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 II:

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

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, Pro, 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, 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, Pro and Hyp;

X15 is selected from the group consisting of Ala, Glu and Ser;
X16 is selected from the group consisting of 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;
X28 is selected from the group consisting of Trp and Tyr;
X29 is selected from the group consisting of Asn, and Tyr;
X30 is selected from the group consisting of His, Trp, and Tyr;
X31 is selected from the group consisting of Ala, Ile, and Leu;
X32 is selected from the group consisting of Gln, and Thr;

and wherein only one of X6 , X10 and X15 is Ala, and
at least two amino acids from X6, X10, X11, X13 and X23 are selected from the group consisting of Asp and Glu, 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 epsilon amino group of lysine and X is attached to U, 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 γ-Glu, and OEG.

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 the treatment of obesity or obesity-related conditions, 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 obesity or obesity-related conditions, such as type 2 diabetes, hypertension, dyslipidemia, sleep apnea and cardiovascular disease.

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 II:

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

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, Pro, 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, 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, Pro and Hyp;

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

X16 is selected from the group consisting of 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;
X28 is selected from the group consisting of Trp and Tyr;
X29 is selected from the group consisting of Asn, and Tyr;
X30 is selected from the group consisting of His, Trp, and Tyr;
X31 is selected from the group consisting of Ala, Ile, and Leu;
X32 is selected from the group consisting of Gln, and Thr;

and wherein only one of X6 , X10 and X15 is Ala, and
at least two amino acids from X6, X10, X11, X13 and X23 are selected from the group consisting of Asp and Glu, 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 epsilon amino group of lysine and X is attached to U, 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 γ-Glu, and OEG.

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.

3. The PYY analogue according to claim 1, wherein the PYY analogue is a compound having the formula:

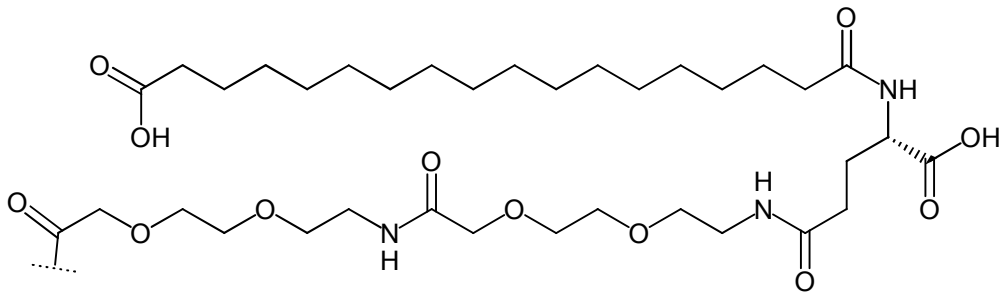
R^1-Z-R^2,
wherein R^1 is hydrogen, -C(O)C_{1-6} alkyl, -C(O)C_6H_6, -C(O)C_{3-6} cycloalkyl or C_{1-6} alkyl:

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 the following sequences:
SEQ ID Nos: 6-8, 10-15, 17-31, 33-35, 37-46, 48-51, 53-58, 60-79, 81-86, 88-95, 97-117, 119-124, 126-133, 135-156, 158-182, 184-190, 192-197, 199, 200, 202-210, 212, 213, 215, 218-241, 243-248.

4. The PYY analogue according to claim 1, wherein X9 is selected from Glu and Gly.

5. The PYY analogue according to claim 1, wherein X9 is Glu.

6. The PYY analogue according to any one of claims 1 to 4, wherein the half-life extending group is C18DA-γ-Glu-OEG-OEG-, i.e.



.

7. The PYY analogue according to any one of the previous claims, wherein the PYY analogue is a compound selected from the group consisting of the following compounds: 2-4, 6-11, 13-27, 29-31, 33-42, 44-47, 49-54, 56-75, 77-82, 84-91, 93-113, 115-120, 122-129, 131-152, 154-178, 180-186, 188-193, 195, 196, 198-206, 208, 209, 211, 214-237, 239-244.

