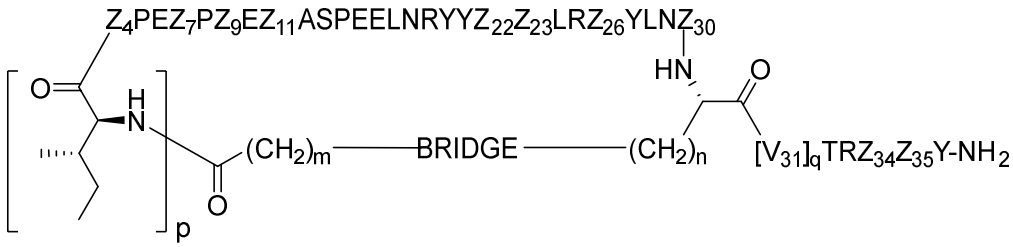
CLAIMS

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 and the GLP-1 fusion peptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 113-224 and 267-274, and

wherein the cyclic PYY peptide is represented by Formula **I** or a derivative or pharmaceutically acceptable salt thereof**:**



Formula **I** (SEQ ID NO:275)

wherein

p is 0 or 1;

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

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 -Ph-CH_2-S-, -triazolyl-, -NHC(O)CH_2S-, -SCH_2C(O)NH-,

-$(OCH_2CH_2)_2$NHC(O)CH_2S, -NHC(O)-, or -CH_2S-;

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

Z_7 is A or K;

Z_9 is G or K;

Z_{11} is D or K;

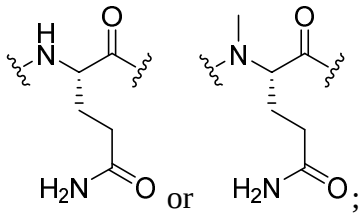
Z_{22} is A or K;

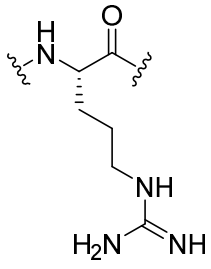
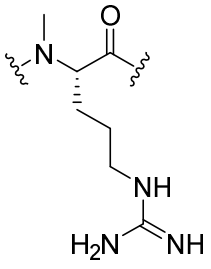
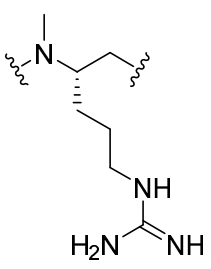
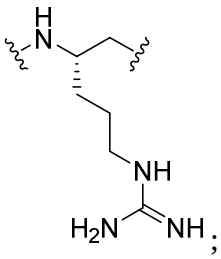
Z_{23} is S or K;

Z_{26} is A or H;

Z_{30} is L, W, or absent,

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

Z_{34} is  or ;

Z_{35} is , , , or ;

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.

2. The conjugate of claim 1, 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;

n is 1, 2, 3, or 4;

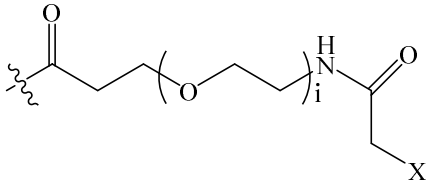
q is 0 or 1; provided that q is 1 only when Z_{30} is absent;

BRIDGE is -Ph-CH_2-S-, -triazolyl-, -NHC(O)CH_2S-, -SCH_2C(O)NH_2-,

-$(OCH_2CH_2)_2$NHC(O)CH_2S, -NHC(O)-, or -CH_2S-;

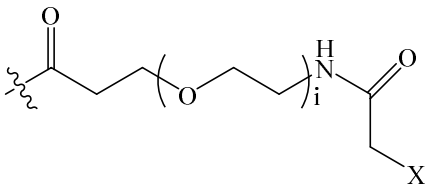
Z_4 is K, A, E, S, or R;

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

, wherein i is an integer of 0 to 24, and X = Br, I or Cl,

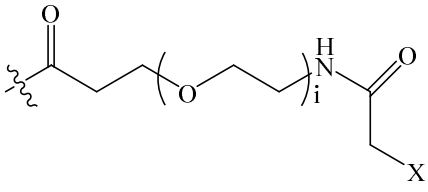
-C(O)CH_2Br, -C(O)CH_2I, or -C(O)CH_2Cl;

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



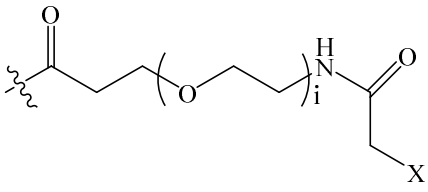
, wherein i is an integer of 0 to 24, and X = Br, I or Cl, -C(O)CH_2Br, -C(O)CH_2I, or -C(O)CH_2Cl;

