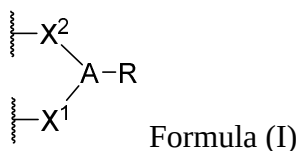


CLAIMS

What is claimed is:

1. A peptide conjugate comprising a peptide and a staple, wherein the peptide comprises: YAiEGTFTSDYSIYLDKXAAAiEFVXWLIAGGPSSGAPPPS (SEQ ID NO: 6), and a staple, wherein the staple is attached to the peptide at each X amino acid of the peptide; wherein each X is a sulfhydryl-containing amino acid, or each X is an amine-containing amino acid; and

wherein the staple is of Formula (I):



wherein

A is -N-;

X^1 and X^2 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 -(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 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 $-CO_2NH(\text{alkyl})$;

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 $-NH_2$;

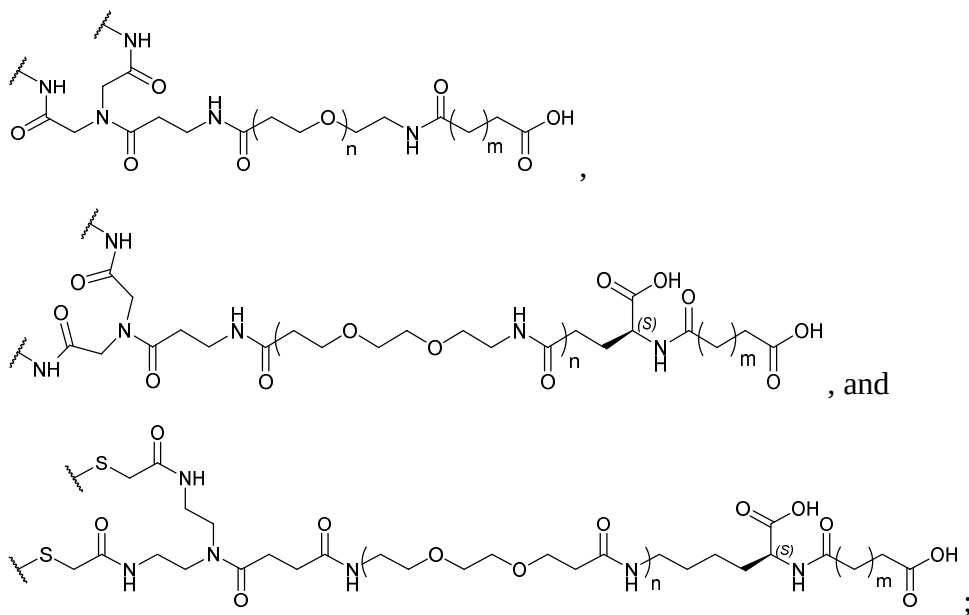
R^b is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 heteroalkyl, C_3 - C_8 cycloalkyl, C_2 - C_8 heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, $-OH$, $-OMe$, or $-NH_2$; and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

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, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, $-OH$, $-OMe$, or $-NH_2$.

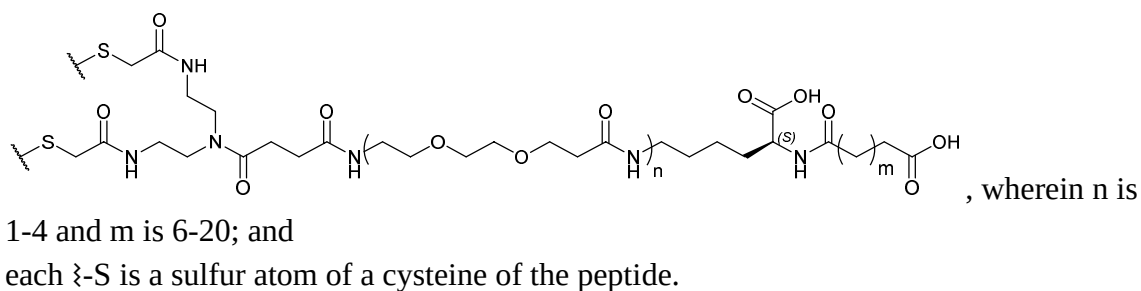
2. The peptide conjugate of claim 1, wherein each X amino acid of the peptide is independently selected from the group consisting of cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, and 2-amino-6-mercaptohexanoic acid; or from the group consisting of lysine, ornithine, diaminobutyric acid, diaminopropionic acid and homolysine.
3. The peptide conjugate of claim 1, wherein each X of the peptide is cysteine, and the peptide comprises the sequence YAibEGTFTSDYSIYLDKCAAAibEFVCWLIAGGPSSGAPPPS (SEQ ID NO: 61).

