

SOLUBLE NPY2 RECEPTOR AGONISTS

BACKGROUND OF THE INVENTION

5 FIELD OF THE INVENTION

The present invention relates to PYY analogues that are neuropeptide Y2 (NPY2) receptor agonists, and to their medical use in the treatment and/or prevention of a variety of diseases, conditions or disorders, such as treatment and/or prevention of excess food intake, excess body weight, obesity, metabolic diseases, and other conditions or disorders
10 related to excess body weight or obesity, e.g. diabetes and cardiovascular diseases.

BACKGROUND INFORMATION

Overweight and obesity are defined as abnormal or excessive fat accumulation that presents a risk to health. In this regard, overweight and obesity are major risk factors for a number of chronic diseases, including type 2 diabetes, cardiovascular diseases and cancer.
15 According to the WHO overweight and obesity are no longer considered a problem limited to high income countries but are now dramatically on the rise in low- and middle-income countries. WHO's Global Health Observatory indicate that, in 2016, 39% of women or men aged 18 and over were overweight and 11% of men and 15% of women were obese.

20 Despite long-standing efforts, the number of overweight and obese patients is still growing. First line therapy for overweight and obese patients comprise diet and exercise but often are not sufficiently efficacious. Second line treatment options are bariatric surgery and pharmacotherapy. Available pharmacological treatments seem to lack in efficacy and/or safety, and only a limited number of approved therapies are available in the US and in
25 Europe.

Therefore, there is still a high medical need for more efficacious and safe treatment options.

30 NPY (Neuropeptide Y; SEQ ID No:1 – human sequence), PYY (Peptide YY; SEQ ID No: 2 – human sequence), and PP (Pancreatic Polypeptide; SEQ ID No:3 – human sequence) are naturally secreted homologous, 36 amino acid, C-terminally amidated peptides and belong to the PP-fold family of peptides.

Sequence of hPYY (3-36):

Ile Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu Asn Arg Tyr Tyr Ala Ser
Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr (SEQ ID No:4)

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PYY is cleaved to PYY(3-36) by dipeptidyl peptidase IV (DPP IV). PYY(3-36) displays increased selectivity for the neuropeptide Y2 receptor over neuropeptide Y1, Y4 and Y5 receptors as compared to PYY(1-36), albeit some Y1 and Y5 affinity is retained. It is believed that PYY or PYY(3-36) exhibits the feeding suppressive action via activation of the neuropeptide Y2 receptor (*Inhibition of Food Intake in Obese Subjects by Peptide YY₃₋₃₆*, N Engl J Med 2003;349:941-8).

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However, PYY and also PYY(3-36) have a short half-life in the body and show undesirable chemical or physical properties, e.g. low stability. Further, the pharmacologic effect, e.g. its efficacy as body weight lowering agent, seems limited.

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WO2014/178018 discloses PYY analogues and their ability to reduce food intake in mice. WO2011/033068 and WO2011/058165 disclose long acting Y2 receptor agonists. WO2015/071355, WO2016/198682 and WO2020/092191 relate to PYY compounds, which are selective Y2 receptor agonists. PYY compounds are disclosed comprising a covalently attached substituent or modifying group also referred therein as a protracting moiety.

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There is a need in the art for further (long acting) PYY analogues selectively acting on the NPY2 receptor. For example, it would be desirable to increase further the solubility of PYY analogues, preferably to increase the solubility around pH 7 and/or around pH 6. This would increase the formulation options for a ready-to-use application and potentially allow combinations with other (peptide) therapeutics to improve their efficacy.

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It has been found that the PYY analogues of the present invention generally are soluble around pH 6 and pH 7.

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BRIEF SUMMARY OF THE INVENTION

- In a first aspect, the invention 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)
 - 5 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.
- 10 In some embodiments, 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)
 - iv) glutamine at the position corresponding to position 18 of hPYY(3-36)
 - 15 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)
 - ix) the sequence QRY at its C-terminal end,
- 20 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 of the present invention, 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;
- 30 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)

wherein

- 5
- 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;
X10 is selected from the group consisting of Ala and Glu;
10 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;
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;
15 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;
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;
20 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 Val;
X27 is selected from the group consisting of Gln and Tyr;
X28 is selected from the group consisting of Gln and Tyr;
25 X29 is selected from the group consisting of His, Asn and Gln;
X30 is selected from the group consisting of Trp and Lys;
X32 is selected from the group consisting of Gln, Leu, Ser and Thr;
X33 is selected from the group consisting of Lys and Arg;
30 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 at position 7.

In some embodiments, 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
5 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.

In some embodiments, the lipophilic substituent X is selected from the group consisting of 15-carboxy-pentadecanoyl, 17-carboxy-heptadecanoyl (C18DA) and 19-carboxy-
10 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 OEG, or independently selected from the group consisting of γ -Glu, Ahx and OEG.

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

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

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

The present invention 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,
25 diseases, or disorders such as type 2 diabetes, NAFLD or NASH.

The invention provides a PYY analogue of the invention for use in a method of treating, inhibiting or reducing weight gain, promoting weight loss and/or reducing excess body weight.
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DETAILED DESCRIPTION OF THE INVENTION

TERMS, DEFINITIONS AND CONVENTIONS

Terms not specifically defined herein should be given the meanings that would be given to them by one of skill in the art in light of the disclosure and the context. As used in the specification, however, unless specified to the contrary, the following terms have the
5 meaning indicated and the following conventions are adhered to.

Throughout this specification, amino acid positions of the PYY analogues are numbered according to the corresponding position in native human PYY having the sequence shown above.

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PYY analogues

A PYY analogue is a peptide comprising an amino acid sequence corresponding to the amino acid sequence of hPYY(3-36). In other words a PYY analogue is a peptide, whose structure is related to PYY, in which one or more amino acid residues have been modified
15 when compared to hPYY(3-36). Possible modifications are substitutions, insertions, or deletions of amino acids at specific positions. A PYY analogue of the invention relates to a peptide that has retained a certain binding affinity (K_i) towards the hNPY2 receptor.

The term "PYY analogue" comprises the peptide itself, i.e. in a non-ionized state, as well
20 as the peptide in ionized state (e.g. when one or more side chains of its amino acids are ionized, i.e. (de)protonated).

The term "PYY analogue" may also refer to peptides, in which a half-life extending group is attached to one or more amino acids of the peptide. In such cases, a side chain of an
25 amino acid bears a covalently attached half-life extending group.

As used herein, the term "pharmaceutically acceptable salt" is intended to indicate a salt which is not harmful to a patient or subject to which the salt in question is administered. It may suitably be a salt chosen, e.g., among acid addition salts and basic salts. As used
30 herein, "pharmaceutically acceptable salt" refer to derivatives of the disclosed analogues or compounds wherein the parent analogue or compound is modified by making acid or base salts thereof. Examples of acid addition salts include chloride salts, citrate salts and acetate salts. Examples of basic salts include salts, where the cation is selected among alkali metal

cations, such as sodium or potassium ions, alkaline earth metal cations, such as calcium or magnesium ions, as well as substituted ammonium ions, such as ions of the type $N(R^1)(R^2)(R^3)(R^4)^+$, where R^1 , R^2 , R^3 and R^4 independently will typically designate hydrogen or optionally substituted C_{1-6} -alkyl. Other examples of pharmaceutically acceptable salts are described in "Remington's Pharmaceutical Sciences", 17th edition, Alfonso R. Gennaro (Ed.), Mark Publishing Company, Easton, PA, USA, 1985 (and more recent editions thereof), in the "Encyclopaedia of Pharmaceutical Technology", 3rd edition, James Swarbrick (Ed.), Informa Healthcare USA (Inc.), NY, USA, 2007, Vol. 5, p. 3177, and in *J. Pharm. Sci.* 66: 2 (1977).

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The term "agonist" as employed in the context of the invention refers to a substance that activates the receptor type in question, typically by binding to it (i.e. as a ligand).

Each embodiment of the invention described herein may be taken alone or in combination with one or more other embodiments of the invention.

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Throughout the present specification, unless naturally occurring amino acids are referred to by their full name (e.g. alanine, arginine, etc.), they are designated by their conventional three-letter or single-letter abbreviations (e.g. Ala or A for alanine, Arg or R for arginine, etc.).

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Unless otherwise indicated, reference is made to the L-isomeric forms of the amino acids in question.