8. 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 IV:

Ala-Pro-X6-Lys-Pro-Glu-X10-X11-Ala-X13-X14-Glu-Glu-X17-Gln-X19-Tyr-Tyr-Val-X23-Leu-Arg-His-Tyr-Tyr-Asn-Trp-Leu-Thr-Arg-Gln-Arg-Tyr (IV)

wherein
X6 is selected from the group consisting of Ala and Glu;
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 Ala, Glu, Ser, and Thr;
X14 is selected from the group consisting of Ala, Pro and Hyp;
X17 is selected from the group consisting of Ile and Leu;

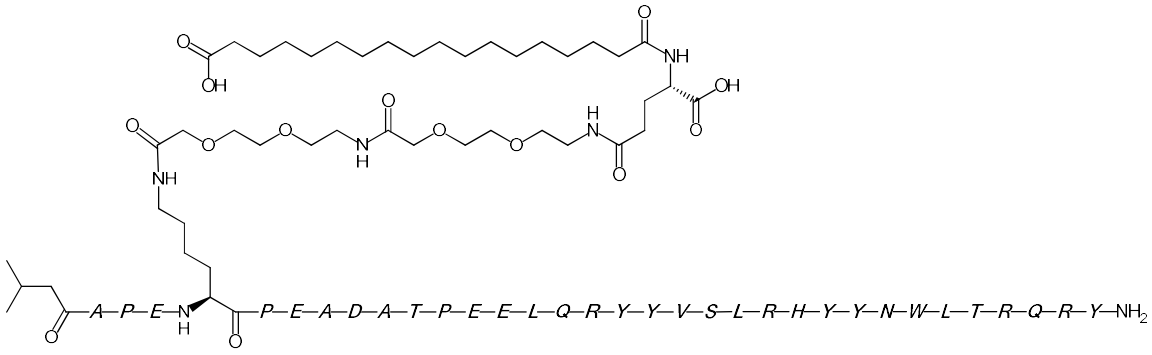
X19 is selected from the group consisting of Arg, Lys, and Gln;
X23 is selected from the group consisting of Ala, Glu, and Ser.

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.

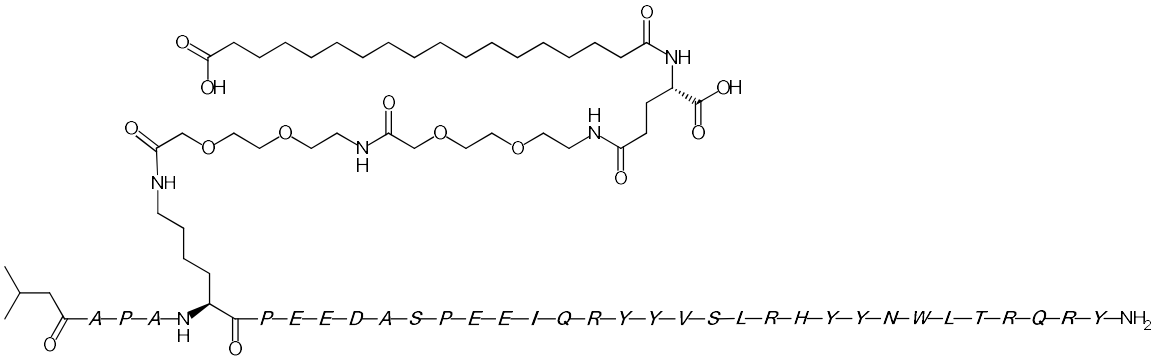
11. The PYY analogue according to any one of the previous claims, wherein the solubility of the PYY analogue is greater than 1.0 mg/ml at pH 6.

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



(Compound 14)
or a pharmaceutically acceptable salt thereof.

