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(54) Title: PEPTIDE COMPOSITIONS TARGETING GLYPICAN-3 AND USES THEREOF

(57) Abstract: The present technology generally relates to peptides that bind to phosphatidylinositol proteoglycan 3 (GPC3), to peptides that bind to the GPC3, and to compositions comprising such peptides.

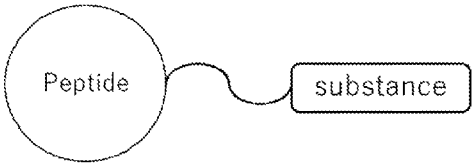

FIG. 1

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PEPTIDE COMPOSITIONS TARGETING GLYPICAN-3 AND USES THEREOF

JOINT RESEARCH AGREEMENT

[0001] Subject matter disclosed herein was developed, and the claimed invention was made by, or on behalf of, one or more parties to a Joint Research Agreement (JRA), within the meaning of 35 U.S.C. § 100(h) and 37 C.F.R. § 1.9(e), that was in effect on or before the effective filing date of the claimed invention. Said one or more parties to the JRA consist of PeptiDream, Inc. (Kanagawa, Japan) and RayzeBio, Inc. (San Diego, CA, U.S.A.). The claimed invention was made as a result of activities undertaken within the scope of said Joint Research Agreement.

RELATED APPLICATIONS

[0002] This application claims priority to U.S. Provisional Application No. 63/506,651, filed on June 7, 2023. The entire contents of the foregoing application are expressly incorporated herein by reference.

SEQUENCE LISTING

The present application contains a Sequence Listing XML file, which has been submitted electronically in .xml format as part of the specification, is incorportate herein by reference in its entirety. Said XML file, created on May 28, 2024, is named 137521-00320_SL.xml, and is 505,650 bytes in size.

TECHNICAL FIEL

[0003] The present technology relates to peptides that bind to Glypican-3 (GPC3) and to compositions comprising such peptides. The invention also includes conjugates comprising said peptides, conjugated to one or more effector and/or functional groups, to any substance such as pharmaceutical compositions, comprising said peptide ligands and the substance conjugates and to the use of said peptide ligands and substance conjugates in preventing, suppressing or treating a disease or disorder characterized by either overexpression or decreased expression of GPC3 in diseased tissue, such as in a tumor when GPC3 is overexpressed.

BACKGROUND OF THE INVENTION

[0004] Glypican-3 (GPC3) is a heparan sulfate (HS) glycoprotein, belonging to the sulfate heparan proteoglycan family, and which is anchored on the cell membrane surface by phosphatidylinositol (GPI) anchor. The GPC3 core protein comprises 580 amino acids, with a molecular weight of about 70 KDa. It is cut by furin (Furin), generating a 40 kDa N-terminal subunit and a 30 kDa C-terminal subunit, connected to each other by a disulfide bond. GPC3's two HS side chain is combined at the position close to the C end (Takahiro Nishida, Hiroaki Kataoka. Glypican 3-Targeted Therapy in Hepatocellular Carcinoma, Cancer 2019; 11 (9): 1339).

[0005] GPC3 can play an important role in the cell proliferation of embryo layer tissue. Deletion of GPC3 gene can cause excessive growth syndrome, namely Simpson-Golabi-Behmel syndrome (SGBS). GPC3 can be clearly

expressed throughout the entire fetal stage, and after birth to adult stage, except for placental, breast, mesodermal, ovarian, lung and kidney tissue with weak expression, other normal tissues have no obvious expression.

[0006] Abnormal GPC3 expression has been found in multiple tumour tissues of adult, such as hepatocellular carcinoma (HCC), lung squamous carcinoma, gastric cancer, ovarian cancer and so on. Especially highly expressed in HCC cells, GPC3 improves autocrine/paracrine canonical Wnt signal transmission, and promotes growth and invasion of HCC cells (Capurro MI, Xiang Y-Y, Lobe C, Filmus J. Glypican-3 promotes the growth of hepatocellular carcinoma by-stimulating canonical Wnt signaling; Canser Res 2005, 65 (14): 6245-54.). Immunohistochemical staining detection shows that about 70% of HCC patient tumor tissue exhibits high GPC3 protein expression (Capurro M, Wanless IR, Sherman M, et al.Glypican-3: a novel serum and histochemical marker for hepatocellular carcinoma; Gastroenterology 2003, 125 (1) :89-97). Thus, GPC3 is considered as a candidate target for tumor treatment.

[0007] Codrituzumab (also known as GC33 antibody) is a recombinant humanized monoclonal antibody developed in Japan by Chugai Pharmaceutical Co., which binds to the region of GPC3 protein proximal membrane end. Codrituzumab targets GPC3 positive HCC cells, and can generate antibody dependent cell toxicity (ADCC). In phase I clinical trials, Codrituzumab shows good immune tolerance. The HCC patient can generate an anti-tumour effect (Ikeda M, Ohkawa S, Okusaka T, et al. Japanese phase I study of GC33, a-antibody against glypican-3 for advanced hepatocellular carcinoma. Cancer Sci. 2014, 105, 455-462). However, in the II clinical trial with 185 late-stage liver cancer patients, the therapeutic efficacy of Codrituzumab was not impressive when compared with the control group.

[0008] Therefore, novel GPC3-binding peptides and compositions comprising the GPC3-binding peptide are both useful and desired.

INCORPORATION BY REFERENCE

[0009] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference for the specific purposes identified herein.

SUMMARY OF THE INVENTION

[0010] The invention described herein provides, *inter alia*, a peptide (*e.g.*, a cyclic peptide) that binds to GPC3, in particular to human GPC3; a linker-attached peptide thereof; a conjugate thereof; a kit thereof (*e.g.*, a kit for use in a method of diagnosing disease or disorder characterized by overexpression or decreased expression of GPC3 by determination of the expression level of GPC3); a composition (*e.g.*, pharmaceutical composition) comprising such GPC3-binding peptide or conjugate thereof; and methods of use thereof.

[0011] Specific, non-limiting, and illustrative aspects and embodiments of the invention described herein are provided herein below as numbered embodiments. As used herein, "a (cyclic) peptide" means "a peptide, such as a cyclic peptide."

[0012] 1. A peptide that has avidity for Glypican 3 (GPC3), or a pharmaceutically acceptable salt

thereof, wherein the peptide comprises an amino acid sequence including deletion, substitution, and/or addition of one or several (*e.g.*, 1-6) amino acids in the amino acid sequence of SEQ ID NO: 1:

MeK-MeI-D-MeQ-F4COO-I-I-Y-MeNal27N-G-3Py6Ph-MeC (SEQ ID NO: 1),

wherein the peptide consists of 10 to 12 amino acid residues.

[0013] 2. The peptide of embodiment 1, or a pharmaceutically acceptable salt thereof, wherein 1, 2, 3, 4 or 5 amino acids are added.

[0014] 3. The peptide of embodiment 1 or 2, or a pharmaceutically acceptable salt thereof, wherein the peptide is a cyclic peptide.

[0015] 4. A peptide that has avidity for Glypican 3 (GPC3), or a pharmaceutically acceptable salt thereof, wherein the peptide comprises an amino acid sequence of Formula (I),

X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12

Formula (I)

wherein,

X1 is any amino acid;

X2 is any amino acid;

X3 is any amino acid;

X4 is any amino acid;

X5 is an amino acid comprising an aromatic ring (*e.g.*, W, F, Y, or a variant thereof), cycloalkyl, or heterocycloalkyl group, or X5 is a peptoid (*e.g.*, Cha4cH, Cha4tH, A1mor, Atp, Cha4cOMe);

X6 is a hydrophobic amino acid, a hydrophilic amino acid, or a polar amino acid wherein the polar amino acid has a substituted side chain;

X7 is a hydrophobic amino acid comprising a C_1-C_8 alkyl, cycloalkyl, or heterocycloalkyl, wherein the alkyl, cycloalkyl, and heterocycloalkyl are each independently, optionally substituted (*e.g.*, X7 is I, Eva, aII, TMe, SMe, Gcpr, Gcpe, Gthp, dMeS, TdMe, or Cbg);

X8 is a A, I, L, V, Y or F, or a variant thereof;

X9 is an N-alkylated amino acid comprising an aromatic ring;

X10 is G, A, or a D-amino acid (e.g, da, ds, de, or dp);

X11 is an amino acid comprising an aromatic ring (*e.g.*, F, Y, or a variant thereof); and,

X12 is N-alkylated cysteine (*e.g.*, MeC).

[0016] 5. The peptide of embodiment 4, or a pharmaceutically acceptable salt thereof, wherein X1 is an N-methylated amino acid.

[0017] 6. The peptide of embodiment 4 or 5, or a pharmaceutically acceptable salt thereof, wherein X1 is an N-methylated amino acid comprising a polar side chain (*e.g.*, MeK, MeQ, or a variant thereof).

[0018] 7. The peptide of any one of embodiments 4 to 6, or a pharmaceutically acceptable salt thereof, wherein X2 is a L-amino acid.

[0019] 8. The peptide of embodiment 7, or a pharmaceutically acceptable salt thereof, wherein X2 is a N-methylated amino acid.

[0020] 9. The peptide of any one of embodiments 4 to 8, or a pharmaceutically acceptable salt thereof, wherein X3 is a polar and/or an L-amino acid.

[0021] 10. The peptide of embodiment 9, or a pharmaceutically acceptable salt thereof, wherein X3 is an amino acid comprising a hydrophilic side chain (*e.g.*, D, K, Q, or a variant thereof) or an N-methylated variant thereof.

[0022] 11. The peptide of any one of embodiments 4 to 10, or a pharmaceutically acceptable salt thereof, wherein X4 is a polar and/or an L-amino acid.

[0023] 12. The peptide of embodiment 11, or a pharmaceutically acceptable salt thereof, wherein X4 is an N-methylated amino acid, a polar amino acid (*e.g.*, D, K, Q, S, or a variant thereof), or peptoid (e.g. EtG, MeeG, CmG, CmpG CrmG CeG CrpG).

[0024] 13. The peptide of any one of embodiments 4 to 12, or a pharmaceutically acceptable salt thereof, wherein X5 has an aromatic side chain, such as F, Y, or a variant thereof.

[0025] 14. The peptide of embodiment 13, or a pharmaceutically acceptable salt thereof, wherein X5 is:

F, or a variant thereof comprising a phenyl, pyridinyl, or naphthalyl, wherein said phenyl, pyridinyl, or naphthalyl is optionally substituted with one or more substituents each independently selected from halogen, -C_{1-3}alkyl, -OH, -NH_2, -CN, -C(=O)OH, -C(=O)NH_2, -NHC(=O)CH_3, -C_{1-3}alkylene-C(=O)OH, -C_{1-3}alkylene-C(=O)NH_2, -O-C_{1-3}alkylene-C(=O)OH, -O-C_{1-3}alkylene-C(=O)NH_2, -C_{1-3}alkylene-C(=O)-5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH, -O-C_{1-3}alkylene-C(=O)- 5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH, -C_{1-3}alkylene-NHC(=O)- 5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH, -O-C_{1-3}alkylene-NHC(=O)- 5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH, and -NH-C_{1-3}alkylene-C(=O)OH; or

Y, or a variant thereof comprising a hydroxyphenyl, wherein the hydrogen atom in hydroxyphenyl of Y or of the variant is optionally substituted with one or more substituents selected from -C_{1-3}alkyl, , and -C_{1-3}alkylene-C(=O)OH.

[0026] 15. The peptide of any one of embodiments 4 to 14, or a pharmaceutically acceptable salt thereof, wherein X6 is an aliphatic amino acid (*e.g.*, V, L, I, A, G, or a variant thereof), a hydrophilic amino acid (*e.g.*, D, E, or a variant thereof), threonine (T) or a variant thereof (e.g., O-methyl threonine (TMe)), serine (S), or methionine (M).

[0027] 16. The peptide of any one of embodiment 4 to 15, or a pharmaceutically acceptable salt thereof, wherein X7 is an amino acid comprising a branched alkyl side chain, a C_{3-5}cycloalkyl side chain, or a 3- to 5- membered heterocycloalkyl side chain, or an N-methylated variant thereof.

[0028] 17. The peptide of embodiment 16, or a pharmaceutically acceptable salt thereof, wherein the

branched alkyl side chain comprises 3-5 carbon atoms.

[0029] 18. The peptide of embodiment 16 or 17, or a pharmaceutically acceptable salt thereof, wherein the alkyl, cycloalkyl, or heterocycloalkyl side chain is optionally substituted with -O-C_1-C_6 alkyl.

[0030] 19. The peptide of any one of embodiment 4 to 18, or a pharmaceutically acceptable salt thereof, wherein X8 is:

an aliphatic amino acid (e.g., A, I, L, or V);

Y, or a variant thereof comprising a hydroxyphenyl ring, wherein the hydroxyphenyl ring of Y or of the variant is optionally substituted with one or more substituents selected from halogen, -C_{1-3}alkyl, -OH, -C(=O)OH, -O-CH_3, -C_{1-3}alkylene-C(=O)OH, -C_{1-3}alkylene-C(=O)- 5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH, and -C_{1-3}alkylene-NHC(=O)- 5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH; or

F, or a variant thereof comprising a phenyl, pyridinyl, or indazolyl, wherein the phenyl of F or the phenyl, pyridinyl, or indazolyl of the variant is optionally substituted with one or more substituents each independently selected from halogen, -C_{1-3}alkyl, -OH, -C(=O)OH, -C(=O)NH_2, -NHC(=O)NH_2, -C_{1-3}alkylene-C(NH_2)-COOH, -NH-CO-CH_3, -NH-C_{1-3}alkylene-NH_2, -C(=O)-N(CH_2)$_2$, -S(=O)$_2$-CH_3, -C_{1-3}alkylene-NH-C(=O)- 5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH, and -O-C_{1-3}alkylene-NH-C(=O)- 5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH.

[0031] 20. The peptide of any one of embodiment 4 to 19, or a pharmaceutically acceptable salt thereof, wherein X9 is an N-methyl aromatic amino acid, optionally a bicyclic aromatic amino acid.

[0032] 21. The peptide of embodiment 20, or a pharmaceutically acceptable salt thereof, wherein the N-methyl aromatic amino acid is:

N-methyl monocyclic aromatic amino acid comprising a phenyl or pyridinyl optionally substituted with one or more substituents each independently selected from halogen, -C_{1-3}alkyl, and trifluoromethyl; or

N-methyl bicyclic aromatic amino acid comprising a naphthalyl, quinolyl, or indazolyl optionally substituted with one or more substituents each independently selected from H or C_{1-3}alkyl.

[0033] 22. The peptide of any one of embodiments 4 to 21, or a pharmaceutically acceptable salt thereof, wherein X10 is G or a D-amino acid (e.g., da, ds, de, or dp).

[0034] 23. The peptide of any one of embodiments 4 to 22, or a pharmaceutically acceptable salt thereof, wherein X11 is F or a variant thereof, or an amino acid comprising -C_{1-6}alkylene-phenyl.

[0035] 24. The peptide of embodiment 23, or a pharmaceutically acceptable salt thereof, wherein F or the variant thereof is:

F, or a variant thereof comprising a phenyl, or pyridinyl, optionally substituted with one or more substituents each independently selected from phenyl, -O-phenyl, -O-C_{1-3}alkylene-phenyl, pyridinyl,

imidazolyl, pyrazolyl, N-C_{1-3}alkylene pyrazolyl, N-C_{1-3}alkylene(-O-C_{1-3}alkyl) pyrazolyl, pyranyl, tetrahydropyranyl, piperidinyl, N-C_{1-3}alkylene-C(=O)-piperidinyl.

[0036] 25. The peptide of any one of embodiments 1 to 24, or a pharmaceutically acceptable salt thereof, wherein the peptide has an amino acid sequence according to Formula (I), or a pharmaceutically acceptable salt thereof,

X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12

Formula (I)

wherein,

X1 is I, R, Cit, F4G, 4Py, 3Py, KCOpipzaa, V, Eva, Q, E, MeI, Ahp, F4COO, KCOpip4COO, MeQdMe, MeA, MeSMe, MeG, MeV, MeHseMe, Aib, MeT, all, TMe, MeKCOpipzaa, MeQ, Hpr, MeTMe, MeDapCOpipzaa, MeK, MeKAc, MeK(de), MeK(H), MeK(df), or MeK(datb);

X2 is I, K, Cit, F4G, 4Py, 3Py, KCOpipzetOH, V, KCOpipzaa, Eva, Q, E, S, Ahp, F4COO, KCOpip4COO, MeQdMe, MeA, MeSMe, MeG, MeI, MeV, MeL, HseMe, MeY, Me3Py, MeHseMe, MeKAc, all, TMe, MeKCOpipzaa, MeQ, Hpr, MeTMe, or MeDapCOpipzaaa;

X3 is D, Har, KCOpipzetOH, Cit, KCOmeglumine, KCOpipzaa, A4paa, Q, A, E, MeD, S, N, Hgl, F4COO, KCOpip4COO, KAc, Hgn, MeY, or DapCOpipzaa;

X4 is D, Har, KCOpipzetOH, KCOmeglumine, KCOpipzaa, A4paa, Q, A, E, MeD, S, N, Hgl, F4COO, KCOpip4COO, dd, MeQ, MeQdMe, MeA, MeSMe, MeG, EtG, MeeG, CmG, CmpG, CrmG, CeG, CrpG, MeK, MeKAc, MeHgl, Hgn, MeDapCOpipzaa, MeKCOpipzaa, Medd, Cit, MeCit, MeN, MeS, MeE, MeY, W5N or Mae4paa;

X5 is Y, F3G, 3Py6COO,4Py2NH2, 3Py5COO, F3COO, 3Py6NHAc, F, F4C, F4OMe, F4COO, Nal2, F3aao, F4aa, F4aao, 3Py6NHaa, 5Pdo, F3CON, F4F, F4OEt, F4Me, F4CON, F4CONPEG4Me, F3OMe, Yae, YaeCOpipzaa, F4aaopipzaa, 4Pdo, 3Py6CON, Atp, Cha4cH, Cha4tH, Cha4cOMe, A1mor, or F4amCOpipzaa;

X6 is I, V, Eva, Chg, Tbg, A, L, Ahp, F4COO, Gcpr, Gcpe, all, Cle , S3REt, TMe, Acpr, Cba, Gthp, NleCOO, NleOH, P, Atb, Nva, Nle, N, DapAc, Abu, Nmm, Ndm, Ncit, Cit, SMe, HseMe, HseEt, HseiPr, dMeS, TdMe, Cbg, NvaOMe, SiPr, Spr, NleOMe, Sbu, Scbm, Scpe, AhpOMe, HseBu, Spent or Hsecpe;

X7 is I, Eva, all, TMe, SMe, Gcpr, Gcpe, Gthp, dMeS, TdMe, or Cbg;

X8 is A, I, L, V, Y, F4OMe, F4COO, F4Oet, F4u, F4Me, F4CONdMe, F4CON, F4ms, F4CONPEG4Me, F34dOMe, F3OMe, F3C, F3CON, F3CONdMe, 3Py6CON, Yae, YaeCOpipzaa, 5Inda, F3aao, F3aa, F4aao, F3aa, 3Py6Nhae, 3Py6NHAc, 3Py6OMe, F4aaopipzaa, or F4amCOpipzaa;

X9 is MeNal2, MeNal27N, MeF34diox, MeF34dOMe, MeF4T, MeY, MeW1Me, MeW7N, MeF3C4Me, or MeF3Me4C;

X10 is G, A, or a D-amino acid (e.g., da, ds, de, or dp);

X11 is Bph, 3Py6Ph, F41Me4Pyz, F43Pyz, F44Pyz, F41Pyz, F41Me3Pyz, F41Et4Pyz, F41MeOe4Pyz, F41MeOp4Pyz, F44thp, F4Ac4pip, PhNva, PhNle, Yph, Ybn, F4tb, F4oPr, or F4CONdMe; and

X12 is MeC.

[0037] 26. A peptide having avidity for Glypican 3 (GPC3), or a pharmaceutically acceptable salt thereof, wherein the peptide has an amino acid sequence of Formula (I),

X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12

Formula (I)

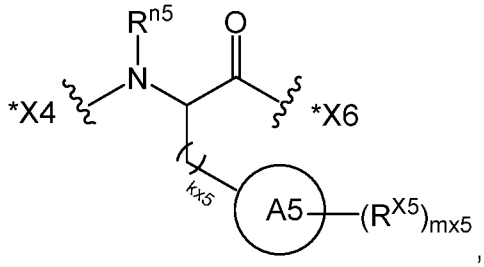
wherein,

X1 is any amino acid;

X2 is any amino acid;

X3 is any amino acid;

X4 is any amino acid;

X5 is 

, wherein:

R^{n5} is hydrogen or C_{1-3} alkyl;

ring A5 is an aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

each R^{X5} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halogen, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-SF_5$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-S(=O)(=NR^a)R^a$, $-N=S(=O)NR^cR^d$, $-NR^aS(=O)_2R^a$, amidinyl, $-NR^aC(=NH)NR^cR^d$, $-NR^aS(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, $-P(=O)(OR^c)(OR^d)$, $-P(=O)R^cR^d$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, $-L^{X5}$-heterocycloalkyl, $-L^{X5}$-cycloalkyl, $-L^{X5}$-aryl, or $-L^{X5}$-heteroaryl, wherein the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl are optionally substituted with one or more R^{X5a}; or

two R^{X5} are taken together to form =O, =S, or $=N(R^a)$;

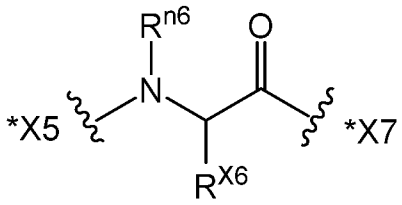
L^{X5} is C_{1-6}alkylene, C_{1-6}heteroalkylene, -O-, -S-, or $-NR^a-$, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X5a};

kx5 is 0, 1, 2, or 3;

mx5 is 0, 1, 2, 3, 4, or 5;

*X4 represents the point of attachment to X4; and

*X6 represents the point of attachment to X6;



X6 is , wherein;

R^{n6} is hydrogen or C_{1-3} alkyl;

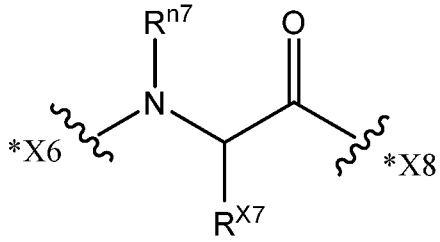
R^{X6} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -L^{X6}-heterocycloalkyl, -L^{X6}-cycloalkyl, -L^{X6}-aryl, or -L^{X6}-heteroaryl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X6a}; or

R^{n6} and R^{x6} are taken together with the intervening atoms to form a 5- to 6- membered heterocycloalkyl, which is optionally substituted with one or more R^{X6a};

L^{X6} is C_{1-6}alkylene, C_{1-6}heteroalkylene, -O-, -S-, or -NR^a-, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X6a};

*X5 represents the point of attachment to X5; and

*X7 represents the point of attachment to X7;



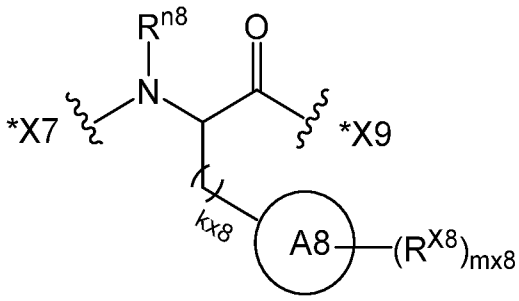
X7 is , wherein:

R^{n7} is hydrogen or C_{1-3} alkyl ;

R^{X7} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, cycloalkyl, or heterocycloalkyl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X7a};

*X6 represents the point of attachment to X6; and

*X8 represents the point of attachment to X8;



X8 is , wherein;

R^{n8} is hydrogen or C_{1-3}alkyl;

ring A8 is an aryl or heteroaryl;

each R^{X8} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halogen, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-SF_5$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2R^cR^d$, $-S(=O)(=NR^a)R^a$, $-N=S(=O)\ R^cR^d$, $-NR^aS(=O)_2R^a$, amidinyl, $-NR^aC(=NH)NR^cR^d$, $-NR^aS(=O)_2R^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, $-P(=O)(OR^c)(OR^d)$, $-P(=O)R^cR^d$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, $-L^{X8}$-heterocycloalkyl, $-L^{X8}$-cycloalkyl, $-L^{X8}$-aryl, or $-L^{X8}$-heteroaryl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X8a}; or

two R^{X8} are taken together to form =O, =S, or $=N(R^a)$;

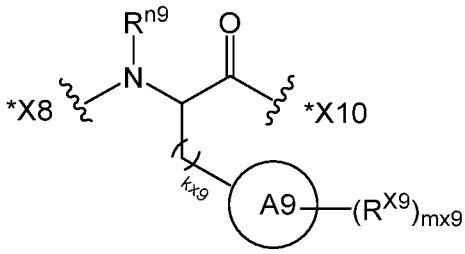
L^{X8} is C_{1-6}alkylene, C_{1-6}heteroalkylene, -O-, -S-, or $-NR^a-$, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X8a};

kx8 is 0, 1, 2, or 3;

mx8 is 0, 1, 2, 3, 4, or 5;

*X7 represents the point of attachment to X7; and

*X9 represents the point of attachment to X9;

X9 is 

, wherein:

R^{n9} is hydrogen or C_{1-3} alkyl;

ring A9 is an aryl or heteroaryl;

each R^{X9} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halogen, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-SF_5$, or $-NR^cR^d$, wherein each of the alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^{X9a}; or

two R^{X9} are taken together to form =O, =S, or $=N(R^a)$;

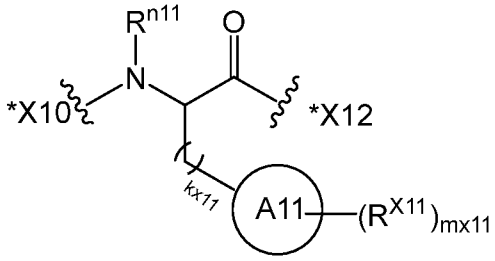
kx9 is 0, 1, 2, or 3;

mx9 is 0, 1, 2, 3, 4, or 5;

*X8 represents the point of attachment to X8; and

*X10 represents the point of attachment to X10;

X10 is glycine or a D-amino acid (e.g., da, ds, de, or dp);

X11 is  , wherein:

R^{n11} is hydrogen or C_{1-3} alkyl;

ring A11 is an aryl or heteroaryl;

each R^{X11} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, halogen, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-SF_5$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2R^cR^d$, $-S(=O)(=NR^a)R^a$, $-N=S(=O)R^cR^d$, $-NR^aS(=O)_2R^a$, amidinyl, $-NR^aC(=NH)NR^cR^d$, $-NR^aS(=O)_2R^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, $-P(=O)(OR^c)(OR^d)$, $-P(=O)R^cR^d$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, $-L^{X11}$-heterocycloalkyl, $-L^{X11}$-cycloalkyl, $-L^{X11}$-aryl, or $-L^{X11}$-heteroaryl, wherein each of the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X11a}; or

two R^{X11} are taken together to form =O, =S, or $=N(R^a)$;

L^{X11} is C_{1-6}alkylene, C_{1-6}heteroalkylene, -O-, -S-, or $-NR^a$-, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X11a};

kx11 is 0, 1, 2, 3, 4, or 5;

mx11 is 0, 1, 2, 3, 4, or 5;

*X10 represents the point of attachment to X10; and,

*X12 represents the point of attachment to X12;

X12 is N-alkylated cysteine;

each of R^{X5a}, R^{X6a}, R^{X7a}, R^{X8a}, R^{X9a}, and R^{X11a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-SF_5$, $-S(=O)_2NR^cR^d$, $-S(=O)(=NR^a)R^a$, $-N=S(=O)R^cR^d$, $-NR^aS(=O)_2R^a$, amidinyl, $-NR^aC(=NH)(NR^a)_2$, $-NR^aS(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, $-P(=O)(OR^c)(OR^d)$, $-P(=O)R^cR^d$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O, =S, or $=N(R^a)$, wherein each of the alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e.

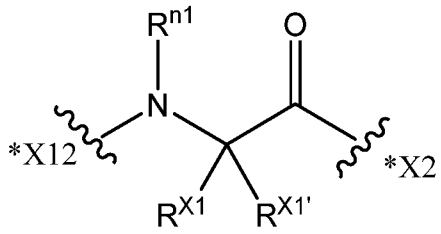
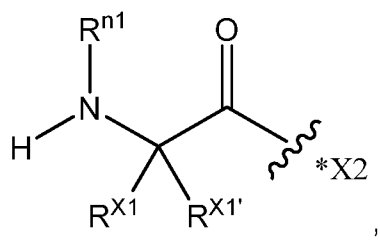
each R^a is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl),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

each R^e is independently halogen, -CN, -OH, -O-C_1-C_6alkyl, -SF_5, -S(=O)C_1-C_6alkyl, -$S(=O)_2C_1$-C_6alkyl, -$S(=O)_2NH_2$, -$S(=O)_2$-halogen, -$S(=O)_2NHC_1$-C_6alkyl, -$S(=O)_2N(C_1$-C_6alkyl$)_2$, -NH_2, -NHC_1-C_6alkyl, -$N(C_1$-C_6alkyl$)_2$, -NHC(=NH)NH_2, -NHC(=O)OC_1-C_6alkyl, -C(=O)C_1-C_6alkyl, -C(=O)OH, C_1-C_6alkyl-C(=O)OH, -C(=O)OC_1-C_6alkyl, -C(=O)NH_2, -C(=O)$N(C_1$-C_6alkyl$)_2$, -C(=O)NHC_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl; or two R^e are taken together to form =O; and

each R^c and R^d are 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 each of the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^e; 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^e.

[0038] 27. The peptide of embodiment 26, or a pharmaceutically acceptable salt thereof, wherein X1 is an N-alkylated amino acid.

[0039] 28. The peptide of embodiment 26 or 27, or a pharmaceutically acceptable salt thereof, wherein:

X1 is  or  ,

wherein:

R^{n1} is hydrogen or C_{1-3} alkyl;

R^{X1} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -L^{X1}-heterocycloalkyl, -L^{X1}-cycloalkyl, -L^{X1}-aryl, or -L^{X1}-heteroaryl, wherein each of the alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X1a};

$R^{X1'}$ is hydrogen or C_{1-6}alkyl, wherein the alkyl is optionally substituted with one or more R^{X1a}; or

R^{n1} and $R^{X1'}$ are taken together with the intervening atoms to form a 5- to 6- membered heterocycloalkyl, which is optionally substituted with one or more R^{X1a};

L^{X1} is C_{1-6}alkylene, C_{1-6}heteroalkylene, -O-, -S-, or -NR^a-, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X1a};

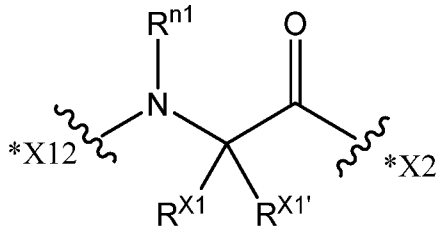
each R^{X1a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -S(=O)R^a, -$S(=O)_2R^a$, -SF_5, -$S(=O)_2NR^cR^d$, -S(=O)(=NR^a)R^a, -N=S(=O)R^cR^d, -$NR^aS(=O)_2R^a$, amidinyl, -

$NR^aC(=NH)(NR^a)_2$, $-NR^aS(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, $-P(=O)(OR^c)(OR^d)$, $-P(=O)R^cR^d$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O, =S, or $=N(R^a)$, wherein each of the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e;

*X12 represents the point of attachment to X12; and

*X2 represents the point of attachment to X2.

[0040] 29. The peptide of any one of embodiments 26 to 28, or a pharmaceutically acceptable salt thereof, wherein:

X1 is  , wherein:

R^{n1} is hydrogen or methyl;

R^{X1} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, $-L^{X1}$-5-6 membered heterocycloalkyl, $-L^{X1}$-C_{4-6}cycloalkyl, $-L^{X1}$-C_{6-10}aryl, or $-L^{X1}$-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X1a};

$R^{X1'}$ is hydrogen or methyl; or

R^{n1} and $R^{X1'}$ are taken together with the intervening atoms to form a 5- to 6- membered heterocycloalkyl, which is optionally substituted with one or more R^{X1a};

L^{X1} is C_{1-6}alkylene or C_{1-6}heteroalkylene, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X1a};

each R^{X1a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-SF_5$, $-S(=O)_2NR^cR^d$, $-S(=O)(=NR^a)R^a$, $-N=S(=O)R^cR^d$, $-NR^aS(=O)_2R^a$, amidinyl, $-NR^aC(=NH)(NR^a)_2$, $-NR^aS(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, $-P(=O)(OR^c)(OR^d)$, $-P(=O)R^cR^d$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O, =S, or $=N(R^a)$, wherein each of the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e;

*X12 represents the point of attachment to X12; and

*X2 represents the point of attachment to X2.

[0041] 30. The peptide of embodiment 28 or 29, or a pharmaceutically acceptable salt thereof, wherein:

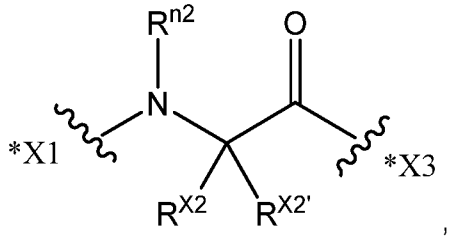
R^{X1} is hydrogen, C_{1-6}alkyl, C_{1-6}heteroalkyl, -L^{X1}-piperidinyl, -L^{X1}-piperazinyl, -L^{X1}-phenyl, or -L^{X1}-pyridinyl, wherein each of the alkyl, heteroalkyl, phenyl, pyridinyl, piperidinyl, and piperazinyl is optionally substituted with one or more R^{X1a}.

[0042] 31. The peptide of any one of embodiments 28 to 30, or a pharmaceutically acceptable salt thereof, wherein:

each R^{X1a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^aS(=O)_2R^a$, -$NR^aC(=NH)(NR^a)_2$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e.

[0043] 32. The peptide of any one of embodiments 26 to 31, or a pharmaceutically acceptable salt thereof, wherein X2 is an N-alkylated amino acid.

[0044] 33. The peptide of any one of embodiments 26 to 32, or a pharmaceutically acceptable salt thereof, wherein:

X2 is 

,

wherein,

R^{n2} is hydrogen or C_{1-3} alkyl, wherein the alkyl is optionally substituted with one or more R^{X2a};

R^{X2} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -L^{X2}-heterocycloalkyl, -L^{X2}-cycloalkyl, -L^{X2}-aryl, or -L^{X2}-heteroaryl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X2a};

$R^{X2'}$ is hydrogen or C_{1-6}alkyl, wherein the alkyl is optionally substituted with one or more R^{X2a}; or

R^{n2} and $R^{X2'}$ are taken together with the intervening atoms to form a 5- to 6- membered heterocycloalkyl, which is optionally substituted with one or more R^{X2a};

L^{X2} is C_{1-6}alkylene, C_{1-6}heteroalkylene, -O-, -S-, or -NR^a-, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X2a};

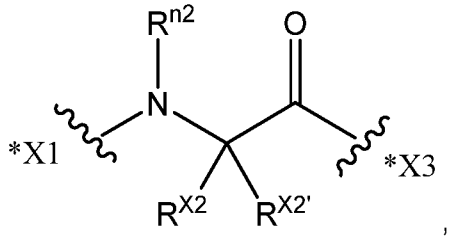
each R^{X2a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -SF_5, -$S(=O)_2NR^cR^d$, -$S(=O)(=NR^a)R^a$, -$N=S(=O)R^cR^d$, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)(NR^a)_2$, -$NR^aS(=O)_2NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, -$P(=O)(OR^c)(OR^d)$, -$P(=O)R^cR^d$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O, =S, =$N(R^a)$, aryl, heteroaryl, cycloalkyl, or

heterocycloalkyl, wherein each of the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e;

*X1 represents the point of attachment to X1; and

*X3 represents the point of attachment to X3.

[0045] 34. The peptide of any one of embodiments 26 to 33, or a pharmaceutically acceptable salt thereof, wherein

X2 is 

,

wherein:

R^{n2} is hydrogen or methyl;

R^{X2} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, -L^{X2}-5-6 membered heterocycloalkyl, -L^{X2}-C_{4-6}cycloalkyl, -L^{X2}-C_{6-10}aryl, or -L^{X2}-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X2a};

$R^{X2'}$ is hydrogen or methyl; or

R^{n2} and $R^{X2'}$ are taken together with the intervening atoms to form a 5- to 6- membered heterocycloalkyl, which is optionally substituted with one or more R^{X2a};

L^{X2} is C_{1-6}alkylene or C_{1-6}heteroalkylene, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X2a};

each R^{X2a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -S(=O)R^a, -$S(=O)_2R^a$, -SF_5, -$S(=O)_2NR^cR^d$, -S(=O)(=NR^a)R^a, -N=S(=O)R^cR^d, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)(NR^a)_2$, -$NR^aS(=O)_2NR^cR^d$, -C(=O)R^a, -C(=O)OR^a, -OC(=O)R^a, -OC(=O)OR^a, -OC(=O)NR^cR^d, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -C(=O)NR^cR^d, -P(=O)(OR^c)(OR^d), -P(=O)R^cR^d, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O, =S, or =N(R^a), wherein each of the alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e;

*X1 represents the point of attachment to X1; and

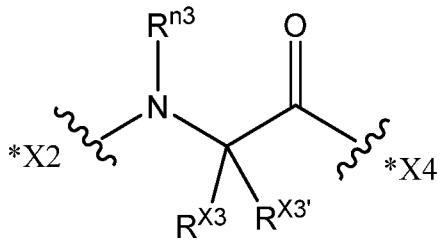
*X3 represents the point of attachment to X3.

[0046] 35. The peptide of embodiment 33 or 34, or a pharmaceutically acceptable salt thereof, wherein R^{X2} is hydrogen, C_{1-6}alkyl, C_{1-6}heteroalkyl, -L^{X2}-piperidinyl, L^{X2}-piperazinyl, -L^{X2}-phenyl, or -L^{X2}-pyridinyl, wherein each of the alkyl, heteroalkyl, phenyl, pyridinyl, piperidinyl, and piperazinyl is optionally substituted with one or more R^{X2a}.

[0047] 36. The peptide of any one of embodiments 33 to 35, or a pharmaceutically acceptable salt thereof, wherein each R^{X2a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-

C_6aminoalkyl, C_1-C_6heteroalkyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^aS(=O)_2R^a$, -$NR^aC(=NH)(NR^a)_2$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e.

[0048] 37. The peptide of any one of embodiments 26 to 36, or a pharmaceutically acceptable salt thereof, wherein

X3 is 

,

wherein:

R^{n3} is hydrogen or C_{1-3}alkyl, wherein the alkyl is optionally substituted with one or more R^{X3a};

R^{X3} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -L^{X3}-heterocycloalkyl, -L^{X3}-cycloalkyl, -L^{X3}-aryl, or -L^{X3}-heteroaryl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X3a};

$R^{X3'}$ is hydrogen or C_{1-6}alkyl, wherein the alkyl is optionally substituted with one or more R^{X3a}; or

R^{n3} and $R^{X3'}$ are taken together with the intervening atoms to form a 5- to 6- membered heterocycloalkyl, which is optionally substituted with one or more R^{X3a};

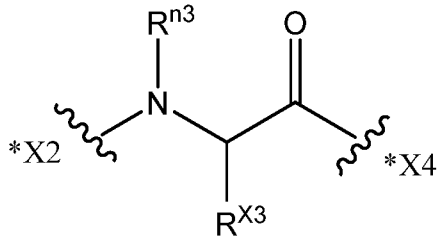
L^{X3} is C_{1-6}alkylene, C_{1-6}heteroalkylene, -O-, -S-, or -NR^a-, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X3a};

each R^{X3a} is independently halogen, C_{1-6}alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -SF_5, -$S(=O)_2NR^cR^d$, -$S(=O)(=NR^a)R^a$, -$N=S(=O)R^cR^d$, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)(NR^a)_2$, -$NR^aS(=O)_2NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, -$P(=O)(OR^c)(OR^d)$, -$P(=O)R^cR^d$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O, =S, or =$N(R^a)$, wherein each of the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e;

*X2 represents the point of attachment to X2; and

*X4 represents the point of attachment to X4.

[0049] 38. The peptide of any one of embodiments 26 to 37, or a pharmaceutically acceptable salt thereof, wherein



X3 is , wherein:

R^{n3} is hydrogen or methyl;

R^{X3} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, -L^{X3}-5-6 membered heterocycloalkyl, -L^{X3}-C_{3-6}cycloalkyl, -L^{X3}-C_{6-10}aryl, or -L^{X3}-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X3a};

L^{X3} is C_{1-6}alkylene or C_{1-6}heteroalkylene, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X3a};

each R^{X3a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -SF_5, -$S(=O)_2NR^cR^d$, -$S(=O)(=NR^a)R^a$, -$N=S(=O)R^cR^d$, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)(NR^a)_2$, -$NR^aS(=O)_2NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, -$P(=O)(OR^c)(OR^d)$, -$P(=O)R^cR^d$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O, =S, or =$N(R^a)$, wherein each of the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e;

*X2 represents the point of attachment to X2; and

*X4 represents the point of attachment to X4.

[0050] 39. The peptide of embodiment 37 to 38, or a pharmaceutically acceptable salt thereof, wherein R^{X3} is C_{1-6}alkyl, C_{1-6}heteroalkyl, -L^{X3}-piperidinyl, L^{X3}-piperazinyl, -L^{X3}-phenyl, or -L^{X3}-pyridinyl, wherein each of the alkyl, heteroalkyl, phenyl, pyridinyl, piperidinyl, and piperazinyl is optionally substituted with one or more R^{X2a}.

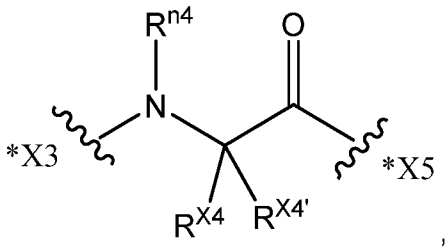
[0051] 40. The peptide of any one of embodiments 37 to 39, or a pharmaceutically acceptable salt thereof, wherein each R^{X3a} is independently halogen, C_{1-6}alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^aS(=O)_2R^a$, -$NR^aC(=NH)(NR^a)_2$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e.

[0052] 41. The peptide of any one of embodiments 26 to 40, or a pharmaceutically acceptable salt thereof, wherein X4 is an N-alkylated amino acid.

[0053] 42. The peptide of any one of embodiments 26 to 40, or a pharmaceutically acceptable salt

thereof, wherein X4 is a peptoid.

[0054] 43. The peptide of any one of embodiments 26 to 42, or a pharmaceutically acceptable salt thereof, wherein

X4 is 

,

wherein:

R^{n4} is hydrogen or C_{1-3} alkyl, wherein the alkyl is optionally substituted with one or more R^{X4a};

R^{X4} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -L^{X4}-heterocycloalkyl, -L^{X4}-cycloalkyl, -L^{X4}-aryl, or -L^{X4}-heteroaryl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X4a};

$R^{X4'}$ is hydrogen or C_{1-6}alkyl, wherein the alkyl is optionally substituted with one or more R^{X4a}; or

R^{n4} and $R^{X4'}$ are taken together with the intervening atoms to form a 5- to 6- membered heterocycloalkyl, which is optionally substituted with one or more R^{X4a};

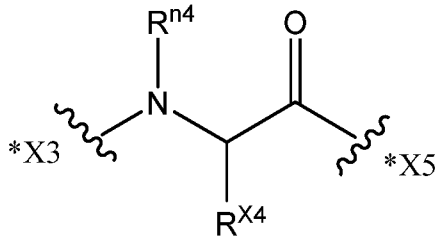
L^{X4} is C_{1-6}alkylene or C_{1-6}heteroalkylene, -O-, -S-, or -NR^a-, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X4a};

each R^{X4a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -SF_5, -$S(=O)_2NR^cR^d$, -$S(=O)(=NR^a)R^a$, -$N=S(=O)R^cR^d$, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)(NR^a)_2$, -$NR^aS(=O)_2NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, -$P(=O)(OR^c)(OR^d)$, -$P(=O)R^cR^d$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O, =S, or =$N(R^a)$, wherein each of the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e;

*X3 represents the point of attachment to X3; and

*X5 represents the point of attachment to X5.

[0055] 44. The peptide of any one of embodiments 26 to 43, or a pharmaceutically acceptable salt thereof, wherein

X4 is 

,

wherein:

R^{n4} is hydrogen or C_{1-3} alkyl, wherein the alkyl is optionally substituted with one or more R^{X4a};

R^{X4} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, -L^{X4}-5-6 membered heterocycloalkyl, -L^{X4}-C_{3-6}cycloalkyl, -L^{X4}-C_{6-10}aryl, or -L^{X4}-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X4a};

L^{X4} is C_{1-6}alkylene or C_{1-6}heteroalkylene, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X4a};

each R^{X4a} is independently halogen, C_{1-6}alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -SF_5, -$S(=O)_2NR^cR^d$, -$S(=O)(=NR^a)R^a$, -$N=S(=O)R^cR^d$, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)(NR^a)_2$, -$NR^aS(=O)_2NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, -$P(=O)(OR^c)(OR^d)$, -$P(=O)R^cR^d$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O, =S, or =$N(R^a)$, wherein each of the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e;

*X3 represents the point of attachment to X3; and

*X5 represents the point of attachment to X5.

[0056] 45. The peptide of embodiment 43 or 44, or a pharmaceutically acceptable salt thereof, wherein R^{X4} is C_{1-6}alkyl, C_{1-6}heteroalkyl, -L^{X4}-piperidinyl, L^{X4}-piperazinyl, -L^{X4}-phenyl, or -L^{X4}-pyridinyl, wherein each of the alkyl, heteroalkyl, phenyl, pyridinyl, piperidinyl, and piperazinyl is optionally substituted with one or more R^{X4a}.

[0057] 46. The peptide of any one of embodiments 43 to 45, or a pharmaceutically acceptable salt thereof, wherein

each R^{X4a} is independently halogen, C_{1-6}alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^aS(=O)_2R^a$, -$NR^aC(=NH)(NR^a)_2$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e.

[0058] 47. The peptide of any one of embodiments 26 to 46, or a pharmaceutically acceptable salt thereof, wherein

R^{n5} is hydrogen or methyl;

ring A5 is a C_{6-10}aryl, 5-10 membered heteroaryl, C_{6-10}cycloalkyl, or 5-10 membered heterocycloalkyl;

each R^{X5} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halogen, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-SF_5$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-S(=O)(=NR^a)R^a$, $-N=S(=O)NR^cR^d$, $-NR^aS(=O)_2R^a$, amidinyl, $-NR^aC(=NH)NR^cR^d$, $-NR^aS(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, $-P(=O)(OR^c)(OR^d)$, $-P(=O)R^cR^d$, C_{6-10}aryl, 5-10 membered heteroaryl, C_{3-6}cycloalkyl, 5-6 membered heterocycloalkyl, $-L^{X5}$-5-6 membered heterocycloalkyl, $-L^{X5}$-C_{3-6}cycloalkyl, $-L^{X5}$-C_{6-10}aryl, or $-L^{X5}$-5-10 membered heteroaryl, wherein the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl are optionally substituted with one or more R^{X5a}; or

two R^{X5} are taken together to form =O; and

L^{X5} is C_{1-6}alkylene or C_{1-6}heteroalkylene, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X5a}.

[0059] 48. The peptide of any one of embodiments 26 to 47, or a pharmaceutically acceptable salt thereof, wherein

ring A5 is a phenyl, naphthyl, pyridinyl, cyclohexyl, piperidinyl, piperazinyl, morpholinyl, or tetrahydropyranyl;

each R^{X5} is independently halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^aS(=O)_2R^a$, $-NR^aC(=NH)NR^cR^d$, $-NR^aS(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, $-L^{X5}$-piperidinyl, or L^{X5}-piperazinyl, wherein each of the alkyl, heteroalkyl, piperidinyl, and piperazinyl are optionally substituted with one or more R^{X5a}; or

two R^{X5} are taken together to form =O;

kx5 is 1 or 2; and

mx5 is 0, 1, or 2.

[0060] 49. The peptide of any one of embodiments 26 to 48, or a pharmaceutically acceptable salt thereof, wherein each R^{X5a} is independently halogen, C_{1-6}alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^aS(=O)_2R^a$, $-NR^aC(=NH)(NR^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e.

[0061] 50. The peptide of any one of embodiments 26 to 49, or a pharmaceutically acceptable salt thereof, wherein

R^{n6} is hydrogen or methyl;

R^{X6} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{6-10}aryl, 5-10 membered heteroaryl, C_{3-6}cycloalkyl, 5-6 membered heterocycloalkyl, -L^{X6}-5-6 membered heterocycloalkyl, -L^{X6}-C_{3-6}cycloalkyl, -L^{X6}-C_{6-10}aryl, or -L^{X6}-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X6a}; and

L^{X6} is C_{1-6}alkylene or C_{1-6}heteroalkylene, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X6a}.

[0062] 51. The peptide of any one of embodiments 26 to 50, or a pharmaceutically acceptable salt thereof, wherein R^{X6} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{3-6}cycloalkyl, 5-6 membered heterocycloalkyl, -L^{X6}-5-6 membered heterocycloalkyl, -L^{X6}- C_{3-6}cycloalkyl, -L^{X6}-phenyl or -L^{X6}-6 membered heteroaryl, wherein each of the alkyl, heteroalkyl, phenyl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X6a}.

[0063] 52. The peptide of any one of embodiments 26 to 51, or a pharmaceutically acceptable salt thereof, wherein each R^{X6a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^aS(=O)_2R^a$, -$NR^aC(=NH)(NR^a)_2$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e.

[0064] 53. The peptide of any one of embodiments 26 to 52, or a pharmaceutically acceptable salt thereof, wherein

R^{n7} is hydrogen or methyl; and

R^{X7} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, or 5-6 membered heterocycloalkyl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X7a}.

[0065] 54. The peptide of any one of embodiments 26 to 53, or a pharmaceutically acceptable salt thereof, wherein R^{X7} is C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{3-6}cycloalkyl, or 5-6 membered heterocycloalkyl, wherein each of the alkyl, heteroalkyl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X7a}.

[0066] 55. The peptide of any one of embodiments 26 to 54, or a pharmaceutically acceptable salt thereof, wherein each R^{X7a} is independently halogen, -CN, -OR^a, -SR^a, -NR^cR^d, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, or =O.

[0067] 56. The peptide of any one of embodiments 26 to 55, or a pharmaceutically acceptable salt thereof, wherein

ring A8 is a C_{6-10}aryl or 5-10 membered heteroaryl;

each R^{X8} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halogen, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-SF_5$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2R^cR^d$, $-S(=O)(=NR^a)R^a$, $-N=S(=O)\ R^cR^d$, $-NR^aS(=O)_2R^a$, amidinyl, $-NR^aC(=NH)NR^cR^d$, $-NR^aS(=O)_2R^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, $-P(=O)(OR^c)(OR^d)$, $-P(=O)R^cR^d$, C_{6-10}aryl, 5-10 membered heteroaryl, C_{3-6}cycloalkyl, 5-6 membered heterocycloalkyl, $-L^{X8}$-5-6 membered heterocycloalkyl, $-L^{X8}$- C_{3-6}cycloalkyl, $-L^{X8}$- C_{6-10}aryl, or $-L^{X8}$-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X8a}; or

two R^{X8} are taken together to form =O; and

L^{X8} is C_{1-6}alkylene or C_{1-6}heteroalkylene, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X8a}.

[0068] 57. The peptide of any one of embodiments 26 to 56, or a pharmaceutically acceptable salt thereof, wherein

ring A8 is a phenyl, pyridinyl, indolyl, azaindolyl, indazolyl, or benzimidazolyl;

each R^{X8} is independently halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^aS(=O)_2R^a$, $-NR^aC(=NH)NR^cR^d$, $-NR^aS(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, $-L^{X8}$-piperidinyl, or L^{X8}-piperazinyl, wherein each of the alkyl, heteroalkyl, piperidinyl, and piperazinyl are optionally substituted with one or more R^{X8a}; or

two R^{X5} are taken together to form =O;

kx8 is 1 or 2; and

mx8 is 0, 1, or 2.

[0069] 58. The peptide of any one of embodiments 26 to 57, or a pharmaceutically acceptable salt thereof, wherein each R^{X8a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^aS(=O)_2R^a$, $-NR^aC(=NH)(NR^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e.

[0070] 59. The peptide of any one of embodiments 26 to 58, or a pharmaceutically acceptable salt thereof, wherein

R^{n9} is hydrogen or methyl;

ring A9 is a C_{6-10}aryl or 5-10 membered heteroaryl; and

each R^{X9} is independently halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-SF_5$, or $-NR^cR^d$, wherein each of the alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^{X9a}; or

two R^{X9} are taken together to form =O.

[0071] 60. The peptide of any one of embodiments 26 to 59, or a pharmaceutically acceptable salt thereof, wherein

ring A9 is a phenyl, naphthyl, pyridinyl, indolyl, azaindolyl, indazolyl, benzimidazolyl, or isoquinolinyl;

each R^{X9} is independently halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, -CN, $-OR^a$, $-SR^a$, or $-NR^cR^d$, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^{X9a};

kx9 is 1 or 2; and

mx9 is 0, 1, or 2.

[0072] 61. The peptide of any one of embodiments 26 to 60, or a pharmaceutically acceptable salt thereof, wherein each R^{X9a} is independently halogen, C_{1-6}alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^aS(=O)_2R^a$, $-NR^aC(=NH)(NR^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e.

[0073] 62. The peptide of any one of embodiments 26 to 61, or a pharmaceutically acceptable salt thereof, wherein

ring A11 is a C_{6-10}aryl or 5-10 membered heteroaryl;

each R^{X11} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, halogen, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-SF_5$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2R^cR^d$, $-S(=O)(=NR^a)R^a$, $-N=S(=O)R^cR^d$, $-NR^aS(=O)_2R^a$, amidinyl, $-NR^aC(=NH)NR^cR^d$, $-NR^aS(=O)_2R^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, $-P(=O)(OR^c)(OR^d)$, $-P(=O)R^cR^d$, C_{6-10}aryl, 5-10 membered heteroaryl, C_{3-6}cycloalkyl, 5-6 membered heterocycloalkyl, $-L^{X11}$-5-6 membered heterocycloalkyl, $-L^{X11}$-C_{3-6}cycloalkyl, $-L^{X11}$-C_{6-10}aryl, or $-L^{X11}$-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X11a}; or

two R^{X11} are taken together to form =O; and

L^{X11} is C_{1-6}alkylene, C_{1-6}heteroalkylene, or -O-, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X11a}.

[0074] 63. The peptide of any one of embodiments 26 to 62, or a pharmaceutically acceptable salt thereof, wherein

ring A11 is a phenyl or pyridinyl;

each R^{X11} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, halogen, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2R^cR^d$, $-NR^aS(=O)_2R^a$, $-NR^aC(=NH)NR^cR^d$, $-NR^aS(=O)_2R^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, C_{6-10}aryl, 5-10 membered heteroaryl, C_{3-6}cycloalkyl, 5-6 membered heterocycloalkyl, $-L^{X11}$-5-6 membered heterocycloalkyl, $-L^{X11}$- C_{3-6}cycloalkyl, $-L^{X11}$- C_{6-10}aryl, or $-L^{X11}$-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X11a}; or

two R^{X11} are taken together to form =O;

kx11 is 1, 2, 3, or 4; and

mx11 is 0, 1, or 2.

[0075] 64. The peptide of any one of embodiments 26 to 63, or a pharmaceutically acceptable salt thereof, wherein each R^{X11} is independently phenyl, pyridinyl, pyrrolyl, pyrazolyl, imidazolyl, cyclohexyl, piperidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, $-L^{X11}$-5-6 membered heterocycloalkyl, - $-L^{X11}$-phenyl, or - L^{X11}-pyridinyl, wherein each of the phenyl, pyridinyl, pyrrolyl, pyrazolyl, imidazolyl, cyclohexyl, piperidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, and heterocycloalkyl is optionally substituted with one or more R^{X11a}.

[0076] 65. The peptide of any one of embodiments 26 to 64, or a pharmaceutically acceptable salt thereof, wherein each R^{X11a} is independently halogen, C_{1-6}alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^aS(=O)_2R^a$, $-NR^aC(=NH)(NR^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e.

[0077] 66. The peptide of any one of embodiments 1-65, wherein the peptide or the pharmaceutically acceptable salt thereof has a cyclic structure.

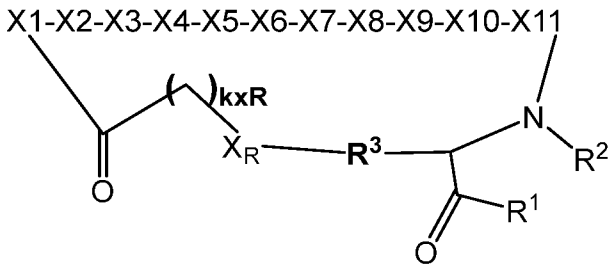
[0078] 67. The peptide of any one of embodiments 1-66, wherein the peptide or the pharmaceutically acceptable salt thereof has a cyclic structure, wherein the first amino acid (or X1) is covalently linked to the last amino acid (or X12).

[0079] 68. The peptide of any one of embodiments 1-67, wherein the peptide or the pharmaceutically acceptable salt thereof has a cyclic structure having an amino acid in the first residue X1 and a N-methylated cysteine residue, and wherein the amino acid in X1 and the N-methylated cysteine residue or variant thereof form a covalent bond.

[0080] 69. The peptide of any one of embodiments 1-68, or a pharmaceutically acceptable salt thereof, wherein the peptide has a monocyclic structure.

[0081] 70. The peptide of embodiment 69, or a pharmaceutically acceptable salt thereof, wherein the monocyclic structure is formed by a covalent bond between the amino acid X1 and a cysteine or a variant thereof.

[0082] 71. The peptide of any one of embodiments 1-70, or a pharmaceutically acceptable salt thereof, wherein the peptide has a structure of Formula (I-1),



Formula (I-1),

wherein,

R^1 is selected from the group consisting of $-NH_2$ and -OH;

R^2 is C_{1-3} alkyl;

R^3 is C_{1-3} alkylene, optionally substituted with one or more R^4, wherein;

each R^4 is independently C_{1-3} alkyl or C_{3-6} cycloalkyl,;

kxR is 1, 2, 3, 4, 5, or 6;

X_R is selected from the group consisting of S, C or O; and

wherein X1 to X11 have the definitions described in Formula (I).

[0083] 72. The peptide of any one of embodiments 1-71, wherein the peptide or the pharmaceutically acceptable salt thereof comprises a sequence with up to 1, 2, 3, 4, or 5 substitutions by a conserved variant compared to any one of the sequences selected from SEQ ID NOs: 1-72.

[0084] 73 The peptide of any one of embodiments 1-72, wherein the peptide or the pharmaceutically acceptable salt thereof consists of an amino acid sequence selected from SEQ ID NOs: 1-72.

[0085] 74. The peptide of any one of embodiments 1-73, or a pharmaceutically acceptable salt thereof, wherein the peptide has a binding affinity to a human GPC3 of at most 100 nM as determined by Kd in surface plasmon resonance (SPR) analysis.

[0086] 75. A peptide of any one of embodiments 1-74, or a pharmaceutically acceptable salt thereof, covalently linked to a linker that is capable of connecting the peptide to a payload molecule.

[0087] 76. The peptide of embodiment 75, or a pharmaceutically acceptable salt thereof, wherein the linker is attached to a lysine of the peptide.

[0088] 77. The peptide of embodiment 75 or 76, or a pharmaceutically acceptable salt thereof, wherein the linker is attached to the peptide via the N terminus of the peptide.

[0089] 78. The peptide of embodiment 75 or 76, or a pharmaceutically acceptable salt thereof, wherein the linker is attached to the peptide via the C terminus of the peptide.

[0090] 79. The peptide of embodiment 75 or 76, or a pharmaceutically acceptable salt thereof, wherein the linker is attached to the peptide via a non-terminal amino acid residue of the peptide.

[0091] 80. The peptide of embodiment 75 or 76, or a pharmaceutically acceptable salt thereof, wherein

the linker is attached to the 1st amino acid residue (or X1), the 2nd amino acid residue (or X2), the 3rd amino acid residue (or X3), the 4th amino acid residue (or X4), the 8th amino acid residue (or X8), or the 12th amino acid residue (or X12).

[0092] 81. The peptide of embodiment 80, or a pharmaceutically acceptable salt thereof, wherein the linker is attached to the 1st amino acid residue or X1.

[0093] 82. The peptide of embodiment 80, or a pharmaceutically acceptable salt thereof, wherein the linker is attached to the last amino acid residue, or X12.

[0094] 83. The peptide of embodiment 80, or a pharmaceutically acceptable salt thereof, wherein the linker is attached to the 2nd amino acid residue (or X2).

[0095] 84. The peptide of embodiment 80, or a pharmaceutically acceptable salt thereof, wherein the linker is attached to the 3rd amino acid residue (or X3).

[0096] 85. The peptide of embodiment 80, or a pharmaceutically acceptable salt thereof, wherein the linker is attached to the 4th amino acid residue (or X4).

[0097] 86. The peptide of embodiment 80, or a pharmaceutically acceptable salt thereof, wherein the linker is attached to the 8th amino acid residue (or X8).

[0098] 87. The peptide of any one of embodiments 75 to 86, or a pharmaceutically acceptable salt thereof, wherein the linker is a bond.

[0099] 88. The peptide of any one of embodiments 75 to 86, or a pharmaceutically acceptable salt thereof, wherein the linker comprises 3 to 30 intervening non-hydrdogen, organic atoms between the payload molecule and the peptide.

[00100] 89. The peptide of any one of embodiments 75 to 86, or a pharmaceutically acceptable salt thereof, wherein the linker comprises 6 to 18 intervening non-hydrogen, organic atoms between the payload molecule and the peptide.

[00101] 90. The peptide of embodiments 88 or 89, or a pharmaceutically acceptable salt thereof, wherein the intervening atoms comprise 1 to 6 nitrogen atoms and 0 to 4 oxygen atoms.

[00102] 91. The peptide of any one of embodiments 75 to 86 or 88 to 90, or a pharmaceutically acceptable salt thereof, wherein the linker comprises one or more amino acid residues.

[00103] 92. The peptide of embodiment 91, pharmaceutically acceptable salt thereof, wherein the linker comprises one amino acid residue.

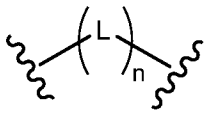
[00104] 93. The peptide of embodiment 91, or a pharmaceutically acceptable salt thereof, wherein the linker comprises at least two contiguous amnio acid residues.

[00105] 94. The peptide of any one of embodiments 91 to 93, wherein the one or more amino acid residues are selected from a lysine residue, an alanine residue, a glycine residue, a D-phenylalanine residue, a histidine residue, a dAtb residue, or a D-glutamate residue.

[00106] 95. The peptide of any one of embodiments 75 to 86, wherein the linker comprises one or more structures selected from AEEA, AEEP, AEEEP, and AEEEEP.

[00107] 96. The peptide of any one of embodiments 75 to 86, wherein the linker has a structure of

Formula (II-1)



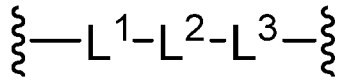
Formula (II-1)

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)$_2NR^L$C(=O)-, substituted or unsubstituted C_{3-15} cycloalkyl, substituted or unsubstituted C_{1-12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_{1-30} alkylene, substituted or unsubstituted C_{2-30} alkenylene, substituted or unsubstituted C_{2-30} alkynylene, substituted or unsubstituted C_{1-30} heteroalkylene, -(C_{1-30} alkylene)-O-, -O-(C_{1-30} alkylene)-, -(C_{1-30} alkylene)-NR^L-, -NR^L-(C_{1-30} alkylene)-, -(C_{1-30} alkylene)-$N(R^L)_2$-, or -$N(R^L)_2$-(C_{1-30} alkylene)-; and

each R^L is independently hydrogen, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} heteroalkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-5} alkynyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{2-7} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

n is 1 to 20.

[00108] 97. The peptide of embodiment 96, 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)$_2NR^L$C(=O)-; and

L^2 is absent, substituted or unsubstituted C_{1-30} alkylene, or substituted or unsubstituted C_{1-30} heteroalkylene.

[00109] 98. The peptide of embodiment 97, wherein L^1 is -NH-.

[00110] 99. The peptide of embodiment 97 or 98, wherein L^2 is substituted or unsubstituted C_{1-30} alkylene, or substituted or unsubstituted C_{1-30} heteroalkylene.

[00111] 100. The peptide of embodiment 97 or 98, wherein L^2 is substituted or unsubstituted C_{1-18} alkylene, or substituted or unsubstituted C_{1-18} heteroalkylene.

[00112] 101. The peptide of any one of embodiments 97 to 100, wherein L^2 is optionally substituted with one or more substituents selected from -OH, -SH, oxo, amino, C_{1-6} alkyl, C_{1-6} hydroxyalkyl, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, -C(=O)OR^L, -OC(=O)R^L, -OC(=O)OR^L, -C(=O)$N(R^L)_2$, -NR^LC(=O)R^L, -OC(=O)$N(R^L)_2$, and -NR^LC(=O)OR^L; and the C_{1-6} alkyl is further optionally substituted with one or more substituents chosen from -OH, -SH, oxo, amino, C_{6-10} aryl, 6- to 10- membered heteroaryl, -C(=O)OR^L, -OC(=O)R^L, -OC(=O)OR^L, -C(=O)$N(R^L)_2$, -NR^LC(=O)R^L, -OC(=O)$N(R^L)_2$, and -NR^LC(=O)OR^L.

[00113] 102. The peptide of any one of embodiments 97 to 101, wherein L^3 is -NH-.

[00114] 103. A pharmaceutical composition comprising the peptide or pharmaceutically acceptable salt thereof according to any one of embodiments 1 to 102, and a pharmaceutically acceptable excipient or carrier.

[00115] 104. A conjugate comprising the peptide or pharmaceutically acceptable salt thereof according to any one of embodiments 1 to 102, and a substance or a payload molecule, wherein the substance or payload molecule is selected from the group consisting of: a nucleotide, a small molecule, a medium sized molecule (e.g., with a M.W. of about 1,000-2,500 Da), a large sized molecule (e.g., with a M.W. of >2,500 Da), a polymer compound, a protein, a peptide, a tag, a biological fragment, a carrier including pharmaceutical compound, or a combination thereof.

[00116] 105. A method of treating a disease or disorder characterized by overexpression of GPC3, in a subject in need of treatment, the method comprising administering to the subject the peptide or pharmaceutically acceptable salt thereof according to any one of embodiments 1 to 102, the conjugate of embodiment 104, or the pharmaceutical composition of embodiment 103.

[00117] 106. The method of embodiment 105, wherein the disease or disorder is cancer.

[00118] 107. The method of embodiment 106, wherein the cancer is a solid tumor or hematological cancer.

[00119] 108. A kit, tester, or composition for determining the expression level of GPC3 in a sample, wherein the kit, tester, or composition comprises the peptide or a salt thereof according to any one of embodiments 1 to 102, the conjugate of embodiment 104, or the pharmaceutical composition of embodiment 103.

[00120] 109. The kit, tester, or composition of embodiment 108, adapted for use in a method of diagnosing disease or disorder characterized by an overexpression or a decreased expression of GPC3.

[00121] 110. The kit, tester, or composition of embodiment 108 or 109, wherein the sample is from a subject having a disease or disorder characterized by an overexpression or a decreased expression of GPC3.

[00122] 111. Use of the peptide or pharmaceutically acceptable salt thereof according to any one of the preceding embodiments in the manufacture of a medicament for diagnosing and/or treating a disease or disorder characterized by an overexpression or a decreased expression of GPC3.

[00123] 112. The peptide or pharmaceutically acceptable salt thereof according to any one of the preceding embodiments, for use in diagnosing and/or treating a disease or disorder characterized by an overexpression or a decreased expression of GPC3.

[00124] In some embodiments, the peptide of the present technology is an isolated peptide.

[00125] In some embodiments, the peptide of the present technology is a purified peptide.

[00126] In all aspects of this disclosure, however, the substance or payload molecule excludes any radioactive materials. Examples of the substance that are excluded are: radioisotope, radiopharmaceutical, or any compound having radioactive component. In all aspects of this disclosure, the substance further excludes any chelators for radioisotope conjugation, regardless of whether the chelator is connected to the peptide directly or via a linker. Accordingly, a complex, conjugate or PDC described herein does not encompass any compound containing a

chelator for radioisotope conjugation, and does not encompass a radioisotope.

[00127] Since the peptide of the present technology has the ability to bind to the GPC3, it is possible for the peptide to target and transport compounds having pharmacological actions to the GPC3, such as low molecular weight compounds, middle molecular weight compounds, high molecular weight compounds, peptides, proteins, antibodies, and nucleic acids.

[00128] Other aspects and features of the present disclosure will become apparent to those ordinarily skilled in the art upon review of the following description of specific embodiments in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[00129] All features of embodiments which are described in this disclosure are not mutually exclusive and can be combined with one another. For example, elements of one embodiment can be utilized in the other embodiments without further mention. A detailed description of specific embodiments is provided herein below with reference to the accompanying drawings in which:

[00130] FIG. 1 illustrates exemplary PDC of the present disclosure, wherein  represents the linker, and the peptide covalently connected to the payload represented by rounded square shown in the circle.

[00131] FIG. 2 illustrates a flow chart of HepG2 cells, which have GPC3 on the cell surface, stained with biotinylated peptides followed by Streptavidin, R-Phycoerythrin Conjugate.

[00132] FIG. 3 illustrates a flow chart of Huh-7 cells, which have GPC3 on the cell surface, stained with biotinylated peptides followed by Streptavidin, R-Phycoerythrin Conjugate.

[00133] FIG. 4 illustrates a flow chart of SK-Hep1 cells, which was a negative control cell line, stained with biotinylated peptides followed by Streptavidin, R-Phycoerythrin Conjugate.

[00134] FIG. 5A illustrates a flow chart of HepG2 cells, which have GPC3 expresion on the cell surface, stained with a biotinylated GPC3-binding peptide of the invention (PLD-45), or a negative control, followed by Streptavidin, R-Phycoerythrin Conjugate.

[00135] FIG. 5B illustrates a flow chart of Huh-7 cells, which have GPC3 expresion on the cell surface, stained with a biotinylated GPC3-binding peptide of the invention (PLD-45), or a negative control, followed by Streptavidin, R-Phycoerythrin Conjugate.

[00136] FIG. 5C illustrates a flow chart of SK-Hep1 cells, which do not have GPC3 expresion on the cell surface, stained with a biotinylated GPC3-binding peptide of the invention (PLD-45), or a negative control, followed by Streptavidin, R-Phycoerythrin Conjugate.

[00137] FIG. 6A illustrates a flow chart of HepG2 cells, which have GPC3 expresion on the cell surface, stained with a biotinylated GPC3-binding peptide of the invention (PLD-30), or a negative control, followed by Streptavidin, R-Phycoerythrin Conjugate.

[00138] FIG. 6B illustrates a flow chart of Huh-7 cells, which have GPC3 expresion on the cell surface, stained with a biotinylated GPC3-binding peptide of the invention (PLD-30), or a negative control, followed by Streptavidin, R-Phycoerythrin Conjugate.

[00139] FIG. 6C illustrates a flow chart of SK-Hep1 cells, which do not have GPC3 expresion on the cell surface, stained with a biotinylated GPC3-binding peptide of the invention (PLD-30), or a negative control, followed by Streptavidin, R-Phycoerythrin Conjugate.

[00140] FIG. 7A illustrates a flow chart of HepG2 cells, which have GPC3 expresion on the cell surface, stained with a biotinylated GPC3-binding peptide of the invention (PLD-1), or a negative control, followed by Streptavidin, R-Phycoerythrin Conjugate.

[00141] FIG. 7B illustrates a flow chart of Huh-7 cells, which have GPC3 expresion on the cell surface, stained with a biotinylated GPC3-binding peptide of the invention (PLD-1), or a negative control, followed by Streptavidin, R-Phycoerythrin Conjugate.

[00142] FIG. 7C illustrates a flow chart of SK-Hep1 cells, which do not have GPC3 expresion on the cell surface, stained with a biotinylated GPC3-binding peptide of the invention (PLD-1), or a negative control, followed by Streptavidin, R-Phycoerythrin Conjugate.

[00143] FIG. 8A illustrates a flow chart of HepG2 cells, which have GPC3 expresion on the cell surface, stained with a biotinylated GPC3-binding peptide of the invention (Mod-3), or a negative control, followed by Streptavidin, R-Phycoerythrin Conjugate.

[00144] FIG. 8B illustrates a flow chart of Huh-7 cells, which have GPC3 expresion on the cell surface, stained with a biotinylated GPC3-binding peptide of the invention (Mod-3), or a negative control, followed by Streptavidin, R-Phycoerythrin Conjugate.

[00145] FIG. 8C illustrates a flow chart of SK-Hep1 cells, which do not have GPC3 expresion on the cell surface, stained with a biotinylated GPC3-binding peptide of the invention (Mod-3), or a negative control, followed by Streptavidin, R-Phycoerythrin Conjugate.

[00146] FIG. 9A illustrates a flow chart of HepG2 cells, which have GPC3 expresion on the cell surface, stained with a biotinylated GPC3-binding peptide of the invention (Mod-5), or a negative control, followed by Streptavidin, R-Phycoerythrin Conjugate.

[00147] FIG. 9B illustrates a flow chart of Huh-7 cells, which have GPC3 expresion on the cell surface, stained with a biotinylated GPC3-binding peptide of the invention (Mod-5), or a negative control, followed by Streptavidin, R-Phycoerythrin Conjugate.

[00148] FIG. 9C illustrates a flow chart of SK-Hep1 cells, which do not have GPC3 expresion on the cell surface, stained with a biotinylated GPC3-binding peptide of the invention (Mod-5), or a negative control, followed by Streptavidin, R-Phycoerythrin Conjugate.

[00149] FIG. 10A illustrates a flow chart of HepG2 cells, which have GPC3 expresion on the cell surface, stained with a biotinylated GPC3-binding peptide of the invention (Mod-6), or a negative control, followed by Streptavidin, R-Phycoerythrin Conjugate.

[00150] FIG. 10B illustrates a flow chart of Huh-7 cells, which have GPC3 expresion on the cell surface, stained with a biotinylated GPC3-binding peptide of the invention (Mod-6), or a negative control, followed by Streptavidin, R-Phycoerythrin Conjugate.

[00151] FIG. 10C illustrates a flow chart of SK-Hep1 cells, which do not have GPC3 expresion on the cell surface,

stained with a biotinylated GPC3-binding peptide of the invention (Mod-6), or a negative control, followed by Streptavidin, R-Phycoerythrin Conjugate.

[00152] FIG. 11A illustrates a flow chart of HepG2 cells, which have GPC3 expresion on the cell surface, stained with a biotinylated GPC3-binding peptide of the invention (Mod-7), or a negative control, followed by Streptavidin, R-Phycoerythrin Conjugate.

[00153] FIG. 11B illustrates a flow chart of Huh-7 cells, which have GPC3 expresion on the cell surface, stained with a biotinylated GPC3-binding peptide of the invention (Mod-7), or a negative control, followed by Streptavidin, R-Phycoerythrin Conjugate.

[00154] FIG. 11C illustrates a flow chart of SK-Hep1 cells, which do not have GPC3 expresion on the cell surface, stained with a biotinylated GPC3-binding peptide of the invention (Mod-7), or a negative control, followed by Streptavidin, R-Phycoerythrin Conjugate.

DETAILED DESCRIPTION OF THE INVENTION

[00155] It should be understood that both the general descriptions and the detailed description below are merely illustrative and descriptive and do not limit the present technology of the present application. 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.

[00156] 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.

[00157] The headings used in the present specification are for structural purposes only and must not be construed as limiting the subject matter described.

[00158] In the present specification, the use of the singular form includes the plural form unless otherwise specified. In the present specification, the use of “or (or)” means “and/or (and/or)” unless otherwise stated. Furthermore, terms such as “element” or “component” encompass both an element and a component including one unit and an element and a component including two or more subunits unless when otherwise specified.

[00159] The recitation herein of numerical ranges by endpoints is intended to include all numbers subsumed within that range (*e.g.*, a recitation of 1 to 5 includes 1, 1.5, 2, 2.75, 3, 3.80, 4, 4.32, and 5).

[00160] 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.

[00161] 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

[00162] 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.

[00163] 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.

[00164] The term "comprising" (and related terms such as "comprise" or "comprises" or "having" or "including") are to be construed in an open, inclusive sense, that is, as "including, but not limited to." 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.

[00165] "Amino" refers to the $-NH_2$ radical.

[00166] "Cyano" refers to the -CN radical.

[00167] "Nitro" refers to the $-NO_2$ radical.

[00168] "Oxo" refers to the =O radical.

[00169] "Imino" refers to the =N-H radical.

[00170] "Oximo" refers to the =N-OH radical.

[00171] "Hydrazino" refers to the $=N-NH_2$ radical.

[00172] "Hydroxy" or "hydroxyl" refers to the -OH radical.

[00173] "Hydroxyamino" refers to the -NH-OH radical.

[00174] "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.

[00175] "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.

[00176] "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 -$CH_2CH_2CH_2$-.

[00177] "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.

[00178] 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-.

[00179] "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.

[00180] "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.

[00181] "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.

[00182] "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.

[00183] 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 $-NO_2$.

[00184] 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 (e.g., C_3-C_{15} fully saturated cycloalkyl or C_3-C_{15} cycloalkenyl), from three to ten carbon atoms (e.g., C_3-C_{10} fully saturated cycloalkyl or C_3-C_{10} cycloalkenyl), from three to eight carbon atoms (e.g., C_3-C_8 fully saturated cycloalkyl or C_3-C_8 cycloalkenyl), from three to six carbon atoms (e.g.,

C_3-C_6 fully saturated cycloalkyl or C_3-C_6 cycloalkenyl), from three to five carbon atoms (e.g., C_3-C_5 fully saturated cycloalkyl or C_3-C_5 cycloalkenyl), or three to four carbon atoms (e.g., C_3-C_4 fully saturated cycloalkyl or C_3-C_4 cycloalkenyl).. 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.

[00185] "Halo" or "halogen" refers to bromo, chloro, fluoro, or iodo. In some embodiments, halogen is fluoro or chloro. In some embodiments, halogen is fluoro.

[00186] "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.

[00187] "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.

[00188] As used herein, a "heteroalkylene" refers to divalent heteroalkyl group. Examples of such heteroalkylene

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 -$OCH_2CH_2OCH_2CH_2OCH_2CH_2O$-.

[00189] 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. 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. Representative heterocycloalkyls include, but are not limited to, heterocycloalkyls having from two to fifteen carbon atoms (e.g., C_2-C_{15} fully saturated heterocycloalkyl or C_2-C_{15} heterocycloalkenyl), from two to ten carbon atoms (e.g., C_2-C_{10} fully saturated heterocycloalkyl or C_2-C_{10} heterocycloalkenyl), from two to eight carbon atoms (e.g., C_2-C_8 fully saturated heterocycloalkyl or C_2-C_8 heterocycloalkenyl), from two to seven carbon atoms (e.g., C_2-C_7 fully saturated heterocycloalkyl or C_2-C_7 heterocycloalkenyl), from two to six carbon atoms (e.g., C_2-C_6 fully saturated heterocycloalkyl or C_2-C_7 heterocycloalkenyl), from two to five carbon atoms (e.g., C_2-C_5 fully saturated heterocycloalkyl or C_2-C_5 heterocycloalkenyl), or two to four carbon atoms (e.g., C_2-C_4 fully saturated heterocycloalkyl or C_2-C_4 heterocycloalkenyl). 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.

[00190] "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.

[00191] The term “moiety” (i.e. in Table 1.1) 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. In some embociments, the term “moiety” describes a conjugate or payload molecule added at the defined position or amino acid. Some examples of a “moiety” are, but are not limited to, a chemical compound, payload molecule, or a linker, wherein the linker is optionally connected to a chemical compound, wherein the chemical compound is, for example, a payload molecule, chemical label, capture agent, or fluorphore.

[00192] 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.

[00193] In certain embodiments, "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. In certain embodiments, 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.

[00194] In certain embodiments, the term "prevent" or "preventing" as related to a disease or disorder can refer to a compound that in a statistical sample, reduces the occurrences 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.

[00195] 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.

[00196] 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.*).

[00197] 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.

[00198] For the purpose of the disclosure, one event of "substitution" of an amino acid or an amino sequence is not considered two separate events of one deletion plus one addition. Thus, for the avoidance of doubt, as an example, a sequence change of "up to two deletion, substitution and/or addition" includes one deletion and one substitution, one deletion and one addition (at a different position), one substitution and one addition, one deletion only, one substitution only, one addition only, two deletions, two substitutions, two additions, *etc*. The deletion, addition, or substitution position may be at one or both ends of the peptide, or in the middle of the peptide.

[00199] The term "optionally substituted" or "substituted" means that the referenced group is optionally substituted with one or more additional group(s). For example, "optionally substituted" or "substituted" can mean that the referenced group is optionally substituted with one or more substituents 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, an "optionally substituted" group is independently substitued with 1-6 substituents selected from halogen, -CN, oxo, -OH, $-SF_5$, -SH, $-S(=O)C_1$-C_3alkyl, $-S(=O)_2C_1$-C_3alkyl, $-S(=O)_2NH_2$, $-S(=O)_2NHC_1$-C_3alkyl, $-S(=O)_2N(C_1$-C_3alkyl)$_2$, $-S(=O)(=NC_1$-C_3alkyl)(C_1-C_3alkyl), $-NH_2$, $-NHC_1$-C_3alkyl, $-N(C_1$-C_3alkyl)$_2$, $-N=S(=O)(C_1$-C_3alkyl)$_2$, $-C(=O)C_1$-C_3alkyl, -C(=O)OH, $-C(=O)OC_1$-C_3alkyl, $-C(=O)NH_2$, $-C(=O)NHC_1$-C_3alkyl, $-C(=O)N(C_1$-C_3alkyl)$_2$, $-P(=O)(C_1$-C_3alkyl)$_2$, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, aryl, heteroaryl, heterocycloalkyl and cycloalkyl. In some embodiments, an "optionally substituted" group is independently substitued with 1-6 substituents selected from halogen, -CN, oxo, -OH, $-SF_5$, -SH, $-S(=O)C_1$-C_3alkyl, $-S(=O)_2C_1$-C_3alkyl, $-S(=O)_2NH_2$, $-S(=O)_2NHC_1$-C_3alkyl, $-S(=O)_2N(C_1$-C_3alkyl)$_2$, $-S(=O)(=NC_1$-C_3alkyl)(C_1-C_3alkyl), $-NH_2$, $-NHC_1$-C_3alkyl, $-N(C_1$-C_3alkyl)$_2$, $-N=S(=O)(C_1$-C_3alkyl)$_2$, $-C(=O)C_1$-C_3alkyl, -C(=O)OH, $-C(=O)OC_1$-C_3alkyl, $-C(=O)NH_2$, $-C(=O)NHC_1$-C_3alkyl, $-C(=O)N(C_1$-C_3alkyl)$_2$, $-P(=O)(C_1$-C_3alkyl)$_2$, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3haloalkyl, C_1-C_3haloalkoxy, C_1-C_3hydroxyalkyl, C_1-C_3aminoalkyl, C_1-C_3heteroalkyl, 5-6 membered heterocycloalkyl and C_3-C_6cycloalkyl. In some embodiments, an "optionally substituted" group is independently substitued with 1-6 substituents selected from halogen, oxo, -OH, $-NH_2$, $-NHC_1$-C_3alkyl, $-N(C_1$-C_3alkyl)$_2$, -C(=O)OH, $-C(=O)NH_2$, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3haloalkyl, C_1-C_3haloalkoxy, C_1-C_3hydroxyalkyl, C_1-C_3aminoalkyl, C_1-C_3heteroalkyl, and C_3-C_6cycloalkyl. 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. In some embodiments, an "optionally substituted" group is unsubstituted. In some embodiments, an "optionally substituted" group is independently substitued with 1-6 substituents. In some embodiments, an "optionally substituted" group is independently substitued with 1-3 substituents. In some embodiments, an "optionally substituted" group is independently substitued with 1-2 substituents.

[00200] The term "unsubstituted" means that the specified group bears no substituents.

[00201] Certain compounds described herein may exist in tautomeric forms, and all such tautomeric forms of the compounds being within the scope of the disclosure.

[00202] 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.

[00203] 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.

[00204] The term "peptoid" as used herein refers to an N-substituted glycine. A peptoid can be optionally substituted. A peptoid can optionally comprise additional substitutions at the alpha-carbon.

[00205] As used herein, the term "unnatural amino acid" refers to an amino acid other than the 20 canonical amino acids. The 20 canonical amino acids refer to alanine (ala or A), arginine (arg or R), asparagine (asn or N), aspartic acid (asp or D), cysteine (cys or C), glutamine (gln or Q), glutamic acid (glu or E), glycine (gly or G), histidine (his or H), isoleucine (ile or I), leucine (leu or L), lysine (lys or K), methionine (met or M), phenylalanine (phe or F), proline (pro or P), serine (ser or S), threonine (thr or T), tryptophan (trp or W), tyrosine (tyr or Y), and valine (val or V).

[00206] 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.

[00207] 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.

[00208] The term "organic atoms" refers to atoms which would be found in organic compounds, such as carbon, hydrogen, nitrogen, oxygen, surfur, phosphorus, fluorine, chlorine, bromine, or iodine.

[00209] 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. 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.

[00210] 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.

[00211] 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.

[00212] 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.

[00213] 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 companion animal such as a dog or a cat. In one aspect, the mammal is a human.

[00214] 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.

[00215] It is appreciated that certain features of the disclosure, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the disclosure, which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination. For example, a conjugate of this disclosure can comprise any peptide ligand described herein (*e.g.*, a peptide ligand of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), or Table 1), any payload molecule described herein, optionally a linker described herein (*e.g.*, a linker of Formula (II-1), (II-1a), or (II-1b)), and optionally a payload molecule described herein. For another example, a peptide of Formula (I) (or any other Formulae such as (III-1) and (III-2)) can comprise X1 to X12 amino acids as described herein, and any combinations of the embodiments of amino acids are encompassed by this disclosure (even though, in some cases, they are described in the context of separate embodiments).

[00216] Unless special definitions are given, the terminology used in relation to analytical chemistry, synthetic organic chemistry, and medical chemistry and pharmaceutical chemistry described in the present specification, as well as their procedures and techniques, are well known and commonly used in the field of the present art. Standard techniques may be used for chemical synthesis and chemical analysis. Those defined from among such techniques and procedures can be found in, for example, "K.J. Jensen, P.T. Shelton, S.L. Pedersen, Peptide Synthesis and Applications, 2nd Edition, Springer, 2013" and the like, and these are incorporated into the present specification by reference for all purposes. All patents, applications, published applications, and other publications, and other data referred to throughout the entire disclosure, when permitted, are incorporated into the present specification by reference.

Peptide:

[00217] In one aspect, the disclosure relates to a peptide (*e.g.*, a binding peptide) that has avidity for Glypican-3 (GPC3). The GPC3 can be a mammalian GPC3. The GPC3 can be a human GPC3. The GPC3 can be a wild-type or mutated GPC3. In some embodiments, the conjugate of the disclosure comprises two or more peptides,

which can be the same or different. The peptide can be linear or cyclic. In some embodiments, the peptide is monocyclic. 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 5 to 14 amino acid residues. In some embodiments, the peptide comprises from 7 to 12 amino acid residues. In some embodiments, the peptide comprises from 8 to 12 amino acid residues. In some embodiments, the peptide comprises from 8 to 10 amino acid residues. In some embodiments, the peptide comprises from 7 to 13 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 14 amino acid residues. In some embodiments, the peptide comprises 6 amino acid residues. In some embodiments, the peptide comprises 7 amino acid residues. In some embodiments, the peptide comprises 8 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 consists of 6 amino acid residues. In some embodiments, the peptide consists of 7 amino acid residues. In some embodiments, the peptide consists of 8 amino acid residues. In some embodiments, the peptide consists of 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 conjugate comprises a monocyclic peptide of 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 amino acid residues. A peptide described herein can be a binding peptide that binds to GPC3. In some embodiments, the binding peptide consists of 6 to 20 amino acid residues. In some embodiments, the binding peptide consists of 7 to 12 amino acid residues. In some embodiments, the binding peptide consists of 10 to 12 amino acid residues. In some embodiments, the binding peptide consists of 8 to 12 amino acid residues. In some embodiments, the binding peptide is monocyclic. In some embodiments, the peptide of the present technology is an isolated peptide. In some embodiments, the peptide of the present technology is a purified peptide.

[00218] In one aspect, described herein is a peptide that has an avidity for Glypican 3 (GPC3), or a pharmaceutically acceptable salt thereof, wherein the peptide comprises an amino acid sequence including deletion, substitution, and/or addition of one or several (e.g., 1-6) amino acids in the amino acid sequence of SEQ ID NO: 1:

MeK-MeI-D-MeQ-F4COO-I-I-Y-MeNal27N-G-3Py6Ph-MeC (SEQ ID NO: 1),

wherein the peptide consists of 10 to 12 amino acid residues.

[00219] In some embodiments, 1, 2, 3, 4 or 5 amino acids are added to the amino acid sequence of SEQ ID NO: 1.

[00220] In some embodiments, the peptide comprises an amino acid sequence with deletion of 2 or fewer amino acids in the amino acid SEQ ID NO: 1. In some embodiments, 1 amino acid is deleted from SEQ ID NO: 1. In some embodiments, the 1 amino acid deleted form SEQ ID NO: 1 is the D at position 3. In some embodiments, 1, 2, 3, 4, or 5 amino acids are added to the peptide of SEQ ID NO: 1. In some embodiments, 1, 2, or 3 amino acids are added to the peptide of SEQ ID NO: 1. In some embodiments, 1 or 2 amino acids are added to the peptide of SEQ ID NO: 1. In some embodiments, 1 amino acid is added to the peptide of SEQ ID NO: 1. In some embodiments, 2 amino acids are added to the peptide of SEQ ID NO: 1.

[00221] In some embodiments, the peptide is a cyclic peptide.

[00222] In another aspect, described herein is a peptide that has an avidity for Glypican 3 (GPC3), or a pharmaceutically acceptable salt thereof, wherein the peptide omprises an amino acid sequence of Formula (I),

X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12

Formula (I)

wherein,

X1 is any amino acid;

X2 is any amino acid;

X3 is absent or any amino acid;

X4 is any amino acid;

X5 is an amino acid comprising an aromatic ring (e.g., W, F, Y, or a variant thereof), cycloalkyl, or heterocycloalkyl group, or X5 is a peptoid (e.g., Cha4cH, Cha4tH, A1mor, Atp, Cha4cOMe);

X6 is a hydrophobic amino acid, a hydrophilic amino acid, or a polar amino acid wherein the polar amino acid has a substituted side chain;

X7 is a hydrophobic amino acid comprising a C1-C8 alkyl, cycloalkyl, or heterocycloalkyl, wherein the alkyl, cycloalkyl, and heterocycloalkyl are each independently, optionally substituted (e.g., X7 is I, Eva, all, TMe, SMe, Gcpr, Gcpe, Gthp, dMeS, TdMe, or Cbg);

X8 is a A, I, L, V, Y or F, or a variant thereof;

X9 is an N-alkylated amino acid comprising an aromatic ring;

X10 is G, A, or a D-amino acid (e.g, da, ds, de, or dp);

X11 is an amino acid comprising an aromatic ring (e.g., F, Y, or a variant thereof); and,

X12 is N-alkylated cysteine (e.g., MeC).

[00223] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, X1 is an N-methylated amino acid, and the remaining variables are as described above.

[00224] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, X1 is an N-methylated amino acid comprising a polar side chain (*e.g.*, MeK, MeQ, or a variant thereof), and the remaining variables are as described above.

[00225] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, X2 is a L-amino acid, and the remaining variables are as described above.

[00226] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, X2 is

a N-methylated amino acid, and the remaining variables are as described above.

[00227] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, X3 is a polar and/or an L-amino acid, and the remaining variables are as described above.

[00228] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, X3 is an amino acid comprising a hydrophilic side chain (*e.g.*, D, K, Q, or a variant thereof) or an N-methylated variant thereof, and the remaining variables are as described above.

[00229] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, X4 is a polar and/or an L-amino acid, and the remaining variables are as described above.

[00230] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, X4 is an N-methylated amino acid, a polar amino acid (*e.g.*, D, K, Q, S, or a variant thereof), or peptoid (e.g. EtG, MeeG, CmG, CmpG CrmG CeG CrpG), and the remaining variables are as described above.

[00231] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, X5 has an aromatic side chain, such as F, Y, or a variant thereof, and the remaining variables are as described above.

[00232] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, F, or a variant thereof comprising a phenyl, pyridinyl, or naphthalyl, wherein said phenyl, pyridinyl, or naphthalyl is optionally substituted with one or more substituents each independently selected from halogen, -C_{1-3}alkyl, -OH, -NH_2, -CN, -C(=O)OH, -C(=O)NH_2, -NHC(=O)CH_3, -C_{1-3}alkylene-C(=O)OH, -C_{1-3}alkylene-C(=O)NH_2, -O-C_{1-3}alkylene-C(=O)OH, -O-C_{1-3}alkylene-C(=O)NH_2, -C_{1-3}alkylene-C(=O)-5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH, -O-C_{1-3}alkylene-C(=O)- 5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH, -C_{1-3}alkylene-NHC(=O)- 5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH, -O-C_{1-3}alkylene-NHC(=O)- 5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH, and -NH-C_{1-3}alkylene-C(=O)OH; or Y, or a variant thereof comprising a hydroxyphenyl, wherein the hydrogen atom in hydroxyphenyl of Y or of the variant is optionally substituted with one or more substituents selected from -C_{1-3}alkyl, , and -C_{1-3}alkylene-C(=O)OH, and the remaining variables are as described above.

[00233] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, X6 is an aliphatic amino acid (*e.g.*, V, L, I, A, G, or a variant thereof), a hydrophilic amino acid (*e.g.*, D, E, or a variant thereof), threonine (T) or a variant thereof (e.g., O-methyl threonine (TMe)), serine (S), or methionine (M), and the remaining variables are as described above.

[00234] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, X7 is an amino acid comprising a branched alkyl side chain, a C_{3-5}cycloalkyl side chain, or a 3- to 5- membered heterocycloalkyl side chain, or an N-methylated variant thereof, and the remaining variables are as described above.

[00235] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, the branched alkyl side chain comprises 3-5 carbon atoms, and the remaining variables are as described above.

[00236] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, the alkyl, cycloalkyl, or heterocycloalkyl side chain is optionally substituted with -O-C_1-C_6 alkyl, and the remaining variables are as described above.

[00237] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, X8 is: an aliphatic amino acid (e.g., A, I, L, or V); Y, or a variant thereof comprising a hydroxyphenyl ring, wherein the hydroxyphenyl ring of Y or of the variant is optionally substituted with one or more substituents selected from halogen, -C_{1-3}alkyl, -OH, -C(=O)OH, -O-CH_3, -C_{1-3}alkylene-C(=O)OH, -C_{1-3}alkylene-C(=O)- 5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH, and -C_{1-3}alkylene-NHC(=O)- 5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH; or F, or a variant thereof comprising a phenyl, pyridinyl, or indazolyl, wherein the phenyl of F or the phenyl, pyridinyl, or indazolyl of the variant is optionally substituted with one or more substituents each independently selected from halogen, -C_{1-3}alkyl, -OH, -C(=O)OH, -C(=O)NH_2, -NHC(=O)NH_2, -C_{1-3}alkylene-C(NH_2)-COOH, -NH-CO-CH_3, -NH-C_{1-3}alkylene-NH_2, -C(=O)-N(CH_2)$_2$, -S(=O)$_2$-CH_3, -C_{1-3}alkylene-NH-C(=O)- 5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH, and -O-C_1.3alkylene-NH-C(=O)- 5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH, and the remaining variables are as described above.

[00238] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, X9 is an N-methyl aromatic amino acid, optionally a bicyclic aromatic amino acid, and the remaining variables are as described above.