Additional abbreviations include the following:

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Hyp: 4-hydroxyproline, e.g. (2S,4R)-4-hydroxyproline
[also denoted (4R)-4-hydroxy-L-proline]
 γ -Glu: γ -glutamic acid [also denoted gGlu]

The term " C_{1-n} alkyl", wherein n is an integer selected from 2, 3, 4, 5 or 6, either alone or in combination with another radical, denotes an acyclic, saturated, branched or linear hydrocarbon radical with 1 to n C atoms. For example the term C_{1-5} -alkyl embraces the radicals H_3C- , H_3C-CH_2- , $H_3C-CH_2-CH_2-$, $H_3C-CH(CH_3)-$, $H_3C-CH_2-CH_2-CH_2-$, H_3C-

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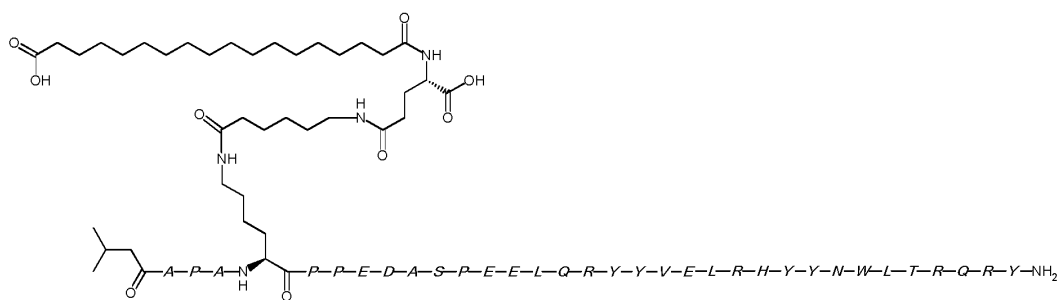
CH₂-CH(CH₃)-, H₃C-CH(CH₃)-CH₂-, H₃C-C(CH₃)₂-, H₃C-CH₂-CH₂-CH₂-CH₂-, H₃C-CH₂-CH₂-CH(CH₃)-, H₃C-CH₂-CH(CH₃)-CH₂-, H₃C-CH(CH₃)-CH₂-CH₂-, H₃C-CH₂-C(CH₃)₂-, H₃C-C(CH₃)₂-CH₂-, H₃C-CH(CH₃)-CH(CH₃)- and H₃C-CH₂-CH(CH₂CH₃)-.

- 5 The term "C_{3-n}-cycloalkyl", wherein n is an integer from 4 to n, either alone or in combination with another radical denotes a cyclic, saturated, unbranched hydrocarbon radical with 3 to n C atoms. For example, the term C₃₋₆-cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.
- 10 "C(O)" or "C(=O)" refers to a carbonyl group.

Nomenclature of compounds:

As an example,

- iVal-APAK(C18DA-gGlu-Ahx)PPEDASPEELQRYVELRHYYNWLTRQRY-NH₂,
 15 wherein iVal represents 3-methylbutanoyl (-C(O)CH₂CH(CH₃)₂),
 C18DA represents 17-carboxyheptadecanoyl,
 gGlu represents L-γ-glutamyl, connected via its amino-group to C18DA and via its γ-carboxy-group to Ahx, and
 Ahx represents 6-amino-hexanoyl, connected via its amino-group to gGlu and via its
 20 carboxy-group to ε-amino-group of lysine (K),
 completely defines the PYY analogue of the following structure:



Alternatively, the same compound can be defined in the following way:

- 25 N{α-4}-(3-methylbutanoyl)-N{ε-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido)butanamido]hexanoyl)-
 [4A,6A,7K,9P,18Q,22V,23E,28Y,30W,31L]-hPYY(4-36).

The terms "treatment" and grammatical variants thereof (e.g. "treated", "treating", "treat") as employed in the present context refer to an approach for obtaining beneficial or desired clinical results. For the purposes of this invention, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilization (i.e. not worsening) of state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival relative to expected survival time if not receiving treatment. A subject (e.g. a human) in need of treatment may thus be a subject already afflicted with the disease or disorder in question. The term "treatment" includes inhibition or reduction of an increase in severity of a pathological state or symptoms (e.g. weight gain or hyperglycemia) relative to the absence of treatment and is not necessarily meant to imply complete cessation of the relevant disease, disorder or condition.

The terms "prevention" and grammatical variants thereof (e.g., "prevented", "preventing", "prevent") as employed in the present context refer to an approach for hindering or preventing the development of, or altering the pathology of, a condition, disease or disorder. Accordingly, "prevention" may refer to prophylactic or preventive measures. For the purposes of this invention, beneficial or desired clinical results include, but are not limited to, prevention or slowing of symptoms, progression or development of a disease, whether detectable or undetectable. A subject (e.g. a human) in need of "prevention" may thus be a subject not yet afflicted with the disease or disorder in question. The term "prevention" thus includes inhibiting or slowing the onset of disease relative to the absence of treatment and is not necessarily meant to imply permanent prevention of the relevant disease, disorder or condition.

Half-life extending group

As described herein, a half-life extending group is covalently attached to a functional group of a side chain of an amino acid of the PYY analogue. The half-life extending group comprises or consists of a lipophilic substituent (X) and optionally a linker (U), wherein one end of the linker U (if present) is attached to an amino acid of the PYY analogue and the other end is connected to the lipophilic substituent (-U-X).

Without wishing to be bound by any particular theory, it is thought that such lipophilic substituents (and other classes of half-life extending moieties) bind albumin and other plasma components in the blood stream, thereby shielding the compound of the invention from renal filtration as well as enzymatic degradation and thus possibly enhancing the half-life of the compound *in vivo*. The lipophilic substituent may also modulate the potency of the compound as an agonist to the NPY2 receptor or other receptors of the NPY receptor family.

The lipophilic substituent X is attached to the linker U via an ester, ether, a sulfonyl ester, a thioester, an amide, an amine, triazole or a sulfonamide. Accordingly, it will be understood that preferably the lipophilic substituent X includes an acyl group, a sulfonyl group, an alkyne, an azide, an N atom, an O atom or an S atom, which forms part of the ester, sulfonyl ester, thioester, triazole, amide, amine or sulfonamide. Preferably, an acyl group, or an O or N atom in the lipophilic substituent X forms part of an amide or ester with the linker U.

The half-life extending group (the linker U thereof, if present) is attached to an amino acid residue of the PYY analogue via an ester, a sulfonyl ester, a thioester, an amide, an amine or a sulfonamide. Accordingly, it will be understood that preferably the half-life extending group (the linker U thereof, if present) includes an acyl group, a sulfonyl group, an N atom, an O atom or an S atom, which forms part of the ester, sulfonyl ester, thioester, amide, amine or sulfonamide. Preferably, an acyl group, or an O or N atom in the linker U forms part of an amide or ester with the amino acid residue.

The lipophilic substituent X may comprise a hydrocarbon chain having from 10 to 24 C atoms, e.g. from 14 to 22 C atoms, e.g. from 16 to 20 C atoms. Preferably, it has at least 14 C atoms, and preferably has 20 C atoms or fewer. For example, the hydrocarbon chain may contain 14, 15, 16, 17, 18, 19 or 20 carbon atoms. The hydrocarbon chain may be linear or branched and may be saturated or unsaturated. Furthermore, it can include a functional group at the end of the hydrocarbon chain, e.g. a carboxylic acid group, a sulphonic acid group, or a tetrazole group. From the discussion above it will also be understood that the hydrocarbon chain is preferably substituted with a moiety, which forms part of the attachment to an amino acid residue of the PYY analogue or to the linker U, for example an acyl group, a sulfonyl group, an N atom, an O atom or an S atom.

Most preferably, the hydrocarbon chain is substituted with an acyl group (for the attachment to the linker U), and accordingly the hydrocarbon chain may be part of an alkanoyl group, for example a dodecanoyl, 2-butyloctanoyl, tetradecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl or eicosanoyl group. These hydrocarbon chains substituted with an acyl group at one end may further be functionalized with a carboxylic acid group at the other end of the chain. Examples of functionalized hydrocarbon chains (e.g. lipophilic substituents X) are 15-carboxy-pentadecanoyl, 17-carboxy-heptadecanoyl and 19-carboxy-nonadecanoyl.