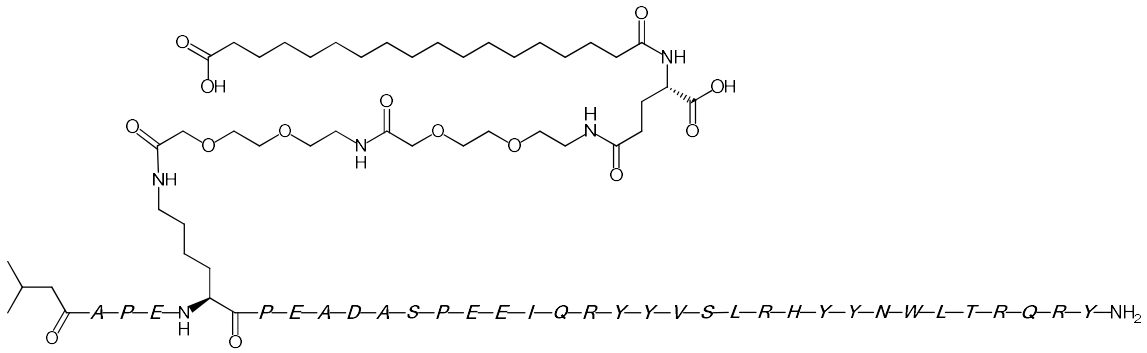
13. The PYY analogue according to claim 1, wherein the compound is



(Compound 23)

or a pharmaceutically acceptable salt thereof.

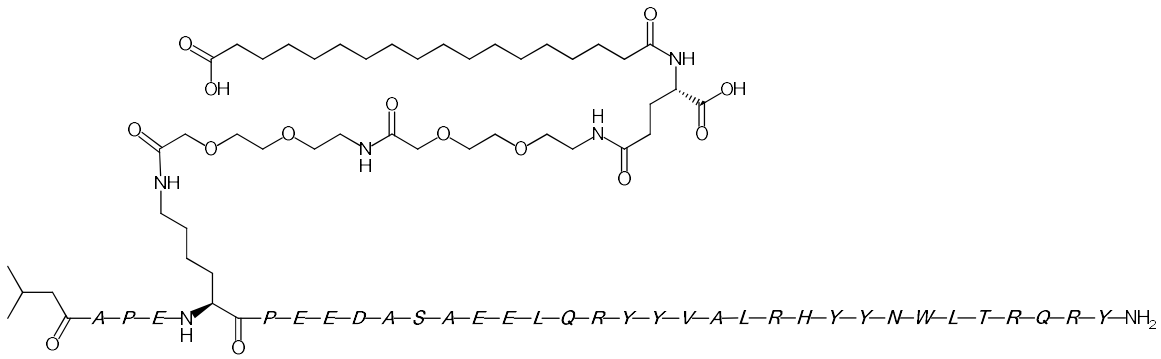
14. The PYY analogue according to claim 1, wherein the compound is



(Compound 53)

or a pharmaceutically acceptable salt thereof.

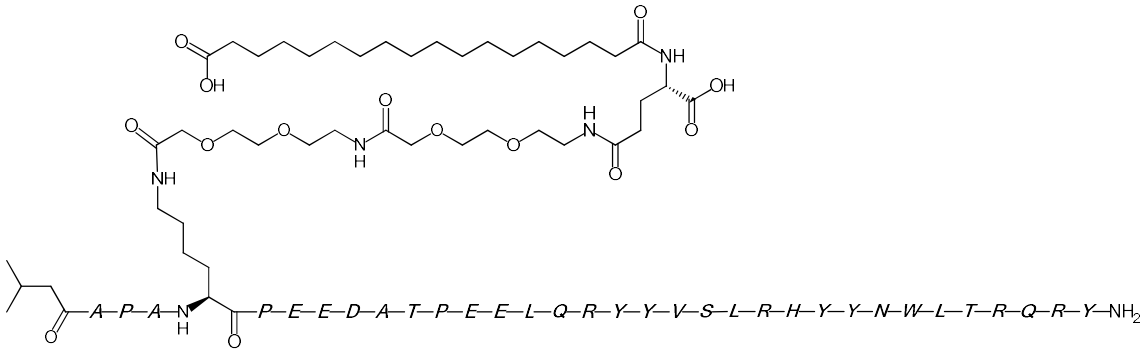
15. The PYY analogue according to claim 1, wherein the compound is



(Compound 74)

or a pharmaceutically acceptable salt thereof.

