

LONG-ACTING DUAL GIP/GLP-1 PEPTIDE CONJUGATES AND METHODS OF USE

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application Serial No. 63/208,952 filed June 9, 2021, which is incorporated by reference herein in its entirety.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on June 2, 2022, is named 36271-714_601_SL.txt and is 46,765 bytes in size.

BACKGROUND OF THE INVENTION

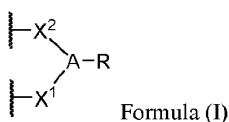
[0003] The development of therapeutic agents is often hampered by short half-lives. The biological half-life of an agent is the time it takes for the agent to lose half of its pharmacologic, physiologic, or radiologic activity. As a result, patients are often administered higher dosages of a therapeutic agent more frequently, which can lead to reduced compliance, higher costs and greater risk of side effects. Accordingly, there is a need for generation of therapeutic agents with extended half-lives.

SUMMARY OF THE INVENTION

[0004] Disclosed herein is a peptide conjugate comprising:

- a) a peptide and
- b) a staple attached to the peptide at a first amino acid and a second amino acid;

wherein the staple is of Formula (I):



wherein

A is -N-;

X¹ and X² are a bond, -C(=O)-, -alkylene-C(=O)-, -C(=O)-alkylene-, -alkylene-C(=O)NR³-, -alkylene-NR³C(=O)-, -C(=O)NR³-alkylene-, -NR³C(=O)-alkylene-, -alkylene-C(=O)NR³-alkylene-, or -alkylene-NR³C(=O)-alkylene-;

wherein X¹ is attached to the first amino acid of the peptide, X² is attached to the second amino acid of the peptide, and X¹ and X² are identical;

R is hydrogen or -(L)_s-Y;

each L is independently -(CR¹R²)_n-, -alkylene-O-, -O-alkylene-, -C(=O)-alkylene-, -alkylene-C(=O)-, -NR³-alkylene-, -alkylene-NR³-, -S-alkylene-, -alkylene-S-, -S(=O)-alkylene-, -alkylene-S(=O)-, -S(=O)₂-alkylene-, -alkylene-S(=O)₂-, -C(=O)-, -C(=O)NR³-, -NR³C(=O)-, -NR³C(=O)NR³-, -NR³C(=O)NR³-alkylene-, -NR³C(=O)-alkylene-NR³-, -alkylene-C(=O)NR³-, -C(=O)NR³-alkylene-, -alkylene-NR³C(=O)-, or -NR³C(=O)-alkylene-;

v is 2-20;

each R^1 or R^2 is independently hydrogen, halogen, -CN, -OR^a, -SR^a, -S(=O)R^b, -NO₂, -NR^cR^d, -S(=O)₂R^d, -NR^aS(=O)₂R^d, -S(=O)₂NR^cR^d, -C(=O)R^b, -OC(=O)R^b, -CO₂R^a, -OCO₂R^a, -C(=O)NR^cR^d, -OC(=O)NR^cR^d, -NR^aC(=O)NR^cR^d, -NR^aC(=O)R^b, -NR^aC(=O)OR^a, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, C₃-C₈ cycloalkyl, C₂-C₈ heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, -OR^a, or -NR^cR^d; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -OR^a, or -NR^cR^d;

or R^1 and R^2 are taken together to form a C₁-C₆ cycloalkyl or C₁-C₆ heterocycloalkyl;

each R^3 is independently hydrogen, -S(=O)R^b, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -C(=O)R^b, -CO₂R^a, -C(=O)NR^cR^d, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, C₃-C₈ cycloalkyl, C₂-C₈ heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, -OR^a, or -NR^cR^d; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -OR^a, or -NR^cR^d;

Y is hydrogen, C₁-C₆ alkyl, -CO₂H, -CO₂(C₁-C₆ alkyl), -CO₂NH₂, -CO₂N(alkyl)₂, or -CO₂NH(alkyl);

s is 0-20;

R^a is hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, C₃-C₈ cycloalkyl, C₂-C₈ heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, -OH, -OMe, or -NH₂; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -OH, -OMe, or -NH₂;

R^b is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, C₃-C₈ cycloalkyl, C₂-C₈ heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, -OH, -OMe, or -NH₂; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -OH, -OMe, or -NH₂; and

each R^c and R^d is independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, C₃-C₈ cycloalkyl, C₂-C₈ heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, -OH, -OMe, or -NH₂; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -OH, -OMe, or -NH₂;

or R^c and R^d, together with the nitrogen atom to which they are attached, form a heterocycloalkyl or heteroaryl; wherein the heterocycloalkyl and heteroaryl is optionally substituted with one, two, or three of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -OH, -OMe, or -NH₂.

[0005] Also provided herein is a peptide comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of any one of SEQ ID NOs: 1-61.

[0006] Also provided herein is a peptide comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to any one of SEQ ID NOs: 1-61. Also provided herein is a peptide comprising a sequence at least 95% identical to SEQ ID NO. 6 (YAibEGT-FTSDY-SIYLD-KX1AAAib-EFVX2W-LIAGG-PSSGA-PPPS).

[0007] Also provided herein is a peptide comprising SEQ ID NO: 6 (YAibEGT-FTSDY-SIYLD-KX1AAAib-EFVX2W-LIAGG-PSSGA-PPPS), or a peptide having 1 amino acid substitution, deletion, or insertion, or any combination thereof, as compared to SEQ ID NO: 6 (YAibEGT-FTSDY-SIYLD-KX1AAAib-EFVX2W-LIAGG-PSSGA-PPPS).

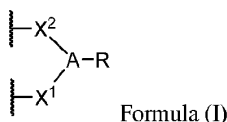
[0008] In some embodiments, the peptide comprises a sequence at least 98% identical to SEQ ID NO. 6. In some embodiments, the peptide comprises SEQ ID NO. 6. In some embodiments, the peptide comprises X1 and/or X2. In some embodiments, the peptide comprises X1, wherein X1 is a cysteine or lysine. In some embodiments, the peptide comprises X2, wherein X2 is a cysteine or lysine. In some embodiments, the peptide comprises X1 and X2, wherein X1 is cysteine and X2 is cysteine.

[0009] Also provided herein are peptide conjugates comprising any peptide herein, and a staple.

[0010] Also provided herein are peptide conjugates comprising a peptide at least 79% identical to SEQ ID NO: 6 (YAibEGT-FTSDY-SIYLD-KX1AAAib-EFVX2W-LIAGG-PSSGA-PPPS), and a staple.

[0011] In some embodiments, the peptide comprises X1 and/or X2 of SEQ ID NO: 6, and the staple is attached at the X1 and/or X2. In some embodiments, the peptide conjugate further comprising a fatty acid and/or half life extending moiety.

[0012] In some embodiments, the staple is attached to the peptide at a first amino acid and a second amino acid; wherein the staple is of Formula (I):



wherein

A is -N-;

X¹ and X² are a bond, -C(=O)-, -alkylene-C(=O)-, -C(=O)-alkylene-, -alkylene-C(=O)NR³-, -alkylene-NR³C(=O)-, -C(=O)NR³-alkylene-, -NR³C(=O)-alkylene-, -alkylene-C(=O)NR³-alkylene-, or -alkylene-NR³C(=O)-alkylene-;

wherein X¹ is attached to the first amino acid of the peptide, X² is attached to the second amino acid of the peptide, and X¹ and X² are identical;

R is hydrogen or -(L)_v-Y;

each L is independently -(CR¹R²)_v-, -alkylene-O-, -O-alkylene-, -C(=O)-alkylene-, -alkylene-C(=O)-, -NR³-alkylene-, -alkylene-NR³-, -S-alkylene-, -alkylene-S-, -S(=O)-alkylene-, -alkylene-S(=O)-, -S(=O)₂-alkylene-, -alkylene-S(=O)₂-, -C(=O)-, -C(=O)NR³-, -NR³C(=O)-, -NR³C(=O)NR³-, -NR³C(=O)NR³-alkylene-, -NR³C(=O)-alkylene-NR³-, -alkylene-C(=O)NR³-, -C(=O)NR³-alkylene-, -alkylene-NR³C(=O)-, or -NR³C(=O)-alkylene-;

v is 2-20;

each R^1 or R^2 is independently hydrogen, halogen, $-\text{CN}$, $-\text{OR}^a$, $-\text{SR}^a$, $-\text{S}(=\text{O})\text{R}^b$, $-\text{NO}_2$, $-\text{NR}^c\text{R}^d$, $-\text{S}(=\text{O})_2\text{R}^d$, $-\text{NR}^a\text{S}(=\text{O})_2\text{R}^d$, $-\text{S}(=\text{O})_2\text{NR}^c\text{R}^d$, $-\text{C}(=\text{O})\text{R}^b$, $-\text{OC}(=\text{O})\text{R}^b$, $-\text{CO}_2\text{R}^a$, $-\text{OCO}_2\text{R}^a$, $-\text{C}(=\text{O})\text{NR}^c\text{R}^d$, $-\text{OC}(=\text{O})\text{NR}^c\text{R}^d$, $-\text{NR}^a\text{C}(=\text{O})\text{NR}^c\text{R}^d$, $-\text{NR}^a\text{C}(=\text{O})\text{R}^b$, $-\text{NR}^a\text{C}(=\text{O})\text{OR}^a$, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_1\text{-C}_6$ heteroalkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_2\text{-C}_8$ heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, $-\text{OR}^a$, or $-\text{NR}^c\text{R}^d$; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $-\text{OR}^a$, or $-\text{NR}^c\text{R}^d$;

or R^1 and R^2 are taken together to form a $\text{C}_1\text{-C}_6$ cycloalkyl or $\text{C}_1\text{-C}_6$ heterocycloalkyl;

each R^3 is independently hydrogen, $-\text{S}(=\text{O})\text{R}^b$, $-\text{S}(=\text{O})_2\text{R}^a$, $-\text{S}(=\text{O})_2\text{NR}^c\text{R}^d$, $-\text{C}(=\text{O})\text{R}^b$, $-\text{CO}_2\text{R}^a$, $-\text{C}(=\text{O})\text{NR}^c\text{R}^d$, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_1\text{-C}_6$ heteroalkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_2\text{-C}_8$ heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, $-\text{OR}^a$, or $-\text{NR}^c\text{R}^d$; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $-\text{OR}^a$, or $-\text{NR}^c\text{R}^d$;

Y is hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $-\text{CO}_2\text{H}$, $-\text{CO}_2(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{CO}_2\text{NH}_2$, $-\text{CO}_2\text{N}(\text{alkyl})_2$, or $-\text{CO}_2\text{NH}(\text{alkyl})$; s is 0-20;

R^a is hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_1\text{-C}_6$ heteroalkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_2\text{-C}_8$ heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, $-\text{OH}$, $-\text{OMe}$, or $-\text{NH}_2$; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $-\text{OH}$, $-\text{OMe}$, or $-\text{NH}_2$;

R^b is $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_1\text{-C}_6$ heteroalkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_2\text{-C}_8$ heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, $-\text{OH}$, $-\text{OMe}$, or $-\text{NH}_2$; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $-\text{OH}$, $-\text{OMe}$, or $-\text{NH}_2$; and

each R^c and R^d is independently hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_1\text{-C}_6$ heteroalkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_2\text{-C}_8$ heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, $-\text{OH}$, $-\text{OMe}$, or $-\text{NH}_2$; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $-\text{OH}$, $-\text{OMe}$, or $-\text{NH}_2$;

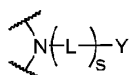
or R^c and R^d , together with the nitrogen atom to which they are attached, form a heterocycloalkyl or heteroaryl; wherein the heterocycloalkyl and heteroaryl is optionally substituted with one, two, or three of halogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $-\text{OH}$, $-\text{OMe}$, or $-\text{NH}_2$, and

wherein optionally the peptide comprises $X1$ and $X2$, and the first amino acid is $X1$ and the second amino acid is $X2$.

[0013] In some embodiments, the first amino acid and the second amino acid are independently a sulfhydryl containing amino acid. In some embodiments, the first amino acid and the second amino acid are

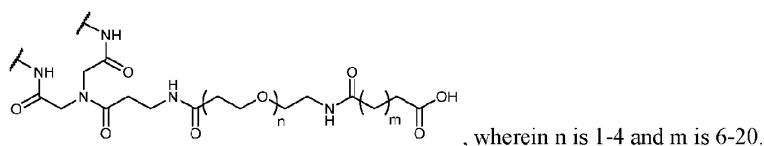
independently selected from cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, and 2-amino-6-mercaptohexanoic acid. In some embodiments, the first amino acid and second amino acids are cysteines. In some embodiments, the first amino acid and the second amino acid are independently an amine-containing amino acid. In some embodiments, the amine-containing amino acid is selected from lysine, ornithine, diaminobutyric acid, diaminopropionic acid and homolysine. In some embodiments, the first amino acid and the second amino acids are lysines. In some embodiments, the first amino acid has a position i in the peptide and the second amino acid has a position $i + n$ in the peptide, wherein n is 4-16. In some embodiments, the peptide modulates a GLP-1 receptor. In some embodiments, the peptide binds to a GLP-1 receptor. In some embodiments, the peptide modulates a GIP receptor. In some embodiments, the peptide binds to a GIP receptor. In some embodiments, the peptide is a GLP-1 receptor agonist. In some embodiments, the peptide is a GIP receptor agonist. In some embodiments, the peptide is a dual GLP-1 receptor and GIP receptor agonist. In some embodiments, the peptide is resistant to proteolysis by a gastrointestinal protease. In some embodiments, the half-life of the peptide conjugate is at least about 2-fold greater than the half-life of an unmodified form of the peptide. In some embodiments, the binding affinity of the peptide conjugate is within about 5-20% of the binding affinity of an unmodified form of the peptide.

[0014] In some embodiments, X¹ and X² are -C(=O)-. In some embodiments, X¹ and X² are -alkylene-C(=O)- or -C(=O)alkylene-. In some embodiments, X¹ and X² are -CH₂-C(=O)- or -C(=O)-CH₂-. In some embodiments, X¹ and X² are -alkylene-C(=O)NR³- or -C(=O)NR³-alkylene-. In some embodiments, X¹ and X² are -CH₂-C(=O)NR³- or -C(=O)NR³-CH₂-. In some embodiments, X¹ and X² are -alkylene-C(=O)NR³-alkylene- or -alkylene-NR³C(=O)-alkylene-. In some embodiments, X¹ and X² are -CH₂-C(=O)NR³-CH₂CH₂- or -CH₂-NR³C(=O)-CH₂CH₂-. In some embodiments, X¹ and X² are -CH₂-C(=O)NH-CH₂CH₂- or -CH₂-NHC(=O)-CH₂CH₂-. In some embodiments, >A-R has the following structure:



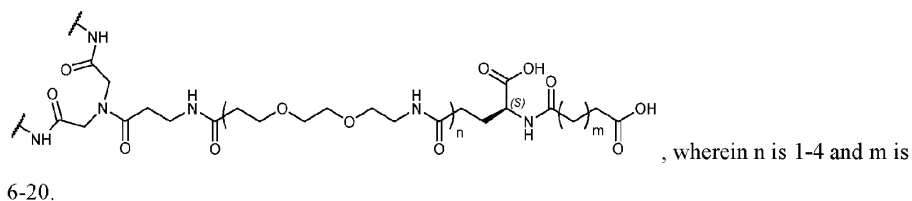
[0015] In some embodiments, s is 1-15. In some embodiments, s is 1-10. In some embodiments, s is 5-15. In some embodiments, s is 5-10. In some embodiments, Y is hydrogen or -CO₂H. In some embodiments, each L is independently -(CR¹R²)-, -alkylene-O-, -C(=O)-, -C(=O)NR³-, -NR³C(=O)-, -alkylene-C(=O)NR³-, or -alkylene-NR³C(=O)-; and v is 2-20.

[0016] In some embodiments, the peptide conjugate comprises:



In some embodiments, n is 3 and m is 15.

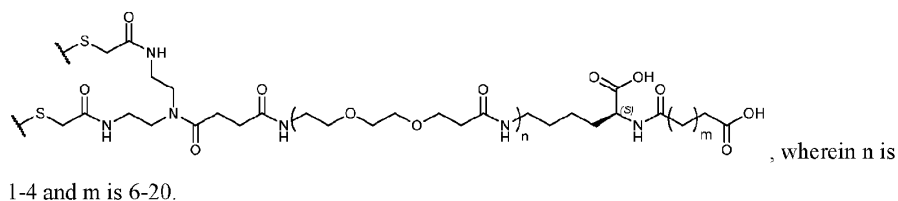
In some embodiments, the peptide conjugate comprises:



In some embodiments, n is 2 and m is 15.

In some embodiments, n is 2 and m is 17.

In some embodiments, the peptide conjugate comprises:

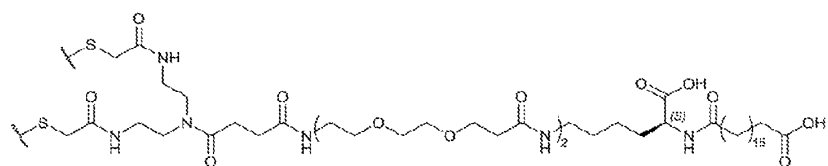


In some embodiments, n is 2 and m is 15.

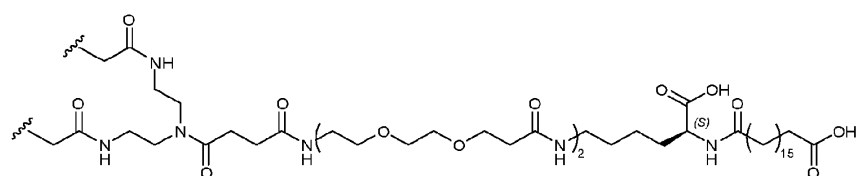
In some embodiments, n is 2 and m is 17.

In some embodiments, n is 2 and m is 13.

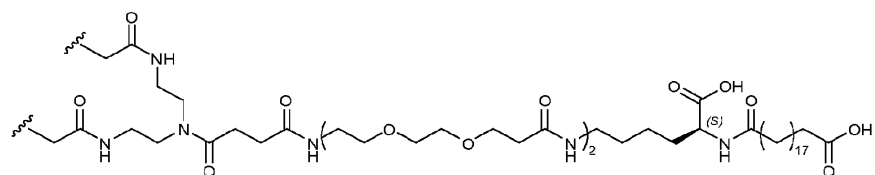
In some embodiments, the peptide conjugate comprises: L5A(S)



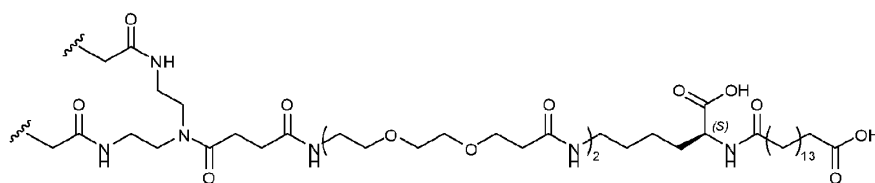
In some embodiments, the peptide conjugate comprises: L5A



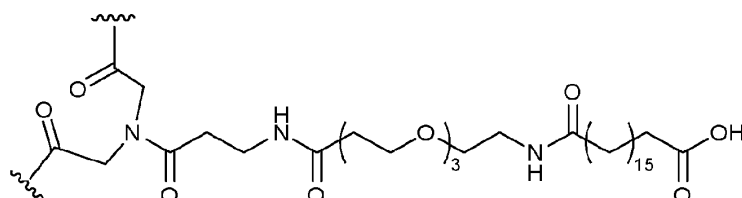
In some embodiments, the peptide conjugate comprises: C20L5A



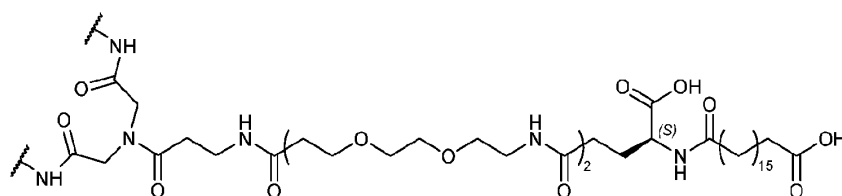
In some embodiments, the peptide conjugate comprises: C16L5A



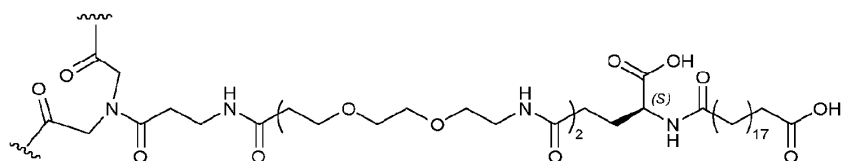
In some embodiments, the peptide conjugate comprises: K4



In some embodiments, the peptide conjugate comprises: K5



In some embodiments, the peptide conjugate comprises: C20K5



[0017] Also provided herein is a pharmaceutical composition comprising the peptide or peptide conjugate described herein and a pharmaceutically acceptable excipient.

[0018] Also provided herein is a method for treating a disease or condition in a subject in need thereof, the method comprising administering to the subject a composition comprising a therapeutically effective amount of a peptide or peptide conjugate described herein. The peptide or peptide conjugate may be administered about once every week, or about once every two weeks.

[0019] In some embodiments, the disease or condition is diabetes or obesity. In some embodiments, the diabetes is Type 1 diabetes mellitus, Type 2 diabetes mellitus, gestational diabetes, neonatal diabetes, maturity onset diabetes of the young, or latent autoimmune diabetes in adults, or any combination thereof. In some embodiments, the disease or condition is non-alcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), or cardiovascular disease. In some embodiments, the disease or condition is short bowel syndrome (SBS). In some embodiments, the disease or condition is inflammatory bowel disease (IBD), inflammatory bowel syndrome (IBS), or psoriasis. In some embodiments, the disease or condition is Crohn's disease or ulcerative colitis. In some embodiments, the disease or condition is Alzheimer's disease, Parkinson's disease or Huntington's disease.

[0020] In some embodiments, the method further comprises administering to the subject one or more additional therapeutic agents. In some embodiments, the one or more additional therapeutic agents comprises an incretin hormone or a derivative thereof. In some embodiments, the incretin hormone or derivative thereof is selected from GLP-1, exendin-4, glucagon (GCG), glucose-dependent insulinotropic polypeptide (GIP), oxyntomodulin, and combinations thereof.

[0021] In some embodiments, the peptide conjugate is administered about once every 7 days. In some embodiments, the peptide conjugate is administered about once every 14 days. In some embodiments, the peptide conjugate is administered about once a month. In some embodiments, the peptide conjugate is administered about once every two months. In some embodiments, the peptide conjugate is administered about once every three months.

BRIEF DESCRIPTION OF FIGURES

[0022] FIG. 1A and FIG. 1B display example components of a peptide, such as amino acids.

[0023] FIGS. 2A-2B are graphs showing plasma glucose excursion during oral glucose tolerance tests (OGTT) in normal mice after 2 h (FIG. 2A) and 96 h (FIG. 2B) post injection. C57B6 mice were s.c. injected with vehicle, L5A (mCMC759), K5 (mCLZ715), K4 (mCMD307), or semaglutide (at 10 nmol/kg each) 2 h prior to the glucose challenge. The bar graph shows the levels of glucose in mice obtained by measuring the area under curve [AUC] as well as the effects on fasted blood glucose. Data are means $\pm$ SE, n = 6 per group. Statistics: AUC and fasted glucose data were compared by one-way ANOVA followed by Dunnett's multiple comparison tests vs. PBS-treated mice: ****P<.0001; ***P<.001.

[0024] FIG. 3 is a graph showing the pharmacokinetic profile of peptide mCMD307 (K4) after a single s.c. administration (1 mg kg⁻¹) or i.v. administration (0.3 mg kg⁻¹) in mice. Peptide dissolved in PBS (pH 8.2) was administered via i.v. or s.c. route into CD1 mice (n = 3 per group). Blood samples were collected at the indicated time points and analyzed by in vitro GLP-1R activity assay. The assay was performed in triplicate. Pharmacokinetic analyses were determined by noncompartmental analysis with WinNonLin.

[0025] FIGS. 4A-4B show in vivo efficacy of mCMD307 (K4) in DIO mice treated for 7 days. Effects on body weight change (FIG. 4A, top), crude body weight (FIG. 4A, middle), cumulative food intake (FIG. 4A, bottom), OGTT on day 7 (FIG. 4B, top and middle), and fasted blood glucose on day 7 (FIG. 4B, bottom). C57BL/6 mice (male, 37 weeks old) were treated with PBS (s.c., twice daily), mCMD307 (K4) (s.c. once daily; 10 nmol kg⁻¹) or semaglutide (s.c. once daily; 10 nmol kg⁻¹) for 7 days. The arrows indicate the day of administration. Data are means $\pm$ SE, n = 6 per group. Statistics: AUC and fasted glucose data were compared by one-way ANOVA followed by Dunnett's multiple comparison tests vs. PBS-treated mice: ****P<.0001; ***P<.001; **P<.01.

[0026] FIGS. 5A-5E show in vivo efficacy of mCMD307 (2050-K4) in high-fat-diet-induced obesity (DIO) mice treated for 24 days. Effects on body weight and food intake change (FIG. 5A), oral glucose tolerance test at day 21, fasted blood glucose prior to the OGTT (day 20) and fed glucose after the OGTT (day 21) (FIG. 5B). Upon termination at day 24, measurement of liver enzyme ALT, AST, ALP levels and plasma cholesterol and triglyceride levels (FIG. 5C) and liver weight, liver triglyceride, liver/body weight ratio and fat weight (FIG. 5D); and steatosis score and liver lipid accumulation measurement by Oil-red

staining (FIG. 5E). C57BL/6 mice (male, 37 weeks old) were treated with PBS (s.c., twice daily), mCMD307 (K4) (s.c. once daily; 10 nmol kg⁻¹) or semaglutide (s.c. once daily; 10 nmol kg⁻¹) for 24 days. Data are means $\pm$ SE, n = 6 per group. Statistics: AUC and fasted glucose data were compared by one-way ANOVA followed by Dunnett's multiple comparison tests vs. PBS-treated mice: ****P<.0001; ***P<.001; **P<.01.

[0027] FIG. 6A depicts the results of a GLP1 receptor activation reporter assay comparing the activity of semaglutide with the activities of various peptide conjugates.

[0028] FIG. 6B depicts the results of a GIP receptor activation reporter assay comparing the activity of semaglutide with the activities of various peptide conjugates.

[0029] FIG. 7A depicts the results of a GLP1 receptor activation reporter assay comparing the activity of semaglutide with the activities of various peptide conjugates.

[0030] FIG. 7B depicts the results of a GIP receptor activation reporter assay comparing the activity of semaglutide with the activities of various peptide conjugates.

[0031] FIG. 8A depicts the results of a GLP1 receptor activation reporter assay comparing the activity of semaglutide with the activities of various peptide conjugates.

[0032] FIG. 8B depicts the results of a GIP receptor activation reporter assay comparing the activity of semaglutide with the activities of various peptide conjugates.

[0033] FIG. 9A depicts the results of a GIP1 receptor activation reporter assay comparing the activity of semaglutide with the activities of various peptide conjugates.

[0034] FIG. 9B depicts the results of a GIP receptor activation reporter assay comparing the activity of semaglutide with the activities of various peptide conjugates.

[0035] FIG. 10 depicts the results of a GIP1 receptor activation reporter assay comparing the activity of semaglutide with the activities of various peptide conjugates.

[0036] FIGS. 11A-11B show the plasma concentration in mice versus time for peptide mCMV266 (FIG. 11A) and mCMV268 (FIG. 11B) administered via IV and SC.

[0037] FIG. 12 demonstrate extended PD effects of mCMV266 and mCMV268 peptide conjugates on fed glucose in C57B6 mice after a single SC dose of mCMV266 (3, 10 and 30 nmol/kg) and mCMV268(3, 10 and 30 nmol/kg).

[0038] FIG. 13 demonstrate the effects of mCMV266 and mCMV268 peptide conjugates on body weight and food consumption in wild-type C57B6 mice after a single SC dose of mCMV266 (3, 10 and 30 nmol/kg) and mCMV268(3, 10 and 30 nmol/kg).

[0039] FIG. 14 shows the plasma concentration in mice versus time for peptide mCMZ370 and mCMZ371 administered via IV and SC.

[0040] FIG. 15 demonstrates extended PD effects of mCMZ371 and mCMV268 peptide conjugates on fed glucose in C57B6 mice after a single SC dose of mCMZ371 (1, 3, 10 and 30 nmol/kg) and mCMV268(3nmol/kg). Results are compared to those testing Tirzepatide (kCMC760) after a single SC dose (10 nmol/kg). Effects on body weight in the same animals was also graphed at each time point.

[0041] FIG. 16 shows plasma glucose excursion during oral glucose tolerance tests (OGTT) in normal mice after 12 h post injection. C57B6 mice were single-dose SC injected with vehicle, Tirzepatide

(kCMC760) (10 nmol/kg), kCLD385 (10nmol/kg), or mCMZ371 (1, 3, 10 or 30 nmol/kg) 12 hours prior to glucose challenge. **FIG. 16** also shows a graph of AUC calculations from this experiment.

[0042] **FIG. 17** shows the plasma concentration in cynomolgus monkeys versus time for peptide mCMZ371 (CTR371) and mCMV268 administered via IV and SC.

[0043] **FIG. 18** shows the plasma concentration in dogs versus time for peptide mCMZ371 (CTR371) and mCMV268. CTR371 was administered via IV and SC. mCMV268 was administered via IV and PO.

DETAILED DESCRIPTION OF THE INVENTION

[0044] G protein-coupled receptors (GPCRs) are membrane-bound proteins that have seven transmembrane domains linked by three intracellular and three extracellular loops. Their ligand-binding sites are highly specialized so that each receptor responds only to a limited variety of chemicals which bind with high affinity. Examples of GPCR ligands are peptides, proteins, lipid-derived molecules, small organic compounds and ions. GPCRs have been of long-standing interest as pharmaceutical drug targets, as they are involved in a plethora of pathophysiological processes, including the regulation of neuronal excitability, metabolism, reproduction, hormonal homeostasis, and behavior. It is estimated that around 34% of all Food and Drug Administration (FDA) approved drugs target 108 members of the GPCR family. GPCRs are generally classified into multiple superfamilies. Family B GPCRs, or the so-called secretin receptor family, are a small but structurally and functionally diverse set of receptors. These proteins are vital to many physiological functions and serve as key drug targets for several human diseases such as type 2 diabetes mellitus (T2DM), migraine, osteoporosis, depression, and anxiety. Members of this family include receptors for polypeptide hormones of 27–141 residues in length. Nine of these receptors are targeted by ligands that are structurally related to one another, examples of which include glucagon-like peptides (GLP-1 and GLP-2), glucagon, glucose-dependent insulintropic polypeptide (GIP), vasoactive intestinal peptide (VIP), pituitary adenylate cyclase-activating polypeptide (PACAP) and growth hormone-releasing hormone (GHRH).

[0045] Glucagon-like peptide 1 (GLP-1) is a naturally-occurring incretin hormone released into the circulation by the L cells of the gut in response to ingested nutrients. By binding to its cognate receptor (GLP-1R) GLP-1 is able to promote insulin secretion while suppressing glucagon secretion, but only when glucose levels are raised, thus offering the potential to lower plasma glucose levels while reducing the risk of hypoglycemia. Furthermore, GLP-1 decreases the rate of gastric emptying, and reduces appetite, thus resulting in weight loss.

[0046] GLP-1 receptor agonists (GLP-1RAs) represent a unique approach to the treatment of diabetes, with benefits beyond glucose control, including favorable effects on body weight, blood pressure, cholesterol levels, and beta-cell function. Two short-acting (exenatide and liraglutide; once- or twice-daily administration) and three long-acting (albiglutide, dulaglutide, and exenatide LAR; weekly administration) GLP-1RAs are currently approved in the United States. In particular, exenatide, a GLP-1 analog originally isolated from the saliva of the Gila monster, has a half-life of 30 min after i.v. administration and a half-life of 2–3 h after s.c. administration in humans. These drugs mimic the effects of the naturally occurring incretin hormone GLP-1 by activating GLP-1 receptors in the pancreas, which leads to enhanced insulin

release and reduced glucagon release in a glucose-dependent manner—with a consequently low risk of hypoglycemia. The effects of these GLP-IRAs on GLP-1 receptors in the CNS and the gastrointestinal tract also lead to reduced appetite and delayed glucose absorption, with concomitant weight loss. Given their limited oral bioavailability, these GLP-IRAs are currently given as an s.c. injection. In some aspects, provided herein are GLP-IRAs connected to a fatty-acid derived side-chain staple to increase half-life.

[0047] Incretin-based peptides are effective therapeutics for treating type 2 diabetes mellitus (T2DM). Oxyntomodulin (OXM), a dual agonist of GLP-1R and GCGR, has shown superior weight loss and glucose lowering effects, compared to single GLP-1R agonists. To overcome the short half-life and rapid renal clearance of OXM, which limit its therapeutic potential, both lipid and PEG modified OXM analogs have been reported. However, these approaches often result in reduced potency or PEG-associated toxicity. In certain embodiments, provided herein are GLP-1R and GCGR dual agonists having increased plasma stability and higher potency in activating both GLP-1R and GCGR.

[0048] GIP is also characterized as an incretin that stimulates insulin secretion in a glucose-dependent manner. A GIP and GLP-1 receptor dual agonist has been shown to reduce fasting serum glucose compared to placebo and to reduce body weight. This dual agonist, LY3298176, is administered once-weekly subcutaneously. In certain embodiments, further provided herein are GIPR and GLP-1R dual agonists comprising a stapled feature to increase serum stability and half-life.

[0049] Provided herein are peptides and peptide conjugates comprising a therapeutic peptide stapled to a molecule, such as a half-life extending molecule.

[0050] In certain embodiments, the stapled peptides comprise incretin peptides or incretin peptide mimetics. Incretin peptides generally bind to their cognate receptors in an α -helical conformation, therefore certain embodiments herein provide for modifications that stabilize the α -helix, which in some cases may increase binding affinity to their receptors. Moreover, proteolytic stability may also be enhanced in a helical rather than an extended conformation. In some aspects, provided herein are such conjugated peptides having increased circulatory half-life and potency toward their cognate receptors.

[0051] In some aspects, described herein is a peptide engineering strategy used to generate stapled long-acting peptide analogs with comparable potency as native peptides and significantly enhanced pharmacokinetic properties.

Peptides

[0052] In one aspect, provided herein are peptides and peptide conjugates comprising a peptide that modulates the GLP-1 receptor and/or the GIP receptor. In some embodiments, the peptide modulates both the GLP-1 receptor and the GIP receptor. In some embodiments, a peptide that modulates the GLP-1 receptor is a GLP-1 receptor agonist. In some embodiments, a peptide that modulates the GIP receptor is a GIP receptor agonist.

[0053] The binding affinity of the peptide conjugate as described herein may be within about 5% of the binding affinity of an unmodified form of the peptide to a receptor (e.g., GLP-1 and/or GIP receptor). The binding affinity of the peptide conjugate as described herein may be within about 10% of the binding affinity of an unmodified form of the peptide. The binding affinity of the peptide conjugate as described

herein may be within about 15% of the binding affinity of an unmodified form of the peptide. The binding affinity of the peptide conjugate as described herein may be within about 20% of the binding affinity of an unmodified form of the peptide.

[0054] The peptide may comprise one or more sulfhydryl containing amino acid residues. The one or more sulfhydryl containing amino acid residues may be used for connecting a staple. The one or more sulfhydryl containing amino acid residues may be used for connecting a HEM (half-life extending molecule). The one or more sulfhydryl containing amino acid residues may be naturally occurring in the peptide. The one or more sulfhydryl containing amino acid residues may be inserted into the peptide. The one or more sulfhydryl containing amino acid residues may replace one or more amino acid residues in the peptide. Methods for amino acid substitution and/or insertion are known in the art.

[0055] The peptide may comprise one or more amine containing residues. Non-limiting examples of amine containing residues include lysine, ornithine, diaminobutyric acid, diaminopropionic acid and homolysine. The one or more amine containing residues may be used for connecting a staple. The one or more one or more amine containing residues may be used for connecting a HEM. The one or more one or more amine containing residues may be naturally occurring in the peptide. The one or more one or more amine containing residues may be inserted into the peptide. The one or more one or more amine containing residues may replace one or more amino acid residues in the peptide.

[0056] The peptide may comprise at least a portion of a wild-type peptide comprising one or more amino acid mutations. The one or more amino acid mutations may comprise a deletion, substitution, addition or a combination thereof. The one or more amino acid mutations may comprise adding one or more amino acid residues to a wild-type peptide. The one or more amino acid mutations may comprise deletion of one or more amino acid residues of the wild-type peptide. The one or more amino acid mutations may comprise substitution of one or more amino acid residues of the wild-type peptide. The one or more amino acid mutations may comprise substituting one or more amino acid residues of the wild-type peptide with one or more cysteine, lysine or other sulfhydryl or amine containing residues. The one or more amino acid mutations may comprise substituting one or more amino acid residues of the wild-type peptide with one or more D-amino acid residues. The one or more amino acid residues of the wild-type peptide may comprise one or more alanines, methionines, arginines, serines, threonines, and tyrosines.

[0057] The peptide may be modified with, for example, acetylation, phosphorylation, and methylation. The peptide modification may comprise a chemical modification. Peptide modifications may occur on the N-terminus of the peptide. Peptide modifications may comprise acetyling the amino group at the N-terminus of the peptide. Alternatively, or additionally, peptide modifications may occur on the C-terminus of the peptide. Peptide modifications may occur at one or more internal amino acids of the peptide. Peptide modifications may comprise replacing the carboxyl group at the C-terminus of the peptide. Peptide modifications may comprise modifying the carboxyl group at the C-terminus of the peptide. The carboxyl group at the C-terminus of the peptide may be modified to produce an amide group. The carboxyl group at the C-terminus of the peptide may be modified to produce an amine group.

[0058] In some embodiments, the peptide may be a modified peptide with a D-serine in place of L-serine. In some embodiments, the peptide may be a modified with an aminoisobutyric acid [Aib] in place of L-

serine. In some embodiments, the peptide may be a modified peptide with a neuroleucine [Nle] in place of leucine (Leu). In some embodiments, the peptide comprises aMeF (alpha-methyl Phe). In some embodiments, the peptide comprises 4Pal (4-pyridyl-Ala). In some embodiments, the peptide comprises aMeL (alpha-methyl Leu). In some embodiments, the peptide comprises Orn (ornithine). In some embodiments, the peptide comprises aMeY (alpha-methyl tyrosine).

[0059] In some embodiments, the peptide comprises one or more of the following amino acids: N-methyl-Phe, D-Phe, alpha-methyl-Phe, Phe (2-F), Phe (3-F), Phe (4-F), 4-Pyridyl-Ala, Aib, N-methyl-Leu, D-Leu, alpha-methyl-Leu, beta-3-Leu, beta-3-Phe, beta-3-Asn, beta-3-Trp, D-Asn, D-Glu, D-Gln, D-Asp. In some embodiments, the peptide comprises an amino acid of **FIGS. 1A-1B**.

[0060] In some embodiments, the peptide comprises a sequence of any one of SEQ ID NOs: 1-61. In some cases, the peptide comprises a sequence at least about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to any one of SEQ ID NOs: 1-61. In some cases, the peptide comprises a sequence at least about 90% identical to any one of SEQ ID NOs: 1-61. In some cases, the peptide comprises a sequence at least about 95% identical to any one of SEQ ID NOs: 1-61. In some cases, the peptide comprises a sequence at least about 99% identical to any one of SEQ ID NOs: 1-61. In some cases, the peptide comprises an amino acid sequence having up to about 1, 2, 3, 4, or 5 amino acid insertions, deletions, modifications, or substitutions as compared to any one of SEQ ID NOS: 1-61.

[0061] Non-limiting examples of peptides are shown in **Table 1**. X refers to any natural or unnatural amino acid. Lower case letters refer to D-amino acids (e.g., "s" is D-serine). In some cases, an X comprises a sulfhydryl containing amino acid. In some cases, an X comprises an amine-containing amino acid. In some cases, an X is Lys. In some cases, an X is a Cys. In some cases, a first X of the peptide is an amine-containing amino acid and a second X of the peptide is a sulfhydryl containing amino acid. In some cases, a second X of the peptide is an amine-containing amino acid and a first X of the peptide is a sulfhydryl containing amino acid. In some embodiments, a peptide is resistant to a GI protease. In some cases, a GI protease resistant peptide comprises SEQ ID NO: 7. In some cases, a GI protease resistant peptide comprises SEQ ID NO: 9. In some cases, a GI protease resistant peptide comprises SEQ ID NO: 6. In some embodiments, the peptide comprises SEQ ID NO: 6, and the first X is a cysteine and the second X is a cysteine.

Table 1. Peptide SEQ ID

SEQ ID NO.	Sequence
1	YAibEGT-FTSDY-SIYXD-KQAAAib-XFVNW-LLAGG-PSSGA-PPPS-NH2
2	YAibEGT-FHSDY-DIYXD-KQAAAib-XFVQW-LLAGG-PSSGA-PPPS-NH2
3	YAibEGT-FHSDY-DIYXD-KQAANle-XFVAW-LLAGG-PSSGA-PPPS-NH2
4	YAibEGT-FTsDY-sIYXD-KQAANle-XFVAW-LLAGG-PSSGA-PPPS-NH2
5	YAibEGT-FTSDY-SIYXD-KQAAAib-XFVNW-LIAGG-PSSGA-PPPS-NH2
6	YAibEGT-FTSDY-SIYLD-KXAAAib-EFVXW-LIAGG-PSSGA-PPPS-NH2

SEQ ID NO.	Sequence
30	YAibEGT-FTSDY-SIYXD-KXAAAib-XFVXW-LIAGG-PSSGA-PPPS-NH2
7	YAibEGT-aa6TSDaa10-SIaa13LD-aa16XAAAib-EFVXaa25-LIaa33GG-PSSGA-PPPS-NH2 aa6: alpha-methyl Phe, N-methyl Phe, D-Phe, beta3-Phe, alpha-methyl Phe, alpha-methyl Phe (2-F), alpha-methyl Phe (3-F), and alpha-methyl (4-F), Phe (2-F), Phe (3-F), or Phe (4-F) aa10: alpha-methyl Tyr, N-methyl Tyr, D-Tyr, beta3-Tyr, 4-Pyr-Ala, Phe (2-F), Phe (3-F), or Phe (4-F) aa13: alpha-methyl Leu, N-methyl Leu, D-Leu, beta3-Leu, Leu, Val, Ile, Aib, alpha-methyl Tyr, N-methyl Tyr, D-Tyr, beta3-Tyr, 4-Pyr-Ala, Phe (2-F), Phe (3-F), or Phe (4-F) aa16: L-Orn, alpha-methyl Lys, N-methyl Lys, D-Lys, or beta3-Lys aa25: alpha-methyl Trp, N-methyl Trp, D-Trp, beta3-Trp, alpha-methyl Tyr, or Aib aa33: A or E
8	YAibEGT-aa6TSDaa10-SIaa13LD-aa16XAAAib-EFVXaa25-LIaa33GG-PSSGA-PPPS-NH2
9	YAibEGT-aa6TSDaa10-SIaa13XD-aa16QAAAib-XFVaa24aa25-LIaa33GG-PSSGA-PPPS-NH2 aa6: alpha-methyl Phe, N-methyl Phe, D-Phe, beta3-Phe, alpha-methyl Phe (2-F), alpha-methyl Phe (3-F), and alpha-methyl (4-F), Phe (2-F), Phe (3-F), or Phe (4-F) aa10: alpha-methyl Tyr, N-methyl Tyr, D-Tyr, beta3-Tyr, 4-Pyr-Ala, Phe (2-F), Phe (3-F), Phe (4-F), or 4-pyridyl-Ala aa13: alpha-methyl Leu, N-methyl Leu, D-Leu, beta3-Leu, Val, Ile, or Aib aa16: alpha-methyl Leu, N-methyl Leu, D-Leu, beta3-Leu, Val, Ile, or Aib aa24: alpha-methyl Asn, N-methyl Asn, beta3-Asn, Aib, D-Asn, D-Asp, D-Glu, or D-Gln aa25: alpha-methyl Trp, N-methyl Trp, D-Trp, beta3-Trp, alpha-methyl Tyr, or Aib aa33: A or E
10	Yaa2EGT-FTSDY-SIaa13LD-KXAAaa20-EFVXW-LIAGG-PSSGA-PPPS-NH2 aa2: Gly, Val, Leu, Ile, or Aib aa13: alpha-methyl Leu, N-methyl Leu, D-Leu, beta3-Leu, Leu, Val, Ile, Aib, alpha-methyl Tyr, N-methyl Tyr, D-Tyr, beta3-Tyr, 4-Pyr-Ala, Phe (2-F), Phe (3-F), or Phe (4-F)

SEQ ID NO.	Sequence
	aa20: Gly, Val, Leu, Ile, or Aib
11	Yaa2EGT-FTSDY-Slaa13LD-KXAAaa20-EFVXW-LIA-NH2 aa2: Gly, Val, Leu, Ile, or Aib aa13: alpha-methyl Leu, N-methyl Leu, D-Leu, beta3-Leu, Leu, Val, Ile, Aib, alpha-methyl Tyr, N-methyl Tyr, D-Tyr, beta3-Tyr, 4-Pyr-Ala, Phe (2-F), Phe (3-F), Phe (4-F) aa20: Gly, Val, Leu, Ile, or Aib
12	Yaa2EGT-FTSDY-Slaa13XD-KQAAaa20-XFVNW-LIAGG-PSSGA-PPPS-NH2 aa2: Gly, Val, Leu, Ile, or Aib aa13: alpha-methyl Leu, N-methyl Leu, D-Leu, beta3-Leu, Leu, Val, Ile, Aib, alpha-methyl Tyr, N-methyl Tyr, D-Tyr, beta3-Tyr, 4-Pyr-Ala, Phe (2-F), Phe (3-F), or Phe (4-F) aa20: Gly, Val, Leu, Ile, or Aib
13	Yaa2EGT-FTSDV-Slaa13XD-KQAAaa20-XFVNW-LIA-NH2 aa2: Gly, Val, Leu, Ile, or Aib aa13: alpha-methyl Leu, N-methyl Leu, D-Leu, beta3-Leu, Leu, Val, Ile, Aib, alpha-methyl Tyr, N-methyl Tyr, D-Tyr, beta3-Tyr, 4-Pyr-Ala, Phe (2-F), Phe (3-F), or Phe (4-F) aa20: Gly, Val, Leu, Ile, or Aib
14	YAibEGT-aMeFTSD-4Pal-SlaMeLLD-OrnXAAAib-EFVXaMeY-LIAGG-PSSGA-PPPS-NH2
15	YAibEGT-aMeFTSD-4Pal-SlaMeLXD-OrnQAAAib-XFV(D-Glu)aMeY-LIAGG-PSSGA-PPPS-NH2
16	YAibEGT-FTSDY-SIYXD-KQAAAib-XFVQW-LLAGG-PSSGA-PPPS-NH2
17	YAibEGT-FISDV-SIYXD-KQAAAib-XFVNW-LIAGG-PSSGA-PPPS-NH2
18	YAibEGT-FTSDY-SIYLD-KXAAAib-EFVXW-LLAGG-PSSGA-PPPS-NH2
19	YAibEGT-FTSDY-SIYLD-KXAQAib-AFVXW-LIAQG-PSSGA-PPPS-NH2
20	YAibEGT-YTSDY-SIYLD-KXAAAib-EFVXW-LIAGG-PSSGA-PPPS-NH2
21	YAibEGT-YTNDY-SIYLD-KXAAAib-EFVXW-LIAGG-PSSGA-PPPS-NH2
22	YAibEGT-YTSDY-SIYXD-KQAAAib-XFVNW-LIAGG-PSSGA-PPPS-NH2
23	HGEFT-FTSDL-SKQME-EEAVR-LFIEW-LKNKG-PSSGA-PPPS-NH2 (extendin)
24	HDEFE-RHAEG-TFTSD-VSSYL-EGQAA-KEFIA-WLVKG-R-NH2 (GLP1)
25	HADGS-FSDEM-NTILD-NLAAR-DFINW-LIQTK-ITDR (GLP2)
26	YAEGT-FISDY-SIAMD-KIHQQ-DFVNW-LLAQK-GKKNDWKHNITQ-NH2 (GIP)
27	YAibEGT-FTSDY-SIAibLD-KIAQK-AFVQW-LIAGG-PSSGA-PPPS-NH2
28	YAibEGT-FTSDY-SIYLD-KQAAAib-EFVNW-LLAGG-PSSGA-PPPS
29	YAibEGT-FTSDY-SIYKD-KQAAAib-KFXNW-LXAGG-PSSGA-PPPS

[0062] In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of any one of SEQ ID NOs: 1-61. In some aspects, provided is a peptide or peptide conjugate comprising the first 28 amino acids of any one of SEQ ID NOs: 1-61.

[0063] In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to any one of SEQ ID NOs: 1-61. In some aspects, provided is a peptide or peptide conjugate comprising the peptide comprises any one of SEQ ID NOs: 1-61.

[0064] In various embodiments, each X of any one of SEQ ID NOS: 1-61 is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid. In some cases, an X is a cysteine. In some cases, an X is a lysine.

[0065] In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 1. In some aspects, provided is a peptide or peptide conjugate comprising the first 28 amino acids of SEQ ID NO: 1. In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 1. In some aspects, provided is a peptide or peptide conjugate comprising SEQ ID NO: 1. In various embodiments, each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid. In some cases, an X is a cysteine. In some cases, an X is a lysine.

[0066] In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 2. In some aspects, provided is a peptide or peptide conjugate comprising the first 28 amino acids of SEQ ID NO: 2. In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 2. In some aspects, provided is a peptide or peptide conjugate comprising SEQ ID NO: 2. In various embodiments, each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid. In some cases, an X is a cysteine. In some cases, an X is a lysine.

[0067] In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 3. In some aspects, provided is a peptide or peptide conjugate comprising the first 28 amino acids of SEQ ID NO: 3. In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 3. In some aspects, provided is a peptide or peptide conjugate

comprising SEQ ID NO: 3. In various embodiments, each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid. In some cases, an X is a cysteine. In some cases, an X is a lysine.

[0068] In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 4. In some aspects, provided is a peptide or peptide conjugate comprising the first 28 amino acids of SEQ ID NO: 4. In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4. In some aspects, provided is a peptide or peptide conjugate comprising SEQ ID NO: 4. In various embodiments, each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid. In some cases, an X is a cysteine. In some cases, an X is a lysine.

[0069] In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 5. In some aspects, provided is a peptide or peptide conjugate comprising the first 28 amino acids of SEQ ID NO: 5. In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5. In some aspects, provided is a peptide or peptide conjugate comprising SEQ ID NO: 5. In various embodiments, each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid. In some cases, an X is a cysteine. In some cases, an X is a lysine.

[0070] In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 6. In some aspects, provided is a peptide or peptide conjugate comprising the first 28 amino acids of SEQ ID NO: 6. In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 6. In some aspects, provided is a peptide or peptide conjugate comprising SEQ ID NO: 6. In various embodiments, each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid. In some cases, an X is a cysteine. In some cases, an X is a lysine. In some cases, the first X is a cysteine and the second X is a cysteine.

[0071] In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 7. In some aspects, provided is a peptide or peptide conjugate comprising the first 28 amino acids of SEQ ID NO: 7. In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%,

98%, or 99% identical to SEQ ID NO: 7. In some aspects, provided is a peptide or peptide conjugate comprising SEQ ID NO: 7. In various embodiments, each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid. In some cases, an X is a cysteine. In some cases, an X is a lysine. In some cases, aa6 is alpha-methyl Phe, N-methyl Phe, D-Phe, beta3-Phe, alpha-methyl Phe, alpha-methyl Phe (2-F), alpha-methyl Phe (3-F), and alpha-methyl (4-F), Phe (2-F), Phe (3-F), or Phe (4-F). In some cases, aa10 is alpha-methyl Tyr, N-methyl Tyr, D-Tyr, beta3-Tyr, 4-Pyr-Ala, Phe (2-F), Phe (3-F), or Phe (4-F). In some cases, aa13 is alpha-methyl Leu, N-methyl Leu, D-Leu, beta3-Leu, Leu, Val, Ile, Aib, alpha-methyl Tyr, N-methyl Tyr, D-Tyr, beta3-Tyr, 4-Pyr-Ala, Phe (2-F), Phe (3-F), or Phe (4-F). In some cases, aa16 is L-Orn, alpha-methyl Lys, N-methyl Lys, D-Lys, or beta3-Lys. In some cases, aa25 is alpha-methyl Trp, N-methyl Trp, D-Trp, beta3-Trp, alpha-methyl Tyr, or Aib. In some cases, aa33 is A or E.

[0072] In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 8. In some aspects, provided is a peptide or peptide conjugate comprising the first 28 amino acids of SEQ ID NO: 8. In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 8. In some aspects, provided is a peptide or peptide conjugate comprising SEQ ID NO: 8. In various embodiments, each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid. In some cases, an X is a cysteine. In some cases, an X is a lysine.

[0073] In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 9. In some aspects, provided is a peptide or peptide conjugate comprising the first 28 amino acids of SEQ ID NO: 9. In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 9. In some aspects, provided is a peptide or peptide conjugate comprising SEQ ID NO: 9. In various embodiments, each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid. In some cases, an X is a cysteine. In some cases, an X is a lysine. In some cases, aa6 is alpha-methyl Phe, N-methyl Phe, D-Phe, beta3-Phe, alpha-methyl Phe (2-F), alpha-methyl Phe (3-F), and alpha-methyl (4-F), Phe (2-F), Phe (3-F), or Phe (4-F). In some cases, aa10 is alpha-methyl Tyr, N-methyl Tyr, D-Tyr, beta3-Tyr, 4-Pyr-Ala, Phe (2-F), Phe (3-F), Phe (4-F), or 4-pyridyl-Ala. In some cases, aa13 is alpha-methyl Leu, N-methyl Leu, D-Leu, beta3-Leu, Val, Ile, or Aib. In some cases, aa16 is alpha-methyl Leu, N-methyl Leu, D-Leu, beta3-Leu, Val, Ile, or Aib. In some cases, aa24 is alpha-methyl Asn, N-methyl Asn, beta3-Asn, Aib, D-Asn, D-Asp, D-Glu, or D-Gln. In some cases, aa25 is alpha-methyl Trp, N-methyl Trp, D-Trp, beta3-Trp, alpha-methyl Tyr, or Aib. In some cases, aa33 is A or E.

[0074] In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 10. In some aspects, provided is a peptide or peptide conjugate comprising the first 28 amino acids of SEQ ID NO: 10. In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 10. In some aspects, provided is a peptide or peptide conjugate comprising SEQ ID NO: 10. In various embodiments, each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid. In some cases, an X is a cysteine. In some cases, an X is a lysine. In some cases, aa2 is Gly, Val, Leu, Ile, or Aib. In some cases, aa20 is Gly, Val, Leu, Ile, or Aib. In some cases, aa13 is alpha-methyl Leu, N-methyl Leu, D-Leu, beta3-Leu, Leu, Val, Ile, Aib, alpha-methyl Tyr, N-methyl Tyr, D-Tyr, beta3-Tyr, 4-Pyr-Ala, Phe (2-F), Phe (3-F), or Phe (4-F).

[0075] In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 11. In some aspects, provided is a peptide or peptide conjugate comprising the first 28 amino acids of SEQ ID NO: 11. In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 11. In some aspects, provided is a peptide or peptide conjugate comprising SEQ ID NO: 11. In various embodiments, each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid. In some cases, an X is a cysteine. In some cases, an X is a lysine. In some cases, aa2 is Gly, Val, Leu, Ile, or Aib. In some cases, aa20 is Gly, Val, Leu, Ile, or Aib. In some cases, aa13 is alpha-methyl Leu, N-methyl Leu, D-Leu, beta3-Leu, Leu, Val, Ile, Aib, alpha-methyl Tyr, N-methyl Tyr, D-Tyr, beta3-Tyr, 4-Pyr-Ala, Phe (2-F), Phe (3-F), or Phe (4-F).

[0076] In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 12. In some aspects, provided is a peptide or peptide conjugate comprising the first 28 amino acids of SEQ ID NO: 12. In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 12. In some aspects, provided is a peptide or peptide conjugate comprising SEQ ID NO: 12. In various embodiments, each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid. In some cases, an X is a cysteine. In some cases, an X is a lysine. In some cases, aa2 is Gly, Val, Leu, Ile, or Aib. In some cases, aa20 is Gly, Val, Leu, Ile, or Aib. In some cases, aa13 is alpha-methyl Leu, N-methyl Leu, D-Leu, beta3-Leu, Leu, Val, Ile, Aib, alpha-methyl Tyr, N-methyl Tyr, D-Tyr, beta3-Tyr, 4-Pyr-Ala, Phe (2-F), Phe (3-F), or Phe (4-F).

[0077] In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 13. In some aspects,

provided is a peptide or peptide conjugate comprising the first 28 amino acids of SEQ ID NO: 13. In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 13. In some aspects, provided is a peptide or peptide conjugate comprising SEQ ID NO: 13. In various embodiments, each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid. In some cases, an X is a cysteine. In some cases, an X is a lysine. In some cases, aa2 is Gly, Val, Leu, Ile, or Aib. In some cases, aa20 is Gly, Val, Leu, Ile, or Aib. In some cases, aa13 is alpha-methyl Leu, N-methyl Leu, D-Leu, beta3-Leu, Leu, Val, Ile, Aib, alpha-methyl Tyr, N-methyl Tyr, D-Tyr, beta3-Tyr, 4-Pyr-Ala, Phe (2-F), Phe (3-F), or Phe (4-F).

[0078] In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 14. In some aspects, provided is a peptide or peptide conjugate comprising the first 28 amino acids of SEQ ID NO: 14. In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 14. In some aspects, provided is a peptide or peptide conjugate comprising SEQ ID NO: 14. In various embodiments, each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid. In some cases, an X is a cysteine. In some cases, an X is a lysine.

[0079] In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 15. In some aspects, provided is a peptide or peptide conjugate comprising the first 28 amino acids of SEQ ID NO: 15. In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 15. In some aspects, provided is a peptide or peptide conjugate comprising SEQ ID NO: 15. In various embodiments, each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid. In some cases, an X is a cysteine. In some cases, an X is a lysine.

[0080] In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 16. In some aspects, provided is a peptide or peptide conjugate comprising the first 28 amino acids of SEQ ID NO: 16. In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 16. In some aspects, provided is a peptide or peptide conjugate comprising SEQ ID NO: 16. In various embodiments, each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid. In some cases, an X is a cysteine. In some cases, an X is a lysine.

[0081] In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 17. In some aspects, provided is a peptide or peptide conjugate comprising the first 28 amino acids of SEQ ID NO: 17. In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 17. In some aspects, provided is a peptide or peptide conjugate comprising SEQ ID NO: 17. In various embodiments, each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid. In some cases, an X is a cysteine. In some cases, an X is a lysine.

[0082] In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 18. In some aspects, provided is a peptide or peptide conjugate comprising the first 28 amino acids of SEQ ID NO: 18. In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 18. In some aspects, provided is a peptide or peptide conjugate comprising SEQ ID NO: 18. In various embodiments, each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid. In some cases, an X is a cysteine. In some cases, an X is a lysine.

[0083] In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 19. In some aspects, provided is a peptide or peptide conjugate comprising the first 28 amino acids of SEQ ID NO: 19. In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 19. In some aspects, provided is a peptide or peptide conjugate comprising SEQ ID NO: 19. In various embodiments, each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid. In some cases, an X is a cysteine. In some cases, an X is a lysine.

[0084] In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 20. In some aspects, provided is a peptide or peptide conjugate comprising the first 28 amino acids of SEQ ID NO: 20. In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 20. In some aspects, provided is a peptide or peptide conjugate comprising SEQ ID NO: 20. In various embodiments, each X is independently selected from a sulfhydryl-

containing amino acid and an amine-containing amino acid. In some cases, an X is a cysteine. In some cases, an X is a lysine.

[0085] In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 21. In some aspects, provided is a peptide or peptide conjugate comprising the first 28 amino acids of SEQ ID NO: 21. In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 21. In some aspects, provided is a peptide or peptide conjugate comprising SEQ ID NO: 21. In various embodiments, each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid. In some cases, an X is a cysteine. In some cases, an X is a lysine.

[0086] In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 22. In some aspects, provided is a peptide or peptide conjugate comprising the first 28 amino acids of SEQ ID NO: 22. In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 22. In some aspects, provided is a peptide or peptide conjugate comprising SEQ ID NO: 22. In various embodiments, each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid. In some cases, an X is a cysteine. In some cases, an X is a lysine.