[00239] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the N-methyl aromatic amino acid is: N-methyl monocyclic aromatic amino acid comprising a phenyl or pyridinyl optionally substituted with one or more substituents each independently selected from halogen, -C_{1-3}alkyl, and trifluoromethyl; or N-methyl bicyclic aromatic amino acid comprising a naphthalyl, quinolyl, or indazolyl optionally substituted with one or more substituents each independently selected from H or C_{1-3}alkyl.

[00240] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, X10 is G or a D-amino acid (e.g., da, ds, de, or dp), and the remaining variables are as described above.

[00241] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, X11 is F or a variant thereof, or an amino acid comprising -C_{1-6}alkylene-phenyl, and the remaining variables are as described above.

[00242] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, F or the variant thereof is: F, or a variant thereof comprising a phenyl, or pyridinyl, optionally substituted with one or more substituents each independently selected from phenyl, -O-phenyl, -O-C_{1-3}alkylene-phenyl, pyridinyl, imidazolyl, pyrazolyl, N-C_{1-3}alkylene pyrazolyl, N-C_{1-3}alkylene(-O-C_{1-3}alkyl) pyrazolyl, pyranyl, tetrahydropyranyl, piperidinyl, N-C_{1-3}alkylene-C(=O)-piperidinyl, and the remaining variables are as described above.

[00243] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the peptide has an amino acid sequence according to Formula (I), or a pharmaceutically acceptable salt thereof,

X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12

Formula (I)

wherein,

X1 is I, R, Cit, F4G, 4Py, 3Py, KCOpipzaa, V, Eva, Q, E, Mel, Ahp, F4COO, KCOpip4COO, MeQdMe,

MeA, MeSMe, MeG, MeV, MeHseMe, Aib, MeT, all, TMe, MeKCOpipzaa, MeQ, Hpr, MeTMe, MeDapCOpipzaa, MeK, MeKAc, MeK(de), MeK(H), MeK(df), or MeK(datb);

X2 is I, K, Cit, F4G, 4Py, 3Py, KCOpipzetOH, V, KCOpipzaa, Eva, Q, E, S, Ahp, F4COO, KCOpip4COO, MeQdMe, MeA, MeSMe, MeG, MeI, MeV, MeL, HseMe, MeY, Me3Py,MeHseMe, MeKAc, all, TMe MeKCOpipzaa, MeQ, Hpr, MeTMe, or MeDapCOpipzaaa;

X3 is D, Har, KCOpipzetOH, Cit, KCOmeglumine, KCOpipzaa, A4paa, Q, A, E, MeD, S, N, Hgl, F4COO, KCOpip4COO, KAc, Hgn, MeY, or DapCOpipzaa;

X4 is D, Har, KCOpipzetOH, KCOmeglumine, KCOpipzaa, A4paa, Q, A, E, MeD, S, N, Hgl, F4COO, KCOpip4COO, dd, MeQ, MeQdMe, MeA, MeSMe, MeG, EtG, MeeG, CmG, CmpG, CrmG, CeG, CrpG, MeK, MeKAc, MeHgl, Hgn, MeDapCOpipzaa, MeKCOpipzaa, Medd, Cit, MeCit, MeN, MeS, MeE, MeY, W5N or Mae4paa;

X5 is Y, F3G, 3Py6COO,4Py2NH2, 3Py5COO, F3COO, 3Py6NHAc, F, F4C, F4OMe, F4COO, Nal2, F3aao, F4aa, F4aao, 3Py6Nhaa, 5Pdo, F3CON, F4F, F4OEt, F4Me, F4CON, F4CONPEG4Me, F3OMe, Yae, YaeCOpipzaa, F4aaopipzaa, 4Pdo, 3Py6CON, Atp, Cha4cH, Cha4tH, Cha4cOMe, A1mor, or F4amCOpipzaa;

X6 is I, V, Eva, Chg, Tbg, A, L, Ahp, F4COO, Gcpr, Gcpe, all, Cle , S3REt, TMe, Acpr, Cba, Gthp, NleCOO, NleOH, P, Atb, Nva, Nle, N, DapAc, Abu, Nmm, Ndm, Ncit, Cit, SMe, HseMe, HseEt, HseiPr, dMeS, TdMe, Cbg, NvaOMe, SiPr, Spr, NleOMe, Sbu, Scbm, Scpe, AhpOMe, HseBu, Spent or Hsecpe;

X7 is I, Eva, all, TMe, SMe, Gcpr, Gcpe, Gthp, dMeS, TdMe, or Cbg;

X8 is A, I, L, V, Y, F4OMe, F4COO, F4OEt, F4u, F4Me, F4CONdMe, F4CON, F4ms, F4CONPEG4Me, F34dOMe, F3OMe, F3C, F3CON, F3CONdMe, 3Py6CON, Yae, YaeCOpipzaa, 5Inda, F3aao, F3aa, 3Py6Nhae, 3Py6NHAc, 3Py6OMe, F4aaopipzaa, or F4amCOpipzaa;

X9 is MeNal2, MeNal27N, MeF34diox, MeF34dOMe, MeF4T, MeY, MeW1Me, MeW7N, MeF3C4Me, or MeF3Me4C;

X10 is G, A, or a D-amino acid (e.g., da, ds, de, or dp);

X11 is Bph, 3Py6Ph, F41Me4Pyz, F43Pyz, F44Pyz, F41Pyz, F41Me3Pyz, F41Et4Pyz, F41MeOe4Pyz, F41MeOp4Pyz, F44thp, F4Ac4pip, PhNva, PhNle, Yph, Ybn, F4tb, F4oPr, or F4CONdMe; and

X12 is MeC, and the remaining variables are as described above.

[00244] In another aspect, described herein is a peptide that has an avidity for Glypican 3 (GPC3), or a pharmaceutically acceptable salt thereof, wherein the peptide omprises an amino acid sequence of Formula (I),

X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12

Formula (I)

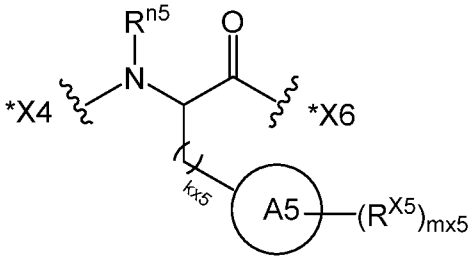
wherein,

X1 is any amino acid;

X2 is any amino acid;

X3 is any amino acid;

X4 is any amino acid;

X5 is  , wherein:

R^{n5} is hydrogen or C_{1-3} alkyl;

ring A5 is an aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

each R^{X5} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halogen, -CN, -NO_2, -OR^a, -SR^a, -SF_5, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$S(=O)(=NR^a)R^a$, -$N=S(=O)NR^cR^d$, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)NR^cR^d$, -$NR^aS(=O)_2NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, -$P(=O)(OR^c)(OR^d)$, -$P(=O)R^cR^d$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -L^{X5}-heterocycloalkyl, -L^{X5}-cycloalkyl, -L^{X5}-aryl, or -L^{X5}-heteroaryl, wherein the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl are optionally substituted with one or more R^{X5a}; or

two R^{X5} are taken together to form =O, =S, or =N(R^a);

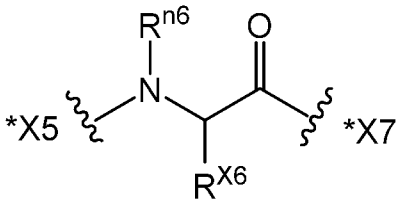
L^{X5} is C_{1-6}alkylene, C_{1-6}heteroalkylene, -O-, -S-, or -NR^a- , wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X5a};

kx5 is 0, 1, 2, or 3;

mx5 is 0, 1, 2, 3, 4, or 5;

*X4 represents the point of attachment to X4; and

*X6 represents the point of attachment to X6;

X6 is  , wherein;

R^{n6} is hydrogen or C_{1-3} alkyl;

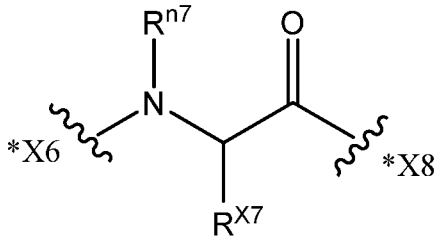
R^{X6} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -L^{X6}-heterocycloalkyl, -L^{X6}-cycloalkyl, -L^{X6}-aryl, or -L^{X6}-heteroaryl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X6a}; or

R^{n6} and R^{x6} are taken together with the intervening atoms to form a 5- to 6- membered heterocycloalkyl, which is optionally substituted with one or more R^{X6a};

L^{X6} is C_{1-6}alkylene, C_{1-6}heteroalkylene, -O-, -S-, or -NR^a-, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X6a};

*X5 represents the point of attachment to X5; and

*X7 represents the point of attachment to X7;

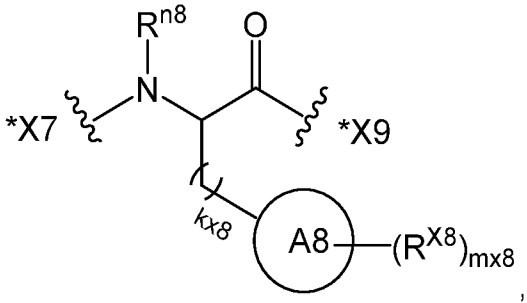
X7 is  , wherein:

R^{n7} is hydrogen or C_{1-3} alkyl ;

R^{X7} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, cycloalkyl, or heterocycloalkyl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X7a};

*X6 represents the point of attachment to X6; and

*X8 represents the point of attachment to X8;

X8 is  , wherein;

R^{n8} is hydrogen or C_{1-3}alkyl;

ring A8 is an aryl or heteroaryl;

each R^{X8} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halogen, -CN, -NO_2, -OR^a, -SR^a, -SF_5, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2R^cR^d$, -$S(=O)(=NR^a)R^a$, -$N=S(=O)$ R^cR^d, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)NR^cR^d$, -$NR^aS(=O)_2R^cR^d$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, -$P(=O)(OR^c)(OR^d)$, -$P(=O)R^cR^d$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -L^{X8}-heterocycloalkyl, -L^{X8}-cycloalkyl, -L^{X8}-aryl, or -L^{X8}-heteroaryl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X8a}; or

two R^{X8} are taken together to form =O, =S, or =N(R^a);

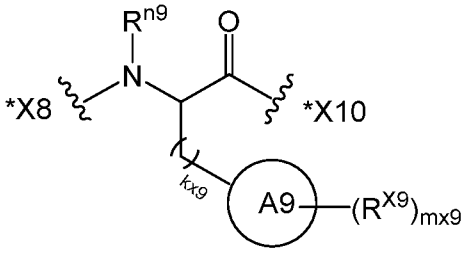
L^{X8} is C_{1-6}alkylene, C_{1-6}heteroalkylene, -O-, -S-, or -NR^a-, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X8a};

kx8 is 0, 1, 2, or 3;

mx8 is 0, 1, 2, 3, 4, or 5;

*X7 represents the point of attachment to X7; and

*X9 represents the point of attachment to X9;

X9 is  , wherein:

R^{n9} is hydrogen or C_{1-3} alkyl;

ring A9 is an aryl or heteroaryl;

each R^{X9} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halogen, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-SF_5$, or $-NR^cR^d$, wherein each of the alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^{X9a}; or

two R^{X9} are taken together to form =O, =S, or =N(R^a);

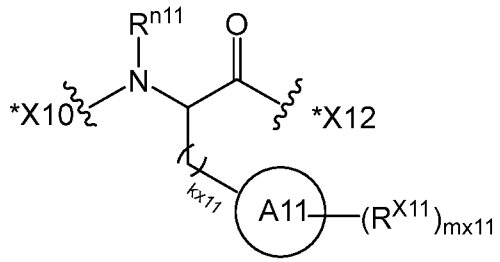
kx9 is 0, 1, 2, or 3;

mx9 is 0, 1, 2, 3, 4, or 5;

*X8 represents the point of attachment to X8; and

*X10 represents the point of attachment to X10;

X10 is glycine or a D-amino acid (e.g., da, ds, de, or dp);

X11 is  , wherein:

R^{n11} is hydrogen or C_{1-3} alkyl;

ring A11 is an aryl or heteroaryl;

each R^{X11} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, halogen, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-SF_5$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2R^cR^d$, $-S(=O)(=NR^a)R^a$, $-N=S(=O)R^cR^d$, $-NR^aS(=O)_2R^a$, amidinyl, $-NR^aC(=NH)NR^cR^d$, $-NR^aS(=O)_2R^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, $-P(=O)(OR^c)(OR^d)$, $-P(=O)R^cR^d$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, $-L^{X11}$-heterocycloalkyl, $-L^{X11}$-cycloalkyl, $-L^{X11}$-aryl, or $-L^{X11}$-heteroaryl, wherein each of the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X11a}; or

two R^{X11} are taken together to form =O, =S, or =N(R^a);

L^{X11} is C_{1-6}alkylene, C_{1-6}heteroalkylene, -O-, -S-, or $-NR^a$-, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X11a};

kx11 is 0, 1, 2, 3, 4, or 5;

mx11 is 0, 1, 2, 3, 4, or 5;

*X10 represents the point of attachment to X10; and,

*X12 represents the point of attachment to X12;

X12 is N-alkylated cysteine;

each of R^{X5a}, R^{X6a}, R^{X7a}, R^{X8a}, R^{X9a}, and R^{X11a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -SF_5, -$S(=O)_2NR^cR^d$, -$S(=O)(=NR^a)R^a$, -$N=S(=O)R^cR^d$, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)(NR^a)_2$, -$NR^aS(=O)_2NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, -$P(=O)(OR^c)(OR^d)$, -$P(=O)R^cR^d$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O, =S, or =$N(R^a)$, wherein each of the alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e.

each R^a 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 each of the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^e;

each R^e is independently halogen, -CN, -OH, -O-C_1-C_6alkyl, -SF_5, -$S(=O)C_1$-C_6alkyl, -$S(=O)_2C_1$-C_6alkyl, -$S(=O)_2NH_2$, -$S(=O)_2$-halogen, -$S(=O)_2NHC_1$-C_6alkyl, -$S(=O)_2N(C_1$-C_6alkyl$)_2$, -NH_2, -NHC_1-C_6alkyl, -$N(C_1$-C_6alkyl$)_2$, -$NHC(=NH)NH_2$, -$NHC(=O)OC_1$-C_6alkyl, -$C(=O)C_1$-C_6alkyl, -C(=O)OH, C_1-C_6alkyl-C(=O)OH, -$C(=O)OC_1$-C_6alkyl, -$C(=O)NH_2$, -$C(=O)N(C_1$-C_6alkyl$)_2$, -$C(=O)NHC_1$-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl; or two R^e are taken together to form =O; and

each R^c and R^d are 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 each of the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^e; 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^e.

[00245] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, X1 is an N-alkylated amino acid, and the remaining variables are as described above.

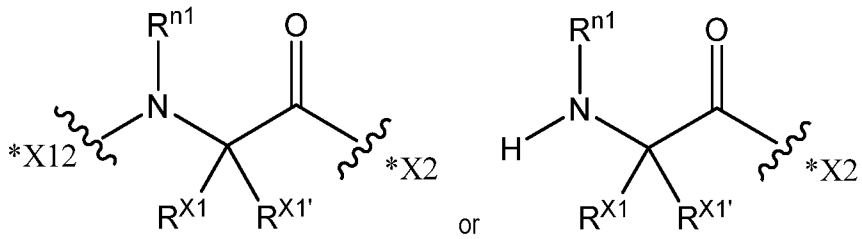
[00246] In some embodiments of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X1 is an N-methylated amino acid. In some embodiments X1 is an N-methylated amino acid comprising a polar side chain (*e.g.*, MeK, MeQ, or a variant thereof).

[00247] In some embodiments of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X1 is I, R, Cit, F4G, 4Py, 3Py, KCOpipzaa, V, Eva, Q, E, MeI, Ahp, F4COO, KCOpip4COO, MeQdMe, MeA, MeSMe, MeG, MeV, MeHseMe, Aib, MeT, aII, Tme, MeKCOpipzaa, MeQ, Hpr, MeTMe, MeDapCOpipzaa, MeK, MeK(de), MeK(H), MeK(df), or MeK(datb). In some embodiments of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X1 is I, R, Cit, F4G, 4Py, 3Py, KCOpipzaa, V, Eva, Q, E, MeI, Ahp, F4COO, KCOpip4COO, MeQdMe, MeA, MeSMe, MeG, MeV, MeHseMe, Aib, MeT, aII, Tme, MeKCOpipzaa, MeQ, Hpr, MeTMe, MeDapCOpipzaa, MeK, MeK(de), MeK(H), MeK(df), or MeK(datb), each of which is optionally substituted. In

some embodiments, X1 is optionally substituted I. In some embodiments, X1 is optionally substituted R. In some embodiments, X1 is optionally substituted Cit. In some embodiments, X1 is optionally substituted F4G. In some embodiments, X1 is optionally substituted 4Py. In some embodiments, X1 is optionally substituted 3Py. In some embodiments, X1 is optionally substituted KCOpipzaa. In some embodiments, X1 is optionally substituted V. In some embodiments, X1 is optionally substituted Eva. In some embodiments, X1 is optionally substituted Q. In some embodiments, X1 is optionally substituted E. In some embodiments, X1 is optionally substituted MeI. In some embodiments, X1 is optionally substituted Ahp. In some embodiments, X1 is optionally substituted F4COO. In some embodiments, X1 is optionally substituted KCOpip4COO. In some embodiments, X1 is optionally substituted MeQdMe. In some embodiments, X1 is optionally substituted MeA. In some embodiments, X1 is optionally substituted MeSMe. In some embodiments, X1 is optionally substituted MeG. In some embodiments, X1 is optionally substituted MeV. In some embodiments, X1 is optionally substituted MeHseMe. In some embodiments, X1 is optionally substituted Aib. In some embodiments, X1 is optionally substituted MeT. In some embodiments, X1 is optionally substituted all. In some embodiments, X1 is optionally substituted Tme. In some embodiments, X1 is optionally substituted MeKCOpipzaa. In some embodiments, X1 is optionally substituted MeQ. In some embodiments, X1 is optionally substituted Hpr. In some embodiments, X1 is optionally substituted MeTMe. In some embodiments, X1 is optionally substituted MeDapCOpipzaa. In some embodiments, X1 is optionally substituted MeK. In some embodiments, X1 is optionally substituted MeK(de). In some embodiments, X1 is optionally substituted MeK(H). In some embodiments, X1 is optionally substituted MeK(df). In some embodiments, X1 is optionally substituted MeK(datb). In some embodiments, X1 is MeQ or a derivative thereof. In some embodiments, X1 is MeK or a derivative thereof.

[00248] In some embodiments of a peptide of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X1 is any amino acid. In some embodiments, X1 is a D-amino acid. In some embodiments, X1 is an L-amino acid. In some embodiments, X1 is an N-alkylated amino acid. . In some embodiments, X1 is an N-methylated amino acid. In some embodiments, X1 does not comprise a cyclic group. In some embodiments, X1 comprises a cyclic group. In some embodiments, X1 comprises a 5-6 membered heterocycloalkyl group. In some embodiments, X1 comprises a 5-6 membered heteroaryl group. In some embodiments, X1 comprises a phenyl group. In some embodiments, X1 is a peptoid.

[00249] In some embodiments of a peptide of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X1 has a structure of



wherein:

R^{n1} is hydrogen or C_{1-3} alkyl;

R^{X1} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -L^{X1}-heterocycloalkyl, -L^{X1}-cycloalkyl, -L^{X1}-aryl, or -L^{X1}-heteroaryl, wherein each of the alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X1a};

$R^{X1'}$ is hydrogen or C_{1-6}alkyl, wherein the alkyl is optionally substituted with one or more R^{X1a}; or

R^{n1} and $R^{X1'}$ are taken together with the intervening atoms to form a 5- to 6- membered heterocycloalkyl, which is optionally substituted with one or more R^{X1a};

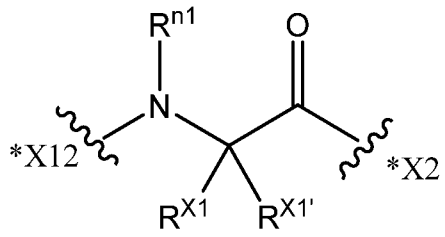
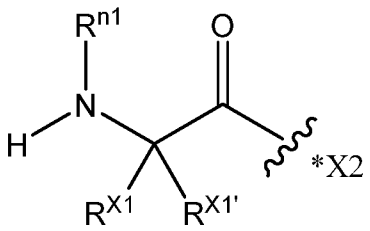
L^{X1} is C_{1-6}alkylene, C_{1-6}heteroalkylene, -O-, -S-, or -NR^a-, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X1a};

each R^{X1a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -S(=O)R^a, -$S(=O)_2R^a$, -SF_5, -$S(=O)_2NR^cR^d$, -S(=O)(=NR^a)R^a, -N=S(=O)R^cR^d, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)(NR^a)_2$, -$NR^aS(=O)_2NR^cR^d$, -C(=O)R^a, -C(=O)OR^a, -OC(=O)R^a, -OC(=O)OR^a, -OC(=O)NR^cR^d, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -C(=O)NR^cR^d, -P(=O)(OR^c)(OR^d), -P(=O)R^cR^d, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O, =S, or =N(R^a), wherein each of the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e;

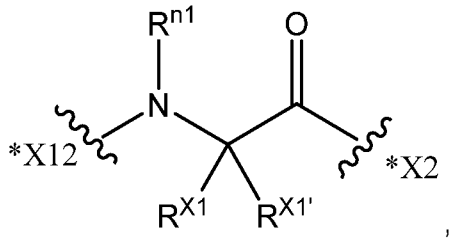
*X12 represents the point of attachment to X12;

*X2 represents the point of attachment to X2; and

other groups (such as R^a, R^c, R^d, and R^e) have the meanings defined in Formula (I).

In some embodiments, X1 has a structure of  . In some embodiments, X1 has a structure of  .

[00250] In some embodiments of a peptide of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X1 has a structure of

 ,

wherein:

R^{n1} is hydrogen or methyl;

R^{X1} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, -L^{X1}-5-6 membered heterocycloalkyl, -L^{X1}-C_{4-6}cycloalkyl, -L^{X1}-C_{6-10}aryl, or -L^{X1}-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X1a};

$R^{X1'}$ is hydrogen or methyl; or

R^{n1} and $R^{X1'}$ are taken together with the intervening atoms to form a 5- to 6- membered heterocycloalkyl, which is optionally substituted with one or more R^{X1a};

L^{X1} is C_{1-6}alkylene or C_{1-6}heteroalkylene, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X1a};

each R^{X1a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -SF_5, -$S(=O)_2NR^cR^d$, -$S(=O)(=NR^a)R^a$, -$N=S(=O)R^cR^d$, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)(NR^a)_2$, -$NR^aS(=O)_2NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, -$P(=O)(OR^c)(OR^d)$, -$P(=O)R^cR^d$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O, =S, or =$N(R^a)$, wherein each of the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e;

*X12 represents the point of attachment to X12;

*X2 represents the point of attachment to X2; and

other groups (such as R^a, R^c, R^d, and R^e) have the meanings defined in Formula (I).

[00251] In some embodiments, R^{n1} is hydrogen. In some embodiments, R^{n1} is C_{1-3} alkyl. In some embodiments, R^{n1} is methyl.

[00252] In some embodiments, R^{X1} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -L^{X1}-heterocycloalkyl, -L^{X1}-cycloalkyl, -L^{X1}-aryl, or -L^{X1}-heteroaryl, wherein each of the alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X1a}.

[00253] In some embodiments, R^{X1} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, -L^{X1}-5-6 membered heterocycloalkyl, -L^{X1}-C_{4-6}cycloalkyl, -L^{X1}-C_{6-10}aryl, or -L^{X1}-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X1a}. In some embodiments, R^{X1} is hydrogen, C_{1-6}alkyl, C_{1-6}heteroalkyl, -L^{X1}-piperidinyl, -L^{X1}-piperazinyl, -L^{X1}-phenyl, or -L^{X1}-pyridinyl, wherein each of the alkyl, heteroalkyl, phenyl, pyridinyl, piperidinyl, and piperazinyl is optionally substituted with one or more R^{X1a}.

[00254] In some embodiments, R^{X1} is hydrogen. In some embodiments, R^{X1} is optionally substituted C_{1-6}alkyl. In some embodiments, R^{X1} is C_{1-6}alkyl optionally substituted with one or more R^{X1a}. In some embodiments, R^{X1} is optionally substituted C_{1-6}heteroalkyl. In some embodiments, R^{X1} is C_{1-6}heteroalkyl optionally substituted with one or more R^{X1a}. In some embodiments, R^{X1} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, or C_{1-6}heteroalkyl, wherein each of which is optionally substituted with one or more R^{X1a}. In some embodiments, R^{X1} is

C_{2-6}alkenyl or C_{2-6}alkynyl, wherein each of which is optionally substituted with one or more R^{X1a}. In some embodiments, R^{X1} is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein each of which is optionally substituted with one or more R^{X1a}. In some embodiments, R^{X1} is aryl or heteroaryl, wherein each of which is optionally substituted with one or more R^{X1a}. In some embodiments, R^{X1} is cycloalkyl or heterocycloalkyl, wherein each of which is optionally substituted with one or more R^{X1a}. In some embodiments, R^{X1} is -L^{X1}-heterocycloalkyl, -L^{X1}-cycloalkyl, -L^{X1}-aryl, or -L^{X1}-heteroaryl, wherein each of which is optionally substituted with one or more R^{X1a}. In some embodiments, R^{X1} is -L^{X1}-heterocycloalkyl, which is optionally substituted with one or more R^{X1a}. In some embodiments, R^{X1} is -L^{X1}- cycloalkyl, which is optionally substituted with one or more R^{X1a}. In some embodiments, R^{X1} is -L^{X1}-aryl, which is optionally substituted with one or more R^{X1a}. In some embodiments, R^{X1} is -L^{X1}-heteroaryl, which is optionally substituted with one or more R^{X1a}.

[00255] In some embodiments, $R^{X1'}$ is hydrogen. In some embodiments, $R^{X1'}$ is C_{1-6}alkyl, wherein the alkyl is optionally substituted with one or more R^{X1a}. In some embodiments, $R^{X1'}$ is C_{1-6}alkyl. In some embodiments, $R^{X1'}$ is methyl.

[00256] In some embodiments, R^{n1} and $R^{X1'}$ are taken together with the intervening atoms to form a 5- to 6-membered heterocycloalkyl, which is optionally substituted with one or more R^{X1a}.

[00257] In some embodiments, L^{X1} is C_{1-6}alkylene, wherein the alkylene is optionally substituted with one or more R^{X1a}. In some embodiments, L^{X1} is C_{1-6}alkylene. In some embodiments, L^{X1} is C_{1-6}heteroalkylene, wherein the heteroalkylene is optionally substituted with one or more R^{X1a}. In some embodiments, L^{X1} is C_{1-6}heteroalkylene. In some embodiments, L^{X1} is -O-. In some embodiments, L^{X1} is -S-. In some embodiments, L^{X1} is -NR^a-. In some embodiments, L^{X1} is -NH-.

[00258] In some embodiments, each R^{X1a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, cycloalkyl, heterocycloalkyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^aS(=O)_2R^a$, -$NR^aC(=NH)(NR^a)_2$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e.

[00259] In some embodiments, each R^{X1a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^aS(=O)_2R^a$, -$NR^aC(=NH)(NR^a)_2$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e.

[00260] In some embodiments, each R^{X1a} is independently C_{1-6} alkyl, C_{1-6} alkoxyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, OH, -CN, -NO_2, NH_2, -$C(=O)R^a$, -$C(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, or oxo.

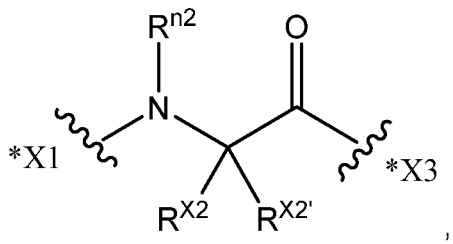
[00261] In some embodiments of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X2 is absent or an L-amino acid. In some embodiments, X2 is absent. In some embodiments, X2 is an L-amino acid. In some embodiments, X2 is a N-methylated amino acid.

[00262] In some embodiments of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X2 is I, K, Cit, F4G, 4Py, 3Py, KCOpipzetOH, V, KCOpipzaa, Eva, Q, E, MeI, Ahp, F4COO, KCOpip4COO, MeQdMe,

MeA, MeSMe, MeG, MeI, MeV, MeHseMe, MeKAc, aII, TMe MeKCOpipzaa, MeQ, Hpr, MeTMe, or MeDapCOpipzaaa. In some embodiments of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X2 is I, K, Cit, F4G, 4Py, 3Py, KCOpipzetOH, V, KCOpipzaa, Eva, Q, E, MeI, Ahp, F4COO, KCOpip4COO, MeQdMe, MeA, MeSMe, MeG, MeI, MeV, MeHseMe, MeKAc, aII, TMe MeKCOpipzaa, MeQ, Hpr, MeTMe, or MeDapCOpipzaaa, each of which is optionally substituted. In some embodiments, X2 is optionally substituted I. In some embodiments, X2 is optionally substituted K. In some embodiments, X2 is optionally substituted Cit. In some embodiments, X2 is optionally substituted F4G. In some embodiments, X2 is optionally substituted 4Py. In some embodiments, X2 is optionally substituted 3Py. In some embodiments, X2 is optionally substituted KCOpipzetOH. In some embodiments, X2 is optionally substituted V. In some embodiments, X2 is optionally substituted KCOpipzaa. In some embodiments, X2 is optionally substituted Eva. In some embodiments, X2 is optionally substituted Q. In some embodiments, X2 is optionally substituted E. In some embodiments, X2 is optionally substituted MeI. In some embodiments, X2 is optionally substituted Ahp. In some embodiments, X2 is optionally substituted F4COO. In some embodiments, X2 is optionally substituted KCOpip4COO. In some embodiments, X2 is optionally substituted MeQdMe. In some embodiments, X2 is optionally substituted MeA. In some embodiments, X2 is optionally substituted MeSMe. In some embodiments, X2 is optionally substituted MeG. In some embodiments, X2 is optionally substituted MeI. In some embodiments, X2 is optionally substituted MeV. In some embodiments, X2 is optionally substituted MeHseMe. In some embodiments, X2 is optionally substituted MeKAc. In some embodiments, X2 is optionally substituted aII. In some embodiments, X2 is optionally substituted TMe. In some embodiments, X2 is optionally substituted MeKCOpipzaa. In some embodiments, X2 is optionally substituted MeQ. In some embodiments, X2 is optionally substituted Hpr. In some embodiments, X2 is optionally substituted MeTMe. In some embodiments, X2 is optionally substituted. In some embodiments, X2 is optionally substituted MeDapCOpipzaaa.

[00263] In some embodiments of a peptide of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X2 is any amino acid. In some embodiments, X2 is a D-amino acid. In some embodiments, X2 is an L-amino acid. In some embodiments, X2 is an N-alkylated amino acid. In some embodiments, X2 is an N-methylated amino acid. In some embodiments, X2 does not comprise a cyclic group. In some embodiments, X2 comprises a cyclic group. In some embodiments, X2 comprises a 5-6 membered heterocycloalkyl group. In some embodiments, X2 comprises a 5-6 membered heteroaryl group. In some embodiments, X2 comprises a phenyl group. In some embodiments, X2 is a peptoid.

[00264] In some embodiments of a peptide of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X2 has a structure of



,

wherein,

R^{n2} is hydrogen or C_{1-3} alkyl, wherein the alkyl is optionally substituted with one or more R^{X2a};

R^{X2} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -L^{X2}-heterocycloalkyl, -L^{X2}-cycloalkyl, -L^{X2}-aryl, or -L^{X2}-heteroaryl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X2a};

$R^{X2'}$ is hydrogen or C_{1-6}alkyl, wherein the alkyl is optionally substituted with one or more R^{X2a}; or

R^{n2} and $R^{X2'}$ are taken together with the intervening atoms to form a 5- to 6- membered heterocycloalkyl, which is optionally substituted with one or more R^{X2a};

L^{X2} is C_{1-6}alkylene, C_{1-6}heteroalkylene, -O-, -S-, or -NR^a-, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X2a};

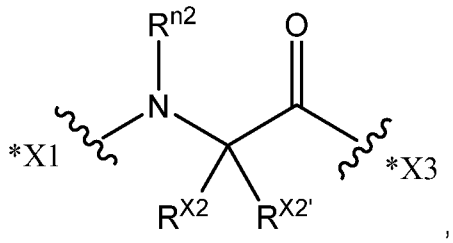
each R^{X2a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -SF_5, -$S(=O)_2NR^cR^d$, -$S(=O)(=NR^a)R^a$, -$N=S(=O)R^cR^d$, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)(NR^a)_2$, -$NR^aS(=O)_2NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, -$P(=O)(OR^c)(OR^d)$, -$P(=O)R^cR^d$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O, =S, or =$N(R^a)$, wherein each of the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e;

*X1 represents the point of attachment to X1;

*X3 represents the point of attachment to X3; and

other groups (such as R^a, R^c, R^d, and R^e) have the meanings defined in Formula (I).

[00265] In some embodiments of a peptide of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X2 has a structure of



,

wherein:

R^{n2} is hydrogen or methyl;

R^{X2} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, -L^{X2}-5-6 membered heterocycloalkyl, -L^{X2}-C_{4-6}cycloalkyl, -L^{X2}-C_{6-10}aryl, or -L^{X2}-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X2a};

$R^{X2'}$ is hydrogen or methyl; or

R^{n2} and $R^{X2'}$ are taken together with the intervening atoms to form a 5- to 6- membered heterocycloalkyl, which is optionally substituted with one or more R^{X2a};

L^{X2} is C_{1-6}alkylene or C_{1-6}heteroalkylene, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X2a};

each R^{X2a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-SF_5$, $-S(=O)_2NR^cR^d$, $-S(=O)(=NR^a)R^a$, $-N=S(=O)R^cR^d$, $-NR^aS(=O)_2R^a$, amidinyl, $-NR^aC(=NH)(NR^a)_2$, $-NR^aS(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, $-P(=O)(OR^c)(OR^d)$, $-P(=O)R^cR^d$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O, =S, or $=N(R^a)$, wherein each of the alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e;

*X1 represents the point of attachment to X1;

*X3 represents the point of attachment to X3; and

other groups (such as R^a, R^c, R^d, and R^e) have the meanings defined in Formula (I).

[00266] In some embodiments, R^{n2} is hydrogen. In some embodiments, R^{n2} is C_{1-3} alkyl. In some embodiments, R^{n2} is methyl.

[00267] In some embodiments, R^{X2} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, $-L^{X2}$-heterocycloalkyl, $-L^{X2}$-cycloalkyl, $-L^{X2}$-aryl, or $-L^{X2}$-heteroaryl, wherein each of the alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X2a}.

[00268] In some embodiments, R^{X2} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, $-L^{X2}$-5-6 membered heterocycloalkyl, $-L^{X2}$-C_{4-6}cycloalkyl, $-L^{X2}$-C_{6-10}aryl, or $-L^{X2}$-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X2a}. In some embodiments, R^{X2} is hydrogen, C_{1-6}alkyl, C_{1-6}heteroalkyl, $-L^{X2}$-piperidinyl, L^{X2}-piperazinyl, $-L^{X2}$-phenyl, or $-L^{X2}$-pyridinyl, wherein each of the alkyl, heteroalkyl, phenyl, pyridinyl, piperidinyl, and piperazinyl is optionally substituted with one or more R^{X2a}.

[00269] In some embodiments, R^{X2} is hydrogen. In some embodiments, R^{X2} is optionally substituted C_{1-6}alkyl. In some embodiments, R^{X2} is C_{1-6}alkyl optionally substituted with one or more R^{X2a}. In some embodiments, R^{X2} is optionally substituted C_{1-6}heteroalkyl. In some embodiments, R^{X2} is C_{1-6}heteroalkyl optionally substituted with one or more R^{X2a}. In some embodiments, R^{X2} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, or C_{1-6}heteroalkyl, wherein each of which is optionally substituted with one or more R^{X2a}. In some embodiments, R^{X2} is C_{2-6}alkenyl or C_{2-6}alkynyl, wherein each of which is optionally substituted with one or more R^{X2a}. In some embodiments, R^{X2} is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein each of which is optionally substituted with one or more R^{X2a}. In some embodiments, R^{X2} is aryl or heteroaryl, wherein each of which is optionally substituted with one or more R^{X2a}. In some embodiments, R^{X2} is cycloalkyl or heterocycloalkyl, wherein each of which is optionally substituted with one or more R^{X2a}. In some embodiments, R^{X2} is $-L^{X2}$-heterocycloalkyl, $-L^{X2}$-cycloalkyl, $-L^{X2}$-aryl, or $-L^{X2}$-heteroaryl, wherein each of which is optionally substituted with one or more R^{X2a}. In some embodiments, R^{X2} is $-L^{X2}$-heterocycloalkyl, which is optionally substituted with one or more R^{X2a}. In some embodiments, R^{X2} is $-L^{X2}$- cycloalkyl, which is optionally substituted with one or more R^{X2a}. In some embodiments, R^{X2} is $-L^{X2}$-aryl, which is optionally substituted with one or more R^{X2a}. In some embodiments, R^{X2} is $-L^{X2}$-heteroaryl,

which is optionally substituted with one or more R^{X2a}.

[00270] In some embodiments, $R^{X2'}$ is hydrogen. In some embodiments, $R^{X2'}$ is C_{1-6}alkyl, wherein the alkyl is optionally substituted with one or more R^{X2a}. In some embodiments, $R^{X2'}$ is C_{1-6}alkyl. In some embodiments, $R^{X2'}$ is methyl.

[00271] In some embodiments, R^{n2} and $R^{X2'}$ are taken together with the intervening atoms to form a 5- to 6-membered heterocycloalkyl, which is optionally substituted with one or more R^{X2a}.

[00272] In some embodiments, L^{X2} is C_{1-6}alkylene, wherein the alkylene is optionally substituted with one or more R^{X2a}. In some embodiments, L^{X2} is C_{1-6}alkylene. In some embodiments, L^{X2} is C_{1-6}heteroalkylene, wherein the heteroalkylene is optionally substituted with one or more R^{X2a}. In some embodiments, L^{X2} is C_{1-6}heteroalkylene. In some embodiments, L^{X2} is -O-. In some embodiments, L^{X2} is -S-. In some embodiments, L^{X2} is $-NR^a-$. In some embodiments, L^{X2} is -NH-.

[00273] In some embodiments, each R^{X2a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, cycloalkyl, heterocycloalkyl, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^aS(=O)_2R^a$, $-NR^aC(=NH)(NR^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e.

[00274] In some embodiments, each R^{X2a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^aS(=O)_2R^a$, $-NR^aC(=NH)(NR^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e.

[00275] In some embodiments, each R^{X2a} is independently C_{1-6} alkyl, C_{1-6} alkoxyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, OH, -CN, $-NO_2$, NH_2, $-C(=O)R^a$, $-C(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, or oxo.

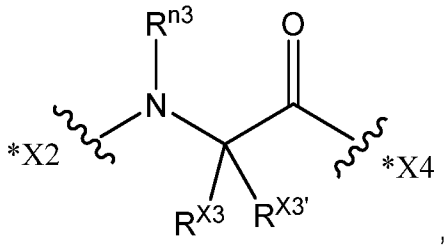
[00276] In some embodiments of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X3 is a polar and/or an L-amino acid. In some embodiments, X3 is an amino acid comprising a hydrophilic side chain (*e.g.*, D, K, Q, or a variant thereof) or an N-methylated variant thereof. In some embodiments, X3 is absent.

[00277] In some embodiments of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X3 is D, Har, KCOpipzetOH, Cit, KCOmeglumine, KCOpipzaa, A4paa, Q, A, E, MeD, S, N, Hgl, F4COO, KCOpip4COO, Kac, Hgn, or DapCOpipzaa. In some embodiments of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X3 is D, Har, KCOpipzetOH, Cit, KCOmeglumine, KCOpipzaa, A4paa, Q, A, E, MeD, S, N, Hgl, F4COO, KCOpip4COO, Kac, Hgn, or DapCOpipzaa, each of which is optionally substituted. In some embodiments, X3 is optionally substituted D. In some embodiments, X3 is optionally substituted Har. In some embodiments, X3 is optionally substituted KCOpipzetOH. In some embodiments, X3 is optionally substituted Cit. In some embodiments, X3 is optionally substituted KCOmeglumine. In some embodiments, X3 is optionally substituted KCOpipzaa. In some embodiments, X3 is optionally substituted A4paa. In some embodiments, X3 is optionally substituted Q. In some embodiments, X3 is optionally substituted A. In some embodiments, X3 is optionally substituted E. In some embodiments, X3 is optionally substituted MeD. In some embodiments, X3 is optionally substituted S. In some

embodiments, X3 is optionally substituted N. In some embodiments, X3 is optionally substituted Hgl. In some embodiments, X3 is optionally substituted F4COO. In some embodiments, X3 is optionally substituted KCOpip4COO. In some embodiments, X3 is optionally substituted Kac. In some embodiments, X3 is optionally substituted Hgn. In some embodiments, X3 is optionally substituted DapCOpipzaa.

[00278] In some embodiments of a peptide of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X3 is any amino acid. In some embodiments, X3 is a D-amino acid. In some embodiments, X3 is an L-amino acid. In some embodiments, X3 is an N-alkylated amino acid. In some embodiments, X3 is an N-methylated amino acid. In some embodiments, X3 does not comprise a cyclic group. In some embodiments, X3 comprises a cyclic group. In some embodiments, X3 comprises a 5-6 membered heterocycloalkyl group. In some embodiments, X3 comprises a 5-6 membered heteroaryl group. In some embodiments, X3 comprises a phenyl group. In some embodiments, X3 is a peptoid. In some embodiments, X3 is a polar amino acid.

[00279] In some embodiments of a peptide of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X3 has a structure of



,

wherein:

R^{n3} is hydrogen or C_{1-3}alkyl, wherein the alkyl is optionally substituted with one or more R^{X3a};

R^{X3} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -L^{X3}-heterocycloalkyl, -L^{X3}-cycloalkyl, -L^{X3}-aryl, or -L^{X3}-heteroaryl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X3a};

$R^{X3'}$ is hydrogen or C_{1-6}alkyl, wherein the alkyl is optionally substituted with one or more R^{X3a}; or

R^{n3} and $R^{X3'}$ are taken together with the intervening atoms to form a 5- to 6- membered heterocycloalkyl, which is optionally substituted with one or more R^{X3a};

L^{X3} is C_{1-6}alkylene, C_{1-6}heteroalkylene, -O-, -S-, or -NR^a-, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X3a};

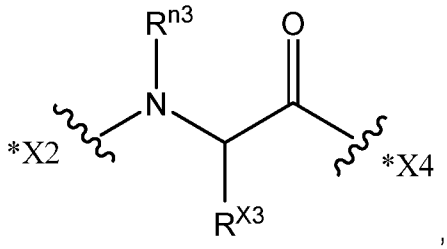
each R^{X3a} is independently halogen, C_{1-6}alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -SF_5, -$S(=O)_2NR^cR^d$, -$S(=O)(=NR^a)R^a$, -$N=S(=O)R^cR^d$, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)(NR^a)_2$, -$NR^aS(=O)_2NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, -$P(=O)(OR^c)(OR^d)$, -$P(=O)R^cR^d$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O, =S, or =$N(R^a)$, wherein each of the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e;

*X2 represents the point of attachment to X2;

*X4 represents the point of attachment to X4;

other groups (such as R^a, R^c, R^d, and R^e) have the meanings defined in Formula (I).

[00280] In some embodiments of a peptide of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X3 has a structure of



,

wherein:

R^{n3} is hydrogen or methyl;

R^{X3} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, -L^{X3}-5-6 membered heterocycloalkyl, -L^{X3}-C_{3-6}cycloalkyl, -L^{X3}-C_{6-10}aryl, or -L^{X3}-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X3a};

L^{X3} is C_{1-6}alkylene or C_{1-6}heteroalkylene, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X3a};

each R^{X3a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -S(=O)R^a, -$S(=O)_2R^a$, -SF_5, -$S(=O)_2NR^cR^d$, -S(=O)(=NR^a)R^a, -N=S(=O)R^cR^d, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)(NR^a)_2$, -$NR^aS(=O)_2NR^cR^d$, -C(=O)R^a, -C(=O)OR^a, -OC(=O)R^a, -OC(=O)OR^a, -OC(=O)NR^cR^d, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -C(=O)NR^cR^d, -P(=O)(OR^c)(OR^d), -P(=O)R^cR^d, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O, =S, or =N(R^a), wherein each of the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e;

*X2 represents the point of attachment to X2;

*X4 represents the point of attachment to X4; and

other groups (such as R^a, R^c, R^d, and R^e) have the meanings defined in Formula (I).

[00281] In some embodiments, R^{n3} is hydrogen. In some embodiments, R^{n3} is C_{1-3} alkyl. In some embodiments, R^{n3} is methyl.

[00282] In some embodiments, R^{X3} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -L^{X3}-heterocycloalkyl, -L^{X3}-cycloalkyl, -L^{X3}-aryl, or -L^{X3}-heteroaryl, wherein each of the alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X3a}. In some embodiments, R^{X3} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, -L^{X3}-5-6 membered heterocycloalkyl, -L^{X3}-C_{3-6}cycloalkyl, -L^{X3}-C_{6-10}aryl, or -L^{X3}-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X3a}.

[00283] In some embodiments, R^{X3} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, -L^{X3}-5-6 membered heterocycloalkyl, -L^{X3}-C_{4-6}cycloalkyl, -L^{X3}-C_{6-10}aryl, or -L^{X3}-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X3a}. In some embodiments, R^{X3} is hydrogen, C_{1-6}alkyl, C_{1-6}heteroalkyl, -L^{X3}-piperidinyl, L^{X3}-piperazinyl, -L^{X3}-phenyl, or -L^{X3}-pyridinyl, wherein each of the alkyl, heteroalkyl, phenyl, pyridinyl, piperidinyl, and piperazinyl is optionally substituted with one or more R^{X3a}.

[00284] In some embodiments, R^{X3} is hydrogen. In some embodiments, R^{X3} is optionally substituted C_{1-6}alkyl. In some embodiments, R^{X3} is C_{1-6}alkyl optionally substituted with one or more R^{X3a}. In some embodiments, R^{X3} is optionally substituted C_{1-6}heteroalkyl. In some embodiments, R^{X3} is C_{1-6}heteroalkyl optionally substituted with one or more R^{X3a}. In some embodiments, R^{X3} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, or C_{1-6}heteroalkyl, wherein each of which is optionally substituted with one or more R^{X3a}. In some embodiments, R^{X3} is C_{2-6}alkenyl or C_{2-6}alkynyl, wherein each of which is optionally substituted with one or more R^{X3a}. In some embodiments, R^{X3} is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein each of which is optionally substituted with one or more R^{X3a}. In some embodiments, R^{X3} is aryl or heteroaryl, wherein each of which is optionally substituted with one or more R^{X3a}. In some embodiments, R^{X3} is cycloalkyl or heterocycloalkyl, wherein each of which is optionally substituted with one or more R^{X3a}. In some embodiments, R^{X3} is -L^{X3}-heterocycloalkyl, -L^{X3}-cycloalkyl, -L^{X3}-aryl, or -L^{X3}-heteroaryl, wherein each of which is optionally substituted with one or more R^{X3a}. In some embodiments, R^{X3} is -L^{X3}-heterocycloalkyl, which is optionally substituted with one or more R^{X3a}. In some embodiments, R^{X3} is -L^{X3}- cycloalkyl, which is optionally substituted with one or more R^{X3a}. In some embodiments, R^{X3} is -L^{X3}-aryl, which is optionally substituted with one or more R^{X3a}. In some embodiments, R^{X3} is -L^{X3}-heteroaryl, which is optionally substituted with one or more R^{X3a}.

[00285] In some embodiments, $R^{X3'}$ is hydrogen. In some embodiments, $R^{X3'}$ is C_{1-6}alkyl, wherein the alkyl is optionally substituted with one or more R^{X3a}. In some embodiments, $R^{X3'}$ is C_{1-6}alkyl. In some embodiments, $R^{X3'}$ is methyl.

[00286] In some embodiments, R^{n3} and $R^{X3'}$ are taken together with the intervening atoms to form a 5- to 6-membered heterocycloalkyl, which is optionally substituted with one or more R^{X3a}.

[00287] In some embodiments, L^{X3} is C_{1-6}alkylene, wherein the alkylene is optionally substituted with one or more R^{X3a}. In some embodiments, L^{X3} is C_{1-6}alkylene. In some embodiments, L^{X3} is C_{1-6}heteroalkylene, wherein the heteroalkylene is optionally substituted with one or more R^{X3a}. In some embodiments, L^{X3} is C_{1-6}heteroalkylene. In some embodiments, L^{X3} is -O-. In some embodiments, L^{X3} is -S-. In some embodiments, L^{X3} is -NR^a-. In some embodiments, L^{X3} is -NH-.

[00288] In some embodiments, each R^{X3a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, cycloalkyl, heterocycloalkyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^aS(=O)_2R^a$, -$NR^aC(=NH)(NR^a)_2$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e.

[00289] In some embodiments, each R^{X3a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl,

C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^aS(=O)_2R^a$, -$NR^aC(=NH)(NR^a)_2$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e.

[00290] In some embodiments, each R^{X3a} is independently C_{1-6} alkyl, C_{1-6} alkoxyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, OH, -CN, -NO_2, NH_2, -$C(=O)R^a$, -$C(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, or oxo.

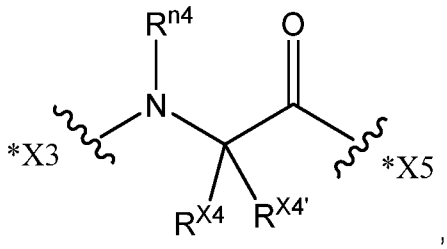
[00291] In some embodiments of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X4 is a polar and/or an L-amino acid. In some embodiments, X4 is an N-methylated amino acid, a polar amino acid (*e.g.*, D, K, Q, S, or a variant thereof), or peptoid (e.g. EtG, MeeG, CmG, CmpG CrmG, CeG, or CrpG).

[00292] In some embodiments of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X4 is D, Har, KCOpipzetOH, KCOmeglumine, KCOpipzaa, A4paa, Q, A, E, MeD, S, N, Hgl, F4COO, KCOpip4COO, dd, MeQ, MeQdMe, MeA, MeSMe, MeG, EtG, MeeG, CmG, CmpG, CrmG, CeG, CrpG, MeK, MeKAc, MeHgl, Hgn, MeDapCOpipzaa, MeKCOpipzaa, Medd, Cit, MeCit, MeN, MeS, MeE, or Mae4paa. In some embodiments of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X4 is D, Har, KCOpipzetOH, KCOmeglumine, KCOpipzaa, A4paa, Q, A, E, MeD, S, N, Hgl, F4COO, KCOpip4COO, dd, MeQ, MeQdMe, MeA, MeSMe, MeG, EtG, MeeG, CmG, CmpG, CrmG, CeG, CrpG, MeK, MeKAc, MeHgl, Hgn, MeDapCOpipzaa, MeKCOpipzaa, Medd, Cit, MeCit, MeN, MeS, MeE, or Mae4paa, each of which is optionally substituted. In some embodiments, X4 is optionally substituted D. In some embodiments, X4 is optionally substituted Har. In some embodiments, X4 is optionally substituted KCOpipzetOH. In some embodiments, X4 is optionally substituted KCOmeglumine. In some embodiments, X4 is optionally substituted KCOpipzaa. In some embodiments, X4 is optionally substituted A4paa. In some embodiments, X4 is optionally substituted Q. In some embodiments, X4 is optionally substituted A. In some embodiments, X4 is optionally substituted E. In some embodiments, X4 is optionally substituted MeD. In some embodiments, X4 is optionally substituted S. In some embodiments, X4 is optionally substituted N. In some embodiments, X4 is optionally substituted Hgl. In some embodiments, X4 is optionally substituted F4COO. In some embodiments, X4 is optionally substituted KCOpip4COO. In some embodiments, X4 is optionally substituted dd. In some embodiments, X4 is optionally substituted MeQ. In some embodiments, X4 is optionally substituted MeQdMe. In some embodiments, X4 is optionally substituted MeA. In some embodiments, X4 is optionally substituted MeSMe. In some embodiments, X4 is optionally substituted MeG. In some embodiments, X4 is optionally substituted EtG. In some embodiments, X4 is optionally substituted MeeG. In some embodiments, X4 is optionally substituted CmG. In some embodiments, X4 is optionally substituted CmpG. In some embodiments, X4 is optionally substituted CrmG. In some embodiments, X4 is optionally substituted CeG. In some embodiments, X4 is optionally substituted CrpG. In some embodiments, X4 is optionally substituted MeK. In some embodiments, X4 is optionally substituted MeKAc. In some embodiments, X4 is optionally substituted MeHgl. In some embodiments, X4 is optionally substituted Hgn. In some embodiments, X4 is optionally substituted MeDapCOpipzaa. In some embodiments, X4 is optionally substituted MeKCOpipzaa. In some embodiments, X4 is optionally substituted Medd. In some embodiments, X4 is optionally substituted Cit. In some embodiments, X4 is optionally substituted MeCit. In some embodiments, X4 is optionally substituted MeN. In some embodiments,

X4 is optionally substituted MeS. In some embodiments, X4 is optionally substituted MeE. In some embodiments, X4 is optionally substituted Mae4paa.

[00293] In some embodiments of a peptide of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X4 is any amino acid. In some embodiments, X4 is a D-amino acid. In some embodiments, X4 is an L-amino acid. In some embodiments, X4 is an N-alkylated amino acid. In some embodiments, X4 is an N-methylated amino acid. In some embodiments, X4 does not comprise a cyclic group. In some embodiments, X4 comprises a cyclic group. In some embodiments, X4 comprises a 5-6 membered heterocycloalkyl group. In some embodiments, X4 comprises a 5-6 membered heteroaryl group. In some embodiments, X4 comprises a phenyl group. In some embodiments, X4 is a peptoid. In some embodiments, X4 is a polar amino acid.

[00294] In some embodiments of a peptide of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X4 has a structure of



,

wherein:

R^{n4} is hydrogen or C_{1-3} alkyl, wherein the alkyl is optionally substituted with one or more R^{X4a};

R^{X4} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -L^{X4}-heterocycloalkyl, -L^{X4}-cycloalkyl, -L^{X4}-aryl, or -L^{X4}-heteroaryl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X4a};

$R^{X4'}$ is hydrogen or C_{1-6}alkyl, wherein the alkyl is optionally substituted with one or more R^{X4a}; or

R^{n4} and $R^{X4'}$ are taken together with the intervening atoms to form a 5- to 6- membered heterocycloalkyl, which is optionally substituted with one or more R^{X4a};

L^{X4} is C_{1-6}alkylene or C_{1-6}heteroalkylene, -O-, -S-, or -NR^a-, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X4a};

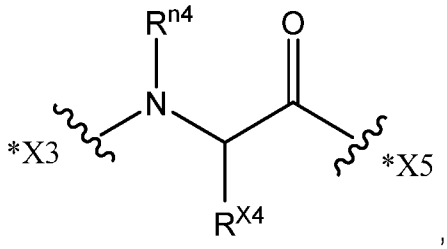
each R^{X4a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -S(=O)R^a, -$S(=O)_2R^a$, -SF_5, -$S(=O)_2NR^cR^d$, -S(=O)(=NR^a)R^a, -N=S(=O)R^cR^d, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)(NR^a)_2$, -$NR^aS(=O)_2NR^cR^d$, -C(=O)R^a, -C(=O)OR^a, -OC(=O)R^a, -OC(=O)OR^a, -OC(=O)NR^cR^d, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -C(=O)NR^cR^d, -P(=O)(OR^c)(OR^d), -P(=O)R^cR^d, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O, =S, or =N(R^a), wherein each of the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e;

*X3 represents the point of attachment to X3;

*X5 represents the point of attachment to X5; and

other groups (such as R^a, R^c, R^d, and R^e) have the meanings defined in Formula (I).

[00295] In some embodiments of a peptide of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X4 has a structure of



,

wherein:

R^{n4} is hydrogen or C_{1-3} alkyl, wherein the alkyl is optionally substituted with one or more R^{X4a};

R^{X4} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, -L^{X4}-5-6 membered heterocycloalkyl, -L^{X4}-C_{3-6}cycloalkyl, -L^{X4}-C_{6-10}aryl, or -L^{X4}-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X4a};

L^{X4} is C_{1-6}alkylene or C_{1-6}heteroalkylene, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X4a};

each R^{X4a} is independently halogen, C_{1-6}alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -SF_5, -$S(=O)_2NR^cR^d$, -$S(=O)(=NR^a)R^a$, -$N=S(=O)R^cR^d$, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)(NR^a)_2$, -$NR^aS(=O)_2NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, -$P(=O)(OR^c)(OR^d)$, -$P(=O)R^cR^d$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O, =S, or =$N(R^a)$, wherein each of the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e;

*X3 represents the point of attachment to X3;

*X5 represents the point of attachment to X5; and

other groups (such as R^a, R^c, R^d, and R^e) have the meanings defined in Formula (I).

[00296] In some embodiments, R^{n4} is hydrogen. In some embodiments, R^{n4} is C_{1-3} alkyl. In some embodiments, R^{n4} is methyl.

[00297] In some embodiments, R^{X4} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -L^{X4}-heterocycloalkyl, -L^{X4}-cycloalkyl, -L^{X4}-aryl, or -L^{X4}-heteroaryl, wherein each of the alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X4a}. In some embodiments, R^{X4} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, -L^{X4}-5-6 membered heterocycloalkyl, -L^{X4}-C_{3-6}cycloalkyl, -L^{X4}-C_{6-10}aryl, or -L^{X4}-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X4a}.

[00298] In some embodiments, R^{X4} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, -L^{X4}-5-6 membered heterocycloalkyl, -L^{X4}-C_{4-6}cycloalkyl, -L^{X4}-C_{6-10}aryl, or -L^{X4}-5-10 membered

heteroaryl, wherein each of the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X4a}. In some embodiments, R^{X4} is hydrogen, C_{1-6}alkyl, C_{1-6}heteroalkyl, -L^{X4}-piperidinyl, L^{X4}-piperazinyl, -L^{X4}-phenyl, or -L^{X4}-pyridinyl, wherein each of the alkyl, heteroalkyl, phenyl, pyridinyl, piperidinyl, and piperazinyl is optionally substituted with one or more R^{X4a}.

[00299] In some embodiments, R^{X4} is hydrogen. In some embodiments, R^{X4} is optionally substituted C_{1-6}alkyl. In some embodiments, R^{X4} is C_{1-6}alkyl optionally substituted with one or more R^{X4a}. In some embodiments, R^{X4} is optionally substituted C_{1-6}heteroalkyl. In some embodiments, R^{X4} is C_{1-6}heteroalkyl optionally substituted with one or more R^{X4a}. In some embodiments, R^{X4} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, or C_{1-6}heteroalkyl, wherein each of which is optionally substituted with one or more R^{X4a}. In some embodiments, R^{X4} is C_{2-6}alkenyl or C_{2-6}alkynyl, wherein each of which is optionally substituted with one or more R^{X4a}. In some embodiments, R^{X4} is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein each of which is optionally substituted with one or more R^{X4a}. In some embodiments, R^{X4} is aryl or heteroaryl, wherein each of which is optionally substituted with one or more R^{X4a}. In some embodiments, R^{X4} is cycloalkyl or heterocycloalkyl, wherein each of which is optionally substituted with one or more R^{X4a}. In some embodiments, R^{X4} is -L^{X4}-heterocycloalkyl, -L^{X4}-cycloalkyl, -L^{X4}-aryl, or -L^{X4}-heteroaryl, wherein each of which is optionally substituted with one or more R^{X4a}. In some embodiments, R^{X4} is -L^{X4}-heterocycloalkyl, which is optionally substituted with one or more R^{X4a}. In some embodiments, R^{X4} is -L^{X4}- cycloalkyl, which is optionally substituted with one or more R^{X4a}. In some embodiments, R^{X4} is -L^{X4}-aryl, which is optionally substituted with one or more R^{X4a}. In some embodiments, R^{X4} is -L^{X4}-heteroaryl, which is optionally substituted with one or more R^{X4a}.

[00300] In some embodiments, $R^{X4'}$ is hydrogen. In some embodiments, $R^{X4'}$ is C_{1-6}alkyl, wherein the alkyl is optionally substituted with one or more R^{X4a}. In some embodiments, $R^{X4'}$ is C_{1-6}alkyl. In some embodiments, $R^{X4'}$ is methyl.

[00301] In some embodiments, R^{n4} and $R^{X4'}$ are taken together with the intervening atoms to form a 5- to 6-membered heterocycloalkyl, which is optionally substituted with one or more R^{X4a}.

[00302] In some embodiments, L^{X4} is C_{1-6}alkylene, wherein the alkylene is optionally substituted with one or more R^{X4a}. In some embodiments, L^{X4} is C_{1-6}alkylene. In some embodiments, L^{X4} is C_{1-6}heteroalkylene, wherein the heteroalkylene is optionally substituted with one or more R^{X4a}. In some embodiments, L^{X4} is C_{1-6}heteroalkylene. In some embodiments, L^{X4} is -O-. In some embodiments, L^{X4} is -S-. In some embodiments, L^{X4} is -NR^a-. In some embodiments, L^{X4} is -NH-.

[00303] In some embodiments, each R^{X4a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, cycloalkyl, heterocycloalkyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^aS(=O)_2R^a$, -$NR^aC(=NH)(NR^a)_2$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e.

[00304] In some embodiments, each R^{X4a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^aS(=O)_2R^a$, -$NR^aC(=NH)(NR^a)_2$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -

$NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e.

[00305] In some embodiments, each R^{X4a} is independently C_{1-6} alkyl, C_{1-6} alkoxyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, OH, -CN, $-NO_2$, NH_2, $-C(=O)R^a$, $-C(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, or oxo. In some embodiments, each R^{X4a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, $-OR^a$, -CN, $-NO_2$, NH_2, $-C(=O)R^a$, $-C(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, or oxo.

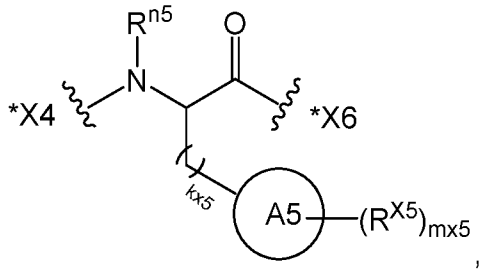
[00306] In some embodiments of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X5 has an aromatic side chain, such as F, Y, or a variant thereof. In some embodiments, X5 is F, or a variant thereof comprising a phenyl, pyridinyl, or naphthalyl, wherein said phenyl, pyridinyl, or naphthalyl is optionally substituted with one or more substituents each independently selected from halogen, $-C_{1-3}$alkyl, -OH, $-NH_2$, -CN, $-C(=O)OH$, $-C(=O)NH_2$, $-NHC(=O)CH_3$, $-C_{1-3}$alkylene-$C(=O)OH$, $-C_{1-3}$alkylene-$C(=O)NH_2$, $-O-C_{1-3}$alkylene-$C(=O)OH$, $-O-C_{1-3}$alkylene-$C(=O)NH_2$, $-C_{1-3}$alkylene-C(=O)-5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-$C(=O)OH$, $-O-C_{1-3}$alkylene-C(=O)- 5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-$C(=O)OH$, $-C_{1-3}$alkylene-NHC(=O)- 5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-$C(=O)OH$, $-O-C_{1-3}$alkylene-NHC(=O)- 5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-$C(=O)OH$, and $-NH-C_{1-3}$alkylene-$C(=O)OH$. In some embodiments, X5 is Y, or a variant thereof comprising a hydroxyphenyl, wherein the hydrogen atom in hydroxyphenyl of Y or of the variant is optionally substituted with one or more substituents selected from $-C_{1-3}$alkyl, , and $-C_{1-3}$alkylene-$C(=O)OH$.

[00307] In some embodiments of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X5 is Y, F3G, 3Py6COO,4Py2NH2, 3Py5COO, F3COO, 3Py6NHAc, F, F4C, F4OMe, F4COO, Nal2, F3aao, F4aa, F4aao, 3Py6Nhaa, 5Pdo, F3CON, F4F, F4Oet, F4Me, F4CON, F4CONPeg4Me, F3OMe, F3CON, YaeCOpipzaa, F4aaopipzaa, 4Pdo, 3Py6CON, Atp, Cha4cH, Cha4tH, Cha4cOMe, A1mor, or F4amCOpipzaa. In some embodiments of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X5 is Y, F3G, 3Py6COO,4Py2NH2, 3Py5COO, F3COO, 3Py6NHAc, F, F4C, F4OMe, F4COO, Nal2, F3aao, F4aa, F4aao, 3Py6Nhaa, 5Pdo, F3CON, F4F, F4Oet, F4Me, F4CON, F4CONPeg4Me, F3OMe, F3CON, YaeCOpipzaa, F4aaopipzaa, 4Pdo, 3Py6CON, Atp, Cha4cH, Cha4tH, Cha4cOMe, A1mor, or F4amCOpipzaa, each of which is optionally substituted. In some embodiments, X5 is optionally substituted Y. In some embodiments, X5 is optionally substituted F3G. In some embodiments, X5 is optionally substituted 3Py6COO. In some embodiments, X5 is optionally substituted 4Py2NH2. In some embodiments, X5 is optionally substituted 3Py5COO. In some embodiments, X5 is optionally substituted F3COO. In some embodiments, X5 is optionally substituted 3Py6NHAc. In some embodiments, X5 is optionally substituted F. In some embodiments, X5 is optionally substituted F4C. In some embodiments, X5 is optionally substituted F4OMe. In some embodiments, X5 is optionally substituted F4COO. In some embodiments, X5 is optionally substituted Nal2. In some embodiments, X5 is optionally substituted F3aao. In some embodiments, X5 is optionally substituted F4aa. In some embodiments, X5 is optionally substituted F4aao. In some embodiments, X5 is optionally substituted 3Py6Nhaa. In some embodiments, X5 is optionally substituted 5Pdo. In some embodiments, X5 is optionally substituted F3CON. In some embodiments, X5 is optionally substituted F4F. In some embodiments, X5 is optionally substituted F4Oet. In some embodiments, X5 is optionally substituted F4Me. In some embodiments, X5 is optionally substituted F4CON. In some

embodiments, X5 is optionally substituted F4CONPeg4Me. In some embodiments, X5 is optionally substituted F3OMe. In some embodiments, X5 is optionally substituted F3CON. In some embodiments, X5 is optionally substituted YaeCOpipzaa. In some embodiments, X5 is optionally substituted F4aaopipzaa. In some embodiments, X5 is optionally substituted 4Pdo. In some embodiments, X5 is optionally substituted 3Py6CON. In some embodiments, X5 is optionally substituted Atp. In some embodiments, X5 is optionally substituted Cha4cH. In some embodiments, X5 is optionally substituted Cha4tH. In some embodiments, X5 is optionally substituted Cha4cOMe. In some embodiments, X5 is optionally substituted A1mor. In some embodiments, X5 is optionally substituted F4amCOpipzaa.

[00308] In some embodiments of a peptide of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X5 is any amino acid. In some embodiments, X5 is a D-amino acid. In some embodiments, X5 is an L-amino acid. In some embodiments, X5 is an N-alkylated amino acid. In some embodiments, X5 is an N-methylated amino acid. In some embodiments, X5 does not comprise a cyclic group. In some embodiments, X5 comprises a cyclic group. In some embodiments, X5 comprises a 5-6 membered heterocycloalkyl group. In some embodiments, X5 comprises a 5-6 membered heteroaryl group. In some embodiments, X5 comprises a phenyl group. In some embodiments, X5 is a peptoid.

[00309] In some embodiments of a peptide of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X5 has a structure of



,

wherein:

R^{n5} is hydrogen or C_{1-3} alkyl;

ring A5 is an aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

each R^{X5} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halogen, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-SF_5$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-S(=O)(=NR^a)R^a$, $-N=S(=O)NR^cR^d$, $-NR^aS(=O)_2R^a$, amidinyl, $-NR^aC(=NH)NR^cR^d$, $-NR^aS(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, $-P(=O)(OR^c)(OR^d)$, $-P(=O)R^cR^d$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, $-L^{X5}$-heterocycloalkyl, $-L^{X5}$-cycloalkyl, $-L^{X5}$-aryl, or $-L^{X5}$-heteroaryl, wherein the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl are optionally substituted with one or more R^{X5a}; or

two R^{X5} are taken together to form =O, =S, or $=N(R^a)$;

L^{X5} is C_{1-6}alkylene, C_{1-6}heteroalkylene, -O-, -S-, or $-NR^a-$, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X5a};

kx5 is 0, 1, 2, or 3;

mx5 is 0, 1, 2, 3, 4, or 5;

*X4 represents the point of attachment to X4;

*X6 represents the point of attachment to X6; and

other groups (such as R^a, R^c, R^d, and R^e) have the meanings defined in Formula (I).

[00310] In some embodiments of a peptide of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), wherein:

R^{n5} is hydrogen or methyl;

ring A5 is a C_{6-10}aryl, 5-10 membered heteroaryl, C_{6-10}cycloalkyl, or 5-10 membered heterocycloalkyl;

each R^{X5} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halogen, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-SF_5$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-S(=O)(=NR^a)R^a$, $-N=S(=O)NR^cR^d$, $-NR^aS(=O)_2R^a$, amidinyl, $-NR^aC(=NH)NR^cR^d$, $-NR^aS(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, $-P(=O)(OR^c)(OR^d)$, $-P(=O)R^cR^d$, C_{6-10}aryl, 5-10 membered heteroaryl, C_{3-6}cycloalkyl, 5-6 membered heterocycloalkyl, $-L^{X5}$-5-6 membered heterocycloalkyl, $-L^{X5}$-C_{3-6}cycloalkyl, $-L^{X5}$-C_{6-10}aryl, or $-L^{X5}$-5-10 membered heteroaryl, wherein the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl are optionally substituted with one or more R^{X5a}; or

two R^{X5} are taken together to form =O; and

L^{X5} is C_{1-6}alkylene or C_{1-6}heteroalkylene, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X5a}.

[00311] In some embodiments of a peptide of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), wherein:

ring A5 is a phenyl, naphthyl, pyridinyl, cyclohexyl, piperidinyl, piperazinyl, morpholinyl, or tetrahydropyranyl;

each R^{X5} is independently halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^aS(=O)_2R^a$, $-NR^aC(=NH)NR^cR^d$, $-NR^aS(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, $-L^{X5}$-piperidinyl, or L^{X5}-piperazinyl, wherein each of the alkyl, heteroalkyl, piperidinyl, and piperazinyl are optionally substituted with one or more R^{X5a}; or

two R^{X5} are taken together to form =O;

kx5 is 1 or 2; and

mx5 is 0, 1, or 2.

[00312] In some embodiments, R^{n5} is hydrogen. In some embodiments, R^{n5} is C_{1-3} alkyl. In some embodiments, R^{n5} is methyl.

[00313] In some embodiments, ring A5 is a C_{6-10}aryl, 5-10 membered heteroaryl, C_{3-10}cycloalkyl, or 3-10 membered heterocycloalkyl. In some embodiments, ring A5 is a C_{6-10}aryl, 5-10 membered heteroaryl, C_{6-10}cycloalkyl, or 5-10 membered heterocycloalkyl. In some embodiments, ring A5 is phenyl, naphthyl, pyridinyl, cyclohexyl, piperidinyl, piperazinyl, morpholinyl, or tetrahydropyranyl. In some embodiments, ring A5 is C_{6-10}aryl. In some embodiments, ring A5 is phenyl. In some embodiments, ring A5 is naphthyl. In some embodiments, ring

A5 is 5-10 membered heteroaryl. In some embodiments, ring A5 is 6-10 membered heteroaryl. In some embodiments, ring A5 is 5-6 membered heteroaryl. In some embodiments, ring A5 is pyridine. In some embodiments, ring A5 is pyridine. In some embodiments, ring A5 is C_{3-10}cycloalkyl. In some embodiments, ring A5 is C_{5-10}cycloalkyl. In some embodiments, ring A5 is C_{5-6}cycloalkyl. In some embodiments, ring A5 is C_{3-6}cycloalkyl. In some embodiments, ring A5 is cyclohexane. In some embodiments, ring A5 is 3-10 membered heterocycloalkyl. In some embodiments, ring A5 is 5-6 membered heterocycloalkyl. In some embodiments, ring A5 is tetrahydropyran. In some embodiments, ring A5 is morpholine.

[00314] In some embodiments, each R^{X5} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halogen, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-SF_5$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-S(=O)(=NR^a)R^a$, $-N=S(=O)NR^cR^d$, $-NR^aS(=O)_2R^a$, amidinyl, $-NR^aC(=NH)NR^cR^d$, $-NR^aS(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, $-P(=O)(OR^c)(OR^d)$, $-P(=O)R^cR^d$, C_{6-10}aryl, 5-10 membered heteroaryl, C_{3-6}cycloalkyl, 5-6 membered heterocycloalkyl, $-L^{X5}$-5-6 membered heterocycloalkyl, $-L^{X5}$-C_{3-6}cycloalkyl, $-L^{X5}$-C_{6-10}aryl, or $-L^{X5}$-5-10 membered heteroaryl, wherein the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl are optionally substituted with one or more R^{X5a}. In some embodiments, each R^{X5} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halogen, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-NR^cR^d$, $-NR^aC(=NH)NR^cR^d$, $-NR^aS(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-C(=O)NR^cR^d$, C_{6-10}aryl, 5-10 membered heteroaryl, C_{3-6}cycloalkyl, 5-6 membered heterocycloalkyl, $-L^{X5}$-5-6 membered heterocycloalkyl, $-L^{X5}$-C_{3-6}cycloalkyl, $-L^{X5}$-C_{6-10}aryl, or $-L^{X5}$-5-10 membered heteroaryl, wherein the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl are optionally substituted with one or more R^{X5a}. In some embodiments, each R^{X5} is independently halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^aS(=O)_2R^a$, $-NR^aC(=NH)NR^cR^d$, $-NR^aS(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, $-L^{X5}$-piperidinyl, or L^{X5}-piperazinyl, wherein each of the alkyl, heteroalkyl, piperidinyl, and piperazinyl are optionally substituted with one or more R^{X5a}.

[00315] In some embodiments, each R^{X5a} is independently halogen, C_{1-6}alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^aS(=O)_2R^a$, $-NR^aC(=NH)(NR^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e.

[00316] In some embodiments, two R^{X5} are taken together to form =O.

[00317] In some embodiments, kx5 is 0. In some embodiments, kx5 is 1. In some embodiments, kx5 is 2. In some embodiments, kx5 is 3.

[00318] In some embodiments, mx5 is 0. In some embodiments, mx5 is 1. In some embodiments, mx5 is 2. In some embodiments, mx5 is 3. In some embodiments, mx5 is 4. In some embodiments, mx5 is 5.

[00319] In some embodiments of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X6 is an

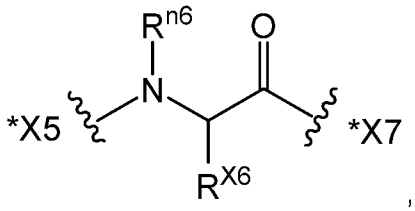
aliphatic amino acid (*e.g.*, V, L, I, A, G, or a variant thereof), a hydrophilic amino acid (*e.g.*, D, E, or a variant thereof), threonine (T), serine (S), O-methyl threonine (TMe), or methionine (M).

[00320] In some embodiments of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X6 is I, V, Eva, Chg, Tbg, A, L, Ahp, F4COO, Gcpr, Gcpe, all, Tme, Acpr, Cba, Gthp, NleCOO, NleOH, P, Atb, Nva, Nle, N, DapAc, Abu, Nmm, Ndm, Ncit, Cit, Sme, HseMe, HseEt, HseiPr, dMeS, TdMe, Cbg, NvaOme, SiPr, Spr, NleOme, Sbu, Scbm, Scpe, AhpOMe, HseBu, Spent or Hsecpe. In some embodiments of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X6 is I, V, Eva, Chg, Tbg, A, L, Ahp, F4COO, Gcpr, Gcpe, all, Tme, Acpr, Cba, Gthp, NleCOO, NleOH, P, Atb, Nva, Nle, N, DapAc, Abu, Nmm, Ndm, Ncit, Cit, Sme, HseMe, HseEt, HseiPr, dMeS, TdMe, Cbg, NvaOme, SiPr, Spr, NleOme, Sbu, Scbm, Scpe, AhpOMe, HseBu, Spent or Hsecpe, each of which is optionally substituted. In some embodiments, X6 is optionally substituted I. In some embodiments, X6 is optionally substituted V. In some embodiments, X6 is optionally substituted Eva. In some embodiments, X6 is optionally substituted Chg. In some embodiments, X6 is optionally substituted Tbg. In some embodiments, X6 is optionally substituted A. In some embodiments, X6 is optionally substituted L. In some embodiments, X6 is optionally substituted Ahp. In some embodiments, X6 is optionally substituted F4COO. In some embodiments, X6 is optionally substituted Gcpr. In some embodiments, X6 is optionally substituted Gcpe. In some embodiments, X6 is optionally substituted all. In some embodiments, X6 is optionally substituted Tme. In some embodiments, X6 is optionally substituted Acpr. In some embodiments, X6 is optionally substituted Cba. In some embodiments, X6 is optionally substituted Gthp. In some embodiments, X6 is optionally substituted NleCOO. In some embodiments, X6 is optionally substituted NleOH. In some embodiments, X6 is optionally substituted P. In some embodiments, X6 is optionally substituted Atb. In some embodiments, X6 is optionally substituted Nva. In some embodiments, X6 is optionally substituted Nle. In some embodiments, X6 is optionally substituted N. In some embodiments, X6 is optionally substituted DapAc. In some embodiments, X6 is optionally substituted Abu. In some embodiments, X6 is optionally substituted Nmm. In some embodiments, X6 is optionally substituted Ndm. In some embodiments, X6 is optionally substituted Ncit. In some embodiments, X6 is optionally substituted Cit. In some embodiments, X6 is optionally substituted Sme. In some embodiments, X6 is optionally substituted HseMe. In some embodiments, X6 is optionally substituted HseEt. In some embodiments, X6 is optionally substituted HseiPr. In some embodiments, X6 is optionally substituted dMeS. In some embodiments, X6 is optionally substituted TdMe. In some embodiments, X6 is optionally substituted Cbg. In some embodiments, X6 is optionally substituted NvaOme. In some embodiments, X6 is optionally substituted SiPr. In some embodiments, X6 is optionally substituted Spr. In some embodiments, X6 is optionally substituted NleOme. In some embodiments, X6 is optionally substituted Sbu. In some embodiments, X6 is optionally substituted Scbm. In some embodiments, X6 is optionally substituted Scpe. In some embodiments, X6 is optionally substituted AhpOMe. In some embodiments, X6 is optionally substituted HseBu. In some embodiments, X6 is optionally substituted Spent. In some embodiments, X6 is optionally substituted Hsecpe.

[00321] In some embodiments of a peptide of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X6 is any amino acid. In some embodiments, X6 is a D-amino acid. In some embodiments, X6 is an L-amino acid. In some embodiments, X6 is an N-alkylated amino acid. In some embodiments, X6 is an N-methylated amino

acid. In some embodiments, X6 does not comprise a cyclic group. In some embodiments, X6 comprises a cyclic group. In some embodiments, X6 comprises a 5-6 membered heterocycloalkyl group. In some embodiments, X6 comprises a 5-6 membered heteroaryl group. In some embodiments, X6 comprises a phenyl group. In some embodiments, X6 is a peptoid.

[00322] In some embodiments of a peptide of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X6 has a structure of



,

wherein;

R^{n6} is hydrogen or C_{1-3} alkyl;

R^{X6} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -L^{X6}-heterocycloalkyl, -L^{X6}-cycloalkyl, -L^{X6}-aryl, or -L^{X6}-heteroaryl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X6a}; or

R^{n6} and R^{x6} are taken together with the intervening atoms to form a 5- to 6- membered heterocycloalkyl, which is optionally substituted with one or more R^{X6a};

L^{X6} is C_{1-6}alkylene, C_{1-6}heteroalkylene, O, S, or NR^a, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X6a};

*X5 represents the point of attachment to X5;

*X7 represents the point of attachment to X7; and

other groups (such as R^a, R^c, R^d, and R^e) have the meanings defined in Formula (I).

[00323] In some embodiments of a peptide of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), wherein

R^{n6} is hydrogen or methyl;

R^{X6} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{6-10}aryl, 5-10 membered heteroaryl, C_{3-6}cycloalkyl, 5-6 membered heterocycloalkyl, -L^{X6}-5-6 membered heterocycloalkyl, -L^{X6}-C_{3-6}cycloalkyl, -L^{X6}-C_{6-10}aryl, or -L^{X6}-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X6a}; and

L^{X6} is C_{1-6}alkylene or C_{1-6}heteroalkylene, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X6a}.

[00324] In some embodiments, R^{n6} is hydrogen. In some embodiments, R^{n6} is C_{1-3} alkyl. In some embodiments, R^{n6} is methyl.

[00325] In some embodiments, R^{X6} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{3-6}cycloalkyl, 5-6 membered heterocycloalkyl, -L^{X6}-5-6 membered heterocycloalkyl, -L^{X6}- C_{3-6}cycloalkyl, -L^{X6}-

phenyl or -L^{X6}-6 membered heteroaryl, wherein each of the alkyl, heteroalkyl, phenyl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X6a}.

[00326] In some embodiments, R^{X6} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, -L^{X6}-5-6 membered heterocycloalkyl, -L^{X6}-C_{3-6}cycloalkyl, -L^{X6}-C_{6-10}aryl, or -L^{X6}-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X6a}.

[00327] In some embodiments, R^{X6} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, -L^{X6}-5-6 membered heterocycloalkyl, -L^{X6}-C_{4-6}cycloalkyl, -L^{X6}-C_{6-10}aryl, or -L^{X6}-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X6a}. In some embodiments, R^{X6} is C_{1-6}alkyl, C_{1-6}heteroalkyl, 6 -L^{X6}-phenyl, or -L^{X6}-pyridinyl, wherein each of the alkyl, heteroalkyl, phenyl, and pyridinyl is optionally substituted with one or more R^{X6a}.

[00328] In some embodiments, R^{X6} is optionally substituted C_{1-6}alkyl. In some embodiments, R^{X6} is C_{1-6}alkyl optionally substituted with one or more R^{X6a}. In some embodiments, R^{X6} is optionally substituted C_{1-6}heteroalkyl. In some embodiments, R^{X6} is C_{1-6}heteroalkyl optionally substituted with one or more R^{X6a}. In some embodiments, R^{X6} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, or C_{1-6}heteroalkyl, wherein each of which is optionally substituted with one or more R^{X6a}. In some embodiments, R^{X6} is C_{2-6}alkenyl or C_{2-6}alkynyl, wherein each of which is optionally substituted with one or more R^{X6a}. In some embodiments, R^{X6} is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein each of which is optionally substituted with one or more R^{X6a}. In some embodiments, R^{X6} is aryl or heteroaryl, wherein each of which is optionally substituted with one or more R^{X6a}. In some embodiments, R^{X6} is cycloalkyl or heterocycloalkyl, wherein each of which is optionally substituted with one or more R^{X6a}. In some embodiments, R^{X6} is C_{3-6} cycloalkyl, which is optionally substituted with one or more R^{X6a}. In some embodiments, R^{X6} is -L^{X6}-heterocycloalkyl, -L^{X6}-cycloalkyl, -L^{X6}-aryl, or -L^{X6}-heteroaryl, wherein each of which is optionally substituted with one or more R^{X6a}. In some embodiments, R^{X6} is -L^{X6}-heterocycloalkyl, which is optionally substituted with one or more R^{X6a}. In some embodiments, R^{X6} is -L^{X6}- cycloalkyl, which is optionally substituted with one or more R^{X6a}. In some embodiments, R^{X6} is -L^{X6}-aryl, which is optionally substituted with one or more R^{X6a}. In some embodiments, R^{X6} is -L^{X6}-heteroaryl, which is optionally substituted with one or more R^{X6a}.

[00329] In some embodiments, R^{n6} and R^{x6} are taken together with the intervening atoms to form a 5- to 6-membered heterocycloalkyl, which is optionally substituted with one or more R^{X6a}.

[00330] In some embodiments, each R^{X6a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^aS(=O)_2R^a$, -$NR^aC(=NH)(NR^a)_2$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e.

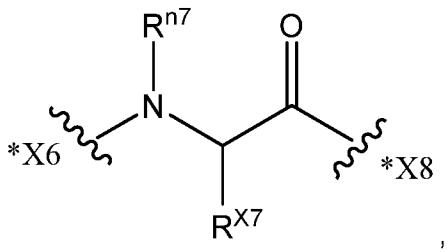
[00331] In some embodiments of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X7 is an amino acid comprising a branched alkyl side chain, a C_{3-5}cycloalkyl side chain, or a 3- to 5- membered heterocycloalkyl side chain, or an N-methylated variant thereof. In some embodiments, the branched alkyl side chain comprises 3-5 carbon atoms. In some embodiments, the alkyl, cycloalkyl, or heterocycloalkyl side chain is

optionally substituted with -O-C_1-C_6 alkyl.

[00332] In some embodiments of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X7 is I, Eva, all, Tme, Sme, Gcpr, Gcpe, Gthp, dMeS, TdMe, or Cbg. In some embodiments of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X7 is I, Eva, all, Tme, Sme, Gcpr, Gcpe, Gthp, dMeS, TdMe, or Cbg, each of which is optionally substituted. In some embodiments, X7 is optionally substituted I. In some embodiments, X7 is optionally substituted Eva. In some embodiments, X7 is optionally substituted all. In some embodiments, X7 is optionally substituted Tme. In some embodiments, X7 is optionally substituted Sme. In some embodiments, X7 is optionally substituted Gcpr. In some embodiments, X7 is optionally substituted Gcpe. In some embodiments, X7 is optionally substituted Gthp. In some embodiments, X7 is optionally substituted dMeS. In some embodiments, X7 is optionally substituted TdMe. In some embodiments, X7 is optionally substituted Cbg.

[00333] In some embodiments of a peptide of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X7 is any amino acid. In some embodiments, X7 is a D-amino acid. In some embodiments, X7 is an L-amino acid. In some embodiments, X7 is an N-alkylated amino acid. In some embodiments, X7 is an N-methylated amino acid. In some embodiments, X7 does not comprise a cyclic group. In some embodiments, X7 comprises a cyclic group. In some embodiments, X7 comprises a 5-6 membered heterocycloalkyl group. In some embodiments, X7 comprises a 5-6 membered heteroaryl group. In some embodiments, X7 comprises a phenyl group. In some embodiments, X7 is a peptoid.

[00334] In some embodiments of a peptide of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X7 has a structure of



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wherein:

R^{n7} is hydrogen or C_{1-3} alkyl ;

R^{X7} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, cycloalkyl, or heterocycloalkyl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X7a};

*X6 represents the point of attachment to X6; and

*X8 represents the point of attachment to X8;

other groups (such as R^a, R^c, R^d, and R^e) have the meanings defined in Formula (I).

[00335] In some embodiments, wherein R^{n7} is hydrogen or methyl; and R^{X7} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, or 5-6 membered heterocycloalkyl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X7a}.

[00336] In some embodiments, R^{n7} is hydrogen. In some embodiments, R^{n7} is C_{1-3} alkyl. In some embodiments, R^{n7} is methyl.

[00337] In some embodiments, R^{X7} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, or 5-6 membered heterocycloalkyl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X7a}. In some embodiments, R^{X7} is C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{3-6}cycloalkyl, or 5-6 membered heterocycloalkyl, wherein each of the alkyl, heteroalkyl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X7a}. In some embodiments, R^{X7} is C_{1-6}alkyl, which is optionally substituted with one or more R^{X7a}. In some embodiments, R^{X7} is C_{1-6}alkyl. In some embodiments, R^{X7} is a branched C_{1-6}alkyl. In some embodiments, R^{X7} is C_{1-6}heteroalkyl, which is optionally substituted with one or more R^{X7a}. In some embodiments, R^{X7} is C_{1-6}heteroalkyl. In some embodiments, R^{X7} is C_{3-6}cycloalkyl, which is optionally substituted with one or more R^{X7a}. In some embodiments, R^{X7} is C_{3-6}cycloalkyl. In some embodiments, R^{X7} is 5-6 membered heterocycloalkyl, which is optionally substituted with one or more R^{X7a}. In some embodiments, R^{X7} is 5-6 membered heterocycloalkyl.

[00338] In some embodiments, each R^{X7a} is independently halogen, -CN, -OR^a, -SR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^a, -OC(=O)R^a, -OC(=O)OR^a, -OC(=O)NR^cR^d, -NR^aC(=O)R^a, -NR^aC(=O)OR^a, -NR^aC(=O)NR^cR^d, -C(=O)NR^cR^d, or =O.

[00339] In some embodiments of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X8 is Y, or a variant thereof comprising a hydroxyphenyl ring, wherein the hydroxyphenyl ring of Y or of the variant is optionally substituted with one or more substituents selected from halogen, -C_{1-3}alkyl, -OH, -C(=O)OH, -O-CH_3, -C_{1-3}alkylene-C(=O)OH, -C_{1-3}alkylene-C(=O)- 5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH, and -C_{1-3}alkylene-NHC(=O)- 5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH. In some embodiments of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X8 is F, or a variant thereof comprising a phenyl, pyridinyl, or indazolyl, wherein the phenyl of F or the phenyl, pyridinyl, or indazolyl of the variant is optionally substituted with one or more substituents each independently selected from halogen, -C_{1-3}alkyl, -OH, -C(=O)OH, -C(=O)NH_2, -NHC(=O)NH_2, -C_{1-3}alkylene-C(NH_2)-COOH, -NH-CO-CH_3, -NH-C_{1-3}alkylene-NH_2, -C(=O)-N(CH_2)$_2$, -S(=O)$_2$-CH_3, -C_{1-3}alkylene-NH-C(=O)- 5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH, and -O-C_{1-3}alkylene-NH-C(=O)- 5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH.

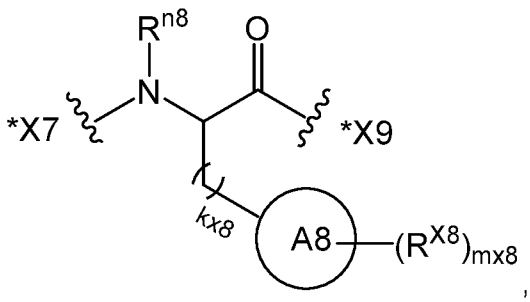
[00340] In some embodiments of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X8 is Y, F4OMe, F4COO, F4Oet, F4u, F4Me, F4CONdMe, F4CON, F4ms, F4CONPEG4Me, F34dOMe, F3OMe, F3C, F3CON, F3CONdMe, 3Py6CON, YaeCOpipzaa, 5Inda, F3aao, F3aa, 3Py6Nhae, 3Py6NHAc, 3Py6OMe, F4aaopipzaa, or F4amCOpipzaa. In some embodiments of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X8 is Y, F4OMe, F4COO, F4Oet, F4u, F4Me, F4CONdMe, F4CON, F4ms, F4CONPEG4Me, F34dOMe, F3OMe, F3C, F3CON, F3CONdMe, 3Py6CON, YaeCOpipzaa, 5Inda, F3aao, F3aa, 3Py6Nhae, 3Py6NHAc, 3Py6OMe, F4aaopipzaa, or F4amCOpipzaa, each of which is optionally substituted. In some embodiments, X8 is optionally substituted Y. In some embodiments, X8 is optionally substituted F4OMe. In some embodiments, X8 is optionally substituted F4COO. In some embodiments, X8 is optionally substituted F4Oet. In some embodiments, X8 is optionally substituted F4u. In some embodiments, X8 is optionally substituted F4Me. In

some embodiments, X8 is optionally substituted F4CONdMe. In some embodiments, X8 is optionally substituted F4CON. In some embodiments, X8 is optionally substituted F4ms. In some embodiments, X8 is optionally substituted F4CONPEG4Me. In some embodiments, X8 is optionally substituted F34dOMe. In some embodiments, X8 is optionally substituted F3OMe. In some embodiments, X8 is optionally substituted F3C. In some embodiments, X8 is optionally substituted F3CON. In some embodiments, X8 is optionally substituted F3CONdMe. In some embodiments, X8 is optionally substituted 3Py6CON. In some embodiments, X8 is optionally substituted YaeCOpipzaa. In some embodiments, X8 is optionally substituted 5Inda. In some embodiments, X8 is optionally substituted F3aao. In some embodiments, X8 is optionally substituted F3aa. In some embodiments, X8 is optionally substituted 3Py6Nhae. In some embodiments, X8 is optionally substituted 3Py6NHAc. In some embodiments, X8 is optionally substituted 3Py6OMe. In some embodiments, X8 is optionally substituted F4aaopipzaa. In some embodiments, X8 is optionally substituted F4amCOpipzaa.

[00341] In some embodiments of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X8 is A, I, L, or V. In some embodiments, X8 is A. In some embodiments, X8 is A or a derivative thereof. In some embodiments, X8 is I or a derivative thereof. In some embodiments, X8 is L or a derivative thereof. In some embodiments, X8 is V or a derivative thereof.

[00342] In some embodiments of a peptide of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X8 is any amino acid. In some embodiments, X8 is a D-amino acid. In some embodiments, X8 is an L-amino acid. In some embodiments, X8 is an aliphatic-amino acid. In some embodiments, X8 is an N-alkylated amino acid. In some embodiments, X8 is an N-methylated amino acid. In some embodiments, X8 does not comprise a cyclic group. In some embodiments, X8 comprises a cyclic group. In some embodiments, X8 comprises a 5-6 membered heterocycloalkyl group. In some embodiments, X8 comprises a 5-6 membered heteroaryl group. In some embodiments, X8 comprises a phenyl group. In some embodiments, X8 is a peptoid.

[00343] In some embodiments of a peptide of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X8 has a structure of



,

wherein,

R^{n8} is hydrogen or C_{1-3}alkyl;

ring A8 is an aryl or heteroaryl;

each R^{X8} is independently halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-SF_5$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2R^cR^d$, $-S(=O)(=NR^a)R^a$, $-N=S(=O)R^cR^d$, $-NR^aS(=O)_2R^a$, amidinyl, $-NR^aC(=NH)NR^cR^d$, $-NR^aS(=O)_2R^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$,

-OC(=O)OR^a, -OC(=O)NR^{c}R^d, -NR^{a}C(=O)R^a, -NR^{a}C(=O)OR^a, -NR^{a}C(=O)NR^{c}R^d, -C(=O)NR^{c}R^d, -P(=O)(OR^c)(OR^d), -P(=O)R^{c}R^d, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -L^{X8}-heterocycloalkyl, -L^{X8}-cycloalkyl, -L^{X8}-aryl, or -L^{X8}-heteroaryl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X8a}; or

two R^{X8} are taken together to form =O, =S, or =N(R^a);

L^{X8} is C_{1-6}alkylene, C_{1-6}heteroalkylene, -O-, -S-, or -NR^a-, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X8a};

kx8 is 0, 1, 2, or 3;

mx8 is 0, 1, 2, 3, 4, or 5;

*X7 represents the point of attachment to X7;

*X9 represents the point of attachment to X9; and

other groups (such as R^a, R^c, R^d, and R^e) have the meanings defined in Formula (I).

[00344] In some embodiments of a peptide of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), wherein

ring A8 is a C_{6-10}aryl or 5-10 membered heteroaryl;

each R^{X8} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halogen, -CN, -NO$_2$, -OR^a, -SR^a, -SF$_5$, -NR^{c}R^d, -S(=O)R^a, -S(=O)$_2$R^a, -S(=O)$_2$R^{c}R^d, -S(=O)(=NR^a)R^a, -N=S(=O) R^{c}R^d, -NR^{a}S(=O)$_2$R^a, amidinyl, -NR^{a}C(=NH)NR^{c}R^d, -NR^{a}S(=O)$_2$R^{c}R^d, -C(=O)R^a, -C(=O)OR^a, -OC(=O)R^a, -OC(=O)OR^a, -OC(=O)NR^{c}R^d, -NR^{a}C(=O)R^a, -NR^{a}C(=O)OR^a, -NR^{a}C(=O)NR^{c}R^d, -C(=O)NR^{c}R^d, -P(=O)(OR^c)(OR^d), -P(=O)R^{c}R^d, C_{6-10}aryl, 5-10 membered heteroaryl, C_{3-6}cycloalkyl, 5-6 membered heterocycloalkyl, -L^{X8}-5-6 membered heterocycloalkyl, -L^{X8}- C_{3-6}cycloalkyl, -L^{X8}- C_{6-10}aryl, or -L^{X8}-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X8a}; or

two R^{X8} are taken together to form =O; and

L^{X8} is C_{1-6}alkylene or C_{1-6}heteroalkylene, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X8a}.