In certain embodiments, the linker moiety U may itself comprise one, two, three or more linked sub-moieties (U^1 , U^2 , U^3 , etc). In some of these embodiments the linker may comprise one or more (e.g. one, two or three) linked amino acid residues, which may each independently be a residue of any naturally occurring or non-naturally occurring amino acid. For example, the linker may comprise one, two or three linked amino acid residues, each of which may independently be a residue of Gly, Pro, Ala, Val, Leu, Ile, Cys, Phe, Tyr, His, Lys, Arg, Gln, Asn, α -Glu, γ -Glu, ϵ -Lys, Asp, β -Asp, Ser, Thr, Aib, AEA (2-(2-aminoethoxy)acetic acid), Ahx (6-aminohexanoic acid), AEEEA (2-{2-[2-(2-aminoethoxy)ethoxy]ethoxy}acetic acid), H_2N -dPEG(4)-COOH (15-amino-4,7,10,13-tetraoxa-pentadecanoic acid), H_2N -dPEG(6)-COOH (1-amino-3,6,9,12,15,18-hexaoxaheptadecanoic acid), H_2N -dPEG(12)-COOH (1-amino-3,6,9,12,15,18,21,24,27,30,33,36-dodecaoxanonatriacontan-39-oic acid), OEG-OEG (2-[2-(2-{2-[2-(2-aminoethoxy)ethoxy]acetamido}ethoxy)ethoxy]acetic acid), H-Ebes (3-({2-[2-(2-aminoethoxy)ethoxy]ethyl}carbamoyl)propanoic acid), H-DOOA-DIG-OH (2-[(2-[2-(2-aminoethoxy)ethoxy]ethyl}carbamoyl)methoxy]acetic acid), H-TTD-DIG-OH (2-[(3-{2-[2-(3-aminopropoxy)ethoxy]ethoxy}propyl)carbamoyl]methoxy}acetic acid), H-TTDS-OH (3-[(3-{2-[2-(3-aminopropoxy)ethoxy]ethoxy}propyl)-carbamoyl]propanoic acid), or 8Ado (i.e. 8-amino-3,6-dioxaoctanoyl also denoted OEG herein).

References to γ -Glu, ϵ -Lys, and β -Asp indicate residues of amino acids which participate in bonds via their side chain carboxyl or amine functional groups. Thus γ -Glu, and β -Asp participate in bonds via their alpha amino and side chain carboxyl groups, while ϵ -Lys participates via its carboxyl and side chain amino groups. In the context of the present invention, γ -Glu, gGlu and isoGlu are used interchangeably.

In certain embodiments, the linker U consists of one, two or three independently selected sub-moieties (U^1 , U^2 , U^3) selected from the group consisting of Ala, Glu, γ -Glu, Gly, ϵ -Lys, Ser, Ahx, Ahx-Ahx, OEG and OEG-OEG.

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Linkers comprising Ahx as sub-moiety (e.g. γ -Glu-Ahx, Ahx- γ -Glu, Ahx-Ahx, γ -Glu- γ -Glu-Ahx, Ahx- γ -Glu- γ -Glu) may be preferred.

Synthesis of PYY analogues

- 10 The invention provides a method of synthesis of a PYY analogue of the invention. The PYY analogues may be manufactured by standard synthetic methods, including standard solid-phase or liquid-phase methodology. Peptides are assembled either stepwise or by merging fragments, and optionally isolated and purified yielding the final peptide product. Synthesis examples are described in numerous publications, including Fields, G.B. et al.,
15 "Principles and Practice of Solid-Phase Peptide Synthesis" in Synthetic Peptides, Grant G.A. (ed.), Oxford University Press (2nd edition, 2002).

EMBODIMENTS

- 20 In a first aspect, the invention 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
25 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 embodiments, the PYY analogue comprises proline at the position corresponding
30 to position 5 of hPYY(3-36).

In some embodiments, the PYY analogue comprises glutamine at the position corresponding to position 18 of hPYY(3-36).

In some embodiment, the PYY analogue comprises leucine at the position corresponding to position 24 of hPYY(3-36).

- 5 In some embodiments, the PYY analogue comprises arginine at the position corresponding to position 25 of hPYY(3-36).

In some embodiments, the PYY analogue comprises histidine at the position corresponding to position 26 of hPYY(3-36).

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In some embodiments, the PYY analogue comprises leucine at the position corresponding to position 31 of hPYY(3-36).

- 15 In some embodiments, the PYY analogue comprises arginine or lysine at the position corresponding to position 33 of hPYY(3-36).

In some embodiments, the PYY analogue bears a half-life extending group, which is attached to the epsilon amino group of the lysine at position 7.

- 20 In some embodiments of the present invention, 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.

In some embodiments the linker U consists of one, two or three sub-moieties (U1, U2, U3), wherein at least one sub-moiety is Ahx.

- 25 In some embodiments, 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)
 - iv) glutamine at the position corresponding to position 18 of hPYY(3-36)
 - 30 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)

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.

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In some embodiments, the PYY analogue comprises arginine at the position corresponding to position 33 of hPYY(3-36).

10 In some embodiments, the PYY analogue comprises tryptophan or lysine at the position corresponding to position 30 of hPYY(3-36).

In some embodiments, the PYY analogue comprises glutamine or tyrosine at the position corresponding to position 28 of hPYY(3-36).

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In some embodiments, the PYY analogue comprises glutamine or tyrosine at the position corresponding to position 27 of hPYY(3-36).

20 In some embodiments, the PYY analogue comprises glutamine or tyrosine at the position corresponding to position 21 of hPYY(3-36).

In some embodiments, the PYY analogue comprises glutamine or tyrosine at the position corresponding to position 20 of hPYY(3-36).

25 In some embodiments, the PYY analogue comprises alanine or glutamic acid at the position corresponding to position 15 of hPYY(3-36).

In some embodiments, the PYY analogue comprises alanine or glutamic acid at the position corresponding to position 10 of hPYY(3-36).

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In some embodiments, the PYY analogue comprises alanine or proline at the position corresponding to position 8 of hPYY(3-36).

In some embodiments, the PYY analogue comprises alanine or glutamic acid at the position corresponding to position 6 of hPYY(3-36).

In some embodiments, the PYY analogue bears a half-life extending group, which is
5 attached to the epsilon amino group of the lysine at position 7.

In some embodiments, the PYY analogue comprises

- i) alanine at the position corresponding to position 4 of hPYY(3-36)
 - 10 iii) proline at the position corresponding to position 5 of hPYY(3-36)
 - iv) alanine or glutamic acid at the position corresponding to position 6 of hPYY(3-36)
 - v) lysine at the position corresponding to position 7 of hPYY(3-36)
 - vi) alanine or proline at the position corresponding to position 8 of hPYY(3-36)
 - vii) alanine or glutamic acid at the position corresponding to position 10 of hPYY(3-36)
 - 15 viii) alanine or glutamic acid at the position corresponding to position 15 of hPYY(3-36)
 - ix) glutamine at the position corresponding to position 18 of hPYY(3-36)
 - x) glutamine or tyrosine at the position corresponding to position 20 of hPYY(3-36)
 - xi) glutamine or tyrosine at the position corresponding to position 21 of hPYY(3-36)
 - xii) leucine at the position corresponding to position 24 of hPYY(3-36)
 - 20 xiii) arginine at the position corresponding to position 25 of hPYY(3-36)
 - xiv) histidine at the position corresponding to position 26 of hPYY(3-36)
 - xv) glutamine or tyrosine at the position corresponding to position 27 of hPYY(3-36)
 - xvi) glutamine or tyrosine at the position corresponding to position 28 of hPYY(3-36)
 - xvii) tryptophan or lysine at the position corresponding to position 30 of hPYY(3-36)
 - 25 xviii) leucine at the position corresponding to position 31 of hPYY(3-36)
 - xix) 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 11, 14, 17, or 22, or to the carboxylic acid group of the side chain of an aspartate or a glutamate at position 14.

30

In some embodiments, exactly one half-life extending group is attached to the PYY analogue, said half-life extending group being attached to the epsilon amino group of the lysine at position 7.

In some embodiments according the previous paragraph, the linker U of the half-life
 5 extending group consists of one, two or three sub-moieties (U1, U2, U3), wherein at least one sub-moiety is Ahx.

In some embodiments of the present invention, the PYY analogue is a compound having
 10 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:

15 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)

20 wherein

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

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

25 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;

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

30 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;

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 HisAsn and Gln;
10 X30 is selected from the group consisting of Trp and Lys;
X32 is selected from the group consisting of Gln, Leu, Ser and Thr;
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.

In a further embodiment the PYY analogue is according to the previous embodiment,
20 wherein one of X6, X8-17, X19-X23 and X27-X32 is absent.

In a further embodiment the PYY analogue is according to the previous embodiment,
wherein none of X6, X8-17, X19-X23 and X27-X32 is absent.

25 In a further embodiment R^1 is $-C(O)C_{1-4}$ alkyl, $-C(O)C_{3-5}$ cycloalkyl, $-C(O)C_{1-3}$ alkyl- C_{3-4} cycloalkyl, C_{1-4} alkyl or C_{1-3} alkyl- C_{3-4} cycloalkyl.

In a further embodiment R^1 is $-C(O)CH_2CH(CH_3)_2$, $-C(O)CH_2$ -cyclobutyl,
30 $-C(O)CH_2$ -cyclopropyl.

It has been found that the PYY analogues of the present invention – bearing alanine at position 4 and lysine at position 7 - generally are soluble around pH 6 and pH 7.

