

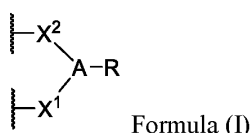
CLAIMS

What is claimed is:

1. A peptide conjugate comprising:
 - a) a peptide that modulates the GLP-2 receptor; and
 - b) a staple attached to the peptide at a first amino acid and a second amino acid.
2. The peptide conjugate of claim 1, wherein the first amino acid and the second amino acid are independently an amine-containing amino acid or a sulfhydryl-containing amino acid.
3. The peptide conjugate of claim 1 or 2, wherein the first amino acid and second amino acid is independently cysteine, homocysteine, 2-amino-5-mercaptopentanoic acid, or 2-amino-6-mercaptohexanoic acid.
4. The peptide conjugate of any one of claims 1-3, wherein the first amino acid and second amino acid are cysteines.
5. The peptide conjugate of claim 1 or 2, wherein the first amino acid and second amino acid is independently lysine, ornithine, diaminobutyric acid, diaminopropionic acid, or homolysine.
6. The peptide conjugate of any one of claims 1 or 2 or 5, wherein the first amino acid and second amino acid are lysines.
7. The peptide conjugate of any one of claims 1 or 2 or 5, wherein the first amino acid and second amino acid are ornithine.
8. The peptide conjugate of any one of claims 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 claims 1-8, 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 4-10.
10. The peptide conjugate of any one of claims 1-9, 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 6-8.
11. The peptide conjugate of any one of claims 1-10, 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.
12. The peptide conjugate of any one of claims 1-11, wherein the peptide comprises a sequence having at least about 80% identity to any one of SEQ ID NOs: 1-9, 21-29.
13. The peptide conjugate of any one of claims 1-11, wherein the peptide comprises a sequence having at least about 90% identity to any one of SEQ ID NOs: 1-9, 21-29.
14. The peptide conjugate of any one of claims 1-11, wherein the peptide comprises a sequence having at least about 95% identity to any one of SEQ ID NOs: 1-9, 21-29.
15. The peptide conjugate of any one of claims 1-11, wherein the peptide comprises a sequence having at least about 99% identity to any one of SEQ ID NOs: 1-9, 21-29.
16. The peptide conjugate of any one of claims 1-11, wherein the peptide comprises a sequence that is any one of SEQ ID NOs: 1-9, 21-29.
17. The peptide conjugate of any one of claims 1-11, wherein the peptide comprises a sequence having at least about 80% identity to SEQ ID NO: 1 or 21.

18. The peptide conjugate of any one of claims 1-11, wherein the peptide comprises a sequence having at least about 90% identity to SEQ ID NO: 1 or 21.
19. The peptide conjugate of any one of claims 1-11, wherein the peptide comprises a sequence having at least about 95% identity to SEQ ID NO: 1 or 21.
20. The peptide conjugate of any one of claims 1-11, wherein the peptide comprises a sequence having at least about 99% identity to SEQ ID NO: 1 or 21.
21. The peptide conjugate of any one of claims 1-11, wherein the peptide comprises a sequence that is SEQ ID NO: 1 or 21.
22. The peptide conjugate of any one of claims 1-11, wherein the peptide comprises a sequence having at least about 80% identity to SEQ ID NO: 2 or 22.
23. The peptide conjugate of any one of claims 1-11, wherein the peptide comprises a sequence having at least about 90% identity to SEQ ID NO: 2 or 22.
24. The peptide conjugate of any one of claims 1-11, wherein the peptide comprises a sequence having at least about 95% identity to SEQ ID NO: 2 or 22.
25. The peptide conjugate of any one of claims 1-11, wherein the peptide comprises a sequence having at least about 99% identity to SEQ ID NO: 2 or 22.
26. The peptide conjugate of any one of claims 1-11, wherein the peptide comprises a sequence that is SEQ ID NO: 2 or 22.
27. The peptide conjugate of any one of claims 1-11, wherein the peptide comprises a sequence having at least about 80% identity to any one of SEQ ID NOs: 10-20, 30-40.
28. The peptide conjugate of any one of claims 1-11, wherein the peptide comprises a sequence having at least about 90% identity to any one of SEQ ID NOs: 10-20, 30-40.
29. The peptide conjugate of any one of claims 1-11, wherein the peptide comprises a sequence having at least about 95% identity to any one of SEQ ID NOs: 10-20, 30-40.
30. The peptide conjugate of any one of claims 1-11, wherein the peptide comprises a sequence having at least about 99% identity to any one of SEQ ID NOs: 10-20, 30-40.
31. The peptide conjugate of any one of claims 1-11, wherein the peptide comprises a sequence that is any one of SEQ ID NOs: 10-20, 30-40.
32. The peptide conjugate of any one of claims 1-11, wherein the peptide comprises a sequence having at least about 80% identity to SEQ ID NO: 10 or 30.
33. The peptide conjugate of any one of claims 1-11, wherein the peptide comprises a sequence having at least about 90% identity to SEQ ID NO: 10 or 30.
34. The peptide conjugate of any one of claims 1-11, wherein the peptide comprises a sequence having at least about 95% identity to SEQ ID NO: 10 or 30.
35. The peptide conjugate of any one of claims 1-11, wherein the peptide comprises a sequence having at least about 99% identity to SEQ ID NO: 10 or 30.
36. The peptide conjugate of any one of claims 1-11, wherein the peptide comprises a sequence that is SEQ ID NO: 10 or 30.

