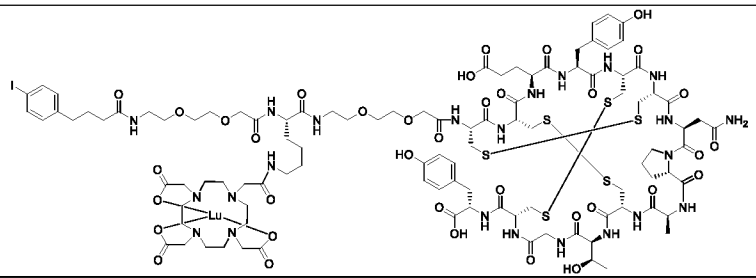
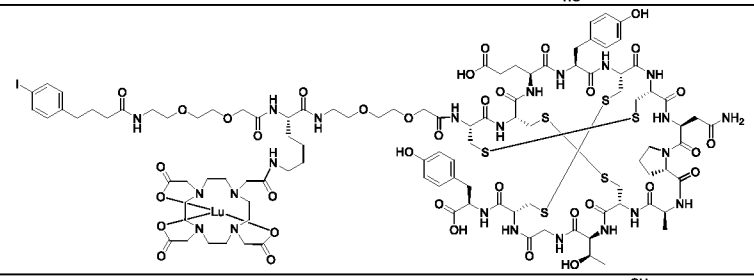
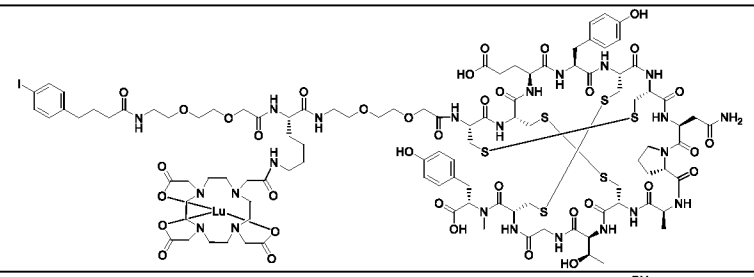
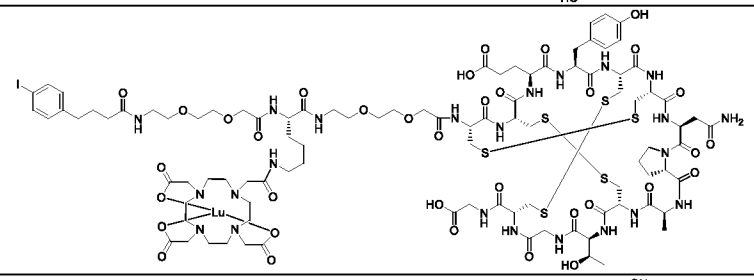
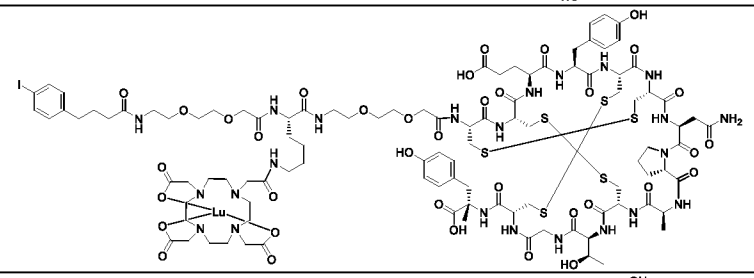
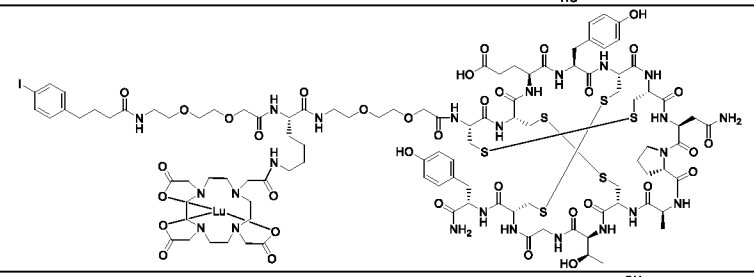
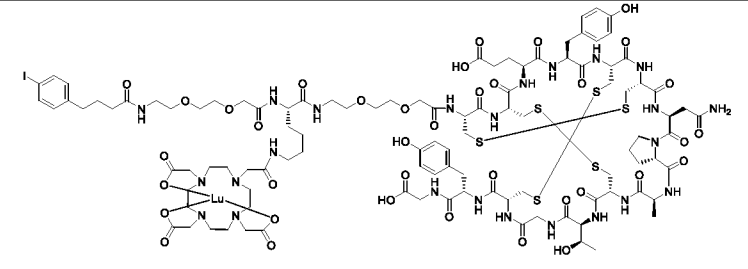
[0356] Conjugates in Table 1 and their corresponding Lu complexed conjugates of Table 7 were synthesized similarly according to the methods described above.

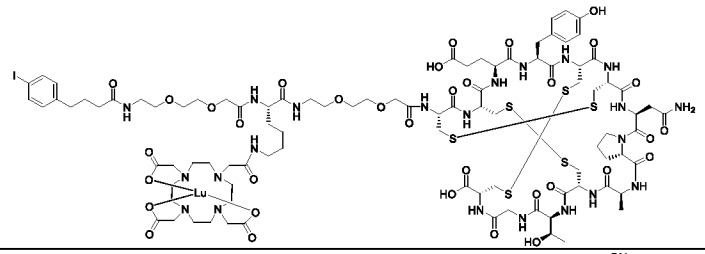
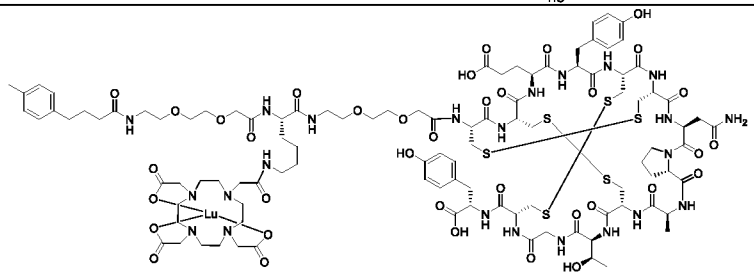
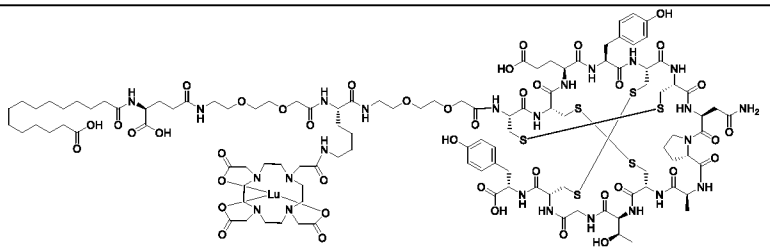
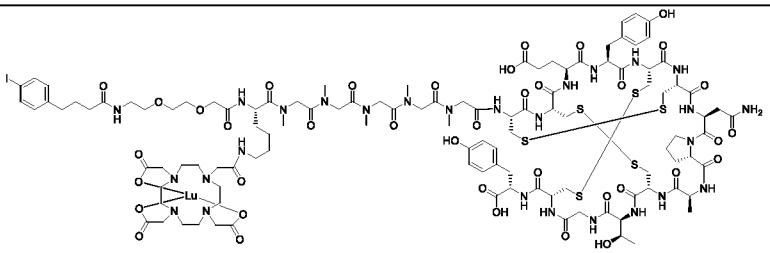
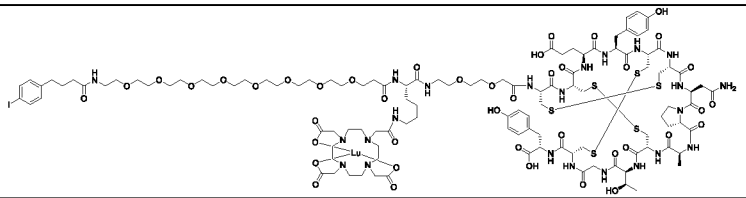
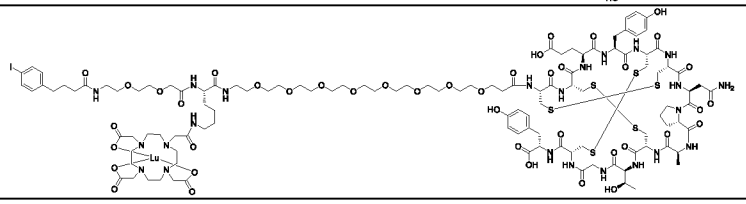
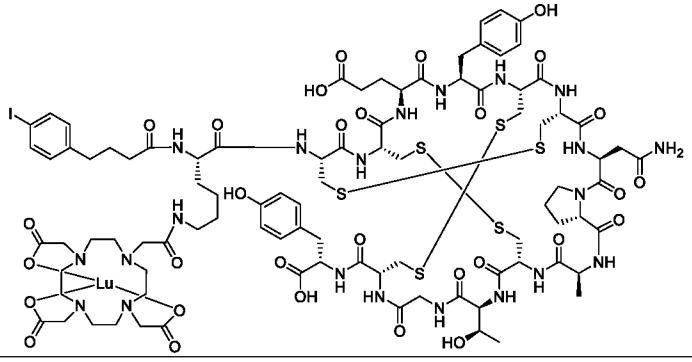
Table 7. Exemplary [175]Lu labelled conjugates

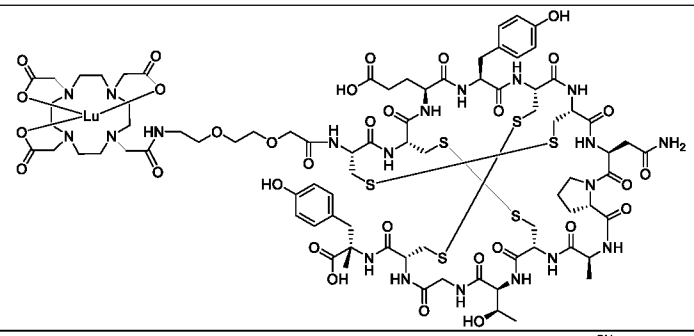
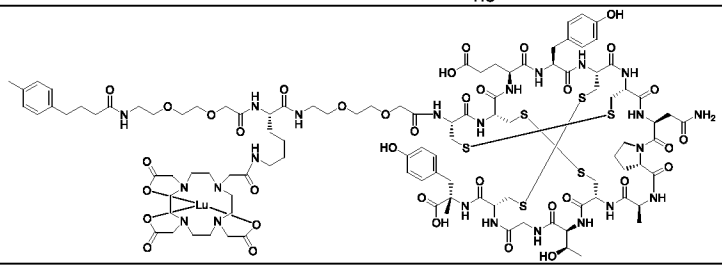
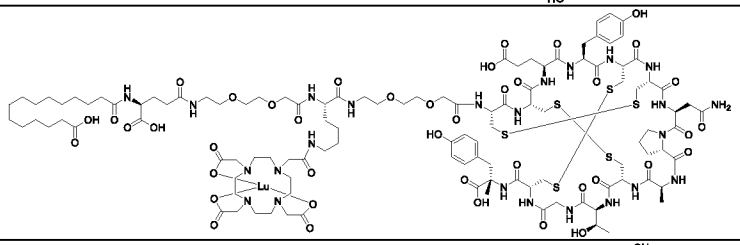
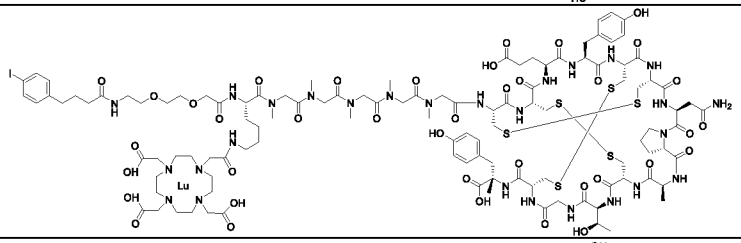
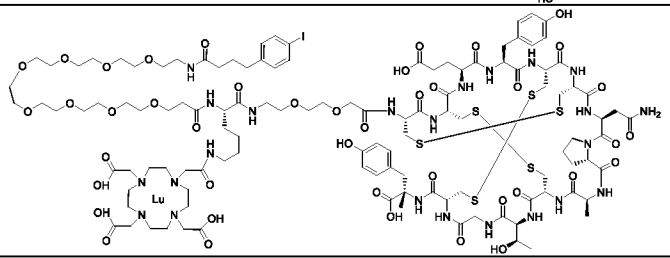
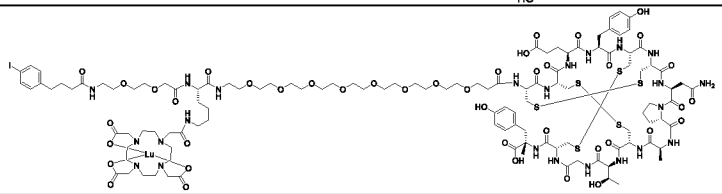
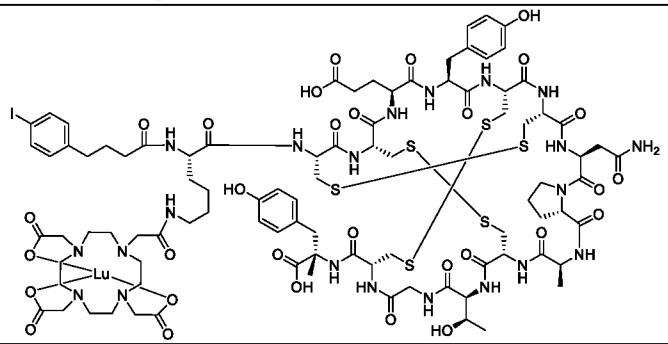
Compound No.	Chemical structure	LC-MS Method	MS (ESI) *m/e*
Lu-C-10		-	-
Lu-C-14		-	-

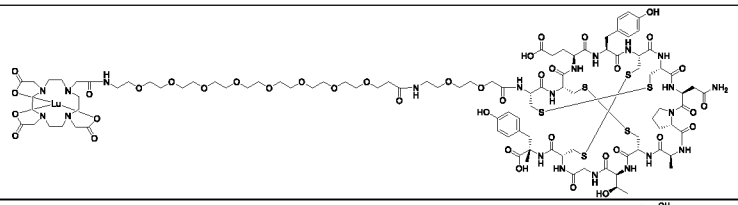
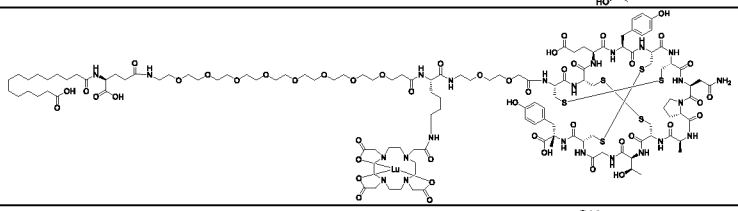
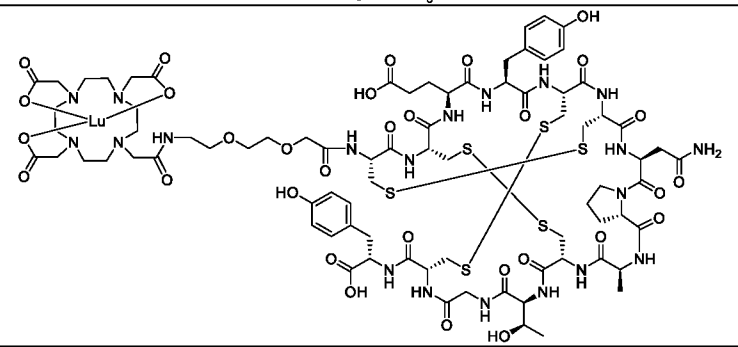
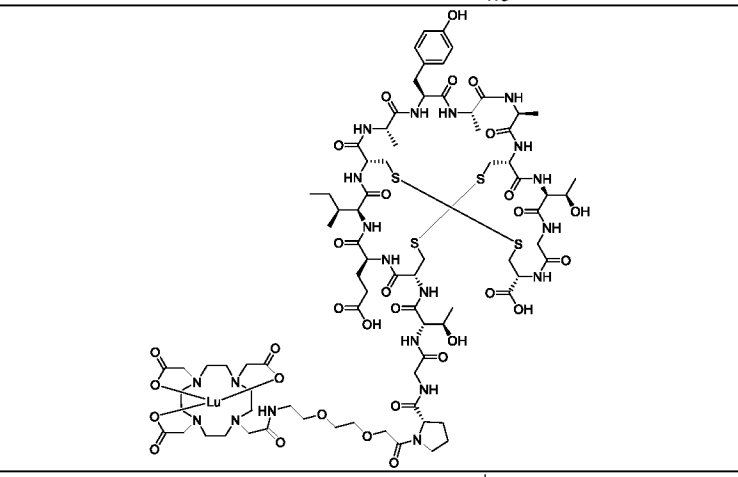
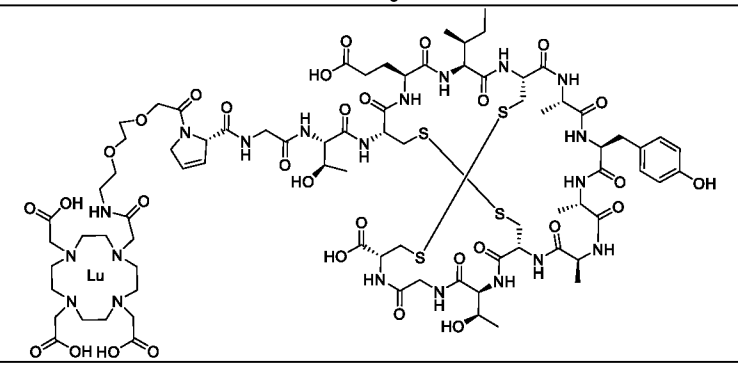
Lu-C-15		-	-
Lu-C-16		-	-
Lu-C-17		-	-
Lu-C-18		-	-

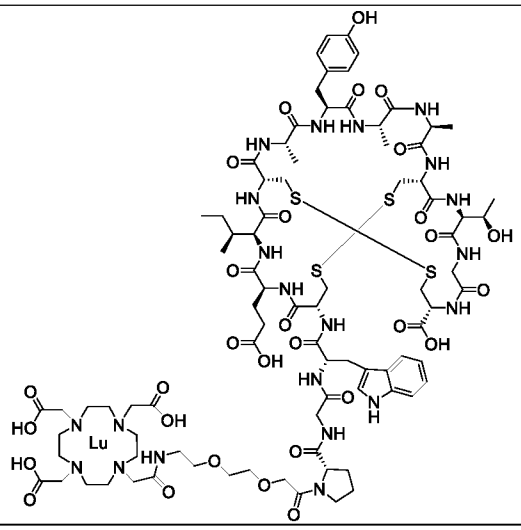
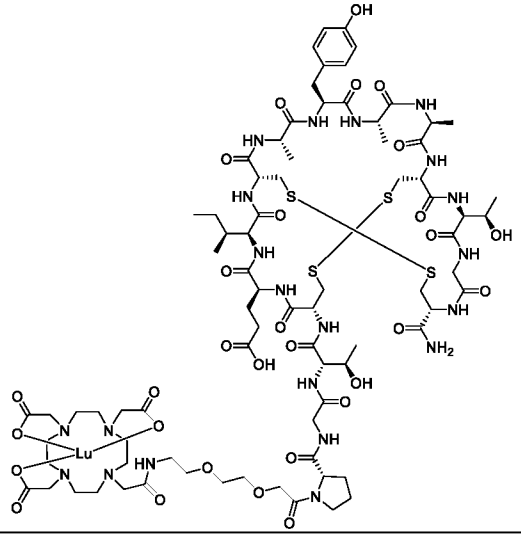
Lu-C-21		-	-
Lu-C-22		-	-
Lu-C-23		-	-
Lu-C-24		-	-
Lu-C-26		-	-

Lu-C-30		B	2774.4 [M + H]$^+$
Lu-C-31		-	-
Lu-C-32		B	2788.8 [M + H]$^+$
Lu-C-33		B	2669.4 [M + H]$^+$
Lu-C-34		B	2789.6 [M + H]$^+$
Lu-C-35		B	2774.6 [M + H]$^+$
Lu-C-36		B	2832.8 [M + H]$^+$

Lu-C-37		B	2612.6 [M + H]$^+$
Lu-C-48		-	-
Lu-C-49		-	-
Lu-C-50		-	-
Lu-C-51		-	-
Lu-C-52		-	-
Lu-C-53		-	-

Lu-C-54		E	2243.4 $[M + H]^+$
Lu-C-55		B	2677.2 $[M + H]^+$
Lu-C-56		D	1934.2 $[M + H]^+$
Lu-C-57		B	3001.0 $[M + H]^+$
Lu-C-58		D	3069.1 $[M + H]^+$
Lu-C-59		B	2045.4 $[M + H]^+$
Lu-C-60		B	2498.6 $[M + H]^+$

Lu-C-67		E	2667.8 [M + H]$^+$
Lu-C-68		D	2119.6 [M + H]$^+$
Lu-C-70		E	2230 [M + H]$^+$
Lu-C-87		E	2161.2 [M + H]$^+$
Lu-C-88		G	2160.2 [M + H]$^+$

Lu-C-89		H	2246 [M + H]$^+$
Lu-C-96		G	2160.4 [M + H]$^+$

[0357] Example A5: Synthesis of C-25 and La-C-25

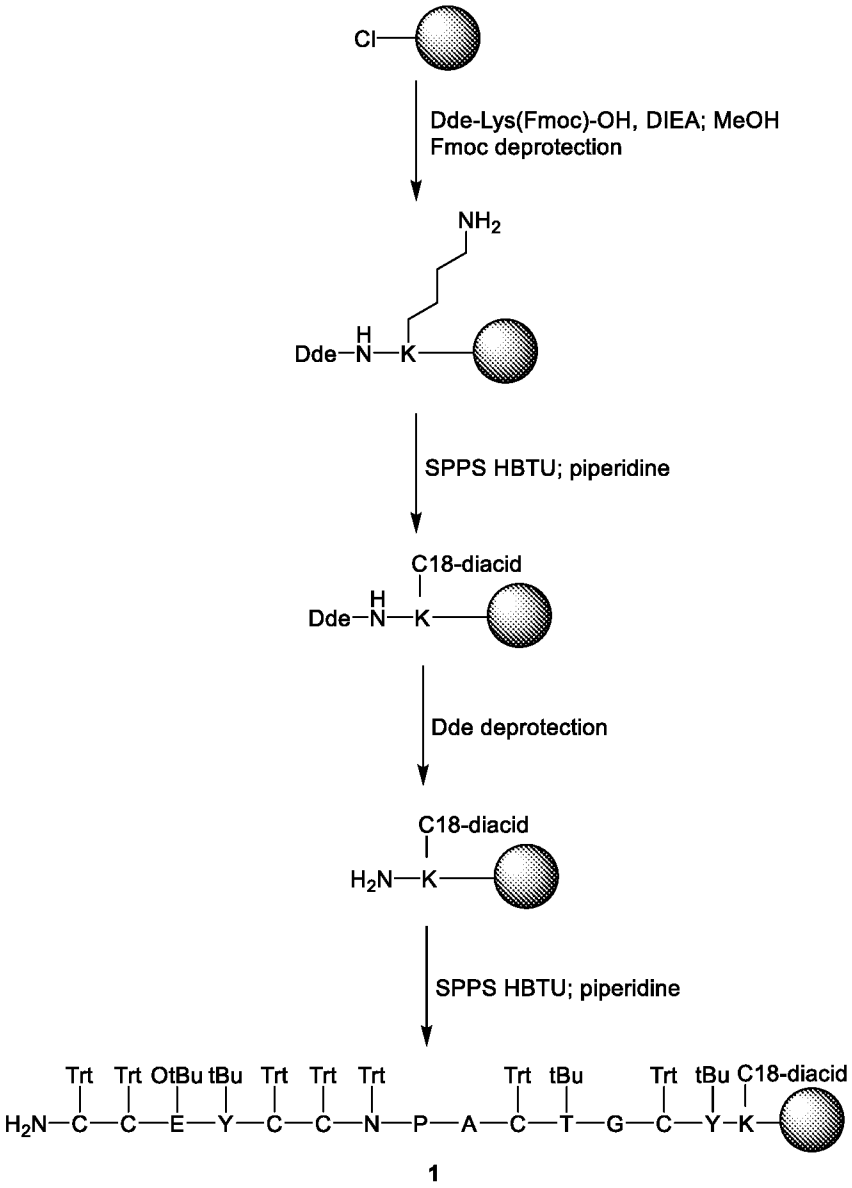
[0358] Solid phase peptide synthesis (SPPS) was performed in a standard manual reaction vessel under nitrogen. 2-CTC resin was purchased from Sunresin New Materials Co. (China). Fmoc protected amino acids were purchased from GL Biochem (China). HBTU and HATU were purchased from Highfine Biotech Co. (China). Piperidine was purchased from Damao Chemical Reagent Factory (China). The peptides and their derivatives were purified on a Gilson GX-281 preparative HPLC system using reverse-phase C18 columns (Gemini, 5 μm, 110 Å + luna, 10 μm, 100 Å) at 30 °C. HPLC solvents consisted of H_2O containing 0.075% trifluoroacetic acid (mobile phase A) and acetonitrile (mobile phase B).

[0359] High performance liquid chromatography (HPLC) analyses were performed on an Agilent 1260 series equipped with a binary pump G7112A, micro vacuum degasser, standard autosampler ALS G7129A, thermostatted column compartment TCC G7116A, variable wavelength detector VWD G7114A, and data were analyzed by OpenLab CDS 2.2 network workstation software from Agilent Technologies. HPLC solvents consisted of H_2O containing 0.1% trifluoroacetic acid (mobile phase A) and acetonitrile containing 0.075% trifluoroacetic acid

(mobile phase B). Conditions: a Phenomenex Gemini-NX C-18 (5 μm, 110 Å, 4.6 × 250 mm) column was used with a flow rate of 1.0 mL/min.

[0360] LC-MS analyses were carried out on an Agilent 1200 series coupled to an Agilent MSD G6125C, equipped with a binary pump G7112A, micro vacuum degasser, standard autosampler ALS G7129A, thermostatted column compartment TCC G7116A, variable wavelength detector VWD G7114A, and data were analyzed by OpenLab CDS 2.3 standalone workstation software from Agilent Technologies. HPLC solvents consisted of H_2O containing 0.1% trifluoroacetic acid (mobile phase A) and acetonitrile containing 0.075% trifluoroacetic acid (mobile phase B). Conditions: a Waters Xbridge C-18 (3.5 μm, 3.1× 30mm) column was used with a flow rate of 1.2 mL/min.

*Synthesis of peptidyl-resin **1***



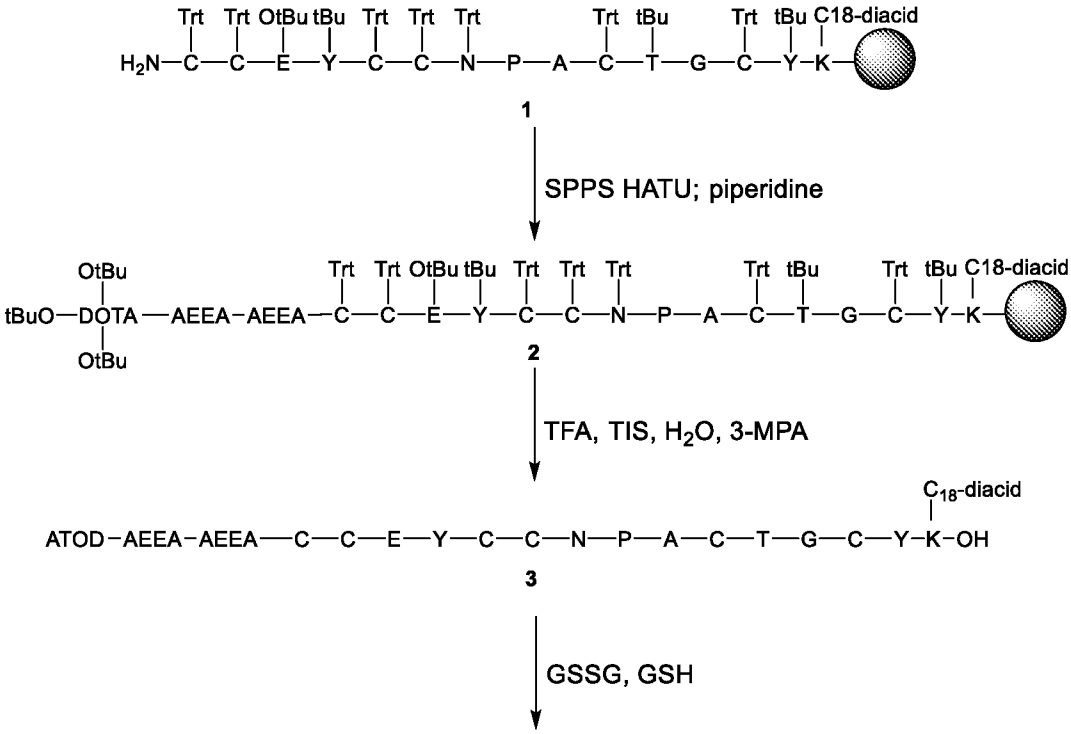
Scheme 1. Synthesis of peptidyl-resin **1**

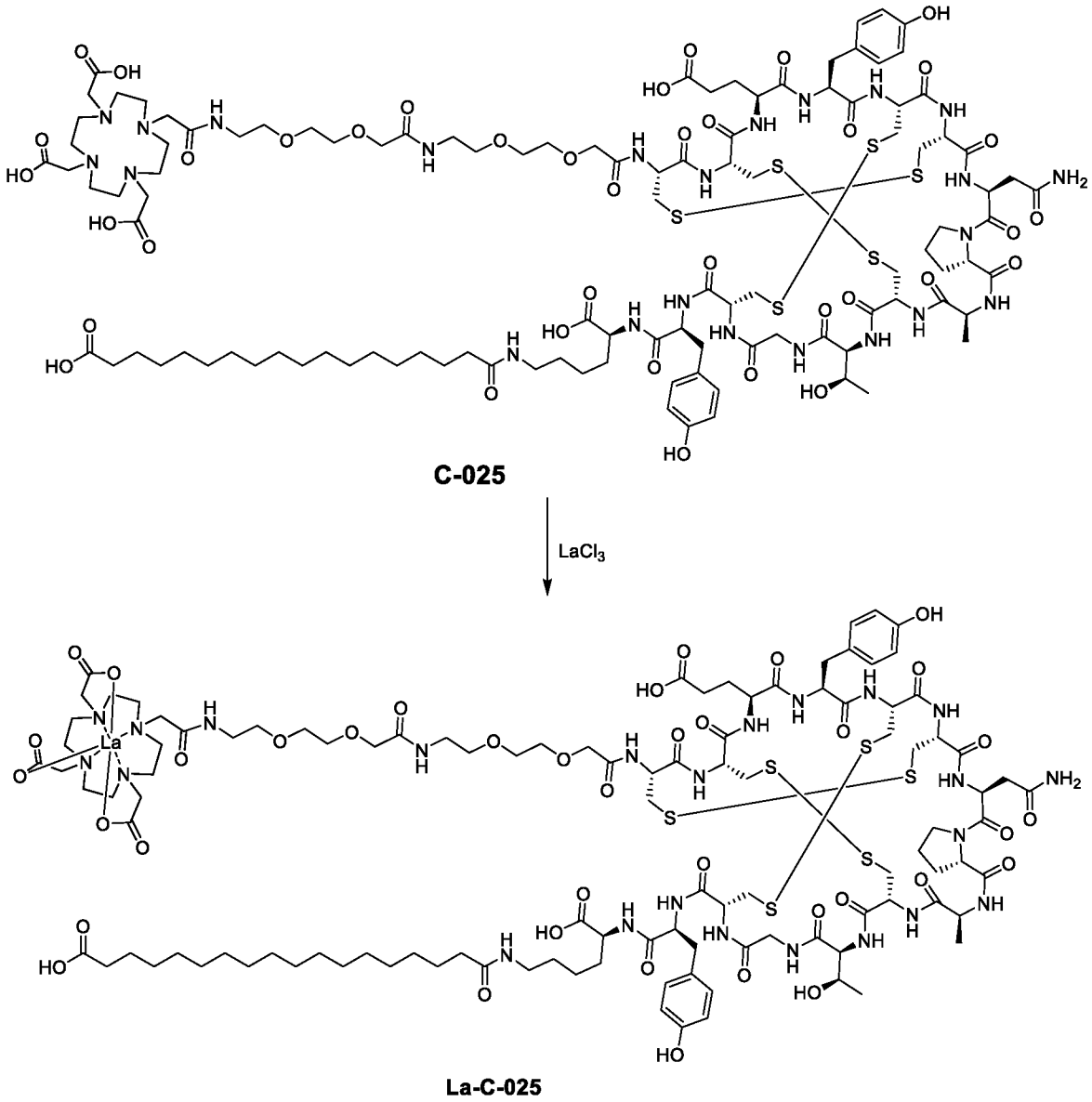
[0361] To the swollen 2-CTC resin (1.00 mmol, 1.10 mmol/g, 1.00 equiv) were added Dde-Lys(Fmoc)-OH (0.53 g, 1.00 mmol) and DIEA (0.70 mL, 4.00 mmol) in DCM (8.00 mL). The mixture was agitated for 2 h under nitrogen. MeOH (1.00 mL) was then added. The resulting mixture was agitated for 30 min. After the reaction solution was removed through filtration, the resin was washed three times with DMF (10 mL). The Fmoc protecting group was removed via 30 min agitation with 20% piperidine in DMF followed by filtration and washing.

[0362] 18-(tert-butoxy)-18-oxooctadecanoic acid (2.00 equiv), HBTU (1.90 equiv) and DIEA (4.00 equiv) were dissolved in dry DMF. The solution was mixed with the resin-bound peptide and then agitated for 30 min under nitrogen. The resin was then washed three times with DMF. Dde removal was carried out while the peptide was on resin using 3% hydrazine hydrate in DMF followed by filtration and washing.

[0363] Subsequent amino acids were coupled using Fmoc-protected amino acid (3.00 equiv), HBTU (2.85 equiv) and DIEA (6.00 equiv) in dry DMF, shaking for 30 min. Pre-activation of any amino acid was not performed prior to coupling. Between amino acid couplings, the Fmoc protecting group was removed via 30 min agitation with 20% piperidine in DMF followed by filtration and washing. Success of Fmoc removal steps and amino acid couplings were monitored qualitatively using a ninhydrin test.

Synthesis of ***C-025***





Scheme 1. Synthesis of **C-25 and La-C-25**

[0364] Fmoc-AEEA-OH (2.00 equiv), HATU (1.90 equiv) and DIEA (4.00 equiv) were dissolved in dry DMF. The solution was mixed with the resin-bound peptide and then agitated for 30 min under nitrogen. The resin was then washed three times with DMF. Fmoc removal was carried out while the peptide was on resin using 20% piperidine in DMF followed by filtration and washing.

[0365] Fmoc-AEEA-OH (2.00 equiv), HATU (1.90 equiv) and DIEA (4.00 equiv) were dissolved in dry DMF. The solution was mixed with the resin-bound peptide and then agitated for 30 min under nitrogen. The resin was then washed three times with DMF. Fmoc removal was carried out while the peptide was on resin using 20% piperidine in DMF followed by filtration and washing.

[0366] 2-(4,7,10-Tris(2-(tert-butoxy)-2-oxoethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid (DOTA-$(OtBu)_3$-OH, 1.50 equiv), HATU (1.90 equiv) and DIEA (4.00 equiv) were dissolved in dry DMF. The solution was mixed with the resin-bound peptide-**2** and then agitated for 30 min under nitrogen. The resin was then washed three times with DMF.

[0367] After the resin was washed three times with MeOH and dried under vacuum, a cocktail of trifluoroacetic acid/H_2O/triisopropylsilane/3-mercaptopropionic acid (90:2.5:2.5:5.0) was added. The resulting mixture was stirred for 2 h at room temperature. Cold isopropyl ether was added. The precipitated crude linear peptide-DOTA **3** was collected through filtration and dried under vacuum.

[0368] *Oxidative folding of DOTA-linker-peptide 3*: To a solution of crude **3** (2.34 g) in water (700 mL) and MeCN (300 mL) were added GSSG (1.63 g) and GSH (1.63 g). The pH of the solution was adjusted to 8.0 using saturated NH_4HCO_3 solution. The resulting mixture was stirred at room temperature for 12 h. The pH of the solution was then adjusted to 5.0 using 1.0 N HCl. After lyophilization, the crude was purified by preparative HPLC to afford **C-25** (8.0 mg, 95.59% purity; 13.6 mg, 94.78% purity and 54 mg, 70% purity) as a white solid.

