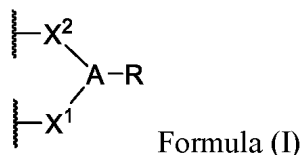


CLAIMS

What is claimed is:

1. A peptide conjugate comprising:

- a) a peptide comprising an amino acid sequence selected from SEQ ID NO: 21, 1, 23, 3, 22, 2, 30, 10, 4-9, and 24-29, or an amino acid sequence having one amino acid addition, deletion, or substitution relative to a sequence selected from SEQ ID NO: 21, 1, 23, 3, 22, 2, 30, 10, 4-9, and 24-29; and
- b) a staple attached to the peptide at a first amino acid and a second amino acid, wherein the first amino acid and second amino acid are independently cysteine, lysine, homocysteine, homolysine, 2-amino-5-mercaptopentanoic acid, 2-amino-6- mercaptohexanoic acid, ornithine, diaminobutyric acid, or diaminopropionic acid, 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, wherein the staple 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, $-CO_2H$, $-CO_2(C_1-C_6 \text{ alkyl})$, $-CO_2NH_2$, $-CO_2N(\text{alkyl})_2$, or $-CO_2NH(\text{alkyl})$; and

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;

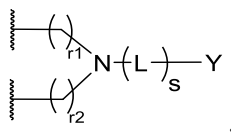
each R^c and R^d is independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, C₃-C₈ cycloalkyl, C₂-C₈ heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, -OH, -OMe, or -NH₂;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

2. The peptide conjugate of claim 1, wherein the peptide comprises the amino acid sequence selected from SEQ ID NO: 21, 1, 23, 3, 22, 2, 30, and 10, or the amino acid sequence having one amino acid addition, deletion, or substitution relative to the sequence selected from SEQ ID NO: 21, 1, 23, 3, 22, 2, 30, and 10; and wherein first amino acid is independently cysteine, homocysteine, lysine, or homolysine, and the second amino acid is independently cysteine, homocysteine, lysine, or homolysine.

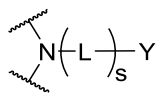
3. The peptide conjugate of claim 1, wherein the first amino acid and the second amino acid are independently cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, or 2-amino-6-mercaptohexanoic acid.
4. The peptide conjugate of claim 1 or claim 2, wherein the first amino acid and second amino acid are each cysteine.
5. The peptide conjugate of claim 1, wherein the first amino acid and second amino acid are independently lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine.
6. The peptide conjugate of claim 1 or 2, wherein the first amino acid and second amino acid are each lysine.
7. The peptide conjugate of claim 1 or 5, wherein the first amino acid and second amino acid are each ornithine.
8. The peptide conjugate of claim 1 or 2, wherein the peptide comprises a sequence that is any one of SEQ ID NOs: 1-9, 21-29.
9. The peptide conjugate of claim 1 or claim 4, wherein the peptide comprises SEQ ID NO: 1.
10. The peptide conjugate of claim 1 or 2, wherein the peptide comprises a sequence that is SEQ ID NO: 2 or 22.
11. The peptide conjugate of claim 1 or 2, 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.
12. The peptide conjugate of claim 1 or 2, 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.
13. The peptide conjugate of claim 12, 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.
14. The peptide conjugate of claim 1 or claim 2, wherein the binding affinity of the peptide conjugate is within about 5% of the binding affinity of an unmodified form of the peptide.
15. The peptide conjugate of claim 1 or claim 2, wherein the binding affinity of the peptide conjugate is within about 10% of the binding affinity of an unmodified form of the peptide.
16. The peptide conjugate of claim 1 or claim 2, wherein the binding affinity of the peptide conjugate is within about 15% of the binding affinity of an unmodified form of the peptide.
17. The peptide conjugate of claim 1 or claim 2, wherein the binding affinity of the peptide conjugate is within about 20% of the binding affinity of an unmodified form of the peptide.

18. The peptide conjugate of claim 1 or 2, wherein A is optionally substituted alkylene.
19. The peptide conjugate of claim 1 or 2, wherein A is $-(CH_2)_t-$, wherein t is 1-12.
20. The peptide conjugate of claim 1 or 2, wherein A is optionally substituted arylene.
21. The peptide conjugate of claim 1 or 2, wherein A is $-NR^3$ -alkylene- NR^3 -.
22. The peptide conjugate of claim 1 or 2, wherein A is $-N-$, and wherein X^1 and X^2 are independently $-CH_2-C(=O)NR^3$ -.
23. The peptide conjugate of claim 1 or 2, wherein X^1 and X^2 are $-C(=O)-$.
24. The peptide conjugate of claim 1 or 2, wherein X^1 and X^2 are $-alkylene-C(=O)-$.
25. The peptide conjugate of claim 1 or 2, wherein X^1 and X^2 are $-CH_2-C(=O)-$.
26. The peptide conjugate of claim 1 or 2, wherein X^1 and X^2 are independently $-alkylene-C(=O)NR^3$ -.
27. The peptide conjugate of claim 1 or 2, wherein X^1 and X^2 are independently $-alkylene-C(=O)NR^3$ -alkylene-.
28. The peptide conjugate of claim 1 or 2, wherein X^1 and X^2 are independently $-CH_2-C(=O)NR^3-CH_2CH_2-$.
29. The peptide conjugate of claim 1 or 2, wherein $>A-R$ has the following structure:



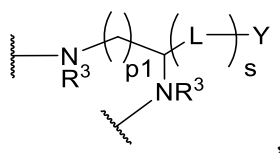
wherein r_1 and r_2 are each independently 0-4, and wherein s is 5-15.

