SUMMARY

The disclosure provides a PYY analogue, wherein the 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) 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 a aspartate or a glutamate at positions 14 or 30.

In some 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) glutamate at the position corresponding to position 9 of hPYY(3-36)

iv) tyrosine at the position corresponding to position 20 of hPYY(3-36)

v) tryptophan at the position corresponding to position 30 of hPYY(3-36)

vi) leucine at the position corresponding to position 31 of hPYY(3-36)

vii) the sequence RQRY 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 a aspartate or a glutamate at position 14.

In some 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) glutamate at the position corresponding to position 9 of hPYY(3-36)

iv) tyrosine at the position corresponding to position 20 of hPYY(3-36)

v) the sequence WLTRQRY 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 a aspartate or a glutamate at positions 14 .

In some examples, the PYY analogue is in accordance to one of the above examples and bears a half-life extending group, which is attached to the epsilon amino group of the lysine at position 7.

In some examples of the present 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_6, -C(O)C_{3-6} cycloalkyl, -C(O)C_{1-6} alkyl-C_{3-6} cycloalkyl, or 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 an amino acid sequence of formula III:

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

wherein

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

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

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

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,

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;

X23 is selected from the group consisting of Ala, Glu, Ser and Thr;

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

In some examples, 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).

Thus, in one aspect, the present disclosure provides a PYY analogue comprising an amino acid sequence corresponding to the amino acid sequence of hPYY(3-36), wherein 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_6, -C(O)C_{3-6} cycloalkyl, -C(O)C_{1-6} alkyl-C_{3-6} cycloalkyl, or 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 I:

Ala-X5-X6-Lys-X8-X9-X10-X11-X12-X13-X14-X15-X16-X17-X18-X19-Tyr-X21-X22-X23-X24-Arg-X26-X27-X28-X29-X30-X31-X32-Arg-Gln-Arg-Tyr (I)

wherein

X5 is selected from the group consisting of Pro and Hyp;

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

X8 is selected from the group consisting of Ala, Ile, Pro, Thr, Val and Hyp;

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

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

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

X12 is selected from the group consisting of Ala, Gly, Ser, Thr and Val;

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

X14 is selected from the group consisting of Ala, Glu, Gly, Pro and Hyp;

X15 is selected from the group consisting of Ala, Glu and Ser;
X16 is selected from the group consisting of Ala, Glu and Ser;
X17 is selected from the group consisting of Ala, 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 Ala, Glu, Gln and Tyr;
X22 is selected from the group consisting of Ile, Ser, Thr and Val;
X23 is selected from the group consisting of Ala, Glu, Ser and Thr;
X24 is selected from the group consisting of Ala, Ile, Leu, Thr and Val;
X26 is selected from the group consisting of Ala, His and Lys;
X27 is selected from the group consisting of Gln and Tyr;
X28 is selected from the group consisting of His, Trp and Tyr;
X29 is selected from the group consisting of Asn, Trp and Tyr;
X30 is selected from the group consisting of Ala, His, Trp, and Tyr;
X31 is selected from the group consisting of Ala, Ile, Leu and Thr;
X32 is selected from the group consisting of Gln, Leu and Thr;

wherein one to three amino acids of X5, X6, X8-X19, X21-X24 and X26-X32 may be absent, and
wherein a half-life extending group is attached to the epsilon amino group of the lysine at position 7.

In some examples, 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, and OEG, or independently selected from the group consisting of γ-Glu, and OEG.

In some embodiment the PYY analogue is selected from the compounds 1 to 244 described herein.

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

The 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 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.

The disclosure provides a PYY analogue of the disclosure for use in a method of treating, inhibiting or reducing weight gain, promoting weight loss and/or reducing excess body weight. In another aspect, the present disclosure provides a PYY analogue as described herein for use in therapy, e.g. for use in the treatment of a condition or disease related or caused by excess body weight or excess body weight gain. 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.