[00345] In some embodiments of a peptide of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), wherein

ring A8 is a phenyl, pyridinyl, indolyl, azaindolyl, indazolyl, or benzimidazolyl;

each R^{X8} is independently halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, -CN, -NO$_2$, -OR^a, -SR^a, -NR^{c}R^d, -S(=O)R^a, -S(=O)$_2$R^a, -S(=O)$_2$NR^{c}R^d , -NR^{a}S(=O)$_2$R^a, -NR^{a}C(=NH)NR^{c}R^d, -NR^{a}S(=O)$_2$NR^{c}R^d , -C(=O)R^a, -C(=O)OR^a, -OC(=O)R^a, -OC(=O)OR^a, -OC(=O)NR^{c}R^d, -NR^{a}C(=O)R^a, -NR^{a}C(=O)OR^a, -NR^{a}C(=O)NR^{c}R^d, -C(=O)NR^{c}R^d, -L^{X5}-piperidinyl, or L^{X5}-piperazinyl, wherein each of the alkyl, heteroalkyl, piperidinyl, and piperazinyl are optionally substituted with one or more R^{X8a}; or

two R^{X5} are taken together to form =O;

kx8 is 1 or 2; and

mx8 is 0, 1, or 2.

[00346] In some embodiments, R^{n8} is hydrogen. In some embodiments, R^{n8} is C_{1-3} alkyl. In some embodiments, R^{n8} is methyl.

[00347] In some embodiments, ring A8 is C_{6-10}aryl. In some embodiments, ring A8 is a phenyl. In some embodiments, ring A8 is naphthyl.

[00348] In some embodiments, ring A8 is 5-10 membered heteroaryl. In some embodiments, ring A8 is 5-6 membered heteroaryl. In some embodiments, ring A8 is monocyclic heteroaryl. In some embodiments, ring A8 is bicyclic heteroaryl. In some embodiments, ring A8 is bicyclic fused heteroaryl. In some embodiments, ring A8 is bicyclic 5-6 or 6-5 fused heteroaryl. In some embodiments, ring A8 is a phenyl, pyridinyl, indolyl, azaindolyl, indazolyl, or benzimidazolyl.

[00349] In some embodiments, each R^{X8} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halogen, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-SF_5$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2R^cR^d$, $-S(=O)(=NR^a)R^a$, $-N=S(=O)R^cR^d$, $-NR^aS(=O)_2R^a$, amidinyl, $-NR^aC(=NH)NR^cR^d$, $-NR^aS(=O)_2R^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, $-P(=O)(OR^c)(OR^d)$, $-P(=O)R^cR^d$, C_{6-10}aryl, 5-10 membered heteroaryl, C_{3-6}cycloalkyl, 5-6 membered heterocycloalkyl, $-L^{X8}$-5-6 membered heterocycloalkyl, $-L^{X8}$-C_{3-6}cycloalkyl, $-L^{X8}$- C_{6-10}aryl, or $-L^{X8}$-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X8a}.

[00350] In some embodiments, each R^{X8} is independently halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^aS(=O)_2R^a$, $-NR^aC(=NH)NR^cR^d$, $-NR^aS(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, or $-L^{X8}$-5-6 membered heterocycloalkyl (e.g., $-L^{X8}$-piperidinyl or L^{X8}-piperazinyl), wherein each of the alkyl, heteroalkyl, heterocycloalkyl (e.g., piperidinyl, and piperazinyl) are optionally substituted with one or more R^{X8a}.

[00351] In some embodiments, R^{X8} are taken together to form an oxo.

[00352] In some embodiments, L^{X8} is C_{1-6}alkylene, which is optionally substituted with one or more R^{X8a}. In some embodiments, L^{X8} is C_{1-6}heteroalkylene, which is optionally substituted with one or more R^{X8a}. In some embodiments, L^{X8} is -O-. In some embodiments, L^{X8} is -S-. In some embodiments, L^{X8} is $-NR^a$-.

[00353] In some embodiments, kx8 is 0. In some embodiments, kx8 is 1. In some embodiments, kx8 is 2. In some embodiments, kx8 is or 3.

[00354] In some embodiments, mx8 is 0. In some embodiments, mx8 is 1. In some embodiments, mx8 is 2. In some embodiments, mx8 is 3. In some embodiments, mx8 is 4. In some embodiments, mx8 is 5.

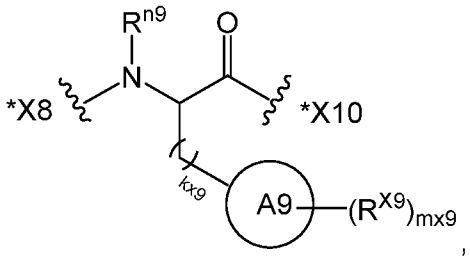
[00355] In some embodiments of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X9 is an N-methyl aromatic amino acid, optionally a bicyclic aromatic amino acid. In some embodiments, X9 is N-methyl amino acid comprising a phenyl or monocyclic heteroaryl, each of which is optionally substituted. In some embodiments, X9 is N-methyl amino acid comprising a naphthalyl or bicyclic heteroaryl, each of which is optionally substituted. In some embodiments, the bicyclic heteroaryl is a 5-6, 6-6, or 6-5 fused heteroaryl. In some embodiments, the heteroaryl comprise 1-3 ring nitrogen atoms. In some embodiments, the heteroaryl comprise 1-

2 ring nitrogen atoms. In some embodiments, the heteroaryl comprise 1 ring nitrogen atom. In some embodiments, the N-methyl aromatic amino acid is N-methyl monocyclic aromatic amino acid comprising a phenyl or pyridinyl optionally substituted with one or more substituents each independently selected from halogen, -C_{1-3}alkyl, and trifluoromethyl. In some embodiments, the N-methyl aromatic amino acid is N-methyl bicyclic aromatic amino acid comprising a naphthalyl, quinolyl, or indazolyl optionally substituted with one or more substituents each independently selected from H or C_{1-3}alkyl.

[00356] In some embodiments of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X9 is MeNal2, MeNal27N, MeF34diox, MeF34dOMe, MeF4T, MeW1Me, MeW7N, MeF3C4Me, or MeF3Me4C. In some embodiments of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X9 is MeNal2, MeNal27N, MeF34diox, MeF34dOMe, MeF4T, MeW1Me, MeW7N, MeF3C4Me, or MeF3Me4C, each of which is optionally substituted. In some embodiments, X9 is optionally substituted MeNal2. In some embodiments, X9 is optionally substituted MeNal27N. In some embodiments, X9 is optionally substituted MeF34diox. In some embodiments, X9 is optionally substituted MeF34dOMe. In some embodiments, X9 is optionally substituted MeF4T. In some embodiments, X9 is optionally substituted MeW1Me. In some embodiments, X9 is optionally substituted MeW7N. In some embodiments, X9 is optionally substituted MeF3C4Me. In some embodiments, X9 is optionally substituted MeF3Me4C.

[00357] In some embodiments of a peptide of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X9 is a D-amino acid. In some embodiments of a peptide of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X9 is an L-amino acid. In some embodiments, X9 is an N-alkylated amino acid. In some embodiments, X9 is an N-methylated amino acid. In some embodiments, X9 comprises a cyclic group. In some embodiments, X9 comprises a 5-6 membered heterocycloalkyl group. In some embodiments, X9 comprises a 5-6 membered heteroaryl group. In some embodiments, X9 comprises a bicyclic heteroaryl group. In some embodiments, X9 comprises a phenyl group. In some embodiments, X9 is a peptoid.

[00358] In some embodiments of a peptide of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X9 has a structure of



,

wherein:

R^{n9} is hydrogen or C_{1-3} alkyl ;

ring A9 is an aryl or heteroaryl;

each R^{X9} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halogen, -CN, -NO_2, -OR^a, -SR^a, -SF_5, or -NR^cR^d, wherein each of the alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^{X9a}; or

two R^{X9} are taken together to form =O, =S, or =N(R^a);

kx9 is 0, 1, 2, or 3;

mx9 is 0, 1, 2, 3, 4, or 5;

*X8 represents the point of attachment to X8;

*X10 represents the point of attachment to X10; and

other groups (such as R^a, R^c, R^d, and R^e) have the meanings defined in Formula (I).

[00359] In some embodiments of a peptide of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), wherein

R^{n9} is hydrogen or methyl;

ring A9 is a C_{6-10}aryl or 5-10 membered heteroaryl; and

each R^{X9} is independently halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, -CN, -NO_2, -OR^a, -SR^a, -SF_5, or -NR^cR^d, wherein each of the alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^{X9a}; or

two R^{X9} are taken together to form =O.

[00360] In some embodiments of a peptide of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), wherein

ring A9 is a phenyl, naphthyl, pyridinyl, indolyl, azaindolyl, indazolyl, benzimidazolyl, or isoquinolinyl;

each R^{X9} is independently halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, -CN, -OR^a, -SR^a, or -NR^cR^d, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^{X9a};

kx9 is 1 or 2; and

mx9 is 0, 1, or 2.

[00361] In some embodiments, R^{n9} is hydrogen. In some embodiments, R^{n9} is C_{1-3} alkyl. In some embodiments, R^{n9} is methyl.

[00362] In some embodiments, ring A9 is C_{6-10}aryl. In some embodiments, ring A9 is 5-10 membered heteroaryl. In some embodiments, ring A9 is monocyclic heteroaryl. In some embodiments, ring A9 is bicyclic heteroaryl. In some embodiments, ring A9 is bicyclic 6-6 fused heteroaryl. In some embodiments, ring A9 is bicyclic 6-5 or 5-6 fused heteroaryl. In some embodiments, ring A9 is phenyl, naphthyl, pyridinyl, indolyl, azaindolyl, indazolyl, benzimidazolyl, or isoquinolinyl.

[00363] In some embodiments, each R^{X9a} is independently halogen, C_{1-6}alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^aS(=O)_2R^a$, -$NR^aC(=NH)(NR^a)_2$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e. In some embodiments, each R^{X9} is independently halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, -CN, -OR^a, -SR^a, or -NR^cR^d, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^{X9a}.

[00364] In some embodiments, kx9 is 0. In some embodiments, kx9 is 1. In some embodiments, kx9 is 2. In some embodiments, kx9 is 3.

[00365] In some embodiments, mx9 is 0. In some embodiments, mx9 is 1. In some embodiments, mx9 is 2. In some embodiments, mx9 is 3. In some embodiments, mx9 is 4. In some embodiments, mx9 is 5.

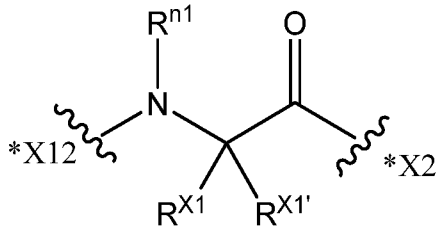
[00366] In some embodiments of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X10 is G. In some embodiments, X10 is a D-amino acid (e.g., da, ds, de, or dp). In some embodiments, X10 is a D amino acid selected from da, ds, de, and dp. In some embodiments, X10 is da.

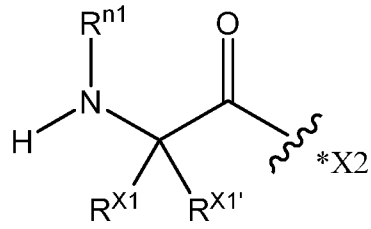
[00367] In some embodiments of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X11 is F or a variant thereof, or an amino acid comprising -C_{1-6}alkylene-phenyl. In some embodiments, the F or the variant thereof is F, or a variant thereof comprising a phenyl or heteroaryl (e.g, monocyclic or bicyclic), each of which is optionally substituted. In some embodiments, the F or the variant thereof is F, or a variant thereof comprising a phenyl, or pyridinyl, optionally substituted with one or more substituents each independently selected from phenyl, -O-phenyl, -O-C_{1-3}alkylene-phenyl, pyridinyl, imidazolyl, pyrazolyl, N-C_{1-3}alkylene pyrazolyl, N-C_{1-3}alkylene(-O-C_{1-3}alkyl) pyrazolyl, pyranyl, tetrahydropyranyl, piperidinyl, N-C_{1-3}alkylene-C(=O)-piperidinyl.

[00368] In some embodiments of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X11 is Bph, 3Py6Ph, F41Me4Pyz, F43Pyz, F44Pyz, F41Pyz, F41Me3Pyz, F41Et4Pyz, F41MeOe4Pyz, F41MeOp4Pyz, F44thp, F4Ac4pip, PhNva, PhNle, Yph, Ybn, F4tb, F4oPr, or F4CONdMe. In some embodiments of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X11 is Bph, 3Py6Ph, F41Me4Pyz, F43Pyz, F44Pyz, F41Pyz, F41Me3Pyz, F41Et4Pyz, F41MeOe4Pyz, F41MeOp4Pyz, F44thp, F4Ac4pip, PhNva, PhNle, Yph, Ybn, F4tb, F4oPr, or F4CONdMe, each of which is optionally substuted. In some embodiments, X11 is optionally substuted Bph. In some embodiments, X11 is optionally substuted 3Py6Ph. In some embodiments, X11 is optionally substuted F41Me4Pyz. In some embodiments, X11 is optionally substuted F43Pyz. In some embodiments, X11 is optionally substuted F44Pyz. In some embodiments, X11 is optionally substuted F41Pyz. In some embodiments, X11 is optionally substuted F41Me3Pyz. In some embodiments, X11 is optionally substuted F41Et4Pyz. In some embodiments, X11 is optionally substuted F41MeOe4Pyz. In some embodiments, X11 is optionally substuted F41MeOp4Pyz. In some embodiments, X11 is optionally substuted F44thp. In some embodiments, X11 is optionally substuted F4Ac4pip. In some embodiments, X11 is optionally substuted PhNva. In some embodiments, X11 is optionally substuted PhNle. In some embodiments, X11 is optionally substuted Yph. In some embodiments, X11 is optionally substuted Ybn. In some embodiments, X11 is optionally substuted F4tb. In some embodiments, X11 is optionally substuted F4oPr. In some embodiments, X11 is optionally substuted F4CONdMe.

[00369] In some embodiments of a peptide of Formula (I), (I-1), (I-2), (I-3), (I-4), (I-5), (III-1), (III-2), (IV-1), or (IV-2), X11 is any amino acid. In some embodiments, X11 is a D-amino acid. In some embodiments, X11 is an L-amino acid. In some embodiments, X11 is an N-alkylated amino acid. In some embodiments, X11 is an N-methylated amino acid. In some embodiments, X11 comprises a cyclic group. In some embodiments, X11 comprises a 5-6 membered heterocycloalkyl group. In some embodiments, X11 comprises a 5-6 membered heteroaryl group. In some embodiments, X11 comprises a bicyclic heteroaryl group. In some embodiments, X11 comprises a phenyl group. In some embodiments, X11 is a peptoid.

[00370] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, X1 is



or


, wherein:

R^{n1} is hydrogen or C_{1-3} alkyl;

R^{X1} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -L^{X1}-heterocycloalkyl, -L^{X1}-cycloalkyl, -L^{X1}-aryl, or -L^{X1}-heteroaryl, wherein each of the alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X1a};

$R^{X1'}$ is hydrogen or C_{1-6}alkyl, wherein the alkyl is optionally substituted with one or more R^{X1a}; or

R^{n1} and $R^{X1'}$ are taken together with the intervening atoms to form a 5- to 6- membered heterocycloalkyl, which is optionally substituted with one or more R^{X1a};

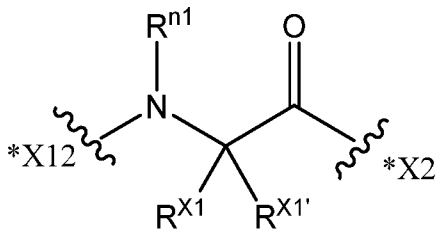
L^{X1} is C_{1-6}alkylene, C_{1-6}heteroalkylene, -O-, -S-, or -NR^a-, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X1a};

each R^{X1a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -S(=O)R^a, -$S(=O)_2R^a$, -SF_5, -$S(=O)_2NR^cR^d$, -S(=O)(=NR^a)R^a, -N=S(=O)R^cR^d, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)(NR^a)_2$, -$NR^aS(=O)_2NR^cR^d$, -C(=O)R^a, -C(=O)OR^a, -OC(=O)R^a, -OC(=O)OR^a, -OC(=O)NR^cR^d, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -C(=O)NR^cR^d, -P(=O)(OR^c)(OR^d), -P(=O)R^cR^d, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O, =S, or =N(R^a), wherein each of the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e;

*X12 represents the point of attachment to X12; and

*X2 represents the point of attachment to X2, and the remaining variables are as described above.

[00371] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof,

X1 is 

, wherein:

R^{n1} is hydrogen or methyl;

R^{X1} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, -L^{X1}-5-6 membered heterocycloalkyl, -L^{X1}-C_{4-6}cycloalkyl, -L^{X1}-C_{6-10}aryl, or -L^{X1}-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X1a};

$R^{X1'}$ is hydrogen or methyl; or

R^{n1} and $R^{X1'}$ are taken together with the intervening atoms to form a 5- to 6- membered heterocycloalkyl, which is optionally substituted with one or more R^{X1a};

L^{X1} is C_{1-6}alkylene or C_{1-6}heteroalkylene, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X1a};

each R^{X1a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -SF_5, -$S(=O)_2NR^cR^d$, -$S(=O)(=NR^a)R^a$, -$N=S(=O)R^cR^d$, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)(NR^a)_2$, -$NR^aS(=O)_2NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, -$P(=O)(OR^c)(OR^d)$, -$P(=O)R^cR^d$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O, =S, or =$N(R^a)$, wherein each of the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e;

*X12 represents the point of attachment to X12; and

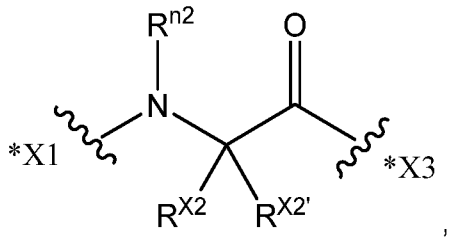
*X2 represents the point of attachment to X2, and the remaining variables are as described above.

[00372] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, R^{X1} is hydrogen, C_{1-6}alkyl, C_{1-6}heteroalkyl, -L^{X1}-piperidinyl, -L^{X1}-piperazinyl, -L^{X1}-phenyl, or -L^{X1}-pyridinyl, wherein each of the alkyl, heteroalkyl, phenyl, pyridinyl, piperidinyl, and piperazinyl is optionally substituted with one or more R^{X1a}, and the remaining variables are as described above.

[00373] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, each R^{X1a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^aS(=O)_2R^a$, -$NR^aC(=NH)(NR^a)_2$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e, and the remaining variables are as described above.

[00374] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, X2 is an N-alkylated amino acid, and the remaining variables are as described above.

[00375] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, X2 is



,

wherein,

R^{n2} is hydrogen or C_{1-3} alkyl, wherein the alkyl is optionally substituted with one or more R^{X2a};

R^{X2} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -L^{X2}-heterocycloalkyl, -L^{X2}-cycloalkyl, -L^{X2}-aryl, or -L^{X2}-heteroaryl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X2a};

$R^{X2'}$ is hydrogen or C_{1-6}alkyl, wherein the alkyl is optionally substituted with one or more R^{X2a}; or

R^{n2} and $R^{X2'}$ are taken together with the intervening atoms to form a 5- to 6- membered heterocycloalkyl, which is optionally substituted with one or more R^{X2a};

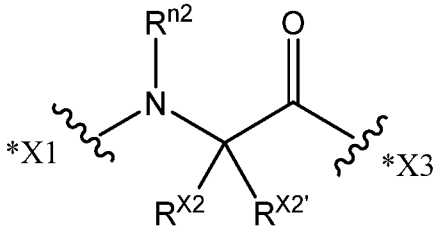
L^{X2} is C_{1-6}alkylene, C_{1-6}heteroalkylene, -O-, -S-, or -NR^a-, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X2a};

each R^{X2a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -SF_5, -$S(=O)_2NR^cR^d$, -$S(=O)(=NR^a)R^a$, -$N=S(=O)R^cR^d$, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)(NR^a)_2$, -$NR^aS(=O)_2NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, -$P(=O)(OR^c)(OR^d)$, -$P(=O)R^cR^d$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O, =S, =$N(R^a)$, aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein each of the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e;

*X1 represents the point of attachment to X1; and

*X3 represents the point of attachment to X3, and the remaining variables are as described above.

[00376] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof,

X2 is 

,

wherein:

R^{n2} is hydrogen or methyl;

R^{X2} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, -L^{X2}-5-6 membered heterocycloalkyl, -L^{X2}-C_{4-6}cycloalkyl, -L^{X2}-C_{6-10}aryl, or -L^{X2}-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X2a};

$R^{X2'}$ is hydrogen or methyl; or

R^{n2} and $R^{X2'}$ are taken together with the intervening atoms to form a 5- to 6- membered heterocycloalkyl, which is optionally substituted with one or more R^{X2a};

L^{X2} is C_{1-6}alkylene or C_{1-6}heteroalkylene, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X2a};

each R^{X2a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -SF_5, -$S(=O)_2NR^cR^d$, -$S(=O)(=NR^a)R^a$, -$N=S(=O)R^cR^d$, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)(NR^a)_2$, -$NR^aS(=O)_2NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, -$P(=O)(OR^c)(OR^d)$, -$P(=O)R^cR^d$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O,

=S, or =N(R^a), wherein each of the alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e;

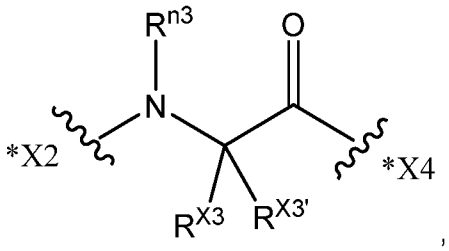
*X1 represents the point of attachment to X1; and

*X3 represents the point of attachment to X3, and the remaining variables are as described above.

[00377] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, R^{X2} is hydrogen, C_{1-6}alkyl, C_{1-6}heteroalkyl, -L^{X2}-piperidinyl, L^{X2}-piperazinyl, -L^{X2}-phenyl, or -L^{X2}-pyridinyl, wherein each of the alkyl, heteroalkyl, phenyl, pyridinyl, piperidinyl, and piperazinyl is optionally substituted with one or more R^{X2a}, and the remaining variables are as described above.

[00378] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, R^{X2a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -S(=O)R^a, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^aS(=O)_2R^a$, -$NR^aC(=NH)(NR^a)_2$, -C(=O)R^a, -C(=O)OR^a, -OC(=O)R^a, -OC(=O)OR^a, -OC(=O)NR^cR^d, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -C(=O)NR^cR^d, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e, and the remaining variables are as described above.

[00379] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof,

X3 is 

,

wherein:

R^{n3} is hydrogen or C_{1-3}alkyl, wherein the alkyl is optionally substituted with one or more R^{X3a};

R^{X3} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -L^{X3}-heterocycloalkyl, -L^{X3}-cycloalkyl, -L^{X3}-aryl, or -L^{X3}-heteroaryl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X3a};

$R^{X3'}$ is hydrogen or C_{1-6}alkyl, wherein the alkyl is optionally substituted with one or more R^{X3a}; or

R^{n3} and $R^{X3'}$ are taken together with the intervening atoms to form a 5- to 6- membered heterocycloalkyl, which is optionally substituted with one or more R^{X3a};

L^{X3} is C_{1-6}alkylene, C_{1-6}heteroalkylene, -O-, -S-, or -NR^a-, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X3a};

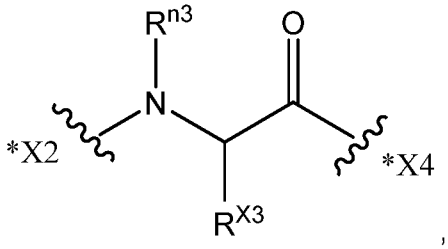
each R^{X3a} is independently halogen, C_{1-6}alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -S(=O)R^a, -$S(=O)_2R^a$, -SF_5, -$S(=O)_2NR^cR^d$, -S(=O)(=NR^a)R^a, -N=S(=O)R^cR^d, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)(NR^a)_2$, -$NR^aS(=O)_2NR^cR^d$, -C(=O)R^a, -C(=O)OR^a, -OC(=O)R^a, -OC(=O)OR^a, -OC(=O)NR^cR^d, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -C(=O)NR^cR^d, -P(=O)(OR^c)(OR^d), -P(=O)R^cR^d, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O,

=S, or =N(R^a), wherein each of the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e;

*X2 represents the point of attachment to X2; and

*X4 represents the point of attachment to X4, and the remaining variables are as described above.

[00380] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof,



X3 is ,

wherein:

R^{n3} is hydrogen or methyl;

R^{X3} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, -L^{X3}-5-6 membered heterocycloalkyl, -L^{X3}-C_{3-6}cycloalkyl, -L^{X3}-C_{6-10}aryl, or -L^{X3}-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X3a};

L^{X3} is C_{1-6}alkylene or C_{1-6}heteroalkylene, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X3a};

each R^{X3a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -S(=O)R^a, -$S(=O)_2R^a$, -SF_5, -$S(=O)_2NR^cR^d$, -S(=O)(=NR^a)R^a, -N=S(=O)R^cR^d, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)(NR^a)_2$, -$NR^aS(=O)_2NR^cR^d$, -C(=O)R^a, -C(=O)OR^a, -OC(=O)R^a, -OC(=O)OR^a, -OC(=O)NR^cR^d, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -C(=O)NR^cR^d, -P(=O)(OR^c)(OR^d), -P(=O)R^cR^d, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O, =S, or =N(R^a), wherein each of the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e;

*X2 represents the point of attachment to X2; and

*X4 represents the point of attachment to X4, and the remaining variables are as described above.

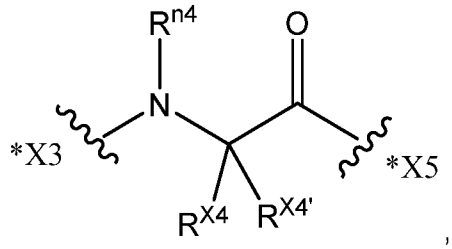
[00381] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, R^{X3} is C_{1-6}alkyl, C_{1-6}heteroalkyl, -L^{X3}-piperidinyl, L^{X3}-piperazinyl, -L^{X3}-phenyl, or -L^{X3}-pyridinyl, wherein each of the alkyl, heteroalkyl, phenyl, pyridinyl, piperidinyl, and piperazinyl is optionally substituted with one or more R^{X2a}, and the remaining variables are as described above.

[00382] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, R^{X3a} is independently halogen, C_{1-6}alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -S(=O)R^a, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^aS(=O)_2R^a$, -$NR^aC(=NH)(NR^a)_2$, -C(=O)R^a, -C(=O)OR^a, -OC(=O)R^a, -OC(=O)OR^a, -OC(=O)NR^cR^d, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -C(=O)NR^cR^d, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e, and

the remaining variables are as described above.

[00383] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, X4 is an N-alkylated amino acid, and the remaining variables are as described above.

[00384] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, X4 is a peptoid, and the remaining variables are as described above.

[00385] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, X4 is  ,

wherein:

R^{n4} is hydrogen or C_{1-3} alkyl, wherein the alkyl is optionally substituted with one or more R^{X4a};

R^{X4} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -L^{X4}-heterocycloalkyl, -L^{X4}-cycloalkyl, -L^{X4}-aryl, or -L^{X4}-heteroaryl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X4a};

$R^{X4'}$ is hydrogen or C_{1-6}alkyl, wherein the alkyl is optionally substituted with one or more R^{X4a}; or

R^{n4} and $R^{X4'}$ are taken together with the intervening atoms to form a 5- to 6- membered heterocycloalkyl, which is optionally substituted with one or more R^{X4a};

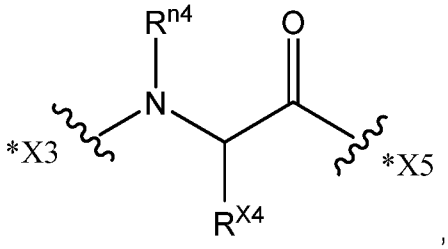
L^{X4} is C_{1-6}alkylene or C_{1-6}heteroalkylene, -O-, -S-, or -NR^a-, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X4a};

each R^{X4a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -S(=O)R^a, -$S(=O)_2R^a$, -SF_5, -$S(=O)_2NR^cR^d$, -S(=O)(=NR^a)R^a, -N=S(=O)R^cR^d, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)(NR^a)_2$, -$NR^aS(=O)_2NR^cR^d$, -C(=O)R^a, -C(=O)OR^a, -OC(=O)R^a, -OC(=O)OR^a, -OC(=O)NR^cR^d, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -C(=O)NR^cR^d, -P(=O)(OR^c)(OR^d), -P(=O)R^cR^d, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O, =S, or =N(R^a), wherein each of the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e;

*X3 represents the point of attachment to X3; and

*X5 represents the point of attachment to X5, and the remaining variables are as described above.

[00386] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof,

X4 is 

,

wherein:

R^{n4} is hydrogen or C_{1-3} alkyl, wherein the alkyl is optionally substituted with one or more R^{X4a};

R^{X4} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, -L^{X4}-5-6 membered heterocycloalkyl, -L^{X4}-C_{3-6}cycloalkyl, -L^{X4}-C_{6-10}aryl, or -L^{X4}-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X4a};

L^{X4} is C_{1-6}alkylene or C_{1-6}heteroalkylene, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X4a};

each R^{X4a} is independently halogen, C_{1-6}alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -SF_5, -$S(=O)_2NR^cR^d$, -$S(=O)(=NR^a)R^a$, -$N=S(=O)R^cR^d$, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)(NR^a)_2$, -$NR^aS(=O)_2NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, -$P(=O)(OR^c)(OR^d)$, -$P(=O)R^cR^d$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O, =S, or =$N(R^a)$, wherein each of the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e;

*X3 represents the point of attachment to X3; and

*X5 represents the point of attachment to X5, and the remaining variables are as described above.

[00387] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, R^{X4} is C_{1-6}alkyl, C_{1-6}heteroalkyl, -L^{X4}-piperidinyl, L^{X4}-piperazinyl, -L^{X4}-phenyl, or -L^{X4}-pyridinyl, wherein each of the alkyl, heteroalkyl, phenyl, pyridinyl, piperidinyl, and piperazinyl is optionally substituted with one or more R^{X4a}, and the remaining variables are as described above.

[00388] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, each R^{X4a} is independently halogen, C_{1-6}alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^aS(=O)_2R^a$, -$NR^aC(=NH)(NR^a)_2$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e, and the remaining variables are as described above.

[00389] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, R^{n5} is hydrogen or methyl; ring A5 is a C_{6-10}aryl, 5-10 membered heteroaryl, C_{6-10}cycloalkyl, or 5-10 membered heterocycloalkyl; each R^{X5} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halogen, -CN, -NO_2, -OR^a, -SR^a, -SF_5, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -

$S(=O)_2NR^cR^d$, $-S(=O)(=NR^a)R^a$, $-N=S(=O)NR^cR^d$, $-NR^aS(=O)_2R^a$, amidinyl, $-NR^aC(=NH)NR^cR^d$, $-NR^aS(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, $-P(=O)(OR^c)(OR^d)$, $-P(=O)R^cR^d$, C_{6-10}aryl, 5-10 membered heteroaryl, C_{3-6}cycloalkyl, 5-6 membered heterocycloalkyl, $-L^{X5}$-5-6 membered heterocycloalkyl, $-L^{X5}$-C_{3-6}cycloalkyl, $-L^{X5}$-C_{6-10}aryl, or $-L^{X5}$-5-10 membered heteroaryl, wherein the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl are optionally substituted with one or more R^{X5a}; or two R^{X5} are taken together to form =O; and L^{X5} is C_{1-6}alkylene or C_{1-6}heteroalkylene, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X5a}, and the remaining variables are as described above.

[00390] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, ring A5 is a phenyl, naphthyl, pyridinyl, cyclohexyl, piperidinyl, piperazinyl, morpholinyl, or tetrahydropyranyl; each R^{X5} is independently halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^aS(=O)_2R^a$, $-NR^aC(=NH)NR^cR^d$, $-NR^aS(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, $-L^{X5}$-piperidinyl, or L^{X5}-piperazinyl, wherein each of the alkyl, heteroalkyl, piperidinyl, and piperazinyl are optionally substituted with one or more R^{X5a}; or two R^{X5} are taken together to form =O; kx5 is 1 or 2; and mx5 is 0, 1, or 2, and the remaining variables are as described above.

[00391] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, each R^{X5a} is independently halogen, C_{1-6}alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^aS(=O)_2R^a$, $-NR^aC(=NH)(NR^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e, and the remaining variables are as described above.

[00392] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, R^{n6} is hydrogen or methyl; R^{X6} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{6-10}aryl, 5-10 membered heteroaryl, C_{3-6}cycloalkyl, 5-6 membered heterocycloalkyl, $-L^{X6}$-5-6 membered heterocycloalkyl, $-L^{X6}$-C_{3-6}cycloalkyl, $-L^{X6}$-C_{6-10}aryl, or $-L^{X6}$-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X6a}; and L^{X6} is C_{1-6}alkylene or C_{1-6}heteroalkylene, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X6a}, and the remaining variables are as described above.

[00393] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, R^{X6} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{3-6}cycloalkyl, 5-6 membered heterocycloalkyl, $-L^{X6}$-5-6 membered heterocycloalkyl, $-L^{X6}$- C_{3-6}cycloalkyl, $-L^{X6}$-phenyl or $-L^{X6}$-6 membered heteroaryl, wherein each of the alkyl, heteroalkyl, phenyl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X6a}, and the remaining variables are as described above.

[00394] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, R^{X6a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^aS(=O)_2R^a$, $-NR^aC(=NH)(NR^a)_2$, $-C(=O)R^a$, -

$C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e, and the remaining variables are as described above.

[00395] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, R^{n7} is hydrogen or methyl; and R^{X7} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, or 5-6 membered heterocycloalkyl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X7a}, and the remaining variables are as described above.

[00396] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, R^{X7} is C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{3-6}cycloalkyl, or 5-6 membered heterocycloalkyl, wherein each of the alkyl, heteroalkyl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X7a}, and the remaining variables are as described above.

[00397] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, each R^{X7a} is independently halogen, -CN, $-OR^a$, $-SR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, or =O, and the remaining variables are as described above.

[00398] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, ring A8 is a C_{6-10}aryl or 5-10 membered heteroaryl; each R^{X8} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halogen, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-SF_5$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2R^cR^d$, $-S(=O)(=NR^a)R^a$, $-N=S(=O)\ R^cR^d$, $-NR^aS(=O)_2R^a$, amidinyl, $-NR^aC(=NH)NR^cR^d$, $-NR^aS(=O)_2R^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, $-P(=O)(OR^c)(OR^d)$, $-P(=O)R^cR^d$, C_{6-10}aryl, 5-10 membered heteroaryl, C_{3-6}cycloalkyl, 5-6 membered heterocycloalkyl, $-L^{X8}$-5-6 membered heterocycloalkyl, $-L^{X8}$- C_{3-6}cycloalkyl, $-L^{X8}$- C_{6-10}aryl, or $-L^{X8}$-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X8a}; or two R^{X8} are taken together to form =O; and L^{X8} is C_{1-6}alkylene or C_{1-6}heteroalkylene, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X8a}, and the remaining variables are as described above.

[00399] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, ring A8 is a phenyl, pyridinyl, indolyl, azaindolyl, indazolyl, or benzimidazolyl; each R^{X8} is independently halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^aS(=O)_2R^a$, $-NR^aC(=NH)NR^cR^d$, $-NR^aS(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, $-L^{X8}$-piperidinyl, or L^{X8}-piperazinyl, wherein each of the alkyl, heteroalkyl, piperidinyl, and piperazinyl are optionally substituted with one or more R^{X8a}; or two R^{X5} are taken together to form =O; kx8 is 1 or 2; and mx8 is 0, 1, or 2, and the remaining variables are as described above.

[00400] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, each R^{X8a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-

C_6heteroalkyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^aS(=O)_2R^a$, -$NR^aC(=NH)(NR^a)_2$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e, and the remaining variables are as described above.

[00401] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, R^{n9} is hydrogen or methyl; ring A9 is a C_{6-10}aryl or 5-10 membered heteroaryl; and each R^{X9} is independently halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, -CN, -NO_2, -OR^a, -SR^a, -SF_5, or -NR^cR^d, wherein each of the alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^{X9a}; or two R^{X9} are taken together to form =O, and the remaining variables are as described above.

[00402] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, ring A9 is a phenyl, naphthyl, pyridinyl, indolyl, azaindolyl, indazolyl, benzimidazolyl, or isoquinolinyl; each R^{X9} is independently halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, -CN, -OR^a, -SR^a, or -NR^cR^d, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^{X9a}; kx9 is 1 or 2; and mx9 is 0, 1, or 2, and the remaining variables are as described above.

[00403] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, each R^{X9a} is independently halogen, C_{1-6}alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^aS(=O)_2R^a$, -$NR^aC(=NH)(NR^a)_2$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e, and the remaining variables are as described above.

[00404] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, ring A11 is a C_{6-10}aryl or 5-10 membered heteroaryl; each R^{X11} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, halogen, -CN, -NO_2, -OR^a, -SR^a, -SF_5, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2R^cR^d$, -$S(=O)(=NR^a)R^a$, -$N=S(=O)R^cR^d$, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)NR^cR^d$, -$NR^aS(=O)_2R^cR^d$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, -$P(=O)(OR^c)(OR^d)$, -$P(=O)R^cR^d$, C_{6-10}aryl, 5-10 membered heteroaryl, C_{3-6}cycloalkyl, 5-6 membered heterocycloalkyl, -L^{X11}-5-6 membered heterocycloalkyl, -L^{X11}- C_{3-6}cycloalkyl, -L^{X11}- C_{6-10}aryl, or -L^{X11}-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X11a}; or two R^{X11} are taken together to form =O; and L^{X11} is C_{1-6}alkylene, C_{1-6}heteroalkylene, or -O-, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X11a}, and the remaining variables are as described above.

[00405] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, ring A11 is a phenyl or pyridinyl; each R^{X11} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, halogen, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2R^cR^d$, -$NR^aS(=O)_2R^a$, -$NR^aC(=NH)NR^cR^d$, -$NR^aS(=O)_2R^cR^d$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, C_{6-10}aryl, 5-10 membered heteroaryl, C_{3-6}cycloalkyl, 5-6 membered heterocycloalkyl, -L^{X11}-5-6 membered heterocycloalkyl, -L^{X11}- C_{3-6}cycloalkyl, -L^{X11}- C_{6-}

$_{10}$aryl, or -L^{X11}-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X11a}; or two R^{X11} are taken together to form =O; kx11 is 1, 2, 3, or 4; and mx11 is 0, 1, or 2, and the remaining variables are as described above.

[00406] In one embodiment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, each R^{X11} is independently phenyl, pyridinyl, pyrrolyl, pyrazolyl, imidazolyl, cyclohexyl, piperidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, -L^{X11}-5-6 membered heterocycloalkyl, - -L^{X11}-phenyl, or -L^{X11}-pyridinyl, wherein each of the phenyl, pyridinyl, pyrrolyl, pyrazolyl, imidazolyl, cyclohexyl, piperidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, and heterocycloalkyl is optionally substituted with one or more R^{X11a}, and the remaining variables are as described above.

[00407] In one embodment, for the peptide of Formula (I), or a pharmaceutically acceptable salt thereof, each R^{X11a} is independently halogen, C_{1-6}alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^aS(=O)_2R^a$, -$NR^aC(=NH)(NR^a)_2$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e, and the remaining variables are as described above.

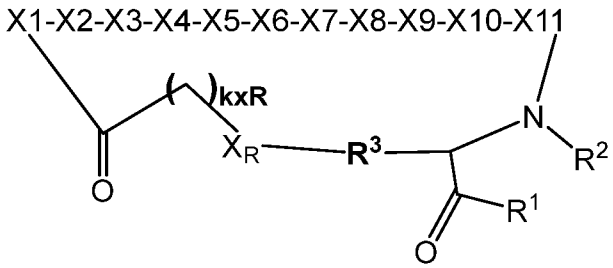
[00408] In some embodiments, the peptide or the pharmaceutically acceptable salt thereof has a cyclic structure.

[00409] In some embodiments, the peptide or the pharmaceutically acceptable salt thereof has a cyclic structure, wherein the first amino acid (or X1) is covalently linked to the last amino acid (or X12).

[00410] In some embodiments, the peptide or the pharmaceutically acceptable salt thereof has a cyclic structure having an amino acid in the first residue X1 and a N-methylated cysteine residue, and wherein the amino acid in X1 and the N-methylated cysteine residue or variant thereof form a covalent bond.

[00411] In some embodiments, the peptide has a monocyclic structure. In some embodiments, the monocyclic structure is formed by a covalent bond between the amino acid X1 and a cysteine or a variant thereof.

[00412] In one embodiment, the peptide of SEQ ID NO: 1 or Formula (I, or a pharmaceutically acceptable salt thereof, has a structure of Formula (I-1),



Formula (I-1),

wherein,

R^1 is selected from the group consisting of -NH_2 and -OH;

R^2 is C_{1-3} alkyl;

R^3 is C_{1-3} alkylene, optionally substituted with one or more R^4, wherein;

each R^4 is independently C_{1-3} alkyl or C_{3-6} cycloalkyl,;

kxR is 1, 2, 3, 4, 5, or 6;

X_R is selected from the group consisting of S, C or O, and the remaining variables are as described above.

[00413] In some embodiments, the peptide or the pharmaceutically acceptable salt thereof comprises a sequence with up to 1, 2, 3, 4, or 5 substitutions by a conserved variant compared to any one of the sequences selected from SEQ ID NOs: 1-72.

[00414] In some embodiments, the peptide or the pharmaceutically acceptable salt thereof consists of an amino acid sequence selected from SEQ ID NOs: 1-72.

[00415] In some embodiments, the peptide or the pharmaceutically acceptable salt thereof has a binding affinity to a human GPC3 of at most 100 nM as determined by Kd in surface plasmon resonance (SPR) analysis.

[00416] In one aspect, the peptide of any of the embodiments described above, or a pharmaceutically acceptable salt thereof, is covalently linked to a linker that is capable of connecting the peptide to a payload molecule.

[00417] In some embodiments, the linker is attached to a lysine of the peptide.

[00418] In some embodiments, the linker is attached to the peptide via the N terminus of the peptide. In other embodiments, the linker is attached to the peptide via the C terminus of the peptide. In other embodiments, the linker is attached to the peptide via a non-terminal amino acid residue of the peptide.

[00419] In some embodiments, the linker is attached to the 1st amino acid residue (or X1), the 2nd amino acid residue (or X2), the 3rd amino acid residue (or X3), the 4th amino acid residue (or X4), the 8th amino acid residue (or X8), or the 12th amino acid residue (or X12). In some embodiments, the linker is attached to the 1st amino acid residue or X1. In some embodiments, the linker is attached to the last amino acid residue, or X12. In some embodiments, the linker is attached to the 2^{nd} amino acid residue (or X2). In some embodiments, the linker is attached to the 3rd amino acid residue (or X3). In some embodiments, the linker is attached to the 4^{th} amino acid residue (or X4). In some embodiments, the linker is attached to the 8th amino acid residue (or X8).

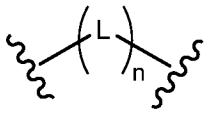
[00420] In some embodiments, the linker is a bond.

[00421] In some embodiments, the linker comprises 3 to 30 intervening non-hydrdogen, organic atoms between the payload molecule and the peptide. In some embodiments, the linker comprises 6 to 18 intervening non-hydrogen, organic atoms between the payload molecule and the peptide. In some embodiments, the intervening atoms comprise 1 to 6 nitrogen atoms and 0 to 4 oxygen atoms.

[00422] In some embodiments, the linker comprises one or more amino acid residues. In some embodiments, the linker comprises one amino acid residue. In some embodiments, the linker comprises at least two contiguous amnio acid residues. In some embodiments, the one or more amino acid residues are selected from a lysine residue, an alanine residue, a glycine residue, a D-phenylalanine residue, a histidine residue, a dAtb residue, or a D-glutamate residue.

[00423] In some embodiments, the linker comprises one or more structures selected from AEEA, AEEP, AEEEP, and AEEEEP.

[00424] In some embodiments, the linker has a structure of Formula (II-1)



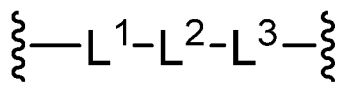
Formula (II-1)

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)$_2$$NR^L$–, -C(=O)$NR^L$S(=O)$_2$-, -S(=O)$_2$$NR^L$C(=O)-, substituted or unsubstituted C_{3-15} cycloalkyl, substituted or unsubstituted C_{1-12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_{1-30} alkylene, substituted or unsubstituted C_{2-30} alkenylene, substituted or unsubstituted C_{2-30} alkynylene, substituted or unsubstituted C_{1-30} heteroalkylene, -(C_{1-30} alkylene)-O-, -O-(C_{1-30} alkylene)-, -(C_{1-30} alkylene)-NR^L–, -NR^L-(C_{1-30} alkylene)-, -(C_{1-30} alkylene)-$N(R^L)_2$-, or -$N(R^L)_2$-(C_{1-30} alkylene)-; and

each R^L is independently hydrogen, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} heteroalkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-5} alkynyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{2-7} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

n is 1 to 20.

[00425] In some embodiments, the linker has 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)$_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_{1-30} alkylene, or substituted or unsubstituted C_{1-30} heteroalkylene.

[00426] In some embodiments, L^1 is -NH-, and the remaining variables are as described above.

[00427] In some embodiments, L^2 is substituted or unsubstituted C_{1-30} alkylene, or substituted or unsubstituted C_{1-30} heteroalkylene, and the remaining variables are as described above.

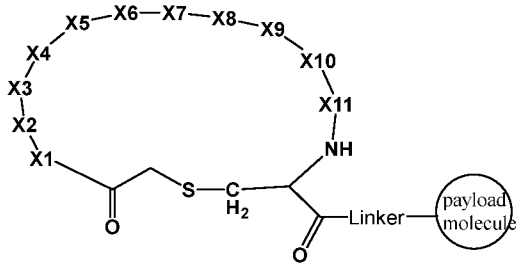
[00428] In some embodiments, L^2 is substituted or unsubstituted C_{1-18} alkylene, or substituted or unsubstituted C_{1-18} heteroalkylene, and the remaining variables are as described above.

[00429] In some embodiments, L^2 is optionally substituted with one or more substituents selected from -OH, -SH, oxo, amino, C_{1-6} alkyl, C_{1-6} hydroxyalkyl, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, -C(=O)OR^L, -OC(=O)R^L, -OC(=O)OR^L, -C(=O)$N(R^L)_2$, -NR^LC(=O)R^L, -OC(=O)$N(R^L)_2$, and -NR^LC(=O)OR^L; and the C_{1-6} alkyl is further optionally substituted with one or more substituents chosen from -OH, -SH, oxo, amino, C_{6-10} aryl, 6- to 10- membered heteroaryl, -

$C(=O)OR^L$, $-OC(=O)R^L$, $-OC(=O)OR^L$, $-C(=O)N(R^L)_2$, $-NR^LC(=O)R^L$, $-OC(=O)N(R^L)_2$, and $-NR^LC(=O)OR^L$, and the remaining variables are as described above.

[00430] In some embodiments, L^3 is -NH-, and the remaining variables are as described above.

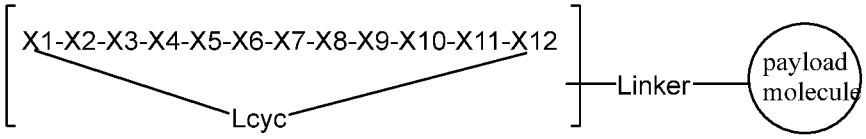
[00431] In some embodiments, a conjugate of the present disclosure has a structure of Formula (III-1),



Formula (III-1)

wherein –Linker– represents the linker.

[00432] In some embodiments, a conjugate comprising a cyclic peptide of formula (I) has a structure of Formula (III-2),



Formula (III-2)

wherein

X1-X12 have the definition described above and Lcyc is a ring closing group that covalently connecting X1 with X12; and

–Linker– represents the linker.

[00433] In some embodiments, the Lcyc is a group selected from Table 4B. In some embodiments, the Lcyc is formed by reacting the first and the second functional groups in Table 4C. In some embodiments, the Lcyc is $-C(=O)-CH_2-$. In some embodiments, the Lcyc is $-C(=O)-CH_2-$, which is formed by reacting with a chloroacetylated (or bromoacetylated) amino acid with a cysteine. In some embodiments, the Lcyc is $-C(=O)-CH_2-S-$, which is formed by reacting with a chloroacetylated (or bromoacetylated) amino acid with an amino acid comprising a SH group.

[00434] In some embodiments, a peptide disclosed herein or a pharmaceutically accepted salt thereof has a cyclic structure having an amino acid (*e.g.*, a chloroacetylated amino acid) in the first residue X1 and a cysteine residue or a variant thereof, and wherein the amino acid (*e.g.*, the chloroacetylated amino acid) in X1 and the cysteine residue or a variant thereof are bound. In some embodiments, a peptide disclosed herein or a pharmaceutically accepted salt thereof has a cyclic structure having an amino acid (*e.g.*, a chloroacetylated amino acid) in the first residue X1 and a cysteine residue or a variant thereof, and wherein the amino acid (*e.g.*, the chloroacetylated amino acid) in X1 and the cysteine residue or a variant thereof form a covalent bond. In some embodiments, a peptide disclosed herein or a pharmaceutically accepted salt thereof has a cyclic structure having a bromoacetylated amino acid in the first residue X1 and a cysteine residue or a variant thereof, and wherein the

bromoacetylated amino acid in X1 and the cysteine residue or a variant thereof form a covalent bond.

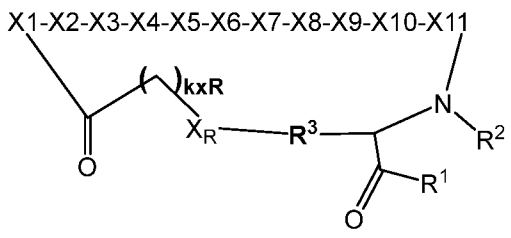
[00435] In some embodiments, the peptide consists of an amino acid sequence selected from SEQ ID NOs: 1-72, and the peptide has a cyclic structure having a cysteine residue or a variant thereof at the 12th residue (X12). In some embodiments, the peptide consists of an amino acid sequence selected from SEQ ID NOs: 1-72, and the peptide has a cyclic structure having a cysteine residue or a variant thereof at the 12th residue (X12), and wherein the chloroacetylated amino acid and the cysteine residue or a variant thereof at 12th residue form a covalent bond. In some embodiments, the chloroacetyl group can be replaced with a bromoacetyl group.

[00436] In some embodiments, the peptide consists of an amino acid sequence selected from any one of SEQ ID NOs: 66-71 that lacks the X3 amnio acid residue, and the peptide has a cyclic structure having a cysteine residue or a variant thereof at the "12th residue" (X12). In some embodiments, the peptide consists of an amino acid sequence selected from SEQ ID NOs: 1-72, and the peptide has a cyclic structure having a cysteine residue or a variant thereof at the 12th residue (X12), and wherein the amino acid at X1 (*e.g.*, a chloroacetylated amino acid) and the cysteine residue or a variant thereof at the 12th residue form a covalent bond. In some embodiments, the chloroacetyl group can be replaced with a bromoacetyl group.

[00437] In some embodiments, a peptide disclosed herein or a pharmaceutically salt thereof has a cyclic structure having the first amino acid covalently linked to the last amino acid.

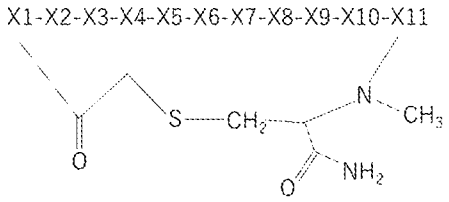
[00438] In some embodiments, the peptide or the pharmaceutically accepted salt thereof has a cyclic structure having a chloroacetylated amino acid in X1 and a cysteine or a cysteine variant thereof, and wherein the chloroacetylated amino acid in X1 and the cysteine or substituted cysteine are bound. In some embodiments, the peptide consists of an amino acid sequence selected from SEQ ID NOs: 1-72. In some embodiments, the peptide consists of an amino acid sequence selected from SEQ ID NOs: 1-72, and the peptide has a cyclic structure. In some embodiments, the peptide consists of an amino acid sequence selected from SEQ ID NOs: 1-72, and the peptide has a cyclic structure having a chloroacetylated amino acid and a cysteine or a cysteine veriant thereof at C-terminus, and wherein the chloroacetylated amino acid and the cysteine or substituted cysteine at C-terminus are bound. In some embodiments, the peptide has a cyclic structure having a chloroacetylated amino acid and; (i) which peptide has 12 or more amino acids, a cysteine or a cysteine variant thereof residue at the 12th residue, and wherein the chloroacetylated amino acid and the cysteine or the systeine variant thereof at the 12th residue are bound; or (ii) which peptide has 11 or less amino acids, especially lacking X3 residue, a cysteine or cysteine variant thereof residue at the 12th residue, and wherein the chloroacetylated amino acid and the cysteine or substituted cysteine at the 12th residue are bound. In some embodiments, the chloroacetyl group can be replaced with a bromoacetyl group.

[00439] For example, a cyclic peptide of formula (I) can have a structure as illustrated below



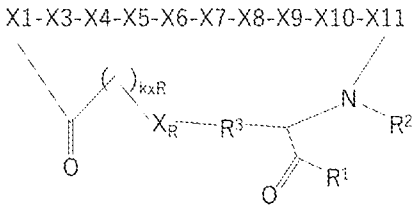
Formula (I-1).

[00440] For example, a cyclic peptide of formula (I) can have a structure as illustrated below



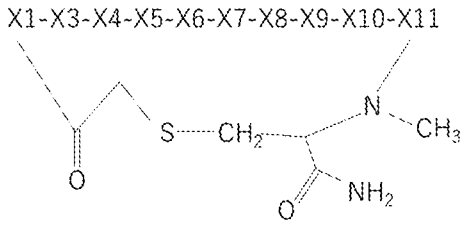
Formula (I-2).

[00441] In some embodiments, a conjugate comprising a cyclic peptide of formula (I) has a structure of as illustarated below



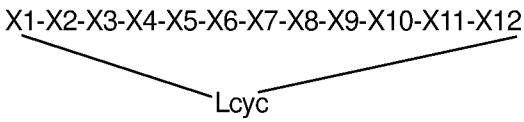
Formula (I-3).

[00442] For example, a cyclic peptide of formula (I) can have a structure as illustrated below.



Formula (I-4).

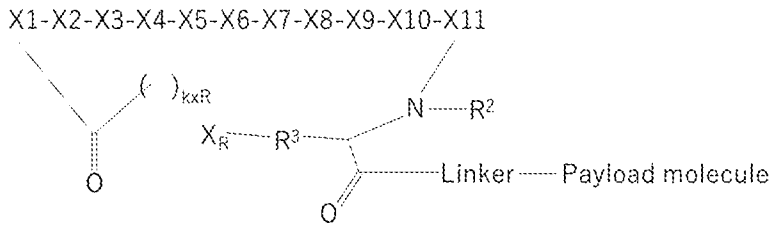
[00443] In some embodiments, the peptide of Formula (I) has a structure of Formula (I-5), or a pharmaceutically acceptable salt thereof:



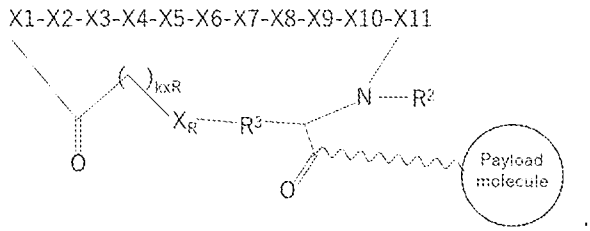
Formula (I-5)

[00444] wherein X1-X12 have the definition described for Formula (I) and Lcyc is a ring closing group that covalently connecting X1 with X12. In some embodiments, the Lcyc is a group selected from Table 4B. In some embodiments, the Lcyc is formed by reacting the first and the second functional groups in Table 4C.

[00445] In some embodiments, a conjugate comprising a cyclic peptide of formula (I) has a structure of



[00446] In some embodiments, a conjugate of the present disclosure has a structure of



[00447] In some embodiments, the peptide or the salt thereof comprises an amino acid sequence that differs by no more than 1, 2, 3, 4, or 5 residues compared to any one of of SEQ ID NOs: 1-72. In some embodiments, the peptide or the salt thereof comprises an amino acid sequence that is identical to at least 7, 8, 9, 10, 11, or 12 amino acid residues compared to a sequence selected from SEQ ID NOs: 1-72. In some embodiments, the peptide or the salt thereof consists of an amino acid sequence of any one of SEQ ID NOs: 1-72. In some embodiments, the peptide or the salt thereof comprises an amino acid sequence that has at most 1, 2, 3, 4, or 5 additions, deletions and/or substitutions (including conservative substitutions) compared to a sequence of any one of SEQ ID NOs: 1-72. In some embodiments, the peptide or the salt thereof comprises an amino acid sequence that has at most 1 addition, deletion, or substitutions (including conservative substitutions) compared to a sequence of any one of SEQ ID NOs: 1-72.

[00448] Exemplary peptides of the present disclosure include the peptides described in Table 1. In some embodiments, the peptides of Table 1 have an -C(=O)-halogen group attached to the N-terminus. In some embodiments, the peptides of Table 1 have a -C(=O)-CH_2-halogen group attached to the N-terminus. In some embodiments, the peptides of Table 1 have an -C(=O)-halogen group attached at residue position 1. In some embodiments, the peptides of Table 1 have a -C(=O)-CH_2-halogen group attached at residue position 1. In some embodiments, the peptides of Table 1 have an -C(=O)-Cl group attached to the N-terminus. In some embodiments, the peptides of Table 1 have a -C(=O)-Cl group attached at residue position 1. In some embodiments, the peptides of Table 1 have an -C(=O)-CH_2-Cl group attached at residue position 1. In some embodiments, the peptides of Table 1 have an -C(=O)-Br group attached at residue position 1. In some embodiments, the peptides of Table 1 have a -C(=O)-CH_2-Br group attached at residue position 1.

[00449] In some embodiments, the conjugates of the disclosure have an -C(=O)-halogen or -C(=O)-CH_2-halogen group attached to the N-terminus. In some embodiments, the conjugates of the disclosure-have an -C(=O)-halogen or -C(=O)-CH_2-halogen group attached at residue position 1. In some embodiments, the conjugates of the disclosure have an -C(=O)-Cl or -C(=O)-CH_2-Cl group attached to the N-terminus. In some embodiments, the conjugates of disclosure have an -C(=O)-Cl or -C(=O)-CH_2-Cl group attached at residue position 1. In some

embodiments, the peptides in the conjugates of the disclosure are monocyclic.

[00450] In some embodiments, the peptides of the conjugates described herein are monocyclic peptides, wherein the -C(=O)-Cl, -C(=O)-CH_2-Cl, or -C(=O)-CH_2-Br group at residue position 1 forms a bond with the cysteine at residue position 12. In some embodiments, the peptides in the conjugates described herein are monocyclic peptides with 12 amino acid residues forming the ring. In some embodiments, the peptides of conjugates described herein are monocyclic peptides, wherein the -C(=O)-Cl, -C(=O)-CH_2-Cl, or -C(=O)-CH_2-Br at residue position 1 forms a bond with the cysteine at residue position 10. In some embodiments, the peptides in the conjugates described herein are monocyclic peptides with 10 amino acid residues forming the ring.

[00451] In one aspect, described herein is a peptide that has avidity for GPC3, wherein the peptide competes for binding to human GPC3 with a peptide that has an amino acid sequence including deletion, substitution, and/or addition of one or several amino acids in the amino acid of SEQ ID NO: 1:

MeK-MeI-D-MeQ-F4COO-I-I-Y-MeNal27N-G-3Py6Ph-MeC (SEQ ID NO: 1)

or a pharmaceutically acceptable salt thereof.

[00452] In one aspect, described herein is a peptide that has avidity for GPC3, wherein the peptide competes for binding to human GPC3 with a peptide that has a structure of Formula (I) as described herein (*e.g.*, Formula (I-1) and Formula (I-2), or a pharmaceutically acceptable salt thereof.

[00453] The structures of exemplary unnatural amino acids that are present in Table 1 can be found in Table 5G.

[00454] As described in Table 1 or other tables, abbreviations have the following meanings:

[00455] Lower case d means D-amino acids, *e.g.*, dF refers to d-phenylalanine;

[00456] Me refers to a methyl group, *e.g.*, MeG represents N-Methyl-Glycine;

[00457] Ala or A refer to alanine;

[00458] Arg or R refer to arginine;

[00459] Asn or N refer to asparagine;

[00460] Asp or D refer to aspartic acid;

[00461] Cys or C refer to cysteine;

[00462] Gln or Q refer to glutamine;

[00463] Gly or G refer to glycine;

[00464] His or H refer to histidine;

[00465] Ile or I refer to isoleucine;

[00466] Leu or L refer to leucine;

[00467] Lys or K refer to lysine;

[00468] Met or M refer to methionine;

[00469] Phe or F refer to phenylalanine;

[00470] Pro or P refer to proline;

[00471] Ser or S refer to serine;

[00472] Thr or T refer to threonine;

[00473] Trp or W refer to tryptophan;

[00474] Tyr or Y refer to tyrosine;

[00475] Val or V refer to valine;

[00476] Unless otherwise stated in the present specification, the following abbreviations for non-natural amino acids are used according to the following meanings:

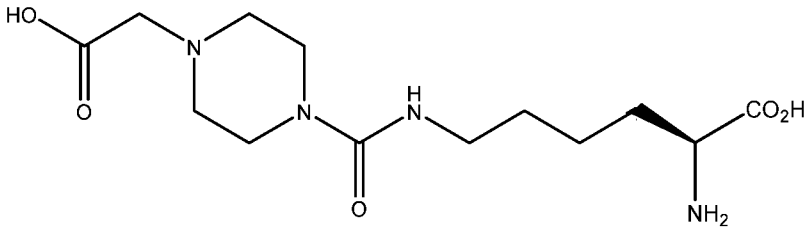
F4G 2-amino-3-(4-guanidinophenyl)propanoic acid, such as (S)-2-amino-3-(4-guanidinophenyl)propanoic acid (CAS 59574-11-7);

4Py 2-amino-3-(pyridin-4-yl)propanoic acid, such as (S)-2-amino-3-(pyridin-4-yl)propanoic acid (CAS 37535-49-2);

3Py 2-amino-3-(pyridin-3-yl)propanoic acid, such as (S)-2-amino-3-(pyridin-3-yl)propanoic acid (CAS 64090-98-8);

Cit 2-amino-5-ureidopentanoic acid, such as (S)-2-amino-5-ureidopentanoic acid (CAS 372-75-8);

KCOpipzaa 2-amino-6-{[4-(carboxymethyl)piperazine-1-carbonyl]amino}hexanoic acid, such as (2S)-2-amino-6-{[4-(carboxymethyl)piperazine-1-carbonyl]amino}hexanoic acid



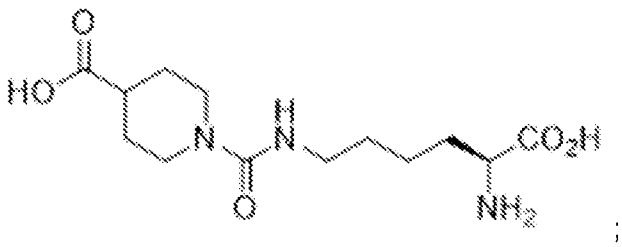
;

Eva 2-amino-3-ethylpentanoic acid, such as (S)-2-amino-3-ethylpentanoic acid (CAS 14328-49-5);

Ahp 2-aminoheptanoic acid, such as (S)-2-aminoheptanoic acid (CAS No. 44902-02-5);

F4COO 4-(2-amino-2-carboxyethyl)benzoic acid, such as (S)-4-(2-amino-2-carboxyethyl)benzoic acid (CAS 126109-42-0);

KCOpip4COO 1-((5-amino-5-carboxypentyl)carbamoyl)piperidine-4-carboxylic acid, such as (S)-1-((5-amino-5-carboxypentyl)carbamoyl)piperidine-4-carboxylic acid



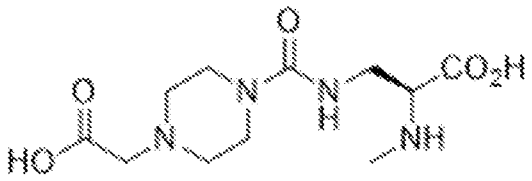
;

Aib 2-amino-2-methylpropanoic acid (CAS 62-57-7);

Hpr piperidine-2-carboxylic acid, such as (S)-piperidine-2-carboxylic acid (CAS 3105-95-1);

Sbu 2-amino-3-butoxypropanoic acid, such as (2S)-2-amino-3-butoxypropanoic acid (CAS 138320-46-4);

MeDapCOpipzaa 3-(4-(carboxymethyl)piperazine-1-carboxamido)-2-(methylamino)propanoic acid, such as (S)-3-(4-(carboxymethyl)piperazine-1-carboxamido)-2-(methylamino)propanoic acid



;

Scbm 2-amino-3-(cyclobutylmethoxy)propanoic acid, such as (2S)-2-amino-3-(cyclobutylmethoxy)propanoic acid

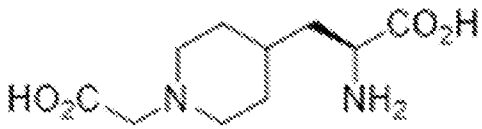
;

Sbu 2-amino-3-butoxypropanoic acid, such as (2S)-2-amino-3-butoxypropanoic acid (CAS 138320-46-4);

Scpe 2-amino-3-(cyclopentyloxy)propanoic acid, such as (2S)-2-amino-3-(cyclopentyloxy)propanoic acid (CAS 1509921-28-1);

HseBu 2-amino-4-butoxybutanoic acid, such as (2S)-2-amino-4-butoxybutanoic acid (CAS 17673-71-1);

A4paa 2-amino-3-(1-(carboxymethyl)piperidin-4-yl)propanoic acid, such as (S)-2-amino-3-(1-(carboxymethyl)piperidin-4-yl)propanoic acid



;

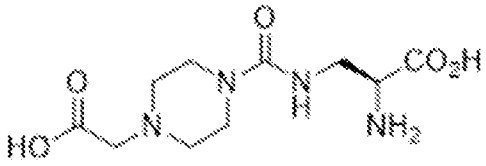
Spent 2-amino-3-(pentyloxy)propanoic acid, such as (2S)-2-amino-3-(pentyloxy)propanoic acid (CAS 1502644-74-7);

Hgl 2-aminohexanedioic acid, such as (S)-2-aminohexanedioic acid (CAS 1118-90-7)

Hsecpe 2-amino-4-(cyclopentyloxy)butanoic acid, such as (2S)-2-amino-4-(cyclopentyloxy)butanoic acid (CAS 1501949-22-9);

Hgn 2,6-diamino-6-oxohexanoic acid, such as (S)-2,6-diamino-6-oxohexanoic acid (CAS 7433-32-1);

DapCOpipzaa 2-amino-3-(4-(carboxymethyl)piperazine-1-carboxamido)propanoic acid, such as (S)-2-amino-3-(4-(carboxymethyl)piperazine-1-carboxamido)propanoic acid



;

MeD 2-(methylamino)butanedioic acid, such as (2S)-2-(methylamino)butanedioic acid (CAS 4226-18-0);

CmG 2-[(2-carbamoylethyl)amino]acetic acid (CAS 34299-32-6);

Medd 2-(methylamino)butanedioic acid, such as (2R)-2-(methylamino)butanedioic acid (CAS 6384-92-5);

HseEt 2-amino-4-ethoxybutanoic acid, such as (2S)-2-amino-4-ethoxybutanoic acid (CAS 17268-93-8);

HseiPr 2-amino-4-(propan-2-yloxy)butanoic acid, such as (2S)-2-amino-4-(propan-2-yloxy)butanoic acid (CAS 685842-10-8);

CrmG 2,2'-azanediyldiacetic acid (CAS 142-73-4);

CeG 3-((carboxymethyl)amino)propanoic acid (CAS 505-72-6);

CrpG 4-((carboxymethyl)amino)butanoic acid (CAS 4386-04-3);

MeHgl 2-(methylamino)hexanedioic acid, such as (S)-2-(methylamino)hexanedioic acid (CAS 261943-13-9);

MeCit 2-(methylamino)-5-ureidopentanoic acid, such as (S)-2-(methylamino)-5-ureidopentanoic acid (CAS 2226129-88-8);

F3G 2-amino-3-(3-guanidinophenyl)propanoic acid, such as (S)-2-amino-3-(3-guanidinophenyl)propanoic acid (CAS 1019057-42-1);

3Py6COO5-(2-amino-2-carboxyethyl)picolinic acid, such as (S)-5-(2-amino-2-carboxyethyl)picolinic acid (CAS 1269945-31-4);

4Py2NH2 2-amino-3-(2-aminopyridin-4-yl)propanoic acid, such as (S)-2-amino-3-(2-aminopyridin-4-yl)propanoic acid (CAS 1269969-46-1);

3Py5COO5-(2-amino-2-carboxyethyl)nicotinic acid, such as (S)-5-(2-amino-2-carboxyethyl)nicotinic acid (CAS 1270138-35-6);

F3COO 3-(2-amino-2-carboxyethyl)benzoic acid, such as (S)-3-(2-amino-2-carboxyethyl)benzoic acid (CAS 13861-02-4)

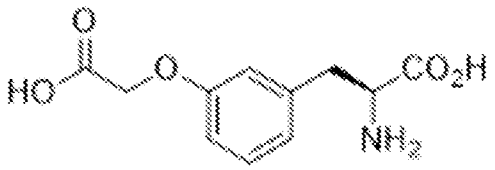
3Py6NHAc 3-(6-acetamidopyridin-3-yl)-2-aminopropanoic acid, such as (S)-3-(6-acetamidopyridin-3-yl)-2-aminopropanoic acid (CAS 1270189-35-9);

F4C 2-amino-3-(4-chlorophenyl)propanoic acid, such as (S)-2-amino-3-(4-chlorophenyl)propanoic acid (CAS 14173-39-8)

F4OMe 2-amino-3-(4-methoxyphenyl)propanoic acid, such as (S)-2-amino-3-(4-methoxyphenyl)propanoic acid (CAS 6230-11-1);

Nal2 2-amino-3-(naphthalen-2-yl)propanoic acid, such as (S)-2-amino-3-(naphthalen-2-yl)propanoic acid (CAS 58438-03-2);

F3aao 2-amino-3-(3-(carboxymethoxy)phenyl)propanoic acid, such as (S)-2-amino-3-(3-(carboxymethoxy)phenyl)propanoic acid



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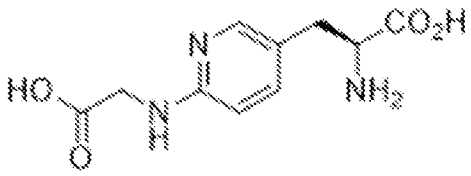
F4aa 2-amino-3-(4-(carboxymethyl)phenyl)propanoic acid, such as (S)-2-amino-3-(4-(carboxymethyl)phenyl)propanoic acid (CAS 140233-60-9);

F4aao 2-amino-3-(4-(carboxymethoxy)phenyl)propanoic acid, such as (S)-2-amino-3-(4-(carboxymethoxy)phenyl)propanoic acid (CAS 24558-63-2);

3Py6NHaa 2-amino-3-(6-((carboxymethyl)amino)pyridin-3-yl)propanoic acid, such as (S)-2-amino-3-(6-((carboxymethyl)amino)pyridin-3-yl)propanoic acid



;

5Pdo 2-amino-3-(6-oxo-1,6-dihydropyridin-3-yl)propanoic acid, such as (S)-2-amino-3-(6-oxo-1,6-dihydropyridin-3-yl)propanoic acid (CAS 140681-92-1);

F3CON 2-amino-3-(3-carbamoylphenyl)propanoic acid, such as (S)-2-amino-3-(3-carbamoylphenyl)propanoic acid (CAS 1217651-22-3);

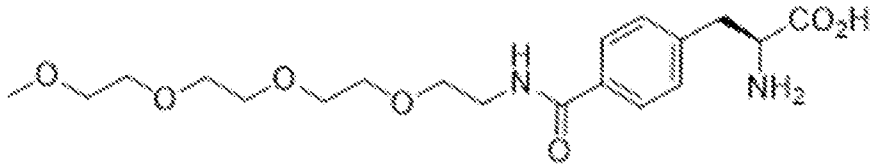
F4F 2-amino-3-(4-fluorophenyl)propanoic acid, such as (S)-2-amino-3-(4-fluorophenyl)propanoic acid (CAS 1132-68-9);

F4OEt 2-amino-3-(4-ethoxyphenyl)propanoic acid, such as (S)-2-amino-3-(4-ethoxyphenyl)propanoic acid (CAS 32795-52-1);

F4Me 2-amino-3-(p-tolyl)propanoic acid, such as (S)-2-amino-3-(p-tolyl)propanoic acid (CAS 1991-87-3);

F4CON 2-amino-3-(4-carbamoylphenyl)propanoic acid, such as (S)-2-amino-3-(4-carbamoylphenyl)propanoic acid (CAS 223593-04-2);

F4CONPEG4Me 3-(4-((2,5,8,11-tetraoxatridecan-13-yl)carbamoyl)phenyl)-2-aminopropanoic acid, such as (S)-3-(4-((2,5,8,11-tetraoxatridecan-13-yl)carbamoyl)phenyl)-2-aminopropanoic acid



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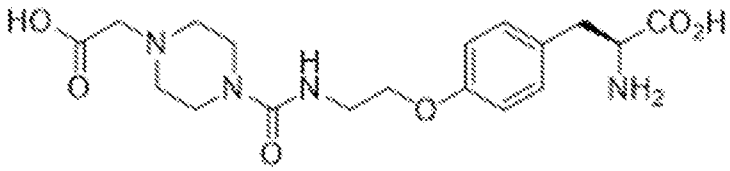
F3OMe 2-amino-3-(3-methoxyphenyl)propanoic acid, such as (S)-2-amino-3-(3-methoxyphenyl)propanoic acid (CAS 33879-32-2);

YaeCOpipzaa 2-amino-3-(4-(2-(4-(carboxymethyl)piperazine-1-carboxamido)ethoxy)phenyl)propanoic acid, such as (S)-2-amino-3-(4-(2-(4-(carboxymethyl)piperazine-1-carboxamido)ethoxy)phenyl)propanoic acid



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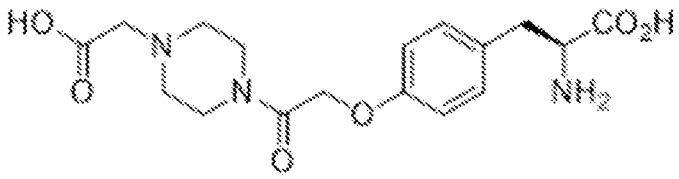
F4aaopipzaa 2-amino-3-(4-(2-(4-(carboxymethyl)piperazin-1-yl)-2-oxoethoxy)phenyl)propanoic acid, such as (S)-2-amino-3-(4-(2-(4-(carboxymethyl)piperazin-1-yl)-2-oxoethoxy)phenyl)propanoic acid



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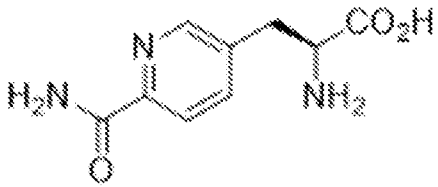
4Pdo 2-amino-3-(2-oxo-1,2-dihydropyridin-4-yl)propanoic acid, such as (S)-2-amino-3-(2-oxo-1,2-dihydropyridin-4-yl)propanoic acid (CAS 1270061-10-3);

3Py6CON 2-amino-3-(6-carbamoylpyridin-3-yl)propanoic acid, such as (S)-2-amino-3-(6-carbamoylpyridin-3-yl)propanoic acid



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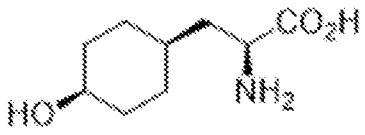
Atp 2-amino-3-(tetrahydro-2H-pyran-4-yl)propanoic acid, such as (S)-2-amino-3-(tetrahydro-2H-pyran-4-yl)propanoic acid (CAS 1344910-91-3);

Cha4cH 2-amino-3-((1s,4R)-4-hydroxycyclohexyl)propanoic acid, such as (S)-2-amino-3-((1s,4R)-4-hydroxycyclohexyl)propanoic acid



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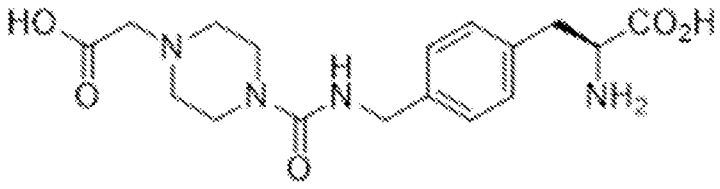
Cha4tH 2-amino-3-((1r,4S)-4-hydroxycyclohexyl)propanoic acid, such as (S)-2-amino-3-((1r,4S)-4-hydroxycyclohexyl)propanoic acid (CAS 221243-22-7);

Cha4cOMe 2-amino-3-((1s,4R)-4-methoxycyclohexyl)propanoic acid, such as (S)-2-amino-3-((1s,4R)-4-methoxycyclohexyl)propanoic acid

;

A1mor 2-amino-3-morpholinopropanoic acid, such as (S)-2-amino-3-morpholinopropanoic acid (CAS 1931924-34-3);

F4amCOpipzaa 2-amino-3-(4-((4-(carboxymethyl)piperazine-1-carboxamido)methyl)phenyl)propanoic acid, such as (S)-2-amino-3-(4-((4-(carboxymethyl)piperazine-1-carboxamido)methyl)phenyl)propanoic acid



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Chg 2-amino-2-cyclohexylacetic acid, such as (S)-2-amino-2-cyclohexylacetic acid (CAS 14328-51-9);

Cle 1-aminocyclopentane-1-carboxylic acid (CAS 52-52-8);

Tbg 2-amino-3,3-dimethylbutanoic acid, such as (S)-2-amino-3,3-dimethylbutanoic acid (CAS 20859-02-3);

Gcpr 2-amino-2-cyclopropylacetic acid, such as (S)-2-amino-2-cyclopropylacetic acid (CAS 49606-99-7);

Gcpe 2-amino-2-cyclopentylacetic acid, such as (S)-2-amino-2-cyclopentylacetic acid (CAS 2521-84-8);

Acpr 2-amino-3-cyclopropylpropanoic acid, such as (S)-2-amino-3-cyclopropylpropanoic acid (CAS 102735-53-5);

Cba 2-amino-3-cyclobutylpropanoic acid, such as (S)-2-amino-3-cyclobutylpropanoic acid (CAS 1201593-

65-8);

Gthp 2-amino-2-(tetrahydro-2H-pyran-4-yl)acetic acid, such as (S)-2-amino-2-(tetrahydro-2H-pyran-4-yl)acetic acid (CAS 811842-25-8);

NleCOO 2-aminoheptanedioic acid, such as (S)-2-aminoheptanedioic acid (CAS 26630-55-7);

NleOH 2-amino-6-hydroxyhexanoic acid, such as (S)-2-amino-6-hydroxyhexanoic acid (CAS 6033-32-5);

Atb 2-amino-4,4-dimethylpentanoic acid, such as (S)-2-amino-4,4-dimethylpentanoic acid (CAS 57224-50-7);

Nva 2-aminopentanoic acid, such as (S)-2-aminopentanoic acid (CAS 6600-40-4);

Nle 2-aminohexanoic acid, such as (S)-2-aminohexanoic acid (CAS 327-57-1);

DapAc 3-acetamido-2-aminopropanoic acid, such as (S)-3-acetamido-2-aminopropanoic acid (CAS 20584-70-7);

Abu 2-aminobutanoic acid, such as (S)-2-aminobutanoic acid (CAS 1492-24-6);

Ncit 2-amino-4-ureidobutanoic acid, such as (S)-2-amino-4-ureidobutanoic acid (CAS 1190-47-2);

dMeS 2-amino-3-hydroxy-3-methylbutanoic acid, such as (S)-2-amino-3-hydroxy-3-methylbutanoic acid (CAS 2280-27-5);

TdMe 2-amino-3-methoxy-3-methylbutanoic acid, such as (S)-2-amino-3-methoxy-3-methylbutanoic acid (CAS 2280-29-7);

Cbg 2-amino-2-cyclobutylacetic acid, such as (S)-2-amino-2-cyclobutylacetic acid (CAS 49607-08-1);

NvaOMe 2-amino-5-methoxypentanoic acid, such as (S)-2-amino-5-methoxypentanoic acid (CAS 1315051-48-9);

NleOMe 2-amino-6-methoxyhexanoic acid, such as (S)-2-amino-6-methoxyhexanoic acid (CAS 1690134-89-4);

AhpOMe 2-amino-7-methoxyheptanoic acid, such as (S)-2-amino-7-methoxyheptanoic acid;

F4u 2-amino-3-(4-ureidophenyl)propanoic acid, such as (S)-2-amino-3-(4-ureidophenyl)propanoic acid (CAS 32401-733-4);

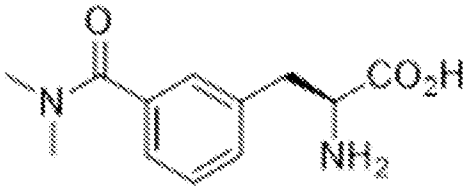
F4CONdMe 2-amino-3-(4-(dimethylcarbamoyl)phenyl)propanoic acid, such as (S)-2-amino-3-(4-(dimethylcarbamoyl)phenyl)propanoic acid (CAS 2349530-31-8);

F4ms 2-amino-3-(4-(methylsulfonyl)phenyl)propanoic acid, such as (S)-2-amino-3-(4-(methylsulfonyl)phenyl)propanoic acid (CAS 1195655-47-0);

F34dOMe 2-amino-3-(3,4-dimethoxyphenyl)propanoic acid, such as (S)-2-amino-3-(3,4-dimethoxyphenyl)propanoic acid (CAS 32161-30-1);

F3C 2-amino-3-(3-chlorophenyl)propanoic acid, such as (S)-2-amino-3-(3-chlorophenyl)propanoic acid (CAS 80126-51-8);

F3CONdMe 2-amino-3-(3-(dimethylcarbamoyl)phenyl)propanoic acid, such as (S)-2-amino-3-(3-(dimethylcarbamoyl)phenyl)propanoic acid



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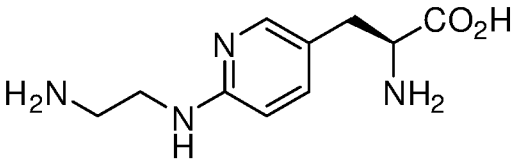
5Inda 2-amino-3-(1H-indazol-5-yl)propanoic acid, such as (S)-2-amino-3-(1H-indazol-5-yl)propanoic acid (CAS 1335577-14-4);

F3aa 2-amino-3-(3-(carboxymethyl)phenyl)propanoic acid, such as (S)-2-amino-3-(3-(carboxymethyl)phenyl)propanoic acid (CAS 1270107-31-7);

3Py6Nhae 2-amino-3-(6-((2-aminoethyl)amino)pyridin-3-yl)propanoic acid, such as (S)-2-amino-3-(6-((2-aminoethyl)amino)pyridin-3-yl)propanoic acid



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3Py6OMe 2-amino-3-(6-methoxypyridin-3-yl)propanoic acid, such as (S)-2-amino-3-(6-methoxypyridin-3-yl)propanoic acid (CAS 1270178-24-9);

MeNal2 2-(methylamino)-3-(naphthalen-2-yl)propanoic acid, such as (S)-2-(methylamino)-3-(naphthalen-2-yl)propanoic acid

;

MeNal27N 3-(isoquinolin-7-yl)-2-(methylamino)propanoic acid, such as (S)-3-(isoquinolin-7-yl)-2-(methylamino)propanoic acid

;

MeF34diox 3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-(methylamino)propanoic acid, such as (S)-3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-(methylamino)propanoic acid

;

MeF34dOMe 3-(3,4-dimethoxyphenyl)-2-(methylamino)propanoic acid, such as (S)-3-(3,4-dimethoxyphenyl)-2-(methylamino)propanoic acid (CAS 52939-34-1);

MeF4T 2-(methylamino)-3-(4-(trifluoromethyl)phenyl)propanoic acid, such as (S)-2-(methylamino)-3-(4-(trifluoromethyl)phenyl)propanoic acid

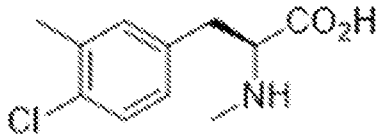
;

MeW7N 2-(methylamino)-3-(1H-pyrrolo[2,3-b]pyridin-3-yl)propanoic acid, such as (S)-2-(methylamino)-3-(1H-pyrrolo[2,3-b]pyridin-3-yl)propanoic acid (CAS 356067-71-5);

MeF3C4Me 3-(3-chloro-4-methylphenyl)-2-(methylamino)propanoic acid, such as (S)-3-(3-chloro-4-methylphenyl)-2-(methylamino)propanoic acid

;

MeF3Me4C 3-(4-chloro-3-methylphenyl)-2-(methylamino)propanoic acid, such as (S)-3-(4-chloro-3-methylphenyl)-2-(methylamino)propanoic acid



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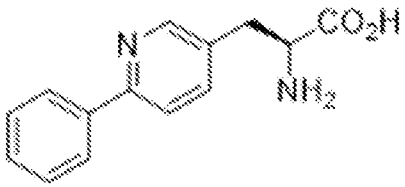
Bph 3-([1,1'-biphenyl]-4-yl)-2-aminopropanoic acid, such as (S)-3-([1,1'-biphenyl]-4-yl)-2-aminopropanoic acid (CAS 155760-02-4);

3Py6Ph 2-amino-3-(6-phenylpyridin-3-yl)propanoic acid, such as (S)-2-amino-3-(6-phenylpyridin-3-yl)propanoic acid



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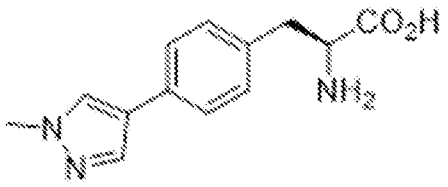
F41Me4Pyz 2-amino-3-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)propanoic acid, such as (S)-2-amino-3-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)propanoic acid



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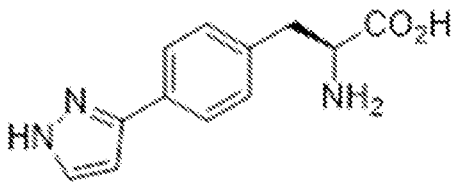
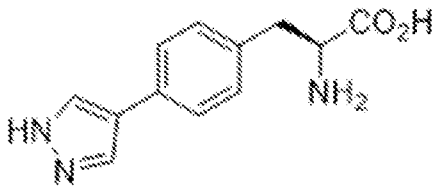
F43Pyz 3-(4-(1H-pyrazol-3-yl)phenyl)-2-aminopropanoic acid, such as (S)-3-(4-(1H-pyrazol-3-yl)phenyl)-2-aminopropanoic acid



;

F44Pyz 3-(4-(1H-pyrazol-4-yl)phenyl)-2-aminopropanoic acid, such as (S)-3-(4-(1H-pyrazol-4-yl)phenyl)-2-aminopropanoic acid



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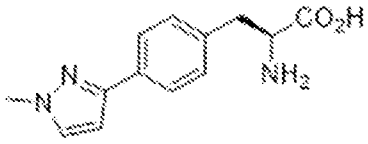
F41Pyz 3-(4-(1H-pyrazol-1-yl)phenyl)-2-aminopropanoic acid, such as (S)-3-(4-(1H-pyrazol-1-yl)phenyl)-2-aminopropanoic acid (CAS 1269982-08-2);

F41Me3Pyz 2-amino-3-(4-(1-methyl-1H-pyrazol-3-yl)phenyl)propanoic acid, such as (S)-2-amino-3-(4-(1-methyl-1H-pyrazol-3-yl)phenyl)propanoic acid



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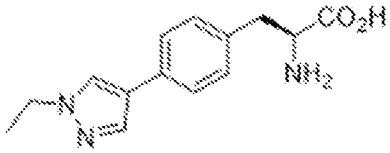
F41Et4Pyz 2-amino-3-(4-(1-ethyl-1H-pyrazol-4-yl)phenyl)propanoic acid, such as (S)-2-amino-3-(4-(1-ethyl-1H-pyrazol-4-yl)phenyl)propanoic acid



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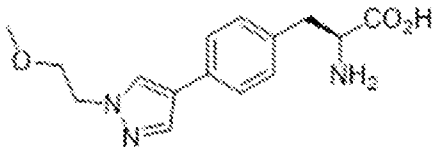
F41MeOe4Pyz 2-amino-3-(4-(1-(2-methoxyethyl)-1H-pyrazol-4-yl)phenyl)propanoic acid, such as (S)-2-amino-3-(4-(1-(2-methoxyethyl)-1H-pyrazol-4-yl)phenyl)propanoic acid



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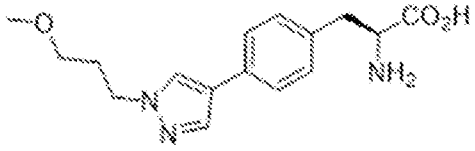
F41MeOp4Pyz 2-amino-3-(4-(1-(3-methoxypropyl)-1H-pyrazol-4-yl)phenyl)propanoic acid, such as (S)-2-amino-3-(4-(1-(3-methoxypropyl)-1H-pyrazol-4-yl)phenyl)propanoic acid



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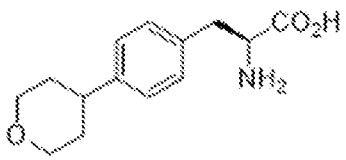
F44thp 2-amino-3-(4-(tetrahydro-2H-pyran-4-yl)phenyl)propanoic acid, such as (S)-2-amino-3-(4-(tetrahydro-2H-pyran-4-yl)phenyl)propanoic acid



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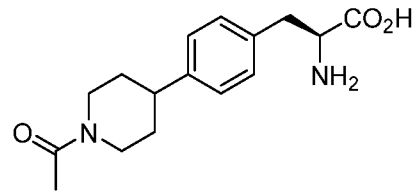
F4Ac4Pip 3-(4-(1-acetylpiperidin-4-yl)phenyl)-2-aminopropanoic acid, such as (S)-3-(4-(1-acetylpiperidin-4-

yl)phenyl)-2-aminopropanoic acid



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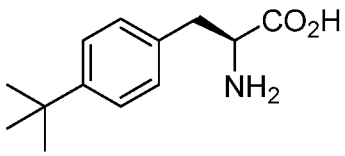
PhNva 2-amino-5-phenylpentanoic acid, such as (S)-2-amino-5-phenylpentanoic acid (CAS 62777-25-7);

PhNle 2-amino-6-phenylhexanoic acid, such as (S)-2-amino-6-phenylhexanoic acid (CAS 80887-26-9);

Yph 2-amino-3-(4-phenoxyphenyl)propanoic acid, such as (S)-2-amino-3-(4-phenoxyphenyl)propanoic acid (CAS 150351-64-7);

Ybn 2-amino-3-(4-(benzyloxy)phenyl)propanoic acid, such as (S)-2-amino-3-(4-(benzyloxy)phenyl)propanoic acid (CAS 16652-64-5);

F4tb 2-amino-3-(4-(tert-butyl)phenyl)propanoic acid, such as (S)-2-amino-3-(4-(tert-butyl)phenyl)propanoic acid



;

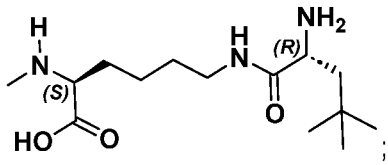
F4Opr 2-amino-3-(4-propoxyphenyl)propanoic acid, such as (S)-2-amino-3-(4-propoxyphenyl)propanoic acid (CAS 32795-53-2);

S3Ret (3R)-2-amino-3-hydroxypentanoic acid, such as (2S,3R)-2-amino-3-hydroxypentanoic acid (CAS 10148-67-1);

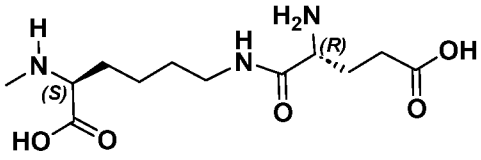
Yae 2-amino-3-(4-(2-aminoethoxy)phenyl)propanoic acid, such as (S)-2-amino-3-(4-(2-aminoethoxy)phenyl)propanoic acid (CAS 1909283-20-0);

datb 2-amino-4,4-dimethylpentanoic acid, such as (R)-2-amino-4,4-dimethylpentanoic acid (CAS 88319-43-1);

Me3Py 2-(methylamino)-3-(pyridin-3-yl)propanoic acid, such as (S)-2-(methylamino)-3-(pyridin-3-yl)propanoic acid (CAS 2651172-69-7);

MeK(datb) N6-(2-amino-4,4-dimethylpentanoyl)-N2-methyl-lysine, such as N6-((R)-2-amino-4,4-dimethylpentanoyl)-N2-methyl-L-lysine  ;

MeK(de) N6-(glutamyl)-N2-methyl-lysine, such as N6-(D-glutamyl)-N2-methyl-L-lysine



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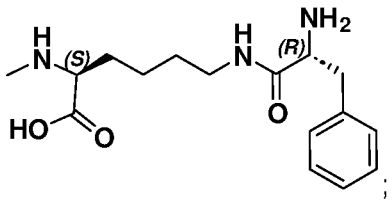
MeK(df) N6-(phenylalanyl)-N2-methyl-lysine, such as N6-(D-phenylalanyl)-N2-methyl-L-lysine



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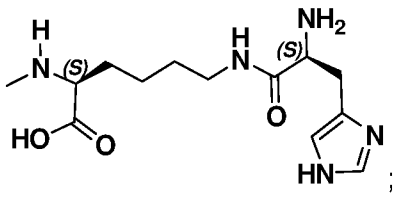
MeK(H) N6-(histidyl)-N2-methyl-lysine, such as N6-(L-histidyl)-N2-methyl-L-lysine



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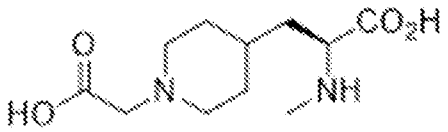
W5N 2-amino-3-(1H-pyrrolo[3,2-c]pyridin-3-yl)propanoic acid, such as (S)-2-amino-3-(1H-pyrrolo[3,2-c]pyridin-3-yl)propanoic acid (CAS 149704-62-1)

MeA4paa 3-(1-(carboxymethyl)piperidin-4-yl)-2-(methylamino)propanoic acid, such as (S)-3-(1-(carboxymethyl)piperidin-4-yl)-2-(methylamino)propanoic acid



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MeI (3S)-3-methyl-2-(methylamino)pentanoic acid, such as (2S,3S)-3-methyl-2-(methylamino)pentanoic acid (CAS 4125-98-8);

MeA 2-(methylamino)propanoic acid, such as (2S)-2-(methylamino)propanoic acid (CAS 3913-67-5);

MeG 2-(methylamino)acetic acid, such as 2-(methylamino)acetic acid (CAS 107-97-1);

MeV 3-methyl-2-(methylamino)butanoic acid, such as (2S)-3-methyl-2-(methylamino)butanoic acid (CAS 2480-23-1)