Peptide therapeutics are usually provided as pharmaceutical liquid formulation in a pre-filled ready-to-use injection device. These peptide formulations for subcutaneous administration have limited application volumes. Therefore, good solubility of the peptides is a requirement for the application in a ready-to-use injection device.

- 5 A further important aspect is the long-term stability and solubility of the peptides in the liquid formulation. A property of fundamental importance for physical stability is the intrinsic solubility (at a given pH value).

- A broad pH range, within which a peptide therapeutic is reasonably soluble (solubility
10 window), is also desirable as it allows more flexibility for pharmaceutical formulation development. This flexibility might be desirable as other factors, such as chemical stability, are also pH dependent. In general, a peptide formulation around pH 6.0 is believed to show reduced rates of oxidation (e.g. Cys oxidation, disulphide crosslinking, and oxidation of Trp residues), deamination and aspartate isomerization as compared to a formulation at pH
15 7. For instance, Bak et al. (A. Bak, D. Leung, S. E. Barrett, S. Forster, E. D. Minnihan, A. W. Leithead, J. Cunningham, N. Toussaint, L. S. Crocker, The AAPS Journal, Vol. 17, No. 1, 2015, p. 144 - 155) states that oxidation propensity generally lessens at lower pH and suggests maintenance at pH <7 as a strategy for mitigation risks related to oxidation. Therefore, it might be desirable to have the option to formulate around pH 6 in case chemical
20 stability of peptides containing asparagine, aspartate or glutamine, tryptophan, cysteine or methionine is an issue.

- Efficacy of obesity therapeutics is limited. However, efficacy might be improved by combining different therapeutic principles. NPY2 receptor agonists seem attractive partners for
25 combination with other weight reducing therapeutics. For example, NPY2 receptor agonists show enhanced weight loss efficacy with GLP-1 receptor agonists (e.g. WO2005/077072, WO2014/178018, WO2018/081370) or amylin (e.g. WO2006/066024, WO2009/064298). Native amylin and many amylin (or calcitonin) analogues comprise a disulphide bridge. Therefore, a fix-dose combination of a PYY analogue with an amylin
30 analogue might benefit from the opportunity to formulate at a lower pH where the disulphide bridge of the amylin analogue potentially shows improved stability (e.g. due to reduced intramolecular disulphide bond crosslinking reactions). This illustrates that the advantage to be able to formulate at a pH below 7 may not (only) be due to a higher stability

of the NPY analogue but may lie therein that the combination partner shows improved stability (or solubility) at a lower pH.

Therefore, to enable co-formulation development with a diverse range of partners, it is highly desirable to identify NPY2 receptor agonists with a wide solubility window.

5

Increased solubility, however, should not come at the cost of reduced activity or potency. It was surprisingly found that the alanine at position 4 increases solubility around pH 6 in the PYY analogues of the invention with no or only small negative effects on activity or potency or other important properties (e.g. chemical or physical stability).

10

Long in-vivo half-life is also a beneficial property for agents to reduce food intake in overweight or obese patients. Compounds with a long-acting profile (as compared to the very short in-vivo half-life of native (human) PYY) reducing the frequency of administration are desirable.

15

In one aspect, the invention relates to PYY analogues being NPY2 receptor agonists.

In one aspect, the invention relates to PYY analogues showing selectivity towards the NPY receptor subtype Y2 as compared to Y receptor subtypes Y1, Y4 and Y5.

In one aspect, the invention relates to PYY analogues with extended half-life, e.g. with

20

longer half-life than the half-life of hPYY(3-36). For example, the PYY analogues of the invention are suitable for once weekly administration.

Additionally or alternatively, the invention relates to PYY analogues having high chemical and/or physical stability, e.g. around pH 6 or pH 7.

25

Further, more specific embodiments are defined below:

In an embodiment of the present invention, the PYY analogue is a compound having the formula:

30

R^1-Z-R^2 ,

wherein R^1 and R^2 are as defined above;

Z is an amino acid sequence of formula Ib; and

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

In a further embodiment of the present invention, the PYY analogue is a compound having the formula:

10 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, 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 IIb:

15
 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

20 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 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;
 25 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;
 X19 is selected from the group consisting of Arg and Gln;
 X22 is selected from the group consisting of Ile, Thr and Val;
 30 X23 is selected from the group consisting of Ala, Glu, Gln and Ser;
 X29 is selected from the group consisting of Asn and Gln;

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

5

According to a further embodiment, up to three residues of X6 to X23 are Ala.

According to a further embodiment, at least four residues of X6 to X23 are Glu. In a further embodiment, at least four residues of X6, X9, X10, X13, X15, X16 and X23 are Glu.

10

According to a further embodiment, up to three residues of X6 to X23 are Ala, and at least four residues of X6, X9, X10, X13, X15, X16 and X23 are Glu.

In an embodiment of the present invention, the PYY analogue is a compound having the formula:

15

$$R^1-Z-R^2,$$

Wherein R^1 and R^2 are as defined above;

Z is an amino acid sequence of formula IIb; and

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

25

In some embodiments of the present invention, the PYY analogue is a compound having the formula:

30 $R^1-Z-R^2,$

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, 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 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)

5

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;

10 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;

15 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;

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

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.

25

In a further embodiment 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)

30

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;
5 X22 is selected from the group consisting of Ile and Val;
X23 is selected from the group consisting of Ala and Ser;

In an embodiment of the present invention, the PYY analogue is a compound having the
10 formula:

- R^1-Z-R^2 ,
Wherein R^1 and R^2 are as defined above;
Z is an amino acid sequence of formula IVb; and
15 wherein a half-life extending group is attached to the epsilon amino group of the lysine at
position 7 and 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.

20

In further embodiments, the PYY analogue is a compound according to formula Ib, IIb,
IIIb, or IVb, wherein up to three residues of X6 to X23 are Ala.

- 25 In further embodiments, the PYY analogue is a compound according to formula Ib, IIb,
IIIb, or IVb, wherein at least four residues of X6, X9, X10, X13, X15, X16 and X23 are
Glu.

- In further embodiments, R^1 is hydrogen, $-C(O)C_{1-6}$ alkyl, $-C(O)C_{3-6}$ cycloalkyl, or C_{1-6} alkyl.
30 In further embodiments, R^1 is hydrogen or $-C(O)C_{1-6}$ alkyl.
In further embodiments, R^1 is hydrogen or $-C(O)C_{1-4}$ alkyl.
In more specific embodiments, R^1 is $-C(O)CH_2CH(CH_3)_2$.

In more specific embodiments, R² is NH₂.

In some embodiments of the present invention, the PYY analogue is a compound having the formula:

5

R¹-Z-R²,

wherein R¹ and R² are as defined in any of the definition above; and Z is an amino acid sequence selected from Table 1:

10

cf. compound No	Sequence	SEQ ID NO
1	APEKPEADAEPEELQRYYYIALRHYYNWLTRQRY	5
2	APEKPEEDASPEELQRYYYIALRHYYNWLTRQRY	6
3	APAKPEADAEPEELQRYYYVALRHYYNWLTRQRY	7
4	APEKPEEAAEPEELQRYYYVSLRHYYNWLTRQRY	8
5	APAKPEEDASPEELQRQYVSLRHYYNWLTRQRY	9
6	APEKPEADAEPEELQRYYYVALRHYYNWLTRQRY	10
7	APEKPEADATPEEIQRYYVSLRHYYNWLTRQRY	11
8	APEKPEEDETPEELQRYYYVSLRHYYNWLTRQRY	12
9	APEKPEEQATPEELQRYYYVSLRHYYNWLTRQRY	13
10	APAKPEAAAEPEELQRYYYVALRHYYNWLTRQRY	14
11	APEKPEADASPEEIQRYYISLRHYYNWLTRQRY	15
12	APEKPEEDASPEELQQYYVSLRHYYHWLTRQRY	16
13	APEKPEADASPEETQRYYVSLRHYYNWLTRQRY	17
14	APEKPPEDASPEELQRYYYVSLRHYYNWLTRQRY	18
15	APEKPEEDASPEEIQQYYVSLRHYYNWLTRQRY	19
16	APEKPEEDATPEELQKYYVSLRHYYNWLTRQRY	20
17	APEKPEEDATPEEIQRYYPSLRHYYNWLTRQRY	21
18	APEKPEEDASPEELQRYYYVALRHYYNWLTRQRY	22
19	APEKPEEDATEEELQRYYYVSLRHYYNWLTRQRY	23
20	APAKPEEDASPEELQRYQVSLRHYYNWLTRQRY	24
21	APEKPEADAEPEELQRYYYVALRHYYNWLTRQRY	25