[0087] In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 23. In some aspects, provided is a peptide or peptide conjugate comprising the first 28 amino acids of SEQ ID NO: 23. In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 23. In some aspects, provided is a peptide or peptide conjugate comprising SEQ ID NO: 23. In various embodiments, each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid. In some cases, an X is a cysteine. In some cases, an X is a lysine.

[0088] In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 24. In some aspects, provided is a peptide or peptide conjugate comprising the first 28 amino acids of SEQ ID NO: 24. In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 24. In some aspects, provided is a peptide or peptide conjugate

comprising SEQ ID NO: 24. In various embodiments, each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid. In some cases, an X is a cysteine. In some cases, an X is a lysine.

[0089] In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 25. In some aspects, provided is a peptide or peptide conjugate comprising the first 28 amino acids of SEQ ID NO: 25. In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 25. In some aspects, provided is a peptide or peptide conjugate comprising SEQ ID NO: 25. In various embodiments, each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid. In some cases, an X is a cysteine. In some cases, an X is a lysine.

[0090] In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 26. In some aspects, provided is a peptide or peptide conjugate comprising the first 28 amino acids of SEQ ID NO: 26. In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 26. In some aspects, provided is a peptide or peptide conjugate comprising SEQ ID NO: 26. In various embodiments, each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid. In some cases, an X is a cysteine. In some cases, an X is a lysine.

[0091] In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 27. In some aspects, provided is a peptide or peptide conjugate comprising the first 28 amino acids of SEQ ID NO: 27. In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 27. In some aspects, provided is a peptide or peptide conjugate comprising SEQ ID NO: 27. In various embodiments, each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid. In some cases, an X is a cysteine. In some cases, an X is a lysine.

[0092] In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 28. In some aspects, provided is a peptide or peptide conjugate comprising the first 28 amino acids of SEQ ID NO: 28. In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%,

98%, or 99% identical to SEQ ID NO: 28. In some aspects, provided is a peptide or peptide conjugate comprising SEQ ID NO: 28. In various embodiments, each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid. In some cases, an X is a cysteine. In some cases, an X is a lysine.

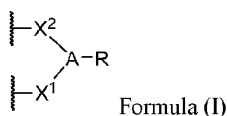
[0093] In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 29. In some aspects, provided is a peptide or peptide conjugate comprising the first 28 amino acids of SEQ ID NO: 29. In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 29. In some aspects, provided is a peptide or peptide conjugate comprising SEQ ID NO: 29. In various embodiments, each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid. In some cases, an X is a cysteine. In some cases, an X is a lysine.

[0094] In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 30. In some aspects, provided is a peptide or peptide conjugate comprising the first 28 amino acids of SEQ ID NO: 30. In some aspects, provided is a peptide or peptide conjugate comprising a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 30. In some aspects, provided is a peptide or peptide conjugate comprising SEQ ID NO: 30. In various embodiments, each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid. In some cases, an X is a cysteine. In some cases, an X is a lysine.

Staples

[0095] Disclosed herein are peptide conjugates comprising a staple.

[0096] In some embodiments, the staple attached to the peptide is of Formula (I):



wherein

A is an optionally substituted alkylene, optionally substituted arylene, optionally substituted heteroarylene, optionally substituted -NR³-alkylene-NR³-, or -N-;

X¹ and X² are independently a bond, -C(=O)-, -alkylene-C(=O)-, -C(=O)-alkylene-, -alkylene-C(=O)NR³-, -alkylene-NR³C(=O)-, -C(=O)NR³-alkylene-, -NR³C(=O)-alkylene-, -alkylene-C(=O)NR³-alkylene-, or -alkylene-NR³C(=O)-alkylene-;

wherein X¹ is attached to a first amino acid of the peptide, and X² is attached to a second amino acid of the peptide;

R is hydrogen or $-(L)_s-Y$;

each L is independently $-(CR^1R^2)_v-$, $-alkylene-O-$, $-O-alkylene-$, $-C(=O)-alkylene-$, $-alkylene-C(=O)-$, $-NR^3-alkylene-$, $-alkylene-NR^3-$, $-S-alkylene-$, $-alkylene-S-$, $-S(=O)-alkylene-$, $-alkylene-S(=O)-$, $-S(=O)_2-alkylene-$, $-alkylene-S(=O)_2-$, $-C(=O)-$, $-C(=O)NR^3-$, $-NR^3C(=O)-$, $-NR^3C(=O)NR^3-$, $-NR^3C(=O)NR^3-alkylene-$, $-NR^3C(=O)-alkylene-NR^3-$, $-alkylene-C(=O)NR^3-$, $-C(=O)NR^3-alkylene-$, $-alkylene-NR^3C(=O)-$, or $-NR^3C(=O)-alkylene-$;

v is 2-20;

each R^1 or R^2 is independently hydrogen, halogen, $-CN$, $-OR^a$, $-SR^a$, $-S(=O)R^b$, $-NO_2$, $-NR^cR^d$, $-S(=O)_2R^d$, $-NR^aS(=O)_2R^d$, $-S(=O)_2NR^cR^d$, $-C(=O)R^b$, $-OC(=O)R^b$, $-CO_2R^a$, $-OCO_2R^a$, $-C(=O)NR^cR^d$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)NR^cR^d$, $-NR^aC(=O)R^b$, $-NR^aC(=O)OR^a$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, $-OR^a$, or $-NR^cR^d$; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-OR^a$, $-NR^cR^d$,

or R^1 and R^2 are taken together to form a C_1-C_6 cycloalkyl or C_1-C_6 heterocycloalkyl;

each R^3 is independently hydrogen, $-S(=O)R^b$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-C(=O)R^b$, $-CO_2R^a$, $-C(=O)NR^cR^d$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, $-OR^a$, or $-NR^cR^d$; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-OR^a$, or $-NR^cR^d$;

Y is hydrogen, C_1-C_6 alkyl, $-CO_2H$, $-CO_2(C_1-C_6$ alkyl), $-CO_2NH_2$, $-CO_2N(alkyl)_2$, or $-CO_2NH(alkyl)$; and

s is 0-20;

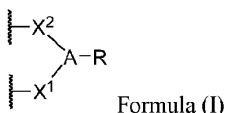
R^a is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, $-OH$, $-OMe$, or $-NH_2$; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-OH$, $-OMe$, or $-NH_2$;

R^b is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, $-OH$, $-OMe$, or $-NH_2$; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-OH$, $-OMe$, or $-NH_2$;

each R^c and R^d is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, $-OH$, $-OMe$, or $-NH_2$;

and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -OH, -OMe, or -NH₂;
or R^c and R^d, together with the nitrogen atom to which they are attached, form a heterocycloalkyl or heteroaryl; wherein the heterocycloalkyl and heteroaryl is optionally substituted with one, two, or three of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -OH, -OMe, or -NH₂.

[0097] In some embodiments, the staple attached to the peptide is of Formula (I):



wherein

A is -N-;

X¹ and X² are a bond, -C(=O)-, -alkylene-C(=O)-, -C(=O)-alkylene-, -alkylene-C(=O)NR³-, -alkylene-NR³C(=O)-, -C(=O)NR³-alkylene-, -NR³C(=O)-alkylene-, -alkylene-C(=O)NR³-alkylene-, or -alkylene-NR³C(=O)-alkylene-;

wherein X¹ is attached to a first amino acid of the peptide, X² is attached to a second amino acid of the peptide, and X¹ and X² are identical;

R is hydrogen or -(L)_v-Y;

each L is independently -(CR¹R²)_v-, -alkylene-O-, -O-alkylene-, -C(=O)-alkylene-, -alkylene-C(=O)-, -NR³-alkylene-, -alkylene-NR³-, -S-alkylene-, -alkylene-S-, -S(=O)-alkylene-, -alkylene-S(=O)-, -S(=O)₂-alkylene-, -alkylene-S(=O)₂-, -C(=O)-, -C(=O)NR³-, -NR³C(=O)-, -NR³C(=O)NR³-, -NR³C(=O)NR³-alkylene-, -NR³C(=O)-alkylene-NR³-, -alkylene-C(=O)NR³-, -C(=O)NR³-alkylene-, -alkylene-NR³C(=O)-, or -NR³C(=O)-alkylene-;

v is 2-20;

each R¹ or R² is independently hydrogen, halogen, -CN, -OR^a, -SR^a, -S(=O)R^b, -NO₂, -NR^cR^d, -S(=O)₂R^d, -NR^aS(=O)₂R^d, -S(=O)₂NR^cR^d, -C(=O)R^b, -OC(=O)R^b, -CO₂R^a, -OCO₂R^a, -C(=O)NR^cR^d, -OC(=O)NR^cR^d, -NR^aC(=O)NR^cR^d, -NR^aC(=O)R^b, -NR^aC(=O)OR^a, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, C₃-C₈ cycloalkyl, C₂-C₈ heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, -OR^a, or -NR^cR^d; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -OR^a, or -NR^cR^d;

or R¹ and R² are taken together to form a C₁-C₆ cycloalkyl or C₁-C₆ heterocycloalkyl;

each R³ is independently hydrogen, -S(=O)R^b, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -C(=O)R^b, -CO₂R^a, -C(=O)NR^cR^d, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, C₃-C₈ cycloalkyl, C₂-C₈ heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, -OR^a, or -NR^cR^d; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -OR^a, or -NR^cR^d;

Y is hydrogen, C₁-C₆ alkyl, -CO₂H, -CO₂(C₁-C₆ alkyl), -CO₂NH₂, -CO₂N(alkyl)₂, or -CO₂NH(alkyl);

s is 0-20;

R^a is hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, C₃-C₈ cycloalkyl, C₂-C₈ heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, -OH, -OMe, or -NH₂; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -OH, -OMe, or -NH₂;

R^b is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, C₃-C₈ cycloalkyl, C₂-C₈ heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, -OH, -OMe, or -NH₂; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -OH, -OMe, or -NH₂; and

each R^c and R^d is independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, C₃-C₈ cycloalkyl, C₂-C₈ heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, -OH, -OMe, or -NH₂; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -OH, -OMe, or -NH₂;

or R^c and R^d, together with the nitrogen atom to which they are attached, form a heterocycloalkyl or heteroaryl; wherein the heterocycloalkyl and heteroaryl is optionally substituted with one, two, or three of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -OH, -OMe, or -NH₂.

[0098] In some embodiments, A is optionally substituted alkylene. In some embodiments, A is -(CH₂)_t-, wherein t is 1-12. In some embodiments, A is -(CH₂)_t-, wherein t is 1-10. In some embodiments, A is -(CH₂)_t-, wherein t is 1-8. In some embodiments, A is -(CH₂)_t-, wherein t is 1-6. In some embodiments, A is -(CH₂)_t-, wherein t is 1-4.

[0099] In some embodiments, A is optionally substituted arylene. In some embodiments, A is arylene optionally substituted with halogen, alkyl, or haloalkyl. In some embodiments, A is unsubstituted arylene.

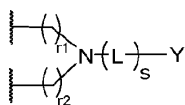
[00100] In some embodiments, A is -NR³-alkylene-NR³-. In some embodiments, A is -N-.

[00101] In some embodiments, X¹ and X² are identical. In some embodiments, X¹ and X² are different.

[00102] In some embodiments, X¹ and X² are -C(=O)-. In some embodiments, X¹ and X² are independently -alkylene-C(=O)- or -C(=O)alkylene-. In some embodiments, X¹ and X² are independently -CH₂-C(=O)- or -C(=O)-CH₂-. In some embodiments, X¹ and X² are independently -alkylene-C(=O)NR³- or -C(=O)NR³-alkylene-. In some embodiments, X¹ and X² are independently -CH₂-C(=O)NR³- or -C(=O)NR³-CH₂-. In some embodiments, X¹ and X² are independently -alkylene-C(=O)NR³-alkylene- or -alkylene-NR³C(=O)-alkylene-. In some embodiments, X¹ and X² are independently -CH₂-C(=O)NR³-CH₂CH₂- or -CH₂-NR³C(=O)-CH₂CH₂-. In some embodiments, X¹ and X² are independently -CH₂-C(=O)NH-CH₂CH₂- or -CH₂-NHC(=O)-CH₂CH₂-.

[00103] In some embodiments, each R³ is independently hydrogen or C₁-C₆ alkyl. In some embodiments, each R³ is hydrogen.

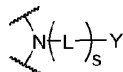
[00104] In some embodiments, >A-R has the following structure:



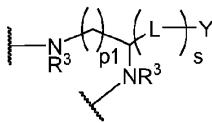
, wherein r_1 and r_2 are each independently 0-4.

[00105] In some embodiments, r_1 and r_2 are each independently 0-2. In some embodiments, r_1 and r_2 are each 0. In some embodiments, r_1 and r_2 are each 1. In some embodiments, r_1 and r_2 are each 3. In some embodiments, r_1 and r_2 are each 2.

[00106] In some embodiments, >A-R has the following structure:



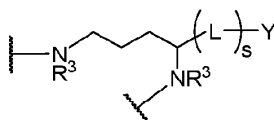
[00107] In some embodiments, >A-R has the following structure:



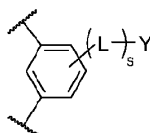
, wherein p_1 is 1-5.

[00108] In some embodiments, p_1 is 1-3. In some embodiments, p_1 is 1-2. In some embodiments, p_1 is 1. In some embodiments, p_1 is 2. In some embodiments, p_1 is 3. In some embodiments, p_1 is 4. In some embodiments, p_1 is 5.

[00109] In some embodiments, >A-R has the following structure:



[00110] In some embodiments, >A-R has the following structure:



[00111] In some embodiments, s is 1-15. In some embodiments, s is 1-10. In some embodiments, s is 5-15. In some embodiments, s is 5-10. In some embodiments, s is 5-20.

[00112] In some embodiments, Y is hydrogen or $-CO_2H$. In some embodiments, Y is hydrogen. In some embodiments, Y is $-CO_2H$.

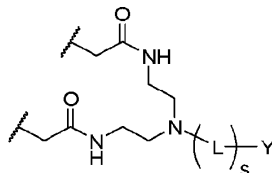
[00113] In some embodiments, each L is independently $-(CR^1R^2)_v-$, $-alkylene-O-$, $-C(=O)-$, $-C(=O)NR^3-$, $-NR^3C(=O)-$, $-alkylene-C(=O)NR^3-$, or $-alkylene-NR^3C(=O)-$; and v is 2-20.

[00114] In some embodiments, each L is independently $-(CR^1R^2)_v-$, $-alkylene-O-$, $-C(=O)-$, $-C(=O)NR^3-$, $-NR^3C(=O)-$, $-alkylene-C(=O)NR^3-$, or $-alkylene-NR^3C(=O)-$; and v is 2-16.

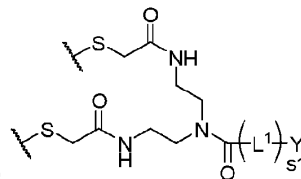
[00115] In some embodiments, v is 2-16. In some embodiments, v is 2-5. In some embodiments, v is 5-16. In some embodiments, v is 5 or 16. In some embodiments, v is 2 or 16.

[00116] In some embodiments, each R^1 or R^2 is independently hydrogen, halogen, $-CN$, $-OR^a$, $-NR^cR^d$, $-C(=O)R^b$, $-CO_2R^a$, $-C(=O)NR^cR^d$, or C_1-C_6 alkyl.

[00117] In some embodiments, each R^1 or R^2 is independently hydrogen, halogen, $-\text{CO}_2\text{R}^a$, $-\text{C}(=\text{O})\text{NR}^b\text{R}^d$, or $\text{C}_1\text{-C}_6$ alkyl. In some embodiments, each R^1 or R^2 is independently hydrogen, $-\text{CO}_2\text{R}^a$, or $-\text{C}(=\text{O})\text{NR}^b\text{R}^d$. In some embodiments, each R^1 or R^2 is independently hydrogen or $-\text{CO}_2\text{R}^a$.

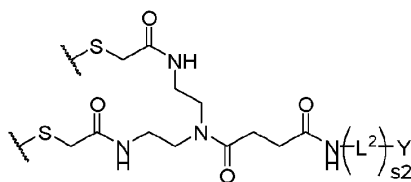


[00118] In some embodiments, the staple is



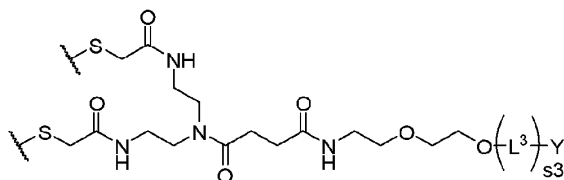
[00119] In some embodiments, the staple attached to the peptide is wherein each L^1 is independently $-(\text{CR}^1\text{R}^2)_v$ -, $-\text{alkylene-O-}$, $-\text{O-alkylene-}$, $-\text{C}(=\text{O})\text{NR}^3$ -, $-\text{NR}^3\text{C}(=\text{O})$ -, $-\text{alkylene-C}(=\text{O})\text{NR}^3$ -, or $-\text{alkylene-NR}^3\text{C}(=\text{O})$ -, v is 2-20; and $s1$ is 1-15.

[00120] In some embodiments, the staple attached to the peptide is



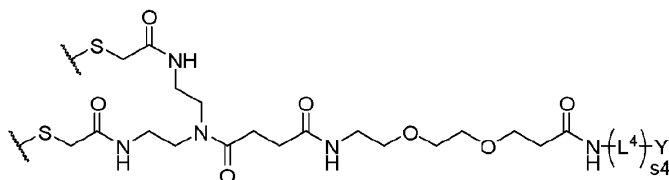
wherein each L^2 is independently $-(\text{CR}^1\text{R}^2)_v$ -, $-\text{alkylene-O-}$, $-\text{O-alkylene-}$, $-\text{C}(=\text{O})\text{NR}^3$ -, $-\text{NR}^3\text{C}(=\text{O})$ -, $-\text{alkylene-C}(=\text{O})\text{NR}^3$ -, or $-\text{alkylene-NR}^3\text{C}(=\text{O})$ -, v is 2-20; and $s2$ is 1-15.

[00121] In some embodiments, the staple attached to the peptide is



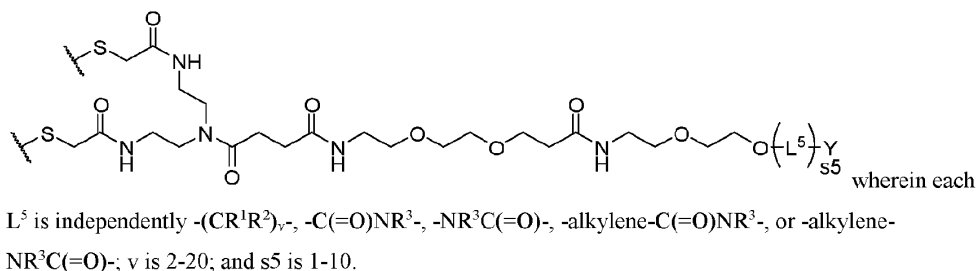
wherein each L^3 is independently $-(\text{CR}^1\text{R}^2)_v$ -, $-\text{alkylene-O-}$, $-\text{O-alkylene-}$, $-\text{C}(=\text{O})\text{NR}^3$ -, $-\text{NR}^3\text{C}(=\text{O})$ -, $-\text{alkylene-C}(=\text{O})\text{NR}^3$ -, or $-\text{alkylene-NR}^3\text{C}(=\text{O})$ -, v is 2-20; and $s3$ is 1-15.

[00122] In some embodiments, the staple attached to the peptide is

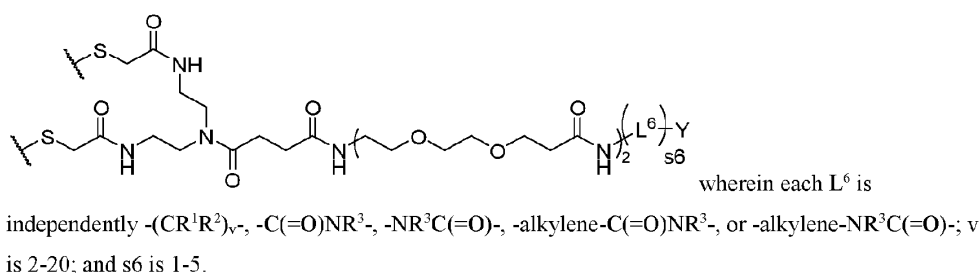


wherein each L^4 is independently $-(\text{CR}^1\text{R}^2)_v$ -, $-\text{alkylene-O-}$, $-\text{O-alkylene-}$, $-\text{C}(=\text{O})\text{NR}^3$ -, $-\text{NR}^3\text{C}(=\text{O})$ -, $-\text{alkylene-C}(=\text{O})\text{NR}^3$ -, or $-\text{alkylene-NR}^3\text{C}(=\text{O})$ -, v is 2-20; and $s4$ is 1-15.

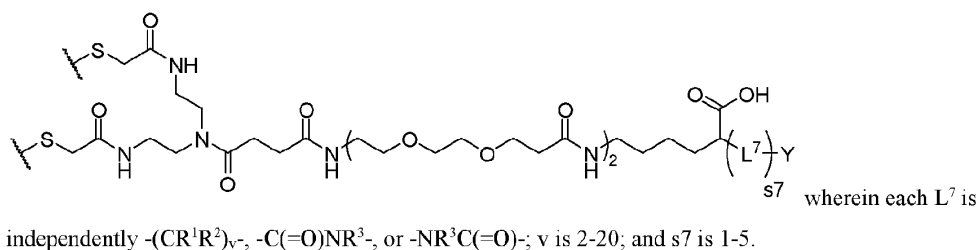
[00123] In some embodiments, the staple attached to the peptide is



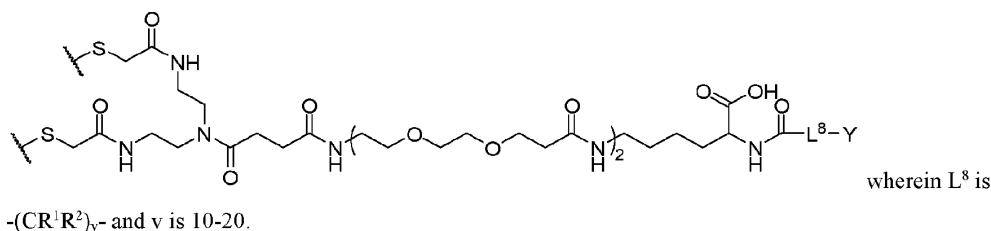
[00124] In some embodiments, the staple attached to the peptide is



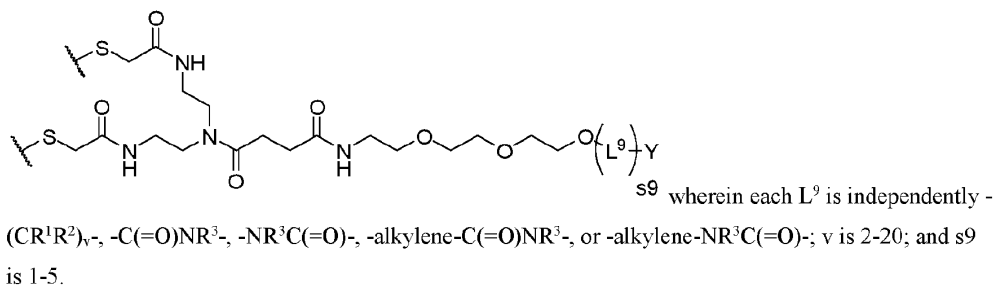
[00125] In some embodiments, the staple attached to the peptide is



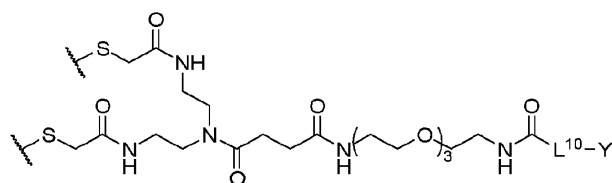
[00126] In some embodiments, the staple attached to the peptide is



[00127] In some embodiments, the staple attached to the peptide is



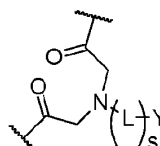
[00128] In some embodiments, the staple attached to the peptide is



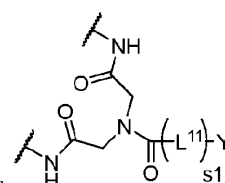
wherein L^{10} is $-(CR^1R^2)_v-$ and v is 10-

20.

[00129] In some embodiments, the staple attached to the peptide is



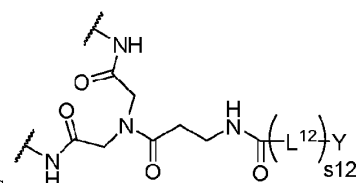
[00130] In some embodiments, the staple attached to the peptide is



wherein each

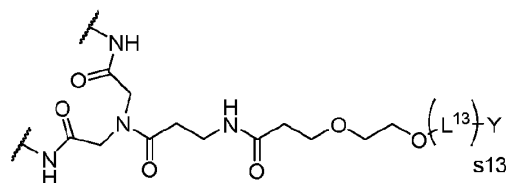
L¹¹ is independently -(CR¹R²)_v-, -alkylene-O-, -O-alkylene-, -C(=O)NR³-, -NR³C(=O)-, -alkylene-C(=O)NR³-, or -alkylene-NR³C(=O)-; v is 2-20; and s11 is 1-15.

[00131] In some embodiments, the staple attached to the peptide is



wherein each L¹² is independently -(CR¹R²)_v-, -alkylene-O-, -O-alkylene-, -C(=O)NR³-, -NR³C(=O)-, -alkylene-C(=O)NR³-, or -alkylene-NR³C(=O)-; v is 2-20; and s12 is 1-15.

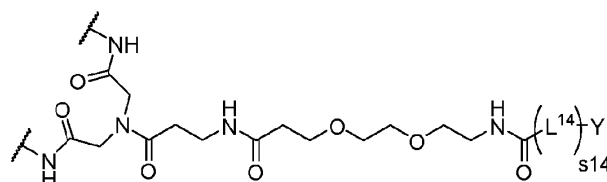
[00132] In some embodiments, the staple attached to the peptide is



wherein each L^{13} is independently $-(CR^1R^2)_v-$, -

alkylene-O-, -O-alkylene-, -C(=O)NR³-, -NR³C(=O)-, -alkylene-C(=O)NR³-, or -alkylene-NR³C(=O)-; v is 2-20; and s13 is 1-15.

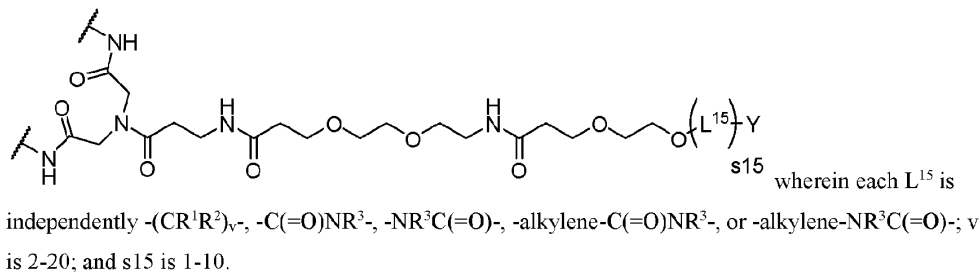
[00133] In some embodiments, the staple attached to the peptide is



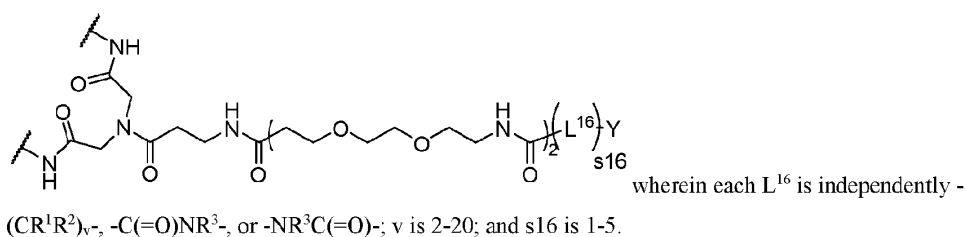
wherein each L^{14} is independently -

$(\text{CR}^1\text{R}^2)_v$ -, -alkylene-O-, -O-alkylene-, $-\text{C}(=\text{O})\text{NR}^3$ -, $-\text{NR}^3\text{C}(=\text{O})$ -, -alkylene- $\text{C}(=\text{O})\text{NR}^3$ -, or -alkylene- $\text{NR}^3\text{C}(=\text{O})$ -; v is 2-20; and $s14$ is 1-15.

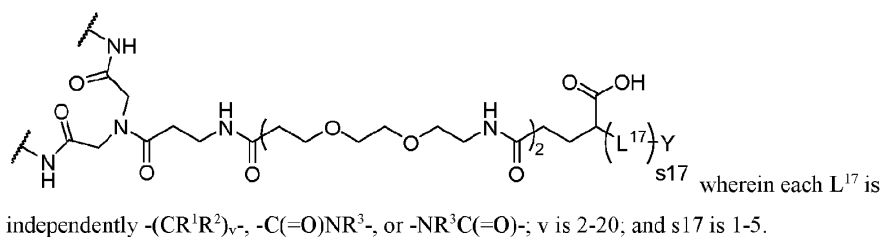
[00134] In some embodiments, the staple attached to the peptide is



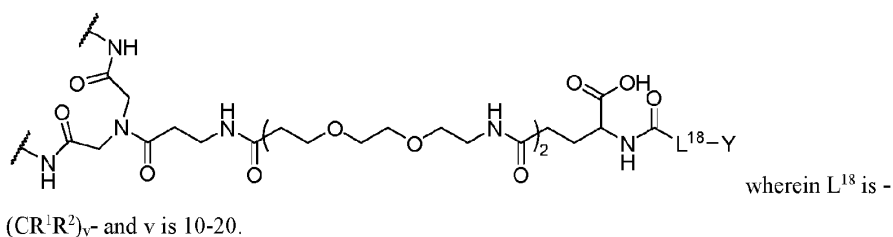
[00135] In some embodiments, the staple attached to the peptide is



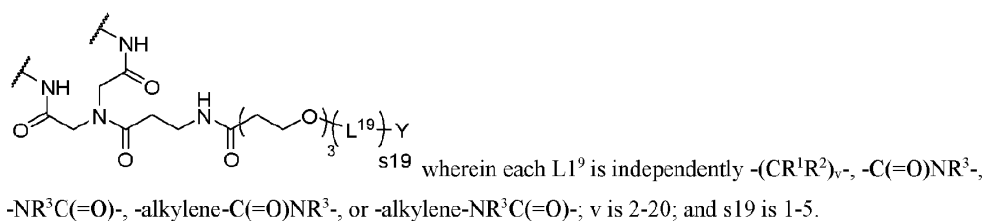
[00136] In some embodiments, the staple attached to the peptide is



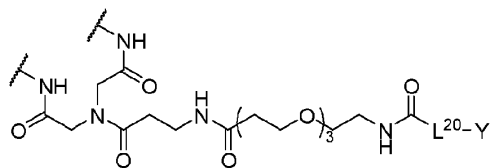
[00137] In some embodiments, the staple attached to the peptide is



[00138] In some embodiments, the staple attached to the peptide is

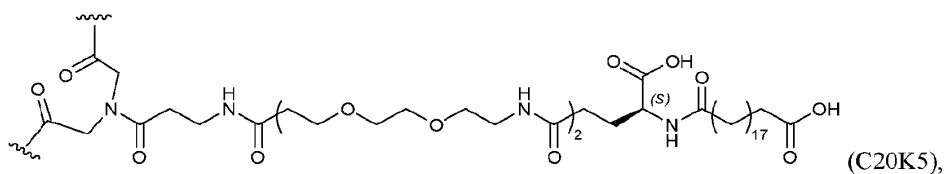
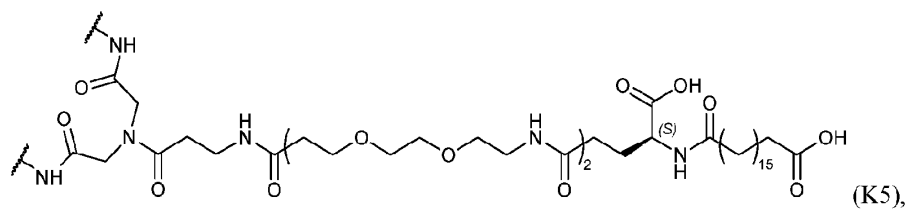
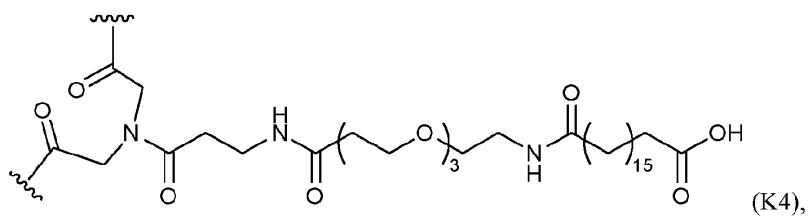
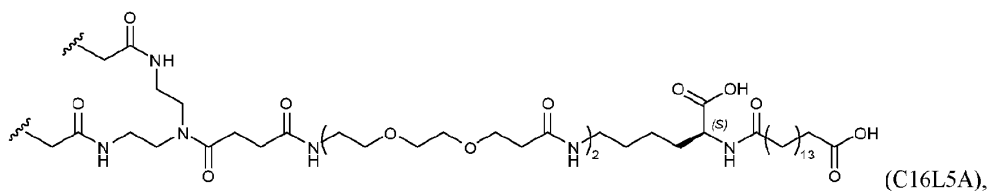
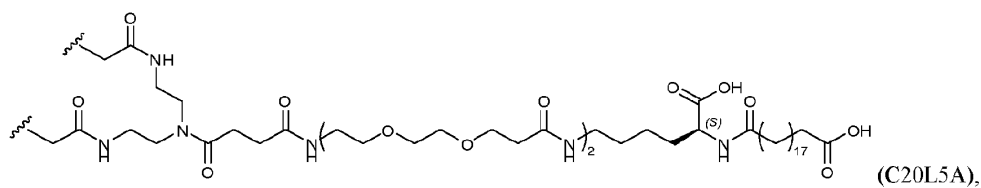
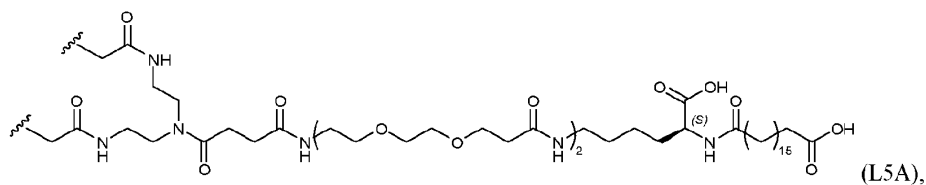


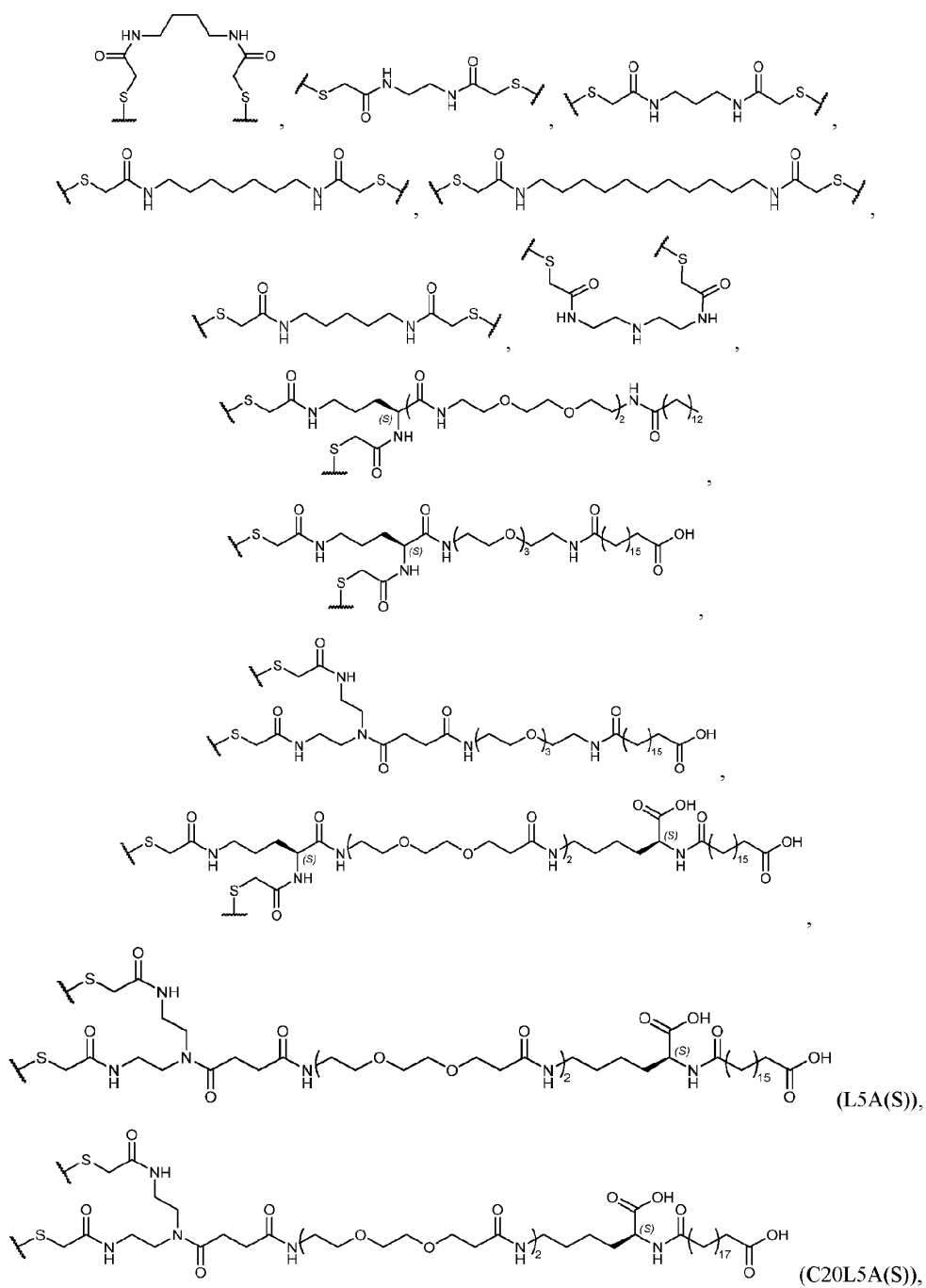
[00139] In some embodiments, the staple attached to the peptide is

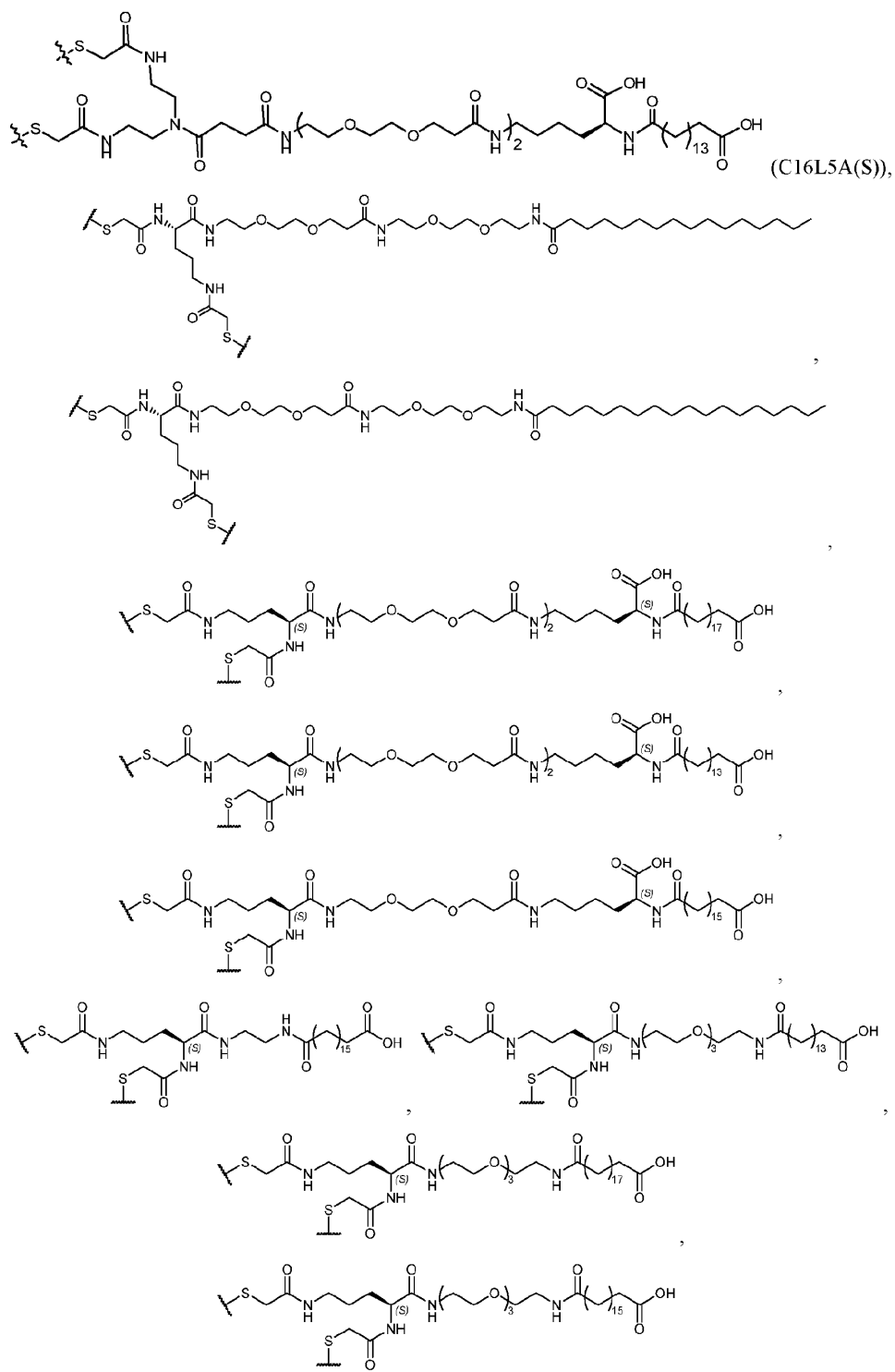


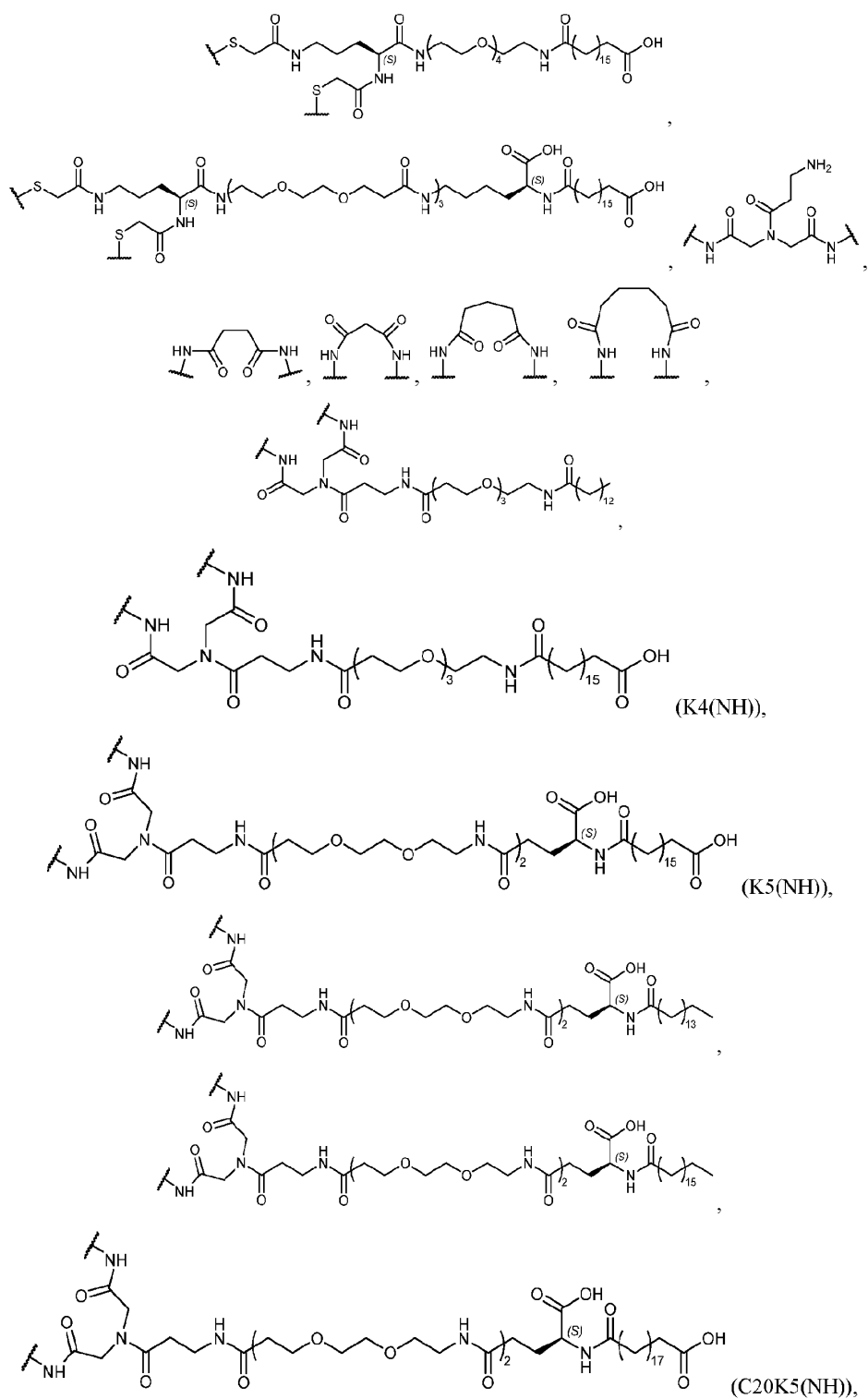
wherein L^{20} is $-(CR^1R^2)_v-$ and v is 10-20.

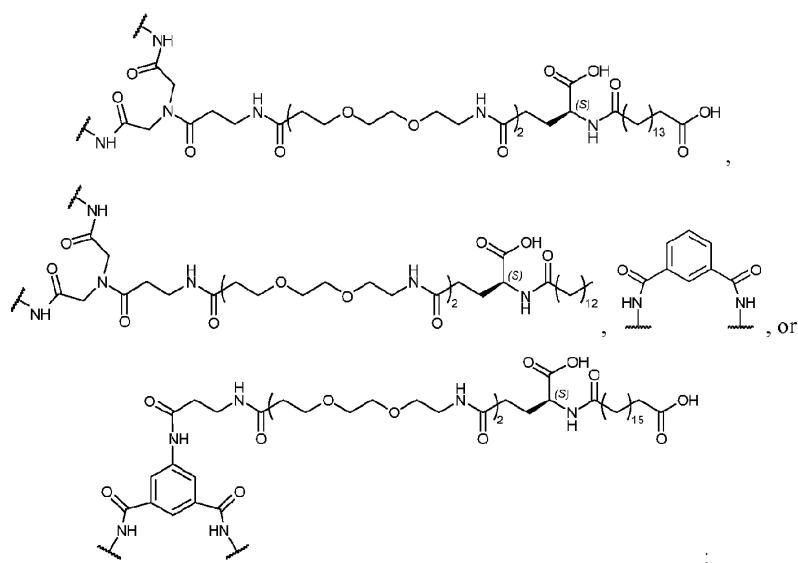
[00140] In some embodiments, the staple attached to the peptide is:





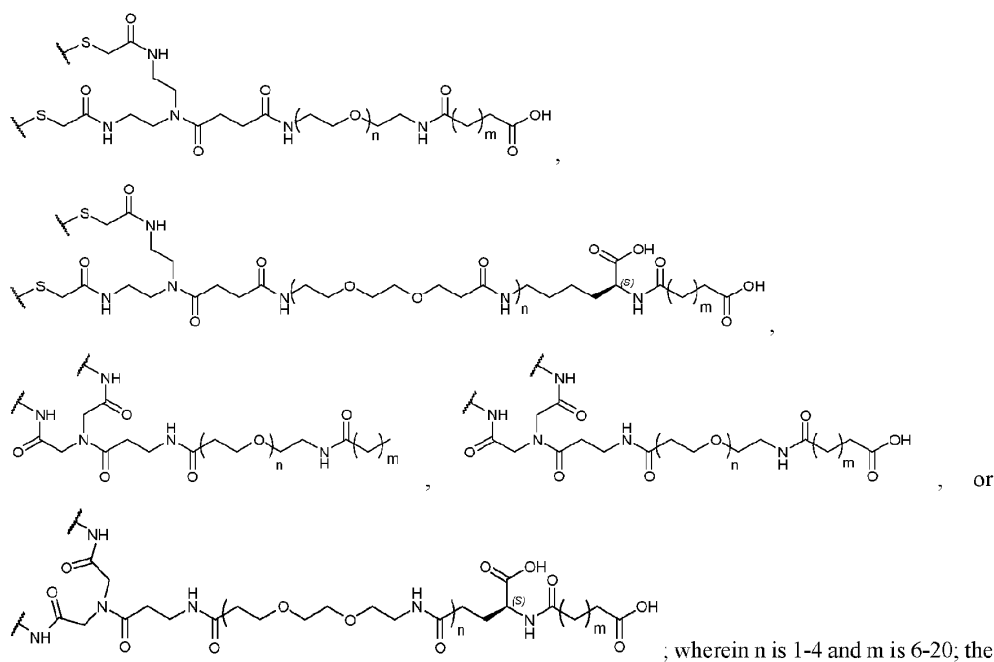






the “ γ -S” being part of a cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, or 2-amino-6-mercaptohexanoic acid residue and the “ γ -NH” being part of a lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine residue.

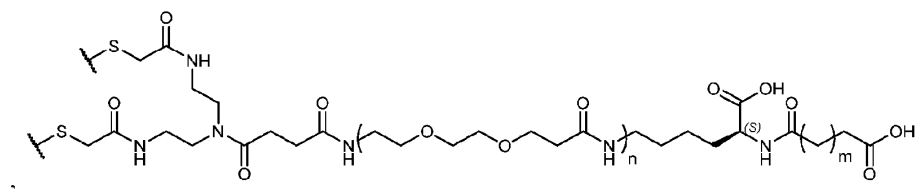
[00141] In some embodiments, the staple attached to the peptide is:



wherein n is 1-4 and m is 6-20; the “ γ -S” being part of a cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, or 2-amino-6-mercaptohexanoic acid residue and the “ γ -NH” being part of a lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine residue. In some embodiments, n is 1 and m is 6. In some embodiments, n is 1 and m is 7. In some embodiments, n is 1 and m is 8. In some embodiments, n is 1 and

m is 9. In some embodiments, n is 1 and m is 10. In some embodiments, n is 1 and m is 11. In some embodiments, n is 1 and m is 12. In some embodiments, n is 1 and m is 13. In some embodiments, n is 1 and m is 14. In some embodiments, n is 1 and m is 15. In some embodiments, n is 1 and m is 16. In some embodiments, n is 1 and m is 17. In some embodiments, n is 1 and m is 18. In some embodiments, n is 1 and m is 19. In some embodiments, n is 1 and m is 20. In some embodiments, n is 2 and m is 6. In some embodiments, n is 2 and m is 7. In some embodiments, n is 2 and m is 8. In some embodiments, n is 2 and m is 9. In some embodiments, n is 2 and m is 10. In some embodiments, n is 2 and m is 11. In some embodiments, n is 2 and m is 12. In some embodiments, n is 2 and m is 13. In some embodiments, n is 2 and m is 14. In some embodiments, n is 2 and m is 15. In some embodiments, n is 2 and m is 16. In some embodiments, n is 2 and m is 17. In some embodiments, n is 2 and m is 18. In some embodiments, n is 2 and m is 19. In some embodiments, n is 2 and m is 20. In some embodiments, n is 3 and m is 6. In some embodiments, n is 3 and m is 7. In some embodiments, n is 3 and m is 8. In some embodiments, n is 3 and m is 9. In some embodiments, n is 3 and m is 10. In some embodiments, n is 3 and m is 11. In some embodiments, n is 3 and m is 12. In some embodiments, n is 3 and m is 13. In some embodiments, n is 3 and m is 14. In some embodiments, n is 3 and m is 15. In some embodiments, n is 3 and m is 16. In some embodiments, n is 3 and m is 17. In some embodiments, n is 3 and m is 18. In some embodiments, n is 3 and m is 19. In some embodiments, n is 3 and m is 20. In some embodiments, n is 4 and m is 6. In some embodiments, n is 4 and m is 7. In some embodiments, n is 4 and m is 8. In some embodiments, n is 4 and m is 9. In some embodiments, n is 4 and m is 10. In some embodiments, n is 4 and m is 11. In some embodiments, n is 4 and m is 12. In some embodiments, n is 4 and m is 13. In some embodiments, n is 4 and m is 14. In some embodiments, n is 4 and m is 15. In some embodiments, n is 4 and m is 16. In some embodiments, n is 4 and m is 17. In some embodiments, n is 4 and m is 18. In some embodiments, n is 4 and m is 19. In some embodiments, n is 4 and m is 20.

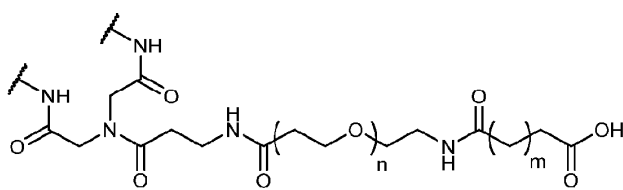
[00142] In some embodiments, the staple attached to the peptide is:



wherein n is 1-4 and m is 6-20; the “-S-” being part of a cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, or 2-amino-6-mercaptohexanoic acid residue and the “-NH-” being part of a lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine residue. In some embodiments, n is 1 and m is 6. In some embodiments, n is 1 and m is 7. In some embodiments, n is 1 and m is 8. In some embodiments, n is 1 and m is 9. In some embodiments, n is 1 and m is 10. In some embodiments, n is 1 and m is 11. In some embodiments, n is 1 and m is 12. In some embodiments, n is 1 and m is 13. In some embodiments, n is 1 and m is 14. In some embodiments, n is 1 and m is 15. In some embodiments, n is 1 and m is 16. In some embodiments, n is 1 and m is 17. In some embodiments, n is 1 and m is 18. In some embodiments, n is 1 and m is 19. In some embodiments, n is 1 and m is 20. In some embodiments, n is 2 and m is 6. In some embodiments, n is 2 and m is 7. In some embodiments, n is 2 and

m is 8. In some embodiments, n is 2 and m is 9. In some embodiments, n is 2 and m is 10. In some embodiments, n is 2 and m is 11. In some embodiments, n is 2 and m is 12. In some embodiments, n is 2 and m is 13. In some embodiments, n is 2 and m is 14. In some embodiments, n is 2 and m is 15. In some embodiments, n is 2 and m is 16. In some embodiments, n is 2 and m is 17. In some embodiments, n is 2 and m is 18. In some embodiments, n is 2 and m is 19. In some embodiments, n is 2 and m is 20. In some embodiments, n is 3 and m is 6. In some embodiments, n is 3 and m is 7. In some embodiments, n is 3 and m is 8. In some embodiments, n is 3 and m is 9. In some embodiments, n is 3 and m is 10. In some embodiments, n is 3 and m is 11. In some embodiments, n is 3 and m is 12. In some embodiments, n is 3 and m is 13. In some embodiments, n is 3 and m is 14. In some embodiments, n is 3 and m is 15. In some embodiments, n is 3 and m is 16. In some embodiments, n is 3 and m is 17. In some embodiments, n is 3 and m is 18. In some embodiments, n is 3 and m is 19. In some embodiments, n is 3 and m is 20. In some embodiments, n is 4 and m is 6. In some embodiments, n is 4 and m is 7. In some embodiments, n is 4 and m is 8. In some embodiments, n is 4 and m is 9. In some embodiments, n is 4 and m is 10. In some embodiments, n is 4 and m is 11. In some embodiments, n is 4 and m is 12. In some embodiments, n is 4 and m is 13. In some embodiments, n is 4 and m is 14. In some embodiments, n is 4 and m is 15. In some embodiments, n is 4 and m is 16. In some embodiments, n is 4 and m is 17. In some embodiments, n is 4 and m is 18. In some embodiments, n is 4 and m is 19. In some embodiments, n is 4 and m is 20.

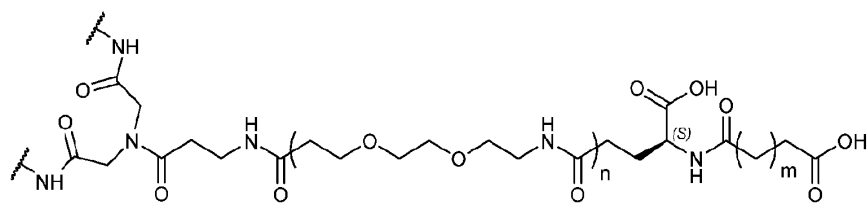
[00143] In some embodiments, the staple attached to the peptide is:



wherein n is 1-4 and m is 6-20; the “-S” being part of a cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, or 2-amino-6-mercaptohexanoic acid residue and the “-NH” being part of a lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine residue. In some embodiments, n is 1 and m is 6. In some embodiments, n is 1 and m is 7. In some embodiments, n is 1 and m is 8. In some embodiments, n is 1 and m is 9. In some embodiments, n is 1 and m is 10. In some embodiments, n is 1 and m is 11. In some embodiments, n is 1 and m is 12. In some embodiments, n is 1 and m is 13. In some embodiments, n is 1 and m is 14. In some embodiments, n is 1 and m is 15. In some embodiments, n is 1 and m is 16. In some embodiments, n is 1 and m is 17. In some embodiments, n is 1 and m is 18. In some embodiments, n is 1 and m is 19. In some embodiments, n is 1 and m is 20. In some embodiments, n is 2 and m is 6. In some embodiments, n is 2 and m is 7. In some embodiments, n is 2 and m is 8. In some embodiments, n is 2 and m is 9. In some embodiments, n is 2 and m is 10. In some embodiments, n is 2 and m is 11. In some embodiments, n is 2 and m is 12. In some embodiments, n is 2 and m is 13. In some embodiments, n is 2 and m is 14. In some embodiments, n is 2 and m is 15. In some embodiments, n is 2 and m is 16. In some embodiments, n is 2 and m is 17. In some embodiments, n is 2 and m is 18. In some embodiments, n is 2 and m is 19. In some embodiments, n is 2 and m is 20. In some embodiments, n is 3 and m is 6. In some embodiments, n is 3 and m is 7. In some embodiments, n is 3 and

m is 8. In some embodiments, n is 3 and m is 9. In some embodiments, n is 3 and m is 10. In some embodiments, n is 3 and m is 11. In some embodiments, n is 3 and m is 12. In some embodiments, n is 3 and m is 13. In some embodiments, n is 3 and m is 14. In some embodiments, n is 3 and m is 15. In some embodiments, n is 3 and m is 16. In some embodiments, n is 3 and m is 17. In some embodiments, n is 3 and m is 18. In some embodiments, n is 3 and m is 19. In some embodiments, n is 3 and m is 20. In some embodiments, n is 4 and m is 6. In some embodiments, n is 4 and m is 7. In some embodiments, n is 4 and m is 8. In some embodiments, n is 4 and m is 9. In some embodiments, n is 4 and m is 10. In some embodiments, n is 4 and m is 11. In some embodiments, n is 4 and m is 12. In some embodiments, n is 4 and m is 13. In some embodiments, n is 4 and m is 14. In some embodiments, n is 4 and m is 15. In some embodiments, n is 4 and m is 16. In some embodiments, n is 4 and m is 17. In some embodiments, n is 4 and m is 18. In some embodiments, n is 4 and m is 19. In some embodiments, n is 4 and m is 20.