4. The peptide conjugate of claim 1, wherein each X of the peptide is lysine and the peptide comprises the sequence YAibEGTFTSDYSIYLDKKAaAibEFVKWLIAGGPSSGAPPPS (SEQ ID NO: 42).
5. The peptide conjugate of claim 1, wherein the peptide modulates a GLP-1 receptor and/or a GIP receptor.
6. The peptide conjugate of claim 1, wherein the peptide is a dual GLP-1 receptor agonist and GIP receptor agonist.
7. The peptide conjugate of claim 1, wherein X^1 and X^2 are each $-C(=O)alkylene-$, $-alkylene-C(=O)NR^3-alkylene-$, or $-alkylene-NR^3C(=O)-alkylene-$.
8. The peptide conjugate of claim 1, wherein R is $-(L)_s-Y$; s is 1-15; Y is hydrogen or $-CO_2H$; and 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 $-alkylene-NR^3C(=O)-$; wherein v is 2-20, each R^1 or R^2 is independently hydrogen or $-CO_2R^a$, wherein R^a is hydrogen, and each R^3 is independently hydrogen or C_1-C_6 alkyl.
9. The peptide conjugate of claim 1, wherein the peptide conjugate comprises a staple selected from the group consisting of:



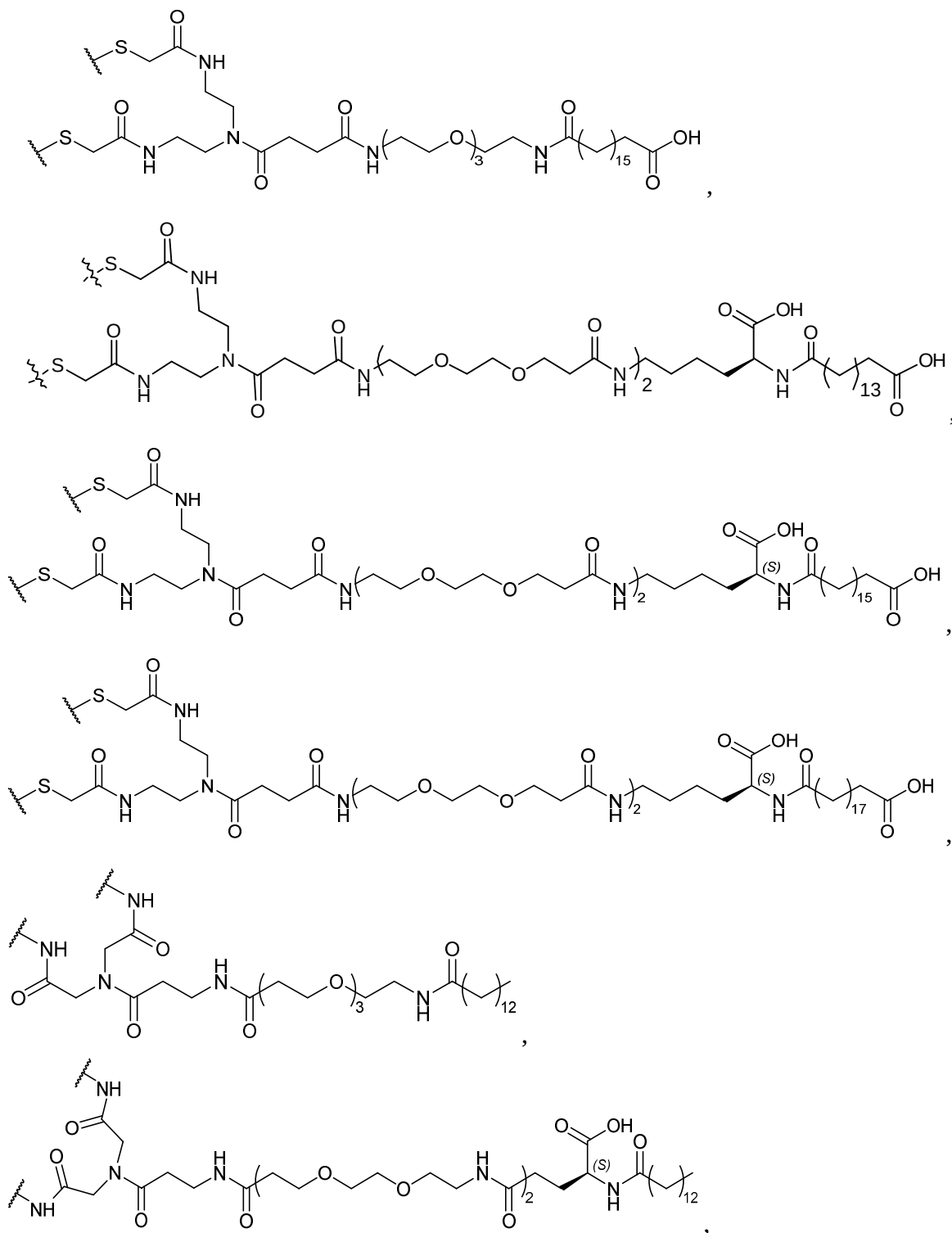
wherein each n is 1-4 and each m is 6-20; each $\zeta-S$ is a sulfur atom of a sulfhydryl-containing amino acid of the peptide; and each $\zeta-NH$ is an amine of the amine-containing amino acid of the peptide.