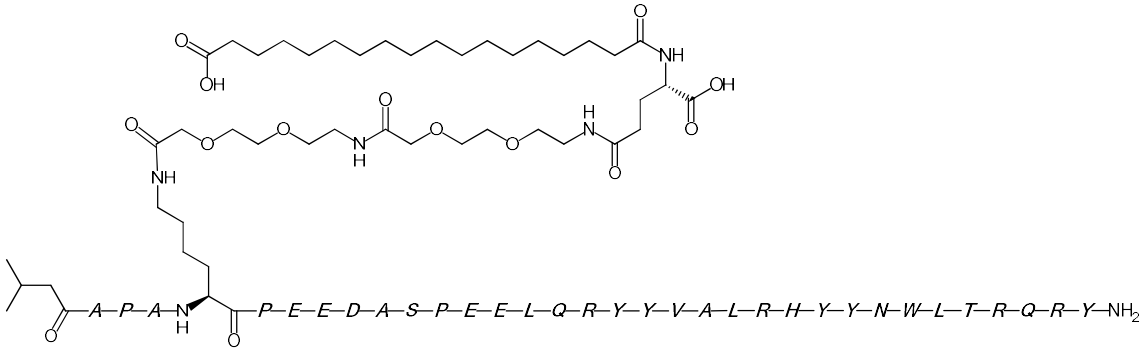
16. The PYY analogue according to claim 1, wherein the compound is



(Compound 106)

or a pharmaceutically acceptable salt thereof.

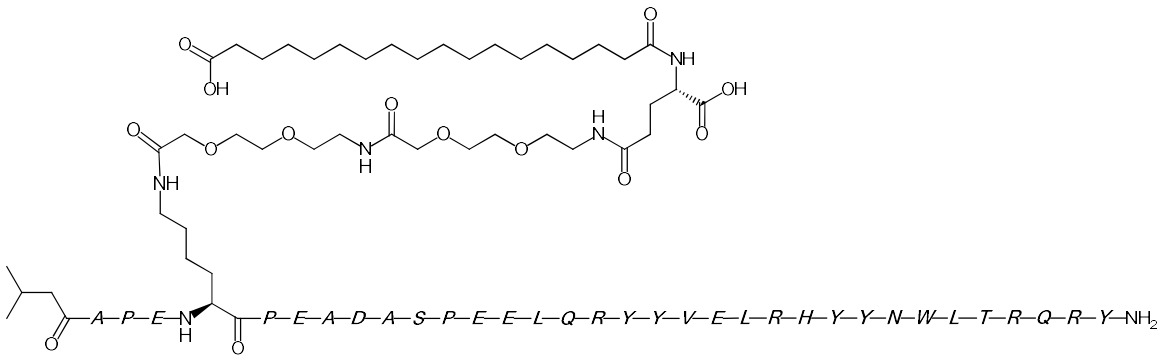
17. The PYY analogue according to claim 1, wherein the compound is



(Compound 117)

or a pharmaceutically acceptable salt thereof.

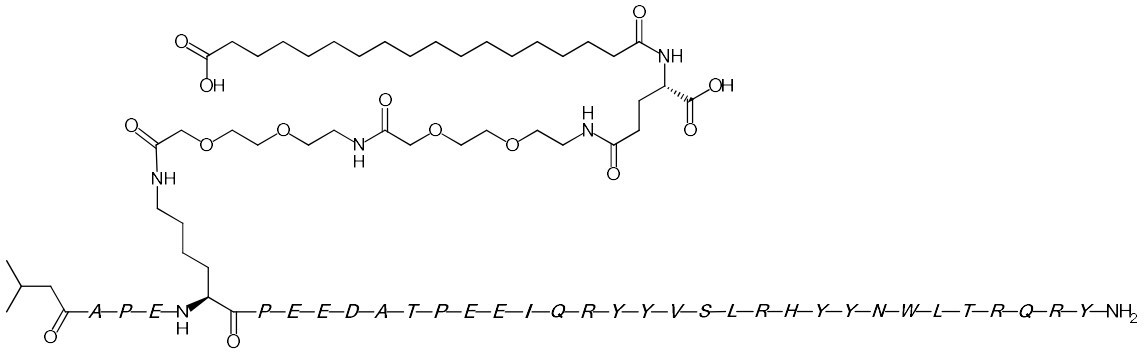
18. The PYY analogue according to claim 1, wherein the compound is



(Compound 135)

or a pharmaceutically acceptable salt thereof.