30. The peptide conjugate of claim 1 or claim 2, wherein $>A-R$ has the following structure:



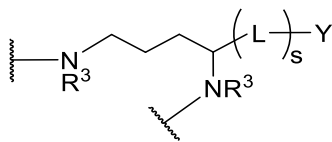
and wherein s is 5-15.

31. The peptide conjugate of claim 1 or 2, wherein $>A-R$ has the following structure:

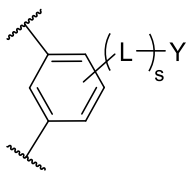


wherein p1 is 1-5.

32. The peptide conjugate of claim 1 or 2, wherein >A-R has the following structure:



33. The peptide conjugate of claim 1 or 2, wherein >A-R has the following structure:



34. The peptide conjugate of claim 1 or 2, wherein s is 1-15.

35. The peptide conjugate of claim 1 or 2, wherein s is 1-10.

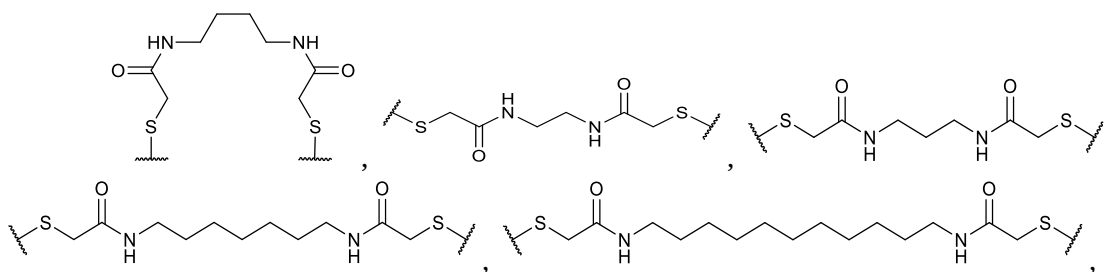
36. The peptide conjugate of claim 1 or 2, wherein s is 5-15.

37. The peptide conjugate of claim 1 or 2, wherein s is 5-10.

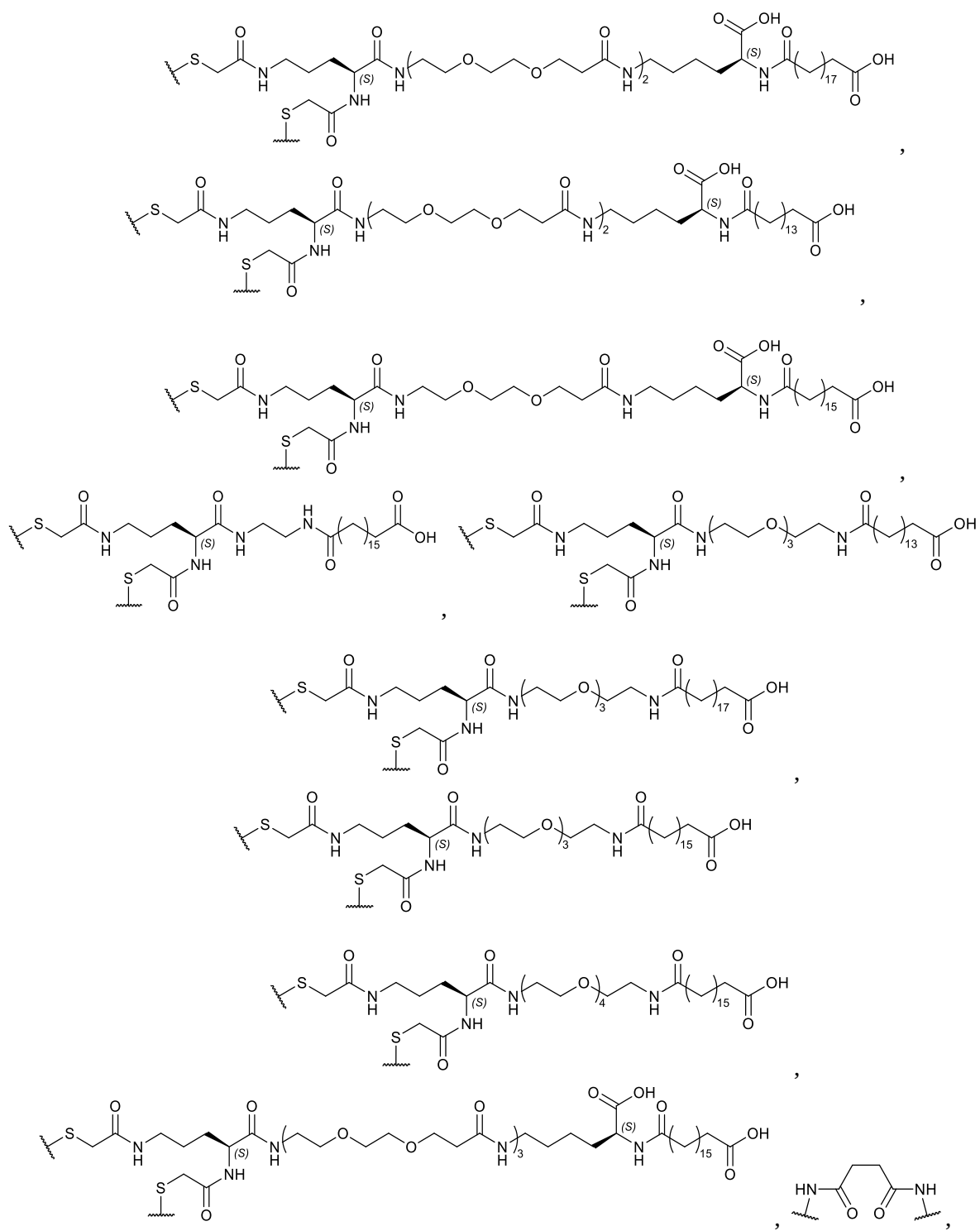
38. The peptide conjugate of claim 1 or 2, wherein Y is hydrogen or -CO₂H.

