

~~BRIEF SUMMARY OF THE INVENTION~~

~~In a first aspect, the invention~~The disclosure provides a PYY analogue, wherein the analogue comprises

- i) alanine at the position corresponding to position 4 of hPYY(3-36)
 - 5 ii) lysine at the position corresponding to position 7 of hPYY(3-36)
 - iii) the sequence QRY at its C-terminal end,
- and wherein a half-life extending group is attached to the epsilon amino group of the lysine at position 7 or of a lysine at positions 6, 10, 11, 14, 17, 21, 22 or 30, or to the carboxylic acid group of the side chain of an aspartate or a glutamate at positions 14 or 30.

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In some ~~embodiments~~examples, the PYY analogue comprises

- i) alanine at the position corresponding to position 4 of hPYY(3-36)
 - ii) lysine at the position corresponding to position 7 of hPYY(3-36)
 - iii) proline at the position corresponding to position 5 of hPYY(3-36)
 - 15 iv) glutamine at the position corresponding to position 18 of hPYY(3-36)
 - v) leucine at the position corresponding to position 24 of hPYY(3-36)
 - vi) arginine at the position corresponding to position 25 of hPYY(3-36)
 - vii) histidine at the position corresponding to position 26 of hPYY(3-36)
 - viii) leucine at the position corresponding to position 31 of hPYY(3-36)
 - 20 ix) the sequence QRY at its C-terminal end,
- and wherein a half-life extending group is attached to the epsilon amino group of the lysine at position 7 or of a lysine at positions 6, 10, 11, 14, 17, 21 or 22, or to the carboxylic acid group of the side chain of an aspartate or a glutamate at position 14.

- 25 In some ~~embodiments~~examples of the present ~~invention~~disclosure, the PYY analogue is a compound having the formula:

R^1-Z-R^2 ,

- wherein R^1 is hydrogen, $-C(O)C_{1-6}$ alkyl, $-C(O)C_6H_5$, $-C(O)C_{3-6}$ cycloalkyl, $-C(O)C_{1-6}$ alkyl- C_{3-6} cycloalkyl, C_{1-6} alkyl or C_{1-6} alkyl- C_{3-6} cycloalkyl:

R^2 is OH or NHR^3 , wherein R^3 is hydrogen or C_{1-3} alkyl; and

Z is a peptide comprising an amino acid sequence of formula Ib:

In some embodimentsexamples, the half-life extending group consists of a lipophilic substituent X and a linker U, wherein the linker U is attached to the amino acid side chain and X is attached to U, and the linker U consists of one, two or three sub-moieties (U1, U2, U3), wherein at least one sub-moiety is Ahx.

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In one aspect, the present disclosure provides a PYY analogue, wherein the PYY analogue is a compound having the formula:

R¹-Z-R²,

10 wherein R¹ is hydrogen, -C(O)C₁₋₆ alkyl, -C(O)C₆H₅, -C(O)C₃₋₆ cycloalkyl, -C(O)C₁₋₆ alkyl-C₃₋₆ cycloalkyl, C₁₋₆ alkyl or C₁₋₆ alkyl-C₃₋₆ cycloalkyl;

R² is OH or NHR³, wherein R³ is hydrogen or C₁₋₃ alkyl; and

Z is a peptide comprising an amino acid sequence of formula Ib:

15 Ala-Pro-X6-Lys-X8-X9-X10-X11-X12-X13-X14-X15-X16-X17-Gln-X19-X20-X21-X22-X23-Leu-Arg-His-X27-X28-X29-X30-Leu-X32-X33-Gln-Arg-Tyr (Ib)

wherein

X6 is selected from the group consisting of Ala and Glu;

20 X8 is selected from the group consisting of Ala and Pro;

X9 is selected from the group consisting of Glu, Gly and Pro;

X10 is selected from the group consisting of Ala and Glu;

X11 is selected from the group consisting of Ala, Asp, Glu, Ile, Leu, Pro, Gln and Ser;

X12 is selected from the group consisting of Ala, Glu, Leu, Pro, Gln and Ser;