WHAT WE CLAIM

1. A PYY analogue comprising an amino acid sequence corresponding to the amino acid sequence of hPYY(3-36), wherein 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_6, -C(O)C_{3-6} cycloalkyl, -C(O)C_{1-6} alkyl-C_{3-6} cycloalkyl, or 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 I:

Ala-X5-X6-Lys-X8-X9-X10-X11-X12-X13-X14-X15-X16-X17-X18-X19-Tyr-X21-X22-X23-X24-Arg-X26-X27-X28-X29-X30-X31-X32-Arg-Gln-Arg-Tyr (I)

wherein

X5 is selected from the group consisting of Pro and Hyp;

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

X8 is selected from the group consisting of Ala, Ile, Pro, Thr, Val and Hyp;

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

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

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

X12 is selected from the group consisting of Ala, Gly, Ser, Thr and Val;

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

X14 is selected from the group consisting of Ala, Glu, Gly, Pro and Hyp;

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

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

X17 is selected from the group consisting of Ala, 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 Ala, Glu, Gln and Tyr;

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

X23 is selected from the group consisting of Ala, Glu, Ser and Thr;

X24 is selected from the group consisting of Ala, Ile, Leu, Thr and Val;
X26 is selected from the group consisting of Ala, His and Lys;
X27 is selected from the group consisting of Gln and Tyr;
X28 is selected from the group consisting of His, Trp and Tyr;
X29 is selected from the group consisting of Asn, Trp and Tyr;
X30 is selected from the group consisting of Ala, His, Trp, and Tyr;
X31 is selected from the group consisting of Ala, Ile, Leu and Thr;
X32 is selected from the group consisting of Gln, Leu and Thr;

wherein one to three amino acids of X5, X6, X8-X19, X21-X24 and X26-X32 may be absent, and
wherein a half-life extending group is attached to the epsilon amino group of the lysine at position 7.

2. The PYY analogue according to claim 1, wherein 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_6, -C(O)C_{3-6} cycloalkyl, -C(O)C_{1-6} alkyl-C_{3-6} cycloalkyl, or 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 an amino acid sequence of formula III:

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

wherein
X6 is selected from the group consisting of Ala and Glu;
X9 is selected from the group consisting of Glu and Gly;
X10 is selected from the group consisting of Ala and Glu;
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,
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;
X23 is selected from the group consisting of Ala, Glu, Ser and Thr;

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

3. The PYY analogue according to claim 1, wherein 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_6, -C(O)C_{3-6} cycloalkyl or C_{1-6} alkyl:

R^2 is OH or NHR^3, wherein R^3 is hydrogen or C_{1-3} alkyl; and
Z is an amino acid sequence selected from Table 1.

4. The PYY analogue according to any one of claims 1 to 3, wherein at least two amino acids from X6, X10, X11, X13 and X23 are selected from the group consisting of Asp and Glu.

5. The PYY analogue according to any of claims 1 to 4, wherein only one of X6, X10 and X15 is Ala.

6. The PYY analogue according to any of the previous claims, wherein 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.

7. The PYY analogue according to claim 6, wherein X is selected from the group consisting of 15-carboxy-pentadecanoyl, 17-carboxy-heptadecanoyl (C18DA) and 19-carboxy-nonadecanoyl, and U consists of one, two or three sub-moieties independently selected from the group consisting of Gly, Glu, γ-Glu, ε-Lys, Ser and OEG.

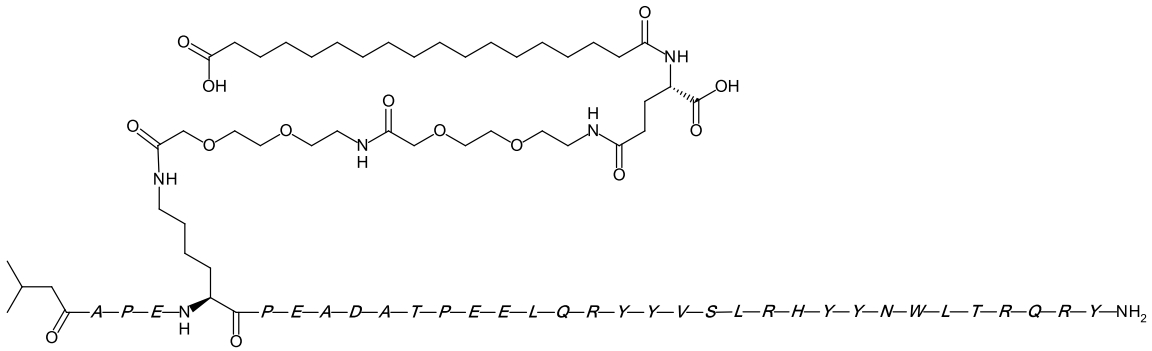
8. The PYY analogue according to any one of the previous claims, wherein the PYY analogue is a compound selected from the group consisting of compound 1 to compound 244.