La^{3+} complexation: To a solution of **La-C-25** (54 mg, 20.0 μmol) in H_2O (2.50 mL) and MeCN (0.5 mL) was added $LaCl_3$ (4.43 mg, 18.0 μmol) and Na_2CO_3 (0.19 mg, 1.8 μmol). The resulting mixture was stirred at 70 °C for 1 h. After filtration, the crude product was purified by preparative HPLC to afford **La-C-25** (10.9 mg, 95.6% purity) as a white solid.

[0369] Example A6: Synthesis of conjugate of C-35 and **Lu-C-35**

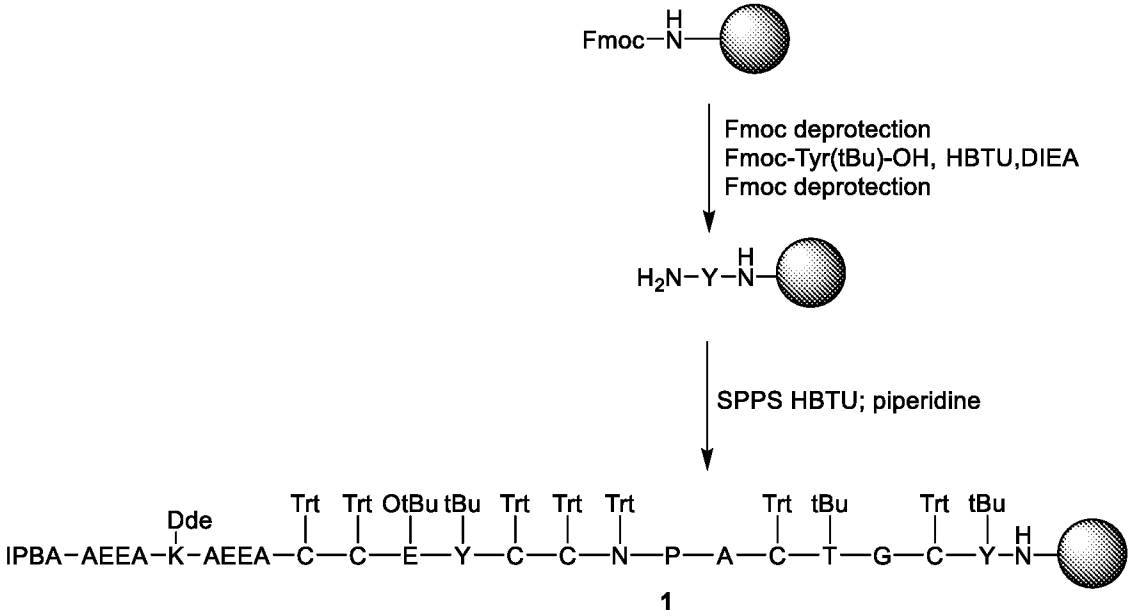
[0370] Solid phase peptide synthesis (SPPS) was performed in a standard manual reaction vessel under nitrogen. 2-CTC resin was purchased from Sunresin New Materials Co. (China). Fmoc protected amino acids were purchased from GL Biochem (China). HBTU and HATU were purchased from Highfine Biotech Co. (China). Piperidine was purchased from Damao Chemical Reagent Factory (China). The peptides and their derivatives were purified on a Gilson GX-281 preparative HPLC system using reverse-phase C18 columns (Gemini, 5 μm, 110 Å + luna, 10 μm, 100 Å) at 30 °C. HPLC solvents consisted of H_2O containing 0.075% trifluoroacetic acid (mobile phase A) and acetonitrile (mobile phase B).

[0371] High performance liquid chromatography (HPLC) analyses were performed on an Agilent 1260 series equipped with a binary pump G7112A, micro vacuum degasser, standard autosampler ALS G7129A, thermostatted column compartment TCC G7116A, variable wavelength detector VWD G7114A, and data were analyzed by OpenLab CDS 2.2 network workstation software from Agilent Technologies. HPLC solvents consisted of H_2O containing 0.1% trifluoroacetic acid (mobile phase A) and acetonitrile containing 0.075% trifluoroacetic acid

(mobile phase B). Conditions: a Phenomenex Gemini-NX C-18 (5 μm, 110 Å, 4.6 × 250 mm) column was used with a flow rate of 1.0 mL/min.

[0372] LC-MS analyses were carried out on an Agilent 1200 series coupled to an Agilent MSD G6125C, equipped with a binary pump G7112A, micro vacuum degasser, standard autosampler ALS G7129A, thermostatted column compartment TCC G7116A, variable wavelength detector VWD G7114A, and data were analyzed by OpenLab CDS 2.3 standalone workstation software from Agilent Technologies. HPLC solvents consisted of H_2O containing 0.1% trifluoroacetic acid (mobile phase A) and acetonitrile containing 0.075% trifluoroacetic acid (mobile phase B). Conditions: a Waters Xbridge C-18 (3.5 μm, 3.1× 30mm) column was used with a flow rate of 1.2 mL/min.

*Synthesis of peptidyl-resin **1***



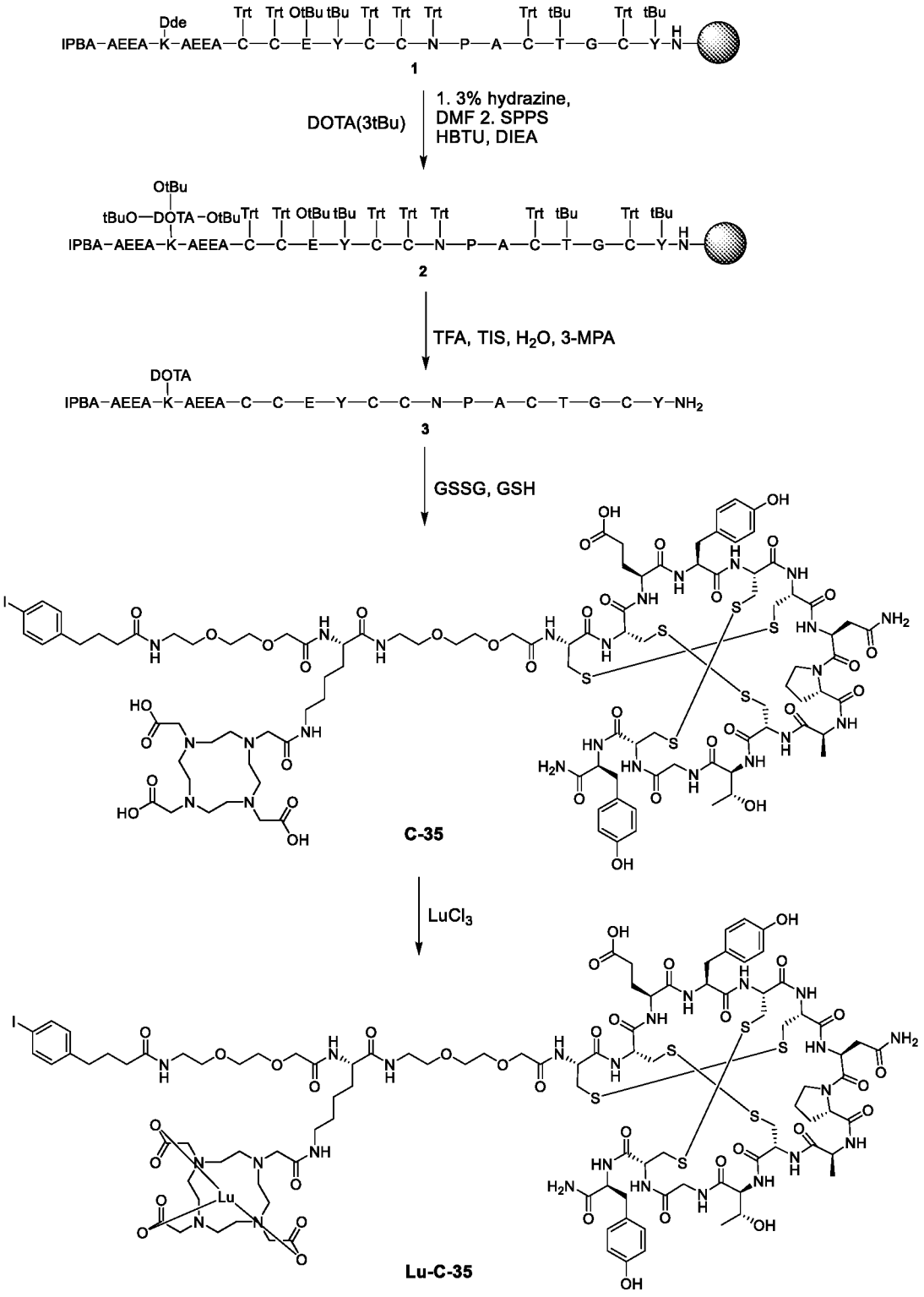
Scheme 2. Synthesis of peptidyl-resin **1**

[0373] To the Rink amide-MBHA resin (0.50 mmol, 0.5 mmol/g, 1.00 equiv) were added in DMF (20mL). Then the mixture was agitated with N_2 for 30 min. After the solution was removed through filtration, The Fmoc protecting group was removed via 30 min agitation with 20% piperidine in DMF followed by filtration and washing. A solution of Fmoc-Tyr(tBu)-OH (0.69 g, 1.50 mmol), HBTU (542mg, 1.43mmol) and DIEA (0.35 mL, 2.00 mmol) in DMF (5 mL) was added to the resin and agitated with N_2 for 30 min at 20°C. The resin was then washed with DMF (15 mL * 3). The Fmoc protecting group was removed via 30 min agitation with 20% piperidine in DMF followed by filtration and washing.

[0374] Subsequent amino acids were coupled using Fmoc-protected amino acid (3.00 equiv), HBTU (2.85 equiv) and DIEA (6.00 equiv) in dry DMF, shaking for 30 min. Pre-activation of any

amino acid was not performed prior to coupling. Between amino acid couplings, the Fmoc protecting group was removed via 30 min agitation with 20% piperidine in DMF followed by filtration and washing. Success of Fmoc removal steps and amino acid couplings were monitored qualitatively using a ninhydrin test.

[0375] Synthesis of **C-35**



Scheme 3. Synthesis of **C-35** and **Lu-C-35**

[0376] The resin was agitated in 3% hydrazine in DMF for 20 min. After the solvent was removed through filtration, the peptidyl-resin was washed five times with DMF.

[0377] 2-(4,7,10-Tris(2-(tert-butoxy)-2-oxoethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid (DOTA-$(OtBu)_3$-OH, 1.50 equiv), HBTU (1.90 equiv) and DIEA (4.00 equiv) were dissolved in dry DMF. The solution was mixed with the resin-bound peptide **2** and then agitated for 30 min under nitrogen. The resin-bound peptide **2** was washed three times with DMF.

[0378] After the resin was washed three times with MeOH and dried under vacuum, a cocktail of trifluoroacetic acid/H_2O/triisopropylsilane/3-mercaptopropionic acid (90:2.5:2.5:5.0) was added. The resulting mixture was stirred for 2.5 h at room temperature. Cold isopropyl ether was used to precipitate the cleaved peptide-linker-DOTA. The crude linear peptide-DOTA **3** (1.2 g) was collected through filtration and dried under vacuum.

[0379] *Oxidative folding of DOTA-linker-peptide **3***: To a solution of crude **3** (1.2 g) in water (400 mL) and MeCN (200 mL) was added GSSG (845 mg, 3eq) and GSH (845 mg, 6eq). The pH of the solution was adjusted to 8.0 using saturated NH_4HCO_3 solution. The resulting mixture was stirred at room temperature for 24 h. The pH of the solution was then adjusted to 5.0 using 1.0 N HCl. After lyophilization, the crude was purified by preparative HPLC to afford compound **C-35** (2.1 mg, 95.06% purity and 67mg 70% purity) as a white solid.

[0380] *Lu^{3+} complexation*: To a solution of **C-35** (67 mg, 70% purity) in H_2O (3.00 mL) and MeCN (1.00 mL) was added $LuCl_3$ (36mg, 5eq) and then 1M Na_2CO_3 aqueous solution was adjusted to pH = 5~6. Then the mixture was heated to 40°C and stirred at 40 °C for 1h. The crude product was purified by preparative HPLC to afford **Lu-C-35** (15.5 mg , 95.06% purity) as a white solid.

[0381] Example A7: Synthesis of 177-Lutetium chelated conjugates

[0382] Conjugates of Table 1 and Table 2 are synthesized according to the same methods described in Examples A1-A6.

[0383] ***General procedure for ^{177}Lu-labeling*** [^{177}Lu]$LuCl_3$ in HCl (50 MBq) is added to a mixture of a DOTA-GCC construct (1 nmol) in NaOAc buffer (5% EtOH, 0.25 M, pH 5.0-5.5, total volume 120 µL) in a 1.8 mL Eppendorf tube. The resulting mixture is heated at 80 °C in a thermal mixer at a shaking speed of 600 rpm for 15-30 min. If necessary, the mixture is purified using a C8 column. Radiochemical purity is determined by radio-RP-HPLC and iTLC.

[0384] Accordingly, conjugates of Table 8 can be synthesized according to this Example A7.

Table 8. Exemplary 177-Lu labelled conjugates

Compound #	Radionuclide bound to the metal chelator	Metal chelator, linker and peptide structure (see compound structures in Table 1)

177Lu-C-01	177-Lu	C-01
177Lu-C-02	177-Lu	C-02
177Lu-C-03	177-Lu	C-03
177Lu-C-04	177-Lu	C-04
177Lu-C-05	177-Lu	C-05
177Lu-C-06	177-Lu	C-06
177Lu-C-07	177-Lu	C-07
177Lu-C-08	177-Lu	C-08
177Lu-C-09	177-Lu	C-09
177Lu-C-10	177-Lu	C-10
177Lu-C-13	177-Lu	C-13
177Lu-C-14	177-Lu	C-14
177Lu-C-15	177-Lu	C-15
177Lu-C-16	177-Lu	C-16
177Lu-C-17	177-Lu	C-17
177Lu-C-18	177-Lu	C-18
177Lu-C-19	177-Lu	C-19
177Lu-C-20	177-Lu	C-20
177Lu-C-21	177-Lu	C-21
177Lu-C-22	177-Lu	C-22
177Lu-C-23	177-Lu	C-23
177Lu-C-24	177-Lu	C-24
177Lu-C-25	177-Lu	C-25
177Lu-C-26	177-Lu	C-26
177Lu-C-27	177-Lu	C-27
177Lu-C-30	177-Lu	C-30
177Lu-C-31	177-Lu	C-31
177Lu-C-32	177-Lu	C-32
177Lu-C-33	177-Lu	C-33
177Lu-C-34	177-Lu	C-34
177Lu-C-35	177-Lu	C-35
177Lu-C-36	177-Lu	C-36
177Lu-C-37	177-Lu	C-37
177Lu-C-40	177-Lu	C-40
177Lu-C-41	177-Lu	C-41
177Lu-C-48	177-Lu	C-48
177Lu-C-49	177-Lu	C-49
177Lu-C-50	177-Lu	C-50
177Lu-C-51	177-Lu	C-51
177Lu-C-52	177-Lu	C-52
177Lu-C-53	177-Lu	C-53
177Lu-C-54	177-Lu	C-54
177Lu-C-55	177-Lu	C-55
177Lu-C-56	177-Lu	C-56
177Lu-C-57	177-Lu	C-57
177Lu-C-58	177-Lu	C-58
177Lu-C-59	177-Lu	C-59
177Lu-C-60	177-Lu	C-60
177Lu-C-67	177-Lu	C-67
177Lu-C-68	177-Lu	C-68

177Lu-C-70	177-Lu	C-70
177Lu-C-87	177-Lu	C-87
177Lu-C-88	177-Lu	C-88
177Lu-C-89	177-Lu	C-89
177Lu-C-96	177-Lu	C-96

[0385] Example A8: Synthesis of 225-Actinium chelated conjugates

[0386] Conjugates of Table 1 and Table 2 are synthesized according to the same methods described in Examples A1-A6.

[0387] ***General procedure for ^{225}Ac-labeling*** [^{225}Ac]Ac$(NO_3)_3$ in 1 mM HCl (50 kBq) is added to a mixture of a DOTA-GCC construct (1 nmol) in NaOAc buffer (100 µL, 0.4 M, pH 5.5-6.5) in a 1.8 mL Eppendorf tube. The resulting mixture is heated at 80-100 °C in a thermal mixer at a shaking speed of 500 rpm for 15-30 min. Radiochemical purity is determined by iTLC.

[0388] Accordingly, conjugates of Table 9 can be synthesized according to this Example A8.

Table 9. Exemplary 225-Actinium labelled conjugates

Compound #	**Radionuclide bound to the metal chelator**	**Metal chelator, linker and peptide structure (see compound structures in Table 1)**
225Ac-C-01	225-Ac	C-01
225Ac-C-02	225-Ac	C-02
225Ac-C-03	225-Ac	C-03
225Ac-C-04	225-Ac	C-04
225Ac-C-05	225-Ac	C-05
225Ac-C-06	225-Ac	C-06
225Ac-C-07	225-Ac	C-07
225Ac-C-08	225-Ac	C-08
225Ac-C-09	225-Ac	C-09
225Ac-C-10	225-Ac	C-10
225Ac-C-13	225-Ac	C-13
225Ac-C-14	225-Ac	C-14
225Ac-C-15	225-Ac	C-15
225Ac-C-16	225-Ac	C-16
225Ac-C-17	225-Ac	C-17
225Ac-C-18	225-Ac	C-18
225Ac-C-19	225-Ac	C-19
225Ac-C-20	225-Ac	C-20
225Ac-C-21	225-Ac	C-21
225Ac-C-22	225-Ac	C-22
225Ac-C-23	225-Ac	C-23
225Ac-C-24	225-Ac	C-24
225Ac-C-25	225-Ac	C-25
225Ac-C-26	225-Ac	C-26
225Ac-C-27	225-Ac	C-27
225Ac-C-30	225-Ac	C-30
225Ac-C-31	225-Ac	C-31
225Ac-C-32	225-Ac	C-32

225Ac-C-33	225-Ac	C-33
225Ac-C-34	225-Ac	C-34
225Ac-C-35	225-Ac	C-35
225Ac-C-36	225-Ac	C-36
225Ac-C-37	225-Ac	C-37
225Ac-C-40	225-Ac	C-40
225Ac-C-41	225-Ac	C-41
225Ac-C-48	225-Ac	C-48
225Ac-C-49	225-Ac	C-49
225Ac-C-50	225-Ac	C-50
225Ac-C-51	225-Ac	C-51
225Ac-C-52	225-Ac	C-52
225Ac-C-53	225-Ac	C-53
225Ac-C-54	225-Ac	C-54
225Ac-C-55	225-Ac	C-55
225Ac-C-56	225-Ac	C-56
225Ac-C-57	225-Ac	C-57
225Ac-C-58	225-Ac	C-58
225Ac-C-59	225-Ac	C-59
225Ac-C-60	225-Ac	C-60
225Ac-C-67	225-Ac	C-67
225Ac-C-68	225-Ac	C-68
225Ac-C-70	225-Ac	C-70
225Ac-C-87	225-Ac	C-87
225Ac-C-88	225-Ac	C-88
225Ac-C-89	225-Ac	C-89
225Ac-C-96	225-Ac	C-96

B: Biological Evaluation

[0389] Example B1. Plasma stability study

[0390] The pooled frozen CD-1 (ICR) mouse plasma was thawed in a water bath at 37 ℃ prior to experiment. Plasma was centrifuged at 4000 rpm for 5 min and the clots were removed if any. The pH would be adjusted to 7.4 ± 0.1 if required.

[0391] Plasma (98 μL) and test compounds (2 μL, 100 μM in DMSO) or reference compound propantheline bromide (2 μL, 100 μM in 40% v/v MeOH/H_2O) were added to the individual wells of a 96-well microtiter plate in duplicate. The plate was incubated at 37 ℃. During the incubation, aliquots were withdrawn at 0, 10, 30, 60, 120 and 300 minutes. 100 μL 4% H_3PO_4 and 800 μL of stop solution (200 ng/mL tolbutamide and 200 ng/mL labetalol in 100% acetonitrile) were added to precipitate proteins. After mixing thoroughly, the quenched aliquots were centrifuged at 4,000 rpm for 20 min. Aliquots (100 μL) of supernatant were transferred to a new plate. The samples were shaken at 800 rpm for 10 min before performing LC-MS/MS analysis.

[0392] The analytes were detected by a multiple reaction monitoring method using a SCIEX Triple Quad 6500+ system equipped with an ACQUITY UPLC HSS T3 column (100 Å, 1.8 μm,

2.1 mm × 30 mm). Mobile phase A: water with 0.1% formic acid; Mobile phase B: acetonitrile with 0.1% formic acid.

The % remaining of test compound after incubation in plasma was calculated using the following equation:

$$\% \text{ Remaining} = 100 \times \frac{PAR\ (t)}{PAR\ (t0)}$$ *PAR is the peak area ratio of analyte versus internal standard (IS)*

[0393] Example B2. In vivo pharmacokinetic studies in female CD-1(ICR) mice

[0394] The pharmacokinetics of linaclotide and the La^{3+}-labelled peptide surrogates were determined using female CD-1 (ICR) mice purchased from Vital River Laboratory Animal Co., Ltd., Beijing, China. All animal studies were conducted in accordance with the highest standards of care as outlined in the NIH Guide for Care and Use of Laboratory. Following injection of the mice (10 mg/kg, 3 mice per test compound) with aliquots of the peptides in PBS (10 mM, pH 7.4) *via* the tail vein, blood samples were collected into pre-chilled tubes containing Heparin-Na (3 µL, 1000 I.U./mL) at 5, 30, 60, and 240 minutes.

[0395] *General sample processing procedure*: An aliquot of 12 µL diluted blood sample (10× dilution factor for 30, 60, and 240 min blood samples; 20× dilution factor for 5 min blood samples), calibration standard, dilution quality control, single blank or double blank samples were added to the individual wells of a low binding 96-well plate. Each sample (except the double blank) was quenched with 120 µL IS in methanol respectively (double blank sample was quenched with 120 µL MeOH). The resulting mixtures were mixed for 10 min at 800 rpm and centrifuged at 3220 g (4000 rpm) for 15 min at 4 °C. Supernatant aliquots (50 µL) were transferred to a clean low binding 96-well plate and centrifuged at 3220 g (4000 rpm) for 5 min at 4 ℃, then the samples were directly injected for LC-MS/MS analysis.

[0396] The analytes were detected by a multiple reaction monitoring method using a SCIEX Triple Quad 6500+ system equipped with an ACQUITY UPLC HSS T3 column (100 Å, 1.8 µm, 2.1 mm × 30 mm). Mobile phase A: water/acetonitrile (95/5, v/v) with 0.1% formic acid and 2 mM ammonium formate; Mobile phase B: acetonitrile/water (95/5, v/v) with 0.1% formic acid and 2 mM ammonium formate. Or Mobile phase A: water with 0.1% formic acid; Mobile phase B: acetonitrile with 0.1% formic acid. Column temperature: 60 °C.

[0397] The plasma concentration-time data was subjected to IV-noncompartmental pharmacokinetics analysis by using Phoenix WinNonlin (version 6.3, Pharsight Corp., Mountain View, CA, USA). The linear/log trapezoidal rule was applied in obtaining the PK parameters.

[0398] Pharmacokinetics of linaclotide and compounds of the present disclosure are given in Table 10 below.

Table 10. Pharmacokinetics of linaclotide and compounds of the present disclosure

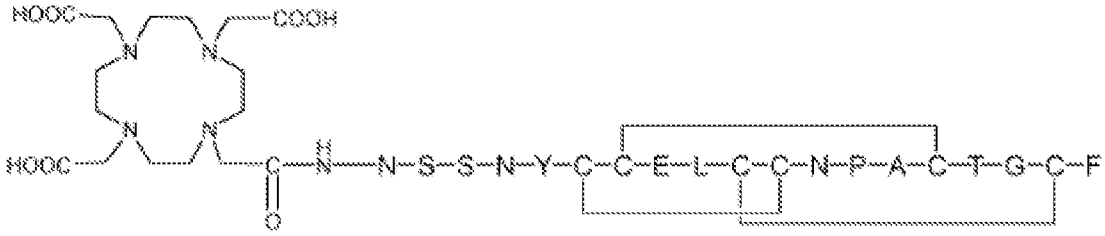
Compound	CL (mL/min/kg)	$AUC_{0\text{-}inf}$ (h*mg/mL)	$T_{1/2}$ (h)
Linaclotide	20.4	0.0084	0.173
La-C-01	23.1	0.0075	0.192
La-C-02	1.24	0.14	1.62
La-C-03	0.8	0.21	2.01
La-C-04	0.555	0.31	2.90
La-C-05	5.58	0.030	0.323
La-C-06	0.364	0.229	2.86
La-C-07	2.30	0.073	0.698
La-C-08	1.29	0.13	1.56
La-C-09	1.21	0.14	1.67
La-C-10	0.249	0.67	3.8

[0399] Example B3. In vitro IC_{50} values for the GCC constructs determined by competitive radioligand displacement cell binding assay

[0400] The IC_{50} values for the GCC constructs were determined by a competitive radioligand displacement cell binding assay, using compound Reference-043 radiolabeled with ^{125}I, Reference-043-[^{125}I]. In a 96 well plate, each well was added T84 cell membrane protein 20 µg in 100 µL assay buffer (DMEM/20 mM HEPES, pH 7.4, 0.5% BSA), Reference-043-[^{125}I] (100 pM, 50 µL) and an unlabeled GCC construct (50 µL) at varying concentrations (0.3 pM – 5 uM). The plate was sealed and incubated at room temperature for 1 h with gentle agitation on a shaker set to 300 rpm. The incubation is stopped by filtration onto a Unifilter-96 GF/C filter plate (presoaked with 50 µL of 0.3% polyethyleneimine per well for at least 0.5 h at room temperature) using a Perkin Elmer Filtermate Harvester. The plate was washed with cold Dulbecco-PBS washing buffer (200 µL x 5 times) then dried at 50 °C for 1 h. The bottom of the filter plate was sealed using Perkin Elmer Unifilter-96 backing seal tape and the Perkin Elmer Microscint 20 cocktail

(50 μL) was added to the wells. The top of the filter plate was sealed with Perkin Elmer TopSeal-A sealing film and the radioactivity was counted with a Perkin Elmer MicroBeta2 Reader. For statistical considerations, each GCC construct was tested in two separate competitive radioligand cell binding experiments performed in duplicate. IC_{50} calculations were performed using the four-parameter logistic model within GraphPad Prism 5.0 software.

[0401] The structure of Reference-043 is the following:



[0402] IC_{50} values of compounds of the present disclosure are given in Table 11 below, where IC_{50} 0nM<A≤30nM; 30nM<B≤ 100nM; 100nM<C≤ 1000nM; and 1000nM<D≤ 6000nM.

Table 11. IC_{50} values of exemplary compounds of the present disclosure

Compound No.	**IC_{50} (nM)**
La-C-13	A
La-C-23	D
C-28	A
C-29	A
Lu-C-30	A
Lu-C-31	A
Lu-C-32	C
Lu-C-33	A
Lu-C-34	A
Lu-C-35	A
Lu-C-36	A
Lu-C-37	A
Lu-C-38	C
Lu-C-54	A
Lu-C-55	B
Lu-C-56	C
Lu-C-57	B
Lu-C-58	C
Lu-C-59	A
Lu-C-60	B
C-66	C
Lu-C-67	A
Lu-C-68	D
Lu-C-70	A
C-84	A
C-85	A

Lu-C-87	B
Lu-C-88	A
Lu-C-89	A
Lu-C-96	A
C-182	A

[0403] Example B4. In vitro determination of bound and unbound fraction of GCC binding constructs to Human Serum Albumin (HSA)

[0404] *HSA-HPLC method (measurement of drug protein binding by immobilized human serum albumin-HPLC).* A 13-minute HPLC (Thermo Vanquish Horizon with Diode Array Detector) gradient method was used to determine the HSA (Human Serum Albumin) binding of novel compounds using a chemically bonded protein stationary phase (ChiralPAK HSA HPLC column, 50 x 4 mm). The HSA binding values were derived from the gradient retention times that were converted to the logarithm of the equilibrium constant using data from a calibration set of molecules. The % bound to plasma values for the calibrator compounds were converted to the linear free energy values using the following equation: LogK = log[%PPB/(101-%PPB)]. The logarithmic value of the gradient retention times from the experiment were plotted against the linearized values of the percent bound to plasma. The slope and the intercept were used to convert the retention times to linear free energy values (LogK), from which the estimated % protein binding was calculated using the following equation: %Binding = $[(101 \cdot 10^{LogK})/(1+10^{LogK})]$. Aqueous mobile phase (mobile phase A) was 50 mM ammonium acetate solution, pH 7.4 and the organic mobile phase (mobile phase B) was 2-propanol. The flow rate was set at 0.350mL/min and injection volume was 5uL, with samples prepared at 0.5mg/mL concentration in 50:50 mobile phase. The initial LC conditions were set at 0% B and ramped to 50% B over 8.5 minutes, then held at 50% B for 1.5 minutes before going back to initial conditions and re-equilibrating the column for 2.5 minutes. Chromatograms were recorded at 280 nm by a diode array UV absorption detector .

[0405] The percent binding values of Table 12 are defined as the following:

90% bound to HSA < A ≤100% bound to HSA;

70% bound to HSA < B ≤ 90% bound to HSA;

20% bound to HSA < C ≤ 70% bound to HSA; and

0% bound to HSA < D ≤ 20% bound to HSA.

Table 12. Percent HSA binding of compounds of the present disclosure

Compound No.	% Bound to HSA
Lu-C-38	B
Lu-C-54	C
Lu-C-55	B

Lu-C-56	A
Lu-C-57	B
Lu-C-58	B
Lu-C-59	B
Lu-C-60	B
Lu-C-67	D
Lu-C-68	A
Lu-C-70	C
Lu-C-87	D
C-182	D

[0406] The examples and embodiments described herein are for illustrative purposes only and various modifications or changes suggested to persons skilled in the art are to be included within the spirit and purview of this application and scope of the appended claims.

CLAIMS

We Claim:

1. A conjugate comprising

   a guanylyl cyclase C (GCC) binding peptide, wherein the GCC binding peptide comprises an amino acid sequence that has at least 85% identity to any one of SEQ ID NOs: 1-42;

   a metal chelator configured to bind with a radionuclide;

   a linker that covalently attaches the GCC binding peptide with the metal chelator; and

   an alpha-particle emitting radionuclide bound to the metal chelator.

2. A conjugate comprising

   a guanylyl cyclase C (GCC) binding peptide;

   a metal chelator configured to bind with a radionuclide; and

   a linker that covalently attaches the GCC binding peptide with the metal chelator,

   wherein 5% to 99% of the conjugate binds to Human Serum Albumin (HSA) in vitro as determined by HSA-HPLC method.

3. The conjugate of claim 2, wherein the GCC binding peptide comprises an amino acid sequence that has at least 85% identity to any one of SEQ ID NOs: 1-42.

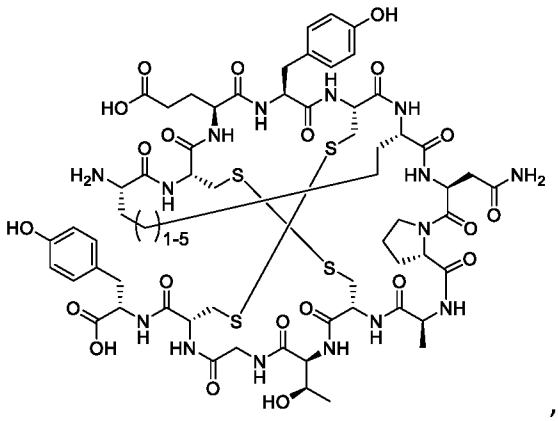
4. The conjugate of claim 1 or 3, wherein the GCC binding peptide consists of an amino acid sequence of any one of SEQ ID NOs: 1-19.

5. The conjugate of claim 1 or 3, wherein the GCC binding peptide comprises SEQ ID NO: 1.

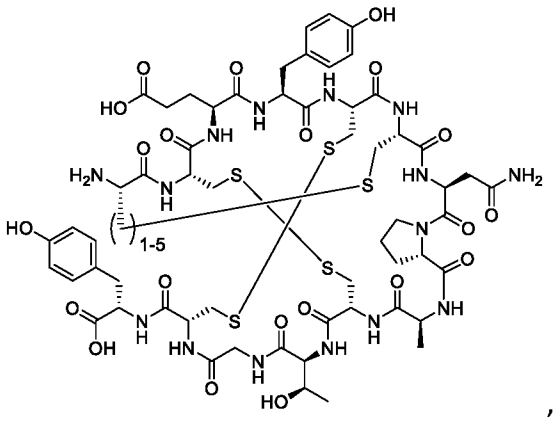
6. The conjugate of any one of claims 1 to 5, wherein the binding peptide further comprises 1, 2 or 3 intramolecular disulfide bonds.

7. The conjugate of any one of claims 1 to 6, wherein the binding peptide further comprises one or more of alkylene, alkenylene, heteroalkylene, and heteroaryl.

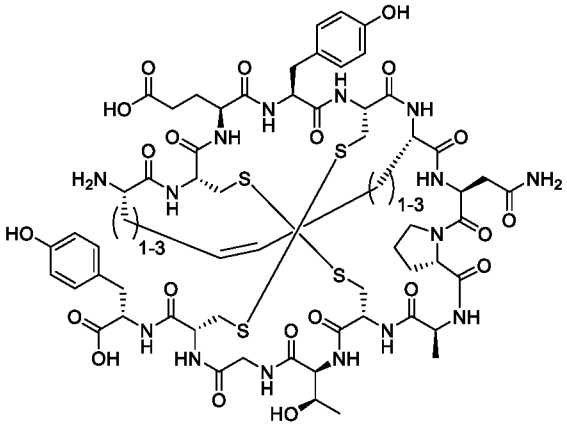
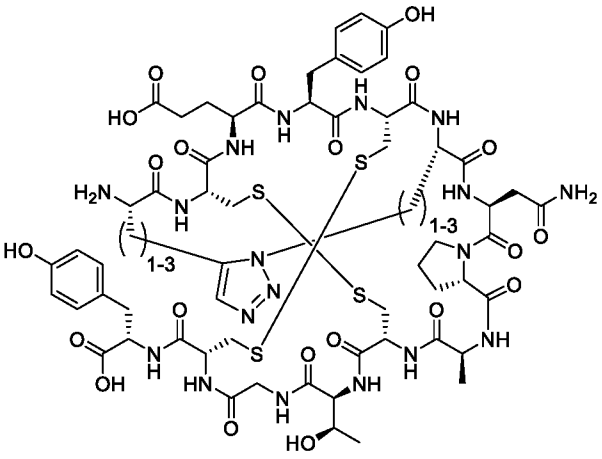
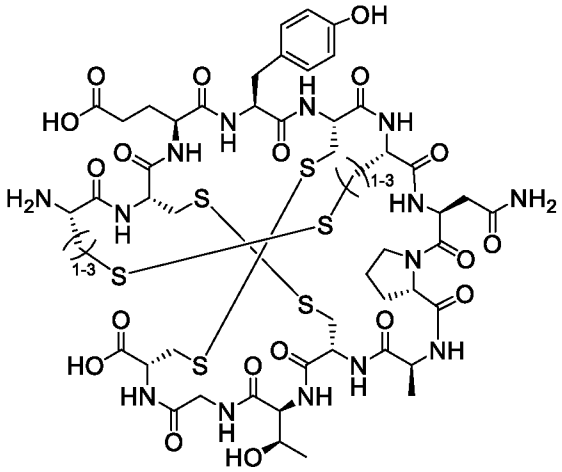
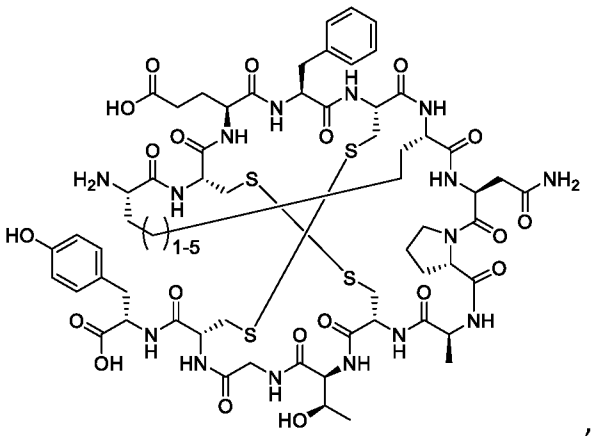
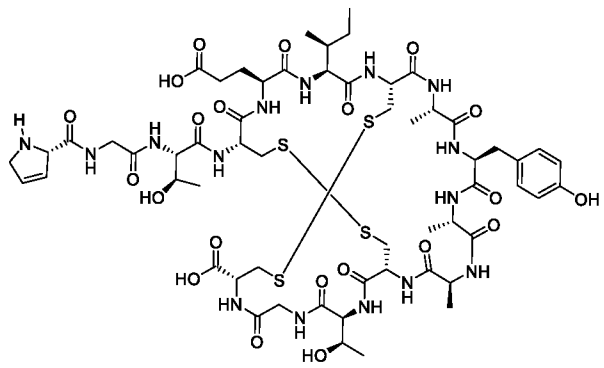
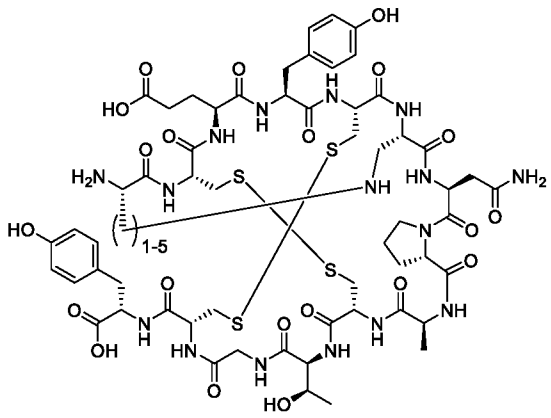
8. The conjugate of claim 7, wherein the binding peptide is selected from:



,



,

and .