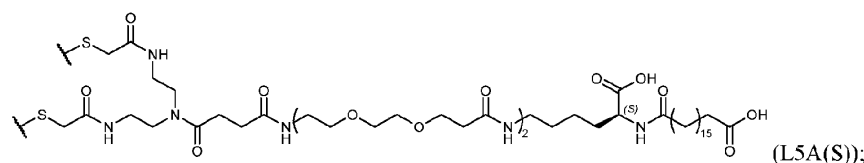
[00144] In some embodiments, the staple attached to the peptide is:



wherein n is 1-4 and m is 6-20; the “-S-” being part of a cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, or 2-amino-6-mercaptohexanoic acid residue and the “-NH-” being part of a lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine residue. In some embodiments, n is 1 and m is 6. In some embodiments, n is 1 and m is 7. In some embodiments, n is 1 and m is 8. In some embodiments, n is 1 and m is 9. In some embodiments, n is 1 and m is 10. In some embodiments, n is 1 and m is 11. In some embodiments, n is 1 and m is 12. In some embodiments, n is 1 and m is 13. In some embodiments, n is 1 and m is 14. In some embodiments, n is 1 and m is 15. In some embodiments, n is 1 and m is 16. In some embodiments, n is 1 and m is 17. In some embodiments, n is 1 and m is 18. In some embodiments, n is 1 and m is 19. In some embodiments, n is 1 and m is 20. In some embodiments, n is 2 and m is 6. In some embodiments, n is 2 and m is 7. In some embodiments, n is 2 and m is 8. In some embodiments, n is 2 and m is 9. In some embodiments, n is 2 and m is 10. In some embodiments, n is 2 and m is 11. In some embodiments, n is 2 and m is 12. In some embodiments, n is 2 and m is 13. In some embodiments, n is 2 and m is 14. In some embodiments, n is 2 and m is 15. In some embodiments, n is 2 and m is 16. In some embodiments, n is 2 and m is 17. In some embodiments, n is 2 and m is 18. In some embodiments, n is 2 and m is 19. In some embodiments, n is 2 and m is 20. In some embodiments, n is 3 and m is 6. In some embodiments, n is 3 and m is 7. In some embodiments, n is 3 and m is 8. In some embodiments, n is 3 and m is 9. In some embodiments, n is 3 and m is 10. In some embodiments, n is 3 and m is 11. In some embodiments, n is 3 and m is 12. In some embodiments, n is 3 and m is 13. In some embodiments, n is 3 and m is 14. In some embodiments, n is 3 and m is 15. In some embodiments, n is 3 and m is 16. In some embodiments, n is 3 and m is 17. In some embodiments, n is 3 and m is 18. In some embodiments, n is 3 and m is 19. In some embodiments, n is 3 and m is 20. In some embodiments, n is 4 and m is 6. In some embodiments, n is 4 and m is 7. In some embodiments, n is 4 and

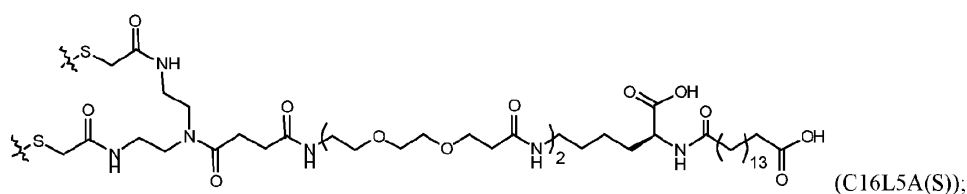
m is 8. In some embodiments, n is 4 and m is 9. In some embodiments, n is 4 and m is 10. In some embodiments, n is 4 and m is 11. In some embodiments, n is 4 and m is 12. In some embodiments, n is 4 and m is 13. In some embodiments, n is 4 and m is 14. In some embodiments, n is 4 and m is 15. In some embodiments, n is 4 and m is 16. In some embodiments, n is 4 and m is 17. In some embodiments, n is 4 and m is 18. In some embodiments, n is 4 and m is 19. In some embodiments, n is 4 and m is 20.

[00145] In some embodiments, the staple attached to the peptide is:



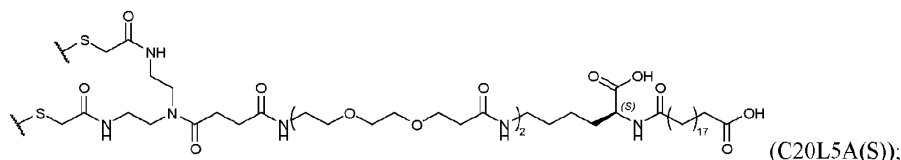
the “λ-S” being part of a cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, or 2-amino-6-mercaptohexanoic acid residue.

[00146] In some embodiments, the staple attached to the peptide is:



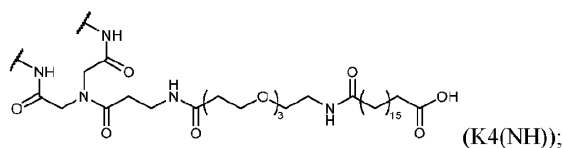
the “λ-S” being part of a cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, or 2-amino-6-mercaptohexanoic acid residue.

[00147] In some embodiments, the staple attached to the peptide is:



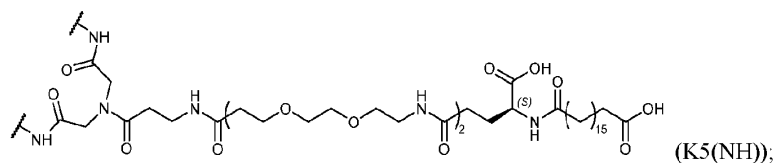
the “λ-S” being part of a cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, or 2-amino-6-mercaptohexanoic acid residue.

[00148] In some embodiments, the staple attached to the peptide is:



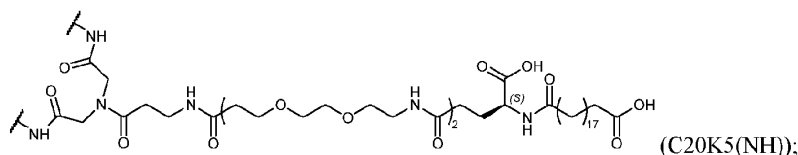
[00149] the “λ-NH” being part of a lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine residue.

[00150] In some embodiments, the staple attached to the peptide is:



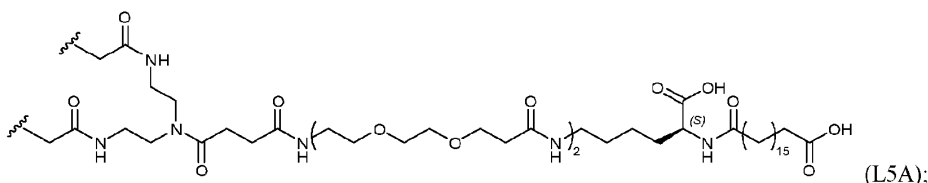
the “-NH” being part of a lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine residue.

[00151] In some embodiments, the staple attached to the peptide is:



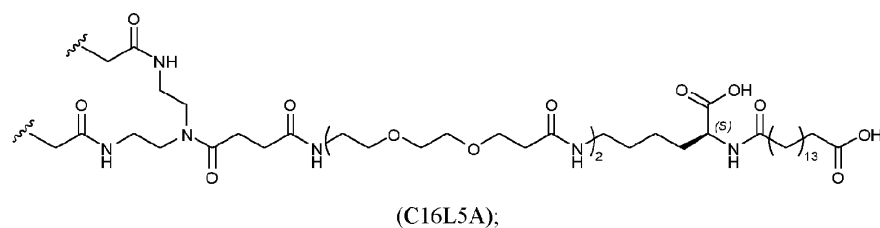
the “-NH” being part of a lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine residue.

[00152] In some embodiments, the staple attached to the peptide is:



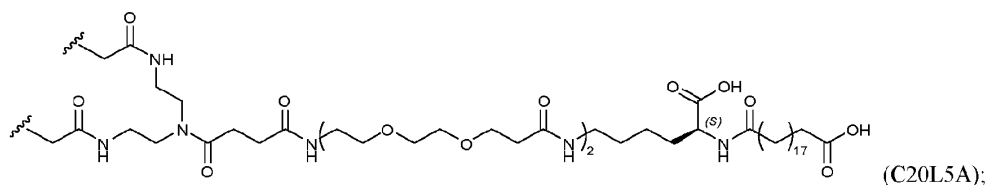
wherein each “-” is connected to an amino acid of the peptide. For instance, the amino acid is a cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, 2-amino-6-mercaptohexanoic acid, lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine residue of the peptide.

[00153] In some embodiments, the staple attached to the peptide is:



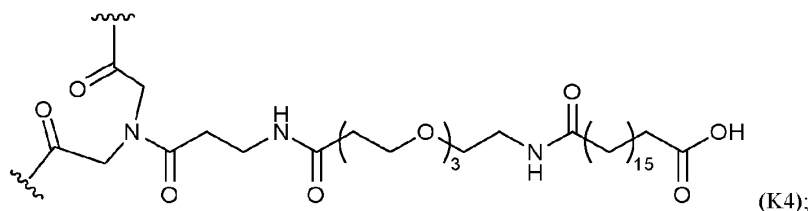
wherein each “-” is connected to an amino acid of the peptide. For instance, the amino acid is a cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, 2-amino-6-mercaptohexanoic acid, lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine residue of the peptide.

[00154] In some embodiments, the staple attached to the peptide is:



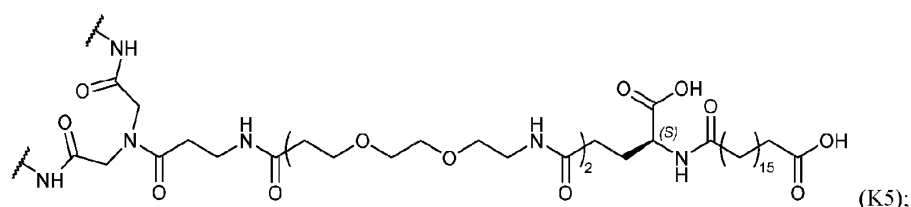
wherein each “ R^2 ” is connected to an amino acid of the peptide. For instance, the amino acid is a cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, 2-amino-6-mercaptohexanoic acid, lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine residue of the peptide.

[00155] In some embodiments, the staple attached to the peptide is:



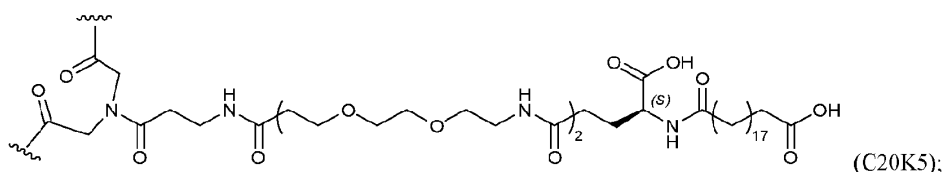
wherein each “ - ” is connected to an amino acid of the peptide. For instance, the amino acid is a cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, 2-amino-6-mercaptohexanoic acid, lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine residue of the peptide.

[00156] In some embodiments, the staple attached to the peptide is:



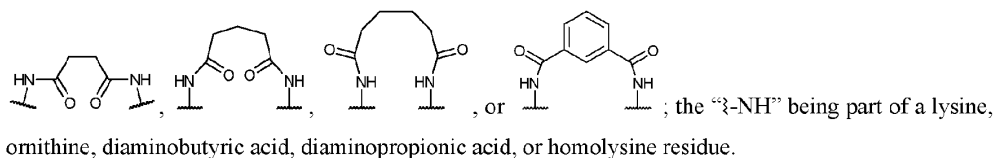
wherein each “ - ” is connected to an amino acid of the peptide. For instance, the amino acid is a cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, 2-amino-6-mercaptohexanoic acid, lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine residue of the peptide.

[00157] In some embodiments, the staple attached to the peptide is:

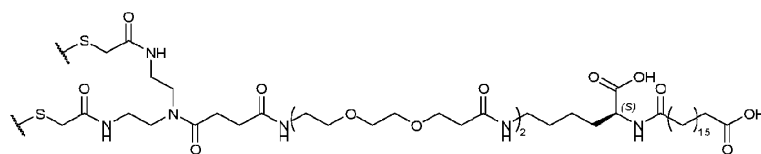


wherein each “ Z^- ” is connected to an amino acid of the peptide. For instance, the amino acid is a cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, 2-amino-6-mercaptohexanoic acid, lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine residue of the peptide.

[00158] In some embodiments, the staple attached to the peptide is:

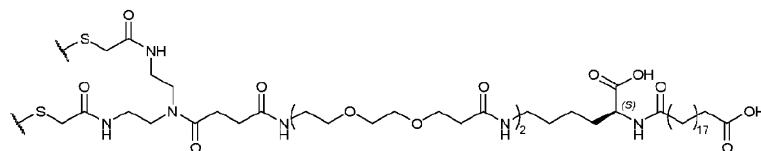


[00159] In some embodiments, the staple attached to the peptide is:



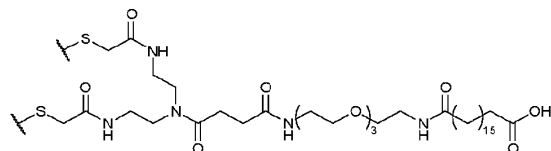
; the “-S-” being part of a cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, or 2-amino-6-mercaptohexanoic acid residue.

[00160] In some embodiments, the staple attached to the peptide is:



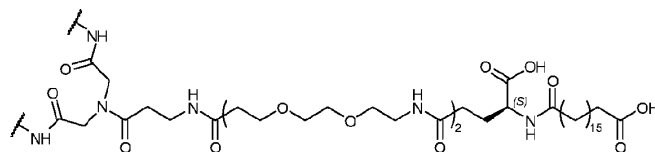
; the “-S-” being part of a cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, or 2-amino-6-mercaptohexanoic acid residue.

[00161] In some embodiments, the staple attached to the peptide is:



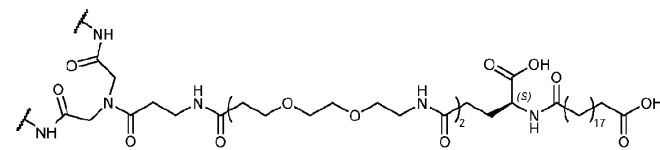
; the “-S-” being part of a cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, or 2-amino-6-mercaptohexanoic acid residue.

[00162] In some embodiments, the staple attached to the peptide is:



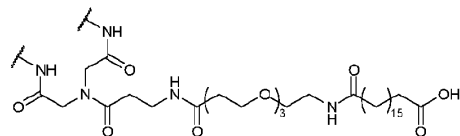
; the “-NH-” being part of a lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine residue.

[00163] In some embodiments, the staple attached to the peptide is:



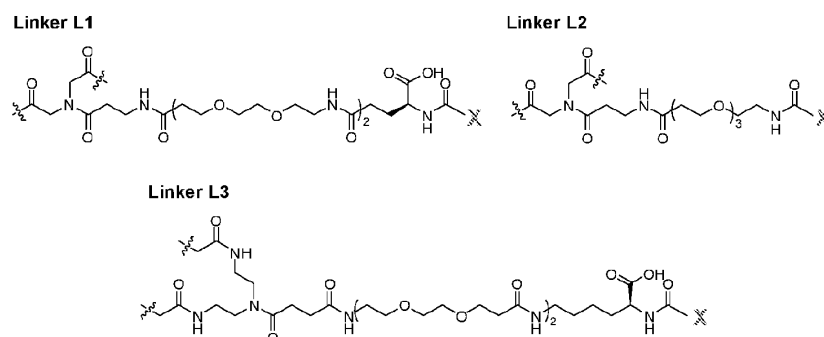
; the “-NH-” being part of a lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine residue.

[00164] In some embodiments, the staple attached to the peptide is:



; the “-NH-” being part of a lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine residue.

[00165] In some embodiments, the staple attached to the peptide comprises Linker L1, Linker L2, or Linker L3:



In some embodiments, X independently comprises C14, C14 diacid, C16, C16 diacid, C18, C18 diacid, C20 or C20 diacid. In some embodiments, X comprises Propionic acid (CH₃CH₂COOH, C3:0). In some embodiments, X comprises Butyric acid (Butanoic acid, CH₃(CH₂)₂COOH, C4:0). In some embodiments, X is Valeric acid (Pentanoic acid, CH₃(CH₂)₃COOH, C5:0). In some embodiments, X comprises Caproic acid (Hexanoic acid, CH₃(CH₂)₄COOH, C6:0). In some embodiments, X comprises Enanthic acid (Heptanoic acid, CH₃(CH₂)₅COOH, C7:0). In some embodiments, X comprises Caprylic acid (Octanoic acid, CH₃(CH₂)₆COOH, C8:0). In some embodiments, X comprises Pelargonic acid (Nonanoic acid, CH₃(CH₂)₇COOH, C9:0). In some embodiments, X comprises Capric acid (Decanoic acid, CH₃(CH₂)₈COOH, C10:0). In some embodiments, X comprises Undecylic acid (Undecanoic acid, CH₃(CH₂)₉COOH, C11:0). In some embodiments, X comprises Lauric acid (Dodecanoic acid, CH₃(CH₂)₁₀COOH, C12:0). In some embodiments, X comprises Tridecylic acid (Tridecanoic acid, CH₃(CH₂)₁₁COOH, C13:0). In some embodiments, X comprises Myristic acid (Tetradecanoic acid, CH₃(CH₂)₁₂COOH, C14:0). In some embodiments, X comprises Pentadecylic acid (Pentadecanoic acid, CH₃(CH₂)₁₃COOH, C15:0). In some embodiments, X comprises Palmitic acid (Hexadecanoic acid, CH₃(CH₂)₁₄COOH, C16:0). In some embodiments, X comprises Margaric acid (Heptadecanoic acid, CH₃(CH₂)₁₅COOH, C17:0). In some embodiments, X comprises Stearic acid (Octadecanoic acid, CH₃(CH₂)₁₆COOH, C18:0). In some embodiments, X comprises Nonadecylic acid (Nonadecanoic acid, CH₃(CH₂)₁₇COOH, C19:0). In some embodiments, X comprises Arachidic acid (Eicosanoic acid, CH₃(CH₂)₁₈COOH, C20:0). In some embodiments, X comprises Heneicosylic acid (Heneicosanoic acid, CH₃(CH₂)₁₉COOH, C21:0). In some embodiments, X comprises Behenic acid (Docosanoic acid, CH₃(CH₂)₂₀COOH, C22:0). In some embodiments, X comprises Tricosylic acid (Tricosanoic acid, CH₃(CH₂)₂₁COOH, C23:0). In some embodiments, X comprises Lignoceric acid (Tetracosanoic acid, CH₃(CH₂)₂₂COOH, C24:0). In some embodiments, X comprises Pentacosylic acid (Pentacosanoic acid, CH₃(CH₂)₂₃COOH, C25:0).

Half-Life Extending Moiety (HEM)

[00166] Disclosed herein are peptide conjugates comprising a HEM.

[00167] In some embodiments, the HEM attached to the peptide is of Formula (II):



wherein

X^3 is a bond, $-C(=O)-$, $-alkylene-C(=O)-$, $-C(=O)-alkylene-$, $-alkylene-C(=O)NR^3-$, $-alkylene-NR^3C(=O)-$, $-C(=O)NR^3-alkylene-$, $-NR^3C(=O)-alkylene-$, $-alkylene-C(=O)NR^3-alkylene-$, or $-alkylene-NR^3C(=O)-alkylene-$;

wherein X^3 is attached to a first amino acid of the peptide;

each L is independently $-(CR^1R^2)_v-$, $-alkylene-O-$, $-O-alkylene-$, $-C(=O)-alkylene-$, $-alkylene-C(=O)-$, $-NR^3-alkylene-$, $-alkylene-NR^3-$, $-S-alkylene-$, $-alkylene-S-$, $-S(=O)-alkylene-$, $-alkylene-S(=O)-$, $-S(=O)_2-alkylene-$, $-alkylene-S(=O)_2-$, $-C(=O)-$, $-C(=O)NR^3-$, $-NR^3C(=O)-$, $-NR^3C(=O)NR^3-$, $-NR^3C(=O)NR^3-alkylene-$, $-NR^3C(=O)-alkylene-NR^3-$, $-alkylene-C(=O)NR^3-$, $-C(=O)NR^3-alkylene-$, $-alkylene-NR^3C(=O)-$, or $-NR^3C(=O)-alkylene-$;

v is 2-20;

each R^1 or R^2 is independently hydrogen, halogen, $-CN$, $-OR^a$, $-SR^a$, $-S(=O)R^b$, $-NO_2$, $-NR^cR^d$, $-S(=O)_2R^d$, $-NR^aS(=O)_2R^d$, $-S(=O)_2NR^cR^d$, $-C(=O)R^b$, $-OC(=O)R^b$, $-CO_2R^a$, $-OCO_2R^a$, $-C(=O)NR^cR^d$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)NR^cR^d$, $-NR^aC(=O)R^b$, $-NR^aC(=O)OR^a$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, $-OR^a$, or $-NR^cR^d$; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-OR^a$, $-NR^cR^d$,

or R^1 and R^2 are taken together to form a C_1-C_6 cycloalkyl or C_1-C_6 heterocycloalkyl;

each R^3 is independently hydrogen, $-S(=O)R^b$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-C(=O)R^b$, $-CO_2R^a$, $-C(=O)NR^cR^d$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, $-OR^a$, or $-NR^cR^d$; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-OR^a$, or $-NR^cR^d$;

Y is hydrogen, C_1-C_6 alkyl, $-CO_2H$, $-CO_2(C_1-C_6 \text{ alkyl})$, $-CO_2NH_2$, $-CO_2N(alkyl)_2$, or $-CO_2NH(alkyl)$; and

s is 0-20;

R^a is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, $-OH$, $-OMe$, or $-NH_2$; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-OH$, $-OMe$, or $-NH_2$;

R^b is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, $-OH$, $-OMe$, or $-NH_2$; and the cycloalkyl,

heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -OH, -OMe, or -NH₂;

each R^c and R^d is independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, C₃-C₈ cycloalkyl, C₂-C₈ heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, -OH, -OMe, or -NH₂; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -OH, -OMe, or -NH₂;

or R^c and R^d, together with the nitrogen atom to which they are attached, form a heterocycloalkyl or heteroaryl; wherein the heterocycloalkyl and heteroaryl is optionally substituted with one, two, or three of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -OH, -OMe, or -NH₂.

[00168] In some embodiments, X³ is a bond.

[00169] In some embodiments, X³ is -alkylene-C(=O)- or -C(=O)alkylene-. In some embodiments, X³ is -CH₂-C(=O)- or -C(=O)-CH₂-. In some embodiments, X³ is -alkylene-C(=O)NR³- or -C(=O)NR³-alkylene-. In some embodiments, X³ is -CH₂-C(=O)NR³- or -C(=O)NR³-CH₂-. In some embodiments, X³ is -alkylene-C(=O)NR³-alkylene- or -alkylene-NR³C(=O)-alkylene-. In some embodiments, X³ is -CH₂-C(=O)NR³-CH₂CH₂- or -CH₂-NR³C(=O)-CH₂CH₂-. In some embodiments, X³ is -CH₂-C(=O)NH-CH₂CH₂- or -CH₂-NHC(=O)-CH₂CH₂-.

[00170] In some embodiments, each R³ is independently hydrogen or C₁-C₆ alkyl. In some embodiments, each R³ is hydrogen.

[00171] In some embodiments, s is 1-15. In some embodiments, s is 1-10. In some embodiments, s is 5-15. In some embodiments, s is 5-10. In some embodiments, s is 5-20.

[00172] In some embodiments, Y is hydrogen or -CO₂H. In some embodiments, Y is hydrogen. In some embodiments, Y is -CO₂H.

[00173] In some embodiments, each L is independently -(CR¹R²)_v-, -alkylene-O-, -C(=O)-, -C(=O)NR³-, -NR³C(=O)-, -alkylene-C(=O)NR³-, or -alkylene-NR³C(=O)-; and v is 2-20.

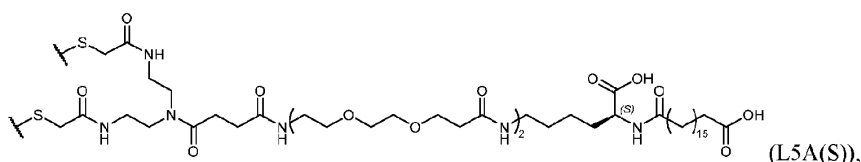
[00174] In some embodiments, each L is independently -(CR¹R²)_v-, -alkylene-O-, -C(=O)-, -C(=O)NR³-, -NR³C(=O)-, -alkylene-C(=O)NR³-, or -alkylene-NR³C(=O)-; and v is 2-16.

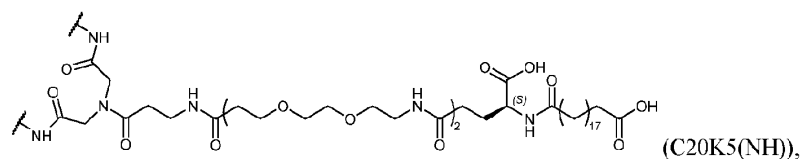
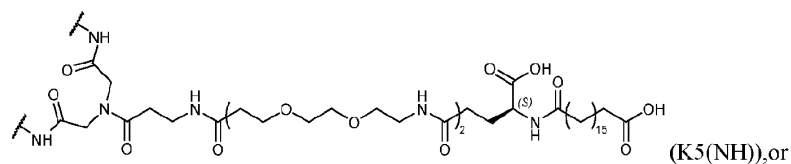
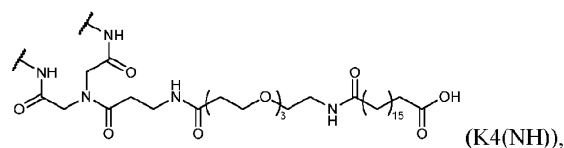
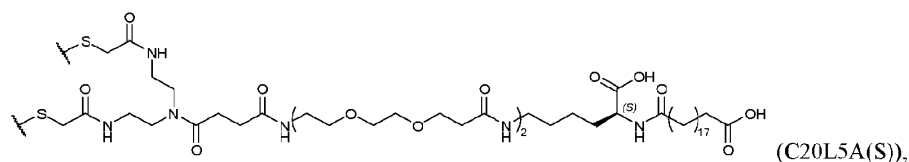
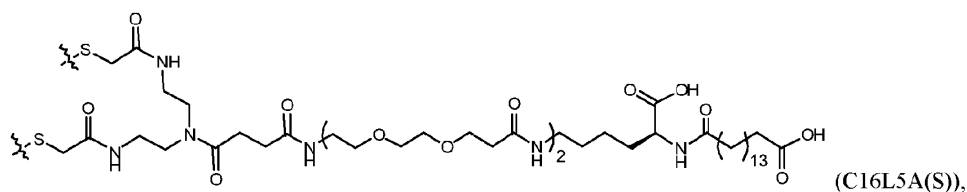
[00175] In some embodiments, v is 2-16. In some embodiments, v is 2-5. In some embodiments, v is 5-16. In some embodiments, v is 5 or 16. In some embodiments, v is 2 or 16.

[00176] In some embodiments, each R¹ or R² is independently hydrogen, halogen, -CN, -OR^a, -NR^cR^d, -C(=O)R^b, -CO₂R^a, -C(=O)NR^cR^d, or C₁-C₆ alkyl.

[00177] In some embodiments, each R¹ or R² is independently hydrogen, halogen, -CO₂R^a, -C(=O)NR^cR^d, or C₁-C₆ alkyl. In some embodiments, each R¹ or R² is independently hydrogen, -CO₂R^a, or -C(=O)NR^cR^d. In some embodiments, each R¹ or R² is independently hydrogen or -CO₂R^a.

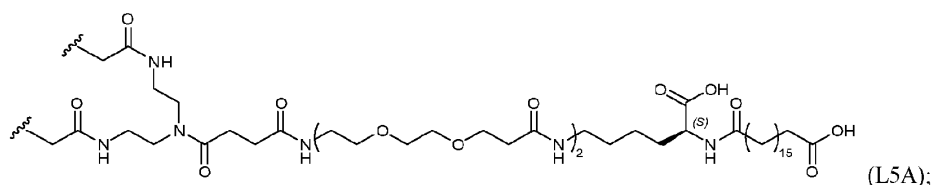
[00178] In some embodiments, the HEM attached to the peptide is:





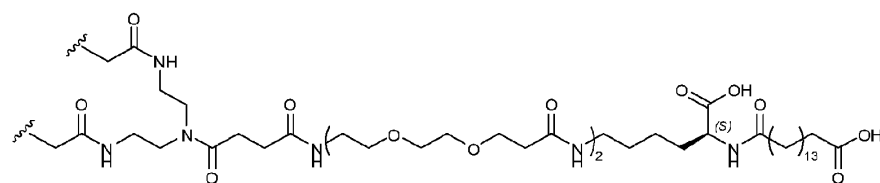
the “ γ -S” being part of a cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, or 2-amino-6-mercaptohexanoic acid residue, and the “ γ -NH” being part of a lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine residue.

[00179] In some embodiments, the HEM attached to the peptide is:



wherein each “ γ -” is connected to an amino acid of the peptide. For instance, the amino acid is a cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, 2-amino-6-mercaptohexanoic acid, lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine residue of the peptide.

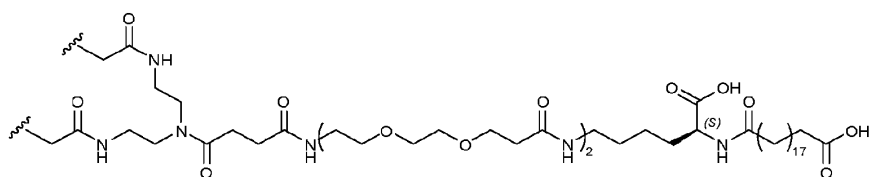
[00180] In some embodiments, the HEM attached to the peptide is:



(C16L5A);

wherein each “ λ ” is connected to an amino acid of the peptide. For instance, the amino acid is a cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, 2-amino-6-mercaptohexanoic acid, lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine residue of the peptide.

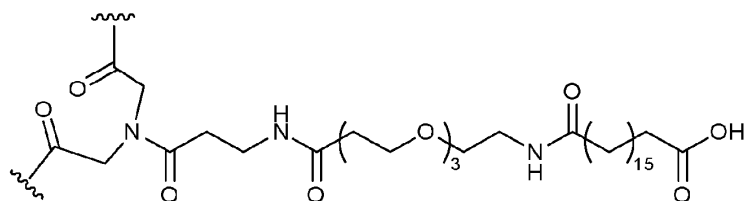
[00181] In some embodiments, the HEM attached to the peptide is:



(C20L5A);

wherein each “ λ ” is connected to an amino acid of the peptide. For instance, the amino acid is a cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, 2-amino-6-mercaptohexanoic acid, lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine residue of the peptide.

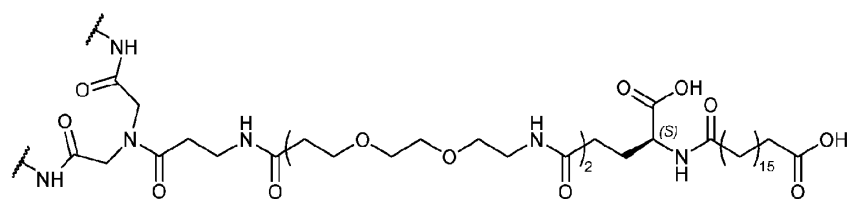
[00182] In some embodiments, the HEM attached to the peptide is:



(K4);

wherein each “ λ ” is connected to an amino acid of the peptide. For instance, the amino acid is a cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, 2-amino-6-mercaptohexanoic acid, lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine residue of the peptide.

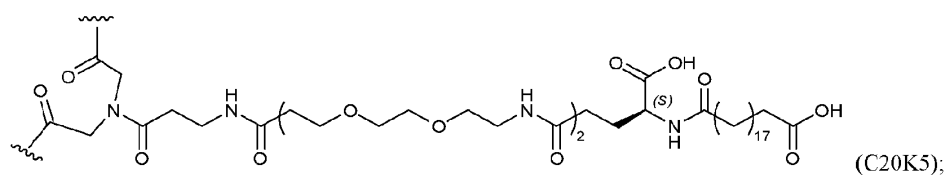
[00183] In some embodiments, the HEM attached to the peptide is:



(K5);

wherein each “ λ ” is connected to an amino acid of the peptide. For instance, the amino acid is a cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, 2-amino-6-mercaptohexanoic acid, lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine residue of the peptide.

[00184] In some embodiments, the HEM attached to the peptide is:



wherein each “ $\sim$ ” is connected to an amino acid of the peptide. For instance, the amino acid is a cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, 2-amino-6-mercaptohexanoic acid, lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine residue of the peptide.

Peptide Conjugates with a Staple

[00185] In one aspect, disclosed herein are peptide conjugates comprising: a peptide and a staple attached to the peptide at a first amino acid and a second amino acid.

[00186] In some embodiments, the peptide conjugates comprise (a) a peptide that modulates a GIP-1R receptor; and (b) a staple attached to the peptide at a first amino acid and a second amino acid.

[00187] In some embodiments, the peptide conjugates comprise (a) a peptide that binds to a GLP-1 receptor; and (b) a staple attached to the peptide at a first amino acid and a second amino acid.

[00188] In some embodiments, the peptide conjugates comprise (a) a peptide that modulates a GIP receptor; and (b) a staple attached to the peptide at a first amino acid and a second amino acid.

[00189] In some embodiments, the peptide conjugates comprise (a) a peptide that binds a GIP receptor; and (b) a staple attached to the peptide at a first amino acid and a second amino acid.

[00190] Non-limiting examples of amino acids for use in conjugation include cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, 2-amino-6-mercaptohexanoic acid, lysine, ornithine, diaminobutyric acid, diaminopropionic acid, homolysine, other sulfhydryl containing amino acids, or other amine containing amino acids. In some embodiments, the two amino acids connected by a staple are about or at least about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or more amino acids apart. For example, the first amino acid has position i , and the second amino acid has position $i + 7$, $i + 11$, $i + 13$, $i + 15$, or $i + 16$. For example, the first amino acid has a position i in the peptide and the second amino acid has a position $i + n$ in the peptide, wherein n is 4-16. In some embodiments, the first amino acid is at the 14 position and the second amino acid is at the 21 position in the peptide. In some embodiments, the first amino acid is at the 17 position and the second amino acid is at the 24 position in the peptide.

[00191] For example, the first amino acid has a position i in the peptide and the second amino acid has a position $i + 4$ in the peptide. For example, the first amino acid has a position i in the peptide and the second amino acid has a position $i + 5$ in the peptide. For example, the first amino acid has a position i in the peptide and the second amino acid has a position $i + 6$ in the peptide. For example, the first amino acid has a position i in the peptide and the second amino acid has a position $i + 7$ in the peptide. For example, the first amino acid has a position i in the peptide and the second amino acid has a position $i + 8$ in the peptide. For example, the first amino acid has a position i in the peptide and the second amino acid has a position $i + 9$ in the peptide. For example, the first amino acid has a position i in the peptide and the second amino acid has a position $i + 10$ in the peptide. For example, the first amino acid has a position i in the peptide and the second amino acid has a position $i + 11$ in the peptide. For example, the first amino acid has a

position i in the peptide and the second amino acid has a position $i + 12$ in the peptide. For example, the first amino acid has a position i in the peptide and the second amino acid has a position $i + 13$ in the peptide. For example, the first amino acid has a position i in the peptide and the second amino acid has a position $i + 14$ in the peptide. For example, the first amino acid has a position i in the peptide and the second amino acid has a position $i + 15$ in the peptide. For example, the first amino acid has a position i in the peptide and the second amino acid has a position $i + 16$ in the peptide.

[00192] In some embodiments, the first amino acid and the second amino acid are independently selected from the group consisting of an amine-containing amino acid and a sulfhydryl-containing amino acid.

[00193] In some embodiments, the first amino acid and second amino acid is independently selected from cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, and 2-amino-6-mercaptohexanoic acid. In some embodiments, the first amino acid and second amino acid are cysteines.

[00194] In some embodiments, the first amino acid and second amino acid is independently selected from lysine, ornithine, diaminobutyric acid, diaminopropionic acid and homolysine.

[00195] In some embodiments, the first amino acid and second amino acid are lysines.

[00196] In some embodiments, the first amino acid and second amino acid are ornithines.

[00197] In some embodiments, the peptide conjugate further comprises a half-life extending molecule attached to a sulfhydryl containing amino acid or an amine-containing amino acid residue in the peptide.

[00198] In some embodiments, the amine-containing amino acid is selected from lysine, ornithine, diaminobutyric acid, diaminopropionic acid, and homolysine.

[00199] In some embodiments, the amine-containing amino acid is lysine.

[00200] In some embodiments, the sulfhydryl-containing amino acid is selected from cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, and 2-amino-6-mercaptohexanoic acid.

[00201] In some embodiments, the sulfhydryl-containing amino acid is cysteine.

[00202] In some embodiments, the peptide comprises a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of any one of SEQ ID NOs: 1-61. In some embodiments, the peptide comprises a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to any one of SEQ ID NOs: 1-61. As a non-limiting example, the peptide comprises a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 6.

Peptide Conjugates

[00203] In one aspect, disclosed herein are peptide conjugates comprising: a peptide and a staple. The staple and/or peptide may comprise a half-life extending moiety (HEM).

[00204] In some embodiments, the peptide conjugates comprise (a) a peptide that modulates a GIP-1R receptor; and (b) a half-life extending moiety (HEM) attached to the peptide at a first amino acid.

[00205] In some embodiments, the peptide conjugates comprise (a) a peptide that binds to a GLP-1 receptor; and (b) a half-life extending moiety (HEM) attached to the peptide at a first amino acid.

[00206] In some embodiments, the peptide conjugates comprise (a) a peptide that modulates a GIP receptor; and (b) a half-life extending moiety (HEM) attached to the peptide at a first amino acid.

[00207] In some embodiments, the peptide conjugates comprise (a) a peptide that binds a GIP receptor; and (b) a half-life extending moiety (HEM) attached to the peptide at a first amino acid.

[00208] Non-limiting examples of amino acids for use in conjugation include cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, 2-amino-6-mercaptohexanoic acid, lysine, ornithine, diaminobutyric acid, diaminopropionic acid, homolysine, other sulfhydryl containing amino acids, or other amine containing amino acids. In some embodiments, the first amino acid is selected from the group consisting of an amine-containing amino acid and a sulfhydryl-containing amino acid. In some embodiments, the first amino acid is selected from cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, and 2-amino-6-mercaptohexanoic acid. In some embodiments, the first amino acid is cysteine. In some embodiments, the first amino acid is selected from lysine, ornithine, diaminobutyric acid, diaminopropionic acid and homolysine. In some embodiments, the first amino acid is lysine. In some embodiments, the first amino acid is ornithine. In some embodiments, the peptide conjugate further comprises a second half-life extending moiety attached to a sulfhydryl containing amino acid or an amine-containing amino acid residue in the peptide. In some embodiments, the amine-containing amino acid is selected from lysine, ornithine, diaminobutyric acid, diaminopropionic acid, and homolysine. In some embodiments, the amine-containing amino acid is lysine. In some embodiments, the sulfhydryl-containing amino acid is selected from cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, and 2-amino-6-mercaptohexanoic acid. In some embodiments, the sulfhydryl-containing amino acid is cysteine.

[00209] The peptide may modulate and/or bind to: a GLP-1 receptor, a GIP receptor, or a GLP-1 receptor and GIP receptor. In exemplary cases, the peptide comprises two amino acids connected by a staple. Non-limiting examples of amino acids for use in conjugation include cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, 2-amino-6-mercaptohexanoic acid, or other sulfhydryl containing amino acids. The two amino acids may be about or at least about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or more amino acids apart. For example, the first amino acid has position i , and the second amino acid has position $i + 7$, $i + 11$, $i + 13$, $i + 15$, or $i + 16$. For example, the first amino acid has a position i in the peptide and the second amino acid has a position $i + n$ in the peptide, wherein n is 4-16. For example, the first amino acid has a position i in the peptide and the second amino acid has a position $i + 7$ in the peptide. For example, the first amino acid has a position i in the peptide and the second amino acid has a position $i + 11$ in the peptide. For example, the first amino acid has a position i in the peptide and the second amino acid has a position $i + 15$ in the peptide. For example, the first amino acid has a position i in the peptide and the second amino acid has a position $i + 16$ in the peptide.

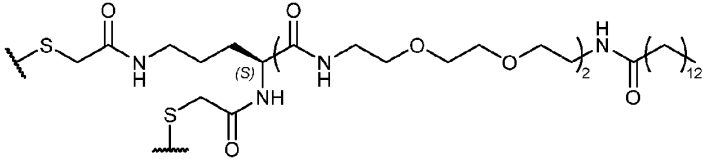
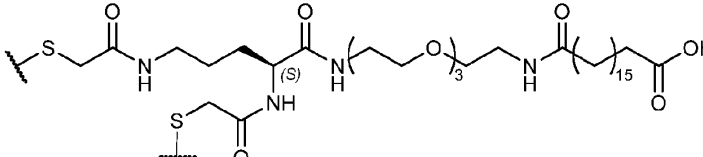
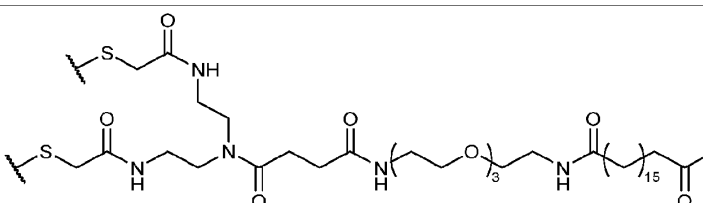
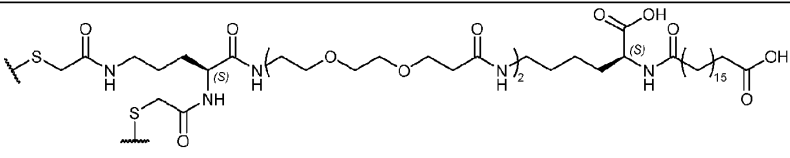
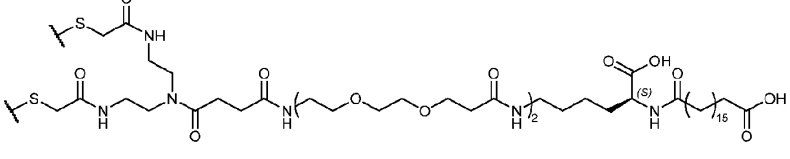
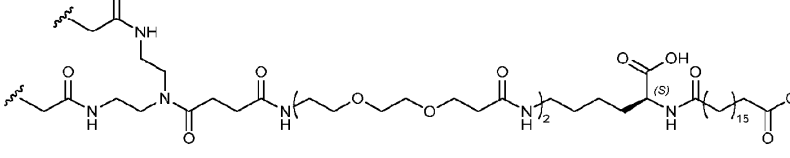
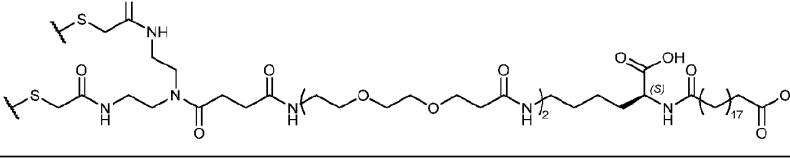
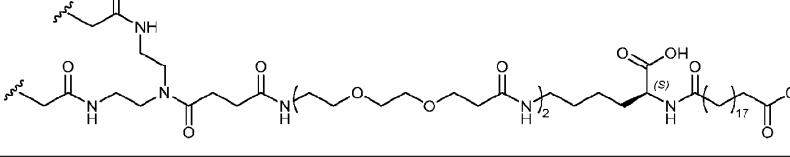
[00210] In some embodiments, the first amino acid and the second amino acid are independently selected from sulfhydryl-containing amino acids.

[00211] In some embodiments, the first amino acid and second amino acid is independently selected from cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, and 2-amino-6-mercaptohexanoic acid. In some embodiments, the first amino acid and second amino acid are cysteines.

[00212] In some embodiments, a peptide herein is conjugated to a structure of Table 2.

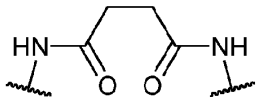
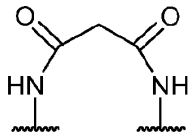
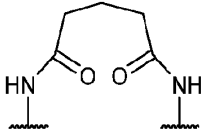
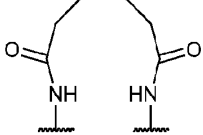
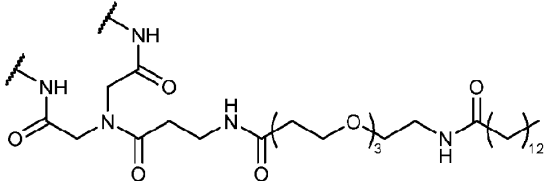
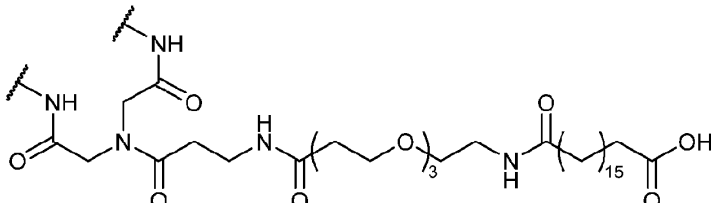
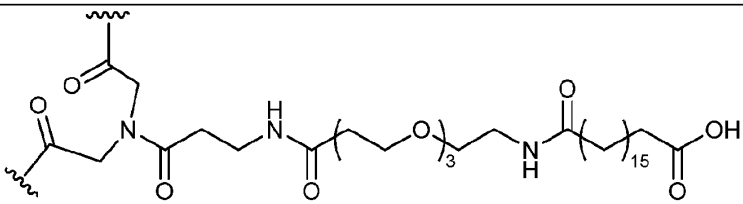
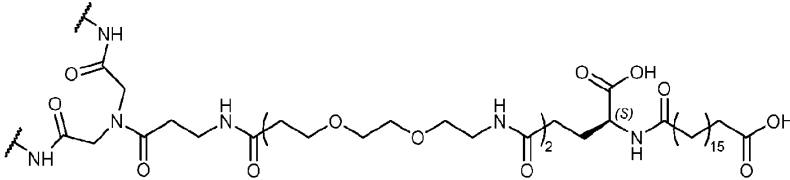
Table 2. Example Structures

Ex	ID	Structure
1	FA2	
2	L1	
3	L1B	
4	L1C	
5	L1D	
6	L1E	
7	L1F	
8	L1G	
	L2	

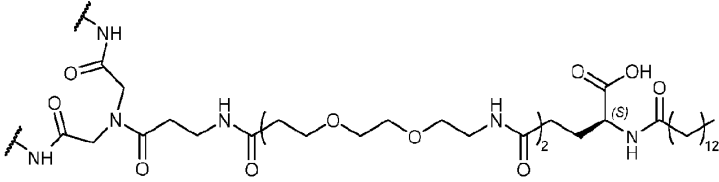
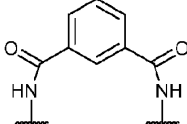
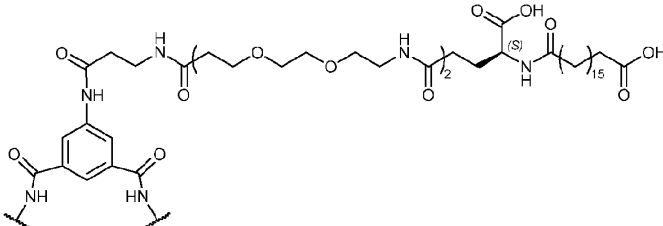
Ex	ID	Structure
9	L3	
10	L4	
11	L4 A	
12	L5	
13	L5 A(S)	
	L5 A	
13	C20 L5 A(S)	
	C20 L5 A	

Ex	ID	Structure
	C16 L5 A(S))	
	C16 L5 A	
14	L6	
15	L7	
16	L8	
17	L9	
18	L12	

Ex	ID	Structure
	L13	
19	L14	
20	L15	
21	L16	
22	L17	
23	L18	
	L19	
	K0	

Ex	ID	Structure
	K1	
	K1 C	
	K1 F	
	K1 H	
	K3	
	K4(NH)	
	K4	
	K5(NH)	

Ex	ID	Structure
	K5	
	C20 K5(NH)	
	C20 K5	
	K6	
	K7	
	K8	
	K9	

Ex	ID	Structure
	K20	
	A1	
	A5	

The “-S-” being part of a cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, or 2-amino-6-mercaptohexanoic acid residue, and the “-N-” being part of a lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine residue. Each “-” of L5A, C20L5A, C16L5A, K4, K5, and C20K5 is connected to an amino acid of the peptide. For instance, the amino acid is a cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, 2-amino-6-mercaptohexanoic acid, lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine residue of the peptide

[00213] In some embodiments, the peptide comprises a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of any one of SEQ ID NOs: 1-61. In some embodiments, the peptide comprises a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to any one of SEQ ID NOs: 1-61.

[00214] In some embodiments, a peptide conjugate comprises:

- a peptide comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of any one of SEQ ID NOs: 1-61; and
- a staple comprising Linker L1 attached to the peptide at a first amino acid and a second amino acid.

[00215] In some embodiments, a peptide conjugate comprises:

- a peptide comprising the first 28 amino acids of any one of SEQ ID NOs: 1-61; and
- a staple comprising Linker L1 attached to the peptide at a first amino acid and a second amino acid.

[00216] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of any one of SEQ ID NOs: 1-61; and

- b) a staple comprising Linker L1 attached to the peptide at a first amino acid and a second amino acid.

[00217] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising any one of SEQ ID NOs: 1-61; and

- b) a staple comprising Linker L1 attached to the peptide at a first amino acid and a second amino acid.

[00218] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of any one of SEQ ID NOs: 1-61; and

- b) a staple comprising Linker L2 attached to the peptide at a first amino acid and a second amino acid.

[00219] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising the first 28 amino acids of any one of SEQ ID NOs: 1-61; and

- b) a staple comprising Linker L2 attached to the peptide at a first amino acid and a second amino acid.

[00220] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of any one of SEQ ID NOs: 1-61; and

- b) a staple comprising Linker L2 attached to the peptide at a first amino acid and a second amino acid.

[00221] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising any one of SEQ ID NOs: 1-61; and

- b) a staple comprising Linker L2 attached to the peptide at a first amino acid and a second amino acid.

[00222] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of any one of SEQ ID NOs: 1-61; and

- b) a staple comprising Linker L3 attached to the peptide at a first amino acid and a second amino acid.

[00223] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising the first 28 amino acids of any one of SEQ ID NOs: 1-61; and

- b) a staple comprising Linker L3 attached to the peptide at a first amino acid and a second amino acid.

[00224] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of any one of SEQ ID NOs: 1-61; and

- b) a staple comprising Linker L3 attached to the peptide at a first amino acid and a second amino acid.

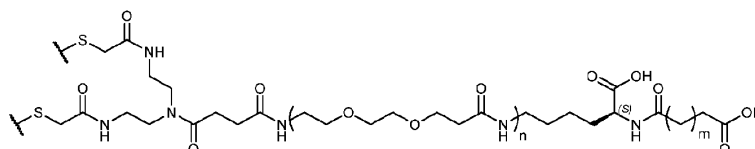
[00225] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising any one of SEQ ID NOs: 1-61; and

- b) a staple comprising Linker L3 attached to the peptide at a first amino acid and a second amino acid.

[00226] In some embodiments, a peptide conjugate comprises:

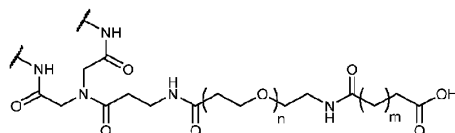
- a) a peptide comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of any one of SEQ ID NOs: 1-61; and
- b) a staple comprising



attached to the peptide at a first amino acid and a second amino acid. In some cases, n is 1-4 and m is 6-20. For example, n is 2 and m is 15, n is 2 and m is 17, or n is 2 and m is 13.

[00227] In some embodiments, a peptide conjugate comprises:

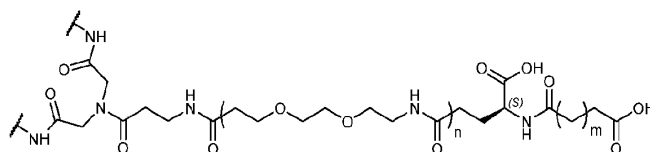
- a) a peptide comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of any one of SEQ ID NOs: 1-61; and
- b) a staple comprising



attached to the peptide at a first amino acid and a second amino acid. In some cases, n is 1-4 and m is 6-20. For example, n is 3 and m is 15.

[00228] In some embodiments, a peptide conjugate comprises:

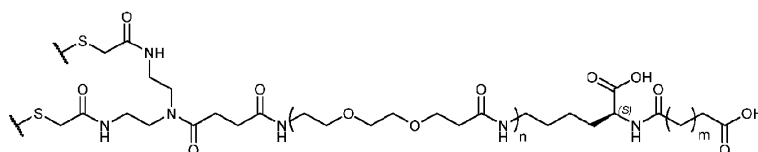
- a) a peptide comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of any one of SEQ ID NOs: 1-61; and
- b) a staple comprising



attached to the peptide at a first amino acid and a second amino acid. In some cases, n is 1-4 and m is 6-20. For example, n is 2 and m is 15, or n is 2 and m is 17.

[00229] In some embodiments, a peptide conjugate comprises:

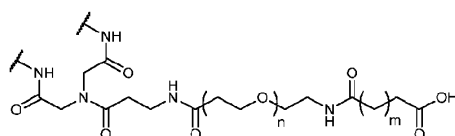
- a) a peptide comprising the first 28 amino acids of any one of SEQ ID NOs: 1-61; and
- b) a staple comprising



attached to the peptide at a first amino acid and a second amino acid. In some cases, n is 1-4 and m is 6-20. For example, n is 2 and m is 15, n is 2 and m is 17, or n is 2 and m is 13.

[00230] In some embodiments, a peptide conjugate comprises:

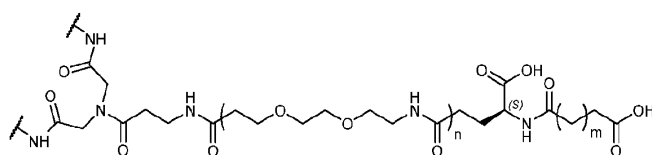
- a peptide comprising the first 28 amino acids of any one of SEQ ID NOs: 1-61; and
- a staple comprising



attached to the peptide at a first amino acid and a second amino acid. In some cases, n is 1-4 and m is 6-20. For example, n is 3 and m is 15.

[00231] In some embodiments, a peptide conjugate comprises:

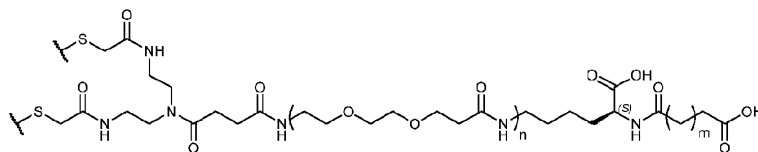
- a peptide comprising the first 28 amino acids of any one of SEQ ID NOs: 1-61; and
- a staple comprising



attached to the peptide at a first amino acid and a second amino acid. In some cases, n is 1-4 and m is 6-20. For example, n is 2 and m is 15, or n is 2 and m is 17.

[00232] In some embodiments, a peptide conjugate comprises:

- a peptide comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to any one of SEQ ID NOs: 1-61; and
- a staple comprising

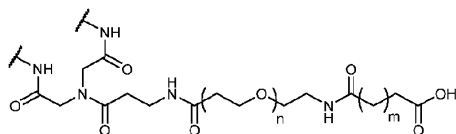


attached to the peptide at a first amino acid and a second amino acid. In some cases, n is 1-4 and m is 6-20. For example, n is 2 and m is 15, n is 2 and m is 17, or n is 2 and m is 13.

[00233] In some embodiments, a peptide conjugate comprises:

- a peptide comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to any one of SEQ ID NOs: 1-61; and

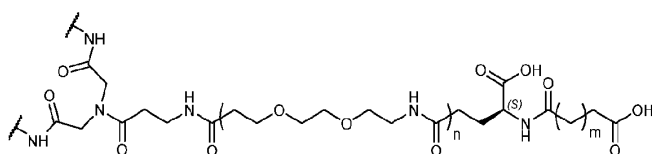
- b) a staple comprising



attached to the peptide at a first amino acid and a second amino acid. In some cases, n is 1-4 and m is 6-20. For example, n is 3 and m is 15.

[00234] In some embodiments, a peptide conjugate comprises:

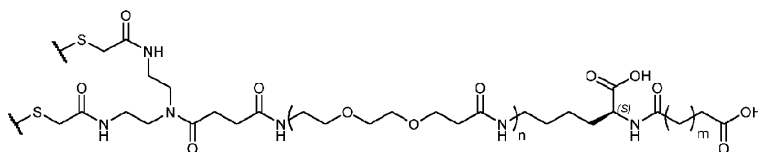
- a) a peptide comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to any one of SEQ ID NOs: 1-61; and
- b) a staple comprising



attached to the peptide at a first amino acid and a second amino acid. In some cases, n is 1-4 and m is 6-20. For example, n is 2 and m is 15, or n is 2 and m is 17.

[00235] In some embodiments, a peptide conjugate comprises:

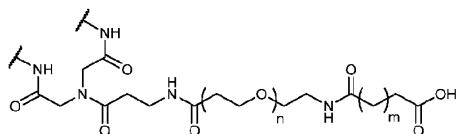
- a) a peptide comprising the peptide comprises any one of SEQ ID NOs: 1-61; and
- b) a staple comprising



attached to the peptide at a first amino acid and a second amino acid. In some cases, n is 1-4 and m is 6-20. For example, n is 2 and m is 15, n is 2 and m is 17, or n is 2 and m is 13.

[00236] In some embodiments, a peptide conjugate comprises:

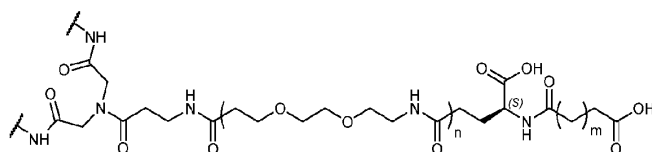
- a) a peptide comprising the peptide comprises any one of SEQ ID NOs: 1-61; and
- b) a staple comprising



attached to the peptide at a first amino acid and a second amino acid. In some cases, n is 1-4 and m is 6-20. For example, n is 3 and m is 15.

[00237] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising the peptide comprises any one of SEQ ID NOs: 1-61; and
- b) a staple comprising



attached to the peptide at a first amino acid and a second amino acid. In some cases, n is 1-4 and m is 6-20. For example, n is 2 and m is 15, or n is 2 and m is 17.

[00238] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of any one of SEQ ID NOs: 1-61; and
- b) a staple comprising L5A attached to the peptide at a first amino acid and a second amino acid. In some cases, the L5A is L5A(S).

[00239] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising the first 28 amino acids of any one of SEQ ID NOs: 1-61; and
- b) a staple comprising L5A attached to the peptide at a first amino acid and a second amino acid. In some cases, the L5A is L5A(S).

[00240] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of any one of SEQ ID NOs: 1-61; and
- b) a staple comprising L5A attached to the peptide at a first amino acid and a second amino acid. In some cases, the L5A is L5A(S).

[00241] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising any one of SEQ ID NOs: 1-61; and
- b) a staple comprising L5A attached to the peptide at a first amino acid and a second amino acid. In some cases, the L5A is L5A(S).

[00242] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of any one of SEQ ID NOs: 1-61; and
- b) a staple comprising C16L5A attached to the peptide at a first amino acid and a second amino acid. In some cases, the C16L5A is C16L5A(S).

[00243] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising the first 28 amino acids of any one of SEQ ID NOs: 1-61; and
- b) a staple comprising C16L5A attached to the peptide at a first amino acid and a second amino acid. In some cases, the C16L5A is C16L5A(S).

[00244] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of any one of SEQ ID NOs: 1-61; and
- b) a staple comprising C16L5A attached to the peptide at a first amino acid and a second amino acid. In some cases, the C16L5A is C16L5A(S).

[00245] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising any one of SEQ ID NOs: 1-61; and
- b) a staple comprising C16L5A attached to the peptide at a first amino acid and a second amino acid. In some cases, the C16L5A is C16L5A(S).

[00246] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of any one of SEQ ID NOs: 1-61; and
- b) a staple comprising C20L5A attached to the peptide at a first amino acid and a second amino acid. In some cases, the C20L5A is C20L5A(S).

[00247] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising the first 28 amino acids of any one of SEQ ID NOs: 1-61; and
- b) a staple comprising C20L5A attached to the peptide at a first amino acid and a second amino acid. In some cases, the C20L5A is C20L5A(S).