25 X13 is selected from the group consisting of Ala, Glu, Leu, Ser, Gln, Thr and Pro;

X14 is selected from the group consisting of Ala, Glu, Leu, Pro, Gln and Ser;

X15 is selected from the group consisting of Ala, and Glu;

X16 is selected from the group consisting of Ala, Glu and Lys;

X17 is selected from the group consisting of Ala, Glu, Ile, Leu, Pro, Gln, Ser, Thr and Val;

30 X19 is selected from the group consisting of Ala, Glu, Leu, Arg, Lys, Pro, Ser and Gln;

X20 is selected from the group consisting of Gln and Tyr;

X21 is selected from the group consisting of Gln and Tyr;

X22 is selected from the group consisting of Ala, Glu, Ile, Leu, Pro, Gln, Ser, Thr and Val;

X23 is selected from the group consisting of Ala, Glu, Gly, Leu, Pro, Gln, Ser, Thr and

5 Val;

X27 is selected from the group consisting of Gln and Tyr;

X28 is selected from the group consisting of Gln and Tyr;

X29 is selected from the group consisting of His, Asn and Gln;

X30 is selected from the group consisting of Trp and Lys;

10 X32 is selected from the group consisting of Gln, Leu, Ser and Thr; and

X33 is selected from the group consisting of Lys and Arg;

wherein one to three amino acids of X6, X8-17, X19-X23 and X27-X32 may be absent,

and wherein a half-life extending group is attached to the epsilon amino group of the lysine

15 at position 7,

the half-life extending group consists of a lipophilic substituent X and a linker U, wherein

the linker U is attached to the amino acid side chain, and X is attached to U, and the linker

U consists of one, two or three sub-moieties (U1, U2, U3), wherein at least one sub-moiety is Ahx (6-aminohexanoic acid).

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In some embodimentexamples, the lipophilic substituent X is selected from the group consisting of 15-carboxy-pentadecanoyl, 17-carboxy-heptadecanoyl (C18DA) and 19-

carboxy-nonadecanoyl, and the linker U consists of one, two or three sub-moieties

independently selected from the group consisting of Gly, Glu, γ -Glu, ϵ -Lys, Ser, Ahx and

25 OEG, or independently selected from the group consisting of γ -Glu, Ahx and OEG.

In some embodimentexamples the PYY analogue is selected from the compounds 245 to 443 described herein.

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In some ~~embodiment~~examples the PYY analogue is in the form of a salt, preferably in the form of a pharmaceutically acceptable salt.

The ~~invention~~disclosure further provides a composition comprising a PYY analogue as described herein.

In another aspect, the present disclosure provides a pharmaceutical composition comprising at least one PYY analogue as described herein and one or more pharmaceutically acceptable excipient.

The present ~~invention~~disclosure further provides a PYY analogue for use in a method of medical treatment, e.g. for use in the treatment of obesity and various obesity-related conditions, diseases, or disorders such as type 2 diabetes, NAFLD or NASH.

In another aspect, the present disclosure provides a PYY analogue as described herein for use in the treatment of obesity or obesity-related conditions or diseases, such as type 2 diabetes, hypertension, dyslipidemia, sleep apnea and cardiovascular disease.

In another aspect, the present disclosure provides a PYY analogue as described herein for use in the treatment of atherogenic dyslipidemia, hepatic steatosis, NAFLD, NASH, kidney failure or atherosclerosis.

In another aspect, the present disclosure provides use of a PYY analogue as described herein in the manufacture of a medicament for the treatment of obesity or obesity-related conditions or diseases, such as type 2 diabetes, hypertension, dyslipidemia, sleep apnea and cardiovascular disease.

In another aspect, the present disclosure provides use of a PYY analogue as described herein in the manufacture of a medicament for the treatment of atherogenic dyslipidemia, hepatic steatosis, NAFLD, NASH, kidney failure or atherosclerosis.

The ~~invention~~disclosure provides a PYY analogue of the ~~invention~~disclosure for use in a method of treating, inhibiting or reducing weight gain, promoting weight loss and/or reducing excess body weight.

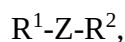
5 In another aspect, the present disclosure provides a PYY analogue as described herein for use in a medical treatment, e.g. for use in the treatment of a condition or disease related or caused by excess body weight or excess body weight gain.