9. The conjugate of any one of claims 1 to 6, wherein the binding peptide further comprises one intramolecular heteroalkylene, alkylene or alkenylene bond.

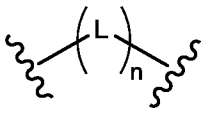
10. The conjugate of claim 9, wherein the heteroalkylene, alkylene or alkenylene is optionally substituted with one or more R^{10}, wherein

each R^{10} is independently halogen, amino, -OH, -SH, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{10} on the same atoms are taken together to form a cycloalkyl or heterocycloalkyl;

or two R^{10} on different atoms are taken together to form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

11. The conjugate of any one of claims 1 to 10, wherein the binding peptide comprises an unnatural amino acid at the N-terminus, the C-terminus, or both.
12. The conjugate of claim 11, wherein the binding peptide comprises a modified tyrosine at the C-terminus.
13. The conjugate of claim 12, wherein the modified tyrosine is a D-tyrosine, N-methyl-L-tyrosine, α-methyl-L-tyrosine, or L-tyrosinamide.
14. The conjugate of any one of claims 1 to 13, wherein the metal chelator is selected from DOTA, DOTP, DOTMA, DOTAGA, DOTAM, DTPA, NTA, EDTA, DO3A, DO2A, NOC, NOTA, TETA, DiAmSar, CB-Cyclam, CB-TE2A, DOTA-4AMP, and NOTP.
15. The conjugate of any one of claims 1 to 14, wherein the metal chelator is DOTA.
16. The conjugate of any one of claims 1 to 15, wherein the linker is a bond.
17. The conjugate of any one of claims 1 to 15, wherein the linker has a structure of Formula (II-1)



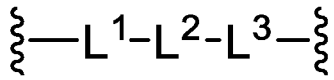
Formula (II-1)

wherein each L is independently -O-, $-NR^L$-, $-N(R^L)_2$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, =CH-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LC(=S)NR^L$-, $-CR^L=N$-, $-N=CR^L$, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, $-S(=O)_2NR^LC(=O)$-, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{30} alkylene, substituted or unsubstituted C_2-C_{30} alkenylene, substituted or unsubstituted C_2-C_{30} alkynylene, substituted or unsubstituted C_1-C_{30} heteroalkylene, -(C_1-C_{30} alkylene)-O-, -O-(C_1-C_{30} alkylene)-, -(C_1-C_{30} alkylene)-NR^L-, $-NR^L$-(C_1-C_{30} alkylene)-, -(C_1-C_{30} alkylene)-$N(R^L)_2$-, or $-N(R^L)_2$-(C_1-C_{30} alkylene)-; and

each R^L is independently hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

n is 1 to 20.

18. The conjugate of claim 17, wherein the linker comprises a structure of Formula (II-1a),



Formula (II-1a)

wherein each of L^1 and L^3 is independently -O-, $-NR^L-$, $-N(R^L)_2-$, $-OP(=O)(OR^L)O-$, -S-, -S(=O)-, $-S(=O)_2-$, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L-$, $-NR^LC(=O)-$, $-OC(=O)NR^L-$, $-NR^LC(=O)O-$, $-NR^LC(=O)NR^L-$, $-NR^LS(=O)_2-$, $-S(=O)_2NR^L-$, $-C(=O)NR^LS(=O)_2-$, or $-S(=O)_2NR^LC(=O)-$; and

L^2 is absent, substituted or unsubstituted C_1-C_{30} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene.

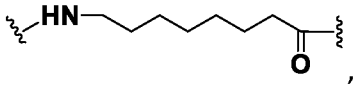
19. The conjugate of claim 18, wherein

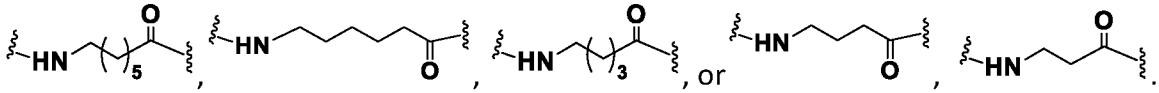
L^1 is -NH-;

L^3 is -C(=O)-;

L^2 is unsubstituted C_1-C_{12} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene, wherein the heteroalkylene is optionally substituted with one or more substituents selected from -OH, -SH, oxo, amino, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, and C_1-C_6 aminoalkyl.

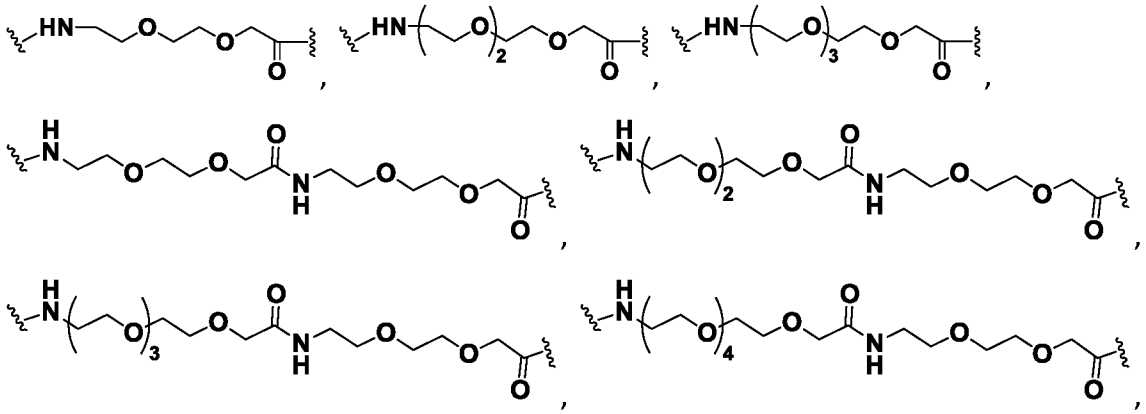
20. The conjugate of claim 18 or 19, wherein L^2 is unsubstituted C_1-C_{12} alkylene.

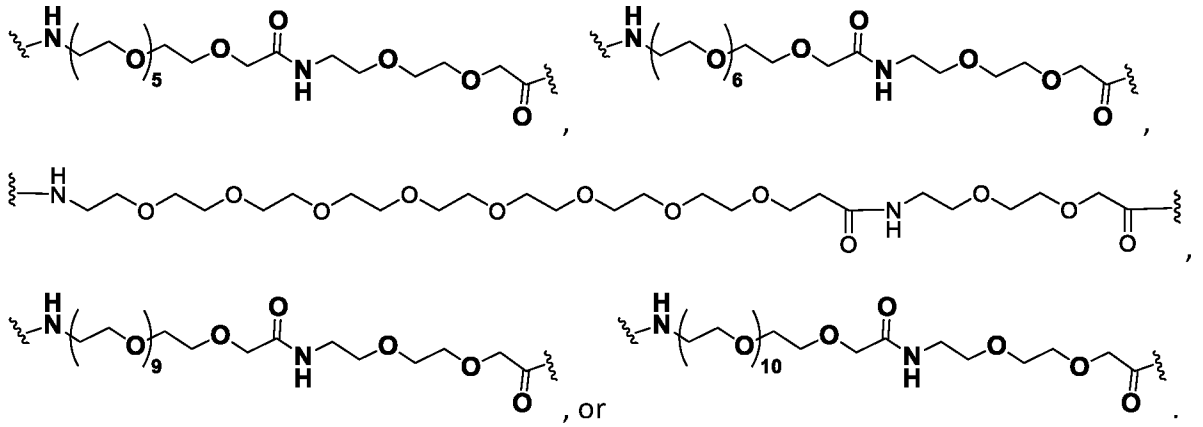
21. The conjugate of claim 20, wherein the linker has a structure of  ,



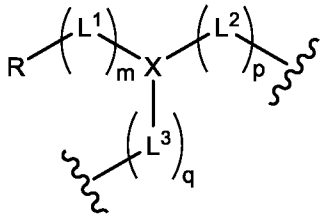
22. The conjugate of claim 18 or 19, wherein L^2 is C_1-C_{30} heteroalkylene that is optionally substituted with one or more substituents selected from -OH, -SH, oxo, amino, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, and C_1-C_6 aminoalkyl.

23. The conjugate of any one of claims 18, 19 or 22, wherein the linker has a structure of





24. The conjugate of any one of claims 1 to 15, wherein the linker has a structure of Formula (II-2)



Formula (II-2),

wherein each L^1, L^2, and L^3 is independently -O-, $-NR^L$-, $-N(R^L)_2$-, -OP(=O)(OR^L)O-, -S-, -S(=O)-, $-S(=O)_2$-, =CH-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, -C(=O)NR^L-, -NR^LC(=O)-, -OC(=O)NR^L-, -NR^LC(=O)O-, -NR^LC(=O)NR^L-, -NR^LC(=S)NR^L-, -CR^L=N-, -N=CR^L, -NR^LS(=O)$_2$-, -S(=O)$_2NR^L$-, -C(=O)NR^LS(=O)$_2$-, -S(=O)$_2NR^L$C(=O)-, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{30} alkylene, substituted or unsubstituted C_2-C_{30} alkenylene, substituted or unsubstituted C_2-C_{30} alkynylene, substituted or unsubstituted C_1-C_{30} heteroalkylene, -(C_1-C_{30} alkylene)-O-, -O-(C_1-C_{30} alkylene)-, -(C_1-C_{30} alkylene)-NR^L-, -NR^L-(C_1-C_{30} alkylene)-, -(C_1-C_{30} alkylene)-$N(R^L)_2$-, or -$N(R^L)_2$-(C_1-C_{30} alkylene)-; and

R is hydrogen, azide, substituted or unsubstituted C_1-C_{30} alkyl, substituted or unsubstituted C_1-C_{30} heteroalkyl, substituted or unsubstituted C_2-C_{30} alkenyl, substituted or unsubstituted C_2-C_{30} alkynyl, substituted or unsubstituted C_3-C_{30} cycloalkyl, substituted or unsubstituted C_2-C_{30} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R^L is independently hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted C_3-C_{30} cycloalkyl,

substituted or unsubstituted C_2-C_{30} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^X is independently hydrogen, halo, -CN, -NO_2, -OH, -SH, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted C_3-C_8 cycloalkyl, or substituted or unsubstituted C_2-C_7 heterocycloalkyl,

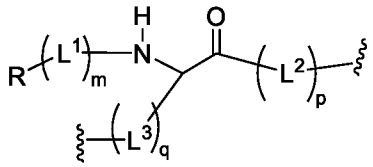
X is N or CR^X;

m is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

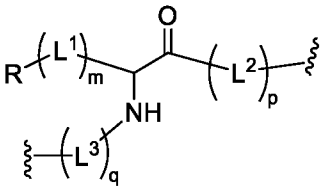
p is 0, 1, 2, 3, 4, 5, or 6; and

q is 0, 1, 2, 3, 4, 5, and 6.

25. The conjugate of claim 24, wherein the linker has a structure of Formula (II-2a) or Formula (II-2b)



Formula (II-2a) or



Formula (II-2b),

wherein

each L^1, L^2, and L^3 is independently -O-, –NR^L-, –$N(R^L)_2$-, -OP(=O)(OR^L)O-, -S-, -S(=O)-, -$S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, -C(=O)NR^L-, -NR^LC(=O)-, -OC(=O)NR^L-, -NR^LC(=O)O-, -NR^LC(=O)NR^L-, -$NR^L$$S(=O)_2$-, -$S(=O)_2NR^L$-, -C(=O)$NR^L$$S(=O)_2$-, -$S(=O)_2NR^L$C(=O)-, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{20} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene;

R^L is hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted C_3-C_8 cycloalkyl, or substituted or unsubstituted C_2-C_7 heterocycloalkyl;

R is hydrogen, azide, substituted or unsubstituted C_1-C_{30} alkyl, substituted or unsubstituted C_1-C_{30} heteroalkyl, substituted or unsubstituted C_2-C_{30} alkenyl, substituted or unsubstituted C_2-C_{30} alkynyl, substituted or unsubstituted C_3-C_{30} cycloalkyl, substituted or unsubstituted C_2-C_{30} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

m is 0, 1, 2, 3, 4, 5, 6, 7, 8, or 9;

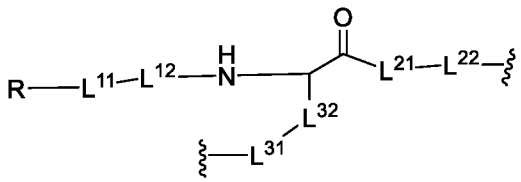
p is 0, 1, 2, 3, 4, or 5; and

q is 0, 1, 2, 3, 4, or 5.

26. The conjugate of claim 25, wherein the linker connects to the metal chelator through L^3 and to the peptide through L^2.

27. The conjugate of claim 25 or 26, wherein the linker has a structure of Formula (II-2a).

28. The conjugate of claim 27, wherein the linker of Formula (II-2a) has a structure of Formula (II-2aa),



Formula (II-2aa)

wherein,

L^{11} is absent, -O-, $-NR^L$-, $-N(R^L)_2$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, or $-S(=O)_2NR^LC(=O)$-;

L^{12} is absent, -O-, $-NR^L$-, $-N(R^L)_2$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, $-S(=O)_2NR^LC(=O)$-, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{20} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene;

L^{21} is absent, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{20} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene;

L^{22} is absent, -O-, $-NR^L$-, $-N(R^L)_2$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, or $-S(=O)_2NR^LC(=O)$-;

L^{31} is absent, -O-, $-NR^L$-, $-N(R^L)_2$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, or $-S(=O)_2NR^LC(=O)$-;

L^{32} is absent, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{20} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene;

R^L is hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted C_3-C_8 cycloalkyl, or substituted or unsubstituted C_2-C_7 heterocycloalkyl;

R is hydrogen, substituted or unsubstituted C_1-C_{30} alkyl, substituted or unsubstituted C_1-C_{30} heteroalkyl, substituted or unsubstituted C_2-C_{30} alkenyl, substituted or unsubstituted C_3-C_{30} cycloalkyl, substituted or unsubstituted C_2-C_{30} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

q is 0, 1, 2, 3, 4, or 5.

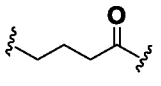
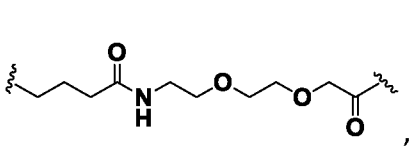
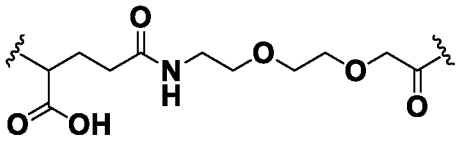
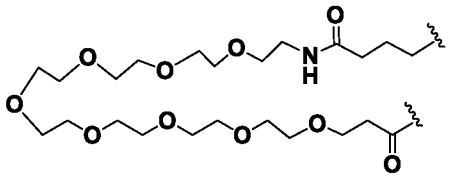
29. The conjugate of claim 28, wherein L^{31} is -NH- and L^{32} is substituted or unsubstituted C_1-C_{12} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene.

30. The conjugate of claim 29, wherein L^{31} is -NH- and L^{32} is $-(CH_2)_4-$.

31. The conjugate of any one of claims 28 to 30, wherein L^{11} is absent, -O-, $-OP(=O)(OR^L)O-$, -S-, $-S(=O)_2-$, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L-$, $-NR^LC(=O)-$, $-OC(=O)NR^L-$, $-NR^LC(=O)O-$, $-NR^LC(=O)NR^L-$, $-NR^LS(=O)_2-$, $-S(=O)_2NR^L-$, $-C(=O)NR^LS(=O)_2-$, or $-S(=O)_2NR^LC(=O)-$.

32. The conjugate of any one of claims 28 to 30, wherein L^{11} is absent, -OP(=O)(OH)O-, -NHC(=O)-, -C(=O)NH-, or $-S(=O)_2NH-$.

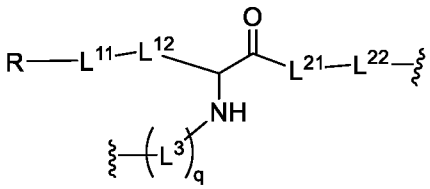
33. The conjugate of any one of claims 28 to 32, wherein L^{12} is absent, -O-, $-OP(=O)(OR^L)O-$, -S-, $-S(=O)_2-$, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L-$, $-NR^LC(=O)-$, $-OC(=O)NR^L-$, $-NR^LC(=O)O-$, $-NR^LC(=O)NR^L-$, $-NR^LS(=O)_2-$, $-S(=O)_2NR^L-$, $-C(=O)NR^LS(=O)_2-$, or $-S(=O)_2NR^LC(=O)-$, substituted or unsubstituted C_1-C_{12} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene.

34. The conjugate of any one of claims 28 to 33, wherein L^{12} is  ,  ,  , or  .

35. The conjugate of any one of claims 28 to 33, wherein L^{12} is -C(=O)- and L^{11} is absent.

36. The conjugate of claim 25 or 26, wherein the linker has a structure of Formula (II-2b).

37. The conjugate of claim 36, wherein the linker of Formula (II-2b) has a structure of Formula (II-2ba),



Formula (II-2ba)

wherein,

L^{11} is absent, -O-, $-NR^L$-, $-N(R^L)_2$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, or $-S(=O)_2NR^LC(=O)$-;

L^{12} is absent, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{20} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene;

L^{21} is absent, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{20} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene;

L^{22} is absent, -O-, $-NR^L$-, $-N(R^L)_2$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, or $-S(=O)_2NR^LC(=O)$-;

L^3 is -O-, $-NR^L$-, $-N(R^L)_2$-, -OP(=O)(OR^L)O-, -S-, -S(=O)-, $-S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, $-S(=O)_2NR^LC(=O)$-, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{20} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene;

R^L is hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted C_3-C_8 cycloalkyl, or substituted or unsubstituted C_2-C_7 heterocycloalkyl;

R is hydrogen, substituted or unsubstituted C_1-C_{30} alkyl, substituted or unsubstituted C_1-C_{30} heteroalkyl, substituted or unsubstituted C_2-C_{30} alkenyl, substituted or unsubstituted C_3-C_{30} cycloalkyl, substituted or unsubstituted C_2-C_{30} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

q is 0, 1, 2, 3, 4, or 5.

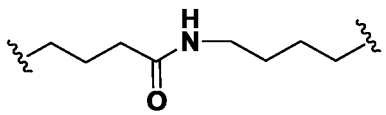
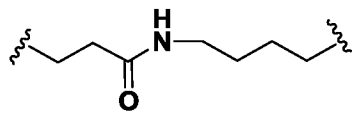
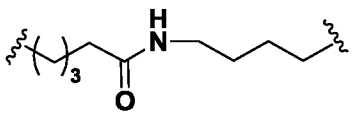
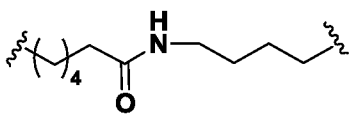
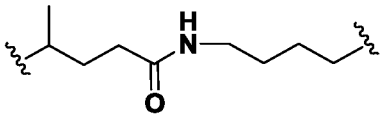
38. The conjugate of claim 36 or 37, wherein q is 0.

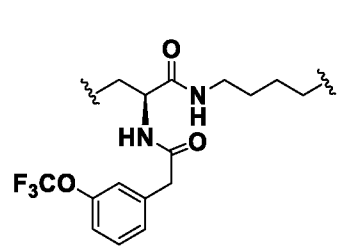
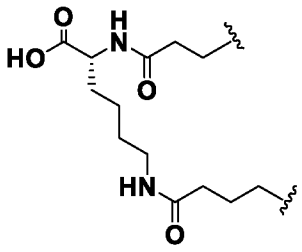
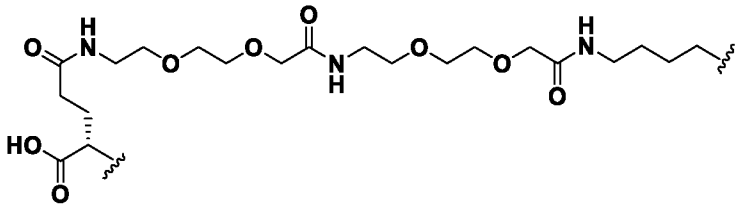
39. The conjugate of claim 37 or 38, wherein L^{11} is absent, -O-, -OP(=O)(OR^L)O-, -S-, $-S(=O)_2$-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, or $-S(=O)_2NR^LC(=O)$-.

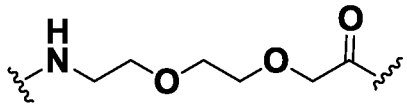
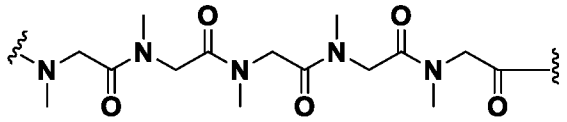
40. The conjugate of claim 37 or 38, wherein L^{11} is absent, -OP(=O)(OH)O-, -NHC(=O)-, -C(=O)NH-, or $-S(=O)_2NH$-.

41. The conjugate of any one of claims 37 to 40, wherein L^{12} is substituted or unsubstituted C_1-C_{12} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene.

42. The conjugate of any one of claims 37 to 41, wherein L^{12} is

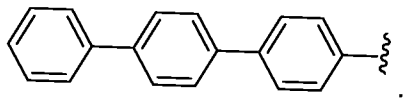

, 
, 
, 
, 
, $-(CH_2)_2$-, $-(CH_2)_3$-, $-(CH_2)_4$-,

-$(CH_2)_5$-, -$(CH_2)_6$-,  ,  , or  .

43. The conjugate of any one of claims 28 to 42, wherein L^{22} and L^{21} are both absent.
44. The conjugate of any one of claims 28 to 42, wherein L^{22} is -C(=O)- and L^{21} is substituted or unsubstituted C_1-C_{12} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene.
45. The conjugate of claim 44, wherein -L^{21}-L^{22}- is  or  .
46. The conjugate of any one of claims 24 to 45, wherein R is hydrogen, substituted or unsubstituted C_6-C_{10} aryl, substituted or unsubstituted C_5-C_9 heteroaryl, or a sterol.
47. The conjugate of claim 46, wherein R is phenyl, naphthyl, monocyclic heteroaryl, or bicyclic heteroaryl, each of which is optionally substituted with one or more substituents selected from halogen, -CN, -NO_2, -OR^a, -$N(R^a)_2$, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^aR^a, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl, wherein each R^a is independently H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl).
48. The conjugate of claim 46 or 47, wherein R is a phenyl optionally substituted with one or more substituents selected from halogen, -CN, -NO_2, -OH, amino, -$N(C_1$-C_6alkyl$)_2$, -$NH(C_1$-C_6alkyl), -C(=O)H, -C(=O)OH, -$C(=O)NH_2$, C_1-C_6alkyl, C_1-C_6alkoxyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-

C_6alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl.

49. The conjugate of any one of claims 46 to 48, wherein R is iodophenyl or



50. The conjugate of any one of claims 24 to 45, wherein R is substituted or unsubstituted C_1-C_{30} alkyl or substituted or unsubstituted C_2-C_{30} alkenyl, each of which is optionally substituted with one or more substituents selected from halogen, -CN, -NO_2, -OR^a, -$N(R^a)_2$, -$C(=O)R^a$, -$C(=O)OR^a$, -$C(=O)NR^aR^a$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl, wherein each R^a is independently H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl).

51. The conjugate of claim 50, wherein R is C_6-C_{30} fatty acid, C_6-C_{30} fatty alcohol or C_6-C_{30} alkyl.

52. The conjugate of any one of claims 1 to 15, 17, or 24, wherein the linker comprises a click chemistry residue.

53. The conjugate of any one of claims 1 to 52, wherein the linker comprises one or more of substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and one or more amino acids.

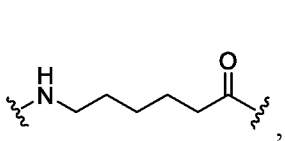
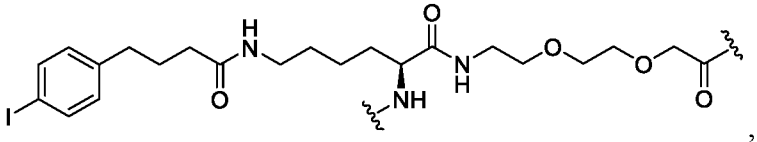
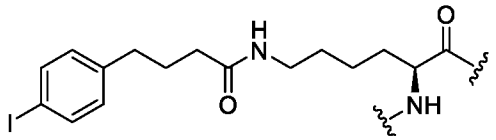
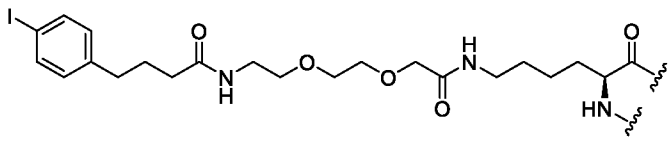
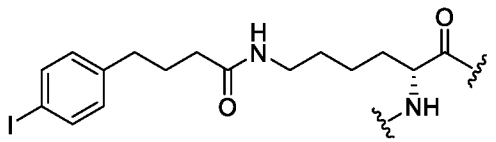
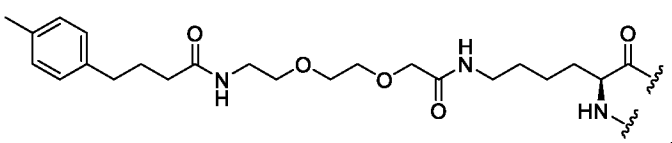
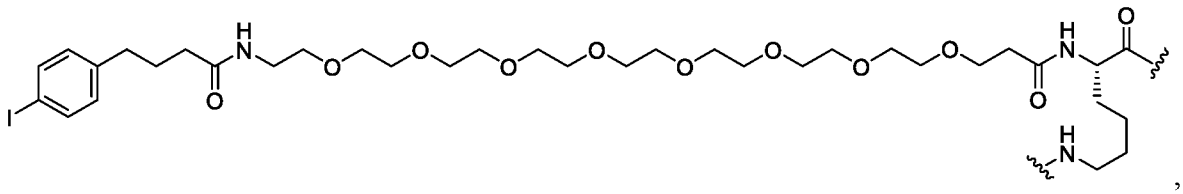
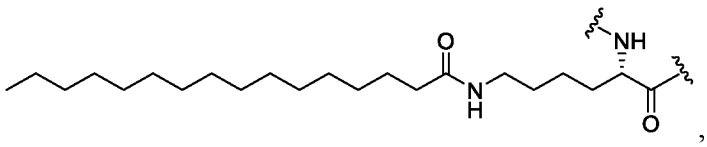
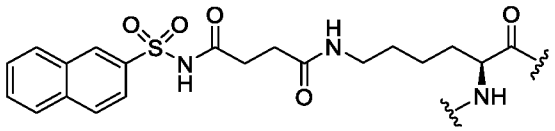
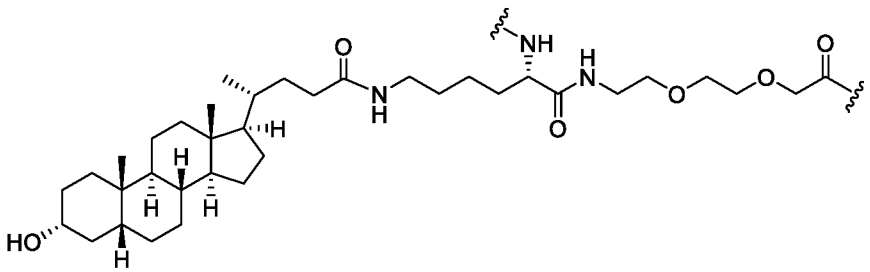
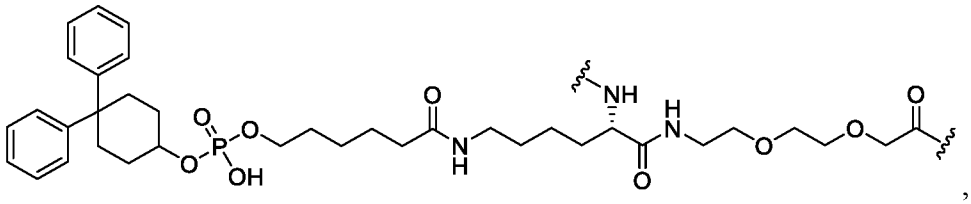
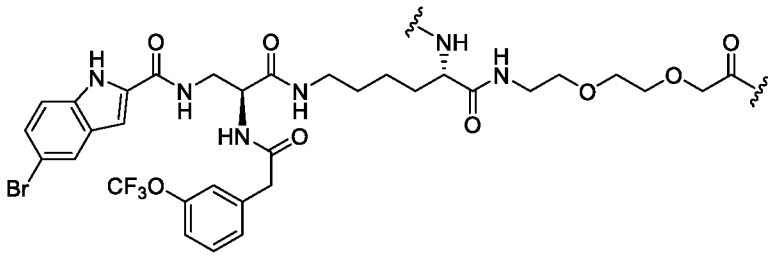
54. The conjugate of any one of claims 1 to 52, wherein the linker comprises one or more of a substituted or unsubstituted C_6-C_{10} aryl, substituted or unsubstituted C_5-C_9 heteroaryl, a sterol, sulfonamide, phosphate ester, polyethylene glycol, C_3-C_{20} alkylene, or amino acid residues.

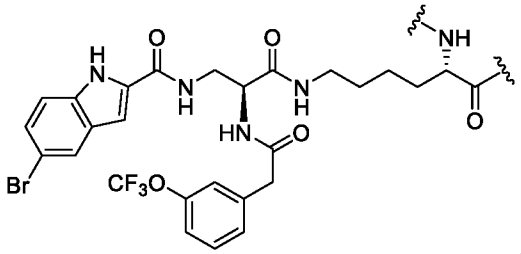
55. The conjugate of any one of claims 1 to 54, wherein the linker comprises one or more lysine residues.

56. The conjugate of any one of claims 1 to 55, wherein the linker comprises one or more glutamate residues.

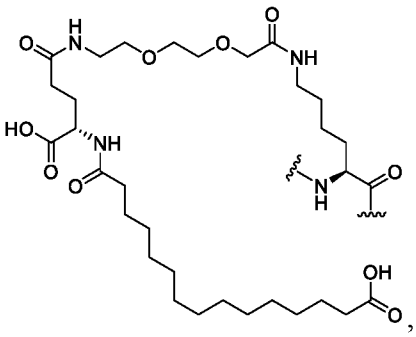
57. The conjugate of any one of claims 1 to 56, wherein the linker comprises phenyl iodide or carboxylic acid.

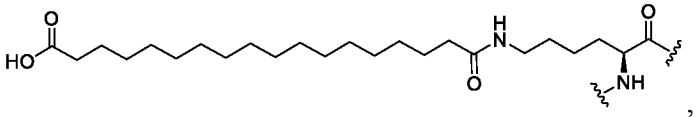
58. The conjugate of any one of claims 1 to 15, wherein the linker comprises or has a structure selected from:


,

,

,

,

,

,

,

,

,

,

,

,

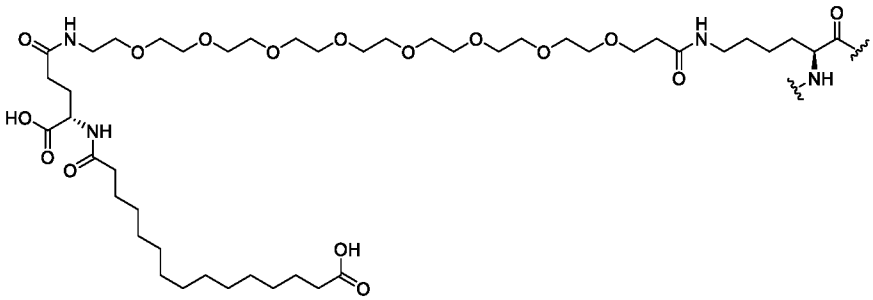


,

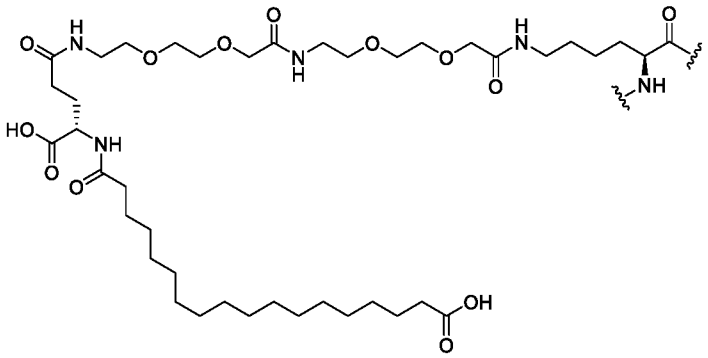




,



, and



.

59. The conjugate of any one of claims 1 to 58, wherein the linker comprises 3 to 30 intervening atoms between the metal chelator and the binding peptide.
60. The conjugate of any one of claims 1 to 58, wherein the linker comprises 6 to 18 intervening atoms between the metal chelator and the binding peptide.
61. The conjugate of any one of claims 1 to 60, wherein a dissociation constant (Kd) between the linker and human serum albumin is at most 25 μM, as determined in vitro at room temperature in human serum condition.
62. The conjugate of any one of claims 1 to 61, wherein about 40%-60% of the conjugate binds to HSA in vitro as determined by HSA-HPLC method.
63. The conjugate of any one of claims 1 to 61, wherein about 60%-80% of the conjugate binds to HSA in vitro as determined by HSA-HPLC method .