[00248] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of any one of SEQ ID NOs: 1-61; and
- b) a staple comprising C20L5A attached to the peptide at a first amino acid and a second amino acid. In some cases, the C20L5A is C20L5A(S).

[00249] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising any one of SEQ ID NOs: 1-61; and
- b) a staple comprising C20L5A attached to the peptide at a first amino acid and a second amino acid. In some cases, the C20L5A is C20L5A(S).

[00250] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of any one of SEQ ID NOs: 1-61; and
- b) a staple comprising K4 attached to the peptide at a first amino acid and a second amino acid. In some cases, the K4 is K4(NH).

[00251] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising the first 28 amino acids of any one of SEQ ID NOs: 1-61; and
- b) a staple comprising K4 attached to the peptide at a first amino acid and a second amino acid. In some cases, the K4 is K4(NH).

[00252] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of any one of SEQ ID NOs: 1-61; and
- b) a staple comprising K4 attached to the peptide at a first amino acid and a second amino acid. In some cases, the K4 is K4(NH).

[00253] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising any one of SEQ ID NOs: 1-61; and
- b) a staple comprising K4 attached to the peptide at a first amino acid and a second amino acid. In some cases, the K4 is K4(NH).

[00254] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of any one of SEQ ID NOs: 1-61; and
- b) a staple comprising K5 attached to the peptide at a first amino acid and a second amino acid. In some cases, the K5 is K5(NH).

[00255] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising the first 28 amino acids of any one of SEQ ID NOs: 1-61; and
- b) a staple comprising K5 attached to the peptide at a first amino acid and a second amino acid. In some cases, the K5 is K5(NH).

[00256] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of any one of SEQ ID NOs: 1-61; and
- b) a staple comprising K5 attached to the peptide at a first amino acid and a second amino acid. In some cases, the K5 is K5(NH).

[00257] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising any one of SEQ ID NOs: 1-61; and
- b) a staple comprising K5 attached to the peptide at a first amino acid and a second amino acid. In some cases, the K5 is K5(NH).

[00258] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of any one of SEQ ID NOs: 1-61; and
- b) a staple comprising C20K5 attached to the peptide at a first amino acid and a second amino acid. In some cases, the C20K5 is C20K5(NH).

[00259] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising the first 28 amino acids of any one of SEQ ID NOs: 1-61; and

- b) a staple comprising C20K5 attached to the peptide at a first amino acid and a second amino acid.
In some cases, the C20K5 is C20K5(NH).

[00260] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of any one of SEQ ID NOs: 1-61; and
- b) a staple comprising C20K5 attached to the peptide at a first amino acid and a second amino acid.
In some cases, the C20K5 is C20K5(NH).

[00261] In some embodiments, a peptide conjugate comprises:

- a) a peptide comprising any one of SEQ ID NOs: 1-61; and
- b) a staple comprising C20K5 attached to the peptide at a first amino acid and a second amino acid.
In some cases, the C20K5 is C20K5(NH).

[0262] In some embodiments, a peptide conjugate described herein is as shown in Table 3.

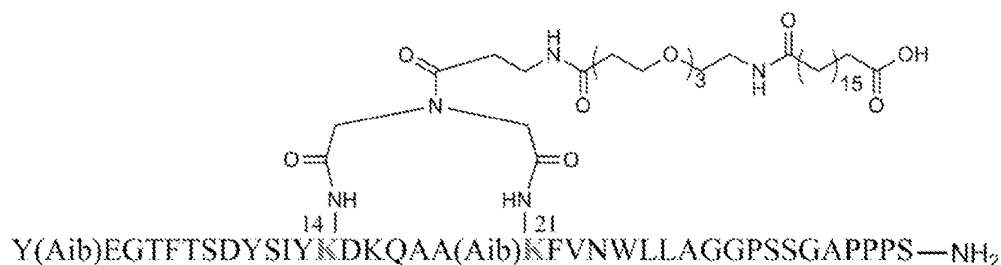
Table 3: Peptide Conjugates

Conjugate	Sequence	Conjugation position	Staple	Calc mass [M+4H] ⁴ ₊	Mass found
mCMD307 (2050-K4)	YAibEGT-FTSDY-SIYXD-KQAAAIb-XFVNW-LLAGG-PSSGA-PPPS-NH2 (where each X is K) (SEQ ID NO: 39)	14, 21	K4	1197.86	1197.87
mCLZ715	YAibEGT-FTSDY-SIYXD-KQAAAIb-XFVNW-LLAGG-PSSGA-PPPS-NH2 (where each X is K) (SEQ ID NO: 40)	14, 21	K5	1259.14	1258.9
mCMD307 C20K5 ZA-39-C20K5	YAibEGT-FTSDY-SIYXD-KQAAAIb-XFVNW-LLAGG-PSSGA-PPPS-NH2 (where each X is K) (SEQ ID NO: 41)	14, 21	C20K5	1265.91	1266.41
mCLZ715-C20K5 ZA-40-/C20K5	YAibEGT-FTSDY-SIYLD-KXAAAIb-EFVXW-LLAGG-PSSGA-PPPS-NH2 (where each X is K) (SEQ ID NO: 42)	17, 24	C20K5	1265.91	1266.42
mCMG681 K4	YAibEGT-FHSDY-DIYXD-KQAAAIb-XFVQW-LLAGG-PSSGA-PPPS-NH2 (where each X is K) (SEQ ID NO: 43)	14, 21	K4	1217.87	1217.96
mCMG679 K4	YAibEGT-FHSDY-DIYXD-KQAANle-XFVAW-LLAGG-PSSGA-PPPS-NH2 (where each X is K) (SEQ ID NO: 44)	14, 21	K4	1210.62	1210.94
mCMG683 K4	YAibEGT-FTsDY-sIYXD-KQAANle-XFVAW-LLAGG-PSSGA-PPPS-NH2 (where each X is K) (SEQ ID NO: 45)	14, 21	K4	1194.37	1194.70
mCMG682 K5	YAibEGT-FHSDY-DIYXD-KQAAAIb-XFVQW-LLAGG-PSSGA-PPPS-NH2 (where each X is K) (SEQ ID NO: 46)	14, 21	K5	1278.89	1279.32
mCMG680 K5	YAibEGT-FHSDY-DIYXD-KQAANle-XFVAW-LLAGG-PSSGA-PPPS-NH2 (where each X is K) (SEQ ID NO: 47)	14, 21	K5	1271.65	1271.73
mCMG684 K5	YAibEGT-FTsDY-sIYXD-KQAANle-XFVAW-LLAGG-PSSGA-PPPS-NH2	14, 21	K5	1255.65	1255.99

Conjugate	Sequence	Conjugation position	Staple	Calc mass [M+4H] ⁴⁺	Mass found
	(where each X is K) (SEQ ID NO: 48)				
mCMC759 (C(14-21) - L5A)	YAibEGT-FTSDY-SIYXD-KQAAAib-XFVNW-LLAGG-PSSGA-PPPS-NH2 (where each X is C) (SEQ ID NO: 49)	14, 21	L5A	1274.88	1275.13
C(14-21) - C20L5A	YAibEGT-FTSDY-SIYXD-KQAAAib-XFVNW-LLAGG-PSSGA-PPPS-NH2 (where each X is C) (SEQ ID NO: 50)	14, 21	C20L5A	1281.89	
27I, C(14-21) - L5A	YAibEGT-FTSDY-SIYXD-KQAAAib-XFVNW-LIAGG-PSSGA-PPPS-NH2 (where each X is C) (SEQ ID NO: 51)	14, 21	L5A	1274.88	
mCMV266 (27I, C(14-21) - C20L5A)	YAibEGT-FTSDY-SIYXD-KQAAAib-XFVNW-LIAGG-PSSGA-PPPS-NH2 (where each X is C) (SEQ ID NO: 52)	14, 21	C20L5A	1281.89	1282.20
7I, 10V, 27I, C(14-21) - L5A	YAibEGT-FISDV-SIYXD-KQAAAib-XFVNW-LIAGG-PSSGA-PPPS-NH2 (where each X is C) (SEQ ID NO: 53)	14, 21	L5A	1261.89	
7I, 10V, 27I, C(14-21) - C20L5A	YAibEGT-FISDV-SIYXD-KQAAAib-XFVNW-LIAGG-PSSGA-PPPS-NH2 (where each X is C) (SEQ ID NO: 54)	14, 21	C20L5A	1268.90	
C(17-24)-L5A	YAibEGT-FTSDY-SIYLD-KXAAAib-EFVXW-LLAGG-PSSGA-PPPS-NH2 (where each X is C) (SEQ ID NO: 55)	17, 24	L5A	1275.13	
C(17-24)-C20L5A	YAibEGT-FTSDY-SIYLD-KXAAAib-EFVXW-LLAGG-PSSGA-PPPS-NH2 (where each X is C) (SEQ ID NO: 56)	17, 24	C20L5A	1282.14	
19Q, 21A, 27I, 29Q, C(17-24)-C20L5A	YAibEGT-FTSDY-SIYLD-KXAQAib-AFVXW-LIAQG-PSSGA-PPPS-NH2 (where each X is C) (SEQ ID NO: 57)	17, 24	C20L5A	1299.40	
6Y, 27I, C(14-21) - C20L5A	YAibEGT-YTSDY-SIYXD-KQAAAib-XFVNW-LIAGG-PSSGA-PPPS-NH2 (where each X is C) (SEQ ID NO: 58)	14, 21	C20L5A	1285.64	

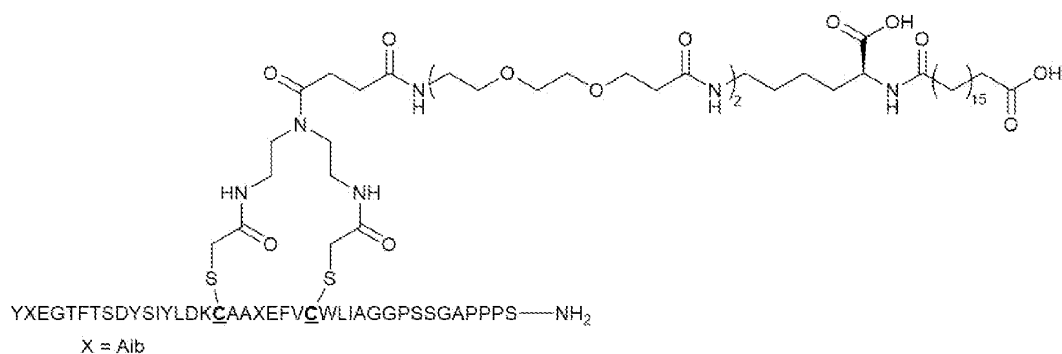
Conjugate	Sequence	Conjugation position	Staple	Calc mass [M+4H] ⁴ ₊	Mass found
6Y, 27I, C(17-24) – C20L5A	YAibEGT-YTSDY-SIYLD-KXAAAIb-EFVXW-LIAGG-PSSGA-PPPS-NH ₂ (where each X is C) (SEQ ID NO: 59)	17, 24	C20L5A	1285.89	
6Y, 8N, 27I, C(17-24) – C20L5A	YAibEGT-YTNDY-SIYLD-KXAAAIb-EFVXW-LIAGG-PSSGA-PPPS-NH ₂ (where each X is C) (SEQ ID NO: 60)	17, 24	C20L5A	1292.64	
mCMV268 (27I, C(17-24) – C20L5A)	YAibEGT-FTSDY-SIYLD-KXAAAIb-EFVXW-LIAGG-PSSGA-PPPS-NH ₂ (where each X is C) (SEQ ID NO: 61)	17, 24	C20L5A	1282.14	1282.20
mCMZ370(C(14-21) – L5A(S))	YAibEGT-FTSDY-SIYXD-KQAAAIb-XFVNW-LIAGG-PSSGA-PPPS-NH ₂ (where each X is C) (SEQ ID NO: 52)	14, 21	L5A(S)		
mCMZ371(C(17-24) – L5A(S))	YAibEGT-FTSDY-SIYLD-KXAAAIb-EFVXW-LIAGG-PSSGA-PPPS-NH ₂ (where each X is C) (SEQ ID NO: 61)	17, 24	L5A(S)		

An example peptide conjugate is shown below, where the -NH- is part of the Lys (K) in the peptide. The example below discloses SEQ ID NO: 62.



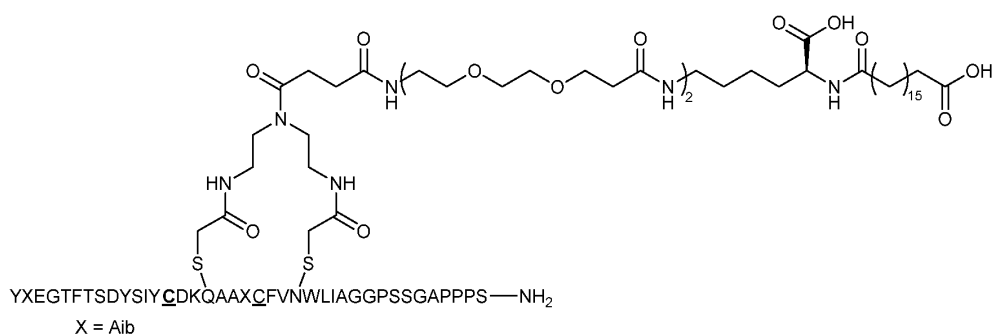
mCMD307

Another example peptide conjugate is shown below.



mCMZ371

A further example peptide conjugate is shown below.

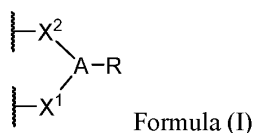


mCMZ370

mCMZ370

Non-limiting example peptide and peptide conjugate embodiments

1. A peptide conjugate comprising:
 - a) a peptide; and
 - b) a staple attached to the peptide at a first amino acid and a second amino acid;
 wherein the staple is of Formula (I):



wherein

A is -N-;

X¹ and X² are a bond, -C(=O)-, -alkylene-C(=O)-, -C(=O)-alkylene-, -alkylene-C(=O)NR³-, -alkylene-NR³C(=O)-, -C(=O)NR³-alkylene-, -NR³C(=O)-alkylene-, -alkylene-C(=O)NR³-alkylene-, or -alkylene-NR³C(=O)-alkylene-;

wherein X^1 is attached to the first amino acid of the peptide, X^2 is attached to the second amino acid of the peptide, and X^1 and X^2 are identical;

R is hydrogen or $-(L)_s-Y$;

each L is independently $-(CR^1R^2)_v-$, $-alkylene-O-$, $-O-alkylene-$, $-C(=O)-alkylene-$, $-alkylene-C(=O)-$, $-NR^3-alkylene-$, $-alkylene-NR^3-$, $-S-alkylene-$, $-alkylene-S-$, $-S(=O)-alkylene-$, $-alkylene-S(=O)-$, $-S(=O)_2-alkylene-$, $-alkylene-S(=O)_2-$, $-C(=O)-$, $-C(=O)NR^3-$, $-NR^3C(=O)-$, $-NR^3C(=O)NR^3-$, $-NR^3C(=O)NR^3-alkylene-$, $-NR^3C(=O)-alkylene-NR^3-$, $-alkylene-C(=O)NR^3-$, $-C(=O)NR^3-alkylene-$, $-alkylene-NR^3C(=O)-$, or $-NR^3C(=O)-alkylene-$;

v is 2-20;

each R^1 or R^2 is independently hydrogen, halogen, $-CN$, $-OR^a$, $-SR^a$, $-S(=O)R^b$, $-NO_2$, $-NR^cR^d$, $-S(=O)_2R^d$, $-NR^aS(=O)_2R^d$, $-S(=O)_2NR^cR^d$, $-C(=O)R^b$, $-OC(=O)R^b$, $-CO_2R^a$, $-OCO_2R^a$, $-C(=O)NR^cR^d$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)NR^cR^d$, $-NR^aC(=O)R^b$, $-NR^aC(=O)OR^a$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, $-OR^a$, or $-NR^cR^d$; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-OR^a$, or $-NR^cR^d$;

or R^1 and R^2 are taken together to form a C_1-C_6 cycloalkyl or C_1-C_6 heterocycloalkyl;

each R^3 is independently hydrogen, $-S(=O)R^b$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-C(=O)R^b$, $-CO_2R^a$, $-C(=O)NR^cR^d$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, $-OR^a$, or $-NR^cR^d$; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-OR^a$, or $-NR^cR^d$;

Y is hydrogen, C_1-C_6 alkyl, $-CO_2H$, $-CO_2(C_1-C_6$ alkyl), $-CO_2NH_2$, $-CO_2N(alkyl)_2$, or $-CO_2NH(alkyl)$;

s is 0-20;

R^a is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, $-OH$, $-OMe$, or $-NH_2$; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-OH$, $-OMe$, or $-NH_2$;

R^b is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, $-OH$, $-OMe$, or $-NH_2$; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-OH$, $-OMe$, or $-NH_2$; and

each R^c and R^d is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, C_2-C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl,

- and heteroalkyl is optionally substituted with one, two, or three of halogen, -OH, -OMe, or -NH₂;
and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -OH, -OMe, or -NH₂;
or R^c and R^d, together with the nitrogen atom to which they are attached, form a heterocycloalkyl or heteroaryl; wherein the heterocycloalkyl and heteroaryl is optionally substituted with one, two, or three of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -OH, -OMe, or -NH₂.
2. The peptide conjugate of embodiment 1, wherein the first amino acid and the second amino acid are independently a sulfhydryl containing amino acid.
 3. The peptide conjugate of embodiment 1 or embodiment 2, wherein the first amino acid and the second amino acid are independently selected from cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, and 2-amino-6-mercaptohexanoic acid.
 4. The peptide conjugate of any one of embodiments 1-3, wherein the first amino acid and second amino acids are cysteines.
 5. The peptide conjugate of embodiment 1, wherein the first amino acid and the second amino acid are independently an amine-containing amino acid.
 6. The peptide conjugate of embodiment 5, wherein the amine-containing amino acid is selected from lysine, ornithine, diaminobutyric acid, diaminopropionic acid and homolysine.
 7. The peptide conjugate of embodiment 5 or 6, wherein the first amino acid and the second amino acids are lysines.
 8. The peptide conjugate of any one of embodiments 1-7, wherein the first amino acid has a position i in the peptide and the second amino acid has a position i + n in the peptide, wherein n is 4-16.
 9. The peptide conjugate of any one of embodiments 1-7, wherein the first amino acid has a position i in the peptide and the second amino acid has a position i + 4 in the peptide.
 10. The peptide conjugate of any one of embodiments 1-7, wherein the first amino acid has a position i in the peptide and the second amino acid has a position i + 7 in the peptide.
 11. The peptide conjugate of any one of embodiments 1-7, wherein the first amino acid has a position i in the peptide and the second amino acid has a position i + 11 in the peptide.
 12. The peptide conjugate of any one of embodiments 1-7, wherein the first amino acid has a position i in the peptide and the second amino acid has a position i + 15 in the peptide.
 13. The peptide conjugate of any one of embodiments 1-7, wherein the first amino acid has a position i in the peptide and the second amino acid has a position i + 16 in the peptide.
 14. The peptide conjugate of any one of embodiments 1-13, wherein the peptide modulates a GLP-1 receptor.
 15. The peptide conjugate of any one of embodiments 1-14, wherein the peptide binds to a GLP-1 receptor.
 16. The peptide conjugate of any one of embodiments 1-15, wherein the peptide modulates a GIP receptor.

17. The peptide conjugate of any one of embodiments 1-16, wherein the peptide binds to a GIP receptor.
18. The peptide conjugate of any one of embodiments 1-17, wherein the peptide is a GLP-1 receptor agonist.
19. The peptide conjugate of any one of embodiments 1-18, wherein the peptide is a GIP receptor agonist.
20. The peptide conjugate of any one of embodiments 1-19, wherein the peptide is a dual GLP-1 receptor and GIP receptor agonist.
21. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of any one of SEQ ID NOs: 1-61.
22. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises the first 28 amino acids of any one of SEQ ID NOs: 1-61.
23. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to any one of SEQ ID NOs: 1-61.
24. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises any one of SEQ ID NOs: 1-61.
25. The peptide conjugate of any one of embodiments 21-24, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
26. The peptide conjugate of any one of embodiments 21-25, wherein each X is a cysteine.
27. The peptide conjugate of any one of embodiments 21-25, wherein each X is a lysine.
28. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 1.
29. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 1.
30. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 1.
31. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises SEQ ID NO: 1.
32. The peptide conjugate of any one of embodiments 28-31, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
33. The peptide conjugate of any one of embodiments 28-31, wherein each X is a cysteine.
34. The peptide conjugate of any one of embodiments 28-31, wherein each X is a lysine.

35. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 2.
36. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 2.
37. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 2.
38. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises SEQ ID NO: 2.
39. The peptide conjugate of any one of embodiments 35-38, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
40. The peptide conjugate of any one of embodiments 35-38, wherein each X is a cysteine.
41. The peptide conjugate of any one of embodiments 35-38, wherein each X is a lysine.
42. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 3.
43. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 3.
44. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 3.
45. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises SEQ ID NO: 3.
46. The peptide conjugate of any one of embodiments 42-45, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
47. The peptide conjugate of any one of embodiments 42-45, wherein each X is a cysteine.
48. The peptide conjugate of any one of embodiments 42-45, wherein each X is a lysine.
49. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 4.
50. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 4.
51. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4.
52. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises SEQ ID NO: 4.

53. The peptide conjugate of any one of embodiments 49-52, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
54. The peptide conjugate of any one of embodiments 49-52, wherein each X is a cysteine.
55. The peptide conjugate of any one of embodiments 49-52, wherein each X is a lysine.
56. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 5.
57. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 5.
58. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5.
59. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises SEQ ID NO: 5.
60. The peptide conjugate of any one of embodiments 56-59, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
61. The peptide conjugate of any one of embodiments 56-59, wherein each X is a cysteine.
62. The peptide conjugate of any one of embodiments 56-59, wherein each X is a lysine.
63. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 6.
64. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 6.
65. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 6.
66. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises SEQ ID NO: 6.
67. The peptide conjugate of any one of embodiments 63-66, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
68. The peptide conjugate of any one of embodiments 63-66, wherein each X is a cysteine.
69. The peptide conjugate of any one of embodiments 63-66, wherein each X is a lysine.
70. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 7.
71. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 7.

72. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 7.
73. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises SEQ ID NO: 7.
74. The peptide conjugate of any one of embodiments 70-73, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
75. The peptide conjugate of any one of embodiments 70-73, wherein each X is a cysteine.
76. The peptide conjugate of any one of embodiments 70-73, wherein each X is a lysine.
77. The peptide conjugate of any one of embodiments 70-76, wherein aa6 is alpha-methyl Phe, N-methyl Phe, D-Phe, beta3-Phe, alpha-methyl Phe, alpha-methyl Phe (2-F), alpha-methyl Phe (3-F), and alpha-methyl (4-F), Phe (2-F), Phe (3-F), or Phe (4-F).
78. The peptide conjugate of any one of embodiments 70-77, wherein aa10 is alpha-methyl Tyr, N-methyl Tyr, D-Tyr, beta3-Tyr, 4-Pyr-Ala, Phe (2-F), Phe (3-F), or Phe (4-F).
79. The peptide conjugate of any one of embodiments 70-78, wherein aa13 is alpha-methyl Leu, N-methyl Leu, D-Leu, beta3-Leu, Leu, Val, Ile, Aib, alpha-methyl Tyr, N-methyl Tyr, D-Tyr, beta3-Tyr, 4-Pyr-Ala, Phe (2-F), Phe (3-F), or Phe (4-F).
80. The peptide conjugate of any one of embodiments 70-79, wherein aa16 is L-Orn, alpha-methyl Lys, N-methyl Lys, D-Lys, or beta3-Lys.
81. The peptide conjugate of any one of embodiments 70-80, wherein aa25 is alpha-methyl Trp, N-methyl Trp, D-Trp, beta3-Trp, alpha-methyl Tyr, or Aib.
82. The peptide conjugate of any one of embodiments 70-81, wherein aa33 is A or E.
83. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 8.
84. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 8.
85. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 8.
86. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises SEQ ID NO: 8.
87. The peptide conjugate of any one of embodiments 83-86, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
88. The peptide conjugate of any one of embodiments 83-86, wherein each X is a cysteine.
89. The peptide conjugate of any one of embodiments 83-86, wherein each X is a lysine.

90. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 9.
91. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 9.
92. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 9.
93. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises SEQ ID NO: 9.
94. The peptide conjugate of any one of embodiments 90-93, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
95. The peptide conjugate of any one of embodiments 90-93, wherein each X is a cysteine.
96. The peptide conjugate of any one of embodiments 90-93, wherein each X is a lysine.
97. The peptide conjugate of any one of embodiments 90-96, wherein aa6 is alpha-methyl Phe, N-methyl Phe, D-Phe, beta3-Phe, alpha-methyl Phe (2-F), alpha-methyl Phe (3-F), and alpha-methyl (4-F), Phe (2-F), Phe (3-F), or Phe (4-F).
98. The peptide conjugate of any one of embodiments 90-97, wherein aa10 is alpha-methyl Tyr, N-methyl Tyr, D-Tyr, beta3-Tyr, 4-Pyr-Ala, Phe (2-F), Phe (3-F), Phe (4-F), or 4-pyridyl-Ala.
99. The peptide conjugate of any one of embodiments 90-98, wherein aa13 is alpha-methyl Leu, N-methyl Leu, D-Leu, beta3-Leu, Val, Ile, or Aib.
100. The peptide conjugate of any one of embodiments 90-99, wherein aa16 is alpha-methyl Leu, N-methyl Leu, D-Leu, beta3-Leu, Val, Ile, or Aib.
101. The peptide conjugate of any one of embodiments 90-100, wherein aa24 is alpha-methyl Asn, N-methyl Asn, beta3-Asn, Aib, D-Asn, D-Asp, D-Glu, or D-Gln.
102. The peptide conjugate of any one of embodiments 90-101, wherein aa25 is alpha-methyl Trp, N-methyl Trp, D-Trp, beta3-Trp, alpha-methyl Tyr, or Aib.
103. The peptide conjugate of any one of embodiments 90-102, wherein aa33 is A or E.
104. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 10.
105. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 10.
106. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 10.
107. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises SEQ ID NO: 10.

108. The peptide conjugate of any one of embodiments 104-107, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
109. The peptide conjugate of any one of embodiments 104-107, wherein each X is a cysteine.
110. The peptide conjugate of any one of embodiments 104-107, wherein each X is a lysine.
111. The peptide conjugate of any one of embodiments 104-110, wherein aa2 is Gly, Val, Leu, Ile, or Aib.
112. The peptide conjugate of any one of embodiments 104-111, wherein aa20 is Gly, Val, Leu, Ile, or Aib.
113. The peptide conjugate of any one of embodiments 104-112, wherein aa13 is alpha-methyl Leu, N-methyl Leu, D-Leu, beta3-Leu, Leu, Val, Ile, Aib, alpha-methyl Tyr, N-methyl Tyr, D-Tyr, beta3-Tyr, 4-Pyr-Ala, Phe (2-F), Phe (3-F), or Phe (4-F).
114. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 11.
115. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 11.
116. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 11.
117. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises SEQ ID NO: 11.
118. The peptide conjugate of any one of embodiments 114-117, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
119. The peptide conjugate of any one of embodiments 114-117, wherein each X is a cysteine.
120. The peptide conjugate of any one of embodiments 114-117, wherein each X is a lysine.
121. The peptide conjugate of any one of embodiments 114-120, wherein aa2 is Gly, Val, Leu, Ile, or Aib.
122. The peptide conjugate of any one of embodiments 114-121, wherein aa20 is Gly, Val, Leu, Ile, or Aib.
123. The peptide conjugate of any one of embodiments 114-122, wherein aa13 is alpha-methyl Leu, N-methyl Leu, D-Leu, beta3-Leu, Leu, Val, Ile, Aib, alpha-methyl Tyr, N-methyl Tyr, D-Tyr, beta3-Tyr, 4-Pyr-Ala, Phe (2-F), Phe (3-F), or Phe (4-F).
124. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 12.
125. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 12.

126. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 12.
127. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises SEQ ID NO: 12.
128. The peptide conjugate of any one of embodiments 124-127, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
129. The peptide conjugate of any one of embodiments 124-127, wherein each X is a cysteine.
130. The peptide conjugate of any one of embodiments 124-127, wherein each X is a lysine.
131. The peptide conjugate of any one of embodiments 124-130, wherein aa2 is Gly, Val, Leu, Ile, or Aib.
132. The peptide conjugate of any one of embodiments 124-131, wherein aa20 is Gly, Val, Leu, Ile, or Aib.
133. The peptide conjugate of any one of embodiments 124-132, wherein aa13 is alpha-methyl Leu, N-methyl Leu, D-Leu, beta3-Leu, Leu, Val, Ile, Aib, alpha-methyl Tyr, N-methyl Tyr, D-Tyr, beta3-Tyr, 4-Pyr-Ala, Phe (2-F), Phe (3-F), or Phe (4-F).
134. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 13.
135. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 13.
136. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 13.
137. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises SEQ ID NO: 13.
138. The peptide conjugate of any one of embodiments 134-137, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
139. The peptide conjugate of any one of embodiments 134-137, wherein each X is a cysteine.
140. The peptide conjugate of any one of embodiments 134-137, wherein each X is a lysine.
141. The peptide conjugate of any one of embodiments 134-140, wherein aa2 is Gly, Val, Leu, Ile, or Aib.
142. The peptide conjugate of any one of embodiments 134-141, wherein aa20 is Gly, Val, Leu, Ile, or Aib.
143. The peptide conjugate of any one of embodiments 134-142, wherein aa13 is alpha-methyl Leu, N-methyl Leu, D-Leu, beta3-Leu, Leu, Val, Ile, Aib, alpha-methyl Tyr, N-methyl Tyr, D-Tyr, beta3-Tyr, 4-Pyr-Ala, Phe (2-F), Phe (3-F), or Phe (4-F).

144. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 14.
145. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 14.
146. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 14.
147. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises SEQ ID NO: 14.
148. The peptide conjugate of any one of embodiments 144-147, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
149. The peptide conjugate of any one of embodiments 144-147, wherein each X is a cysteine.
150. The peptide conjugate of any one of embodiments 144-147, wherein each X is a lysine.
151. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 15.
152. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 15.
153. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 15.
154. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises SEQ ID NO: 15.
155. The peptide conjugate of any one of embodiments 151-154, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
156. The peptide conjugate of any one of embodiments 151-154, wherein each X is a cysteine.
157. The peptide conjugate of any one of embodiments 151-154, wherein each X is a lysine.
158. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 16.
159. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 16.
160. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 16.
161. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises SEQ ID NO: 16.

162. The peptide conjugate of any one of embodiments 158-161, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
163. The peptide conjugate of any one of embodiments 158-161, wherein each X is a cysteine.
164. The peptide conjugate of any one of embodiments 158-161, wherein each X is a lysine.
165. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 17.
166. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 17.
167. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 17.
168. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises SEQ ID NO: 17.
169. The peptide conjugate of any one of embodiments 165-168, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
170. The peptide conjugate of any one of embodiments 165-168, wherein each X is a cysteine.
171. The peptide conjugate of any one of embodiments 165-168, wherein each X is a lysine.
172. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 18.
173. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 18.
174. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 18.
175. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises SEQ ID NO: 18.
176. The peptide conjugate of any one of embodiments 172-175, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
177. The peptide conjugate of any one of embodiments 172-175, wherein each X is a cysteine.
178. The peptide conjugate of any one of embodiments 172-175, wherein each X is a lysine.
179. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 19.
180. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 19.

181. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 19.
182. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises SEQ ID NO: 19.
183. The peptide conjugate of any one of embodiments 179-182, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
184. The peptide conjugate of any one of embodiments 179-182, wherein each X is a cysteine.
185. The peptide conjugate of any one of embodiments 179-182, wherein each X is a lysine.
186. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 20.
187. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 20.
188. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 20.
189. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises SEQ ID NO: 20.
190. The peptide conjugate of any one of embodiments 186-189, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
191. The peptide conjugate of any one of embodiments 186-189, wherein each X is a cysteine.
192. The peptide conjugate of any one of embodiments 186-189, wherein each X is a lysine.
193. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 21.
194. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 21.
195. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 21.
196. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises SEQ ID NO: 21.
197. The peptide conjugate of any one of embodiments 193-196, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
198. The peptide conjugate of any one of embodiments 193-196, wherein each X is a cysteine.
199. The peptide conjugate of any one of embodiments 193-196, wherein each X is a lysine.

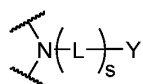
200. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 22.
201. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 22.
202. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 22.
203. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises SEQ ID NO: 22.
204. The peptide conjugate of any one of embodiments 200-203, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
205. The peptide conjugate of any one of embodiments 200-203, wherein each X is a cysteine.
206. The peptide conjugate of any one of embodiments 200-203, wherein each X is a lysine.
207. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 23.
208. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 23.
209. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 23.
210. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises SEQ ID NO: 23.
211. The peptide conjugate of any one of embodiments 207-210, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
212. The peptide conjugate of any one of embodiments 207-210, wherein each X is a cysteine.
213. The peptide conjugate of any one of embodiments 207-210, wherein each X is a lysine.
214. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 24.
215. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 24.
216. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 24.
217. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises SEQ ID NO: 24.

218. The peptide conjugate of any one of embodiments 214-217, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
219. The peptide conjugate of any one of embodiments 214-217, wherein each X is a cysteine.
220. The peptide conjugate of any one of embodiments 214-217, wherein each X is a lysine.
221. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 25.
222. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 25.
223. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 25.
224. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises SEQ ID NO: 25.
225. The peptide conjugate of any one of embodiments 221-224, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
226. The peptide conjugate of any one of embodiments 221-224, wherein each X is a cysteine.
227. The peptide conjugate of any one of embodiments 221-224, wherein each X is a lysine.
228. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 26.
229. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 26.
230. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 26.
231. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises SEQ ID NO: 26.
232. The peptide conjugate of any one of embodiments 228-231, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
233. The peptide conjugate of any one of embodiments 228-231, wherein each X is a cysteine.
234. The peptide conjugate of any one of embodiments 228-231, wherein each X is a lysine.
235. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 27.
236. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 27.

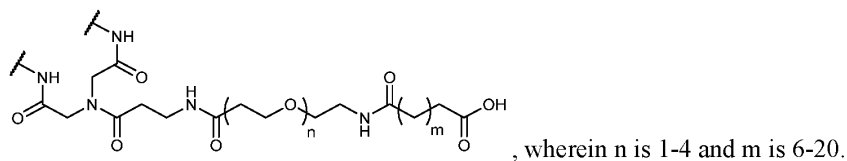
237. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 27.
238. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises SEQ ID NO: 27.
239. The peptide conjugate of any one of embodiments 235-238, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
240. The peptide conjugate of any one of embodiments 235-238, wherein each X is a cysteine.
241. The peptide conjugate of any one of embodiments 235-238, wherein each X is a lysine.
242. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 28.
243. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 28.
244. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 28.
245. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises SEQ ID NO: 28.
246. The peptide conjugate of any one of embodiments 242-245, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
247. The peptide conjugate of any one of embodiments 242-245, wherein each X is a cysteine.
248. The peptide conjugate of any one of embodiments 242-245, wherein each X is a lysine.
249. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 29.
250. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 29.
251. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 29.
252. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises SEQ ID NO: 29.
253. The peptide conjugate of any one of embodiments 249-252, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
254. The peptide conjugate of any one of embodiments 249-252, wherein each X is a cysteine.
255. The peptide conjugate of any one of embodiments 249-252, wherein each X is a lysine.

256. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 30.
257. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 30.
258. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 30.
259. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises SEQ ID NO: 30.
260. The peptide conjugate of any one of embodiments 256-259, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
261. The peptide conjugate of any one of embodiments 256-259, wherein each X is a cysteine.
262. The peptide conjugate of any one of embodiments 256-259, wherein each X is a lysine.
263. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of any one of SEQ ID NOS: 31-61.
264. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises the first 28 amino acids of any one of SEQ ID NOS: 31-61.
265. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to any one of SEQ ID NOS: 31-61.
266. The peptide conjugate of any one of embodiments 1-20, wherein the peptide comprises any one of SEQ ID NOS: 31-61.
267. The peptide conjugate of any one of embodiments 263-266, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
268. The peptide conjugate of any one of embodiments 263-266, wherein each X is a cysteine.
269. The peptide conjugate of any one of embodiments 263-266, wherein each X is a lysine.
270. The peptide conjugate of any one of embodiments 1-269, wherein the peptide is resistant to proteolysis by a gastrointestinal protease.
271. The peptide conjugate of any one of embodiments 1-270, wherein the half-life of the peptide conjugate is at least about 2-fold greater than the half-life of an unmodified form of the peptide.
272. The peptide conjugate of any one of embodiments 1-270, wherein the half-life of the peptide conjugate is at least about 5-fold greater than the half-life of an unmodified form of the peptide.
273. The peptide conjugate of any one of embodiments 1-270, wherein the half-life of the peptide conjugate is at least about 10-fold greater than the half-life of an unmodified form of the peptide.

274. The peptide conjugate of any one of embodiments 1-273, wherein the binding affinity of the peptide conjugate is within about 5% of the binding affinity of an unmodified form of the peptide.
275. The peptide conjugate of any one of embodiments 1-273, wherein the binding affinity of the peptide conjugate is within about 10% of the binding affinity of an unmodified form of the peptide.
276. The peptide conjugate of any one of embodiments 1-273, wherein the binding affinity of the peptide conjugate is within about 15% of the binding affinity of an unmodified form of the peptide.
277. The peptide conjugate of any one of embodiments 1-273, wherein the binding affinity of the peptide conjugate is within about 20% of the binding affinity of an unmodified form of the peptide.
278. The peptide conjugate of any one of embodiments 1-277, wherein X^1 and X^2 are $-C(=O)-$.
279. The peptide conjugate of any one of embodiments 1-277, wherein X^1 and X^2 are $-alkylene-C(=O)-$ or $-C(=O)alkylene-$.
280. The peptide conjugate of any one of embodiments 1-277, wherein X^1 and X^2 are $-CH_2-C(=O)-$ or $-C(=O)-CH_2-$.
281. The peptide conjugate of any one of embodiments 1-277, wherein X^1 and X^2 are $-alkylene-C(=O)NR^3-$ or $-C(=O)NR^3-alkylene-$.
282. The peptide conjugate of any one of embodiments 1-277, wherein X^1 and X^2 are $-CH_2-C(=O)NR^3-$ or $-C(=O)NR^3-CH_2-$.
283. The peptide conjugate of any one of embodiments 1-277, wherein X^1 and X^2 are $-alkylene-C(=O)NR^3-alkylene-$ or $-alkylene-NR^3C(=O)-alkylene-$.
284. The peptide conjugate of any one of embodiments 1-277, wherein X^1 and X^2 are $-CH_2-C(=O)NR^3-CH_2CH_2-$ or $-CH_2-NR^3C(=O)-CH_2CH_2-$.
285. The peptide conjugate of any one of embodiments 1-277, wherein X^1 and X^2 are $-CH_2-C(=O)NH-CH_2CH_2-$ or $-CH_2-NHC(=O)-CH_2CH_2-$.
286. The peptide conjugate of any one of embodiments 1-285, wherein $>A-R$ has the following structure:

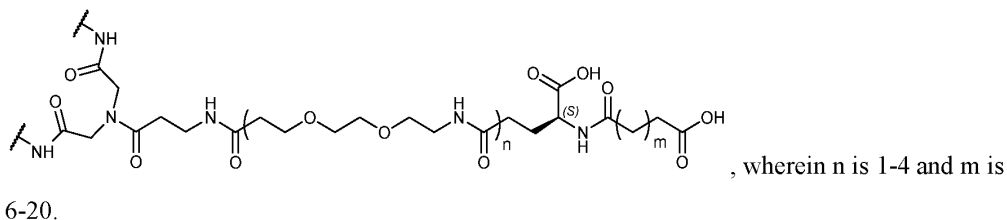


287. The peptide conjugate of any one of embodiments 1-286, wherein s is 1-15.
288. The peptide conjugate of any one of embodiments 1-287, wherein s is 1-10.
289. The peptide conjugate of any one of embodiments 1-288, wherein s is 5-15.
290. The peptide conjugate of any one of embodiments 1-289, wherein s is 5-10.
291. The peptide conjugate of any one of embodiments 1-290, wherein Y is hydrogen or $-CO_2H$.
292. The peptide conjugate of any one of embodiments 1-291, wherein each L is independently $-(CR^1R^2)_v-$, $-alkylene-O-$, $-C(=O)-$, $-C(=O)NR^3-$, $-NR^3C(=O)-$, $-alkylene-C(=O)NR^3-$, or $-alkylene-NR^3C(=O)-$; and v is 2-20.
293. The peptide conjugate of any one of embodiments 1-277, wherein the peptide conjugate comprises:



294. The peptide conjugate of embodiment 293, wherein n is 3 and m is 15.

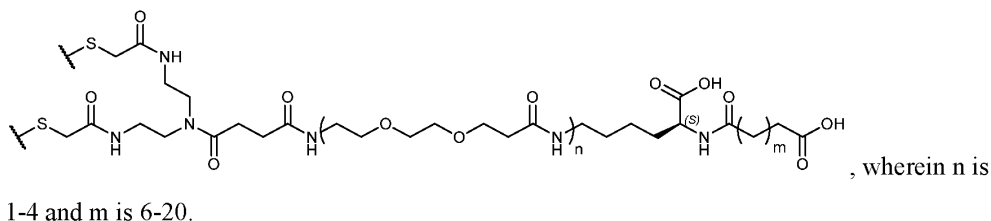
295. The peptide conjugate of any one of embodiments 1-277, wherein the peptide conjugate comprises:



296. The peptide conjugate of embodiment 295, wherein n is 2 and m is 15.

297. The peptide conjugate of embodiment 295, wherein n is 2 and m is 17.

298. The peptide conjugate of any one of embodiments 1-277, wherein the peptide conjugate comprises:

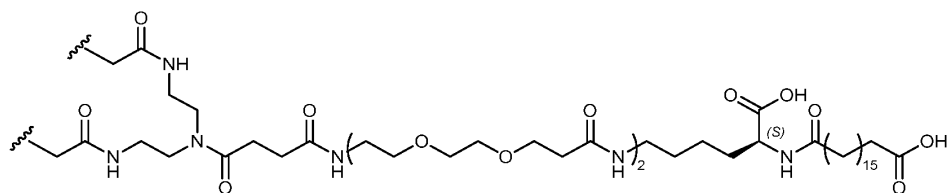


299. The peptide conjugate of embodiment 298, wherein n is 2 and m is 15.

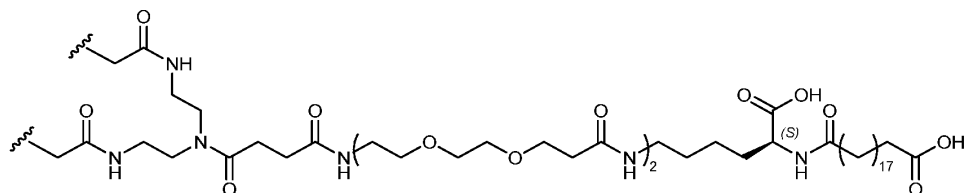
300. The peptide conjugate of embodiment 298, wherein n is 2 and m is 17.

301. The peptide conjugate of embodiment 298, wherein n is 2 and m is 13.

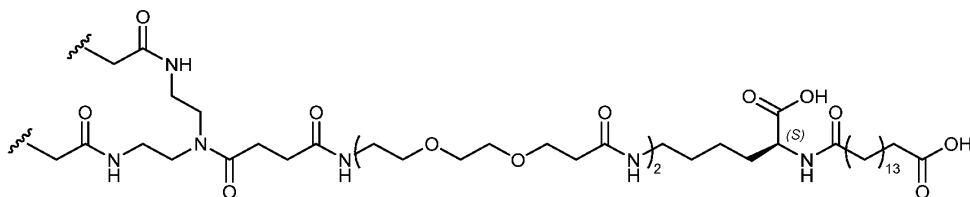
302. The peptide conjugate of any one of embodiments 1-277, wherein the peptide conjugate comprises:
L5A



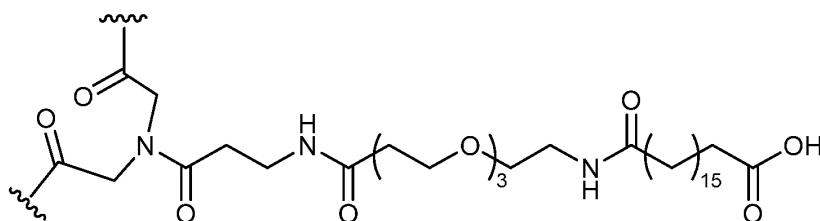
303. The peptide conjugate of any one of embodiments 1-277, wherein the peptide conjugate comprises: C20L5A



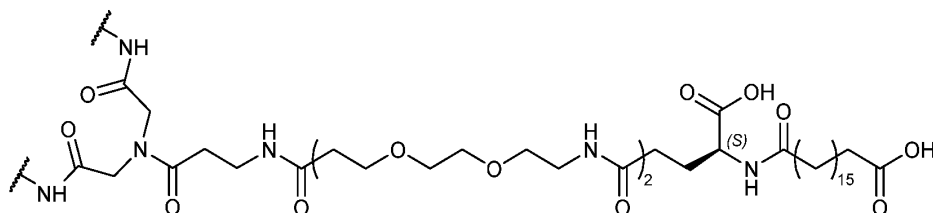
304. The peptide conjugate of any one of embodiments 1-277, wherein the peptide conjugate comprises: C16L5A



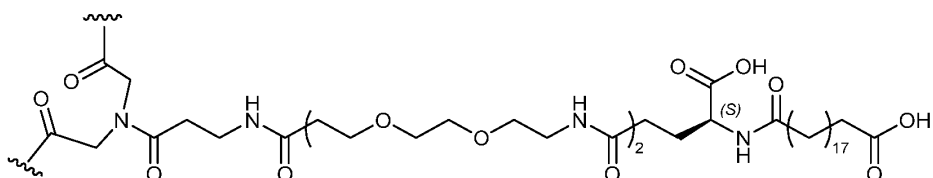
305. The peptide conjugate of any one of embodiments 1-277, wherein the peptide conjugate comprises: K4



306. The peptide conjugate of any one of embodiments 1-277, wherein the peptide conjugate comprises: K5



307. The peptide conjugate of any one of embodiments 1-277, wherein the peptide conjugate comprises: C20K5



308. A peptide conjugate comprising mCMD307 (Table 3).
309. A peptide conjugate comprising: mCMV266 (Table 3).
310. A peptide conjugate comprising: mCMV268 (Table 3).
311. A peptide conjugate comprising any molecule of Table 3.
312. A peptide conjugate comprising:
- a peptide, and
 - a staple attached to the peptide at a first amino acid and a second amino acid.
313. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of any one of SEQ ID NOs: 1-61.
314. The peptide conjugate of embodiment 312, wherein the peptide comprises the first 28 amino acids of any one of SEQ ID NOs: 1-61.

315. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to any one of SEQ ID NOs: 1-61.
316. The peptide conjugate of embodiment 312, wherein the peptide comprises any one of SEQ ID NOs: 1-61.
317. The peptide conjugate of any one of embodiments 313-316, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
318. The peptide conjugate of any one of embodiments 313-316, wherein each X is a cysteine.
319. The peptide conjugate of any one of embodiments 313-316, wherein each X is a lysine.
320. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 1.
321. The peptide conjugate of embodiment 312, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 1.
322. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 1.
323. The peptide conjugate of embodiment 312, wherein the peptide comprises SEQ ID NO: 1.
324. The peptide conjugate of any one of embodiments 320-323, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
325. The peptide conjugate of any one of embodiments 320-323, wherein each X is a cysteine.
326. The peptide conjugate of any one of embodiments 320-323, wherein each X is a lysine.
327. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 2.
328. The peptide conjugate of embodiment 312, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 2.
329. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 2.
330. The peptide conjugate of embodiment 312, wherein the peptide comprises SEQ ID NO: 2.
331. The peptide conjugate of any one of embodiments 327-330, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
332. The peptide conjugate of any one of embodiments 327-330, wherein each X is a cysteine.
333. The peptide conjugate of any one of embodiments 327-330, wherein each X is a lysine.
334. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 3.

335. The peptide conjugate of embodiment 312, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 3.
336. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 3.
337. The peptide conjugate of embodiment 312, wherein the peptide comprises SEQ ID NO: 3.
338. The peptide conjugate of any one of embodiments 334-337, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
339. The peptide conjugate of any one of embodiments 334-337, wherein each X is a cysteine.
340. The peptide conjugate of any one of embodiments 334-337, wherein each X is a lysine.
341. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 4.
342. The peptide conjugate of embodiment 312, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 4.
343. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4.
344. The peptide conjugate of embodiment 312, wherein the peptide comprises SEQ ID NO: 4.
345. The peptide conjugate of any one of embodiments 341-344, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
346. The peptide conjugate of any one of embodiments 341-344, wherein each X is a cysteine.
347. The peptide conjugate of any one of embodiments 341-344, wherein each X is a lysine.
348. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 5.
349. The peptide conjugate of embodiment 312, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 5.
350. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5.
351. The peptide conjugate of embodiment 312, wherein the peptide comprises SEQ ID NO: 5.
352. The peptide conjugate of any one of embodiments 348-351, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
353. The peptide conjugate of any one of embodiments 348-351, wherein each X is a cysteine.
354. The peptide conjugate of any one of embodiments 348-351, wherein each X is a lysine.

355. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 6.
356. The peptide conjugate of embodiment 312, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 6.
357. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 6.
358. The peptide conjugate of embodiment 312, wherein the peptide comprises SEQ ID NO: 6.
359. The peptide conjugate of any one of embodiments 355-358, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
360. The peptide conjugate of any one of embodiments 355-358, wherein each X is a cysteine.
361. The peptide conjugate of any one of embodiments 355-358, wherein each X is a lysine.
362. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 7.
363. The peptide conjugate of embodiment 312, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 7.
364. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 7.
365. The peptide conjugate of embodiment 312, wherein the peptide comprises SEQ ID NO: 7.
366. The peptide conjugate of any one of embodiments 362-365, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
367. The peptide conjugate of any one of embodiments 362-365, wherein each X is a cysteine.
368. The peptide conjugate of any one of embodiments 362-365, wherein each X is a lysine.
369. The peptide conjugate of any one of embodiments 362-368, wherein aa6 is alpha-methyl Phe, N-methyl Phe, D-Phe, beta3-Phe, alpha-methyl Phe, alpha-methyl Phe (2-F), alpha-methyl Phe (3-F), and alpha-methyl (4-F), Phe (2-F), Phe (3-F), or Phe (4-F).
370. The peptide conjugate of any one of embodiments 362-369, wherein aa10 is alpha-methyl Tyr, N-methyl Tyr, D-Tyr, beta3-Tyr, 4-Pyr-Ala, Phe (2-F), Phe (3-F), or Phe (4-F).
371. The peptide conjugate of any one of embodiments 362-370, wherein aa13 is alpha-methyl Leu, N-methyl Leu, D-Leu, beta3-Leu, Leu, Val, Ile, Aib, alpha-methyl Tyr, N-methyl Tyr, D-Tyr, beta3-Tyr, 4-Pyr-Ala, Phe (2-F), Phe (3-F), or Phe (4-F).
372. The peptide conjugate of any one of embodiments 362-371, wherein aa16 is L-Orn, alpha-methyl Lys, N-methyl Lys, D-Lys, or beta3-Lys.
373. The peptide conjugate of any one of embodiments 362-372, wherein aa25 is alpha-methyl Trp, N-methyl Trp, D-Trp, beta3-Trp, alpha-methyl Tyr, or Aib.

374. The peptide conjugate of any one of embodiments 362-373, wherein aa33 is A or E.
375. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 8.
376. The peptide conjugate of embodiment 312, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 8.
377. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 8.
378. The peptide conjugate of embodiment 312, wherein the peptide comprises SEQ ID NO: 8.
379. The peptide conjugate of any one of embodiments 375-378, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
380. The peptide conjugate of any one of embodiments 375-378, wherein each X is a cysteine.
381. The peptide conjugate of any one of embodiments 375-378, wherein each X is a lysine.
382. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 9.
383. The peptide conjugate of embodiment 312, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 9.
384. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 9.
385. The peptide conjugate of embodiment 312, wherein the peptide comprises SEQ ID NO: 9.
386. The peptide conjugate of any one of embodiments 382-385, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
387. The peptide conjugate of any one of embodiments 382-385, wherein each X is a cysteine.
388. The peptide conjugate of any one of embodiments 382-385, wherein each X is a lysine.
389. The peptide conjugate of any one of embodiments 382-388, wherein aa6 is alpha-methyl Phe, N-methyl Phe, D-Phe, beta3-Phe, alpha-methyl Phe (2-F), alpha-methyl Phe (3-F), and alpha-methyl (4-F), Phe (2-F), Phe (3-F), or Phe (4-F).
390. The peptide conjugate of any one of embodiments 382-389, wherein aa10 is alpha-methyl Tyr, N-methyl Tyr, D-Tyr, beta3-Tyr, 4-Pyr-Ala, Phe (2-F), Phe (3-F), Phe (4-F), or 4-pyridyl-Ala.
391. The peptide conjugate of any one of embodiments 382-390, wherein aa13 is alpha-methyl Leu, N-methyl Leu, D-Leu, beta3-Leu, Val, Ile, or Aib.
392. The peptide conjugate of any one of embodiments 382-391, wherein aa16 is alpha-methyl Leu, N-methyl Leu, D-Leu, beta3-Leu, Val, Ile, or Aib.
393. The peptide conjugate of any one of embodiments 382-392, wherein aa24 is alpha-methyl Asn, N-methyl Asn, beta3-Asn, Aib, D-Asn, D-Asp, D-Glu, or D-Gln.

394. The peptide conjugate of any one of embodiments 382-393, wherein aa25 is alpha-methyl Trp, N-methyl Trp, D-Trp, beta3-Trp, alpha-methyl Tyr, or Aib.
395. The peptide conjugate of any one of embodiments 382-394, wherein aa33 is A or E.
396. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 10.
397. The peptide conjugate of embodiment 312, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 10.
398. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 10.
399. The peptide conjugate of embodiment 312, wherein the peptide comprises SEQ ID NO: 10.
400. The peptide conjugate of any one of embodiments 396-399, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
401. The peptide conjugate of any one of embodiments 396-399, wherein each X is a cysteine.
402. The peptide conjugate of any one of embodiments 396-399, wherein each X is a lysine.
403. The peptide conjugate of any one of embodiments 396-402, wherein aa2 is Gly, Val, Leu, Ile, or Aib.
404. The peptide conjugate of any one of embodiments 396-403, wherein aa20 is Gly, Val, Leu, Ile, or Aib.
405. The peptide conjugate of any one of embodiments 396-404, wherein aa13 is alpha-methyl Leu, N-methyl Leu, D-Leu, beta3-Leu, Leu, Val, Ile, Aib, alpha-methyl Tyr, N-methyl Tyr, D-Tyr, beta3-Tyr, 4-Pyr-Ala, Phe (2-F), Phe (3-F), or Phe (4-F).
406. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 11.
407. The peptide conjugate of embodiment 312, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 11.
408. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 11.
409. The peptide conjugate of embodiment 312, wherein the peptide comprises SEQ ID NO: 11.
410. The peptide conjugate of any one of embodiments 406-409, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
411. The peptide conjugate of any one of embodiments 406-409, wherein each X is a cysteine.
412. The peptide conjugate of any one of embodiments 406-409, wherein each X is a lysine.
413. The peptide conjugate of any one of embodiments 406-412, wherein aa2 is Gly, Val, Leu, Ile, or Aib.

414. The peptide conjugate of any one of embodiments 406-413, wherein aa20 is Gly, Val, Leu, Ile, or Aib.
415. The peptide conjugate of any one of embodiments 406-414, wherein aa13 is alpha-methyl Leu, N-methyl Leu, D-Leu, beta3-Leu, Leu, Val, Ile, Aib, alpha-methyl Tyr, N-methyl Tyr, D-Tyr, beta3-Tyr, 4-Pyr-Ala, Phe (2-F), Phe (3-F), or Phe (4-F).
416. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 12.
417. The peptide conjugate of embodiment 312, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 12.
418. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 12.
419. The peptide conjugate of embodiment 312, wherein the peptide comprises SEQ ID NO: 12.
420. The peptide conjugate of any one of embodiments 416-419, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
421. The peptide conjugate of any one of embodiments 416-419, wherein each X is a cysteine.
422. The peptide conjugate of any one of embodiments 416-419, wherein each X is a lysine.
423. The peptide conjugate of any one of embodiments 416-422, wherein aa2 is Gly, Val, Leu, Ile, or Aib.
424. The peptide conjugate of any one of embodiments 416-423, wherein aa20 is Gly, Val, Leu, Ile, or Aib.
425. The peptide conjugate of any one of embodiments 416-424, wherein aa13 is alpha-methyl Leu, N-methyl Leu, D-Leu, beta3-Leu, Leu, Val, Ile, Aib, alpha-methyl Tyr, N-methyl Tyr, D-Tyr, beta3-Tyr, 4-Pyr-Ala, Phe (2-F), Phe (3-F), or Phe (4-F).
426. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 13.
427. The peptide conjugate of embodiment 312, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 13.
428. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 13.
429. The peptide conjugate of embodiment 312, wherein the peptide comprises SEQ ID NO: 13.
430. The peptide conjugate of any one of embodiments 426-429, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
431. The peptide conjugate of any one of embodiments 426-429, wherein each X is a cysteine.
432. The peptide conjugate of any one of embodiments 426-429, wherein each X is a lysine.

433. The peptide conjugate of any one of embodiments 426-432, wherein aa2 is Gly, Val, Leu, Ile, or Aib.
434. The peptide conjugate of any one of embodiments 426-433, wherein aa20 is Gly, Val, Leu, Ile, or Aib.
435. The peptide conjugate of any one of embodiments 426-434, wherein aa13 is alpha-methyl Leu, N-methyl Leu, D-Leu, beta3-Leu, Leu, Val, Ile, Aib, alpha-methyl Tyr, N-methyl Tyr, D-Tyr, beta3-Tyr, 4-Pyr-Ala, Phe (2-F), Phe (3-F), or Phe (4-F).
436. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 14.
437. The peptide conjugate of embodiment 312, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 14.
438. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 14.
439. The peptide conjugate of embodiment 312, wherein the peptide comprises SEQ ID NO: 14.
440. The peptide conjugate of any one of embodiments 436-439, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
441. The peptide conjugate of any one of embodiments 436-439, wherein each X is a cysteine.
442. The peptide conjugate of any one of embodiments 436-439, wherein each X is a lysine.
443. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 15.
444. The peptide conjugate of embodiment 312, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 15.
445. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 15.
446. The peptide conjugate of embodiment 312, wherein the peptide comprises SEQ ID NO: 15.
447. The peptide conjugate of any one of embodiments 443-446, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
448. The peptide conjugate of any one of embodiments 443-446, wherein each X is a cysteine.
449. The peptide conjugate of any one of embodiments 443-446, wherein each X is a lysine.
450. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 16.
451. The peptide conjugate of embodiment 312, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 16.

452. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 16.
453. The peptide conjugate of embodiment 312, wherein the peptide comprises SEQ ID NO: 16.
454. The peptide conjugate of any one of embodiments 450-453, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
455. The peptide conjugate of any one of embodiments 450-453, wherein each X is a cysteine.
456. The peptide conjugate of any one of embodiments 450-453, wherein each X is a lysine.
457. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 17.
458. The peptide conjugate of embodiment 312, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 17.
459. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 17.
460. The peptide conjugate of embodiment 312, wherein the peptide comprises SEQ ID NO: 17.
461. The peptide conjugate of any one of embodiments 457-460, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
462. The peptide conjugate of any one of embodiments 457-460, wherein each X is a cysteine.
463. The peptide conjugate of any one of embodiments 457-460, wherein each X is a lysine.
464. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 18.
465. The peptide conjugate of embodiment 312, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 18.
466. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 18.
467. The peptide conjugate of embodiment 312, wherein the peptide comprises SEQ ID NO: 18.
468. The peptide conjugate of any one of embodiments 464-467, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
469. The peptide conjugate of any one of embodiments 464-467, wherein each X is a cysteine.
470. The peptide conjugate of any one of embodiments 464-467, wherein each X is a lysine.
471. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 19.