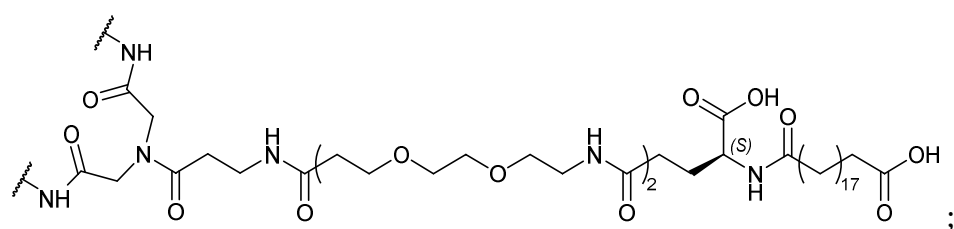
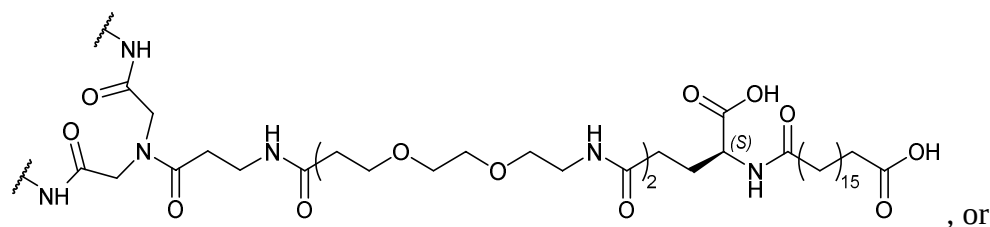
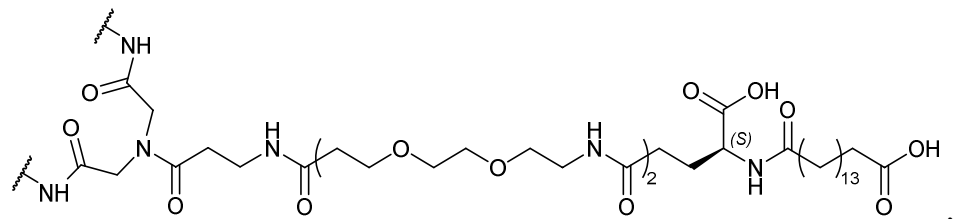
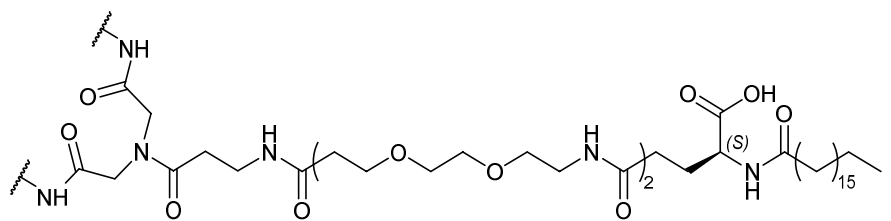
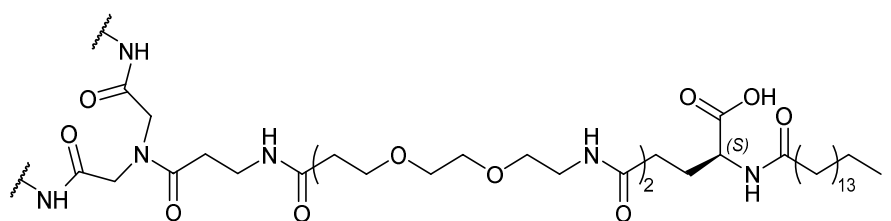
10. The peptide conjugate of claim 3, wherein the staple is:



11. The peptide conjugate of claim 10, wherein n is 2 and m is 15.

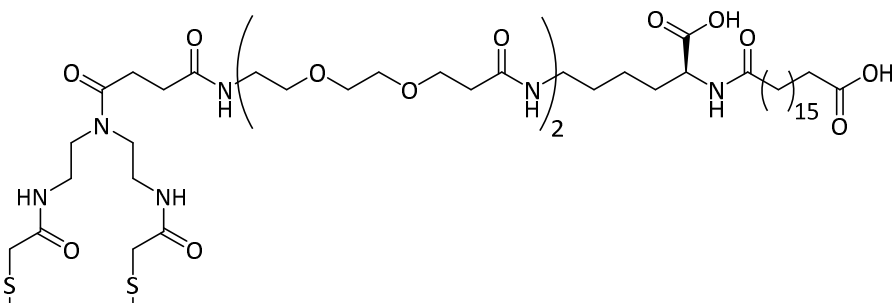
12. The peptide conjugate of claim 1, wherein the staple is:





wherein each ζ -S is a sulfur atom of a sulfhydryl-containing amino acid of the peptide,
and each ζ -NH is an amine of the amine-containing amino acid of the peptide.