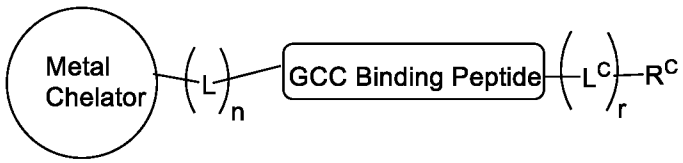
64. The conjugate of any one of claims 1 to 63, wherein the linker is attached to the binding peptide via the N terminus of the binding peptide.
65. The conjugate of claim 64, wherein the conjugate comprises a second linker attached to the C terminus of the binding peptide.
66. The conjugate of any one of claims 1 to 65, wherein the conjugate comprises an alpha particle-emitting radionuclide bound to the metal chelator.
67. The conjugate of claim 66, wherein the alpha particle-emitting radionuclide is actinium-225, astatine-211, radium-223, or thorium-227.
68. The conjugate of claim 66, wherein the alpha particle-emitting radionuclide is actinium-225.
69. The conjugate of any one of claims 1 to 68, wherein the conjugate comprises two or more metal chelators.
70. The conjugate of any one of claims 1 to 69, wherein the conjugate has an elimination half-life in rats of about 1 to 120 hours.
71. The conjugate of any one of claims 1 to 69, wherein the conjugate has an elimination half-life in rats of about 2 to 24 hours.
72. The conjugate of any one of claims 1 to 71, wherein a half-life of the conjugate in human serum condition is about 2 to 20 hours, 5 to 20 hours, 8 to 15 hours, or 10 to 14 hours at 37 °C.
73. A conjugate comprising

a guanylyl cyclase C (GCC) binding peptide;

a metal chelator configured to bind with a radionuclide; and

a linker that covalently attaches the GCC binding peptide with the metal chelator,

wherein the conjugate has a structure of Formula (I)



Formula (I)

wherein,

the linker $-(L)_n-$ comprises 2 to 50 intervening atoms between the metal chelator and the binding peptide;

each L is independently -O-, $-NR^L-$, $-OP(=O)(OR^L)O-$, -S-, -S(=O)-, $-S(=O)_2-$, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L-$, $-NR^LC(=O)-$, $-OC(=O)NR^L-$, $-NR^LC(=O)O-$, $-NR^LC(=O)NR^L-$, $-NR^LC(=S)NR^L-$, $-CR^L=N-$, $-N=CR^L$, $-NR^LS(=O)_2-$, $-S(=O)_2NR^L-$, $-C(=O)NR^LS(=O)_2-$, $-S(=O)_2NR^LC(=O)-$, substituted or unsubstituted C_1-C_{30} alkylene, substituted or unsubstituted C_2-C_{30} alkenylene, substituted or unsubstituted

C_2-C_{30} alkynylene, substituted or unsubstituted C_1-C_{30} heteroalkylene, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

L^C is absent, -O-, $-NR^L$-, -OP(=O)(OR^L)O-, -S-, -S(=O)-, -S(=O)$_2$-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, -C(=O)NR^L-, -NR^LC(=O)-, -OC(=O)NR^L-, -NR^LC(=O)O-, -NR^LC(=O)NR^L-, -NR^LC(=S)NR^L-, -CR^L=N-, -N=CR^L, -NR^LS(=O)$_2$-, -S(=O)$_2$$NR^L$-, -C(=O)$NR^L$S(=O)$_2$-, -S(=O)$_2$$NR^L$C(=O)-, substituted or unsubstituted C_1-C_{30} alkylene, substituted or unsubstituted C_2-C_{30} alkenylene, substituted or unsubstituted C_2-C_{30} alkynylene, substituted or unsubstituted C_1-C_{30} heteroalkylene, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or an amino acid;

each R^L is independently hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^C is hydrogen, halogen, -CN, -NO_2, -SR^a, -OR^a, -N(R^a)$_2$, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^aR^a, azide, substituted or unsubstituted C_1-C_{30} alkyl, substituted or unsubstituted C_1-C_{30} heteroalkyl, substituted or unsubstituted C_2-C_{30} alkenyl, substituted or unsubstituted C_2-C_{30} alkynyl, substituted or unsubstituted C_3-C_{30} cycloalkyl, substituted or unsubstituted C_2-C_{30} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl,

wherein each R^a is independently H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl);

n is 0 or an integer from 1 to 20; and

r is 0 or an integer from 1 to 5.

74. The conjugate of claim 73, wherein the linker –(L)$_n$- comprises 3 to 20 intervening atoms between the metal chelator and the binding peptide

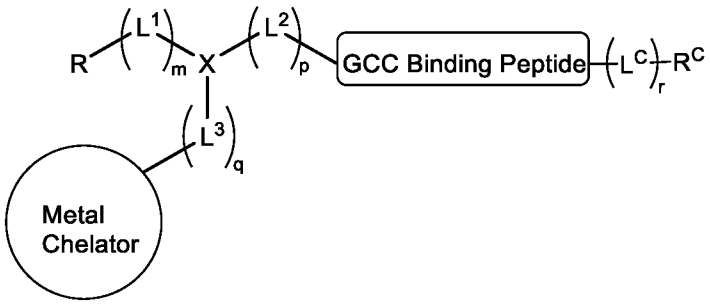
75. The conjugate of claim 73 or 74, wherein –(L)$_n$- is bound to the N-terminus of the GCC binding peptide and L^C is bound to the C-terminus of the GCC binding peptide.

76. The conjugate of any one of claims 73 to 75, wherein the linker –(L)$_n$- comprises a hydrophobic group selected from a C_8-C_{30} fatty acid, C_8-C_{30} fatty alcohol, C_8-C_{30} alkyl, aryl, heteroaryl, one or more amino acid residues, or a combination thereof.

77. The conjugate of any one of claims 73 to 76, wherein $-(L)_n-$ comprises one or more lysine residues.

78. The conjugate of any one of claims 73 to 76, wherein $-(L)_n-$ comprises one or more glutamate residues.

79. The conjugate of any one of claims 73 to 75, wherein the conjugate has a structure of Formula (Ia),



Formula (Ia)

wherein,

each L^1, L^2, and L^3 is independently -O-, $-NR^L-$, $-OP(=O)(OR^L)O-$, -S-, -S(=O)-, $-S(=O)_2-$, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L-$, $-NR^LC(=O)-$, $-OC(=O)NR^L-$, $-NR^LC(=O)O-$, $-NR^LC(=O)NR^L-$, $-NR^LC(=S)NR^L-$, $-CR^L=N-$, $-N=CR^L$, $-NR^LS(=O)_2-$, $-S(=O)_2NR^L-$, $-C(=O)NR^LS(=O)_2-$, $-S(=O)_2NR^LC(=O)-$, substituted or unsubstituted C_1-C_{30} alkylene, substituted or unsubstituted C_2-C_{30} alkenylene, substituted or unsubstituted C_2-C_{30} alkynylene, substituted or unsubstituted C_1-C_{30} heteroalkylene, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R and R^C are each independently hydrogen, halogen, -CN, $-NO_2$, $-SR^a$, $-OR^a$, $-N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, azide, substituted or unsubstituted C_1-C_{30} alkyl, substituted or unsubstituted C_1-C_{30} heteroalkyl, substituted or unsubstituted C_2-C_{30} alkenyl, substituted or unsubstituted C_2-C_{30} alkynyl, substituted or unsubstituted C_3-C_{30} cycloalkyl, substituted or unsubstituted C_2-C_{30} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl,

wherein each R^a is independently H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl);

R^L is hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted C_3-C_{30} cycloalkyl, substituted or unsubstituted C_2-C_{30} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^X is independently hydrogen, halo, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted C_3-C_8 cycloalkyl, or substituted or unsubstituted C_2-C_7 heterocycloalkyl,

X is N or CR^X;

m is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

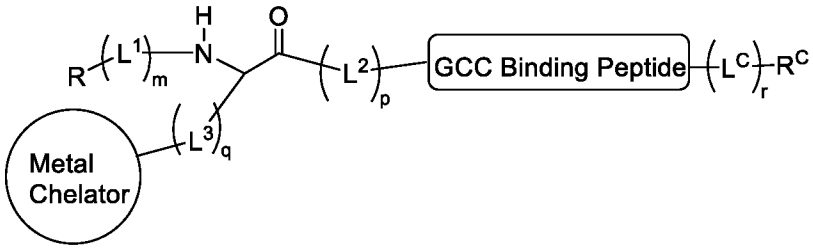
p is 0, 1, 2, 3, 4, 5, or 6;

q is 0, 1, 2, 3, 4, 5, or 6; and

r is 0, 1, 2, 3, 4, or 5.

80. The conjugate of claim 79, wherein at least one of L^1, L^2, and L^3 comprises a hydrophobic group selected from a C_8-C_{30} fatty acid, C_8-C_{30} fatty alcohol, C_4-C_{12} alkylene chain, heteroaryl, or aryl group, each of which is optionally substituted.

81. The conjugate of claim 79 or 80, wherein the conjugate has a structure of Formula (Iaa),



Formula (Iaa)

wherein

each L^1, L^2, and L^3 is independently -O-, $-NR^L$-, $-N(R^L)_2$-, $-OP(=O)(OR^L)O$-, -S-, -S(=O)-, $-S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, $-C(=O)NR^L$-, $-NR^LC(=O)$-, $-OC(=O)NR^L$-, $-NR^LC(=O)O$-, $-NR^LC(=O)NR^L$-, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, $-S(=O)_2NR^LC(=O)$-, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{20} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene;

R^L is hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted C_3-C_8 cycloalkyl, or substituted or unsubstituted C_2-C_7 heterocycloalkyl;

R is hydrogen, azide, substituted or unsubstituted C_1-C_{30} alkyl, substituted or unsubstituted C_1-C_{30} heteroalkyl, substituted or unsubstituted C_2-C_{30} alkenyl, substituted or unsubstituted C_2-C_{30} alkynyl, substituted or unsubstituted C_3-C_{30} cycloalkyl, substituted

or unsubstituted C_2-C_{30} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

L^C is absent, -O-, $-NR^L$-, -OP(=O)(OR^L)O-, -S-, -S(=O)-, -$S(=O)_2$-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, -C(=O)NR^L-, -NR^LC(=O)-, -OC(=O)NR^L-, -NR^LC(=O)O-, -NR^LC(=O)NR^L-, -NR^LC(=S)NR^L-, -CR^L=N-, -N=CR^L, -$NR^L$$S(=O)_2$-, -$S(=O)_2NR^L$-, -C(=O)$NR^L$$S(=O)_2$-, -$S(=O)_2NR^L$C(=O)-, substituted or unsubstituted C_1-C_{30} alkylene, substituted or unsubstituted C_2-C_{30} alkenylene, substituted or unsubstituted C_2-C_{30} alkynylene, substituted or unsubstituted C_1-C_{30} heteroalkylene, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or an amino acid;

R^C is hydrogen, halogen, -CN, -NO_2, -SR^a, -OR^a, -$N(R^a)_2$, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^aR^a, azide, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_1-C_{12} heteroalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl,

wherein each R^a is independently H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl);

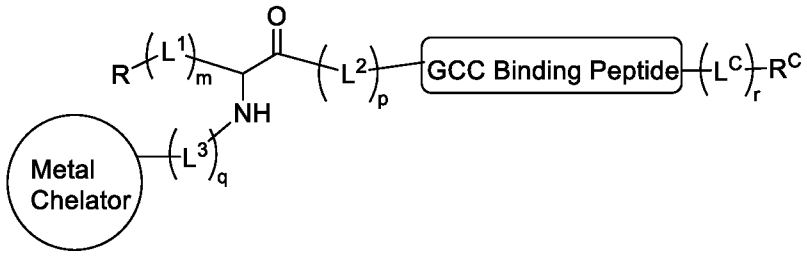
m is 0, 1, 2, 3, 4, 5, 6, 7, 8, or 9;

r is 0, 1, 2, 3, 4, or 5;

p is 0, 1, 2, 3, 4, or 5; and

q is 0, 1, 2, 3, 4, or 5.

82. The conjugate of 79 or 80, wherein the conjugate has a structure of Formula (Iab),



Formula (Iab)

wherein

each L^1, L^2, and L^3 is independently -O-, $-NR^L$-, $-N(R^L)_2$-, -OP(=O)(OR^L)O-, -S-, -S(=O)-, -$S(=O)_2$-, -CH=CH-, =CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, -C(=O)NR^L-, -NR^LC(=O)-, -OC(=O)NR^L-, -NR^LC(=O)O-, -NR^LC(=O)NR^L-, -$NR^L$$S(=O)_2$-, -$S(=O)_2NR^L$-, -C(=O)$NR^L$$S(=O)_2$-, -$S(=O)_2NR^L$C(=O)-, substituted or

unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_{20} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene;

R^L is hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 heteroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_5 alkynyl, substituted or unsubstituted C_3-C_8 cycloalkyl, or substituted or unsubstituted C_2-C_7 heterocycloalkyl;

R is hydrogen, azide, substituted or unsubstituted C_1-C_{30} alkyl, substituted or unsubstituted C_1-C_{30} heteroalkyl, substituted or unsubstituted C_2-C_{30} alkenyl, substituted or unsubstituted C_2-C_{30} alkynyl, substituted or unsubstituted C_3-C_{30} cycloalkyl, substituted or unsubstituted C_2-C_{30} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

L^C is absent, -O-, $-NR^L$-, -OP(=O)(OR^L)O-, -S-, -S(=O)-, -S(=O)$_2$-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, -C(=O)NR^L-, -NR^LC(=O)-, -OC(=O)NR^L-, -NR^LC(=O)O-, -NR^LC(=O)NR^L-, -NR^LC(=S)NR^L-, -CR^L=N-, -N=CR^L, -NR^LS(=O)$_2$-, -S(=O)$_2$$NR^L$-, -C(=O)$NR^L$S(=O)$_2$-, -S(=O)$_2$$NR^L$C(=O)-, substituted or unsubstituted C_1-C_{30} alkylene, substituted or unsubstituted C_2-C_{30} alkenylene, substituted or unsubstituted C_2-C_{30} alkynylene, substituted or unsubstituted C_1-C_{30} heteroalkylene, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or an amino acid;

R^C is hydrogen, halogen, -CN, -NO_2, -SR^a, -OR^a, -$N(R^a)_2$, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^aR^a, azide, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_1-C_{12} heteroalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl,

wherein each R^a is independently H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl);

m is 0, 1, 2, 3, 4, 5, 6, 7, 8, or 9;

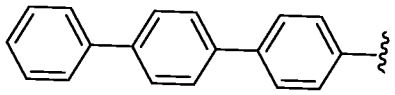
r is 0, 1, 2, 3, 4, or 5;

p is 0, 1, 2, 3, 4, or 5; and

q is 0, 1, 2, 3, 4, or 5.

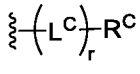
83. The conjugate of any one of claims 73 to 82, R is hydrogen, substituted or unsubstituted C_6-C_{10} aryl, substituted or unsubstituted C_5-C_9 heteroaryl, or a sterol.

84. The conjugate of claim 83, wherein R is phenyl, naphthyl, monocyclic heteroaryl, or bicyclic heteroaryl, each of which is optionally substituted with one or more substituents selected from halogen, -CN, -NO_2, -OR^a, -$N(R^a)_2$, -$C(=O)R^a$, -$C(=O)OR^a$, -$C(=O)NR^aR^a$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl, wherein each R^a is independently H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl).

85. The conjugate of claim 83, wherein R is iodophenyl or  .

86. The conjugate of any one of claims 73 to 82, wherein R is C_6-C_{30} fatty acid, C_6-C_{30} fatty alcohol or C_6-C_{30} alkyl.

87. The conjugate of any one of claims 73 to 86, wherein R^c is a C_6-C_{30} fatty acid, C_6-C_{30} fatty alcohol or C_6-C_{30} alkyl.

88. The conjugate of any one of claims 73 to 86, wherein  is -OH or NH_2.

89. The conjugate of any one of claims 73 to 88, wherein the binding peptide comprises an unnatural amino acid, e.g., at the C-terminus.

90. The conjugate any one of claims 73 to 89, wherein the binding peptide comprises a modified tyrosine at the C-terminus.

91. The conjugate of any one of claims 73 to 90, wherein the GCC binding peptide comprises an amino acid sequence that has at least 85% identity to any one of SEQ ID NOs: 1-42.

92. The conjugate of any one of claims 73 to 90, wherein the GCC binding peptide comprises an amino acid sequence selected from SEQ ID NOs: 1-42.

93. The conjugate of any one of claims 73 to 92, wherein the GCC binding peptide further comprises 1 to 3 intramolecular bonds selected from heteroalkylene, alkylene and alkenylene bonds.

94. The conjugate of any one of claims 73 to 93, wherein the metal chelator is selected from DOTA, DOTP, DOTMA, DOTAGA, DOTAM, DTPA, NTA, EDTA, DO3A, DO2A, NOC, NOTA, TETA, DiAmSar, CB-Cyclam, CB-TE2A, DOTA-4AMP, or NOTP.

95. The conjugate of claim 93, wherein the metal chelator is DOTA.

96. The conjugate of any one of claims 73 to 95, wherein the conjugate comprises a radionuclide bound to the metal chelator.

97. The conjugate of claim 96, wherein the radionuclide is an alpha particle-emitting radionuclide selected from actinium-225, astatine-211, radium-223, and thorium-227.

98. The conjugate of claim 96, wherein the radionuclide is lutetium-177 or actinium-225.

99. A conjugate having a structure selected from Table 1.

100. A conjugate comprising: a structure selected from Table 1 and a radionuclide bound to a metal chelator of the structure.

101. A conjugate, wherein the conjugate is a salt or solvate of a conjugate of any one of the preceding claims.

102. A pharmaceutical composition comprising a conjugate of any one of claims 1 to 101, and a pharmaceutically acceptable excipient or carrier.

103. A method of treating a gastrointestinal tract cancer in a subject in need thereof, comprising administering to the subject a conjugate of any one of claims 1 to 101, or a pharmaceutical composition of claim 102.

104. The method of claim 103, wherein the cancer is colorectal cancer.

105. The method of claim 103 or 104, wherein the method comprises administering a second therapeutic agent that is a GCC receptor agonist.

106. The method of claim 103 or 104, wherein the method comprises administering (i) a first conjugate comprising a radionuclide configured for companion diagnostic and (ii) a second conjugate comprising a radionuclide selected from an alpha or beta-particle emitter, wherein the first and the second conjugate have the same structure except for the radionuclide.

107. The method of claim 106, wherein the radionuclide of the first conjugate is selected from Lu-177, In-111, Ga-68, Cu-64, and Zr-89.

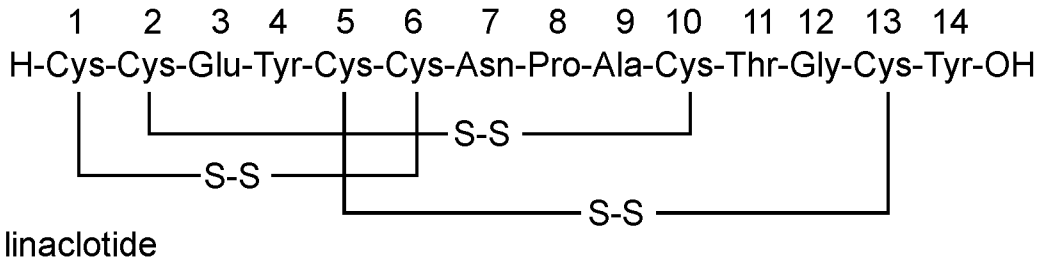


FIG. 1A

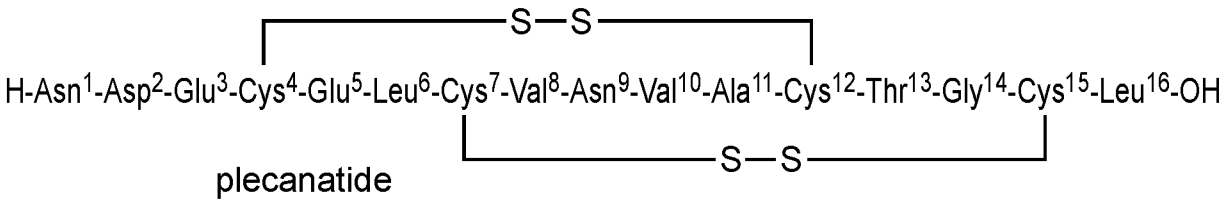


FIG. 1B

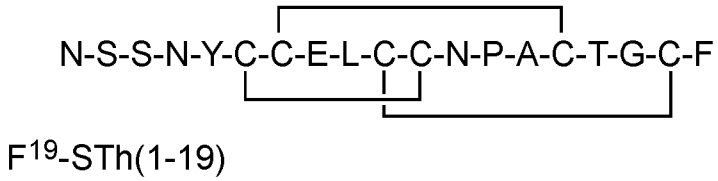


FIG. 1C

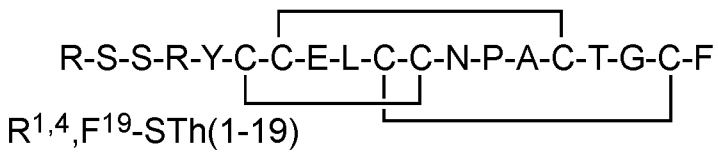


FIG. 1D

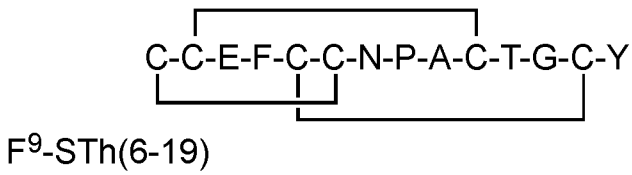
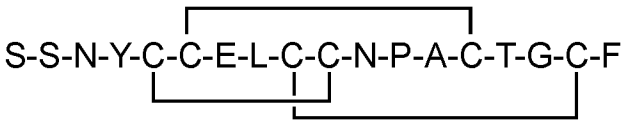


FIG. 1E



F^{19}-STh(2-19)

FIG. 1F

uroguanylin

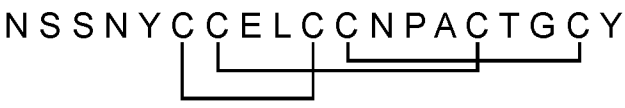
FIG. 1G

guanylin

FIG. 1H

lymphoguanylin

FIG. 1I



E. coli ST

FIG. 1J

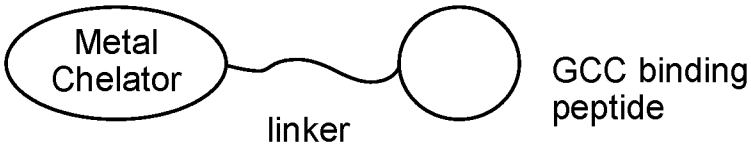


FIG. 2A

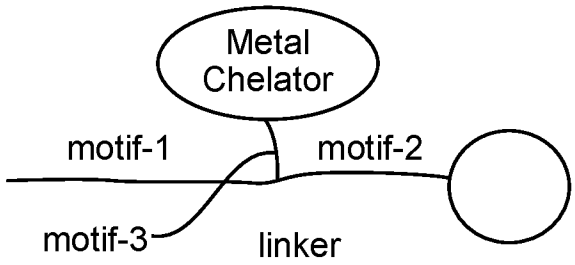


FIG. 2B

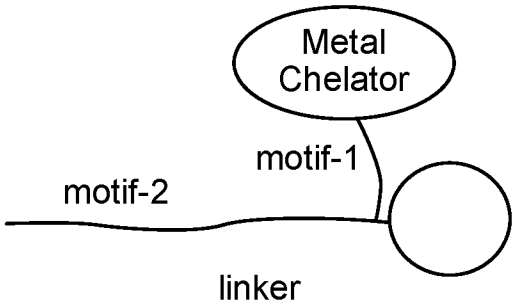


FIG. 2C

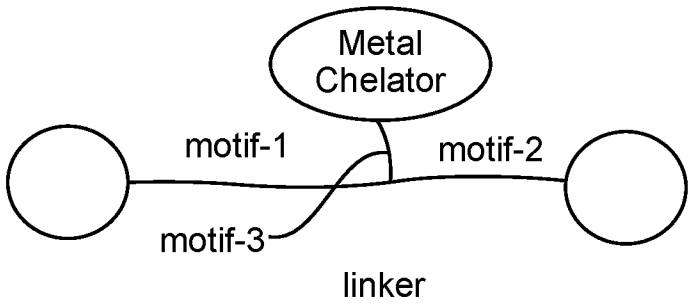
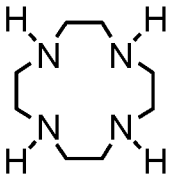
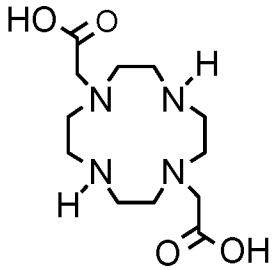


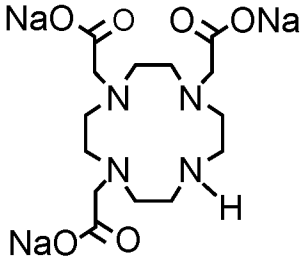
FIG. 2D



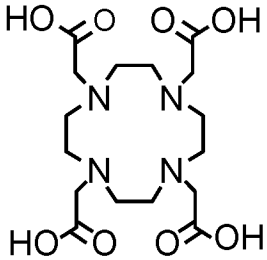
Cyclen



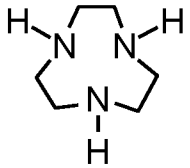
DO2A



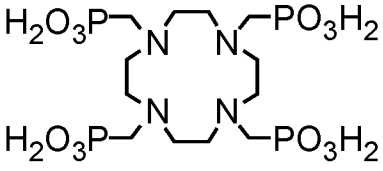
DO3A



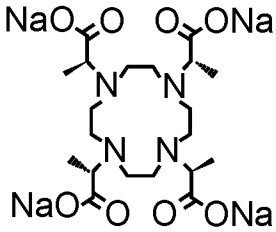
DOTA



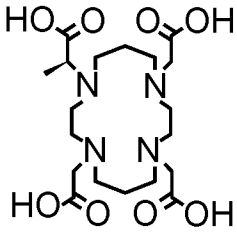
TACN



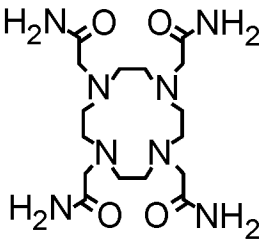
DOTP



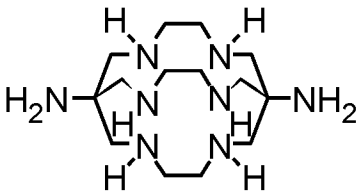
DOTMA



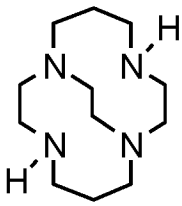
TETA



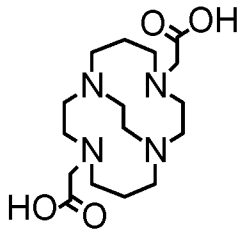
DOTAM



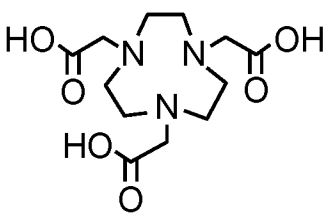
DiAmSar



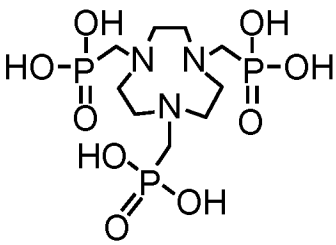
CB-Cyclam



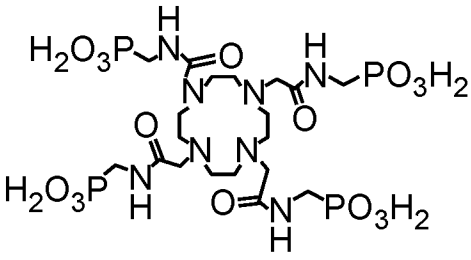
CB-TE2A



NOTA



NOTP



DOTA-4AMP

FIG. 3

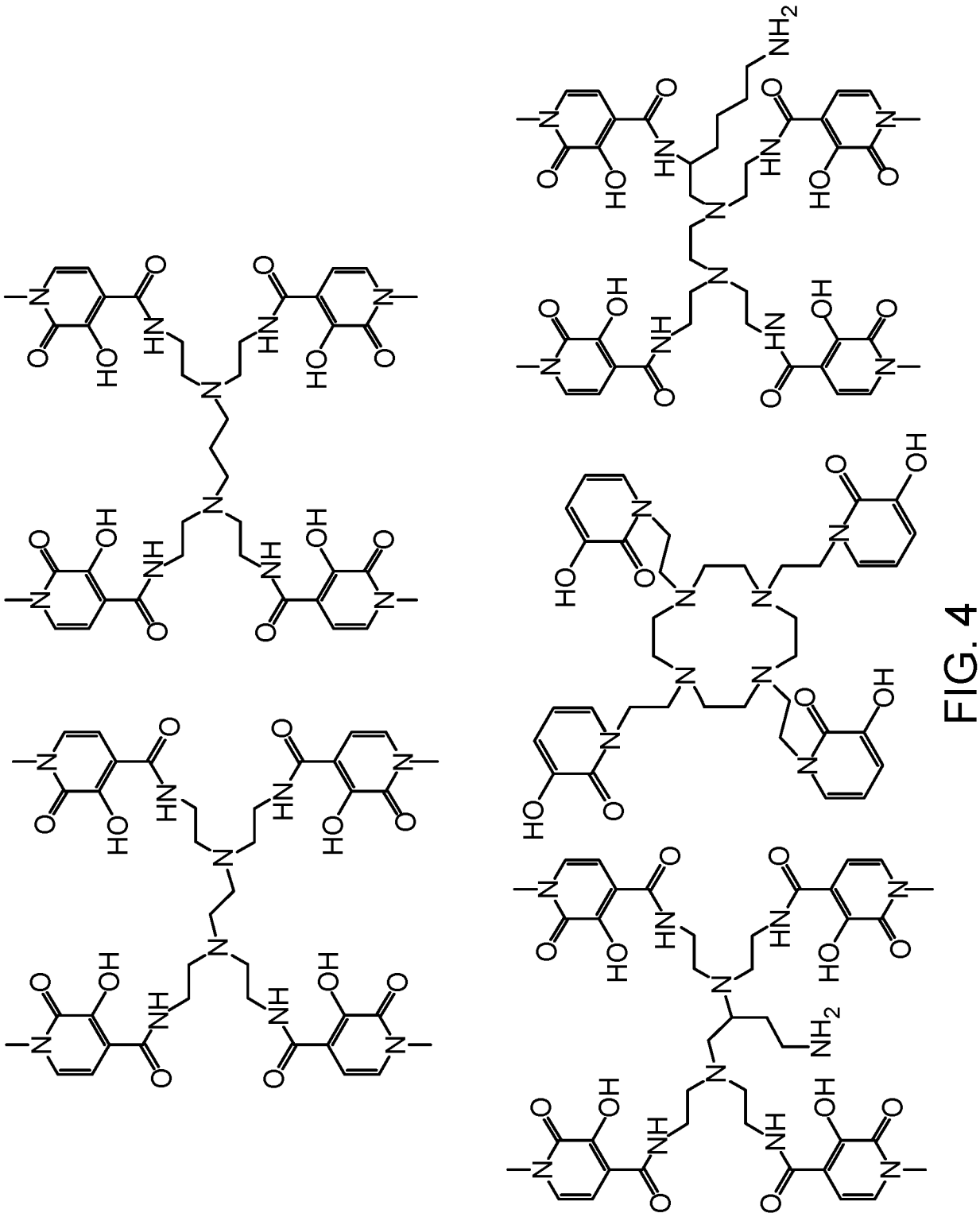


FIG. 4

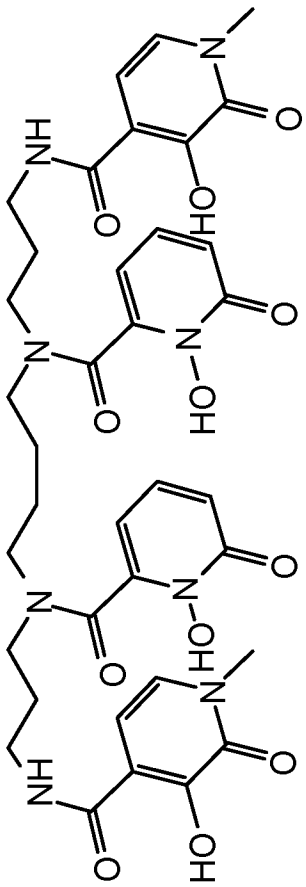


FIG. 4 (Cont.)

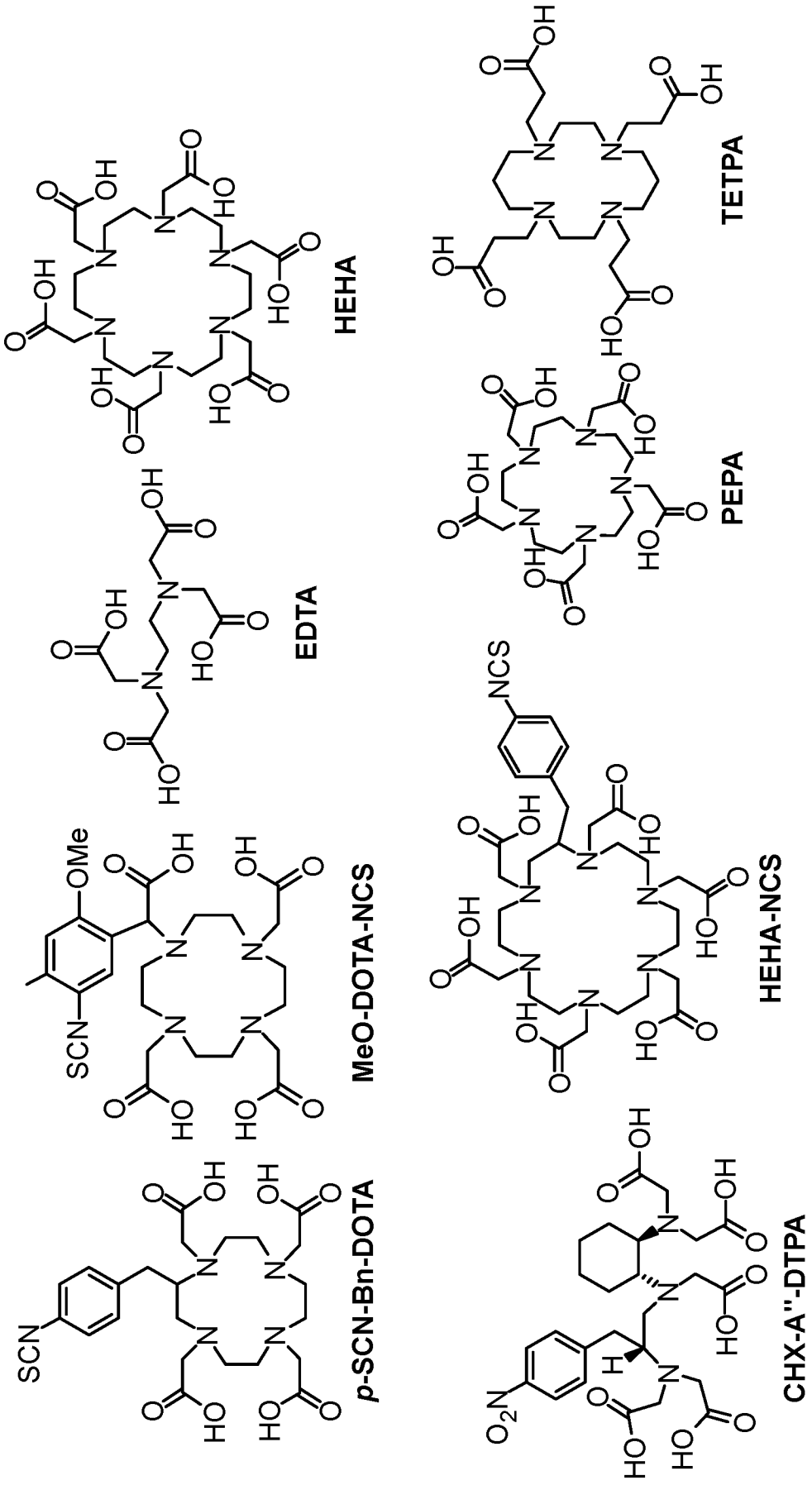

HEHA
TETPA
EDTA
PEPA
MeO-DOTA-NCS
HEHA-NCS
p-SCN-Bn-DOTA
CHX-A''-DTPA

FIG. 5

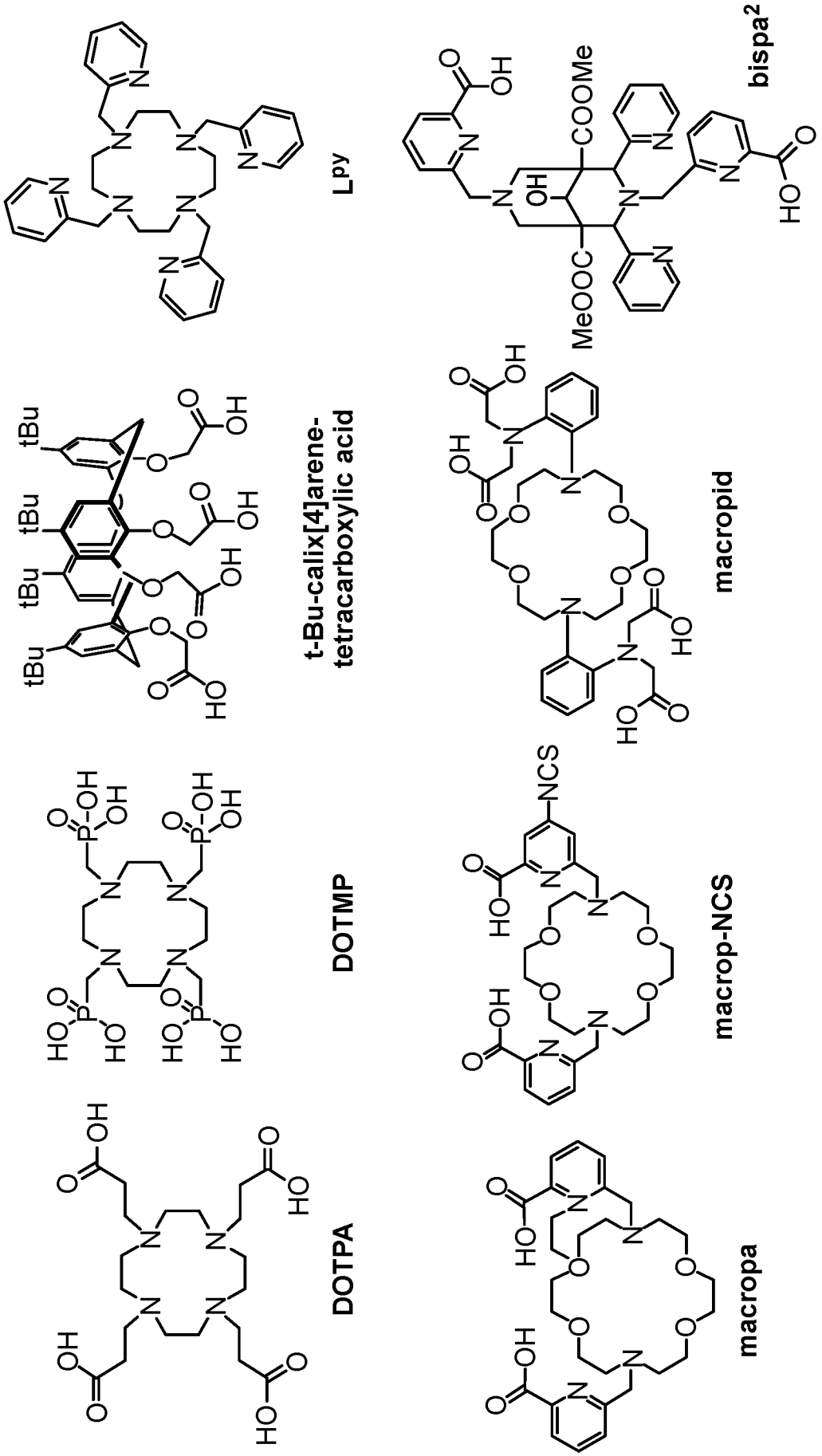
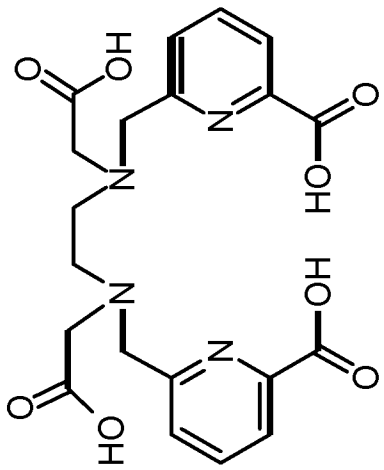
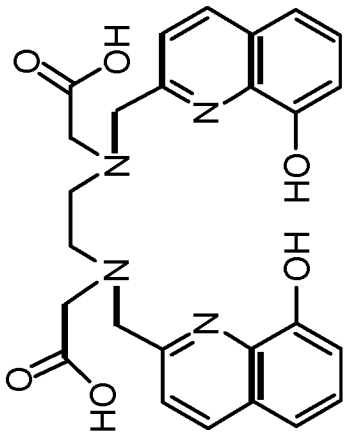

L^py
bispa^2
t-Bu-calix[4]arene-tetracarboxylic acid
macropid
DOTMP
macrop-NCS
DOTPA
macropa

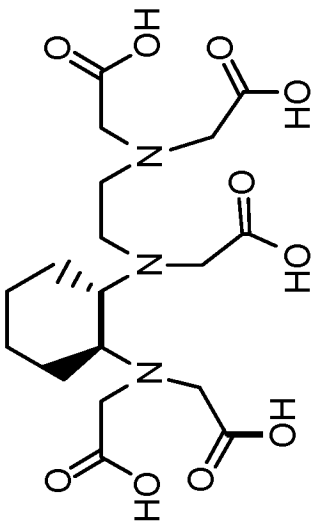
FIG. 5 (Cont.)