22	APEKPEEDPTPEELQRYYYVSLRHYYNWLTRQRY	26
23	APEKPEEEASPEELQRYYYVSLRHYYNWLTRQRY	27
24	APEKPEEDSSPEELQRYYYVALRHYYNWLTRQRY	28
25	APEKPEADATPEELQRYYYISLRHYYNWLTRQRY	29
26	APAKPEEDATPEELQRYYYVSLRHYYNWLTRQRY	30
27	APEKPEEDAEPEESQRYYYVSLRHYYNWLTRQRY	31
28	APEKPPEDATPEEIQRYYYVSLRHYYNWLTRQRY	32
29	APEKPEADSSPEELQRYYYVSLRHYYNWLTRQRY	33
30	APEKPPADATPEELQRYYYVSLRHYYNWLTRQRY	34
31	APEKPEEDATPEELQPYYVSLRHYYNWLTRQRY	35
32	APAKPEEDASPEELQRYYYVSLRHQYNWLTRQRY	36
33	APAKPEEDAEPEELQRYYYISLRHYYNWLTRQRY	37
34	APEKPEEDASAEELQQYYVSLRHYYNWLTRQRY	38
35	APAKPEEAATPEELQRYYYVSLRHYYNWLTRQRY	39
36	APAKPEEAATPEEIQRYYYVSLRHYYNWLTRQRY	40
37	APEKPEEDAEPEELQRYYTSLRHYYNWLTRQRY	41
38	APEKPEEDATPEELQEYYVSLRHYYNWLTRQRY	42
39	APEKPEEDASPEALQEYYVSLRHYYNWLTRQRY	43
40	APEKPEADASPEEIQRYYYIALRHYYNWLTRQRY	44
41	APEKPEEDAEPEELQRYYTSLRHYYQWLTRQRY	45
42	APEKPEEPATPEELQRYYYVSLRHYYNWLTRQRY	46
43	APAKPEAAAEPEELQRYYYVSLRHYYNWLTRQRY	47
44	APEKPEEDATPEELQRYYYVGLRHYYNWLTRQRY	48
45	APEKPEEIATPEELQRYYYVSLRHYYNWLTRQRY	49
46	APEKPEEDAEPEELQRYYASLRHYYNWLTRQRY	50
47	APEKPPEDASPEEIQRYYYVALRHYYNWLTRQRY	51
48	APAKPEEAATPEELQRYYYISLRHYYNWLTRQRY	52
49	APEKPEEDATPEELQRYYYVLLRHYYNWLTRQRY	53
50	APEKPEEDATPEEIQRYYYVALRHYYNWLTRQRY	54
51	APEKPEEDATPEELQRYYYVQLRHYYNWLTRQRY	55
52	APEKPEEDASPEEIQRYYYVELRHYYNWLTRQRY	56
53	APEKPEEDAEPEEVQRYYYVSLRHYYNWLTRQRY	57
54	APEKPEEDATPEEAQRYYYVSLRHYYNWLTRQRY	58

55	APEKPEEDASEEEIQRYVSLRHYYNWLTRQRY	59
56	APEKPEEDATAEELQRYVSLRHYYNWLTRQRY	60
57	APAKPEEDATPEEAQRYVSLRHYYNWLTRQRY	61
58	APEKPEEDATPEEVQRYVSLRHYYNWLTRQRY	62
59	APAKPEEDASPEELQRYVQLRHYYNWLTRQRY	63
60	APEKPEEDASPEELQRYVSLRHYYQWLTRQRY	64
61	APEKPPADASPEEIQRYVSLRHYYNWLTRQRY	65
62	APAKPPEDASPEELQRYVELRHYYNWLTRQRY	66
63	APAKPEEDASPEEIQRYVSLRHYYNWLTRQRY	67
64	APEKPPEDATPEEIQRYVALRHYYNWLTRQRY	68
65	APAKPEEDASPEEIQRYIALRHYYNWLTRQRY	69
66	APEKPEEDATPEELQRYISLRHYYNWLTRQRY	70
67	APEKPEEDASPEETQRYVALRHYYNWLTRQRY	71
68	APEKPEEDAEPEELQRYVSLRHYYQWLTRQRY	72
69	APEKPPADASPEETQRYVSLRHYYNWLTRQRY	73
70	APAKPEEDATPEELQRYIALRHYYNWLTRQRY	74
71	APAKPEEDAEPEELQRYVALRHYYNWLTRQRY	75
72	APEKPEADAEPEELQRYVSLRHYYNWLTRQRY	76
73	APEKPEEAASPEELQRYVALRHYYNWLTRQRY	77
74	APEKPEEDATPEELQRYVALRHYYNWLTRQRY	78
75	APEKPEEDAPPEEIQRYVSLRHYYNWLTRQRY	79
76	APEKPEEDASPEELQRYISLRHYYNWLTRQRY	80
77	APAKPEEDASPEELQRYVSLRHYQNWLTQRY	81
78	APAKPEEDASPEELQRYVSLRHYYQWLTRQRY	82
79	APEKPEEDASPEELQRYVSLRHYYNWLTRQRY	83
80	APEKPEEDASEAELQRYVSLRHYYNWLTRQRY	84
81	APEKPEEDAQPEEIQRYVSLRHYYNWLTRQRY	85
82	APAKPPEDASPEEIQRYVSLRHYYNWLTRQRY	86
83	APEKPEEDATSEELQRYVSLRHYYNWLTRQRY	87
84	APEKPEEDATPEEIQRYVALRHYYNWLTRQRY	88
85	APAKPEEDASPEETQRYVSLRHYYNWLTRQRY	89
86	APEKPEEDATPEEIQRYASLRHYYNWLTRQRY	90
87	APEKPEEDATPEELQRYVPLRHYYNWLTRQRY	91

88	APEKPEEDATPEELQRQYVSLRHYYNWLTRQRY	92
89	APAKPPEDASPEELQRYYVALRHYYNWLTRQRY	93
90	APEKPEEDATPEELQRYYVVL RHYYNWLTRQRY	94
91	APEKPEEDAEPEELQRYYTSLRHYYHWLTRQRY	95
92	APEKPGEDASPEELQRYYISLRHYYNWLTRQRY	96
93	APEKPEEDASPEEIQRYYVQLRHYYNWLTRQRY	97
94	APAKPEADASPEELQRYYVELRHYYNWLTRQRY	98
95	APEKPEEDATPEELQAYYVSLRHYYNWLTRQRY	99
96	APEKPEESATPEELQRYYVSLRHYYNWLTRQRY	100
97	APEKPEEDATPEEIQRYYLSLRHYYNWLTRQRY	101
98	APEKPEADATPEEIQRYYVSLRHYYNWLTRQRY	102
99	APAKPEEDATPEEIQRYYVALRHYYNWLTRQRY	103
100	APEKPEADATPEELQRYYIALRHYYNWLTRQRY	104
101	APAKPEEDATPEELQRYYVALRHYYNWLTRQRY	105
102	APEKPEEDATLEELQRYYVSLRHYYNWLTRQRY	106
103	APEKPEEDASAEELQRYYVALRHYYNWLTRQRY	107
104	APEKPEEDAEPEEAQRYYVSLRHYYNWLTRQRY	108
105	APEKPEEDATQEELQRYYVSLRHYYNWLTRQRY	109
106	APAKPEEDASPEELQRYYVALRHYYNWLTRQRY	110
107	APEKPEEDAEPEETQRYYVSLRHYYNWLTRQRY	111
108	APEKPEADASEEELQRYYVSLRHYYNWLTRQRY	112
109	APEKPEEDLTPEELQRYYVSLRHYYNWLTRQRY	113
110	APEKPEEDATPEELQRYYVELRHYYNWLTRQRY	114
111	APAKPEAAAEPEEIQRYYVSLRHYYNWLTRQRY	115
112	APEKPEEDAEPEEIQRYYVSLRHYYNWLTRQRY	116
113	APEKPEEDATPEEIQRYYVSLRHYQNWLTQRQY	117
114	APAKPEEDATPEEIQRYYVSLRHYYNWLTRQRY	118
115	APEKPEEDATPEELQRYYQVSLRHYYNWLTRQRY	119
116	APAKPEAAAEPEEIQRYYVALRHYYNWLTRQRY	120
117	APEKPEEDASPEEAQRYYVALRHYYNWLTRQRY	121
118	APEKPPEDAEPEEIQRYYVSLRHYYNWLTRQRY	122
119	APEKPEEDATPEESQRYYVSLRHYYNWLTRQRY	123
120	APAKPEEAATPEEIQRYYVALRHYYNWLTRQRY	124