13. The peptide conjugate of claim 3, wherein the peptide conjugate has the following structure:



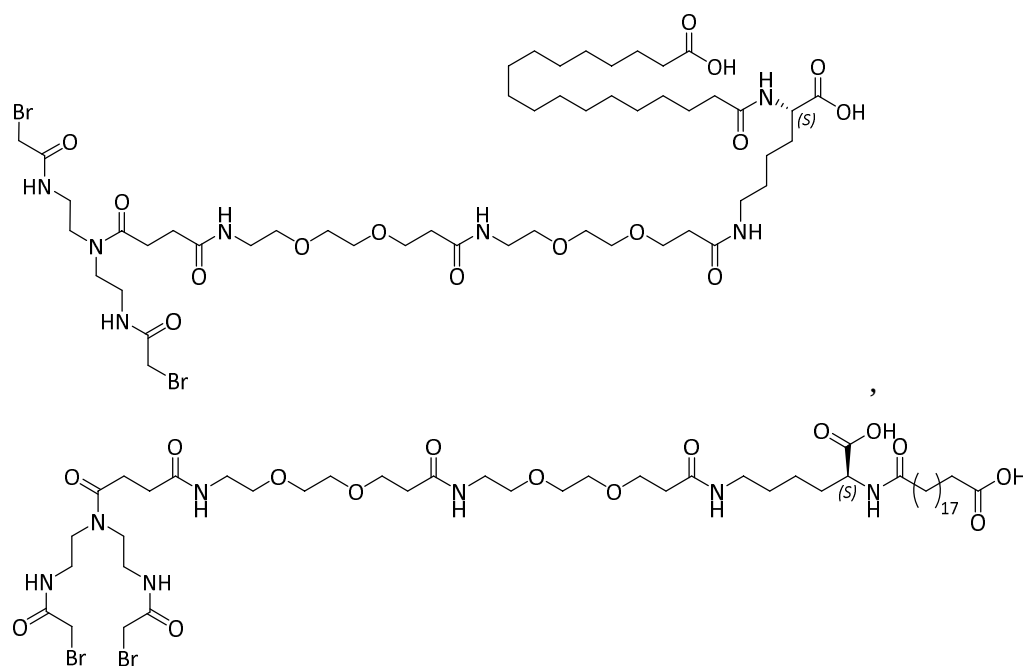
YAibEGTFTSDYSIYLDKCAAAibEFVCWLIAGGPSSGAPPPS (SEQ ID NO: 61)

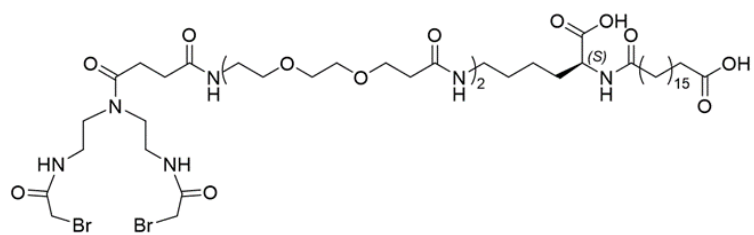
14. A peptide comprising YAibEGTFTSDYSIYLDKXAAAibEFVXWLIAGGPSSGAPPPS
(SEQ ID NO: 6), wherein each X is a sulfhydryl-containing amino acid or an amine-
containing amino acid.

15. The peptide of claim 14, wherein each X is a cysteine, and the peptide comprises:

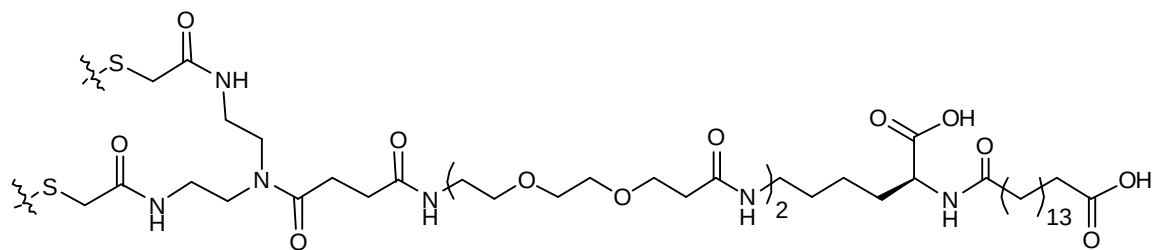
YAibEGTFTSDYSIYLDKCAAAibEFVCWLIAGGPSSGAPPPS (SEQ ID NO: 61).