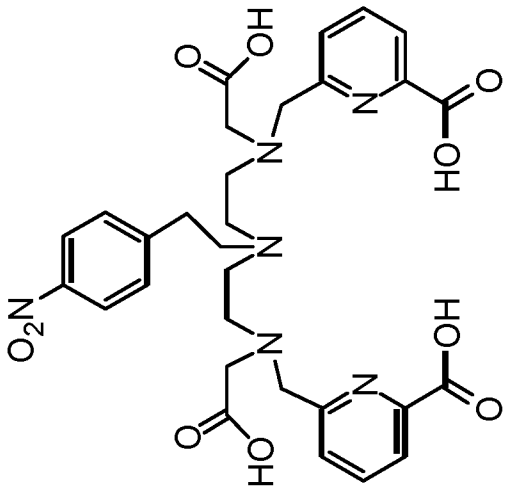
H_4octapa



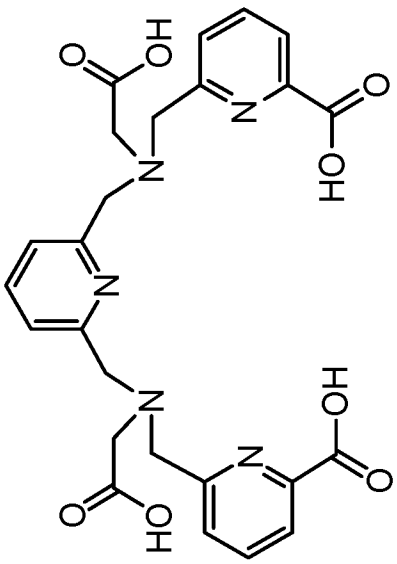
H_4octox



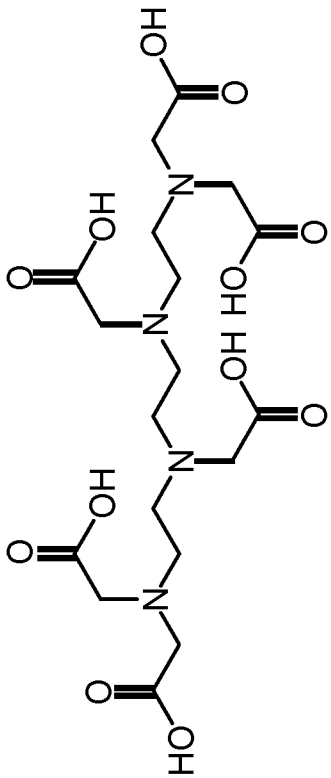
CHX-A''-DTPA



p-NO_2-Bn-neunpa

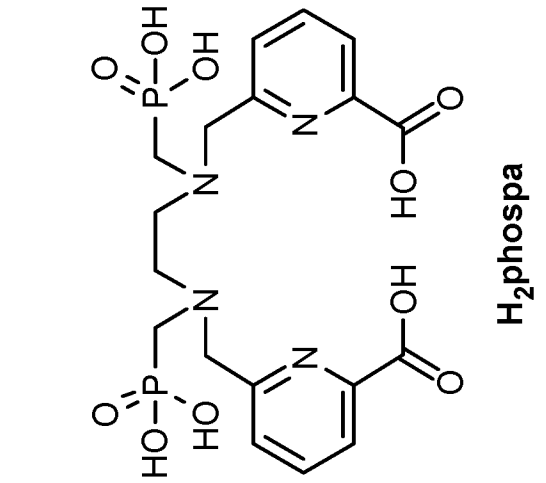


H_4pypa

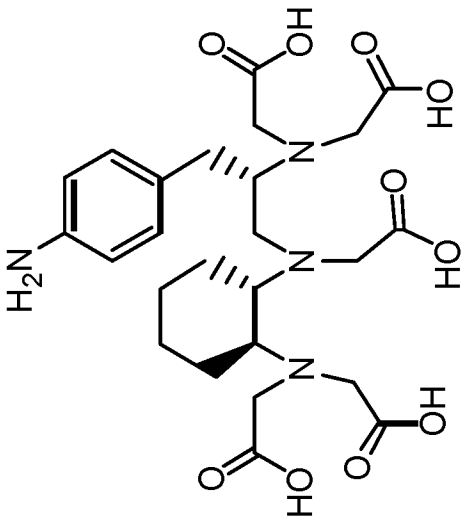


TTHA

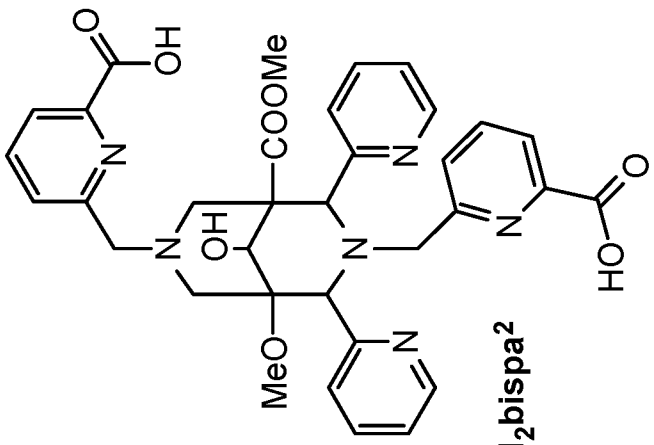
FIG. 6



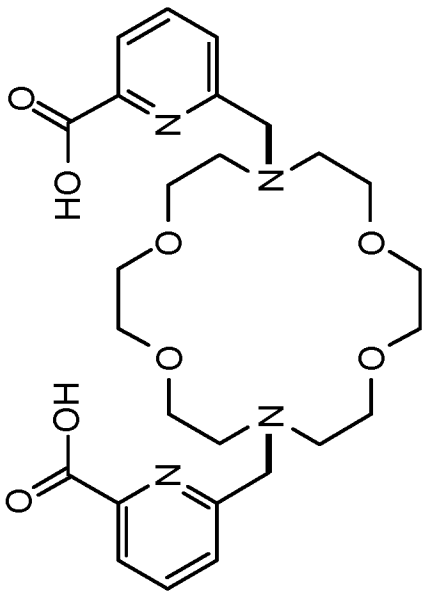
H_2phospa



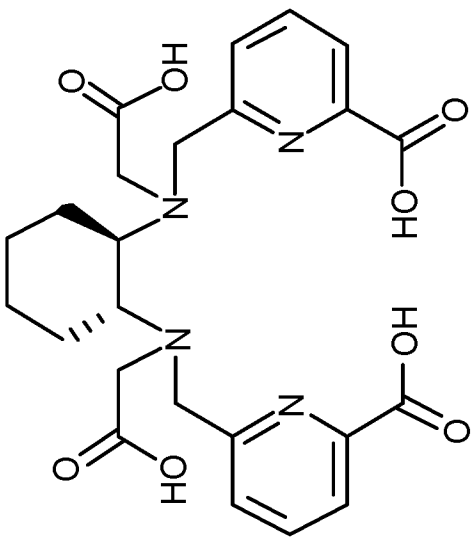
p-NH_2-Bn-CHX-A''-DTPA



H_2bispa^2



H_2macropa



H_4*CH*Xoctapa

FIG. 6 (Cont.)

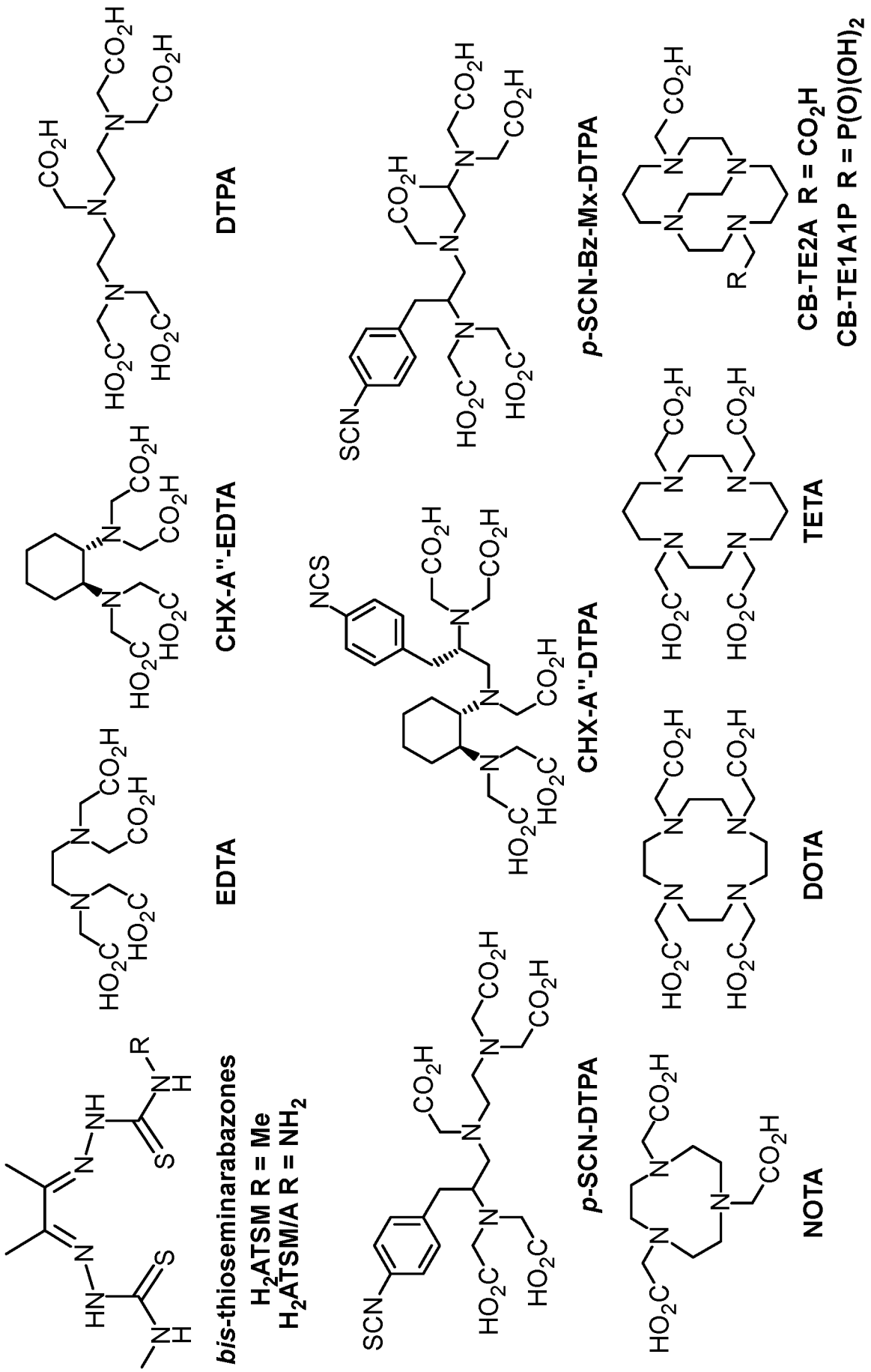

bis-thioseminarabazones
H2ATSM R = Me
H2ATSM/A R = NH2
EDTA
DTPA
CHX-A''-EDTA
p-SCN-DTPA
CHX-A''-DTPA
p-SCN-Bz-Mx-DTPA
DOTA
TETA
NOTA
CB-TE2A R = CO2H
CB-TE1A1P R = P(O)(OH)2

FIG. 7

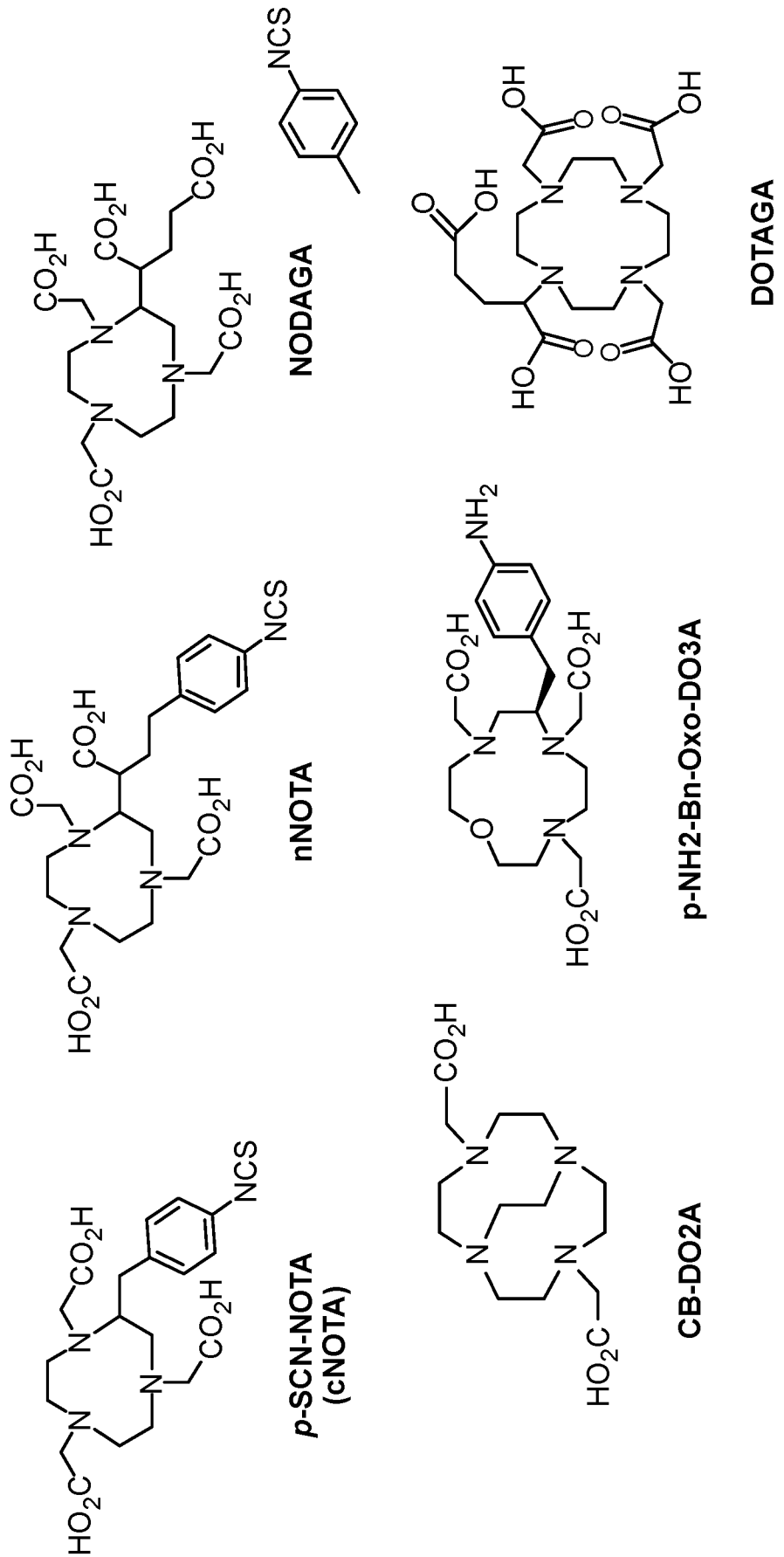


FIG. 7 (Cont.)

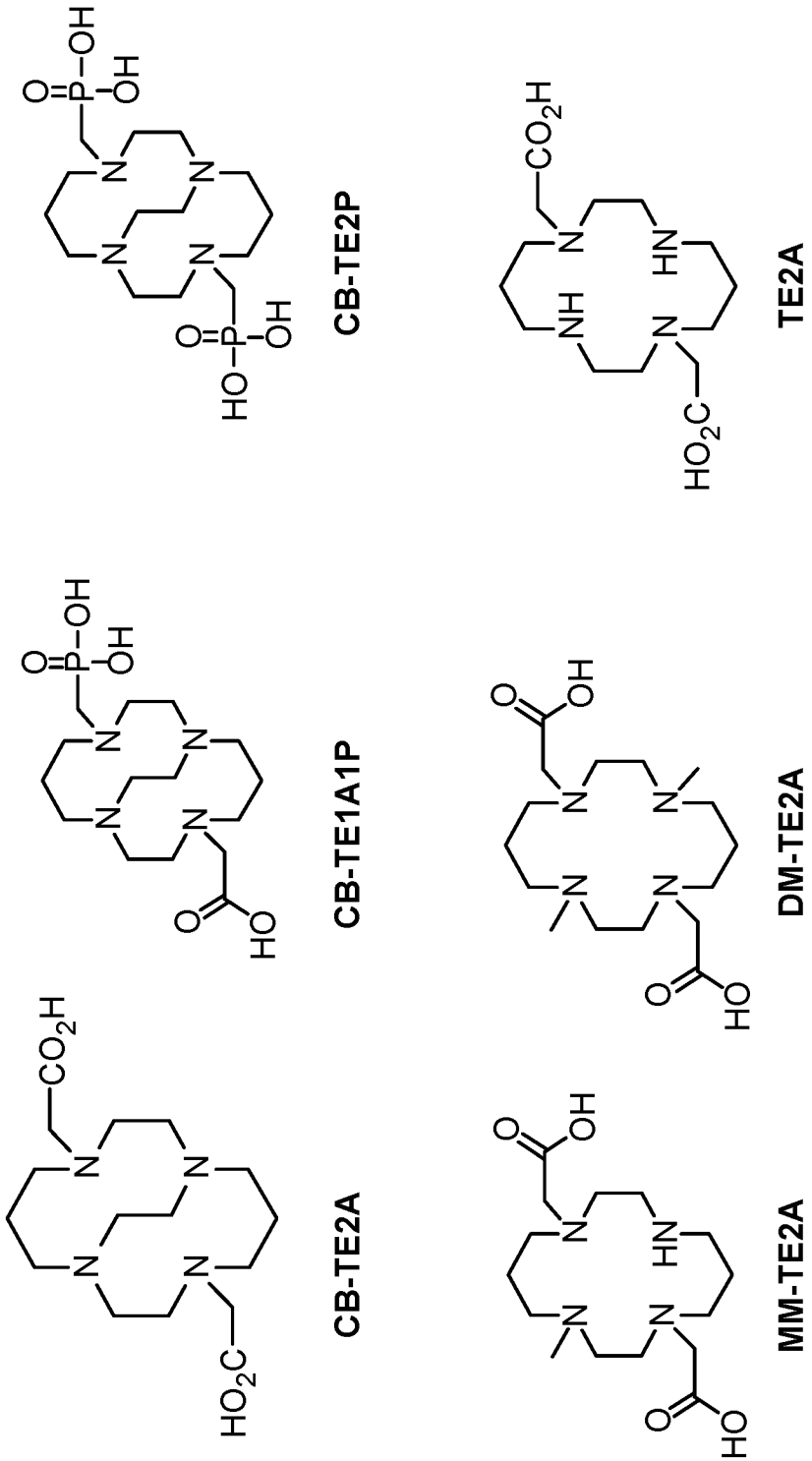


FIG. 8

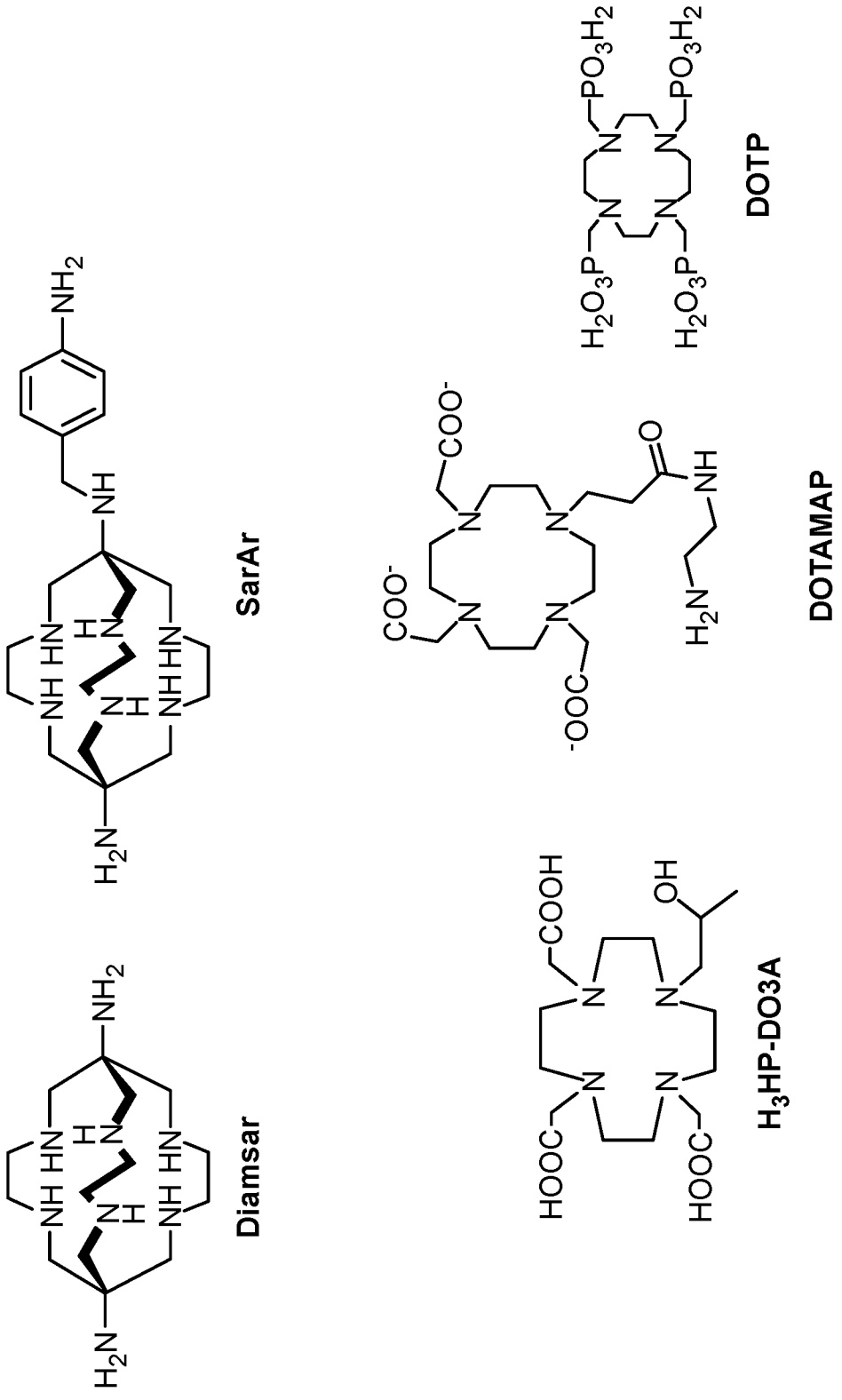


FIG. 8 (Cont.)

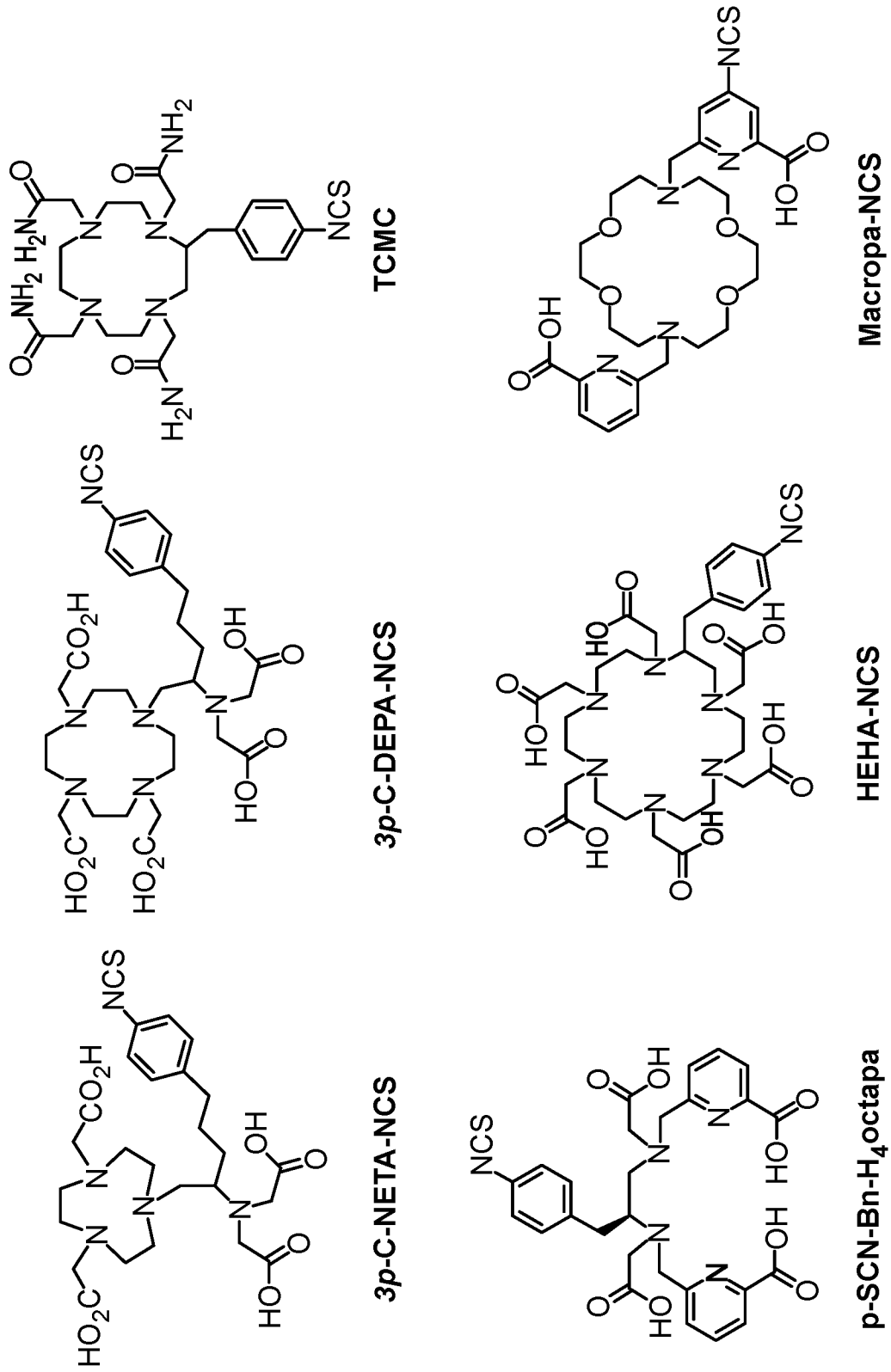

TCMC
Macropa-NCS
3p-C-DEPA-NCS
HEHA-NCS
3p-C-NETA-NCS
p-SCN-Bn-H4octapa

FIG. 9

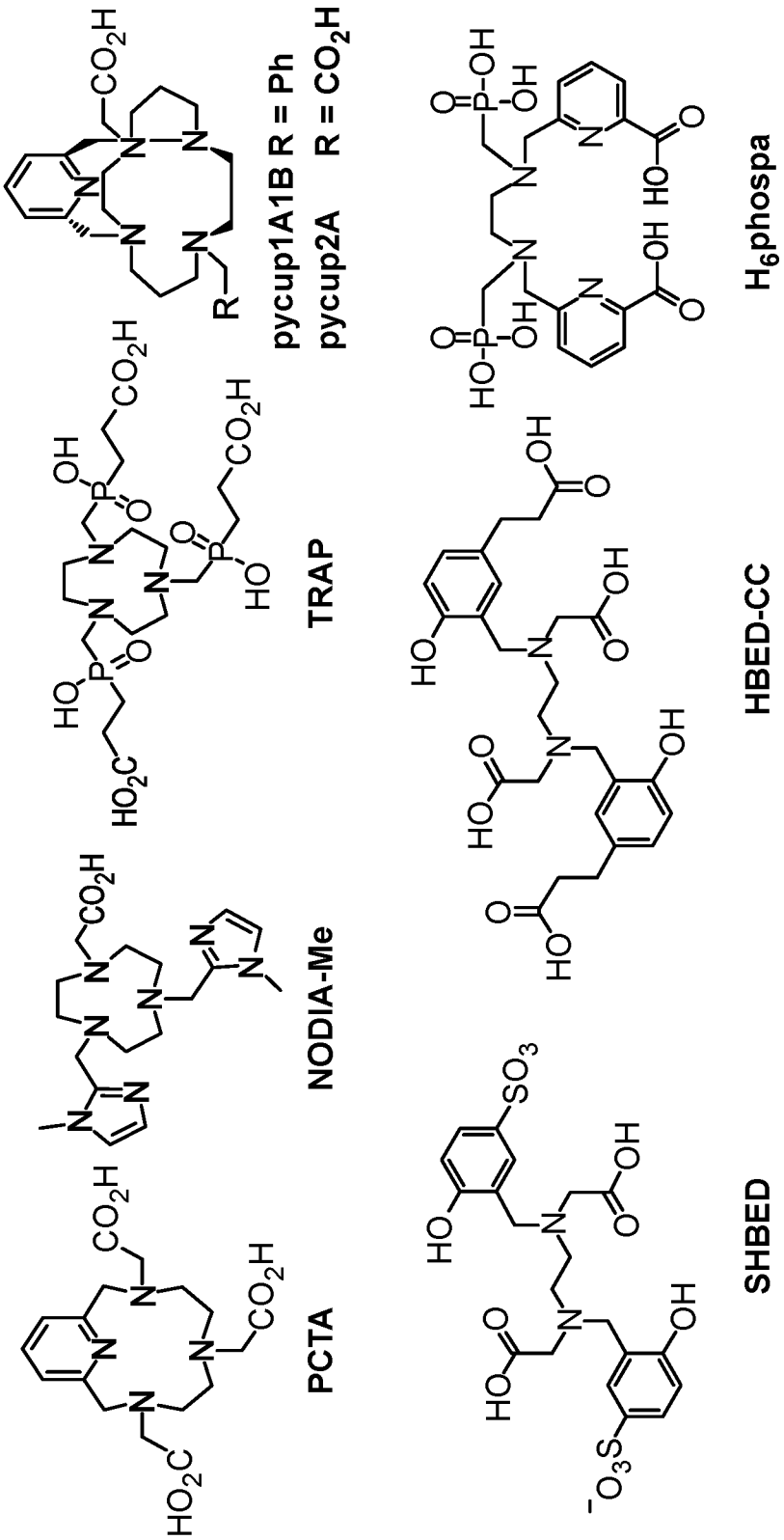

pycup1A1B R = Ph
pycup2A R = CO2H
TRAP
NODIA-Me
PCTA
H6phospa
HBED-CC
SHBED

FIG. 9 (Cont.)