121	APEKPEADASPEELQRYYYVQLRHYYNWLTRQRY	125
122	APEKPEAEASPEELQRYYYVSLRHYYNWLTRQRY	126
123	APEKPEEDAAPEELQKYYVSLRHYYNWLTRQRY	127
124	APEKPEAAAEPEEIQRYYYVSLRHYYNWLTRQRY	128
125	APEKPEEDASPEELQRYYYVELRHYYNWLTRQRY	129
126	APEKPEEDAEPEELQRYYYVSLRHYYNWLTRQRY	130
127	APEKPEAAAEPEELQRYYYVALRHYYNWLTRQRY	131
128	APEKPEEAATPEELQRYYYVSLRHYYNWLTRQRY	132
129	APEKPEEDASAEIIRYYYVSLRHYYNWLTRQRY	133
130	APEKPEEDATPEELQLYYVSLRHYYNWLTRQRY	134
131	APEKPEADAEPEEIQRYYYVALRHYYNWLTRQRY	135
132	APEKPEADATPEELQRYYYVSLRHYYNWLTRQRY	136
133	APAKPEEDAEPEELQRYYYVSLRHYYNWLTRQRY	137
134	APEKPEEDATPEEQRYYYVSLRHYYNWLTRQRY	138
135	APEKPEAAAEPEEIQRYYYVALRHYYNWLTRQRY	139
136	APEKPEADATPEELQRYYYVALRHYYNWLTRQRY	140
137	APEKPEEDATPEELQRYYYVSLRHYYNWLLRQRY	141
138	APEKPEEDAEPEELQEYYVSLRHYYNWLTRQRY	142
139	APEKPEEEASPAELQRYYYVSLRHYYNWLTRQRY	143
140	APEKPEADASPEEIQRYYYVSLRHYYNWLTRQRY	144
141	APEKPEEDATPEELQSYVSLRHYYNWLTRQRY	145
142	APEKPEEDALPEEIQRYYYVSLRHYYNWLTRQRY	146
143	APEKPEEDSTPEELQRYYYVSLRHYYNWLTRQRY	147
144	APEKPEEDQTPEELQRYYYVSLRHYYNWLTRQRY	148
145	APAKPEEDASPEELQRYYYVSLRHYYNWLTRQRY	149
146	APEKPEEEATPEELQRYYYVSLRHYYNWLTRQRY	150
147	APEKPEEDASPEEIQRYYYVSLRHYYNWLTRQRY	151
148	APEKPEEDATPEELQRYYYVTLRHYYNWLTRQRY	152
149	APAKPEEDASPEESQRYYYVSLRHYYNWLTRQRY	153
150	APEKPEEAASPEEIQRYYYVSLRHYYNWLTRQRY	154
151	APEKPEEDSSPEELQRYYYVALRHYYNWLTRQRY	155
152	APEKPEEDATPEETQRYYYVSLRHYYNWLTRQRY	156
153	APEKPEELATPEELQRYYYVSLRHYYNWLTRQRY	157

154	APEKPEEAATPEEIQRYYVALRHYYNWLTRQRY	158
155	APEKPEEDATPEELQRYYVSLRHYYNWLTRQRY	159
156	APEKPEEAAEPEEIQRYYVALRHYYNWLTRQRY	160
157	APAKPEEAAASPEELQRYYVALRHYYNWLTRQRY	161
158	APEKPPEAASPEEIQRYYVALRHYYNWLTRQRY	162
159	APEKPEADAEPEELQRYYISLRHYYNWLTRQRY	163
160	APAKPEEDASPEELQRYYIALRHYYNWLTRQRY	164
161	APAKPEEAAEPEELQRYYVALRHYYNWLTRQRY	165
162	APEKPEEDATPEEEQRYYVSLRHYYNWLTRQRY	166
163	APEKPEADASPEELQRYYVALRHYYNWLTRQRY	167
164	APEKPEEDATPEEIQRYYQSLRHYYNWLTRQRY	168
165	APAKPPEDAEPEELQRYYVSLRHYYNWLTRQRY	169
166	APAKPEEDASPEELQRYYVELRHYYNWLTRQRY	170
167	APAKPEEAAEPEEIQRYYVALRHYYNWLTRQRY	171
168	APEKPEEDATPEEIQRYYSSLRHYYNWLTRQRY	172
169	APEKPEADAEPEELQAYYVSLRHYYNWLTRQRY	173
170	APEKPEEDAAPPEEIQRYYVSLRHYYNWLTRQRY	174
171	APEKPEADASPEELQRYYVELRHYYNWLTRQRY	175
172	APEKPPEDASPEEIQRYYVSLRHYYNWLTRQRY	176
173	APEKPEEDATPEELQRYYVSLRHYYNWLTRQRY	177
174	APEKPGADASPEKLQRYYVSLRHHYHKLTRQRY	178
175	APAKPEEDAEPEELQRYYIALRHYYNWLTRQRY	179
176	APEKPEEDATPEEIQRYYVSLRHYYNWLTRQRY	180
177	APEKPEEDATPEELQQYYVSLRHYYNWLTRQRY	181
178	APEKPEAAATPEEIQRYYVALRHYYNWLTRQRY	182
179	APEKPEADASPEETQRYYVALRHYYNWLTRQRY	183
180	APEKPEEDATPEELQRYYVSLRHYYNWLTKQRY	184
181	APAKPEADAEPEEIQRYYVALRHYYNWLTRQRY	185
182	APAKPEEDASPEEAQRYYVALRHYYNWLTRQRY	186
183	APEKAEEDASPEEIQRYYVSLRHYYNWLTRQRY	187
184	APEKPEADATPEEIQRYYVALRHYYNWLTRQRY	188
185	APAKPEEDASEEELQRYYVSLRHYYNWLTRQRY	189
186	APEKPEEDAEPEEAQRYYVSLRHYYNWLTRQRY	190

187	APEKPEEDATPEEPQRYYYVSLRHYYNWLTRQRY	191
188	APEKPEEDATPEELQRYYYVSLRHYYNWLQRQRY	192
189	APAKPEEDASPEETQRYYYVALRHYYNWLTRQRY	193
190	APAKPEEDATPEELQRYYYISLRHYYNWLTRQRY	194
191	APEKPEEDATPEEIQRYYESLRHYYNWLTRQRY	195
192	APEKPEAPASPEELQRYYYVSLRHYYNWLTRQRY	196
193	APEKPEEEASPEEIQRYYVSLRHYYNWLTRQRY	197
194	APAKPEEDAEPEEIQRYYVALRHYYNWLTRQRY	198
195	APAKPEEDASPEEIQRYYISLRHYYNWLTRQRY	199
196	APEKPEADASPEELQRYYYVSLRHYYNWLTRQRY	200
197	APEKPEEDASPEEIQRYYVALRHYYNWLTRQRY	201
198	APAKPEADAEPEEIQRYYVSLRHYYNWLTRQRY	202
199	APAKPEEEASPEELQRYYYVSLRHYYNWLTRQRY	203

Table 1

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.

In an embodiment of the present invention, the PYY analogue is a compound having the formula:

R^1-Z-R^2 ,

Wherein R^1 and R^2 are as defined above;

Z is an amino acid sequence of selected from Table 1; and

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

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

- 5 In some embodiments the linker U consists of one, two or three sub-moieties (U^1 , U^2 , U^3) independently selected from the group consisting of Gly, Glu, γ -Glu, ϵ -Lys, Ser, Ahx and OEG, or independently selected from the group consisting of γ -Glu, Ahx and OEG.

In some embodiments the linker U comprises one or more Ahx as (sub-)moiety.

10

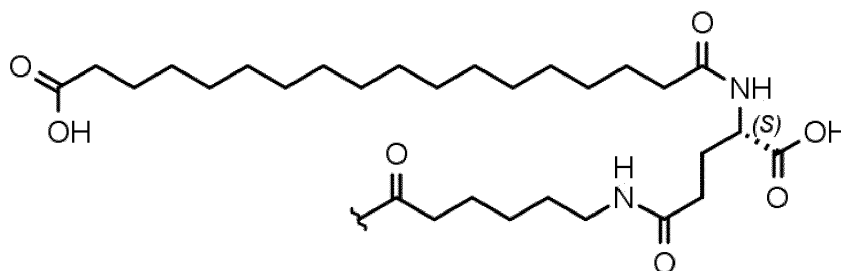
In certain embodiments, the linker U is selected from the group consisting of γ -Glu, γ -Glu- γ -Glu, γ -Glu-OEG, OEG- γ -Glu, γ -Glu-Ahx, Ahx- γ -Glu, OEG-OEG, Ahx-Ahx, γ -Glu- γ -Glu-OEG, OEG- γ -Glu- γ -Glu, γ -Glu- γ -Glu-Ahx, Ahx- γ -Glu- γ -Glu, γ -Glu-OEG-OEG, OEG-OEG- γ -Glu, γ -Glu-Ahx-Ahx and Ahx-Ahx- γ -Glu.