MeT (3R)-3-hydroxy-2-(methylamino)butanoic acid, such as (2S,3R)-3-hydroxy-2-(methylamino)butanoic acid (CAS 2812-28-4)

all (3R)-2-amino-3-methylpentanoic acid, such as (2S,3R)-2-amino-3-methylpentanoic acid (CAS 1509-34-8)

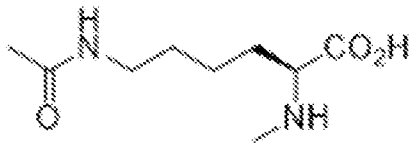
TMe (3R)-2-amino-3-methoxybutanoic acid, such as (2S,3R)-2-amino-3-methoxybutanoic acid (CAS 4144-02-9)

MeQ 4-carbamoyl-2-(methylamino)butanoic acid, such as (2S)-4-carbamoyl-2-(methylamino)butanoic acid (CAS 300560-56-9)

MeTMe (3R)-3-methoxy-2-(methylamino)butanoic acid, such as (2S,3R)-3-methoxy-2-(methylamino)butanoic acid (CAS 594865-59-5)

MeK 6-amino-2-(methylamino)hexanoic acid, such as (2S)-6-amino-2-(methylamino)hexanoic acid (CAS 7431-89-2)

MeKAc 6-acetamido-2-(methylamino)hexanoic acid, such as (2S)-6-acetamido-2-(methylamino)hexanoic acid



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Har 2-amino-6-carbamimidamidohexanoic acid, such as (2S)-2-amino-6-carbamimidamidohexanoic acid (CAS 156-86-5)

KAc 2-amino-6-acetamidohexanoic acid, such as (2S)-2-amino-6-acetamidohexanoic acid (CAS 692-04-6)

dd 2-aminobutanedioic acid, such as (2R)-2-aminobutanedioic acid

EtG 2-(ethylamino)acetic acid (CAS 627-01-0)

K(biotin) 6-{5-[(3aS,4S,6aR)-2-oxo-hexahydro-1H-thieno[3,4-d]imidazol-4-yl]pentanamido}-2-aminohexanoic acid, such as (2S)-6-{5-[(3aS,4S,6aR)-2-oxo-hexahydro-1H-thieno[3,4-d]imidazol-4-yl]pentanamido}-2-aminohexanoic acid (CAS 576-19-2);

MeeG 2-[(2-methoxyethyl)amino]acetic acid (CAS 205124-55-6);

CmpG 2-[(3-carbamoylpropyl)amino]acetic acid (CAS 1182825-67-7)

Nmm 2-amino-3-(methylcarbamoyl)propanoic acid, such as (2S)-2-amino-3-(methylcarbamoyl)propanoic acid (CAS 149204-93-3)

Ndm 2-amino-3-(dimethylcarbamoyl)propanoic acid, such as (2S)-2-amino-3-(dimethylcarbamoyl)propanoic acid (CAS 138585-02-1);

SMe 2-amino-3-methoxypropanoic acid, such as (2S)-2-amino-3-methoxypropanoic acid (CAS 32620-11-4);

HseMe 2-amino-4-methoxybutanoic acid, such as (2S)-2-amino-4-methoxybutanoic acid (CAS 3311-01-1);

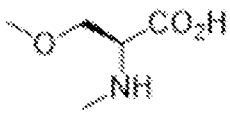
SiPr 2-amino-3-(propan-2-yloxy)propanoic acid, such as (2S)-2-amino-3-(propan-2-yloxy)propanoic acid (CAS 83824-92-4)

SPr 2-amino-3-propoxypropanoic acid, such as (2S)-2-amino-3-propoxypropanoic acid (CAS 113576-31-1)

MeW1Me 3-(1-methyl-1H-indol-3-yl)-2-(methylamino)propanoic acid, such as (2S)-3-(1-methyl-1H-indol-3-yl)-2-(methylamino)propanoic acid (CAS 1152412-98-0)

MeQdMe 4-(dimethylcarbamoyl)-2-(methylamino)butanoic, (2S)-4-(dimethylcarbamoyl)-2-(methylamino)butanoic (CAS 2255323-71-6)

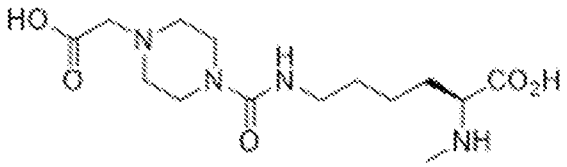
MeSMe 3-methoxy-2-(methylamino)propanoic acid, such as (2S)-3-methoxy-2-(methylamino)propanoic acid



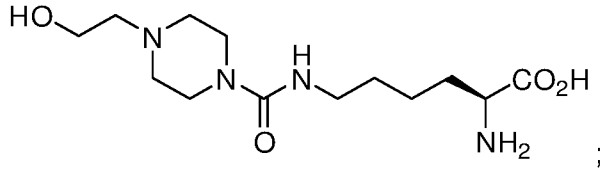
;

MeHseMe4-methoxy-2-(methylamino)butanoic acid, such as (2S)-4-methoxy-2-(methylamino)butanoic acid (CAS 1500648-79-2)

MeKCOpipzaa (2S)-6-{[4-(carboxymethyl)piperazine-1-carbonyl]amino}-2-(methylamino)hexanoic acid



KCOpipzetOH 2-amino-6-{[4-(2-hydroxyethyl)piperazine-1-carbonyl]amino}hexanoic acid, such as (2S)-2-amino-6-{[4-(2-hydroxyethyl)piperazine-1-carbonyl]amino}hexanoic acid



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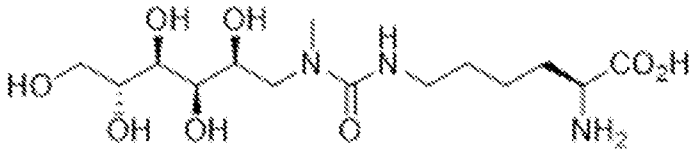
KCOmeglumine 2-amino-6-({methyl[(2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl]carbamoyl}amino)hexanoic acid, such as (2S)-2-amino-6-({methyl[(2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl]carbamoyl}amino)hexanoic acid



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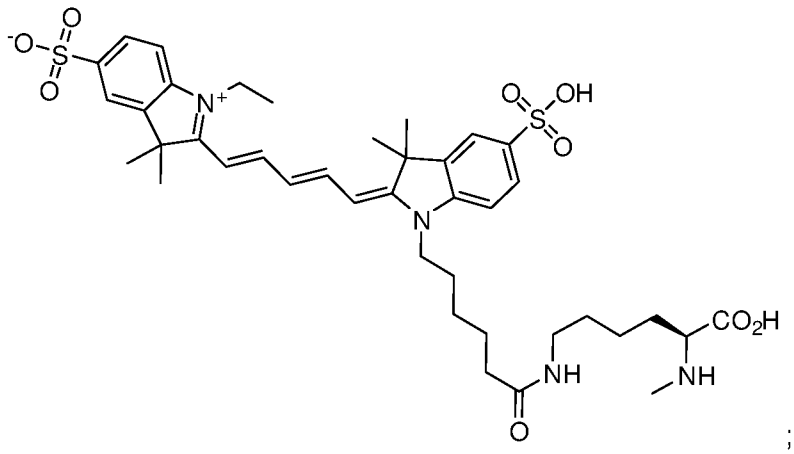
MeK(SulfoCy5) 2-[(1E,3E)-5-[(2E)-1-(5-{[(5S)-5-carboxy-5-(methylamino)pentyl]carbamoyl}pentyl)-3,3-dimethyl-5-sulfo-2,3-dihydro-1H-indol-2-ylidene]penta-1,3-dien-1-yl]-1-ethyl-3,3-dimethyl-3H-indol-1-ium-5-sulfonate



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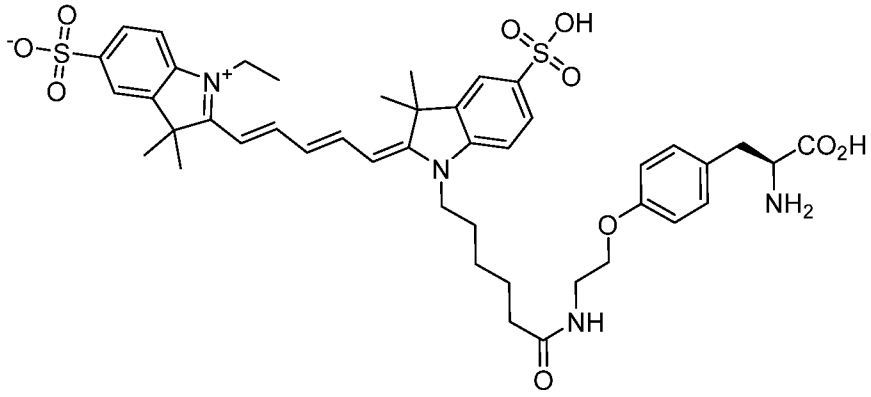
Yae(SulfoCy5) 2-[(1E,3E)-5-[(2E)-1-{5-[(2-{4- [(2S) -2-amino-2-carboxyethyl]phenoxy}ethyl)carbamoyl]pentyl}-3,3-dimethyl-5-sulfo-2,3-dihydro-1H-indol-2-ylidene]penta-1,3-dien-1-yl] -1-ethyl-3,3-dimethyl-3H-indol-1-ium-5-sulfonate



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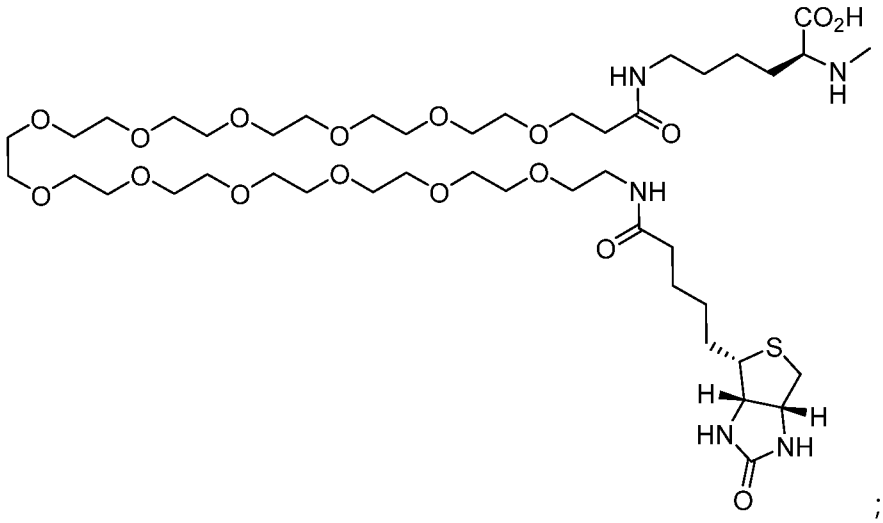
MeK(Biotin-PEG12c) 51-(methylamino)-5,45-dioxo-1-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)-9,12,15,18,21,24,27,30,33,36,39,42-dodecaoxa-6,46-diazadopentacontan-52-oic acid, such as (S)-51-(methylamino)-5,45-dioxo-1-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)-9,12,15,18,21,24,27,30,33,36,39,42-dodecaoxa-6,46-diazadopentacontan-52-oic acid



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Yae(Biotin-PEG12c) 2-amino-3-(4-((4,44-dioxo-48-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)-7,10,13,16,19,22,25,28,31,34,37,40-dodecaoxa-3,43-diazaoctatetracontyl)oxy)phenyl)propanoic acid, such as (S)-2-amino-3-(4-((4,44-dioxo-48-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)-7,10,13,16,19,22,25,28,31,34,37,40-dodecaoxa-3,43-diazaoctatetracontyl)oxy)phenyl)propanoic acid

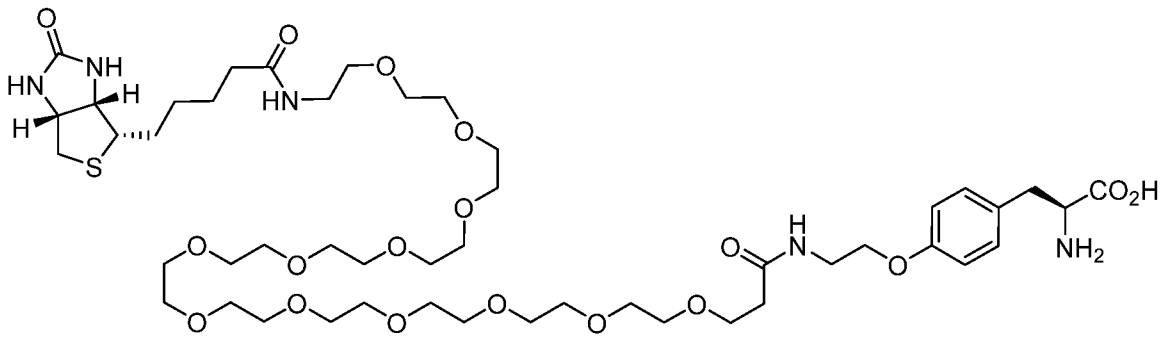


Table 1. Exemplary peptide sequences with avidity to GPC3

Seq. ID No.	Peptide Sequence (from residue position 1 to residue position 14, if present)															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1	MeK	MeI	D	MeQ	F4COO	I	I	Y	MeNal27N	G	3Py6Ph	MeC				
2	MeKAc	MeI	D	MeQ	F4COO	I	I	F4COO	MeNal2	G	3Py6Ph	MeC	NH2			
3	MeKAc	MeI	D	MeQ	F4COO	I	I	F4COO	MeNal2	G	F41Me4Pyz	MeC	NH2			
4	MeKAc	MeI	Q	MeQ	F4COO	I	I	F4COO	MeNal2	G	F41Me4Pyz	MeC	NH2			
5	MeK	MeI	D	MeQ	F4COO	I	I	F4COO	MeNal2	G	F41Me4Pyz	MeC	NH2			
6	MeK	MeI	Q	MeQ	F4COO	I	I	F4COO	MeNal2	G	F41Me4Pyz	MeC	NH2			
7	MeKAc	MeI	D	MeQ	F4COO	I	I	Y	MeNal27N	G	3Py6Ph	MeC	NH2			
8	MeQ	MeQ	D	MeQ	F4COO	I	I	F4COO	MeNal2	G	F41Me4Pyz	MeC	NH2			
9	MeA	MeQ	D	MeQ	F4COO	I	I	F4COO	MeNal2	G	F41Me4Pyz	MeC	NH2			
10	MeQ	MeL	D	MeQ	F4COO	I	I	F4COO	MeNal2	G	F41Me4Pyz	MeC	NH2			
11	MeQ	MeHseMe	D	MeQ	F4COO	I	I	F4COO	MeNal2	G	F41Me4Pyz	MeC	NH2			
12	MeQ	HseMe	D	MeQ	F4COO	I	I	F4COO	MeNal2	G	F41Me4Pyz	MeC	NH2			
13	MeQ	MeQ	Hgn	MeQ	F4COO	I	I	F4COO	MeNal2	G	F41Me4Pyz	MeC	NH2			
14	MeQ	MeQ	KAc	MeQ	F4COO	I	I	F4COO	MeNal2	G	F41Me4Pyz	MeC	NH2			
15	MeQ	MeQ	D	MeA4paa	F4COO	I	I	F4COO	MeNal2	G	F41Me4Pyz	MeC	NH2			
16	MeQ	MeQ	D	MeD	F4COO	I	I	F4COO	MeNal2	G	F41Me4Pyz	MeC	NH2			

17	MeQ	MeQ	D	MeQ	F4aao	I	I	F4COO	MeNal2	G	F41Me4Pyz	MeC	NH2							
18	MeQ	MeQ	D	MeQ	F4COO	TMe	I	F4COO	MeNal2	G	F41Me4Pyz	MeC	NH2							
19	MeQ	MeQ	D	MeQ	F4COO	I	I	F4aa	MeNal2	G	F41Me4Pyz	MeC	NH2							
20	MeQ	MeQ	D	MeQ	F4COO	I	I	F4aao	MeNal2	G	F41Me4Pyz	MeC	NH2							
21	MeK	MeHseMe	D	MeQ	F4COO	I	I	F4aa	MeNal2	G	3Py6Ph	MeC	NH2							
22	MeK	MeHseMe	D	MeQ	F4COO	I	I	F4aa	MeNal2	G	F41Me4Pyz	MeC	NH2							
23	MeK	MeHseMe	D	MeA4paa	F4COO	I	I	F4aa	MeNal2	G	F41Me4Pyz	MeC	NH2							
24	MeK	MeQ	D	MeQ	F4COO	TMe	I	F4aa	MeNal2	G	F41Me4Pyz	MeC	NH2							
25	MeK	MeQ	D	MeA4paa	F4COO	TMe	I	F4aa	MeNal2	G	F41Me4Pyz	MeC	NH2							
26	MeQ	MeQ	D	MeK	F4COO	I	I	F4aa	MeNal2	G	F41Me4Pyz	MeC	NH2							
27	MeQ	MeQ	D	MeQ	Yae	I	I	F4aa	MeNal2	G	F41Me4Pyz	MeC	NH2							
28	MeQ	MeQ	D	MeQ	F4COO	I	I	Yae	MeNal2	G	F41Me4Pyz	MeC	NH2							
29	MeK	MeQ	Hgn	MeQ	F4COO	TMe	I	Y	MeNal2	G	F41Me4Pyz	MeC	NH2							
30	MeK	Mel	D	MeQ	F4COO	TMe	I	F4aao	MeNal27N	G	3Py6Ph	MeC	NH2							
31	MeK	Mel	D	MeQ	F4COO	TMe	I	F4aao	MeNal27N	G	3Py6Ph	MeC	de	NH2						
32	MeK	Mel	D	MeQ	F4COO	TMe	I	F4aao	MeNal27N	G	3Py6Ph	MeC	E	NH2						
33	MeK(de)	Mel	D	MeQ	F4COO	I	I	F4aao	MeNal27N	G	3Py6Ph	MeC	NH2							
34	MeK(H)	Mel	D	MeQ	F4COO	I	I	F4aao	MeNal27N	G	3Py6Ph	MeC	NH2							
35	MeK	MeQ	D	MeQ	F4COO	TMe	I	F4aao	MeNal27N	G	3Py6Ph	MeC	NH2							

36	MeQ	MeHseMe	D	MeQ	F4COO	TMe	I	F4aao	MeNal27N	G	F41Me4Pyz	MeC	NH2		
37	MeQ	MeHseMe	D	MeQ	F4COO	TMe	I	YaeCOpipzaa	MeNal2	G	3Py6Ph	MeC	NH2		
38	MeQ	MeHseMe	D	MeQ	F4COO	TMe	I	F4amCOpipzaa	MeNal2	G	3Py6Ph	MeC	NH2		
39	MeQ	MeHseMe	D	MeQ	F4COO	TMe	I	F4u	MeNal2	G	3Py6Ph	MeC	NH2		
40	MeQ	MeHseMe	D	MeQ	F4COO	TMe	I	F4aaopipzaa	MeNal2	G	3Py6Ph	MeC	NH2		
41	MeK(df)	MeI	D	MeQ	F4COO	I	I	F4aao	MeNal27N	G	3Py6Ph	MeC	NH2		
42	MeK(datb)	MeI	D	MeQ	F4COO	I	I	F4aao	MeNal27N	G	3Py6Ph	MeC	NH2		
43	MeA	MeQ	D	MeQ	F4COO	I	I	F4COO	MeNal2	G	3Py6Ph	MeC	NH2		
44	MeA	MeHseMe	D	MeQ	F4COO	TMe	I	Yae	MeNal2	G	3Py6Ph	MeC	NH2		
45	MeK	MeHseMe	D	MeQ	F4COO	TMe	I	Y	MeNal27N	G	3Py6Ph	MeC	NH2		
46	MeK	MeKCOpipzaa	D	MeDapCOpipzaa	F4COO	TMe	I	F4aao	MeNal27N	G	3Py6Ph	MeC	NH2		
47	MeK	MeKCOpipzaa	D	MeDapCOpipzaa	3Py6NHaa	TMe	I	F4aao	MeNal27N	G	3Py6Ph	MeC	NH2		
48	MeK	MeKCOpipzaa	D	MeKCOpipzaa	F4COO	TMe	I	YaeCOpipzaa	MeNal27N	G	3Py6Ph	MeC	NH2		
49	MeK	MeKCOpipzaa	D	MeKCOpipzaa	F4COO	TMe	I	F4aaopipzaa	MeNal27N	G	3Py6Ph	MeC	NH2		
50	MeDapCOpipzaa	MeHseMe	D	MeDapCOpipzaa	F4COO	TMe	I	Yae	MeNal2	G	3Py6Ph	MeC	NH2		
51	MeDapCOpipzaa	MeHseMe	D	MeDapCOpipzaa	3Py6NHaa	TMe	I	Yae	MeNal27N	G	3Py6Ph	MeC	NH2		
52	MeK	MeHseMe	D	MeDapCOpipzaa	F4COO	TMe	I	F4aao	MeNal27N	G	3Py6Ph	MeC	NH2		
53	MeK	MeHseMe	D	MeDapCOpipzaa	3Py6NHaa	TMe	I	F4aao	MeNal27N	G	3Py6Ph	MeC	NH2		
54	MeDapCOpipzaa	MeHseMe	D	MeDapCOpipzaa	F4COO	TMe	I	Yae	MeNal27N	G	3Py6Ph	MeC	NH2		

55	MeKCOpipzaa	MeHseMe	D	MeDapCOpipzaa	F4COO	TMe	I	Yae	MeNal27N	G	3Py6Ph	MeC	NH2		
56	MeKCOpipzaa	MeA	D	MeY	F4COO	TMe	I	Yae	MeY	G	3Py6Ph	MeC	NH2		
57	MeKCOpipzaa	MeA	MeY	D	F4COO	TMe	I	Yae	MeY	G	3Py6Ph	MeC	NH2		
58	MeKCOpipzaa	MeHseMe	D	MeQ	F4COO	TMe	I	Y	MeNal27N	G	3Py6Ph	MeC	NH2		
59	MeKCOpipzaa	MeHseMe	D	MeQ	F4COO	S3REt	I	Y	MeNal27N	G	3Py6Ph	MeC	NH2		
60	MeKAc	Mel	D	MeQ	F4COO	I	I	Y	MeNal27N	G	3Py6Ph	MeC	G	PEG10c	K	NH_2
61	MeK	MeHseMe	D	MeQ	F4COO	I	I	F4aao	MeNal27N	G	3Py6Ph	MeC	NH2			
62	MeK	Mel	D	MeQ	F4COO	TMe	I	Y	MeNal27N	G	3Py6Ph	MeC	NH2			
63	MeK	MeHseMe	D	MeQ	F4COO	TMe	I	F4aao	MeNal27N	G	3Py6Ph	MeC	NH2			
64	MeK	Mel	D	MeQ	F4COO	I	I	F4aao	MeNal27N	G	3Py6Ph	MeC	NH2			
65	MeK	MeQ	Hgn	MeQ	F4COO	TMe	I	F4aa	MeNal2	G	F41Me4Pyz	MeC	NH2			
66	MeA	MeY		D	Y	TMe	I	Y	MeNal2	G	3Py6Ph	MeC	NH2			
67	MeA	S		D	Y	I	I	Y	MeNal2	G	3Py6Ph	MeC	NH2			
68	MeA	S		W5N	Y	I	I	Y	MeNal2	G	3Py6Ph	MeC	NH2			
69	MeA	Me3Py		D	Y	all	I	Y	MeNal2	G	3Py6Ph	MeC	NH2			
70	MeA	S		Q	Y	I	I	Y	MeNal2	G	3Py6Ph	MeC	NH2			
71	MeA	TMe		D	Y	Cle	I	Y	MeNal2	G	3Py6Ph	MeC	NH2			
72	MeK	MeHseMe	D	MeQ	F4COO	I	I	Y	MeNal27N	G	3Py6Ph	MeC	NH2			

Table 1.1. Exemplary peptide conjugate sequences with avidity to GPC3

SEQ ID No.	Conjugate ID No.	Peptide Sequence (from residue position 1 to residue position 14, if present)															
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
73	PLB-1	MeK(Biotin-PEG12c)	MeI	D	MeQ	F4COO	I	I	Y	MeNal27N	G	3Py6Ph	MeC	NH2			
74	PLB-35	MeK(Biotin-PEG12c)	MeQ	D	MeQ	F4COO	TMe	I	F4aao	MeNal27N	G	3Py6Ph	MeC	NH2			
75	PLB-28	MeQ	MeQ	D	MeQ	F4COO	I	I	Yae(Biotin-PEG12c)	MeNal2	G	F41Me4Pyz	MeC	NH2			
76	PLB-64	MeK(Biotin-PEG12c)	MeI	D	MeQ	F4COO	I	I	F4aao	MeNal27N	G	3Py6Ph	MeC	NH2			
77	PLB-30	MeK(Biotin-PEG12c)	MeI	D	MeQ	F4COO	TMe	I	F4aao	MeNal27N	G	3Py6Ph	MeC	NH2			
78	PLB-60	MeKAc	MeI	D	MeQ	F4COO	I	I	Y	MeNal27N	G	3Py6Ph	MeC	G	PEG10c	K(Biotin)	NH2
79	PLD-45	MeK(SulfoCy5)	MeHseMe	D	MeQ	F4COO	TMe	I	Y	MeNal27N	G	3Py6Ph	MeC	NH2			
80	PLD-30	MeK(SulfoCy5)	MeI	D	MeQ	F4COO	TMe	I	F4aao	MeNal27N	G	3Py6Ph	MeC	NH2			
81	PLD-1	MeK(SulfoCy5)	MeI	D	MeQ	F4COO	I	I	Y	MeNal27N	G	3Py6Ph	MeC	NH2			
82	Mod3	MeA	MeHseMe	D	MeQ	F4COO	TMe	I	Yae(SulfoCy5)	MeNal2	G	3Py6Ph	MeC	NH2			
83	Mod5	MeK(SulfoCy5)	MeHseMe	D	MeQ	F4COO	I	I	F4aao	MeNal27N	G	3Py6Ph	MeC	NH2			
84	Mod6	MeK(SulfoCy5)	MeI	D	MeQ	F4COO	TMe	I	Y	MeNal27N	G	3Py6Ph	MeC	NH2			
85	Mod7	MeK(SulfoCy5)	MeHseMe	D	MeQ	F4COO	TMe	I	F4aao	MeNal27N	G	3Py6Ph	MeC	NH2			
86	C-M-1	MeK(Moiety)	MeI	D	MeQ	F4COO	I	I	Y	MeNal27N	G	3Py6Ph	MeC	NH2			
87	C-M-21	MeK(Moiety)	MeHseMe	D	MeQ	F4COO	I	I	F4aa	MeNal2	G	3Py6Ph	MeC	NH2			
88	C-M-22	MeK(Moiety)	MeHseMe	D	MeQ	F4COO	I	I	F4aa	MeNal2	G	F41Me4Pyz	MeC	NH2			
89	C-M-24	MeK(Moiety)	MeQ	D	MeQ	F4COO	TMe	I	F4aa	MeNal2	G	F41Me4Pyz	MeC	NH2			

90	C-M-26	MeQ	MeQ	D	MeK(Moiety)	F4COO	I	I	F4aa	MeNal2	G	F41Me4Pyz	MeC	NH2		
91	C-M-28	MeQ	MeQ	D	MeQ	F4COO	I	I	Yae(Moiety)	MeNal2	G	F41Me4Pyz	MeC	NH2		
92	C-M-30	MeK(Moiety)	Mel	D	MeQ	F4COO	TMe	I	F4aao	MeNal27N	G	3Py6Ph	MeC	NH2		
93	C-M-31	MeK(Moiety)	Mel	D	MeQ	F4COO	TMe	I	F4aao	MeNal27N	G	3Py6Ph	MeC	de	NH2	
94	C-M-32	MeK(Moiety)	Mel	D	MeQ	F4COO	TMe	I	F4aao	MeNal27N	G	3Py6Ph	MeC	E	NH2	
95	C-M-33	MeK(Moiety)	Mel	D	MeQ	F4COO	I	I	F4aao	MeNal27N	G	3Py6Ph	MeC	NH2		
96	C-M-34	MeK(Moiety)	Mel	D	MeQ	F4COO	I	I	F4aao	MeNal27N	G	3Py6Ph	MeC	NH2		
97	C-M-35	MeK(Moiety)	MeQ	D	MeQ	F4COO	TMe	I	F4aao	MeNal27N	G	3Py6Ph	MeC	NH2		
98	C-M-41	MeK(df)(Moiety)	Mel	D	MeQ	F4COO	I	I	F4aao	MeNal27N	G	3Py6Ph	MeC	NH2		
99	C-M-42	MeK(datb)(Moiety)	Mel	D	MeQ	F4COO	I	I	F4aao	MeNal27N	G	3Py6Ph	MeC	NH2		
100	C-M-44	MeA	MeHseMe	D	MeQ	F4COO	TMe	I	Yae(Moiety)	MeNal2	G	3Py6Ph	MeC	NH2		
101	C-M-45	MeK(Moiety)	MeHseMe	D	MeQ	F4COO	TMe	I	Y	MeNal27N	G	3Py6Ph	MeC	NH2		
102	C-M-62	MeK(Moiety)	Mel	D	MeQ	F4COO	TMe	I	Y	MeNal27N	G	3Py6Ph	MeC	NH2		
103	C-M-63	MeK(Moiety)	MeHseMe	D	MeQ	F4COO	TMe	I	F4aao	MeNal27N	G	3Py6Ph	MeC	NH2		
104	C-M-64	MeK(Moiety)	Mel	D	MeQ	F4COO	I	I	F4aao	MeNal27N	G	3Py6Ph	MeC	NH2		
105	C-M-72	MeK(Moiety)	MeHseMe	D	MeQ	F4COO	I	I	Y	MeNal27N	G	3Py6Ph	MeC	NH2		

[00477] The molecular weight of the described peptide can vary. In some embodiments, the peptide has a molecular weight of about 0.1 to about 25 kDa. In some embodiments, the peptide has a molecular weight of about 0.2 to about 20 kDa, about 0.5 to about 15 kDa, about 0.75 to about 10 kDa, about 0.5 to about 10 kDa, about 0.5 to about 5 kDa, about 0.5 to about 2.5 kDa, about 0.5 to about 2 kDa, about 0.5 to about 1.5 kDa, about 0.5 to about 1 kDa, about 1 to about 10 kDa, about 1 to about 5 kDa, about 1 to about 2.5 kDa, about 1 to about 2 kDa, about 1 to about 1.5 kDa, about 1 to about 1.25 kDa, or about 0.5 to about 1.25 kDa. In some embodiments, the peptide has a molecular weight of about 0.5 to 5 kDa. In some embodiments, the peptide has a molecular weight of about 0.5 to 2 kDa. In some embodiments, the peptide has a molecular weight of about 0.75 to 1.75 kDa. In some embodiments, the peptide has a molecular weight of about 1 to 1.5 kDa. In some embodiments, the peptide is monocyclic.

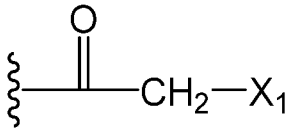
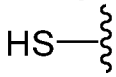
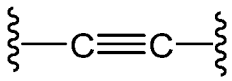
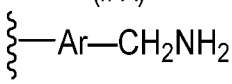
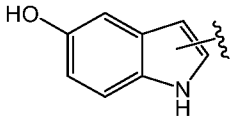
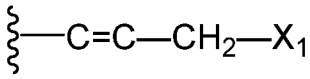
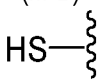
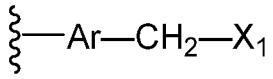
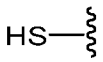
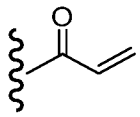
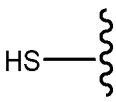
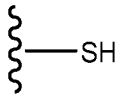
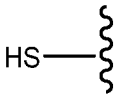
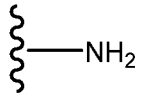
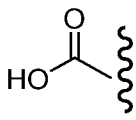
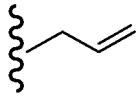
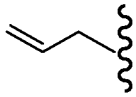
[00478] A peptide described herein can be cyclized (*i.e.*, macrocyclized). Cyclization can be achieved less ideally via a single disulfide bond, or more ideally via a peptide bond, alkyl bond, alkenyl bond, ester bond, thioester bond, ether bond, thioether bond, phosphate ether bond, azo bond, C—S—C bond, C—N—C bond, C═N—C bond, C═N—O bond, amide bond, lactam bridge, carbamoyl bond, urea bond, thiourea bond, amine bond, thioamide bond, or the like, but not limited to them. In some embodiments, the peptide is a cyclic peptide that is cyclized by a peptide bond, alkyl bond, alkenyl bond, ester bond, thioester bond, ether bond, thioether bond, phosphate ether bond, azo bond, C—N—C bond, C═N—C bond, C═N—O bond, amide bond, lactam bridge, carbamoyl bond, urea bond, thiourea bond, amine bond, or thioamide bond. In some embodiments, the cyclic peptide is cyclized by a thioether bond. In some embodiments, the cyclic peptide is cyclized via an oxime cyclization reaction. A cyclization of a peptide sometimes stabilizes the peptide structure and thereby enhance affinity for a target. 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 cyclized via oxime cyclization. In some embodiments, the peptide is cyclized between cysteine and haloacyl. In some embodiments, the peptide comprises a haloacetyl group (*e.g.*, chloroacetyl or bromoacetyl) at the N-terminus. In some embodiments, the peptide comprises a haloacetyl group (*e.g.*, chloroacetyl or bromoacetyl) at the C-terminus. In some embodiments, the peptide comprises a Cys at the C-terminus. In some embodiments, the peptide comprises a Cys at the N-terminus. In some embodiments, the cyclization occurs via a thioether bond between Cys and a haloacetyl group. In some embodiments, the cyclization occurs between the N-terminus and the C-terminus of the peptide.

[00479] As amino acids for macrocyclization, for example, an amino acid having the following functional group A and an amino acid having a corresponding functional group B can be used (see Table 4A). Either the functional group A or the functional group B may be placed on the N-terminal side. The amino acid having the functional group A and the amino acid having the functional group B can each be an N-terminal amino acid or C-terminal amino acid or a non-terminal amino acid. In some embodiments, an amino acid having the functional group A is placed at the N-terminus. In some embodiments, an amino acid having the functional group A is placed at the C-terminus. In some embodiments, an amino acid having the functional group A is placed at a non-terminal amino acid. In some embodiments, an amino acid having the functional group B is placed at the N-terminus. In some

embodiments, an amino acid having the functional group B is placed at the C-terminus. In some embodiments, an amino acid having the functional group B is placed at a non-terminal amino acid.

[00480]

Table 4A. Functional groups for cyclization

	Functional group A	Functional group B
(I)	 (I-A) X_1 is a halogen such as Cl, Br or I	 (I-B)
(II)	 (II-A)	 (II-B)
(III)	 (III-A) Ar is substituted or unsubstituted aryl or heteroaryl	 (III-B)
(IV)	 (IV-A) X_1 is a halogen such as Cl, Br or I	 (IV-B)
(V)	 (V-A) X_1 is a halogen such as Cl, Br or I; Ar is substituted or unsubstituted aryl or heteroaryl	 (V-B)
(VI)	 (VI-A)	 (VI-B)
(VII)	 (VII-A)	 (VII-B)
(VIII)	 (VIII-A)	 (VIII-B)
(IX)	 (IX-A)	 (IX-B)

[00481] In some embodiments, as the amino acid (I-A) in Table 4A can be, for example, a chloroacetylated amino acid can be used. Examples of the chloroacetylated amino acids include N-chloroacetyl-L-alanine, N-chloroacetyl-L-phenylalanine, N-chloroacetyl-L-tyrosine, N-chloroacetyl-L-tryptophan, N-3-(2-chloroacetamido)benzoyl-L-phenylalanine, N-3-(2-chloroacetamido)benzoyl-L-tyrosine, N-3-(2-

chloroacetamido)benzoyl-L-tryptophan, β-N-chloroacetyl-L-diaminopropanoic acid, γ-N-chloroacetyl-L-diaminobutyric acid, σ-N-chloroacetyl-L-ornithine, ε-N-chloroacetyl-L-lysine, N-3-chloromethylbenzoyl-L-tyrosine, and N-3-chloromethylbenzoyl-L-tryptophane and D-amino acid derivatives corresponding thereto (for example, N-Chloroacetyl-D-alanine, N-Chloroacetyl-D-phenylalanine, N-Chloroacetyl-D-tyrosine, and N-Chloroacetyl-D-tryptophan).

[00482] Examples of the amino acid (I-B) include, but are not limited to, cysteine, homocysteine, mercaptonorvaline, mercaptonorleucine, 2-amino-7-mercaptoheptanoic acid, 2-amino-8-mercaptooctanoic acid, and amino acids obtained by protecting the SH group of these amino acids and then eliminating the protecting group, and D-amino acid derivatives corresponding thereto.

[00483] The cyclization method can be carried out, for example, according to the method described in Kawakami, T. *et al.*, Nature Chemical Biology 5, 888-890 (2009); Yamagishi, Y. *et al.*, ChemBioChem 10, 1469-1472 (2009); Sako, Y. *et al.*, Journal of American Chemical Society 130, 7932-7934 (2008); or WO2008/117833.

[00484] In some embodiments, for example, the amino acid (II-A) is selected from propargylglycine, homopropargylglycine, 2-amino-6-heptynoic acid, 2-amino-7-octynoic acid, and 2-amino-8-nonynoic acid can be used. In addition, 4-pentynoylated or 5-hexynoylated amino acids can also be used. Examples of the 4-pentynoylated amino acids include N-(4-pentenoyl)-L-alanine, N-(4-pentenoyl)-L-phenylalanine, N-(4-pentenoyl)-L-tyrosine, N-(4-pentenoyl)-L-tryptophan, N-3-(4-pentynoylamido)benzoyl-L-phenylalanine, N-3-(4-pentynoylamido)benzoyl-L-tyrosine, N-3-(4-pentynoylamido)benzoyl-L-tryptophan, β-N-(4-pentenoyl)-L-diaminopropanoic acid, γ-N-(4-pentenoyl)-L-diaminobutyric acid, σ-N-(4-pentenoyl)-L-ornithine, and ε-N-(4-pentenoyl)-L-lysine, and D-amino acid derivatives corresponding thereto.

[00485] In some embodiments, for example, the amino acid (II-B) is selected from azidoalanine, 2-amino-4-azidobutanoic acid, azidoptonorvaline, azidonorleucine, 2-amino-7-azidoheptanoic acid, and 2-amino-8-azidooctanoic acid can be used. In addition, azidoacetylated or 3-azidopentanoylated amino acids can also be used. Examples of the azidoacetylated amino acids include N-azidoacetyl-L-alanine, N-azidoacetyl-L-phenylalanine, N-azidoacetyl-L-tyrosine, N-azidoacetyl-L-tryptophan, N-3-(4-pentynoylamido)benzoyl-L-phenylalanine, N-3-(4-pentynoylamido)benzoyl-L-tyrosine, N-3-(4-pentynoylamido)benzoyl-L-tryptophan, β-N-azidoacetyl-L-diaminopropanoic acid, γ-N-azidoacetyl-L-diaminobutyric acid, α-N-azidoacetyl-L-ornithine, and ε-N-azidoacetyl-L-lysine, and D-amino acid derivatives corresponding thereto.

[00486] The cyclization method can be performed, for example, according to the method described in Sako, Y. *et al.*, Journal of American Chemical Society 130, 7932-7934 (2008) or WO2008/117833.

[00487] Examples of amino acid (III-A) include, but are not limited to, N-(4-aminomethyl-benzoyl)-phenylalanine (AMBF) and 4-3-aminomethyltyrosine.

[00488] Examples of the amino acid (III-B) include, but are not limited to, 5-hydroxytryptophan (WoH). The cyclization method can be performed, for example, according to the method described in Yamagishi, Y. *et al.*, ChemBioChem 10, 1469-1472 (2009) or WO2008/117833.

[00489] Examples of the amino acid (IV-A) include, but are not limited to, 2-amino-6-chloro-hexynoic acid, 2-amino-7-chloro-heptynoic acid, and 2-amino-8-chloro-octynoic acid.

[00490] Examples of the amino acid (IV-B) include, but are not limited to, cysteine, homocysteine, mercaptonorvaline, mercaptonorleucine, 2-amino-7-mercaptoheptanoic acid, and 2-amino-8-mercaptooctanoic acid, amino acids obtained by protecting the SH group of these amino acids and then eliminating the protecting group, and D-amino acid derivatives corresponding thereto. The cyclization method can be performed, for example, according to the method described in WO2012/074129.

[00491] Examples of the amino acid (V-A) include, but are not limited to, N-3-chloromethylbenzoyl-L-phenylalanine, N-3-chloromethylbenzoyl-L-tyrosine, and N-3-chloromethylbenzoyl-L-tryptophane.

[00492] Examples of the amino acid (V-B) include, but are not limited to, cysteine, homocysteine, mercaptonorvaline, mercaptonorleucine, 2-amino-7-mercaptoheptanoic acid, and 2-amino-8-mercaptooctanoic acid, and amino acids obtained by protecting the SH group of these amino acids and then eliminating the protecting group, and D-amino acid derivatives corresponding thereto.

[00493] The amino acids I-A to V-A and I-B to V-B can be introduced into the peptide in a known manner by chemical synthesis or translation and synthesis described herein. In some embodiments, the cyclization reaction comprises forming a thioether bond using an amino acid comprising a sulfanyl group, *e.g.*, cysteine, homocysteine, mercaptonorvaline, mercaptovaline, mercaptonorleucine, 2-amino-7-mercaptoheptanoic acid, and 2-amino-8-mercaptooctanoic acid.

[00494] A peptide described herein can comprise one or more negatively charged amino acids and/or one or more positively charged amino acids. Positively charged amino acids include, for example, lysine, arginine, histidine, and amino acids that contain additional amine groups. Positively charged amino acids can comprise a heteroaryl substitution such as pyridine, imidazole, pyrazole, or triazole that has one or more ring nitrogen atoms. Negatively charged amino acids include, for example, amino acids that contain an additional carboxylic acid group such as glutamic acid or the like.

[00495] In some embodiments, a cyclic peptide of Formula (I), Formula (I-1), Formula (I-2), Formula (I-3), or Formula (I-4) 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. In some embodiments, a cyclic peptide of Formula (I), Formula (I-1), Formula (I-2), Formula (I-3), or Formula (I-4) 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 peptide of Formula (I), Formula (I-1), Formula (I-2), Formula (I-3), or Formula (I-4) 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. The net charge can be determined by aggregating the charge of each of the X1 to X12 amino acids (or each of the amino acid 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.

[00496] In some embodiments, a (cyclic) peptide of formula (I) 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 of the (cyclic) peptide.

[00497] In some embodiments, a (cyclic) peptide described herein (*e.g.*, a (cyclic) peptide of Formula (I), Formula (I-1), Formula (I-2), Formula (I-3), or Formula (I-4)) is configured to bind to 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 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. 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*.

[00498] In some embodiments, a conjugate described herein (*e.g.*, a conjugate comprising a (cyclic) peptide of Formula (I), Formula (I-1), Formula (I-2), Formula (I-3), or Formula (I-4)) is configured to bind to a plasma protein with a prescribed affinity, for example, measured as Plasma Protein Albumin Binding (PPB) percentage. PPB can be determined *in vitro* by HPLC 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. 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*.

[00499] In some embodiments, a (cyclic) peptide of Formula (I), Formula (I-1), Formula (I-2), Formula (Ia), Formula (Ib), or Formula (Ic) does not contain any S-S bond.

[00500] In some embodiments, a peptide of the present disclosure can be cyclized by forming a group as illustrated in Table 4B.

Table 4B. Ring Closing Groups (m and n are independently 0 or an integer from 1 to 6.)

-C(=O)-CH_2-
-C(=O)-CH_2-S-
-C(=O)-CH_2-S-CH_2-
-C(=O)-CH_2-S-CH_2-CH_2-
-$(CH_2)_m$-NH-CO-$(CH_2)_n$-
-$(CH_2)_m$-CO-NH-$(CH_2)_n$-
-$(CH_2)_m$-S-$(CH_2)_n$-
-$(CH_2)_m$-CH=CH-$(CH_2)_n$-
-$(CH_2)_m$-NH-$(CH_2)_n$-
-$(CH_2)_m$-S-CH_2-benzene-CH_2-S-$(CH_2)_n$-
-$(CH_2)_m$-triazole-$(CH_2)_n$-
-$(CH_2)_m$-succinimide-S-$(CH_2)_n$-
-C(=O)-CH_2-NH-CH_2-
-C(=O)-CH_2-O-CH_2-
-C(=O)-CH_2-CH_2-S-
-$(CH_2)_m$-S-S-$(CH_2)_n$-
-$(CH_2)_m$-C(=O)-NH-$(CH_2)_n$-
-$(CH_2)_m$-CH_2-CH_2-$(CH_2)_n$-

[00501] In some embodiments, m is 0 and n is 0. 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, 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.

[00502] In some embodiments, a peptide of the present disclosure, *e.g.*, peptides of Formulae (I), (I-1), (I-2), (I-3), (I-4), (III-1), or (III-2), can be cyclized by reacting a first functional group with a second functional group, see

Table 4C. In some embodiments, the first functional group is located at the N-terminus. In some embodiments, the first functional group is located at a non-terminal amino acid. In some embodiments, the second functional group is located at the C-terminus. In some embodiments, the second functional group is located at a non-terminal amino acid.

Table 4C. Formation of Ring Closing Groups

First Functional group (*e.g.*, at N-terminus)	Second Functional group (or amino acid) (*e.g.*, at C-terminus or at a non-terminal amino acid)
-C(=O)-CH_2Cl	Cysteine, homocysteine, lysine, homolysine, ornithine, diaminobutric acid, serine, homoserine, threonine, homothreonine
-$(CH_2)_n$-NH_2	Aspartic acid, glutamic acid, homoglutamic acid
-$(CH_2)_n$-CO_2H	Lysine, homolysine, ornithine, diaminobutric acid,
-$(CH_2)_n$-Br	Cysteine, homocysteine
-$(CH_2)_n$-CH=CH_2	Allyl-glycine, homoallyl-glycine
-$(CH_2)_n$-NH_2	Aspartate-4-semialdehyde, glutamate-5-semialdehyde
-$(CH_2)_n$-SH	Cysteine, homocysteine conjugated with 1,2- or 1,3- or 1,4-bis-(bromomethyl)benzene
-$(CH_2)_n$-alkyne	XaaC is an amino acid with a side chain with azide
-$(CH_2)_n$-N_3	Alkynyl-glycine, homoalkynyl-glycine
-$(CH_2)_n$-maleimide	Cysteine, homocysteine

[00503] In some embodiments, a conjugate comprising any one of peptide of Table 1 may further comprise amino acid residues at the N and/or C terminus of the peptide, which is not part of the cyclic structure. In some embodiments, the conjugate further comprises a linker.

[00504] 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.

[00505] 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.

[00506] A peptide described herein can comprise an N-substituted amino acid. In some embodiments, the N-substituted amino acid is a derivative of tryptophan, phenylalanine, tyrosine, arginine, histidine, isoleucine, leucine, lysine, or valine. In some embodiments, the N-substitution is an N-alkyl, such as N-methyl and N-ethyl. In some embodiments, the N-substitution is N-methyl. In some embodiments, the N-substitution is an N-aryl, such as N-

phenyl or N-biphenyl. In some embodiments, the N-substitution is an N-heteroaryl such as N-pyridyl. In some embodiments, the N-substituted amino acid is at the N-terminus of the peptide. In some embodiments, the N-substituted amino acid is a non-terminal amino acid.

[00507] In some embodiments, peptides described herein comprise one or more amino acids in Tables 5A to 5G.

Table 5A. Exemplary Amino Acids at N or C-terminus

N - Chloroacetyl - L - alanine	Acetyl - L - alanine
N - Chloroacetyl - L - phenylalanine	Acetyl - L - phenylalanine
N - Chloroacetyl - L - phenylalanine	Acetyl - L - tyrosine
N - Chloroacetyl - L - tyrosine	Acetyl - L - tryptophan
N - Chloroacetyl - L - tryptophan	Acetyl - D - alanine
N - Chloroacetyl - D - alanine	Acetyl - D - phenylalanine
N - Chloroacetyl - D - phenylalanine	Acetyl - D - tyrosine
N - Chloroacetyl - D - tyrosine	Acetyl - D - tryptophan
N - Chloroacetyl - D - tryptophan	N - 3 - chloromethylbenzoyl - L - tyrosine
	N - 3 - chloromethylbenzoyl - L - tryptophan

Table 5B. Exemplary Amino Acids That Crosslink With A Peptide

Nγ-(2-chloroacetyl)-α,γ-diaminobutylic acid
Nγ-(2-chloroacetyl)-α,γ-diaminopropanoic acid

Table 5C. D-amino Acids

D-Serine
D-Phenylalanine
D-Tyrosine
D-Tryptophan

Table 5D. Exemplary N-alkylamino Acids

N-alkyl-Glycine
N-alkyl-Alanine
N-alkyl-Phenylalanine
N-alkyl-Tyrosine
N-alkyl-Serine
N-alkyl-Histidine
N-alkyl-Tryptophan

Exemplary alkyl groups for Table 5D include methyl, ethyl, and propyl groups.

Table 5E. Exemplary Peptoid Blocks

N-ethyl-Glycine
N-n-propyl-Glycine
N-n-butyl-Glycine
N-n-pentyl-Glycine
N-n-hexyl-Glycine
N-n-heptyl-Glycine

N-n-octyl-Glycine
N-isopentyl-Glycine
N-(2-phenylethyl)-Glycine
N-(3-phenylpropyl)-Glycine
N-[2-(p-hydroxyphenyl)ethyl]-Glycine

Table 5F. Exemplary Unnatural Amino Acids

p-biphenylalanine
p-trifluoromethylphenylalanine
p-azidophenylalanine
p-biotinyl-aminophenylalanine
e-N-Biotinyl-lysine
e-N-Acetyl-lysine
L-Citrulline
L-5-Hydroxytryptphan
L-1,2,3,4,-Tetrahydroisoquinoline-3-carboxylic acid
Aminoisobutyric acid
N-methyl-aminoisobutyric acid
N-methyl-Phenylglycine

[00508] Amino acids used in the disclosed peptides can be substituted with similar amino acids. In some embodiments, an amino acid can be substituted with another amino acid with similar hydrophobicity. In some embodiments, an amino acid can be substituted with another amino acid with similar hydrophilicity. In some embodiments, an amino acid can be substituted with another amino acid with similar size. In some embodiments, an amino acid can be substituted with another amino acid with similar charge. In some embodiment, an amino acid can be substituted with another amino acid with a similar functional group. In some embodiments, an amino acid can be substituted with another amino acid with the same functional group.

[00509] In some embodiments, an amino acid described herein can be replaced with a variant thereof. Examples of an amino acid substitution or variant include derivatives having an amine, amide, ester, or carboxyl group as the C-terminus and/or N-terminus thereof. Additional examples of amino acid/peptide variants include those obtained by modification such as phosphorylation, alkylation (*e.g.*, methylation), acetylation, adenylylation, ADP-ribosylation, or glycosylation and fused protein obtained by fusion with another peptide or protein. These variants can be prepared by those skilled in the art in a known manner or a method based thereon. An amino acid variant further encompasses the amino acids that have the same functional groups but with different lengths of the side chain (*e.g.*, LysAc vs. OrnAc and cysteine vs. homocysteine). An amino acid variant further encompasses amino acids with a different aromatic moiety compared to the canonical amino acid (*e.g.*, the indole in tryptophan vs the 7-azaindole in 7-AzaTrp; the phenyl in phenylalanine vs the pyridine in 4Py). An amino acid variant further encompasses amino acids with optional substituents, *i.e.*, optionally substituted amino acid. In some embodiments, the optionally substituted amino acid is optionally substituted with one or more substituents independently selected from halogen, hydroxyl, cyano, amino, amide, nitro, ureido, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, C_3-C_6 cycloalkyl, 6-10 membered heterocycloalkyl, and 6-10 membered heteroaryl. In

some embodiments, the optionally substituted amino acid is optionally substituted with one or more substituents independently selected from halogen, -CN, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, oxo, -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 embodiments, substituents may include any substituents described herein, for example: halogen, hydroxy, oxo (=O), thioxo (=S), cyano (-CN), nitro ($-NO_2$), imino (=N-H), oximo (=N-OH), hydrazino ($=N-NH_2$), SF^5, $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2), and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2); and alkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, aralkynyl, cycloalkyl, cycloalkylalkyl, and heterocycle, any of which may be optionally substituted by alkyl, alkenyl, alkynyl, halogen, haloalkyl, haloalkenyl, haloalkynyl, oxo (=O), thioxo (=S), cyano (-CN), nitro ($-NO_2$), imino (=N-H), oximo (=N-OH), hydrazine ($=N-NH_2$), $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2) and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2); wherein each R^a is independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, and heterocycle, wherein each R^a, valence permitting, may be optionally substituted with alkyl, alkenyl, alkynyl, halogen, haloalkyl, haloalkenyl, haloalkynyl, oxo (=O), thioxo (=S), cyano (-CN), nitro ($-NO_2$), imino (=N-H), oximo (=N-OH), hydrazine ($=N-NH_2$), $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2) and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2); and wherein each R^b is independently selected from a direct bond or a straight or branched alkylene, alkenylene, or alkynylene chain, and each R^c is a straight or branched alkylene, alkenylene or alkynylene chain.

[00510] In some embodiments, a variant of an amino acid is selected from amino acids having one, two or three substituents based on the amino acid, and wherein the substituents are independently selected from halogen, -CN, $-NH_2$, -NH(C_1-C_3alkyl), $-N(C_1$-$C_3alkyl)_2$, oxo, -OH, $-CO_2H$, $-CO_2-C_1-C_3$alkyl, $-C(=O)NH_2$, -C(=O)NH(C_1-C_3alkyl), $-C(=O)N(C_1$-$C_3alkyl)_2$, $-S(=O)_2NH_2$, $-S(=O)_2$NH(C_1-C_3alkyl), $-S(=O)_2N(C_1$-$C_3alkyl)_2$, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 alkoxy, C_6-C_{10} aryl, C_3-C_6 cycloalkyl, 6-10 membered heterocycloalkyl, and 6-10 membered heteroaryl.

[00511] In some embodiments, the variant is selected from amino acids having one or two substituents based on the amino acid, and wherein the substituents are independently selected from halogen, -CN, $-NH_2$, -NH(C_1-C_3alkyl), $-N(C_1$-$C_3alkyl)_2$, oxo, -OH, $-CO_2H$, $-CO_2-C_1-C_3$alkyl, $-C(=O)NH_2$, -C(=O)NH(C_1-C_3alkyl), $-C(=O)N(C_1$-$C_3alkyl)_2$, and C_1-C_6 alkyl. In some embodiments, the variant is selected from amino acids having one or two substituents based on the amino acid, and wherein the substituents are independently selected from halogen, -CN, $-NH_2$, -NH(C_1-C_3alkyl), $-N(C_1$-$C_3alkyl)_2$, and C_1-C_6 alkyl. In some embodiments, the variant is selected from amino acids having one or two substituents based on the amino acid, and wherein the substituents are

independently selected from C_1-C_6 alkyl.

[00512] In some embodiments, a variant of an amino acid is selected from amino acids that have the similar hydrophilicity or hydrophobicity compared to the amino acid. Thus, in some embodiments, a positively charged amino acid can be a variant of another positively charged amino acid. In some embodiments, a negatively charged amino acid can be a variant of another negatively charged amino acid. In some embodiments, a zwitterionic amino acid can be a variant of another zwitterionic amino acid.

[00513] In some embodiments, a hydrophilic amino acid has an electrically charged side chain. In some embodiments, a hydrophilic amino acid has a positive charge. In some embodiments, a hydrophilic amino acid has a negative charge. In some embodiments, a hydrophilic amino acid is zwitterionic (*e.g.*, KCOpipzaa). In some embodiments, a hydrophilic amino acid comprises a -OH, COOH, -NH- or NH_2 moiety. In some embodiments, a hydrophilic amino acid comprises -OH, -C(O)OH, -NHC(=NH)NH_2, -NHC(O)NH_2, -C(O)NH_2, or -NHC(O)CH_3. In some embodiments, a hydrophilic amino acid comprises a side chain of C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, -$C_{0\text{-}6}$ alkylene-NH-C(=NH)-NH_2, -$C_{0\text{-}6}$ alkylene-CO-NH_2, -$C_{0\text{-}6}$ alkylene-COOH, or -NH-CO-$C_{1\text{-}6}$ alkyl.

[00514] In some embodiments, a hydrophobic amino acid is not charged. In some embodiments, a hydrophobic amino acid contains at least 2 contiguous carbon atoms. In some embodiments, a hydrophobic amino acid comprises at least 3 contiguous carbon atoms, either linear or branched. In some embodiments, a hydrophobic amino acid comprises at least 4 contiguous carbon atoms, either linear or branched. In some embodiments, a hydrophobic amino acid comprises at least 5 contiguous carbon atoms, either linear or branched. In some embodiments, a hydrophobic amino acid comprises an ethylene moiety in the side chain. In some embodiments, a hydrophobic amino acid comprises a propylene moiety in the side chain. In some embodiments, a hydrophobic amino acid comprises a butylene moiety in the side chain. In some embodiments, a hydrophobic amino acid comprises phenyl moiety. In some embodiments, a hydrophobic amino acid comprises a heteroaryl moiety. In some embodiments, a hydrophobic amino acid is Trp, Tyr, Phe, or derivatives thereof.

[00515] In some embodiments, a variant of an amino acid is selected from amino acids that have the same functional group as the amino acid, and wherein the variant has a different length of a side chain compared to the amino acid. In some embodiments, a variant of an amino acid is selected from amino acids that have the same charge compared to the amino acid. In some embodiments, a variant of an amino acid is selected from amino acids that have the same polarity compared to the amino acid. In some embodiments, an amino acid comprising an aromatic group can be a variant of another amino acid having an aromatic group. In some embodiments, an amino acid comprising a phenyl can be a variant of another amino acid having a phenyl. In some embodiments, an amino acid comprising a heteroaryl can be a variant of another amino acid having a heteroaryl. Amino acids having an aromatic group include, but are not limited to, F, W, F4G, 4Py ,3Py, F4COO, F3G, 3Py6COO, 4Py2NH2, 3Py5COO, F3COO, 3Py6NHAc, F4C, F4OMe, Nal2, F3aao, F4aa, F4aao, 3Py6NHaa, F3CON, F4F, F4OEt, F4Me, F4CON, F4CONPEG4Me, F3OMe, YaeCOpipzaa, F4aaopipzaa, 4Pdo, 3Py6CON, F4amCOpipzaa, F4u, F4CONdMe, F4ms, F34dOMe, F3C, F3CONdMe, 5Inda, F3aa, 3Py6Nhae, 3Py6OMe, MeNal2, MeNal27N, MeF34diox, MeF34dOMe, MeF4T, MeW7N, MeF3C4Me, MeF3Me4C, Bph,

3Py6Ph, F41Me4Pyz, F43Pyz, F44Pyz, F41Pyz, F41Me3Pyz, F41Et4Pyz, F41MeOe4Pyz, F41MeOp4Pyz, F44thp, F4Ac4Pip, PhNva, PhNle, Yph, Ybn, F4tb, F4OPr, Yae, Me3Py, W5N and MeW1Me.

[00516] In some embodiments, an amino acid comprising a cycloalkyl group can be a variant of another amino acid having a cycloalkyl group. In some embodiments, an amino acid comprising a heterocycloalkyl group can be a variant of another amino acid having a heterocycloalkyl group.

[00517] In some embodiments, a variant of an amino acid is selected from amino acids that have similar polarity and/or charge with the amino acid. For example, in some embodiments, a polar, uncharged amino acid can be a variant of another polar, uncharged amino acid (*e.g.*, Hgn, Q, S, T, Qglucamine),

[00518] In some embodiments, a variant of an amino acid has the same number of hydrogen donor as the amino acid. In some embodiments, a variant of an amino acid has the same number of hydrogen acceptor as the amino acid.

[00519] In some embodiments, the variant has a molecular weight that does not vary for more than 14, 28, 30, 45 or 60 g/mol compared to the amino acid. In some embodiments, the variant has a molecular weight that does not vary for more than 14 g/mol compared to the amino acid. In some embodiments, the variant has a molecular weight that does not vary for more than 50 g/mol compared to the amino acid. In some embodiments, the variant has a molecular weight that does not vary for more than 28 g/mol compared to the amino acid.

[00520] An amino acid variant further encompasses amino acids wherein a functional group is substituted with another functional group having similar properties, *e.g.*, a cysteine can be substituted with a homocysteine. In some embodiments, an aryl functional group can be substituted with an aryl or heteroaryl group. In some embodiments, a heteroaryl functional group can be substituted with an aryl or heteroaryl group. In some embodiments, an amino functional group can be substituted with a NH(alkyl) group.

[00521] As used herein, the expression “conservative amino acid substitution” refers to a substitution of functionally equivalent or similar amino acids. A conservative amino acid substitution in a peptide brings about a static change to the amino acid sequence of the peptide. For example, one or two or more amino acids having similar polarity act functionally equivalent to each other and bring about a static change in the amino acid sequence of the peptide. In general, a substitution within a certain group may be considered conservative regarding structure and function. However, as is clear to a person having ordinary skill in the art, the role played by a defined amino acid residue may be determined by its implication in the three-dimensional structure of the molecule containing the amino acid. For example, a cysteine residue in an oxidized-type (disulfide) form may have a lower polarity than that of a reduced-type (thiol) form. The long aliphatic part of the arginine side chain may constitute structurally and functionally important features. Furthermore, the side chain (tryptophan, tyrosine, phenylalanine) including an aromatic ring may contribute to ion-aromatic interaction or cation-pi interaction. In such a case, even if the amino acids having these side chains are substituted for amino acids belonging to the acidic or non-polar groups, they may be structurally and functionally conservative. There is a possibility that residues such as proline, glycine, cysteine (disulfide foam) have a direct effect on the three-dimensional structure of the main chain and often may not be substituted without structural distortion.

[00522] Conservative amino acid substitution, as shown below, includes specific substitution based on the

similarity of side chains (for example, substitutions are described in Lehninger, Biochemistry, Revised 2nd Edition, published in 1975, pp. 73 to 75: L. Lehninger, Biochemistry, 2nd edition, pp. 73 to 75, Worth Publisher, New York (1975)), incorporated herein by reference, and typical substitution.

[00523] Hydrophobic amino acids include amino acids that exhibit hydrophobicity, including alanine (also referred to as "Ala" or simply "A"), glycine (also referred to as "Gly" or simply "G"), valine (also referred to as "Val" or simply "V"), leucine (also referred to as "Leu" or simply "L"), isoleucine (also referred to as "Ile" or simply "I"), proline (also referred to as "Pro" or simply "P"), phenylalanine (also referred to as "Phe" or simply "F"), tryptophan (also referred to as Trp" or simply "W"), tyrosine (also referred to as "Tyr" or simply "Y"), and methionine (also referred to as "Met" or simply "M").

[00524] Exemplary hydrophobic amino acids may be further divided into the following groups:

- Aliphatic amino acids: Amino acids having a fatty acid or hydrogen in the side chain, including *e.g.*, Ala, Gly, Val, Ile, and Leu.
- Aliphatic/branched-chain amino acids: Amino acids having a branched fatty acid in the side chain, including *e.g.*, Val, Ile, and Leu.
- Aromatic amino acids: Amino acids having an aromatic ring in the side chain, including *e.g.*, Trp, Tyr, and Phe.

[00525] In some embodiments, a hydrophobic amino acid has a C1-C8 alkyl, cycloalkyl, or heterocycloalkyl, wherein the alkyl, cycloalkyl, and heterocycloalkyl are each independently, optionally substituted. In certain embodiments, a hydrophobic amino acid is I, Eva, all, TMe, SMe, Gcpr, Gcpe, Gthp, dMeS, TdMe, or Cbg.

[00526] Hydrophilic amino acids or amino acids comprising a hydrophilic side chain, include amino acids that exhibit hydrophilicity, including *e.g.*, serine (also referred to as "Ser" or simply "S"), threonine (also referred to as "Thr" or simply "T"), cysteine (also referred to as "Cys" or simply "C"), asparagine (also referred to as "Asn" or simply "N"), glutamine (also referred to as "Gln" or simply "Q"), aspartic acid (also referred to as "Asp" or simply "D"), glutamic acid (also referred to as "Glu" or simply "E"), Elysine (also referred to as "Lys" or simply "K"), arginine (also referred to as "Arg" or simply "R"), and histidine (also referred to as "His" or "H").

[00527] Exemplary hydrophilic amino acids may be further divided into the following groups:

- Acidic amino acids: Amino acids whose side chains exhibit acidity, including Asp and Glu.
- Basic amino acids: Amino acids whose side chains exhibit basicity, including Lys, Arg, and His.
- Neutral amino acids: Amino acids whose side chains exhibit neutrality, including Ser, Thr, Asn, Gln, and Cys.

[00528] Exemplary hydrophilic amino acids include, for example, D, Q, A, E, S, N, T, C, H, or a variant thereof (including D-amino acid such as da and variations such as KCOpipzetOH, Cit, COmeglumine, KCOpipzaa, A4paa, Hgl, F4COO, KCOpip4COO, KAc, Hgn, Har, DapCOpipzaa, Acpr, Cba, NleCOO, NleOH, Atb, Nva, Nle, DapAc, Abu, Nmm, Ndm, Ncit, Cit or the like). In some aspect, hydrophilic amino acid is optionally N-methylated such as MeD.

[00529] In some embodiments, a peptide described herein comprises an amino acid that affects the direction of

the main chain, *e.g.*, Gly and Pro. In some embodiments, a peptide described herein comprises a sulfur-containing amino acid, *e.g.*, Cys and Met. In some embodiments, a peptide described herein comprises an amino acid that comprises an aromatic ring, or aromatic amino acids, which can be optionally substituted. Amino acids comprising an aromatic ring or armatic amino acids include, *e.g.*, F (Phe; phenylalanine), Y (Tyr: tyrosine), W (Trp; tryptophan).

[00530] In some embodiments, W or a variant thereof can be W, an amino acid having a heteroatom in the indole ring of W in the side chain, an amino acid in which the hydrogen of NH in the indole ring of W is substituted, or an amino acids having a substituent in the benzene ring of W, or the like.

[00531] In some embodiments, F or a variant thereof can be F (phenylalanine), an amino acid comprising a phenyl, pyridinyl, indazolyl, or naphthalyl in its side chain, wherein said phenyl, pyridinyl, indazolyl or naphthalyl is optionally substituted with one or more substituents each independently selected from halogen, -C_{1-3}alkyl, -OH, -NH_2, -CN, -C(=O)OH, -C(=O)NH_2, -NHC(=O)CH_2, -C_{1-3}alkylene-C(=O)OH, -C_{1-3}alkylene-C(=O)NH_2, -O-C_{1-3}alkylene-C(=O)OH, -O-C_{1-3}alkylene-C(=O)NH_2, -C_{1-3}alkylene-C(=O)-5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH, -O-C1-3alkylene-C(=O)- 5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH, -C1-3alkylene-NHC(=O)- 5- to 6-membered heterocycloalkylene-C1-3alkylene-C(=O)OH, -O-C_{1-3}alkylene-NHC(=O)-5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH, and -NH-C_{1-3}alkylene-C(=O)OH, -NHC(=O)NH_2, -C_{1-3}alkylene-C(NH_2)-COOH, -NH-CO-CH_3, -NH-C_{1-3}alkylene-NH_2, -C(=O)-N(CH_2)$_2$, -S(=O)$_2$-CH_3, -C_{1-3}alkylene-NH-C(=O)- 5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH, and -O-C_{1}.3alkylene-NH-C(=O)- 5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH, -O-phenyl, -O-C_{1-3}alkylene-phenyl, pyridinyl, imidazolyl, pyrazolyl, N-C_{1-3}alkylene pyrazolyl, N-C_{1-3}alkylene(-O-C_{1-3}alkyl) pyrazolyl, pyranyl, tetrahydropyranyl, piperidinyl, N-C_{1-3}alkylene-C(=O)-piperidiny ; or the like. In some aspect, F or a variant thereof is optionally N-methylated.

[00532] In some embodiments, Y or a variant thereof can be Y, an amino acid having a hydroxyphenyl ring, wherein the hydrogen atom in hydroxyphenyl of Y or of the variant is optionally substituted with one or more substituents selected from -C1-3alkyl, -C1-3alkylene-C(=O)OH, halogen, -OH, -C(=O)OH, -O-CH_3, -C_{1-3}alkylene-C(=O)- 5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH, and -C_{1-3}alkylene-NHC(=O)- 5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH. In some embodiments, a variant of W or a variant thereof can be W, W1Me, or W7N or the like. In some embodiments, W or a variant thereof is optionally N-methylated (e.g., MeW1Me or MeW7N).

[00533] In certain embodiments, F or Y or a variants thereof is Y, F3G, 3Py6COO, 4Py2NH2, 3Py5COO, F3COO, 3Py6NHAc, F, F4C, F4OMe, F4COO, Nal2, F3aao, F4aa, F4aao, 3Py6Nhaa, 5Pdo, F3CON, F4F, F4OEt, F4Me, F4CON, F4CONPEG4Me, F3OMe, YaeCOpipzaa, F4aaopipzaa, 4Pdo, 3Py6CON, Atp, Cha4cH, Cha4tH, Cha4cOMe, A1mor, F4amCOpipzaa, F4OMe, F4u, F4CONdMe, F4ms, F34dOMe, F3C, F3CONdMe, 5Inda, F3aa, 3Py6Nhae, 3Py6OMe, F4amCOpipzaa, Bph, 3Py6Ph, F41Me4Pyz, F43Pyz, F44Pyz, F41Pyz, F41Me3Pyz, F41Et4Pyz, F41MeOe4Pyz, F41MeOp4Pyz, F44thp, F4Ac4pip, PhNva, PhNle, Yph, Ybn, F4tb, or F4oPr.

[00534] In some embodiments, a monocyclic aromatic amino acid can be amino an amino acid having a phenyl or pyridinyl optionally substituted with one or more substituents each independently selected from halogen, -C1-

3alkyl, and trifluoromethy.In some embodiment, a bicyclic aromatic amino acid can be an amino acid having a naphthalyl, quinolyl, or indazolyl optionally substituted with one or more substituents each independently selected from H or C1-3alkyl. In some embodiments, bicyclic aromatic acid can be W (tryprophan), or a variant thereof, or N-methylated thereof. In certain embodiments, a monocycic aromatic amimo acid is MeF3C3Me, MeF34dOMe, MeF4T,or M3FMe4C. In certain embodiments, a bucyclic aromatic amino acid is MeNal2, MeNal27N, MeF34diox, MeW1Me, or MeW7N.

[00535] In some embodiments, an amino acid described herein is N-alkylated.

[00536] In some embodiments, an amino acid described herein is not N-alkylated (*e.g.*, an amino acid with -H on the alpha-amino group).

[00537] 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.

[00538] In some embodiments, an amino acid described herein is N-alkylated. In some embodiments, an amino acid described herein is not N-alkylated (*e.g.*, an amino acid with -H on the alpha-amino group).

[00539] The peptides described herein can comprise one or more unnatural amino acids. Unnatural amino acids include, but are not limited to, (1) amino acids corresponding to an amino acid residue on a polypeptide subjected to modification after expression (ex. phosphorylated tyrosine, acetylated lysine, or farnesylated cysteine), (2) amino acids that cannot be used in expression on a ribosome but occur naturally, and (3) artificial amino acids that do not occur naturally (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, 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 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.

[00540] Unnatural amino acids include, for example, N-alkyl amino acids in which a natural amino acid described above is N-alkylated, *e.g.*, those modified with lower alkyl groups (for example, of C1 to C5, C1 to C3, and C1) in which the nitrogen forming a peptide bond is branched or not branched. Exemplary N-alkyl amino acids include, *e.g.*, N-ethyl amino acid, N-butyl amino acid, and N-methyl amino acid. Also included are amino acids to which a functional group is further added to the side chain of a natural amino acid or substituted for another functional group (for example, an amino acid having a substitution or an addition in a part such as an arylene group, an alkylene group, or the like of the side chain; an amino acid wherein the arylene group or the alkyl group of the side chain has an increased C-number; an amino acid having a substitution in the aromatic ring of the side chain; a heterocyclic or condensed cyclic amino acid; or the like). Exemplary N-alkyl amino acids further include, *e.g.*, N-alkyllysine and N-methyllysine. Exemplary N-alkyl amino acids further include, *e.g.*, N-methyllysine in which an albumin binder is bound.

[00541] In a non-limiting manner, unnatural amino acids include, but are not limited to N-methyl amino acids, F4G, 4Py, 3Py, Cit, KCOpipzaa, Eva, Ahp, F4COO, KCOpip4COO, Aib, Hpr, Sbu, MeDapCOpipzaa, Scbm, Scpe, HseBu, A4paa, Spent, Hgl, Hsecpe, Hgn, DapCOpipzaa, MeD, CmG, Medd, HseEt, HseiPr, CrmG, CeG, CrpG, MeHgl, MeCit, F3G, 3Py6COO, 4Py2NH2, 3Py5COO, F3COO, 3Py6NHAc, F4C, F4OMe, Nal2, F3aao, F4aa, F4aao, 3Py6Nhaa, 5Pdo, F3CON, F4F, F4OEt, F4Me, F4CON, F4CONPEG4Me, F3OMe, YaeCOpipzaa, F4aaopipzaa, 4Pdo, 3Py6CON, Atp, Cha4cH, Cha4tH, Cha4cOMe, A1mor, F4amCOpipzaa, Chg, Tbg, Gcpr, Gcpe, Acpr, Cba, Gthp, NleCOO, NleOH, Atb, Nva, Nle, DapAc, Abu, Ncit, dMeS, TdMe, Cbg, NvaOMe, NleOMe, AhpOMe, F4u, F4CONdMe, F4ms, F34dOMe, F3C, F3CONdMe, 5Inda, F3aa, 3Py6Nhae, 3Py6OMe, MeNal2, MeNal27N, MeF34diox, MeF34dOMe, MeF4T, MeW7N, MeF3C4Me, MeF3Me4C, Bph, 3Py6Ph, F41Me4Pyz, F43Pyz, F44Pyz, F41Pyz, F41Me3Pyz, F41Et4Pyz, F41MeOe4Pyz, F41MeOp4Pyz, F44thp, F4Ac4Pip, PhNva, PhNle, Yph, Ybn, F4tb, F4OPr, S3REt, Yae, datb, Me3Py, W5N, MeA4paa, Mel, MeA, MeG, MeV, MeT, all, TMe, MeQ, MeTMe, MeK, MeKAc, Har, KAc, dd, EtG, K(biotin), MeeG, CmpG, Nmm, Ndm, SMe, HseMe, SiPr, SPr, MeW1Me, MeQdMe, MeSMe, MeHseMe, MeKCOpipzaa, KCOpipzetOH, KCOmeglumine, MeK, MeK(de), MeK(H), MeK(df), MeK(datb) and the like. Note that D-amino acids such as da may be classified as D-amino acids, but they may also be classified according to the properties of their side chains, and N-methyl amino acids may be classified as N-alkyl amino acids and may also be classified according to the property of the side chain.

[00542] 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), and 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).

[00543] 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.

[00544] In some embodiments, the peptide described herein comprises a basic amino acid. Examples of the basic amino acid include arginine, lysine, citrulline, ornithine, creatine, histidine, diaminobutanoic acid, and diaminopropionic acid.

[00545] In some embodiments, provided herein is a peptide having 90% or more sequence identity to any of sequences disclosed herein. In some embodiments, the sequence identity is at least 95% or 99%.

[00546] In some embodiments, the 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. In some cases, when a peptide is cyclized, protease resistance is improved, metabolic stability is improved, and restrictions are also added to conformational change, so that rigidity is increased and membrane permeability and affinity for the target protein is improved.

[00547] In some embodiments, the peptide of the present disclosure has a cyclic structure in which a chloroacetylated amino acid and a cysteine or cysteine variant such as MeC residue present in the peptide are bound. In one aspect, the peptide has a cyclic structure in which an N-terminal amino acid and a cysteine or cysteine variant such as MeC residue present in the peptide are bound. In some embodiments, the peptide has a cyclic structure in which an N-terminal amino acid and the twelve cysteine or cysteine variant such as MeC residue present in the peptide are bound. In some embodiments, the peptide has a cyclic structure in which a chloroacetylated N-terminal amino acid and the 12th cysteine or cysteine variant such as MeC residue present in the peptide are bound. “Chloroacetylation” may be replaced with “haloacetylation” using another halogen. Furthermore, “acetylation” may be “acylation” using an acyl group other than an acetyl group.

[00548] In some embodiments, the 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.

[00549] Further exemplary peptides include BMS-753493, Somatostatins, Octreotide, Octreotate, Lanreotide, Pasireotide, JR-11, L-779,976, BIM-23120, Satoreotide, depreotide, 18F-KYNDRLPLYISNP (SEQ ID NO: 106), CalX-P1, and FAP-2286.

[00550] The peptide of the present disclosure embraces salts thereof. As the salts of the peptide, salts with physiologically acceptable base or acid are used. Examples include addition salts with an inorganic acid (such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, or phosphoric acid), addition salts with an organic acid (such as p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carboxylic acid, succinic acid, citric acid, benzoic acid, or acetic acid), inorganic bases (such as ammonium hydroxide, alkali or alkaline earth metal hydroxide, carbonate, or bicarbonate), and an amino acid.

GPC3-Binding Peptide and Peptide Having GPC3 Antagonistic Activity

[00551] Glypican-3 (GPC3) is a protein that in humans is encoded by the GPC3 gene. GPC3 may be upregulated in multiple cancers, often correlating with disease progression, metastasis and poor prognosis *e.g.*, in solid tumors such as hepatocellular, lung, gastric, and ovarian.

[00552] GPH3 belongs to the sulfate heparin proteoglycan family, and which is anchored on the cell membrane surface by phosphatidylinositol (GPI) anchor.

[00553] GPC3 plays an important role in the cell proliferation of embryo layer tissue. Deletion of GPC3 gene causes excessive growth syndrome, namely Simpson-Golabi-Behmel syndrome (SGBS). GPC3 was clearly

expressed throughout the entire fetal stage, and after birth to adult stage, except for placental, breast, mesodermal, ovarian, lung and kidney tissue with weak expression, other normal tissues have no obvious expression.

[00554] In some embodiments, the peptide of the present technology binds to GPC3. In some implementations of these embodiments, the peptide has GPC3 antagonistic activity. In some instances, the peptide binds to human GPC3 (hGPC3) and has hGPC3 antagonistic activity, such as inhibiting the ability of GPC3 to promote or stabilize Wnt / Frizzled interaction and/or downstream signaling.

[00555] As used herein, the term "GPC3" refers to any form of GPC3 and a variant thereof for retaining at least a part of the activity of GPC3. The GPC3 includes all the native sequences of GPC3 in mammals such as, for example, humans, dogs, cats, horses, and cows, unless otherwise specifically described as human GPC3 (hGPC3). One exemplification of GPC3 is hGPC3 (Gene ID:2719), which is human GPC3 and is a protein having an amino acid sequence (SEQ ID NO: 107, Isoform 1, P51654-1).

[00556] MAGTVRTACLVVAMLLSLDFPGQAQPPPPPPDATCHQVRSFFQRLQPGLKWVPETPVPGSDLQVCL PKGPTCCSRKMEEKYQLTARLNMEQLLQSASMELKFLIIQNAAVFQEAFEIVVRHAKNYTNAMFKNNYPSLTPQA FEFVGEFFTDVSLYILGSDINVDDMVNELFDSLFPVIYTQLMNPGLPDSALDINECLRGARRDLKVFGNFPKLIMTQ VSKSLQVTRIFLQALNLGIEVINTTDHLKFSKDCGRMLTRMWYCSYCQGLMMVKPCGGYCNVVMQGCMAGVVEI DKYWREYILSLEELVNGMYRIYDMENVLLGLFSTIHDSIQYVQKNAGKLTTTIGKLCAHSQQRQYRSAYYPEDLFI DKKVLKVAHVEHEETLSSRRRELIQKLKSFISFYSALPGYICSHSPVAENDTLCWNGQELVERYSQKAARNGMKN QFNLHELKMKGPEPVVSQIIDKLKHINQLLRTMSMPKGRVLDKNLDEEGFESGDCGDDEDECIGGSGDGMIKVK NQLRFLAELAYDLDVDDAPGNSQQATPKDNEISTFHNLGNVHSPLKLLTSMAISVVCFFFLVH.

[00557] As used herein, the expression "has avidity for GPC3" or "binds to GPC3" indicates having the activity of binding to GPC3. Binding site of the peptide of the present invention on the GPC3 is not limited, the peptide can bind to anywhere on the GPC3 protein. Binding to GPC3 may be measured by any method for measuring known intermolecular binding. In a non-limiting manner, for example, this may be determined by competitive binding assays such as surface plasmon resonance (SPR) assays, scatter analysis and/or radioimmunoassays (RIA), enzyme immunoassays (EIA), and sandwich and competitive assays, and in any suitable manner which is known, including different variants of the examples given that are known in the technical field.

[00558] In one aspect, the binding affinity of the peptide of the present technology is at most 100 nM as determined by Kd in surface plasmon resonance (SPR) analysis. In some implementations, the Kd of the peptides of the present technology is 100 nM ore less, 50 nM or less, 30 nM or less, 20 nM or less, 10 nM or less, 5 nM or less, 4 nM or less, 3 nM or less, 2 nM or less, 1 nM or less, 0.9 nM or less, 0.5 nM or less, 0.4 nM or less, 0.3 nM or less, 0.2 nM or less, 0.1 nM or less, 0.09 nM or less, 0.08 nM or less, 0.07 nM or less, 0.06 nM or less, 0.05 nM or less, 0.04 nM or less, 0.03 nM or less, 0.02 nM or less, 0.01 nM or less.

[00559] In some embodiments, a peptide described herein has a binding affinity to a human GPC3 of at most 1, 5, 10, 50, 100, 200, 500, 1000, 5000 or 10,000 nM as determined by Kd in surface plasmon resonance (SPR) analysis. In some embodiments, a peptide described herein has a binding affinity to a human GPC3 of at most 100nM as determined by Kd in surface plasmon resonance (SPR) analysis. In some embodiments, a peptide described herein has a binding affinity to a human GPC3 of at most 1 nM as determined by Kd in surface plasmon

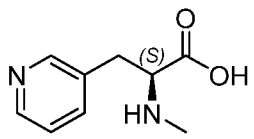
resonance (SPR) analysis. In some embodiments, a peptide described herein has a binding affinity to a human GPC3 of at most 2 nM as determined by Kd in surface plasmon resonance (SPR) analysis. In some embodiments, a peptide described herein has a binding affinity to a human GPC3 of at most 5 nM as determined by Kd in surface plasmon resonance (SPR) analysis. In some embodiments, a peptide described herein has a binding affinity to a human GPC3 of at most 10 nM as determined by Kd in surface plasmon resonance (SPR) analysis.

[00560] In some embodiments, a conjugate described herein has a binding affinity to a human GPC3 of at most 1, 5, 10, 50, 100, 200, 500, 1000, 5000 or 10,000 nM as determined by Kd in surface plasmon resonance (SPR) analysis. In some embodiments, a conjugate described herein has a binding affinity to a human GPC3 of at most 100nM as determined by Kd in surface plasmon resonance (SPR) analysis. In some embodiments, a conjugate described herein has a binding affinity to a human GPC3 of at most 1 nM as determined by Kd in surface plasmon resonance (SPR) analysis. In some embodiments, a conjugate described herein has a binding affinity to a human GPC3 of at most 2 nM as determined by Kd in surface plasmon resonance (SPR) analysis. In some embodiments, a conjugate described herein has a binding affinity to a human GPC3 of at most 5 nM as determined by Kd in surface plasmon resonance (SPR) analysis. In some embodiments, a conjugate described herein has a binding affinity to a human GPC3 of at most 10 nM as determined by Kd in surface plasmon resonance (SPR) analysis.

[00561] In one aspect, the binding affinity of the peptide or conjugate of the present disclosure is at most 100 nM as determined by Kd in surface plasmon resonance (SPR) analysis. In some implementations, the Kd of the peptide or conjugate of the present disclosure is 100 nM ore less, 50 nM or less, 30 nM or less, 20 nM or less, 10 nM or less, 5 nM or less, 4 nM or less, 3 nM or less, 2 nM or less, 1 nM or less, 0.9 nM or less, 0.5 nM or less, 0.4 nM or less, 0.3 nM or less, 0.2 nM or less, 0.1 nM or less, 0.09 nM or less, 0.08 nM or less, 0.07 nM or less, 0.06 nM or less, 0.05 nM or less, 0.04 nM or less, 0.03 nM or less, 0.02 nM or less, 0.01 nM or less.

[00562] In certain embodiments, the peptides and conjugates described herein comprises one or more unnatural amino acids that are not any one of the 20 canonical amino acids found in proteins. Representative unnatural amino acids that can be incorporated into the peptides and conjugates described herein are provided in the table below.

Table 5G. Structures of exemplary unnatural amino acids
that can be incorporated into a peptide / conjugate described herein



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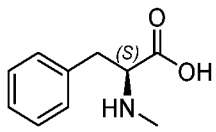
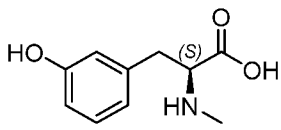


MeF



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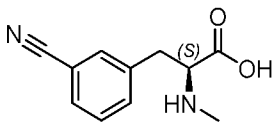

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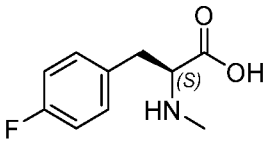
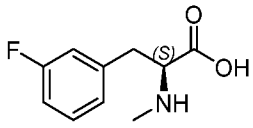


MeF4F



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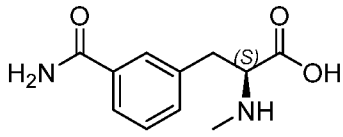
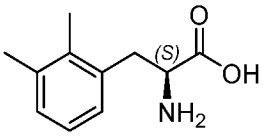
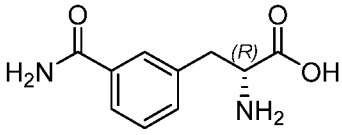


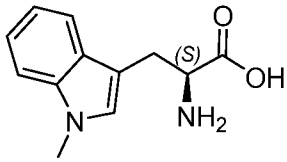
MeF3CON



F23dMe



df3CON



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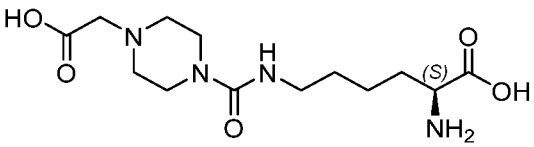
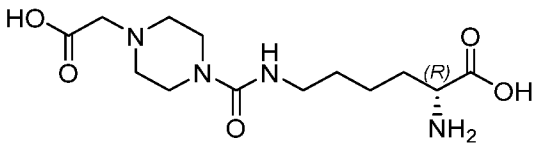


KCOpipzaa



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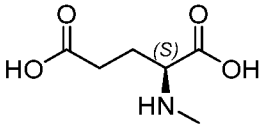

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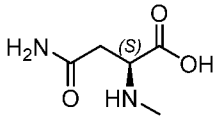

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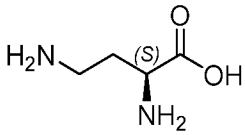
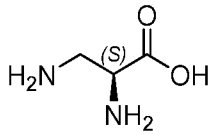
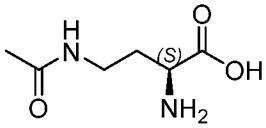


Dab



Dap



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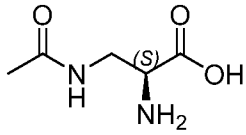

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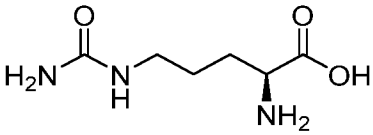

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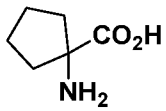

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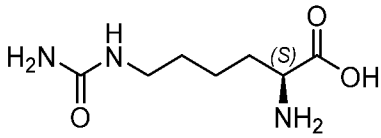

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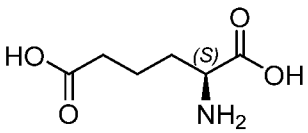

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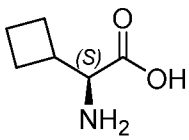
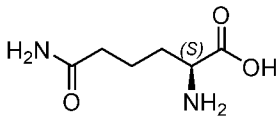


Cbg



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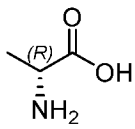

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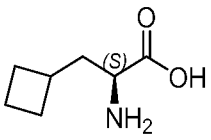

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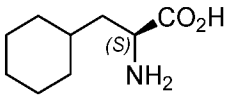

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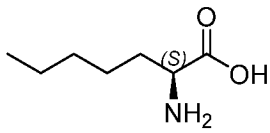

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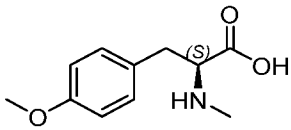

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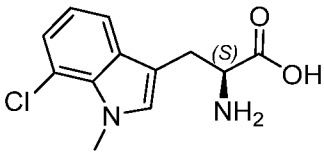

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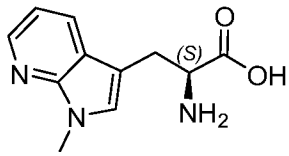

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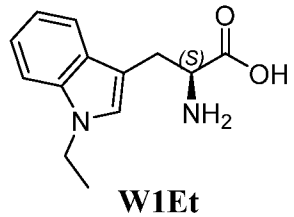

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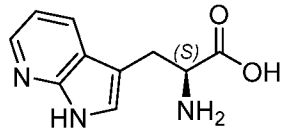

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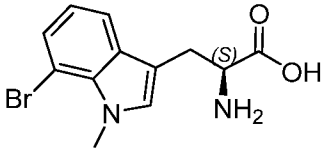

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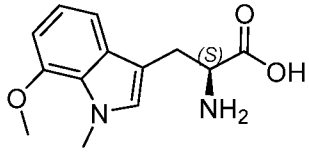

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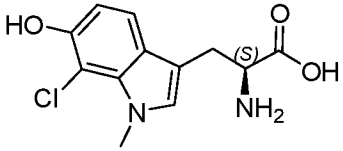

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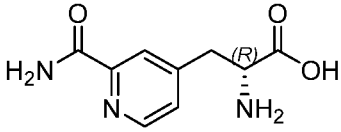

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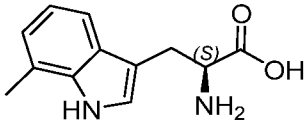

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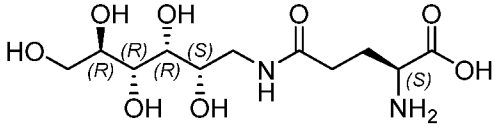
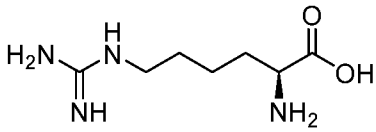


Qglucamine



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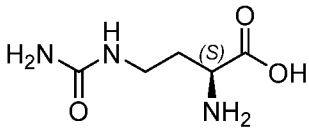

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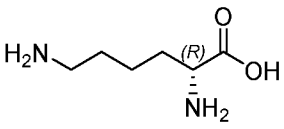

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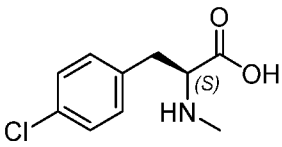

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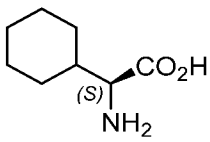

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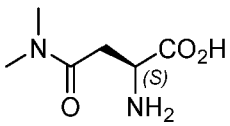

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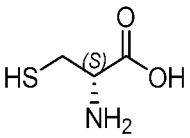

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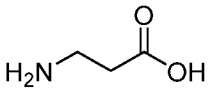

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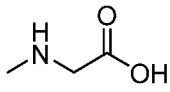

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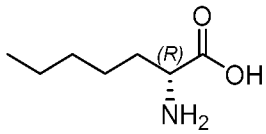

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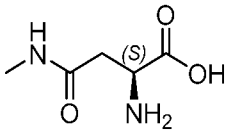

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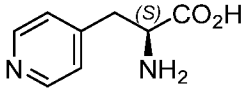

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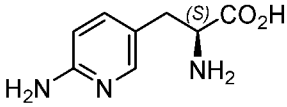

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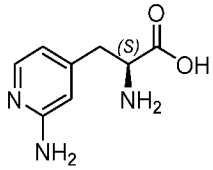

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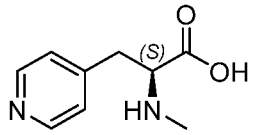

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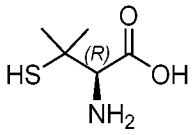

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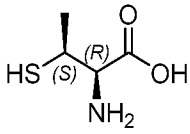

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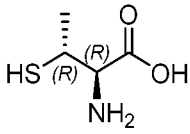

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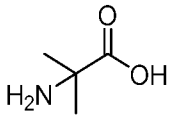

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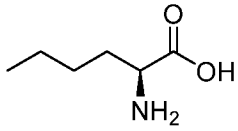

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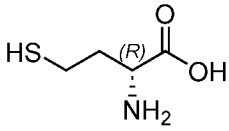

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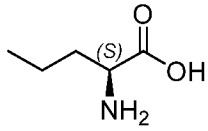

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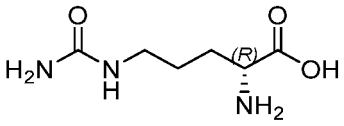

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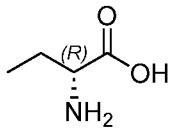

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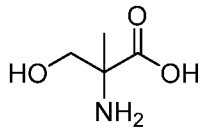

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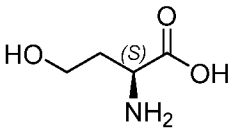

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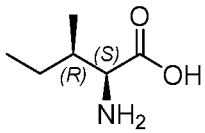

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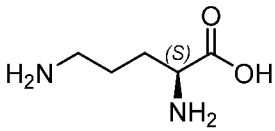

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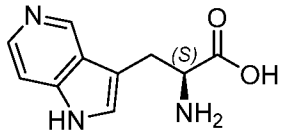

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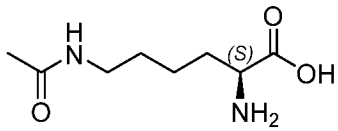

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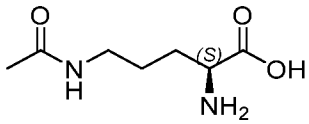

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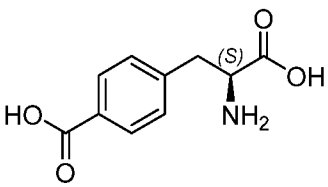

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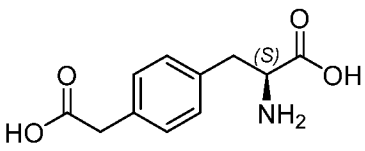

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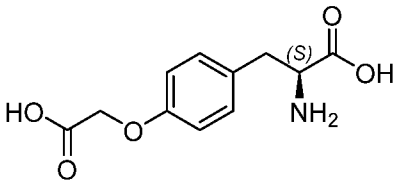

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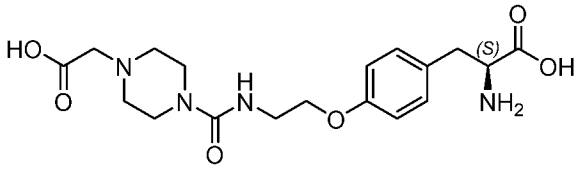

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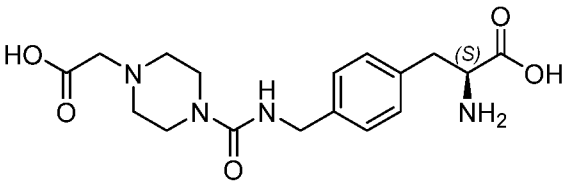

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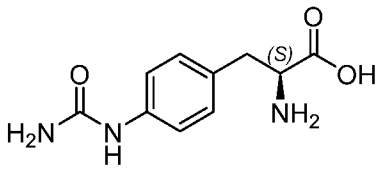

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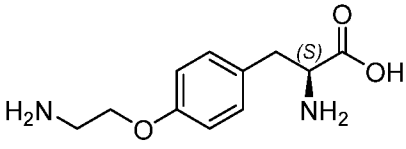

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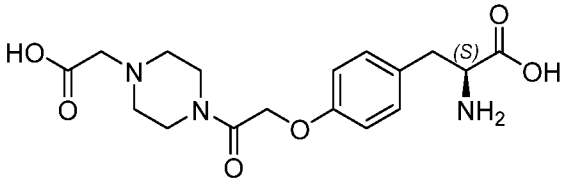

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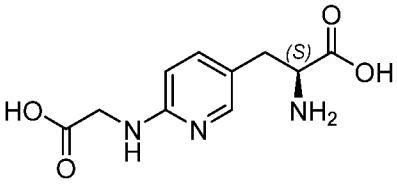

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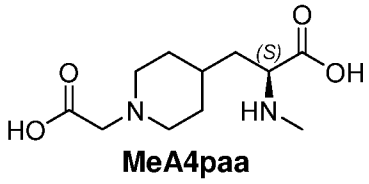

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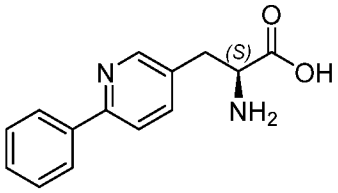

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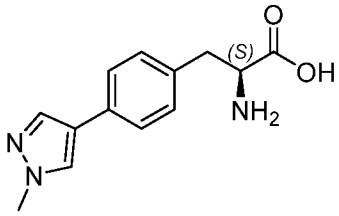

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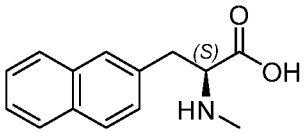

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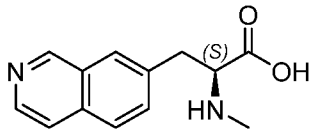

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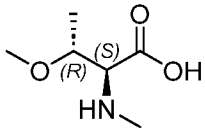

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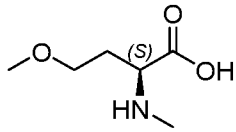

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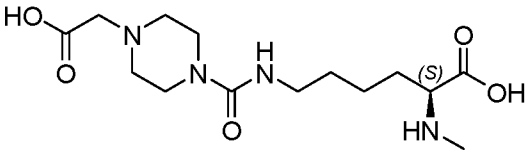

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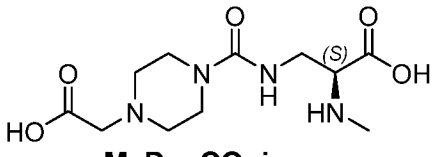


MeDapCOpipzaa

Linkers & Peptide-Linkers

[00563] A peptide described herein may be linked to one or more linkers, before such peptide-linker intermediate is further linked to a payload molecule to form the conjuate described herein. Thus, a conjugate described herein can comprise one or more linkers. In some embodiments, the linker covalently attaches the peptide with the payload molecule in the conjugate. In some other embodiments, the peptide attaches directly to the payload molecule without a linker. In some embodiments, the present disclosure describes linkers that function as a spacer.

