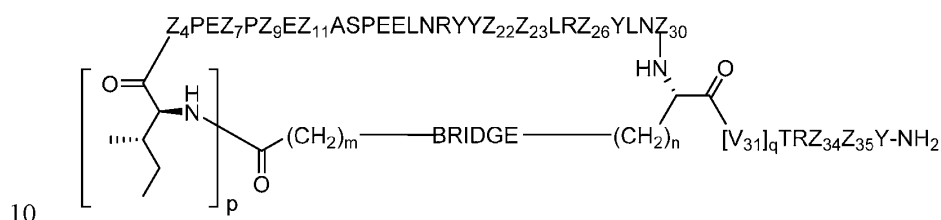


CLAIMS

It is claimed:

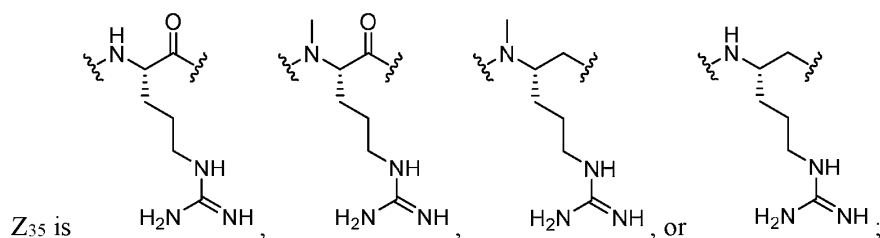
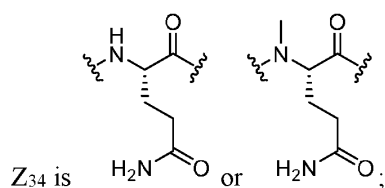
1. A conjugate comprising a glucagon-like peptide 1 (GLP-1) fusion peptide coupled to a cyclic PYY peptide, wherein the GLP-1 fusion peptide comprises a GLP-1 peptide, a first linker peptide, a hinge-Fc region peptide, and a second linker peptide, wherein the first linker peptide is optionally missing.
2. The conjugate of claim 1, wherein the cyclic PYY peptide is represented by Formula I or a derivative or pharmaceutically acceptable salt thereof:



Formula I

wherein

- p is 0 or 1;
- m is 0, 1, 2, 3, 4, or 5;
- 15 n is 1, 2, 3, or 4;
- q is 0 or 1; provided that q is 1 only when Z₃₀ is absent;
- BRIDGE is -Ph-CH₂-S-, -triazolyl-, -NHC(O)CH₂S-, -SCH₂C(O)NH-,
-(OCH₂CH₂)₂NHC(O)CH₂S-, -NHC(O)-, or -CH₂S-;
- Z₄ is K, A, E, S, or R;
- 20 Z₇ is A or K;
- Z₉ is G or K;
- Z₁₁ is D or K;
- Z₂₂ is A or K;
- Z₂₃ is S or K;
- 25 Z₂₆ is A or H;
- Z₃₀ is L, W, or absent,
provided that Z₃₀ is absent only when q is 1;



wherein the derivative is the compound of Formula I that is modified by one or more processes selected from the group consisting of amidation, acylation, and pegylation.

3. The conjugate of claim 2, wherein the cyclic PYY peptide is represented by Formula I or the derivative or pharmaceutically acceptable salt thereof, wherein:

p is 0 or 1;

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

10 n is 1, 2, 3, or 4;

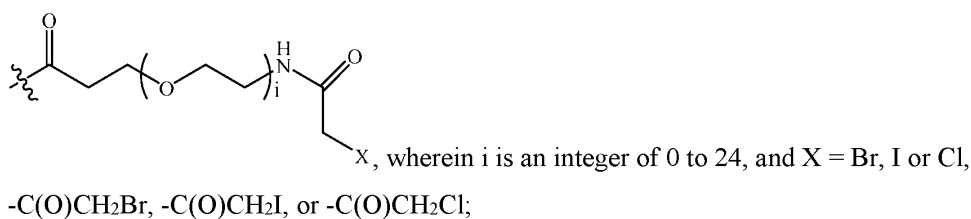
q is 0 or 1; provided that q is 1 only when Z_{30} is absent;