9. 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.

10. The PYY analogue according to any one of the previous claims, wherein the binding affinity (Ki) towards hNPY2R is below 100 nM.

11. 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.

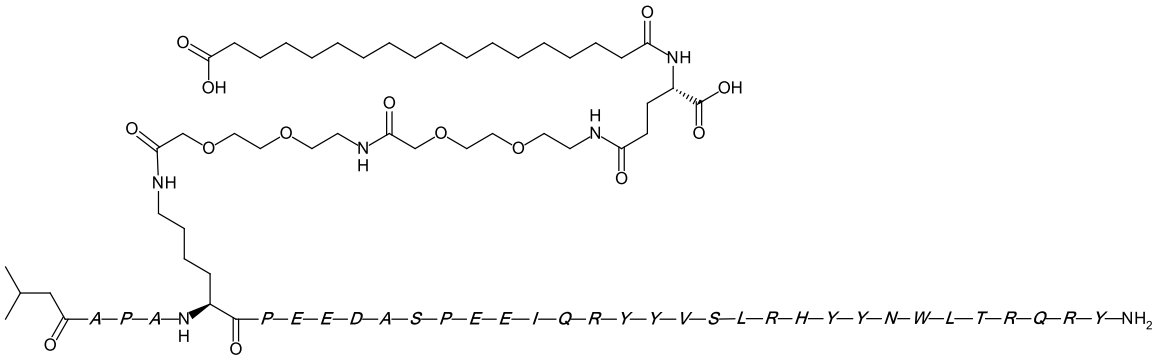
12. The PYY analogue according to claim 1, wherein the compound is



(Compound 14)

or a pharmaceutically acceptable salt thereof.

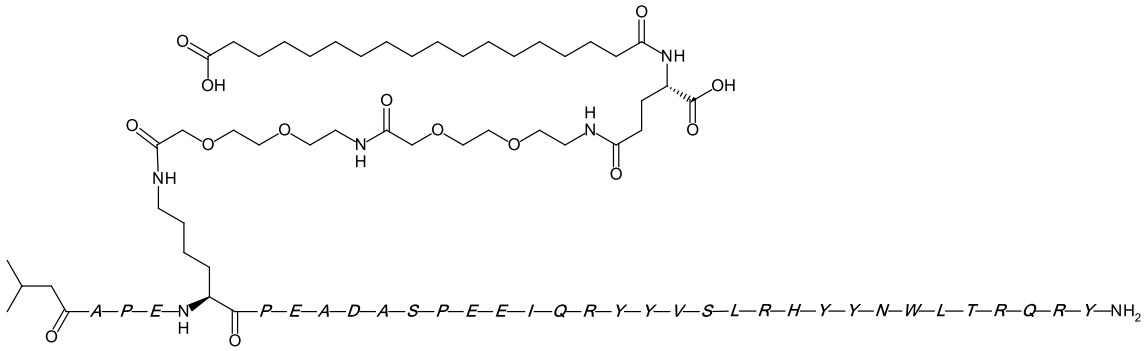
13. The PYY analogue according to claim 1, wherein the compound is



(Compound 23)

or a pharmaceutically acceptable salt thereof.