[00564] A linker can comprise a number of intervening atoms (on a linear chain, excluding pendant groups or substituents) between the payload molecule and the binding peptide described herein, thereby creating a distance between the payload molecule and the binding peptide. In some embodiments, a linker comprises 10-100 intervening atoms between the payload molecule and the binding peptide. In some embodiments, a linker comprises 2-60 intervening atoms between the payload molecule 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 payload molecule and the binding peptide. In some embodiments, a linker comprises 3 to 30 intervening atoms between the payload molecule and the binding peptide. In some embodiments, a linker comprises 5 to 25 intervening atoms between the payload molecule and the binding peptide. In some

embodiments, a linker comprises 6 to 18 intervening atoms between the payload molecule and the binding peptide. In some embodiments, a linker comprises 10 to 20 intervening atoms between the payload molecule 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. In some embodiments, the intervening atoms comprise 1 to 6 nitrogen and 0 to 4 oxygen.

[00565] 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, the linker comprises a lysine or a derivative thereof. In some embodiments, the linker comprises a lysine. In some embodiments, one or more amino acids of the linker are unnatural amino acids. In some embodiments, the linker comprises a lysine residue, an alanine residue, or both. In certain embodiments, the linker comprises one or more amino acids chosen from a lysine residue, an alanine residue, or a phenylalanine residue. In some embodiments, the linker comprises a lysine residue. In some embodiments, the linker comprises an alanine residue. In some embodiments, the linker comprises a lysine residue, an alanine residue, a glycine residue, a D-phenylalanine residue, a histidine residue, a dAtb residue, or a D-glutamate residue. In some embodiments, the linker comprises 2 amino acids selected from the group consisting of lysine, alanine, glycine, D-phenylalanine, histidine, dAtb, and D-glutamate.

[00566] 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, the linker is attached to the peptide via its N-terminus. In some embodiments, the linker is attached to the peptide via a cysteine residue at the C-terminus. In some embodiments, the linker is attached to the peptide via a cysteine residue at the N-terminus. In some embodiments, the linker is attached to the peptide via its C-terminus. In some embodiments, the linker is attached to the peptide via a non-terminal amino acid. The linker can be bonded to the peptide, the payload molecule, 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.

[00567] The linker can have a prescribed length thereby linking the payload molecule 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.

[00568] 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. 108)), proline-rich sequences, and regions rich in double and/or triple bonds.

[00569] In some embodiment, a linker may be further added to the (cyclic) peptide. Examples of the linker include the foregoing amino acid linker (peptide linker), a chemical linker, a fatty acid linker, a nucleic acid linker, a sugar chain linker, any of the likers described herein, or the like, or it may be a complex, for example, a chemical linker, a peptide linker, or the like. Examples of the chemical linker include a PEG (polyethylene glycol) linker. For example, the PEG linker may comprise between 1 to 24 ethylene glycol units. Furthermore, the linker may be a fatty acid linker containing a divalent chemical moiety derived from a fatty acid. The linker includes at least one amino acid, and, for example, a glycine-rich peptide such as a peptide having a sequence [Gly-Gly-Gly-Gly-Ser] n (in the formula, n is 1, 2, 3, 4, 5, or 6, (SEQ ID No. 109)) such as that according to US Patent No. 7,271,149, incorporated by reference herein, or a serine-rich peptide linker according to US Patent No. 5,525,491, incorporated by reference herein, may be used. In a non-limiting manner, there are some cases where a physical property (for example, solubility) of the peptide may be changed by the addition of a linker. In one aspect, the amino acid linker includes an amino acid sequence according to any one of SEQ ID NOs: 1 to 72.

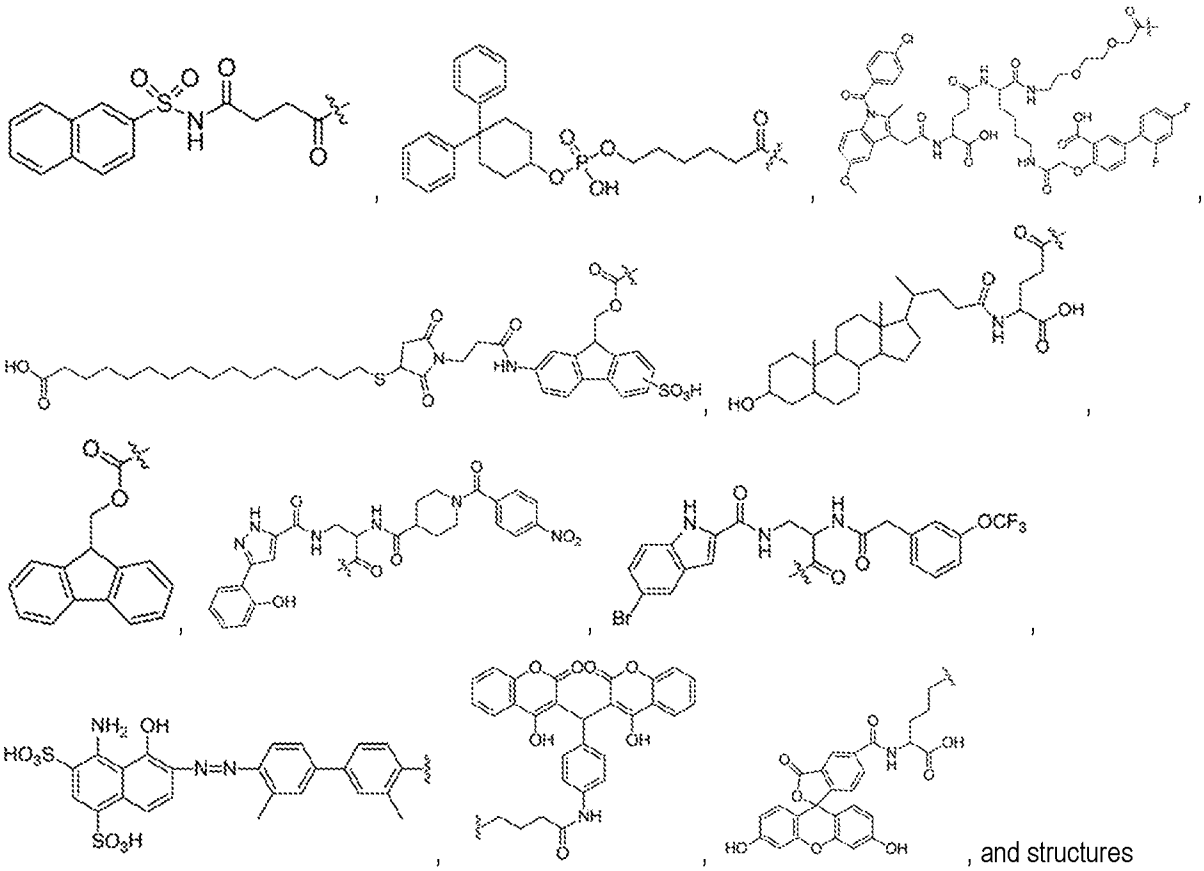
[00570] The linker may be added at any position. For example, it may be bound to Cys positioned on the C-terminal side or may be bound to an amino acid comprised in the cyclic peptide. In some instances, it is bound to Cys or variant thereof positioned on the C-terminal side. In this case, linker is added to the -COOH on the Cys or variant residue. It may be possible to add one to several amino acid to the C-terminus of such Cys or cysteine variant such as MeC residue and then the liker is added to its terminus; for example, Gly is added to the C-terminus of Cys or cysteine variant such as MeC within the cyclic structure peptide, then the -COOH of the Gly is bound to linker such as PEG linker or amino acid linker. In other instances, linker is added to the side chain on amino acid, preferably Lys, within the cyclic peptide. In this case, for example, linker is added to the side chain of Lys at X1, X2, X3, X4, X8, or X12.

[00571] The linker can be cleavable, *e.g.*, under physiological conditions, *e.g.*, under intracellular conditions, such that cleavage of the linker releases the payload molecule 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.

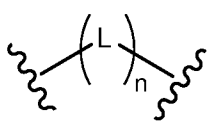
[00572] In some embodiments, the linker comprises an amino acid sequence, such as a combination of amino acid sequence and a flexible and/or rigid region.

[00573] 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 substituted or unsubstituted C_1-C_{30} heteroalkylene. 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.

[00574] In some embodiments, the linker has a structure of



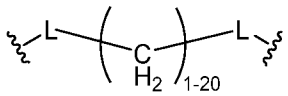
Formula (II-1)

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-, $-C(=O)NR^L-$, $-NR^LC(=O)-$, $-OC(=O)NR^L-$, $-NR^LC(=O)O-$, -

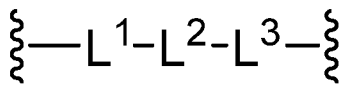
$NR^LC(=O)NR^L$-, $-NR^LC(=S)NR^L$-, $-CR^L=N$-, $-N=CR^L$-, $-NR^LS(=O)_2$-, $-S(=O)_2NR^L$-, $-C(=O)NR^LS(=O)_2$-, $-S(=O)_2NR^LC(=O)$-, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_1-C_{12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted 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)-$N(R^L)_2^+$-, $-N(R^L)_2^+$-(C_1-C_{30} alkylene)-, or a click chemistry residue; 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 (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20).

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 $-S(=O)_2NR^LC(=O)$-.

[00575] In some embodiments, the linker of Formula (II-1) has a structure of Formula (II-1a),



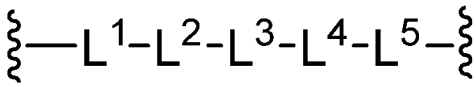
Formula (II-1a)

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.

[00576] In some embodiments, the linker comprises a structure of Formula (II-1b),



Formula (II-1b)

wherein

each of L^1 and L^5 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 5-6 membered cycloalkyl, or substituted or unsubstituted 5-6 membered heterocycloalkyl; and

L^2, L^3 and L^4 are each independently absent, substituted or unsubstituted 5-6 membered cycloalkyl, substituted or unsubstituted 5-6 membered heterocycloalky, substituted or unsubstituted C_1-C_{30} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene.

[00577] In some embodiments, L^1 is -NH-.

[00578] In some embodiments, L^2 is absent. In some embodiments, L^2 is substituted or unsubstituted C_1-C_{30} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene. In some embodiments, L^2 is substituted or unsubstituted C_1-C_{30} alkylene. In some embodiments, L^2 is substituted or unsubstituted C_1-C_{30} heteroalkylene. In some embodiments, L^2 is substituted or unsubstituted C_1-C_{18} alkylene, or substituted or unsubstituted C_1-C_{18} heteroalkylene. In some embodiments, L^2 is optionally substituted. In some embodiments, L^2 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, C_1-C_6 aminoalkyl, -$C(=O)OR^L$, -$OC(=O)R^L$, -$OC(=O)OR^L$, -$C(=O)N(R^L)_2$, -$NR^LC(=O)R^L$, -$OC(=O)N(R^L)_2$, and -$NR^LC(=O)OR^L$. In some embodiments, 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. In some embodiments, L2 is optionally substituted with C_1-C_6 alkyl which is further optionally substituted with one or more substituents chosen from -OH, -SH, oxo, amino, C_6-C_{10} aryl, 6- to 10- membered heteroaryl, -$C(=O)OR^L$, -$OC(=O)R^L$, -$OC(=O)OR^L$, -$C(=O)N(R^L)_2$, -$NR^LC(=O)R^L$, -$OC(=O)N(R^L)_2$, and -$NR^LC(=O)OR^L$.

[00579] In some embodiments, L^3 is -NH-. In some embodiments, L^3 is absent.

[00580] In some embodiments, L^4 is absent. In some embodiments, L^4 is substituted or unsubstituted 5-6 membered cycloalkyl, substituted or unsubstituted 5-6 membered heterocycloalky, substituted or unsubstituted C_1-C_{30} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene.

[00581] In some embodiments, L^5 is -NH-. In some embodiments, L^5 is absent.

[00582] In some embodiments for Formula (II-1b), L^1 is -O-, -N(methyl)-, -NH- or -C(=O)-; L^5 is -O-, -N(methyl)-, -NH- or -C(=O)-; L^2, L^3 and L^4 are each independently absent, substituted or unsubstituted 5-6 membered cycloalkyl, substituted or unsubstituted 5-6 membered heterocycloalky, substituted or unsubstituted C_1-C_{12} alkylene, or substituted or unsubstituted C_1-C_{30} heteroalkylene, wherein L^1 is connected to the payload molecule and L^5 is connected to the GPC3 binding peptide.

[00583] In some embodiments for Formula (II-1b), L^2 is unsubstituted C_1-C_{12} alkylene, and L^3 and L^4 are absent.

[00584] In some embodiments, the linker comprises substituted or unsubstituted C_1-C_{30} alkylene, C_1-C_{12} alkylene, C_1-C_8 alkylene, C_1-C_6 alkylene, or C_2-C_6 alkylene. In some embodiments, the linker comprises C_2-C_6 alkylene. In some embodiments, the linker comprises C_4-C_6 alkylene.

[00585] In some embodiments, 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, -$NR^LS(=O)_2$-, -$S(=O)_2NR^L$-, -$C(=O)NR^LS(=O)_2$-, -$S(=O)_2NR^LC(=O)$-, 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^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 -$S(=O)_2NR^LC(=O)$-. 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.

[00586] In some embodiments, 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.

[00587] In some embodiments, 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^{L}C(=O)-, -OC(=O)NR^L-, -NR^{L}C(=O)O-, -NR^{L}C(=O)NR^L-, -NR^{L}C(=S)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)-. 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. In some embodiments, L^3 is absent.

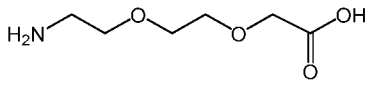
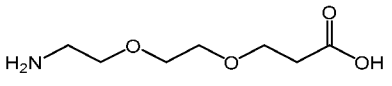
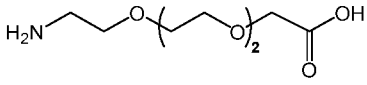
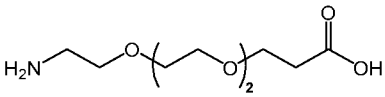
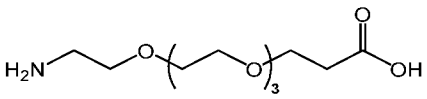
[00588] In some embodiments, each of L^4 is independently -O-, –NR^L–, –N(R^L)$_2$-, -OP(=O)(OR^L)O-, -S-, -S(=O)-, -S(=O)$_2$-, =CH-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, -C(=O)NR^L-, -NR^{L}C(=O)-, -OC(=O)NR^L-, -NR^{L}C(=O)O-, -NR^{L}C(=O)NR^L-, -NR^{L}C(=S)NR^L-, -CR^L=N-, -N=CR^L, -NR^{L}S(=O)$_2$-, -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$_{30}$ 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^4 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^{L}C(=O)-, -OC(=O)NR^L-, -NR^{L}C(=O)O-, -NR^{L}C(=O)NR^L-, -NR^{L}C(=S)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)-. In some embodiments, L^4 is -O-, –NH-, -S(=O)-, -S(=O)$_2$-, or -C(=O)-. In some embodiments, L^4 is -C(=O)NH- or -NHC(=O)-. In some embodiments, L^4 is substituted or unsubstituted C$_3$-C$_{15}$ cycloalkyl, or substituted or unsubstituted C$_1$-C$_{12}$ heterocycloalkyl. In some embodiments, L^4 is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl. In some embodiments, L^4 is substituted or unsubstituted C$_1$-C$_{30}$ alkylene. In some embodiments, L^4 is substituted or unsubstituted C$_2$-C$_{30}$ alkenylene. In some embodiments, L^4 is substituted or unsubstituted C$_1$-C$_{30}$ heteroalkylene. In some embodiments, L^4 is substituted or unsubstituted C$_5$-C$_{25}$ heteroalkylene. In some embodiments, L^4 is substituted or unsubstituted C$_5$-C$_{12}$ heteroalkylene. In some embodiments, L^4 is absent.

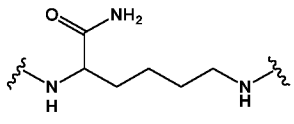
[00589] In some embodiments, each of L^5 is independently -O-, –NR^L–, –N(R^L)$_2$-, -OP(=O)(OR^L)O-, -S-, -S(=O)-, -S(=O)$_2$-, =CH-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, -C(=O)NR^L-, -NR^{L}C(=O)-, -OC(=O)NR^L-, -NR^{L}C(=O)O-, -NR^{L}C(=O)NR^L-, -NR^{L}C(=S)NR^L-, -CR^L=N-, -N=CR^L, -NR^{L}S(=O)$_2$-, -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$_{30}$ 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^5 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^{L}C(=O)-, -OC(=O)NR^L-, -NR^{L}C(=O)O-, -NR^{L}C(=O)NR^L-, -NR^{L}C(=S)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)-. In some embodiments, L^5 is -O-, –NH-, -S(=O)-, -S(=O)$_2$-, or -C(=O)-. In some embodiments,

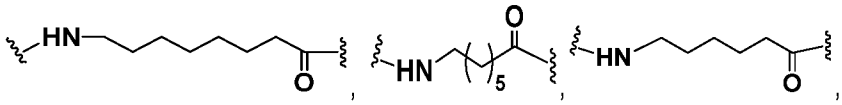
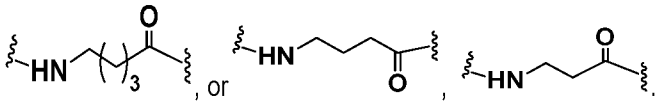
L^5 is -C(=O)NH- or -NHC(=O)-. In some embodiments, L^5 is substituted or unsubstituted C_3-C_{15} cycloalkyl, or substituted or unsubstituted C_1-C_{12} heterocycloalkyl. In some embodiments, L^5 is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl. In some embodiments, L^5 is substituted or unsubstituted C_1-C_{30} alkylene. In some embodiments, L^5 is substituted or unsubstituted C_2-C_{30} alkenylene. In some embodiments, L^5 is substituted or unsubstituted C_1-C_{30} heteroalkylene. In some embodiments, L^5 is substituted or unsubstituted C_5-C_{25} heteroalkylene. In some embodiments, L^5 is substituted or unsubstituted C_5-C_{12} heteroalkylene. In some embodiments, L^5 is absent.

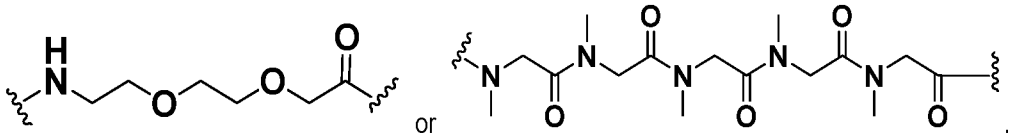
[00590] In some embodiments, at least one L^1 is unsubstituted C_3-C_{20} alkylene.

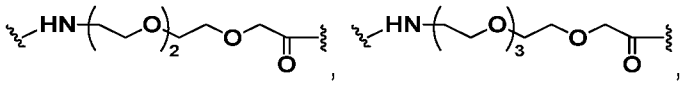
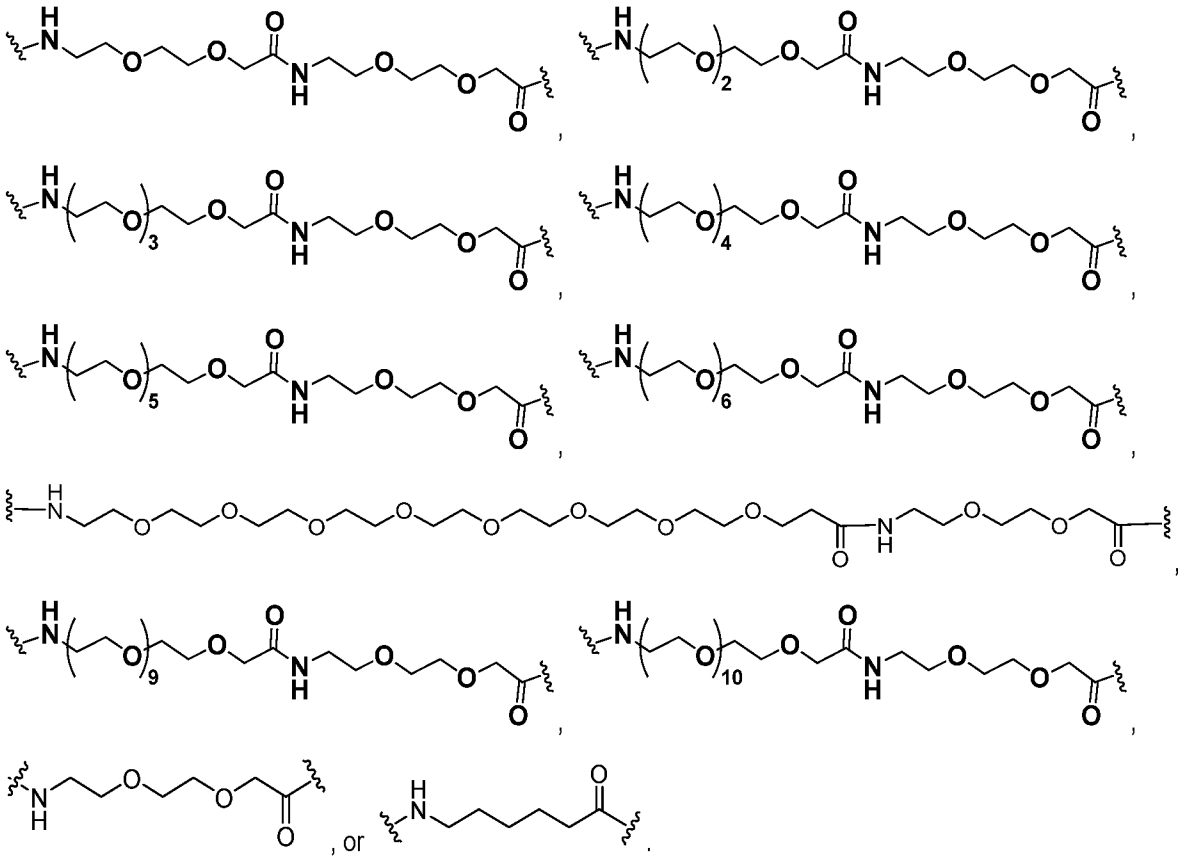
[00591] In some embodiments, the linker comprises one or more of a substituted or unsubstituted C_6-C_{10} aryl, substituted or unsubstituted C_5-C_9 heteroaryl, a sterol, sulfonamide, phosphate ester, polyethylene glycol, or C_3-C_{20} alkylene, or amino acid residues.

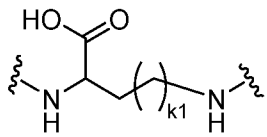
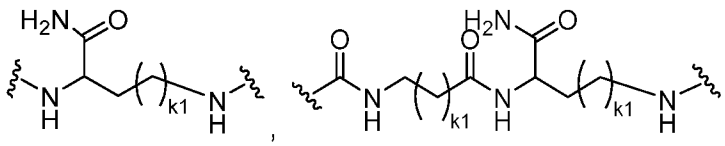
[00592] In some embodiments, the linker comprises one or more selected from AEEA, AEEP, AEEEP, and AEEEEP groups. In some embodiments, the linker comprises  (AEEA). In some embodiments, the linker comprises  (AEEP). In some embodiments, the linker comprises  (AEEEA). In some embodiments, the linker comprises  (AEEEP). In some embodiments, the linker comprises  (AEEEEP).

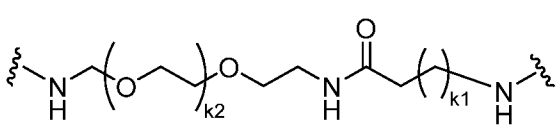
[00593] In some embodiments, the linker is  . In some embodiments, the linker is or comprises lysine. In some embodiments, the linker comprises C_1-C_{12} alkylene. In some embodiments, the linker comprises C_3-C_9 alkylene. In some embodiments, the linker comprises C_2-C_8 alkylene. In some embodiments, the linker comprises 1 to 10 repeating ethylene glycol units. In some embodiments, the linker comprises 2 to 4 repeating ethylene glycol units. In some embodiments, the linker comprises 5 to 8 repeating ethylene glycol units. In some embodiments, the linker comprises NH_2-$(CH_2)_n$-COOH, wherein n is 1 to 12. In some embodiments, the linker comprises NH_2-$(CH_2)_2$-COOH. In some embodiments, the linker comprises NH_2-$(CH_2)_3$-COOH. In some embodiments, the linker comprises NH_2-$(CH_2)_4$-COOH. In some embodiments, the linker comprises NH_2-$(CH_2)_5$-COOH. In some embodiments, the linker comprises NH_2-$(CH_2)_6$-COOH. In some embodiments, the linker comprises NH_2-$(CH_2)_7$-COOH. In some embodiments, the linker comprises NH_2-$(CH_2)_8$-COOH. In some embodiments, the linker comprises NH_2-$(CH_2)_{10}$-COOH. In some embodiments, the linker is absent.

[00594] In some embodiments, a linker of the present disclosure (*e.g.*, a linker of Formula (II-1), (II-1a) or (II-1b)) comprises a structure of  ,  .

[00595] In some embodiments, a linker of the present disclosure comprises a structure of  .

[00596] In some embodiments, a linker of the present disclosure (*e.g.*, a linker of Formula (II-1), (II-1a) or (II-1b)) comprises a structure of  ,  .

[00597] In some embodiments, the linker comprises a structure selected from:  ,  .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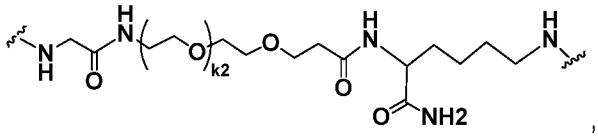
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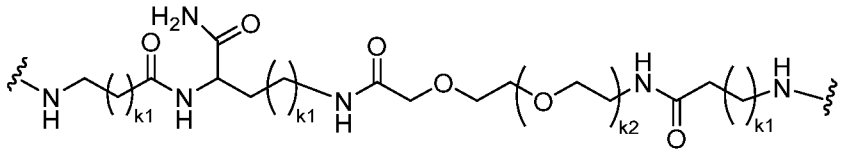
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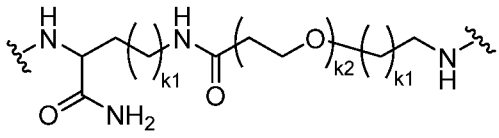
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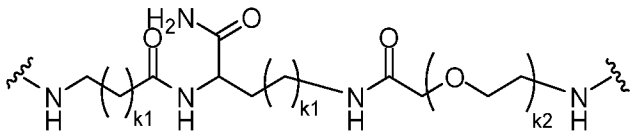
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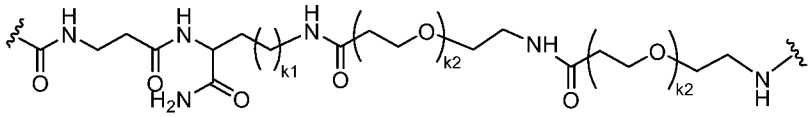
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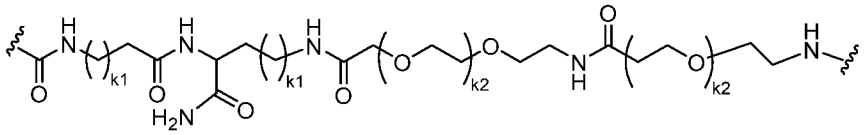
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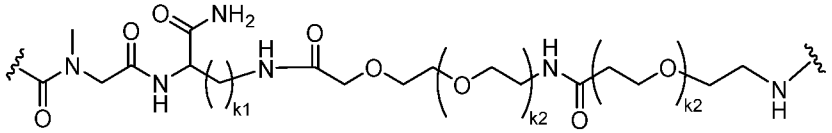
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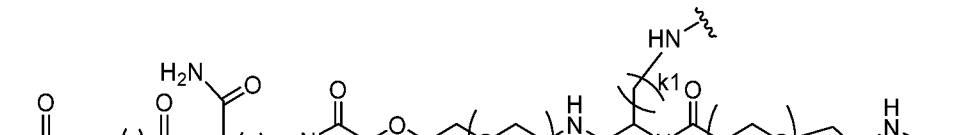
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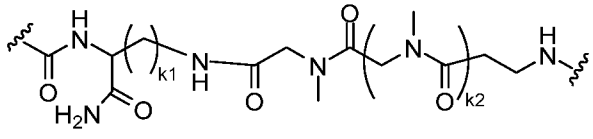
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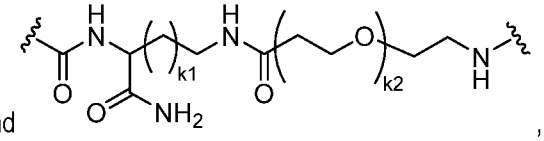
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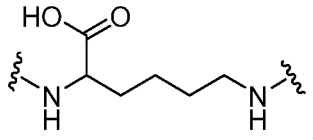
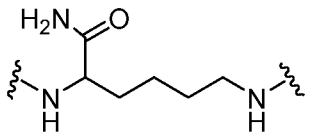
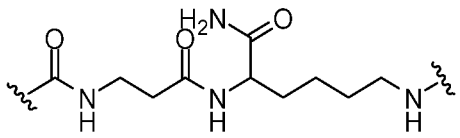
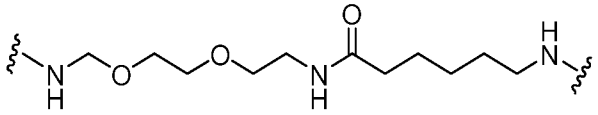
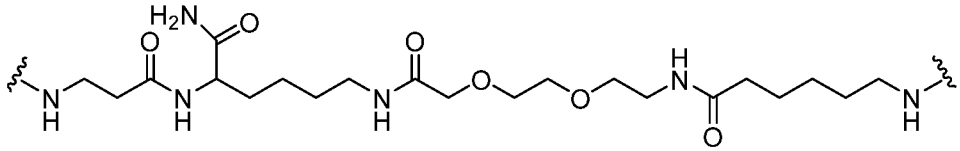
wherein each k1 is independently 0 or an integer from 1 to 20; and each k2 is independently 0 or an integer from 1 to 15. In some embodiments, k1 is 0. In some embodiments, k1 is 1. In some embodiments, k1 is 2. In some embodiments, k1 is 3. In some embodiments, k1 is 4. In some embodiments, k1 is 5. In some embodiments, k1 is 6. In some embodiments, k1 is 7. In some embodiments, k1 is 8. In some embodiments, k1 is 9. In some embodiments, k1 is 10. In some embodiments, k1 is 11. In some embodiments, k1 is 12. In some embodiments, k1 is 13. In some embodiments, k1 is 14. In some embodiments, k1 is 15. In some embodiments, k1 is 16. In some embodiments, k1 is 17. In some embodiments, k1 is 18. In some embodiments, k1 is 19. In some embodiments, k1 is 20. In some embodiments, k2 is 0. In some embodiments, k2 is 1. In some embodiments, k2 is 2. In some embodiments, k2 is 3. In some embodiments, k2 is 4. In some embodiments, k2 is 5. In some embodiments, k2 is 6. In some embodiments, k2 is 7. In some embodiments, k2 is 8. In some embodiments, k2 is 9. In some embodiments, k2 is 10. In some embodiments, k2 is 11. In some embodiments, k2 is 12. In some

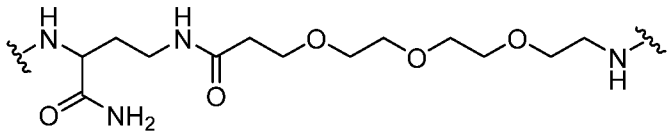
embodiments, k2 is 13. In some embodiments, k2 is 14. In some embodiments, k2 is 15.

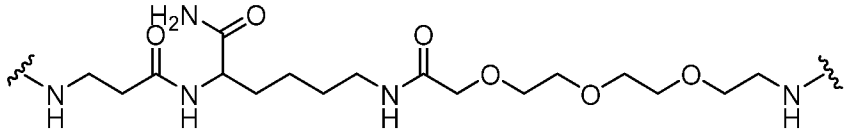
[00598] In some embodiments, the linker comprises a structure selected from:  ,

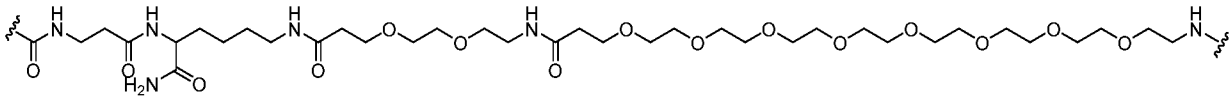
 ,  ,

 ,

 ,

 ,

 ,



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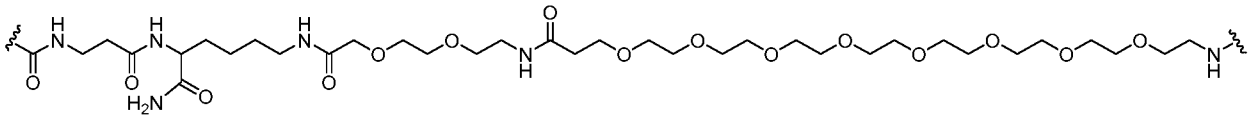

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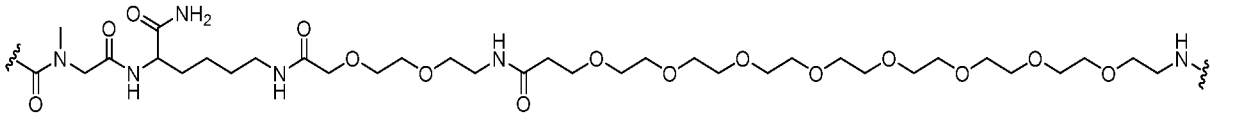

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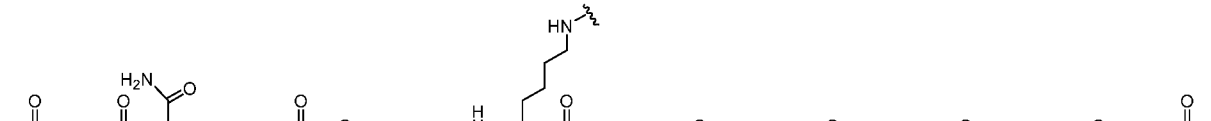

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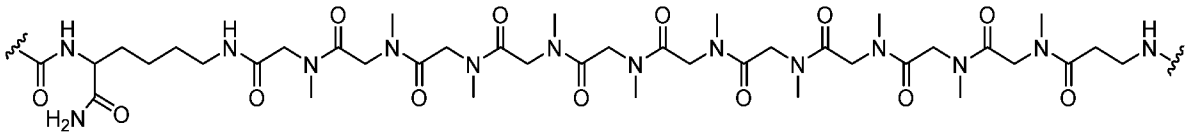

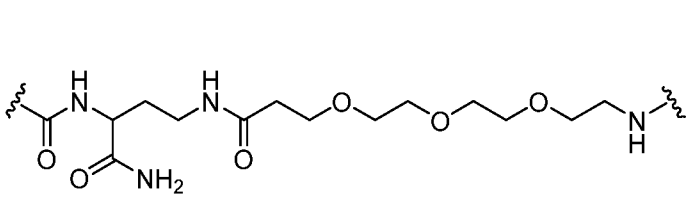

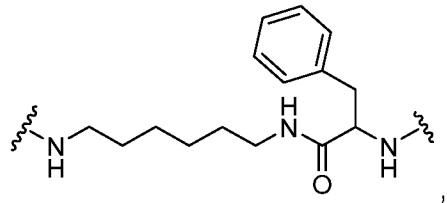

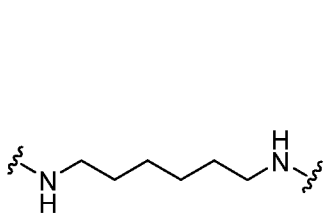

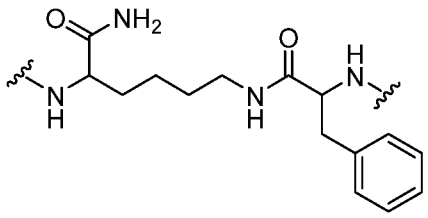

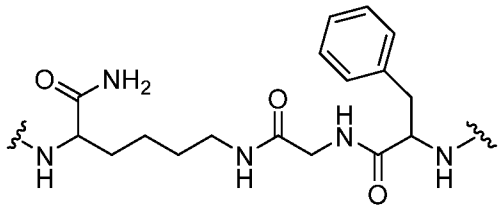

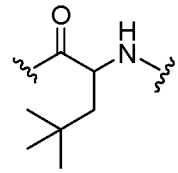

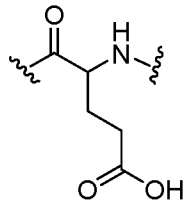

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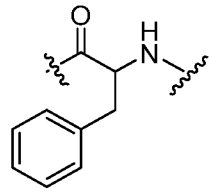
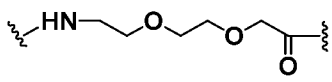
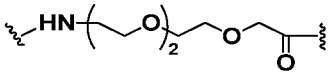
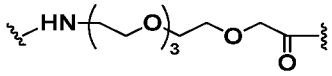
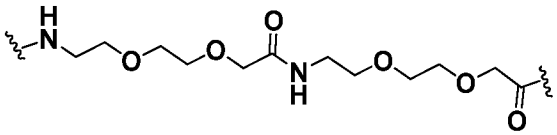


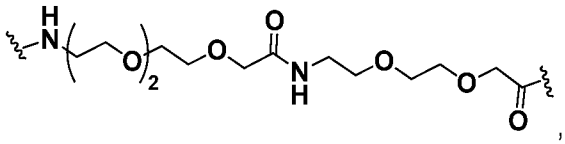


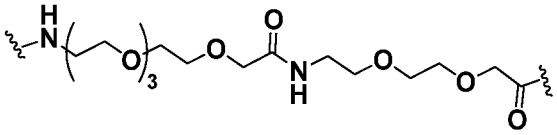
[00599] In some embodiments, the linker comprises a structure selected from:

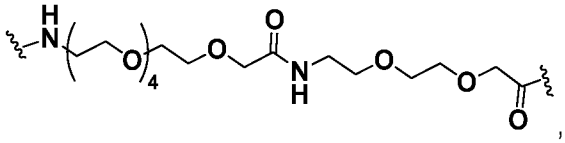


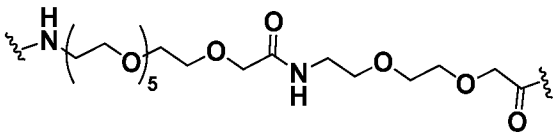


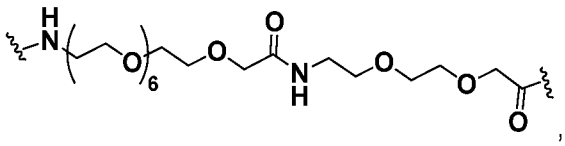


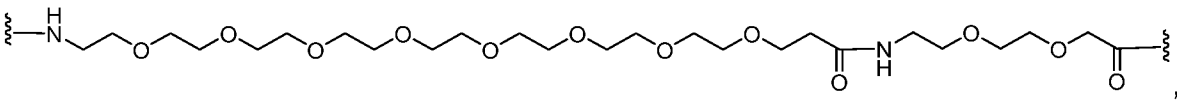


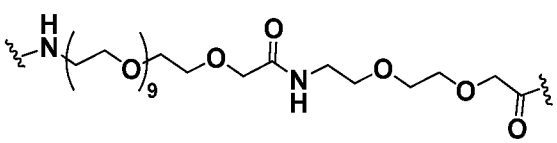


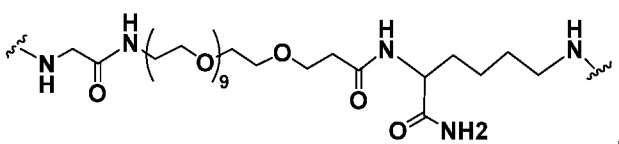


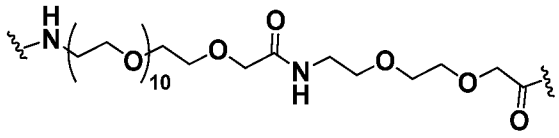












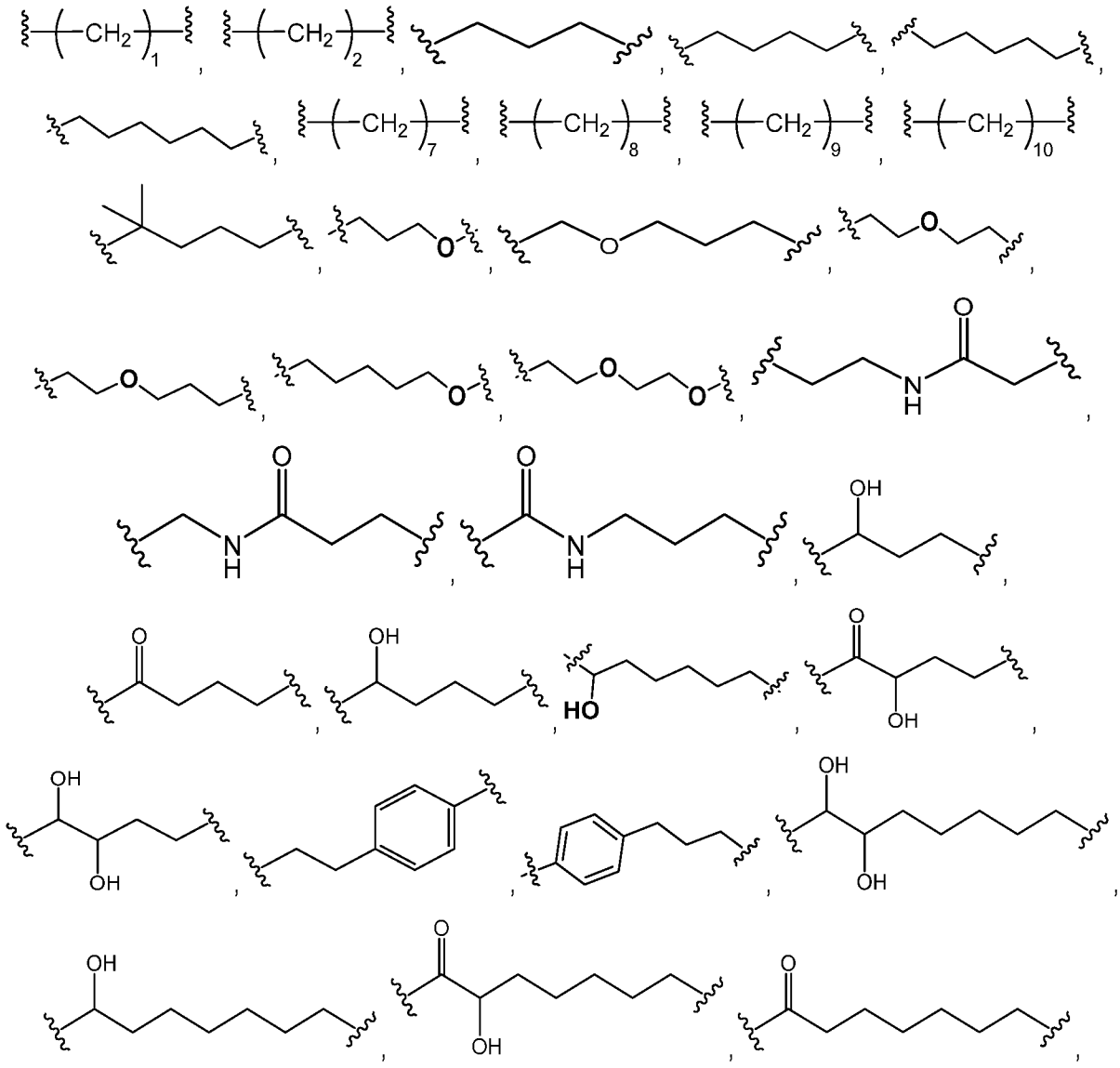
or .

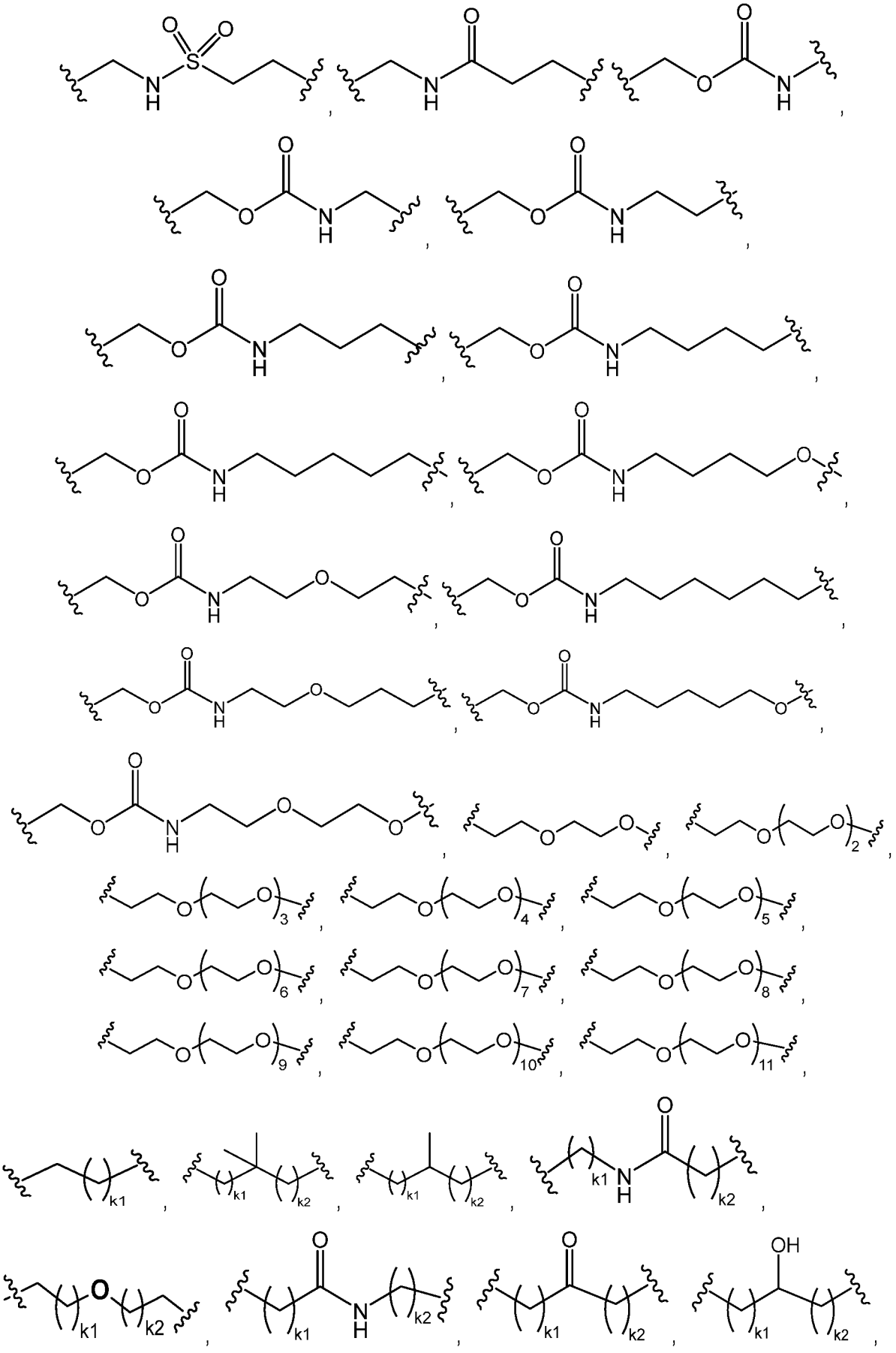
[00600] In some embodiments, the linker is configured to reversibly bind to a plasma protein such as albumin. In some embodiments, a dissociation constant (Kd) between the linker and human serum albumin is at most 15 μM, as determined at room temperature in human serum condition. In some embodiments, 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.

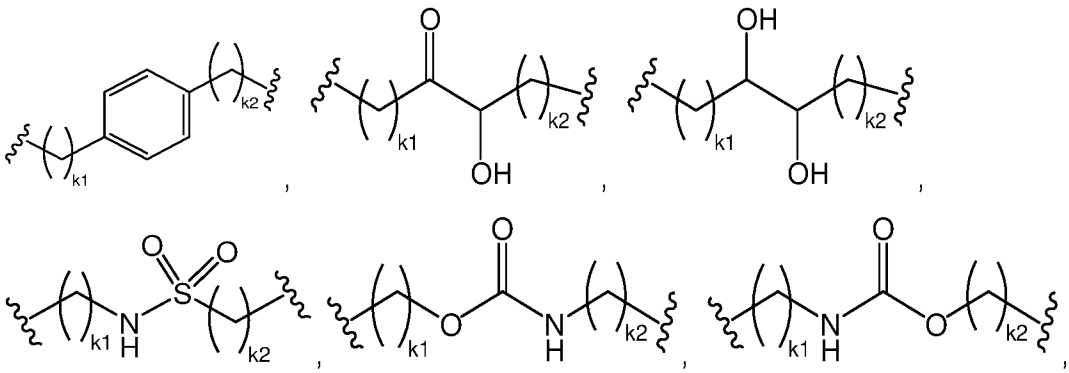
[00601] In some embodiments, the linker is a bond.

[00602] In some embodiments, a conjugate comprises a linker structure selected from Table 6

Table 6







wherein each k1 and k2 is independently 0 or an integer selected from 1 to 20.

[00603] In some embodiments of Table 6, k1 is selected from 0-12. In some embodiments, k1 is 0. In some embodiments, k1 is 1. In some embodiments, k1 is 2. In some embodiments, k1 is 3. In some embodiments, k1 is 4. In some embodiments, k1 is 5. In some embodiments, k1 is 6. In some embodiments, k1 is 7. In some embodiments, k1 is 8. In some embodiments, k1 is 9. In some embodiments, k1 is 10. In some embodiments of Table 6, k2 is selected from 0-12. In some embodiments, k2 is 0. In some embodiments, k2 is 1. In some embodiments, k2 is 2. In some embodiments, k2 is 3. In some embodiments, k2 is 4. In some embodiments, k2 is 5. In some embodiments, k2 is 6. In some embodiments, k2 is 7. In some embodiments, k2 is 8. In some embodiments, k2 is 9. In some embodiments, k2 is 10.

Payload-Bound PDC (Peptide-Drug Conjugate, or" Conjugate")

[00604] In one embodiment, the present technology relates to a complex or conjugate. This complex / conjugate comprises any of the peptides described herein, any of the linkers described herein bound to the peptide, and/or a substance (*e.g.*, a payload molecule) bound to this linker (PDC). Since the peptide is capable of binding to the GPC3, the complex / conjugate can transport the substance / payload molecule to the GPC3.

[00605] In one aspect, described herein is a PDC with structure of FIG. 1, wherein the  represents the linker connected to the peptide.

[00606] In some embodiments, the linker is connected to the peptide at the side chain of any amino acid included in the peptide of the invention, such as the amino acid at the C-terminus of the peptide. For example, but not limited to, the linker bound to the substance is connected to the Cys or cysteine variant such as MeCat the C-terminus of the peptide, or any amino acid within the peptide, preferably amino acid at X1, X4, X5, X8, or X12.

[00607] The substance or payload molecule may be any substance desired by a person having ordinary skill in the art, as long as it is a substance the skilled person desires to be delivered to the GPC3. Examples of the substance are not limited, but include the following:

- A compound: Including low molecular weight compounds, middle molecular weight compounds, and examples include known low/middle molecular weight drugs. Examples includes any ligand for a receptor, antagonist, agonist or like. Examples also includes any compound that is not used as drugs such as fluorescent molecules or tags. Further to examples, any chemical compound that is used for connecting

or conjugating to a substance (*e.g.*, biotin/avidin, click chemistry compounds) or conjugations thereof is included.

- A peptide: May be a peptide that binds to a target in the body and exhibits some kind of effect, for example, a cyclic peptide.
- A protein: May be any protein that exhibits a useful function in the body, such as an antibody or an enzyme. Examples include enzymes used in enzyme replacement therapy.
- A nucleic acid: Any substance having a base sequence, such as DNA and RNA, and combination thereof (*e.g.* heteroduplex oligonucleotide). Examples include nucleic acid medicines.
- Any molecule used in a drug delivery system (DDS): May be a known molecule used in DDS, such as a liposome or a micelle. The DDS molecule may further comprise a compound therein such as a pharmaceutical.

[00608] In all aspects of this disclosure, however, the substance, moiety, and payload molecule excludes any radioactive materials. Examples of the radioactive materials that are excluded are: radioisotope, radiopharmaceutical, or any compound having radioactive component. In all aspects of this disclosure, the substance, moiety, and payload further exclude any chelators for radioisotope conjugation, regardless of whether the chelator is connected to the peptide directly or via a linker. Accordingly, a complex, conjugate or PDC described herein does not encompass any compound containing a chelator for radioisotope conjugation, and does not encompass a radioisotope.

[00609] Moreover, the DDS molecule may be a complex in which several of the examples given above are combined.

Peptide Production

[00610] The peptide of the present technology may be produced by, for example, any known method for producing a peptide, such as the following:

- a chemical synthesis method such as a liquid phase method, a solid phase method, a hybrid method combining a liquid phase method and a solid phase method, or the like;
- a genetic recombination method; or the like.

[00611] In some of the instances where the peptide of the present technology is produced by a chemical synthesis method, it can be said that the peptide of the present technology is a synthetic peptide.

[00612] In the solid phase method, for example, a hydroxy group of a resin having a hydroxy group and a carboxy group of a first amino acid (normally a C-terminal amino acid of a target peptide) in which an α-amino group is protected by a protecting group are subjected to an esterification reaction. For the esterification catalyst, a known dehydrating and condensing agent such as 1-mesitylenesulfonyl-3-nitro-1, 2, 4-triazole (MSNT), dicyclohexylcarbodiimide (DCC), and diisopropylcarbodiimide (DIPCDI) may be used.

[00613] Next, the protecting group of the α-amino group of the first amino acid is removed, a second amino acid in which all functional groups except the carboxy group of the main chain are protected is added, and the

carboxy group is activated, binding the first and second amino acids. Furthermore, the α-amino group of the second amino acid is deprotected, a third amino acid in which all functional groups except the carboxy group of the main chain are protected is added, the carboxy group is activated, binding the second and third amino acids. This is repeated, and after a peptide having a target length is synthesized, all of the functional groups are deprotected.

[00614] Examples of the resin for solid-phase synthesis include Merrifield resin, MBHA resin, Cl-Trt resin, SASRIN resin, Wang resin, Rink amide resin, HMFS resin, Amino-PEGA resin (Merck KGaA), HMPA-PEGA resin (Merck KGaA), and the like. These resins may be used after being washed using a solvent (dimethylformamide (DMF), 2-propanol, methylene chloride, and the like). A peptide chain can be cleaved from the resin by treating it with an acid such as TFA or hydrogen fluoride (HF).

[00615] Examples of the protecting group of the α-amino group include a benzyloxycarbonyl (Cbz or Z) group, tert-butoxycarbonyl (Boc) group, fluorenylmethoxycarbonyl (Fmoc) group, benzyl group, allyl group, allyloxycarbonyl (Alloc) group, and the like. The Cbz group may be deprotected by a treatment using hydrofluoric acid, hydrogenation, or the like, the Boc group may be deprotected by a treatment using trifluoroacetic acid (TFA), and the Fmoc group may be deprotected by a treatment using pipericine or pyrrolysine.

[00616] Examples, such as methyl ester, ethyl ester, allyl ester, benzyl ester, tert-butyl ester, cyclohexyl ester, and the like may be used to protect the α-carboxy group.

[00617] As other functional groups of an amino acid, the hydroxyl group of serine or threonine can be protected with a benzyl group or a tert-butyl group and the hydroxyl group of tyrosine can be protected with a 2-bromobenzyloxycarbonyl group or a tert-butyl group. The amino group of a lysine side chain or the carboxyl group of glutamic acid or aspartic acid can be protected in a manner similar to the a-amino group or a-carboxyl group.

[00618] Activation of the carboxy group may be performed using a condensing agent. Examples of the condensing agent include dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIPCDI), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC or WSC), (1H-benzotriazole-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP), 1-[bis(dimethylamino)methyl]-1H-benzotriazolium-3-oxide hexafluorophosphate (HBTU), and the like.

[00619] Cleavage of the peptide chain from the resin may be performed by treating the peptide chain using an acid such as TFA, hydrogen fluoride (HF), or the like.

[00620] Production of a peptide by a gene recombination method (translation/synthesis system) may be performed using a nucleic acid encoding the peptide. The nucleic acid encoding the peptide may be DNA or RNA.

[00621] The nucleic acid encoding the peptide may be prepared by a known method or a method equivalent thereto. For example, the peptide may be synthesized by an automated synthesizer. A restriction enzyme recognition site may be added to insert the obtained DNA into a vector. Alternatively, a base sequence encoding an amino acid sequence for splicing a formed peptide chain using an enzyme or the like may be incorporated. The peptide obtained may be converted from a free peptide to a salt thereof or from a salt thereof to a free

peptide by a known method or a method based thereon.

[00622] As described above, when the peptide is fused to a cell-penetrating peptide or the like, the nucleic acid also includes a nucleic acid encoding the cell-penetrating peptide.

[00623] A chimeric protein expression method for expressing the target peptide as a chimeric peptide of another peptide may also be used to suppress degradation by a host-derived protease. In this case, a nucleic acid encoding the target peptide and the peptide bound thereto may be used as the nucleic acid.

[00624] Subsequently, an expression vector is prepared using the nucleic acid encoding the peptide. The nucleic acid may be digested as is or by a restriction enzyme, and alternatively, the nucleic acid may be inserted downstream of a promotor of the expression vector by adding a linker, or the like. Examples of the vector include an *Escherichia coli*-derived plasmid (pBR322, pBR325, pUC12, pUC13, pUC18, pUC19, pUC118, pBluescript II, and the like), a *Bacillus subtilis*-derived plasmid (pUB110, pTP5, pC1912, pTP4, pE194, pC194, and the like), a yeast-derived plasmid (pSH19, pSH15, YEp, YRp, YIp, YAC, and the like), a bacteriophage (e phage, M13 phage, and the like), a virus (retrovirus, vaccinia virus, adenovirus, adeno-associated virus (AAV), cauliflower mosaic virus, tobacco mosaic virus, baculovirus, and the like), a cosmid, and the like.

[00625] The promoter may be selected appropriately according to the type of host. When the host is an animal cell, for example, a promoter derived from SV40 (simian virus 40) or a promoter derived from CMV (cytomegalovirus) may be used. When the host is *Escherichia coli*, a trp promoter, a T7 promoter, a lac promoter, or the like may be used.

[00626] The expression vector may incorporate, for example, a DNA replication starting point (ori), a selective marker (antibiotic resistance, auxotrophy, or the like), an enhancer, a splicing signal, a poly-A addition signal, a nucleic acid encoding a tag (FLAG, HA, GST, GFP, or the like), or the like.

[00627] Next, an appropriate host cell is transformed by the expression vector. The host may be appropriately selected in relation to the vector. Examples such as *Escherichia coli*, *Bacillus subtilis* (*Bacillus*), yeast, insects or insect cells, animal cells, or the like may be used as the host. As the animal cells, for example, HEK293T cells, CHO cells, COS cells, myeloma cells, HeLa cells, and Vero cells may be used. Transformation may be carried out according to a known method, such as a lipofection method, a calcium phosphate method, an electroporation method, a microinjection method, a gene gun method, or the like depending on the type of host. The target peptide is expressed by culturing a transformant according to a conventional method.

[00628] As for purification of the peptide from the transformant culture, cultured cells are recovered and then suspended in an appropriate buffer solution, followed by disruption of cells by a method such as sonication, freeze-thawing, or the like, and then a crude extract is obtained by centrifugation or filtration. When the peptide is secreted into the culture solution, a supernatant is recovered.

[00629] Purification of the crude extract or the culture supernatant may also be performed by a known method or a method equivalent thereto (for example, salting-out, dialysis, an ultrafiltration method, gel filtration method, SDS-PAGE method, ion exchange chromatography, affinity chromatography, reversed-phase high-performance liquid chromatography, and the like).

[00630] The obtained peptide may be converted from a free body to a salt or from a salt to a free body by a

known method or a method equivalent thereto.

[00631] In one aspect, the translation/synthesis system may be a cell-free translation system. According to the cell-free translation system, a highly pure form of an expression product can generally be obtained without purification. The cell-free translation system includes, for example, a ribosome protein, an aminoacyl-tRNA synthase (ARS), a ribosome RNA, an amino acid, rRNA, GTP, ATP, a translation initiation factor (IF), an elongation factor (EF), a release factor (RF), and a ribosome regeneration factor (RRF), or another factor required for translation. An *Escherichia coli* extract or a wheat embryo extract may be added to increase expression efficiency. In addition, a rabbit red blood cell extract or an insect cell extract may be added.

[00632] By continuously supplying energy to a system including these using dialysis, a protein of several hundred μg to several mg/mL may be produced in a non-limiting manner. The system may include an RNA polymerase to concurrently perform transcription of genomic DNA. Examples of commercially available cell-free translation systems that may be used include RTS-100 (registered trademark) by Roche Diagnostics K.K., PURE System by GeneFrontier Corporation, PURExpress *In vitro* Protein Synthesis Kit by New England Biolabs Inc., and the like for a system derived from *Escherichia coli*, and a system by ZOIGENE, CellFree Sciences Co., Ltd., or the like for a system using wheat embryo extract.

[00633] In the cell translation system, artificial aminoacyl-tRNA may be used and a desired amino acid or hydroxy acid may be linked (acylated) to a tRNA in place of an aminoacyl-tRNA synthesized by a natural aminoacyl-tRNA synthase. The aminoacyl-tRNA may be synthesized using an artificial ribozyme.

[00634] An example of the ribozyme includes a flexizyme (flexizyme) (H. Murakami, H. Saito, and H. Suga, (2003), Chemistry & Biology, Vol. 10, 655-662; and WO 2007/066627 and the like), all incorporated herein by reference. Flexizymes are also known under the names of prototype flexizyme (Fx), newly modified dinitrobenzyl flexizyme (dFx), enhanced flexizyme (eFx), aminoflexizyme (aFx), and the like.

[00635] A desired codon may be translated in association with the desired amino acid or hydroxy acid by using the tRNA produced by flexizyme and to which the desired amino acid or hydroxy acid is linked. A specialty amino acid may be used as the desired amino acid. For example, an unnatural amino acid required for the above circularization may also be introduced into the binding peptide by this method.

[00636] Various methods commonly used in the technical field may be used for chemical synthesis of the peptide, including, for example, stepwise solid-phase synthesis, semisynthesis of peptide fragments undergoing conformationally supported religation, and chemical ligation. Synthesis of the peptide is chemical synthesis using various solid phase technologies described in, for example, K. J. Jensen, P. T. Shelton, S. L. Pedersen, Peptide Synthesis and Applications, 2nd Edition, Springer, 2013, and the like. A preferable strategy is based on a combination of an Fmoc group capable of temporarily protecting the α-amino group and being selectively removed using a base, and a protecting group that temporarily protects a side chain functional group and is stable under Fmoc deprotection conditions. Selection of this kind of general peptide side chain is known according to the aforementioned Peptide Synthesis and Applications, 2nd Edition; G. B. Fields, R. L. Noble, Solid Phase Peptide Synthesis Utilizing 9-Fluorenylmethoxycarbonyl Amino Acids, Int. J. Peptide Protein Res. 35, 1990, 161-214, and the like; however, preferable peptide side chain protecting groups include, for example, a

benzyl group or a tert-butyl group and a trityl (Trt) group for the hydroxy group of serine or threonine; a 2-bromobenzyloxycarbonyl group or a tert-butyl group for the hydroxy group of tyrosine; a Boc group, a methyltetrazole thiol (Mtt) group, an Alloc group, and an ivDde group for the amino group of the lysine side chain; a Trt group or a Boc group for the imidazole group of histidine; a 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl group (Pbf) group for the guanidyl group of arginine; a tert-butyl group, an allyl group, and a 3-methylpentane (Mpe) group for carboxyl groups, such as glutamic acid and aspartic acid; a Trt group for the carboxamide group of glutamine or asparagine; or a Trt group and a monomethoxytrityl (Mmt) group for the thiol group of cysteine.

[00637] The peptide may be synthesized by a stepwise method on the solid-phase resin described above. The C-terminal amino acid to be used and all of the amino acids or peptides to be used for synthesis must be selectively removed during the process of synthesizing the α-amino protecting group. Preferably, the solid-phase resin described above is used, and once a C-terminal carboxyl group of a peptide having its N-terminal properly protected by Fmoc or the like or a C-terminal carboxyl group of an amino acid having its N-terminal protected by Fmoc is made into an activated ester by an appropriate reagent, this is then added to the amino group on the solid-phase resin to start. Subsequent elongation of the peptide chain may be achieved by removing the N-terminal protecting group (Fmoc group) then successively repeating condensation of the protected amino acid derivative according to the amino acid sequence of the target peptide. Note that these may release the target peptide in a final stage. Examples of releasing conditions are given in Teixeira, W. E. Benckhuijsen, P. E. de Koning, A. R. P. M. Valentijn, J. W. Drijfhout, Protein Pept. Lett., 2002, 9, 379-385, and the like, and the peptide may be released in a TFA solution containing water/silyl hydride/thiol as a scavenger in TFA. Typical examples include TFA/Water/TIS/DODT (volume ratio 92.5:2.5:2.5:2.5).

[00638] Synthesis of the peptide described in the present specification may be carried out using a single or multi-channel peptide synthesizer, for example, a Liberty Blue synthesizer from CEM Corporation, a Syro I synthesizer or a successor machine thereof from Biotage Japan, Ltd., or the like.

[00639] Activation of the carboxy group may be performed using a condensing agent. Examples of the condensing agent include dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIPCDI), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC or WSC), (1H-benzotriazole-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP), 1-[bis(dimethylamino)methyl]-1H-benzotriazolium-3-oxide hexafluorophosphate (HBTU), and the like.

[00640] Cyclization of the peptide may be carried out according to a known method. In a non-limiting manner, by designing the peptide to comprise two or more cysteine residues, for example, a cyclic structure may be formed by a disulfide bond after translation. Furthermore, according to the method of Goto *et al.* (Y. Goto, *et al.* ACS Chem. Biol. 3 120-129 (2008)), a peptide having a chloroacetyl group at its N-terminal may be synthesized by genetic code reprogramming technology and may also be circularized by disposing a cysteine residue containing a sulfur molecule in the peptide. Thus, a mercapto group spontaneously performs a nucleophilic attack on the chloroacetyl group after translation, and the peptide is circularized by thioether binding. Other amino acid combinations that bind to form a ring may be disposed within the peptide and circularized by genetic

code reprogramming technology. Alternatively, circularization may be carried out by disposing an L-2-aminoadipic acid residue in the peptide and binding it to the main chain amino group of the N-terminal. In this manner, a known circularization method may be used without any particular limitation.

Pharmaceutical Composition and Uses Thereof

[00641] The present technology also relates to a pharmaceutical composition that comprises the peptide of the present technology. Diseases targeted by the pharmaceutical composition of the present technology are those associated with overexpression or decreased expression of GPC3, such as certain cancer.

[00642] As used herein, the expression "a disease or disorder characterized by overexpression or decreased expression of GPC3" refers to a disease that exhibits various symptoms mainly caused by excessive or decreased GPC3 expression.

[00643] In some aspect, the diseases targeted by the pharmaceutical composition of the present technology are those associated with overexpression of GPC3.

[00644] In some embodiments, the pharmaceutical composition of the present technology may comprise the peptide itself or may comprise a pharmaceutically acceptable salt of the peptide. The "peptide" in the present specification may comprise a pharmaceutically acceptable salt of the peptide unless otherwise specified. The pharmaceutical composition preferably comprises the peptide as an active ingredient in an effective amount.

[00645] The salt of the peptide (pharmaceutically acceptable salt) is preferably an acid addition salt. For example, a salt of an inorganic acid (such as hydrochloric acid, phosphoric acid, hydrobromic acid, sulfuric acid), a salt of an organic acid (such as acetic acid, formic acid, propionic acid, fumaric acid, maleic acid, succinic acid, tartaric acid, citric acid, malic acid, oxalic acid, benzoic acid, methanesulfonic acid, benzenesulfonic acid), or the like is used as this salt. The peptide or a salt thereof also comprises a solvate such as a hydrate.

[00646] In the present specification, the form of administration of the pharmaceutical composition is not particularly limited and may be oral or parenteral. Examples of parenteral administration include injection, such as intramuscular injection, intravenous injection, or subcutaneous injection; transdermal administration; transmucosal administration (transnasal, transoral, transocular, transpulmonary, transvaginal, or transrectal); or the like.

[00647] The pharmaceutical composition may be modified in various ways, considering a property where a polypeptide is easily metabolized and excreted. For example, polyethylene glycol (PEG) or a sugar chain may be added to the polypeptide to extend its retention time in the blood to reduce antigenicity. Furthermore, an emulsion, nanoparticles, nanospheres, or the like prepared in a biodegradable polymerized compound such as polylactic acid/glycol (PLGA), porous hydroxyapatite, liposomes, surface-modified liposomes, and unsaturated fatty acids are used as a controlled-release base, and the polypeptide may be present in the base. In the case of transdermal administration, a weak current is allowed to pass through the skin surface and penetrate the stratum corneum (iontophoresis).

[00648] As for the pharmaceutical composition, the active ingredient may be used as is, or the pharmaceutical composition may comprise a pharmaceutically acceptable carrier, an excipient, an additive, or the like, or may be

formulated. Examples of the dosage form include a liquid agent (for example, an injection), a dispersant, a suspension, a tablet, a pill, a powder, a suppository, a powdered drug, a fine granule, a granule, a capsule, a syrup, a lozenge, an inhalant, an ointment, an eye drop, a nasal drop, an ear drop, a patch, or the like. The formulation may be carried out by a common method using, for example, an excipient, a binder, a disintegrant, a lubricant, a dissolving agent, a solubilizing agent, a colorant, a flavoring agent, a stabilizer, an emulsifier, an absorption promoter, a surfactant, a pH regulator, a preservative, an antioxidant, or the like as appropriate.

[00649] Examples of ingredients used for formulation include but are not limited to purified water, saline, phosphate buffer solution, dextrose, glycerol, a pharmaceutically acceptable organic solvent such as ethanol, animal and vegetable oil, lactose, mannitol, glucose, sorbitol, crystalline cellulose, hydroxypropyl cellulose, starch, corn starch, anhydrous silicic acid, magnesium aluminum silicate, collagen, polyvinyl alcohol, polyvinyl pyrrolidone, carboxyvinyl polymer, sodium carboxymethylcellulose, sodium polyacrylate, sodium alginate, water-soluble dextran, sodium carboxymethyl starch, pectin, methyl cellulose, ethyl cellulose, xanthan gum, gum arabic, tragacanth, casein, agar, polyethylene glycol, diglycerin, glycerin, propylene glycol, vaseline, paraffin, octyldodecyl myristate, isopropyl myristate, higher alcohol, stearyl alcohol, stearic acid, human serum albumin, or the like.

[00650] The pharmaceutical composition may comprise an absorption promoter for improving absorption of a poorly absorbable drug, in consideration of the fact that it is generally difficult for peptides to be absorbed through mucous membranes. The following may be used as the absorption promoter: a surfactant such as polyoxyethylene lauryl ether, sodium lauryl sulfate, and saponin; a bile salt such as glycocholic acid, deoxycholic acid, and taurocholic acid; a chelating agent such as EDTA and salicylic acid; a fatty acid such as caproic acid, capric acid, lauric acid, oleic acid, linoleic acid, a mixed micelle; an enamine derivative, an N-acyl collagen peptide, an N-acyl amino acid, a cyclodextrin, chitosan, a nitric oxide donor, or the like.

[00651] When the pharmaceutical composition is a pill or tablet, it may be coated using a sugar coating, or a gastric-soluble or enteric-coated substance.

[00652] When the pharmaceutical composition is an injection, it may comprise distilled water for injection, physiological saline, propylene glycol, polyethylene glycol, vegetable oil, alcohol, or the like. Additionally, a humectant, an emulsifier, a dispersant, a stabilizer, a dissolving agent, a solubilizing agent, a preservative, or the like may be added.

[00653] Furthermore, the pharmaceutical composition may be targeted not only to humans but also to non-human mammals or birds. Examples of non-human mammals include primates other than humans (monkeys, chimpanzees, gorillas, and the like), livestock animals (pigs, cows, horses, sheep, and the like), dogs, cats, rats, mice, guinea pigs, rabbits, and the like.

[00654] In particular, the dosage in the case of administering to a human changes depending on symptoms, age, sex, and weight of the patient, sensitivity difference, administration method, administration interval, type of active ingredient, and type of formulation, and it may be administered in a non-limiting manner: for example, by administering between about 30 μg to about 100 g, between about 1 μg to about 10g, between about 1 μg to about 1g, between about 10 μg to about 1g, between about 10 μg to about 500 mg, between about 100 μg to

about 10g, between about 100 µg to about 1g, between about 10 µg to about to about 500 mg, between about 100 µg to about 500 mg, or between about 100 µg to about 100 mg once or divided into several doses. In the case of injection, between about 1 µg/kg and about 3,000 µg/kg or between about 3 µg/kg and about 1,000 µg/kg according to the bodyweight of the patient may be administered once or divided into several doses.

II. METHOD OF USE OR TREATMENT

[00655] The present technology also relates to a method for treating a disease or disorder characterized by overexpression or decreased expression of GPC3 by administering the peptide of the present technology to a subject.

[00656] The present technology also relates to a use of the peptide of the present technology for the treatment of a disease or disorder characterized by overexpression or decreased expression of GPC3.

[00657] The present technology also relates to a use of the peptide for manufacturing a pharmaceutical composition for the treatment of a disease or disorder characterized by overexpresion or decreased expression of GPC3.

[00658] The present technology also relates to the peptide of the present technology for use in a method for treating a disease or disorder characterized by overexpression ordecreased expression of GPC3.

[00659] The present technology also relates to a kit for use in a method of diagnosing disease or disorder characterized by overexpression or decreased expression of GPC3 by determination of the expression level of GPC3.

[00660] The present technology also relates to a composition for use in a method of diagnosing disease or disorder characterized by overexpression or decreased expression of GPC3.

[00661] The present technology also relates to use of a peptide or a salt thereof for use in a method of diagnosing disease or disorder characterized by overexpression or decreased expression of GPC3.

[00662] The present technology also provides methods of treating a disease or condition in a subject in need thereof. In some embodiments, the disease or disorder is characterized by overexpression or decreased expression of GPC3 in diseased tissue. In some embodiments, the disease or disorder is characterized by overexpression of GPC3 in diseased tissue. In some embodiments, the disease or disorder is characterized by decreased expression of GPC3 in diseased tissue. In some embodiments, the methods comprise administering a peptide described herein, a conjugate described herein, 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 peptide, a conjugate, or a pharmaceutical composition described herein.

[00663] In some embodiments, the methods comprise administering to a subject a therapeutically effective amount of a peptide, a conjugate, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the peptide, 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.

[00664] In one aspect, provided herein is a method of treating cancer by administering a herein described peptide, conjugate or a pharmaceutically acceptable salt or solvate thereof to a subject in need thereof. According to a further aspect of the disclosure, there is provided a peptide, or a drug conjugate thereof as defined herein, for use in preventing, suppressing or treating a disease or disorder characterized by overexpression or decreased expression of GPC3 in diseased tissue. In some embodiments, the disease or disorder is characterized by overexpression of GPC3 in diseased tissue (such as a tumor). In one embodiment, the GPC3 is mammalian GPC3. In a further embodiment, the mammalian GPC3 is human GPC3.

[00665] In one aspect, provided herein is a method of preventing, suppressing or treating a disease or disorder characterized by overexpression or decreased expression of GPC3 in diseased tissue. In some embodiments, the disease or disorder is characterized by overexpression of GPC3 in diseased tissue (such as a tumor), which comprises administering to a patient in need thereof a peptide or a conjugate described herein (*e.g.*, including a peptide, a payload molecule, and optionally a linker). In some embodiments, the disease or disorder characterized by overexpression of GPC3 in diseased tissue is a cancer.

[00666] Non-limiting examples of cancers to be treated by the methods of the present disclosure can include hematological cancer or solid tumor, such as melanoma (*e.g.*, metastatic malignant melanoma), renal cancer (*e.g.*, clear cell carcinoma), prostate cancer (*e.g.*, hormone refractory prostate adenocarcinoma), pancreatic adenocarcinoma, breast cancer, colon cancer, lung cancer (*e.g.*, non-small cell lung cancer), esophageal cancer, squamous cell carcinoma of the head and neck, liver cancer, ovarian cancer, cervical cancer, thyroid cancer, glioblastoma, glioma, leukemia, lymphoma, and other neoplastic malignancies. In some embodiments, a subject or population of subjects to be treated with a pharmaceutical composition of the present disclosure have a solid tumor. In some embodiments, a solid tumor is a melanoma, renal cell carcinoma, lung cancer, bladder cancer, breast cancer, cervical cancer, colon cancer, gall bladder cancer, laryngeal cancer, liver cancer, thyroid cancer, stomach cancer, salivary gland cancer, prostate cancer, pancreatic cancer, or Merkel cell carcinoma. In some embodiments, a subject or population of subjects to be treated with a pharmaceutical composition of the present disclosure have a hematological cancer. In some embodiments, the subject has a hematological cancer such as Diffuse large B cell lymphoma ("DLBCL"), Hodgkin's lymphoma ("HL"), Non-Hodgkin's lymphoma ("NHL"), Follicular lymphoma ("FL"), acute myeloid leukemia ("AML"), or Multiple myeloma ("MM"). In some embodiments, a subject or population of subjects to be treated having the cancer selected from the group consisting of ovarian cancer, lung cancer and melanoma. In some embodiments, the cancer is selected from hepatocellular carcinoma, squamous cell carcinoma of the lung, lung adenocarcinoma, germ cell tumors, hepatoblastoma, wilms tumor, malignant rhabdoid tumors, rhabdomyosarcoma, liposarcoma, thyroid cancers, pancreatic cancer, small bowel cancer, small cell neuroendocrine carcinoma (SCNC), hormonally treated, castration resistant prostatic adenocarcinoma, ovarian cancer, gastric cancer, esophageal carcinoma and malignant melanoma.

[00667] In some embodiments, provided herein are methods and compositions for treating a disease or condition. Exemplary disease or condition includes refractory or recurrent malignancies whose growth may be inhibited using the methods of treatment of the present disclosure. In some embodiments, the disease or condition is a cancer. In some embodiments, the cancer is breast cancer, head and neck squamous cell

carcinoma, non-small cell lung cancer, hepatocellular cancer, bladder cancer, colorectal cancer, gastric adenocarcinoma, ovarian cancer, melanoma, or advanced cancer. In some embodiments, a cancer to be treated by the methods of treatment of the present disclosure is selected from the group consisting of carcinoma, squamous carcinoma, adenocarcinoma, sarcomata, endometrial cancer, breast cancer, ovarian cancer, cervical cancer, fallopian tube cancer, primary peritoneal cancer, colon cancer, colorectal cancer, squamous cell carcinoma of the anogenital region, melanoma, renal cell carcinoma, lung cancer, non-small cell lung cancer, squamous cell carcinoma of the lung, stomach cancer, bladder cancer, gall bladder cancer, liver cancer, thyroid cancer, laryngeal cancer, salivary gland cancer, esophageal cancer, head and neck cancer, glioblastoma, glioma, squamous cell carcinoma of the head and neck, prostate cancer, pancreatic cancer, mesothelioma, sarcoma, hematological cancer, leukemia, lymphoma, neuroma, and combinations thereof. In some embodiments, a cancer to be treated by the methods of the present disclosure include, for example, carcinoma, squamous carcinoma (for example, cervical canal, eyelid, tunica conjunctiva, vagina, lung, oral cavity, skin, urinary bladder, tongue, larynx, and gullet), and adenocarcinoma (for example, prostate, small intestine, endometrium, cervical canal, large intestine, lung, pancreas, gullet, rectum, uterus, stomach, mammary gland, and ovary). In some embodiments, a cancer to be treated by the methods of the present disclosure further include sarcomata (for example, myogenic sarcoma), leukosis, neuroma, melanoma, and lymphoma. In some embodiments, a cancer to be treated by the methods of the present disclosure is breast cancer. In some embodiments, a cancer to be treated by the methods of treatment of the present disclosure is triple negative breast cancer (TNBC). In some embodiments, a cancer to be treated by the methods of treatment of the present disclosure is pancreatic cancer. In some embodiments, a cancer to be treated by the methods of the present disclosure is non-small cell lung cancer, ovarian cancer, or bladder cancer. In some embodiments, a cancer to be treated by the methods of the present disclosure is non-small cell lung cancer. In some embodiments, a cancer to be treated by the methods of the present disclosure is bladder cancer. In some embodiments, a cancer to be treated by the methods of the present disclosure is ovarian cancer. In some embodiments, a cancer to be treated by the methods of the present disclosure is hepatocellular carcinoma, squamous cell carcinoma of the lung, lung adenocarcinoma, germ cell tumors, hepatoblastoma, wilms tumor, malignant rhabdoid tumors, rhabdomyosarcoma, liposarcoma, thyroid cancers, pancreatic cancer, small bowel cancer, ovarian cancer, gastric cancer, esophageal carcinoma, or malignant melanoma.

[00668] Further examples of cancers (and their benign counterparts) which may be treated include, but are not limited to tumors of epithelial origin (adenomas and carcinomas of various types including adenocarcinomas, squamous carcinomas, transitional cell carcinomas and other carcinomas) such as carcinomas of the bladder and urinary tract, breast, gastrointestinal tract (including the esophagus, stomach (gastric), small intestine, colon, rectum and anus), liver (hepatocellular carcinoma), gall bladder and biliary system, exocrine pancreas, kidney, lung (for example adenocarcinomas, small cell lung carcinomas, non-small cell lung carcinomas, bronchioalveolar carcinomas and mesotheliomas), head and neck (for example cancers of the tongue, buccal cavity, larynx, pharynx, nasopharynx, tonsil, salivary glands, nasal cavity and paranasal sinuses), ovary, fallopian tubes, peritoneum, vagina, vulva, penis, cervix, myometrium, endometrium, thyroid (for example thyroid follicular

carcinoma), adrenal, prostate, skin and adnexae (for example melanoma, basal cell carcinoma, squamous cell carcinoma, keratoacanthoma, dysplastic naevus); hematological malignancies (*i.e.* leukemias, lymphomas) and premalignant hematological disorders and disorders of borderline malignancy including hematological malignancies and related conditions of lymphoid lineage (for example acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia, B-cell lymphomas such as diffuse large B-cell lymphoma, follicular lymphoma, Burkitt's lymphoma, mantle cell lymphoma, T-cell lymphomas and leukemias, natural killer cell lymphomas, Hodgkin's lymphomas, hairy cell leukemia, monoclonal gammopathy of uncertain significance, plasmacytoma, multiple myeloma, and post-transplant lymphoproliferative disorders), and hematological malignancies and related conditions of myeloid lineage (for example acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelomonocytic leukemia, hypereosinophilic syndrome, myeloproliferative disorders such as polycythemia vera, essential thrombocythemia and primary myelofibrosis, myeloproliferative syndrome, myelodysplastic syndrome, and promyelocytic leukemia); tumors of mesenchymal origin, for example sarcomas of soft tissue, bone or cartilage such as osteosarcomas, fibrosarcoma's, chondrosarcomas, rhabdomyosarcomas, leiomyosarcomas, liposarcomas, angiosarcomas, Kaposi's sarcoma, Ewing's sarcoma, synovial sarcomas, epithelioid sarcomas, gastrointestinal stromal tumors, benign and malignant histiocytomas, and dermatofibrosarcoma protuberans; tumors of the central or peripheral nervous system (for example astrocytoma's, gliomas and glioblastomas, meningiomas, ependymomas, pineal tumors and schwannomas); endocrine tumors (for example pituitary tumors, adrenal tumors, islet cell tumors, parathyroid tumors, carcinoid tumors and medullary carcinoma of the thyroid); ocular and adnexal tumors (for example retinoblastoma); germ cell and trophoblastic tumors (for example teratomas, seminomas, dysgerminomas, hydatidiform moles and choriocarcinomas); and pediatric and embryonal tumors (for example medulloblastoma, neuroblastoma, Wilms tumor, and primitive neuroectodermal tumors); or syndromes, congenital or otherwise, which leave the patient susceptible to malignancy (for example Xeroderma Pigmentosum).

[00669] In some embodiments, the cancer is selected from glioblastoma, prostate cancer, lung cancer, breast cancer, gastric cancer, ovarian cancer, gladder cancer, colon cancer, esophageal cancer, multiple myeloma and fibrosarcoma. In some embodiments, the cancer is selected from: breast cancer, lung cancer, gastric cancer, pancreatic cancer, prostate cancer, liver cancer, glioblastoma and angiogenesis. In some embodiments, the cancer is selected from: prostate cancer, lung cancer (such as non-small cell lung carcinomas (NSCLC)), breast cancer (such as triple negative breast cancer), gastric cancer, ovarian cancer, esophageal cancer, multiple myeloma and fibrosarcoma. In some embodiments, the cancer is prostate cancer. In some embodiments, the conjugate is useful for preventing, suppressing or treating solid tumors such as fibrosarcoma's and breast, and non-small cell lung carcinomas. In some embodiments, the cancer is selected from lung cancer, such as non-small cell lung carcinomas (NSCLC). In some embodiments, the cancer is breast cancer. In some embodiments, the breast cancer is triple negative breast cancer. In some embodiments, the breast cancer is Herceptin resistant breast cancer. In some embodiments, the subject has failed to respond to Herceptin. In some embodiments, the cancer is gastric cancer. In some embodiments, the cancer is ovarian cancer. In some embodiments, the cancer is esophageal cancer. In some embodiments, the cancer is multiple myeloma. In some embodiments, the cancer

is fibrosarcoma.

[00670] In some embodiments, provided herein are methods for killing a cell comprising contacting the cell with a peptide, a conjugate, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the cell expresses GPC3. In some embodiments, the cell over-expresses GPC3. In some embodiments, the conjugate or pharmaceutically acceptable salt or solvate thereof binds to a structure on the cell, wherein the structure is an GPC3.

[00671] After contacting a cell, the described peptide or conjugate can be internalized by the cell. The internalization can be mediated by cell receptors, cell membrane endocytosis, *etc*. In some embodiments, the described peptide or conjugate is internalized by a cell through GPC3. In some embodiments, rapid internalization rate into cancer cells accompanied by a slow externalization rate can offer therapeutic benefit.

[00672] In one aspect, the disclosed peptide, conjugate or a pharmaceutically acceptable salt or solvate thereof is configured to treat cancer by ablating tumor cells. In some embodiments, the peptide, 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.

[00673] In addition to the methods of treatment described above, the peptide, conjugates and compositions described herein can be used to image, and/or as part of a treatment for diseases. Suitable imaging applications include single-photon emission computed tomography (SPECT) and positron emission tomography (PET).

[00674] In one aspect, described herein is a method of diagnosing or imaging a cancer in a subject in need thereof, comprising administering to the subject a peptide, a conjugate or a pharmaceutical composition described herein.

[00675] In some embodiments, the subject is 1 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.

Combination Therapy

[00676] In some embodiments, a peptide or conjugate described herein can be administered alone or in combination with one or more additional therapeutic agents. For example, the combination therapy can include a composition comprising a peptide or 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 immunotherapies. In some embodiments, the peptide or conjugate is administered in combination with other therapeutic treatment

modalities, including surgery, 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.

[00677] 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.

[00678] In some embodiments, the herein-described peptide or conjugate is used in combination with a chemotherapeutic agent, *e.g.*, a DNA damaging chemotherapeutic agent, a platinum based agent, a topoisomerase inhibitor, a taxane, an antimetabolite, a vinca alkaloid, or an anthracycline. In some embodiments, the herein-described peptide or conjugate is used in combination with a radiation sensitizer, which makes tumor cells more sensitive to radiation therapy. In some embodiments, the herein-described peptide or conjugate is used in combination with a DNA damage repair inhibitor (or DNA damage response (DDR) inhibitor). In some embodiments, the DNA damage repair inhibitor or DDR inhibitor is a poly (ADP-ribose) polymerase (PARP) inhibitor. In some embodiments, the herein-described peptide or conjugate is used in combination with an immune checkpoint inhibitor. In some embodiments, the immune checkpoint inhibitor is a PD-L1 inhibitor, a PD-1 inhibitor, or a CTLA-4 inhibitor. In some embodiments, the herein-described peptide or conjugate is used in combination with a chemotherapeutic agent, a PARP inhibitor, and/or an immune checkpoint inhibitor. In some embodiments, the herein-described peptide or conjugate is used in combination with a chemotherapeutic agent, a PARP inhibitor, and an immune checkpoint inhibitor.

[00679] 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.

[00680] 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

Abbreviations:

[00681] Unless otherwise stated in the present specification, the following abbreviations are used according to the following meanings:

Alloc	allyloxycarbonyl
aq.	aqueous
Biotin-OSu	biotin *N*-hydroxysuccinimide ester (CAS 35013-72-0)
Boc	*tert*-butyloxycarbonyl
ClAcOH	chloroacetic acid
ClAcOSu	*N*-succinimidyl 2-chloroacetate (CAS 27243-15-8)
DCM	dichloromethane (CAS 75-09-2)
DIC	*N,N'*-diisopropylcarbodiimide (CAS 693-13-0)
DIPEA, DIEA	*N,N*-diisopropylethylamine (CAS 7087-68-5)
DMEM	Dulbecco's Modified Eagle Medium
DMF	*N,N*-dimethylformamide (CAS 68-12-2)
DODT	2,2'-(ethylenedioxy)diethanethiol (CAS 14970-87-7)
EDCI-HCl	*N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (CAS 25952-53-8)
EDTA	ethylenediaminetetraacetic acid
EMEM	Eagle's minimal essential medium
eq	equivalent
Et	ethyl
Et_3N, TEA	triethylamine (CAS 121-44-8)
FBS	fetal bovine serum
Fmoc	9-fluorenylmethoxycarbonyl
hr	hour
HATU	1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium-3-oxide hexafluorophosphate (CAS 148893-10-1)
HOSu	*N*-hydroxysuccinimide (CAS 6066-82-6)
iPrOH, IPA	isopropanol
M	molar
min	minutes
NHS	*N*-hydroxysuccinimide (CAS 6066-82-6)
NMP	*N*-methylpyrrolidone (CAS 872-50-4)
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0) (CAS 14221-01-3)
PG	protecting group
Ph	phenyl
RP	reverse phase

rpm	rotations per minute
rt	room temperature
SAPE	Streptavidin, R-Phycoerythrin conjugate
SPPS	solid phase peptide synthesis
Su	succinimidyl
SulfoCy5-	sulfo Cyanine5 (CAS 2791287-13-1)
SulfoCy5-OSu,	(CAS 146368-14-1)
SulfoCy5-NHS	see SulfoCy5-OSu
tert	tertiary
TFA	trifluoroacetic acid (CAS 76-05-1)
TIS	triisopropylsilane (CAS 6485-79-6)
tr	retention time
Trt	trityl.
PyAOP	(7-azabenzotriazol-1-yloxy)trispyrrolidinophosphonium hexafluorophosphate (CAS 156311-83-0)
MeCN	acetonitrile
AcOH	acetic acid
Et_2O	diethyl ether
AA	amino acid
Me	methyl
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol (CAS 920-66-1)
$PhSiH_3$	phenylsilane (CAS 694-53-1)
tBu	tertiary butyl
DMSO	dimethylsulfoxide
Mpe	3-Methyl-pent-3-yl

[00682] The present technology is described in detail below based on examples, but the present technology is not limited to these examples. A person having ordinary skill in the art is capable of easily adding modifications and changes to the present technology based on the description of the present specification, and these are included in the technical scope of the present technology.

[00683] Abbreviation for non-natural amino acids used in this invention will be described here.

[00684] Analytical methods, materials, and instruments.

[00685] Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. If not otherwise specified, purity and low-resolution mass spectral data were measured using a Shimadzu Nexera XR system coupled to a LCMS-2020 MS (ESI). Methods are specified below.

Method A-1 (HPLC-MS): Phenomenex Kinetex EVO C18 2.6um, 2.1ID x 150mm, 100Å (with a guard cartridge 2.1mmID); 60 °C; 0.5 mL/min; (A) H_2O + 0.025% TFA / (B) MeCN + 0.025% TFA; gradient: from 5 to 45% B in 7.2 min. Detection: electrospray mass spectra (+) and PDA-UV at UV of 225 nm.

Method A-2 (HPLC-MS): Phenomenex Kinetex EVO C18 2.6um, 2.1ID x 150mm, 100Å (with a guard cartridge 2.1mmID); 60 °C; 0.5 mL/min; (A) H_2O + 0.025% TFA / (B) MeCN + 0.025% TFA; gradient: from 20 to 60% B in 7.2 min. Detection: electrospray mass spectra (+) and PDA-UV at UV of 225 nm.