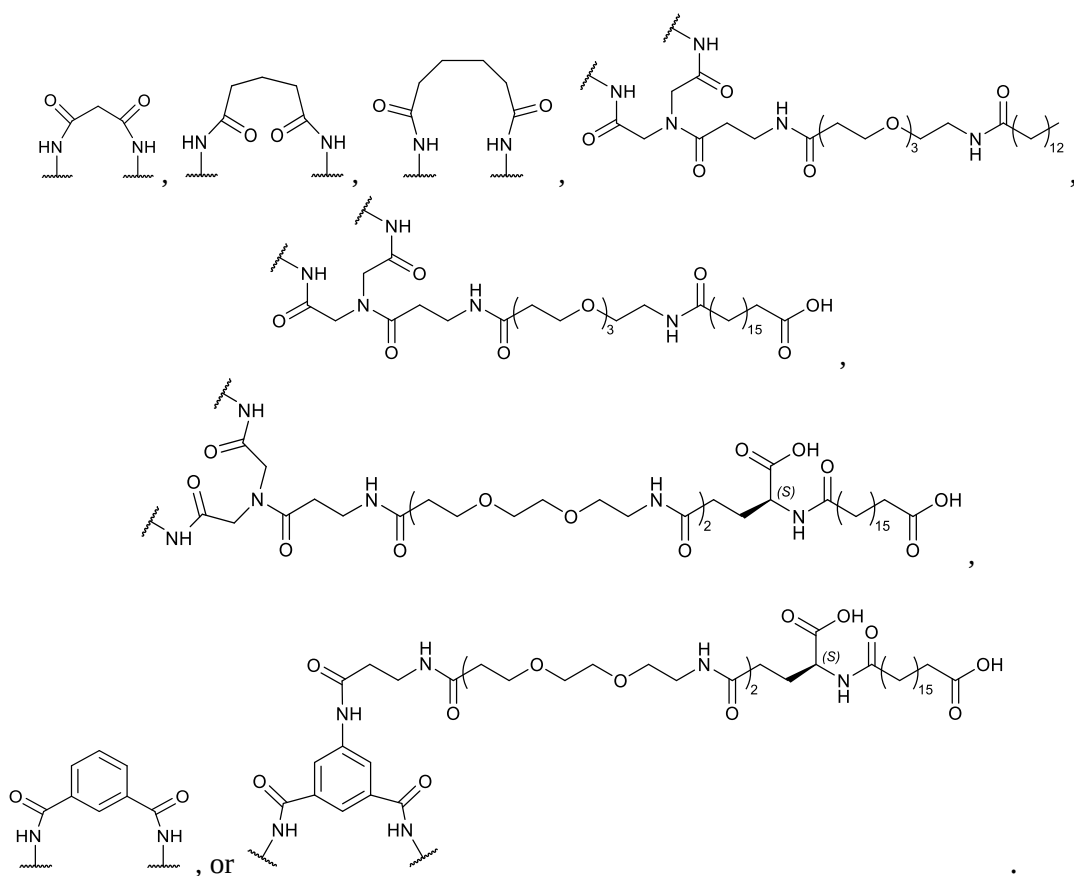
39. The peptide conjugate of claim 1 or 2, wherein each L is independently -(CR¹R²)_v-, -alkylene-O-, -C(=O)-, -C(=O)NR³-, -NR³C(=O)-, -alkylene-C(=O)NR³-, or -alkylene-NR³C(=O)-; and v is 2-20.