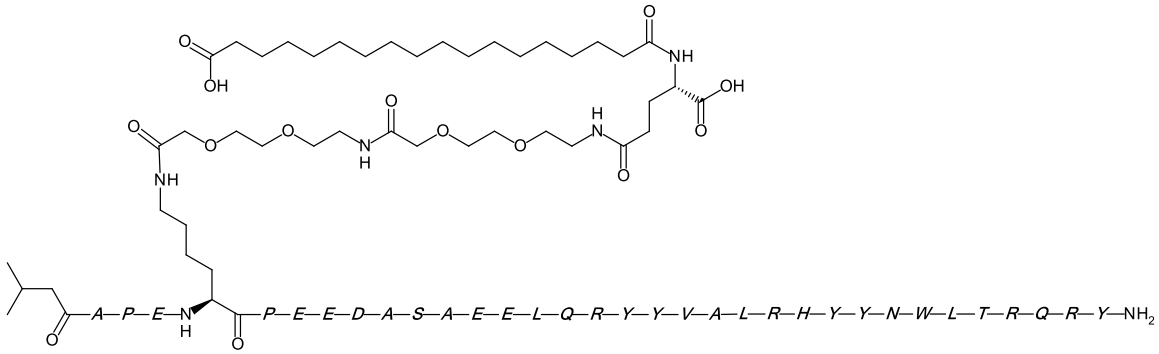
14. The PYY analogue according to claim 1, wherein the compound is



(Compound 53)

or a pharmaceutically acceptable salt thereof.

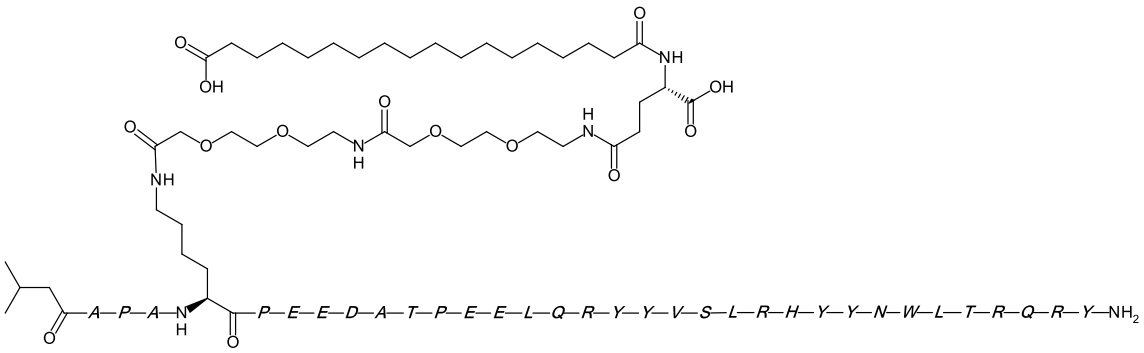
15. The PYY analogue according to claim 1, wherein the compound is



(Compound 74)

or a pharmaceutically acceptable salt thereof.

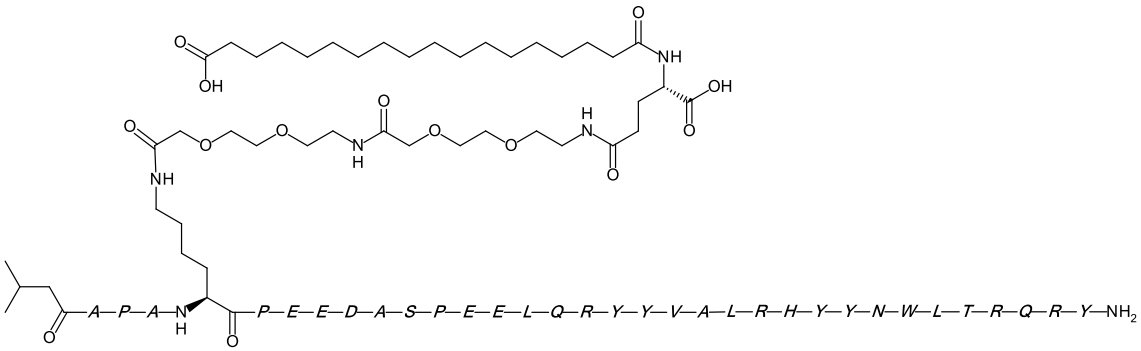
16. The PYY analogue according to claim 1, wherein the compound is



(Compound 106)

or a pharmaceutically acceptable salt thereof.