472. The peptide conjugate of embodiment 312, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 19.
473. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 19.
474. The peptide conjugate of embodiment 312, wherein the peptide comprises SEQ ID NO: 19.
475. The peptide conjugate of any one of embodiments 471-474, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
476. The peptide conjugate of any one of embodiments 471-474, wherein each X is a cysteine.
477. The peptide conjugate of any one of embodiments 471-474, wherein each X is a lysine.
478. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 20.
479. The peptide conjugate of embodiment 312, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 20.
480. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 20.
481. The peptide conjugate of embodiment 312, wherein the peptide comprises SEQ ID NO: 20.
482. The peptide conjugate of any one of embodiments 478-481, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
483. The peptide conjugate of any one of embodiments 478-481, wherein each X is a cysteine.
484. The peptide conjugate of any one of embodiments 478-481, wherein each X is a lysine.
485. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 21.
486. The peptide conjugate of embodiment 312, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 21.
487. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 21.
488. The peptide conjugate of embodiment 312, wherein the peptide comprises SEQ ID NO: 21.
489. The peptide conjugate of any one of embodiments 485-488, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
490. The peptide conjugate of any one of embodiments 485-488, wherein each X is a cysteine.
491. The peptide conjugate of any one of embodiments 485-488, wherein each X is a lysine.

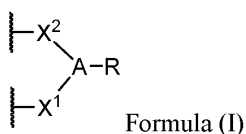
492. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 22.
493. The peptide conjugate of embodiment 312, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 22.
494. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 22.
495. The peptide conjugate of embodiment 312, wherein the peptide comprises SEQ ID NO: 22.
496. The peptide conjugate of any one of embodiments 492-495, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
497. The peptide conjugate of any one of embodiments 492-495, wherein each X is a cysteine.
498. The peptide conjugate of any one of embodiments 492-495, wherein each X is a lysine.
499. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 23.
500. The peptide conjugate of embodiment 312, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 23.
501. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 23.
502. The peptide conjugate of embodiment 312, wherein the peptide comprises SEQ ID NO: 23.
503. The peptide conjugate of any one of embodiments 499-502, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
504. The peptide conjugate of any one of embodiments 499-502, wherein each X is a cysteine.
505. The peptide conjugate of any one of embodiments 499-502, wherein each X is a lysine.
506. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 24.
507. The peptide conjugate of embodiment 312, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 24.
508. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 24.
509. The peptide conjugate of embodiment 312, wherein the peptide comprises SEQ ID NO: 24.
510. The peptide conjugate of any one of embodiments 506-509, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
511. The peptide conjugate of any one of embodiments 506-509, wherein each X is a cysteine.

512. The peptide conjugate of any one of embodiments 506-509, wherein each X is a lysine.
513. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 25.
514. The peptide conjugate of embodiment 312, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 25.
515. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 25.
516. The peptide conjugate of embodiment 312, wherein the peptide comprises SEQ ID NO: 25.
517. The peptide conjugate of any one of embodiments 513-516, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
518. The peptide conjugate of any one of embodiments 513-516, wherein each X is a cysteine.
519. The peptide conjugate of any one of embodiments 513-516, wherein each X is a lysine.
520. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 26.
521. The peptide conjugate of embodiment 312, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 26.
522. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 26.
523. The peptide conjugate of embodiment 312, wherein the peptide comprises SEQ ID NO: 26.
524. The peptide conjugate of any one of embodiments 520-523, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
525. The peptide conjugate of any one of embodiments 520-523, wherein each X is a cysteine.
526. The peptide conjugate of any one of embodiments 520-523, wherein each X is a lysine.
527. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 27.
528. The peptide conjugate of embodiment 312, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 27.
529. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 27.
530. The peptide conjugate of embodiment 312, wherein the peptide comprises SEQ ID NO: 27.
531. The peptide conjugate of any one of embodiments 527-530, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.

532. The peptide conjugate of any one of embodiments 527-530, wherein each X is a cysteine.
533. The peptide conjugate of any one of embodiments 527-530, wherein each X is a lysine.
534. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 28.
535. The peptide conjugate of embodiment 312, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 28.
536. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 28.
537. The peptide conjugate of embodiment 312, wherein the peptide comprises SEQ ID NO: 28.
538. The peptide conjugate of any one of embodiments 534-537, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
539. The peptide conjugate of any one of embodiments 534-537, wherein each X is a cysteine.
540. The peptide conjugate of any one of embodiments 534-537, wherein each X is a lysine.
541. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 29.
542. The peptide conjugate of embodiment 312, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 29.
543. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 29.
544. The peptide conjugate of embodiment 312, wherein the peptide comprises SEQ ID NO: 29.
545. The peptide conjugate of any one of embodiments 541-544, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
546. The peptide conjugate of any one of embodiments 541-544, wherein each X is a cysteine.
547. The peptide conjugate of any one of embodiments 541-544, wherein each X is a lysine.
548. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of SEQ ID NO: 30.
549. The peptide conjugate of embodiment 312, wherein the peptide comprises the first 28 amino acids of SEQ ID NO: 30.
550. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 30.
551. The peptide conjugate of embodiment 312, wherein the peptide comprises SEQ ID NO: 30.

552. The peptide conjugate of any one of embodiments 548-551, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
553. The peptide conjugate of any one of embodiments 548-551, wherein each X is a cysteine.
554. The peptide conjugate of any one of embodiments 548-551, wherein each X is a lysine.
555. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the first 28 amino acids of any one of SEQ ID NOS: 31-61.
556. The peptide conjugate of embodiment 312, wherein the peptide comprises the first 28 amino acids of any one of SEQ ID NOS: 31-61.
557. The peptide conjugate of embodiment 312, wherein the peptide comprises a sequence about or at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to any one of SEQ ID NOS: 31-61.
558. The peptide conjugate of embodiment 312, wherein the peptide comprises any one of SEQ ID NOS: 31-61.
559. The peptide conjugate of any one of embodiments 555-558, wherein each X is independently selected from a sulfhydryl-containing amino acid and an amine-containing amino acid.
560. The peptide conjugate of any one of embodiments 555-558, wherein each X is a cysteine.
561. The peptide conjugate of any one of embodiments 555-558, wherein each X is a lysine.
562. The peptide conjugate of any one of embodiments 312-561, wherein the peptide is resistant to proteolysis by a gastrointestinal protease.
563. The peptide conjugate of any one of embodiments 312-562, wherein the first amino acid and the second amino acid are independently an amine-containing amino acid or a sulfhydryl-containing amino acid.
564. The peptide conjugate of any one of embodiments 312-562, wherein the first amino acid and second amino acid are independently selected from cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, and 2-amino-6-mercaptohexanoic acid.
565. The peptide conjugate of any one of embodiments 312-562, wherein the first amino acid and second amino acid are each cysteines.
566. The peptide conjugate of any one of embodiments 312-562, wherein the first amino acid and second amino acid is independently selected from lysine, ornithine, diaminobutyric acid, diaminopropionic acid and homolysine.
567. The peptide conjugate of any one of embodiments 312-562, wherein the first amino acid and second amino acid are each lysines.
568. The peptide conjugate of any one of embodiments 312-562 further comprising a half-life extending molecule attached to a sulfhydryl containing amino acid.
569. The peptide conjugate of any one of embodiments 312-562 further comprising a half-life extending molecule attached to an amine-containing amino acid residue in the peptide.

570. The peptide conjugate of embodiment 569, wherein the amine-containing amino acid is selected from lysine, ornithine, diaminobutyric acid, diaminopropionic acid and homolysine.
571. The peptide conjugate of embodiment 569, wherein the amine-containing amino acid is lysine.
572. The peptide conjugate of embodiment 568, wherein the sulfhydryl-containing amino acid is selected from cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, and 2-amino-6-mercaptohexanoic acid.
573. The peptide conjugate of embodiment 568, wherein the sulfhydryl-containing amino acid is cysteine.
574. The peptide conjugate of any one of embodiments 312-573, wherein the first amino acid has a position i in the peptide and the second amino acid has a position $i + n$ in the peptide, wherein n is 4-16.
575. The peptide conjugate of any one of embodiments 312-573, wherein the first amino acid has a position i in the peptide and the second amino acid has a position $i + 7$ in the peptide.
576. The peptide conjugate of any one of embodiments 312-573, wherein the half-life of the peptide conjugate is at least about 2-fold greater than the half-life of an unmodified form of the peptide.
577. The peptide conjugate of any one of embodiments 312-573, wherein the half-life of the peptide conjugate is at least about 5-fold greater than the half-life of an unmodified form of the peptide.
578. The peptide conjugate of any one of embodiments 312-573, wherein the half-life of the peptide conjugate is at least about 10-fold greater than the half-life of an unmodified form of the peptide.
579. The peptide conjugate of any one of embodiments 312-578, wherein the binding affinity of the peptide conjugate is within about 5% of the binding affinity of an unmodified form of the peptide.
580. The peptide conjugate of any one of embodiments 312-578, wherein the binding affinity of the peptide conjugate is within about 10% of the binding affinity of an unmodified form of the peptide.
581. The peptide conjugate of any one of embodiments 312-578, wherein the binding affinity of the peptide conjugate is within about 15% of the binding affinity of an unmodified form of the peptide.
582. The peptide conjugate of any one of embodiments 312-578, wherein the binding affinity of the peptide conjugate is within about 20% of the binding affinity of an unmodified form of the peptide.
583. The peptide conjugate of any one of embodiments 312-582, wherein the staple is of Formula (I):



wherein

A is an optionally substituted alkylene, optionally substituted arylene, optionally substituted heteroarylene, optionally substituted $\text{-NR}^3\text{-alkylene-NR}^3\text{-}$, or -N- ;

X^1 and X^2 are independently a bond, -C(=O)- , -alkylene-C(=O)- , -C(=O)-alkylene- , $\text{-alkylene-C(=O)NR}^3\text{-}$, $\text{-alkylene-NR}^3\text{C(=O)-}$, $\text{-C(=O)NR}^3\text{-alkylene-}$, $\text{-NR}^3\text{C(=O)-alkylene-}$, $\text{-alkylene-C(=O)NR}^3\text{-alkylene-}$, or $\text{-alkylene-NR}^3\text{C(=O)-alkylene-}$;

wherein X^1 is attached to a first amino acid of the peptide, and X^2 is attached to a second amino acid of the peptide;

R is hydrogen or $-(L)_s-Y$;

each L is independently $-(CR^1R^2)_v-$, -alkylene-O-, -O-alkylene-, $-C(=O)$ -alkylene-, -alkylene- $C(=O)-$, $-NR^3$ -alkylene-, -alkylene- NR^3- , -S-alkylene-, -alkylene-S-, $-S(=O)$ -alkylene-, -alkylene- $S(=O)-$, $-S(=O)_2$ -alkylene-, -alkylene- $S(=O)_2-$, $-C(=O)-$, $-C(=O)NR^3-$, $-NR^3C(=O)-$, $-NR^3C(=O)NR^3-$, $-NR^3C(=O)NR^3$ -alkylene-, $-NR^3C(=O)$ -alkylene- NR^3- , -alkylene- $C(=O)NR^3-$, $-C(=O)NR^3$ -alkylene-, -alkylene- $NR^3C(=O)-$, or $-NR^3C(=O)$ -alkylene-;

v is 2-20;

each R^1 or R^2 is independently hydrogen, halogen, -CN, $-OR^a$, $-SR^a$, $-S(=O)R^b$, $-NO_2$, $-NR^cR^d$, $-S(=O)_2R^d$, $-NR^aS(=O)_2R^d$, $-S(=O)_2NR^cR^d$, $-C(=O)R^b$, $-OC(=O)R^b$, $-CO_2R^a$, $-OCO_2R^a$, $-C(=O)NR^cR^d$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)NR^cR^d$, $-NR^aC(=O)R^b$, $-NR^aC(=O)OR^a$, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 heteroalkyl, C_3 - C_8 cycloalkyl, C_2 - C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, $-OR^a$, or $-NR^cR^d$; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, $-OR^a$, $-NR^cR^d$,

or R^1 and R^2 are taken together to form a C_1 - C_6 cycloalkyl or C_1 - C_6 heterocycloalkyl;

each R^3 is independently hydrogen, $-S(=O)R^b$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-C(=O)R^b$, $-CO_2R^a$, $-C(=O)NR^cR^d$, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 heteroalkyl, C_3 - C_8 cycloalkyl, C_2 - C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, $-OR^a$, or $-NR^cR^d$; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, $-OR^a$, or $-NR^cR^d$;

Y is hydrogen, C_1 - C_6 alkyl, $-CO_2H$, $-CO_2(C_1-C_6 \text{ alkyl})$, $-CO_2NH_2$, $-CO_2N(\text{alkyl})_2$, or $-CO_2NH(\text{alkyl})$; and

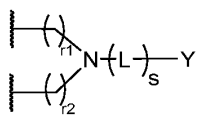
s is 0-20;

R^a is hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 heteroalkyl, C_3 - C_8 cycloalkyl, C_2 - C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, -OH, -OMe, or $-NH_2$; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, -OH, -OMe, or $-NH_2$;

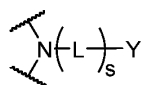
R^b is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 heteroalkyl, C_3 - C_8 cycloalkyl, C_2 - C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, -OH, -OMe, or $-NH_2$; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, -OH, -OMe, or $-NH_2$;

each R^c and R^d is independently hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 heteroalkyl, C_3 - C_8 cycloalkyl, C_2 - C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, -OH, -OMe, or $-NH_2$;

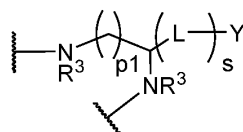
- and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -OH, -OMe, or -NH₂;
- or R^c and R^d, together with the nitrogen atom to which they are attached, form a heterocycloalkyl or heteroaryl; wherein the heterocycloalkyl and heteroaryl is optionally substituted with one, two, or three of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -OH, -OMe, or -NH₂.
584. The peptide conjugate of embodiment 583, wherein A is optionally substituted alkylene.
585. The peptide conjugate of embodiment 583 or 584, wherein A is -(CH₂)_t-, wherein t is 1-12.
586. The peptide conjugate of embodiment 583, wherein A is optionally substituted arylene.
587. The peptide conjugate of embodiment 583, wherein A is -NR³-alkylene-NR³-.
588. The peptide conjugate of embodiment 583, wherein A is -N-.
589. The peptide conjugate of any one of embodiments 583-588, wherein X¹ and X² are identical.
590. The peptide conjugate of any one of embodiments 583-588, wherein X¹ and X² are different.
591. The peptide conjugate of any one of embodiments 583-588, wherein X¹ and X² are -C(=O)-.
592. The peptide conjugate of any one of embodiments 583-588, wherein X¹ and X² are independently -alkylene-C(=O)- or -C(=O)alkylene-.
593. The peptide conjugate of any one of embodiments 583-588, wherein X¹ and X² are independently -CH₂-C(=O)- or -C(=O)-CH₂-.
594. The peptide conjugate of any one of embodiments 583-588, wherein X¹ and X² are independently -alkylene-C(=O)NR³- or -C(=O)NR³-alkylene-.
595. The peptide conjugate of any one of embodiments 583-588, wherein X¹ and X² are independently -CH₂-C(=O)NR³- or -C(=O)NR³-CH₂-.
596. The peptide conjugate of any one of embodiments 583-588, wherein X¹ and X² are independently -alkylene-C(=O)NR³-alkylene- or -alkylene-NR³C(=O)-alkylene-.
597. The peptide conjugate of any one of embodiments 583-588, wherein X¹ and X² are independently -CH₂-C(=O)NR³-CH₂CH₂- or -CH₂-NR³C(=O)-CH₂CH₂-.
598. The peptide conjugate of any one of embodiments 583-588, wherein X¹ and X² are independently -CH₂-C(=O)NH-CH₂CH₂- or -CH₂-NHC(=O)-CH₂CH₂-.
599. The peptide conjugate of any one of embodiments 583-598, wherein >A-R has the following structure:



600. The peptide conjugate of any one of embodiments 583-599, wherein >A-R has the following structure:

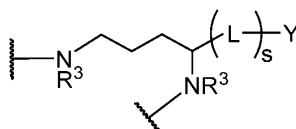


601. The peptide conjugate of any one of embodiments 583-600, wherein >A-R has the following structure:

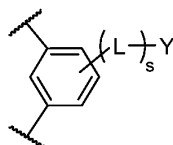


wherein p1 is 1-5.

602. The peptide conjugate of any one of embodiments 583-598 or 601, wherein >A-R has the following structure:

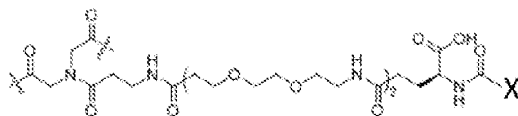


603. The peptide conjugate of any one of embodiments 583-598, wherein >A-R has the following structure:

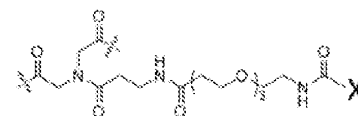


604. The peptide conjugate of any one of embodiments 583-603, wherein s is 1-15.
 605. The peptide conjugate of any one of embodiments 583-603, wherein s is 1-10.
 606. The peptide conjugate of any one of embodiments 583-603, wherein s is 5-15.
 607. The peptide conjugate of any one of embodiments 583-603, wherein s is 5-10.
 608. The peptide conjugate of any one of embodiments 583-607, wherein Y is hydrogen or -CO₂H.
 609. The peptide conjugate of any one of embodiments 583-608, wherein each L is independently - (CR¹R²)_v-, -alkylene-O-, -C(=O)-, -C(=O)NR³-, -NR³C(=O)-, -alkylene-C(=O)NR³-, or -alkylene-NR³C(=O)-; and v is 2-20.
 610. The peptide conjugate of any one of embodiments 312-582, wherein the staple comprises Linker L1, Linker L2, or Linker L3:

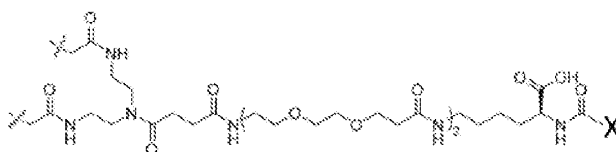
Linker L1



Linker L2



Linker L3



wherein X comprises a fatty acid.

611. The peptide conjugate of embodiment 610, wherein the fatty acid comprises a chain of about 10 to about 22 carbon atoms.

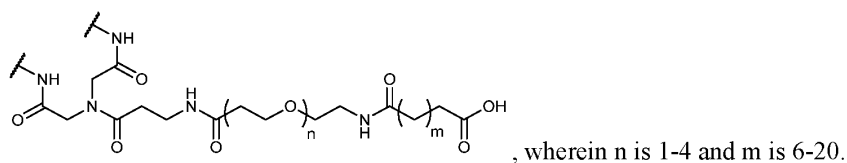
612. The peptide conjugate of embodiment 610, wherein the fatty acid comprises propionic acid, butyric acid, valeric acid, caproic acid, enanthic acid, caprylic acid, pelargonic acid, capric acid, undecylic acid, lauric acid, tridecylic acid, myristic acid, pentadecylic acid, palmitic acid, margaric acid, stearic acid, nonadecylic acid, arachidic acid, heneicosylic acid, behenic acid, tricosylic acid, lignoceric acid, or pentacosylic acid.

613. The peptide conjugate of any one of embodiments 610-612, comprising the Linker L1.

614. The peptide conjugate of any one of embodiments 610-612, comprising the Linker L2.

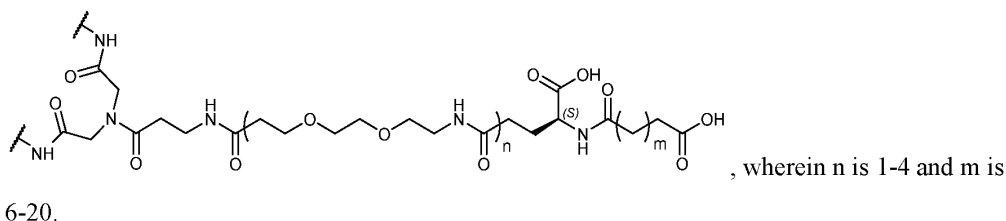
615. The peptide conjugate of any one of embodiments 610-612, comprising the Linker L3.

616. The peptide conjugate of any one of embodiments 312-582, wherein the peptide conjugate comprises:



617. The peptide conjugate of embodiment 616, wherein n is 3 and m is 15.

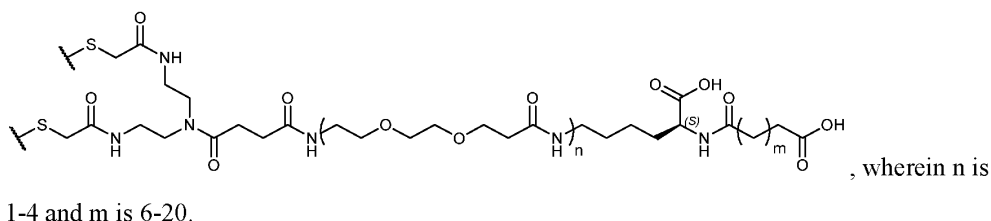
618. The peptide conjugate of any one of embodiments 312-582, wherein the peptide conjugate comprises:



619. The peptide conjugate of embodiment 618, wherein n is 2 and m is 15.

620. The peptide conjugate of embodiment 618, wherein n is 2 and m is 17.

621. The peptide conjugate of any one of embodiments 312-582, wherein the peptide conjugate comprises:

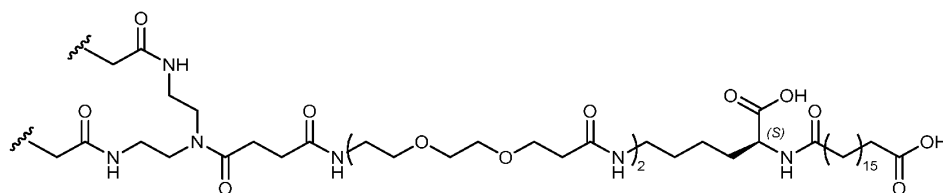


622. The peptide conjugate of embodiment 621, wherein n is 2 and m is 15.

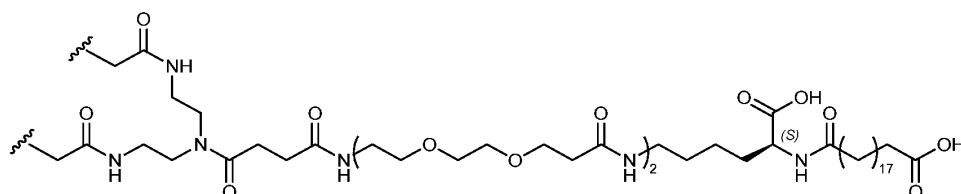
623. The peptide conjugate of embodiment 621, wherein n is 2 and m is 17.

624. The peptide conjugate of embodiment 621, wherein n is 2 and m is 13.

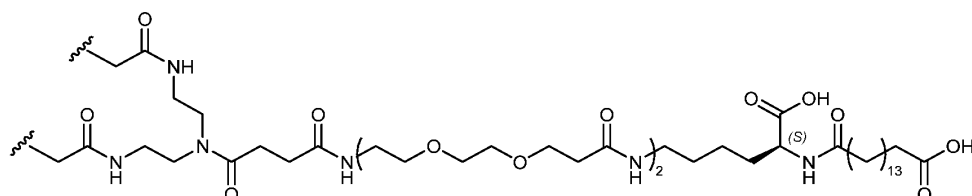
625. The peptide conjugate of any one of embodiments 312-582, wherein the peptide conjugate comprises: L5A



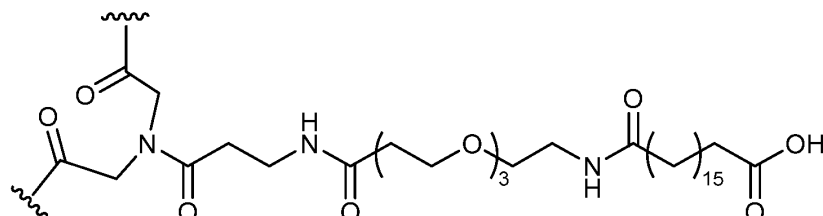
626. The peptide conjugate of any one of embodiments 312-582, wherein the peptide conjugate comprises: C20L5A



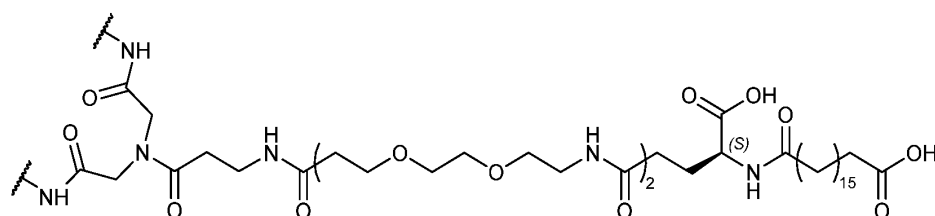
627. The peptide conjugate of any one of embodiments 312-582, wherein the peptide conjugate comprises: C16L5A



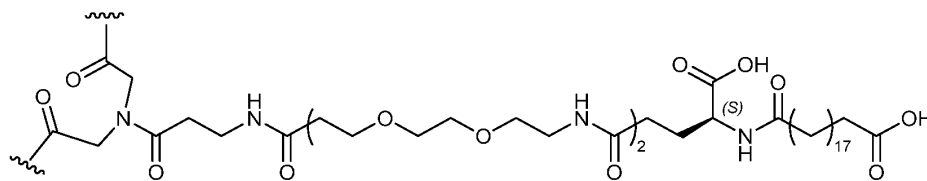
628. The peptide conjugate of any one of embodiments 312-582, wherein the peptide conjugate comprises: K4



629. The peptide conjugate of any one of embodiments 312-582, wherein the peptide conjugate comprises: K5



630. The peptide conjugate of any one of embodiments 312-582, wherein the peptide conjugate comprises: C20K5



631. A peptide comprising the peptide of any one of embodiments 28-270.
632. A pharmaceutical composition comprising the peptide conjugate of any one of embodiments 1-630 or a peptide of embodiment 631, and a pharmaceutically acceptable excipient.
633. A method for treating a disease or condition in a subject in need thereof, the method comprising administering to the subject a composition comprising a therapeutically effective amount of the peptide conjugate of any one of embodiments 1-630 or the peptide of embodiment 631.
634. The method of embodiment 633, wherein the disease or condition is diabetes or obesity.
635. The method of embodiment 633, wherein the disease or condition is non-alcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), or cardiovascular disease.
636. The method of embodiment 633, wherein the disease or condition is short bowel syndrome (SBS).
637. The method of embodiment 633, wherein the disease or condition is inflammatory bowel disease (IBD), inflammatory bowel syndrome (IBS), or psoriasis.
638. The method of embodiment 633, wherein the disease or condition is Crohn's disease or ulcerative colitis.
639. The method of embodiment 633, wherein the disease or condition is Alzheimer's disease, Parkinson's disease or Huntington's disease.
640. The method of any one of embodiments 633-639, further comprising administering to the subject one or more additional therapeutic agents.
641. The method of embodiment 640, wherein the one or more additional therapeutic agents comprises an incretin hormone or a derivative thereof.
642. The method of embodiment 641, wherein the incretin hormone or derivative thereof is selected from GLP-1, exendin-4, glucagon (GCG), glucose-dependent insulinotropic polypeptide (GIP), oxyntomodulin, and combinations thereof.
643. The method of any one of embodiments 633-642, wherein the peptide conjugate is administered about once every 7 days.
644. The method of any one of embodiments 633-642, wherein the peptide conjugate is administered about once every 14 days.
645. The method of any one of embodiments 633-642, wherein the peptide conjugate is administered about once a month.
646. The method of any one of embodiments 633-642, wherein the peptide conjugate is administered about once every two months.
647. The method of any one of embodiments 633-642, wherein the peptide conjugate is administered about once every three months.

Pharmacokinetics

[0263] Mechanisms by which peptides and peptide conjugates positively influence pharmacokinetic or pharmacodynamic behavior include, but are not limited to, (i) preventing or mitigating *in vivo* proteolytic degradation or other activity-diminishing chemical modification of the therapeutic agent; (ii) improving half-life or other pharmacokinetic properties by reducing renal filtration, decreasing receptor-mediated clearance or increasing bioavailability; (iii) reducing toxicity; (iv) improving solubility; and/or (v) increasing biological activity and/or target selectivity of the unconjugated therapeutic agent. The therapeutic agent may comprise a peptide that modulates and/or binds to: a GLP-1 receptor, a GIP receptor, or a GLP-1 receptor and GIP receptor. The therapeutic agent may comprise a peptide comprising a sequence about or at least about 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to any one of SEQ ID NOS: 1-61.

[0264] Peptide conjugates may enhance one or more pharmacokinetic properties of a therapeutic agent when attached to the therapeutic agent. Peptide conjugates disclosed herein may enhance the one or more pharmacokinetic properties of the therapeutic agent by at least about 200% as measured by pharmacodynamics when compared to the therapeutic agent or unmodified therapeutic peptide alone. Peptide conjugates disclosed herein may enhance the one or more pharmacokinetic properties of the therapeutic agent by at least about 300%, 400%, 500%, 600%, 700%, 800%, 900%, 1000% as measured by pharmacodynamics when compared to the therapeutic agent or unmodified therapeutic peptide alone.

[0265] The pharmacokinetic properties may comprise a half-life. The half-life of the peptide conjugate may be at least about two-fold longer compared to the half-life of the unmodified peptide alone. The half-life of the peptide conjugate disclosed herein may be at least about 3-fold, 4-fold, 5-fold, or 10-fold longer compared to the half-life of the therapeutic agent or unmodified therapeutic peptide alone. The half-life of a peptide conjugate disclosed herein may be at least about 6-, 7-, 8-, 9-, 10-, 15-, 20-, 25-, 30-, 35-, 40-, 45-, or 50-fold longer compared to the half-life of the unmodified peptide alone.

[0266] In some embodiments, the half-life of the peptide conjugate is at least about 2-fold greater than the half-life of an unmodified form of the peptide. In some embodiments, the half-life of the peptide conjugate is at least about 5-fold greater than the half-life of an unmodified form of the peptide. In some embodiments, the half-life of the peptide conjugate is at least about 10-fold greater than the half-life of an unmodified form of the peptide.

[0267] In addition, a peptide conjugate as described herein may have a positive effect on terms of increasing manufacturability, and/or reducing immunogenicity of the peptide, compared to an unconjugated form of the unmodified therapeutic peptide.

[0268] In some embodiments, peptides and peptide conjugates disclosed herein are administered weekly, or about every 7 days. In some cases, peptides and peptide conjugates disclosed herein are administered biweekly, or about every 14 days. In some cases, a peptide disclosed herein is administered every week, every two weeks, once a month, or once every three months. In some cases, a peptide conjugate disclosed herein is administered every week, every two weeks, once a month, or once every three months.

Therapeutic Use

[0269] In one aspect, peptides and peptide conjugates disclosed herein are useful for treating, alleviating, inhibiting and/or preventing one or more diseases and/or conditions. The disease and/or condition may be a chronic disease or condition. Alternatively, the disease and/or condition is an acute disease or condition. The disease or condition may be recurrent, refractory, accelerated, or in remission. The disease or condition may affect one or more cell types. The one or more diseases and/or conditions may be an autoimmune disease, inflammatory disease, or metabolic disease.

[0270] Disclosed herein are methods for treating a disease or condition in a subject in need thereof, the method comprising administering to the subject a peptide conjugate described herein. The disease or condition may be diabetes or obesity, or a medical condition associated with diabetes or obesity. The diabetes may be type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, neonatal diabetes, maturity onset diabetes of the young, or latent autoimmune diabetes in adults, or any combination thereof. The disease or condition may be non-alcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), or cardiovascular disease. The disease or condition may be an autoimmune disorder. The disease or condition may be Crohn's disease or ulcerative colitis. The disease or condition may be short bowel syndrome (SBS). The disease or condition may be inflammatory bowel disease (IBD), inflammatory bowel syndrome (IBS), or psoriasis. The disease or condition may be Alzheimer's disease, Parkinson's disease or Huntington's disease. The peptide conjugate may be administered with one or more additional therapeutic agents. Disclosed herein are methods of treating a disease or condition in a subject in need thereof, the method comprising administering to the subject a composition disclosed herein comprising one or more peptide conjugates.

[0271] Provided herein is a method of preventing or treating a metabolic disease or condition in a subject in need thereof, the method comprising administering to the subject a peptide conjugate described herein. The metabolic disease or condition may be diabetes. The metabolic disease or condition may be obesity. The metabolic disease or condition may be glycogen storage disease, phenylketonuria, maple syrup urine disease, glutaric acidemia type 1, Carbamoyl phosphate synthetase I deficiency, alcaptonuria, Medium-chain acyl-coenzyme A dehydrogenase deficiency (MCADD), acute intermittent porphyria, Lesch-Nyhan syndrome, lipoid congenital adrenal hyperplasia, congenital adrenal hyperplasia, POMPC deficiency, LEPR deficiency, Bardet Biedl syndrome, Alstrom syndrome, Prader-Willi Syndrome, Kearns-Sayre syndrome, Zellweger syndrome, Gaucher's disease, or Niemann Pick disease.

[0272] Provided herein is a method of preventing or treating NAFLD, NASH, or cardiovascular disease in a subject in need thereof, the method comprising administering to the subject a peptide conjugate described herein.

[0273] Provided herein is a method of preventing or treating short bowel syndrome (SBS) in a subject in need thereof, the method comprising administering to the subject a peptide conjugate described herein.

[0274] Provided herein is a method of preventing or treating inflammatory bowel disease (IBD), inflammatory bowel syndrome (IBS), or psoriasis in a subject in need thereof, the method comprising administering to the subject a peptide conjugate described herein.

[0275] Provided herein is a method of preventing or treating Crohn's disease or ulcerative colitis in a subject in need thereof, the method comprising administering to the subject a peptide conjugate described herein.

[0276] Provided herein is a method of preventing or treating a sleep disorder.

[0277] Provided herein is a method of preventing or treating absence seizure.

Provided herein is a method of preventing or treating chronic kidney disease (for example complication of diabetes). Provided herein is a method of preventing or treating diabetic heart disease.

Provided herein is a method of preventing or treating cardiovascular events.

[0278] Provided herein is a method of preventing or treating Alzheimer's disease, Parkinson's disease or Huntington's disease in a subject in need thereof, the method comprising administering to the subject a peptide conjugate described herein.

[0279] Provided herein is a method of preventing or treating stomach and bowel-related disorders, such as the treatment of neonatals with compromised intestine function, osteoporosis, and DPP-IV (dipeptidylpeptidase-IV) mediated conditions. By way of example, the stomach and bowel-related disorders include ulcers, gastritis, digestion disorders, malabsorption syndromes, short-gut syndrome, cul-de-sac syndrome, inflammatory bowel disease, celiac sprue (for example arising from gluten induced enteropathy or celiac disease), tropical sprue, hypogammaglobulinemia sprue, enteritis, regional enteritis (Crohn's disease), ulcerative colitis, irritable bowel syndrome associated with diarrhea, Small intestine damage and short bowel syndrome.

[0280] Provided herein is a method of preventing or treating radiation enteritis, infectious or post-infectious enteritis, and small intestinal damage due to toxic or other chemotherapeutic agents. This may require administration of the peptide conjugate prior to, concurrently with or following a course of chemotherapy or radiation therapy in order to reduce side effects of chemotherapy such as diarrhea, abdominal cramping and vomiting, and reduce the consequent structural and functional damage of the intestinal epithelium resulting from the chemotherapy or radiation therapy.

[0281] Provided herein is a method of preventing or treating malnutrition, for example conditions such as the wasting syndrome cachexia and anorexia.

[0282] Provided herein is a method of preventing or treating a disease or condition which benefits from a modulator and/or binder of a GLP-1 receptor in a subject in need thereof comprising administering to the subject a peptide conjugate described herein.

[0283] Provided herein is a method of preventing or treating a disease or condition which benefits from a modulator and/or binder of a GLP-1/GIP receptor in a subject in need thereof comprising administering to the subject a peptide conjugate described herein.

[0284] Provided herein is a method of preventing or treating a disease or condition which benefits from a modulator and/or binder of a GIP receptor in a subject in need thereof comprising administering to the subject a peptide conjugate described herein.

[0285] In some embodiments, peptides disclosed herein are administered weekly, or about every 7 days. In some cases, peptides disclosed herein are administered biweekly, or about every 14 days.

[0286] In some embodiments, peptide conjugates disclosed herein are administered weekly, or about every 7 days. In some cases, peptide conjugates disclosed herein are administered biweekly, or about every 14 days.

Combinations

[0287] Disclosed herein are pharmaceutical compositions comprising a peptide or peptide conjugate described herein and one or more additional therapeutic agents.

[0288] The additional therapeutic agents may comprise one or more other diabetes drugs, DPP4 inhibitors, SGLT2 inhibitors, hypoglycemic drugs and biguanidine drugs, insulin secretagogues and sulfonyl urea drugs, TZD drugs, insulin and insulin analogs, FGF21 and analogs, leptin or leptin analogs, amylin and amylin analogs, an anti-inflammatory drug, cyclosporine A or FK506, 5-ASA, or a statin, or any combination thereof. The additional therapeutic agent may be aspirin.

[0289] The additional therapeutic agents may comprise a therapeutic incretin or derivative thereof. Non-limiting examples of incretins or derivatives thereof include GLP-1, glucagon, oxyntomodulin, exendin-4, GLP-2, GIP, and combinations thereof.

[0290] In some embodiments, combination treatment demonstrates superior glucose control, food intake reduction, and weight loss than administration of a single agent. In some embodiments, combination treatment mimics the beneficial effects of bariatric surgery in an obese patient.

Compositions

[0291] Disclosed herein are pharmaceutical compositions comprising a peptide or peptide conjugate described herein and a pharmaceutically acceptable excipients or vehicles. Pharmaceutically acceptable excipients or vehicles may include carriers, excipients, diluents, antioxidants, preservatives, coloring, flavoring and diluting agents, emulsifying agents, suspending agents, solvents, fillers, bulking agents, buffers, delivery vehicles, tonicity agents, cosolvents, wetting agents, complexing agents, buffering agents, antimicrobials, and surfactants.

[0292] Neutral buffered saline or saline mixed with serum albumin are exemplary appropriate carriers. The pharmaceutical compositions may include antioxidants such as ascorbic acid; low molecular weight polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as Tween, pluronics, or polyethylene glycol (PEG). Also by way of example, suitable tonicity enhancing agents include alkali metal halides (preferably sodium or potassium chloride), mannitol, sorbitol, and the like. Suitable preservatives include benzalkonium chloride, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid and the like. Hydrogen peroxide also may be used as preservative. Suitable cosolvents include glycerin, propylene glycol, and PEG. Suitable complexing agents include caffeine, polyvinylpyrrolidone, beta-cyclodextrin or

hydroxy-propyl-beta-cyclodextrin. Suitable surfactants or wetting agents include sorbitan esters, polysorbates such as polysorbate 80, tromethamine, lecithin, cholesterol, tyloxapal, and the like. The buffers may be conventional buffers such as acetate, borate, citrate, phosphate, bicarbonate, or Tris-HCl. Acetate buffer may be about pH 4-5.5, and Tris buffer can be about pH 7-8.5. Additional pharmaceutical agents are set forth in Remington's Pharmaceutical Sciences, 18th Edition, A. R. Gennaro, ed., Mack Publishing Company, 1990.

[0293] The composition may be in liquid form or in a lyophilized or freeze-dried form and may include one or more lyoprotectants, excipients, surfactants, high molecular weight structural additives and/or bulking agents. In one embodiment, a lyoprotectant is included, which is a non-reducing sugar such as sucrose, lactose or trehalose. The amount of lyoprotectant generally included is such that, upon reconstitution, the resulting formulation will be isotonic, although hypertonic or slightly hypotonic formulations also may be suitable. In addition, the amount of lyoprotectant should be sufficient to prevent an unacceptable amount of degradation and/or aggregation of the protein upon lyophilization. Exemplary lyoprotectant concentrations for sugars (e.g., sucrose, lactose, trehalose) in the pre-lyophilized formulation are from about 10 mM to about 400 mM. In another embodiment, a surfactant is included, such as for example, nonionic surfactants and ionic surfactants such as polysorbates (e.g., polysorbate 20, polysorbate 80); poloxamers (e.g., poloxamer 188); poly(ethylene glycol) phenyl ethers (e.g., Triton); sodium dodecyl sulfate (SDS); sodium laurel sulfate; sodium octyl glycoside; lauryl-, myristyl-, linoleyl-, or stearyl-sulfobetaine; lauryl-, myristyl-, linoleyl- or stearyl-sarcosine; linoleyl, myristyl-, or cetyl-betaine; lauroamidopropyl-, cocamidopropyl-, linoleamidopropyl-, myristamidopropyl-, palmidopropyl-, or isostearamidopropyl-betaine (e.g., lauroamidopropyl); myristamidopropyl-, palmidopropyl-, or isostearamidopropyl-dimethylamine; sodium methyl cocoyl-, or disodium methyl ofeyle-aurate; and the MONAQUAT™ series (Mona Industries, Inc., Paterson, N.J.), polyethyl glycol, polypropyl glycol, and copolymers of ethylene and propylene glycol (e.g., Pluronics, PF68 etc). Exemplary amounts of surfactant that may be present in the pre-lyophilized formulation are from about 0.001-0.5%. High molecular weight structural additives (e.g., fillers, binders) may include for example, acacia, albumin, alginic acid, calcium phosphate (dibasic), cellulose, carboxymethylcellulose, carboxymethylcellulose sodium, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, microcrystalline cellulose, dextran, dextrin, dextrates, sucrose, tylose, pregelatinized starch, calcium sulfate, amylose, glycine, bentonite, maltose, sorbitol, ethylcellulose, disodium hydrogen phosphate, disodium phosphate, disodium pyrosulfite, polyvinyl alcohol, gelatin, glucose, guar gum, liquid glucose, compressible sugar, magnesium aluminum silicate, maltodextrin, polyethylene oxide, polymethacrylates, povidone, sodium alginate, tragacanth microcrystalline cellulose, starch, and zein. Exemplary concentrations of high molecular weight structural additives are from 0.1% to 10% by weight. In other embodiments, a bulking agent (e.g., mannitol, glycine) may be included.

[0294] Compositions may be suitable for parenteral administration. Exemplary compositions are suitable for injection or infusion into an animal by any route available to the skilled worker, such as intraarticular, subcutaneous, intravenous, intramuscular, intraperitoneal, intracerebral (intraparenchymal),

intracerebroventricular, intramuscular, intraocular, intraarterial, or intralesional routes. A parenteral formulation typically may be a sterile, pyrogen-free, isotonic aqueous solution, optionally containing pharmaceutically acceptable preservatives.

[0295] Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringers' dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers, such as those based on Ringer's dextrose, and the like. Preservatives and other additives may also be present, such as, for example, anti-microbials, anti-oxidants, chelating agents, inert gases and the like. See generally, Remington's Pharmaceutical Science, 16th Ed., Mack Eds., 1980.

[0296] Pharmaceutical compositions described herein may be formulated for controlled or sustained delivery in a manner that provides local concentration of the product (e.g., bolus, depot effect) and/or increased stability or half-life in a particular local environment. The compositions can include the formulation of peptide conjugates, polypeptides, nucleic acids, or vectors disclosed herein with particulate preparations of polymeric compounds such as polylactic acid, polyglycolic acid, etc., as well as agents such as a biodegradable matrix, injectable microspheres, microcapsular particles, microcapsules, bioerodible particles beads, liposomes, and implantable delivery devices that provide for the controlled or sustained release of the active agent which then can be delivered as a depot injection. Techniques for formulating such sustained-or controlled-delivery means are known, and a variety of polymers have been developed and used for the controlled release and delivery of drugs. Such polymers are typically biodegradable and biocompatible. Polymer hydrogels, including those formed by complexation of enantiomeric polymer or polypeptide segments, and hydrogels with temperature or pH sensitive properties, may be desirable for providing drug depot effect because of the mild and aqueous conditions involved in trapping bioactive protein agents (e.g., peptide conjugates).

[0297] Suitable and/or preferred pharmaceutical formulations may be determined in view of the present disclosure and general knowledge of formulation technology, depending upon the intended route of administration, delivery format, and desired dosage. Regardless of the manner of administration, an effective dose may be calculated according to patient body weight, body surface area, or organ size. Further refinement of the calculations for determining the appropriate dosage for treatment involving each of the formulations described herein are routinely made in the art and is within the ambit of tasks routinely performed in the art. Appropriate dosages may be ascertained through use of appropriate dose-response data.

Definitions

[0298] 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. The term “about” when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range, in some instances, will vary between 1% and 15% of the stated number or numerical range. 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.

[0299] As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated below.

[0300] “Alkyl” refers to a straight or branched chain hydrocarbon monoradical, which may be fully saturated or unsaturated, having from one to about ten carbon atoms, or from one to six carbon atoms, wherein a sp³-hybridized carbon of the alkyl residue is attached to the rest of the molecule by a single bond. Examples of saturated hydrocarbon monoradical 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 “C₁-C₆ 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 C₁-C₁₀ alkyl, a C₁-C₉ alkyl, a C₁-C₈ alkyl, a C₁-C₇ alkyl, a C₁-C₆ alkyl, a C₁-C₅ alkyl, a C₁-C₄ alkyl, a C₁-C₃ alkyl, a C₁-C₂ alkyl, or a C₁ alkyl. When the alkyl refers to an unsaturated straight or branched chain hydrocarbon monoradical it is known as an “alkenyl” or an “alkynyl”. The alkenyl may be in either the *cis* or *trans* conformation about the double bond(s), and should be understood to include both isomers. Examples of alkenyls include, but are not limited to ethenyl (-CH=CH₂), 1-propenyl (-CH₂CH=CH₂), isopropenyl [-C(CH₃)=CH₂], butenyl, 1,3-butadienyl and the like. Whenever it appears herein, a numerical range such as “C₂-C₆ 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 C₂-C₁₀ alkenyl, a C₂-C₉ alkenyl, a C₂-C₈ alkenyl, a C₂-C₇ alkenyl, a C₂-C₆ alkenyl, a C₂-C₅ alkenyl, a C₂-C₄ alkenyl, a C₂-C₃ alkenyl, or a C₂ alkenyl. Examples of alkynyl include, but are not limited to ethynyl, 2-propynyl, 2- and the like. Whenever it appears herein, a numerical range such as “C₂-C₆ 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 C₂-C₁₀ alkynyl, a C₂-C₉ alkynyl, a C₂-C₈ alkynyl, a C₂-C₇ alkynyl, a C₂-C₆ alkynyl, a C₂-C₅ alkynyl, a C₂-C₄ alkynyl, a C₂-C₃ alkynyl, or a C₂ alkynyl. Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted as described below, 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, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the alkyl is optionally substituted with oxo, halogen, -CN, -CF₃, -OH, or -OMe. In some embodiments, the alkyl is optionally substituted with halogen.

[0301] “Alkylene” refers to a straight or branched divalent hydrocarbon chain. Whenever it appears herein, a numerical range such as “C₁-C₆ alkylene” means that the alkylene 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 “alkylene” where no numerical range is designated. In some embodiments, the alkylene is a C₁-C₁₀ alkylene, a C₁-C₉ alkylene, a C₁-C₈ alkylene, a C₁-C₇ alkylene, a C₁-C₆ alkylene, a C₁-C₅ alkylene, a C₁-C₄ alkylene, a C₁-C₃ alkylene, a C₁-C₂ alkylene, or a C₁ alkylene. 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, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, an alkylene is optionally substituted with oxo, halogen, -CN, -CF₃, -OH, or -OMe. In some embodiments, the alkylene is optionally substituted with halogen.

[0302] “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, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, an alkoxy is optionally substituted with oxo, halogen, -CN, -CF₃, -OH, or -OMe. In some embodiments, the alkoxy is optionally substituted with halogen.

[0303] “Aryl” refers to a radical derived from a hydrocarbon ring system comprising hydrogen, 6 to 30 carbon atoms and at least one aromatic ring. The aryl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused (when fused with a cycloalkyl or heterocycloalkyl ring, the aryl is bonded through an aromatic ring atom) or bridged ring systems. In some embodiments, the aryl is a 6- to 10-membered aryl. In some embodiments, the aryl is a 6-membered aryl. Aryl radicals include, but are not limited to, aryl radicals derived from the hydrocarbon ring systems of anthrylene, naphthylene, phenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, as-indacene, s-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. In some embodiments, the aryl is phenyl. Unless stated otherwise specifically in the specification, an aryl may be 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, an

aryl is optionally substituted with halogen, methyl, ethyl, -CN, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, an aryl is optionally substituted with halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the aryl is optionally substituted with halogen.

[0304] “Cycloalkyl” refers to a stable, partially or fully saturated, monocyclic or polycyclic carbocyclic ring, which may include fused (when fused with an aryl or a heteroaryl ring, the cycloalkyl is bonded through a non-aromatic ring atom) or bridged ring systems. Representative cycloalkyls include, but are not limited to, cycloalkyls having from three to fifteen carbon atoms (C₃-C₁₅ cycloalkyl), from three to ten carbon atoms (C₃-C₁₀ cycloalkyl), from three to eight carbon atoms (C₃-C₈ cycloalkyl), from three to six carbon atoms (C₃-C₆ cycloalkyl), from three to five carbon atoms (C₃-C₅ cycloalkyl), or three to four carbon atoms (C₃-C₄ cycloalkyl). In some embodiments, the cycloalkyl is a 3- to 6-membered cycloalkyl. In some embodiments, the cycloalkyl is a 5- to 6-membered cycloalkyl. Monocyclic cycloalkyls include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyls or carbocycles include, for example, adamantyl, norbornyl, decalyl, 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, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, a cycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the cycloalkyl is optionally substituted with halogen.

[0305] “Halo” or “halogen” refers to bromo, chloro, fluoro, or iodo. In some embodiments, halogen is fluoro or chloro. In some embodiments, halogen is fluoro.

[0306] “Haloalkyl” refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like.

[0307] “Heterocycloalkyl” refers to a stable 3- to 24-membered partially or fully saturated ring radical comprising 2 to 23 carbon atoms and from one to 8 heteroatoms selected from nitrogen, oxygen, phosphorous, and sulfur. Representative heterocycloalkyls include, but are not limited to, heterocycloalkyls having from two to fifteen carbon atoms (C₂-C₁₅ heterocycloalkyl), from two to ten carbon atoms (C₂-C₁₀ heterocycloalkyl), from two to eight carbon atoms (C₂-C₈ heterocycloalkyl), from two to six carbon atoms (C₂-C₆ heterocycloalkyl), from two to five carbon atoms (C₂-C₅ heterocycloalkyl), or two to four carbon atoms (C₂-C₄ heterocycloalkyl). In some embodiments, the heterocycloalkyl is a 3- to 6-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 5- to 6-membered heterocycloalkyl. Unless stated otherwise specifically in the specification, the heterocycloalkyl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic 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; and the nitrogen, carbon or sulfur atoms in the heterocycloalkyl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. Examples of such heterocycloalkyl radicals include, but are not limited to, aziridinyl, azetidiny, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazoliny, imidazolidiny, isothiazolidiny, isoxazolidiny, morpholiny, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidiny, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidiny, quinuclidiny, thiazolidiny, tetrahydrofuryl, trithianyl, tetrahydropyrany, thiomorpholiny, thiamorpholiny, 1-oxo-thiomorpholiny, 1,1-dioxo-thiomorpholiny, 1,3-dihydroisobenzofuran-1-yl, 3-oxo-1,3-dihydroisobenzofuran-1-yl, methyl-2-oxo-1,3-dioxol-4-yl, and 2-oxo-1,3-dioxol-4-yl. The term heterocycloalkyl also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides and the oligosaccharides. Unless otherwise noted, heterocycloalkyls have from 2 to 10 carbons 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). Partially saturated heterocycloalkyls include, for example dihydropyrrolyl or tetrahydropyridine. 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, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, a heterocycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the heterocycloalkyl is optionally substituted with halogen.

[0308] “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 C₁-C₆ 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. 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, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, a heteroalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the heteroalkyl is optionally substituted with halogen.

[0309] “Heteroaryl” refers to a 5- to 14-membered ring system radical comprising hydrogen atoms, one to thirteen carbon atoms, one to six heteroatoms selected from nitrogen, oxygen, phosphorous, and sulfur, and at least one aromatic ring. The heteroaryl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused (when fused with a cycloalkyl or heterocycloalkyl ring, the

heteroaryl is bonded through an aromatic ring atom) or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heteroaryl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. In some embodiments, the heteroaryl is a 5- to 10-membered heteroaryl. In some embodiments, the heteroaryl is a 5- to 6-membered heteroaryl. In some embodiments, the heteroaryl is a 5-membered heteroaryl. In some embodiments, the heteroaryl is a 6-membered heteroaryl. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indoliziny, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1H-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazoliny, quinoxaliny, quinolinyl, quinuclidinyl, isoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (i.e., thienyl). 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, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, a heteroaryl is optionally substituted with halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the heteroaryl is optionally substituted with halogen.

[0310] The term “percent identity” refers to a comparison between two nucleic acid or amino acid sequences. Such comparisons are measured using any number of alignment methods known in the art, including but not limited to global (e.g., Needleman–Wunsch algorithm) or local alignments (e.g., Smith–Waterman, Sellers, or other algorithm). Percent identity often refers to the percentage of matching positions of two sequences for a contiguous section of positions, wherein the two sequences are aligned in such a way to maximize matching positions and minimize gaps of non-matching positions. In some instances, alignments are conducted wherein there are no gaps between the two sequences. In some instances, the alignment results in less than 5% gaps, less than 3% gaps, or less than 1% gaps. Additional methods of sequence comparison or alignment are also consistent with the disclosure.

[0311] Percent (%) sequence identity with respect to a reference polypeptide sequence is the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the reference polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are known for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Appropriate parameters for aligning

sequences are able to be determined, including algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are generated using the sequence comparison computer program ALIGN-2. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc., and the source code has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available from Genentech, Inc., South San Francisco, Calif., or may be compiled from the source code. The ALIGN-2 program should be compiled for use on a UNIX operating system, including digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary. In situations where ALIGN-2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows: 100 times the fraction X/Y , where X is the number of amino acid residues scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program.

[0312] “Pharmaceutically acceptable” refers to approved or approvable by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, including humans.

[0313] “Pharmaceutically acceptable salt” refers to a salt of a compound that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound.

[0314] “Pharmaceutically acceptable excipient, carrier or adjuvant” refers to an excipient, carrier or adjuvant that may be administered to a subject, together with at least one antibody of the present disclosure, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the compound.

[0315] “Pharmaceutically acceptable vehicle” refers to a diluent, adjuvant, excipient, or carrier with which at least one antibody of the present disclosure is administered.

[0316] Terms such as “treating” or “treatment” or “to treat” or “alleviating” or “to alleviate” may refer to: 1) therapeutic measures that cure, slow down, lessen symptoms of, and/or halt progression of a diagnosed pathologic condition or disorder; and/or 2) prophylactic or preventative measures that prevent and/or slow the development of a targeted pathologic condition or disorder. “Treatment” refers to clinical intervention in an attempt to alter the natural course of the individual or cell being treated, and can be performed either for prophylaxis or during the course of clinical pathology. Desirable effects of treatment include preventing occurrence or recurrence of disease, alleviation of symptoms, and diminishment of any direct or indirect

pathological consequences of the disease, preventing metastasis, decreasing the rate of disease progression, amelioration or palliation of the disease state, and remission or improved prognosis. Thus those in need of treatment may include those already with the disorder; those prone to have the disorder; and those in whom the disorder is to be prevented.

[0317] “Amino acid” refers to naturally occurring and synthetic amino acids, as well as amino acid analogs and amino acid mimetics that function similarly to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified, e.g., hydroxyproline, gamma-carboxyglutamate, and O-phosphoserine. Amino acid analogs refers to compounds that have the same basic chemical structure as a naturally occurring amino acid, e.g., an alpha carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, e.g., homoserine, norleucine, methionine sulfoxide, methionine methyl sulfonium. Such analogs can have modified R groups (e.g., norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. Amino acid mimetics refers to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that functions similarly to a naturally occurring amino acid.

[0318] “Disorder” or “disease” refers to a condition that would benefit from treatment with a substance/molecule (e.g., a peptide conjugate disclosed herein) or method disclosed herein. This includes chronic and acute disorders or diseases including those pathological conditions which predispose the mammal to the disorder in question.

[0319] “Mammal” for purposes of treatment refers to any animal classified as a mammal, including humans, rodents (e.g., mice and rats), and monkeys; domestic and farm animals; and zoo, sports, laboratory, or pet animals, such as dogs, cats, cattle, horses, sheep, pigs, goats, rabbits, etc. In some embodiments, the mammal is selected from a human, dog, rodent, or monkey. In some embodiments, the subject having a disease or condition in need of treating is a human. In some embodiments, the subject having a disease or condition in need of treating is a companion animal. In some embodiments, the subject having a disease or condition in need of treating is a dog. In some embodiments, the subject having a disease or condition in need of treating is a cat.

[0320] “Modulate” refers to the ability of a peptide to bind to a protein receptor. In some embodiments, the modulator is a ligand of the receptor. In some embodiments, the modulator is an agonist. In some embodiments, the modulator is an antagonist. For instance, a peptide that modulates the GLP-1 receptor binds to a GLP-1 receptor (GLP-1R). For instance, a peptide that modulates the GCG receptor binds to a GCG receptor (GCGR). For instance, a peptide that modulates the GIP receptor binds to a GIP receptor (GIPR). For instance, a peptide that modulates the PYY receptor binds to a PYY receptor (PYYR). As non-limiting examples, the peptide that modulates the GLP-1 receptor is a GLP-1R agonist. As non-limiting examples, the peptide that modulates both the GLP-1 receptor and the GCG receptor is a dual GLP-1R/GCGR agonist. As non-limiting examples, the peptide that modulates both the GLP-1 receptor and the GIP receptor is a dual GLP-1R/GIPR agonist. As non-limiting examples, the peptide that modulates the PYY receptor is a PYYR agonist.

[0321] "Unmodified peptide" refers to either an unmodified sequence (wild type peptide) or a modified sequence without a staple.

EXAMPLES

[0322] Peptides were synthesized by standard solid-phase peptide synthesis (SPPS) techniques and purified via HPLC.

[0323] Unless otherwise noted, all reagents were purchased from commercial suppliers and used without further purification. All reactions involving air or moisture sensitive reagents or intermediates were performed under an inert atmosphere of nitrogen or argon. All solvents used were of HPLC grade. Reactions were monitored by LC-MS or by thin-layer chromatography (TLC) on Merck 50 × 100 mm silica gel 60 aluminum sheets stained using an aqueous solution of KMnO₄.

[0324] Flash chromatography purifications were performed on silica gel prepacked columns (40 μm, RediSep® Rf from Teledyne Isco) on a CombiFlash® Rf (Teledyne Isco). Purified final compounds were eluted as single and symmetrical peaks (thereby confirming a purity of ≥95%).

Semi-preparative chromatography were performed on a Shimadzu HPLC with a Phenomenex Luna column (C18, 100 Å pore size, 10 μm particle size, 250 × 10.0 mm, flow: 4 mL/min) or on an Agilent 1200 HPLC with a Phenomenex Luna column (C18, 100 Å pore size, 5 μm particle size, 150 × 21.2 mm, flow: 20 mL/min).

[0325] ¹H and ¹³C NMR spectra were recorded on a Bruker 400 system in d₆-DMSO, CDCl₃ or CD₃OD. Chemical shifts are given in parts per million (ppm) with tetramethylsilane as an internal standard. Abbreviations are used as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, dd = doublet of doublets, br = broad. Coupling constants (*J* values) are given in hertz (Hz).

Low resolution mass spectra were recorded on a Waters Acquity UPLC with a Phenomenex Luna Omega C18 column (C18, 100 Å pore size, 1.6 μm particle size, 50 × 2.1 mm, flow: 0.4 mL/min). Solvents: A - H₂O + 0.1% formic acid, B - MeCN + 0.1% formic acid, gradient: 0-1 min 10-90% B, 1-1.6 min 90% B, 1.6-1.7 min 90-10% B, 1.7-2 min 10% B.

[0326] High resolution mass spectra (HRMS) were recorded on an Agilent 1200 Series Accurate Mass Time-of-Flight (TOF) with an Aeris Widespore column (XB-C8, 3.6 μm particle size, 150 × 2.1 mm, flow: 0.5 mL/min). Solvents: A - H₂O + 0.1% formic acid, B - MeCN + 0.1% formic acid, gradient: 0-2 min 5% B, 2-12 min 5-60% B, 12-13 min 60-80% B, 13-14 min 80-20% B, 14-15 min 20-80% B, 15-16 min 80-20% B, 16-17 min 20-95% B, 17-20 min 95% B, 20-21 min 95-5% B.