40. The peptide conjugate of claim 1, wherein the peptide conjugate comprises the structure:

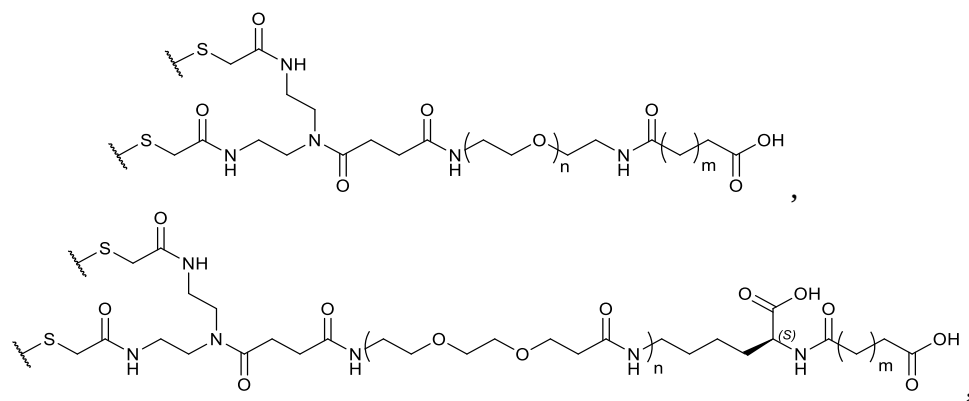


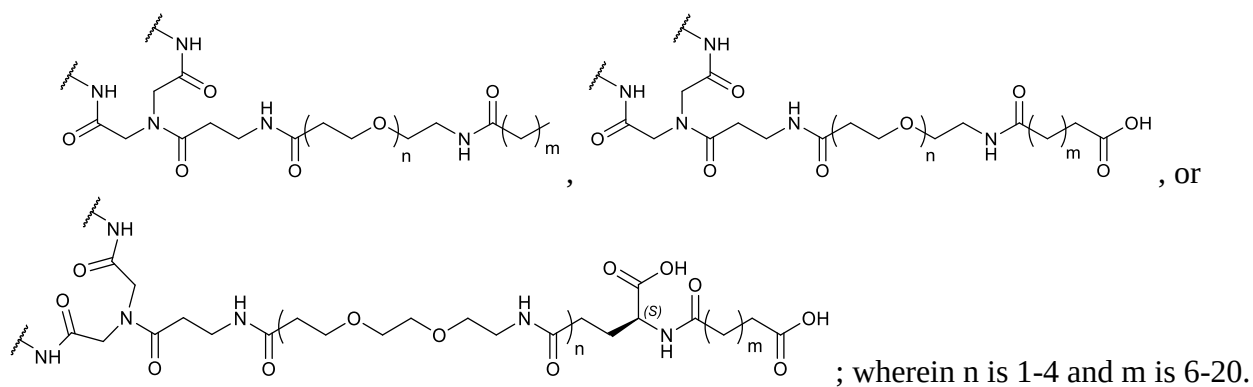




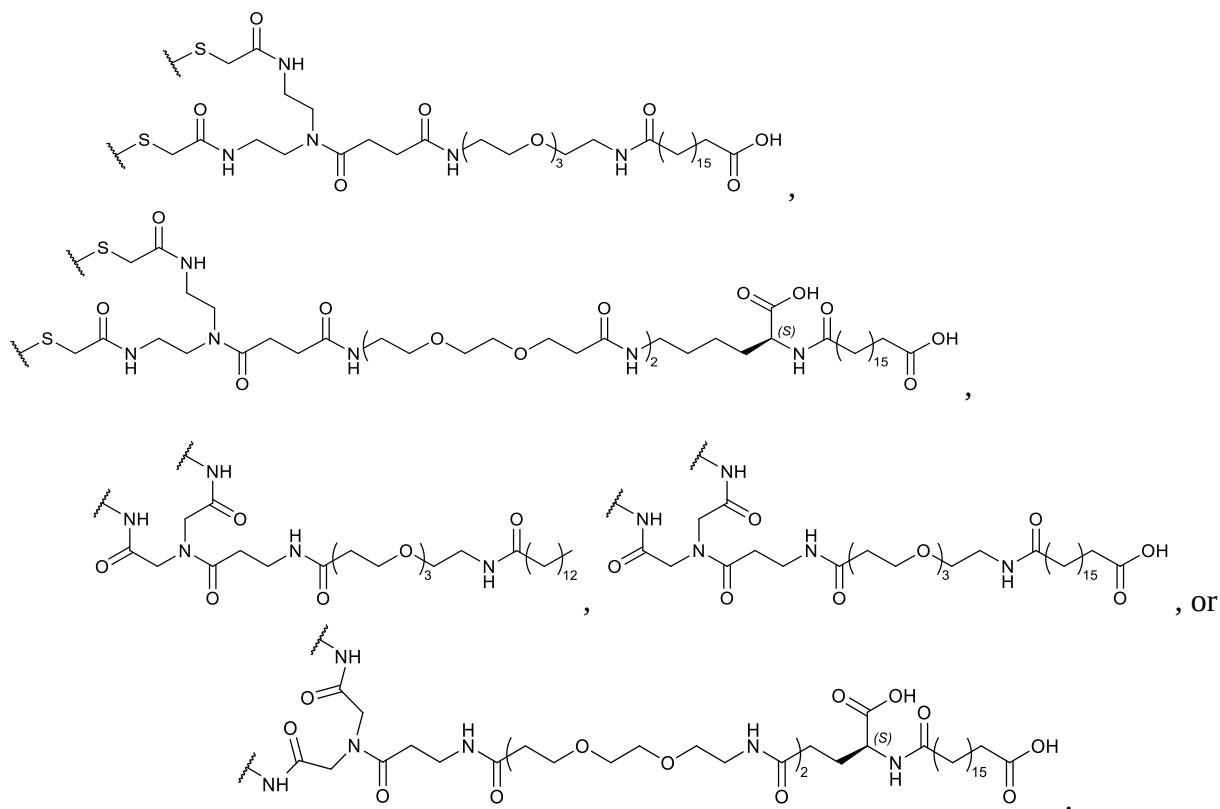


41. The peptide conjugate of claim 1, wherein the peptide conjugate comprises the structure:

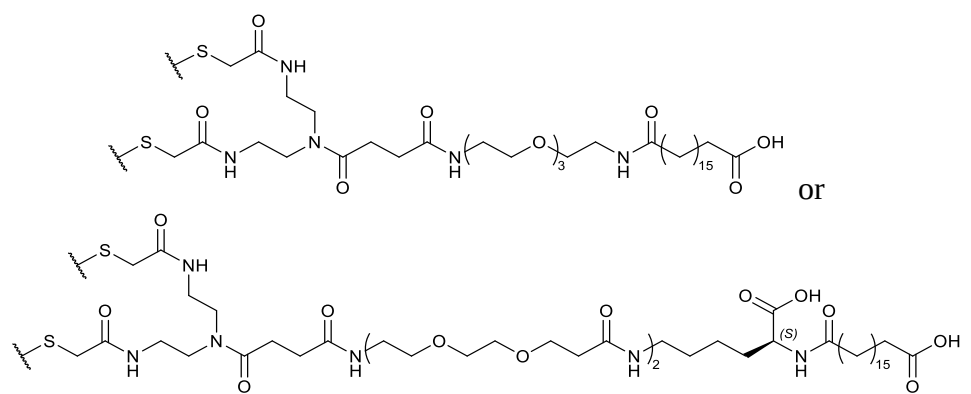




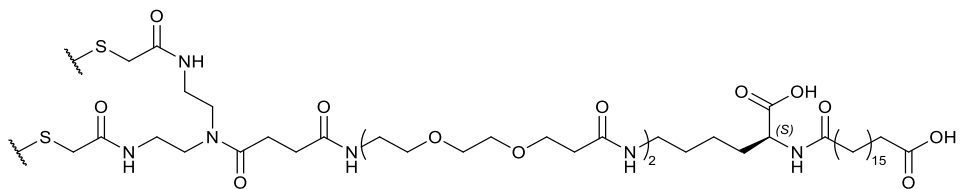
42. The peptide conjugate of claim 1, wherein the peptide conjugate comprises the structure:



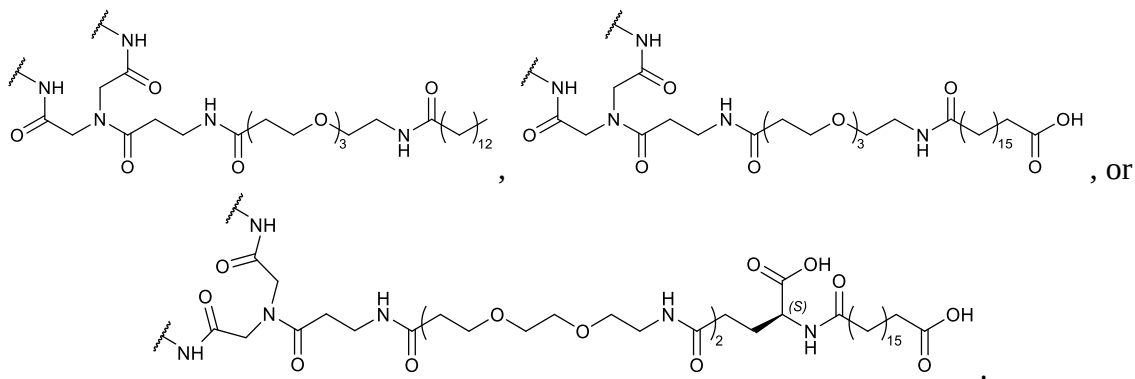
43. The peptide conjugate of claim 1, wherein the peptide conjugate comprises the structure:



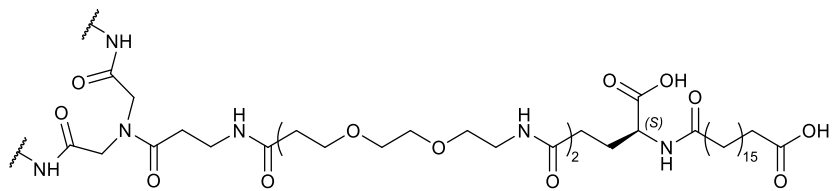
44. The peptide conjugate of claim 1, wherein the peptide conjugate comprises the structure:



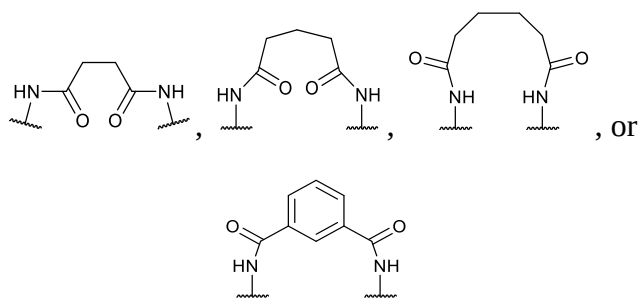
45. The peptide conjugate of claim 1, wherein the peptide conjugate comprises the structure:



46. The peptide conjugate of claim 1, wherein the peptide conjugate comprises the structure:

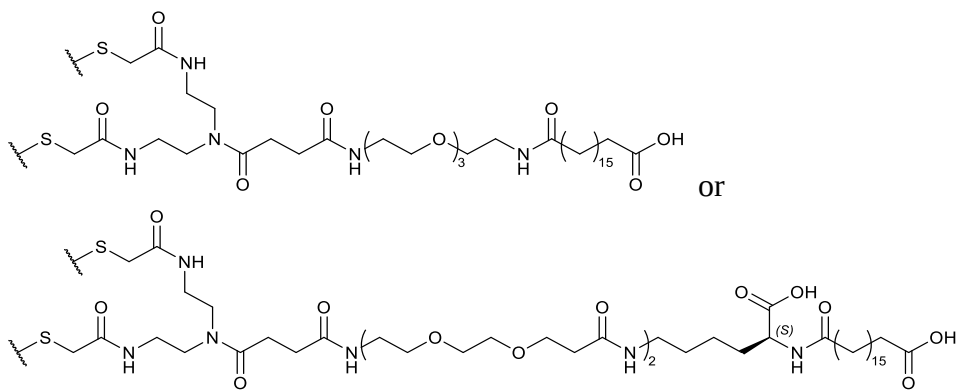


47. The peptide conjugate of claim 1, wherein the peptide conjugate comprises the structure:



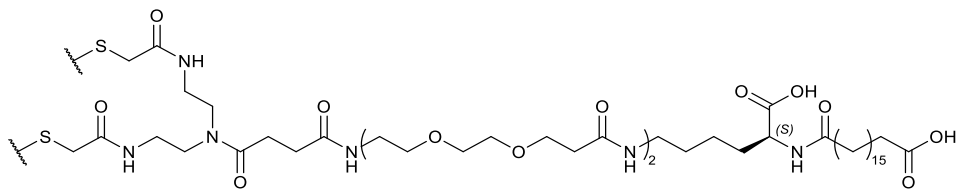
48. The peptide conjugate of claim 1, wherein the peptide conjugate comprises:

- a peptide comprising a sequence that is any one of SEQ ID NOs: 21, 1, 23, 3, 22, and 2; and
- a staple attached to the peptide at a first cysteine and a second cysteine having the following structure (“S” being part of the first cysteine or the second cysteine):



49. A peptide conjugate comprising:

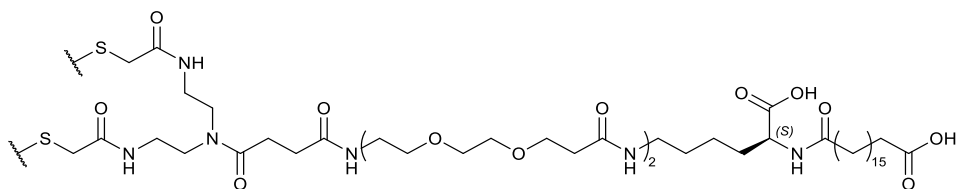
- a peptide comprising SEQ ID NO: 1; and
- a staple attached to the peptide at the first cysteine of SEQ ID NO: 1 and the second cysteine of SEQ ID NO: 1, wherein the staple has the following structure (each “S” being part of the first cysteine or the second cysteine of SEQ ID NO: 1):



50. A peptide conjugate comprising:

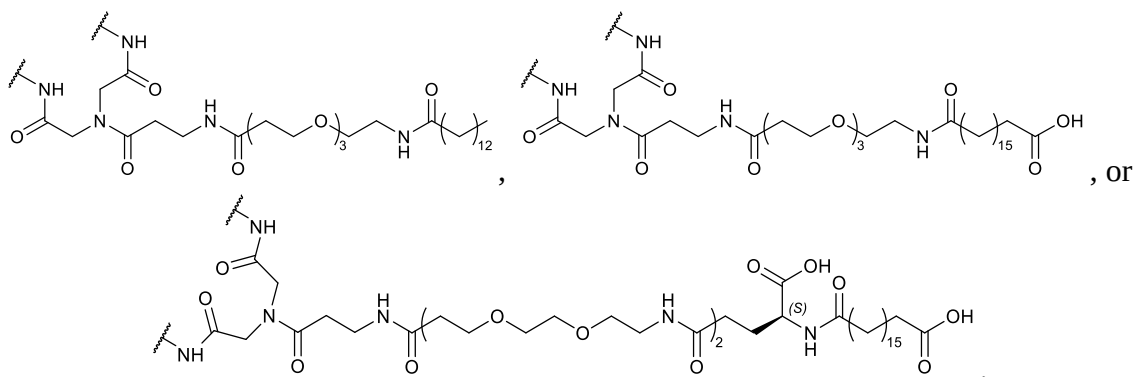
- a peptide comprising SEQ ID NO: 2 or 22; and

- b) a staple attached to the peptide at the first cysteine of SEQ ID NO: 2 or 22 and the second cysteine of SEQ ID NO: 2 or 22, wherein the staple has the following structure (each “S” being part of the first cysteine or the second cysteine of SEQ ID NO: 2 or 22):



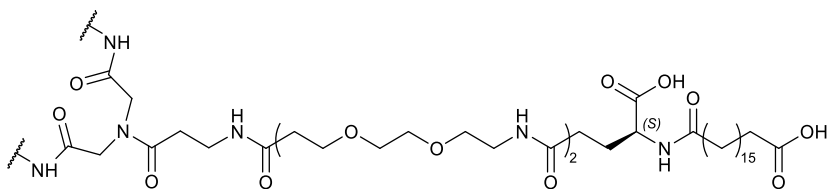
51. A peptide conjugate comprising:

- a peptide comprising any one of SEQ ID NOs: 10-20, 30-40; and
- a staple attached to the peptide at a first lysine and a second lysine having the following structure (each “NH” being part of the first lysine or the second lysine):

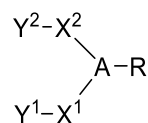


52. A peptide conjugate comprising:

- a peptide comprising SEQ ID NO: 30 or 10, wherein the amino acid at position 10 is L-Norleucine; and
- a staple attached to the peptide at a first lysine and a second lysine having the following structure (each “NH” being part of the first lysine or the second lysine):



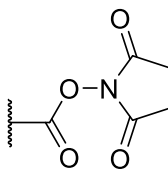
53. A pharmaceutical composition comprising the peptide conjugate of claim 1 or claim 49 and a pharmaceutically acceptable excipient.
54. The peptide conjugate of claim 1 or claim 49, for use as a medicament in treating a disease or condition in a subject in need thereof.
55. Use of the peptide conjugate of claim 1 or claim 49 in the manufacture of a medicament for treating diabetes or obesity, or a medical condition associated with diabetes or obesity.
56. Use of the peptide conjugate of claim 1 or claim 49 in the manufacture of a medicament for treating non-alcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), or cardiovascular disease.
57. Use of the peptide conjugate of claim 1 or claim 49 in the manufacture of a medicament for treating a gastrointestinal (GI) disorder.
58. The use of claim 57, wherein the gastrointestinal (GI) disorder is short bowel syndrome (SBS), inflammatory bowel syndrome (IBS), or inflammatory bowel diseases (IBD).
59. The use of claim 58, wherein the inflammatory bowel diseases (IBD) is Crohn's disease.
60. The use of claim 58, wherein the inflammatory bowel diseases (IBD) is ulcerative colitis.
61. Use of the peptide conjugate of claim 1 or claim 49 in the manufacture of a medicament for treating psoriasis.
62. Use of the peptide conjugate of claim 1 or claim 49 in the manufacture of a medicament for treating Alzheimer's disease, Parkinson's disease, or Huntington's disease.
63. The use of claim 54, wherein the subject in need thereof is undergoing chemotherapy.
64. Use of the peptide conjugate of claim 1 or claim 49 in the manufacture of a medicament for treating radiation-induced GI mucositis.
65. Use of the peptide conjugate of claim 1 or claim 49 in the manufacture of a medicament for treating chemotherapy-induced diarrhea (CID).
66. Use of the peptide conjugate of claim 1 or claim 49 in the manufacture of a medicament for treating total parenteral nutrition (TPN) induced intestinal atrophy.
67. A staple of Formula:



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-, or -alkylene-C(=O)NR³-alkylene-;



Y¹ and Y² are independently halogen, -COOH, , or are independently the -S- of a sulfhydryl-containing amino acid in a peptide or are independently -CONH- wherein the -NH- is part of an amine-containing amino acid in the peptide;

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, -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); and

s is 0-20;

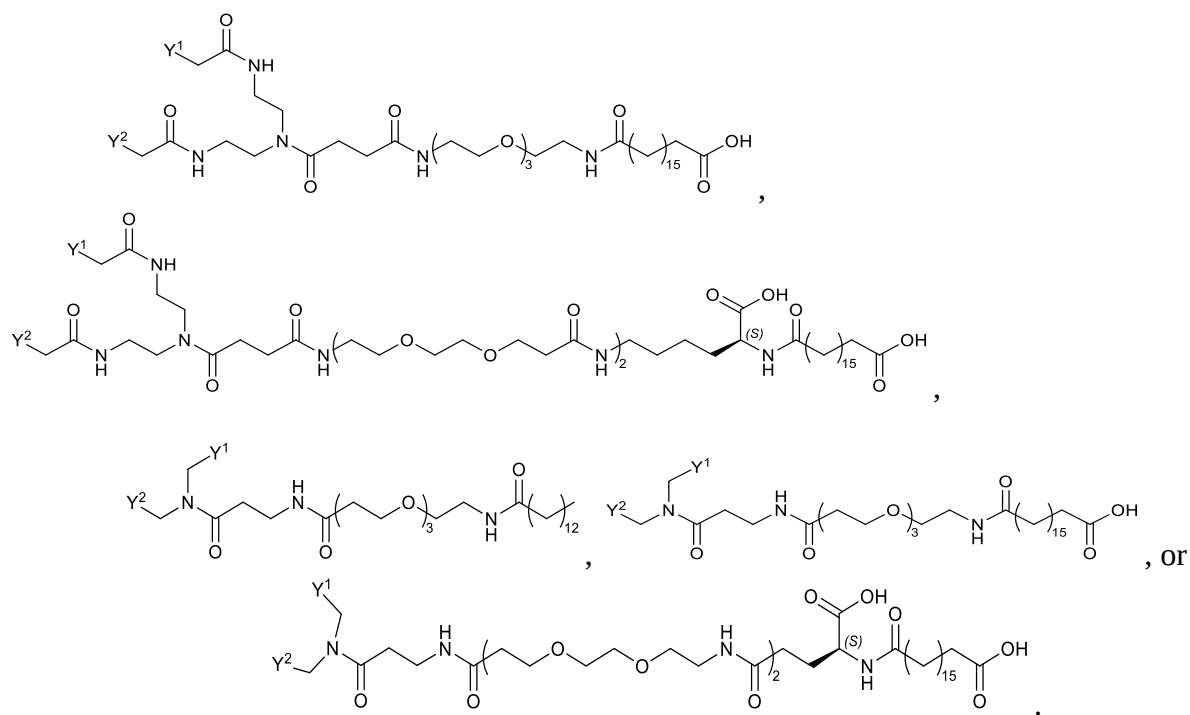
R^a is hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, C₃-C₈ cycloalkyl, C₂-C₈ heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, -OH, -OMe, or -NH₂; and the cycloalkyl, heterocycloalkyl,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