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



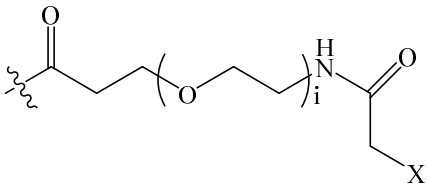
, wherein i is an integer of 0 to 24, and X = Br, I or Cl, -C(O)CH_2Br, -C(O)CH_2I, or -C(O)CH_2Cl;

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



, wherein i is an integer of 0 to 24, and X = Br, I or Cl, -C(O)CH_2Br, -C(O)CH_2I, or -C(O)CH_2Cl;

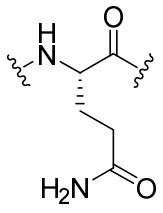
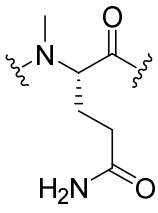
Z_{23} is S or K, wherein, when Z_{23} is K, the amino side chain of said K is substituted with

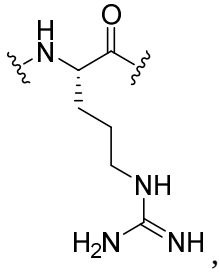
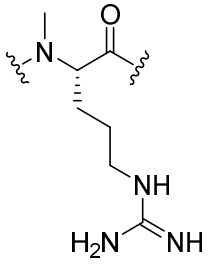
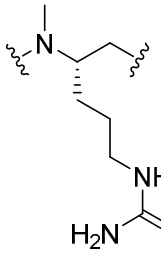
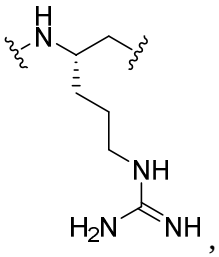


, wherein i is an integer of 0 to 24, and X = Br, I or Cl, -C(O)CH_2Br, -C(O)CH_2I, or -C(O)CH_2Cl;

Z_{26} is A or H;

Z_{30} is L;

Z_{34} is  or ; and

Z_{35} is , , , or ,

wherein only one of Z_7, Z_9, Z_{11}, Z_{22} and Z_{23} in Formula **I** is K.

3. The conjugate of claim 1, 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, or 5;

n is 1, 2, or 4;

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

BRIDGE is -Ph-CH_2-S-, -triazolyl-, -NHC(O)CH_2S-, -$(OCH_2CH_2)_2$NHC(O)CH_2S, -NHC(O)-, or -CH_2S-;

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

Z_7 is A or K, wherein, when Z_7 is K, the amino side chain of said K is substituted with -C(O)CH_2Br,

Z_9 is G or K, wherein, when Z_9 is K, the amino side chain of said K is substituted with -C(O)CH_2Br,

Z_{11} is D or K, wherein, when Z_{11} is K, the amino side chain of said K is substituted with -C(O)CH_2Br,

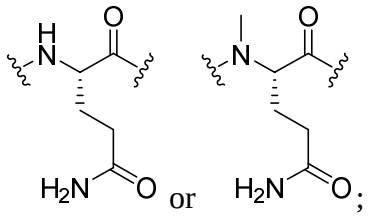
Z_{22} is A or K, wherein, when Z_{22} is K, the amino side chain of said K is substituted with -C(O)CH_2Br,

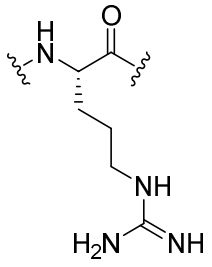
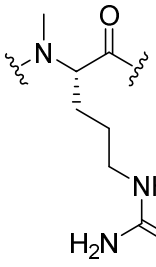
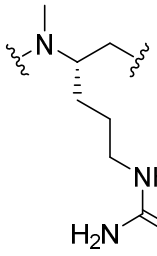
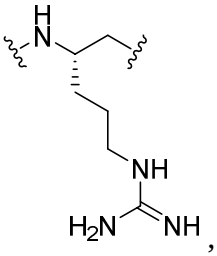
Z_{23} is S or K, wherein, when Z_{23} is K, the amino side chain of said K is substituted with

-C(O)CH_2Br,

Z_{26} is A or H,

Z_{30} is L;

Z_{34} is  or ;

Z_{35} is , , , or ,

wherein only one of Z_7, Z_9, Z_{11}, Z_{22} and Z_{23} in Formula **I** is K.

4. The conjugate of claim 1, wherein the cyclic PYY peptide is selected from the group consisting of SEQ ID NOs:1-54, or a pharmaceutically acceptable salt thereof.

5. The conjugate of claim 4, 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.

6. The conjugate of claim 1, wherein the GLP-1 fusion peptide is covalently linked to the cyclic PYY peptide at a K residue of the cyclic PYY peptide.