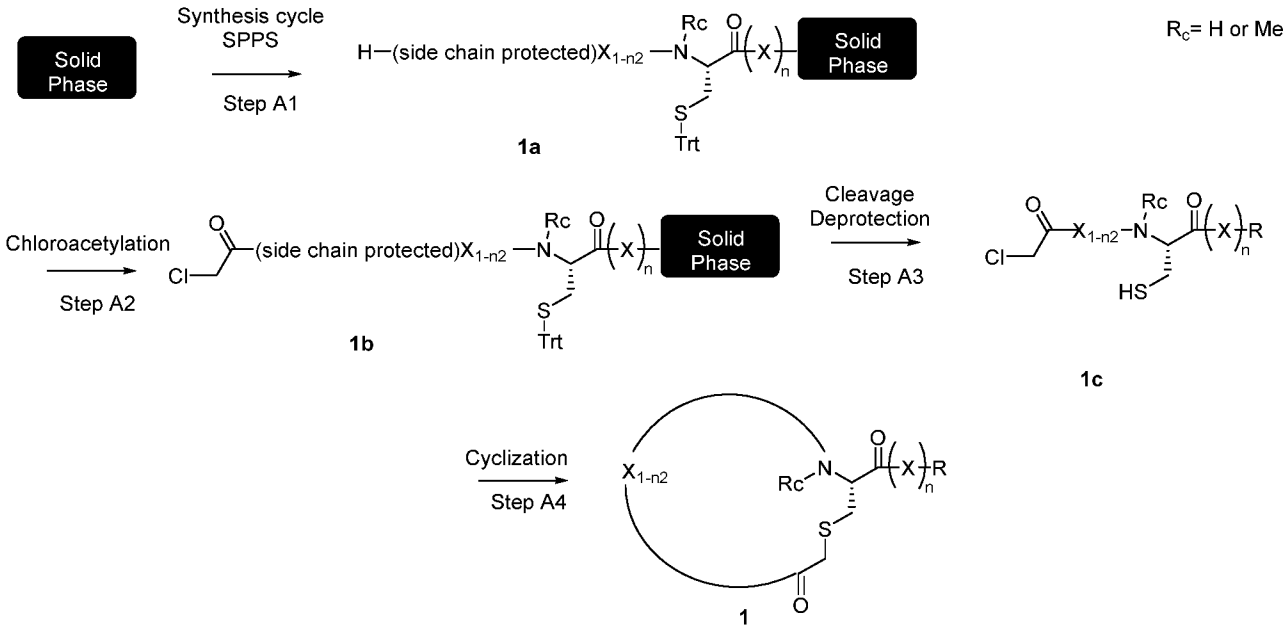
[00686] General preparative HPLC purification method.

[00687] Crude containing the desired polypeptide were purified by preparative RP-HPLC using DAD-UV chromatogram at UV 220 nm and electrospray mass spectra (+) for the detection and employing commercially available RP-HPLC columns such as Waters XBridge C18, Waters XSelect C18, Phenomenex Kinetex EVO C18, and Interchim US5C18HQ-100/300. Otherwise specified, (A) H_2O + 0.1% TFA and (B) MeCN + 0.1% with varying gradients were employed as eluents. Product-containing fractions were collected and lyophilized to obtain the purified product.

[00688] General synthetic aspects.

[00689] Macrocyclic peptides type-A can be synthesized as outlined in Scheme-1.

Scheme-1



[00690] Step-A1: Peptide elongation on resin.

[00691] Th peptide elongations in this invention were performed in automated peptide synthesizers employing conditions as described in Method-S1, Method-S2, and Method-S3 in accordance with the manufacturer's instruction. In addition, the peptide coupling with certain Fmoc-AAs was performed by the synthesizer or by manually as described in the table S1-2. In detail, Fmoc-Sieber amide resin was suspended in the solvent (e.g., DMF or DCM) and then loaded onto the peptide synthesizer. After Fmoc removal of the resin, Fmoc-AA coupling and subsequent Fmoc removal as one cycle was performed employing conditions suitable for each Fmoc-AA as described below. The peptide elongation on resin was continued until the desired linear polypeptide sequence **1a** was obtained. Below described the AA coupling and Fmoc deprotection conditions.

[00692] Method S1 employing Liberty BLUE HT 12TM (CEM. Inc.).

[00693] General AA coupling conditions

Table S1-1

Fmoc-AA	Reagents	Coupling conditions
Fmoc-MeC(Trt)-OH	DIC/ Oxyma Pure® in DMF or NMP	50°C, 1-2x 15-20 min; or 40°C, 1-2x 30 min; or 25°C, 1-2x 30 min
Fmoc-H(Trt)-OH		50°C, 2x 30 min
Other than listed above		90°C, 1-2x 3-10 min or 75°C, 1-2x 10-30 min

[00694] Fmoc deprotection on resin.

Table S1-2

Fmoc-AA on peptide	Reagents	Deprotection conditions
Fmoc-AA coupled with N-Me-AA	pyrrolidine/ DMF (1/ 9) or piperidine/ DMF (1/ 4)	25°C, 1-2x 1-5 min or 25°C, 5 min then 25°C, 15 min
Other than listed above		90°C, 1 min or 75°C, 3 min or 50°C, 1.5 min

[00695] Method S2 employing Liberty Prime (CEM. Inc.).

[00696] General AA coupling on resin.

Table S2-1

Fmoc-AA	Reagents	Coupling conditions
Fmoc-MeC(Trt)-OH	DIC/ Oxyma Pure® in DMF or NMP	50°C, 1-2x 15-20 min or 40°C, 1-2x 30 min
Other than listed above		105°C, 1-2x 1-2 min; or 90°C, 1-2x 3-10 min; or 75°C, 2x 20-30 min

[00697] General method for Fmoc deprotection

Table S2-2

Fmoc-AA on peptide	Reagents	Deprotection conditions
Fmoc-AA coupled with N-Me-AA	pyrrolidine/ DMF (1/ 9)	25°C, 1-2x 1-5 min
Other than listed above	83 mM Oxyma Pure® in pyrrolidine/ DMF (4/ 96)	110°C, 1-1.5 min

[00698] Method S3 employing Cyro I (Biotage. Inc.).

[00699] General AA coupling

[00700] Table S3-1

Fmoc-AA	Reagents	Coupling conditions
Fmoc-MeC(Trt)-OH	HATU/ DIEA in DMF or NMP	25°C, 40 min
Other than listed above		75°C, 2x 20-30 min

[00701] General Fmoc deprotection

[00702] Table S3-2

Fmoc-AA on peptide	Reagents	Deprotection conditions
All AAs	piperidine/ DMF (1/ 4)	25°C, 5 min then 25°C, 15 min

[00703] Method S4: General peptide coupling without automated synthesizers.

[00704] The peptide coupling with the AAs listed below were performed manually without microwave employing conditions in Table S4. (Note: the AAs listed below can be introduced by the peptide synthesizer employing above methods as well).

[00705] Table S4

Fmoc-AA	Reagents	Coupling conditions
Fmoc-MeNal27N-OH	HATU/ DIEA (3-4.2/ 3-4/ 6-12) in NMP	25°C, 1x 30-60 min
Fmoc-SR3Et-OH	HATU/ DIEA (3/ 3/ 6) in DMF	25°C, 1x 40 min
Fmoc-MeA4paa(tBu)-OH	DIC/ Oxyma Pure® (3/ 4/ 8) in DMF	75°C, 1x 30 min

[00706] Step A2: Chloroacetylation.

[00707] The obtained polypeptide **1a** on resin was transferred in a syringe with a flit. The resin was shaken in a reagent mixture (see below) at room temperature for 0.5-2h. The solution was then drained through the frit. The resin was washed successively a few times with DMF, DCM, and Et_2O to afford the linear peptides **1b** on resin.

- Reagent mixture: resin/ ClAcOH in DMF(0.087-0.25M)/ HATU in DMF(0.087-0.25M)/ DIPEA in DMF (0.17-0.5M)= 1 eq/ 4.2-5 eq/ 4-5 eq/ 4.2-10 eq.

[00708] Step A3: Cleavage of polypeptides from the resin along with the global deprotection of side chain protecting groups (PGs).

[00709] Polypeptide **1b** on resin was shaken at rt for 5-90 min in the cleavage cocktail (TFA/ TIS/ DODT/ H_2O = 92.5/ 2.5/ 2.5/ 2.5). The resin was filtered and rinsed with the cocktail used. Combined filtrates were poured into cold diethyl ether. The resulting suspension was centrifuged (9000 rpm, 1 min at 0°C), and then the supernatant was decanted out. The precipitate was suspended in cold ether, vortexed briefly, and then centrifuged. This process was repeated a few times when appropriate and necessary. The crude containing polypeptide **1c** was dried under reduced pressure.

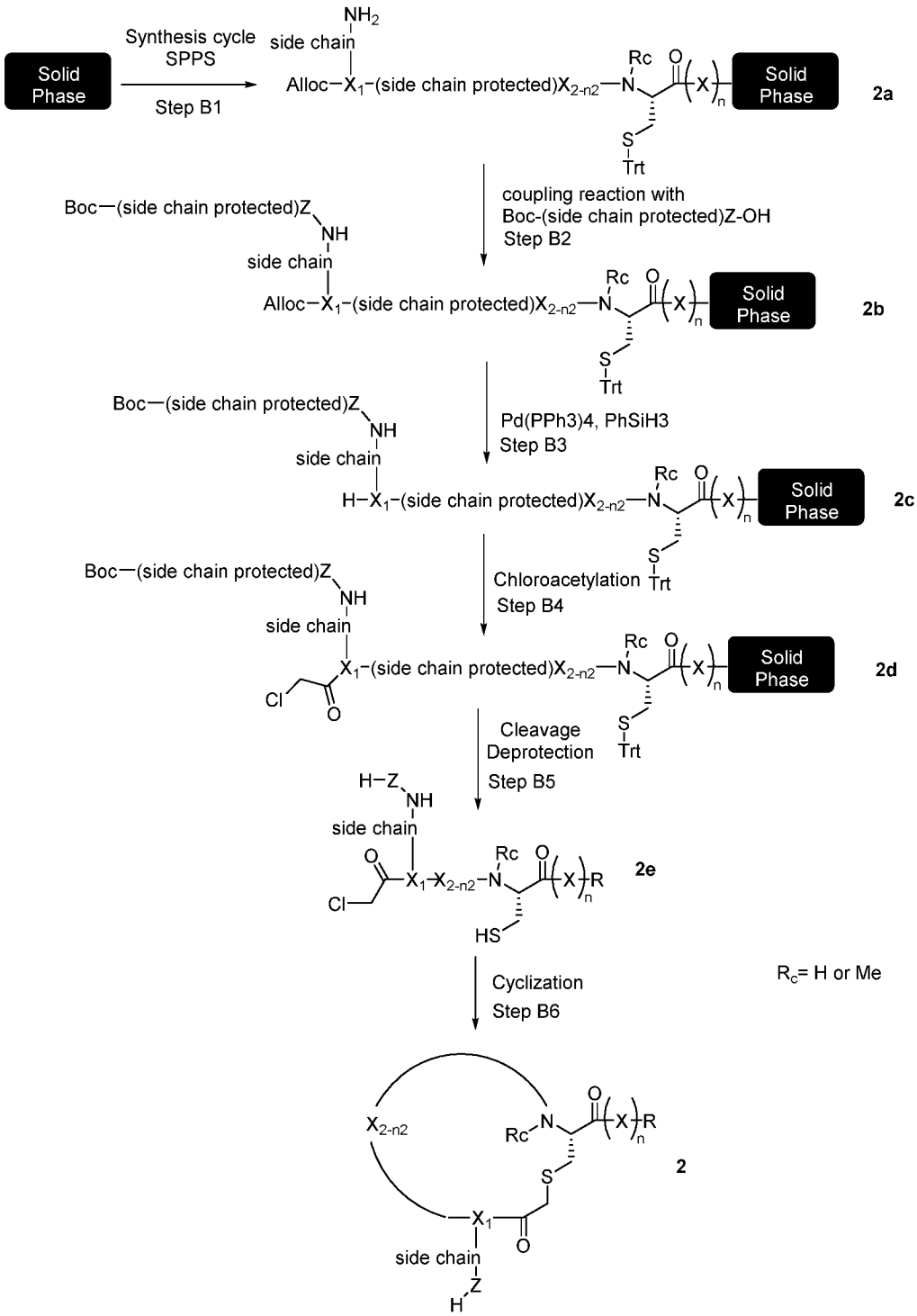
[00710] Step A4: Peptide cyclization and purification.

[00711] The crude containing polypeptide **1c** was dissolved in MeCN/ H_2O (1/ 1). To the solution was added TEA (5-20 eq), and then the mixture was stirred for 1hr to 18 hrs until completion of the reaction. The resulting mixture was rendered acidic by AcOH, and then reaction mixture was concentrated by Genevac EZ-2 Elite or HT-12. The resulting residue was purified by RP-HPLC to afford Macrocyclic peptide type-A.

[00712]

[00713] Macrocyclic peptides type-B in the present invention can be synthesized as outlined in Scheme 2. Note that the following methods can afford desired sidechain branched polypeptide at any AA position by appropriate order of Fmoc-AA used.

[00714] Scheme 2



[00715] Step B1: Polypeptides type **2a** on-resin were synthesized in the fashion analogous to Step-A1 in Scheme-1 but employing appropriately protected AA building blocks such as Alloc-K(Fmoc)-OH. Subsequently, treatment of **2a** with one of the Fmoc deprotection conditions above, followed by the coupling with the Boc-protected AAs employing the described condition in Table S5 afforded **2b**.

[00716] Table S5

Boc-protected AAs (the side chain protected properly	Reagents	Coupling conditions
Boc-df-OH	HATU/ DIEA (3/ 3/ 6) in DMF	25°C, 30 min (coupling manually)
Boc-H(Trt)-OH	DIC/ Oxyma Pure® (4.2/ 8/ 4) in DMF	50°C, 2x 30 min (Liberty Blue)
Boc-de(tBu)-OH	HATU/ DIEA (3/ 3/ 6) in DMF	75°C, 2x 30 min (Liberty Blue)

Step B3: Deprotection of the Alloc protecting group

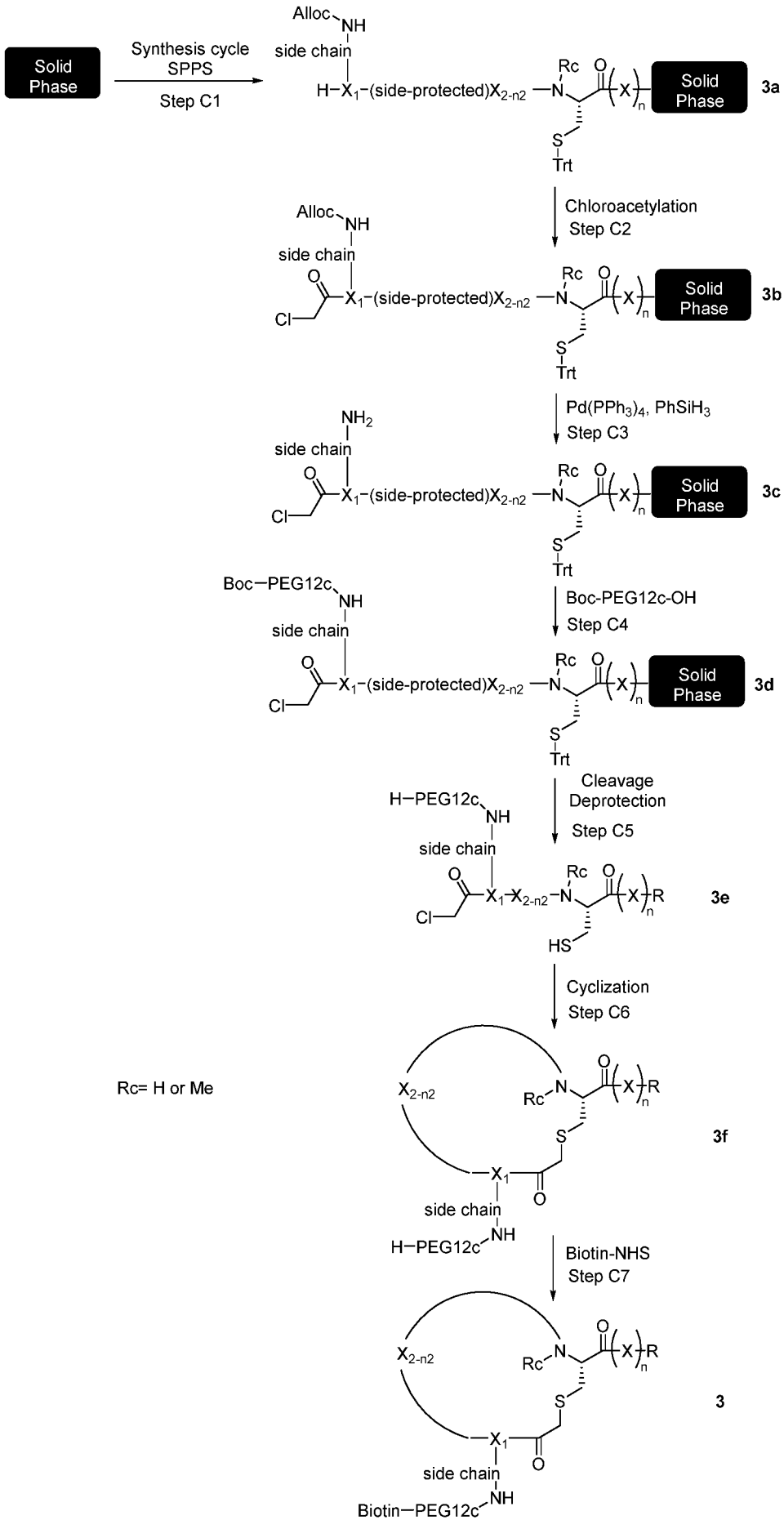
Polypeptides **2b** on resin were swollen in DCM. The resin was shaken with $Pd(PPh_3)_4$ (0.2-0.25 eq) and $PhSiH_3$ (10-15 eq) at room temperature for 1h. The resin was washed with DMF. Then the resin was washed by DCM followed by DMF to afford polypeptides **2c** on resin.

[00717] Step B4, -B5, and -B6:

Subsequently, polypeptide **2c** on resin were transformed to Macrocyclic peptides type-B by similar fashion analogous to the preparation in Scheme-1.

[00718] Macrocyclic peptides type-C in the present invention can be synthesized as outlined in Scheme-3.

[00719] Scheme-3


Solid Phase
Synthesis cycle SPPS
Step C1
Alloc
NH
side chain
H–X1–(side-protected)X2-n2
Rc
O
N
X
n
S
Trt
Solid Phase
3a
Chloroacetylation
Step C2
Cl
3b
Pd(PPh3)4, PhSiH3
Step C3
NH2
3c
Boc–PEG12c
Boc-PEG12c-OH
Step C4
3d
Cleavage
Deprotection
Step C5
H–PEG12c
HS
3e
Cyclization
Step C6
Rc= H or Me
X2-n2
R
3f
Biotin-NHS
Step C7
Biotin–PEG12c
3

[00720] Step C1, C2, and C3:

Polypeptides **3c** were synthesized by methods analogously to the preparation above employing appropriate Fmoc-AA building blocks.

[00721] Step C4: elongation of the side chain with Boc-PEG12c-OH.

[00722] Polypeptides **3c** on resin were suspended in DMF. The resin was shaken with Boc-PEG12c-OH (4.2-5.3 eq)/ HATU (4-5 eq)/ DIEA (8-10 eq) at room temperature for 30 min; or Boc-PEG12c-OH (4.2-5.3 eq)/ PyAOP (4-5 eq)/ DIEA (8-10 eq) at 40°C for 30 min. The resin was washed with DMF. Then the resin was washed by DCM followed by DMF to provide polypeptides **3d** on resin.

[00723] Step C5 and C6:

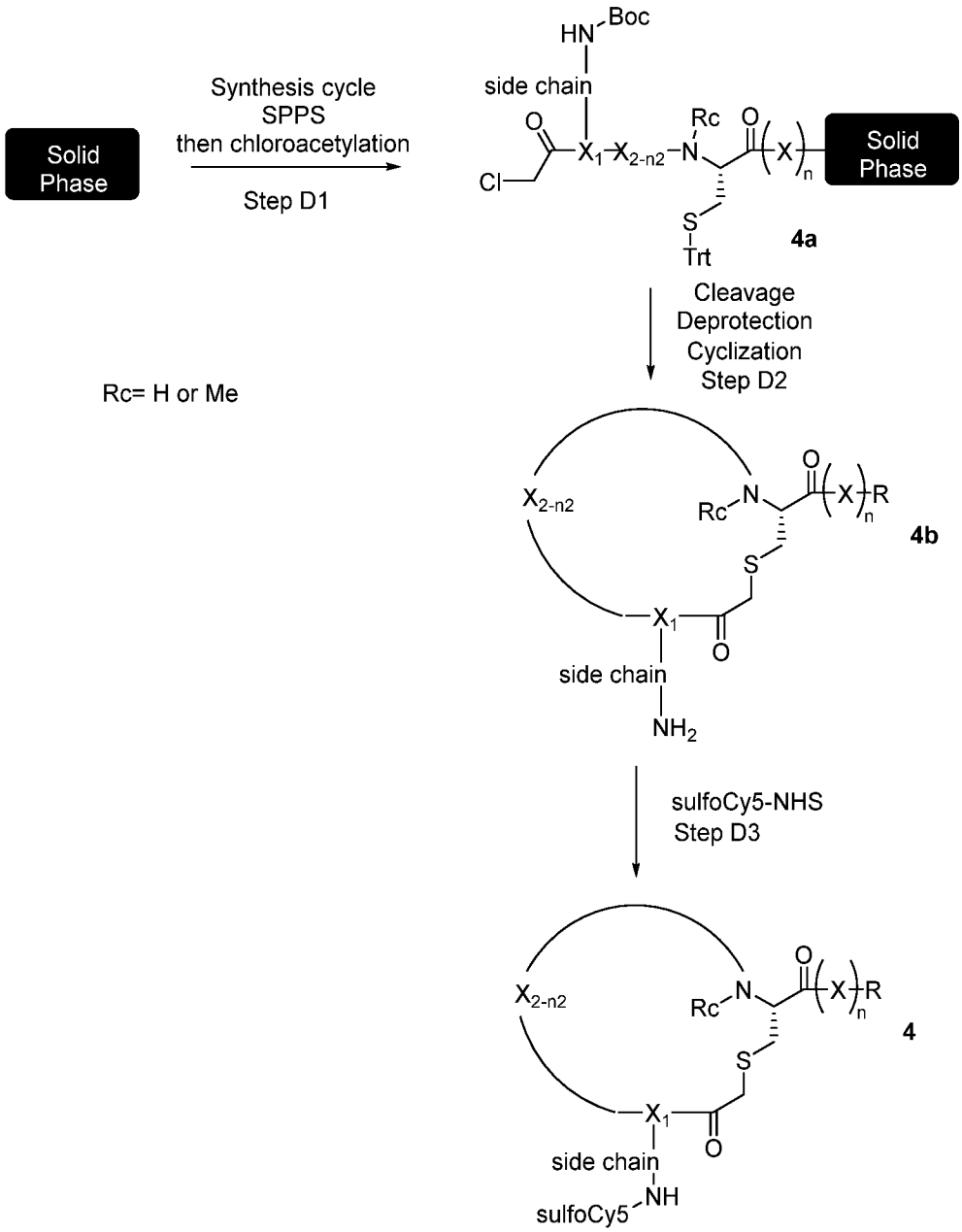
Polypeptides **3f** were synthesized from polypeptides **3d** on resin in the fashion analogous to Scheme-1.

[00724] Step C7: Coupling reaction with Biotin-OSu

[00725] To the polypeptides **3f** in DMSO were added Biotin-OSu (approx. 1 eq) and DIEA (3- 5 eq). The mixture was shaken at room temperature for 0.2-1h. The reaction mixture was directly purified by preparative RP-HPLC to afford Macrocyclic peptides type-C.

[00726] Macrocyclic peptide-conjugates type-D, when one of AA sidechains contains a nucleophilic amine, in the present invention can be synthesized outlined in scheme-4.

[00727] Scheme-4

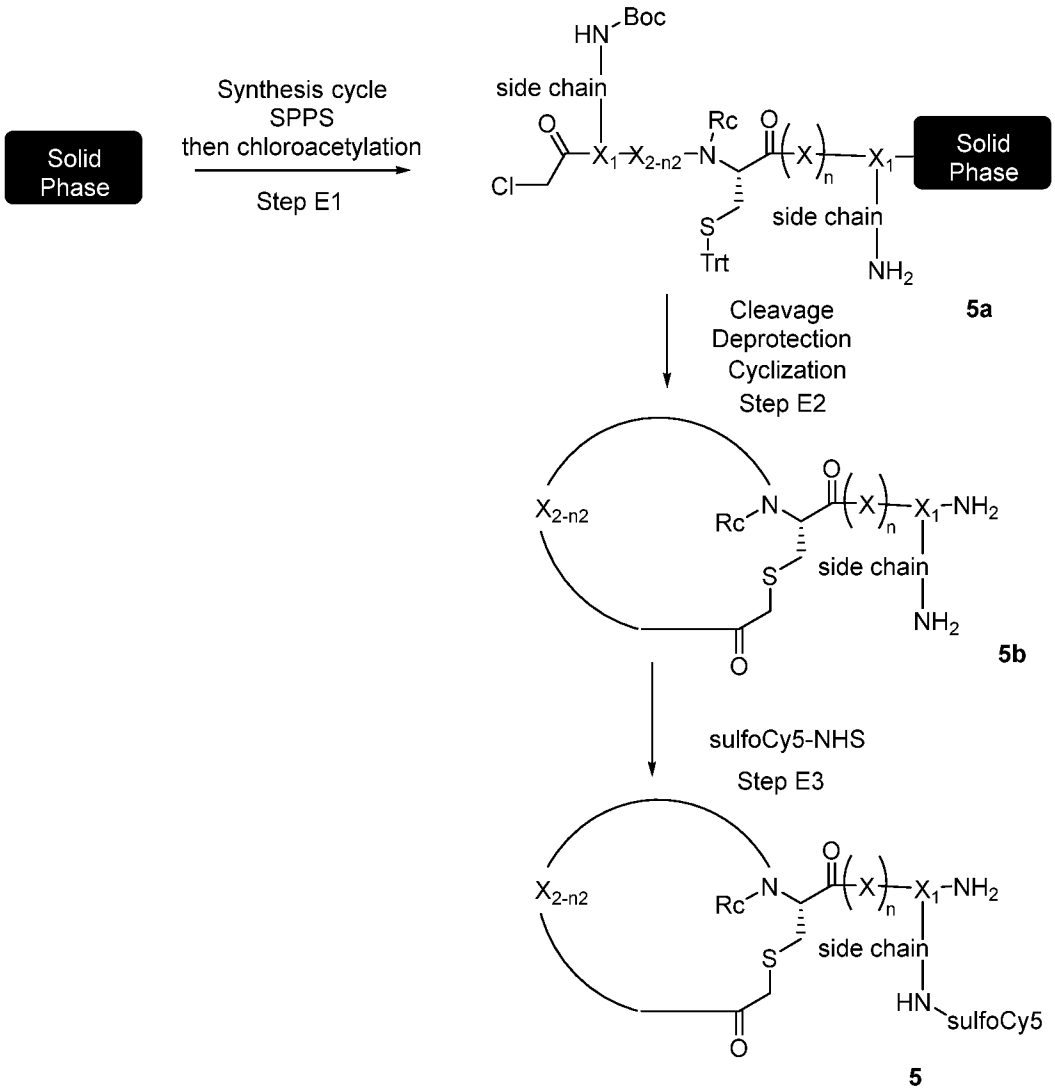


[00728] Polypeptides **4a** on resin were synthesized by methods described above. Subsequently, the cleavage from the resin along with the global deprotection, followed by the cyclization and then RP-HPLC purification were performed similarly by the methods described above to afford polypeptide **4b**. Finally, treatment of **4b** with sulfoCy5-NHS, followed by the RP-HPLC purification afforded Macrocyclic peptide-conjugates type-D.

[00729] Alternatively, the crude containing **4b** was treated with sulfoCy5-NHS, followed by RP-HPLC afforded Macrocyclic peptide-conjugates type-D.

[00730] Macrocyclic peptide-conjugates type-E can be synthesized via appropriate AA sequencing as shown in Scheme-5.

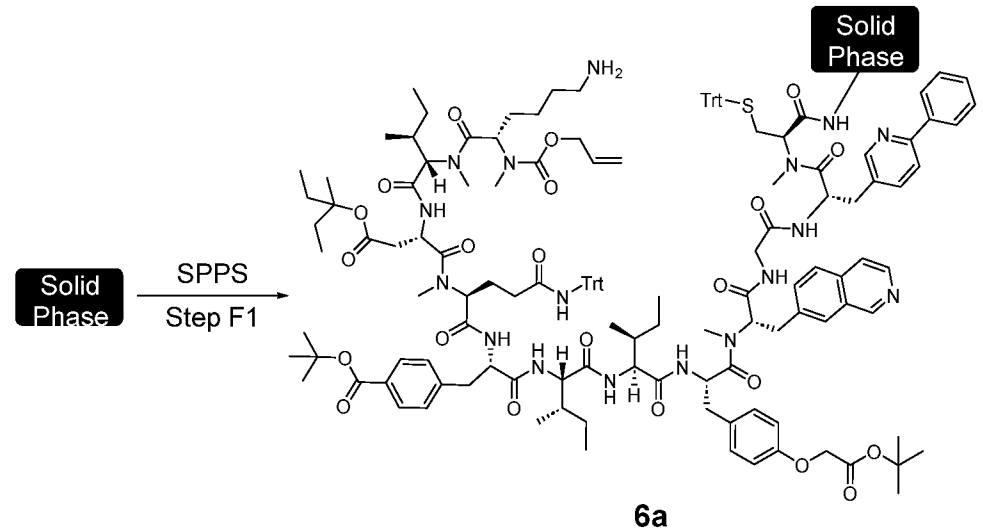
[00731] Scheme-5



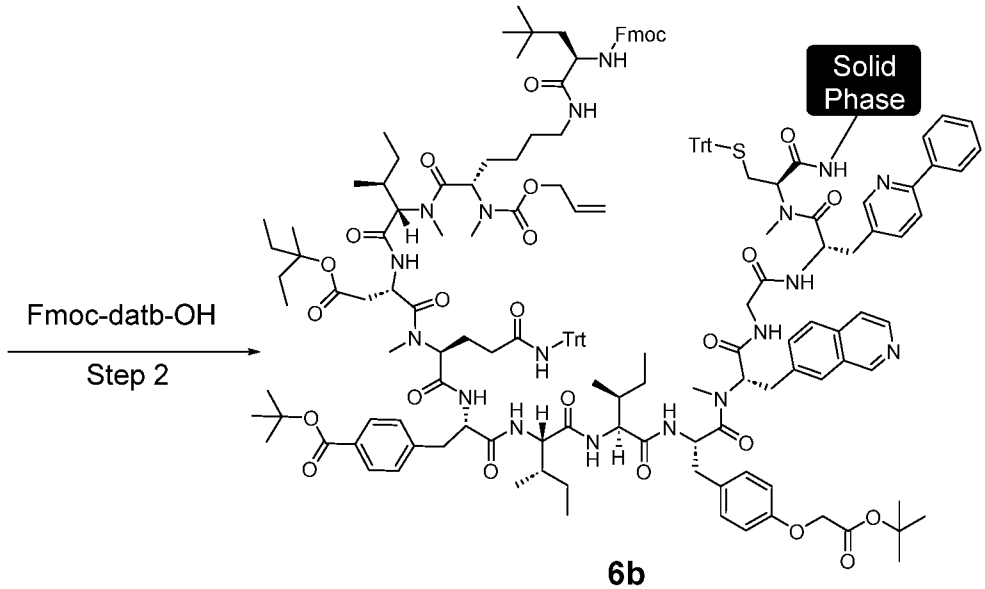
[00732] Polypeptides **5b** were synthesized by methods described above via polypeptides **5a** on resin. After the purification of **5b**, treatment with sulfoCy5-NHS, followed by the RP-HPLC purification afforded Macrocyclic peptide-conjugates type-E.

[00733] Macrocyclic peptide type-F can be synthesized as outlined in Scheme-6.

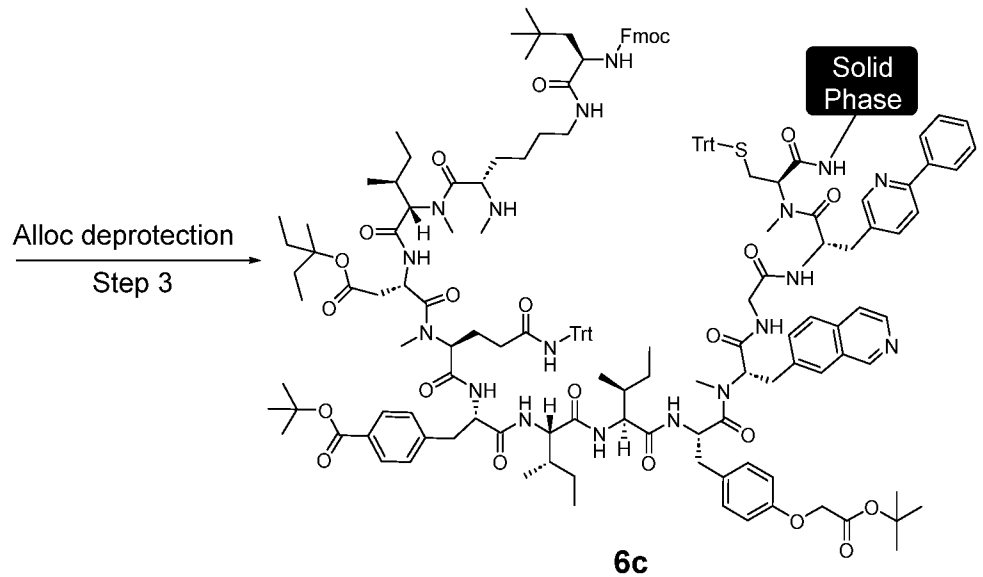
[00734] Scheme-6 (SEQ ID NOS 110-116, respectively, in order of appearance)


Solid Phase
SPPS
Step F1
Solid Phase

6a

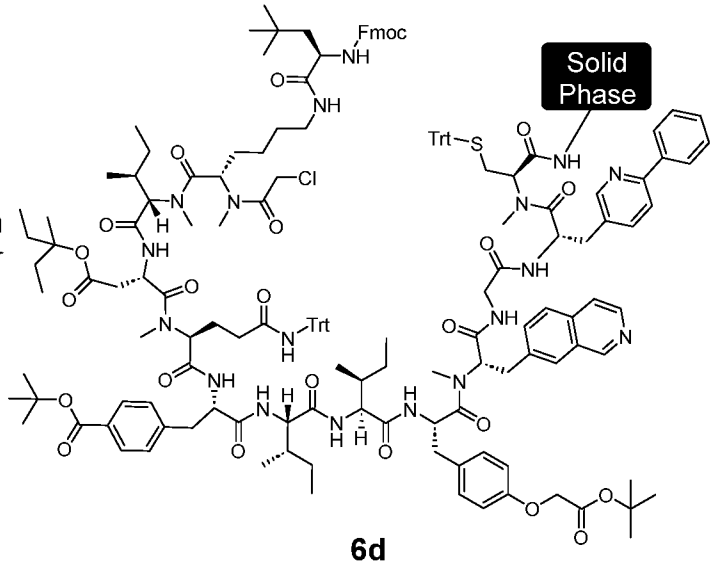

Fmoc-datb-OH
Step 2
Solid Phase

6b


Alloc deprotection
Step 3
Solid Phase

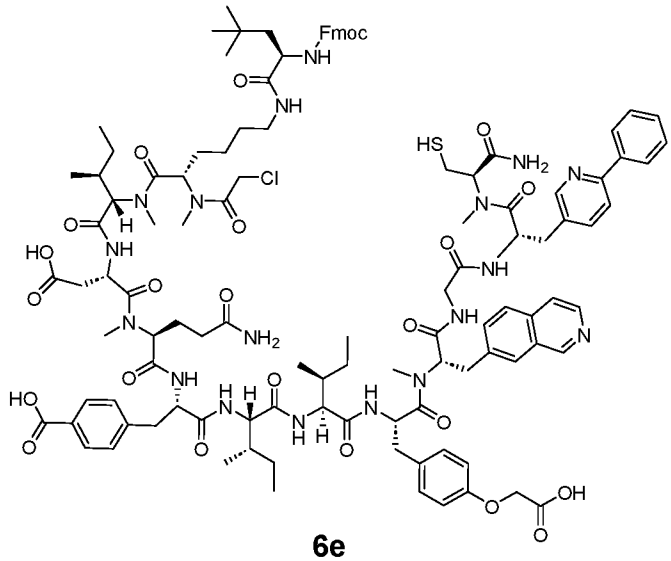
6c

Chloroacetylation
Step 4



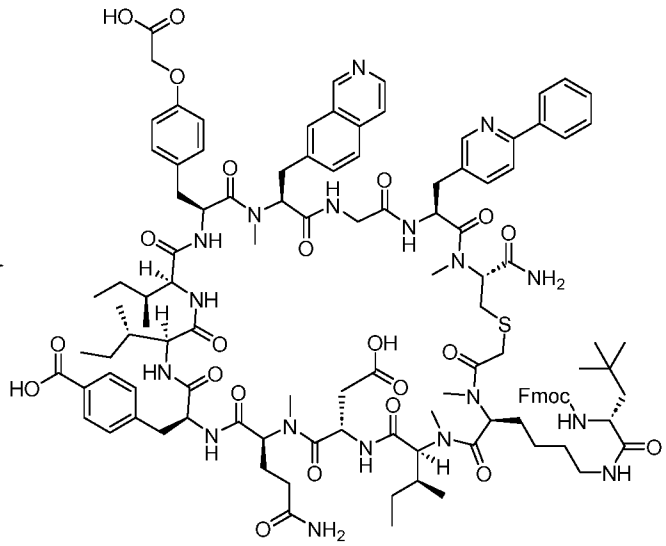
6d

Cleavage
Deprotection
Step 5

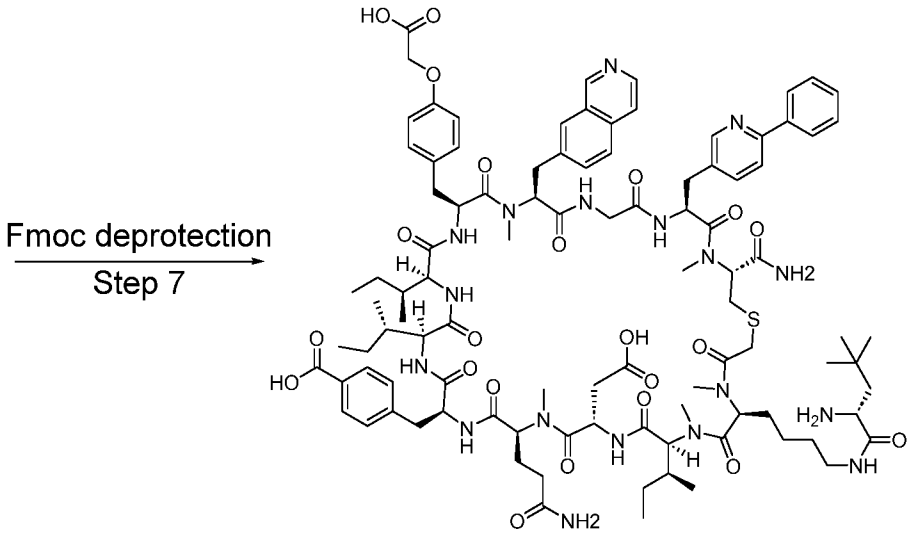


6e

Cyclization
Step 6



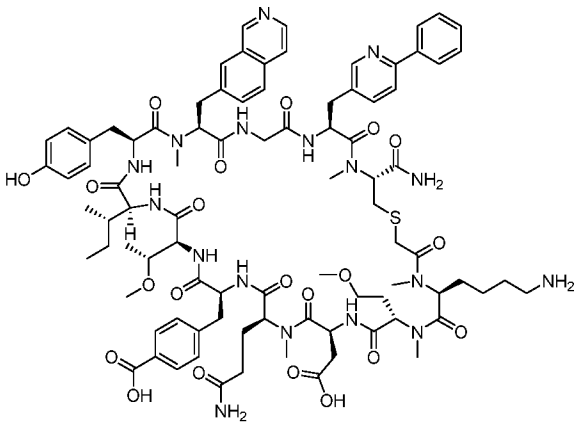
6f



6

[00735] Polypeptides type **6b** via **6a** on-resin were synthesized in the fashion analogous to Step-A1 in Scheme-1 but employing appropriately protected AA building blocks such as Alloc-K(Fmoc)-OH. Subsequently, Alloc deprotection and the chloroacetiylation described in Step-B3 and Step-A2 respectively can afford linear polypeptide type **6d** on resin. Cleavage from the resin along with the removal of the acid labile protecting groups by methods described in Step-A3 can afford **6e**, which was then treated for the macrocyclization by methods described in such as Step-A4 can afford **6f**. Removal of the Fmoc group of **6f** can be achieved by treatment with suitable bases such as pyrrolidine in solvent such as DMF to afford Macrocyclic peptide type **6**.

[00736] Example-1 (SEQ ID NO: 117):



[00737] The desired polypeptide was synthesized as outlined in Scheme-1. The linear polypeptide was synthesized on Fmoc-Sieber amide resin (0.25 mmol) using Fmoc-AAs listed in below table. Method S-1 was employed for the peptide elongation. The obtained peptide on the resin was subjected to the chloroacetylation described in Step-A2 (ClAcOH (1.25 mmol)/ HATU/ DIEA (2.5 mmol) in DMF (12.5 mL), 30 min), followed by treating with the cleavage cocktail (12 mL) for 5 min as outlined in Step-A3 to furnish the linear peptide. The crude containing the linear peptide (0.25 mmol as theoretical based on the resin used) was dissolved in

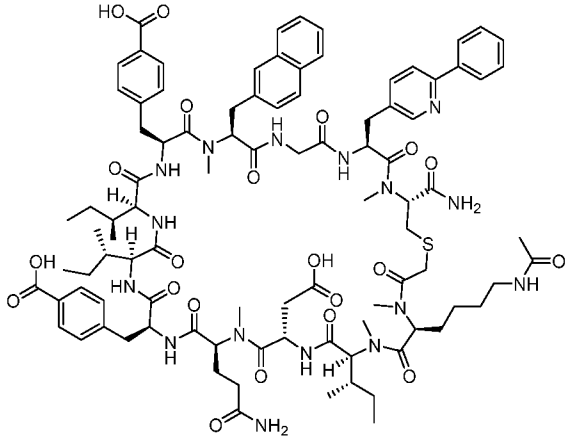
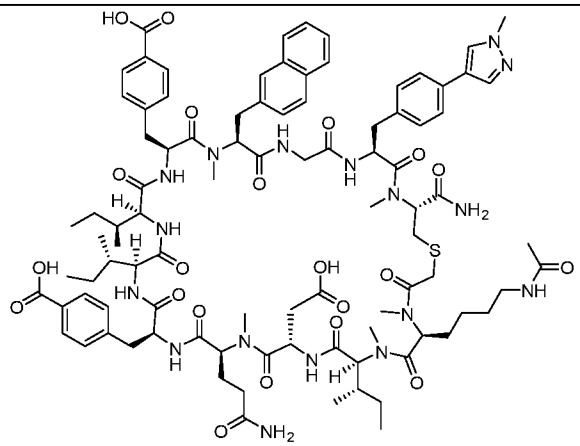
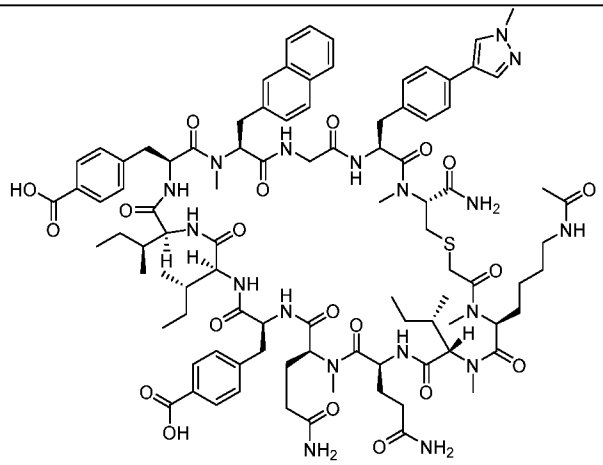
CH_3CN/H_2O (100 mL), and then added Et_3N (2.5 mmol, 348 µL), and then shaken for at room temperature for 18 hrs, and then concentrated as outlined in Step-A4. The resulting residue was purified by preparative RP-HPLC. Pure fractions were combined and lyophilized to afford the title macrocyclic peptide (SEQ ID No:45). HPLC-MS (Method A-1): 4.67 min, ESI-MS m/z: 890.7 [M+2H]2+.

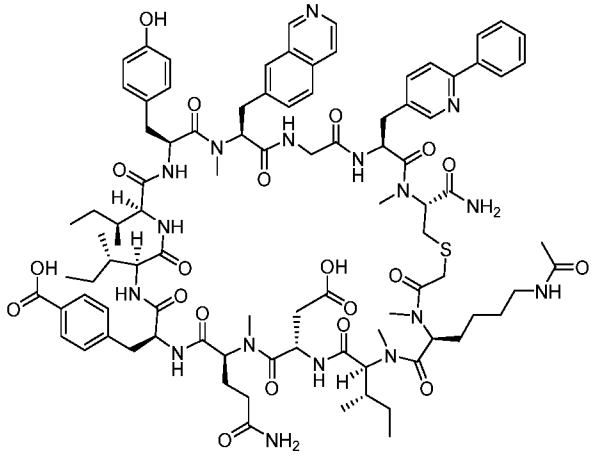
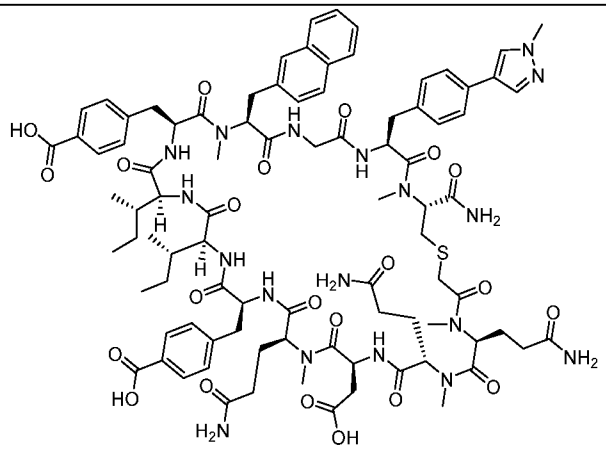
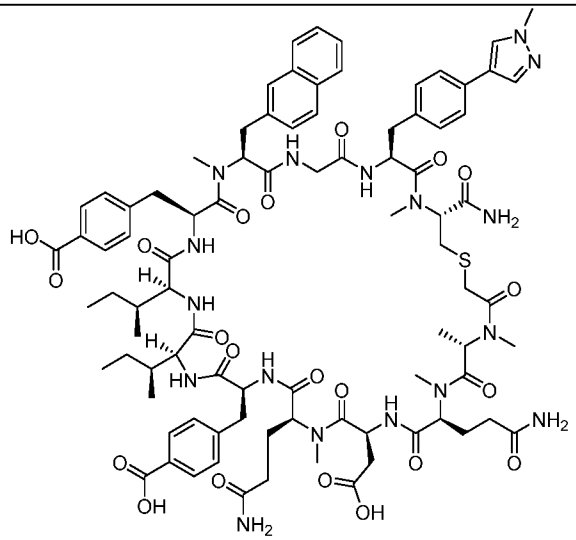
[00738] Table S6

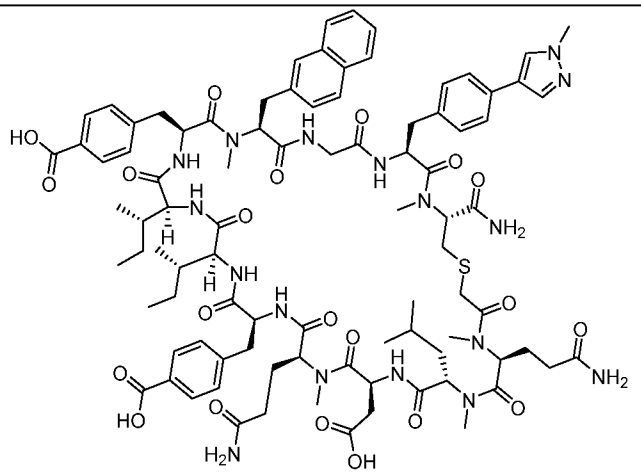
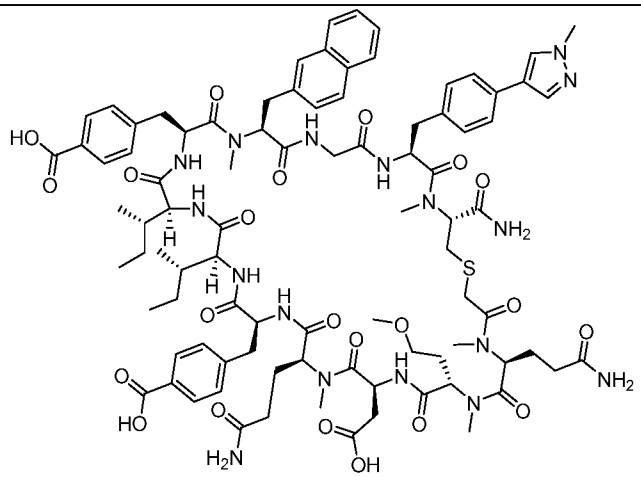
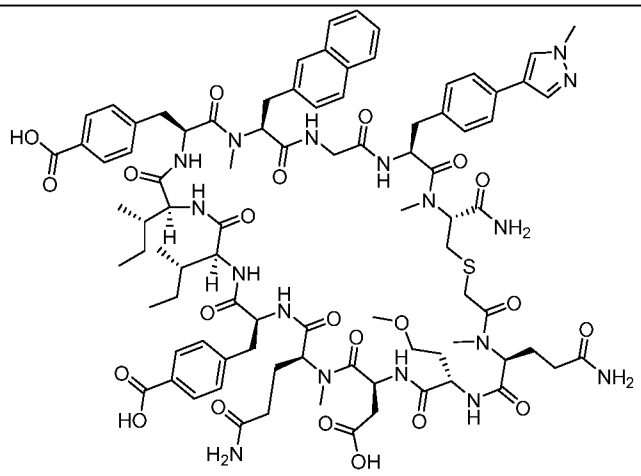
order of Fmoc-AA used in the SPPS	AA position in the cyclic peptide	Fmoc-AA
1	X12	Fmoc-MeC(Trt)-OH
2	X11	Fmoc-3Py6Ph-OH
3	X10	Fmoc-G-OH
4	X9	Fmoc-MeNal27N
5	X8	Fmoc-Y(tBu)-OH
6	X7	Fmoc-I-OH
7	X6	Fmoc-TMe-OH
8	X5	Fmoc-F4COO(tBu)-OH
9	X4	Fmoc-Me(Trt)-OH
10	X3	Fmoc-D(Mpe)-OH
11	X2	Fmoc-MeHseMe-OH
12	X1	Fmoc-MeK(Boc)-OH

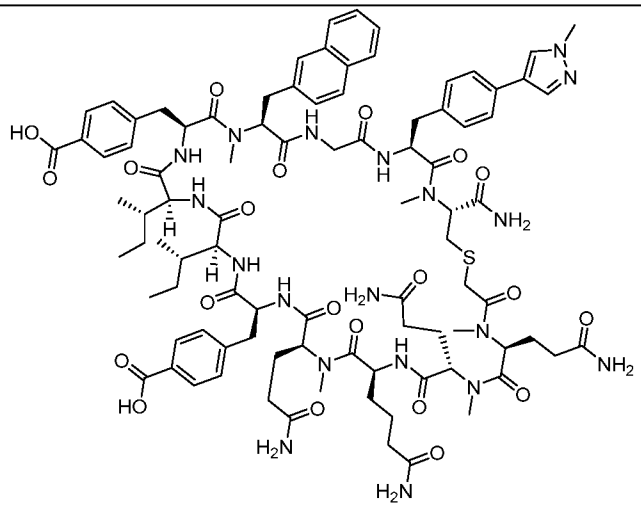
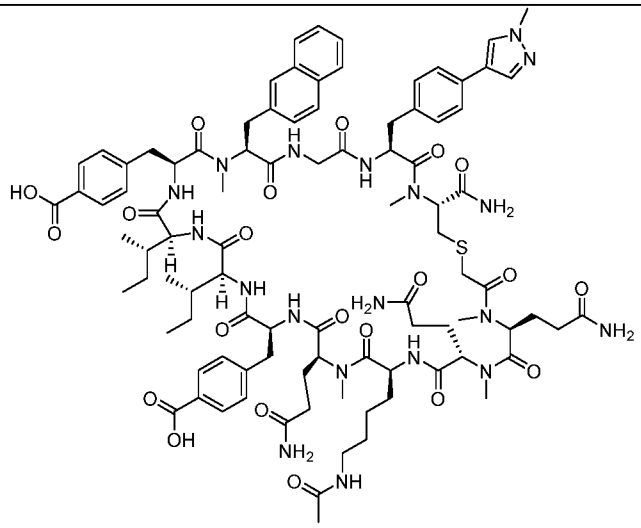
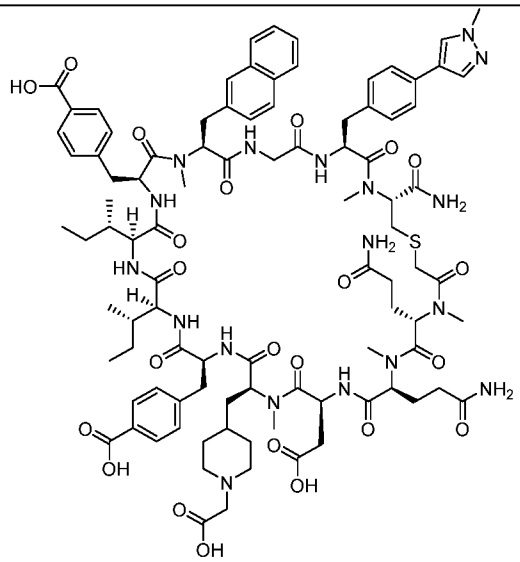
[00739] Example 2: The following peptides were synthesized by similar methods described above.

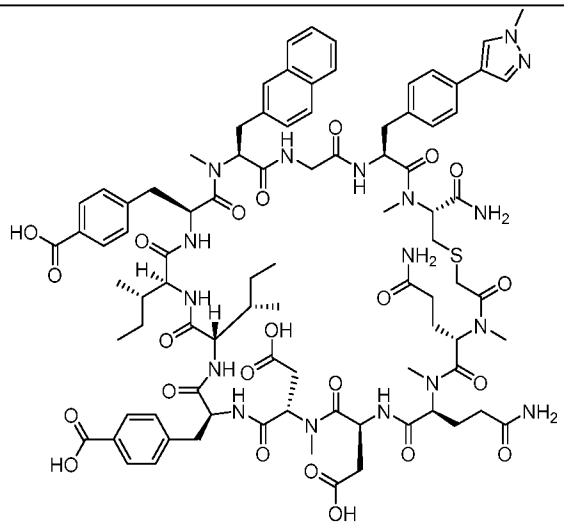
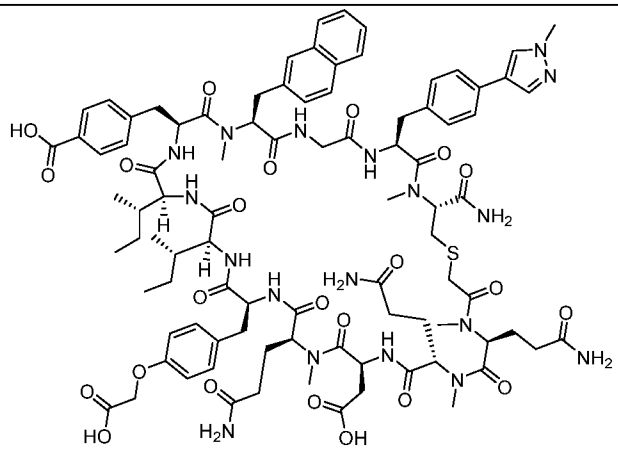
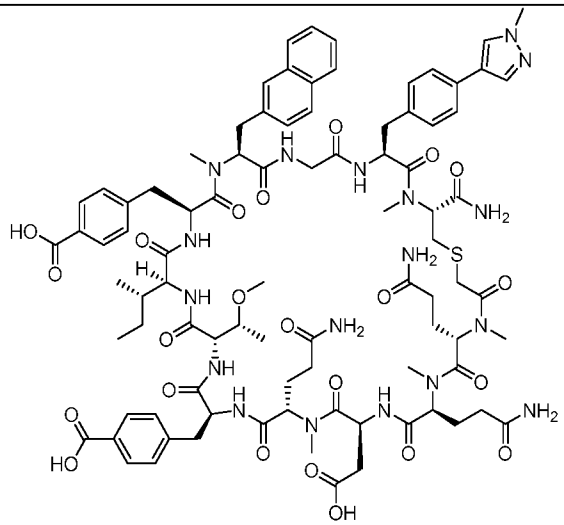
[00740] Table S7

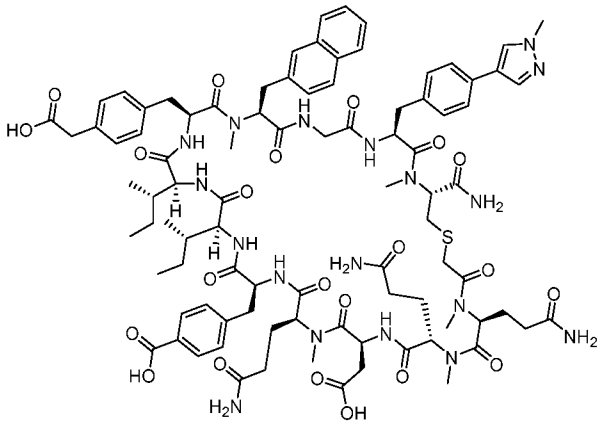
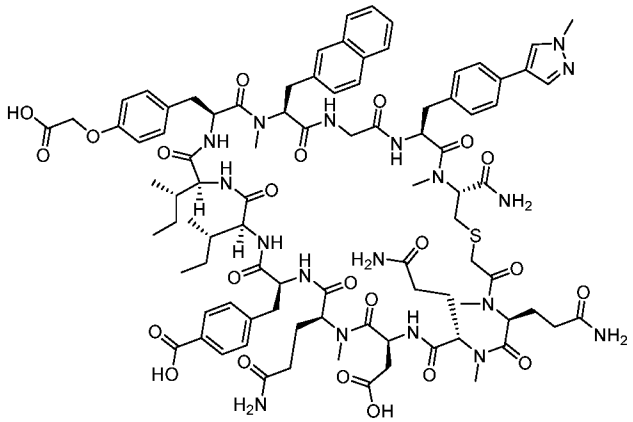
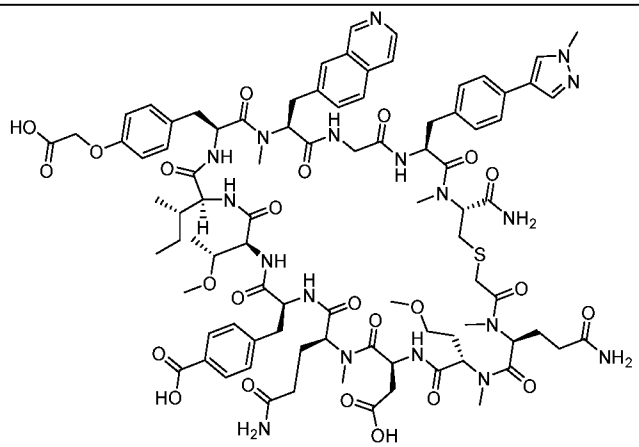
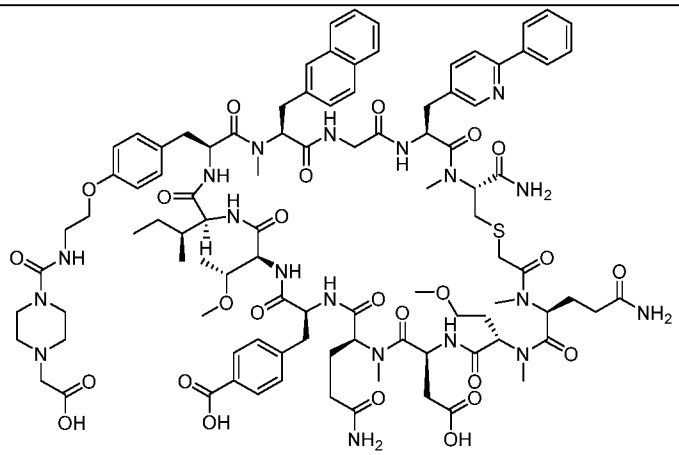
SEQ ID NO	Structure	Analytical Data
2		HPLC-MS (Method A-2): 5.04 min ESI-MS m/z: 923.3 [M+2H]2+
3		HPLC-MS (Method A-2): 5.66 min ESI-MS m/z: 924.9 [M+2H]2+
4		HPLC-MS (Method A-2): 5.55 min ESI-MS m/z: 931.4 [M+2H]2+

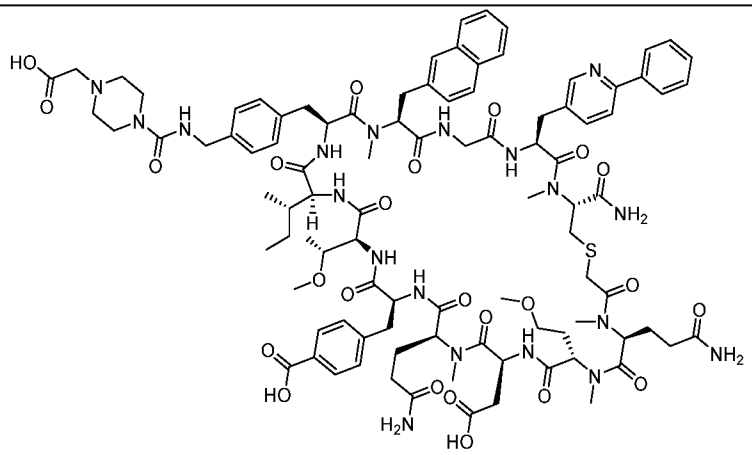
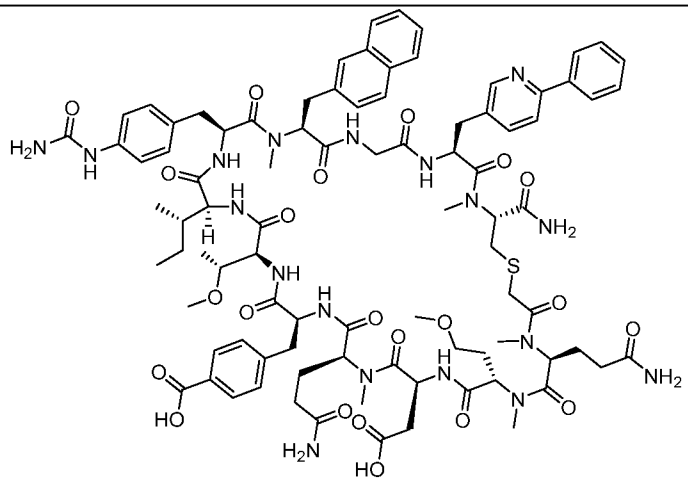
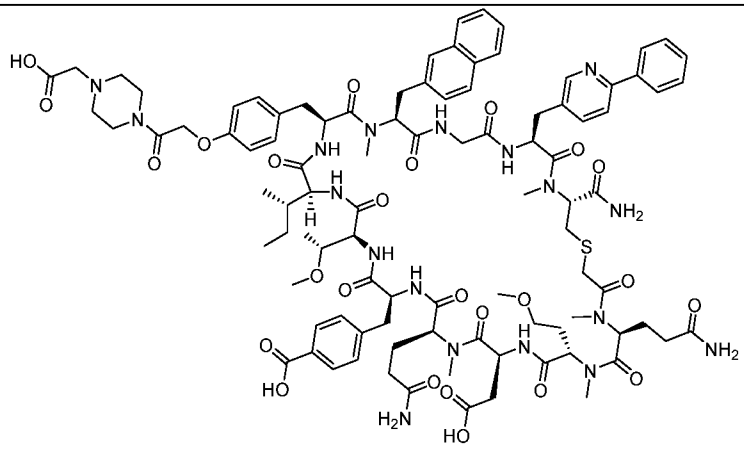
7		HPLC-MS (Method A-2): 3.47 min ESI-MS m/z: 909.4 [M+2H]2+
8		HPLC-MS (Method A-2): 4.96 min ESI-MS m/z: 911.3 [M+2H]2+
9		HPLC-MS (Method A-2): 5.20 min ESI-MS m/z: 882.74 [M+2H]2+

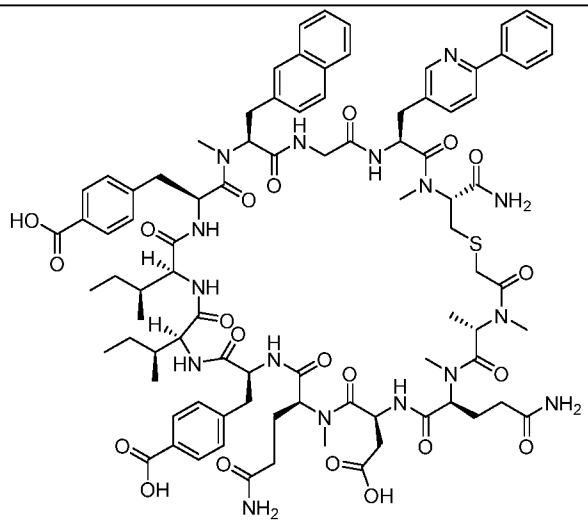
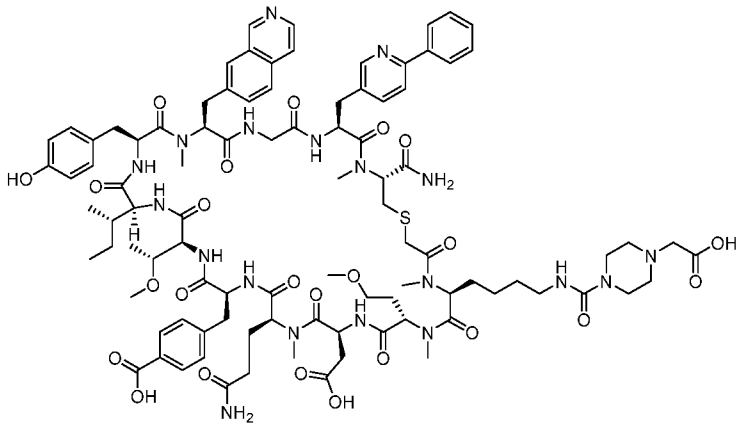
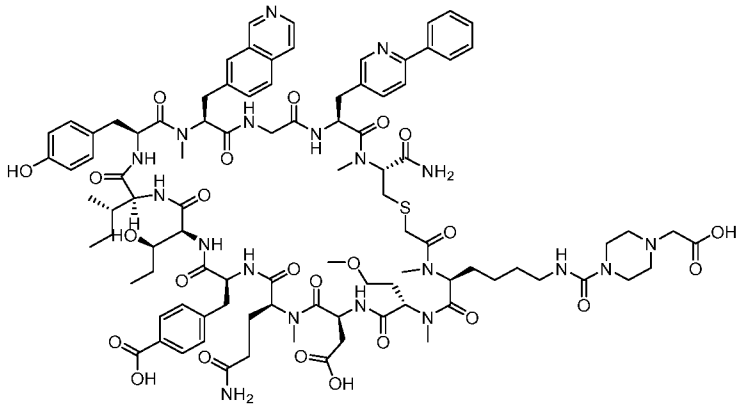
10		HPLC-MS (Method A-2): 5.80 min ESI-MS m/z: 903.5 [M+2H]2+
11		HPLC-MS (Method A-2): 5.50 min ESI-MS m/z: 904.5 [M+2H]2+
12		HPLC-MS (Method A-2): 5.40 min ESI-MS m/z: 897.4 [M+2H]2+

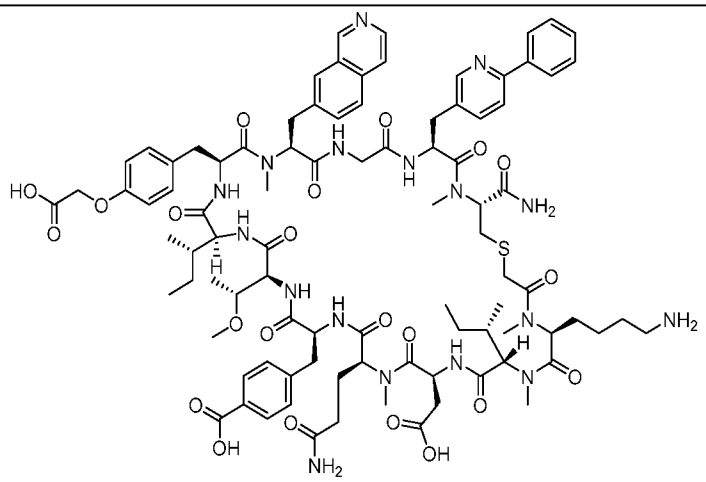
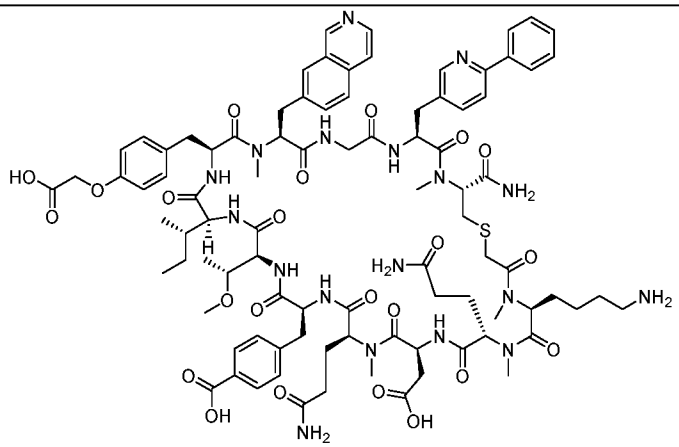
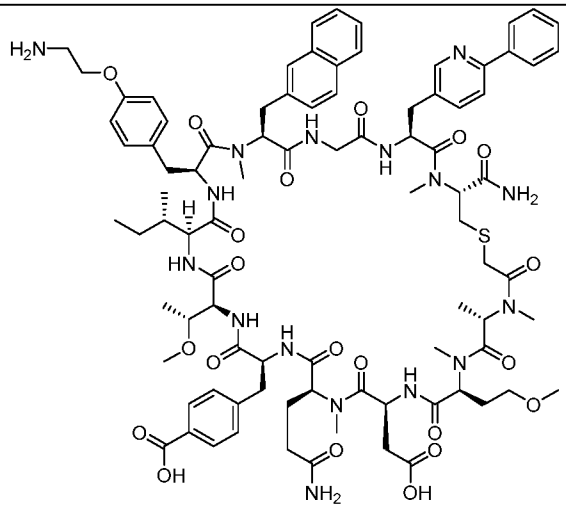
13		HPLC-MS (Method A-2): 4.84 min ESI-MS m/z: 924.8 [M+2H]2+
14		HPLC-MS (Method A-2): 5.34 min ESI-MS m/z: 938.5 [M+2H]2+
15		HPLC-MS (Method A-2): 4.58 min ESI-MS m/z: 953.3 [M+2H]2+

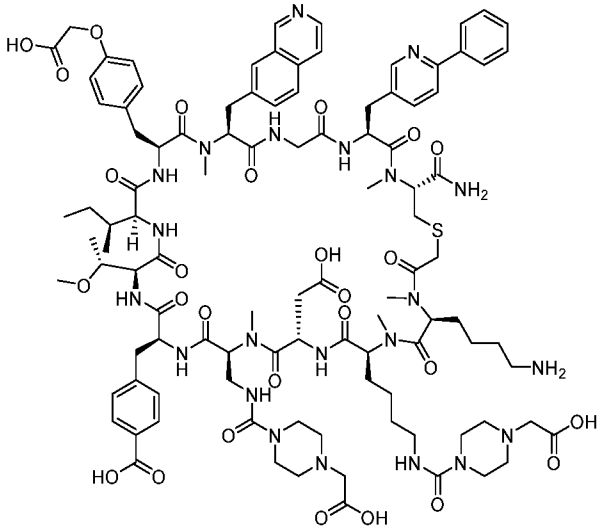
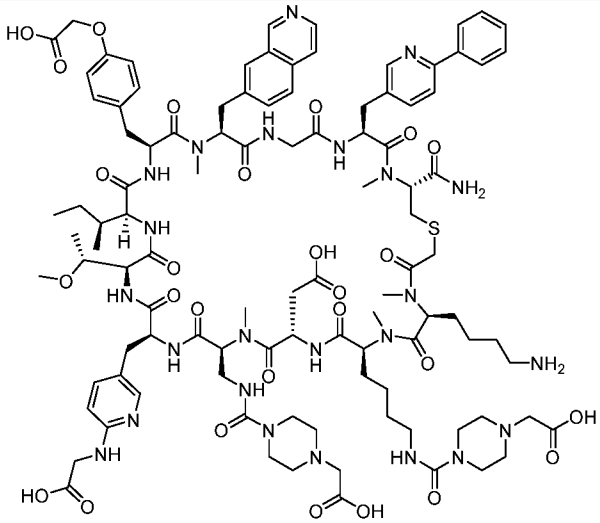
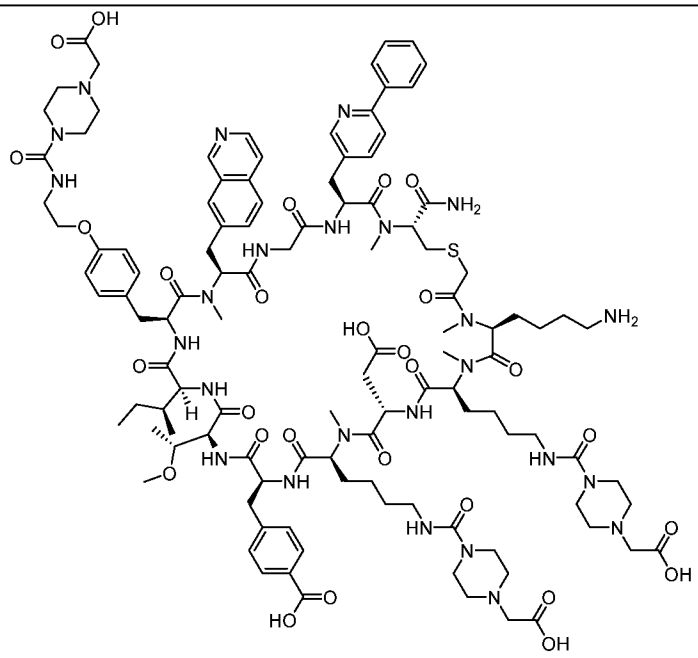
16		HPLC-MS (Method A-2): 5.40 min ESI-MS m/z: 904.4 [M+2H]2+
17		HPLC-MS (Method A-2): 5.30 min ESI-MS m/z: 926.0 [M+2H]2+
18		HPLC-MS (Method A-2): 5.02 min ESI-MS m/z: 911.9 [M+2H]2+

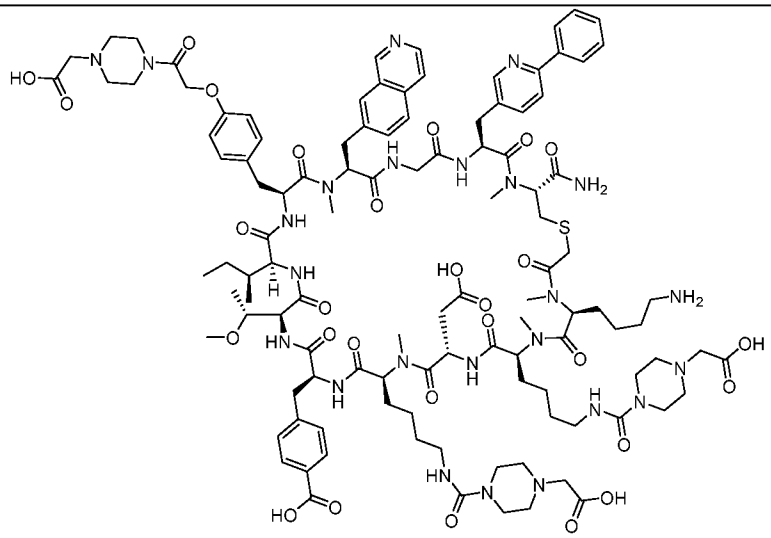
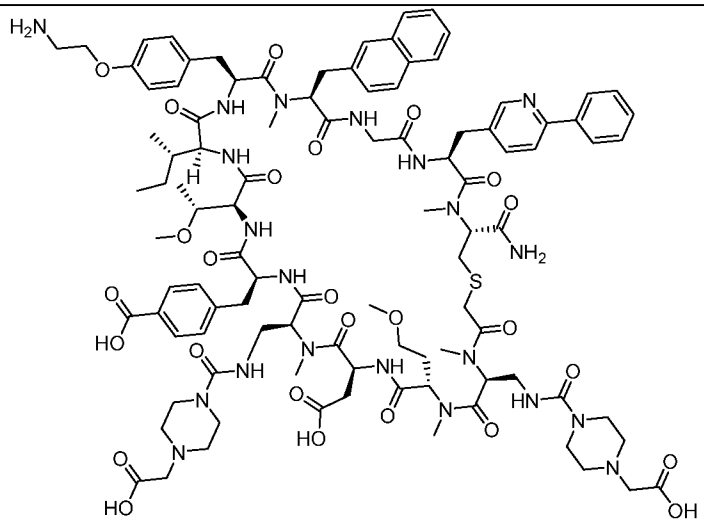
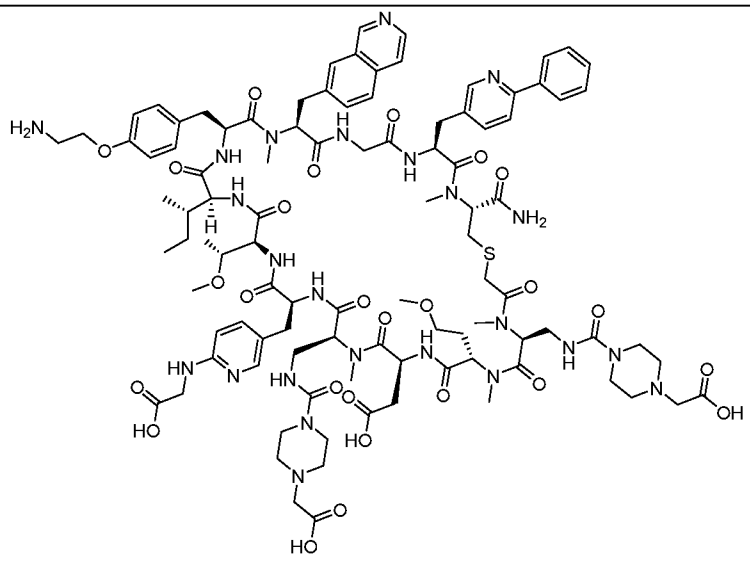
19		HPLC-MS (Method A-2): 5.32 min ESI-MS m/z: 917.9 [M+2H]2+
20		HPLC-MS (Method A-2): 5.25 min ESI-MS m/z: 925.9 [M+2H]2+
36		HPLC-MS (Method A-1): 5.88 min ESI-MS m/z: 920.9 [M+2H]2+
37		HPLC-MS (Method A-2): 3.74 min ESI-MS m/z: 996.8 [M+2H]2+

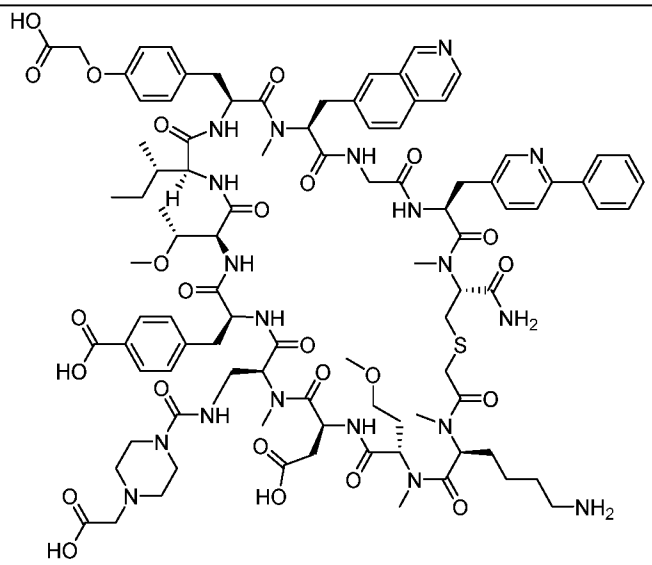
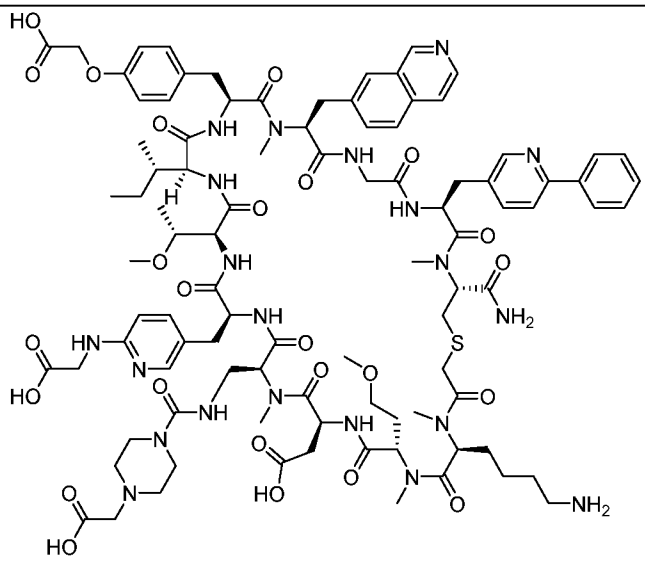
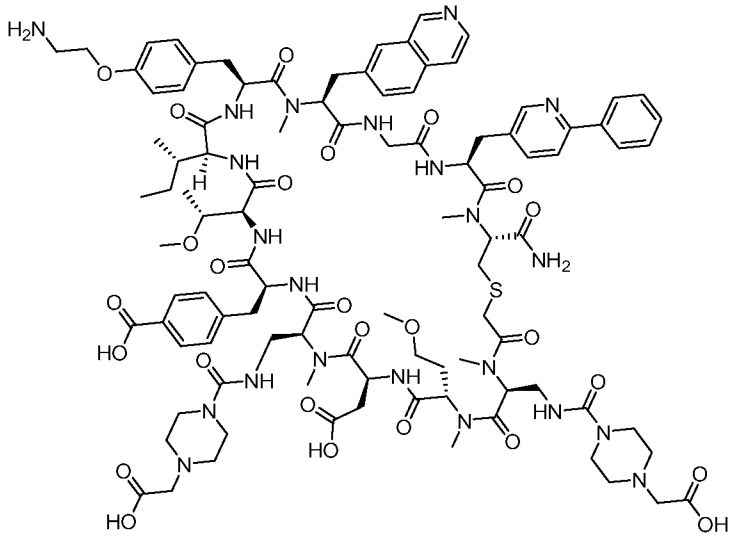
38		HPLC-MS (Method A-2): 3.98 min ESI-MS m/z: 981.4 [M+2H]2+
39		HPLC-MS (Method A-2): 4.50 min ESI-MS m/z: 910.8 [M+2H]2+
40		HPLC-MS (Method A-2): 3.66 min ESI-MS m/z: 982.3 [M+2H]2+

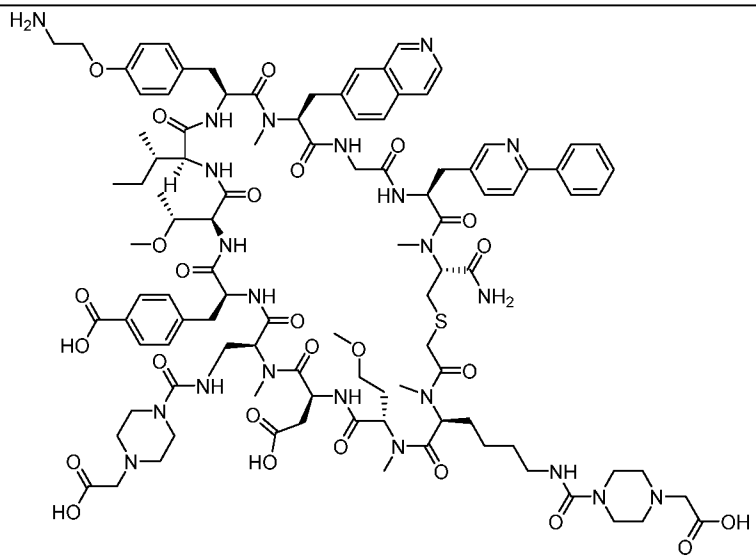
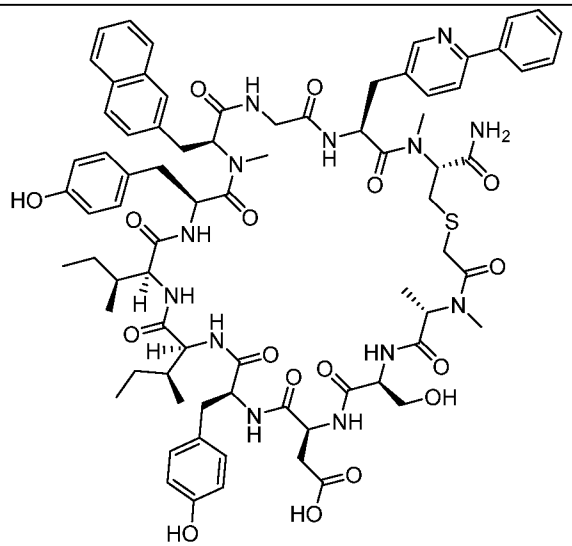
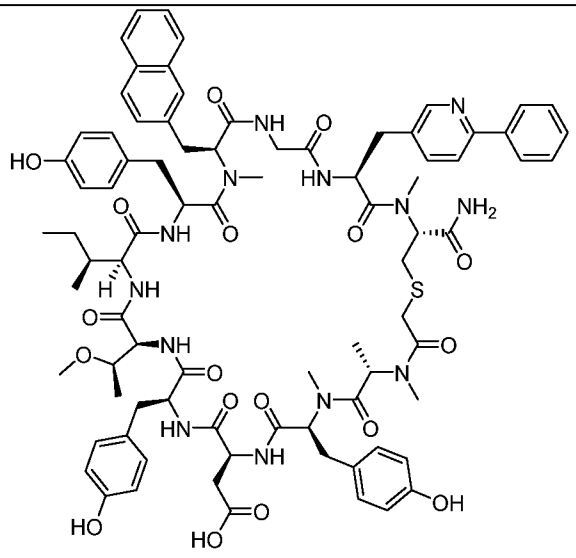
43		HPLC-MS (Method A-2): 4.55 min ESI-MS m/z: 881.3 [M+2H]2+
58		HPLC-MS (Method A-1): 4.98 min ESI-MS m/z: 650.8 [M+3H]3+
59		HPLC-MS (Method A-1): 4.89 min ESI-MS m/z: 975.5 [M+2H]2+

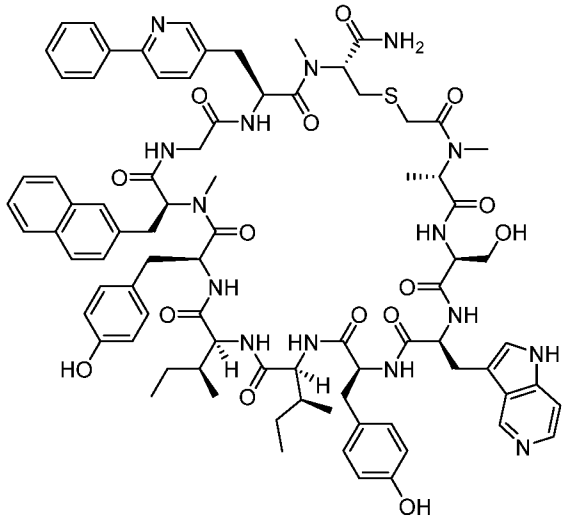
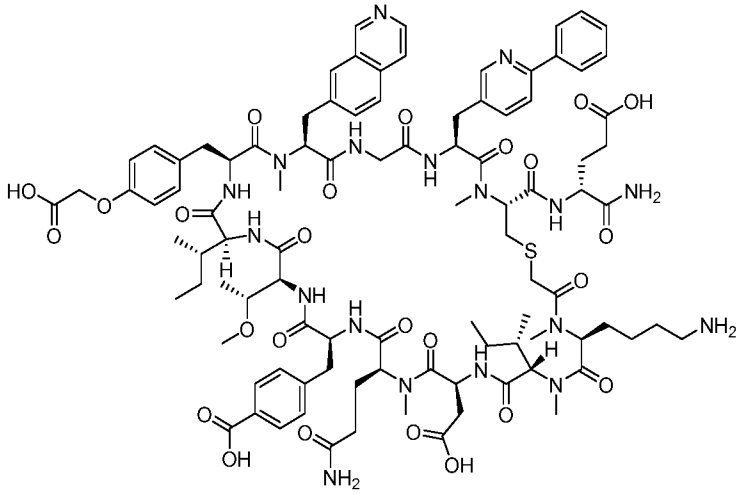
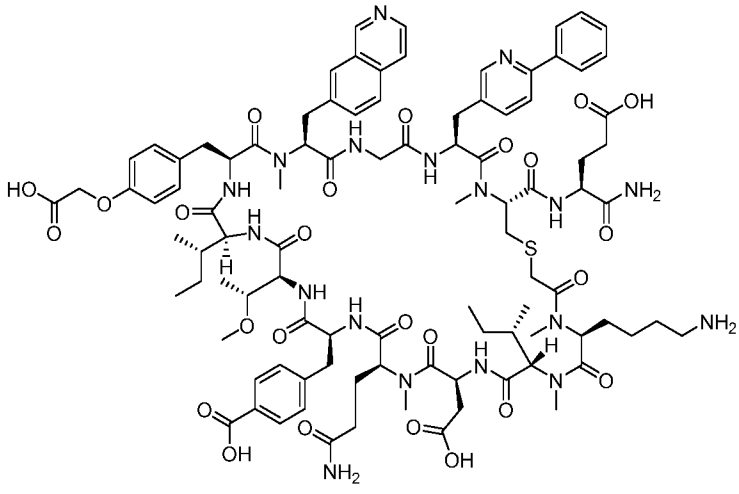
30		HPLC-MS (Method A-1): 5.50 min ESI-MS m/z: 918.4 [M+2H]2+
35		HPLC-MS (Method A-1): 4.98 min ESI-MS m/z: 617.6 [M+3H]3+
44		HPLC-MS (Method A-2): 4.28 min ESI-MS m/z: 882.9 [M+2H]2+

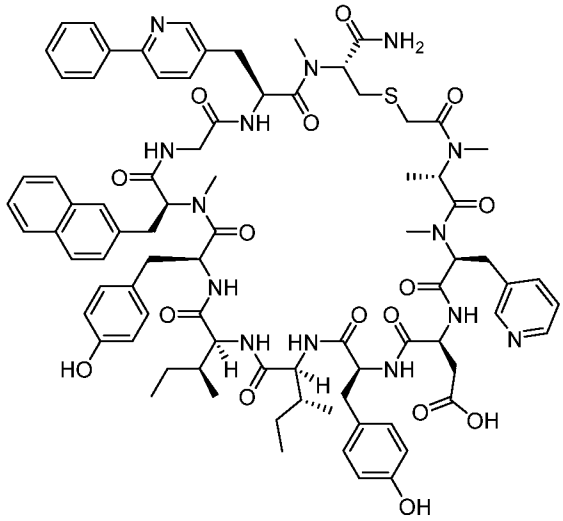
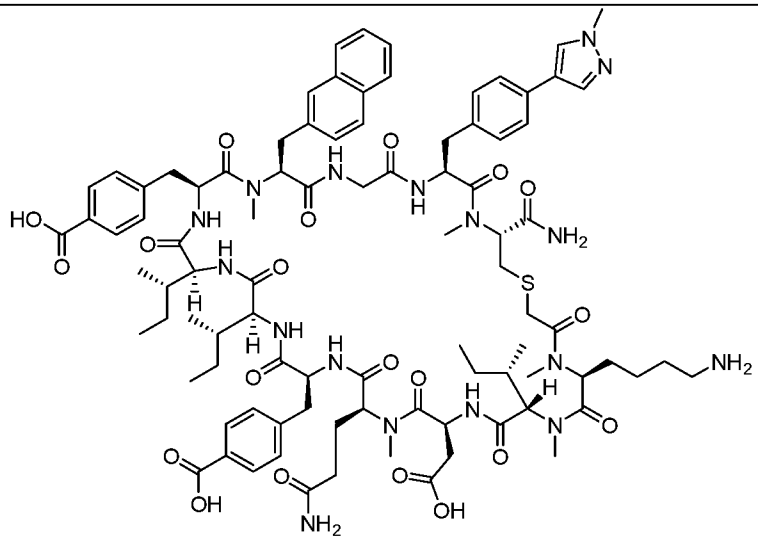
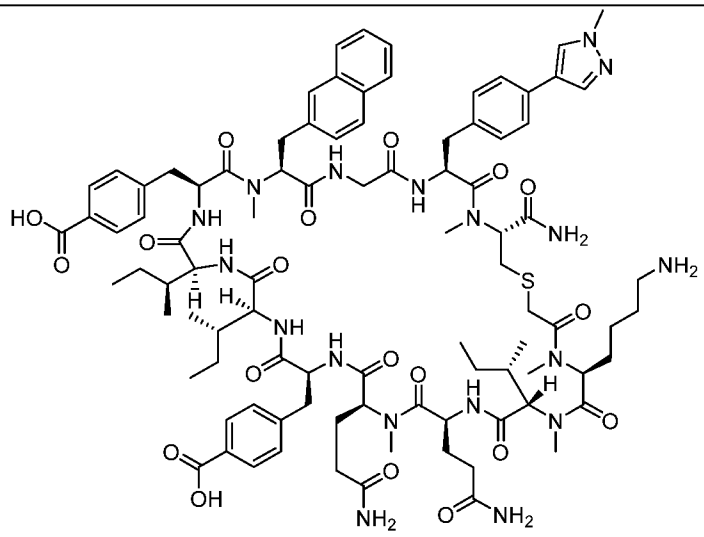
46		HPLC-MS (Method A-1): 4.50 min ESI-MS m/z: 717.0 [M+3H]3+
47		HPLC-MS (Method A-1): 3.98 min ESI-MS m/z: 727.1 [M+3H]3+
48		HPLC-MS (Method A-1): 4.27 min ESI-MS m/z: 782.8 [M+3H]3+