15

In certain embodiments, the linker U is selected from the group consisting of γ -Glu-Ahx, Ahx- γ -Glu, Ahx-Ahx, γ -Glu- γ -Glu-Ahx, Ahx- γ -Glu- γ -Glu, γ -Glu-Ahx-Ahx and Ahx-Ahx- γ -Glu.

20

In specific embodiments, the half-life extending group is C18DA- γ -Glu-Ahx-, i.e.



- 25 In some embodiments of the present invention, the PYY analogue is a compound selected from the group consisting of compound 1 to compound 199 as defined below.

In some embodiments, the PYY analogue has a maximum of 15 amino acid modifications as compared to hPYY(3-36).

5 In some embodiments, the PYY analogue has a maximum of 14 amino acid modifications as compared to hPYY(3-36).

In some embodiments, the PYY analogue has a maximum of 13 amino acid modifications as compared to hPYY(3-36).

10 In some embodiments, the PYY analogue has a maximum of 12 amino acid modifications as compared to hPYY(3-36).

In some embodiments, the PYY analogue has a maximum of 11 amino acid modifications as compared to hPYY(3-36).

15 In some embodiments, the PYY analogue has between 7 and 15 (i.e. 7, 8, 9, 10, 11, 12, 13, 14 or 15) amino acid modifications as compared to hPYY(3-36).

In some embodiments, the PYY analogue has between 8 and 14 (i.e. 8, 9, 10, 11, 12, 13 or 14) amino acid modifications as compared to hPYY(3-36).

In some embodiments, the PYY analogue has between 5 and 13 (i.e. 5, 6, 7, 8, 9, 10, 11, 12 or 13) amino acid modifications as compared to hPYY(3-36).

25 In some embodiments, the PYY analogue has between 7 and 13 (i.e. 7, 8, 9, 10, 11, 12 or 13) amino acid modifications as compared to hPYY(3-36).

In some embodiments, the PYY analogue has between 8 and 13 (i.e. 8, 9, 10, 11, 12 or 13) amino acid modifications as compared to hPYY(3-36).

30 In some embodiments, the PYY analogue has between 9 and 13 (i.e. 9, 10, 11, 12 or 13) amino acid modifications as compared to hPYY(3-36).

In some embodiments, the PYY analogue has between 10 and 13 (i.e. 10, 11, 12 or 13) amino acid modifications as compared to hPYY(3-36).

5 In some embodiments, the PYY analogue has between 8 and 12 (i.e. 8, 9, 10, 11 or 12) amino acid modifications as compared to hPYY(3-36).

In some embodiments, the PYY analogue has between 9 and 12 (i.e. 9, 10, 11 or 12) amino acid modifications as compared to hPYY(3-36).

10 In some embodiments, the PYY analogue has between 10 and 12 (i.e. 10, 11 or 12) amino acid modifications as compared to hPYY(3-36).

In some embodiments, the PYY analogue has between 11 and 12 (i.e. 11 or 12) amino acid modifications as compared to hPYY(3-36).

15

In some embodiments, the PYY analogue has between 9 and 11 (i.e. 9, 10 or 11) amino acid modifications as compared to hPYY(3-36).

20

In some embodiments, the PYY analogue or compound of the above-mentioned embodiments is in the form of a salt, preferably in the form of a pharmaceutically acceptable salt.

25 The PYY analogues of the invention are able to bind to the human NPY2 receptor (hNPY2-R).

Binding to biological receptors can be measured by appropriate assays known in the art. For instance, binding of PYY analogues to the NPY2 receptor can be evaluated by radio-ligand binding competition assays as described in Example 1, below.

30

In some embodiments of compounds of the present invention, the binding affinity (K_i) towards hNPY2 receptor is below 100 nM (e.g. 0.01 to 100 nM).

In some embodiments of compounds of the present invention, the binding affinity (K_i) towards hNPY2 receptor is below 50 nM (e.g. 0.01 to 50 nM).

In some embodiments of compounds of the present invention, the binding affinity (K_i) towards hNPY2 receptor is below 10 nM (e.g. 0.01 to 10 nM).

5 In some embodiments of compounds of the present invention, the binding affinity (K_i) towards hNPY2 receptor is below 5 nM (e.g. 0.01 to 5 nM).

In some embodiments of compounds of the present invention, the binding affinity (K_i) towards hNPY2 receptor is below 2 nM (e.g. 0.01 to 2 nM).

10

The PYY analogues of the invention activate the human NPY2 receptor, i.e. they are NPY2 agonists.

In general, it is preferred to use a biological assay, which measures intracellular signalling caused by binding of the compound to the relevant receptor. Activation of the NPY2
15 receptor by compounds of the invention (which behave as agonists of the receptor) reduces cAMP concentrations effecting intracellular signalling pathways. Thus, reduction of cAMP or any other suitable parameter in cells expressing the receptor can be used to monitor agonist activity towards the receptor. The skilled person will be aware of suitable assay
20 formats, and examples are provided below.

EC_{50} values may be used as a numerical measure of agonist potency at a given receptor. An EC_{50} value is a measure of the concentration of a compound required to achieve half of that compound's maximal activity in a particular assay, e.g. in the assay as described in
25 Example 2, below.

In some embodiments of compounds of the present invention, the EC_{50} towards hNPY2 receptor is below 100 nM (e.g. 0.001 to 100 nM).

30 In some embodiments of compounds of the present invention, the EC_{50} towards hNPY2 receptor is below 50 nM (e.g. 0.001 to 50 nM).

In some embodiments of compounds of the present invention, the EC_{50} towards hNPY2 receptor is below 10 nM (e.g. 0.001 to 10 nM).

In some embodiments of compounds of the present invention, the EC₅₀ towards hNPY2 receptor is below 5 nM (e.g. 0.001 to 5 nM).

In some embodiments of compounds of the present invention, the EC₅₀ towards hNPY2 receptor is below 2 nM (e.g. 0.001 to 2 nM).

5

As mentioned above the PYY analogues or compounds of the present invention are generally soluble around pH 7 and 6. There are several techniques known to the skilled person in the art how to determine solubility. One such experiment is described below under Example 3. If specific solubility in mg/ml is provided herein, it is referred to the solubility determination as in Example 3.

10

In some embodiments, the solubility of the PYY analogues or compounds of the invention is greater than 1.0 mg/ml around pH 6 (e.g. at pH 6.1 ± 0.2).

In some embodiments, the solubility of the PYY analogues or compounds of the invention is greater than 3.0 mg/ml around pH 6 (e.g. at pH 6.1 ± 0.2).

15

In some embodiments, the solubility of the PYY analogues or compounds of the invention is greater than 5.0 mg/ml around pH 6 (e.g. at pH 6.1 ± 0.2).

In some embodiments, the solubility of the PYY analogues or compounds of the invention is equal to or greater than 7.0 mg/ml around pH 6 (e.g. at pH 6.1 ± 0.2).

In some embodiments, the solubility of the PYY analogues or compounds of the invention is equal to or greater than 8.0 mg/ml around pH 6 (e.g. at pH 6.1 ± 0.2).

20

In some embodiments, the solubility of the PYY analogues or compounds of the invention is greater than 1.0 mg/ml around pH 7 (e.g. at pH 6.8 ± 0.2).

25

In some embodiments, the solubility of the PYY analogues or compounds of the invention is greater than 5.0 mg/ml around pH 7 (e.g. at pH 6.8 ± 0.2).

In some embodiments, the solubility of the PYY analogues or compounds of the invention is greater than 7.0 mg/ml around pH 7 (e.g. at pH 6.8 ± 0.2).

In some embodiments, the solubility of the PYY analogues or compounds of the invention is equal to or greater than 8.0 mg/ml around pH 7 (e.g. at pH 6.8 ± 0.2).

30

In some embodiments, the solubility of the PYY analogues or compounds of the invention is greater than 1.0 mg/ml around pH 6 (e.g. at pH 6.1 ± 0.2) and around pH 7 (e.g. at pH 6.8 ± 0.2).

5 In some embodiments, the solubility of the PYY analogues or compounds of the invention is greater than 3.0 mg/ml around pH 6 (e.g. at pH 6.1 ± 0.2) and around pH 7 (e.g. at pH 6.8 ± 0.2).

In some embodiments, the solubility of the PYY analogues or compounds of the invention is greater than 5.0 mg/ml around pH 6 (e.g. at pH 6.1 ± 0.2) and around pH 7 (e.g. at pH 6.8 ± 0.2).

10 In some embodiments, the solubility of the PYY analogues or compounds of the invention is greater than 6.0 mg/ml around pH 6 (e.g. at pH 6.1 ± 0.2) and around pH 7 (e.g. at pH 6.8 ± 0.2).

In some embodiments, the solubility of the PYY analogues or compounds of the invention is greater than 7.0 mg/ml around pH 6 (e.g. at pH 6.1 ± 0.2) and around pH 7 (e.g. at pH 6.8 ± 0.2).