10 In another aspect, the present disclosure provides use of a PYY analogue as described herein in the manufacture of a medicament for the treatment of a condition or disease related or caused by excess body weight or excess body weight gain.

DETAILED DESCRIPTION OF THE INVENTION

WHAT WE CLAIM

- 5 1. A PYY analogue, wherein the PYY analogue is a compound having the formula:



wherein R^1 is hydrogen, $-C(O)C_{1-6}$ alkyl, $-C(O)C_6H_5$, $-C(O)C_{3-6}$ cycloalkyl, $-C(O)C_{1-6}$ alkyl- C_{3-6} cycloalkyl, C_{1-6} alkyl or C_{1-6} alkyl- C_{3-6} cycloalkyl;

10 R^2 is OH or NHR^3 , wherein R^3 is hydrogen or C_{1-3} alkyl; and

Z is a peptide comprising an amino acid sequence of formula Ib:

Ala-Pro-X6-Lys-X8-X9-X10-X11-X12-X13-X14-X15-X16-X17-Gln-X19-X20-
X21-X22-X23-Leu-Arg-His-X27-X28-X29-X30-Leu-X32-X33-Gln-Arg-Tyr (Ib)

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wherein

X6 is selected from the group consisting of Ala and Glu;

X8 is selected from the group consisting of Ala and Pro;

X9 is selected from the group consisting of Glu, Gly and Pro;

20 X10 is selected from the group consisting of Ala and Glu;

X11 is selected from the group consisting of Ala, Asp, Glu, Ile, Leu, Pro, Gln and Ser;

X12 is selected from the group consisting of Ala, Glu, Leu, Pro, Gln and Ser;

X13 is selected from the group consisting of Ala, Glu, Leu, Ser, Gln, Thr and Pro;

25 X14 is selected from the group consisting of Ala, Glu, Leu, Pro, Gln and Ser;

X15 is selected from the group consisting of Ala, and Glu;

X16 is selected from the group consisting of Ala, Glu and Lys;

X17 is selected from the group consisting of Ala, Glu, Ile, Leu, Pro, Gln, Ser, Thr and Val;

30 X19 is selected from the group consisting of Ala, Glu, Leu, Arg, Lys, Pro, Ser and Gln;

X20 is selected from the group consisting of Gln and Tyr;

X21 is selected from the group consisting of Gln and Tyr;

X22 is selected from the group consisting of Ala, Glu, Ile, Leu, Pro, Gln, Ser, Thr and Val;

5 X23 is selected from the group consisting of Ala, Glu, Gly, Leu, Pro, Gln, Ser, Thr and Val;

X27 is selected from the group consisting of Gln and Tyr;

X28 is selected from the group consisting of Gln and Tyr;

X29 is selected from the group consisting of His, Asn and Gln;

X30 is selected from the group consisting of Trp and Lys;

10 X32 is selected from the group consisting of Gln, Leu, Ser and Thr; and

X33 is selected from the group consisting of Lys and Arg;

wherein one to three amino acids of X6, X8-17, X19-X23 and X27-X32 may be absent,

15 and wherein a half-life extending group is attached to the epsilon amino group of the lysine at position 7,

the half-life extending group consists of a lipophilic substituent X and a linker U, wherein the linker U is attached to the amino acid side chain, and X is attached to U, and the linker U consists of one, two or three sub-moieties (U1, U2, U3), wherein at
20 least one sub-moiety is Ahx (6-aminohexanoic acid).