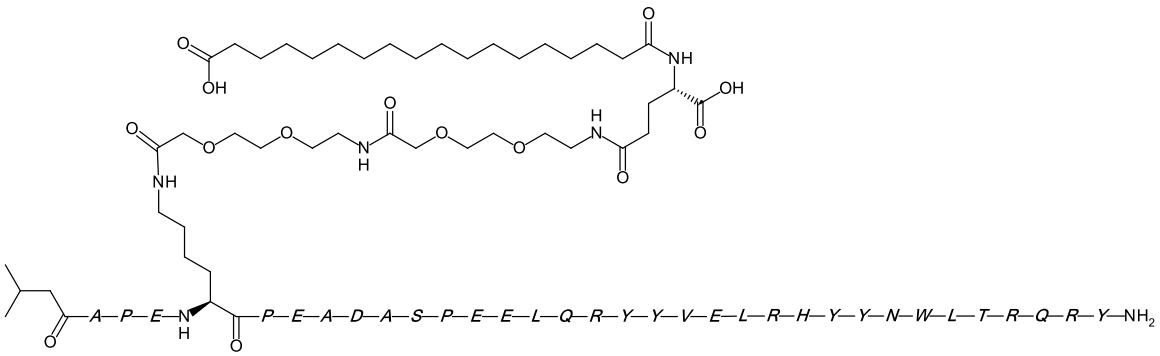
17. The PYY analogue according to claim 1, wherein the compound is



(Compound 117)

or a pharmaceutically acceptable salt thereof.

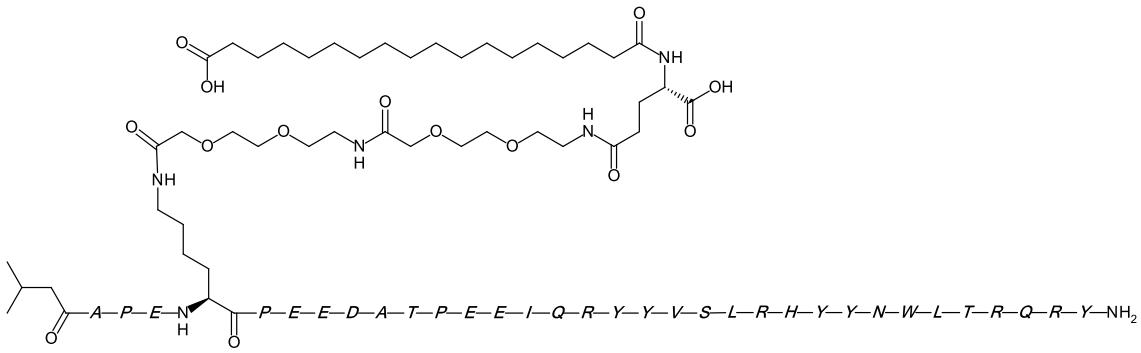
18. The PYY analogue according to claim 1, wherein the compound is



(Compound 135)

or a pharmaceutically acceptable salt thereof.

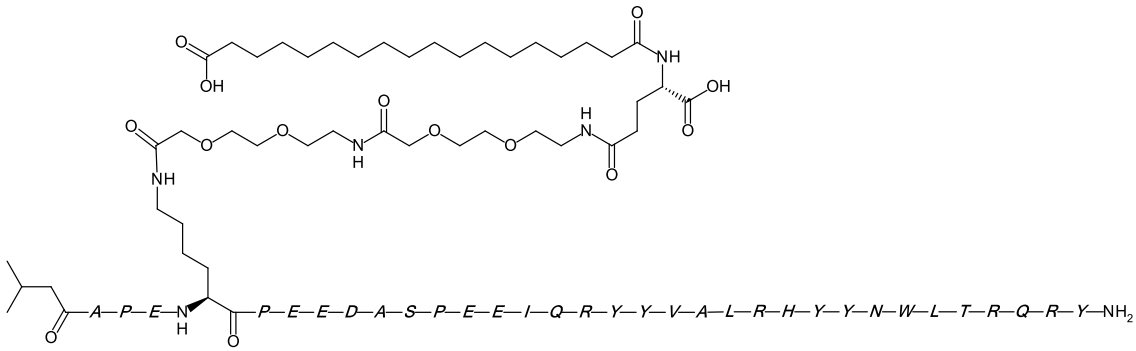
19. The PYY analogue according to claim 1, wherein the compound is