BRIDGE is $-\text{Ph}-\text{CH}_2-\text{S}-$, $-\text{triazolyl}-$, $-\text{NHC}(\text{O})\text{CH}_2\text{S}-$, $-\text{SCH}_2\text{C}(\text{O})\text{NH}_2-$,

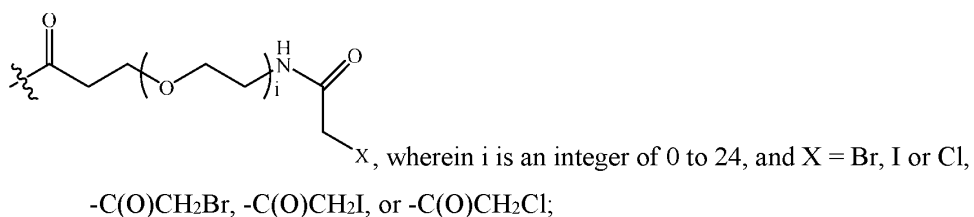
$-(\text{OCH}_2\text{CH}_2)_2\text{NHC}(\text{O})\text{CH}_2\text{S}$, $-\text{NHC}(\text{O})-$, or $-\text{CH}_2\text{S}-$;

Z_4 is K, A, E, S, or R;

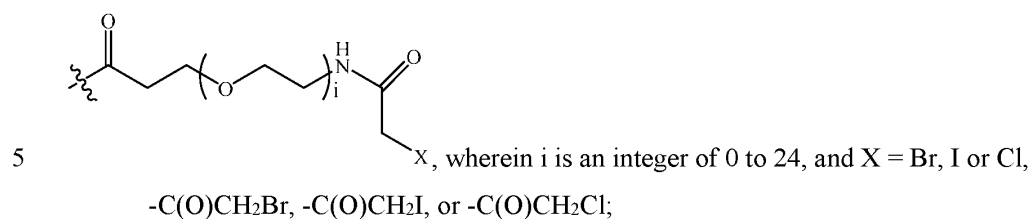
15 Z_7 is A or K, wherein the amino side chain of said K is optionally substituted with



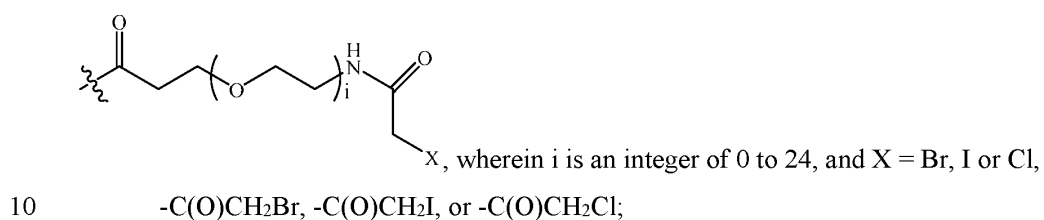
Z_9 is G or K, wherein the amino side chain of said K is optionally substituted with



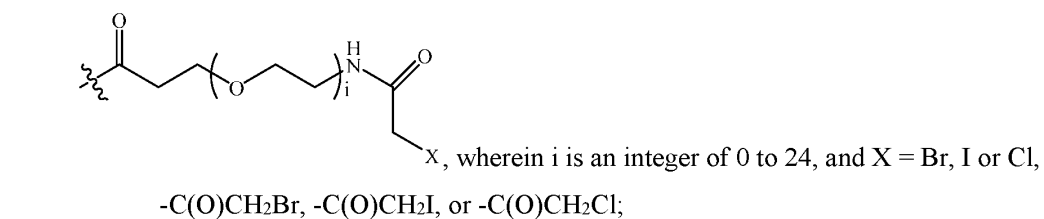
Z_{11} is D or K, wherein the amino side chain of said K is optionally substituted with



Z_{22} is A or K, wherein the amino side chain of said K is optionally substituted with