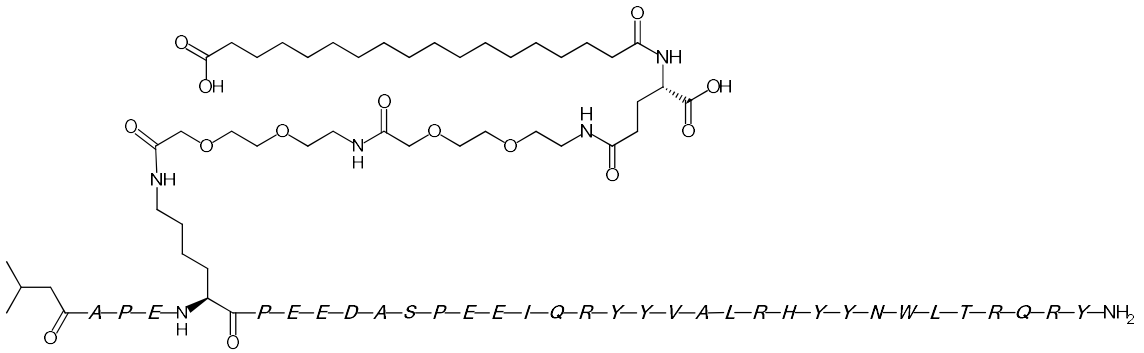
19. The PYY analogue according to claim 1, wherein the compound is



(Compound 171)

or a pharmaceutically acceptable salt thereof.

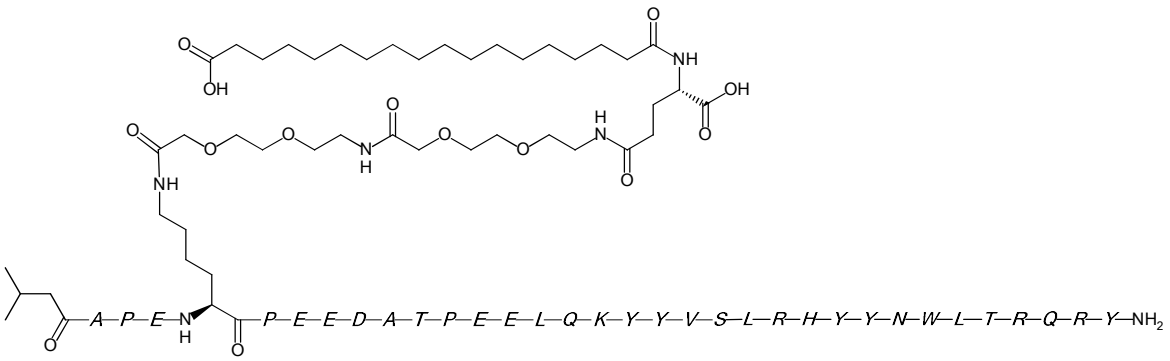
20. The PYY analogue according to claim 1, wherein the compound is



(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 the treatment of obesity or obesity-related conditions, such as type 2 diabetes, hypertension, dyslipidemia, sleep apnea and cardiovascular disease.

24. A PYY analogue for use according to claim 23, wherein the use is for the treatment of atherogenic dyslipidemia, hepatic steatosis, NAFLD, NASH, kidney failure or atherosclerosis.

25. A PYY analogue for use according to claim 23 or 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.

26. A PYY analogue for use according to claim 23 or 24, 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.

27. Use of a PYY analogue according to any one of claims 1 to 21 in the manufacture of a medicament for the treatment of obesity or obesity-related conditions, such as type 2 diabetes, hypertension, dyslipidemia, sleep apnea and cardiovascular disease.

28. The use according to claim 27, wherein the disease is atherogenic dyslipidemia, hepatic steatosis, NAFLD, NASH, kidney failure or atherosclerosis.

29. The use according to claim 27 or 28, 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.

30. The use according to claim 27 or 28, 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.