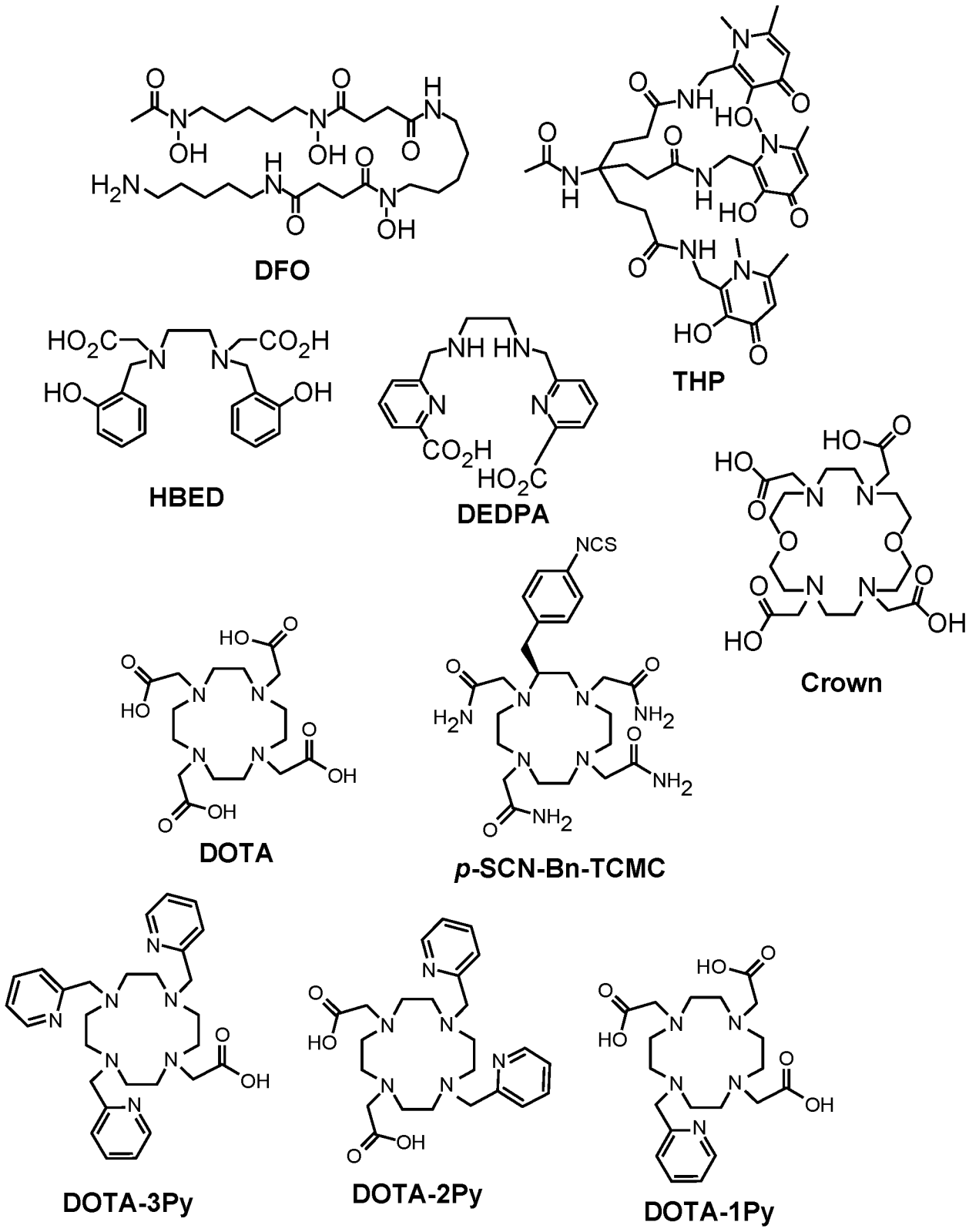

DFO
THP
HBED
DEDPA
Crown
DOTA
p-SCN-Bn-TCMC
DOTA-3Py
DOTA-2Py
DOTA-1Py

FIG. 10

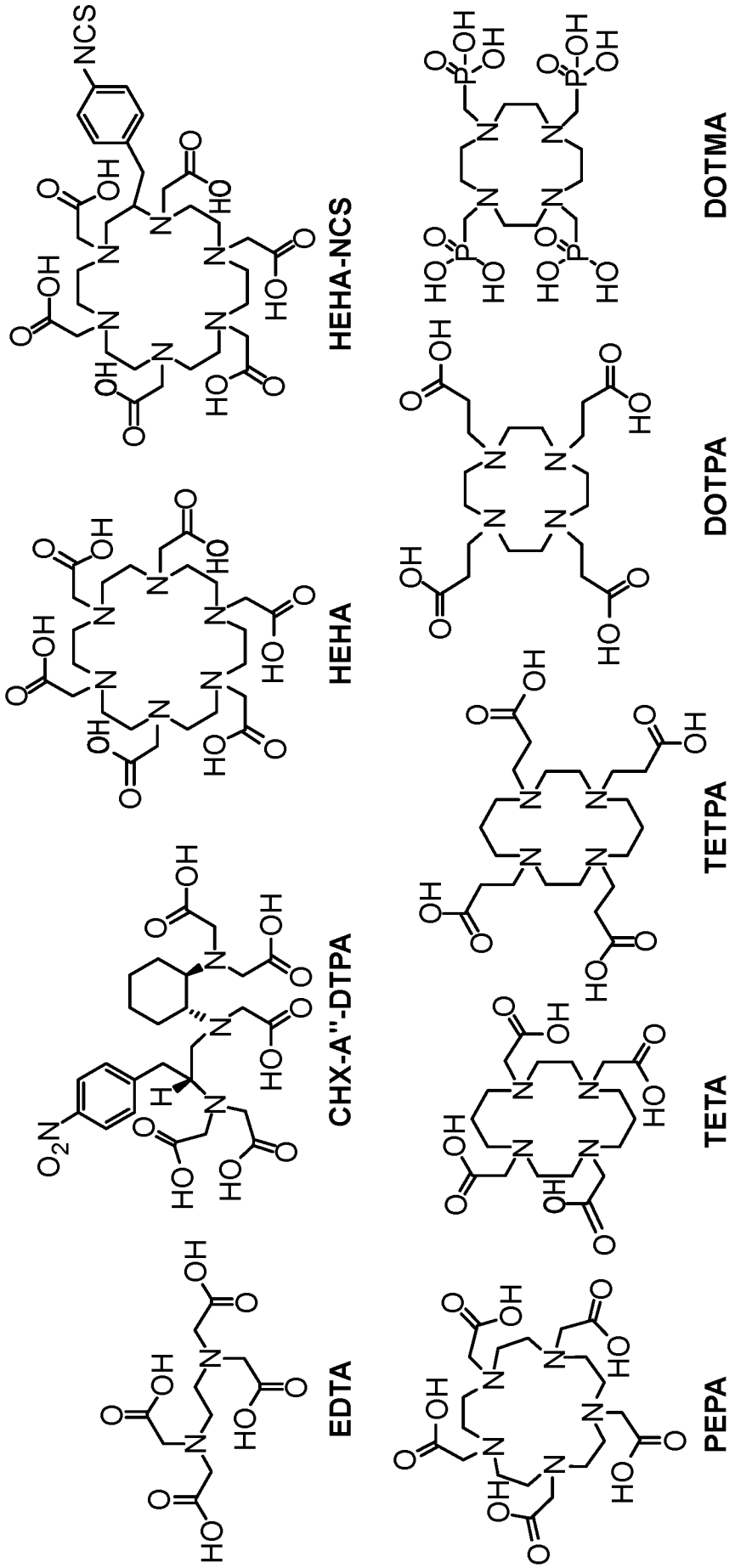


FIG. 11

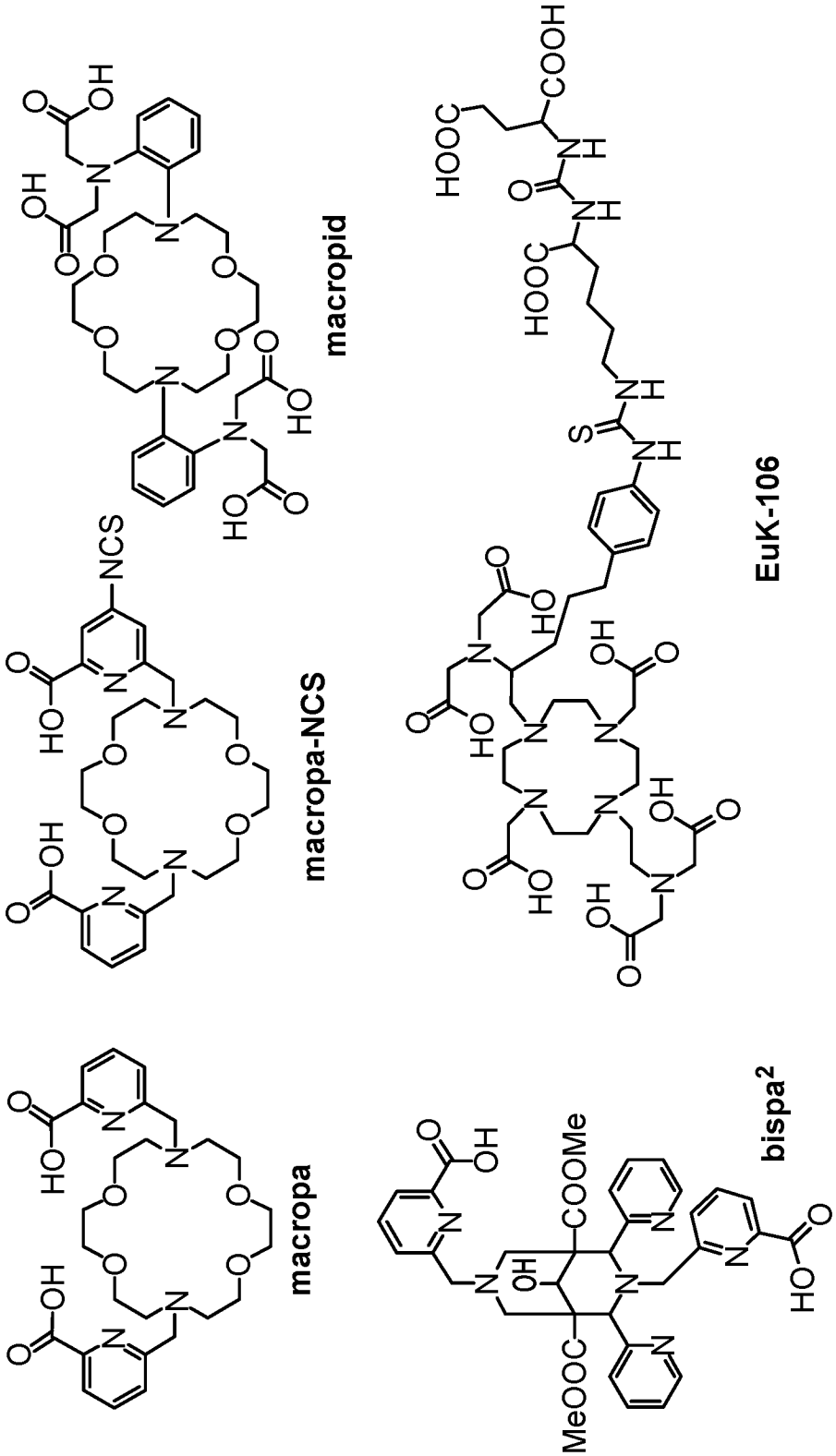


FIG. 11 (Cont. 1)

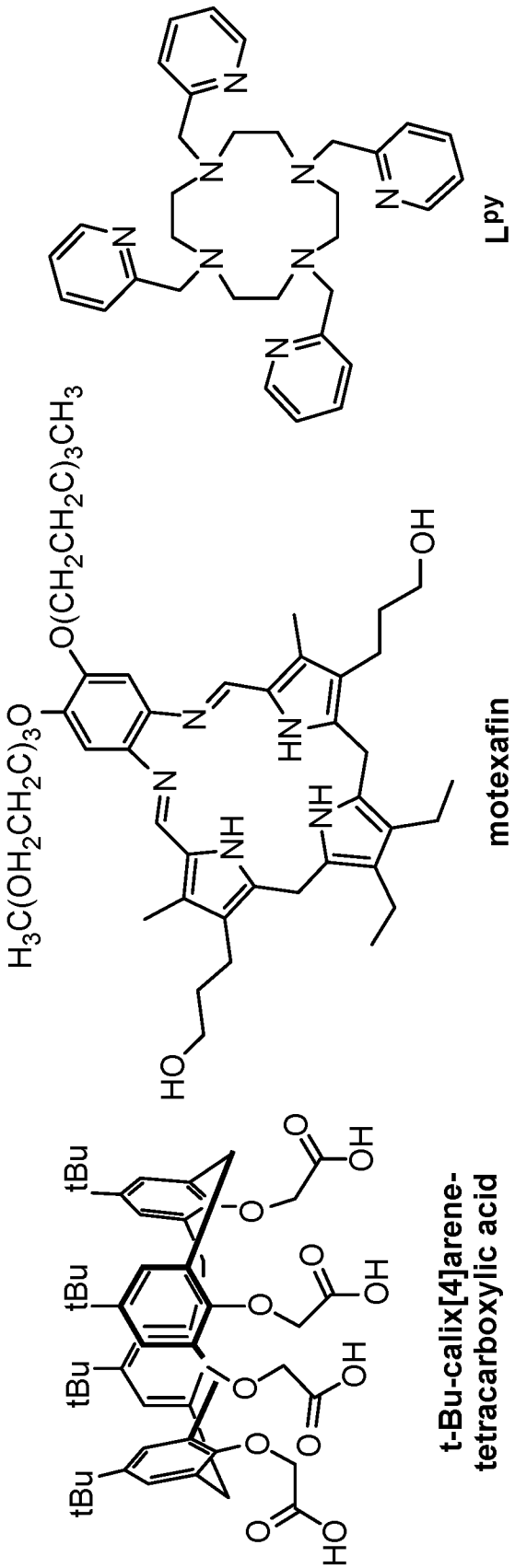


FIG. 11 (Cont. 2)

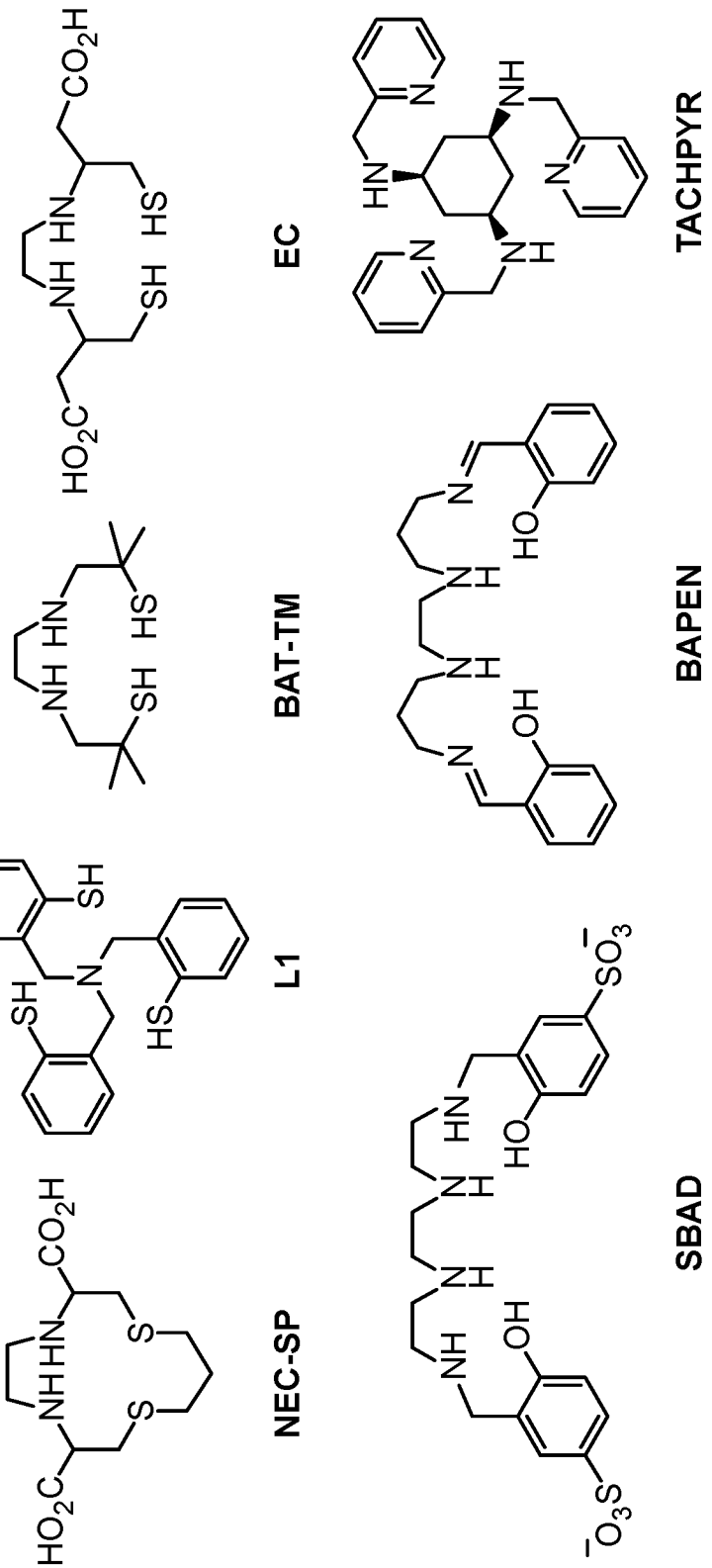
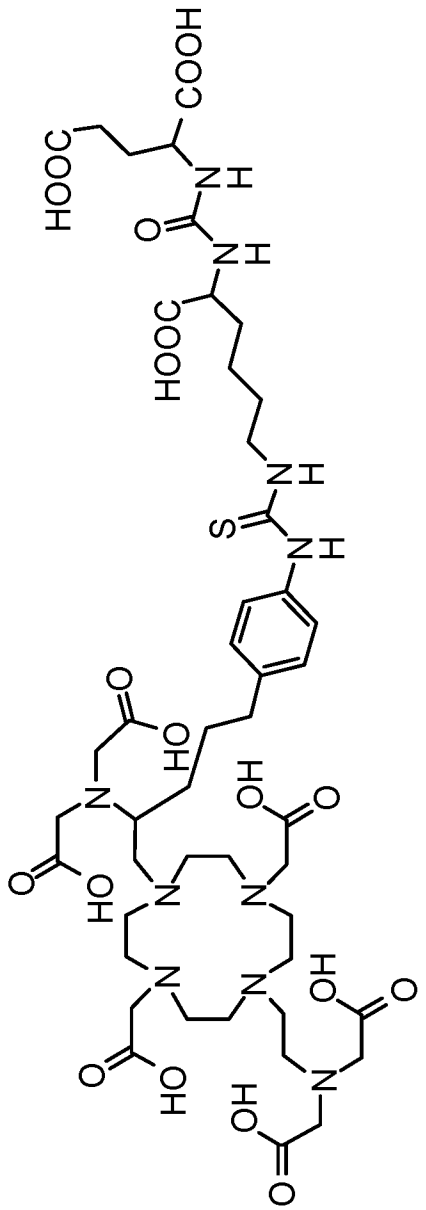
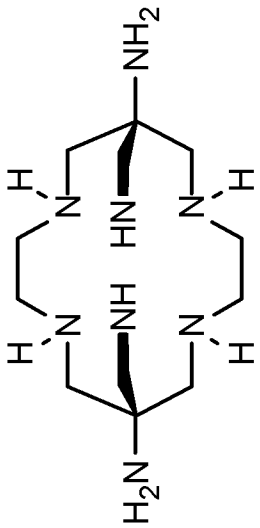


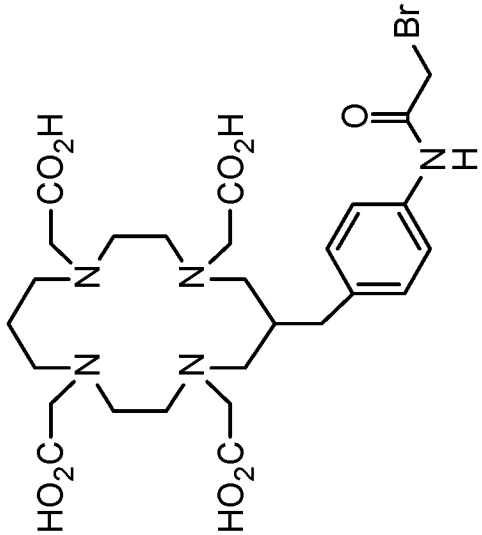
FIG. 12



EuK-108

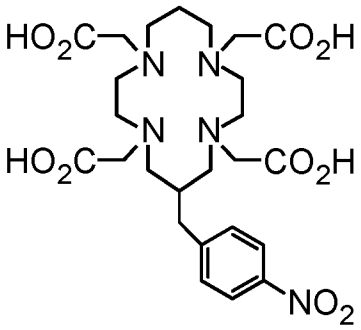


Diamsar

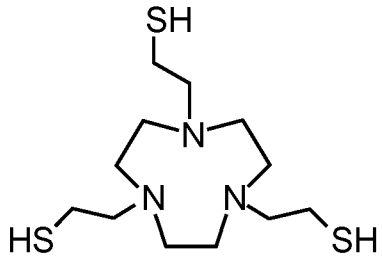


BAT

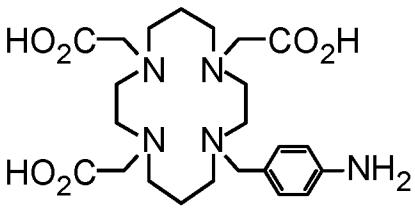
FIG. 12 (Cont.)



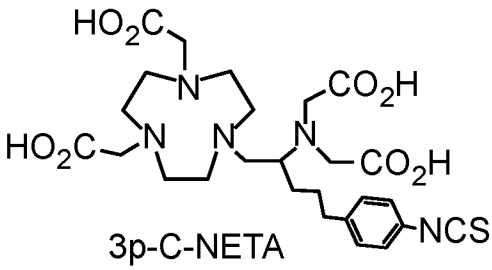
p-NO2-Bn-TETA



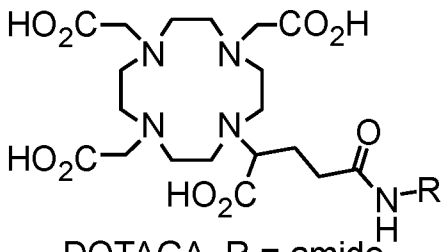
TACN-TM, *N,N′ ,N″*, tris(2-mercaptoethyl)-1,4,7-triazacyclononane



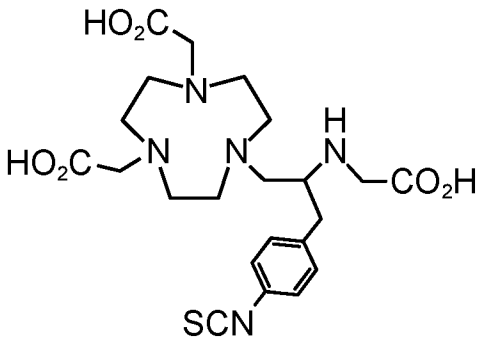
p-NH_2-Bn-TE3A



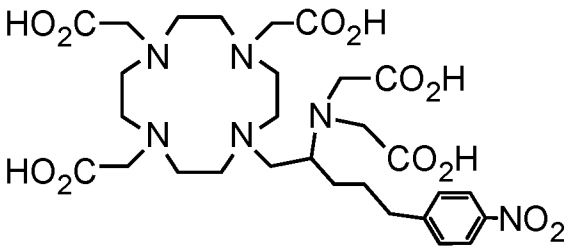
3p-C-NETA



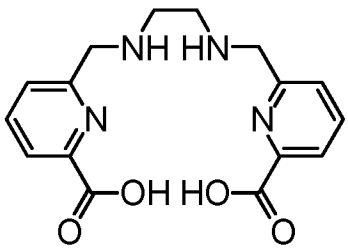
DOTAGA, R = amide, NHS ester



C-NE3TA-NCS



3p-C-DEPA



H_2dedpa, 1,2-[[6-(carboxy)-pyridin-2-yl]-methylamino]ethane

FIG. 13

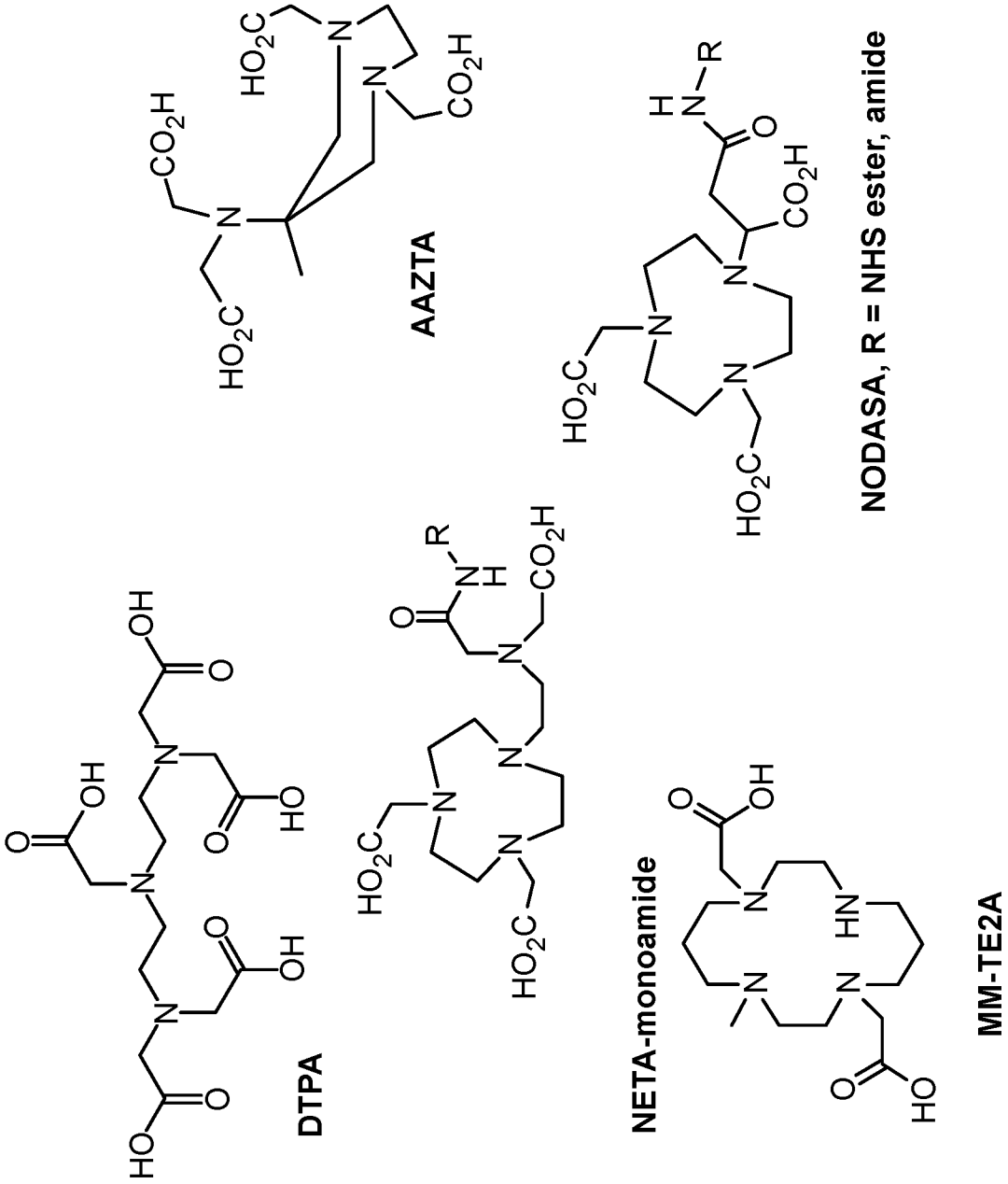
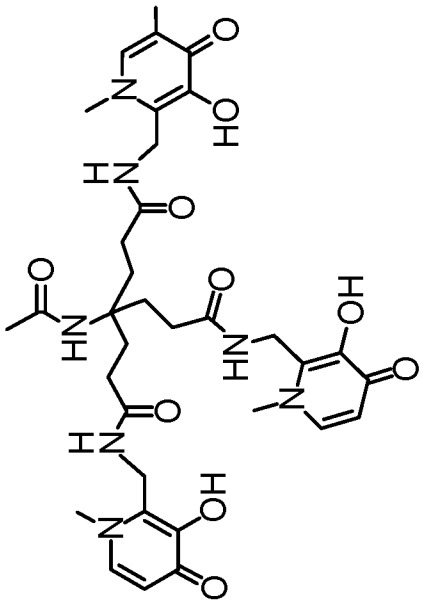
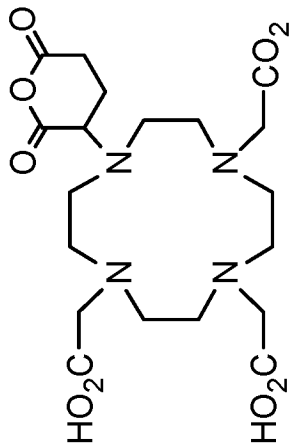


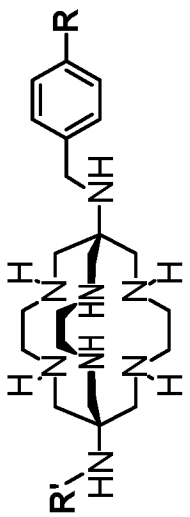
FIG. 14



CP256



DOTAGA-anhydride



1-*N*-(4-Aminobenzyl)-3,6,10,13,16,19-hexaazabicyclo[6.6.6]-eicosane-1,8-diamine (SarAr)
SarAr **R** = NH_2, **R'** = H
SarAr-NCS **R** = NCS, **R'** = H
AmBaSar **R** = COOH, **R'** = H
BaBaSar **R** = – COOH, **R'** = $–CH_2–Ph–COOH$

FIG. 14 (Cont.)

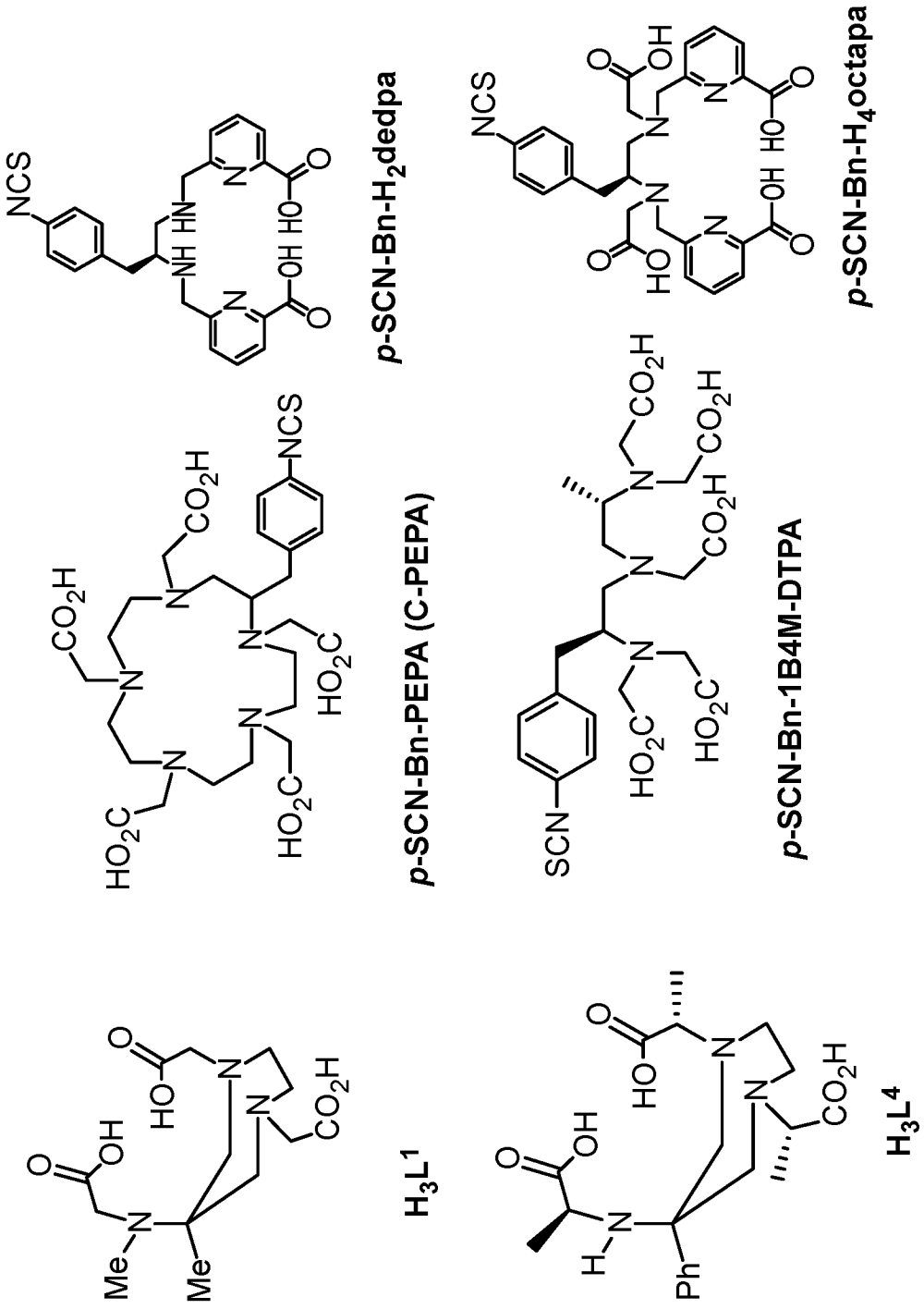
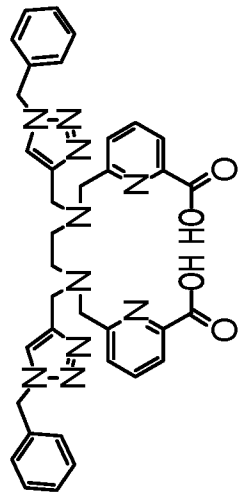
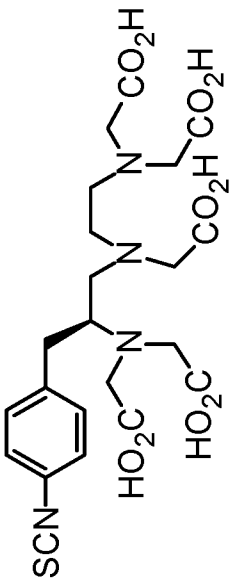

p-SCN-Bn-H2dedpa
p-SCN-Bn-PEPA (C-PEPA)
p-SCN-Bn-1B4M-DTPA
p-SCN-Bn-H4octapa
H3L1
H3L4

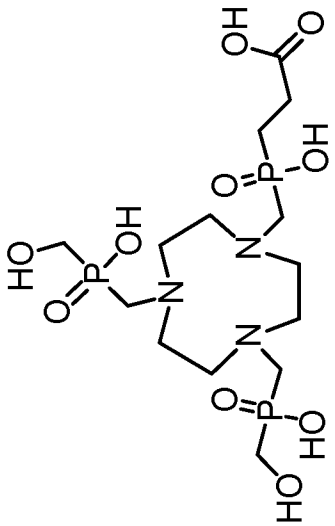
FIG. 15



H_2azapa, *N,N'* -[1-benzyl-1,2,3-triazole-4-yl]methyl-*N,N'*-[6-(carboxy)pyridin-2-yl]-1,2-diaminoethane,

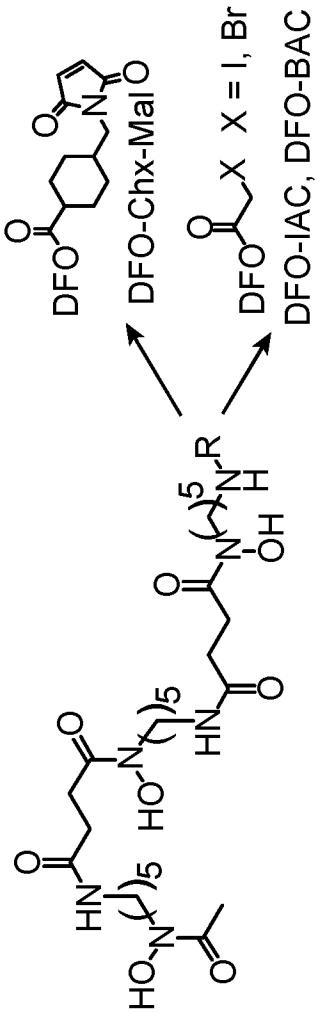


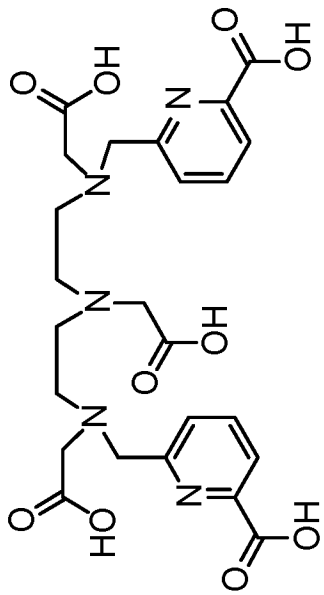
p-SCN-Bn-1B-DTPA



NOPO

FIG. 15 (Cont.)