(Compound 171)

or a pharmaceutically acceptable salt thereof.

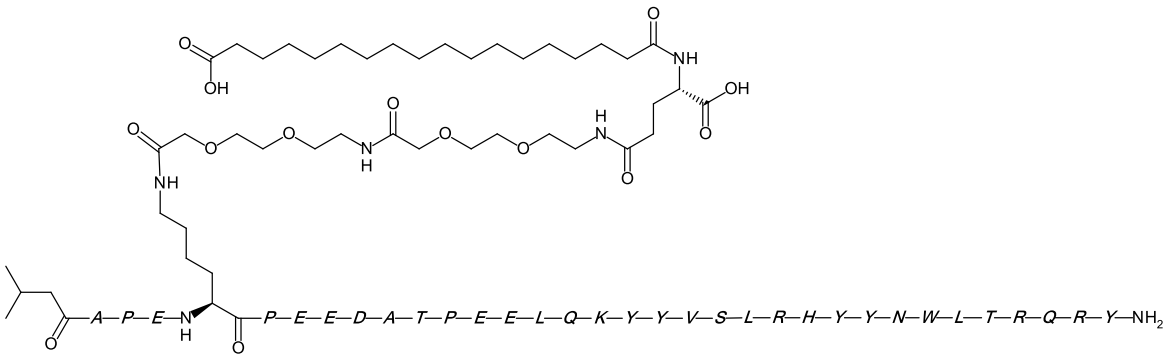
20. The PYY analogue according to claim 1, wherein the compound is



(Compound 230)

or a pharmaceutically acceptable salt thereof.

21. The PYY analogue according to claim 1, wherein the compound is



(Compound 231)

or a pharmaceutically acceptable salt thereof.

22. A pharmaceutical composition comprising at least one PYY analogue according to any one of the previous claims and one or more pharmaceutically acceptable excipient.

23. A PYY analogue according to any one of claims 1 to 21 for use in therapy, e.g. for use in the treatment of a condition or disease related or caused by excess body weight or excess body weight gain.

24. A PYY analogue according to any one of claims 1 to 21 for use according to claim 23, wherein the use is for the treatment of obesity or obesity-related conditions, such as type 2 diabetes, hypertension, dyslipidemia, sleep apnea and cardiovascular disease.

25. A PYY analogue according to any one of claims 1 to 21 for use according to claim 23, wherein the use is for the treatment of atherogenic dyslipidemia, hepatic steatosis, NAFLD, NASH, kidney failure or atherosclerosis.

26. A PYY analogue according to any one of claims 1 to 21 for the treatment according to any one of claims 23 to 25, 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.

27. A PYY analogue according to any one of claims 1 to 21 for the treatment according to any one of claims 23 to 25, wherein the PYY analogue is to be administered as part of a combination therapy together with an agent for 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.

28. Use of a PYY analogue according to any one of claims 1 to 21 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.

29. The use according to claim 28, wherein the disease is obesity or obesity-related conditions, such as type 2 diabetes, hypertension, dyslipidemia, sleep apnea and cardiovascular disease.

30. The use according to claim 28, wherein the disease is atherogenic dyslipidemia, hepatic steatosis, NAFLD, NASH, kidney failure or atherosclerosis.

31. The use according to any one of claims 28 to 30, 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.

32. The use according to any one of claims 28 to 30, wherein the PYY analogue is to be administered as part of a combination therapy together with an agent for 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.