2. The PYY analogue according to claim 1, wherein Z is an amino acid sequence of formula IIb:

25 Ala-Pro-X6-Lys-X8-X9-X10-X11-Ala-X13-X14-Glu-Glu-X17-Gln-X19-Tyr-Tyr-X22-X23-Leu-Arg-His-Tyr-Tyr-X29-Trp-Leu-Thr-Arg-Gln-Arg-Tyr (IIb)

wherein

X6 is selected from the group consisting of Ala and Glu;

30 X8 is selected from the group consisting of Ala and Pro;

X9 is selected from the group consisting of Glu and Pro;

X10 is selected from the group consisting of Ala and Glu;

X11 is selected from the group consisting of Ala, Asp and Glu;
X13 is selected from the group consisting of Glu, Ser and Thr;
X14 is selected from the group consisting of Ala, Glu and Pro;
X17 is selected from the group consisting of Ala, Ile, Leu, Ser and Thr;
5 X19 is selected from the group consisting of Arg and Gln;
X22 is selected from the group consisting of Ile, Thr and Val;
X23 is selected from the group consisting of Ala, Glu, Gln and Ser;
X29 is selected from the group consisting of Asn and Gln.

10 3. The PYY analogue according to claim 1, wherein Z is an amino acid sequence of formula IIIb:

Ala-Pro-X6-Lys-Pro-X9-X10-X11-X12-X13-X14-X15-X16-X17-X18-X19-Tyr-
X21-X22-X23-Leu-Arg-His-Tyr-Tyr-Asn-Trp-Leu-Thr-Arg-Gln-Arg-Tyr (IIIb)

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wherein

X6 is selected from the group consisting of Ala and Glu;
X9 is selected from the group consisting of Glu, Gly and Pro;
X10 is selected from the group consisting of Ala and Glu;
20 X11 is selected from the group consisting of Ala, Asp, Glu and Pro;
X12 is selected from the group consisting of Ala and Ser;
X13 is selected from the group consisting of Ala, Glu, Ser, Thr and Pro;
X14 is selected from the group consisting of Ala, Glu and Pro;
X15 is selected from the group consisting of Ala and Glu;
25 X16 is selected from the group consisting of Ala and Glu;
X17 is selected from the group consisting of Ile, Leu, Thr and Val;
X18 is selected from the group consisting of Glu and Gln;
X19 is selected from the group consisting of Ala, Glu, Arg, Lys, and Gln;
X21 is selected from the group consisting of Glu and Tyr;
30 X22 is selected from the group consisting of Ile and Val;
X23 is selected from the group consisting of Ala, Glu, Ser and Thr.

4. The PYY analogue according to claim 1, wherein Z is an amino acid sequence of formula IVb:

Ala-Pro-X6-Lys-Pro-X9-X10-X11-Ala-X13-Pro-Glu-Glu-X17-Gln-Arg-Tyr-Tyr-
X22-X23-Leu-Arg-His-Tyr-Tyr-Asn-Trp-Leu-Thr-Arg-Gln-Arg-Tyr (IVb)

wherein

X6 is selected from the group consisting of Ala and Glu;

X9 is selected from the group consisting of Glu and Pro;

X10 is selected from the group consisting of Ala and Glu;

X11 is selected from the group consisting of Ala, Asp and Glu;

X13 is selected from the group consisting of Glu, Ser and Thr;

X17 is selected from the group consisting of Ile and Leu;

X22 is selected from the group consisting of Ile and Val;

X23 is selected from the group consisting of Ala and Ser.

5. The PYY analogue according to any one of claim 1 to 4, wherein none of X6, X8-17, X19-X23 and X27-X32 is absent.

6. The PYY analogue according to any one of claim 1 to 5, wherein the PYY analogue has 7 or more but not more than 15 amino acid modifications as compared to hPYY(3-36).

7. The PYY analogue according to claim 1, wherein Z is an amino acid sequence selected from Table 1.

8. The PYY analogue according to any one of claims 1 to 7, wherein R¹ is selected from the group consisting of -C(O)CH₂CH(CH₃)₂, -C(O)CH₂-cyclobutyl and -C(O)CH₂-cyclopropyl.