H_5decapa, *N,N''*-[[6-(carboxy)pyridin-2-yl]methyl]-diethylenetriamine-*N,N',N''* -triacetic Acid,

FIG. 16

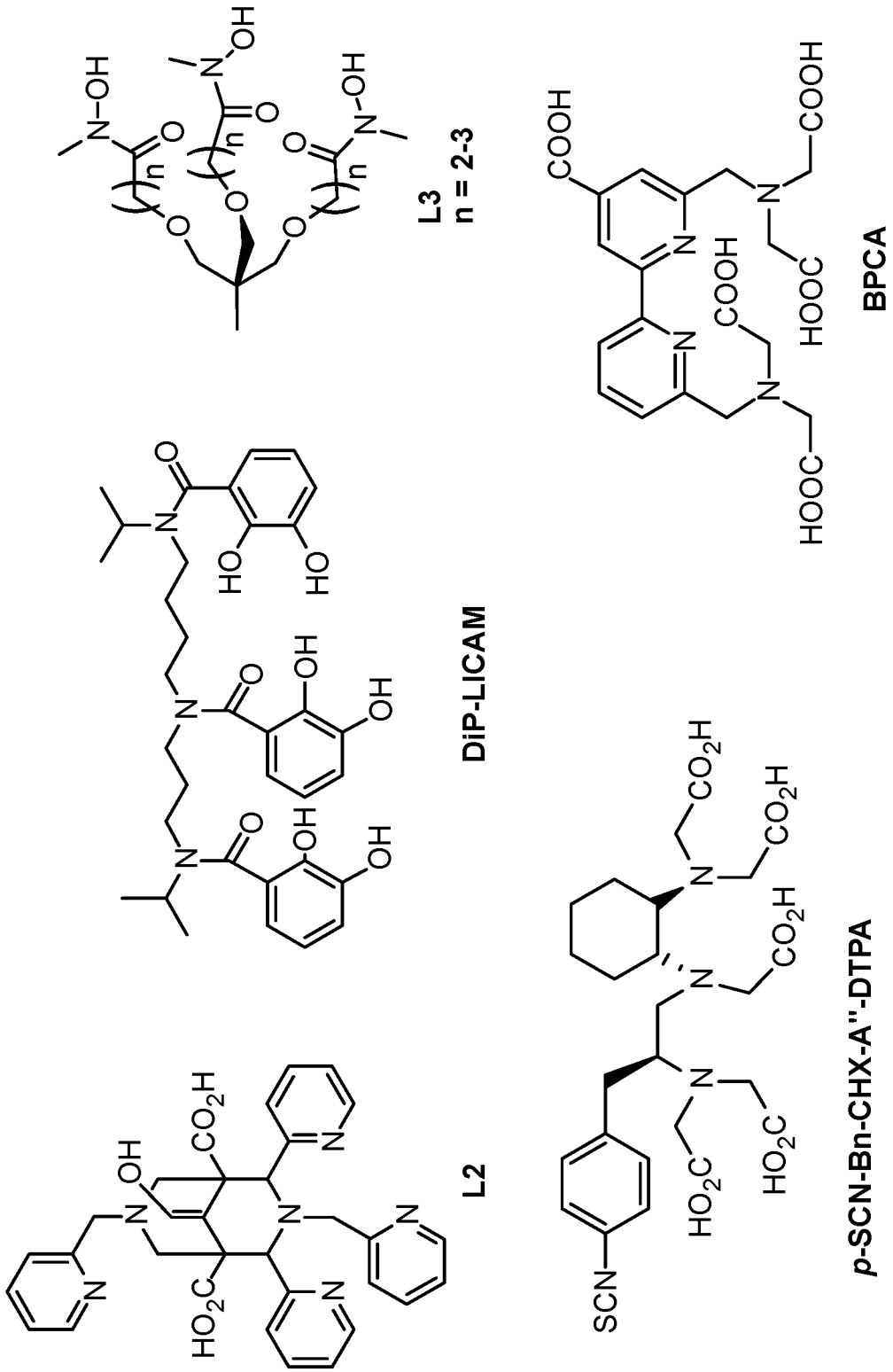
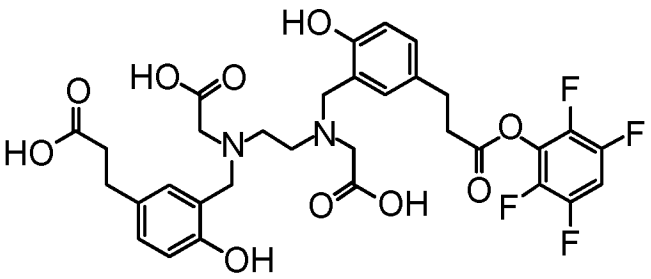
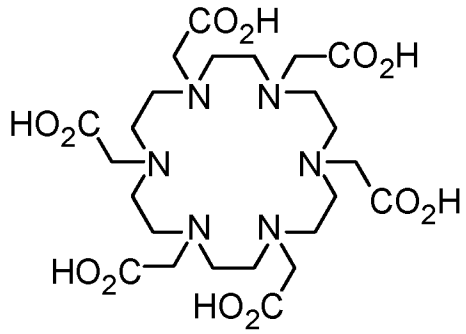


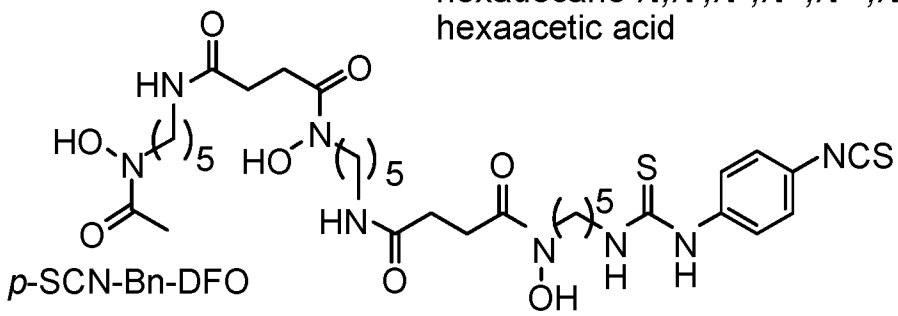
FIG. 16 (Cont.)



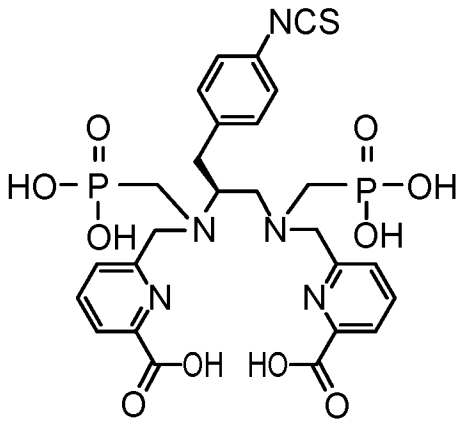
(HBED-CC)TFP



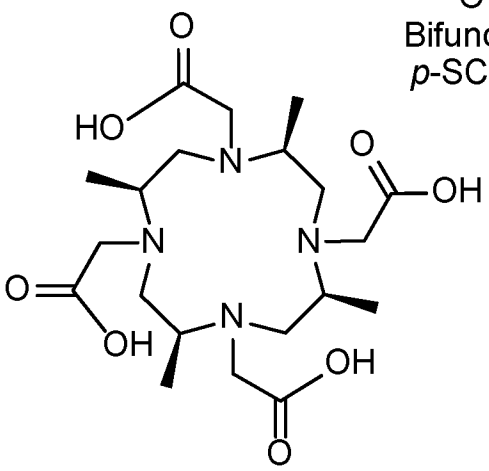
HEHA, 1,4,7,10,13,16-hexaazacyclohexadecane-*N,N',N'',N''',N'''',N'''''*-hexaacetic acid



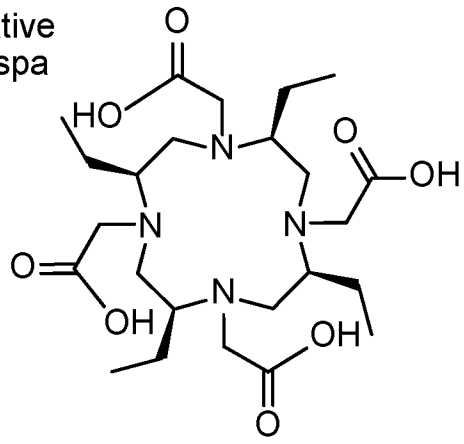
p-SCN-Bn-DFO



Bifunctional derivative *p*-SCN-Bn-H_6phospa



2,2',2'',2'''-((2S,5S,8S,11S)-2,5,8,11-tetramethyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrayl)tetraacetic acid



2,2',2'',2'''-((2S,5S,8S,11S)-2,5,8,11-tetraethyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrayl)tetraacetic acid

FIG. 17

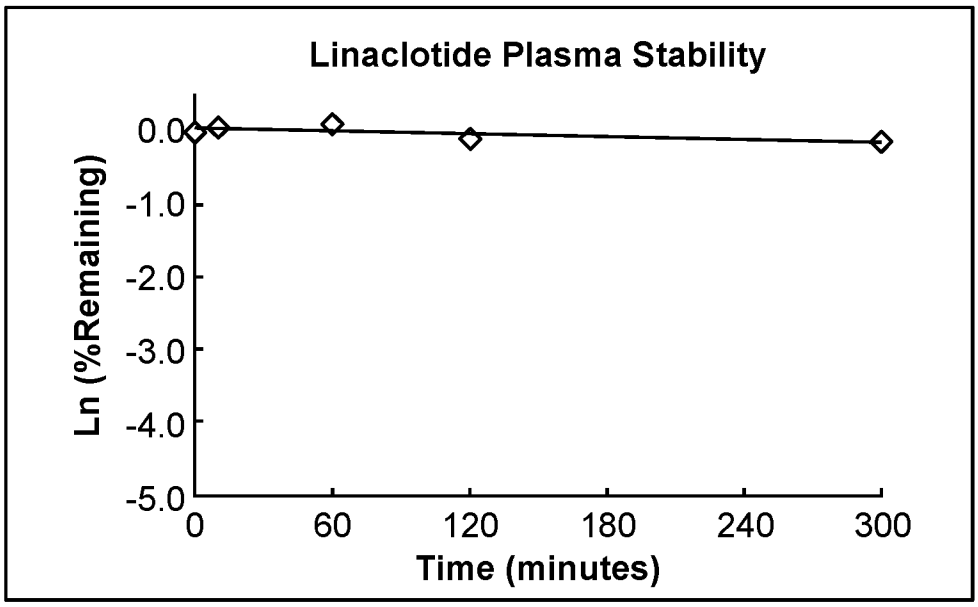


FIG. 18A

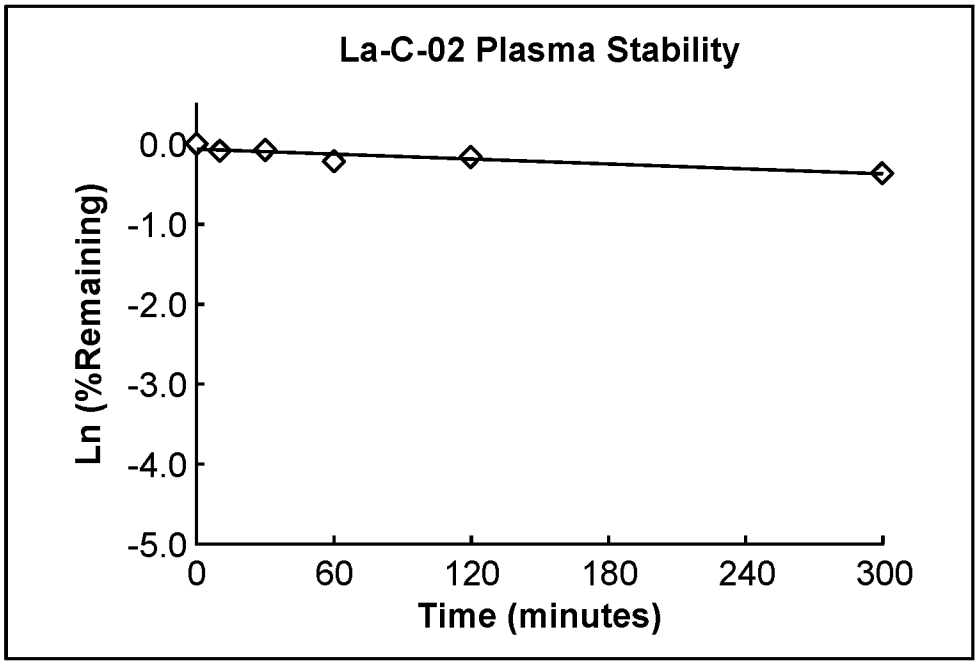


FIG. 18B

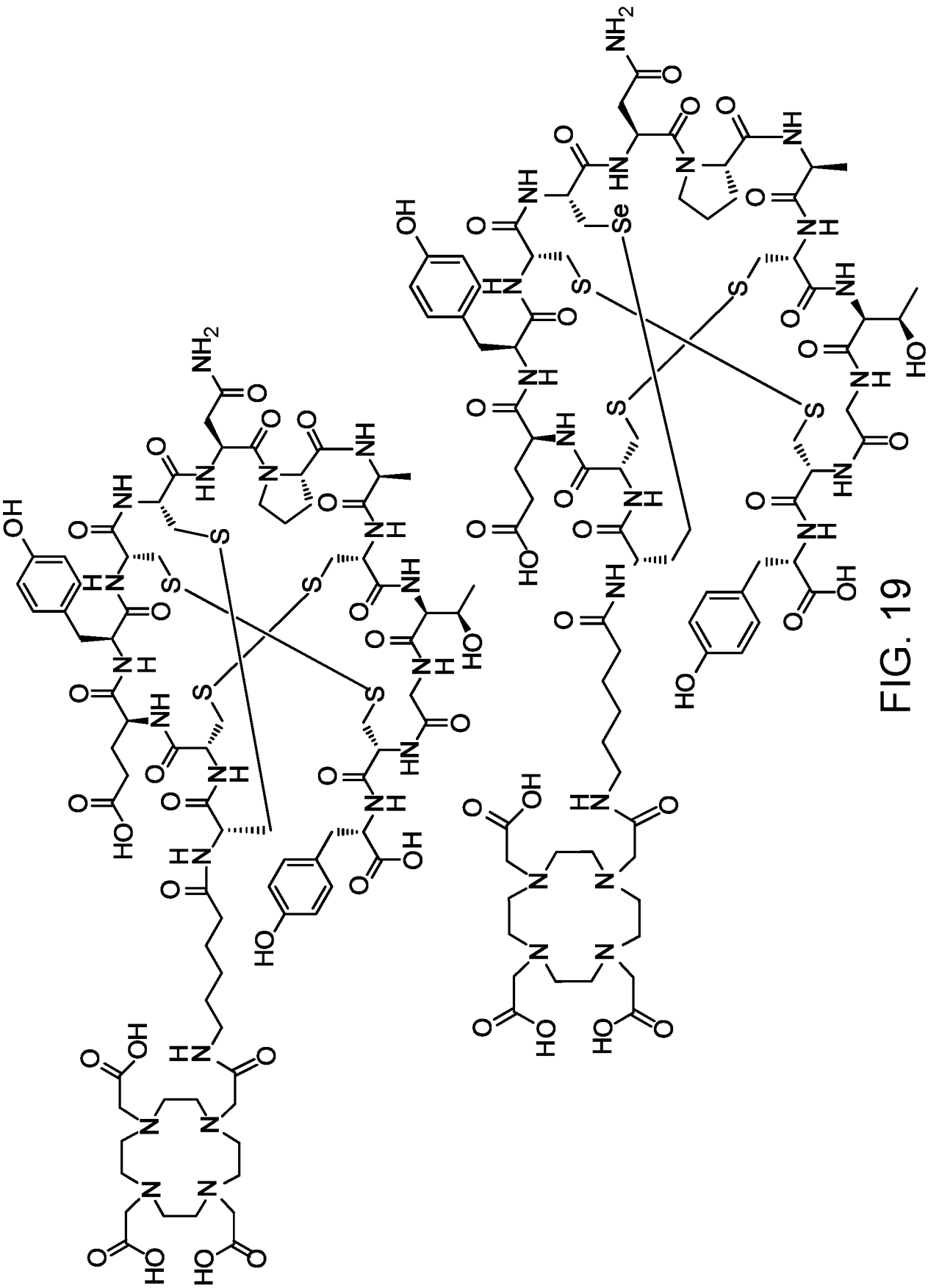


FIG. 19

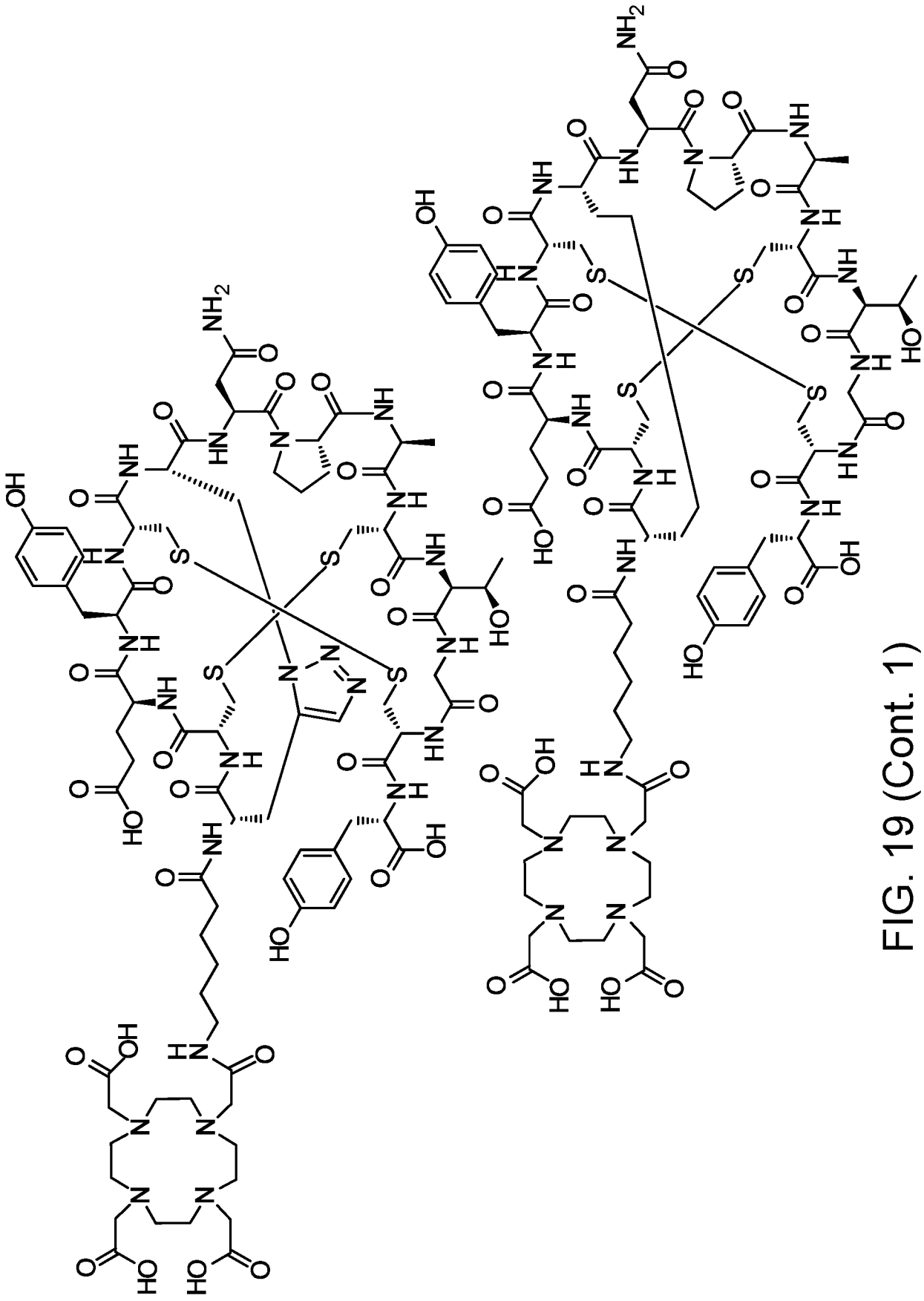


FIG. 19 (Cont. 1)

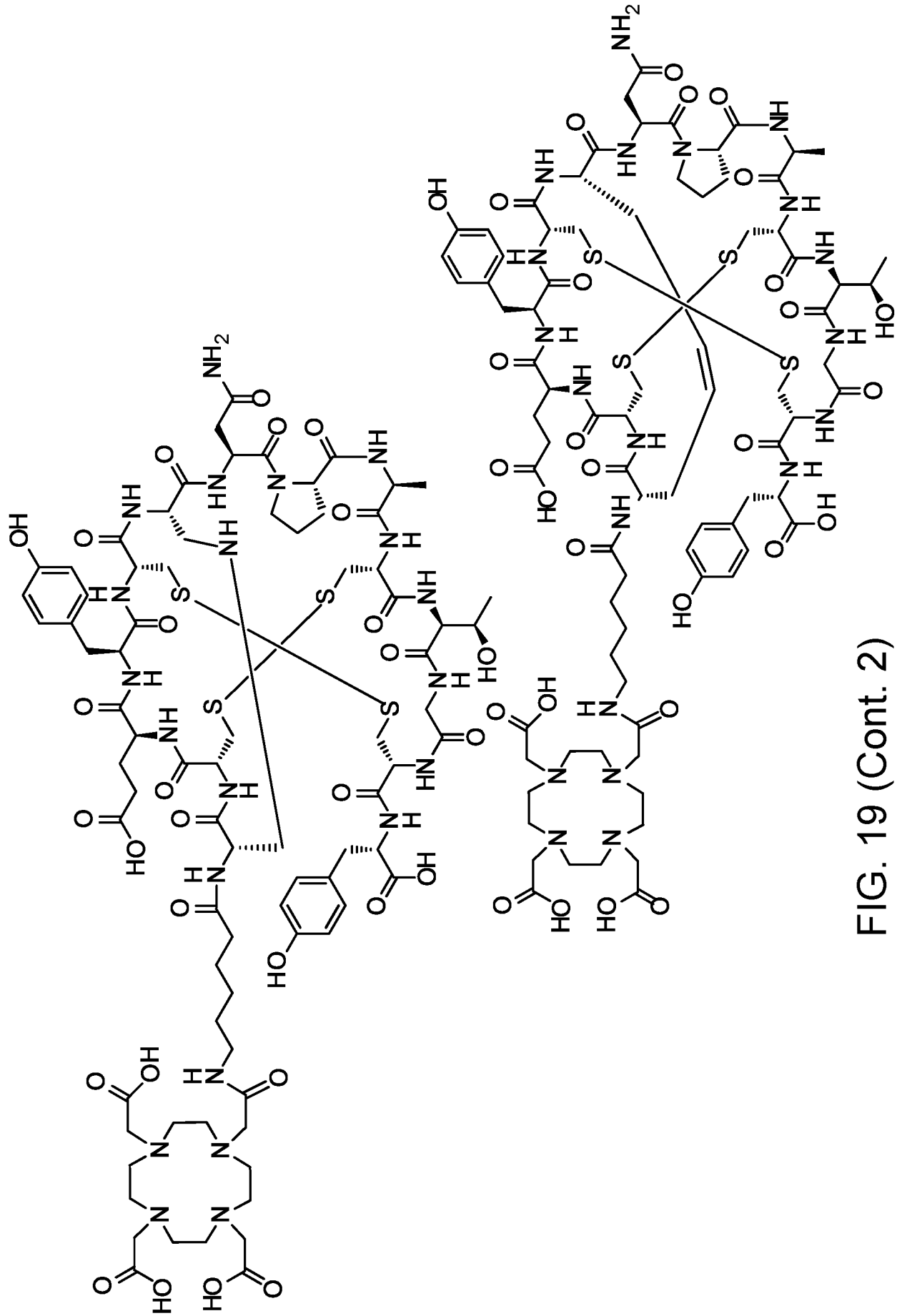


FIG. 19 (Cont. 2)

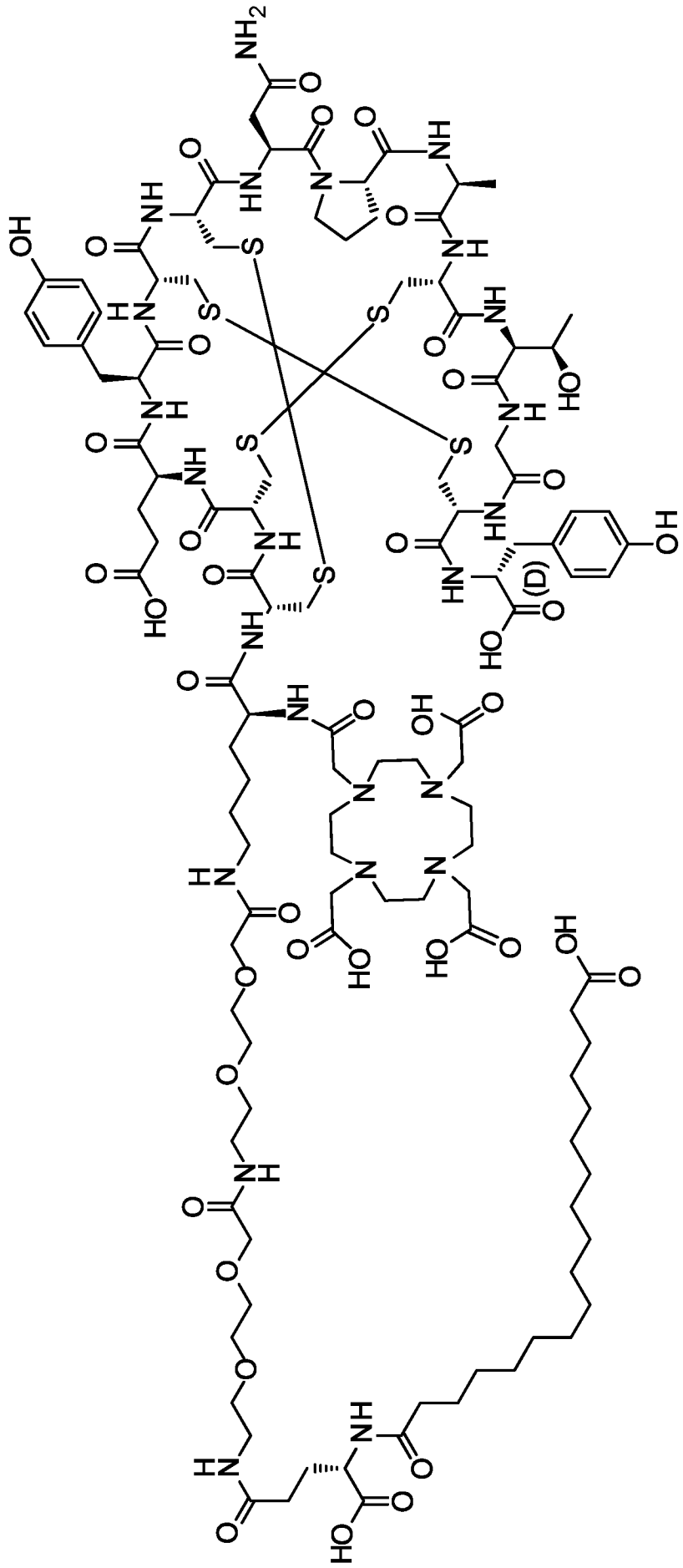


FIG. 20

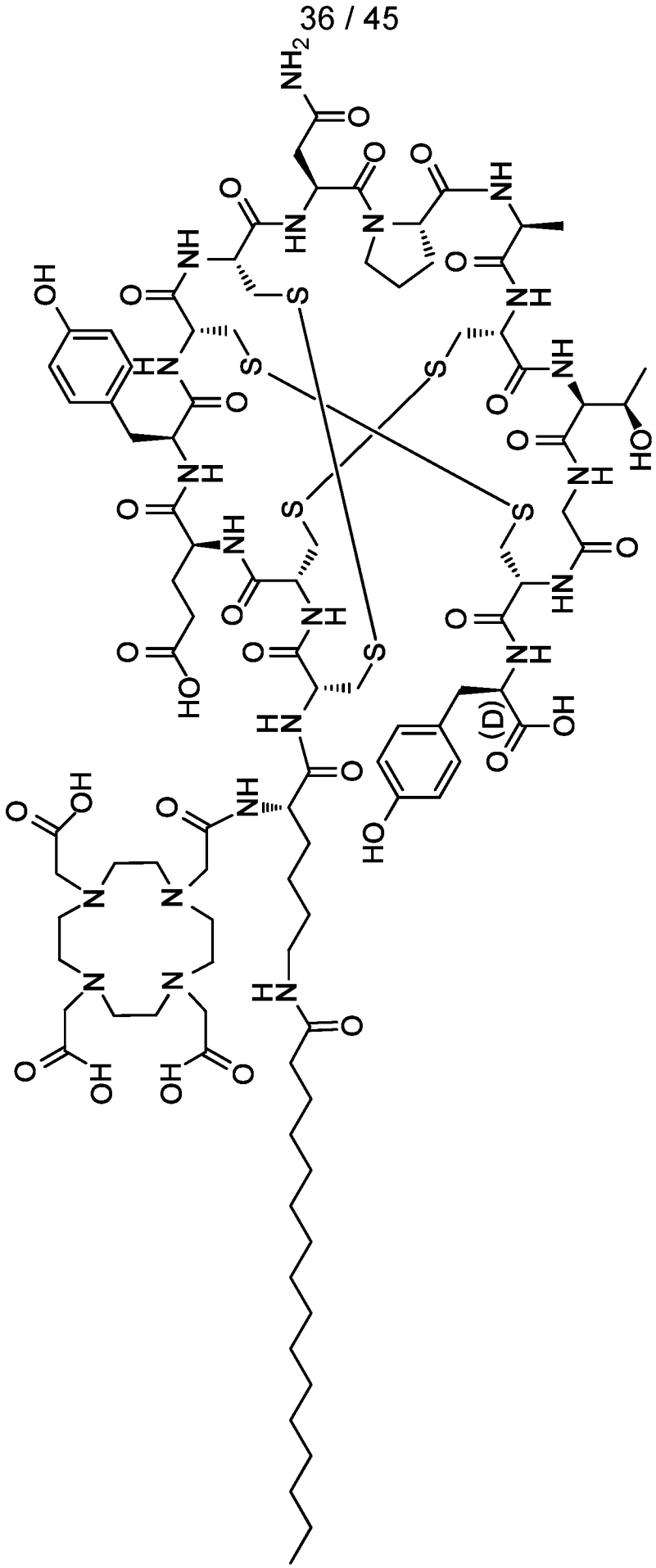


FIG. 20 (Cont. 1)

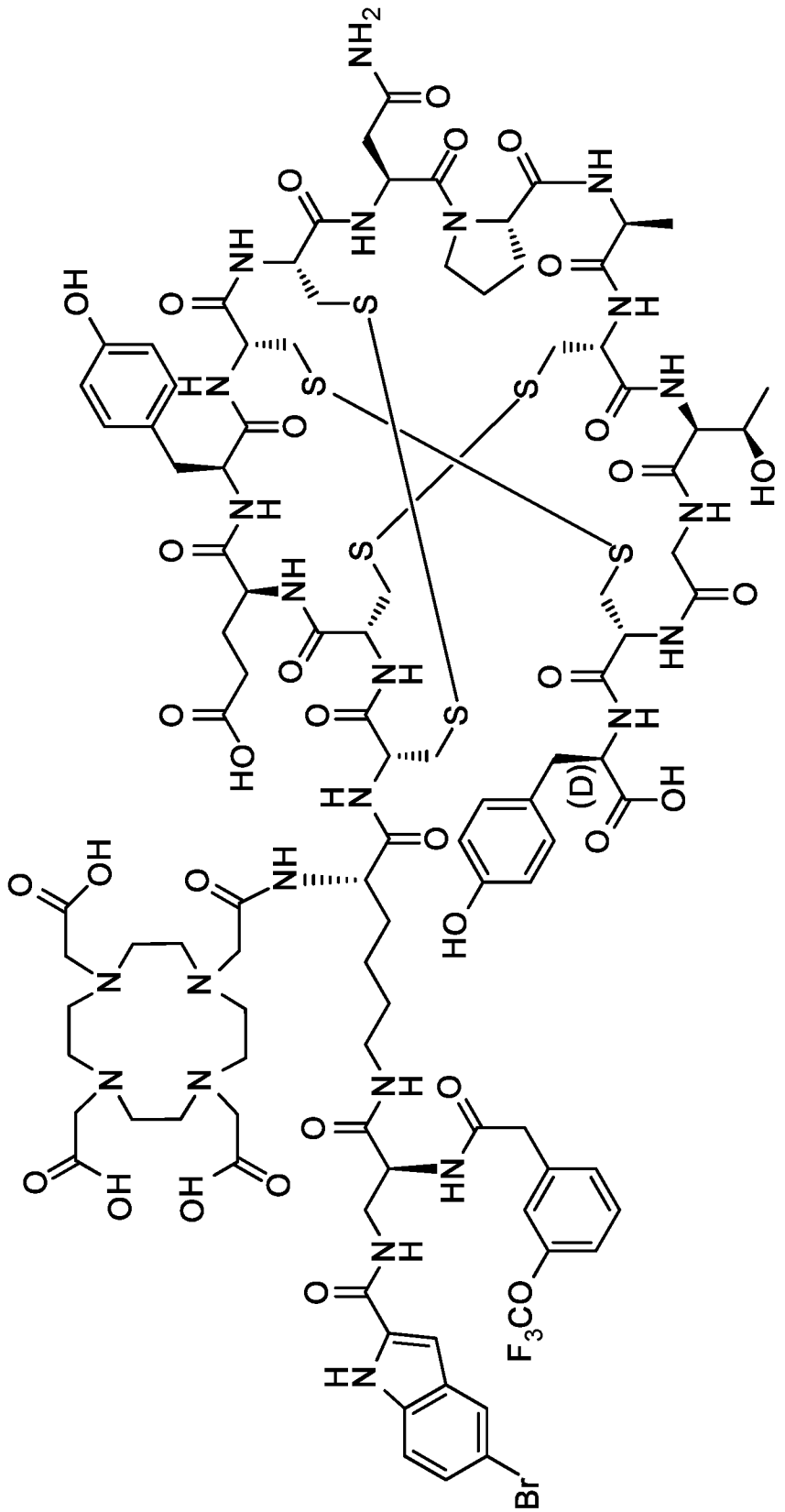


FIG. 20 (Cont. 2)

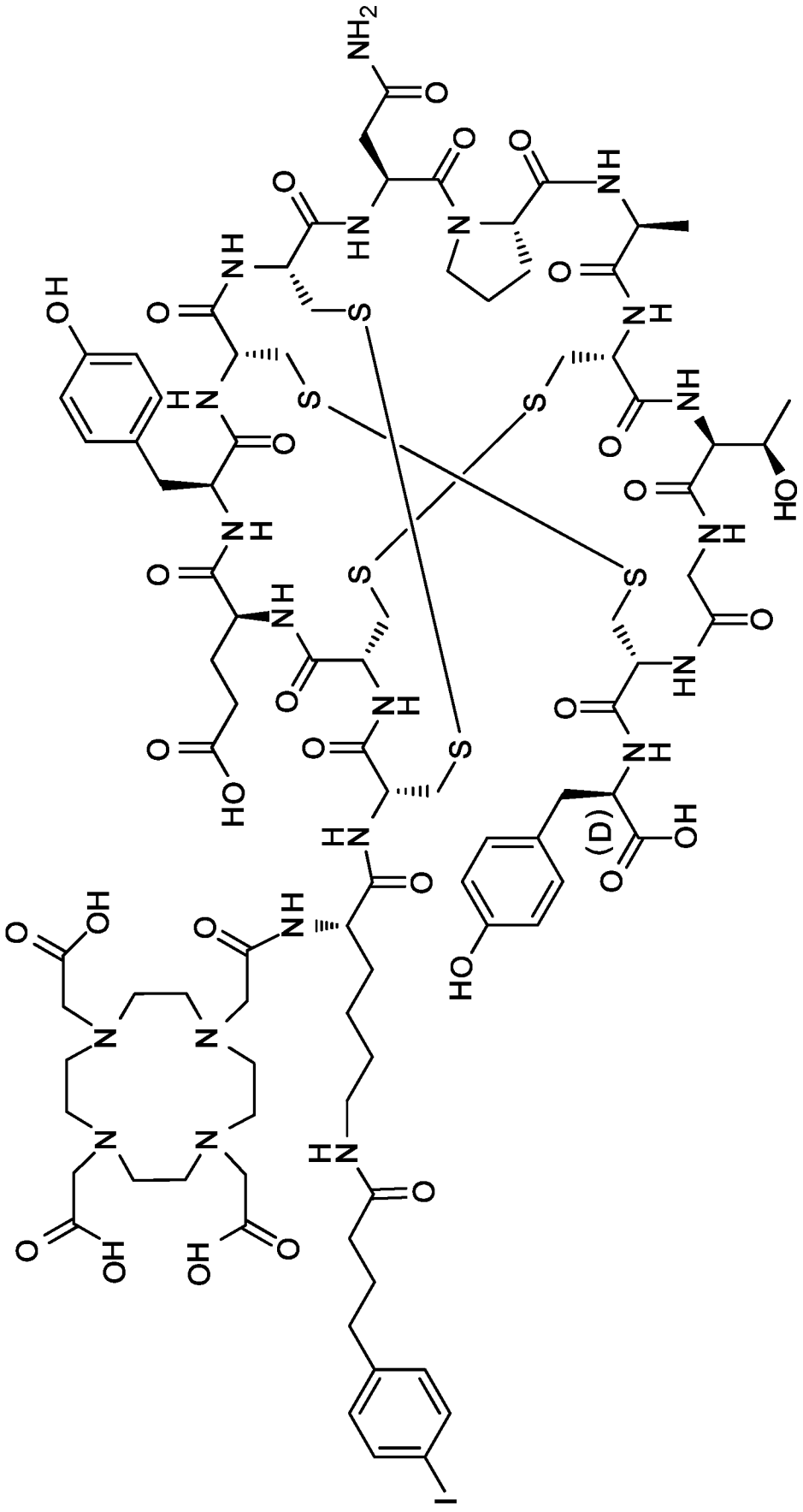


FIG. 20 (Cont. 3)