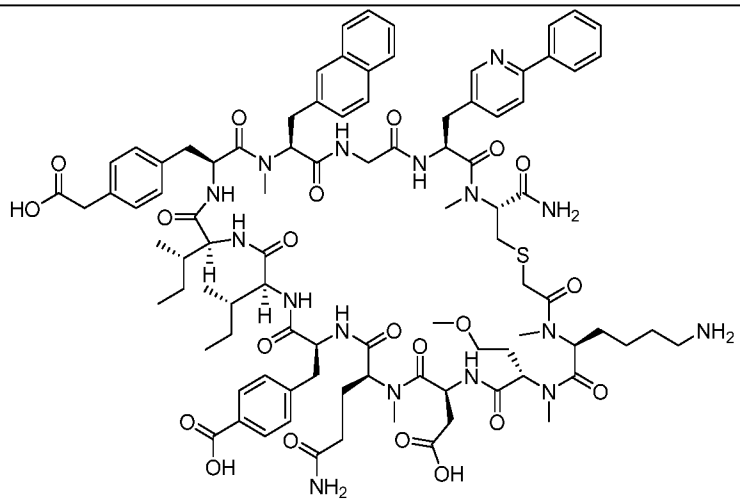
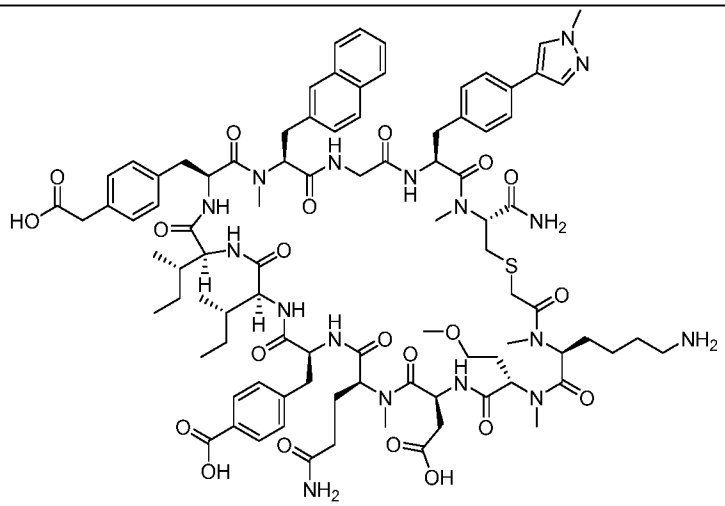
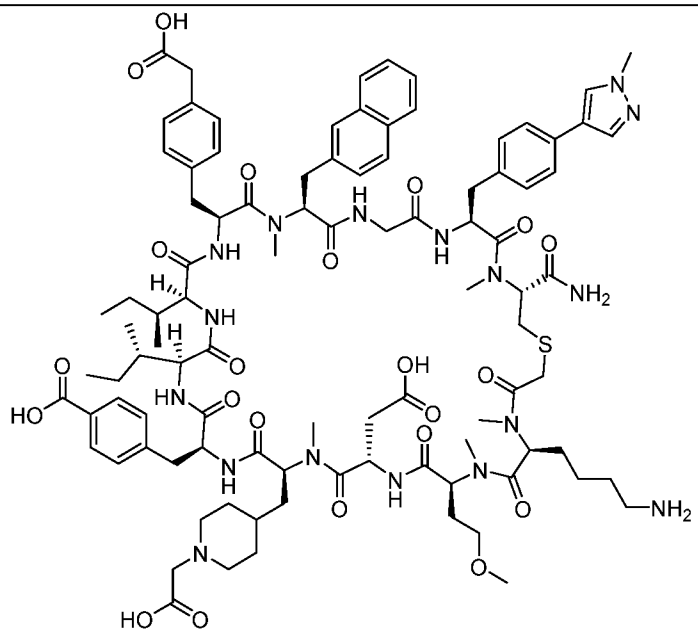
49		HPLC-MS (Method A-1): 4.23 min ESI-MS m/z: 773.1 [M+3H]3+
50		HPLC-MS (Method A-2): 3.30 min ESI-MS m/z: 693.4 [M+3H]3+
51		HPLC-MS (Method A-1): 3.66 min ESI-MS m/z: 703.7 [M+3H]3+

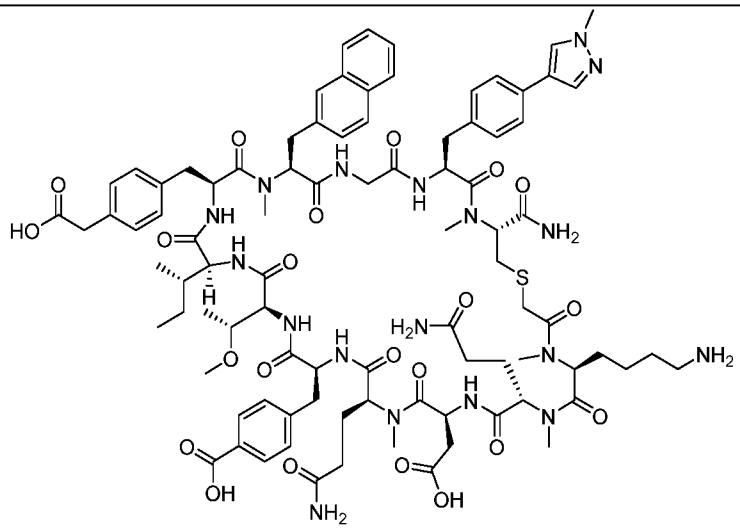
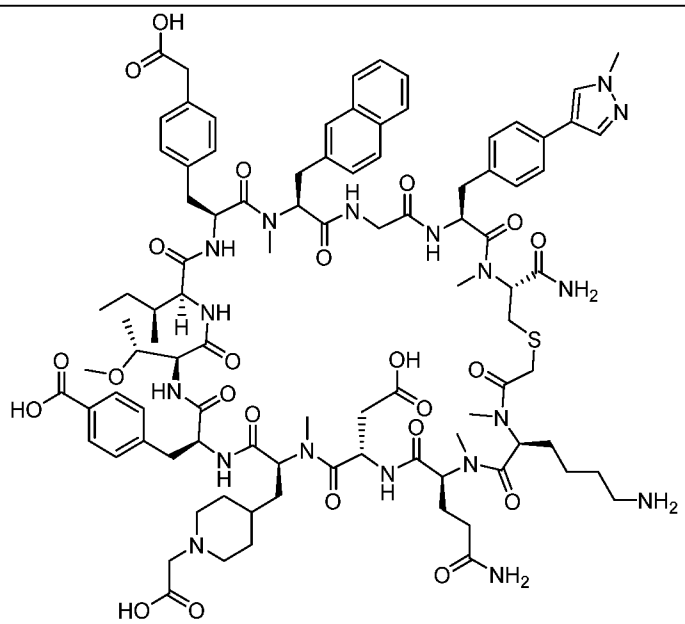
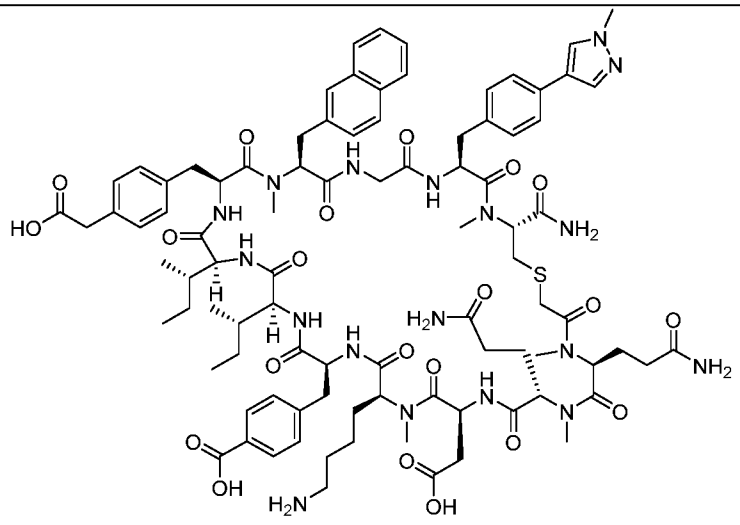
52		HPLC-MS (Method A-1): 4.97 min ESI-MS m/z: 656.0 [M+3H]3+
53		HPLC-MS (Method A-1): 4.28 min ESI-MS m/z: 666.1 [M+3H]3+
54		HPLC-MS (Method A-1): 4.52 min ESI-MS m/z: 693.7 [M+3H]3+

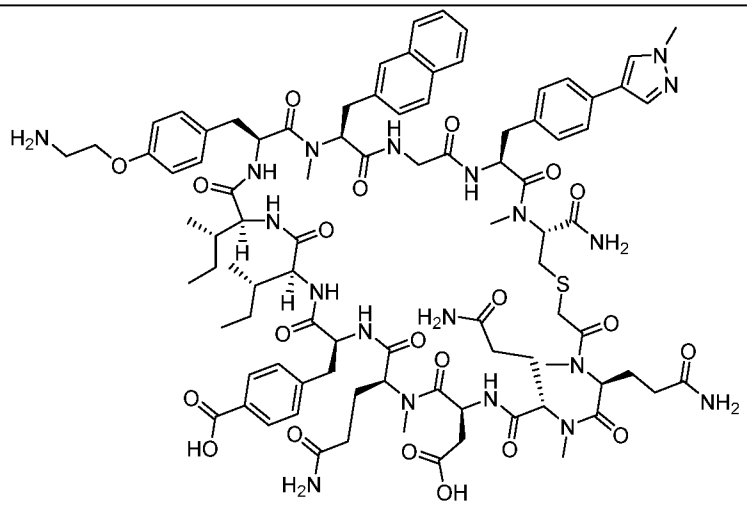
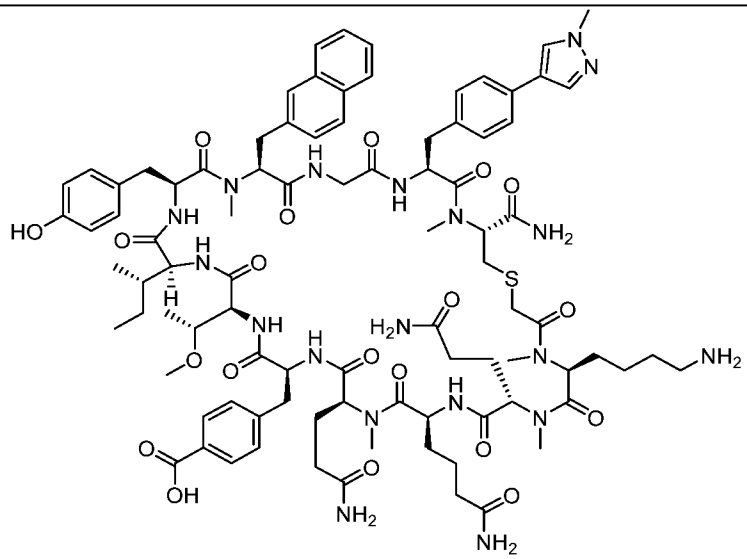
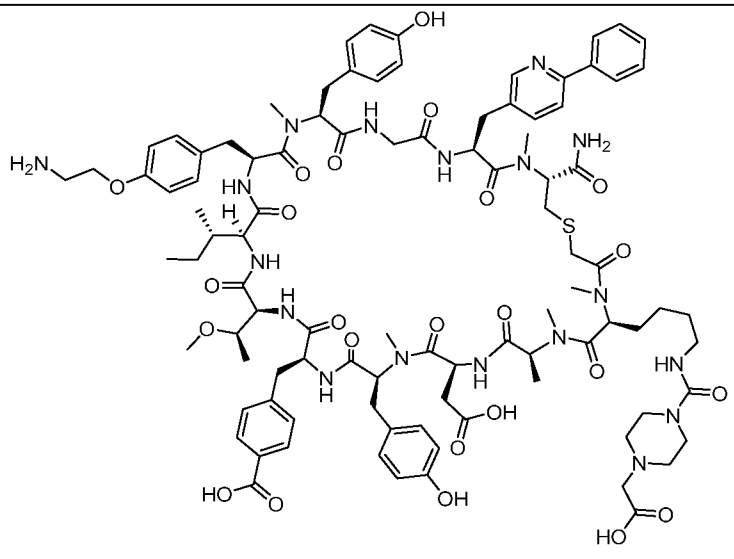
55		HPLC-MS (Method A-1): 4.58 min ESI-MS m/z: 707.7 [M+3H]3+
67		HPLC-MS (Method A-2): 4.80 min ESI-MS m/z: 754.4 [M+2H]2+
66		HPLC-MS (Method A-2): 4.95 min ESI-MS m/z: 800.3 [M+2H]2+

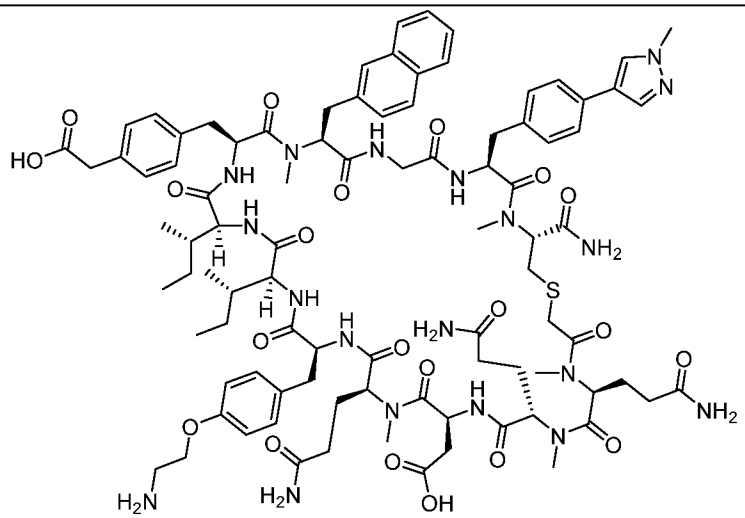
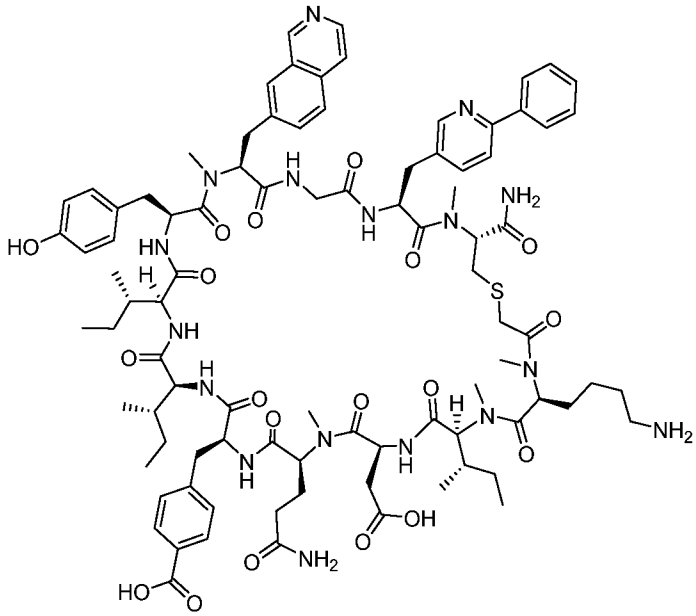
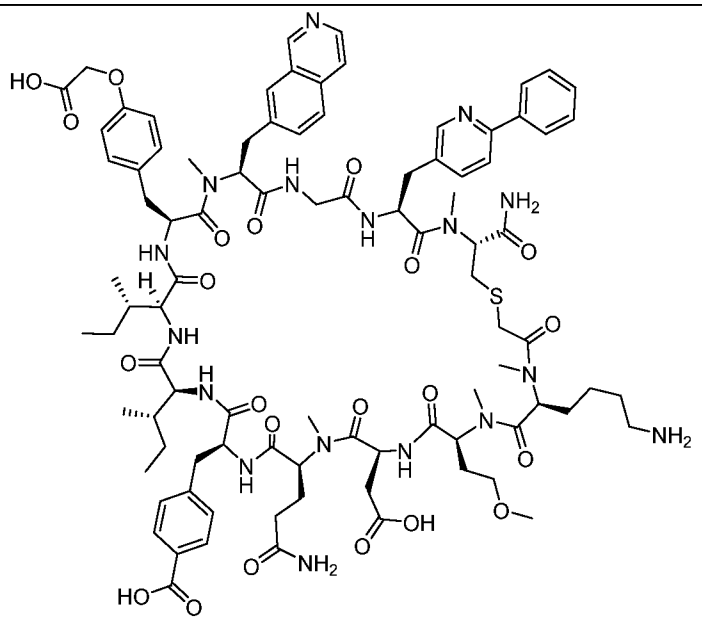
68		HPLC-MS (Method A-2): 4.09 min ESI-MS m/z: 790.4 [M+2H]2+
31		HPLC-MS (Method A-1): 5.46 min ESI-MS m/z: 655.6 [M+3H]3+
32		HPLC-MS (Method A-1): 5.42 min ESI-MS m/z: 655.6 [M+3H]3+

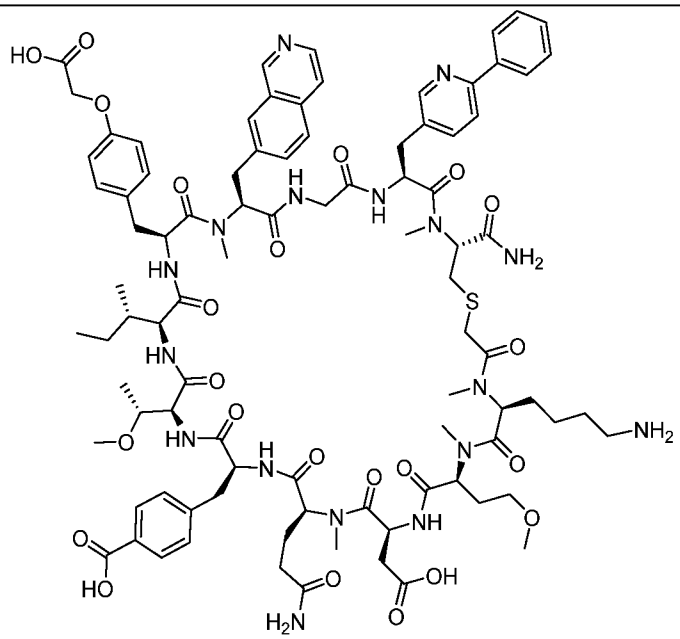
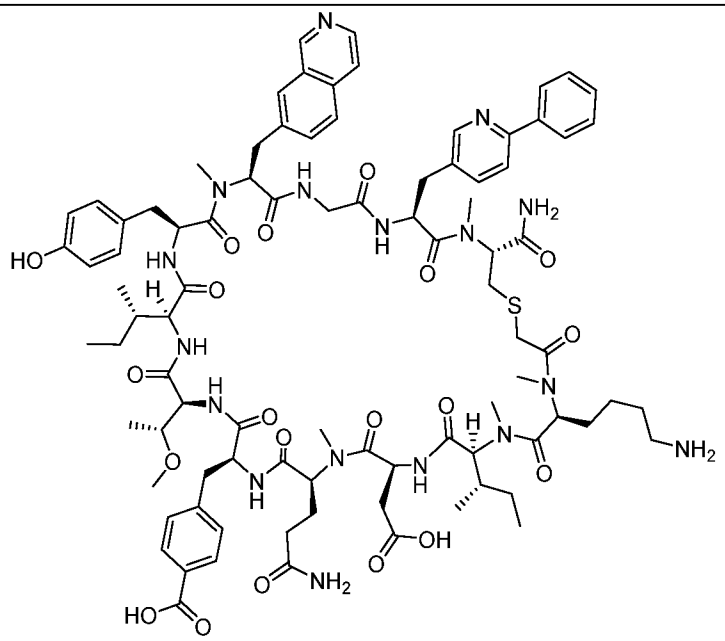
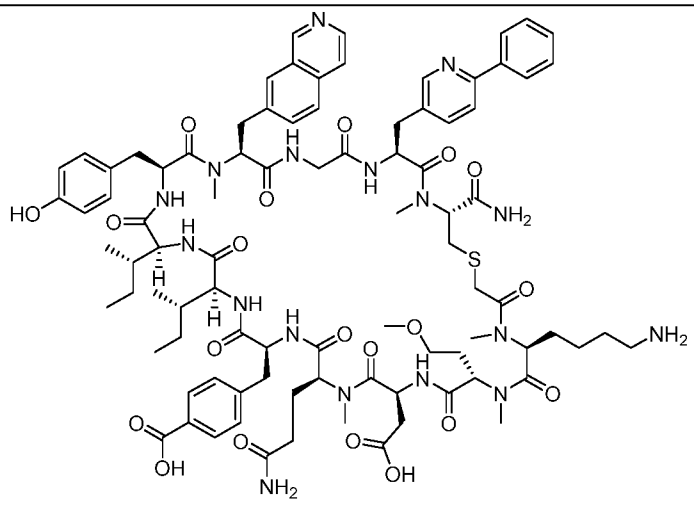
69		HPLC-MS (Method A-2): 4.39 min ESI-MS m/z: 791.8 [M+2H]2+
5		HPLC-MS (Method A-2): 4.93 min ESI-MS m/z: 903.5 [M+2H]2+
6		HPLC-MS (Method A-2): 4.86 min ESI-MS m/z: 910.0 [M+2H]2+

21		HPLC-MS (Method A-2): 4.52 min ESI-MS m/z: 910.0 [M+2H]2+
22		HPLC-MS (Method A-2): 4.58 min ESI-MS m/z: 911.8 [M+2H]2+
23		HPLC-MS (Method A-2): 4.15 min ESI-MS m/z: 953.9 [M+2H]2+

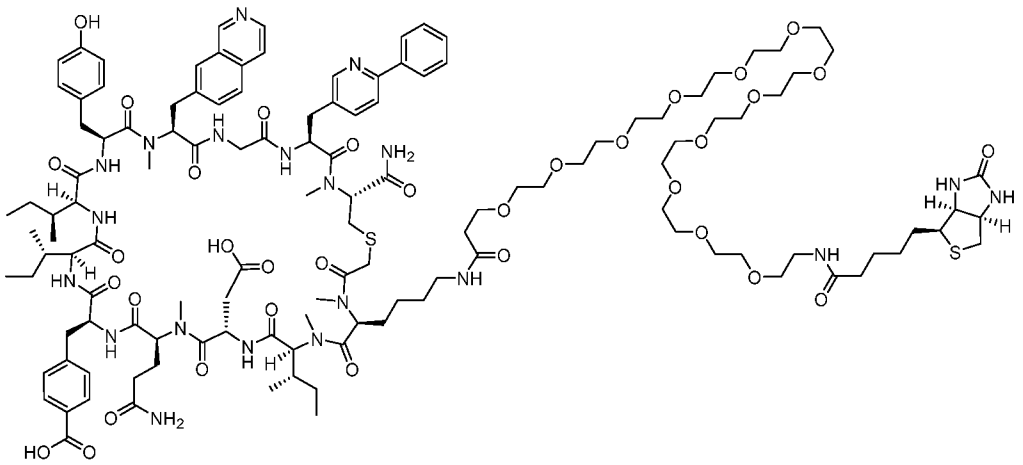
24		HPLC-MS (Method A-2): 4.19 min ESI-MS m/z: 919.3 [M+2H]2+
25		HPLC-MS (Method A-2): 3.98 min ESI-MS m/z: 961.4 [M+2H]2+
26		HPLC-MS (Method A-2): 4.81 min ESI-MS m/z: 917.9 [M+2H]2+

28		HPLC-MS (Method A-2): 4.17 min ESI-MS m/z: 918.4 [M+2H]2+
29		HPLC-MS (Method A-2): 4.30 min ESI-MS m/z: 911.4 [M+2H]2+
56		HPLC-MS (Method A-1): 5.20 min ESI-MS m/z: 975.0 [M+2H]2+

27		HPLC-MS (Method A-2): 4.39 min ESI-MS m/z: 925.5 [M+2H]2+
1		HPLC-MS (Method A-1): 5.79 min ESI-MS m/z: 888.4 [M+2H]2+
61		HPLC-MS (Method A-1): 5.52 min ESI-MS m/z: 918.4 [M+2H]2+

63		HPLC-MS (Method A-1): 4.96 min ESI-MS m/z: 919.4 [M+2H]2+
62		HPLC-MS (Method A-1): 5.32 min ESI-MS m/z: 889.4 [M+2H]2+
72		HPLC-MS (Method A-1): 4.96 min ESI-MS m/z: 889.4 [M+2H]2+

[00741] Example-3: Synthesis of the conjugated form consisting of the GPC binding peptide in this invention and biotin as a payload.



(SEQ ID NO: 118)

[00742] The desired polypeptide was synthesized as outlined in Scheme-3 on Fmoc-Sieber amide resin (0.100 mmol). Elongation of the linear peptide was achieved by Method S-1 employing Fmoc-AAs listed in below table. The obtained peptide on the resin was treated with the reagent mixture (4.5 mL) and performed the chloroacetylation as described in Step-C2 at room temperature for 30 min. Subsequently, the resin was shaken with $Pd(PPh_3)_4$ (23.1 mg, 0.2 eq) and $PhSiH_3$ (123 µL, 10 eq) in DCM (5 mL) at room temperature for 1 hr. The obtained peptide on the resin was shaken with Boc-PEG12c-OH (0.53 mmol) in DMF (2.5 mL)/ PyAOP (0.50 mmol) and DIEA (1.0 mmol) in DMF (2 mL) at 40 °C for 30 min as outlined in step-C3. The polypeptide on the resin was treated with the cleavage cocktail (4.5 mL) for 60 min as outlined in step-C4 to furnish the linear peptide, which was dissolved in $MeCN/H_2O$ (20mL). To the mixture was added Et3N (279 µL), and then the mixture was shaken for at room temperature for 15 hrs, and then concentrated as outlined in Step-C5. The reaction mixture was concentrated in Genevac EZ-2 Elite, and then the resulting residue was dissolved in DMSO (4 mL). To the solution were added Biotin-OSu (34.1 mg, 0.1 mmol) and DIEA (52.3 µL). The mixture was shaken at room temperature for 1 hr as outlined in Step-C6. To the mixture was added AcOH. The mixture was directly purified by preparative RP-HPLC. Pure fractions were combined and lyophilized to afford the title macrocyclic peptide (Conjugate ID No.:PLB-1, SEQ ID NO: 73). HPLC-MS (Method A-2): 4.13 min, ESI-MS m/z: 868.0 [M+3H]3+.

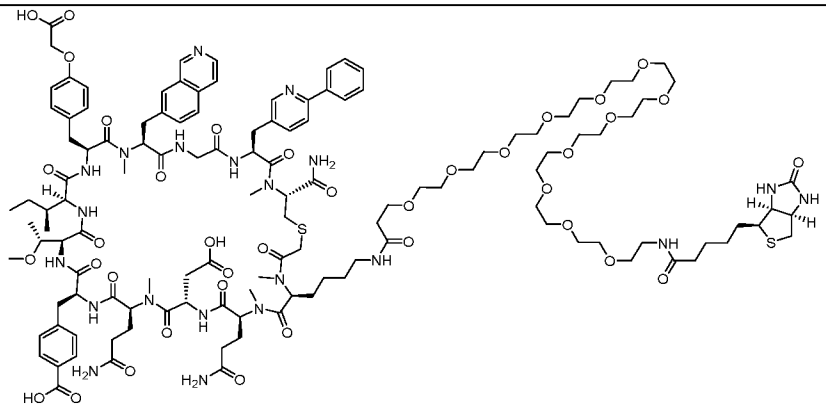
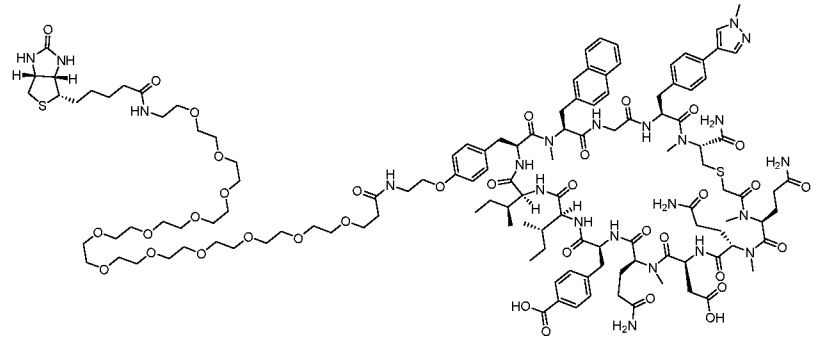
[00743] Table S8

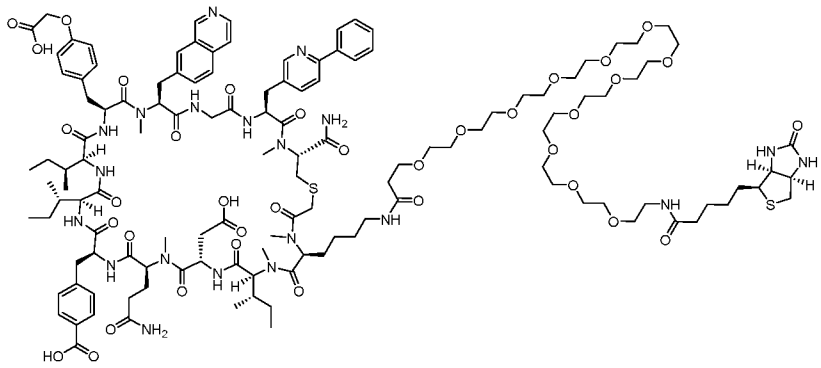
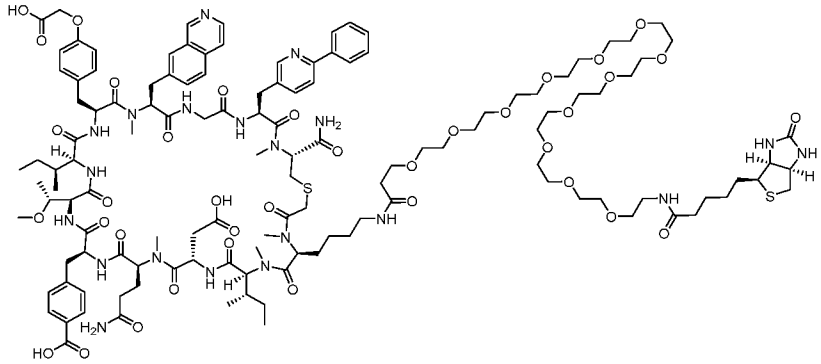
order of Fmoc-AA used in the SPPS	AA position in the cyclic peptide	Fmoc-AA
1	X12	Fmoc-MeC(Trt)-OH
2	X11	Fmoc-3Py6Ph-OH
3	X10	Fmoc-G-OH

4	X9	Fmoc-MeNal27N
5	X8	Fmoc-Y(tBu)-OH
6	X7	Fmoc-I-OH
7	X6	Fmoc-I-OH
8	X5	Fmoc-F4COO(tBu)-OH
9	X4	Fmoc-Q(Trt)-OH
10	X3	Fmoc-D(Mpe)-OH
11	X2	Fmoc-MeI-OH
12	X1	Fmoc-MeK(Alloc)-OH

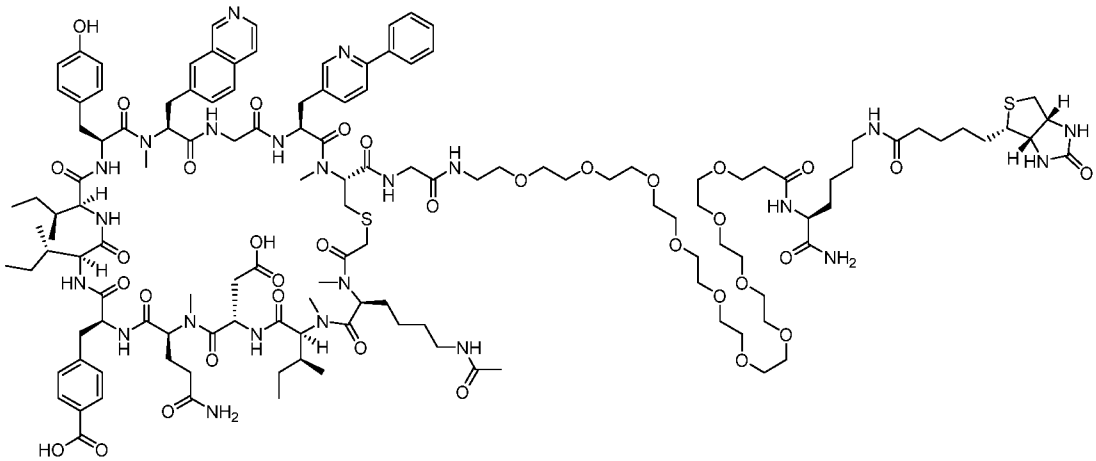
Example-4: The following conjugates were prepared analogously to Example-3.

Table S9

SEQ ID NO	Conjugate ID	Structure	Analytical data
74	PLB-35		HPLC-MS (Method A-2): tr= 3.92 min ESI-MS m/z: 892.9 ([M+3H]3+)
75	PLB-28		HPLC-MS (Method A-2): tr= 5.30 min ESI-MS m/z: 888.3 ([M+3H]3+)

76	PLB-64		HPLC-MS (Method A-2): tr= 4.02 min ESI-MS m/z: 887.3 ([M+3H]3+)
77	PLB-30		HPLC-MS (Method A-2): tr= 4.36 min ESI-MS m/z: 887.9 ([M+3H]3+)

[00744] Example-5: Synthesis of the conjugated form consisting of the GPC binding peptide in this invention and biotin as a payload.



(SEQ ID NO: 78)

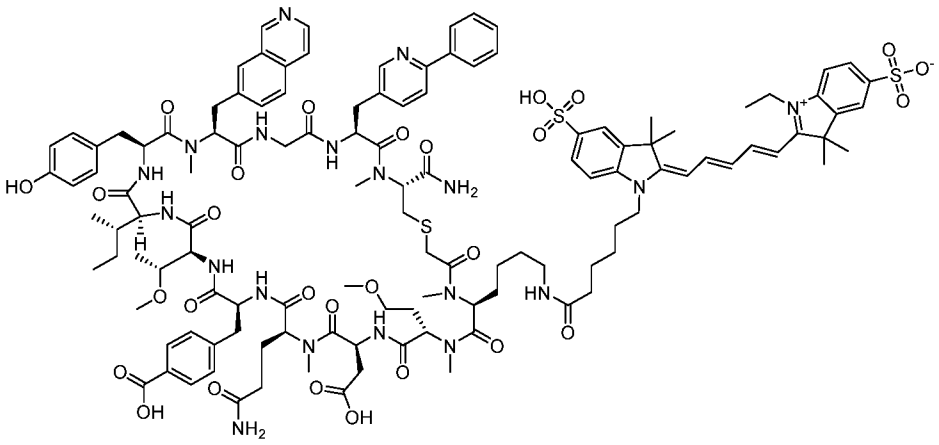
[00745] The desired polypeptide was synthesized as outlined in Scheme-1 on Fmoc-Sieber amide resin (0.050 mmol). Elongation of the linear peptide except for X9 was achieved by Method S-1 employing Fmoc-AAs listed in below table. Coupling reaction of Fmoc-MeNal27N-OH was performed manually as described in Method S4. The obtained peptide on the resin was treated with the reagent mixture (6 mL) and performed the chloroacetylation as described in Step-A2 at room temperature for 30 min. The polypeptide on the resin was treated with the cleavage cocktail (3 mL) for 30 min as outlined in Step-A3 to furnish the linear peptide, which was dissolved in MeCN/H_2O (10 mL). To the mixture was added Et_3N (69.7 µL), and then the mixture was shaken for at room

temperature for 3 hrs, and then concentrated as outlined in Step-A4. The resulting residue was purified by preparative RP-HPLC. Pure fractions were combined and lyophilized to afford the title macrocyclic peptide (SEQ ID No: 78, Conjugate ID No.:PLB-60). HPLC-MS (Method A-2): 3.75 min, ESI-MS m/z: 914.3 [M+3H]3+.

[00746] Table S10

Reaction order	Position no.	Fmoc-AA
1	X15	Fmoc-K(biotin)-OH
2	X14	Fmoc-PEG12c-OH
3	X13	Fmoc-G-OH
4	X12	Fmoc-MeC(Trt)-OH
5	X11	Fmoc-3Py6Ph-OH
6	X10	Fmoc-G-OH
7	X9	Fmoc-MeNal27N-OH
8	X8	Fmoc-Y(tBu)-OH
9	X7	Fmoc-I-OH
10	X6	Fmoc-I-OH
11	X5	Fmoc-F4COO(tBu)-OH
12	X4	Fmoc-MeQ(Trt)-OH
13	X3	Fmoc-D(Mpe)-OH
14	X2	Fmoc-MeI-OH
15	X1	Fmoc-MeKAc-OH

[00747] Example-6: Synthesis of the conjugated form consisting of the GPC binding peptide in this invention and sulfoCy5 as a payload.

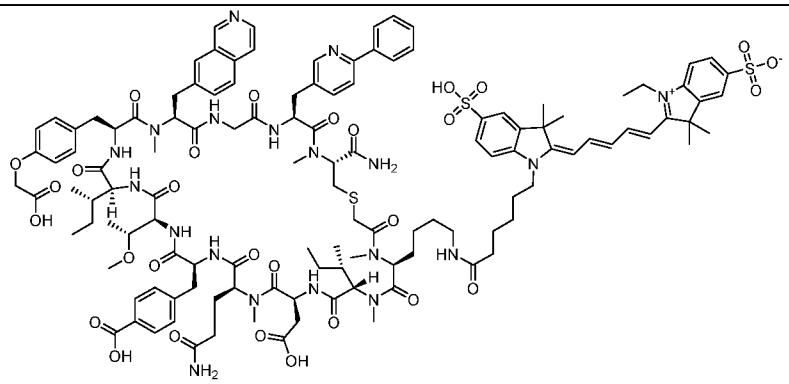
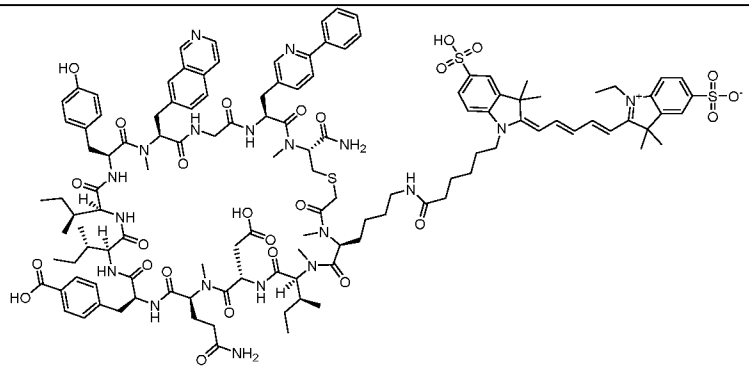


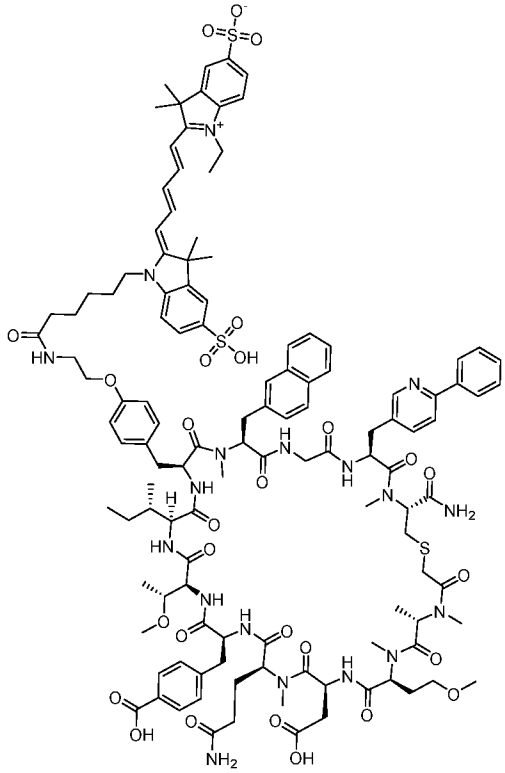
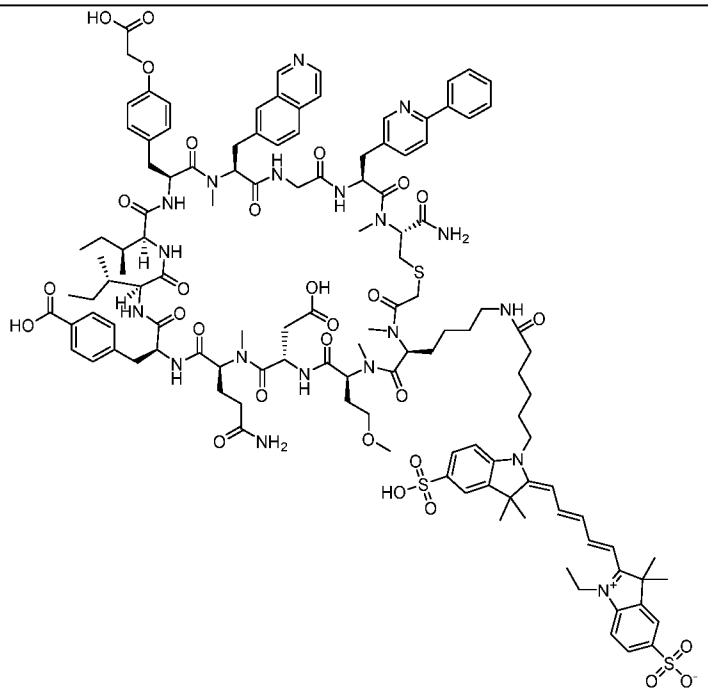
(SEQ ID NO: 119)

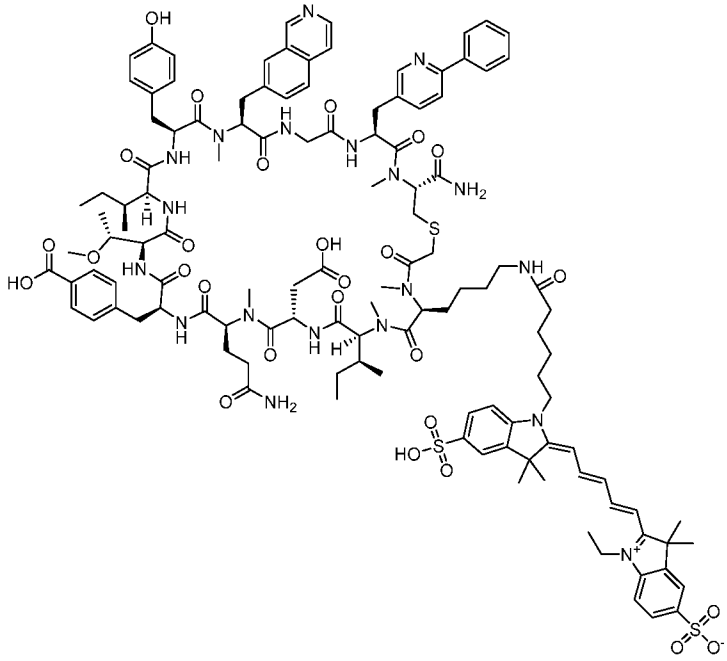
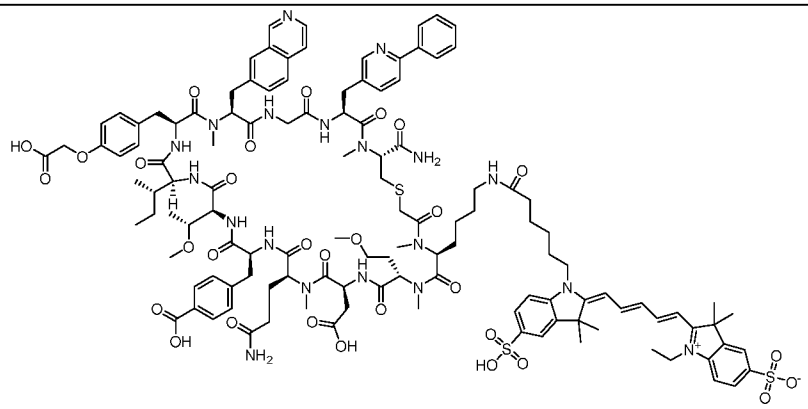
[00748] The desired polypeptide was synthesized as outlined in Scheme-4. To a solution of the GPC binding peptide in Example-1 (10.0 mg, 4.71 µmol) in DMF (150 µL) at room temperature were added triethylamine (6.6 µL, 47.1 µmol) and SulfoCy5-NHS (4.6 mg, 6.13 µmol). The mixture was stirred at room temperature for 18 hrs as outlined in step-D4. The resulting mixture was purified by preparative RP-HPLC. Pure fractions were combined and lyophilized to afford the title macrocyclic peptide (SEQ ID NO: 119, Conjugate ID No.:PLD-45). HPLC-MS (Method A-2): 3.80 min, ESI-MS m/z: 1209.6 [M+2H]2+.

[00749] Example-7: The following compounds were prepared by analogous method described above.

[00750] Table S11

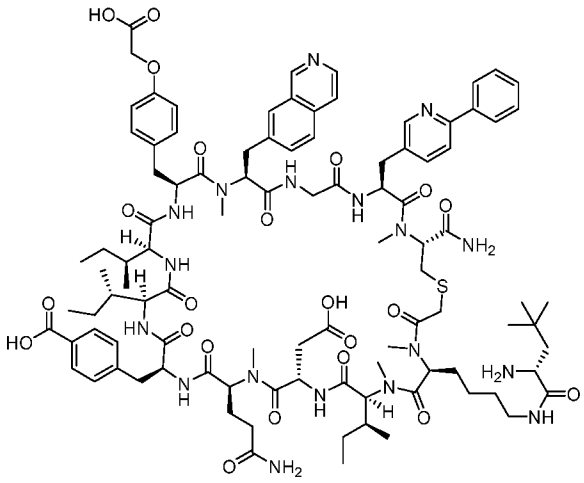
SEQ ID NO	Conjugate ID	Structure	Analytical data
80	PLD-30		HPLC-MS (Method A-2): tr= 4.00 min ESI-MS m/z: 1237.7 ([M+2H]2+)
81	PLD-1		HPLC-MS (Method A-2): tr= 4.14 min ESI-MS m/z: 1207.7 ([M+2H]2+)

82	Mod3		HPLC-MS (Method A-2): tr=5.30 min ESI-MS m/z: 1202.2 [M+2H]2+
83	Mod5		HPLC-MS (Method A-2): tr=4.00 min ESI-MS m/z: 1237.8 [M+2H]2+

84	Mod6		HPLC-MS (Method A-2): tr=4.41 min ESI-MS m/z: 1208.8 [M+2H]2+
85	Mod7		HPLC-MS (Method A-2): tr=4.10 min ESI-MS m/z: 1238.8 [M+2H]2+

[00751] The following compounds were prepared by analogous methods as described above.

[00752] Example-8:



(SEQ ID NO: 42)

[00753] The desired macrocyclic peptide was synthesized as outlined in Scheme-6. Starting with Fmoc-Sieber

amide resin (2x0.250 mmol), elongation of the linear peptide except for X9 was achieved by Method S-1 employing Fmoc-AAs listed in below table. Coupling reaction of Fmoc-MeNal27N-OH for X9 was performed manually as described in Method S4. The obtained peptide on the resin was treated with Fmoc-datb-OH (0.75 mmol)/HATU (0.75 mmol)/DIEA (1.5 mmol) in DMF (10mL) at room temperature for 30 min and then washed with DMF. Subsequently, the resin was shaken with $Pd(PPh_3)_4$ (57.8 mg, 0.2 eq) and $PhSiH_3$ (308 µL, 10 eq) in DCM/AcOH (99/1, 5 mL) at room temperature for 1hr, and then washed successively with DCM and DMF. The resin was treated with the reagent mixture (ClAcOH (1.25 mmol)/HATU (1.25 mmol)/DIEA (2.5 mmol) in DMF (10 mL). The whole mixture was shaken at room temperature for 30 min. The polypeptide on resin was successively washed with DMF, DCM, and then Et_2O. The polypeptide on resin was dried under reducing pressure. The polypeptide on the resin was treated with the cleavage cocktail (10 mL) for 90 min as outlined in Step-A3 to furnish the linear peptide, which was dissolved in DMSO/MeCN/H_2O (1/1/1, 100 mL). The mixture was split into four portions, and each mixture was then added TEA in each mixture (4x 174 µL for the whole crude). The mixture was shaken at room temperature for 2 hrs, and then concentrated in Genevac EZ-2 Elite. The resulting residue was dissolved in DMSO (15 mL). To the solution was added pyrrolidine (310 µL), and then the solution was shaken at room temperature for 1 hr. The reaction mixture was rendered acidic by AcOH, and then directly purified by preparative RP-HPLC. Pure fractions were combined and lyophilized to afford the title macrocyclic peptide (SEQ ID NO: 42). HPLC-MS (Method A-2): 3.67 min, ESI-MS m/z: 654.4 [M+3H]3+.

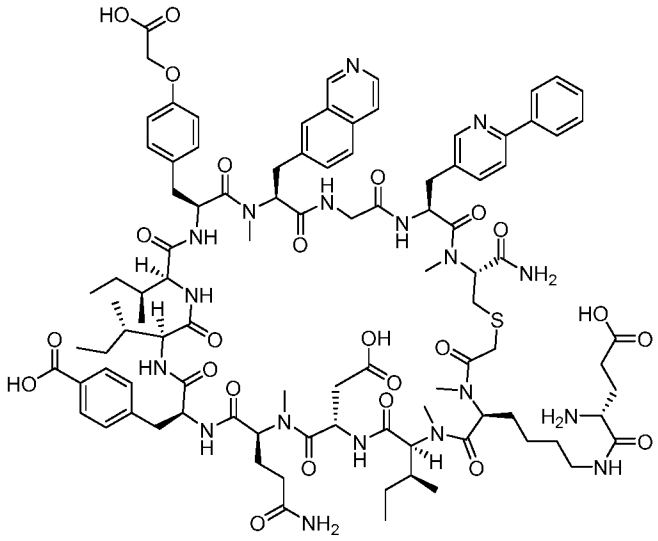
[00754] Table S12

order of Fmoc-AA used in the SPPS	AA position in the cyclic peptide	Fmoc-AA
1	X12	Fmoc-MeC(Trt)-OH
2	X11	Fmoc-3Py6Ph-OH
3	X10	Fmoc-G-OH
4	X9	Fmoc-MeNal27N-OH
5	X8	Fmoc-F4aao(tBu)-OH
6	X7	Fmoc-I-OH
7	X6	Fmoc-I-OH
8	X5	Fmoc-F4COO(tBu)-OH
9	X4	Fmoc-MeQ(Trt)-OH
10	X3	Fmoc-D(Mpe)-OH
11	X2	Fmoc-MeI-OH

12	X1	Alloc-MeK(Fmoc)-OH

[00755] The following compounds were prepared by analogous methods as described above.

[00756] Example-9:



(SEQ ID NO: 33)

[00757] The desired macrocyclic peptide was synthesized as outlined in Scheme-2 on Fmoc-Sieber amide resin (0.50 mmol). Elongation of the linear peptide except for X9 was achieved by Method S-1 employing Fmoc-AAs listed in below table. Coupling reaction of Fmoc-MeNal27N-OH was performed manually as described in Method S4. The obtained peptide on the resin was treated with Boc-de(tBu)-OH (2.1 mmol) in DMF (10 mL)/ DIC (4.0 mmol) in DMF (4 mL)/Oxyma pure® (2.0 mmol) in DMF (4 mL) at 75 °C for 30 min as outlined in Step-B2. Subsequently, the resin was shaken in a mixture of $Pd(PPh_3)_4$ (115.6 mg, 0.2 eq) and $PhSiH_3$ (616 µL, 10 eq) in DCM (25 mL) at room temperature for 1hr as outlined in Step-B3. The resin was treated with the reagent mixture (25 mL) and performed the chloroacetylation as described in Step-B4 at room temperature for 30 min. The polypeptide on the resin was treated with the cleavage cocktail (30 mL) for 10 min as outlined in Step-B5 to furnish the linear peptide, which was dissolved in MeCN/H_2O (100 mL). To the mixture was added TEA (697 µL) and then the mixture was shaken for at room temperature for 14 hrs, and then concentrated as outlined in Step-B6. The resulting residue was purified by preparative RP-HPLC. Pure fractions were combined and lyophilized to afford the title macrocyclic peptide (SEQ ID NO: 33). HPLC-MS (Method A-1): 5.74 min, ESI-MS m/z: 982.9 [M+2H]2+.

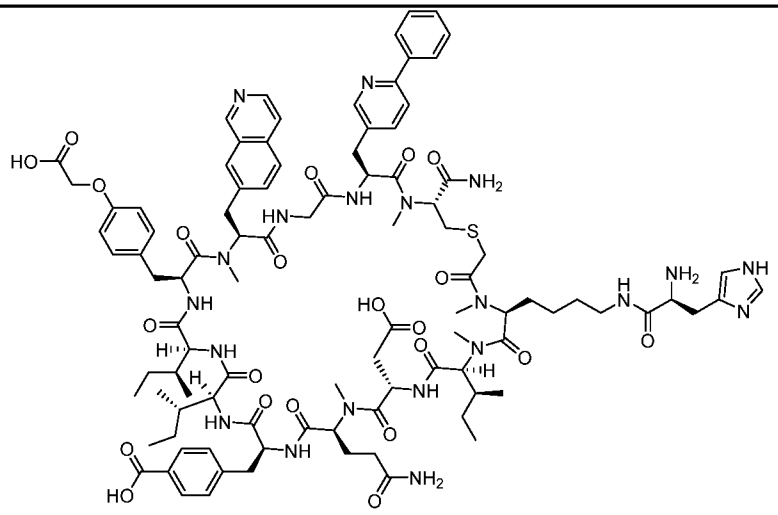
[00758] Table S13

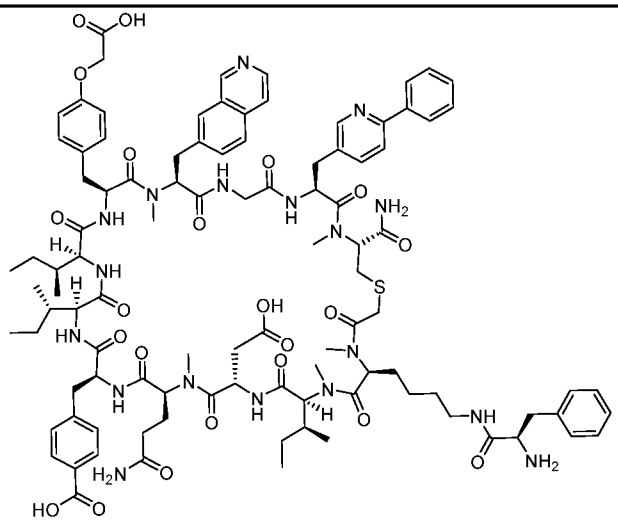
order of Fmoc-AA used in the SPPS	AA position in the cyclic peptide	Fmoc-AA
1	X12	Fmoc-MeC(Trt)-OH
2	X11	Fmoc-3Py6Ph-OH

3	X10	Fmoc-G-OH
4	X9	Fmoc-MeNal27N-OH
5	X8	Fmoc-F4aao(tBu)-OH
6	X7	Fmoc-I-OH
7	X6	Fmoc-I-OH
8	X5	Fmoc-F4COO(tBu)-OH
9	X4	Fmoc-MeQ(Trt)-OH
10	X3	Fmoc-D(Mpe)-OH
11	X2	Fmoc-MeI-OH
12	X1	Alloc-MeK(Fmoc)-OH

[00759] Example-10. The following peptides were prepared by methods analogously to the examples above.

[00760] Table S14

Example No.	**SEQ ID NO:**	**Structure**	**analytical data**
10-1	34		HPLC-MS (Method A-1): 5.43 min ESI-MS m/z: 657.7 [M+3H]3+

10-2	41		HPLC-MS (Method A-2): 5.67 min ESI-MS m/z: 991.4 [M+2H]2+

[00761] Biological example-1.

[00762] Macrocyclic peptides in this invention were tested for binding to Glypican-3 protein by SPR.

[00763] Method B-1.

[00764] A CM3 sensor chip (Cytiva) was inserted into a Biacore T200 (Cytiva), primed three times with a running buffer: HBS-P+, pH 7.4 (Cytiva), and equilibrated at a flow rate of 30 μL/min. Ligand immobilization was performed at a flow rate of 10 μL/min. 50 μL each of 60 mM EDC solution (Cytiva) and 650 mM NHS solution (Cytiva) were mixed, and then reacted at a flow rate of 10 μL/min for 420 seconds. 150 μL of 0.2 μM human Glypican3 (R&D systems, catalog number: 2119-GP) solution which was prepared by diluting with 10 mM acetic acid solution (pH 5.0), was reacted at a flow rate of 10 μL/min for 420 seconds, and Glypican3 was immobilized on the CM3 sensor chip. After immobilization, 1.0 M ethanolamine aqueous solution (Cytiva) was allowed to react for 420 seconds at a flow rate of 10 μL/min for capping. A peptide lysate prepared to 10 mM in DMSO solution was diluted with running buffer to a final concentration of 10 μM peptide lysate. After that, 5 serial dilution series (100 nM, 50 nM, 25 nM, 10 nM, 5 nM) of peptide solutions were prepared. Using the above samples, peptide kinetics for Glypican3 was obtained by SPR measurement. Kinetics evaluation of Glypican3 was performed by SPR measurements at a flow rate of 10 μL/min, setting the association time to 120 seconds and the disassociation time to 600 seconds.

[00765] Method B-2.

[00766] A CM3 sensor chip (Cytiva) was inserted into a Biacore T200 (Cytiva), primed three times with a running buffer: HBS-P+, pH 7.4 (Cytiva), and equilibrated at a flow rate of 30 μL/min. Using the Anti-Fc Capture Kit (Cytiva), 50 μL each of 60 mM EDC solution (Cytiva) and 650 mM NHS solution (Cytiva) were mixed, and then reacted at a flow rate of 10 μL/min for 420 seconds. 150 μL of 20 μL/mL Anti-human IgG (Fc) Antibody solution was prepared by diluting with 10 mM acetic acid solution (pH 5.0), reacted at a flow rate of 10 μL/min for 420 seconds, and immobilized on a CM3 sensor chip. After immobilization, 1.0 M ethanolamine aqueous solution (Cytiva) was allowed to react for 420 seconds at a flow rate of 10 μL/min for capping. Human Glypican3-Fc (ACRO Biosystems, GP3-H5258) was allowed to react for 60 seconds at a flow rate of 10 μL/min. After capturing

human Glypican3-Fc, a peptide solution prepared to 10 mM in DMSO solution was diluted with a running buffer to a final concentration of 10 μM. After that, 5 serial dilution series (100 nM, 50 nM, 25 nM, 10 nM, 5 nM) of peptide solutions were prepared. Using the above samples, peptide kinetics for Glypican3 was obtained by SPR measurement. Kinetics evaluation of Glypican3 was performed by SPR measurements at a flow rate of 10 μL/min, setting the association time to 120 seconds and the disassociation time to 600 seconds.

[00767] Method B-3.

[00768] A Protein A sensor chip (Cytiva) was inserted into a Biacore T200 (Cytiva), priming was performed three times with a running buffer: HBS-P+, pH 7.4 (Cytiva), and equilibration was carried out at a flow rate of 30 μL/min. Glypican3-Fc was allowed to react for 60 seconds at a flow rate of 10 μL/min. After capturing human Glypican3 -Fc, a peptide solution prepared to 10 mM in DMSO solution was diluted with a running buffer to a final concentration of 10 μM. After that, 5 serial dilution series (100 nM, 50 nM, 25 nM, 10 nM, 5 nM) of peptide solutions were prepared. Using the above samples, peptide kinetics for Glypican3 was obtained by SPR measurement. Kinetics evaluation of Glypican3 was performed by SPR measurements at a flow rate of 10 μL/min, setting the association time to 120 seconds and the disassociation time to 600 seconds.

[00769] Method B-4

[00770] A Protein A sensor chip (Cytiva) was inserted into a Biacore T200 (Cytiva), priming was performed three times with a running buffer: HBS-P+, pH 7.4 (Cytiva), and equilibration was carried out at a flow rate of 30 μL/min. Glypican3-Fc was allowed to react for 60 seconds at a flow rate of 10 μL/min. After capturing human Glypican3 -Fc, a peptide solution prepared to 1 mM in DMSO solution was diluted with a running buffer to a final concentration of 1 μM. After that, the peptide solution was diluted to 40 nM in a similar manner. Using the above samples, peptide kinetics for Glypican3 was obtained by SPR measurement. Kinetics evaluation of Glypican3 was performed by SPR measurements at a flow rate of 30 μL/min, setting the association time to 120 seconds and the disassociation time to 600 seconds.

[00771] The obtained data by Method B-1, Method B-2, Method B-3, and Method B-4 were analyzed by follow. Single Cycle Kinetics was used as the kinetics evaluation model, and curve fitting was performed using Biacore T200 Evaluation Software Version 3.0 (Cytiva). The obtained sensorgram was subjected to curve fitting by the method of least squares and obtained KD values of the macrocyclic peptides in this invention for Glypican 3 protein are shown in Biological Table-1.

Biological Table-1.

SEQ ID No.	Conjugate ID	SPR KD (nM)	SPR method
45	-	0.2	B-3
2	-	0.5	B-1
3	-	1.5	B-1
4	-	1.2	B-1
7	-	0.3	B-3

8	-	2.6	B-1
9	-	2.7	B-1
10	-	6.8	B-1
11	-	1.3	B-1
12	-	7.2	B-1
13	-	2.2	B-1
14	-	2.5	B-1
15	-	2.9	B-1
16	-	2.8	B-1
17	-	4.8	B-1
18	-	1.8	B-1
19	-	3.5	B-1
20	-	1.9	B-1
36	-	3.8	B-2
37	-	0.5	B-2
38	-	0.7	B-2
39	-	0.4	B-2
40	-	0.8	B-2
43	-	1.5	B-2
58	-	0.5	B-3
59	-	6.6	B-3
30	-	0.3	B-3
35	-	1.1	B-3
44	-	0.3	B-3
46	-	1	B-3
47	-	6.6	B-3
48	-	1.2	B-3
49	-	1.8	B-3
50	-	0.3	B-3
51	-	-	-
52	-	0.6	B-3
53	-	-	-
54	-	1	B-3
55	-	1.8	B-3
67	-	25.3	B-3
66	-	21.5	B-3
68	-	58.5	B-3
31	-	3.2	B-3

32	-	9.3	B-3
69	-	49.1	B-3
5	-	-	-
6	-	0.2	B-3
21	-	0.2	B-3
22	-	0.5	B-3
23	-	-	-
24	-	2	B-3
25	-	2.5	B-3
26	-	1.6	B-3
28	-	1	B-3
29	-	0.1	B-3
56	-	5.3	B-3
27	-	7.9	B-3
1	-	0.17	B-3
61	-	1.19	B-3
63	-	1.55	B-3
62	-	0.23	B-3
73	PLB-1	0.25	B-3
74	PLB-35	3.63	B-3
75	PLB-28	1.53	B-3
76	PLB-64	1.04	B-3
77	PLB-30	0.75	B-3
78	PLB-60	0.11	B-3
79	PLD-45	0.88	B-3
81	PLD-1	0.32	B-3
42	-	0.57	B-3
33	-	0.52	B-3
34	-	0.51	B-3
41	-	0.54	B-3
72	-	0.23	B-4
82	Mod3	0.90	B-3
83	Mod5	3.6	B-3
84	Mod6	0.24	B-3
85	Mod7	4.2	B-3
104	C-M-64	<1	B-3

Biological example-2.

[00772] Macrocyclic peptide-conjugates in this invention were tested in cells expressing glypican 3 and analyzed by flow cytometry.

[00773] Cell lines

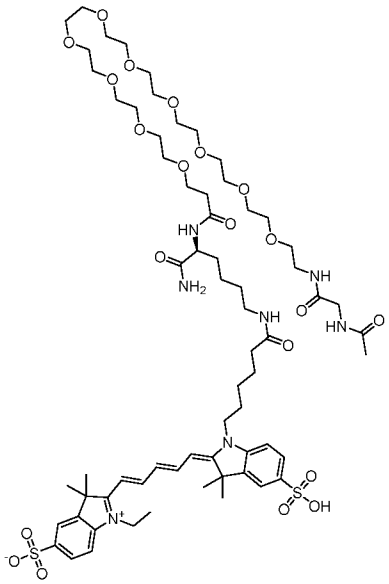
[00774] HepG2 (human hepatocellular carcinoma) and SK-HEP-1 (human hepatic adenocarcinoma) cell lines were purchased from the American Type Culture Collection (ATCC; Manassas, VA). Huh-7 (human hepatoblastoma) cell line was purchased from the Japanese Collection of Research Bioresources Cell Bank (JCRB Cell Bank, Osaka, Japan). HepG2 and SK-HEP-1 were grown in EMEM (FUJIFILM Wako Pure Chemical Corporation, 055-08975) with 10% fetal bovine serum (FBS; Thermo Fisher Scientific, 10270106) and 0.1% gentamicin (NACALAI TESQUE, 11980-14). Huh-7 was grown in DMEM (Thermo Fisher Scientific, 10567014) with 10% FBS and 0.1% gentamicin.

[00775] Flow cytometry

[00776] HepG2, SK-HEP-1 and Huh-7 cells were collected from the culture dish and stained with biotinylated peptides at 100 nM followed by Streptavidin, R-Phycoerythrin Conjugate (SAPE; Thermo Fisher Scientific, S866) (1:250). Cells were washed with phosphate-buffered saline (PBS; FUJIFILM Wako Pure Chemical Corporation, 043-29791) containing 0.5% FBS after addition of peptides or SAPE. All staining procedures were performed on ice. Samples were measured using CytoFLEX S (Beckman Coulter) and CytExpert ver2.4 software. All data were analyzed using FlowJo™ (BD Bioscience). For discrimination of live cells from dead cells, SYTOX™ Blue Dead Cell Stain (Thermo Fisher Scientific, S34857) (1:5000) was added prior to measurement.

[00777] The glypican-3 binding macrocyclic peptide-biotin conjugate in Example 5 (SEQ ID No: 78, Conjugate ID No.:PLB-60) was tested in the condition above. FIGs. 2-4 showed the flow charts of the comparative staining of HepG2 (glypican 3 expressed on the cell surface), Huh-7 (glypican 3 expressed on the cell surface), and SK-Hep1 (negative control) respectively, indicating specific binding to both glypican expressing cells and SAPE.

[00778] 2-[(1E,3E)-5-[(2E)-1-(5-{[(5S)-5-carbamoyl-5-[1-(2-acetamidoacetamido)-3,6,9,12,15,18,21,24,27,30-decaoxatritriacontan-33-amido]pentyl]carbamoyl}pentyl)-3,3-dimethyl-5-sulfo-2,3-dihydro-1H-indol-2-ylidene]penta-1,3-dien-1-yl]-1-ethyl-3,3-dimethyl-3H-indol-1-ium-5-sulfonate (shown below) was used as the negative control compound in the FACS assay.



[00779] SulfoCy5-peptides Flow cytometry

[00780] HepG2, SK-HEP-1 and Huh-7 cells were collected from the culture dish and stained with SulfoCy5-peptides at 100 nM. Cells were washed with phosphate-buffered saline (PBS; FUJIFILM Wako Pure Chemical Corporation, 043-29791) containing 0.5% FBS after addition of SulfoCy5-peptides. All staining procedures were performed on ice. Samples were measured using CytoFLEX S (Beckman Coulter) and CytExpert ver2.4 software. All data were analyzed using FlowJo™ (BD Bioscience). For discrimination of live cells from dead cells, SYTOX™ Blue Dead Cell Stain (Thermo Fisher Scientific, S34857) (1:5000) was added prior to measurement. FIGS. 5A-11C show the flow charts of the comparative staining of HepG2 (glypican 3 expressed on the cell surface), Huh-7 (glypican 3 expressed on the cell surface), and SK-Hep1 (negative control), indicating specific binding to both glypican expressing cells.

[00781] Certain linker-added peptides have identical or substantially the same peptide sequences compared to certain conjugates comprising such linker-added peptides, or “naked” peptides without the linker. Although the GPC3 binding affinity for such linker-added peptides have not been directly tested, they likely bind to GPC3 with similar avidity compared to that of the conjugates comprising such linker-added peptides, or that of the “naked” peptides without the linker portion.

[00782] The present technology may be used in bio-related industries and the pharmaceutical industry.

[00783] All references cited in this specification, and their references, are incorporated by reference herein in their entirety where appropriate for teachings of additional or alternative details, features, and/or technical background.

[00784] While the disclosure has been particularly shown and described with reference to particular embodiments, it will be appreciated that variations of the above-disclosed and other features and functions, or alternatives thereof, may be desirably combined into many other different systems or applications. Also, that various presently unforeseen or unanticipated alternatives, modifications, variations or improvements therein may be subsequently made by those skilled in the art which are also intended to be encompassed by the following claims.

CLAIMS

What is claimed is:

1. A peptide that has avidity for Glypican 3 (GPC3), or a pharmaceutically acceptable salt thereof, wherein the peptide comprises an amino acid sequence including deletion, substitution, and/or addition of one or several (*e.g.*, 1-6) amino acids in the amino acid sequence of SEQ ID NO: 1:

   MeK-MeI-D-MeQ-F4COO-I-I-Y-MeNal27N-G-3Py6Ph-MeC (SEQ ID NO: 1),

   wherein the peptide consists of 10 to 12 amino acid residues.
2. The peptide of claim 1, or a pharmaceutically acceptable salt thereof, wherein 1, 2, 3, 4 or 5 amino acids are added.
3. The peptide of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein the peptide is a cyclic peptide.
4. A peptide that has avidity for Glypican 3 (GPC3), or a pharmaceutically acceptable salt thereof, wherein the peptide comprises an amino acid sequence of Formula (I),

   X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12

   Formula (I)

   wherein,

   X1 is any amino acid;

   X2 is any amino acid;

   X3 is any amino acid;

   X4 is any amino acid;

   X5 is an amino acid comprising an aromatic ring (*e.g.*, W, F, Y, or a variant thereof), cycloalkyl, or heterocycloalkyl group, or X5 is a peptoid (*e.g.*, Cha4cH, Cha4tH, A1mor, Atp, Cha4cOMe);

   X6 is a hydrophobic amino acid, a hydrophilic amino acid, or a polar amino acid wherein the polar amino acid has a substituted side chain;

   X7 is a hydrophobic amino acid comprising a C_1-C_8 alkyl, cycloalkyl, or heterocycloalkyl, wherein the alkyl, cycloalkyl, and heterocycloalkyl are each independently, optionally substituted (*e.g.*, X7 is I, Eva, aII, TMe, SMe, Gcpr, Gcpe, Gthp, dMeS, TdMe, or Cbg);

   X8 is a A, I, L, V, Y or F, or a variant thereof;

   X9 is an N-alkylated amino acid comprising an aromatic ring;

   X10 is G, A, or a D-amino acid (e.g, da, ds, de, or dp);

   X11 is an amino acid comprising an aromatic ring (*e.g.*, F, Y, or a variant thereof); and,

   X12 is N-alkylated cysteine (*e.g.*, MeC).
5. The peptide of claim 4, or a pharmaceutically acceptable salt thereof, wherein X1 is an N-methylated amino acid.
6. The peptide of claim 4 or 5, or a pharmaceutically acceptable salt thereof, wherein X1 is an N-

methylated amino acid comprising a polar side chain (*e.g.*, MeK, MeQ, or a variant thereof).

7. The peptide of any one of claims 4 to 6, or a pharmaceutically acceptable salt thereof, wherein X2 is a L-amino acid.

8. The peptide of claim 7, or a pharmaceutically acceptable salt thereof, wherein X2 is a N-methylated amino acid.

9. The peptide of any one of claims 4 to 8, or a pharmaceutically acceptable salt thereof, wherein X3 is a polar and/or an L-amino acid.

10. The peptide of claim 9, or a pharmaceutically acceptable salt thereof, wherein X3 is an amino acid comprising a hydrophilic side chain (*e.g.*, D, K, Q, or a variant thereof) or an N-methylated variant thereof.

11. The peptide of any one of claims 4 to 10, or a pharmaceutically acceptable salt thereof, wherein X4 is a polar and/or an L-amino acid.

12. The peptide of claim 11, or a pharmaceutically acceptable salt thereof, wherein X4 is an N-methylated amino acid, a polar amino acid (*e.g.*, D, K, Q, S, or a variant thereof), or peptoid (e.g. EtG, MeeG, CmG, CmpG CrmG CeG CrpG).

13. The peptide of any one of claims 4 to 12, or a pharmaceutically acceptable salt thereof, wherein X5 has an aromatic side chain, such as F, Y, or a variant thereof.

14. The peptide of claim 13, or a pharmaceutically acceptable salt thereof, wherein X5 is:

F, or a variant thereof comprising a phenyl, pyridinyl, or naphthalyl, wherein said phenyl, pyridinyl, or naphthalyl is optionally substituted with one or more substituents each independently selected from halogen, -C_{1-3}alkyl, -OH, -NH_2, -CN, -C(=O)OH, -C(=O)NH_2, -NHC(=O)CH_3, -C_{1-3}alkylene-C(=O)OH, -C_{1-3}alkylene-C(=O)NH_2, -O-C_{1-3}alkylene-C(=O)OH, -O-C_{1-3}alkylene-C(=O)NH_2, -C_{1-3}alkylene-C(=O)-5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH, -O-C_{1-3}alkylene-C(=O)- 5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH, -C_{1-3}alkylene-NHC(=O)- 5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH, -O-C_{1-3}alkylene-NHC(=O)- 5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH, and -NH-C_{1-3}alkylene-C(=O)OH; or

Y, or a variant thereof comprising a hydroxyphenyl, wherein the hydrogen atom in hydroxyphenyl of Y or of the variant is optionally substituted with one or more substituents selected from -C_{1-3}alkyl, , and -C_{1-3}alkylene-C(=O)OH.

15. The peptide of any one of claims 4 to 14, or a pharmaceutically acceptable salt thereof, wherein X6 is an aliphatic amino acid (*e.g.*, V, L, I, A, G, or a variant thereof), a hydrophilic amino acid (*e.g.*, D, E, or a variant thereof), threonine (T) or a variant thereof (e.g., O-methyl threonine (TMe)), serine (S), or methionine (M).

16. The peptide of any one of claim 4 to 15, or a pharmaceutically acceptable salt thereof, wherein X7 is an

amino acid comprising a branched alkyl side chain, a C_{3-5}cycloalkyl side chain, or a 3- to 5- membered heterocycloalkyl side chain, or an N-methylated variant thereof.

17. The peptide of claim 16, or a pharmaceutically acceptable salt thereof, wherein the branched alkyl side chain comprises 3-5 carbon atoms.

18. The peptide of claim 16 or 17, or a pharmaceutically acceptable salt thereof, wherein the alkyl, cycloalkyl, or heterocycloalkyl side chain is optionally substituted with -O-C_1-C_6 alkyl.

19. The peptide of any one of claim 4 to 18, or a pharmaceutically acceptable salt thereof, wherein X8 is:

an aliphatic amino acid (e.g., A, I, L, or V);

Y, or a variant thereof comprising a hydroxyphenyl ring, wherein the hydroxyphenyl ring of Y or of the variant is optionally substituted with one or more substituents selected from halogen, -C_{1-3}alkyl, -OH, -C(=O)OH, -O-CH_3, -C_{1-3}alkylene-C(=O)OH, -C_{1-3}alkylene-C(=O)- 5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH, and -C_{1-3}alkylene-NHC(=O)- 5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH; or

F, or a variant thereof comprising a phenyl, pyridinyl, or indazolyl, wherein the phenyl of F or the phenyl, pyridinyl, or indazolyl of the variant is optionally substituted with one or more substituents each independently selected from halogen, -C_{1-3}alkyl, -OH, -C(=O)OH, -C(=O)NH_2, -NHC(=O)NH_2, -C_{1-3}alkylene-C(NH_2)-COOH, -NH-CO-CH_3, -NH-C_{1-3}alkylene-NH_2, -C(=O)-N(CH_2)$_2$, -S(=O)$_2$-CH_3, -C_{1-3}alkylene-NH-C(=O)- 5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH, and -O-C_{1-3}alkylene-NH-C(=O)- 5- to 6-membered heterocycloalkylene-C_{1-3}alkylene-C(=O)OH.

20. The peptide of any one of claim 4 to 19, or a pharmaceutically acceptable salt thereof, wherein X9 is an N-methyl aromatic amino acid, optionally a bicyclic aromatic amino acid.

21. The peptide of claim 20, or a pharmaceutically acceptable salt thereof, wherein the N-methyl aromatic amino acid is:

N-methyl monocyclic aromatic amino acid comprising a phenyl or pyridinyl optionally substituted with one or more substituents each independently selected from halogen, -C_{1-3}alkyl, and trifluoromethyl; or

N-methyl bicyclic aromatic amino acid comprising a naphthalyl, quinolyl, or indazolyl optionally substituted with one or more substituents each independently selected from H or C_{1-3}alkyl.

22. The peptide of any one of claims 4 to 21, or a pharmaceutically acceptable salt thereof, wherein X10 is G or a D-amino acid (e.g., da, ds, de, or dp).

23. The peptide of any one of claims 4 to 22, or a pharmaceutically acceptable salt thereof, wherein X11 is F or a variant thereof, or an amino acid comprising -C_{1-6}alkylene-phenyl.

24. The peptide of claim 23, or a pharmaceutically acceptable salt thereof, wherein F or the variant thereof is:

F, or a variant thereof comprising a phenyl, or pyridinyl, optionally substituted with one or more substituents each independently selected from phenyl, -O-phenyl, -O-C_{1-3}alkylene-phenyl, pyridinyl, imidazolyl, pyrazolyl, N-C_{1-3}alkylene pyrazolyl, N-C_{1-3}alkylene(-O-C_{1-3}alkyl) pyrazolyl, pyranyl, tetrahydropyranyl, piperidinyl, N-C_{1-3}alkylene-C(=O)-piperidinyl.

25. The peptide of any one of claims 1 to 24, or a pharmaceutically acceptable salt thereof, wherein the peptide has an amino acid sequence according to Formula (I), or a pharmaceutically acceptable salt thereof,

X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12

Formula (I)

wherein,

X1 is I, R, Cit, F4G, 4Py, 3Py, KCOpipzaa, V, Eva, Q, E, MeI, Ahp, F4COO, KCOpip4COO, MeQdMe, MeA, MeSMe, MeG, MeV, MeHseMe, Aib, MeT, all, TMe, MeKCOpipzaa, MeQ, Hpr, MeTMe, MeDapCOpipzaa, MeK, MeKAc, MeK(de), MeK(H), MeK(df), or MeK(datb);

X2 is I, K, Cit, F4G, 4Py, 3Py, KCOpipzetOH, V, KCOpipzaa, Eva, Q, E, S, Ahp, F4COO, KCOpip4COO, MeQdMe, MeA, MeSMe, MeG, MeI, MeV, MeL, HseMe, MeY, Me3Py, MeHseMe, MeKAc, all, TMe MeKCOpipzaa, MeQ, Hpr, MeTMe, or MeDapCOpipzaaa;

X3 is D, Har, KCOpipzetOH, Cit, KCOmeglumine, KCOpipzaa, A4paa, Q, A, E, MeD, S, N, Hgl, F4COO, KCOpip4COO, KAc, Hgn, MeY, or DapCOpipzaa;

X4 is D, Har, KCOpipzetOH, KCOmeglumine, KCOpipzaa, A4paa, Q, A, E, MeD, S, N, Hgl, F4COO, KCOpip4COO, dd, MeQ, MeQdMe, MeA, MeSMe, MeG, EtG, MeeG, CmG, CmpG, CrmG, CeG, CrpG, MeK, MeKAc, MeHgl, Hgn, MeDapCOpipzaa, MeKCOpipzaa, Medd, Cit, MeCit, MeN, MeS, MeE, MeY, W5N or Mae4paa;

X5 is Y, F3G, 3Py6COO,4Py2NH2, 3Py5COO, F3COO, 3Py6NHAc, F, F4C, F4OMe, F4COO, Nal2, F3aao, F4aa, F4aao, 3Py6Nhaa, 5Pdo, F3CON, F4F, F4OEt, F4Me, F4CON, F4CONPEG4Me, F3OMe, Yae, YaeCOpipzaa, F4aaopipzaa, 4Pdo, 3Py6CON, Atp, Cha4cH, Cha4tH, Cha4cOMe, A1mor, or F4amCOpipzaa;

X6 is I, V, Eva, Chg, Tbg, A, L, Ahp, F4COO, Gcpr, Gcpe, all, Cle , S3REt, TMe, Acpr, Cba, Gthp, NleCOO, NleOH, P, Atb, Nva, Nle, N, DapAc, Abu, Nmm, Ndm, Ncit, Cit, SMe, HseMe, HseEt, HseiPr, dMeS, TdMe, Cbg, NvaOMe, SiPr, Spr, NleOme, Sbu, Scbm, Scpe, AhpOMe, HseBu, Spent or Hsecpe;

X7 is I, Eva, all, TMe, SMe, Gcpr, Gcpe, Gthp, dMeS, TdMe, or Cbg;

X8 is A, I, L, V, Y, F4OMe, F4COO, F4OEt, F4u, F4Me, F4CONdMe, F4CON, F4ms, F4CONPEG4Me, F34dOMe, F3OMe, F3C, F3CON, F3CONdMe, 3Py6CON, Yae, YaeCOpipzaa, 5Inda, F3aao, F3aa, 3Py6Nhae, 3Py6NHAc, 3Py6OMe, F4aaopipzaa, or F4amCOpipzaa;

X9 is MeNal2, MeNal27N, MeF34diox, MeF34dOMe, MeF4T, MeY, MeW1Me, MeW7N, MeF3C4Me, or MeF3Me4C;

X10 is G, A, or a D-amino acid (e.g., da, ds, de, or dp);

X11 is Bph, 3Py6Ph, F41Me4Pyz, F43Pyz, F44Pyz, F41Pyz, F41Me3Pyz, F41Et4Pyz, F41MeOe4Pyz, F41MeOp4Pyz, F44thp, F4Ac4pip, PhNva, PhNle, Yph, Ybn, F4tb, F4oPr, or F4CONdMe; and

X12 is MeC.

26. A peptide having avidity for Glypican 3 (GPC3), or a pharmaceutically acceptable salt thereof, wherein the peptide has an amino acid sequence of Formula (I),

X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12

Formula (I)

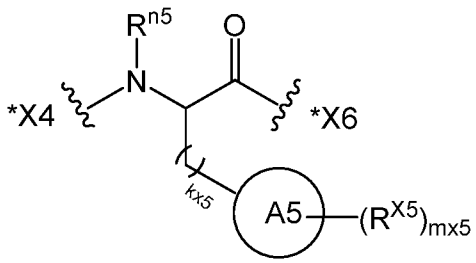
wherein,

X1 is any amino acid;

X2 is any amino acid;

X3 is any amino acid;

X4 is any amino acid;

X5 is 

, wherein:

R^{n5} is hydrogen or C_{1-3} alkyl;

ring A5 is an aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

each R^{X5} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halogen, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-SF_5$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-S(=O)(=NR^a)R^a$, $-N=S(=O)NR^cR^d$, $-NR^aS(=O)_2R^a$, amidinyl, $-NR^aC(=NH)NR^cR^d$, $-NR^aS(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, $-P(=O)(OR^c)(OR^d)$, $-P(=O)R^cR^d$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, $-L^{X5}$-heterocycloalkyl, $-L^{X5}$-cycloalkyl, $-L^{X5}$-aryl, or $-L^{X5}$-heteroaryl, wherein the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl are optionally substituted with one or more R^{X5a}; or

two R^{X5} are taken together to form =O, =S, or $=N(R^a)$;

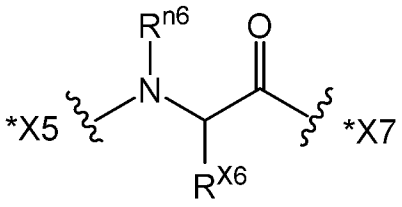
L^{X5} is C_{1-6}alkylene, C_{1-6}heteroalkylene, -O-, -S-, or $-NR^a-$, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X5a};

kx5 is 0, 1, 2, or 3;

mx5 is 0, 1, 2, 3, 4, or 5;

*X4 represents the point of attachment to X4; and

*X6 represents the point of attachment to X6;

X6 is  , wherein;

R^{n6} is hydrogen or C_{1-3} alkyl;

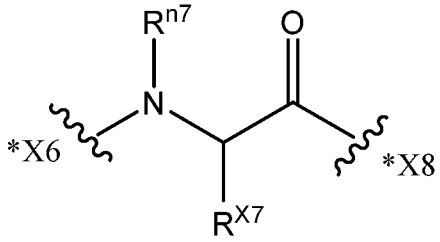
R^{X6} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -L^{X6}-heterocycloalkyl, -L^{X6}-cycloalkyl, -L^{X6}-aryl, or -L^{X6}-heteroaryl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X6a}; or

R^{n6} and R^{x6} are taken together with the intervening atoms to form a 5- to 6- membered heterocycloalkyl, which is optionally substituted with one or more R^{X6a};

L^{X6} is C_{1-6}alkylene, C_{1-6}heteroalkylene, -O-, -S-, or -NR^a-, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X6a};

*X5 represents the point of attachment to X5; and

*X7 represents the point of attachment to X7;

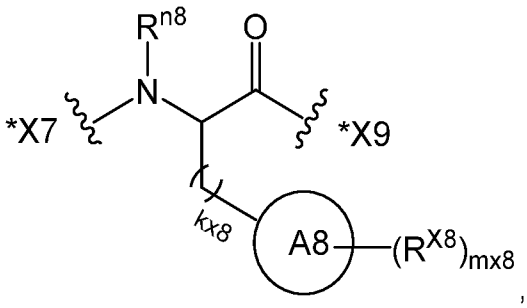
X7 is  , wherein:

R^{n7} is hydrogen or C_{1-3} alkyl ;

R^{X7} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, cycloalkyl, or heterocycloalkyl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X7a};

*X6 represents the point of attachment to X6; and

*X8 represents the point of attachment to X8;

X8 is  , wherein;

R^{n8} is hydrogen or C_{1-3}alkyl;

ring A8 is an aryl or heteroaryl;

each R^{X8} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halogen, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-SF_5$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2R^cR^d$, $-S(=O)(=NR^a)R^a$, $-N=S(=O)\ R^cR^d$, $-NR^aS(=O)_2R^a$, amidinyl, $-NR^aC(=NH)NR^cR^d$, $-NR^aS(=O)_2R^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, $-P(=O)(OR^c)(OR^d)$, $-P(=O)R^cR^d$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, $-L^{X8}$-heterocycloalkyl, $-L^{X8}$-cycloalkyl, $-L^{X8}$-aryl, or $-L^{X8}$-heteroaryl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X8a}; or

two R^{X8} are taken together to form =O, =S, or $=N(R^a)$;

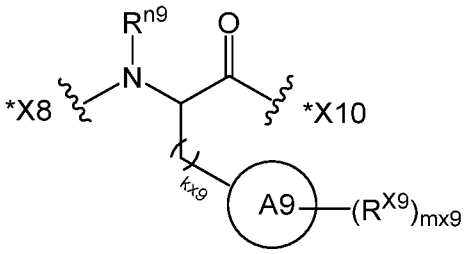
L^{X8} is C_{1-6}alkylene, C_{1-6}heteroalkylene, -O-, -S-, or $-NR^a-$, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X8a};

kx8 is 0, 1, 2, or 3;

mx8 is 0, 1, 2, 3, 4, or 5;

*X7 represents the point of attachment to X7; and

*X9 represents the point of attachment to X9;

X9 is 

, wherein:

R^{n9} is hydrogen or C_{1-3} alkyl;

ring A9 is an aryl or heteroaryl;

each R^{X9} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halogen, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-SF_5$, or $-NR^cR^d$, wherein each of the alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^{X9a}; or

two R^{X9} are taken together to form =O, =S, or $=N(R^a)$;

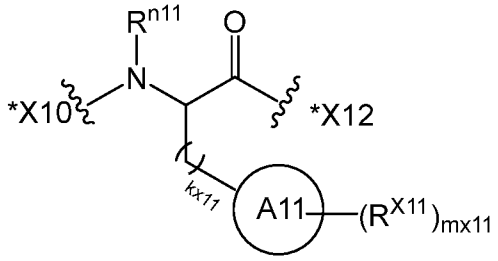
kx9 is 0, 1, 2, or 3;

mx9 is 0, 1, 2, 3, 4, or 5;

*X8 represents the point of attachment to X8; and

*X10 represents the point of attachment to X10;

X10 is glycine or a D-amino acid (e.g., da, ds, de, or dp);

X11 is  , wherein:

R^{n11} is hydrogen or C_{1-3} alkyl;

ring A11 is an aryl or heteroaryl;

each R^{X11} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, halogen, -CN, -NO_2, -OR^a, -SR^a, -SF_5, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2R^cR^d$, -$S(=O)(=NR^a)R^a$, -$N=S(=O)R^cR^d$, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)NR^cR^d$, -$NR^aS(=O)_2R^cR^d$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, -$P(=O)(OR^c)(OR^d)$, -$P(=O)R^cR^d$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -L^{X11}-heterocycloalkyl, -L^{X11}-cycloalkyl, -L^{X11}-aryl, or -L^{X11}-heteroaryl, wherein each of the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X11a}; or

two R^{X11} are taken together to form =O, =S, or =$N(R^a)$;

L^{X11} is C_{1-6}alkylene, C_{1-6}heteroalkylene, -O-, -S-, or -NR^a-, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X11a};

kx11 is 0, 1, 2, 3, 4, or 5;

mx11 is 0, 1, 2, 3, 4, or 5;

*X10 represents the point of attachment to X10; and,

*X12 represents the point of attachment to X12;

X12 is N-alkylated cysteine;

each of R^{X5a}, R^{X6a}, R^{X7a}, R^{X8a}, R^{X9a}, and R^{X11a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -SF_5, -$S(=O)_2NR^cR^d$, -$S(=O)(=NR^a)R^a$, -$N=S(=O)R^cR^d$, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)(NR^a)_2$, -$NR^aS(=O)_2NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, -$P(=O)(OR^c)(OR^d)$, -$P(=O)R^cR^d$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O, =S, or =$N(R^a)$, wherein each of the alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e.

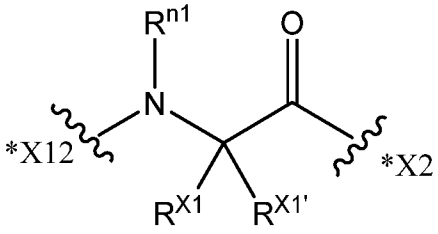
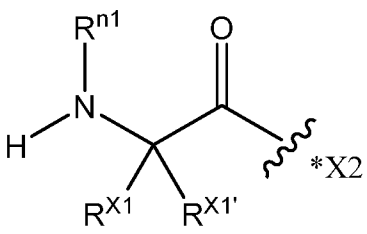
each R^a is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl),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

each R^e is independently halogen, -CN, -OH, -O-C_1-C_6alkyl, -SF_5, -S(=O)C_1-C_6alkyl, -S(=O)$_2$$C_1$-$C_6$alkyl, -S(=O)$_2$$NH_2$, -S(=O)$_2$-halogen, -S(=O)$_2$$NHC_1$-$C_6$alkyl, -S(=O)$_2$$N(C_1$-$C_6$alkyl)$_2$, -$NH_2$, -$NHC_1$-$C_6$alkyl, -$N(C_1$-$C_6$alkyl)$_2$, -NHC(=NH)$NH_2$, -NHC(=O)O$C_1$-$C_6$alkyl, -C(=O)$C_1$-$C_6$alkyl, -C(=O)OH, C_1-C_6alkyl-C(=O)OH, -C(=O)OC_1-C_6alkyl, -C(=O)NH_2, -C(=O)$N(C_1$-C_6alkyl)$_2$, -C(=O)NHC_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl; or two R^e are taken together to form =O; and

each R^c and R^d are 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 each of the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^e; 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^e.

27. The peptide of claim 26, or a pharmaceutically acceptable salt thereof, wherein X1 is an N-alkylated amino acid.

28. The peptide of claim 26 or 27, or a pharmaceutically acceptable salt thereof, wherein

X1 is  or  , wherein:

R^{n1} is hydrogen or C_{1-3} alkyl;

R^{X1} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -L^{X1}-heterocycloalkyl, -L^{X1}-cycloalkyl, -L^{X1}-aryl, or -L^{X1}-heteroaryl, wherein each of the alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X1a};

$R^{X1'}$ is hydrogen or C_{1-6}alkyl, wherein the alkyl is optionally substituted with one or more R^{X1a}; or

R^{n1} and $R^{X1'}$ are taken together with the intervening atoms to form a 5- to 6- membered heterocycloalkyl, which is optionally substituted with one or more R^{X1a};

L^{X1} is C_{1-6}alkylene, C_{1-6}heteroalkylene, -O-, -S-, or -NR^a-, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X1a};

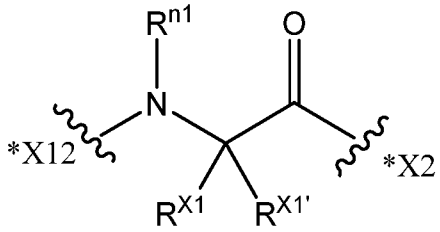
each R^{X1a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -S(=O)R^a, -S(=O)$_2$$R^a$, -$SF_5$, -S(=O)$_2$$NR^cR^d$, -S(=O)(=$NR^a$)$R^a$, -N=S(=O)$R^cR^d$, -$NR^a$S(=O)$_2$$R^a$, amidinyl, -$NR^a$C(=NH)$(NR^a)_2$, -$NR^a$S(=O)$_2$$NR^cR^d$, -C(=O)$R^a$, -C(=O)$OR^a$, -OC(=O)$R^a$, -OC(=O)$OR^a$, -OC(=O)$NR^cR^d$, -$NR^a$C(=O)$R^a$, -$NR^a$C(=O)$OR^a$, -$NR^a$C(=O)$NR^cR^d$, -C(=O)$NR^cR^d$, -P(=O)$(OR^c)(OR^d)$, -P(=O)$R^cR^d$, aryl, heteroaryl,

cycloalkyl, heterocycloalkyl, =O, =S, or =N(R^a), wherein each of the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e;

*X12 represents the point of attachment to X12; and

*X2 represents the point of attachment to X2.

29. The peptide of any one of claims 26 to 28, or a pharmaceutically acceptable salt thereof, wherein:

X1 is  , wherein:

R^{n1} is hydrogen or methyl;

R^{X1} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, -L^{X1}-5-6 membered heterocycloalkyl, -L^{X1}-C_{4-6}cycloalkyl, -L^{X1}-C_{6-10}aryl, or -L^{X1}-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X1a};

$R^{X1'}$ is hydrogen or methyl; or

R^{n1} and $R^{X1'}$ are taken together with the intervening atoms to form a 5- to 6- membered heterocycloalkyl, which is optionally substituted with one or more R^{X1a};

L^{X1} is C_{1-6}alkylene or C_{1-6}heteroalkylene, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X1a};

each R^{X1a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -S(=O)R^a, -$S(=O)_2R^a$, -SF_5, -$S(=O)_2NR^cR^d$, -S(=O)(=NR^a)R^a, -N=S(=O)R^cR^d, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)(NR^a)_2$, -$NR^aS(=O)_2NR^cR^d$, -C(=O)R^a, -C(=O)OR^a, -OC(=O)R^a, -OC(=O)OR^a, -OC(=O)NR^cR^d, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -C(=O)NR^cR^d, -P(=O)(OR^c)(OR^d), -P(=O)R^cR^d, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O, =S, or =N(R^a), wherein each of the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e;

*X12 represents the point of attachment to X12; and

*X2 represents the point of attachment to X2.

30. The peptide of claim 28 or 29, or a pharmaceutically acceptable salt thereof, wherein:

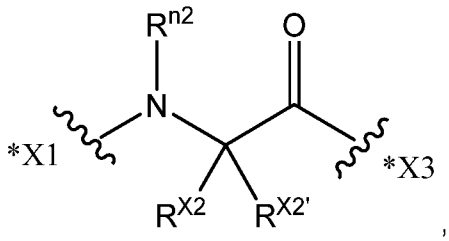
R^{X1} is hydrogen, C_{1-6}alkyl, C_{1-6}heteroalkyl, -L^{X1}-piperidinyl, -L^{X1}-piperazinyl, -L^{X1}-phenyl, or -L^{X1}-pyridinyl, wherein each of the alkyl, heteroalkyl, phenyl, pyridinyl, piperidinyl, and piperazinyl is optionally substituted with one or more R^{X1a}.

31. The peptide of any one of claims 28 to 30, or a pharmaceutically acceptable salt thereof, wherein:

each R^{X1a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^aS(=O)_2R^a$, -$NR^aC(=NH)(NR^a)_2$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e.

32. The peptide of any one of claims 26 to 31, or a pharmaceutically acceptable salt thereof, wherein X2 is an N-alkylated amino acid.