37. The peptide conjugate of any one of claims 1-36, 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.
38. The peptide conjugate of any one of claims 1-36, 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.
39. The peptide conjugate of any one of claims 1-36, 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.
40. The peptide conjugate of any one of claims 1-36, wherein the binding affinity of the peptide conjugate is within about 5% of the binding affinity of an unmodified form of the peptide.
41. The peptide conjugate of any one of claims 1-36, wherein the binding affinity of the peptide conjugate is within about 10% of the binding affinity of an unmodified form of the peptide.
42. The peptide conjugate of any one of claims 1-36, wherein the binding affinity of the peptide conjugate is within about 15% of the binding affinity of an unmodified form of the peptide.
43. The peptide conjugate of any one of claims 1-36, wherein the binding affinity of the peptide conjugate is within about 20% of the binding affinity of an unmodified form of the peptide.
44. The peptide conjugate of any one of claims 1-43, 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 -(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, $-S(=O)R^b$, $-S(=O)_2R^a$, $-S(=O)NR^cR^d$, $-C(=O)R^b$, $-CO_2R^a$, -

$C(=O)NR^cR^d$, 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, $-CO_2H$, $-CO_2(C_1-C_6 \text{ alkyl})$, $-CO_2NH_2$, $-CO_2N(\text{alkyl})_2$, 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 $-NH_2$; 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 $-NH_2$;

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 $-NH_2$; 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 $-NH_2$;

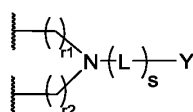
each R^c and R^d is independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, C₃-C₈ cycloalkyl, C₂-C₈ heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one, two, or three of halogen, $-OH$, $-OMe$, or $-NH_2$; 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 $-NH_2$;

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, C₁-C₆ alkyl, C₁-C₆ haloalkyl, $-OH$, $-OMe$, or $-NH_2$.

45. The peptide conjugate of claim 44, wherein A is optionally substituted alkylene.
46. The peptide conjugate of claim 44 or 45, wherein A is $-(CH_2)_t-$, wherein t is 1-12.
47. The peptide conjugate of claim 44, wherein A is optionally substituted arylene.
48. The peptide conjugate of claim 44, wherein A is $-NR^3$ -alkylene- NR^3 -.
49. The peptide conjugate of claim 44, wherein A is $-N-$.
50. The peptide conjugate of any one of claims 44-49, wherein X¹ and X² are $-C(=O)-$.

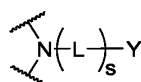
51. The peptide conjugate of any one of claims 44-49, wherein X^1 and X^2 are -alkylene-C(=O)-.
52. The peptide conjugate of any one of claims 44-49, wherein X^1 and X^2 are -CH₂-C(=O)-.
53. The peptide conjugate of any one of claims 44-49, wherein X^1 and X^2 are independently -alkylene-C(=O)NR³-.
54. The peptide conjugate of any one of claims 44-49, wherein X^1 and X^2 are independently -CH₂-C(=O)NR³-.
55. The peptide conjugate of any one of claims 44-49, wherein X^1 and X^2 are independently -alkylene-C(=O)NR³-alkylene-.
56. The peptide conjugate of any one of claims 44-49, wherein X^1 and X^2 are independently -CH₂-C(=O)NR³-CH₂CH₂-.

57. The peptide conjugate of any one of claims 44-56, wherein >A-R has the following structure:

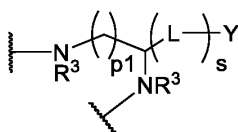


wherein r_1 and r_2 are each independently 0-4.

58. The peptide conjugate of any one of claims 44-56, wherein >A-R has the following structure:

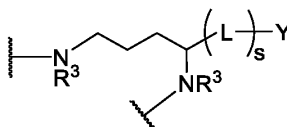


59. The peptide conjugate of any one of claims 44-56, wherein >A-R has the following structure:

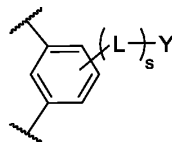


wherein p_1 is 1-5.

60. The peptide conjugate of any one of claims 44-56, wherein >A-R has the following structure:



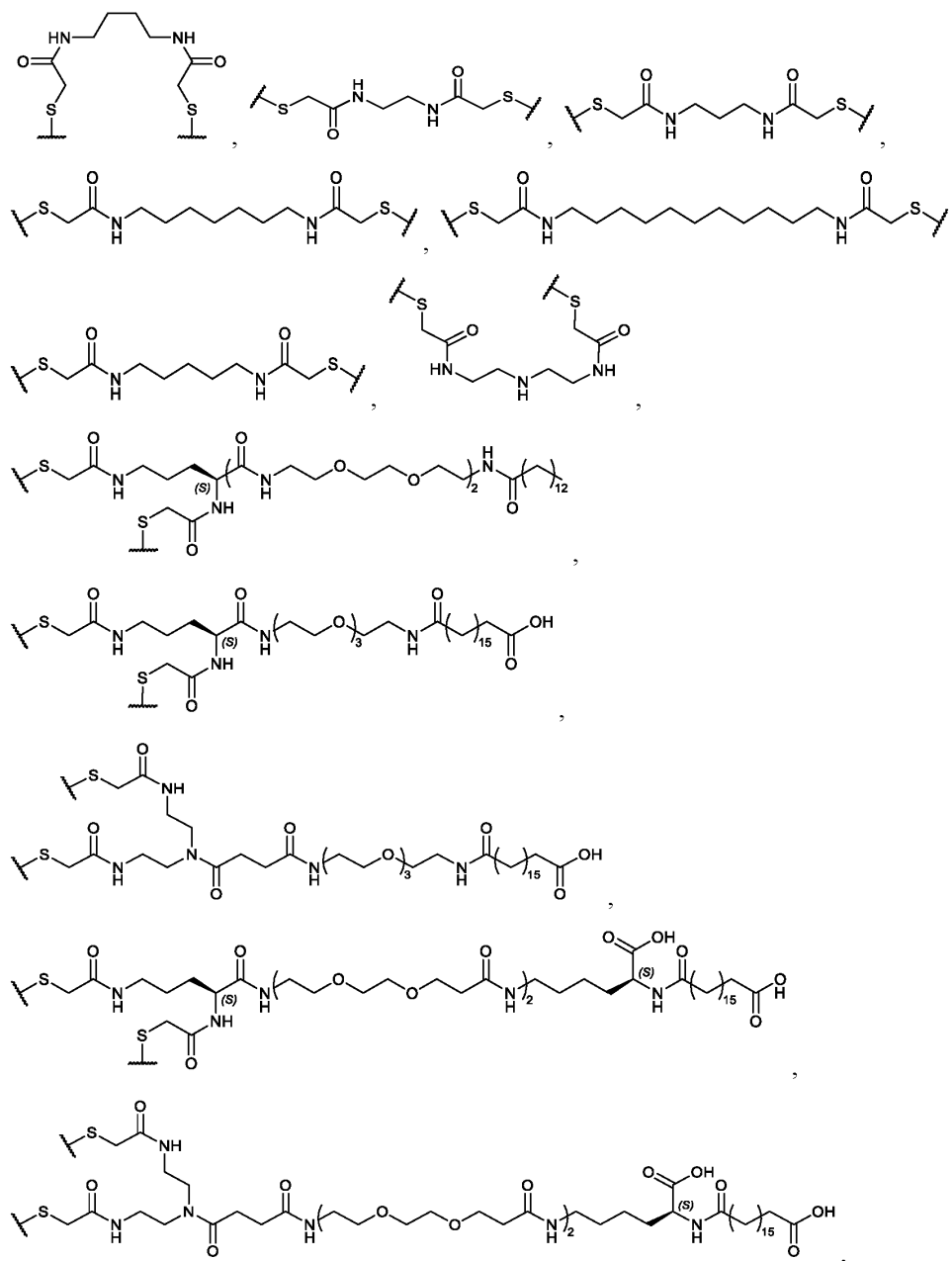
61. The peptide conjugate of any one of claims 44-56, wherein >A-R has the following structure:

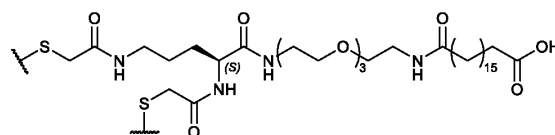
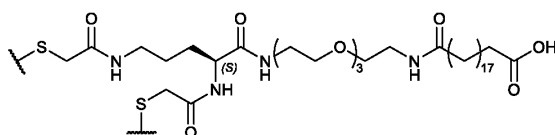
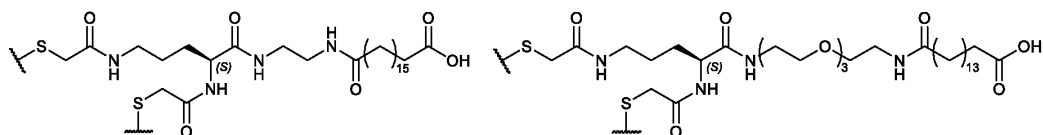
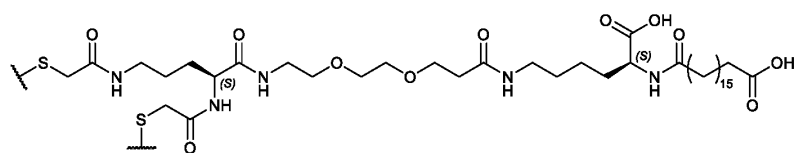
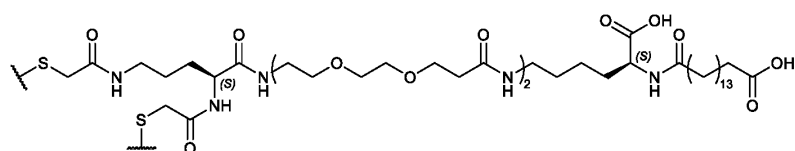
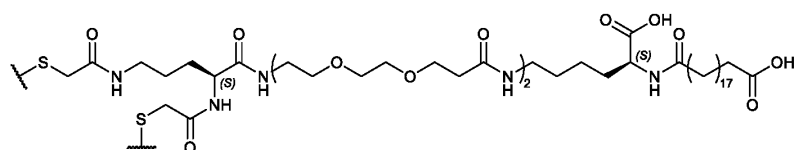
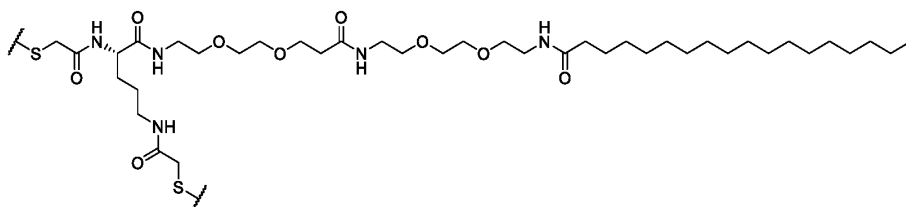
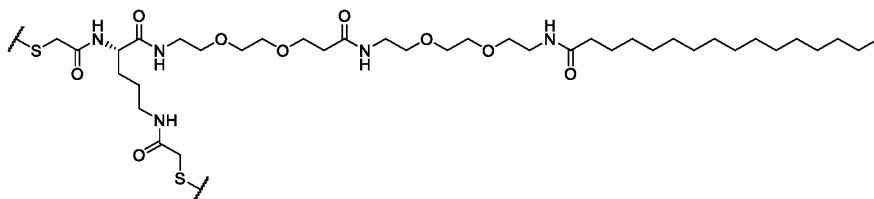