9. The PYY analogue according to any one of claims 1 to 8, wherein up to three residues of X6 to X23 are Ala.

10. The PYY analogue according to any one of claims 1 to 9, wherein at least four residues of X6, X9, X10, X13, X15, X16 and X23 are Glu.
- 5 11. The PYY analogue according to any one of claims 1 to 10, wherein the linker U of the half-life extending group consists of one, two or three sub-moieties independently selected from the group consisting of Gly, Glu, γ -Glu, ϵ -Lys, Ser, Ahx and OEG, wherein at least one sub-moiety is Ahx, and X of the half-life extending group is selected from the group consisting of 15-carboxy-pentadecanoyl, 17-carboxy-heptadecanoyl and 19-carboxy-nonadecanoyl.
- 10 12. The PYY analogue according to any one of the previous claims, wherein the PYY analogue is a compound selected from the group consisting of compound 1 to compound 199.
- 15 13. The PYY analogue according to any one of the previous claims, wherein the PYY analogue is in the form of a salt, preferably in the form of a pharmaceutically acceptable salt.
- 20 14. The PYY analogue according to any one of the previous claims, wherein the binding affinity (K_i) towards hNPY2R is below 100 nM.
15. The PYY analogue according to any one of the previous claims, wherein the solubility of the PYY analogue is greater than 1.0 mg/ml at pH 6.
- 25 16. A pharmaceutical composition comprising at least one PYY analogue according to any one of the previous claims and one or more pharmaceutically acceptable excipient.
- 30 17. A PYY analogue according to any one of claims 1 to 15 for use in a ~~method of~~ medical treatment, e.g. for use in ~~a method of the~~ treatment of a condition or disease related or caused by excess body weight or excess body weight gain.

18. A PYY analogue according to any one of claims 1 to 15 for use in the treatment of obesity or obesity-related conditions or diseases, such as type 2 diabetes, hypertension, dyslipidemia, sleep apnea and cardiovascular disease.

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19. A PYY analogue according to any one of claims 1 to 15 for use in the treatment of atherogenic dyslipidemia, hepatic steatosis, NAFLD, NASH, kidney failure or atherosclerosis.

10 20. ~~A-The~~ PYY analogue ~~according to any one of claims 1 to 15~~ for use ~~in the treatment~~ according to any one of claims 17 to 19, wherein the PYY analogue is to be administered as part of a combination therapy together with an agent for treatment of diabetes, obesity, dyslipidemia or hypertension.

15 21. ~~A-The~~ PYY analogue ~~according to any one of claims 1 to 15~~ for use ~~in the treatment~~ according to any one of claims 17 to 19, wherein the PYY analogue is to be administered as part of a combination therapy together with an agent for the treatment of obesity, wherein the agent for obesity is a GIP or GLP-1 receptor agonist, e.g. GLP-1 or a GLP-1 analogue, exendin-4 or an exendin-4 analogue, any
20 other GLP-1 receptor agonist including Liraglutide, Semaglutide, Dulaglutide or Albiglutide, or a glucagon-GLP-1 dual agonist, GLP-1/GIP dual agonist, or a GLP-1/GIP/glucagon triple agonist, or an amylin receptor agonist.

25 22. Use of a PYY analogue according to any one of claims 1 to 15 in the manufacture of a medicament for the treatment of a condition or disease related or caused by excess body weight or excess body weight gain.

30 23. Use of a PYY analogue according to any one of claims 1 to 15 in the manufacture of a medicament for the treatment of obesity or obesity-related conditions or diseases, such as type 2 diabetes, hypertension, dyslipidemia, sleep apnea and cardiovascular disease.

24. Use of a PYY analogue according to any one of claims 1 to 15 in the manufacture of a medicament for the treatment of atherogenic dyslipidemia, hepatic steatosis, NAFLD, NASH, kidney failure or atherosclerosis.
- 5 25. The use according to any one of claims 22 to 24, wherein the PYY analogue is to be administered as part of a combination therapy together with an agent for treatment of diabetes, obesity, dyslipidemia or hypertension.
- 10 26. The use according to any one of claims 22 to 24, wherein the PYY analogue is to be administered as part of a combination therapy together with an agent for the treatment of obesity, wherein the agent for obesity is a GIP or GLP-1 receptor agonist, e.g. GLP-1 or a GLP-1 analogue, exendin-4 or an exendin-4 analogue, any other GLP-1 receptor agonist including Liraglutide, Semaglutide, Dulaglutide or Albiglutide, or a glucagon-GLP-1 dual agonist, GLP-1/GIP dual agonist, or a GLP-1/GIP/glucagon triple agonist, or an amylin receptor agonist.
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