33. The peptide of any one of claims 26 to 32, or a pharmaceutically acceptable salt thereof, wherein:

X2 is 

,

wherein,

R^{n2} is hydrogen or C_{1-3} alkyl, wherein the alkyl is optionally substituted with one or more R^{X2a};

R^{X2} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -L^{X2}-heterocycloalkyl, -L^{X2}-cycloalkyl, -L^{X2}-aryl, or -L^{X2}-heteroaryl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X2a};

$R^{X2'}$ is hydrogen or C_{1-6}alkyl, wherein the alkyl is optionally substituted with one or more R^{X2a}; or

R^{n2} and $R^{X2'}$ are taken together with the intervening atoms to form a 5- to 6- membered heterocycloalkyl, which is optionally substituted with one or more R^{X2a};

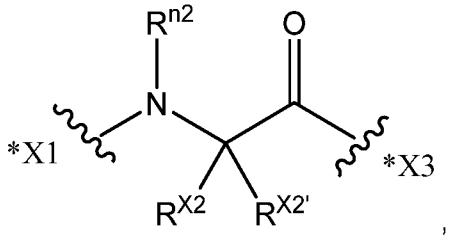
L^{X2} is C_{1-6}alkylene, C_{1-6}heteroalkylene, -O-, -S-, or -NR^a-, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X2a};

each R^{X2a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -SF_5, -$S(=O)_2NR^cR^d$, -$S(=O)(=NR^a)R^a$, -$N=S(=O)R^cR^d$, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)(NR^a)_2$, -$NR^aS(=O)_2NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, -$P(=O)(OR^c)(OR^d)$, -$P(=O)R^cR^d$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O, =S, =$N(R^a)$, aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein each of the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e;

*X1 represents the point of attachment to X1; and

*X3 represents the point of attachment to X3.

34. The peptide of any one of claims 26 to 33, or a pharmaceutically acceptable salt thereof, wherein

X2 is 

,

wherein:

R^{n2} is hydrogen or methyl;

R^{X2} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, -L^{X2}-5-6 membered heterocycloalkyl, -L^{X2}-C_{4-6}cycloalkyl, -L^{X2}-C_{6-10}aryl, or -L^{X2}-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X2a};

$R^{X2'}$ is hydrogen or methyl; or

R^{n2} and $R^{X2'}$ are taken together with the intervening atoms to form a 5- to 6- membered heterocycloalkyl, which is optionally substituted with one or more R^{X2a};

L^{X2} is C_{1-6}alkylene or C_{1-6}heteroalkylene, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X2a};

each R^{X2a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -SF_5, -$S(=O)_2NR^cR^d$, -$S(=O)(=NR^a)R^a$, -$N=S(=O)R^cR^d$, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)(NR^a)_2$, -$NR^aS(=O)_2NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, -$P(=O)(OR^c)(OR^d)$, -$P(=O)R^cR^d$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O, =S, or =$N(R^a)$, wherein each of the alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e;

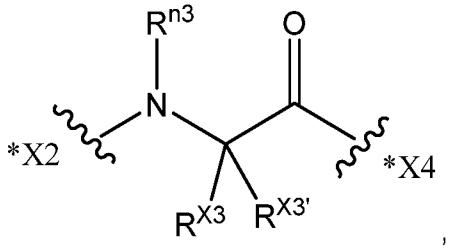
*X1 represents the point of attachment to X1; and

*X3 represents the point of attachment to X3.

35. The peptide of claim 33 or 34, or a pharmaceutically acceptable salt thereof, wherein R^{X2} is hydrogen, C_{1-6}alkyl, C_{1-6}heteroalkyl, -L^{X2}-piperidinyl, L^{X2}-piperazinyl, -L^{X2}-phenyl, or -L^{X2}-pyridinyl, wherein each of the alkyl, heteroalkyl, phenyl, pyridinyl, piperidinyl, and piperazinyl is optionally substituted with one or more R^{X2a}.

36. The peptide of any one of claims 33 to 35, or a pharmaceutically acceptable salt thereof, wherein each R^{X2a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^aS(=O)_2R^a$, -$NR^aC(=NH)(NR^a)_2$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e.

37. The peptide of any one of claims 26 to 36, or a pharmaceutically acceptable salt thereof, wherein

X3 is 

,

wherein:

R^{n3} is hydrogen or C_{1-3}alkyl, wherein the alkyl is optionally substituted with one or more R^{X3a};

R^{X3} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -L^{X3}-heterocycloalkyl, -L^{X3}-cycloalkyl, -L^{X3}-aryl, or -L^{X3}-heteroaryl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X3a};

$R^{X3'}$ is hydrogen or C_{1-6}alkyl, wherein the alkyl is optionally substituted with one or more R^{X3a}; or

R^{n3} and $R^{X3'}$ are taken together with the intervening atoms to form a 5- to 6- membered heterocycloalkyl, which is optionally substituted with one or more R^{X3a};

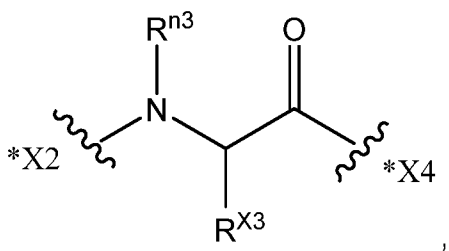
L^{X3} is C_{1-6}alkylene, C_{1-6}heteroalkylene, -O-, -S-, or -NR^a-, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X3a};

each R^{X3a} is independently halogen, C_{1-6}alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -S(=O)R^a, -$S(=O)_2R^a$, -SF_5, -$S(=O)_2NR^cR^d$, -S(=O)(=NR^a)R^a, -N=S(=O)R^cR^d, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)(NR^a)_2$, -$NR^aS(=O)_2NR^cR^d$, -C(=O)R^a, -C(=O)OR^a, -OC(=O)R^a, -OC(=O)OR^a, -OC(=O)NR^cR^d, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -C(=O)NR^cR^d, -P(=O)(OR^c)(OR^d), -P(=O)R^cR^d, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O, =S, or =N(R^a), wherein each of the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e;

*X2 represents the point of attachment to X2; and

*X4 represents the point of attachment to X4.

38. The peptide of any one of claims 26 to 37, or a pharmaceutically acceptable salt thereof, wherein

X3 is 

,

wherein:

R^{n3} is hydrogen or methyl;

R^{X3} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, -L^{X3}-5-6 membered heterocycloalkyl, -L^{X3}-C_{3-6}cycloalkyl, -L^{X3}-C_{6-10}aryl, or -L^{X3}-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X3a};

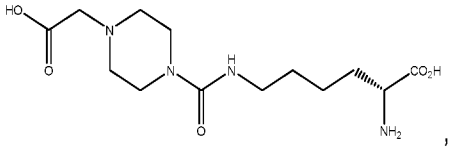
L^{X3} is C_{1-6}alkylene or C_{1-6}heteroalkylene, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X3a};

each R^{X3a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -S(=O)R^a, -$S(=O)_2R^a$, -SF_5, -$S(=O)_2NR^cR^d$, -S(=O)(=NR^a)R^a, -N=S(=O)R^cR^d, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)(NR^a)_2$, -$NR^aS(=O)_2NR^cR^d$, -C(=O)R^a, -C(=O)OR^a, -OC(=O)R^a, -OC(=O)OR^a, -OC(=O)NR^cR^d, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -C(=O)NR^cR^d, -P(=O)(OR^c)(OR^d), -P(=O)R^cR^d, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O, =S, or =N(R^a), wherein each of the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e;

*X2 represents the point of attachment to X2; and

*X4 represents the point of attachment to X4.

39. The peptide of claim 37 to 38, or a pharmaceutically acceptable salt thereof, wherein R^{X3} is C_{1-6}alkyl, C_{1-6}heteroalkyl, -L^{X3}-piperidinyl, L^{X3}-piperazinyl, -L^{X3}-phenyl, or -L^{X3}-pyridinyl, wherein each of the alkyl, heteroalkyl, phenyl, pyridinyl, piperidinyl, and piperazinyl is optionally substituted with one or more R^{X2a}.
40. The peptide of any one of claims 37 to 39, or a pharmaceutically acceptable salt thereof, wherein each R^{X3a} is independently halogen, C_{1-6}alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -S(=O)R^a, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^aS(=O)_2R^a$, -$NR^aC(=NH)(NR^a)_2$, -C(=O)R^a, -C(=O)OR^a, -OC(=O)R^a, -OC(=O)OR^a, -OC(=O)NR^cR^d, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -C(=O)NR^cR^d, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e.
41. The peptide of any one of claims 26 to 40, or a pharmaceutically acceptable salt thereof, wherein X4 is an N-alkylated amino acid.
42. The peptide of any one of claims 26 to 40, or a pharmaceutically acceptable salt thereof, wherein X4 is a peptoid.
43. The peptide of any one of claims 26 to 42, or a pharmaceutically acceptable salt thereof, wherein

X4 is  ,

wherein:

R^{n4} is hydrogen or C_{1-3} alkyl, wherein the alkyl is optionally substituted with one or more R^{X4a};

R^{X4} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -L^{X4}-heterocycloalkyl, -L^{X4}-cycloalkyl, -L^{X4}-aryl, or -L^{X4}-heteroaryl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X4a};

$R^{X4'}$ is hydrogen or C_{1-6}alkyl, wherein the alkyl is optionally substituted with one or more R^{X4a}; or

R^{n4} and $R^{X4'}$ are taken together with the intervening atoms to form a 5- to 6- membered heterocycloalkyl, which is optionally substituted with one or more R^{X4a};

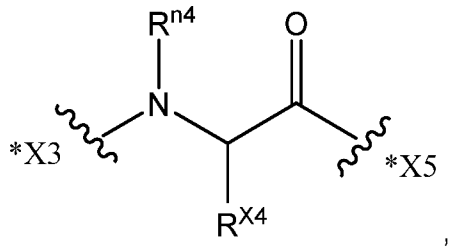
L^{X4} is C_{1-6}alkylene or C_{1-6}heteroalkylene, -O-, -S-, or -NR^a-, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X4a};

each R^{X4a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -S(=O)R^a, -$S(=O)_2R^a$, -SF_5, -$S(=O)_2NR^cR^d$, -S(=O)(=NR^a)R^a, -N=S(=O)R^cR^d, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)(NR^a)_2$, -$NR^aS(=O)_2NR^cR^d$, -C(=O)R^a, -C(=O)OR^a, -OC(=O)R^a, -OC(=O)OR^a, -OC(=O)NR^cR^d, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -C(=O)NR^cR^d, -P(=O)(OR^c)(OR^d), -P(=O)R^cR^d, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O, =S, or =N(R^a), wherein each of the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e;

*X3 represents the point of attachment to X3; and

*X5 represents the point of attachment to X5.

44. The peptide of any one of claims 26 to 43, or a pharmaceutically acceptable salt thereof, wherein

X4 is  ,

wherein:

R^{n4} is hydrogen or C_{1-3} alkyl, wherein the alkyl is optionally substituted with one or more R^{X4a};

R^{X4} is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, -L^{X4}-5-6 membered heterocycloalkyl, -L^{X4}-C_{3-6}cycloalkyl, -L^{X4}-C_{6-10}aryl, or -L^{X4}-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X4a};

L^{X4} is C_{1-6}alkylene or C_{1-6}heteroalkylene, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X4a};

each R^{X4a} is independently halogen, C_{1-6}alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -S(=O)R^a, -S(=O)$_2R^a$, -SF_5, -S(=O)$_2NR^cR^d$, -S(=O)(=NR^a)R^a, -N=S(=O)R^cR^d, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)(NR^a)_2$, -$NR^aS(=O)_2NR^cR^d$, -C(=O)R^a, -C(=O)OR^a, -OC(=O)R^a, -OC(=O)OR^a, -OC(=O)NR^cR^d, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -C(=O)NR^cR^d, -P(=O)(OR^c)(OR^d), -P(=O)R^cR^d, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O, =S, or =N(R^a), wherein each of the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e;

*X3 represents the point of attachment to X3; and

*X5 represents the point of attachment to X5.

45. The peptide of claim 43 or 44, or a pharmaceutically acceptable salt thereof, wherein

R^{X4} is C_{1-6}alkyl, C_{1-6}heteroalkyl, -L^{X4}-piperidinyl, L^{X4}-piperazinyl, -L^{X4}-phenyl, or -L^{X4}-pyridinyl, wherein each of the alkyl, heteroalkyl, phenyl, pyridinyl, piperidinyl, and piperazinyl is optionally substituted with one or more R^{X4a}.

46. The peptide of any one of claims 43 to 45, or a pharmaceutically acceptable salt thereof, wherein

each R^{X4a} is independently halogen, C_{1-6}alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -S(=O)R^a, -S(=O)$_2R^a$, -S(=O)$_2NR^cR^d$, -$NR^aS(=O)_2R^a$, -$NR^aC(=NH)(NR^a)_2$, -C(=O)R^a, -C(=O)OR^a, -OC(=O)R^a, -OC(=O)OR^a, -OC(=O)NR^cR^d, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -C(=O)NR^cR^d, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e.

47. The peptide of any one of claims 26 to 46, or a pharmaceutically acceptable salt thereof, wherein

R^{n5} is hydrogen or methyl;

ring A5 is a C_{6-10}aryl, 5-10 membered heteroaryl, C_{6-10}cycloalkyl, or 5-10 membered heterocycloalkyl;

each R^{X5} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halogen, -CN, -NO_2, -OR^a, -SR^a, -SF_5, -NR^cR^d, -S(=O)R^a, -S(=O)$_2R^a$, -S(=O)$_2NR^cR^d$, -S(=O)(=NR^a)R^a, -N=S(=O)NR^cR^d, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)NR^cR^d$, -$NR^aS(=O)_2NR^cR^d$, -C(=O)R^a, -C(=O)OR^a, -OC(=O)R^a, -OC(=O)OR^a, -OC(=O)NR^cR^d, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -C(=O)NR^cR^d, -P(=O)(OR^c)(OR^d), -P(=O)R^cR^d, C_{6-10}aryl, 5-10 membered heteroaryl, C_{3-6}cycloalkyl, 5-6 membered heterocycloalkyl, -L^{X5}-5-6 membered

heterocycloalkyl, -L^{X5}-C_{3-6}cycloalkyl, -L^{X5}-C_{6-10}aryl, or -L^{X5}-5-10 membered heteroaryl, wherein the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl are optionally substituted with one or more R^{X5a}; or

two R^{X5} are taken together to form =O; and

L^{X5} is C_{1-6}alkylene or C_{1-6}heteroalkylene, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X5a}.

48. The peptide of any one of claims 26 to 47, or a pharmaceutically acceptable salt thereof, wherein ring A5 is a phenyl, naphthyl, pyridinyl, cyclohexyl, piperidinyl, piperazinyl, morpholinyl, or tetrahydropyranyl;

each R^{X5} is independently halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^aS(=O)_2R^a$, -$NR^aC(=NH)NR^cR^d$, -$NR^aS(=O)_2NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, -L^{X5}-piperidinyl, or L^{X5}-piperazinyl, wherein each of the alkyl, heteroalkyl, piperidinyl, and piperazinyl are optionally substituted with one or more R^{X5a}; or

two R^{X5} are taken together to form =O;

kx5 is 1 or 2; and

mx5 is 0, 1, or 2.

49. The peptide of any one of claims 26 to 48, or a pharmaceutically acceptable salt thereof, wherein each R^{X5a} is independently halogen, C_{1-6}alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^aS(=O)_2R^a$, -$NR^aC(=NH)(NR^a)_2$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e.

50. The peptide of any one of claims 26 to 49, or a pharmaceutically acceptable salt thereof, wherein R^{n6} is hydrogen or methyl;

R^{X6} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{6-10}aryl, 5-10 membered heteroaryl, C_{3-6}cycloalkyl, 5-6 membered heterocycloalkyl, -L^{X6}-5-6 membered heterocycloalkyl, -L^{X6}-C_{3-6}cycloalkyl, -L^{X6}-C_{6-10}aryl, or -L^{X6}-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X6a}; and

L^{X6} is C_{1-6}alkylene or C_{1-6}heteroalkylene, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X6a}.

51. The peptide of any one of claims 26 to 50, or a pharmaceutically acceptable salt thereof, wherein R^{X6} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{3-6}cycloalkyl, 5-6 membered heterocycloalkyl, -L^{X6}-5-6 membered heterocycloalkyl, -L^{X6}- C_{3-6}cycloalkyl, -L^{X6}-phenyl or -L^{X6}-6 membered heteroaryl, wherein each of the alkyl, heteroalkyl, phenyl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X6a}.
52. The peptide of any one of claims 26 to 51, or a pharmaceutically acceptable salt thereof, wherein each R^{X6a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^aS(=O)_2R^a$, -$NR^aC(=NH)(NR^a)_2$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e.
53. The peptide of any one of claims 26 to 52, or a pharmaceutically acceptable salt thereof, wherein R^{n7} is hydrogen or methyl; and

R^{X7} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, or 5-6 membered heterocycloalkyl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X7a}.

54. The peptide of any one of claims 26 to 53, or a pharmaceutically acceptable salt thereof, wherein R^{X7} is C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{3-6}cycloalkyl, or 5-6 membered heterocycloalkyl, wherein each of the alkyl, heteroalkyl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X7a}.
55. The peptide of any one of claims 26 to 54, or a pharmaceutically acceptable salt thereof, wherein each R^{X7a} is independently halogen, -CN, -OR^a, -SR^a, -NR^cR^d, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, or =O.

56. The peptide of any one of claims 26 to 55, or a pharmaceutically acceptable salt thereof, wherein ring A8 is a C_{6-10}aryl or 5-10 membered heteroaryl;

each R^{X8} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halogen, -CN, -NO_2, -OR^a, -SR^a, -SF_5, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2R^cR^d$, -$S(=O)(=NR^a)R^a$, -$N=S(=O)$ R^cR^d, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)NR^cR^d$, -$NR^aS(=O)_2R^cR^d$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, -$P(=O)(OR^c)(OR^d)$, -$P(=O)R^cR^d$, C_{6-10}aryl, 5-10 membered heteroaryl, C_{3-6}cycloalkyl, 5-6 membered heterocycloalkyl, -L^{X8}-5-6 membered heterocycloalkyl, -L^{X8}- C_{3-6}cycloalkyl, -L^{X8}- C_{6-10}aryl, or -L^{X8}-5-10 membered heteroaryl, wherein

each of the alkyl, heteroalkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X8a}; or

two R^{X8} are taken together to form =O; and

L^{X8} is C_{1-6}alkylene or C_{1-6}heteroalkylene, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X8a}.

57. The peptide of any one of claims 26 to 56, or a pharmaceutically acceptable salt thereof, wherein ring A8 is a phenyl, pyridinyl, indolyl, azaindolyl, indazolyl, or benzimidazolyl;

each R^{X8} is independently halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^aS(=O)_2R^a$, $-NR^aC(=NH)NR^cR^d$, $-NR^aS(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, $-L^{X8}$-piperidinyl, or L^{X8}-piperazinyl, wherein each of the alkyl, heteroalkyl, piperidinyl, and piperazinyl are optionally substituted with one or more R^{X8a}; or

two R^{X5} are taken together to form =O;

kx8 is 1 or 2; and

mx8 is 0, 1, or 2.

58. The peptide of any one of claims 26 to 57, or a pharmaceutically acceptable salt thereof, wherein each R^{X8a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^aS(=O)_2R^a$, $-NR^aC(=NH)(NR^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e.

59. The peptide of any one of claims 26 to 58, or a pharmaceutically acceptable salt thereof, wherein R^{n9} is hydrogen or methyl;

ring A9 is a C_{6-10}aryl or 5-10 membered heteroaryl; and

each R^{X9} is independently halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-SF_5$, or $-NR^cR^d$, wherein each of the alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^{X9a}; or

two R^{X9} are taken together to form =O.

60. The peptide of any one of claims 26 to 59, or a pharmaceutically acceptable salt thereof, wherein ring A9 is a phenyl, naphthyl, pyridinyl, indolyl, azaindolyl, indazolyl, benzimidazolyl, or isoquinolinyl;

each R^{X9} is independently halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, -CN, -OR^a, -SR^a, or -NR^cR^d, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^{X9a};

kx9 is 1 or 2; and

mx9 is 0, 1, or 2.

61. The peptide of any one of claims 26 to 60, or a pharmaceutically acceptable salt thereof, wherein each R^{X9a} is independently halogen, C_{1-6}alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^aS(=O)_2R^a$, -$NR^aC(=NH)(NR^a)_2$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e.

62. The peptide of any one of claims 26 to 61, or a pharmaceutically acceptable salt thereof, wherein ring A11 is a C_{6-10}aryl or 5-10 membered heteroaryl;

each R^{X11} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, halogen, -CN, -NO_2, -OR^a, -SR^a, -SF_5, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2R^cR^d$, -$S(=O)(=NR^a)R^a$, -$N=S(=O)R^cR^d$, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)NR^cR^d$, -$NR^aS(=O)_2R^cR^d$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, -$P(=O)(OR^c)(OR^d)$, -$P(=O)R^cR^d$, C_{6-10}aryl, 5-10 membered heteroaryl, C_{3-6}cycloalkyl, 5-6 membered heterocycloalkyl, -L^{X11}-5-6 membered heterocycloalkyl, -L^{X11}- C_{3-6}cycloalkyl, -L^{X11}- C_{6-10}aryl, or -L^{X11}-5-10 membered heteroaryl, wherein each of the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X11a}; or

two R^{X11} are taken together to form =O; and

L^{X11} is C_{1-6}alkylene, C_{1-6}heteroalkylene, or -O-, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X11a}.

63. The peptide of any one of claims 26 to 62, or a pharmaceutically acceptable salt thereof, wherein ring A11 is a phenyl or pyridinyl;

each R^{X11} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, halogen, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2R^cR^d$, -$NR^aS(=O)_2R^a$, -$NR^aC(=NH)NR^cR^d$, -$NR^aS(=O)_2R^cR^d$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, C_{6-10}aryl, 5-10 membered heteroaryl, C_{3-6}cycloalkyl, 5-6 membered heterocycloalkyl, -L^{X11}-5-6 membered heterocycloalkyl, -L^{X11}- C_{3-6}cycloalkyl, -L^{X11}- C_{6-10}aryl, or -L^{X11}-5-10 membered heteroaryl, wherein

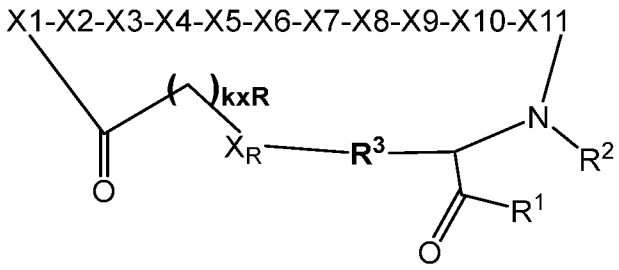
each of the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X11a}; or

two R^{X11} are taken together to form =O;

kx11 is 1, 2, 3, or 4; and

mx11 is 0, 1, or 2.

64. The peptide of any one of claims 26 to 63, or a pharmaceutically acceptable salt thereof, wherein each R^{X11} is independently phenyl, pyridinyl, pyrrolyl, pyrazolyl, imidazolyl, cyclohexyl, piperidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, -L^{X11}-5-6 membered heterocycloalkyl, - -L^{X11}-phenyl, or -L^{X11}-pyridinyl, wherein each of the phenyl, pyridinyl, pyrrolyl, pyrazolyl, imidazolyl, cyclohexyl, piperidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, and heterocycloalkyl is optionally substituted with one or more R^{X11a}.
65. The peptide of any one of claims 26 to 64, or a pharmaceutically acceptable salt thereof, wherein each R^{X11a} is independently halogen, C_{1-6}alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, -CN, -NO_2, -OR^a, -SR^a, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^aS(=O)_2R^a$, -$NR^aC(=NH)(NR^a)_2$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$, or =O, wherein each of the alkyl and heteroalkyl is optionally substituted with one or more R^e.
66. The peptide of any one of claims 1-65, wherein the peptide or the pharmaceutically acceptable salt thereof has a cyclic structure.
67. The peptide of any one of claims 1-66, wherein the peptide or the pharmaceutically acceptable salt thereof has a cyclic structure, wherein the first amino acid (or X1) is covalently linked to the last amino acid (or X12).
68. The peptide of any one of claims 1-67, wherein the peptide or the pharmaceutically acceptable salt thereof has a cyclic structure having an amino acid in the first residue X1 and a N-methylated cysteine residue, and wherein the amino acid in X1 and the N-methylated cysteine residue or variant thereof form a covalent bond.
69. The peptide of any one of claims 1-68, or a pharmaceutically acceptable salt thereof, wherein the peptide has a monocyclic structure.
70. The peptide of claim 69, or a pharmaceutically acceptable salt thereof, wherein the monocyclic structure is formed by a covalent bond between the amino acid X1 and a cysteine or a variant thereof.
71. The peptide of any one of claims 1-70, or a pharmaceutically acceptable salt thereof, wherein the peptide has a structure of Formula (I-1),



Formula (I-1),

wherein,

R^1 is selected from the group consisting of $-NH_2$ and -OH;

R^2 is C_{1-3} alkyl;

R^3 is C_{1-3} alkylene, optionally substituted with one or more R^4, wherein;

each R^4 is independently C_{1-3} alkyl or C_{3-6} cycloalkyl,;

kxR is 1, 2, 3, 4, 5, or 6;

X_R is selected from the group consisting of S, C or O; and

wherein X1 to X11 have the definitions described in Formula (I).

72. The peptide of any one of claims 1-71, wherein the peptide or the pharmaceutically acceptable salt thereof comprises a sequence with up to 1, 2, 3, 4, or 5 substitutions by a conserved variant compared to any one of the sequences selected from SEQ ID NOs: 1-72.

73. The peptide of any one of claims 1-72, wherein the peptide or the pharmaceutically acceptable salt thereof consists of an amino acid sequence selected from SEQ ID NOs: 1-72.

74. The peptide of any one of claims 1-73, or a pharmaceutically acceptable salt thereof, wherein the peptide has a binding affinity to a human GPC3 of at most 100 nM as determined by Kd in surface plasmon resonance (SPR) analysis.

75. A peptide of any one of claims 1-74, or a pharmaceutically acceptable salt thereof, covalently linked to a linker that is capable of connecting the peptide to a payload molecule.

76. The peptide of claim 75, or a pharmaceutically acceptable salt thereof, wherein the linker is attached to a lysine of the peptide.

77. The peptide of claim 75 or 76, or a pharmaceutically acceptable salt thereof, wherein the linker is attached to the peptide via the N terminus of the peptide.

78. The peptide of claim 75 or 76, or a pharmaceutically acceptable salt thereof, wherein the linker is attached to the peptide via the C terminus of the peptide.

79. The peptide of claim 75 or 76, or a pharmaceutically acceptable salt thereof, wherein the linker is attached to the peptide via a non-terminal amino acid residue of the peptide.

80. The peptide of claim 75 or 76, or a pharmaceutically acceptable salt thereof, wherein the linker is

attached to the 1st amino acid residue (or X1), the 2nd amino acid residue (or X2), the 3rd amino acid residue (or X3), the 4th amino acid residue (or X4), the 8th amino acid residue (or X8), or the 12th amino acid residue (or X12).

81. The peptide of claim 80, or a pharmaceutically acceptable salt thereof, wherein the linker is attached to the 1st amino acid residue or X1.

82. The peptide of claim 80, or a pharmaceutically acceptable salt thereof, wherein the linker is attached to the last amino acid residue, or X12.

83. The peptide of claim 80, or a pharmaceutically acceptable salt thereof, wherein the linker is attached to the 2nd amino acid residue (or X2).

84. The peptide of claim 80, or a pharmaceutically acceptable salt thereof, wherein the linker is attached to the 3rd amino acid residue (or X3).

85. The peptide of claim 80, or a pharmaceutically acceptable salt thereof, wherein the linker is attached to the 4th amino acid residue (or X4).

86. The peptide of claim 80, or a pharmaceutically acceptable salt thereof, wherein the linker is attached to the 8th amino acid residue (or X8).

87. The peptide of any one of claims 75 to 86, or a pharmaceutically acceptable salt thereof, wherein the linker is a bond.

88. The peptide of any one of claims 75 to 86, or a pharmaceutically acceptable salt thereof, wherein the linker comprises 3 to 30 intervening non-hydrdogen, organic atoms between the payload molecule and the peptide.

89. The peptide of any one of claims 75 to 86, or a pharmaceutically acceptable salt thereof, wherein the linker comprises 6 to 18 intervening non-hydrogen, organic atoms between the payload molecule and the peptide.

90. The peptide of claims 88 or 89, or a pharmaceutically acceptable salt thereof, wherein the intervening atoms comprise 1 to 6 nitrogen atoms and 0 to 4 oxygen atoms.

91. The peptide of any one of claims 75 to 86 or 88 to 90, or a pharmaceutically acceptable salt thereof, wherein the linker comprises one or more amino acid residues.

92. The peptide of claim 91, pharmaceutically acceptable salt thereof, wherein the linker comprises one amino acid residue.

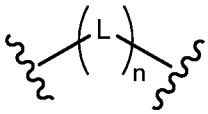
93. The peptide of claim 91, or a pharmaceutically acceptable salt thereof, wherein the linker comprises at least two contiguous amnio acid residues.

94. The peptide of any one of claims 91 to 93, wherein the one or more amino acid residues are selected

from a lysine residue, an alanine residue, a glycine residue, a D-phenylalanine residue, a histidine residue, a dAtb residue, or a D-glutamate residue.

95. The peptide of any one of claims 75 to 86, wherein the linker comprises one or more structures selected from AEEA, AEEP, AEEEP, and AEEEEP.

96. The peptide of any one of claims 75 to 86, wherein the linker has a structure of Formula (II-1)



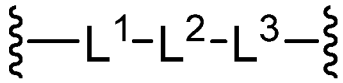
Formula (II-1)

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_{3-15} cycloalkyl, substituted or unsubstituted C_{1-12} heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_{1-30} alkylene, substituted or unsubstituted C_{2-30} alkenylene, substituted or unsubstituted C_{2-30} alkynylene, substituted or unsubstituted C_{1-30} heteroalkylene, -(C_{1-30} alkylene)-O-, -O-(C_{1-30} alkylene)-, -(C_{1-30} alkylene)-NR^L–, -NR^L–(C_{1-30} alkylene)-, -(C_{1-30} alkylene)-$N(R^L)_2$-, or -$N(R^L)_2$-(C_{1-30} alkylene)-; and

each R^L is independently hydrogen, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} heteroalkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-5} alkynyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{2-7} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

n is 1 to 20.

97. The peptide of claim 96, 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_{1-30} alkylene, or substituted or unsubstituted C_{1-30} heteroalkylene.

98. The peptide of claim 97, wherein L^1 is -NH-.

99. The peptide of claim 97 or 98, wherein L^2 is substituted or unsubstituted C_{1-30} alkylene, or substituted or

unsubstituted C_{1-30} heteroalkylene.

100. The peptide of claim 97 or 98, wherein L^2 is substituted or unsubstituted C_{1-18} alkylene, or substituted or unsubstituted C_{1-18} heteroalkylene.

101. The peptide of any one of claims 97 to 100, wherein L^2 is optionally substituted with one or more substituents selected from -OH, -SH, oxo, amino, C_{1-6} alkyl, C_{1-6} hydroxyalkyl, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, $-C(=O)OR^L$, $-OC(=O)R^L$, $-OC(=O)OR^L$, $-C(=O)N(R^L)_2$, $-NR^LC(=O)R^L$, $-OC(=O)N(R^L)_2$, and $-NR^LC(=O)OR^L$; and the C_{1-6} alkyl is further optionally substituted with one or more substituents chosen from -OH, -SH, oxo, amino, C_{6-10} aryl, 6- to 10- membered heteroaryl, $-C(=O)OR^L$, $-OC(=O)R^L$, $-OC(=O)OR^L$, $-C(=O)N(R^L)_2$, $-NR^LC(=O)R^L$, $-OC(=O)N(R^L)_2$, and $-NR^LC(=O)OR^L$.

102. The peptide of any one of claims 97 to 101, wherein L^3 is -NH-.

103. A pharmaceutical composition comprising the peptide or pharmaceutically acceptable salt thereof according to any one of claims 1 to 102, and a pharmaceutically acceptable excipient or carrier.

104. A conjugate comprising the peptide or pharmaceutically acceptable salt thereof according to any one of claims 1 to 102, and a substance or a payload molecule, wherein the substance or payload molecule is selected from the group consisting of: a nucleotide, a small molecule, a medium sized molecule (e.g., with a M.W. of about 1,000-2,500 Da), a large sized molecule (e.g., with a M.W. of >2,500 Da), a polymer compound, a protein, a peptide, a tag, a biological fragment, a carrier including pharmaceutical compound, or a combination thereof.

105. A method of treating a disease or disorder characterized by overexpression of GPC3, in a subject in need of treatment, the method comprising administering to the subject the peptide or pharmaceutically acceptable salt thereof according to any one of claims 1 to 102, the conjugate of claim 104, or the pharmaceutical composition of claim 103.

106. The method of claim 105, wherein the disease or disorder is cancer.

107. The method of claim 106, wherein the cancer is a solid tumor or hematological cancer.

108. A kit, tester, or composition for determining the expression level of GPC3 in a sample, wherein the kit, tester, or composition comprises the peptide or a salt thereof according to any one of claims 1 to 102, the conjugate of claim 104, or the pharmaceutical composition of claim 103.

109. The kit, tester, or composition of claim 108, adapted for use in a method of diagnosing disease or disorder characterized by an overexpression or a decreased expression of GPC3.

110. The kit, tester, or composition of claim 108 or 109, wherein the sample is from a subject having a disease or disorder characterized by an overexpression or a decreased expression of GPC3.

111. Use of the peptide or pharmaceutically acceptable salt thereof according to any one of the preceding claims in the manufacture of a medicament for diagnosing and/or treating a disease or disorder

characterized by an overexpression or a decreased expression of GPC3.

112. The peptide or pharmaceutically acceptable salt thereof according to any one of the preceding claims, for use in diagnosing and/or treating a disease or disorder characterized by an overexpression or a decreased expression of GPC3.

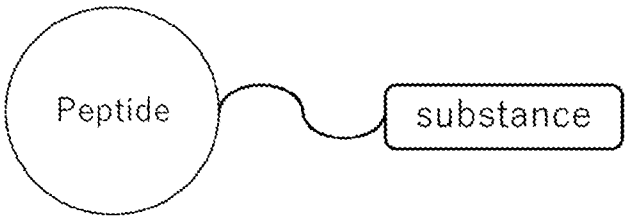
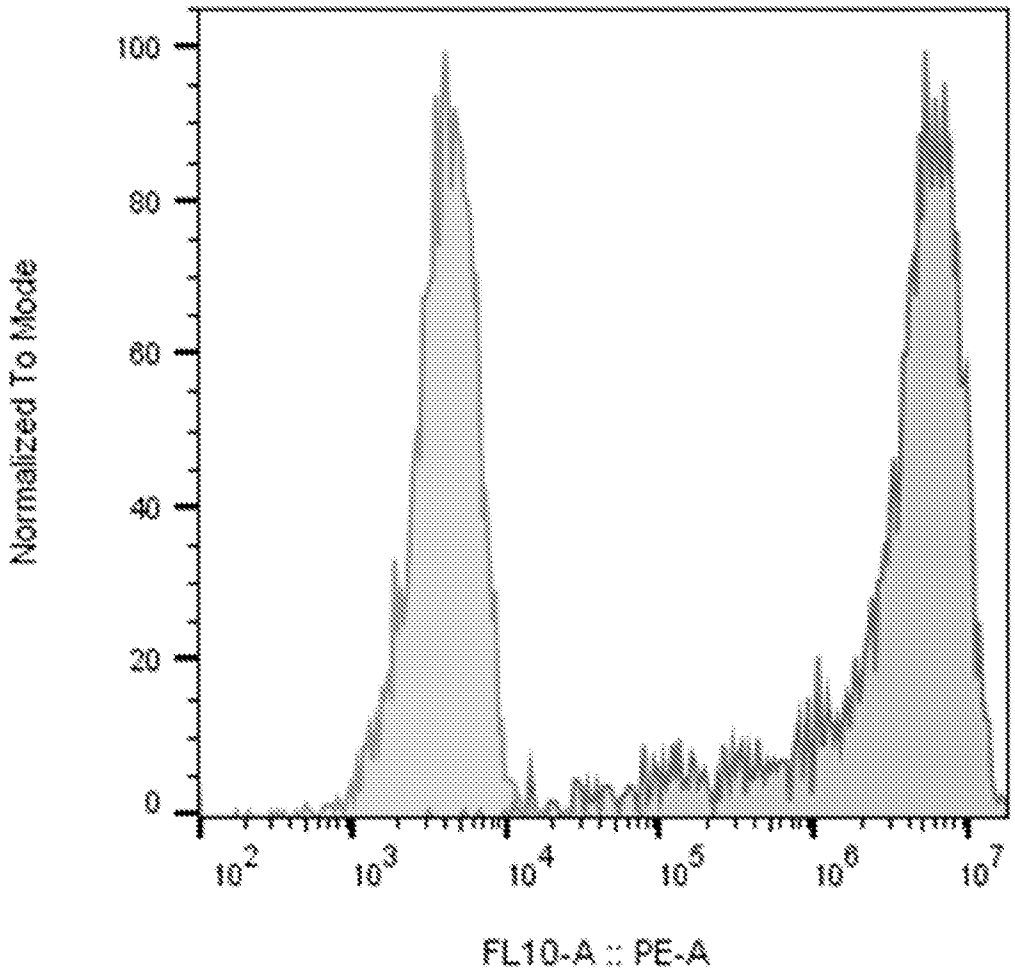

Peptide
substance

FIG. 1


Normalized To Mode
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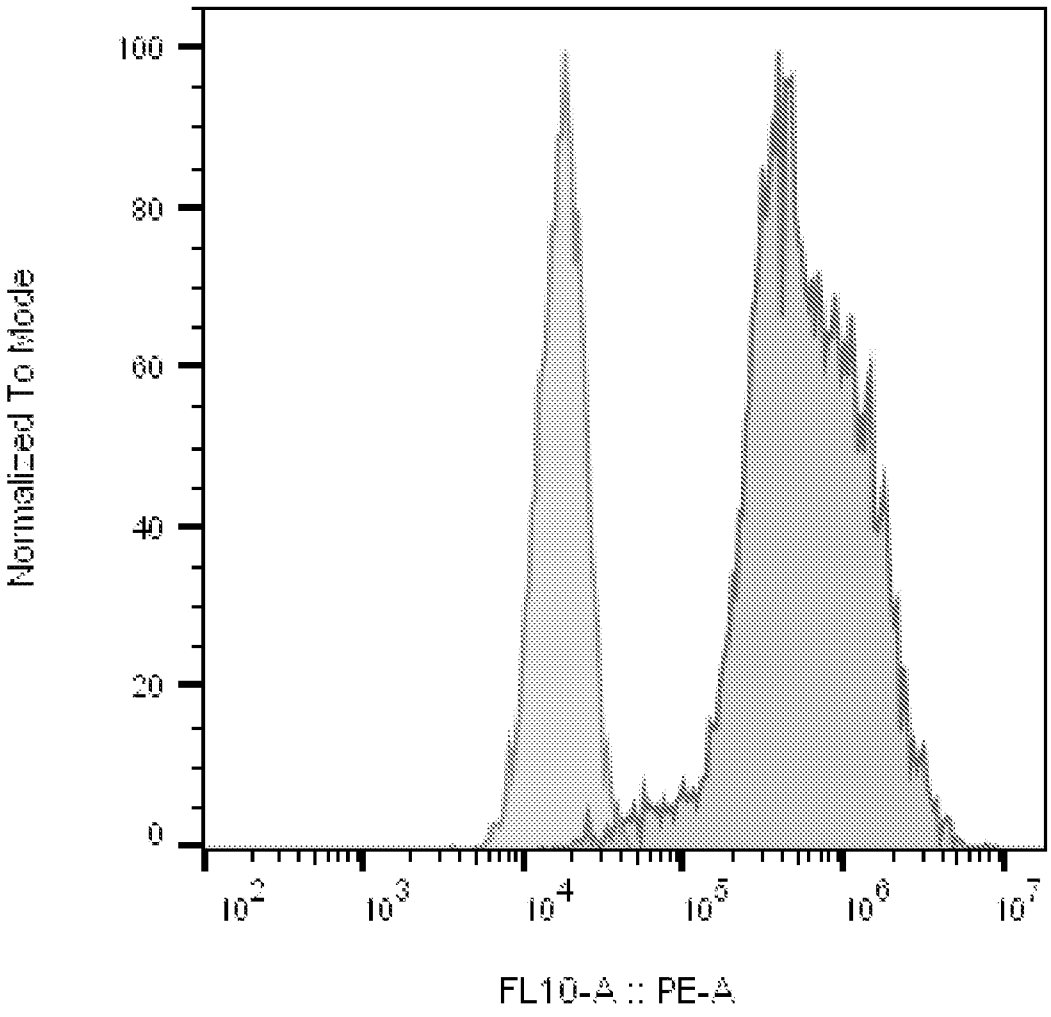
80
60
40
20
0
10^2
10^3
10^4
10^5
10^6
10^7
FL10-A :: PE-A

FIG. 2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10^2
10^3
10^4
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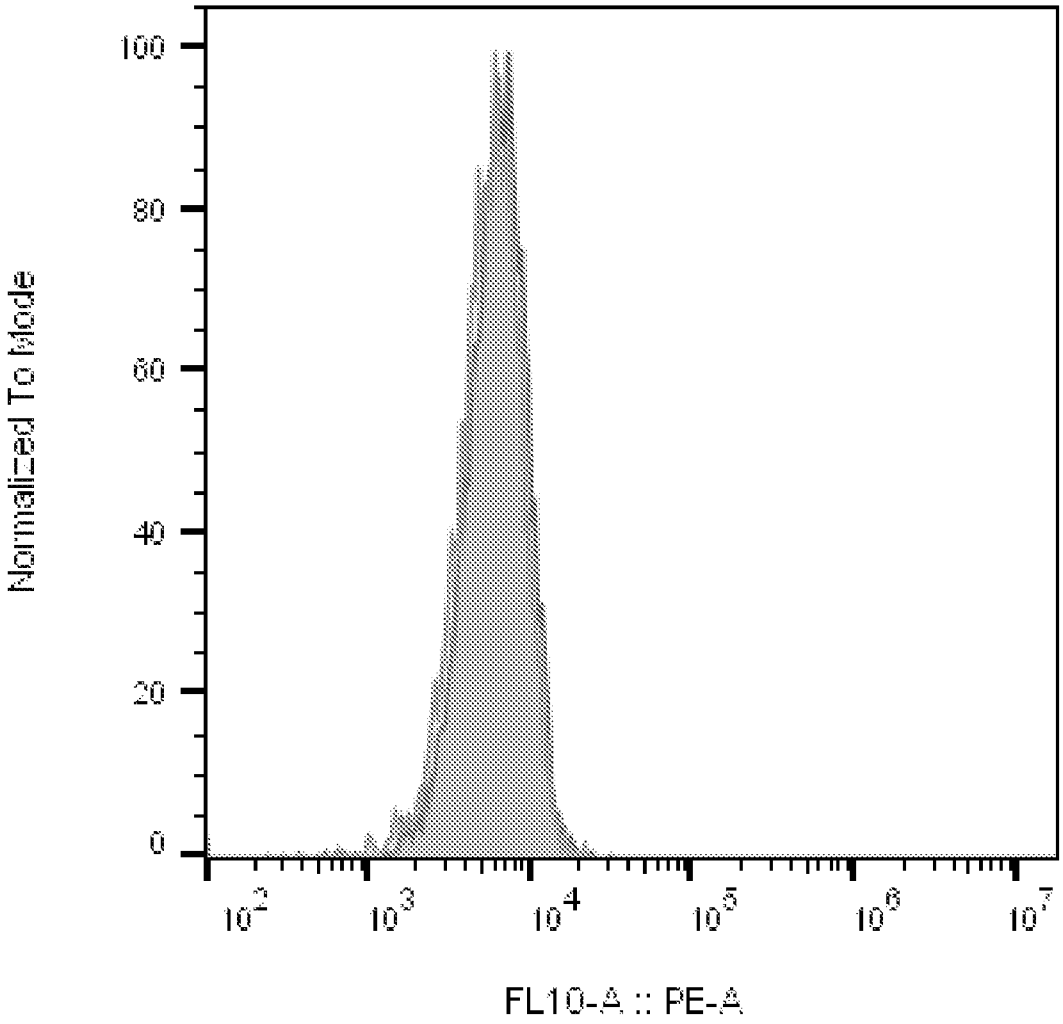
10^6
10^7
FL10-A :: PE-A

FIG. 3


Normalized To Mode
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0
10^2
10^3
10^4
10^5
10^6
10^7
FL10-A :: PE-A

FIG. 4

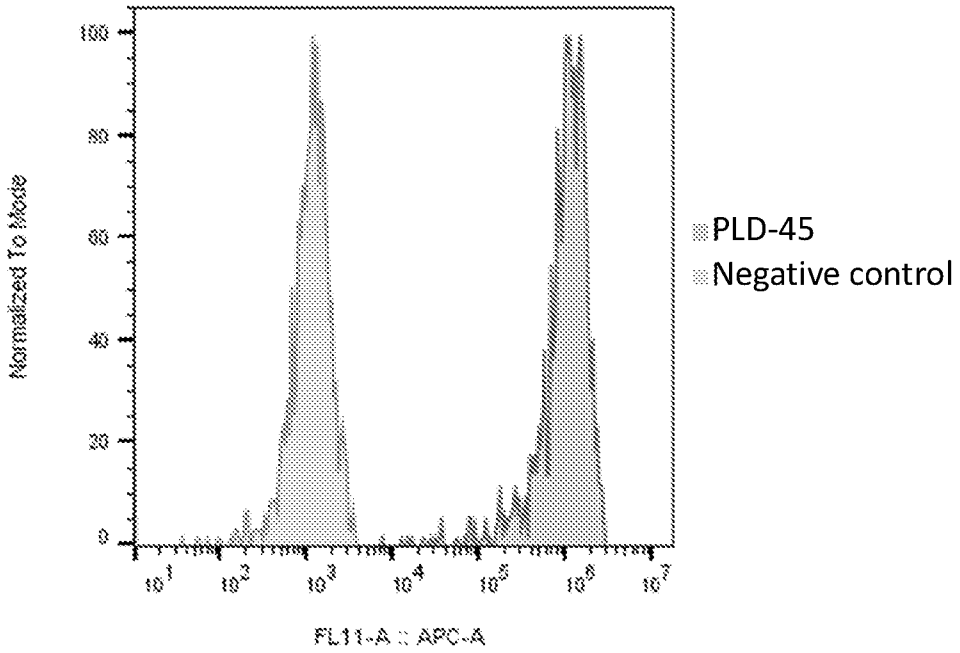
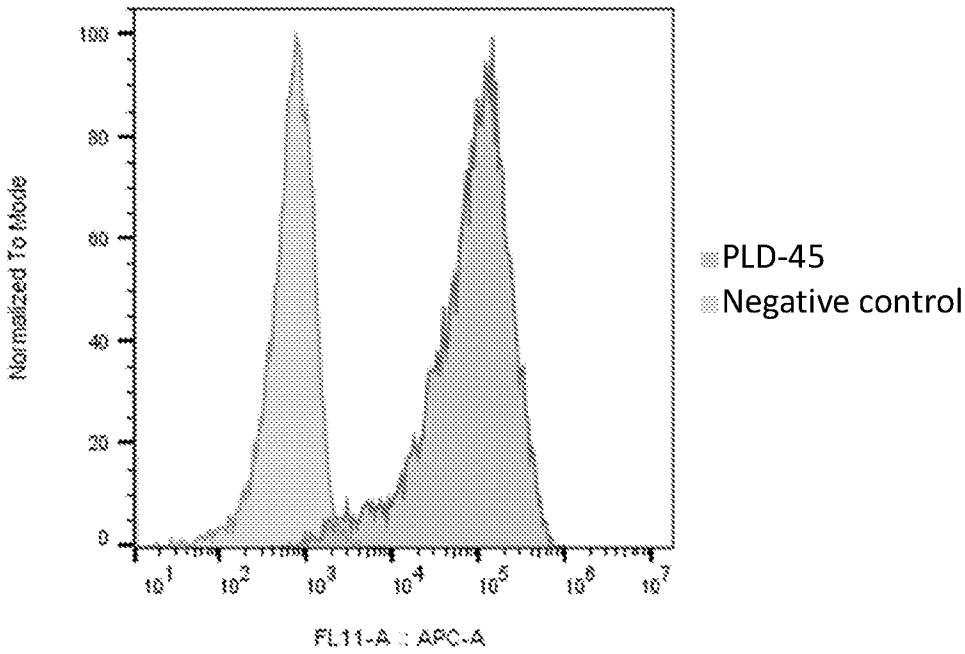

Normalized To Mode
100
80
60
40
20
0
10^1
10^2
10^3
10^4
10^5
10^6
10^7
FL11-A :: APC-A
PLD-45
Negative control

FIG. 5A


Normalized To Mode
100
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60
40
20
0
10^1
10^2
10^3
10^4
10^5
10^6
10^7
FL11-A :: APC-A
PLD-45
Negative control

FIG. 5B

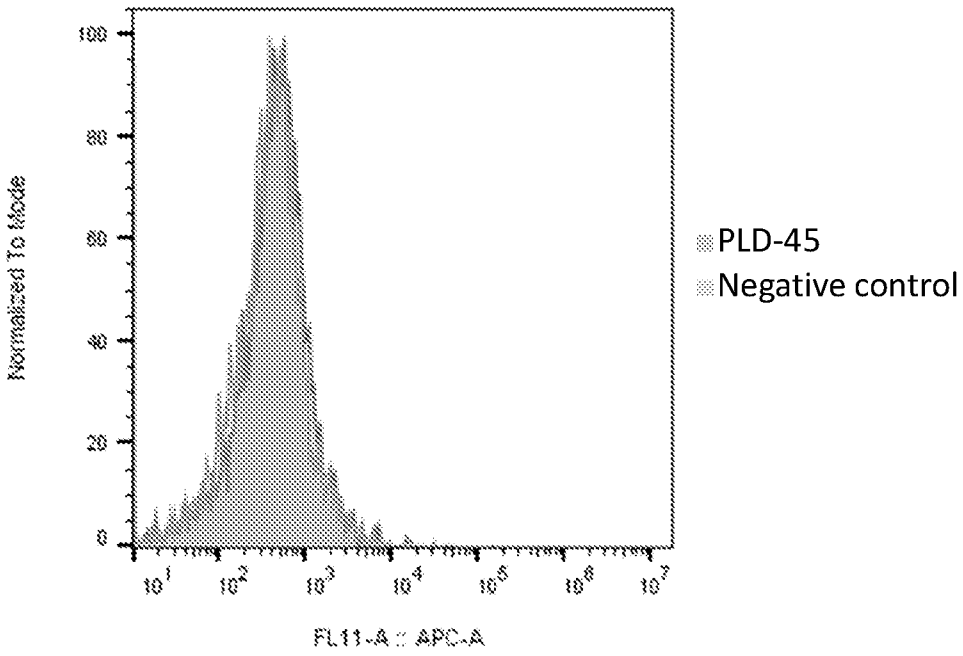

Normalized To Mode
FL11-A :: APC-A
PLD-45
Negative control

FIG. 5C

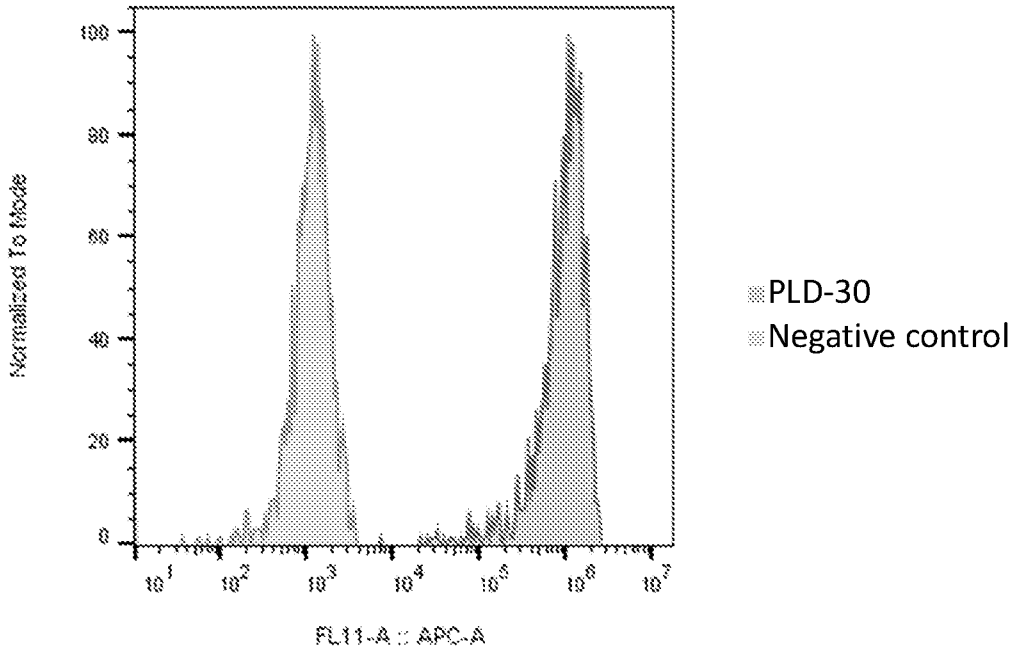
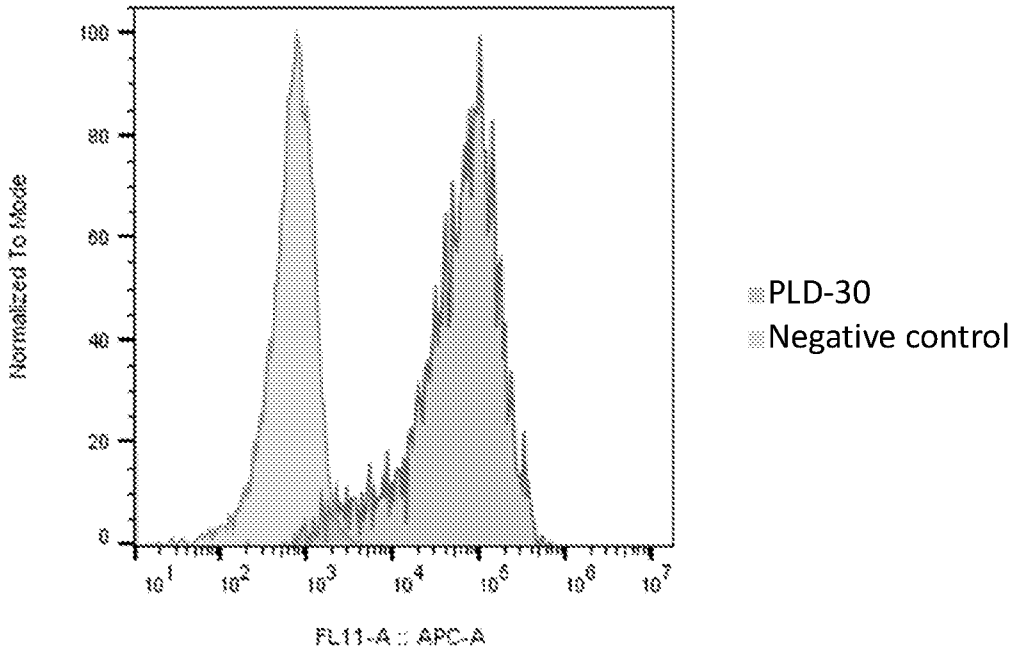

Normalized To Mode
FL11-A :: APC-A
PLD-30
Negative control

FIG. 6A


Normalized To Mode
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40
20
0
10^1
10^2
10^3
10^4
10^5
10^6
10^7
FL11-A :: APC-A
PLD-30
Negative control

FIG. 6B

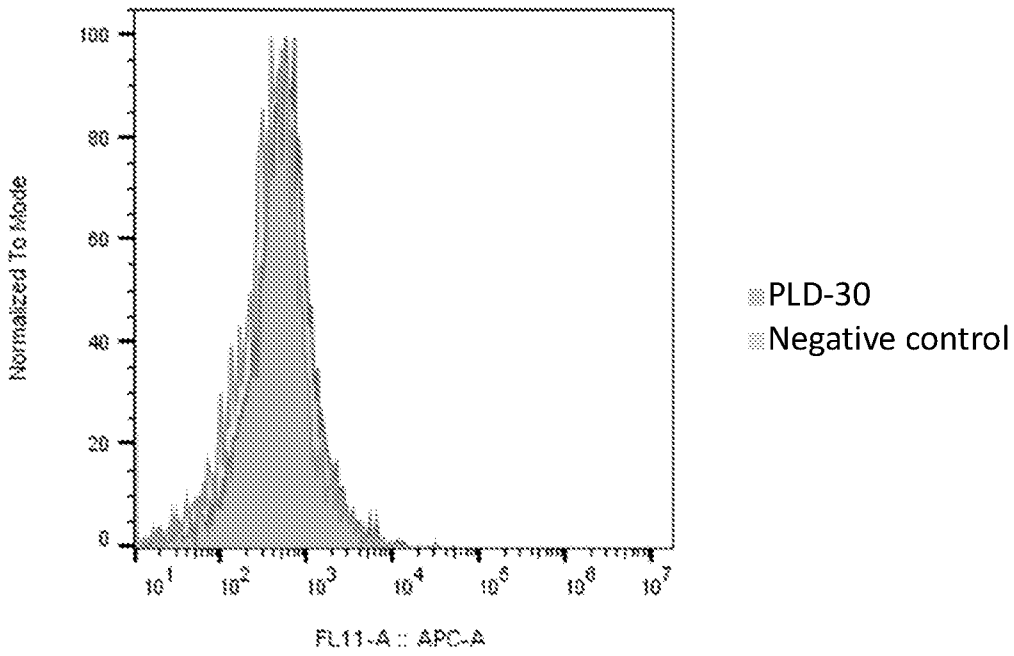
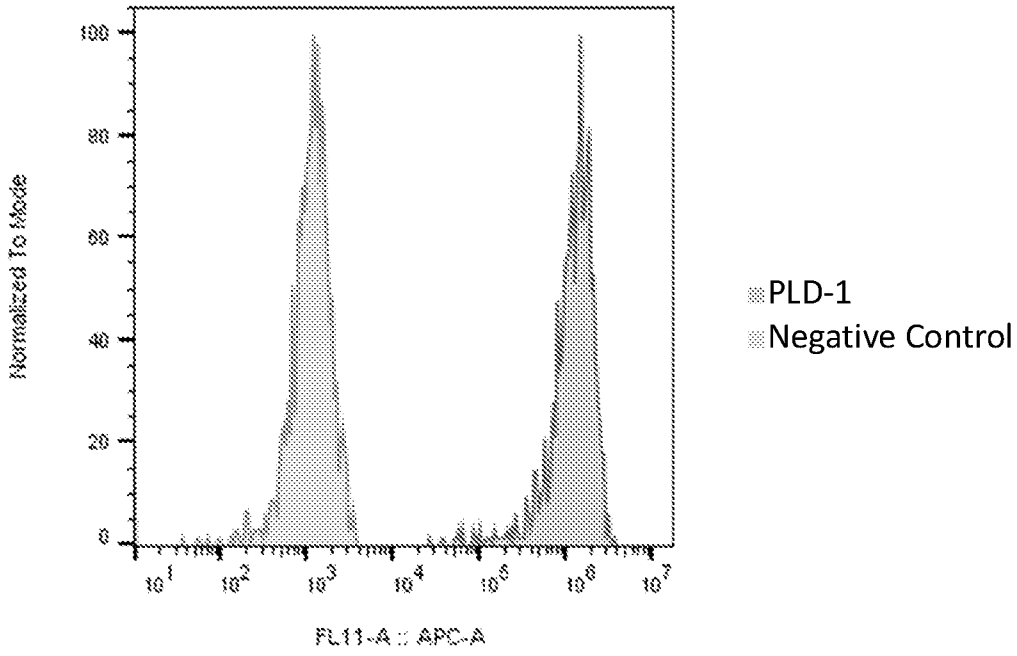

Normalized To Mode
100
80
60
40
20
0
10^1
10^2
10^3
10^4
10^5
10^6
10^7
FL11-A :: APC-A
PLD-30
Negative control

FIG. 6C


Normalized To Mode
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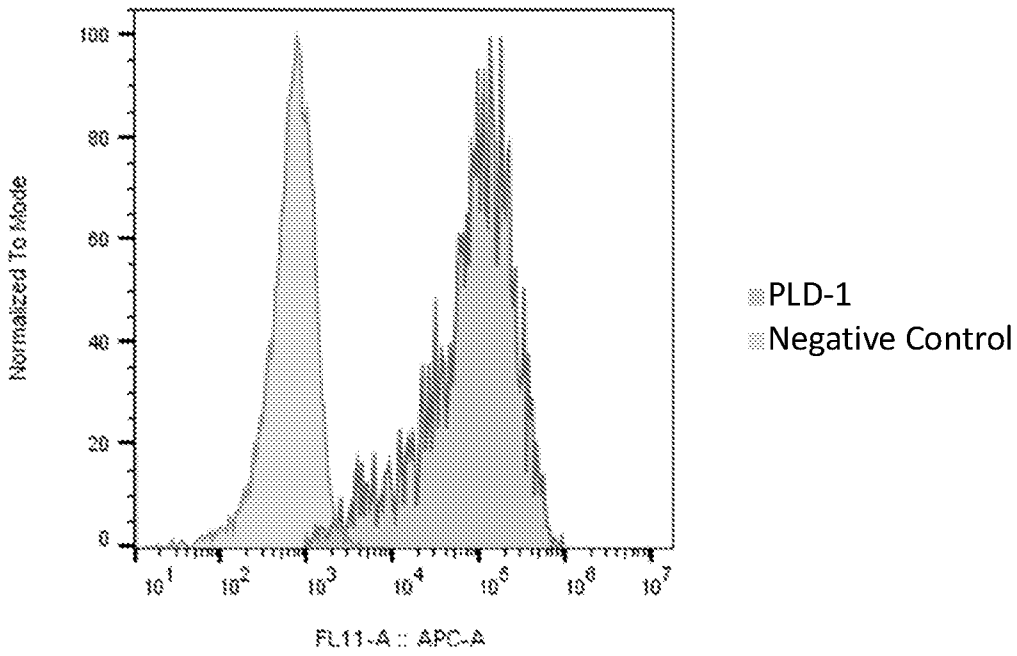
40
20
0
10^1
10^2
10^3
10^4
10^5
10^6
10^7
FL11-A :: APC-A
PLD-1
Negative Control

FIG. 7A


Normalized To Mode
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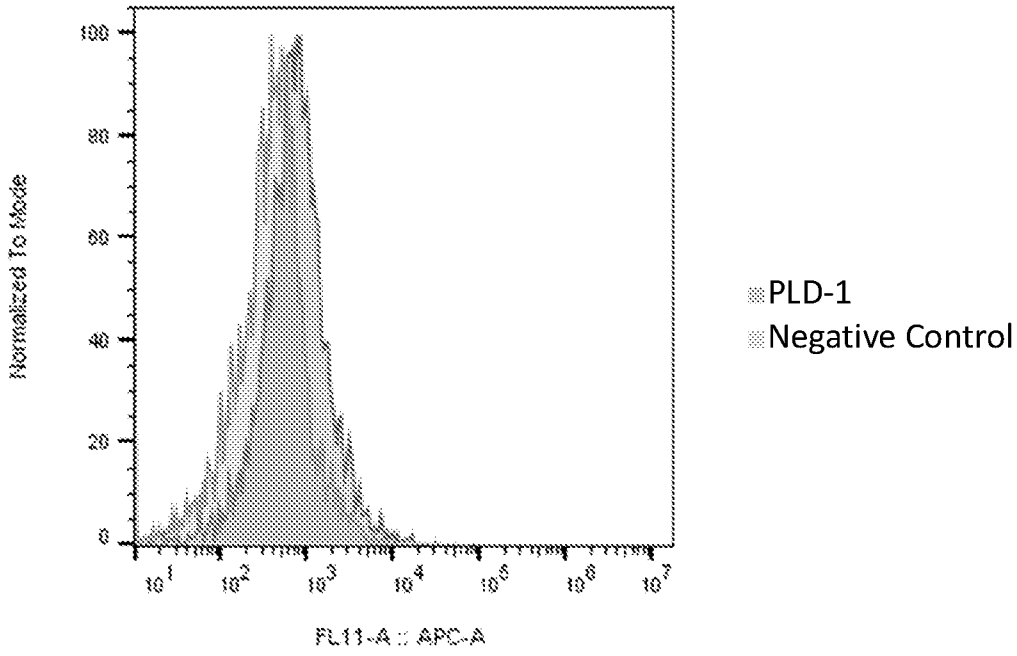
20
0
10^1
10^2
10^3
10^4
10^5
10^6
10^7
FL11-A :: APC-A
PLD-1
Negative Control

FIG. 7B


Normalized To Mode
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0
10^1
10^2
10^3
10^4
10^5
10^6
10^7
FL11-A :: APC-A
PLD-1
Negative Control

FIG. 7C

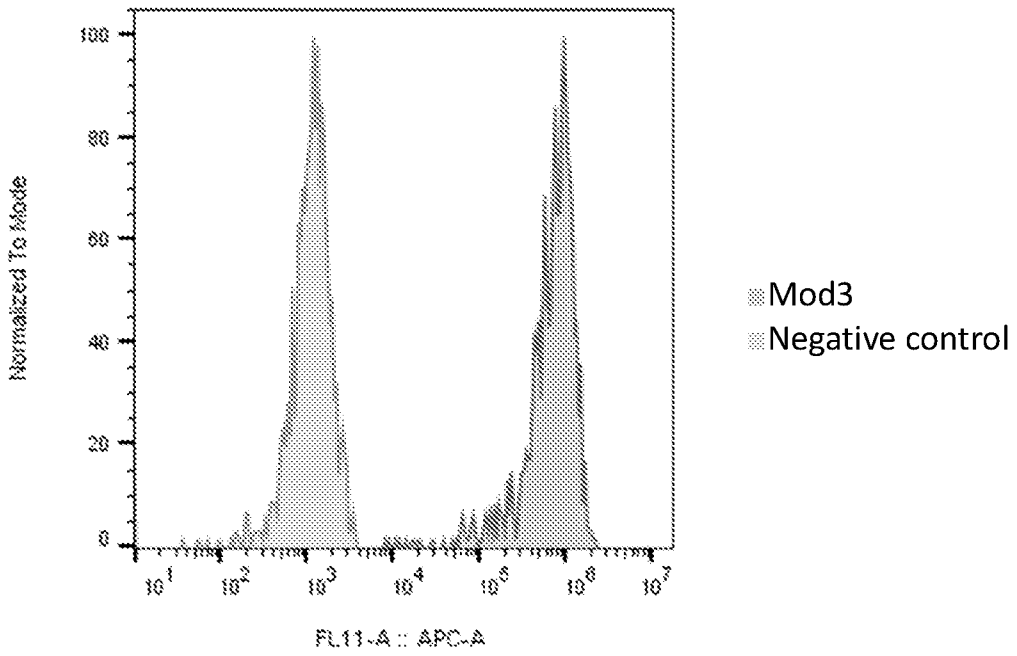

Normalized To Mode
100
80
60
40
20
0
10^1
10^2
10^3
10^4
10^5
10^6
10^7
FL11-A :: APC-A
Mod3
Negative control

FIG. 8A

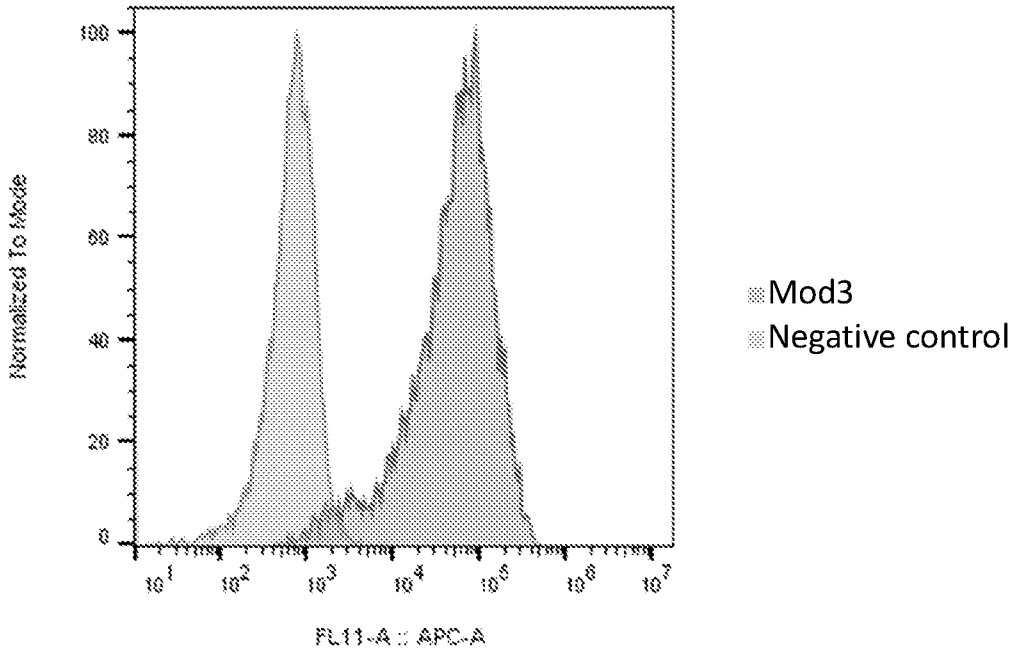
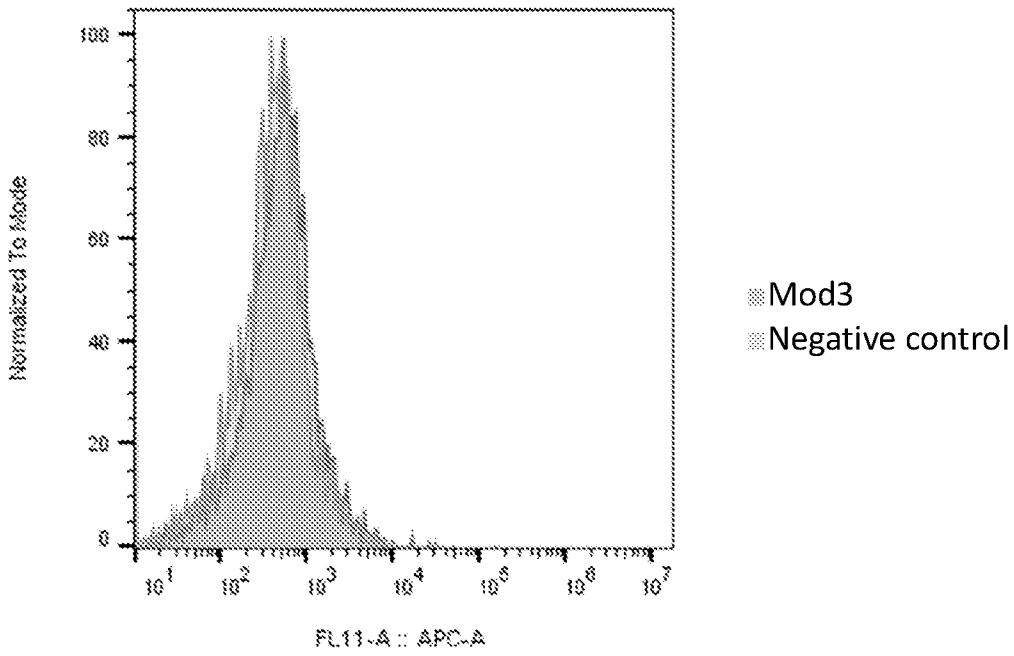

Normalized To Mode
100
80
60
40
20
0
10^1 10^2 10^3 10^4 10^5 10^6 10^7
FL11-A :: APC-A
Mod3
Negative control

FIG. 8B


Normalized To Mode
100
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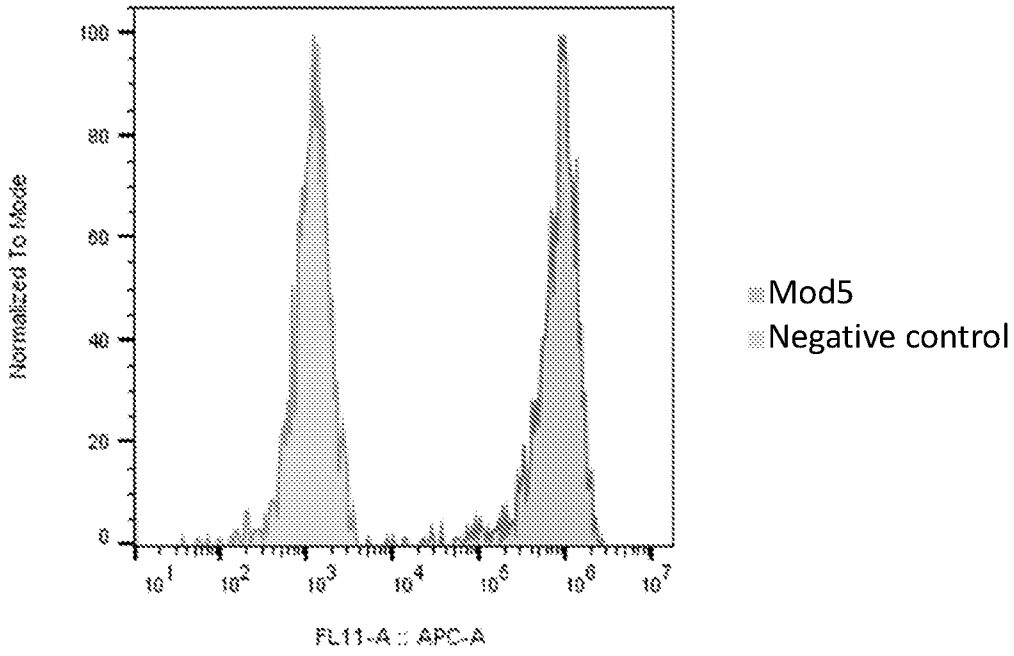
0
10^1 10^2 10^3 10^4 10^5 10^6 10^7
FL11-A :: APC-A
Mod3
Negative control

FIG. 8C


Normalized To Mode
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10^1
10^2
10^3
10^4
10^5
10^6
10^7
FL11-A :: APC-A
Mod5
Negative control

FIG. 9A

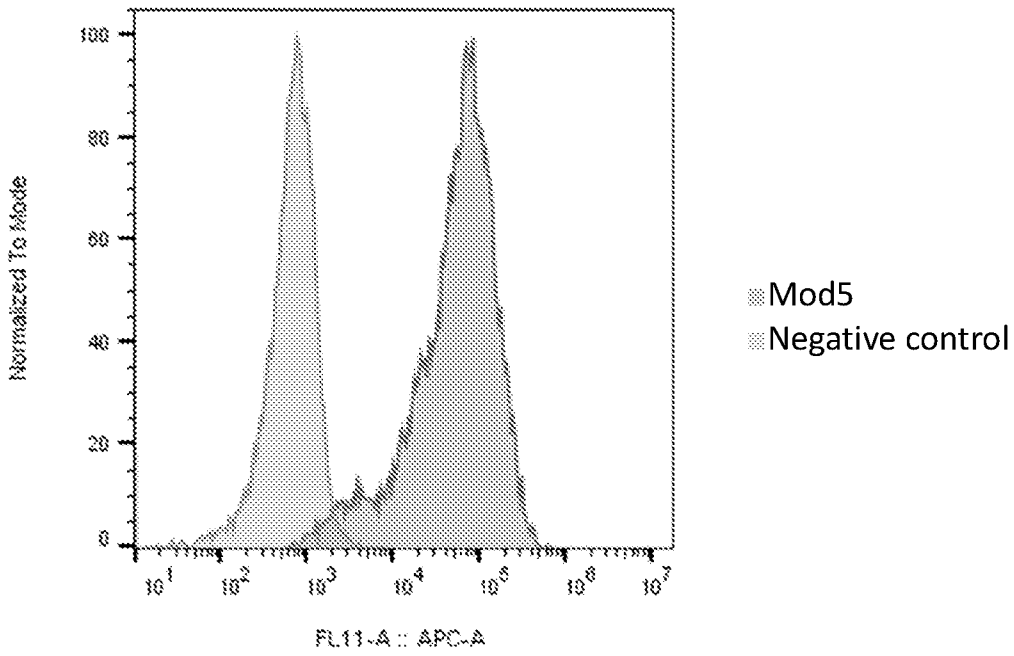
Normalized To Mode
100
80
60
40
20
0
10^1
10^2
10^3
10^4
10^5
10^6
10^7
FL11-A :: APC-A
Mod5
Negative control

FIG. 9B

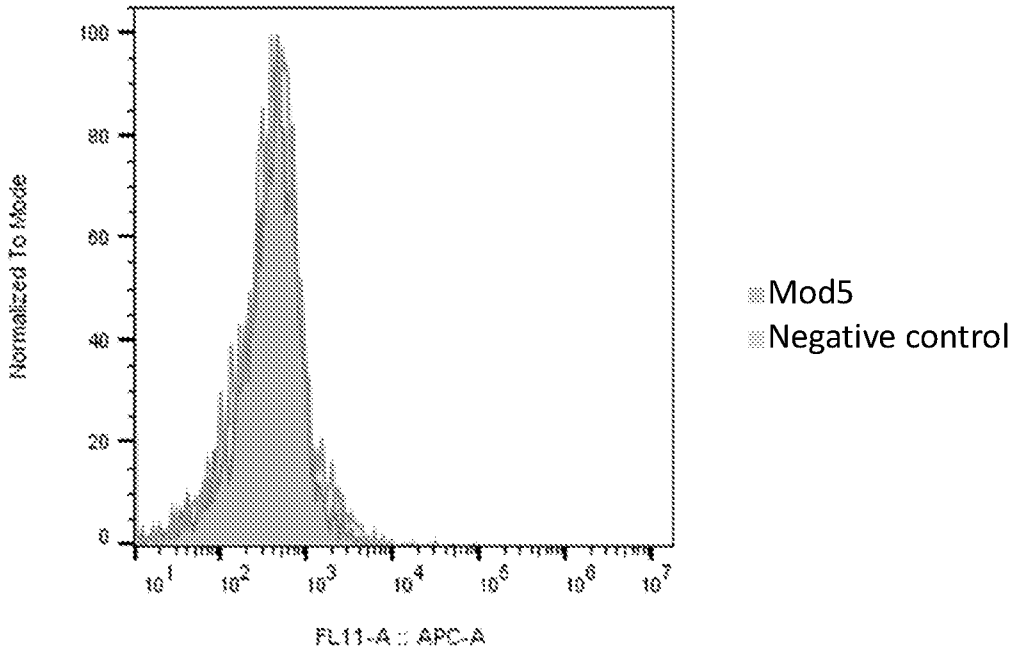

FIG. 9C

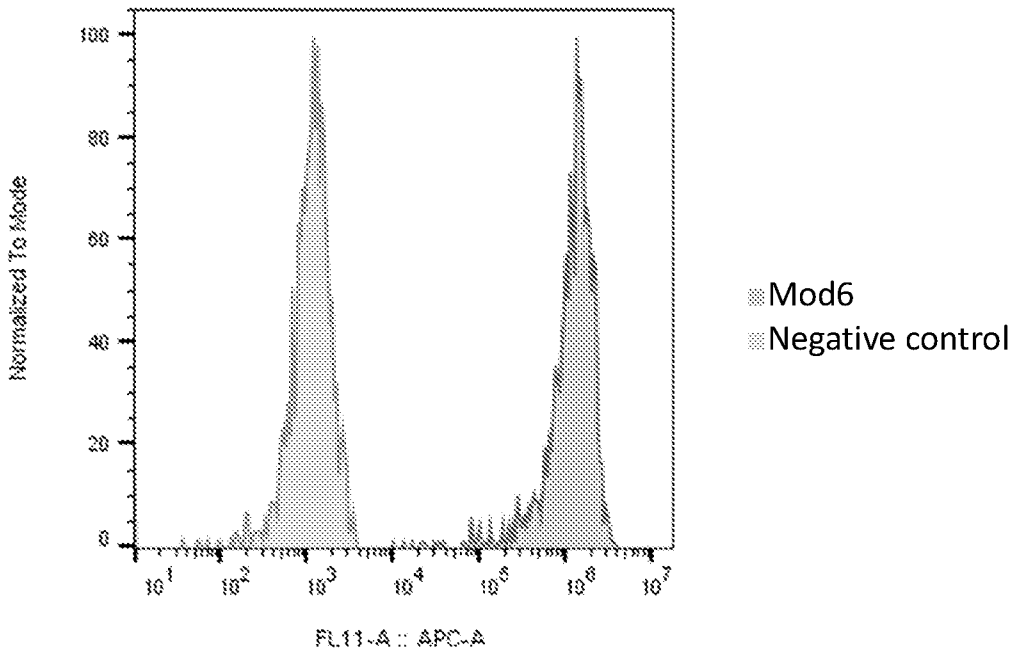

FIG. 10A

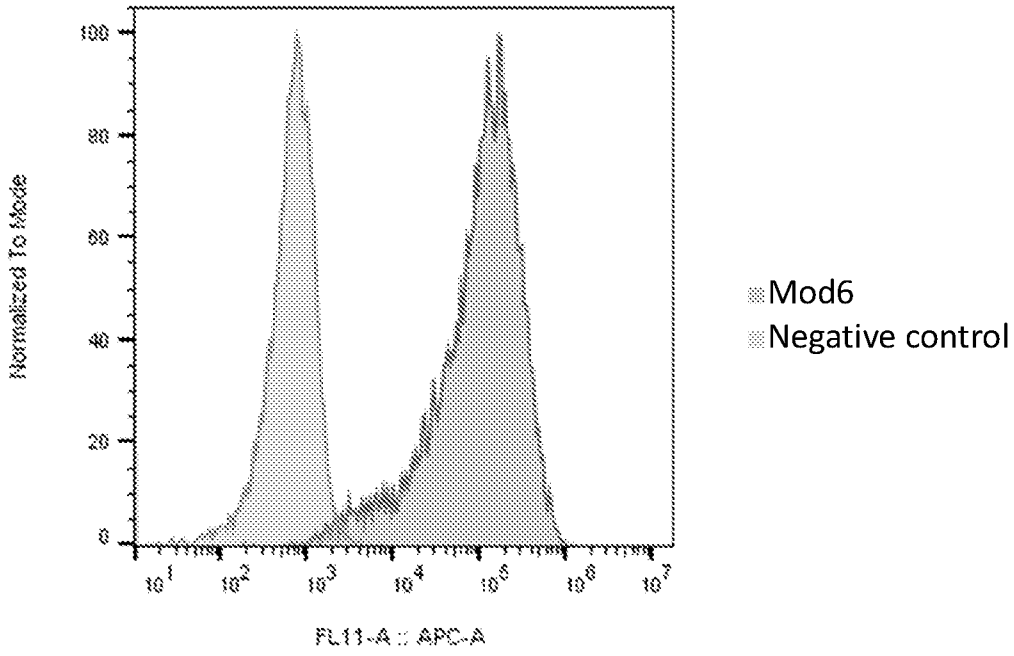

FIG. 10B

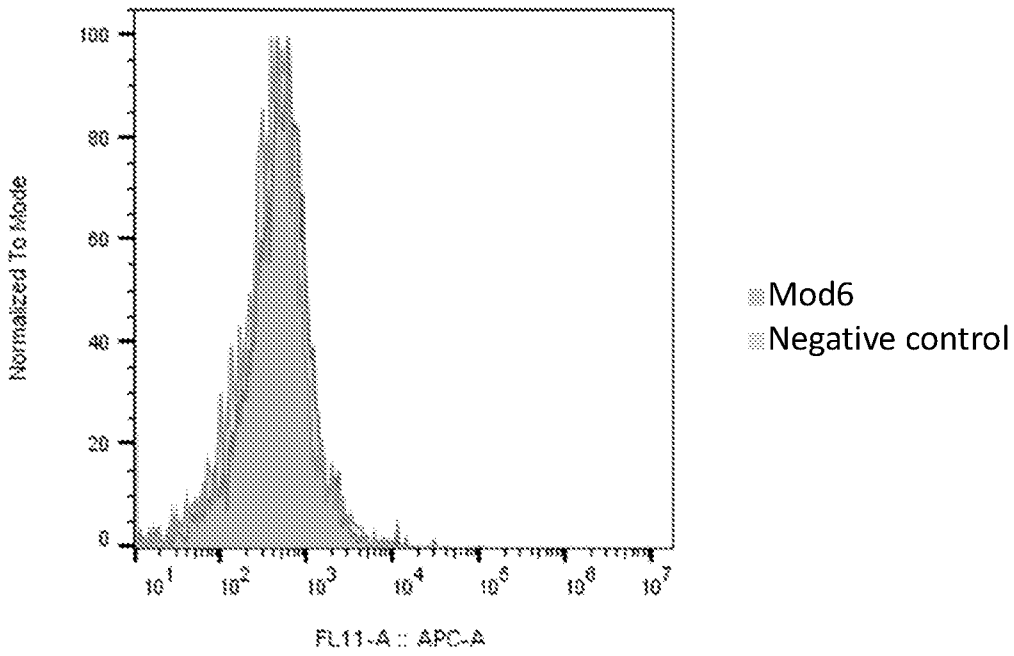

FIG. 10C

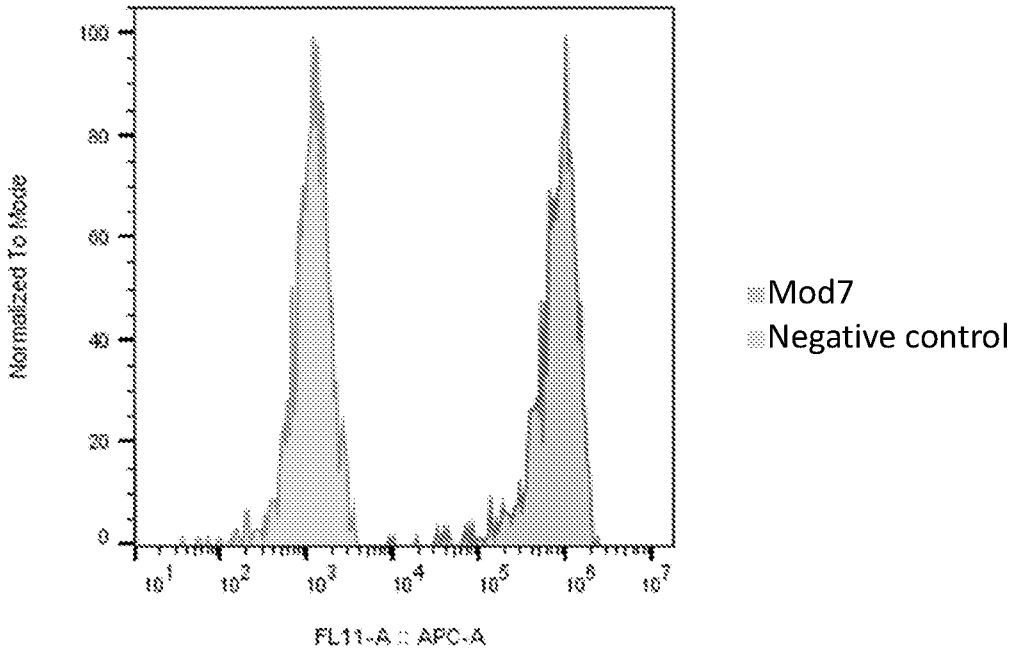

FIG. 11A

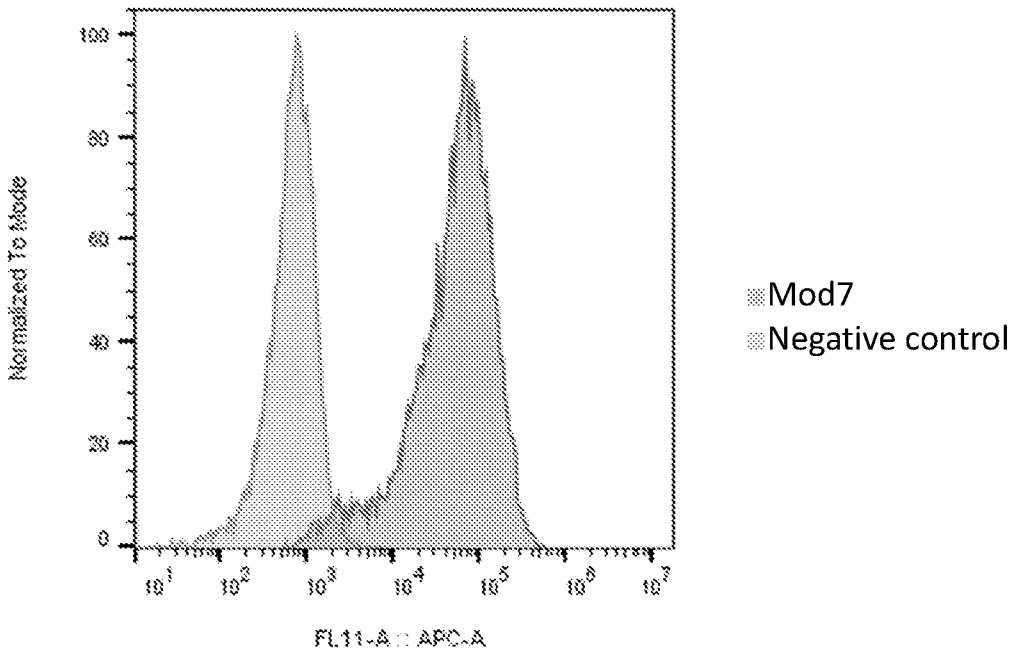

FIG. 11B

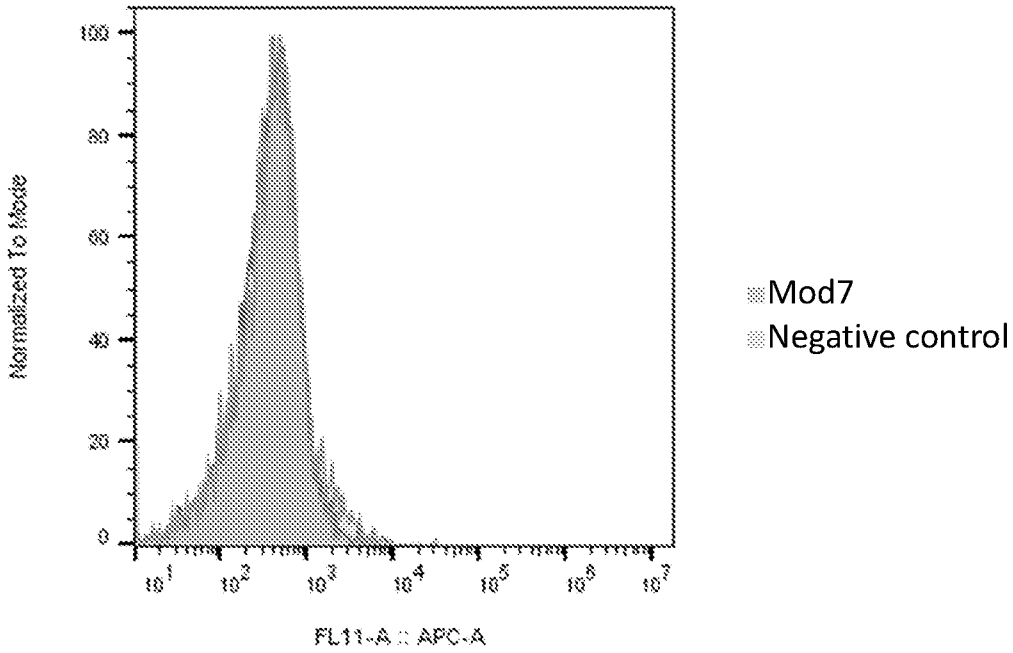
Normalized To Mode
100
80
60
40
20
0
10^1
10^2
10^3
10^4
10^5
10^6
10^7
FL11-A :: APC-A
Mod7
Negative control

FIG. 11C

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2024/055561

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07K7/08 A61K38/00 G01N33/68 A61P35/00
ADD.

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)
C07K A61K G01N A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZHU DONGLING ET AL: "Novel Glypican-3-Binding Peptide for in Vivo Hepatocellular Carcinoma Fluorescent Imaging", BIOCONJUGATE CHEMISTRY, vol. 27, no. 3, 16 March 2016 (2016-03-16) , pages 831-839, XP093201536, US ISSN: 1043-1802, DOI: 10.1021/acs.bioconjchem.6b00030 the whole document table 1 ----- -/--	1-3, 66-112

[X] Further documents are listed in the continuation of Box C.

[X] 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

"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
4 September 2024	05/11/2024

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Cervigni, S

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2024/055561

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FENG SHUO ET AL: "Multi-Modal Imaging Probe for Glypican-3 Overexpressed in Orthotopic Hepatocellular Carcinoma", JOURNAL OF MEDICINAL CHEMISTRY, vol. 64, no. 21, 11 November 2021 (2021-11-11), pages 15639-15650, XP093201539, US ISSN: 0022-2623, DOI: 10.1021/acs.jmedchem.1c00697 the whole document figure 1	1-3, 66-112
X	ZHANG QI ET AL: "An innovative peptide with high affinity to GPC3 for hepatocellular carcinoma diagnosis", BIOMATERIALS SCIENCE, vol. 7, no. 1, 25 October 2018 (2018-10-25), pages 159-167, XP093201545, GB ISSN: 2047-4830, DOI: 10.1039/C8BM01016A abstract	1-3, 66-112
X	LEE Y L ET AL: "Targeting of hepatocellular carcinoma with glypican-3-targeting peptide ligand", JOURNAL OF PEPTIDE SIENCE, JOHN WILEY & SONS, INC, HOBOKEN, USA, vol. 17, no. 11, 1 November 2011 (2011-11-01), pages 763-769, XP002708121, ISSN: 1075-2617, DOI: 10.1002/PSC.1400 [retrieved on 2011-10-04] the whole document table 1	1-3, 66-112
A	Andrew D. Foster1*,: "Methods for the Creation of Cyclic Peptide Libraries for Use in Lead Discovery", Journal of Biomolecular Screening Society for Laboratory Automation and Screening, 2015, pages 563-576, XP055409603, DOI: 10.1177/1087057114566803 Retrieved from the Internet: URL:http://journals.sagepub.com/doi/pdf/10.1177/1087057114566803 [retrieved on 2017-09-25] the whole document	1-3, 66-112
X	WO 2016/100285 A1 (BRISTOL MYERS SQUIBB CO [US]) 23 June 2016 (2016-06-23) the whole document claims	1-3, 66-112

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2024/055561

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. [X] forming part of the international application as filed.

   b. [ ] furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)).

      [ ] accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.

2. [ ] With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2024/055561

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.:
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:

see additional sheet

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 an 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.:
1-3(completely); 66-112(partially)

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-3(completely); 66-112(partially)

   A peptide that has avidity for GPC3 as characterised in independent claim 1. Composition and conjugates comprising it. Methods, kits and uses related thereto.

   ---

2. claims: 4-25(completely); 66-112(partially)

   A peptide that has avidity for GPC3 as characterised in independent claim 4. Composition and conjugates comprising it. Methods, kits and uses related thereto.

   ---

3. claims: 26-65(completely); 66-112(partially)

   A peptide that has avidity for GPC3 as characterised in independent claim 26. Composition and conjugates comprising it. Methods, kits and uses related thereto.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2024/055561

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2016100285 A1	23-06-2016	AR 103093 A1	12-04-2017
		AU 2015362703 A1	03-08-2017
		BR 112017012679 A2	06-03-2018
		CA 2971189 A1	23-06-2016
		CN 107108697 A	29-08-2017
		EA 201791231 A1	31-01-2018
		EP 3233888 A1	25-10-2017
		ES 2940632 T3	10-05-2023
		JP 6625129 B2	25-12-2019
		JP 2018504379 A	15-02-2018
		KR 20170087518 A	28-07-2017
		SG 11201704823T A	28-07-2017
		TW 201629086 A	16-08-2016
		US 2016175386 A1	23-06-2016
		WO 2016100285 A1	23-06-2016