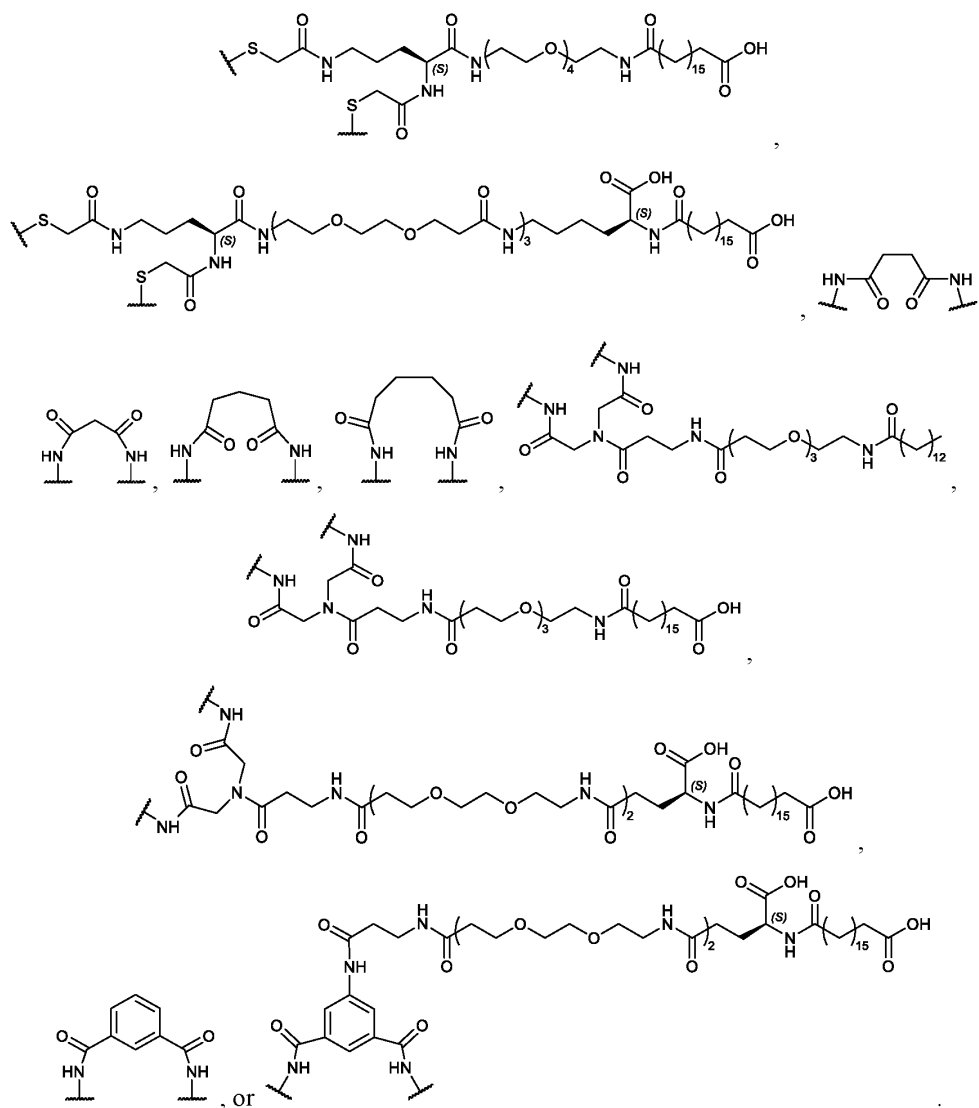
62. The peptide conjugate of any one of claims 44-61, wherein s is 1-15.
63. The peptide conjugate of any one of claims 44-62, wherein s is 1-10.
64. The peptide conjugate of any one of claims 44-62, wherein s is 5-15.
65. The peptide conjugate of any one of claims 44-62, wherein s is 5-10.
66. The peptide conjugate of any one of claims 44-65, wherein Y is hydrogen or -CO₂H.

67. The peptide conjugate of any one of claims 44-66, 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.

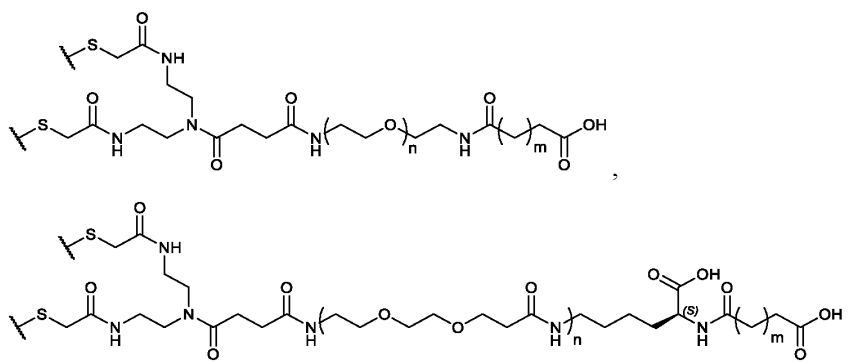
68. The peptide conjugate of claim 1, wherein the peptide conjugate comprises the structure:

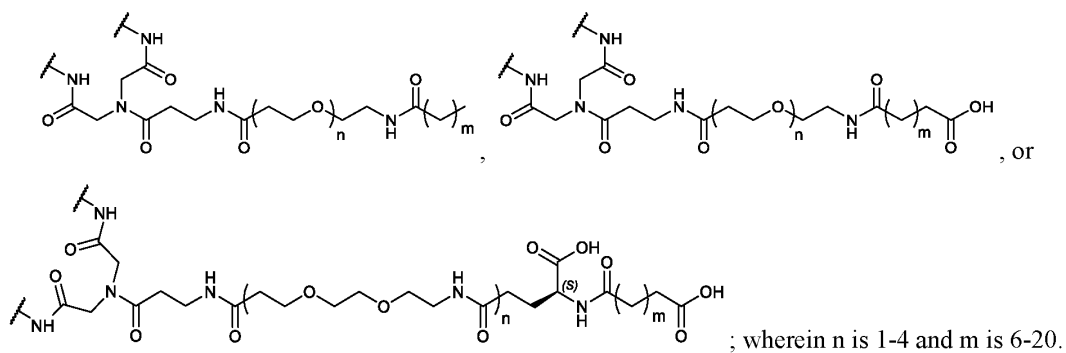




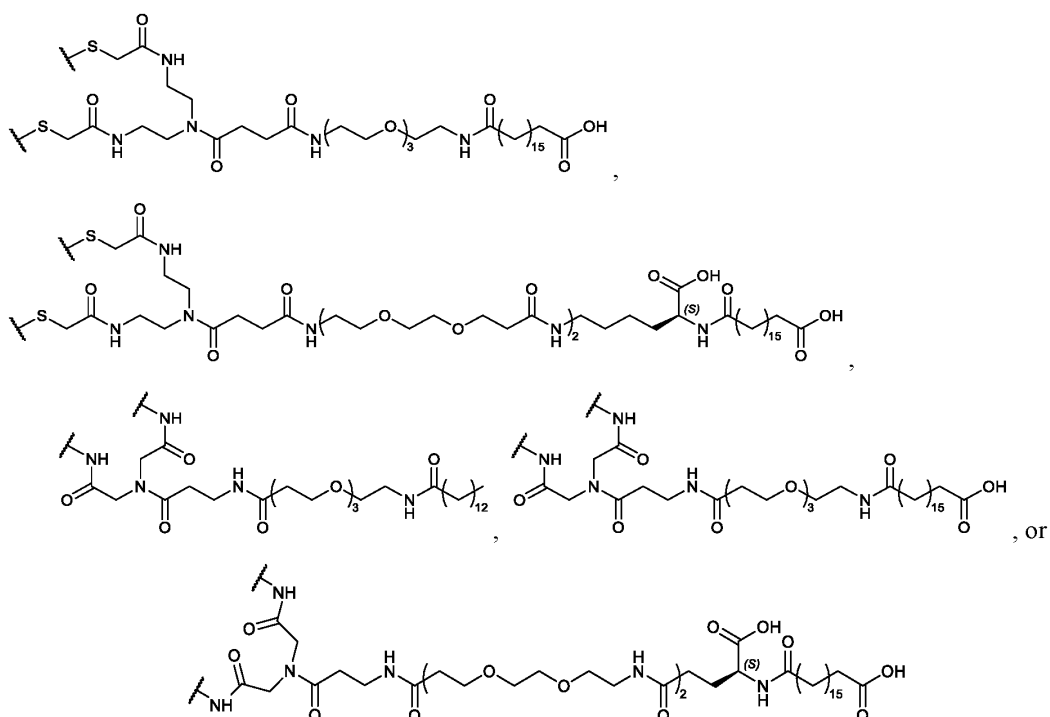


69. The peptide conjugate of claim 1, wherein the peptide conjugate comprises the structure:

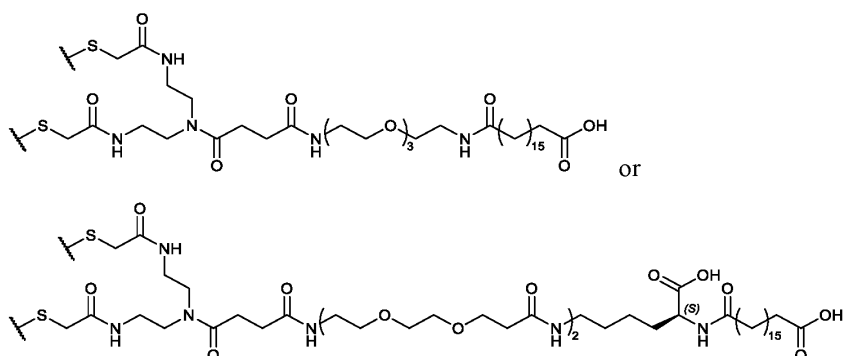




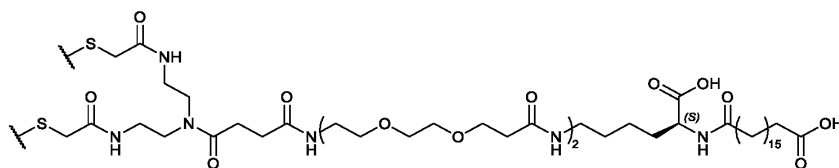
70. The peptide conjugate of claim 1, wherein the peptide conjugate comprises the structure:



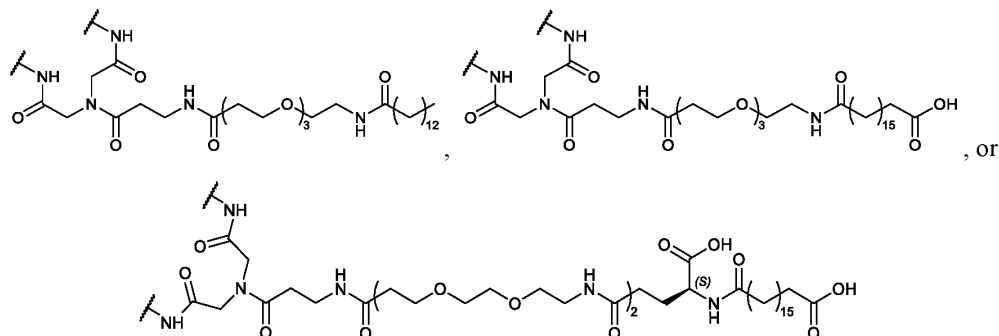
71. The peptide conjugate of claim 1, wherein the peptide conjugate comprises the structure:



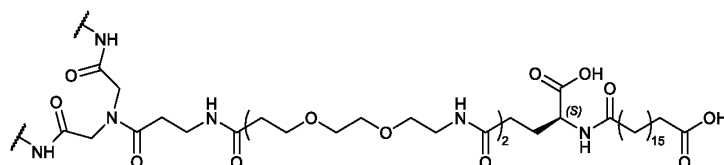
72. The peptide conjugate of claim 1, wherein the peptide conjugate comprises the structure:



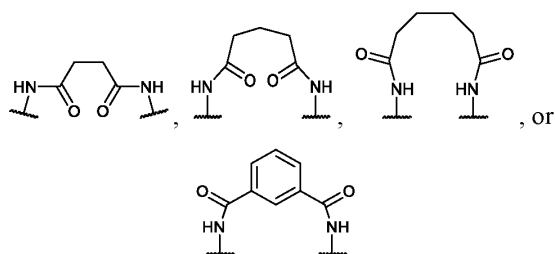
73. The peptide conjugate of claim 1, wherein the peptide conjugate comprises the structure:



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

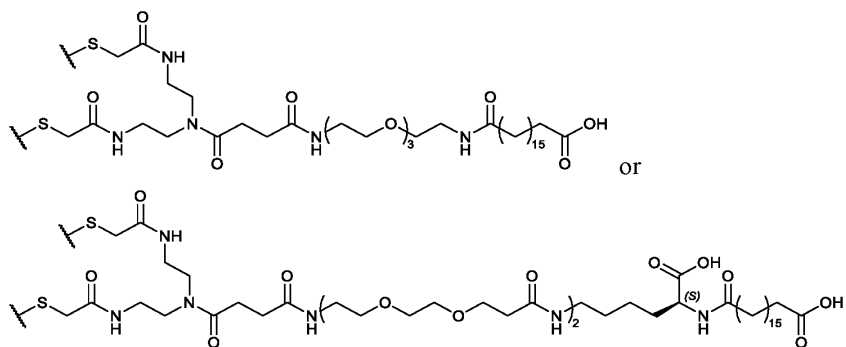


75. The peptide conjugate of claim 1, wherein the peptide conjugate comprises the structure:



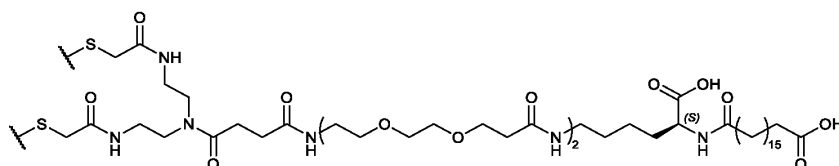
76. The peptide conjugate of claim 1, wherein the peptide conjugate comprises:

- a peptide that modulates the GLP-2 receptor comprising a sequence that is any one of SEQ ID NOs: 1-9, 21-29; and
- a staple attached to the peptide at a first cysteine and a second cysteine having the following structure ("S" being part of the cysteine residue):



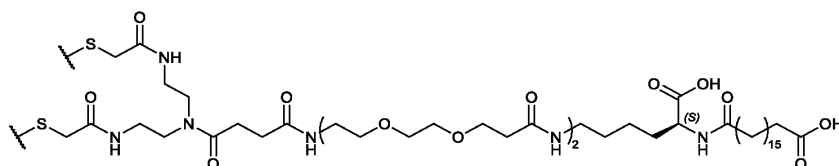
77. The peptide conjugate of claim 1, wherein the peptide conjugate comprises:

- a) a peptide that modulates the GLP-2 receptor comprising a sequence that is SEQ ID NO: 1 or 21;
and
- b) a staple attached to the peptide at a first cysteine and a second cysteine having the following structure ("S" being part of the cysteine residue):



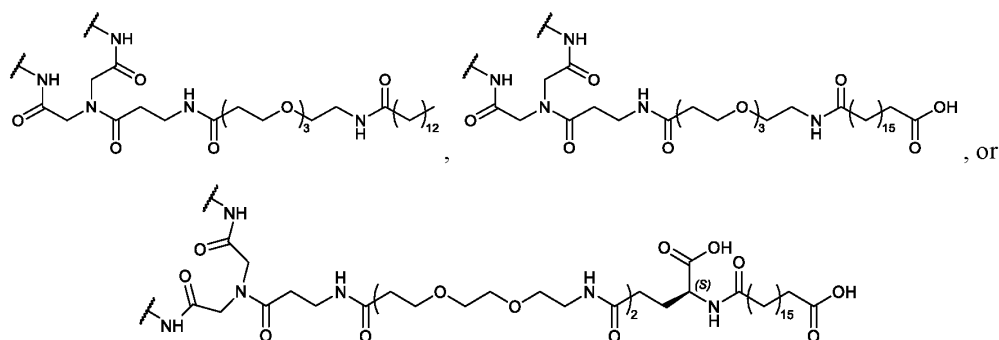
78. The peptide conjugate of claim 1, wherein the peptide conjugate comprises:

- a) a peptide that modulates the GLP-2 receptor comprising a sequence that is SEQ ID NO: 2 or 22;
and
- b) a staple attached to the peptide at a first cysteine and a second cysteine having the following structure ("S" being part of the cysteine residue):

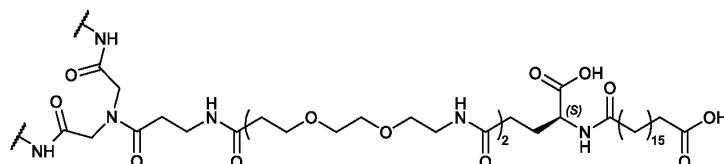


79. The peptide conjugate of claim 1, wherein the peptide conjugate comprises:

- a) a peptide that modulates the GLP-2 receptor comprising a sequence that is any one of SEQ ID NOs: 10-20, 30-40; and
- b) a staple attached to the peptide at a first lysine and a second lysine having the following structure ("NH" being part of the lysine residue):