General protocol A for loading of chlorotrityl chloride resin

[0327] Fmoc-Lys(ivDde)-OH (60 mg, 100 μmol) was coupled to 2-chlorotrityl chloride resin (Novabiochem) (100 mg, 80 μmol) by mixing the amino acid, resin, and DIEA (70 μL, 400 μmol) in 5 mL of DMF and stirring for 30 min. The resin was then washed with DMF (3x), DCM (3x) and treated with CH₃OH/DCM/DIEA (8:1:1) for 10 min to cap the unreacted trityl chloride sites, dried under vacuum and stored in a desiccator.

General protocol B for deprotection of Fmoc protecting group

[0328] To the resin was added piperidine in DMF (20%). The mixture was shaken for 5 min and drained. Fresh 20% piperidine was added and this time the mixture was shaken for 15 min. Positive ninhydrin and/or TNBS test was observed. The resin was then washed with DMF (3x), DCM (3x).

General protocol C for deprotection of ivDde protecting group

[0329] After washing with DMF and DCM, the resin was treated with 2% hydrazine in DMF (5 mL, 2×15 min). Positive ninhydrin and/or TNBS test was observed. The resin was then washed with DMF (3x), DCM (3x).

General protocol D for peptide coupling

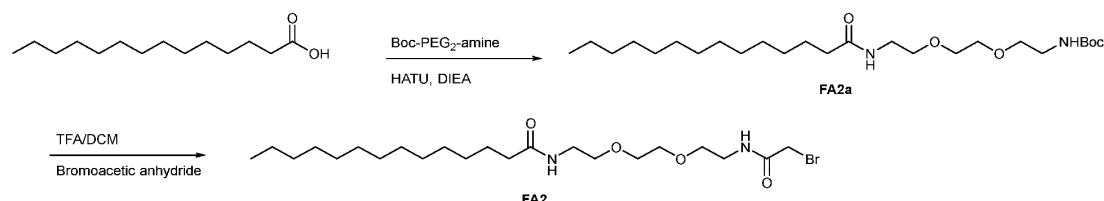
[0330] The resin was treated with the carboxylic acid derivative specified (3 eq) using coupling reagent HATU (3.3 eq), and DIEA (3.3 eq) in DMF (5 mL) for 2 h or repeated until a negative ninhydrin and/or TNBS test was observed. The resin was then washed with DMF (3x), DCM (3x).

General protocol E for on-resin bromoacetylation

[0331] The resin was then treated with bromoacetic anhydride (2.4 eq), and DIEA (2.6 eq) in 200 mL of DCM for 30 min.

General protocol F for cleavage of peptides from chlorotrityl resin

[0332] The resin was washed with DCM (3x), the product was cleaved from the resin using 5 mL of 10% TFA in DCM containing 10% H₂O and 10% triisopropylsilane for 1 h.

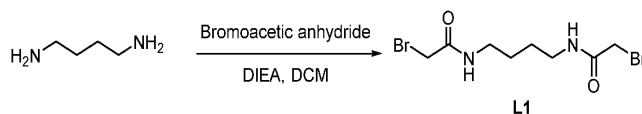
Example 1: Synthesis of a fatty acid conjugation reagent (FA2).

[0333] **Intermediate FA2a.** Myristic acid (0.46 g, 2 mmol) was dissolved in 5 mL of DMF. HATU (0.8 g, 2.1 mmol) and DIEA (0.4 mL, 2.2 mmol) were added followed by the addition of Boc-NH-PEG₂-COOH (0.5 g, 2 mmol). The reaction mixture was then stirred for 6 h, and the solvent was removed. The product was extracted with EtOAc (3×15 mL). The organic layer was successively washed with sat. NaHCO₃, cooled HCl (1 M) and brine, dried over Na₂SO₄, filtered, and concentrated. Purification by flash column chromatography on silica gel provided 0.81 g of *tert*-butyl (2-(2-(2-tetradecanamidoethoxy)ethoxy)ethyl)carbamate (FA2a) as a white solid in 90% product yield. MS (ES⁺) *m/z* 459.6 ([M+H]⁺), calcd MW 458.4.

[0334] **FA2.** A solution of FA2a (0.23 g, 0.5 mmol) in DCM (10 mL) was treated with TFA (2 mL) for 2 h. The mixture was concentrated, followed by the addition of bromoacetic anhydride (0.14 g, 0.55 mmol) and DIEA (0.17 mL, 1 mmol) in 10 mL of DCM at 0 °C. The reaction mixture was then stirred for 2 h, and the solvent was removed. The product was extracted with EtOAc (3×15 mL). The organic layer was successively washed with sat. NaHCO₃, cooled HCl (1 M) and brine, dried over Na₂SO₄, filtered, and

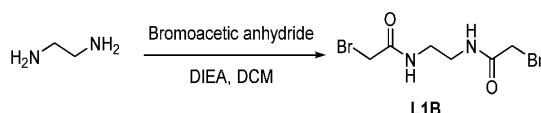
concentrated. Purification by flash column chromatography on silica gel provided 0.2 g of **FA2** as a white solid in 83% product yield. MS (ES⁺) m/z 480.4 ([M+H]⁺), calcd MW 479.5.

Example 2: Synthesis of L1



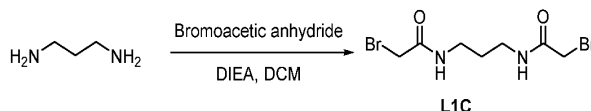
[0335] To a solution of 1,4-diaminobutane (80 μ L, 0.795 mmol, 1 eq) in DCM (10 mL) at 0°C were added DIEA (276 μ L, 1.59 mmol, 2 eq) followed by bromoacetic anhydride (413 g, 1.59 mmol, 2 eq) dissolved in 1 mL of DCM. The reaction mixture was then stirred for 30 min at 0°C, 1.5 h at RT, and the solvent was removed. Purification by flash column chromatography on silica gel afforded **L1** as a white solid (162 mg, 0.49 mmol, 61%). MS (ES⁺) m/z 331.0 ([M+H]⁺). ¹H NMR (400 MHz, methanol-*d*₄) δ 3.94 (s, 4H), 3.40-3.30 (m, 4H), 1.68 (p, J = 3.5 Hz, 4H).

Example 3: Synthesis of L1B



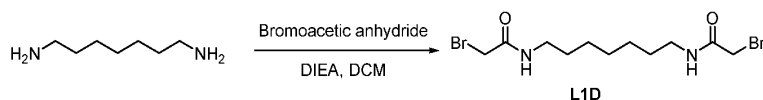
[0336] To a solution of 1,2-ethylenediamine (30 μ L, 0.448 mmol, 1 eq) in DCM (5 mL) at 0°C were added DIEA (172 μ L, 0.985 mmol, 2.2 eq) followed by bromoacetic anhydride (233 mg, 0.897 mmol, 2 eq) dissolved in 1 mL of DCM. The reaction mixture was then stirred for 30 min at 0°C, 1.5 h at RT, and the solvent was removed. Purification by flash column chromatography on silica gel provided **L1B** as a white solid (43.9 mg, 0.145 mmol, 32%). MS (ES⁺) m/z 302.55 ([M+H]⁺), 304.54 ([M+H]⁺). ¹H NMR (400 MHz, methanol-*d*₄) δ 2.49 (s, 4H), 2.06 (s, 4H).

Example 4: Synthesis of L1C



[0337] To a solution of 1,3-diaminopropane (30 μ L, 0.359 mmol, 1 eq) in DCM (5 mL) at 0°C were added DIEA (138 μ L, 0.789 mmol, 2.2 eq) followed by bromoacetic anhydride (186 mg, 0.718 mmol, 2 eq) dissolved in 1 mL of DCM. The reaction mixture was then stirred for 30 min at 0°C, 1.5 h at RT, and the solvent was removed. Purification by flash column chromatography on silica gel afforded **L1C** as a white solid (60.8 mg, 0.19 mmol, 53%). MS (ES⁺) m/z 316.32 ([M+H]⁺), 318.6 ([M+H]⁺). ¹H NMR (400 MHz, methanol-*d*₄) δ 3.86 (s, 4H), 3.27 (t, J = 6.8 Hz, 4H), 1.74 (p, J = 6.8 Hz, 2H).

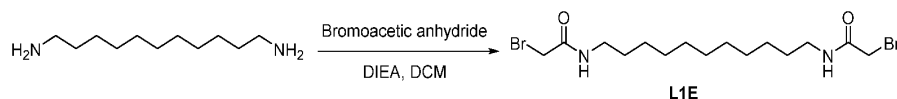
Example 5: Synthesis of L1D



[0338] To a solution of 1,7-diaminohexane (65 mg, 0.499 mmol, 1 eq) in DCM (15 mL) at 0°C were added DIEA (208 μ L, 1.197 mmol, 2.4 eq) followed by bromoacetic anhydride (259 mg, 0.998 mmol, 2 eq) dissolved in 1 mL of DCM. The reaction mixture was then stirred for 30 min at 0°C, 1.5 h at RT, and

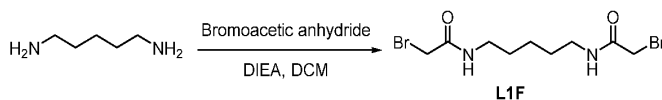
the solvent was removed. Purification by flash column chromatography on silica gel afforded **L1D** as a white solid (120 mg, 0.322 mmol, 64%). MS (ES⁺) m/z 372.71 ([M+H]⁺), 374.70 ([M+3H]⁺). ¹H NMR (400 MHz, chloroform-*d*) δ 6.55 (s, 2H), 3.91 (s, 4H), 3.30 (q, J = 7.1 Hz, 4H), 1.56 (p, J = 7.1 Hz, 4H), 1.45-1.29 (m, 6H).

Example 6: Synthesis of L1E



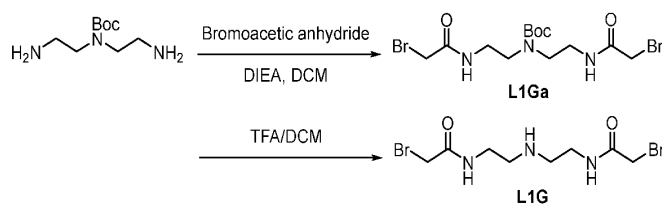
[0339] To a solution of 1,11-diaminoundecane (48 mg, 0.257 mmol, 1 eq) in DCM (10 mL) at 0°C were added DIEA (108 μ L, 0.616 mmol, 2.4 eq) followed by bromoacetic anhydride (134 mg, 0.515 mmol, 2 eq) dissolved in 1 mL of DCM. The reaction mixture was then stirred for 30 min at 0°C, 1.5 h at RT, and the solvent was removed. Purification by flash column chromatography on silica gel afforded **L1E** as a white solid (62.3 mg, 0.145 mmol, 56%). MS (ES⁺) m/z 428.33 ([M+H]⁺). ¹H NMR (400 MHz, chloroform-*d*) δ 6.53 (s, 2H), 3.91 (s, 4H), 3.30 (q, J = 6.8 Hz, 4H), 1.57 (q, J = 7.2 Hz, 4H), 1.42-1.20 (m, 14H).

Example 7: Synthesis of L1F



[0340] To a solution of cadaverine (48 mg, 0.257 mmol, 1 eq) in DCM (20 mL) at 0°C were added DIEA (284 μ L, 1.63 mmol, 2.4 eq) followed by bromoacetic anhydride (353 mg, 1.36 mmol, 2 eq) dissolved in 1 mL of DCM. The reaction mixture was then stirred for 30 min at 0°C, 1.5 h at RT, and the solvent was removed. Purification by flash column chromatography on silica gel afforded **L1F** as a white solid (156mg, 0.453 mmol, 66%). MS (ES⁺) m/z 344.65 ([M+H]⁺), 346.64 ([M+H]⁺). ¹H NMR (400 MHz, methanol-*d*₄) δ 3.83 (s, 4H), 3.23 (q, J = 6.8 Hz, 4H), 1.57 (p, J = 7.2 Hz, 4H), 1.44-1.33 (m, 2H).

Example 8: Synthesis of L1G



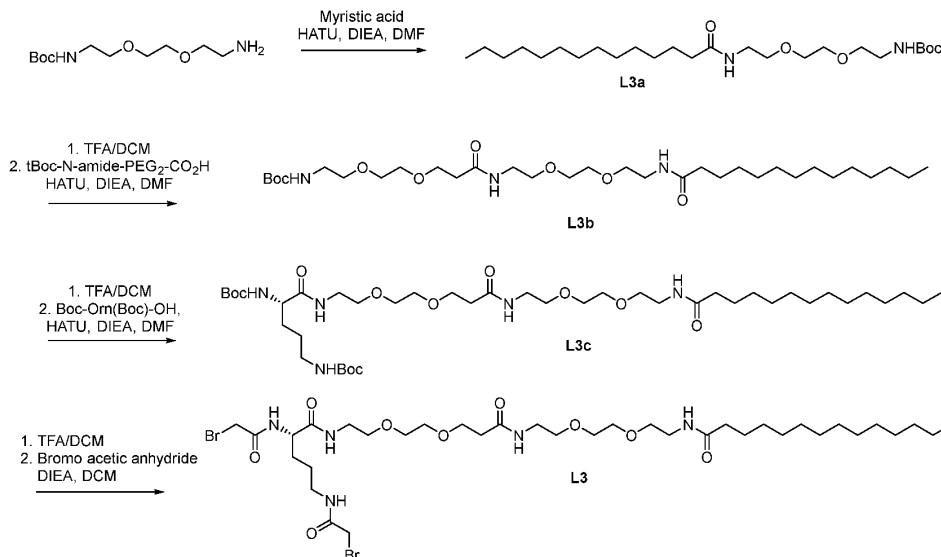
Intermediate L1Ga

[0341] To a solution of *tert*-butyl bis(2-aminoethyl)carbamate (167 mg, 0.82 mmol, 1 eq) in DCM (20 mL) at 0°C were added DIEA (342 μ L, 11.96 mmol, 2.4 eq) followed by bromoacetic anhydride (426 mg, 1.64 mmol, 2 eq) dissolved in 1 mL of DCM. The reaction mixture was then stirred for 30 min at 0°C, 1.5 h at RT, and the solvent was removed. Purification by flash column chromatography on silica gel afforded **L1Ga** as a white solid (289 mg, 0.65 mmol, 79%). MS (ES⁺) m/z 445.71 ([M+H]⁺), 447.7 ([M+H]⁺). ¹H NMR (400 MHz, methanol-*d*₄) δ 3.85 (s, 4H), 3.39 (s, 9H), 1.50 (s, 10H).

L1G

[0342] Compound **L1Ga** (20 mg) was dissolved in TFA/DCM (1:1, v/v, 2 mL), agitated 30 min at RT and evaporated (co-evaporation with hexane) to obtain compound **L1G** as an oil. The product was directly used in further steps. MS (ES⁺) *m/z* 345.2 ([M+H]⁺).

Example 9: Synthesis of L3



Intermediate L3a

[0343] Myristic acid (184 mg, 0.805 mmol, 1 eq) was dissolved in 4 mL of DMF. HATU (321 mg, 0.845 mmol, 1.1 eq) and DIEA (154 μ L, 0.885 mmol, 1.1 eq) were added followed by the addition of BocNH-PEG₂-COOH (200 mg, 0.805 mmol, 1 eq). The reaction mixture was then stirred for 1.5 h, and the solvent was removed. The product was dissolved in EtOAc. The organic layer was successively washed with 1M HCl, sat. NaHCO₃, and brine, dried over Na₂SO₄, filtered, and concentrated. Purification by flash column chromatography on silica gel provided the desired compound **L3a** as a white solid (254 mg, 0.55 mmol, 69%). ¹H NMR (400 MHz, chloroform-*d*) δ 3.66-3.54 (m, 8H), 3.49 (q, *J* = 5.2 Hz, 2H), 3.35 (d, *J* = 6.1 Hz, 2H), 2.20 (t, *J* = 7.7 Hz, 2H), 1.63-1.58 (m, 2H), 1.47 (s, 8H), 1.33-1.24 (m, 21H), 0.90 (t, *J* = 6.9 Hz, 3H). *t_R* = 2.21 min (Agilent). MS (ES⁺) *m/z* 459.6 ([M+H]⁺)

Intermediate L3b

[0344] A solution of compound **L3a** (242 mg, 0.527 mmol, 1 eq) in DCM (2 mL) was treated with TFA (2 mL) for 30 min. The mixture was concentrated, co-evaporated with hexane. To a solution of BocNH-PEG₂-CO₂H (146 mg, 0.527 mmol, 1 eq) dissolved in DMF (5 mL) was added HATU (224 mg, 0.59 mmol, 1.1 eq). Deprotected compound **L3a** and DIEA (183 μ L, 1.05 mmol, 2 eq) in DMF were added to the reaction mixture. The reaction mixture was agitated for 2 h at RT. The product was diluted with EtOAc. The organic layer was successively washed with 1M HCl, sat. NaHCO₃, and brine, dried over Na₂SO₄, filtered, and concentrated. Purification by flash column chromatography on silica gel provided the desired compound **L3b** as an oil (129 mg, 0.209 mmol, 40%). ¹H NMR (400 MHz, chloroform-*d*) δ 6.76 (s, 1H), 6.19 (s, 1H), 5.29 (s, 1H), 3.76 (t, *J* = 5.8 Hz, 2H), 3.69-3.62 (m, 8H), 3.57 (dt, *J* = 12.3, 5.0 Hz, 6H), 3.48

(dt, $J = 10.4, 5.5$ Hz, 4H), 3.33 (s, 2H), 2.51 (t, $J = 5.8$ Hz, 2H), 2.20 (t, $J = 7.0$ Hz, 2H), 1.90-1.75 (m, 4H), 1.64 (p, $J = 7.3$ Hz, 2H), 1.46 (s, 9H), 1.33-1.22 (m, 17H).

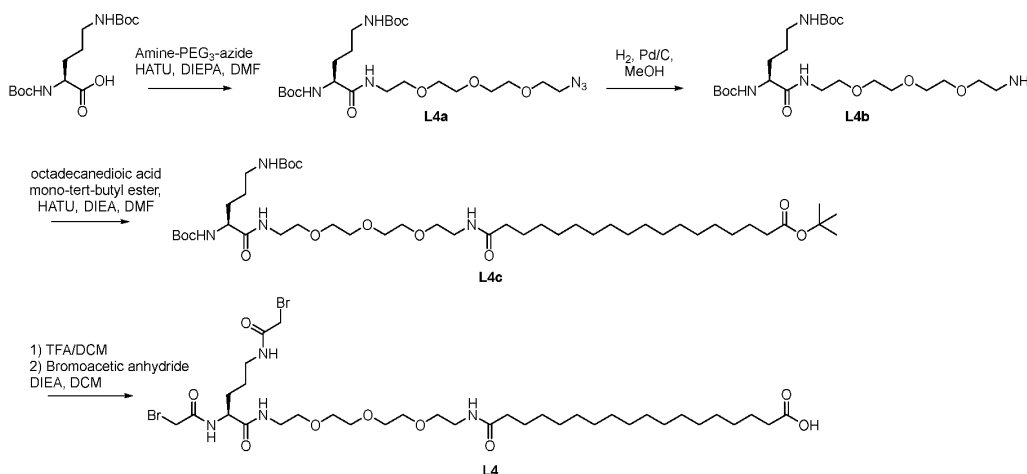
Intermediate L3c

[0345] A solution of Compound **L3b** (129 mg, 0.209 mmol, 1 eq) in DCM (2 mL) was treated with TFA (2 mL) for 30 min. The mixture was concentrated, co-evaporated with hexane. To a solution of Boc-Orn(Boc)-OH (69 mg, 0.209 mmol, 1 eq) dissolved in DMF (5 mL) was added HATU (88 mg, 0.23 mmol 1.1 eq). Deprotected compound **L3b** and DIEA (73 μ L, 0.419 mmol, 2 eq) in DMF were added to the reaction mixture. The reaction mixture was agitated 2 h at RT. The product was diluted with EtOAc. The organic layer was successively washed with 1M HCl, sat. NaHCO_3 , and brine, dried over Na_2SO_4 , filtered, and concentrated. Purification by flash column chromatography on silica gel provided the desired compound **L3c** as an oil (137 mg, 0.164 mmol, 78%). $t_R = 4.07$ min (Agilent). MS (ES^+) m/z 832.9 ($[\text{M}+\text{H}]^+$). ^1H NMR (400 MHz, chloroform- d) δ 7.12 (s, 1H), 6.80 (s, 1H), 6.30 (s, 1H), 4.87 (s, 1H), 3.85-3.73 (m, 2H), 3.68-3.61 (m, 7H), 3.58 (p, $J = 6.1, 5.5$ Hz, 7H), 3.53-3.36 (m, 6H), 3.29-3.00 (m, 2H), 2.51 (t, $J = 5.8$ Hz, 2H), 2.20 (t, $J = 7.7$ Hz, 2H), 2.00-1.74 (m, 6H), 1.71-1.51 (m, 5H), 1.45 (s, 18H), 1.35-1.22 (m, 21H).

L3

[0346] A solution of Compound **L3c** (137 mg, 0.165 mmol, 1 eq) in DCM (2 mL) was treated with TFA (2 mL) for 30 min. The mixture was concentrated, co-evaporated with hexane and dissolved in 10 mL of DCM and cooled at 0°C . DIEA (115 μ L, 0.66 mmol, 4 eq) was added followed by bromoacetic anhydride (85.8 g, 0.33 mmol, 2 eq) dissolved in 1 mL of DCM. The reaction mixture was then stirred for 30 min at 0°C , 1.5 h at RT, and the solvent was removed. Purification by flash column chromatography on silica gel afforded **L3** as a white solid (56 mg, 0.064 mmol, 39%). $t_R = 3.4$ min (Agilent). MS (ES^+) m/z 872.4 ($[\text{M}+\text{H}]^+$), 874.3 ($[\text{M}+\text{H}]^+$).

Example 10: Synthesis of L4



Intermediate L4a

[0347] To a solution of Boc-Orn(Boc)-OH (595 mg, 1.79 mmol, 1 eq) dissolved in DMF (5 mL) was added HATU (750 mg, 1.79 mmol 1.1 eq), DIEA (343 μ L, 1.97 mmol, 1.1 eq) and amine-PEG₃-N₃

(391 mg, 1.79 mmol, 1 eq) dissolved in 1 mL of DMF. The reaction mixture was agitated 16 h at RT. The product was diluted with EtOAc. The organic layer was successively washed with 1M HCl, sat. NaHCO₃, brine, dried over Na₂SO₄, filtered, and concentrated. Purification by flash column chromatography on silica gel provided the desired compound **L4a** as an oil (558 mg, 1.05 mmol, 58%). MS (ES⁺) *m/z* 533.13 ([M+H]⁺). ¹H NMR (400 MHz, chloroform-*d*) δ 6.82 (s, 1H), 5.25 (d, *J* = 8.3 Hz, 1H), 4.75 (s, 1H), 4.19 (s, 1H), 3.76-3.60 (m, 10H), 3.57 (t, *J* = 5.1 Hz, 2H), 3.43 (t, *J* = 4.6 Hz, 2H), 3.30-3.19 (m, 1H), 3.18-3.03 (m, 1H), 1.85 (s, 4H), 1.68-1.49 (m, 2H), 1.45 (s, 18H).

Intermediate L4b

[0348] To a solution of compound **L4a** (548 mg, 1.02 mmol, 1 eq) in anhydrous MeOH (10 mL) and under argon was added Pd/C (10.9 mg, 0.102 mmol, 0.1 eq) and argon was replaced with H₂. The reaction mixture was agitated for 6 h at RT, filtrated on celite and evaporated to afford compound **L4b** as an oil (516 mg, 1.02 mmol, quant). The product was used without any further purification.

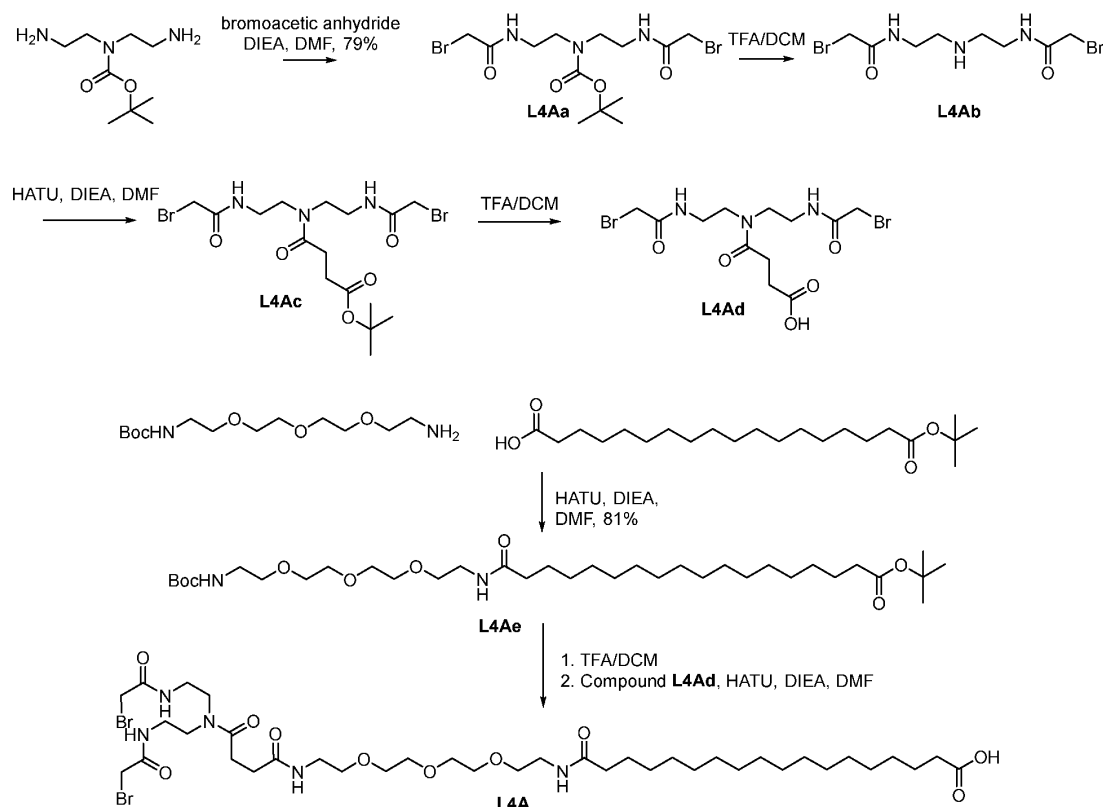
Intermediate L4c

[0349] To a solution of octadecanedioic acid mono *tert*-butyl ester (370 mg, 1.02 mmol, 1 eq) dissolved in DMF (5 mL) was added HATU (387 mg, 1.02 mmol 1.1 eq), DIEA (186 μL, 1.07 mmol, 2 eq) and compound **L4b** (516 mg, 1.02 mmol, 1 eq) dissolved in 1 mL of DMF. The reaction mixture was agitated 3 h at RT. The product was diluted with EtOAc. The organic layer was successively washed with 1M HCl, sat. NaHCO₃, brine, dried over Na₂SO₄, filtered, and concentrated. Purification by flash column chromatography on silica gel provided the desired compound **L4c** as an oil (697 mg, 0.81 mmol, 79%). ¹H NMR (400 MHz, chloroform-*d*) δ 6.94 (s, 1H), 6.42 (s, 1H), 4.81 (s, 1H), 4.20 (s, 1H), 3.65 (d, *J* = 6.7 Hz, 8H), 3.59 (dt, *J* = 9.7, 5.1 Hz, 4H), 3.51-3.35 (m, 4H), 3.31-3.18 (m, 1H), 3.17-3.06 (m, 1H), 2.20 (q, *J* = 8.0 Hz, 4H), 1.87 (s, 4H), 1.71-1.53 (m, 6H), 1.45 (s, 26H), 1.26 (s, 24H).

L4

[0350] A solution of **L4c** (422 mg, 0.49 mmol, 1 eq) in DCM (2 mL) was treated with TFA (2 mL) for 30 min. The mixture was concentrated, co-evaporated with hexane and dissolved in 20 mL of DCM and cooled at 0°C. DIEA (327 μL, 1.96 mmol, 4 eq) was added followed by bromoacetic anhydride (254 mg, 0.98 mmol, 2 eq) dissolved in 1 mL of DCM. The reaction mixture was then stirred for 30 min at 0°C, 1.5 h at RT, and the solvent was removed. Purification by flash column chromatography on silica gel afforded **L4** as a white solid (53 mg, 0.063 mmol, 12%). MS (ES⁺) *m/z* 845.08 ([M+H]⁺), 847.07 ([M+H]⁺) ¹H NMR (400 MHz, methanol-*d*₄) δ 3.68-3.60 (m, 8H), 3.54 (td, *J* = 5.4, 3.4 Hz, 4H), 3.43-3.35 (m, 4H), 3.30-3.16 (m, 2H), 2.27 (t, *J* = 7.5 Hz, 2H), 2.17 (t, *J* = 7.6 Hz, 2H), 1.86-1.73 (m, 1H), 1.72-1.45 (m, 8H), 1.37-1.19 (m, 28H).

Example 11: Synthesis of L4A



Intermediate L4Aa

[0351] To a solution of *tert*-butyl bis(2-aminoethyl)carbamate (500 mg, 2.45 mmol, 1 eq) and DIEA (1.02 mL, 5.88 mmol, 2 eq) in DCM (20 mL) at 0°C was added dropwise bromoacetic anhydride (1.31 g, 5.04 mmol, 2.05 eq in 1 mL DCM). The reaction mixture was agitated 30 min at 0°C, 2 h at RT and evaporated *in vacuo*. Purification by flash chromatography afforded the product as an oil (883 mg, 81%). ¹H NMR (400 MHz, methanol-*d*₄) δ 1.50 (s, 9H), 3.39 (s, 8H), 3.85 (s, 4H). *t_R* = 1.04 min. MS (ES⁺) *m/z* 445.71/447.70 ([M+H]⁺).

Intermediate L4Ab

[0352] A solution of compound **L4Aa** (1 eq) in DCM/TFA (1:1, v/v) was agitated at RT for 30 min and concentrated *in vacuo* (co-evaporated with heptane). Compound **L4Ab** was used directly in further steps without purification. *t_R* = 0.58 min. MS (ES⁺) *m/z* 345.65/347.67 ([M+H]⁺).

Intermediate L4Ac

[0353] To a solution of mono-*tert*-butyl succinate (1.05 eq) in DMF was added HATU (1.05 eq). The reaction mixture was agitated at RT for 5 min. Compound **L4Ab** and DIEA (4 eq) were dissolved in DMF (1 mL) and added to the reaction mixture. The reaction was agitated overnight at RT and diluted with AcOEt. The organic phase was washed with HCl 1N, a solution of saturated NaHCO₃, dried over MgSO₄ and evaporated. Purification by flash chromatography afforded the product as an oil. *t_R* = 1.07 min. MS (ES⁺) *m/z* 501.52/503.80 ([M+H]⁺).

Intermediate L4Ad

[0354] A solution of compound **L4Ac** (1 eq) in DCM/TFA (1:1, v/v) was agitated at RT for 30 min and concentrated *in vacuo* (co-evaporated with heptane). Compound **L4Ad** was used directly in further steps without purification. $t_R = 0.57$ min. MS (ES⁺) m/z 445.71/447.73 ([M+H]⁺).

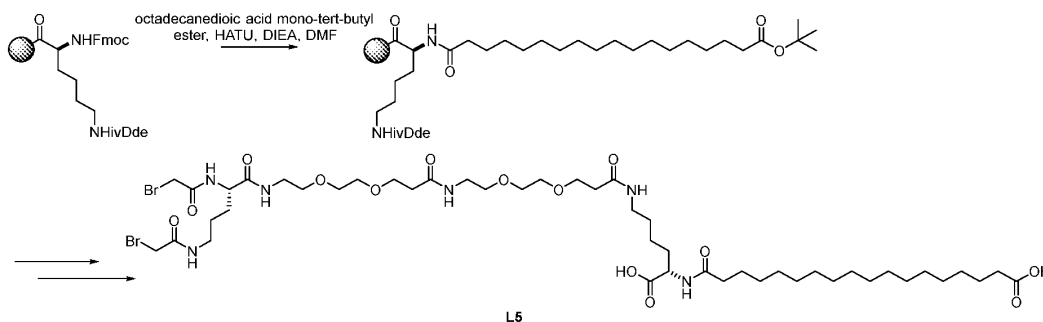
Intermediate L4Ae

[0355] Octadecanedioic acid mono-*tert*-butyl ester acid (200 mg, 0.54 mmol, 1 eq) was dissolved in 5 mL of DMF. HATU (225 mg, 0.59 mmol, 1.1 eq) and DIEA (103 μ L, 0.59 mmol, 1.1 eq) were added followed by the addition of Boc-NH-PEG₃-NH₂ (157.8 g, 0.54 mmol, 1 eq). The reaction mixture was then stirred for 3 h, and the solvent was removed. The product was dissolved in EtOAc. The organic layer was successively washed with sat. NaHCO₃, 1M HCl, brine, dried over Na₂SO₄, filtered, and concentrated. Purification by flash column chromatography on silica gel provided the desired product **L4Ae** as a white solid (281 mg, 0.43 mmol, 81%). MS (ES⁺) m/z 645.5 ([M+H]⁺). ¹H NMR (400 MHz, chloroform-*d*) δ 3.76-3.61 (m, 8H), 3.63-3.54 (m, 4H), 3.48 (q, $J = 5.1$ Hz, 2H), 3.34 (s, 2H), 2.20 (dt, $J = 9.8, 7.6$ Hz, 4H), 1.67-1.55 (m, 4H), 1.49-1.44 (m, 17H), 1.30 (s, 6H), 1.30-1.24 (m, 19H).

L4A

[0356] A solution of compound **L4Ae** in DCM was treated with TFA for 30 min. The mixture was concentrated, co-evaporated with heptane, dissolved in DMF and added to a solution of compound **L4Ad**, HATU and DIEA in DMF. The reaction mixture was agitated 3h and purified by semi-preparative HPLC to provide the desired product **L4A**.

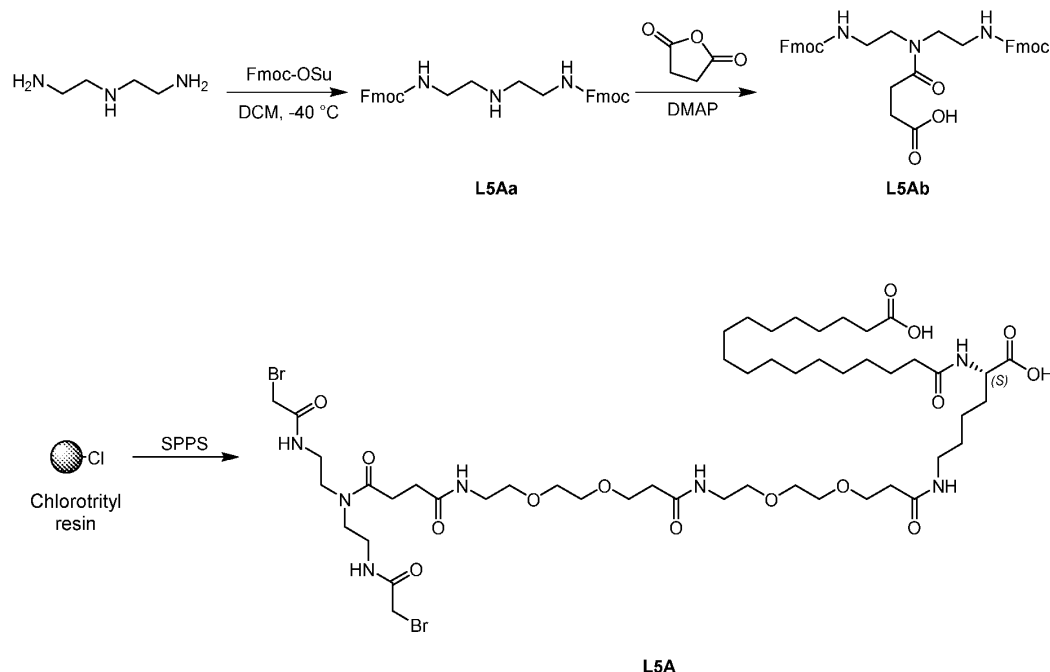
Example 12: Synthesis of L5



[0357] General protocol **A**, **B**, **D** (octadecanedioic acid mono-*tert* butyl ester), **C**, **D** (Fmoc-PEG₂-propionic acid), **B**, **D** (Fmoc-PEG₂-propionic acid), **B**, **D** (Fmoc-Orn(Fmoc)-OH), **B**, **E**, **F**.

[0358] The crude was purified by semi-preparative HPLC with mass detection to afford the product **L5** as a white solid (73 mg, 0.065 mmol, 11%). ¹H NMR (400 MHz, methanol-*d*₄) δ 4.36 (td, $J = 8.9, 5.1$ Hz, 2H), 3.89 (q, $J = 11.4$ Hz, 2H), 3.82 (s, 2H), 3.74 (t, $J = 6.2$ Hz, 2H), 3.60 (s, 4H), 3.54 (t, $J = 5.5$ Hz, 2H), 3.37 (q, $J = 5.2$ Hz, 2H), 3.29-3.11 (m, 5H), 2.44 (t, $J = 6.2$ Hz, 2H), 2.26 (dt, $J = 12.3, 7.5$ Hz, 4H), 1.89-1.77 (m, 2H), 1.76-1.49 (m, 10H), 1.48-1.38 (m, 2H), 1.37-1.25 (m, 25H).

Example 13: Synthesis of L5A and C20L5A



Intermediate L5Aa

[0359] A solution of Fmoc-OSu (131 g, 388 mmol) in DCM (200 mL) was added dropwise to a solution of diethylenetriamine (20 g, 194 mmol) in DCM (200 mL) at $-40\text{ }^\circ\text{C}$ under N_2 , stirred for 2 h. LCMS showed the reaction was complete. The crude product in solution was not purified and used for the next step directly. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.88 (d, $J = 7.6$ Hz, 4H), 7.68 (d, $J = 7.6$ Hz, 4H), 7.43-7.24 (m, 10H), 4.30 (d, $J = 6.4$ Hz, 4H), 4.21 (d, $J = 6.4$ Hz, 2H), 3.06 (d, $J = 5.6$ Hz, 4H), 2.57 (d, $J = 7.6$ Hz, 4H). MS (ES^+) m/z 548.2 ($[\text{M}+\text{H}]^+$).

Intermediate L5Ab

[0360] To a solution of compound L5Aa (106 g, 194 mmol) in DCM (400 mL) was added DMAP (4.74 g, 38.8 mmol) and tetrahydrofuran-2,5-dione (67.9 g, 678 mmol), stirred at $25\text{ }^\circ\text{C}$ for 14 h. LCMS showed the reaction was complete. To the reaction mixture was added 1 N HCl until pH = 5-6, stirred for 15 min, the organic phase was separated, then the organic phase was washed with water and saturated NaCl (500 mL) and the aqueous phase was extracted with DCM (500 mL) twice. The combined DCM was dried over anhydrous Na_2SO_4 , concentrated under vacuum. The crude product was purified by column chromatography on silica gel using DCM/MeOH (80:0-5:1) as eluent to give compound L5Ab (57.6 g, 45% yield) as a white solid powder. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.09 (s, 1 H), 7.87 (d, $J = 7.5$ Hz, 4 H), 7.66 (d, $J = 7.0$ Hz, 4 H), 7.23-7.48 (m, 10 H), 4.24-4.33 (m, 4 H), 4.14-4.22 (m, 2 H), 3.27 (s, 4 H), 2.95-3.19 (m, 4 H), 2.37-2.44 (m, 4 H). MS (ES^+) m/z 648.2 ($[\text{M}+\text{H}]^+$).

L5A

[0361] General protocol A, B, D (octadecanedioic acid mono-tert butyl ester), C, D (Fmoc-PEG₂-propionic acid), B, D (Fmoc-PEG₂-propionic acid), B, D (compound L5Ab), B, E, F.

Synthesis of C20L5A



- 1) Resin preparation: To the 1-chloro-2-[chloro(diphenyl)methyl]benzene (8.00 mmol, 2.00 eq, Sub 1.00 mmol/g) was added Fmoc-Lys(Dde)-OH (2.13g, 4.00mmol, 1.00 eq) and DIEA (2.76mL, 16.0 mmol, 4.00 eq) in DCM (50.0mL). The mixture was agitated with N₂ for 2 h at 20 °C, then added MeOH (8.0mL) and agitated with N₂ for another 30 min. The resin was washed with DMF (100mL) *5. Then 20% PIPERIDINE (100mL) in DMF was added and the mixture was agitated with N₂ for 15 min at 20 °C. Then the mixture was filtered to get the resin. The resin was washed with DMF (100mL) *5 and filtered to get the resin.
- 2) Coupling: a solution of 20-(tert-butoxy)-20-oxooctadecanoic acid (3.19, 8.00 mmol, 2.00 eq), HBTU (2.89g, 7.60 mmol, 1.90 eq) and DIEA (2.06g, 16.0mmol, 2.76mL, 4.00 eq) in DMF (30.00 mL) was added to the resin and agitated with N₂ for 20 min at 20 °C. The resin was then washed with DMF (50.0 mL) *5.
- 3) Add 3% hydrazine hydrate/DMF and react on 15 min*2. Drain and wash with DMF (100 mL*5).
- 4) Repeat Step 2 for the following amino acid: (3)

Note:

#	Materials	Coupling reagents
3	3-[2-[2-(9H-fluoren-9-ylmethoxycarbonylamino)ethoxy]ethoxy]propanoic acid (2.00 eq)	HBTU (1.90 eq) and DIPEA (4.00 eq)

- 5) Deprotection: 20% piperidine in DMF (100 mL) was added and agitated the resin with N₂ for another 30 min. The resin was washed with DMF (100 mL * 5) and filtered to get the resin.
- 6) Repeat above step 2 and 5 for the coupling of following amino acids: (4~6)

Note:

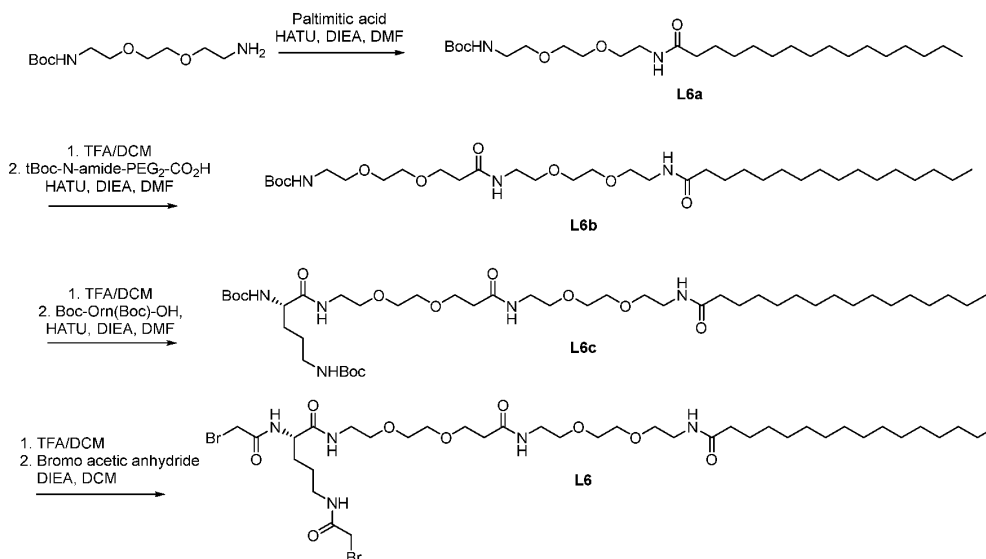
4	3-[2-[2-(9H-fluoren-9-ylmethoxycarbonylamino)ethoxy]ethoxy]propanoic acid (2.00 eq)	HBTU (1.90 eq) and DIPEA (4.00 eq)
5	4-[bis[2-(9H-fluoren-9-ylmethoxycarbonylamino)ethyl]amino]-4-oxo-butanoic acid (1.20 eq)	HATU (1.20 eq) and DIPEA (2.40 eq)
6	2-bromoacetic acid (8.00 eq)	HOBt (4.00 eq) and DIC (8.00 eq)

Peptide Cleavage and Purification:

- 1) Add cleavage buffer (90.0%TFA/2.5%TIS/2.5%H₂O/5%methanolsulfanylbenezene) to the flask containing the side chain protected peptide at room temperature and stir for 2.00 hours.
- 2) Precipitated the peptide was with cold isopropyl ether.
- 3) Filter and collect the filter cake.
- 4) Isopropyl ether washes two more times.
- 5) Dry the crude peptide under vacuum 2 hours.

The crude peptide was purified by prep-HPLC (A: 0.075% TFA in H₂O, B: ACN) to give the final product Compound 1 (1.85 g, 1.32 mmol, 32.95% yield, 86.65% purity) as an off-white solid.

Example 14: Synthesis of L6



Intermediate L6a

[0363] Palmitic acid (235 mg, 0.919 mmol, 1.05 eq) was dissolved in 4 mL of DMF. HATU (349 mg, 0.919 mmol, 1.05 eq) and DIEA (167 μ L, 0.963 mmol, 1.1 eq) were added followed by the addition of Boc-NH-PEG₂-NH₂ (200 mg, 0.875 mmol, 1 eq). The reaction mixture was then stirred for 2 h, and the solvent was removed. The product was dissolved in EtOAc. The organic layer was successively washed with 1M HCl, sat. NaHCO₃, HCl and brine, dried over Na₂SO₄, filtered, and concentrated to provide the desired compound **L6a** as a white solid (412 mg, 0.84 mmol, 97%). ¹H NMR (400 MHz, chloroform-*d*) δ 6.17 (s, 1H), 5.07 (s, 1H), 3.58 (s, 4H), 3.53 (t, *J* = 5.0 Hz, 3H), 3.43 (q, *J* = 5.3 Hz, 2H), 3.36-3.21 (m, 2H), 2.15 (t, *J* = 7.5 Hz, 2H), 1.66-1.54 (m, 2H), 1.32-1.15 (m, 26H), 0.84 (t, *J* = 6.6 Hz, 3H).

Intermediate L6b

[0364] A solution of compound **L6a** (412 mg, 0.84 mmol, 1 eq) in DCM (2 mL) was treated with TFA (2 mL) for 30 min. The mixture was concentrated, co-evaporated with hexane. To a solution of BocNH-PEG₂-CO₂H (258 mg, 0.931 mmol, 1.1 eq) dissolved in DMF (5 mL) was added HATU (353 mg, 0.931 mmol, 1.1 eq). Deprotected compound **L6a** and DIEA (294 μ L, 1.69 mmol, 2 eq) in DMF were added to the reaction mixture. The reaction mixture was agitated 2 h at RT. The product was diluted with EtOAc. The organic layer was successively washed with 1M HCl, sat. NaHCO₃, HCl and brine, dried over Na₂SO₄, filtered, and concentrated. Purification by flash column chromatography on silica gel provided the desired compound **L6b** as an oil (329 mg, 0.51 mmol, 60%). ¹H NMR (400 MHz, chloroform-*d*) δ 6.79 (s, 1H), 6.28 (s, 1H), 5.28 (s, 1H), 3.68 (t, *J* = 5.8 Hz, 2H), 3.61-3.44 (m, 14H), 3.38 (p, *J* = 5.6 Hz, 4H), 3.24 (q, *J* = 5.5 Hz, 2H), 2.42 (t, *J* = 5.8 Hz, 2H), 2.11 (t, *J* = 7.9 Hz, 2H), 1.55 (p, *J* = 7.2 Hz, 2H), 1.38 (s, 9H), 1.32-1.10 (m, 24H), 0.81 (t, *J* = 6.7 Hz, 3H).

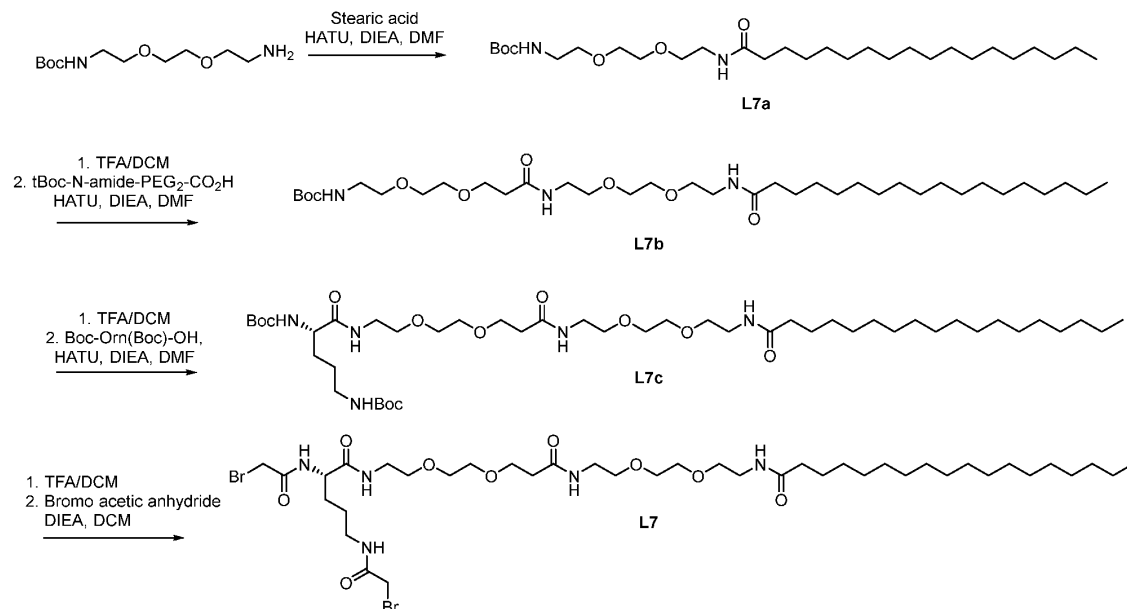
Intermediate L6c

[0365] A solution of compound **L6b** (329 mg, 0.51 mmol, 1 eq) in DCM (2 mL) was treated with TFA (2 mL) for 30 min. The mixture was concentrated, co-evaporated with hexane. To a solution of Boc-

Orn(Boc)-OH (186 mg, 0.56 mmol, 1.1 eq) dissolved in DMF (5 mL) was added HATU (213 mg, 0.56 mmol 1.1 eq). Deprotected compound **L6b** and DIEA (177 μ L, 1.02 mmol, 2 eq) in DMF were added to the reaction mixture. The reaction mixture was agitated 2 h at RT. The product was diluted with EtOAc. The organic layer was successively washed with sat. NaHCO_3 , 1M HCl and brine, dried over Na_2SO_4 , filtered, and concentrated. Purification by flash column chromatography on silica gel provided the desired compound **L6c** as an oil (326 mg, 0.37 mmol, 94%). ^1H NMR (400 MHz, chloroform- d) δ 7.18 (s, 1H), 6.92 (s, 1H), 6.48 (s, 1H), 5.61 (d, J = 8.4 Hz, 1H), 5.08 (t, J = 5.9 Hz, 1H), 4.13 (s, 1H), 3.73-3.65 (m, 2H), 3.59-3.44 (m, 14H), 3.42-3.29 (m, 8H), 3.19-2.86 (m, 2H), 2.42 (t, J = 5.9 Hz, 2H), 2.10 (d, J = 7.3 Hz, 2H), 1.78-1.63 (m, 1H), 1.60-1.40 (m, 5H), 1.35 (s, 18H), 1.26-1.09 (m, 22H), 0.80 (t, J = 6.7 Hz, 3H).

[0366] A solution of compound **L6c** (100 mg, 0.116 mmol, 1 eq) in DCM (2 mL) was treated with TFA (2 mL) for 30 min. The mixture was concentrated, co-evaporated with hexane and dissolved in 10 mL of DCM and cooled at 0°C. DIEA (80.8 μ L, 0.46 mmol, 4 eq) was added followed by bromoacetic anhydride (61.9 mg, 0.238 mmol, 2.05 eq) dissolved in 1 mL of DCM. The reaction mixture was then stirred for 30 min at 0°C, 1.5 h at RT, and the solvent was removed. Purification by flash column chromatography on silica gel afforded **L6** as a white solid (50.1 mg, 0.055 mmol, 40%). ^1H NMR (400 MHz, methanol- d_4) δ 4.39 (dd, J = 8.4, 5.5 Hz, 1H), 3.91 (q, J = 11.4 Hz, 2H), 3.84 (s, 2H), 3.76 (t, J = 6.2 Hz, 2H), 3.63 (d, J = 7.1 Hz, 8H), 3.57 (q, J = 5.5 Hz, 6H), 3.43-3.36 (m, 6H), 3.25 (t, J = 13.9, 6.8 Hz, 2H), 2.49 (t, J = 6.2 Hz, 2H), 2.21 (t, J = 7.5 Hz, 2H), 1.91-1.79 (m, 1H), 1.75-1.53 (m, 5H), 1.42-1.25 (m, 24H), 0.92 (t, J = 6.7 Hz, 3H).

Example 15: Synthesis of L7



Intermediate L7a

[0367] Stearic acid (261 mg, 0.919 mmol, 1.05 eq) was dissolved in 4 mL of DMF. HATU (349 mg, 0.919 mmol, 1.05 eq) and DIEA (167 μ L, 0.963 mmol, 1.1 eq) were added followed by the addition of

Boc-NH-PEG₂-NH₂ (200 mg, 0.875 mmol, 1 eq). The reaction mixture was then stirred for 2 h, and the solvent was removed. The product was dissolved in EtOAc. The organic layer was successively washed with 1M HCl, sat. NaHCO₃, and brine, dried over Na₂SO₄, filtered, and concentrated to provide the desired compound **L7a** as a white solid (430 mg, 0.83 mmol, 95%). ¹H NMR (400 MHz, chloroform-*d*) δ 3.69-3.59 (m, 4H), 3.56 (t, *J* = 5.1 Hz, 4H), 3.46 (q, *J* = 5.2 Hz, 2H), 3.40-3.23 (m, 2H), 2.18 (t, *J* = 7.6 Hz, 2H), 1.62 (t, *J* = 7.3 Hz, 2H), 1.45 (s, 9H), 1.35-1.19 (m, 30H), 0.88 (t, *J* = 6.7 Hz, 4H).

Intermediate L7b

[0368] A solution of compound **L7a** (426 mg, 0.87 mmol, 1 eq) in DCM (2 mL) was treated with TFA (2 mL) for 30 min. The mixture was concentrated, co-evaporated with hexane. To a solution of BocNH-PEG₂-CO₂H (266 mg, 0.96 mmol, 1.1 eq) dissolved in DMF (5 mL) was added HATU (366 mg, 0.96 mmol, 1.1 eq). Deprotected compound **L7a** and DIEA (304 μL, 1.75 mmol, 2 eq) in DMF were added to the reaction mixture. The reaction mixture was agitated 2 h at RT. The product was diluted with EtOAc. The organic layer was successively washed with 1M HCl, sat. NaHCO₃, and brine, dried over Na₂SO₄, filtered, and concentrated. Purification by flash column chromatography on silica gel provided the desired compound **L7b** as an oil (360 mg, 0.53 mmol, 61%). ¹H NMR (400 MHz, chloroform-*d*) δ 6.75 (s, 1H), 6.18 (s, 1H), 5.26 (s, 1H), 3.75 (t, *J* = 5.8 Hz, 2H), 3.69-3.52 (m, 14H), 3.47 (p, *J* = 5.4 Hz, 4H), 3.33 (q, *J* = 5.5 Hz, 2H), 2.50 (t, *J* = 5.8 Hz, 2H), 2.19 (t, *J* = 7.5 Hz, 2H), 2.07 (s, 1H), 1.63 (p, *J* = 7.3 Hz, 2H), 1.46 (s, 9H), 1.37-1.19 (m, 29H), 0.89 (t, *J* = 6.7 Hz, 3H).

Intermediate L7c

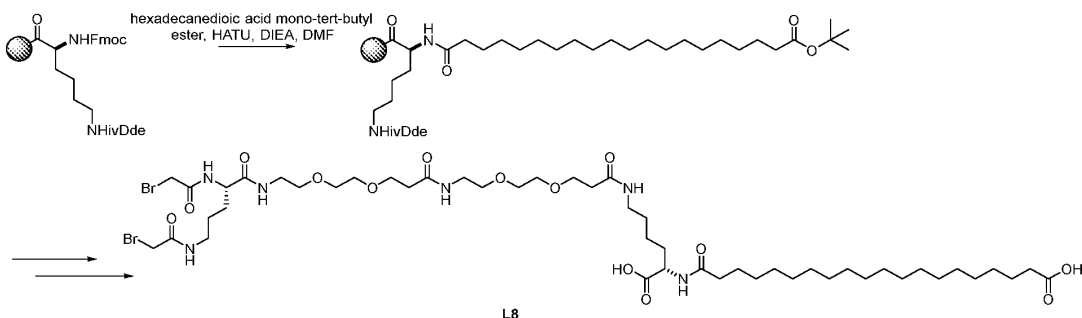
[0369] A solution of compound **L7b** (360 mg, 0.53 mmol, 1 eq) in DCM (2 mL) was treated with TFA (2 mL) for 30 min. The mixture was concentrated, co-evaporated with hexane. To a solution of Boc-Orn(Boc)-OH (195 mg, 0.58 mmol, 1.1 eq) dissolved in DMF (5 mL) was added HATU (223 mg, 0.58 mmol, 1.1 eq). Deprotected compound **L7b** and DIEA (186 μL, 1.07 mmol, 2 eq) in DMF were added to the reaction mixture. The reaction mixture was agitated 2 h at RT. The product was diluted with EtOAc. The organic layer was successively washed with 1M HCl, sat. NaHCO₃, and brine, dried over Na₂SO₄, filtered, and concentrated. Purification by flash column chromatography on silica gel provided the desired compound **L7c** as an oil (373 mg, 0.42 mmol, 78%). ¹H NMR (400 MHz, chloroform-*d*) δ 7.14 (s, 1H), 6.84 (s, 1H), 6.35 (s, 1H), 5.53 (d, *J* = 8.2 Hz, 1H), 5.05-4.88 (m, 1H), 4.20 (s, 1H), 3.82-3.69 (m, 2H), 3.65-3.31 (m, 22H), 3.23-3.00 (m, 2H), 2.48 (t, *J* = 5.8 Hz, 2H), 2.17 (t, *J* = 7.8 Hz, 2H), 1.87-1.72 (m, 1H), 1.67-1.48 (m, 5H), 1.42 (s, 18H), 1.34-1.14 (m, 29H), 0.87 (t, *J* = 6.9 Hz, 3H).

L7

[0370] A solution of compound **L7c** (100 mg, 0.112 mmol, 1 eq) in DCM (2 mL) was treated with TFA (2 mL) for 30 min. The mixture was concentrated, co-evaporated with hexane and dissolved in 10 mL of DCM and cooled at 0°C. DIEA (78 μL, 0.44 mmol, 4 eq) was added followed by bromoacetic anhydride (62 mg, 0.24 mmol, 2.05 eq) dissolved in 1 mL of DCM. The reaction mixture was then stirred for 30 min at 0°C, 1.5 h at RT, and the solvent was removed. The product was dissolved in EtOAc. The organic layer was successively washed with 1M HCl, sat. NaHCO₃, and brine, dried over Na₂SO₄, filtered, and concentrated. Purification by flash column chromatography on silica gel afforded **L7** as a white solid

(95 mg, 0.10 mmol, 91%). MS (ES⁺) m/z 931.31 ([M+H]⁺), 933.25 ([M+H]⁺). ¹H NMR (400 MHz, methanol-*d*₄) δ 4.39 (dd, J = 8.5, 5.4 Hz, 1H), 3.91 (q, J = 11.3 Hz, 2H), 3.84 (s, 2H), 3.76 (t, J = 6.2 Hz, 2H), 3.63 (d, J = 7.0 Hz, 8H), 3.57 (t, J = 5.5 Hz, 6H), 3.42-3.35 (m, 6H), 3.31-3.13 (m, 4H), 2.49 (t, J = 6.2 Hz, 2H), 2.20 (t, J = 7.4 Hz, 2H), 1.91-1.79 (m, 1H), 1.75-1.56 (m, 6H), 1.39-1.26 (m, 26H), 0.92 (t, J = 6.3 Hz, 3H).