16. A pharmaceutical composition comprising the peptide conjugate of any one of claims 1-13, or the peptide of claim 14 or 15, and a pharmaceutically acceptable excipient.
17. Use of the peptide conjugate of any one of claims 1-13, or the peptide of claim 14 or 15, or the pharmaceutical composition of claim 16, in the manufacture of a medicament for treating diabetes, obesity, non-alcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), cardiovascular disease, short bowel syndrome (SBS), inflammatory bowel disease (IBD), inflammatory bowel syndrome (IBS), psoriasis, Crohn's disease, ulcerative colitis, Alzheimer's disease, Parkinson's disease, or Huntington's disease.
18. Use of the peptide conjugate of any one of claims 1-13, or the peptide of claim 14 or 15, or the pharmaceutical composition of claim 16, in the manufacture of a medicament for treating 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.
19. A process for obtaining the peptide conjugate as defined in any one of claims 1-13, or the peptide as defined in claim 14 or 15, comprising the following steps:
(i) synthesizing the peptide comprising using standard solid-phase peptide synthesis (SPPS) techniques; and (ii) purifying the peptide comprising using high pressure liquid chromatography (HPLC).
20. A composition comprising any one of the following compounds:

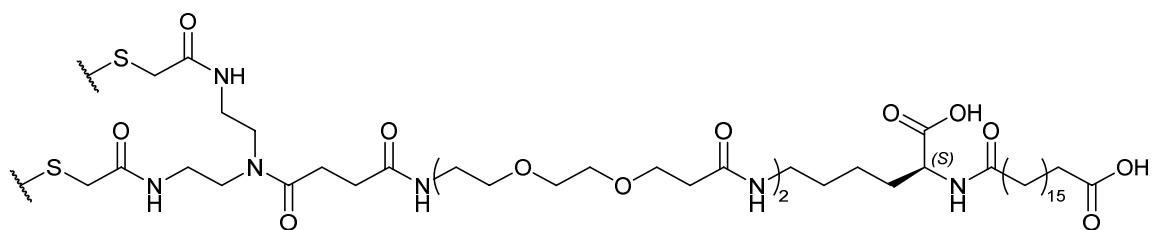




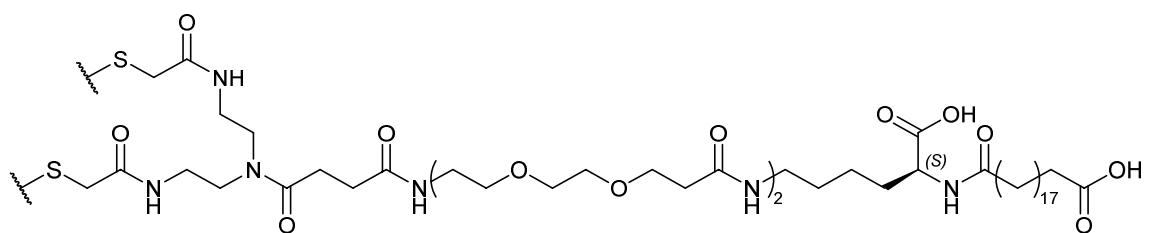
,



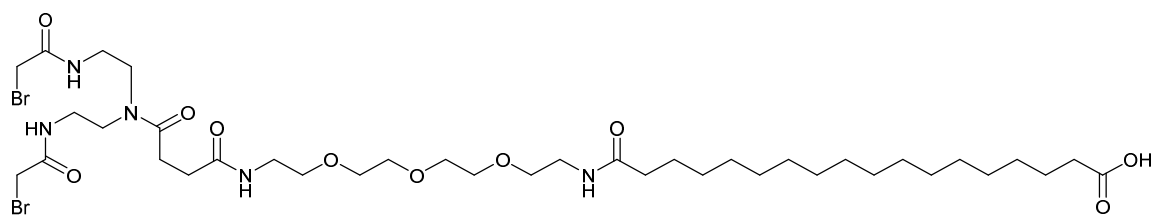
,



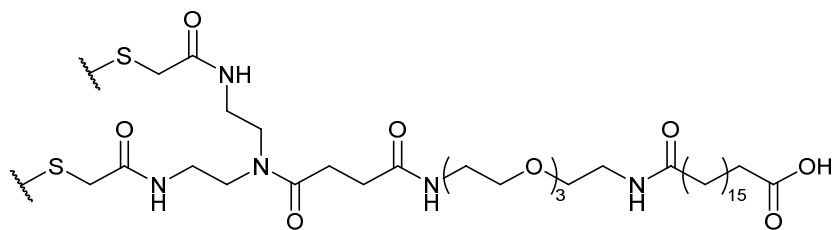
,



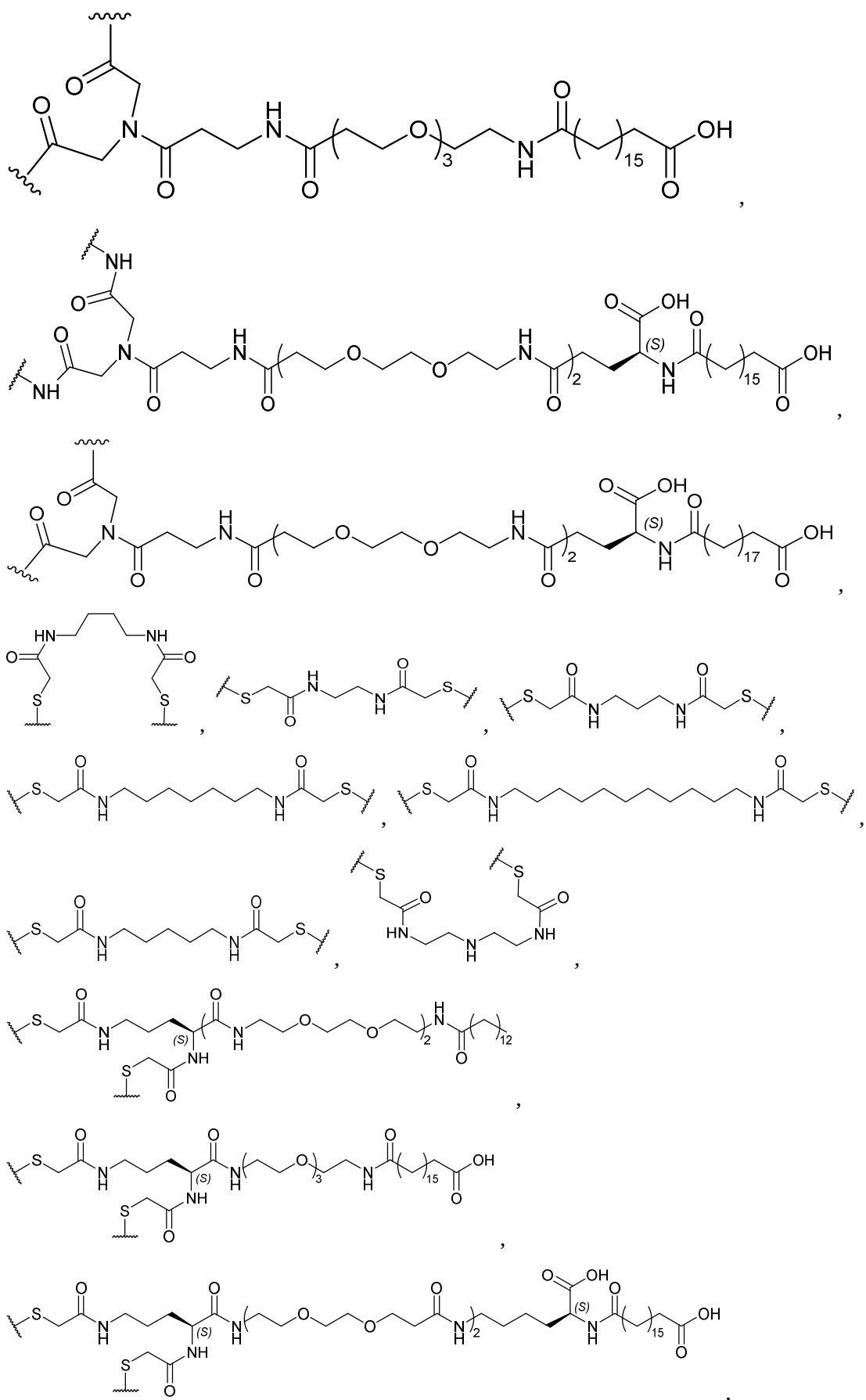
,



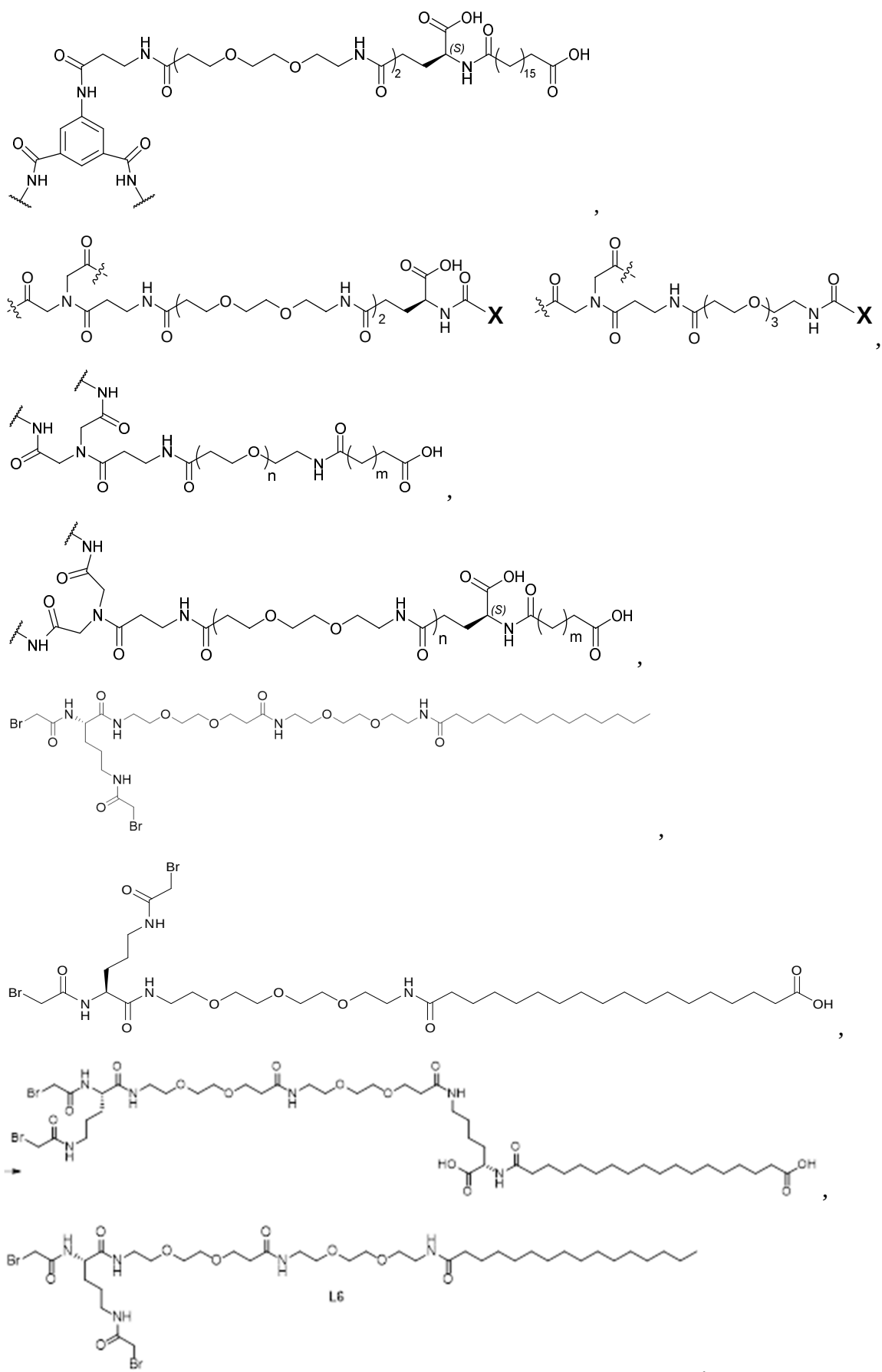
,

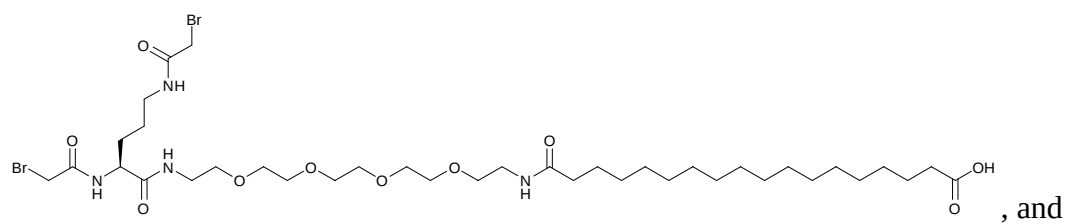
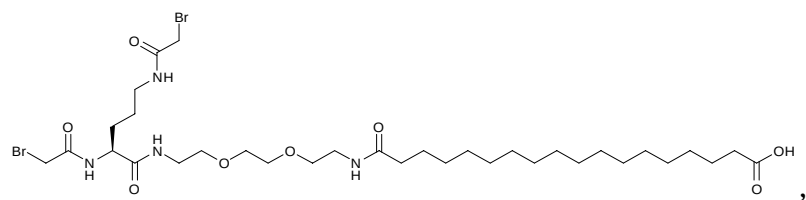
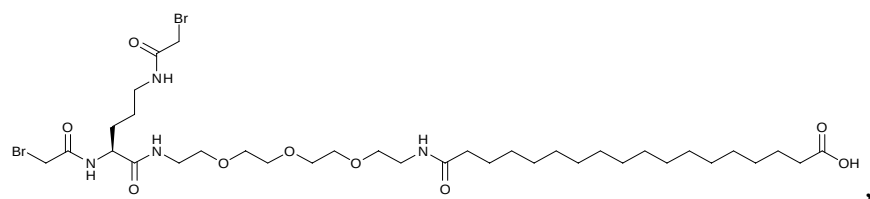
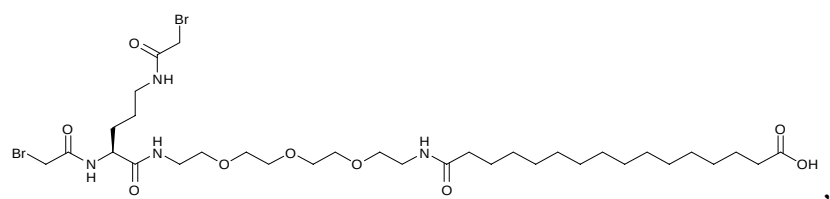
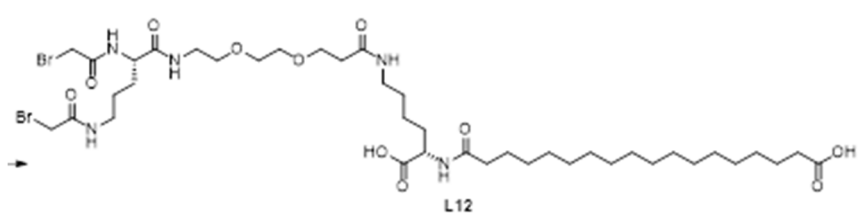
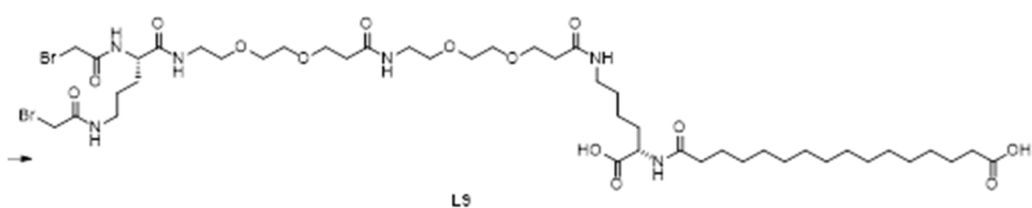
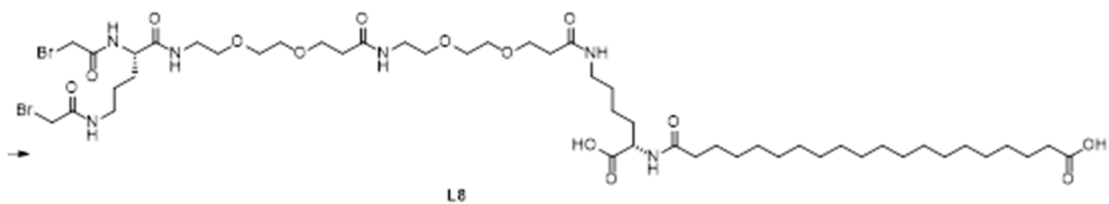