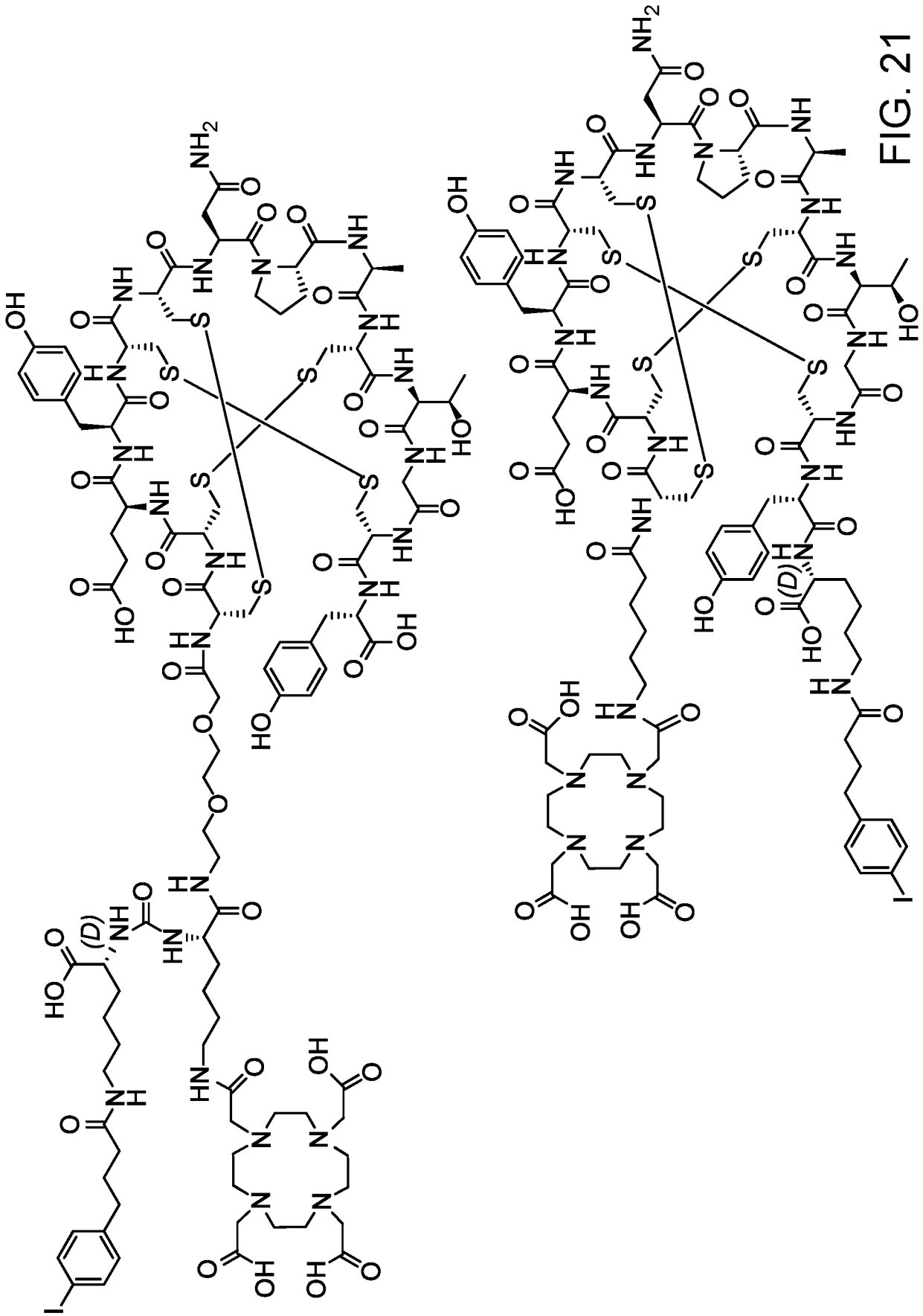


FIG. 21

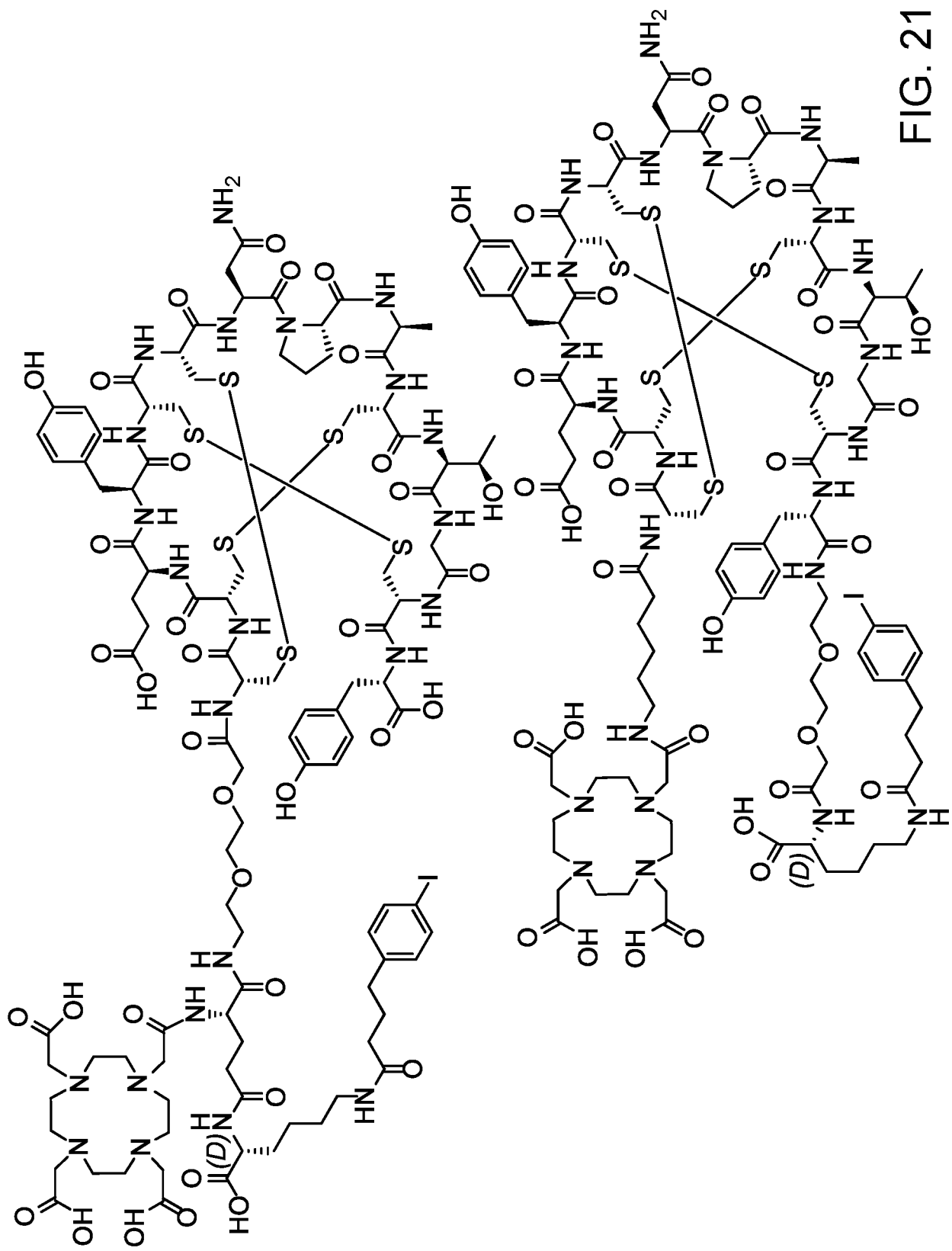


FIG. 21 (Cont.)

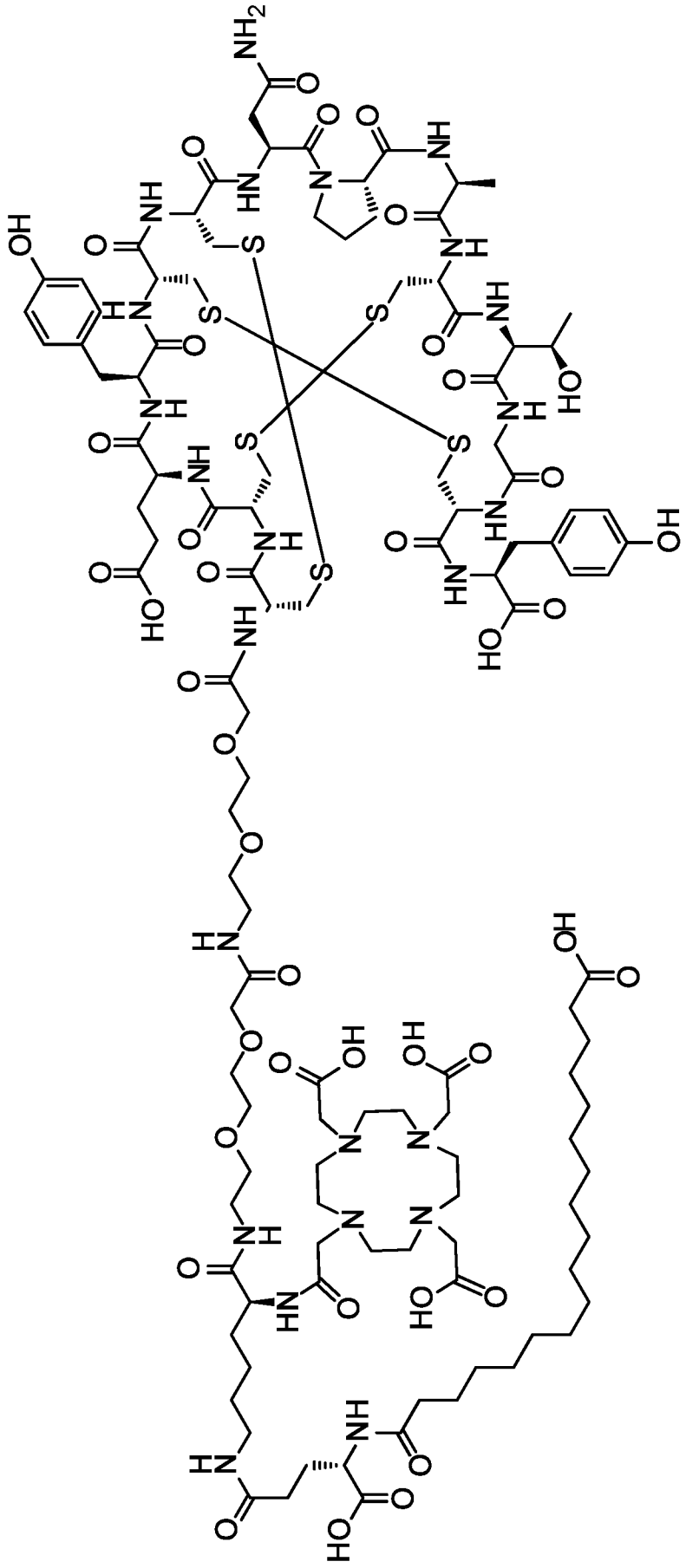


FIG. 22

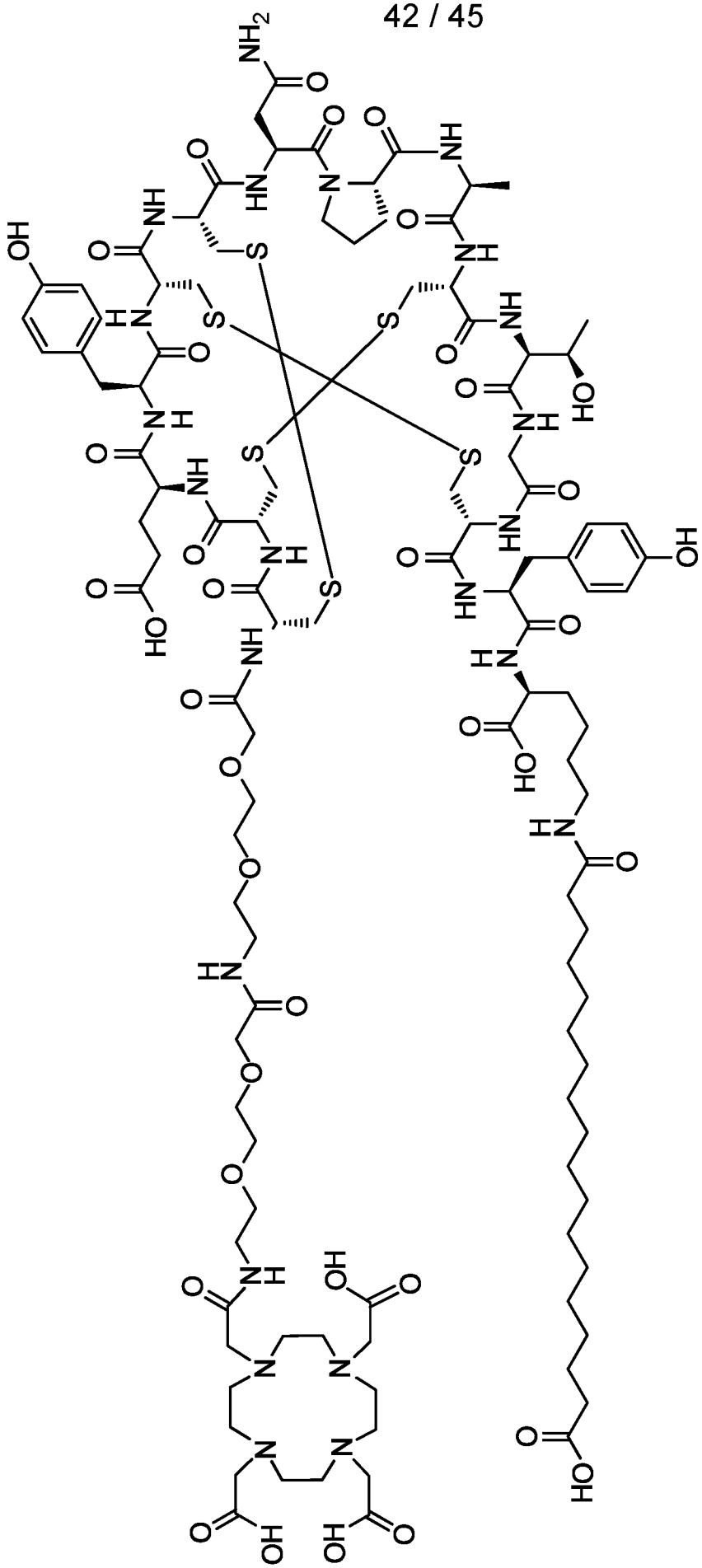


FIG. 22 (Cont. 1)

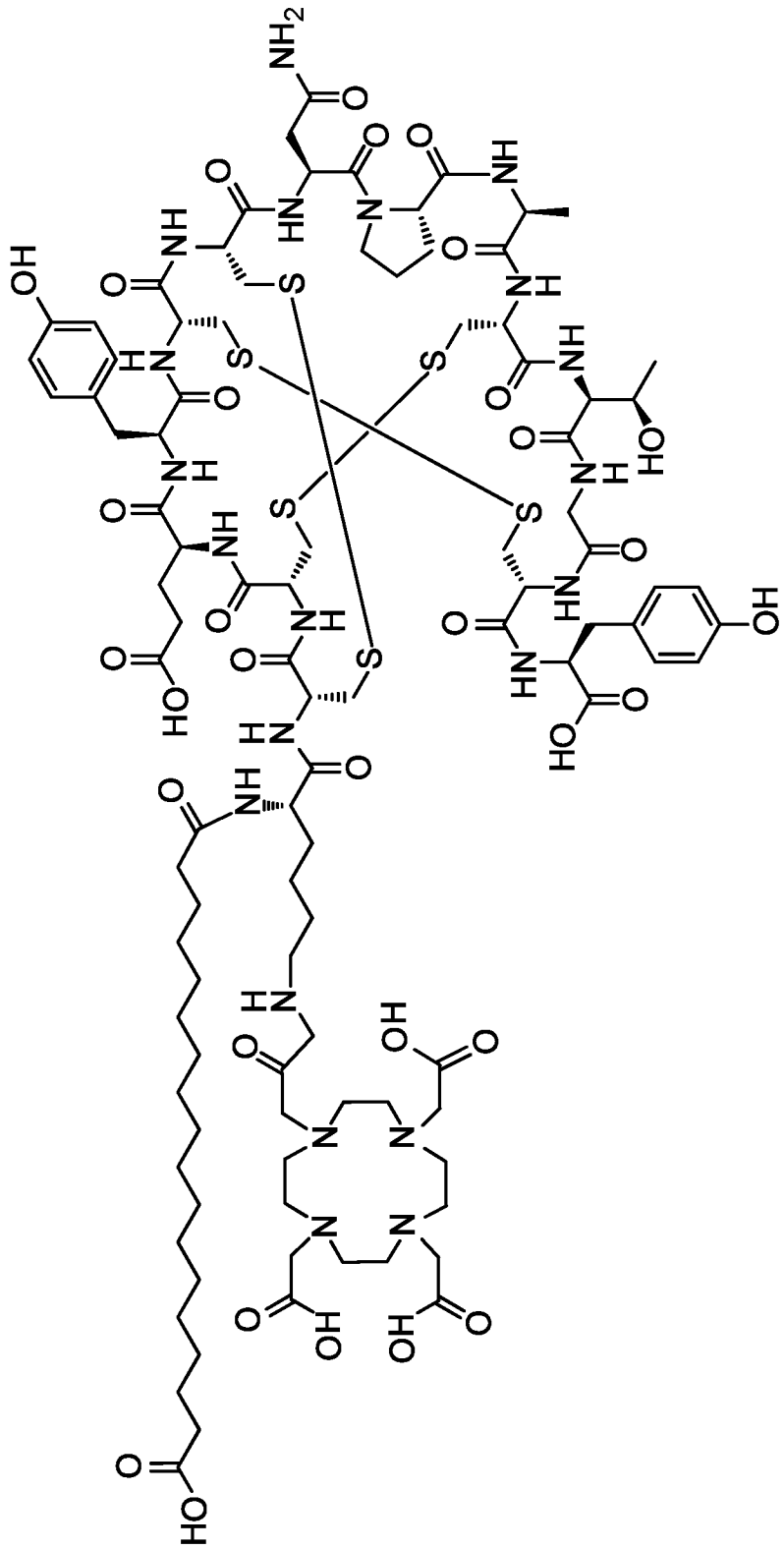


FIG. 22 (Cont. 2)

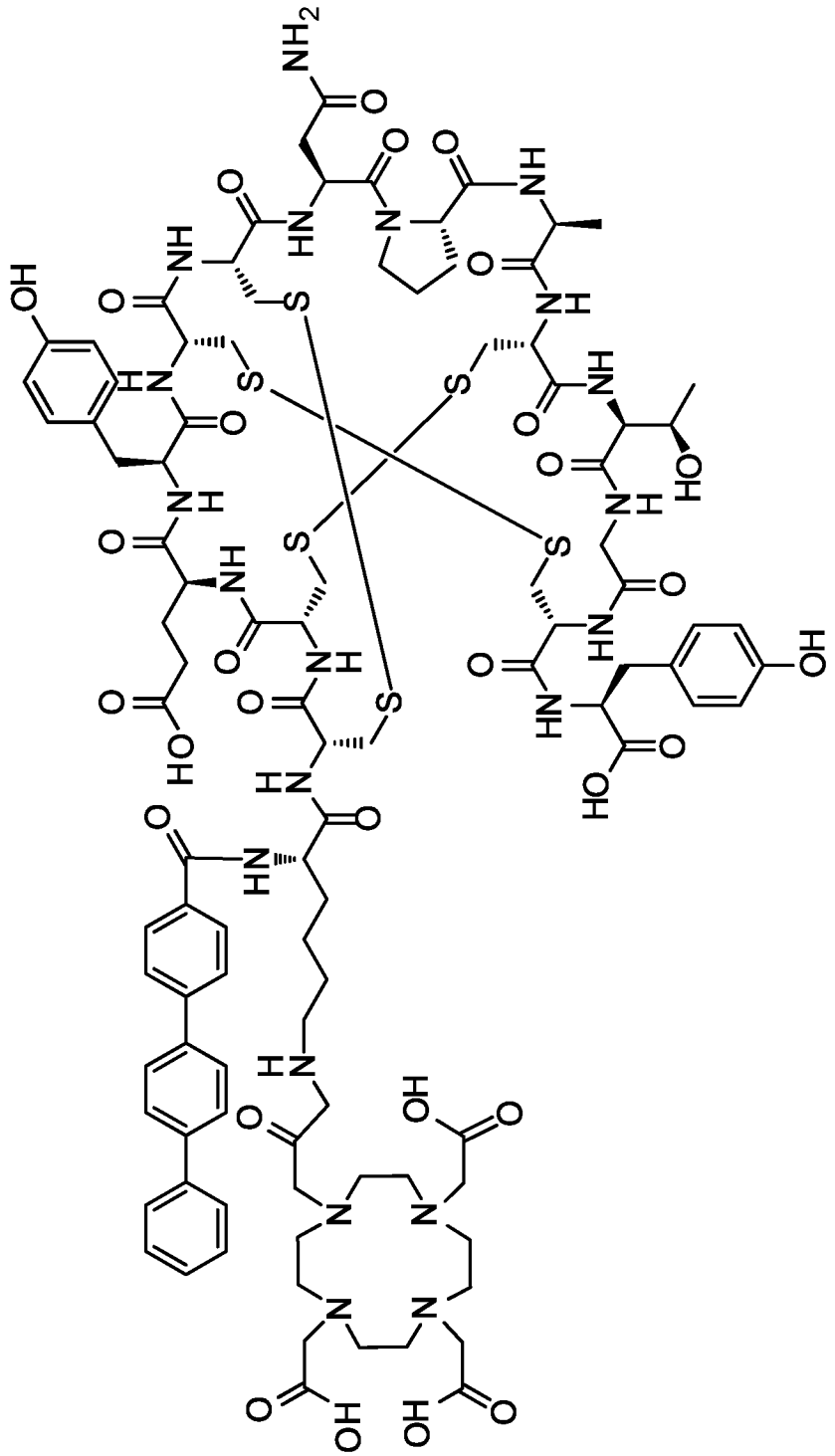


FIG. 22 (Cont. 3)

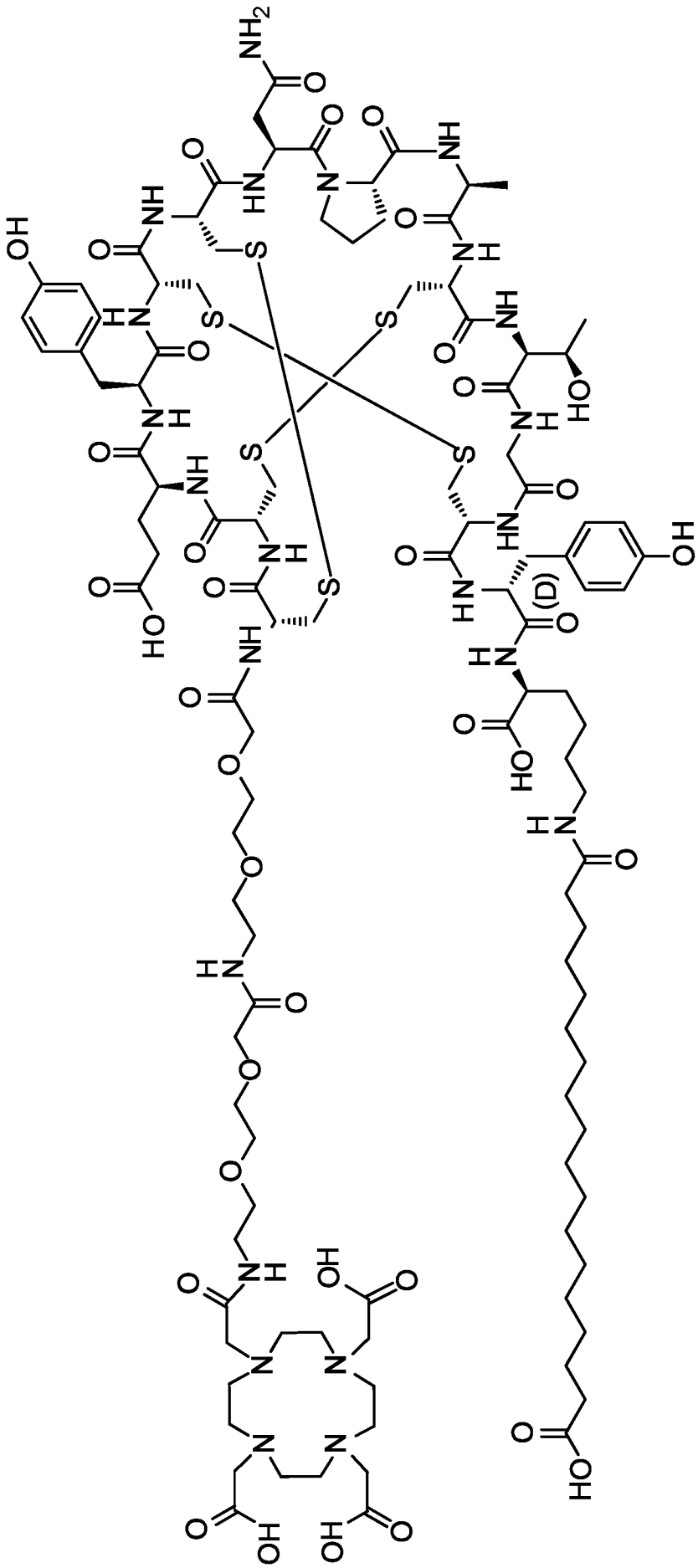


FIG. 22 (Cont. 4)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US21/61252

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 51/04; A61K 38/10; A61K 38/17; C07K 7/08; A61K 49/00; C07K 16/30; A61P 35/00; G01N 30/02 (2021.01)

CPC - A61K 51/04; A61K 38/10; A61K 38/17; C07K 7/08; A61K 49/0002; C07K 16/30; G01N 2030/027; A61P 35/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2006/0258593 A1 (CURRIE, M.G., ET AL.) 16 November 2006; paragraphs [0006], [0011], [0060], [0061], [0098], [0099], [0229]	1, 3-5
Y --- A	WO 2019/177970 A1 (MEMORIAL SLOAN KETTERING CANCER CENTER) 19 September 2019; paragraphs [0006], [0023], [0055], [00157], [00172]	1, 4/1, 5/1 --- 99-100
Y --- A	US 2014/0147380 A1 (THOMAS JEFFERSON UNIVERSITY) 29 May 2014; paragraphs [0013], [0086], [0114], [0330], [0369]	2-3, 4/3, 5/3 --- 73
Y	(VALKO, K., ET AL). "Fast Gradient HPLC Method to Determine Compounds Binding to Human Serum Albumin. Relationships with Octanol/Water and Immobilized Artificial Membrane Lipophilicity" pages 2236-2248. Journal of Pharmaceutical Sciences. Vol. 92, No. 11. November 2003; abstract; page 2237, second column, first paragraph; table 1; DOI: 10.1002/jps.10494	2-3, 4/3, 5/3
A	WO 2019/212357 A1 (TAGWORKS PHARMACEUTICALS B.V.) 07 November 2019; page 5, lines 15-20; page 32, lines 9-11; page 41, lines 9-11; page 108, lines 4-6	73
A	US 2019/0321495 A1 (UNIVERSITY OF IOWA RESEARCH FOUNDATION) 24 October 2019; paragraphs [0007], [0052], [0095], [0107], [0220], [0238], [0250], [0275], [0285]; Figure 17	73, 99-100
A	US 2020/0148791 A1 (IRONWOOD PHARMACEUTICALS, INC.) 14 May 2020; paragraph [0065]	99-100

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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

Date of the actual completion of the international search	Date of mailing of the international search report
03 April 2022 (03.04.2022)	MAY 05 2022
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas Telephone No. PCT Helpdesk: 571-272-4300

Form PCT/ISA/210 (second sheet) (July 2019)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US21/61252

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. ☒ forming part of the international application as filed:

      ☒ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US21/61252

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 6-72, 76-98, 101-107
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
-***-Please See Supplemental Page-***-

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Groups I+, Claims 1-5, 73-75, 99-100 and SEQ ID NO: 1 (GCC amino acid sequence); Formula I, where –(L)n- is 2 atoms, each L is -O-, Lc is absent, Rc is hydrogen, n is 2, r is 0 (Formula I composition); C-01 (table 1 structure)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US21/61252

-***-Continued From Box No. III: Observations where unity of invention is lacking-***-

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups I+, Claims 1-5, 73-75, 99-100 and SEQ ID NO: 1 (GCC amino acid sequence); Formula I, where –(L)n- is 2 atoms, each L is -O-, Lc is absent, Rc is hydrogen, n is 2, r is (Formula I composition); C-01 (table 1 structure) are directed towards conjugates comprising GCC binding peptides and metal chelators.

The conjugates of Claims 1 (in-part), 2, 3-5 (each in-part), 73 (in-part), 99-100 (each in-part) are believed to encompass the first named invention of Groups I+ and are the claims that will be searched without fee to the extent that they encompass SEQ ID NO: 1 (first exemplary GCC amino acid sequence); Formula I, where –(L)n- is 2 atoms, each L is -O-, Lc is absent, Rc is hydrogen, n is 2, r is (first exemplary Formula I composition); C-01 (first exemplary table 1 structure).

Applicant is invited to elect additional Formula I composition(s), table 1 structure(s), and GCC amino acid sequence(s) with specified SEQ ID NO: for each, or with specified substitution(s) at specified site(s) of a SEQ ID NO:, such that the sequence of each elected species is fully specified (i.e. no optional or variable residues or substituents), and where available as an option within at least one searchable claim, to be searched. Additional Formula I composition(s), table 1 structure(s), and GCC amino acid sequence(s) will be searched upon the payment of additional fees. Applicants must specify the searchable claims that encompass any additionally elected Formula I composition(s), table 1 structure(s), and GCC amino acid sequence(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be SEQ ID NO: 2 (GCC amino acid sequence); Formula I, where –(L)n is 3 atoms, each L is -NRL-, Lc is -O-, each RL is hydrogen, n is 3, r is 1 (Formula I composition); C-02 (table 1 structure).

a conjugate comprising a guanylyl cyclase C "GCC" binding peptide, wherein the GCC binding peptide comprises an amino acid sequence that has at least 85% identity to a sequence; a metal chelator configured to bind with a radionuclide; a linker that covalently attaches the GCC binding peptide with the metal chelator; and an alpha-particle emitting radionuclide bound to the metal chelator.

A conjugate comprising a guanylyl cyclase C "GCC" binding peptide; a metal chelator configured to bind with a radionuclide; and a linker that covalently attaches the GCC binding peptide with the metal chelator, wherein 5% to 99% of the conjugate binds to Human Serum Albumin (HSA) in vitro as determined by HSA-HPLC method.

A conjugate comprising a guanylyl cyclase C "GCC" binding peptide; a metal chelator configured to bind with a radionuclide; and a linker that covalently attaches the GCC binding peptide with the metal chelator, wherein the conjugate has a structure of Formula I)

A conjugate having a structure.

A conjugate comprising: a structure and a radionuclide bound to a metal chelator of the structure.

US 2014/0147380 A1 (Thomas Jefferson University) (hereinafter 'Jefferson') in view of the publication entitled 'Radioimmunotherapy with -particle-emittingradionuclides' by Seidl (hereinafter 'Seidl') and further in view of the publication entitled 'Fast Gradient HPLC Method to Determine Compounds Binding to Human Serum Albumin. Relationships with Octanol/Water and Immobilized Artificial Membrane Lipophilicity' by Valko et al. (hereinafter 'Valko').

Jefferson discloses a conjugate (a conjugated compound; paragraphs [0013], [0085]) comprising a guanylyl cyclase C "GCC" binding peptide (compounds the bind to GCC; paragraph [0013]), wherein the GCC binding peptide comprises an amino acid sequence that has at least 85% identity to a sequence (the GCC binding compound comprises an amino acid sequence; paragraphs [0013], [0018]-[0029]); a metal chelator configured to bind with a radionuclide (a metal chelator which binds to a metal that emits 152Eu (radionuclide); paragraphs [0085], [0369]); a linker that covalently attaches the GCC binding peptide with the metal chelator (a linker is used to attach the GCC binding peptide and the metal chelator; paragraphs [0013], [0085], [0114], [0369]); a conjugate (a conjugated compound; paragraphs [0013], [0085]) comprising a guanylyl cyclase C "GCC" binding peptide (compounds the bind to GCC; paragraph [0013]); a metal chelator configured to bind with a radionuclide (a metal chelator which binds to a metal that emits 152Eu (radionuclide); paragraphs [0085], [0369]); and a linker that covalently attaches the GCC binding peptide with the metal chelator (a linker is used to attach the GCC binding peptide and the metal chelator; paragraphs [0013], [0085], [0114], [0369]), a conjugate (a conjugated compound; paragraphs [0013], [0085]) comprising a guanylyl cyclase C "GCC" binding peptide (compounds the bind to GCC; paragraph [0013]); a metal chelator configured to bind with a radionuclide (a metal chelator which binds to a metal that emits 152Eu (radionuclide); paragraphs [0085], [0369]); and a linker that covalently attaches the GCC binding peptide with the metal chelator (a linker is used to attach the GCC binding peptide and the metal chelator; paragraphs [0013], [0085], [0114], [0369]), wherein the conjugate has a structure of Formula I) (a conjugated GCC binding compound of formula I, where R1 is substituted aryls, and where the GCC binding compound is linked to a metal chelator; paragraphs [0013], [0018]-[0019], [0085], [0114], [0369]); a conjugate having a structure (a conjugated GCC binding compound of formula I linked to a metal chelator; paragraphs [0013], [0018], [0085], [0114], [0369]); a conjugate (a conjugated compound; paragraphs [0013], [0085]) comprising: a structure and a radionuclide bound to a metal chelator of the structure (conjugated GCC binding compound of formula I linked to a metal chelator which binds to a metal that emits 152Eu (radionuclide); paragraphs [0013], [0018], [0085], [0114], [0369]).

Jefferson does not disclose an alpha-particle emitting radionuclide bound to the metal chelator; wherein 5% to 99% of the conjugate binds to Human Serum Albumin "HSA" in vitro as determined by HSA-HPLC method.

Seidl discloses an alpha-particle emitting radionuclide bound to a metal chelator (alpha emitting metal radionuclides bound to an appropriate chelating agent; abstract).

Valko discloses wherein 5% to 99% of a compound binds to Human Serum Albumin "HSA" in vitro as determined by HSA-HPLC method

-***-Continued Within the Next Supplemental Box-***-

-***-Continued from previous Supplemental Box-***-

(various compounds bind to HAS in vitro with % HAS of 70-99%; abstract; page 2237, second column, first paragraph; table 1).

It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the metal chelator configured to bind with a radionuclide, as previously disclosed by Jefferson, with the alpha-particle emitting radionuclide bound to a metal chelator, as previously disclosed by Seidl, for a superior conjugate which provides the benefit of using alpha emitting radionuclides that are highly cytotoxic and can be used for targeted radioimmunotherapy (Seidl reference; abstract). Further It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the conjugate, as previously disclosed by Jefferson, with 5%-99% of a compound binds to HSA in vitro as determined by the HSA-HLPC method, as previously disclosed by Valko, for a superior conjugate which provides the benefit of using a method which accurately compares the conjugate to other drugs where the conjugate will have an HSA binding percentage similar to other effective drugs (Valko reference; abstract; page 2237, first column, last paragraph; page 2237, second column, first paragraph; table 1).

Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Jefferson, Seidl, and Valko references, unity of invention is lacking.