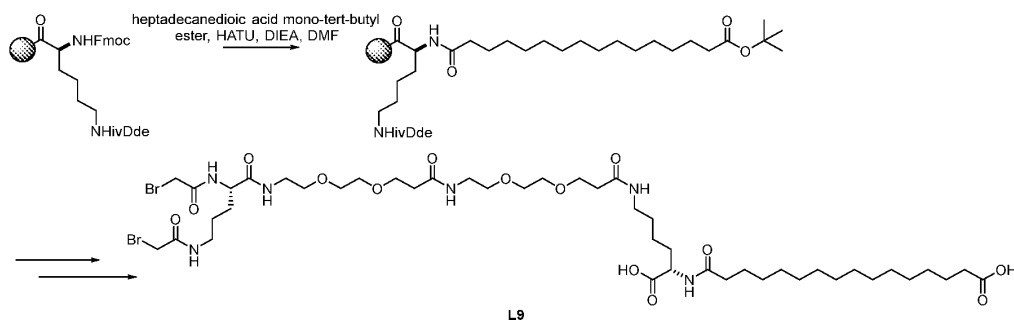
Example 16: Synthesis of L8



[0371] General protocol A, B, D (hexadecanedioic acid mono-tert butyl ester), C, D (Fmoc-PEG₂-propionic acid), B, D (Fmoc-PEG₂-propionic acid), B, D (Fmoc-Orn(Fmoc)-OH), B, E, F.

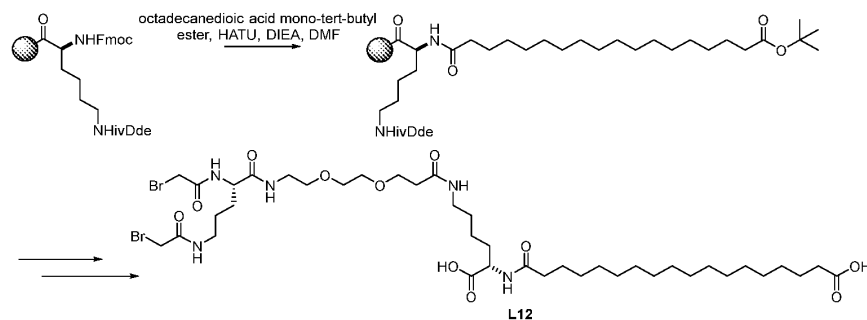
[0372] The crude was purified by semi-preparative HPLC with mass detection to afford the product L8 as a white solid (42.6 mg, 0.038 mmol, 22%). ¹H NMR (400 MHz, methanol-*d*₄) δ 4.38 (td, J = 8.6, 5.1 Hz, 2H), 3.91 (q, J = 11.3 Hz, 2H), 3.84 (s, 2H), 3.76 (q, J = 6.1 Hz, 4H), 3.65-3.59 (m, 8H), 3.56 (td, J = 5.5, 1.7 Hz, 4H), 3.43-3.37 (m, 4H), 3.31-3.16 (m, 4H), 2.48 (dt, J = 15.7, 6.2 Hz, 4H), 2.28 (dt, J = 12.6, 7.5 Hz, 4H), 1.95-1.79 (m, 1H), 1.77-1.51 (m, 10H), 1.49-1.41 (m, 2H), 1.40-1.26 (m, 31H).

Example 17: Synthesis of L9



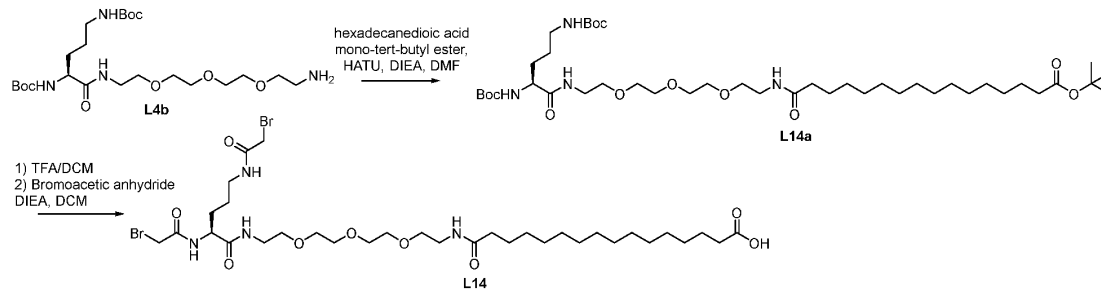
[0373] General protocol A, B, D (heptadecanedioic acid mono-tert butyl ester), C, D (Fmoc-PEG₂-propionic acid), B, D (Fmoc-PEG₂-propionic acid), B, D (Fmoc-Orn(Fmoc)-OH), B, E, F.

[0374] The crude was purified by semi-preparative HPLC with mass detection to afford the product L9 as a white solid (49 mg, 0.089 mmol, 9%). ¹H NMR (400 MHz, methanol-*d*₄) δ 4.45-4.33 (m, 2H), 3.92 (t, J = 10.9 Hz, 2H), 3.85 (d, J = 1.1 Hz, 2H), 3.77 (q, J = 6.0 Hz, 4H), 3.63 (s, 8H), 3.57 (t, J = 5.6 Hz, 4H), 3.40 (t, J = 5.5 Hz, 4H), 3.25 (dq, J = 22.7, 6.7 Hz, 4H), 2.48 (dt, J = 15.6, 6.2 Hz, 4H), 2.29 (dt, J = 13.2, 7.4 Hz, 4H), 1.95-1.79 (m, 2H), 1.80-1.50 (m, 10H), 1.51-1.41 (m, 2H), 1.40-1.27 (m, 20H).

Example 18: Synthesis of L12

[0375] General protocol A, B, D (octadecanedioic acid), C, D (Fmoc-PEG₂-propionic acid), B, D (Fmoc-Orn(Fmoc)-OH), B, E, F.

[0376] The crude was purified by semi-preparative HPLC with mass detection to afford the product **L12** as a white solid (51.7 mg, 0.054 mmol, 3%). ¹H NMR (400 MHz, methanol-*d*₄) δ 4.39 (td, *J* = 9.2, 5.1 Hz, 2H), 3.92 (qd, *J* = 11.4, 1.2 Hz, 2H), 3.85 (s, 2H), 3.76 (t, *J* = 6.2 Hz, 2H), 3.63 (s, 4H), 3.57 (t, *J* = 5.5 Hz, 2H), 3.40 (q, *J* = 5.1 Hz, 2H), 3.30-3.12 (m, 6H), 2.47 (t, *J* = 6.1 Hz, 2H), 2.29 (dt, *J* = 12.1, 7.4 Hz, 4H), 1.95-1.77 (m, 2H), 1.78-1.50 (m, 10H), 1.48-1.40 (m, 2H), 1.39-1.26 (m, 22H).

Example 19: Synthesis of L14*Intermediate L14a*

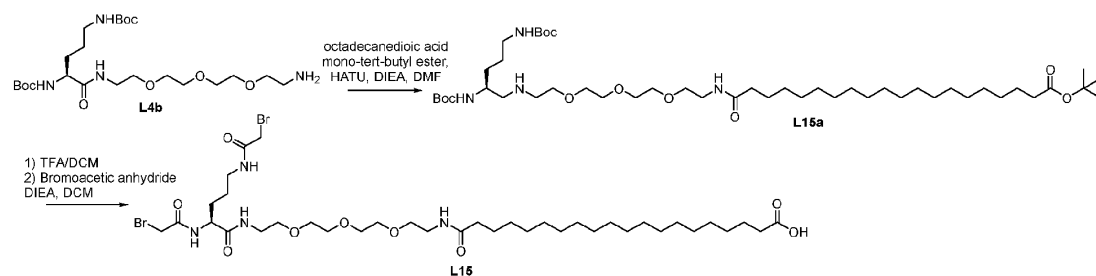
[0377] To a solution of hexadecanedioic acid mono *tert*-butyl ester (102 mg, 0.30 mmol, 1 eq) dissolved in DMF (5 mL) was added HATU (125 mg, 0.33 mmol 1.1 eq), DIEA (51 μL, 0.33 mmol, 1.1 eq) and compound **L4b** (151.9 mg, 0.3 mmol, 1 eq) dissolved in 1 mL of DMF. The reaction mixture was agitated 3h at RT. The product was diluted with EtOAc. The organic layer was successively washed with 1M HCl, sat. NaHCO₃, brine, dried over Na₂SO₄, filtered, and concentrated. Purification by flash column chromatography on silica gel provided the desired compound **L14a** as an oil (147 mg, 0.176 mmol, 59%). ¹H NMR (400 MHz, chloroform-*d*) δ 6.87 (s, 1H), 6.40 (s, 1H), 5.32 (s, 2H), 4.79 (s, 1H), 4.20 (s, 1H), 3.66 (d, *J* = 7.0 Hz, 8H), 3.60 (dt, *J* = 10.0, 5.1 Hz, 4H), 3.49-3.45 (m, 3H), 3.31-3.18 (m, 1H), 3.13-3.06 (m, 1H), 2.21 (td, *J* = 7.8, 6.0 Hz, 4H), 1.88-1.78 (m, 1H), 1.66-1.53 (m, 7H), 1.51-1.42 (m, 27H), 1.36-1.19 (m, 20H).

L14

[0378] A solution of compound **L14a** (40 mg, 0.048 mmol, 1 eq) in DCM (2 mL) was treated with TFA (2 mL) for 30 min. The mixture was concentrated, co-evaporated with hexane and dissolved in 20 mL of DCM and cooled at 0°C. DIEA (34 μL, 0.1924 mmol, 4 eq) was added followed by bromoacetic anhydride

(23.63 mg, 0.098 mmol, 2.05 eq) dissolved in 1 mL of DCM. The reaction mixture was then stirred for 30 min at 0°C, 1.5 h at RT, and the solvent was removed. Purification by flash column chromatography on silica gel afforded **L14** as a white solid (18.3 mg, 0.022 mmol, 46%). MS (ES⁺) m/z 817.1 ([M+H]⁺), 819.09 ([M+H]⁺). ¹H NMR (400 MHz, methanol-*d*₄) δ 4.38 (dd, J = 8.4, 5.5 Hz, 1H), 3.92 (q, J = 11.2, 10.6 Hz, 2H), 3.84 (s, 2H), 3.69-3.61 (m, 8H), 3.56 (td, J = 5.5, 2.6 Hz, 4H), 3.44-3.36 (m, 4H), 3.30-3.14 (m, 2H), 2.29 (t, J = 7.4 Hz, 2H), 2.21 (t, J = 7.5 Hz, 2H), 1.91-1.78 (m, 1H), 1.76-1.67 (m, 1H), 1.67-1.54 (m, 6H), 1.40-1.29 (m, 20H).

Example 20: Synthesis of L15



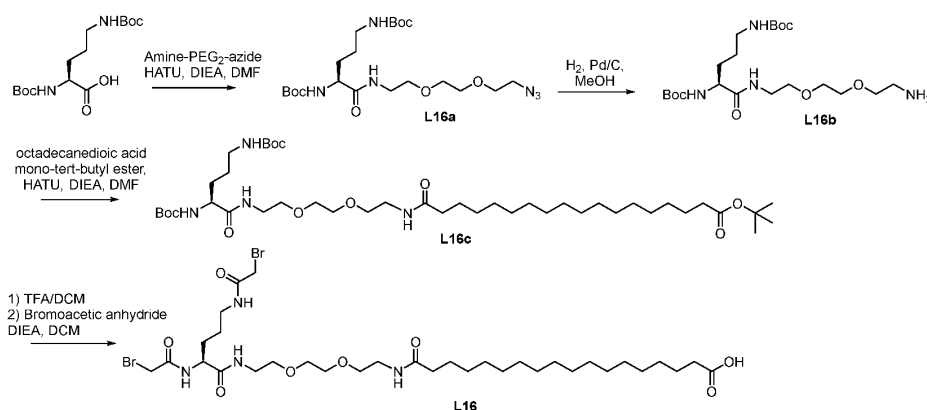
Intermediate L15a

[0379] To a solution of 20-(*tert*-butoxy)-20-oxoicosanoic acid (360 mg, 0.90 mmol, 1.05 eq) dissolved in DMF (5 mL) was added HATU (343 mg, 0.90 mmol, 1.05 eq), DIEA (300 μL, 1.71 mmol, 2 eq) and compound **L4b** (435 mg, 0.858 mmol, 1 eq) dissolved in 1 mL of DMF. The reaction mixture was agitated 3 h at RT. The product was diluted with EtOAc. The organic layer was successively washed with 1M HCl, sat. NaHCO₃, brine, dried over Na₂SO₄, filtered, and concentrated. Purification by flash column chromatography on silica gel provided the desired compound **L15a** as an oil (555 mg, 0.625 mmol, 72%). ¹H NMR (400 MHz, chloroform-*d*) δ 6.87 (s, 1H), 6.40 (s, 1H), 4.79 (s, 1H), 4.21 (s, 1H), 3.76-3.53 (m, 15H), 3.47 (s, 5H), 3.32-3.05 (m, 3H), 2.29-2.17 (m, 4H), 1.90-1.76 (m, 4H), 1.69-1.53 (m, 2H), 1.52-1.41 (m, 33H), 1.36-1.20 (m, 29H).

L15

[0380] A solution of compound **L15a** (100 mg, 0.112 mmol, 1 eq) in DCM (2 mL) was treated with TFA (2 mL) for 30 min. The mixture was concentrated, co-evaporated with hexane and dissolved in 20 mL of DCM and cooled at 0°C. DIEA (79 μL, 0.45 mmol, 4 eq) was added followed by bromoacetic anhydride (60 mg, 0.231 mmol, 2.05 eq) dissolved in 1 mL of DCM. The reaction mixture was then stirred for 30 min at 0°C, 1.5 h at RT, and the solvent was removed. Purification by flash column chromatography on silica gel afforded **L15** as a white solid (17.5 mg, 0.02 mmol, 18%). MS (ES⁺) m/z 873.21 ([M+H]⁺), 875.20 ([M+H]⁺). ¹H NMR (400 MHz, methanol-*d*₄) δ 4.38 (dd, J = 8.4, 5.5 Hz, 1H), 3.91 (q, J = 11.4 Hz, 2H), 3.84 (s, 2H), 3.72-3.61 (m, 8H), 3.56 (td, J = 5.5, 2.7 Hz, 4H), 3.44-3.35 (m, 5H), 3.30-3.17 (m, 2H), 2.29 (t, J = 7.4 Hz, 2H), 2.21 (t, J = 7.5 Hz, 2H), 1.92-1.77 (m, 1H), 1.75-1.53 (m, 7H), 1.40-1.27 (m, 27H).

Example 21: Synthesis of L16



Intermediate L16a

[0381] To a solution of Boc-Orn(Boc)-OH (400 mg, 1.2 mmol, 1 eq) dissolved in DMF (10 mL) was added HATU (504 mg, 1.32 mmol, 1.1 eq), DIEA (230 μ L, 1.32 mmol, 1.1 eq) and amine-PEG₂-N₃ (210 mg, 1.20 mmol, 1 eq) dissolved in 1 mL of DMF. The reaction mixture was agitated 4 h at RT. The product was diluted with EtOAc. The organic layer was successively washed with 1M HCl, sat. NaHCO₃, brine, dried over Na₂SO₄, filtered, and concentrated. Purification by flash column chromatography on silica gel provided the desired compound **L16a** as an oil (471 mg, 0.96 mmol, 80%). ¹H NMR (400 MHz, methanol-*d*₄) δ 4.01 (t, *J* = 6.6 Hz, 1H), 3.71-3.60 (m, 6H), 3.55 (t, *J* = 5.5 Hz, 2H), 3.41-3.37 (m, 3H), 3.04 (t, *J* = 6.2 Hz, 2H), 1.78-1.66 (m, 1H), 1.62-1.48 (m, 3H), 1.48-1.39 (m, 18H).

Intermediate L16b

[0382] To a solution of compound **L16a** (471 mg, 0.9 mmol, 1 eq) in anhydrous MeOH (10 mL) and under argon was added Pd/C (10.2 mg, 0.09 mmol, 0.1 eq) and argon was replaced with H₂. The reaction mixture was agitated for 6 h at RT, filtrated on celite and evaporated to afford compound **L16b** as an oil (295.5 mg, 0.64 mmol, 71%). The product was used without any further purification. MS (ES⁺) *m/z* 462.51 ([M+H]⁺).

Intermediate L16c

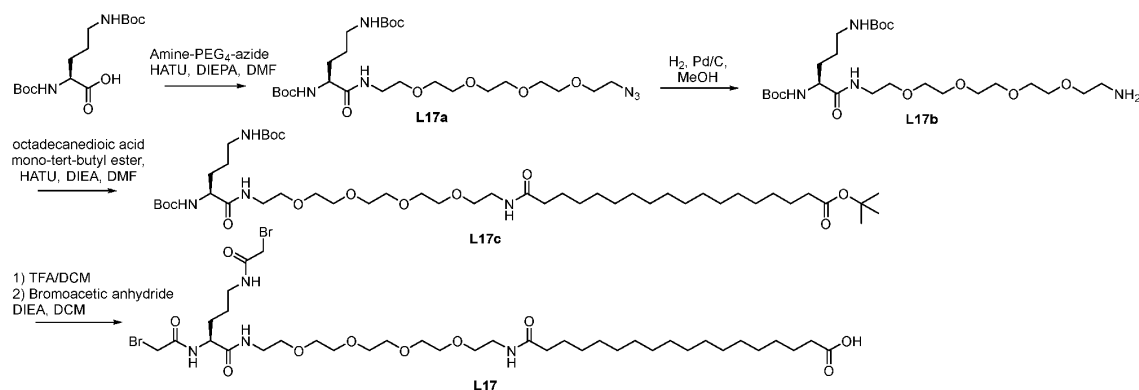
[0383] To a solution of octadecanedioic acid mono *tert*-butyl ester (281 mg, 0.76 mmol, 1 eq) dissolved in DMF (5 mL) was added HATU (288 mg, 0.76 mmol, 1 eq), DIEA (132 μ L, 0.76 mmol, 1 eq) and compound **L16b** (351 mg, 0.76 mmol, 1 eq) dissolved in 1 mL of DMF. The reaction mixture was agitated 3 h at RT. The product was diluted with EtOAc. The organic layer was successively washed with 1M HCl, sat. NaHCO₃, brine, dried over Na₂SO₄, filtered, and concentrated. Purification by flash column chromatography on silica gel provided the desired compound **L16c** as an oil (351 mg, 0.43 mmol, 57%). ¹H NMR (400 MHz, methanol-*d*₄) δ 3.61 (s, 4H), 3.54 (td, *J* = 5.6, 2.3 Hz, 4H), 3.40-3.34 (m, 4H), 3.04 (t, *J* = 6.6 Hz, 2H), 2.20 (td, *J* = 7.6, 5.9 Hz, 4H), 1.77-1.68 (m, 2H), 1.64-1.48 (m, 2H), 1.48-1.42 (m, 28H), 1.35-1.26 (m, 26H).

L16

[0384] A solution of compound **L16c** (31 mg, 0.038 mmol, 1 eq) in DCM (2 mL) was treated with TFA (2 mL) for 30 min. The mixture was concentrated, co-evaporated with hexane and dissolved in 20 mL of

DCM and cooled at 0°C. DIEA (27 μ L, 0.152 mmol, 4 eq) was added followed by bromoacetic anhydride (21 mg, 0.078 mmol, 2.05 eq) dissolved in 1 mL of DCM. The reaction mixture was then stirred for 30 min at 0°C, 1.5 h at RT, and the solvent was removed. Purification by flash column chromatography on silica gel afforded **L16** as a white solid (12.6 mg, 0.015 mmol, 41%). MS (ES⁺) m/z 801.13 ([M+H]⁺), 803.12 ([M+H]⁺). ¹H NMR (400 MHz, methanol-*d*₄) δ 4.37 (dd, J = 8.5, 5.4 Hz, 1H), 3.91 (q, J = 11.3 Hz, 2H), 3.84 (s, 2H), 3.63 (s, 4H), 3.57 (td, J = 5.6, 2.6 Hz, 4H), 3.43-3.36 (m, 4H), 3.31-3.17 (m, 1H), 2.29 (t, J = 7.4 Hz, 2H), 2.21 (t, J = 7.5 Hz, 2H), 1.90-1.79 (m, 1H), 1.76-1.54 (m, 7H), 1.41-1.30 (m, 26H).

Example 22: Synthesis of L17



Intermediate L17a

[0385] To a solution of Boc-Orn(Boc)-OH (400 mg, 1.2 mmol, 1 eq) dissolved in DMF (10 mL) was added HATU (504 mg, 1.32 mmol, 1.1 eq), DIEA (230 μ L, 1.32 mmol, 1.1 eq) and amine-PEG₂-N₃ (316 mg, 1.20 mmol, 1 eq) dissolved in 1 mL of DMF. The reaction mixture was agitated 4 h at RT. The product was diluted with EtOAc. The organic layer was successively washed with 1M HCl, sat. NaHCO₃, brine, dried over Na₂SO₄, filtered, and concentrated. Purification by flash column chromatography on silica gel provided the desired compound **L17a** as an oil (454 mg, 0.78 mmol, 66%). ¹H NMR (400 MHz, methanol-*d*₄) δ 4.04-3.97 (m, 1H), 3.71-3.58 (m, 14H), 3.54 (t, J = 5.4 Hz, 2H), 3.37 (t, J = 5.0 Hz, 4H), 3.04 (t, J = 6.6 Hz, 2H), 1.75-1.67 (m, 1H), 1.62-1.48 (m, 3H), 1.48-1.41 (m, 18H).

Intermediate L17b

[0386] To a solution of compound **L17a** (454 mg, 0.9 mmol, 1 eq) in anhydrous MeOH (10 mL) and under argon was added Pd/C (8.3 mg, 0.078 mmol, 0.1 eq) and argon was replaced with H₂. The reaction mixture was agitated for 6 h at RT, filtrated on celite and evaporated to afford compound **L17b** as an oil (192 mg, 0.35 mmol, 45%). The product was used without any further purification.

Intermediate L17c

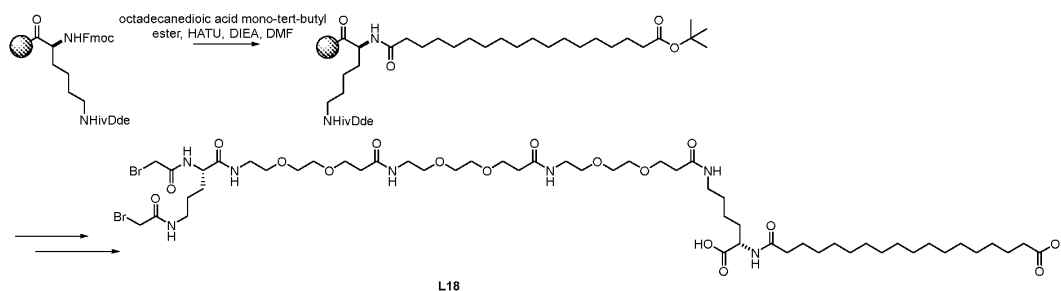
[0387] To a solution of octadecanedioic acid mono *tert*-butyl ester (225 mg, 0.61 mmol, 1 eq) dissolved in DMF (5 mL) was added HATU (231 mg, 0.61 mmol, 1 eq), DIEA (106 μ L, 0.61 mmol, 1 eq) and compound **L17b** (335mg, 0.61 mmol, 1 eq) dissolved in 1 mL of DMF. The reaction mixture was agitated 2 h at RT. The product was diluted with EtOAc. The organic layer was successively washed with 1M HCl, sat. NaHCO₃, brine, dried over Na₂SO₄, filtered, and concentrated. Purification by flash column chromatography on silica gel provided the desired compound **L17c** as an oil (178 mg, 0.20 mmol, 32%).

^1H NMR (400 MHz, chloroform-*d*) δ 5.32 (s, 2H), 3.74-3.63 (m, 11H), 3.59 (dt, $J = 10.9, 5.0$ Hz, 4H), 3.52-3.43 (m, 4H), 3.27-3.08 (m, 2H), 2.22 (d, $J = 7.6$ Hz, 4H), 1.69-1.52 (m, 6H), 1.51-1.42 (m, 27H), 1.27 (s, 26H).

L17

[0388] A solution of compound **L17c** (45.6 mg, 0.05 mmol, 1 eq) in DCM (2 mL) was treated with TFA (2 mL) for 30 min. The mixture was concentrated, co-evaporated with hexane and dissolved in 20 mL of DCM and cooled at 0°C. DIEA (36 μL , 0.202 mmol, 4 eq) was added followed by bromoacetic anhydride (27 mg, 0.103 mmol, 2.05 eq) dissolved in 1 mL of DCM. The reaction mixture was then stirred for 30 min at 0°C, 1.5 h at RT, and the solvent was removed. Purification by flash column chromatography on silica gel afforded **L17** as a white solid (14.9 mg, 0.017 mmol, 33%). MS (ES^+) m/z 889.18 ($[\text{M}+\text{H}]^+$), 891.17 ($[\text{M}+\text{H}]^+$). ^1H NMR (400 MHz, methanol-*d*₄) δ 4.38 (dd, $J = 8.3, 5.5$ Hz, 1H), 3.92 (q, $J = 11.3$ Hz, 2H), 3.84 (s, 2H), 3.67-3.60 (m, 7H), 3.56 (td, $J = 5.5, 3.5$ Hz, 4H), 3.45-3.35 (m, 5H), 3.32-3.15 (m, 3H), 2.29 (t, $J = 7.4$ Hz, 2H), 2.21 (t, $J = 7.5$ Hz, 2H), 1.90-1.76 (m, 1H), 1.74-1.57 (m, 7H), 1.41-1.26 (m, 25H).

Example 23: Synthesis of L18



[0389] General protocol **A**, **B**, **D** (octadecanedioic acid), **C**, **D** (Fmoc-PEG₂-propionic acid), **B**, (Fmoc-PEG₂-propionic acid), **B**, (Fmoc-PEG₂-propionic acid), **B**, **D** (Fmoc-Orn(Fmoc)-OH), **B**, **E**, **F**.

[0390] The crude was purified by semi-preparative HPLC with mass detection to afford the product **L18** as a white solid (47 mg, 0.036 mmol, 10 %). MS (ES^+) m/z 1276.39 ($[\text{M}+\text{H}]^+$), 1278.37 ($[\text{M}+\text{H}]^+$).

General procedure for bromoacetyl peptide stapling/conjugation

[0391] Peptides were dissolved at a concentration of 2 mM with 1.5 eq of bromoacetyl staple in 1:3 (v/v) MeCN / 30 mM NH_4HCO_3 buffer (pH 8.5). The pH of the reaction mixture was readjusted with ammonium hydroxide to correct the drop in pH caused by the peptide TFA counterion. More MeCN was added for particularly insoluble peptides. The reaction was stirred at RT for 2-4 h, before acidification to pH 5 via dropwise addition of acetic acid. The resulting solution was lyophilized and purified by reversed-phase HPLC.

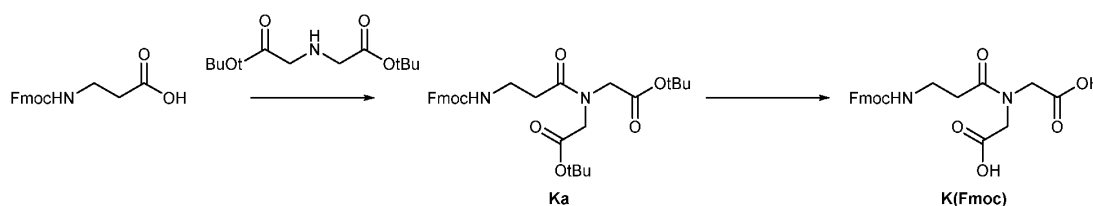
General solid-phase protocols for lactam stapling

[0392] Peptide-resin bearing amine side chain orthogonal protection (Dde/Mmt) at each stapling position was swollen in DMF for 1 h. The Dde protecting group was removed from the first side chain via treatment with 2% hydrazine solution in DMF (2 $\times$ 15 min). Positive TNBS test was observed. The linker building block specified below was coupled as described and a negative TNBS test was observed. The solvent was

exchanged for DCM and the Mmt group was removed from the second side chain via treatment with 1% TFA in DCM containing 5% TIPS, 5×2 min. The resin was washed with DCM, 10% DIEA in DMF, DMF and a positive TNBS test was observed. The linker was cyclized and the PEG-fatty acid portion of the staple (if applicable) elongated as described below. The complete stapled peptide was cleaved from the resin using 95% TFA, 2.5% TIPS, 2.5% H₂O, 3 h. The peptide cleavage mixture was evaporated to an oil, triturated and washed with diethyl ether and purified via reversed-phase HPLC.

A Dde/Alloc protection scheme can also be used for this approach, which requires the addition of allyl alcohol to the Dde deprotection cocktail as a scavenger to prevent concurrent reduction of the Alloc allyl moiety.

Synthesis of K(Fmoc) linker



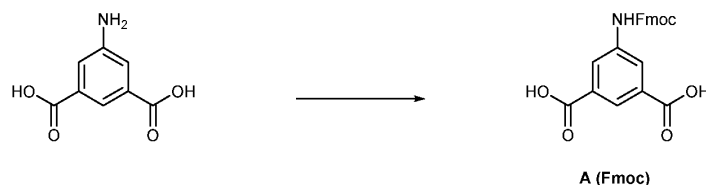
Intermediate Ka

[0393] Fmoc-β-Ala-OH (1.00 g, 3.21 mmol) and di-*tert*-butyl iminodiacetate (0.461 g, 2.68 mmol) were suspended in 100 mL DCM. HATU (1.02 g, 2.68 mmol) and DIEA (3.32 mL, 12.8 mmol) were added and the reaction was stirred at RT for 3.5 h. The solvent was evaporated and the residue dissolved in MeOH and purified via flash column chromatography on silica gel (hexane/EtOAc) to afford the product as a white solid (0.802 g, 56%). ¹H NMR (400 MHz, chloroform-*d*) δ 7.78 (d, *J* = 7.4 Hz, 2H), 7.62 (d, *J* = 7.4 Hz, 2H), 7.42 (t, *J* = 7.4 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 2H), 5.66 (t, *J* = 5.7 Hz, 1H), 4.35 (d, *J* = 7.3 Hz, 2H), 4.23 (t, *J* = 7.3 Hz, 1H), 4.10 (s, 2H), 4.02 (s, 2H), 3.56 (q, *J* = 5.7 Hz, 2H), 2.55 (t, *J* = 5.7 Hz, 2H), 1.49 (s, 18H).

K(Fmoc) linker

[0394] Compound **Ka** was treated with 20 mL 1:1 TFA/DCM for 2 h. The solvent was evaporated and the residue triturated and washed with diethyl ether to afford **K(Fmoc)** linker as a white solid (0.371 g, 58%). MS (ES⁺) *m/z* 427.15 ([M+H]⁺).

Synthesis of A(Fmoc) linker



[0395] A solution of 5-Aminoisophthalic acid (1.00 g, 5.5 mmol) in 10 mL dioxane was added to a degassed solution of Na₂CO₃ (1.46 g, 5.5 mmol) in 15 mL water. The solution was cooled on ice and a solution of Fmoc chloride (1.42 g, 5.5 mmol) in 10 mL dioxane was then added dropwise with stirring over 15 min. The reaction was then stirred for 1 h and then 24 h at RT. The dioxane was removed under vacuum

and the remaining aqueous solution acidified with 1M HCl. The resulting solid precipitate was then washed with diethyl ether (4×10 mL), redissolved in EtOAc, filtered, washed with brine, dried over Na_2SO_4 filtered and concentrated to give **A (Fmoc)** linker as a white solid (119 mg, 5%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 13.24 (s, 2H), 10.12 (s, 1H), 8.33 (d, $J = 1.5$ Hz, 2H), 8.12 (t, $J = 1.5$ Hz, 1H), 7.91 (d, $J = 7.6$ Hz, 2H), 7.76 (dd, $J = 7.6, 1.2$ Hz, 2H), 7.43 (t, $J = 7.6$ Hz, 2H), 7.36 (td, $J = 7.6, 1.2$ Hz, 2H), 4.50 (d, $J = 6.8$ Hz, 2H), 4.33 (t, $J = 6.8$ Hz, 1H).

General protocol G for 'A1' and 'K1' series simple lactam staples

[0396] For linker coupling the appropriate diacid building block (2 eq) was attached using HATU (4 eq) and DIEA (4 eq) in DMF, 1×2 h. The cyclization step was achieved using HATU (1 eq) and DIEA (2 eq) in DMF, 1×2 h.

General protocol H for 'K' PEG-fatty acid trifunctional lactam staples

[0397] For linker coupling the intramolecular symmetric anhydride of building block **K(Fmoc)** linker (2 eq) was preformed using DIC (2 eq) and catalytic DMAP in dry DCM for 10 min at RT. The peptide-resin solvent was exchanged for DCM and the anhydride was then added and agitated overnight. The resin was drained, washed with DCM and DMF. The linker was cyclized overnight via treatment with DIC (1 eq) and HOBt or HOAt (1 eq) in DMF, and a negative TNBS was observed. Remaining uncyclized linker was capped via treatment with 10% acetic anhydride in DMF (30 min). The linker Fmoc group was deprotected via treatment with 20% piperidine in DMF (2×10 min). A positive TNBS was observed. Subsequent staple PEG and fatty acid building blocks were attached sequentially to the linker free amine via standard coupling chemistry: building block (3 eq), HATU (3 eq) and DIEA (6 eq) in DMF, 1 h at RT, using 20% piperidine in DMF for deprotection cycles ($5 + 10$ min, RT).

General protocol I for 'A' PEG-fatty acid trifunctional lactam staples

[0398] For linker coupling the building block **A(Fmoc)** linker (2 eq) was attached using HATU (4 eq) and DIEA (4 eq) in DMF, 1×2 h. The cyclization step was achieved using HATU (1 eq) and DIEA (2 eq) in DMF, 1×2 h. Remaining uncyclized linker was capped via treatment with 10% acetic anhydride in DMF (30 min). The linker Fmoc group was deprotected via treatment with 20% piperidine in DMF (2×10 min). It was not possible to observe a positive TNBS test for the aniline nitrogen. Fmoc- β -Ala-OH (3 eq) was coupled using HATU (3 eq) and DIEA (6 eq) in DMF, 4×1 h at RT or as the symmetric anhydride using DIC/DMAP in DCM (2 h, RT). Subsequent staple PEG and fatty acid building blocks were attached sequentially to the linker free amine via standard coupling chemistry: building block (3 eq), HATU (3 eq) and DIEA (6 eq) in DMF, 1 h at RT, using 20% piperidine in DMF for deprotection cycles ($5 + 10$ min, RT).

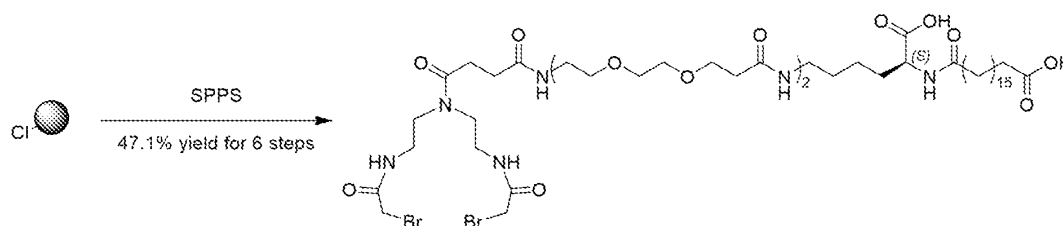
[0399] In some embodiments, the peptide conjugate described herein comprises a half-life extending moiety or a staple of Table 2 or Table 3.

Example 24: Peptide synthesis for mCMZ370(C(14-21) - L5A(S)) and mCMZ371(C(17-24) - L5A(S))

[0400] mCMZ370(C(14-21) - L5A(S)) comprises Compound 2 (266 : SEQ ID NO. 5) and L5A.

[0401] mCMZ371(C(17-24) - L5A(S)) comprises Compound 3 (268 : SEQ ID NO. 6) and L5A.

[0402] General procedure for preparation of **Compound 1**:



The peptide was synthesized using standard Fmoc chemistry.

- 1) Resin preparation: To the 2-CTC 1-chloro-2-[chloro(diphenyl)methyl]benzene (20.0 mmol, 1.00 eq) (Sub: 1.00 mmol/g) was added Fmoc-Lys(Dde)-OH (15.0 mmol, 1.00 eq) and DIEA (10.0 mL, 4.00 eq) in DCM (150 mL). The mixture was agitated with N₂ for 2 hrs at 20 °C, then added MeOH (15.0 mL) and agitated with N₂ for another 30 mins. The resin was washed with DMF (300 mL * 5).
- 2) Deprotection: 20% piperidine in DMF (300 mL) was added and agitated the resin with N₂ for another 30 mins. The resin was washed with DMF (300 mL * 5) and filtered to get the resin.
- 3) Coupling: A solution of 18-(tert-butoxy)-18-oxooctadecanoic acid (2.00 eq) and DIEA (4.00 eq) in DMF (150 mL) was added HATU (1.90 eq) to the resin and agitated with N₂ for 30 mins at 20 °C. The resin was then washed with DMF (300 mL * 5).
- 4) Deprotection: 3% hydrazine hydrate in DMF (300 mL) was added and agitated the resin with N₂ for another 15 min for twice. The resin was washed with DMF (300 mL * 5) and filtered to get the resin.
- 5) Repeat above step 2 to 3 for the coupling of following amino acids: (3~5).
- 6) Repeat above step 3 for the coupling of following amino acids: 2-bromoacetic acid.

Note:

#	Materials	Coupling reagents
3	Fmoc-NH-PEG2-CH ₂ CH ₂ COOH (1.50 eq)	HBTU (1.42 eq) and DIEA (3.00 eq)
4	Fmoc-NH-PEG2-CH ₂ CH ₂ COOH (1.50 eq)	HBTU (1.42 eq) and DIEA (3.00 eq)
5	(2.00 eq)	HBTU (1.90 eq) and DIEA (4.00 eq)
6	2-bromoacetic acid (12.0 eq)	DIC (6.00 eq)

20% piperidine in DMF was used for Fmoc deprotection for 30 mins. The coupling reaction was monitored by ninhydrin test, and the resin was washed with DMF for 5 times.

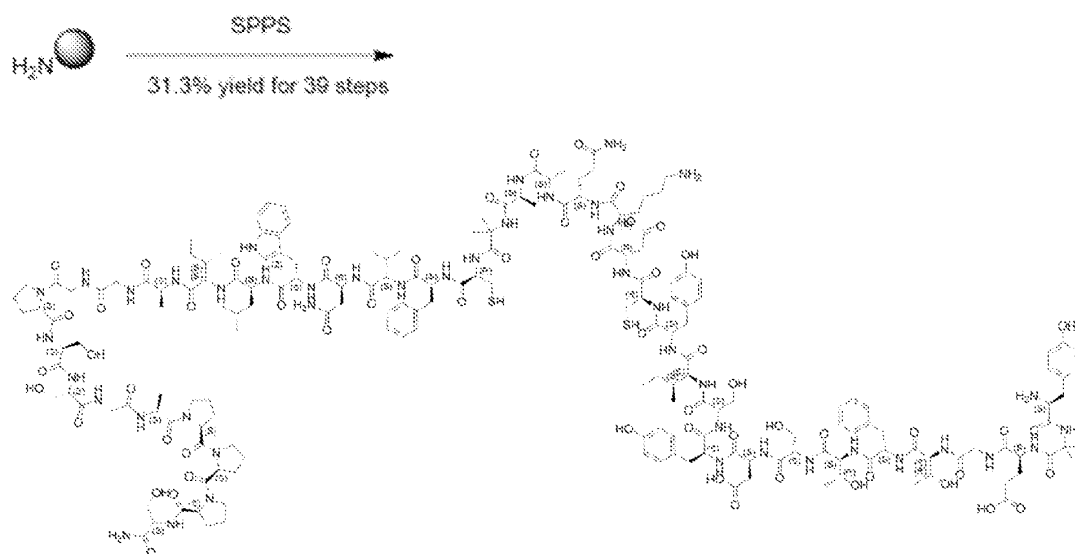
Peptide Cleavage and Purification:

- 1) After coupling, the resin was washed with DMF (200 ml) for 5 times. After last step, the resin was washed with MeOH (200 mL) for 3 times and dried under vacuum. Then the peptide resin (35.0 g) was treated with the cleavage cocktail (350 mL, 95%TFA/5%H₂O) for 1.5 hours. The mixture was filtered to remove the cleavage cocktail, concentrated under reduced pressure to give a residue. LCMS (EW33512-2-P1A1, Rt = 1.524 min).
- 2) The crude peptide was purified by prep-HPLC (A: 0.075% TFA in H₂O, B: ACN) to give the **Compound 1** (8.92 g, 7.07 mmol, 47.11% yield, 94.13% purity) was obtained as a white solid and confirmed by LCMS (EW33512-2-P1A, Rt = 1.544 min), and HPLC (EW33515-2-P1B, Rt = 13.396 min, purity: 94.13%).

Purification conditions:

Separation condition	
Dissolution condition	Dissolve in 50%TFA - H ₂ O
Instrument	Gilson GX-281
Mobile Phase	A: H ₂ O (0.075% TFA in H ₂ O)
	B: CH ₃ CN
Gradient	38-68%-50 min. Retention time: 50 min
Column	luna,C18,10um,100A
Flow Rate	20 mL/Min
Wavelength	214/254 nm
Oven Tem.	30 °C

[0403] General procedure for preparation of Compound 2: (266 : SEQ ID NO. 5)



Peptide Synthesis:

The peptide was synthesized using standard Fmoc chemistry.

- 1) Resin preparation: To the 9H-fluoren-9-ylmethyl N-[(2,4-dimethoxyphenyl)-[4-[2-oxo-2-[[phenyl(p-tolyl)methyl]amino]ethoxy]phenyl]methyl]carbamate (5.00 mmol, 1.00 eq) (Sub: 0.28 mmol/g) in DMF (300 mL) was agitated with N₂ for 2 hrs at 20 °C. Then the mixture was filtered to get the resin.
- 2) Deprotection: 20% piperidine in DMF (300 mL) was added and agitated the resin with N₂ for another 30 mins. The resin was washed with DMF (300 mL * 5) and filtered to get the resin.
- 3) Coupling: A solution of Fmoc-Ser(tBu)-OH (15.0 mmol, 5.75 g, 3.00 eq), DIEA (30.0 mmol, 5.20 mL, 6.00 eq) in DMF (100 mL), then HBTU (5.41 g, 14.2 mmol, 2.85 eq) was added to the resin and agitated with N₂ for 20 mins at 20 °C. The resin was then washed with DMF (450 mL * 5).
- 4) Repeat above step 2 to 3 for the coupling of following amino acids: (2~34).

Note:

#	Materials	Coupling reagents
2	Fmoc-Pro-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
3	Fmoc-Pro-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
4	Fmoc-Pro-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
5	Fmoc-Ala-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
6	Fmoc-Gly-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
7	Fmoc-Ser(tBu)-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
8	Fmoc-Ser(tBu)-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
9	Fmoc-Pro-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)

10	Fmoc-Gly-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
11	Fmoc-Gly-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
12	Fmoc-Ala-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
13	Fmoc-Ile-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
14	Fmoc-Leu-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
15	Fmoc-Trp(Boc)-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
16	Fmoc-Asn(Trt)-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
17	Fmoc-Val-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
18	Fmoc-Phe-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
19	Fmoc-Cys(Trt)-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
20	Fmoc-Aib-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
21	Fmoc-Ala-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
22	Fmoc-Ala-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
23	Fmoc-Gln(Trt)-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
24	Fmoc-Lys(Boc)-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
25	Fmoc-Asp(OtBu)-OH (3.00 eq)	HATU (2.85 eq) and DIEA (6.00 eq)
26	Fmoc-Cys(Trt)-OH (3.00 eq)	HATU (2.85 eq) and DIEA (6.00 eq)
27	Fmoc-Tyr(tBu)-OH (3.00 eq)	HATU (2.85 eq) and DIEA (6.00 eq)
28	Fmoc-Ile-OH (3.00 eq)	HATU (2.85 eq) and DIEA (6.00 eq)
29	Fmoc-Ser(tBu)-OH (3.00 eq)	HATU (2.85 eq) and DIEA (6.00 eq)
30	Fmoc-Tyr(tBu)-OH (3.00 eq)	HATU (2.85 eq) and DIEA (6.00 eq)
31	Fmoc-Asp(OtBu)-OH (3.00 eq)	HATU (2.85 eq) and DIEA (6.00 eq)
32	Fmoc-Ser(tBu)-OH (3.00 eq)	HATU (2.85 eq) and DIEA (6.00 eq)
33	Fmoc-Thr(tBu)-OH (3.00 eq)	HATU (2.85 eq) and DIEA (6.00 eq)
34	Fmoc-Phe-OH (3.00 eq)	HATU (2.85 eq) and DIEA (6.00 eq)
35	Fmoc-Thr(tBu)-OH (3.00 eq)	HATU (2.85 eq) and DIEA (6.00 eq)
36	Fmoc-Gly-OH (3.00 eq)	HATU (2.85 eq) and DIEA (6.00 eq)
37	Fmoc-Glu(OtBu)-OH (3.00 eq)	HATU (2.85 eq) and DIEA (6.00 eq)
38	Fmoc-Aib-OH (3.00 eq)	HATU (2.85 eq) and DIEA (6.00 eq)
39	Boc-Tyr(tBu)-OH (3.00 eq)	HATU (2.85 eq) and DIEA (6.00 eq)

Note: 20% piperidine in DMF was used for Fmoc deprotection for 15 mins. The coupling reaction was monitored by ninhydrin test, and the resin was washed with DMF for 5 times.

Peptide Cleavage and Purification:

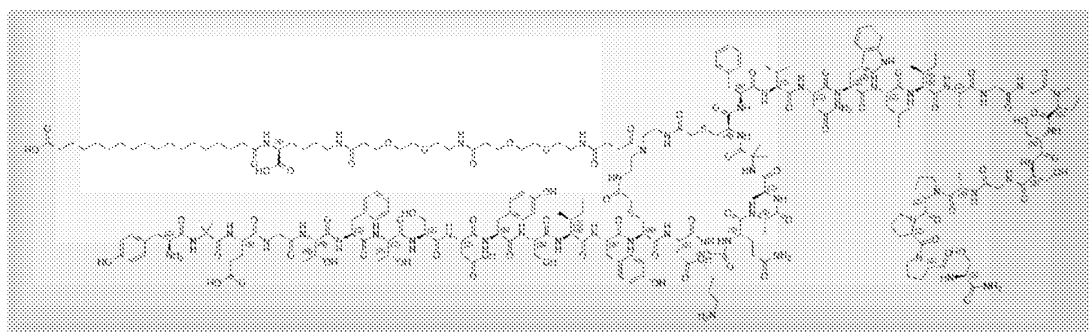
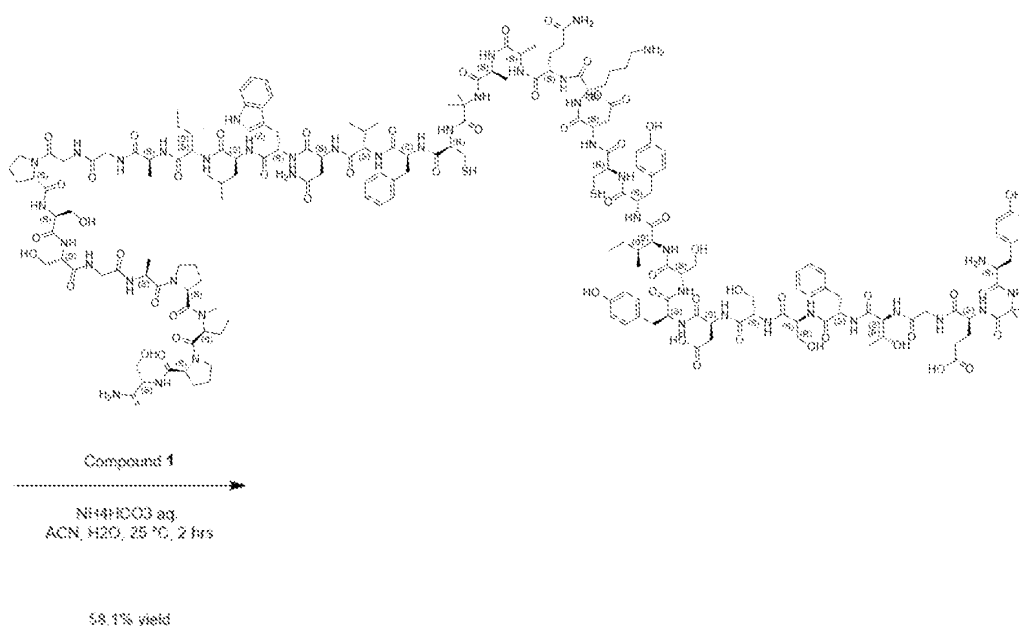
- 1) After coupling, the resin was washed with DMF (200 mL) for 5 times. After last step, the resin was washed with MeOH (200 mL) for 3 times and dried under vacuum. Then the peptide resin (45.6 g) was treated with the cleavage cocktail (460 mL, 92.5%TFA/2.5%TIS/2.5%Mpr/2.5%H₂O) for 2.5 hours. The mixture was filtered to remove the cleavage cocktail. The peptide is precipitated with cold isopropyl ether, filtered and concentrated under reduced pressure to give a residue. LCMS (EW33512-1-P1A1, Rt = 1.539 min).

- 2) The residue was purified by prep-HPLC (A: 0.075% TFA in H₂O, B: ACN) to give the **Compound 2** (7.70 g, 1.57 mmol, 31.33% yield, 85.12% purity, TFA) was obtained as a white solid and confirmed by LCMS (EW33512-1-P1A, Rt = 1.515 min) and HPLC (EW33515-1-P1B, Rt = 12.103 min).

Purification conditions:

Separation condition	
Dissolution condition	Dissolve in 20%ACN - H ₂ O
Instrument	Gilson GX-281
Mobile Phase	A: H ₂ O (0.075% TFA in H ₂ O)
	B: CH ₃ CN
Gradient	20-50%-60 min. Retention time: 45 min
Column	Gemini,5um,c18,110A+luna,c18,10um,100A
Flow Rate	100 mL/Min
Wavelength	214/254 nm
Oven Tem.	30 °C

[0404] General procedure for preparation of **mCMZ370(C(14-21) - L5A(S))**



To a mixture of **compound 2** (2.80 g, 570.44 μmol , 85.12% purity, 1.20 eq, TFA) in MeCN (200 mL) and H_2O (300 mL) was added NH_4HCO_3 (1 M, 475.37 μL , 1.00 eq) until the pH = 8~9, then was added drop-wise **Compound 1** (600 mg, 475.37 μmol , 94.13% purity, 1.00 eq) in MeCN (60.0 mL) and H_2O (90.0 mL). The mixture was stirred at 25 °C for 2 hrs. LCMS (EW33512-3-P1A1, product: R_t = 1.652 min) showed Reactant 1 was consumed completely and one main peak with desired m/z was detected. The reaction mixture was adjusted pH = 5~6 with 1 M HCl aq., then was lyophilized. The residue was purified by prep-HPLC (TFA condition: A: 0.075% TFA in H_2O , B: ACN), and then was second purified by prep-HPLC (HOAc condition: A: 0.5% HOAc in H_2O , B: ACN) to give the **mCMZ370(C(14-21) - L5A(S))** (1.45 g, 276.45 μmol , 58.15% yield, 96.85% purity, HAC) was obtained as a white solid and confirmed by LCMS (EW33512-3-P1A, product: R_t = 1.661 min) & HPLC (EW33512-3-P1B, product: R_t = 13.316 min, purity: 96.85%).

Purification conditions:

Separation condition	
Dissolution condition	Dissolve in 30%ACN - H ₂ O
Instrument	Gilson GX-281
Mobile Phase	A: H ₂ O (0.075% TFA in H ₂ O)
	B: CH ₃ CN
Gradient	24-54%-60 min. Retention time: 30 min
Column	luna,C8,10um,100A
Flow Rate	100 mL/Min
Wavelength	214/254 nm
Oven Tem.	30 °C
Second separation condition	
Dissolution condition	Dissolve in 20%ACN – 50%TFA in H ₂ O
Instrument	Gilson GX-281
Mobile Phase	A: H ₂ O (0.5% HAC in H ₂ O)
	B: CH ₃ CN
Gradient	CH ₃ COONH ₄ (0.2 mol/L in H ₂ O) for 25 min. 0.5%CH ₃ COOH in H ₂ O for 10 min. 32-62%ACN in 0-30min Retention time: 59 min
Column	Gemini,5um,C18,110A+luna,C18,10um,100A
Flow Rate	20 mL/Min
Wavelength	214/254 nm
Oven Tem.	30 °C

[0405] General procedure for preparation of Compound 3: (268 : SEQ ID NO. 6)

Peptide Synthesis:

Compound 1 was synthesized according to the above protocol.

The peptide was synthesized using standard Fmoc chemistry.

- 5) Resin preparation: To the 9H-fluoren-9-ylmethyl N-[(2,4-dimethoxyphenyl)-[4-[2-oxo-2-[[phenyl(p-tolyl)methyl]amino]ethoxy]phenyl]methyl]carbamate (5.00 mmol, 1.00 eq) (Sub: 0.28 mmol/g) in DMF (300 mL) was agitated with N₂ for 2 hrs at 20 °C. Then the mixture was filtered to get the resin.
- 6) Deprotection: 20% piperidine in DMF (300 mL) was added and agitated the resin with N₂ for another 30 mins. The resin was washed with DMF (300 mL * 5) and filtered to get the resin.
- 7) Coupling: A solution of Fmoc-Ser(tBu)-OH (15.0 mmol, 5.75 g, 3.00 eq), DIEA (30.0 mmol, 5.20 mL, 6.00 eq) in DMF (100 mL), then HBTU (5.41 g, 14.2 mmol, 2.85 eq) was added to the resin and agitated with N₂ for 20 mins at 20 °C. The resin was then washed with DMF (450 mL * 5).
- 8) Repeat above step 2 to 3 for the coupling of following amino acids: (2~34).
- 9) Note:

#	Materials	Coupling reagents
2	Fmoc-Pro-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
3	Fmoc-Pro-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
4	Fmoc-Pro-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
5	Fmoc-Ala-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
6	Fmoc-Gly-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
7	Fmoc-Ser(tBu)-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
8	Fmoc-Ser(tBu)-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
9	Fmoc-Pro-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
10	Fmoc-Gly-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
11	Fmoc-Gly-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
12	Fmoc-Ala-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
13	Fmoc-Ile-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
14	Fmoc-Leu-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
15	Fmoc-Trp(Boc)-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
16	Fmoc-Cys(Trt)-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
17	Fmoc-Val-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
18	Fmoc-Phe-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
19	Fmoc-Glu-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
20	Fmoc-Aib-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
21	Fmoc-Ala-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
22	Fmoc-Ala-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
23	Fmoc-Cys(Trt)-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
24	Fmoc-Lys(Boc)-OH (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)
25	Fmoc-Asp(OtBu)-OH (3.00 eq)	HATU (2.85 eq) and DIEA (6.00 eq)

26	Fmoc-Leu-OH (3.00 eq)	HATU (2.85 eq) and DIEA (6.00 eq)
27	Fmoc-Tyr(tBu)-OH (3.00 eq)	HATU (2.85 eq) and DIEA (6.00 eq)
28	Fmoc-Ile-OH (3.00 eq)	HATU (2.85 eq) and DIEA (6.00 eq)
29	Fmoc-Ser(tBu)-OH (3.00 eq)	HATU (2.85 eq) and DIEA (6.00 eq)
30	Fmoc-Tyr(tBu)-OH (3.00 eq)	HATU (2.85 eq) and DIEA (6.00 eq)
31	Fmoc-Asp(OtBu)-OH (3.00 eq)	HATU (2.85 eq) and DIEA (6.00 eq)
32	Fmoc-Ser(tBu)-OH (3.00 eq)	HATU (2.85 eq) and DIEA (6.00 eq)
33	Fmoc-Thr(tBu)-OH (3.00 eq)	HATU (2.85 eq) and DIEA (6.00 eq)
34	Fmoc-Phe-OH (3.00 eq)	HATU (2.85 eq) and DIEA (6.00 eq)
35	Fmoc-Thr(tBu)-OH (3.00 eq)	HATU (2.85 eq) and DIEA (6.00 eq)
36	Fmoc-Gly-OH (3.00 eq)	HATU (2.85 eq) and DIEA (6.00 eq)
37	Fmoc-Glu(OtBu)-OH (3.00 eq)	HATU (2.85 eq) and DIEA (6.00 eq)
38	Fmoc-Aib-OH (3.00 eq)	HATU (2.85 eq) and DIEA (6.00 eq)
39	Boc-Tyr(tBu)-OH (3.00 eq)	HATU (2.85 eq) and DIEA (6.00 eq)

Note: 20% piperidine in DMF was used for Fmoc deprotection for 15 mins. The coupling reaction was monitored by ninhydrin test, and the resin was washed with DMF for 5 times.

Peptide Cleavage and Purification:

- After coupling, the resin was washed with DMF (200 mL) for 5 times. After last step, the resin was washed with MeOH (200 mL) for 3 times and dried under vacuum. Then the peptide resin (45.6 g) was treated with the cleavage cocktail (460 mL, 92.5%TFA/2.5%TIS/2.5%Mpr/2.5%H₂O) for 2.5 hours. The mixture was filtered to remove the cleavage cocktail. The peptide is precipitated with cold isopropyl ether, filtered and concentrated under reduced pressure to give a residue. LCMS (EW33512-1-P1A1, Rt = 1.539 min).
- The residue was purified by prep-HPLC (A: 0.075% TFA in H₂O, B: ACN) to give the **Compound 3** (7.70 g, 1.57 mmol, 31.33% yield, 85.12% purity, TFA) was obtained as a white solid and confirmed by LCMS (EW33512-1-P1A, Rt = 1.515 min) and HPLC (EW33515-1-P1B, Rt = 12.103 min).

Purification conditions:

Separation condition	
Dissolution condition	Dissolve in 20%ACN - H ₂ O
Instrument	Gilson GX-281
Mobile Phase	A: H ₂ O (0.075% TFA in H ₂ O)
	B: CH ₃ CN

Gradient	20-50%-60 min. Retention time: 45 min
Column	Gemini,5um,c18,110A+luna,c18,10um,100A
Flow Rate	100 mL/Min
Wavelength	214/254 nm
Oven Tem.	30 °C

[0406] General procedure for preparation of **mCMZ371(C(17-24) - L5A(S))**

To a mixture of **compound 3** (2.80 g, 570.44 μmol , 85.12% purity, 1.20 eq, TFA) in MeCN (200 mL) and H₂O (300 mL) was added NH₄HCO₃ (1 M, 475.37 μL , 1.00 eq) until the pH = 8~9, then was added drop-wise **Compound 1** (600 mg, 475.37 μmol , 94.13% purity, 1.00 eq) in MeCN (60.0 mL) and H₂O (90.0 mL). The mixture was stirred at 25 °C for 2 hrs. LCMS (EW33512-3-P1A1, product: Rt = 1.652 min) showed Reactant 1 was consumed completely and one main peak with desired m/z was detected. The reaction mixture was adjusted pH = 5~6 with 1 M HCl aq., then was lyophilized. The residue was purified by prep-HPLC (TFA condition: A: 0.075% TFA in H₂O, B: ACN), and then was second purified by prep-HPLC (HOAc condition: A: 0.5% HOAc in H₂O, B: ACN) to give the **mCMZ371(C(17-24) - L5A(S))** (1.45 g, 276.45 μmol , 58.15% yield, 96.85% purity, HAC) was obtained as a white solid and confirmed by LCMS (EW33512-3-P1A, product: Rt = 1.661 min) & HPLC (EW33512-3-P1B, product: Rt = 13.316 min, purity: 96.85%).