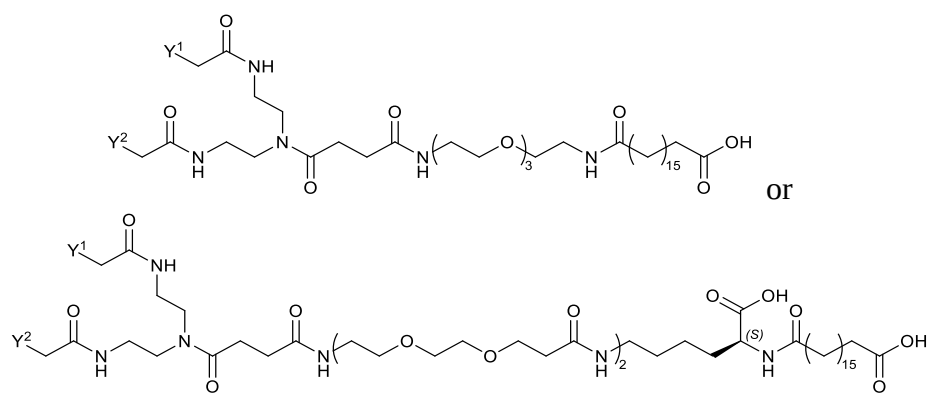
each R^c and R^d is independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, C₃-C₈ cycloalkyl, C₂-C₈ heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, -OH, -OMe, or -NH₂;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

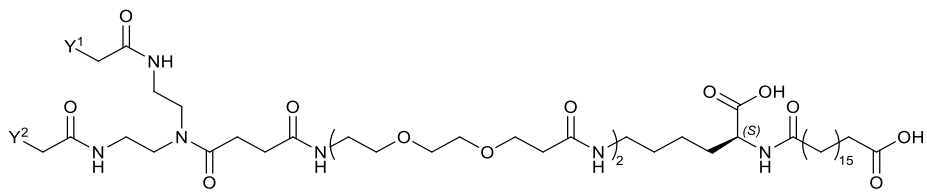
68. The staple of claim 67, wherein Y¹ and Y² are independently the -S- of two sulfhydryl-containing amino acids in the peptide.
69. The staple of claim 68, wherein Y¹ and Y² are 7 amino acid apart.
70. The staple of claim 67, wherein Y¹ and Y² are independently -CONH- wherein each -NH- is part of one of two amine-containing amino acids in the peptide.
71. The staple of claim 69, wherein Y¹ and Y² are 7 amino acids apart.
72. The staple of claim 67, 68, or 70, having the structure:



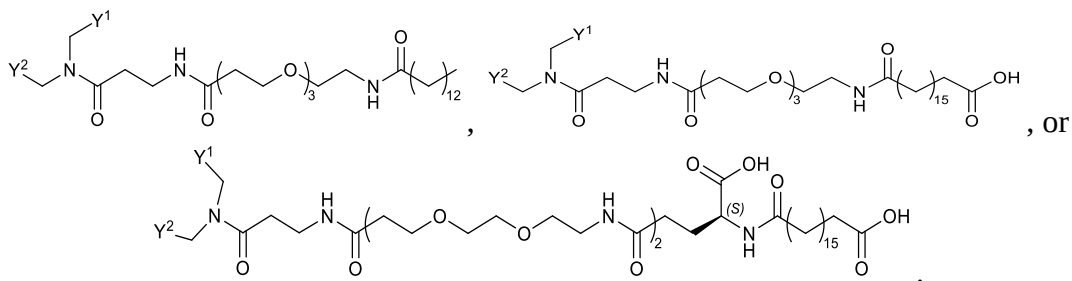
73. The staple of claim 67, 68, or 70, having the structure:



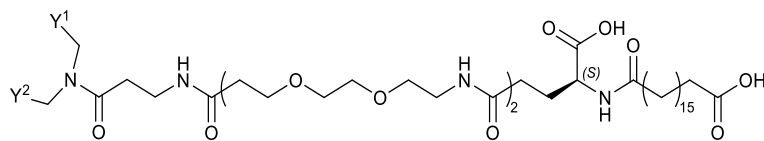
74. The staple of claim 67, 68, or 70, having the structure:



75. The staple of claim 67, 68, or 70, having the structure:



76. The staple of claim 67, 68, or 70, having the structure:



77. A peptide sequence that is SEQ ID NO: 2, 3, 4, 5, 6, 7, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20.