7. The conjugate of claim 6, wherein the K is covalently linked to a cysteine residue in the second linker peptide of the GLP-1 fusion peptide.

8. The conjugate of claim 7, wherein Z_{11} in Formula **I** is K.

9. The conjugate of claim 1, wherein a cysteine residue between amino acid residues 287 to 289 of the GLP-1 fusion peptide is covalently linked to a K residue at residue Z_7, Z_9, Z_{11}, Z_{22}, or Z_{23} of the cyclic PYY peptide via a chemical linker.

10. The conjugate of claim 1, wherein the conjugate comprises an amino acid sequence selected from the group consisting of SEQ ID NOs:225-262 or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition comprising the conjugate of claim 1 and a pharmaceutically acceptable carrier.

12. Use of the pharmaceutical composition of claim 11 in the manufacture of a medicament for the treatment or prevention of 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, hypertension, cardiovascular risk factors related to unmanaged cholesterol, cardiovascular risk factors related to lipid levels, osteoporosis, inflammation, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), renal disease, and/or eczema, and wherein an effective amount of the pharmaceutical composition is to be administered to the subject.

13. Use of the pharmaceutical composition of claim 11 in the manufacture of a medicament for reducing at least one of food intake or body weight in a subject in need thereof, wherein an effective amount of the pharmaceutical composition is to be administered to the subject.

14. A kit comprising the conjugate of claim 1 and a device for injection.

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 the amino acid sequence of

SEQ ID NO:136, and the cyclic PYY peptide comprises an amino acid sequence 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 the conjugate comprises an amino acid sequence selected from the group consisting of SEQ ID NO:229, SEQ ID NO:230, SEQ ID NO:231, and SEQ ID NO:232.

17. A pharmaceutical composition comprising the conjugate of claim 15and a pharmaceutically acceptable carrier.

18. Use of the pharmaceutical composition of claim 17 in the manufacture of a medicament for the treatment or prevention of 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, hypertension, cardiovascular risk factors related to unmanaged cholesterol, cardiovascular risk factors related to lipid levels, osteoporosis, inflammation, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), renal disease, and/or eczema, and wherein an effective amount of the pharmaceutical composition is to be administered to the subject.

19. Use of the pharmaceutical composition of claim 17 in the manufacture of a medicament for reducing at least one of food intake or body weight in a subject in need thereof, wherein an effective amount of the pharmaceutical composition is to be administered to the subject.

20. 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 the amino acid sequence of SEQ ID NO:113, and the cyclic PYY peptide comprises an amino acid sequence selected from SEQ ID NO:24, 25, 27, 28, 29, 30, 33, or 34, or a pharmaceutically acceptable salt thereof.

21. The conjugate of claim 2021, wherein the conjugate comprises an amino acid sequence selected from the group consisting of SEQ ID NO:225, SEQ ID NO:226, SEQ ID NO:227, and SEQ ID NO:228.

22. A pharmaceutical composition comprising the conjugate of claim 20 and a pharmaceutically acceptable carrier.

23. Use of the pharmaceutical composition of claim 22 in the manufacture of a medicament for the treatment or prevention of 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, hypertension, cardiovascular risk factors related to unmanaged cholesterol, cardiovascular risk factors related to lipid levels, osteoporosis, inflammation, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), renal disease, and/or eczema, and wherein an effective amount of the pharmaceutical composition is to be administered to the subject.

24. Use of the pharmaceutical composition of claim 22 in the manufacture of a medicament for reducing at least one of food intake or body weight in a subject in need thereof, wherein an effective amount of the pharmaceutical composition is to be administered to the subject.

25. 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 the amino acid sequence of SEQ ID NO:131, and the cyclic PYY peptide comprises an amino acid sequence selected from SEQ ID NO:24, 25, 27, 28, 29, 30, 33, or 34, or a pharmaceutically acceptable salt thereof.

26. The conjugate of claim 25, wherein the conjugate comprises an amino acid sequence of SEQ ID NO:251.

27. A pharmaceutical composition comprising the conjugate of claim 25 and a pharmaceutically acceptable carrier.

28. Use of the pharmaceutical composition of claim 27in the manufacture of a medicament for the treatment or prevention of 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, hypertension, cardiovascular risk factors related to unmanaged cholesterol, cardiovascular risk factors related to lipid levels, osteoporosis, inflammation, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), renal disease, and/or eczema, and wherein an effective amount of the pharmaceutical composition is to be administered to the subject.

29. Use of the pharmaceutical composition of claim 27 in the manufacture of a medicament for reducing at least one of food intake or body weight in a subject in need thereof, wherein an effective amount of the pharmaceutical composition is to be administered to the subject.

30. The pharmaceutical composition of any one of claims 11, 17, 22 or 27 for use in therapy.