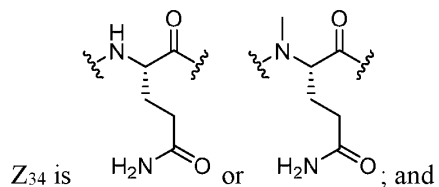


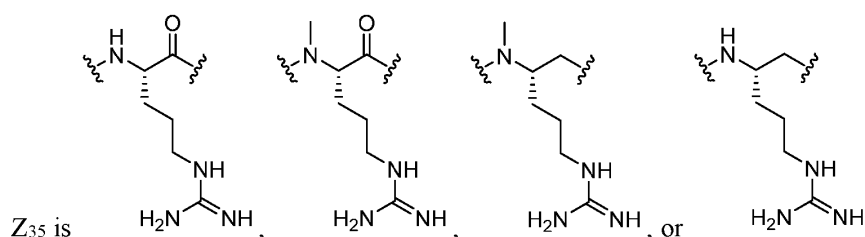
Z_{23} is S or K, wherein the amino side chain of said K is optionally substituted with



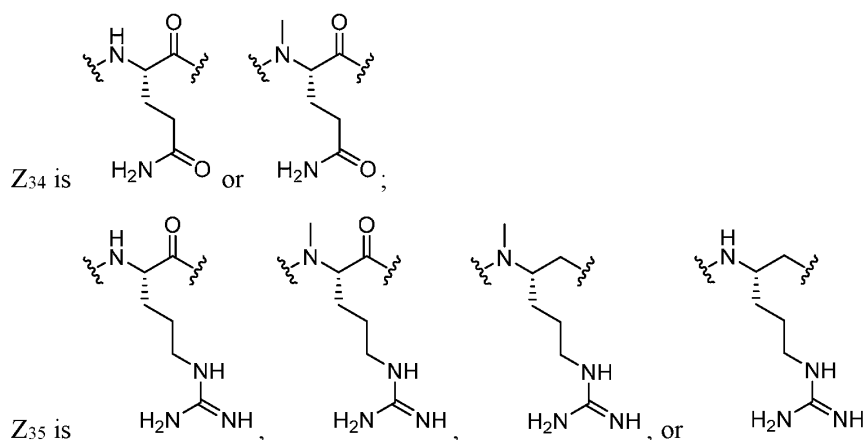
Z_{26} is A or H;

Z_{30} is L;





4. The conjugate of claim 2, wherein the cyclic PYY peptide is represented by
- 5 Formula I or the derivative or pharmaceutically acceptable salt thereof, wherein:
 - p is 0 or 1;
 - m is 0, 1, 2, 3, or 5;
 - n is 1, 2, or 4;
 - q is 0 or 1; provided that q may be 1 only when Z₃₀ is absent;
 - 10 BRIDGE is -Ph-CH₂-S-, -triazolyl-, -NHC(O)CH₂S-, -
(OCH₂CH₂)₂NHC(O)CH₂S-, -NHC(O)-, or -CH₂S-;
 - Z₄ is K, A, E, S, or R;
 - Z₇ is A or K, wherein the amino side chain of said K is substituted with
-C(O)CH₂Br,
 - 15 Z₉ is G or K, wherein the amino side chain of said K is substituted with
-C(O)CH₂Br,
 - Z₁₁ is D or K, wherein the amino side chain of said K is substituted with
-C(O)CH₂Br,
 - Z₂₂ is A or K, wherein the amino side chain of said K is substituted with
20 -C(O)CH₂Br,
 - Z₂₃ is S or K, wherein the amino side chain of said K is substituted with
-C(O)CH₂Br,
 - Z₂₆ is A or H,
 - Z₃₀ is L;



5. The conjugate of claim 2, wherein the cyclic PYY peptide is selected from the group consisting of SEQ ID NOs:1-54, or a pharmaceutically acceptable salt thereof.
6. The conjugate of claim 5, wherein the cyclic PYY peptide is selected from SEQ ID NO:24, 25, 27, 28, 29, 30, 33, or 34, or a pharmaceutically acceptable salt thereof.
7. The conjugate of any one of claims 1-6, wherein the GLP-1 fusion peptide is covalently linked to the cyclic PYY peptide at a lysine residue of the cyclic PYY peptide.
8. The conjugate of claim 7, wherein only one of Z₇, Z₉, Z₁₁, Z₂₂ and Z₂₃ in Formula I is lysine, and the lysine is covalently linked to a cysteine residue in the second linker peptide of the GLP-1 fusion peptide.
9. The conjugate of claim 8, wherein Z₁₁ in Formula I is lysine.
10. The conjugate of any one of claims 1-9, wherein the GLP-1 peptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOs:56-59.
11. The conjugate of any one of claims 1-10, wherein the first linker peptide is present and comprises an amino acid sequence selected from the group consisting of SEQ ID NOs:60-83.
12. The conjugate of any one of claims 1-11, wherein the hinge-Fc region peptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOs:84-90.
13. The conjugate of any one of claims 1-12, wherein the second linker peptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOs:93-112.