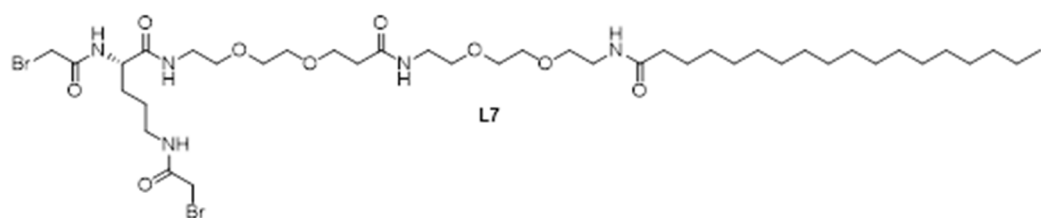


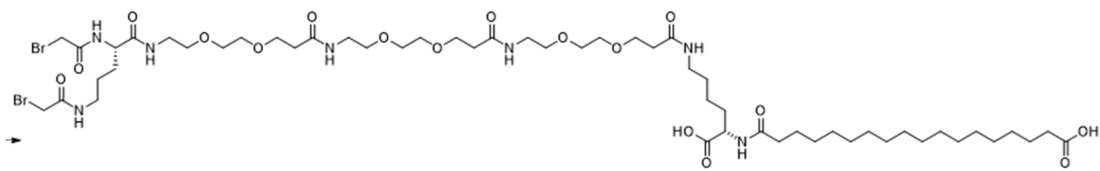
,











wherein:

each “-S-” is a sulfur atom of a sulfhydryl-containing amino acid;

each “-NH-” is an amine of an amine-containing amino acid;

each “-C(=O)-” is a carbonyl of an amide bond to an amine-containing amino acid;

each **X** independently represents a C₁₄ alkyl, C₁₄ diacid, C₁₆ alkyl, C₁₆ diacid, C₁₈ alkyl, C₁₈ diacid, C₂₀ alkyl or C₂₀ diacid;

n is 1-4; and

m is 6-20.

21. The peptide conjugate of any one of claims 1-13, or the peptide of claim 14 or 15, or the pharmaceutical composition of claim 16, for use in therapy.