Purification conditions:

Separation condition	
Dissolution condition	Dissolve in 30%ACN - H ₂ O
Instrument	Gilson GX-281
Mobile Phase	A: H ₂ O (0.075% TFA in H ₂ O)
	B: CH ₃ CN
Gradient	24-54%-60 min. Retention time: 30 min
Column	luna,C8,10um,100A
Flow Rate	100 mL/Min
Wavelength	214/254 nm

Oven Tem.	30 °C
Second separation condition	
Dissolution condition	Dissolve in 20%ACN – 50%TFA in H ₂ O
Instrument	Gilson GX-281
Mobile Phase	A: H ₂ O (0.5% HAC in H ₂ O)
	B: CH ₃ CN
Gradient	CH ₃ COONH ₄ (0.2 mol/L in H ₂ O) for 25 min. 0.5%CH ₃ COOH in H ₂ O for 10 min. 32-62%ACN in 0-30min Retention time: 59 min
Column	Gemini,5um,C18,110A+luna,C18,10um,100A
Flow Rate	20 mL/Min
Wavelength	214/254 nm
Oven Tem.	30 °C

Example A: A Stapled GLP-1R/GIPR Dual Agonist Peptide Exhibit Improved Anorexigenic Properties and Metabolic Parameters Over Commercial GLP-1R agonists and Preclinical GLP-1R/GCGR Candidates

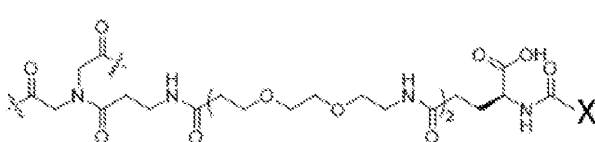
[0407] Peptide conjugates were generated as full dual agonists (Table 4) with EC₅₀ values of 4-35 pM and 11- 40 pM, for the human GIP and GLP-1 receptors respectively. By adjusting the linker, the length of fatty acid chain, functional group at the end of the fatty acid chain and a limited number of amino acid changes in the peptide sequence, it was possible to vary the terminal half-lives of the DI compounds in mice from 2 to 20 hours.

Table 4: Peptide Sequences

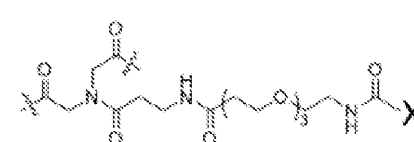
SEQ ID	Label	Peptide sequence	Peptide Name	
31	SEQ-1	H ₂ N-Y(Aib)EGT-FTSDY-SIYLD-KQAA(Aib)-EFVNW-LLAGG-PSSGA-PPPS-CONH ₂		SEQ ID NO: 28
32	SEQ-2	H ₂ N-Y(Aib)EGT-FTSDY-SIYLD-KKAA(Aib)-EFVKW-LLAGG-PSSGA-PPPS-CONH ₂	ZA-40	SEQ ID NO: 18, where each X is K
33	SEQ-3	H ₂ N-Y(Aib)EGT-FTSDY-SIYKD-KQAA(Aib)-KQVNW-LLAGG-PSSGA-PPPS-CONH ₂	ZA-39	SEQ ID NO: 1, where each X is K

34	SEQ-4	H ₂ N-Y(Aib)EGT-FTSDY-SIYKD-KQAA(Aib)-KF $\underline{\text{K}}$ NW-L $\underline{\text{K}}$ AGG-PSSGA-PPPS-CONH ₂	14k, 21k, staple K23-27	SEQ ID NO: 29, where each X is K
35	SEQ-5	H ₂ N-Y(Aib)EGT-FTSDY-SIYLD-K $\underline{\text{K}}$ AA(Aib)-AFV $\underline{\text{K}}$ W-LIAQG-PSSGA-PPPS-CONH ₂	19Q-21A, 27I, 29Q, K17-24 staple	SEQ ID NO: 19, where each X is K
36	SEQ-6	H ₂ N-Y(Aib)EGT-FHSDY-DIY $\underline{\text{K}}$ D-KQAA(Aib)- $\underline{\text{K}}$ FVQW-LLAGG-PSSGA-PPPS-CONH ₂	ZA-41	SEQ ID NO: 2, where each X is K
37	SEQ-7	H ₂ N-Y(Aib)EGT-FHSDY-DIY $\underline{\text{K}}$ D-KQAA(Nle)- $\underline{\text{K}}$ FVAW-LLAGG-PSSGA-PPPS-CONH ₂	ZA-42	SEQ ID NO: 3, where each X is K
38	SEQ-8	H ₂ N-Y(Aib)EGT-FTsDY-sIY $\underline{\text{K}}$ D-KQAA(Nle)- $\underline{\text{K}}$ FVAW-LLAGG-PSSGA-PPPS-CONH ₂	ZA-43	SEQ ID NO: 4, where each X is K

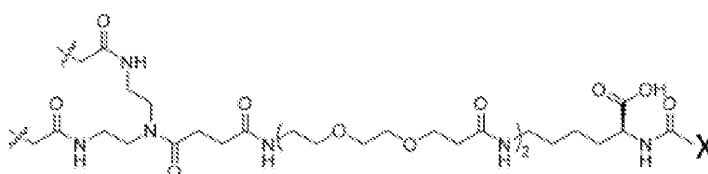
Linker L1



Linker L2



Linker L3



[0408] mCMD307 (2050-K4) Decreased Body Weight and Improved Glucose Intolerance and Dyslipidemia and Attenuated Hepatic Steatosis in DIO Mice

[0409] Encouraged by the preliminary PK and PD results, the efficacy of chronic administration of mCMD307 (2050-K4) was assessed in a high-fat-diet-induced obesity (DIO) mouse model. DIO mice (C57BL/6, male, 25-week old) were randomized based on their body weight and then treated for 5 weeks by *s.c.* dosing of either PBS, mCMD307 (2050-K4) (40 µg/kg), or semaglutide (40 µg/kg; positive control). Wide-type lean mice were used as normal controls.

[0410] Fruitfully, mCMD307 (2050-K4) -treated DIO mice exhibited a steady reduction in body weight and fasting blood glucose levels, with better efficacy than semaglutide-treated group (FIGS. 5A). At an efficacious dose of 40 µg/kg, mCMD307 (2050-K4) significantly reduced body weight food intake (FIG. 5A),

[0411] Apart from a reduction in fasting blood glucose levels, in an OGTT on day 21 and OGTT on day 21, the levels of fed blood glucose in mCMD307 (2050-K4)-treated DIO mice were also significantly lower than compared to PBS-treated DIO mice (Figure 5B). At the termination of the study at day 24, liver enzyme ALT, AST, ALP levels and plasma cholesterol and triglyceride levels (FIG. 5C) and liver weight,

liver triglyceride, liver/body weight ratio and fat weight (FIG. 5D); and steatosis score and liver lipid accumulation measurement by Oil-red staining (Fig. 5E). C57BL/6 mice (male, 37 weeks old) were treated with PBS (s.c., twice daily), **mCMD307 (K4)** (s.c. once daily; 10 nmol kg⁻¹) or semaglutide (s.c. once daily; 10 nmol kg⁻¹) for 24 days. Data are means $\pm$ SE, n = 6 per group. Accordingly, these results suggest that **mCMD307 (2050-K4)** could offer potential clinical benefit for the treatment of fatty liver diseases such as non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).

[0412] The acute effects of dual incretin agonists on glucose tolerance in wild-type mice

[0413] Selected GLP-1R/GIPR dual agonists were evaluated for their acute effects in oral glucose tolerance tests (OGTT) in wild-type mice. The single GLP-1R agonist semaglutide was employed as a positive control in this experiment. All peptides significantly improved glucose tolerance to a similar level after 2 h of from administration when compared to the vehicle (**FIG. 2A**). Similar results were observed for fasted blood glucose for all peptides. However, significant differences in glucose levels were observed after 96 h from administration of the peptides. Semaglutide did not exhibit any improvement over the vehicle after 96 h. On the other hand, mice treated with **mCMD307 (K4)** and **mCLZ715 (K5)** showed more significant improvements in handling glucose (**FIG. 2B**). Moreover, **mCMD307 (K4)** and **mCLZ715 (K5)** were able to significantly reduce fasted glucose levels while the rest of the peptides resulted in no improvements in efficacy. The increased *in vivo* efficacy of **mCMD307 (K4)** and **mCLZ715 (K5)** observed here likely result from both higher dual agonistic activity and the extended *in vivo* half-life. Assuming a direct relationship between pharmacokinetics and pharmacokinetics, the results of this experiment indicate that peptide **mCMD307 (K4)** and **mCLZ715 (K5)** exhibits a longer half-life than semaglutide, and thus has the potential to be developed as a once weekly or semi-monthly with an appropriate formulation.

[0414] Pharmacokinetics in wild-type mice

[0415] To determine the *in vivo* half-life of the potent analog **mCMD307 (2050-K4)**, pharmacokinetic (PK) studies were performed in CD1 female mice by *i.v.* or *s.c.* injection of the peptide at 40 μ g/kg. Plasma level of the peptide at indicated time points was determined using the *in vitro* GLP-1R reporter assay. **mCMD307 (2050-K4)** exhibited higher T_{max} and C_{max} (11.6h and 4710 nM, respectively) after *s.c.* administration (**FIG. 3**). Notably, the terminal mouse plasma half-life of **mCMD307 (2050-K4)** is longer than that of semaglutide (rodent half-life is $\sim$ 8 h), which has been clinically approved for once-weekly application in T2DM patients. It is also noteworthy that although our focus for half-life extension was on the serum-binding ability of the stapled peptide, there may be a combination of effects, for example self-assembly and depotting at the injection site, that led to the delayed onset of C_{max} and the extended half-life.

Table 6: PK Parameters of Peptide mCND307 (K4) in Plasma

$T_{\max}$	2.33 ± 1.16 h	$C_{\max}$	4710 ± 659 ng mL ⁻¹
$T_{1/2}$	11.6 ± 0.85 h	$AUC_{0-\text{last}}$	59200 ± 6810 ng h mL ⁻¹
V_{ss}	0.18 ± 0.05 L Kg ⁻¹	Clearance	0.28 ± 0.04 mL min ⁻¹ kg ⁻¹

[0416] Experimental Procedures

[0417] Peptide cross-linking. The dicysteine-containing peptide (2 mM, >85% pure) (Shanghai Apeptide Co., Shanghai, China) and the cross-linker (1.5 eq) were dissolved in CH₃CN/30 mM NH₄HCO₃ buffer (v/v; 1:3) pH 8.5), and the reaction was stirred at room temperature for 2-4 h. Under ice cooling, acetic acid was then added dropwise to reduce the pH of the mixture to around 5 and the crude cross-linked peptide was then purified by semi-preparative chromatography on Agilent 1200 with a Phenomenex Luna column (C₁₈, 100 Å pore size, 5 µm particle size, 150 x 21.2 mm). A linear gradient from 30% to 60% CH₃CN/H₂O containing 0.05% trifluoroacetic acid was applied for 60 min at a flow rate of 20 mL min⁻¹. The fractions containing the products were collected and lyophilized to afford the products as a powder with >90% purity.

[0418] The identity and purity of the peptide were determined using an Agilent 6520 accurate-mass quadrupole-time-of-light (QTOF) instrument equipped with reversed-phase liquid chromatography and an electrospray ionization (ESI). Aeris Widepore column (XB-C₁₈, 3.6 µm particle size, 150 x 2.1 mm) was used with a flow rate of 0.5 mL min⁻¹ and peptides were detected using a UV-Vis detection wavelength of 214 nm.

[0419] Generation of CRE-Luc stable cell line overexpressing GLP-1R or GIP. HEK293 cells were infected with lentivirus encoding firefly luciferase gene under the control of cAMP responsive element (CRE) promoter (Qiagen, The Netherlands) and then were selected using 1 µg mL⁻¹ puromycin (Life Technologies, Carlsbad) for 1 week. The surviving cells (referred to as CRE-HEK293) were expanded and then transfected with a G418 selective mammalian expression plasmid encoding human GLP-1R or GIPR. In brief, GLP-1R or GIPR plasmid was transfected into CRE-HEK293 cells using Lipofectamine 2000 and selected with 400 µg mL⁻¹ Geneticin (Life Technologies, Carlsbad, CA). Single colony stable cell line overexpressing CRE-luciferase and GLP-1R or GIPR (HEK293-GLP-1R-CRE or HEK293-GIPR-CRE) was then established for *in vitro* activity assay.

[0420] *In vitro* receptor activation reporter assay (receptor-mediated cAMP synthesis) HEK293-GLP-1R-CRE or HEK293-GIPR-CRE cells were seeded in 384-well plates at a density of 5000 cells per well and cultured for 18 h in DMEM with 10% FBS at 37 °C and 5% CO₂. Cells were treated with peptides in a dose-dependent manner for 24 h, and receptor activation was reported by luminescence intensities,

using One-Glo (Promega, WI) luciferase reagent following manufacturer's instruction. The EC₅₀ of each peptide was determined using GraphPad Prism 6 software (GraphPad, San Diego, CA).

[0421] cAMP assay

[0422] CHOK1 cells stably overexpressed human GLP-1R or GIPR (20 µL of 5000 cells per well) were seeded in a white solid 384 well plate covered with metal lid and incubated overnight. On day 2, the culture medium was replaced by fresh medium containing no FBS (for 0% FBS group). Cells were treated with 5 µL peptide in 12-point dose response, in culture medium with 0.5 mM IBMX in triplicate for 30 min at 37 °C, 5% CO₂. cAMP dynamic 2 kit from Cisbio was used to detect cAMP level. Briefly, 25 µL of cAMP detection reagent (1:1:38 of cAMP-d2, Cryptate conjugate, lysis buffer) per well was added and incubated at room temperature for 1 h. For cell negative control wells, cAMP detection reagent without d2 was added. Plates were then read at Ex320 nm, Em-1 665 nm and, EM-2 620 nm. Graphs were plotted with Ratio or ΔF using Prism software and EC₅₀ values were then obtained:

$$\text{Ratio} = A_{665 \text{ nm}} / B_{620 \text{ nm}} \times 10^4$$

$$\% \Delta F = (\text{standard or sample ratio} - \text{ratio}_{\text{neg}}) / \text{ratio}_{\text{neg}} \times 100.$$

Animals Animal care and experimental procedures were approved by the Institutional Animal Care and Use Committee (IACUC) of Calibr at the Scripps Research Institute, strictly following the NIH guidelines for humane treatment of animals.

Pharmacokinetics of peptides in mice Female CD-1 mice (n = 4 per group) from Charles River Laboratory were fasted overnight and administered 100 µL of each peptide in phosphate buffered saline by intravenous (*i.v.*) or subcutaneous (*s.c.*) route. Food was provided to mice after blood collection at 3 h time point. Blood was collected into heparin tubes and centrifuged at 3,000x g for 15 min. The resulting plasma were then stored at -80 °C for peptide concentration determination. The concentrations of peptides in plasma at each time point were determined by in vitro cell based activity assay. Briefly, HEK293-GLP-1R-CRE cells were treated with plasma samples at different time points (5-point dose response, starting from 1:10 to 1:100 dilution of each plasma sample) and incubated for 16 h in DMEM with 10% FBS at 37 °C with 5% CO₂, and the firefly luciferase activity was then measured. Simultaneously, the same peptides were used to obtain standard curves and parameters for Bottom, Top, EC₅₀, and Hill Slope. Relative luciferase unit (RLU) for each plasma sample was used to calculate the peptide concentrations in plasma (nmol/L), using parameters derived from the standard curve:

$$(\text{RLU} = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{((\text{LogEC}_{50} - \text{Conc.}) \times \text{Hill Slope}))})$$

Peptide concentrations in plasma were obtained and plotted against time points to obtain in vivo half-life of each peptide, using WinNonLin Phoenix software (Pharsight Corp, St. Louis, MO).

Oral glucose tolerance test (OGTT) Female Charles River CD-1 mice were fasted overnight and then administrated 150 µL of each peptide in PBS (pH = 8.2) by *i.v.* or *s.c.* route. After 6 h, mice were orally or intraperitoneally administrated with 2 gram of glucose solution per kg body weight and their blood glucose levels were measured (by tail nick) before (0 min) and after glucose challenge for 2 to 3 h.

DIO Study DIO mice (C57BL/6, male, 25 weeks old, or 19 weeks on high fat diet) were randomized based on their body weight and were treated with daily subcutaneous injections of mCMD307 (2050-K4) or

vehicle (n =5). Body weight and food intake were monitored daily throughout the study. At the end of the experiment, mice were sacrificed, and visceral fat mass was weighed. Collected plasma was used for cholesterol level determination according to the manufacturer's guide (cholesterol assay kit, Abcam, Cambridge, England) and triglyceride level using a triglyceride colorimetric assay kit (Cayman chemical, Ann Arbor, Michigan).

Oil red staining Frozen tissue sections of liver were cut at 10 μ m and air dried onto the slides. After fixation in 10% formalin for 5 min, the slides were briefly washed with running tap water for 10 min, followed by rinsing with 60% isopropanol. Subsequently, oil red O working solution (0.3% oil red O) was used to stain lipid for 15 min. Slides were again rinsed with 60% isopropanol, and then nuclei were lightly stained with alum hematoxylin, followed by rinsing with distilled water, and mounted in glycerin jelly. Pictures were taken under a microscope.

[0423] Biochemical and Histological analyses Terminal serum analytes including ALT, AST, and ALP were determined by Alfa Wassermann Vet Axcel clinical analyzer. Hepatic triglycerides were measured in liver homogenates generated with a colorimetric triglyceride kit (Cayman Chemical). Paraformaldehyde-fixed liver were paraffin-embedded, sectioned and stained with hematoxylin-eosin and Picro-Sirius red by HistoTox Labs (Boulder, CO). All histological assessment (steatosis, fibrosis scoring) were performed by a certified histopathologist blind to treatment (HistoTox Labs) based on classification outlined by Kleiner et al.

Example B: *In vitro* receptor activation reporter assay (receptor-mediated cAMP synthesis) HEK293

[00424] *Generation of CRE-Luc stable cell line overexpressing GLP-1R*

[00425] HEK293 cells were infected with lentivirus encoding firefly luciferase gene under the control of cAMP responsive element (CRE) promoter (Qiagen, The Netherlands) and then were selected using 1 μ g/mL puromycin (Life Technologies, Carlsbad) for 1 week. The surviving cells (referred to as CRE-HEK293) were expanded and then transfected with a G418 selective mammalian expression plasmid encoding human GLP-1R. In brief, GLP-1R plasmid was transfected into CRE-HEK293 cells using Lipofectamine 2000 and selected with 400 μ g/mL Geneticin (Life Technologies, Carlsbad, CA). Single colony stable cell line overexpressing CRE-luciferase and GLP1R was then established for *in vitro* activity assay.

[00426] GLP-1R-CRE or HEK293-GIPR-CRE cells were seeded in 384-well plates at a density of 5000 cells per well and cultured for 18 h in DMEM with 10% FBS at 37 °C and 5% CO₂. Cells were treated with peptides in a dose dependent manner for 24 h, and receptor activation was reported by luminescence intensities, using One-Glo (Promega, WI) luciferase reagent following manufacturer's instruction. The EC₅₀ of each peptide was determined using GraphPad Prism 6 software (GraphPad, San Diego, CA). Results are depicted in **FIGS. 6A-6B, FIGS. 7A-7B, FIGS. 8A-8B, FIGS. 9A-9B, and Tables 7-12**. Measurements of peptide conjugate potency were expressed as half maximal effective concentration (EC₅₀) values.

[00427] Measurements indicate distinct and separable *in vitro* activation potencies of a number of peptide conjugates described herein. In some instances, novel peptide conjugates were tested against known GLP1R or dual GLP1R/GIPR agonists under the same assay conditions. Table 11 shows the results of testing mCMZ371, cCMV268, Tirzepatide, Semaglutide and hGIP (as a control) for human GLP1R and GIPR activation in this *in vitro* assay. The testing recapitulated previously published results for Tirzepatide indicating comparable GIPR activation to wild-type human GIP (hGIP). Tirzepatide is known to bind human GIPR with a comparable affinity than that of hGIP and approximately five times lower GLP-1 receptor binding than native hGLP-1 (T. Coskun et al. *Mol Metab.* 2018 Dec;18:3-14). Surprisingly, mCMZ371 showed a much different *in vitro* activation profile compared to Tirzepatide with approximately 4-fold more potency in activating GLP1R but 2-fold less potency in activating GIPR. Thus, mCMZ371 functions as a GLP1R/GIPR dual agonist with a distinct agonist profile when compared with Tirzepatide. mCMZ371 has much stronger activation of GLP1R signaling and weaker activation of GIPR signaling than does Tirzepatide. This profile of mCMZ371 for differentially modulating the extent of two metabolic hormone receptor signaling pathways compared to a known dual agonist creates a unique activation profile of GLP1R and GIPR in subjects upon treatment. This unique activation profile in mCMZ371 is beneficial for treating a subject in need of GLP1R activation to a greater extent and GIPR activation to a lesser extent than that afforded by the use of other known GLP1R/GIPR dual agonists or combination therapy with single GLP1R and GIPR agonists. Also noteworthy in Table 11 is the comparison in activation profiles between mCMZ371 and mCMV268. These two peptide conjugates share identical amino acid sequences but differ in their lipid staples. mCMZ371 showed approximately three-fold more potent activation of GLP1R signaling and a more modest increase in potency of GIPR activation.

Table 7. EC₅₀ of receptor-mediated cAMP synthesis by various peptide conjugates

EC ₅₀ [nM]	GLP1R	GIPR
Semaglutide	0.01	0.41
mCMD307	0.01	0.02
mCLZ715	0.02	0.02
ZA-41- K4	13.77	5.31
ZA-42 - K4	18.77	20.43
ZA-43 - K4	1.32	11.29
ZA-41 - K5	83.92	12.55
ZA-42 - K5	~ 13663	303.00
ZA-43 - K5	3.74	15.66

Table 8. EC₅₀ of receptor-mediated cAMP synthesis by various peptide conjugates

EC ₅₀ [nM]	GLP1R	GIPR
Semaglutide	0.03	-
mCMD307	0.03	0.01
C(14-21) - L5A	0.16	0.03
C(14-21) - C20L5A	0.20	0.05
27I, C(14-21) - L5A	0.04	0.03
27I, C(14-21) - C20L5A	0.05	0.07
7I, 10V, 27I, C(14-21) - L5A	83.92	12.55
7I, 10V, 27I, C(14-21) - C20L5A	~ 13663	303.00

Table 9. EC₅₀ of receptor-mediated cAMP synthesis by various peptide conjugates

EC ₅₀ [nM]	GLP1R	GIPR
Semaglutide	0.03	-
mCMD307	0.03	0.01
C(14-21) - L5A	0.16	0.03
C(17-24) - L5A	0.11	0.05
C(17-24) - C20L5A	0.11	0.05
19Q, 21A, 27I, 29Q, C(17-24) - C20L5A	0.12	0.02

Table 10. EC₅₀ of receptor-mediated cAMP synthesis by various peptide conjugates

	GLP1R (nM)				GIPR (nM)			
	02/19	3/25	03/26	average	02/19	03/25	03/26	average
[EC ₅₀]								
C(14-21) - C20L5A	0.17	0.17	0.19	0.18	0.07	0.04	0.04	0.05
C(17-24) - C20L5A	0.07	0.10	0.09	0.09	0.04	0.02	0.03	0.03
27I, C(14-21) - C20L5A (mCMV266)	0.03	0.05	0.06	0.05	0.08	0.06	0.06	0.07
6Y, 27I, C(14-21) - C20L5A	0.04	0.07	0.07	0.06	0.50	0.58	0.60	0.56
6Y, 27I, C(17-24) - C20L5A	0.05	0.07	0.06	0.06	0.27	0.27	0.25	0.26
27I, C(17-24) - C20L5A (mCMV268)	0.02	0.03	0.03	0.03	0.05	0.04	0.03	0.04
6Y, 8N, 27I, C(17-24) - C20L5A	0.06	0.11	0.07	0.08	2.48	-	3.29	2.88
Semaglutide	0.05	0.02	0.02	0.03	-	-	-	-
mCMD307	0.01	0.01	0.01	0.01	0.04	0.01	0.01	0.02
Tirzepatide		0.15	0.09	0.12		0.02	0.02	0.02

Table 11. Potency summary in human GLP1R and GIPR activation (EC₅₀ of receptor-mediated cAMP synthesis by various peptide conjugates)

Peptide	In Vitro Potency GLP1R EC ₅₀ [nM]		In Vitro Potency GIPR EC ₅₀ [nM]	
	10% FBS	No Serum	10% FBS	No Serum
Semaglutide	0.42 ± 0.10	0.17 ± 0.09	-	-

hGIP	-	-	0.01 ± 0.00	0.05 ± 0.00
mCMV268	1.96 ± 0.46	0.42 ± 0.12	0.09 ± 0.02	0.01 ± 0.01
mCMZ371	0.56 ± 0.15	0.14 ± 0.06	0.04 ± 0.01	0.01 ± 0.00
Tirzepatide	2.35 ± 0.27	0.57 ± 0.25	0.02 ± 0.00	0.006 ± 0.00

Table 12. Potency summary in mouse, cynomolgous monkey, and dog GLP1R and GIPR activation (EC₅₀ of receptor-mediated cAMP synthesis by various peptide conjugates)

Peptide	In Vitro Potency GLP1R EC ₅₀ [nM]			In Vitro Potency GIPR EC ₅₀ [nM]		
	Mouse	Cyno	Dog	Mouse	Cyno	Dog
Semaglutide	0.10 ± 0.01	0.13 ± 0.00	0.67 ± 0.08	-	-	-
hGIP	-	-	-	0.34 ± 0.05	0.69 ± 0.30	0.70 ± 0.25
mCMV268	0.26 ± 0.08	0.22 ± 0.04	1.48 ± 0.20	0.26 ± 0.11	0.16 ± 0.04	0.42 ± 0.13
mCMZ371	0.09 ± 0.01	0.11 ± 0.00	1.34 ± 0.13	0.27 ± 0.08	0.13 ± 0.02	0.47 ± 0.12
Tirzepatide	0.16 ± 0.02	0.55 ± 0.08	6.98 ± 1.23	0.42 ± 0.27	0.08 ± 0.02	0.10 ± 0.15

Example C: Plasma Stability

[0428] To investigate the stability of the conjugates in mouse, cyno monkey, dog, and human plasma, conjugate mCMD307 was incubated in plasma for 24 h (Table 13). At certain time intervals a sample of plasma was taken and plasma proteins precipitated. Samples were analyzed using LC-MS.

Table 13. Plasma stability

24 h Stability Data in Mouse		
	Area under the peak (%)	Cleavage point
mCMD307	53%	N/A
Impurity 1	7.10%	Pro(31) / Ser(32)
Impurity 2	22.4% (Impurities 2 & 3 co-elute)	Thr(7) / Ser(8)
Impurity 3		Phe(6) / Thr(7)
Impurity 4	13.20%	Tyr(10) / Ser(11)
Impurity 5	4.7% (Impurities 5 & 6 co-elute)	Leu(26) / Leu(27)
Impurity 6		Tyr(13) / Lys(14)
24 h Stability Data in Cyno		
mCMD307	87%	N/A

Impurity 1	3.14%	Pro(31) / Ser(32)
Impurity 2	5.39%	Aib(2) / Glu(3)
24 h Stability Data in Dog and Human		
mCMD307	92%	N/A

Example D: Pharmacokinetics Studies

[0429] The pharmacokinetic profile of conjugates (27I, C(14-21)-C20L5A) and (27I, C(17-24)-C20L5A) was evaluated in mice upon s.c. or i.v. injection at 1 mg/kg. The peptide plasma concentration at various time points was determined using LC-MS.

[0430] FIGS. 11A-11B show the plasma concentration in mice versus times for peptides administered via IV and SV.

Table 14. Summary of mCMV266 and mCMV268 Pharmacokinetics in CD-1 Mouse (ng/mL)

Dose (mg/ kg)	Cmpd	Route	T _{1/2} (hr)	C _{max} (ng/mL)	T _{max} (hr)	AUC ₀₋₂₄ (hr*ng/ mL)	AUC _{LAST} (hr*ng/ mL)	AUC _{INF} (hr*ng/ mL)	Vd (L/kg)	Cl (mL/min/ kg)	MRT _{LAST} (hr)	F (%)
1	mCMV 268	IV	14.8	33967	0.5	204267	315067	326967	0.067	0.050	19.5	64%
1	mCMV 268	SC	12.8	4783	24	92093	200467	208433	0.087	0.080	27.8	
1	mCMV 266	IV	11.5	30367	0.50	269233	390433	397167	0.043	0.043	18.6	63%
1	mCMV 266	SC	10.7	6610	12.7	135267	246767	251600	0.063	0.067	24.3	

[0431] The pharmacokinetic profile of conjugates mCMZ370 and mCMZ371 was evaluated in mice upon I.V. or S.C. injection at 1 mg/kg. (Table 15 and Table 16). The peptide plasma concentration at various time points was determined using LC-MS. Notably, mCMZ371 demonstrated a longer half-life ($t_{1/2}$) and significantly larger area under the curve (AUC) calculations than mCMZ370 after either I.V. or S.C. administration. This extended pharmacokinetic profile of mCMZ371 allows for lower effective dosing strategies than would be available for mCMZ370. This feature is important given the desire to mitigate any potential adverse drug reactions which may be dose dependent. Additionally, the extended pharmacokinetic profile of mCMZ371 will allow for a longer dose interval during treatment of a subject in need thereof.

Table 15. Summary of mCMZ370 and mCMZ371 Pharmacokinetics in CD-1 Mouse (I.V. administration)

Sample Name	Animal	Dose (mg/kg)	Route	Rsq_a djuste d	C ₀ (ng/mL)	C _{max} (ng/mL)	t _{1/2} (hr)	T _{max} (hr)	T _{last} (hr)
mCMZ370	1	1	I.V.	0.985	15210	14564	8.82	0.08	72
	2	1	I.V.	0.993	8380	8230	8.82	0.08	72
	3	1	I.V.	0.976	10006	9829	9.87	0.08	72

mCMZ371	7	1	I.V.	0.972	15533	15134	9.13	0.08	72
	8	1	I.V.	0.995	21060	20910	10	0.08	72
	9	1	I.V.	1	24603	24203	10.31	0.08	72
Sample Name	Animal	Dose (mg/kg)	Route	AUC ₀₋₂₄	AUC _{last}	AUC _{INF_{-pred}}	V _{ss_{-pred}}	V _{z_{-pred}}	Cl _{pred}
				(hr*ng/mL)	(hr*ng/mL)	(hr*ng/mL)	(L/kg)	(L/kg)	(mL/min/kg)
mCMZ370	1	1	I.V.	120757	148290	148865	0.098	0.085	0.112
	2	1	I.V.	107856	127615	128099	0.106	0.099	0.13
	3	1	I.V.	85158	102411	103033	0.133	0.138	0.162
mCMZ371	7	1	I.V.	242246	341205	343780	0.054	0.038	0.048
	8	1	I.V.	255418	355565	359258	0.051	0.04	0.046
	9	1	I.V.	285442	403090	407964	0.046	0.036	0.041
Sample Name	Animal	Dose (mg/kg)	Route	MRT _{last}	MRT _{INF_{-pred}}	AUC _{% Extrap_{-pred}}	AUMC _{% Extrap_{-pred}}	No _{-points_{-la}} mbda _{-z}	
				(hr)	(hr)	(%)	(%)	(L/kg)	
mCMZ370	1	1	I.V.	14.35	14.63	0.39	2.24	4	
	2	1	I.V.	13.29	13.56	0.38	2.36	4	
	3	1	I.V.	13.3	13.74	0.6	3.79	4	
mCMZ371	7	1	I.V.	18.19	18.69	0.75	3.41	3	
	8	1	I.V.	17.72	18.43	1.03	4.82	3	
	9	1	I.V.	17.83	18.65	1.19	5.56	3	

Table 16. Summary of mCMZ370 and mCMZ371 Pharmacokinetics in CD-1 Mouse (S.C. administration)

Sample Name	Animal	Dose (mg/kg)	Route	Rs _{q_{-a}} djuste d	C _{max}	t _{1/2}	T _{max}	T _{last}
					(ng/mL)	(hr)	(hr)	(hr)
mCMZ370	4	1	S.C.	1	2460	7.5	7	72
	5	1	S.C.	0.998	2221	7.06	24	72
	6	1	S.C.	0.998	3993	7.05	3	72
mCMZ371	10	1	S.C.	0.999	9259	10.66	24	72
	11	1	S.C.	0.91	3389	12.36	24	72
	12	1	S.C.	0.994	6337	11.01	24	72

Sample Name	Animal	Dose (mg/kg)	Route	AUC ₀₋₂₄	AUC _{all}	AUC _{INF_pred}	V _{F_pred}	Cl _{F_pred}
				(hr*ng/mL)	(hr*ng/mL)	(hr*ng/mL)	(L/kg)	(mL/min/kg)
mCMZ370	4	1	S.C.	41870	53345	53483	0.2	0.24
	5	1	S.C.	44691	68029	68240	0.15	0.21
	6	1	S.C.	63474	80522	80676	0.13	0.06
mCMZ371	10	1	S.C.	127402	267216	273625	0.06	0.12
	11	1	S.C.	67917	138868	143707	0.12	0.08
	12	1	S.C.	95280	197314	202468	0.08	0.24
Sample Name	Animal	Dose (mg/kg)	Route	MRT _{1a}	MRT _{INF_pred}	AUC _{%E}	AUMC _{%Ex}	No_points_lambda_z
				(hr)	(hr)	(%)	(%)	(L/kg)
mCMZ370	4	1	S.C.	16.06	16.23	0.26	1.32	3
	5	1	S.C.	20.45	20.64	0.31	1.23	3
	6	1	S.C.	15.69	15.82	0.19	0.99	3
mCMZ371	10	1	S.C.	27.64	29.04	2.34	7.05	3
	11	1	S.C.	26.63	28.76	3.37	10.52	3
	12	1	I.V.	27.22	28.77	2.55	7.78	3

[0432] mCMZ371 exhibited cross-reactivity with mouse, cynomolgus monkey, dog and human GLP1R and GIPR. Data for cynomolgus monkey assays are shown in FIG. 17 and Table 17. Data for dog assays are shown in FIG. 18 and Table 18. In addition to cross-reactivity, mCMZ371 demonstrated an extended pharmacokinetic profile with a long $t_{1/2}$ in both cynomolgus monkeys and dogs.

Table 17. Summary of mCMZ371 and mCMV268 Pharmacokinetics in cynomolgus monkey mCMZ371 (CTR371)

PK Parameters	CTR371 – I.V.	CTR371 – S.C.
C_{max} (ng/mL)	-	1737
T_{1/2} (h)	60.2	49.3
Vd_{ss} (L/kg)	0.0538	-
Cl (mL/min/kg)	0.0126	-
T_{max} (h)	-	24
T_{last} (h)	240	240
AUC_{0-last}	266594	155915
Bioavailability (%)	-	58.5
PK Parameters	mCMV268 – I.V.	mCMV268 – S.C.
C_{max} (ng/mL)	-	3927
T_{1/2} (h)	58.8	60.5
Vd_{ss} (L/kg)	0.0612	-
Cl (mL/min/kg)	0.0140	-
T_{max} (h)	-	14.7
T_{last} (h)	504	504
AUC_{0-last}	-	437624
Bioavailability (%)	-	73.7

Table 18. Summary of mCMZ371 and mCMV268 Pharmacokinetics in dog mCMZ371 (CTR371)

PK Parameters	CTR371 – I.V.	CTR371 – S.C.
$C_{\max}$ (ng/mL)	-	150
$T_{1/2}$ (h)	71.9	62.7
Vd_{ss} (L/kg)	0.110	-
Cl (mL/min/kg)	0.0198	-
$T_{\max}$ (h)	-	24
T_{last} (h)	240	240
AUC _{0-last}	25585	17575
Bioavailability (%)	-	68.7
PK Parameters	mCMV268 – I.V.	mCMV268 – Oral
$C_{\max}$ (ng/mL)	8497	31.4
$T_{1/2}$ (h)	63.9	77.8
Vd_{ss} (L/kg)	0.0957	-
Cl (mL/min/kg)	0.0181	21.6
$T_{\max}$ (h)	0.693	1.00
T_{last} (h)	168	144
AUC _{0-last}	59235	1699
Bioavailability (%)		0.27%, 0.27%, 0.04%, 0.06%, 0

Example E: *In vivo* oral glucose tolerance test (OGTT)

Mice were fasted overnight prior to the oral glucose tolerance test (OGTT), and then dosed with peptide. After 12 h, 1 g of glucose solution per kg body weight was administered orally, and mouse tail blood glucose levels were measured before (0 min) and after glucose challenge for 90 minutes (with measurements at 15, 30, 60 and 90 minutes) (FIG. 16). The data were compared using the unpaired Student's t test. Where appropriate, data were compared using repeated measures or one-way analysis of variance, followed by the Student-Newman-Keuls post hoc test. Calculations for AUC₀₋₁₂₀ (mg/dL*min) were also analyzed and graphed in FIG. 16. The effects of mCMZ371 at various dosages (1, 3, 10, and 30 nmol/kg S.C.) on oral glucose tolerance was tested and compared to that of Tirzepatide (kCMC760) (10 nmol/kg S.C.) and kCLD385 (10 nmol/kg S.C.). The graphs of AUC₀₋₁₂₀ mean and standard error demonstrate a glucose tolerance response for mCMZ371 at 1 nmol/kg S.C. and more robust responses at the higher dosages (3 nmol/kg S.C., 10 nmol/kg S.C., and 30 nmol/kg S.C.) indicating a clear dose response effect. The response of mice to mCMZ371, tirzepatide (kCMC760), and semaglutide (kCLD385) all at a dosage of 10 nmol/kg S.C. produced indistinguishable effects on glucose tolerance. Of note, mice treated

with a single dose of mCMZ371 at 3 nmol/kg S.C. produced glucose tolerance responses that were indistinguishable from the responses to tirzepatide and semaglutide at 10 nmol/kg S.C. This indicates the extent of pharmacodynamic potency of mCMZ371 at modest concentrations allowing for a lower effective dose than the use of tirzepatide or semaglutide for subjects in need of treatment. This lower effective dose of mCMZ371 reduces both the likelihood and severity of adverse drug responses in subjects in need of treatment.

Example F: Dose related, long-acting PD effects on fed glucose and body weight in mice

[0433] Mice were single dosed with peptide conjugates and assayed for fed glucose level and body weight for up to seven days. As shown in FIG. 12, mCMV266 and mCMV268 demonstrate a robust and durable impact on fed glucose in wild-type mice. A dose response PD effect was observed for both compounds, with a more dramatic effect with high dose mCMV266. The mCMV266 and mCMV268 peptide conjugates demonstrated better efficacy than semaglutide, and more potency *in vivo* than Tirzepatide.

[0434] As shown in FIG. 13, mCMV266 and mCMV268 peptide conjugates demonstrate durable impact on body weight reduction in mice. The peptide conjugates demonstrated better efficacy than semaglutide, and were more potent *in vivo* than tirzepatide.

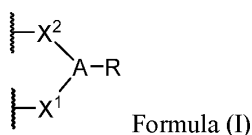
[0435] As shown in FIG. 15, mCMZ371 demonstrated a robust and durable impact on fed glucose in wild-type mice. mCMZ371 was efficacious even from a single dose at 1 nmol/kg. mCMZ371 was more potent in reducing fed levels than mCMV268 treatment at 3 nmol/kg and more potent than Tirzepatide at 10 nmol/kg indicating clear dose response efficacy. mCMZ371 showed a stronger reduction in fed glucose than mCMV268 (both at 3 nmol/kg S.C.) and achieved similar reduction of fed glucose to Tirzepatide at 3 times higher dosages (10 nmol/kg S.C.). As shown in FIG. 15., mCMZ371 peptide conjugate demonstrated durable impact on body weight reduction in mice. A dose response was evident, but all doses of mCMZ371 tested (including 1 nmol/kg S.C.) led to a reduction in body weight. mCMZ371 and mCMV268 treatment (each at 3 nmol/kg S.C.) achieved similar efficacy in weight reduction. These effects of mCMZ371 and mCMV268 (at 3 nmol/kg S.C.) produced similar responses to higher dose treatment with Tirzepatide (at 10 nmol/kg S.C.). At 30 nmol/kg S.C., mCMZ371 treatment produced superior efficacy in reduction of body weight compared with other dosages and molecules tested. These robust pharmacodynamic responses to mCMZ371 provide opportunities for developing a treatment dosing regimen with a lower effective dose range than Tirzepatide thereby mitigating the risk of occurrence and extent of adverse drug responses in subjects in need of treatment. Based on the superior efficacy in reduction of body weight of mCMZ371 at the highest dose tested, a treatment dosing regimen can be developed yielding more extensive weight loss than treatment with Tirzepatide.

CLAIMS

What is claimed is:

1. A peptide comprising a sequence at least 95% identical to SEQ ID NO. 6 (YAibEGT-FTSDY-SIYLD-KX1AAAib-EFVX2W-LIAGG-PSSGA-PPPS).
2. A peptide comprising SEQ ID NO: 6 (YAibEGT-FTSDY-SIYLD-KX1AAAib-EFVX2W-LIAGG-PSSGA-PPPS), or a peptide having 1 amino acid substitution, deletion, or insertion, or any combination thereof, as compared to SEQ ID NO: 6 (YAibEGT-FTSDY-SIYLD-KX1AAAib-EFVX2W-LIAGG-PSSGA-PPPS).
3. The peptide of claim 1, comprising a sequence at least 98% identical to SEQ ID NO. 6.
4. The peptide of claim 1, comprising SEQ ID NO. 6.
5. The peptide of claim 1, comprising X1 and/or X2.
6. The peptide of claim 5, comprising X1, wherein X1 is a cysteine or lysine.
7. The peptide of claim 5, comprising X2, wherein X2 is a cysteine or lysine.
8. The peptide of claim 1, comprising X1 and X2, wherein X1 is cysteine and X2 is cysteine.
9. A peptide conjugate comprising the peptide of any one of claims 1-8, and a staple.
10. A peptide conjugate comprising a peptide at least 79% identical to SEQ ID NO: 6 (YAibEGT-FTSDY-SIYLD-KX1AAAib-EFVX2W-LIAGG-PSSGA-PPPS), and a staple.
11. The peptide conjugate of claim 9 or claim 10, wherein the peptide comprises X1 and/or X2 of SEQ ID NO: 6, and the staple is attached at the X1 and/or X2.
12. The peptide conjugate of any one of claims 9-11, further comprising a fatty acid and/or half life extending moiety.
13. The peptide conjugate of any one of claims of 9-12, wherein the staple is attached to the peptide at a first amino acid and a second amino acid;

wherein the staple is of Formula (I):



wherein

A is -N-;

X¹ and X² are a bond, -C(=O)-, -alkylene-C(=O)-, -C(=O)-alkylene-, -alkylene-C(=O)NR³-, -alkylene-NR³C(=O)-, -C(=O)NR³-alkylene-, -NR³C(=O)-alkylene-, -alkylene-C(=O)NR³-alkylene-, or -alkylene-NR³C(=O)-alkylene-;

wherein X¹ is attached to the first amino acid of the peptide, X² is attached to the second amino acid of the peptide, and X¹ and X² are identical;

R is hydrogen or -(L)_s-Y;

each L is independently -(CR¹R²)_v-, -alkylene-O-, -O-alkylene-, -C(=O)-alkylene-, -alkylene-C(=O)-, -NR³-alkylene-, -alkylene-NR³-, -S-alkylene-, -alkylene-S-, -S(=O)-alkylene-, -alkylene-S(=O)-, -S(=O)₂-alkylene-, -alkylene-S(=O)₂-, -C(=O)-, -C(=O)NR³-, -NR³C(=O)-, -NR³C(=O)NR³-, -

$\text{NR}^3\text{C}(=\text{O})\text{NR}^3\text{-alkylene-}$, $\text{-NR}^3\text{C}(=\text{O})\text{-alkylene-NR}^3\text{-}$, $\text{-alkylene-C}(=\text{O})\text{NR}^3\text{-}$, $\text{-C}(=\text{O})\text{NR}^3\text{-alkylene-}$, $\text{-alkylene-NR}^3\text{C}(=\text{O})\text{-}$, or $\text{-NR}^3\text{C}(=\text{O})\text{-alkylene-}$;

v is 2-20;

each R^1 or R^2 is independently hydrogen, halogen, -CN , -OR^a , -SR^a , -S(=O)R^b , -NO_2 , $\text{-NR}^c\text{R}^d$, $\text{-S(=O)}_2\text{R}^d$, $\text{-NR}^a\text{S(=O)}_2\text{R}^d$, $\text{-S(=O)}_2\text{NR}^c\text{R}^d$, -C(=O)R^b , -OC(=O)R^b , $\text{-CO}_2\text{R}^a$, $\text{-OCO}_2\text{R}^a$, $\text{-C(=O)NR}^c\text{R}^d$, $\text{-OC(=O)NR}^c\text{R}^d$, $\text{-NR}^a\text{C(=O)NR}^c\text{R}^d$, $\text{-NR}^a\text{C(=O)R}^b$, $\text{-NR}^a\text{C(=O)OR}^a$, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_1\text{-C}_6$ heteroalkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_2\text{-C}_8$ heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, -OR^a , or $\text{-NR}^c\text{R}^d$; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, -OR^a , or $\text{-NR}^c\text{R}^d$;

or R^1 and R^2 are taken together to form a $\text{C}_1\text{-C}_6$ cycloalkyl or $\text{C}_1\text{-C}_6$ heterocycloalkyl;

each R^3 is independently hydrogen, -S(=O)R^b , $\text{-S(=O)}_2\text{R}^a$, $\text{-S(=O)}_2\text{NR}^c\text{R}^d$, -C(=O)R^b , $\text{-CO}_2\text{R}^a$, $\text{-C(=O)NR}^c\text{R}^d$, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_1\text{-C}_6$ heteroalkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_2\text{-C}_8$ heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, -OR^a , or $\text{-NR}^c\text{R}^d$; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, -OR^a , or $\text{-NR}^c\text{R}^d$;

Y is hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{-CO}_2\text{H}$, $\text{-CO}_2(\text{C}_1\text{-C}_6 \text{ alkyl})$, $\text{-CO}_2\text{NH}_2$, $\text{-CO}_2\text{N(alkyl)}_2$, or $\text{-CO}_2\text{NH(alkyl)}$;

s is 0-20;

R^a is hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_1\text{-C}_6$ heteroalkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_2\text{-C}_8$ heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, -OH , -OMe , or -NH_2 ; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, -OH , -OMe , or -NH_2 ;

R^b is $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_1\text{-C}_6$ heteroalkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_2\text{-C}_8$ heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, -OH , -OMe , or -NH_2 ; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, -OH , -OMe , or -NH_2 ; and

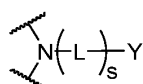
each R^c and R^d is independently hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_1\text{-C}_6$ heteroalkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_2\text{-C}_8$ heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, -OH , -OMe , or -NH_2 ; and the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one, two, or three of halogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, -OH , -OMe , or -NH_2 ;

or R^c and R^d , together with the nitrogen atom to which they are attached, form a heterocycloalkyl or heteroaryl; wherein the heterocycloalkyl and heteroaryl is optionally substituted with one, two, or three of halogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, -OH , -OMe , or -NH_2 , and

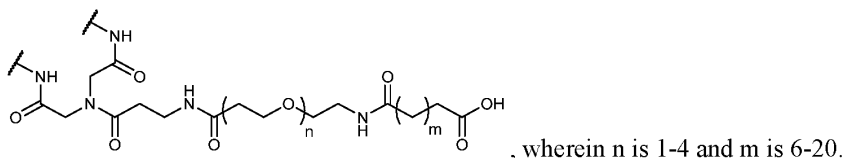
wherein optionally the peptide comprises X1 and X2, and the first amino acid is X1 and the second amino acid is X2.

14. The peptide conjugate of claim 13, wherein the first amino acid and the second amino acid are independently a sulfhydryl containing amino acid.
15. The peptide conjugate of claim 13 or claim 14, wherein the first amino acid and the second amino acid are independently selected from cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, and 2-amino-6-mercaptohexanoic acid.
16. The peptide conjugate of any one of claims 13-15, wherein the first amino acid and second amino acids are cysteines.
17. The peptide conjugate of claim 13, wherein the first amino acid and the second amino acid are independently an amine-containing amino acid.
18. The peptide conjugate of claim 17, wherein the amine-containing amino acid is selected from lysine, ornithine, diaminobutyric acid, diaminopropionic acid and homolysine.
19. The peptide conjugate of claim 17 or claim 18, wherein the first amino acid and the second amino acids are lysines.
20. The peptide conjugate of any one of claims 9-18, wherein the first amino acid has a position i in the peptide and the second amino acid has a position i + n in the peptide, wherein n is 4-16.
21. The peptide conjugate of any one of claims 9-20, wherein the peptide modulates a GLP-1 receptor.
22. The peptide conjugate of any one of claims 9-21, wherein the peptide binds to a GLP-1 receptor.
23. The peptide conjugate of any one of claims 9-22, wherein the peptide modulates a GIP receptor.
24. The peptide conjugate of any one of claims 9-23, wherein the peptide binds to a GIP receptor.
25. The peptide conjugate of any one of claims 9-24, wherein the peptide is a GLP-1 receptor agonist.
26. The peptide conjugate of any one of claims 9-25, wherein the peptide is a GIP receptor agonist.
27. The peptide conjugate of any one of claims 9-26, wherein the peptide is a dual GLP-1 receptor and GIP receptor agonist.
28. The peptide conjugate of any one of claims 9-27, wherein the peptide is resistant to proteolysis by a gastrointestinal protease.
29. The peptide conjugate of any one of claims 9-28, wherein the half-life of the peptide conjugate is at least about 2-fold greater than the half-life of an unmodified form of the peptide.
30. The peptide conjugate of any one of claims 9-29, wherein the binding affinity of the peptide conjugate is within about 5-20% of the binding affinity of an unmodified form of the peptide.
31. The peptide conjugate of any one of claims 9-30, wherein X¹ and X² are -C(=O)-.
32. The peptide conjugate of any one of claims 9-30, wherein X¹ and X² are -alkylene-C(=O)- or -C(=O)alkylene-.
33. The peptide conjugate of any one of claims 9-30, wherein X¹ and X² are -CH₂-C(=O)- or -C(=O)-CH₂-.
34. The peptide conjugate of any one of claims 9-30, wherein X¹ and X² are -alkylene-C(=O)NR³- or -C(=O)NR³-alkylene-.

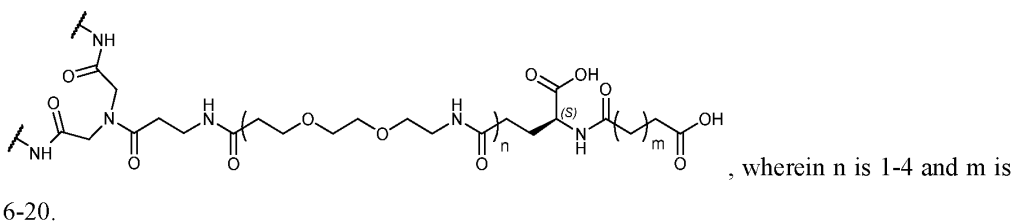
35. The peptide conjugate of any one of claims 9-30, wherein X^1 and X^2 are $-\text{CH}_2-\text{C}(=\text{O})\text{NR}^3-$ or $-\text{C}(=\text{O})\text{NR}^3-\text{CH}_2-$.
36. The peptide conjugate of any one of claims 9-30, wherein X^1 and X^2 are $-\text{alkylene}-\text{C}(=\text{O})\text{NR}^3-\text{alkylene}-$ or $-\text{alkylene}-\text{NR}^3\text{C}(=\text{O})-\text{alkylene}-$.
37. The peptide conjugate of any one of claims 9-30, wherein X^1 and X^2 are $-\text{CH}_2-\text{C}(=\text{O})\text{NR}^3-\text{CH}_2\text{CH}_2-$ or $-\text{CH}_2-\text{NR}^3\text{C}(=\text{O})-\text{CH}_2\text{CH}_2-$.
38. The peptide conjugate of any one of claims 9-30, wherein X^1 and X^2 are $-\text{CH}_2-\text{C}(=\text{O})\text{NH}-\text{CH}_2\text{CH}_2-$ or $-\text{CH}_2-\text{NHC}(=\text{O})-\text{CH}_2\text{CH}_2-$.
39. The peptide conjugate of any one of claims 9-38, wherein $>\text{A}-\text{R}$ has the following structure:



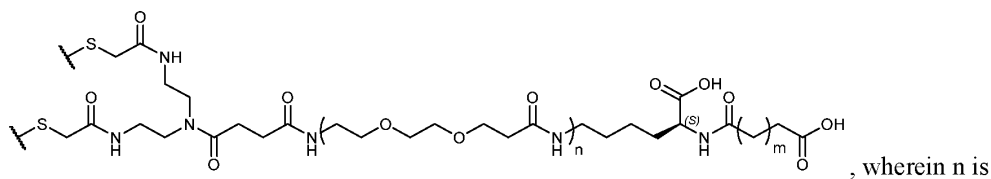
40. The peptide conjugate of claim 39, wherein s is 1-15.
41. The peptide conjugate of claim 39, wherein s is 1-10.
42. The peptide conjugate of claim 39, wherein s is 5-15.
43. The peptide conjugate of claim 39, wherein s is 5-10.
44. The peptide conjugate of any one of claims 9-43, wherein Y is hydrogen or -CO₂H.
45. The peptide conjugate of any one of claims 9-43, wherein each L is independently -(CR¹R²)_v-, -alkylene-O-, -C(=O)-, -C(=O)NR³-, -NR³C(=O)-, -alkylene-C(=O)NR³-, or -alkylene-NR³C(=O)-; and v is 2-20.
46. The peptide conjugate of any one of claims 9-13, wherein the peptide conjugate comprises:



47. The peptide conjugate of claim 46, wherein n is 3 and m is 15.
48. The peptide conjugate of any one of claims 9-13, wherein the peptide conjugate comprises:

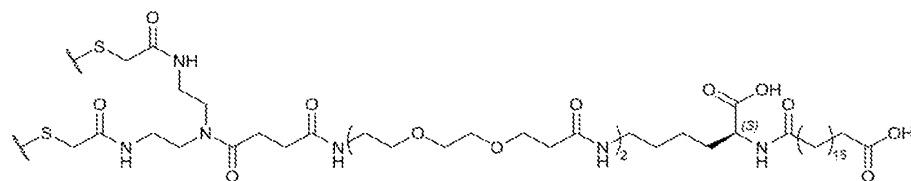


49. The peptide conjugate of claim 48, wherein n is 2 and m is 15.
50. The peptide conjugate of claim 48, wherein n is 2 and m is 17.
51. The peptide conjugate of any one of claims 9-13, wherein the peptide conjugate comprises:

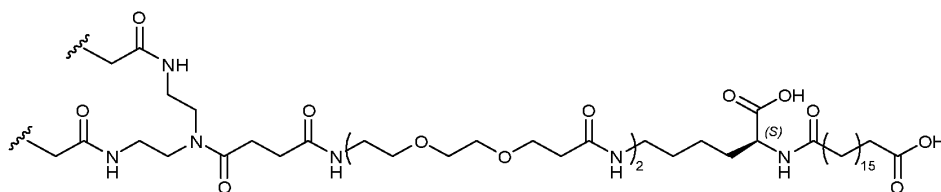


1-4 and m is 6-20.

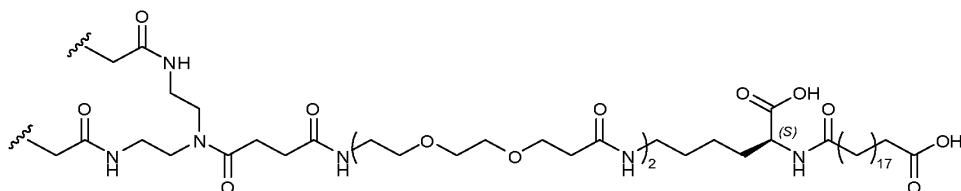
52. The peptide conjugate of claim 51, wherein n is 2 and m is 15.
53. The peptide conjugate of claim 51, wherein n is 2 and m is 17.
54. The peptide conjugate of claim 51, wherein n is 2 and m is 13.
55. The peptide conjugate of any one of claims 9-13, wherein the peptide conjugate comprises: L5A(S)



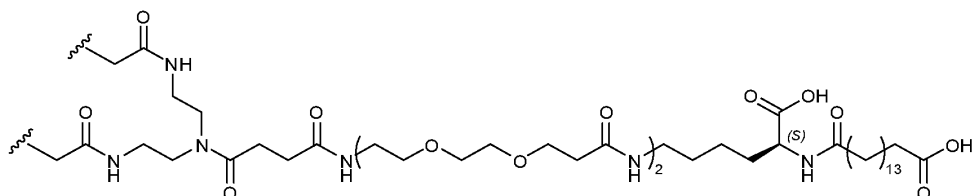
56. The peptide conjugate of any one of claims 9-13, wherein the peptide conjugate comprises: L5A



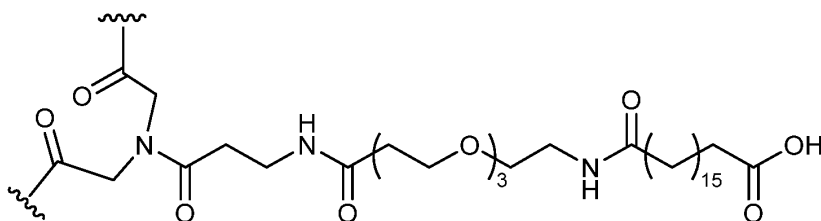
57. The peptide conjugate of any one of claims 9-13, wherein the peptide conjugate comprises: C20L5A



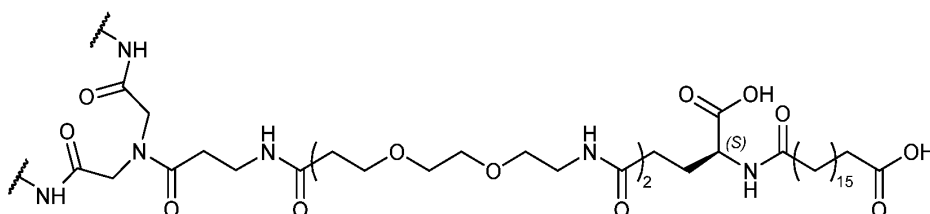
58. The peptide conjugate of any one of claims 9-13, wherein the peptide conjugate comprises:
C16L5A



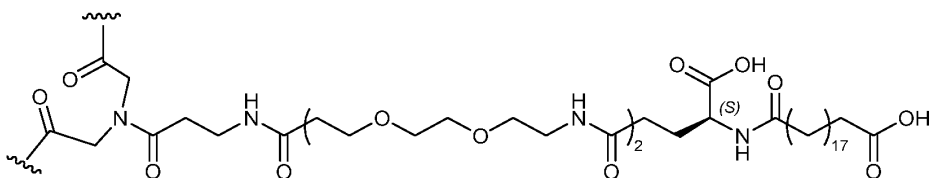
59. The peptide conjugate of any one of claims 9-13, wherein the peptide conjugate comprises: K4



60. The peptide conjugate of any one of claims 9-13, wherein the peptide conjugate comprises: K5



61. The peptide conjugate of any one of claims 9-13, wherein the peptide conjugate comprises: C20K5



62. A pharmaceutical composition comprising the peptide of any one of claims 1-8 or the peptide conjugate of any one of claims 9-61, and a pharmaceutically acceptable excipient.
63. A method for treating a disease or condition in a subject in need thereof, the method comprising administering to the subject a composition comprising a therapeutically effective amount of the peptide of any one of claims 1-8 or the peptide conjugate of any one of claims 9-61.
64. The method of claim 63, wherein the disease or condition is diabetes or obesity.
65. The method of claim 64, wherein the diabetes is Type 1 diabetes mellitus, Type 2 diabetes mellitus, gestational diabetes, neonatal diabetes, maturity onset diabetes of the young, or latent autoimmune diabetes in adults, or any combination thereof.
66. The method of claim 63, wherein the disease or condition is non-alcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), or cardiovascular disease.
67. The method of claim 63, wherein the disease or condition is short bowel syndrome (SBS).
68. The method of claim 63, wherein the disease or condition is inflammatory bowel disease (IBD), inflammatory bowel syndrome (IBS), or psoriasis.
69. The method of claim 68, wherein the disease or condition is Crohn's disease or ulcerative colitis.
70. The method of claim 63, wherein the disease or condition is Alzheimer's disease, Parkinson's disease or Huntington's disease.
71. The method of any one of claims 63-70, further comprising administering to the subject one or more additional therapeutic agents.

72. The method of claim 71, wherein the one or more additional therapeutic agents comprises an incretin hormone or a derivative thereof.
73. The method of claim 72, wherein the incretin hormone or derivative thereof is selected from GLP-1, exendin-4, glucagon (GCG), glucose-dependent insulintropic polypeptide (GIP), oxyntomodulin, and combinations thereof.
74. The method of any one of claims 63-73, wherein the peptide conjugate is administered about once every 7 days, about once every 14 days, about once a month, about once every two months, or about once every three months.