14. The conjugate of any one of claims 1-12, wherein the second linker peptide comprises the amino acid sequence of SEQ ID NO:93, 94, 95, 106, or 111.
15. A conjugate comprising a glucagon-like peptide 1 (GLP-1) fusion peptide coupled to a cyclic PYY peptide, wherein the GLP-1 fusion peptide comprises an amino acid
5 sequence selected from the group consisting of SEQ ID NOs:113-224 and 267-274, and wherein the cyclic PYY peptide comprises an amino acid sequence of selected from SEQ ID NO:24, 25, 27, 28, 29, 30, 33, or 34, or a pharmaceutically acceptable salt thereof.
16. The conjugate of claim 15, wherein a cysteine residue between amino acid residues 287 to 289, preferably cysteine residue 288, of the GLP-1 fusion peptide is
10 covalently linked to a lysine residue at residue 7, 9, 11, 22 or 23 of the cyclic PYY peptide, preferably the lysine residue 11 of the cyclic PYY peptide, via a chemical linker.
17. A conjugate comprising a glucagon-like peptide 1 (GLP-1) fusion peptide coupled to a cyclic PYY peptide, wherein the conjugate comprises an amino acid sequence selected from the group consisting of SEQ ID NOs:225-262 or a pharmaceutically
15 acceptable salt thereof.
18. A method of producing the conjugate of any one of claims 1-17, comprising reacting an electrophile, preferably bromoacetamide or maleimide, introduced onto a sidechain of the cyclic PYY peptide, preferably the sidechain of a lysine residue of the cyclic PYY peptide, with the sulfhydryl group of a cysteine residue of the second linker
20 peptide of the GLP-1 fusion peptide, thereby creating a covalent linkage between the cyclic PYY peptide and the GLP-1 fusion peptide.
19. The method of claim 18, wherein the cysteine residue of the second linker peptide of the GLP-1 fusion peptide is reduced by contacting the GLP-1 fusion peptide with an excess of an azaphosphine reducing agent, and the reduced cysteine residue is reacted
25 with the electrophile.
20. The method of claim 19, wherein the azaphosphine reducing agent is 1,3,5-triaza-7-phosphatricyclo[3.3.1.1] decane (PTA) or a derivative thereof.
21. A pharmaceutical composition comprising the conjugate of any one of claims 1-17 and a pharmaceutically acceptable carrier.
- 30 22. A method for treating or preventing a disease or disorder in a subject in need thereof, wherein said disease or disorder is obesity, type I or type II diabetes, metabolic

- syndrome, insulin resistance, impaired glucose tolerance, hyperglycemia, hyperinsulinemia, hypertriglyceridemia, hypoglycemia due to congenital hyperinsulinism (CHI), dyslipidemia, atherosclerosis, diabetic nephropathy, and other cardiovascular risk factors such as hypertension and cardiovascular risk factors related to unmanaged
- 5 cholesterol and/or lipid levels, osteoporosis, inflammation, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), renal disease, and/or eczema, the method comprising administering to the subject in need thereof an effective amount of the pharmaceutical composition of claim 21.
23. A method of reducing at least one of food intake or body weight in a subject in
- 10 need thereof, the method comprising administering to the subject in need thereof an effective amount of the pharmaceutical composition of claim 21.
24. A method of modulating Y2 receptor activity and/or GLP-1 receptor activity in a subject in need thereof, the method comprising administering to the subject in need thereof an effective amount of the pharmaceutical composition of claim 21.
- 15 25. The method of any one of claims 22-24, wherein the pharmaceutical composition is administered via an injection.
26. A kit comprising the conjugate of any one of claims 1-17, preferably further comprising a device for injection.
27. A method of producing a pharmaceutical composition comprising the conjugate
- 20 of any one of claims 1-17, comprising combining the conjugate with a pharmaceutically acceptable carrier to obtain the pharmaceutical composition.