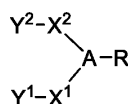


80. The peptide conjugate of claim 1, wherein the peptide conjugate comprises:
- a peptide that modulates the GLP-2 receptor comprising a sequence that is SEQ ID NO: 10 or 30; and
 - a staple attached to the peptide at a first lysine and a second lysine having the following structure (“NH” being part of the lysine residue):



- A pharmaceutical composition comprising the peptide conjugate of any one of claims 1-80 and a pharmaceutically acceptable excipient.
- 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 claims 1-80.
- The method of claim 81, wherein the disease or condition is diabetes or obesity, or a medical condition associated with diabetes or obesity.
- The method of claim 82, wherein the disease or condition is non-alcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), or cardiovascular disease.
- The method of claim 82, wherein the disease or condition is a gastrointestinal (GI) disorder.
- The method of claim 85, wherein the gastrointestinal (GI) disorder is short bowel syndrome (SBS), inflammatory bowel syndrome (IBS), or inflammatory bowel diseases (IBD).
- The method of claim 86, wherein the inflammatory bowel diseases (IBD) is Crohn's disease.
- The method of claim 86, wherein the inflammatory bowel diseases (IBD) is ulcerative colitis.
- The method of claim 82, wherein the disease or condition is psoriasis.
- The method of claim 82, wherein the disease or condition is Alzheimer's disease, Parkinson's disease, or Huntington's disease.
- The method of claim 82, wherein the subject in need thereof is undergoing chemotherapy.
- The method of claim 82, wherein the subject in need thereof has radiation-induced GI mucositis.

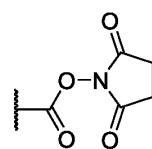
93. The method of claim 82, wherein the subject in need thereof has chemotherapy-induced diarrhea (CID).
94. The method of claim 82, wherein the subject in need thereof has total parenteral nutrition (TPN) induced intestinal atrophy.
95. A staple of Formula:

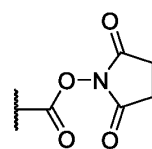


wherein

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 or -CONH- wherein the -NH- is part of an amine-containing amino acid in a peptide that modulates the GLP-2 receptor;

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 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.

96. The staple of claim 95, wherein A is optionally substituted alkylene.

97. The staple of claim 95 or 96, wherein A is -(CH₂)_t-, wherein t is 1-12.

98. The staple of claim 95, wherein A is optionally substituted arylene.

99. The staple of claim 95, wherein A is -NR³-alkylene-NR³-.

100. The staple of claim 95, wherein A is -N-.

101. The staple of any one of claims 95-100, wherein X¹ and X² are -C(=O)-.

102. The staple of any one of claims 95-100, wherein X¹ and X² are -alkylene-C(=O)-.

103. The staple of any one of claims 95-100, wherein X¹ and X² are -CH₂-C(=O)-.

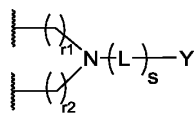
104. The staple of any one of claims 95-100, wherein X¹ and X² are independently -alkylene-C(=O)NR³-.

105. The staple of any one of claims 95-100, wherein X¹ and X² are independently -CH₂-C(=O)NR³-.

106. The staple of any one of claims 95-100, wherein X¹ and X² are independently -alkylene-C(=O)NR³-alkylene-.

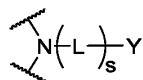
107. The staple of any one of claims 95-100, wherein X^1 and X^2 are independently $-\text{CH}_2-\text{C}(=\text{O})\text{NR}^3-\text{CH}_2\text{CH}_2-$.

108. The staple of any one of claims 95-107, wherein $>\text{A}-\text{R}$ has the following structure:

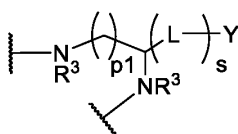


wherein r_1 and r_2 are each independently 0-4.

109. The staple of any one of claims 95-107, wherein $>\text{A}-\text{R}$ has the following structure:

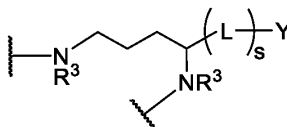


110. The staple of any one of claims 95-107, wherein $>\text{A}-\text{R}$ has the following structure:

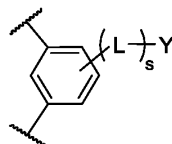


wherein p_1 is 1-5.

111. The staple of any one of claims 95-107, wherein $>\text{A}-\text{R}$ has the following structure:



112. The staple of any one of claims 95-107, wherein $>\text{A}-\text{R}$ has the following structure:



113. The staple of any one of claims 95-112, wherein s is 1-15.

114. The staple of any one of claims 95-113, wherein s is 1-10.

115. The staple of any one of claims 95-113, wherein s is 5-15.

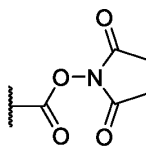
116. The staple of any one of claims 95-113, wherein s is 5-10.

117. The staple of any one of claims 95-116, wherein Y is hydrogen or $-\text{CO}_2\text{H}$.

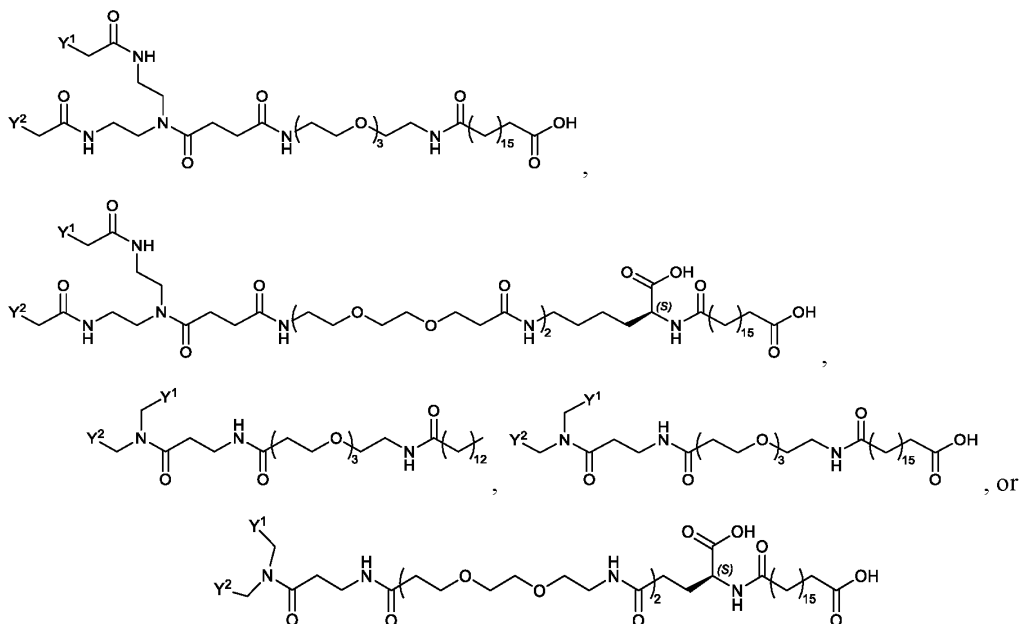
118. The staple of any one of claims 95-117, wherein each L is independently $-(\text{CR}^1\text{R}^2)_v-$, -alkylene-O-, $-\text{C}(=\text{O})-$, $-\text{C}(=\text{O})\text{NR}^3-$, $-\text{NR}^3\text{C}(=\text{O})-$, -alkylene- $\text{C}(=\text{O})\text{NR}^3-$, or -alkylene- $\text{NR}^3\text{C}(=\text{O})-$; and v is 2-20.

119. The staple of claim 94-118, wherein Y^1 and Y^2 are halogen.

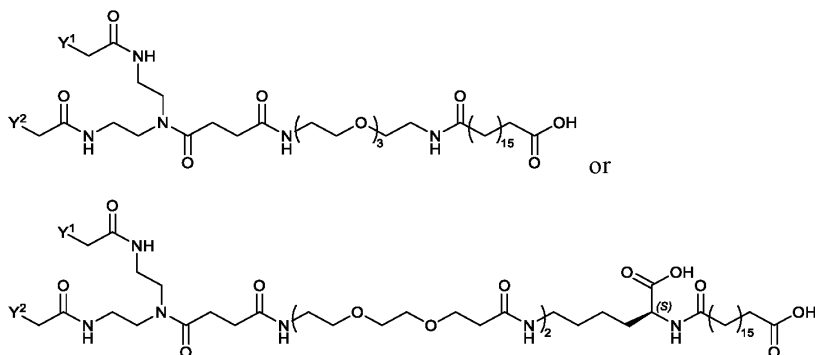
120. The staple of claim 94-118, wherein Y^1 and Y^2 are $-\text{COOH}$.



121. The staple of claim 95-118, wherein Y¹ and Y² are
122. The staple of claim 95-118, wherein Y¹ and Y² are the -S- of two sulfhydryl-containing amino acids in a peptide that modulates the GLP-2 receptor.
123. The staple of claim 95-118, wherein Y¹ and Y² are the -S- of two sulfhydryl-containing amino acids in a peptide that modulates the GLP-2 receptor which are 7 amino acid apart.
124. The staple of claim 95-118, wherein Y¹ and Y² are -CONH- wherein the -NH- is part of two amine-containing amino acids in a peptide that modulates the GLP-2 receptor.
125. The staple of claim 95-118, wherein Y¹ and Y² -CONH- wherein the -NH- is part of two amine-containing amino acids in a peptide that modulates the GLP-2 receptor which are 7 amino acids apart.
126. The staple of claim 95, having the structure:



127. The staple of claim 95, having the structure:



O=C(O)C(=O)[C@H](CCCCNC(=O)CC(C(=O)NCCC(NC(=O)CCY1)CC(=O)NCCC(=O)NCCC(=O)NCCOCOC(=O)NCCC(=O)NCCY2)CCCCC(=O)O
$$\begin{array}{c} \text{Y}^2\text{CH}_2\text{N}(\text{CH}_2\text{Y}^1)\text{C}(=\text{O})\text{CH}_2\text{C}(=\text{O})\text{NH}(\text{CH}_2)_3\text{C}(=\text{O})\text{O}(\text{CH}_2)_3\text{C}(=\text{O})\text{NH}(\text{CH}_2)_{12}\text{C}(=\text{O})\text{OH} \\ \text{Y}^2\text{CH}_2\text{N}(\text{CH}_2\text{Y}^1)\text{C}(=\text{O})\text{CH}_2\text{C}(=\text{O})\text{NH}(\text{CH}_2)_3\text{C}(=\text{O})\text{O}(\text{CH}_2)_3\text{C}(=\text{O})\text{NH}(\text{CH}_2)_{15}\text{C}(=\text{O})\text{OH} \end{array}, \text{ or}$$

$$\text{Y}^2\text{CH}_2\text{N}(\text{CH}_2\text{Y}^1)\text{C}(=\text{O})\text{CH}_2\text{C}(=\text{O})\text{NH}(\text{CH}_2)_3\text{C}(=\text{O})\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{C}(=\text{O})\text{NH}(\text{CH}_2)_2\text{CH}(\text{CH}_2)_{15}\text{C}(=\text{O})\text{OH}$$
O=C(O)CC(=O)N[C@@H](C)CCC(=O)NCCOC(CCO)CCOC(=O)NCCC(=O)N(CC)CCY1

- 114 -