20 In some embodiments the PYY analogues or compounds of the invention have favourable pharmacokinetic properties. In this regard, in some embodiments of the invention, the in-vivo half-life of the PYY analogues or compounds is at least 3 hours in the mouse (NMRI mice, see measurement described in Example 5). In some embodiments, the in-vivo half-life is at least 5 hours in the mouse. In some embodiments, the in-vivo half-life is at least 7 hours in the mouse. In some embodiments, the in-vivo half-life is at least 10 hours in the mouse.

25

The invention further provides a composition comprising a PYY analogue as described above. The composition may be a pharmaceutical composition, and may comprise a pharmaceutically acceptable carrier, excipient or vehicle.

30 The invention further provides a method for the synthesis of a PYY analogue as described above. The method may comprise the steps of synthesising the peptide by solid-phase or liquid-phase methodology, and optionally isolating and/or purifying the final product.

METHOD OF TREATMENT

The present invention is directed to PYY analogues or a compound according to the above-mentioned embodiments, which are useful in the prevention and/or treatment of a disease and/or condition associated with or modulated by NPY2 receptor activity, including but
5 not limited to the treatment and/or prevention of obesity and various obesity-related conditions, diseases, or co-morbidities, such as type 2 diabetes and NASH (non-alcoholic steatohepatitis).

The compounds described herein find use, inter alia, in preventing weight gain or promoting weight loss. By "preventing" is meant inhibiting or reducing when compared to the
10 absence of treatment, and is not necessarily meant to imply complete cessation of weight gain. The peptides may cause a decrease in food intake and/or increased energy expenditure, and may have a beneficial effect on glucose control and/or on circulating cholesterol levels, being capable of lowering circulating LDL levels and increasing HDL/LDL ratio.
15 Thus, the compounds of the invention can be used for direct or indirect therapy of any condition caused or characterised by excess body weight, such as the treatment and/or prevention of obesity, morbid obesity, obesity linked inflammation, obesity linked gallbladder disease, and obesity related sleep apnea. They may also be used for the prevention of conditions or treatment of obesity associated co-morbidities caused or characterised by
20 inadequate glucose control or dyslipidaemia (e.g. elevated LDL levels or reduced HDL/LDL ratio), Type 2 diabetes, metabolic syndrome, hypertension, atherogenic dyslipidemia, and cardiovascular diseases such as atherosclerosis, coronary heart disease, peripheral artery disease, stroke or microvascular disease, and cancer. Their effects in these diseases may be as a result of or associated with their effect on body weight, or may be
25 independent thereof.

As mentioned above the PYY analogues or compounds according to the above mentioned embodiments are useful in the reduction of food intake, promotion of weight loss, and inhibition or reduction of weight gain. As a result, they may be used for treatment of a variety
30 of conditions, diseases, or disorders in a subject, including, but not limited to, obesity and various obesity-related conditions, diseases, or co-morbidities, such as type 2 diabetes, hypertension, dyslipidemia, sleep apnea, cardiovascular disease, hepatic steatosis, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH) and cancer.

The subject may be affected by obesity accompanied by at least one weight-related co-morbid condition, such as type 2 diabetes, hypertension, dyslipidemia, sleep apnea, cardiovascular disease, hepatic steatosis, NAFLD and NASH. It will be understood that the PYY analogues may thus be administered to subjects affected by conditions or diseases
5 characterised by inadequate control of appetite or otherwise over-feeding, such as binge-eating disorder and Prader-Willi syndrome. It will be clear that the analogues can be used for treatment of combinations of the conditions or diseases described.

Thus, the invention provides a PYY analogue for use in a method of medical treatment,
10 e.g. for treating, inhibiting or reducing weight gain, promoting weight loss and/or reducing excess body weight. Treatment may be achieved, for example, by control of appetite, feeding, food intake, caloric intake and/or energy expenditure.

The invention also provides a PYY analogue of the invention for use in a method of treating obesity as well as associated diseases, disorders and health conditions, including,
15 but not limited to, morbid obesity, obesity prior to surgery, obesity-linked inflammation, obesity-linked gallbladder disease and obesity related sleep apnea and respiratory problems, degeneration of cartilage, osteoarthritis, and reproductive health complications of obesity or overweight such as infertility. The subject may be affected by obesity accompanied by at least one weight-related co-morbidity, such as type 2 diabetes, hypertension,
20 dyslipidemia, sleep apnea, cardiovascular disease, cancer, hepatic steatosis, NAFLD and NASH.

The invention also provides a PYY analogue of the invention for use in a method of prevention or treatment of conditions or diseases mentioned above.

25 Accordingly, the present invention relates to a PYY analogue or a compound according to the above-mentioned embodiments for use as a medicament.

Furthermore, the present invention relates to the use of a PYY analogue or a compound according to the above-mentioned embodiments for the treatment and/or prevention of a
30 disease and/or condition associated with or modulated by NPY2 receptor activation.

Furthermore, the present invention relates to the use of a PYY analogue or a compound according to the above mentioned embodiments for the treatment and/or prevention of

obesity and various obesity-related conditions, diseases, or co-morbidities, such as type 2 diabetes and NASH (non-alcoholic steatohepatitis) and others as mentioned above.

In a further aspect the present invention relates to the use of a PYY analogue or a
5 compound according to the above mentioned embodiments for the preparation of a medicament for the treatment and/or prevention of above-mentioned diseases and conditions.

In a further aspect the present invention relates to methods for the treatment or prevention
10 of above mentioned diseases and conditions, which method comprises the administration of an effective amount of a PYY analogue or a compound according to the above-mentioned embodiments to a human being.

The dose range of the compounds of general formula 1 applicable per week is usually from
15 0.01 to 100 mg for humans (subcutaneous administration).

The actual pharmaceutically effective amount or therapeutic dosage will usually depend on factors known by those skilled in the art such as age and weight of the patient, route of administration and severity of disease. In any case, the compounds will be administered at
20 dosages and in a manner, which allows a pharmaceutically effective amount to be delivered based upon patient's unique condition.

COMBINATION THERAPY

25 A PYY analogue of the invention may be administered as part of a combination therapy together with another active agent for the treatment of the disease or disorder in question, e.g. an anti-obesity agent, an anti-diabetic agent, an agent for treatment of metabolic syndrome, an anti-dyslipidemia agent, an anti-hypertensive agent, a proton pump inhibitor, or an anti-inflammatory agent. In such cases, the two active agents may be given together
30 or separately, e.g. as constituents in the same pharmaceutical composition or formulation, or as separate formulations.

Thus, a peptide of the invention may be used in combination with an anti-obesity agent of known type. The anti-obesity agent may be a GIP or GLP-1 receptor agonist (including GLP-1 or a GLP-1 analogue, exendin-4 or an exendin-4 analogue, any other GLP-1 receptor agonist including Liraglutide (Saxenda™), Semaglutide, Dulaglutide, Albiglutide, 5 MK-8521, or a glucagon-GLP-1 dual agonist (e.g. HM-12525, SAR-425899, MEDI-0382, NN-9277 or as described in WO2008/101017, WO2008/152403, WO2010/070252, WO2010/070253, WO2010/070255, WO2010/070251, WO2011/006497, WO2011/160630, WO2011/160633, WO2013/092703, WO2014/041195, WO2015/055801, WO2015/055802, WO2016/166289), oxyntomodulin or an 10 oxyntomodulin analog (e.g. TT-401) or a GLP-1/GIP dual agonist (e.g. Tirzepatide or as described in WO2013/164483), or a GLP-1/GIP/glucagon triple agonists (e.g. NN-9423 or as described in WO2015/067716, WO2016/198624, WO2017/116204, WO2017/116205, WO2018/100134, WO2018/100135).

The anti-obesity agent may be amylin or an amylin analogue, e.g. pramlintide, NN-9838, 15 or an amylin (or calcitonin) analogue disclosed in WO2012/168430, WO2012/168431, WO2012/168432, WO2015/040182, WO2015/071229, WO2016/146739, WO2018/046719, or WO2018/172390.

Alternatively, the anti-obesity agent may be Orlistat™, Sibutramine™, phentermine, a melanin concentrating hormone receptor 1 antagonist, CCK, leptin analogue, a GOAT 20 inhibitor, a ghrelin-receptor antagonist, a further neuropeptide Y (NPY) analogue, a NPY4 receptor agonist, a NPY5 receptor antagonist, a cannabinoid receptor 1 antagonist, a beta-3 agonist, a lipase inhibitor, Human proIslet Peptide (HIP), a melanocortin receptor 4 agonist, as well as analogues thereof.

25 Moreover, a peptide of the invention may have some benefit if administered in combination with an anti-diabetic agent of known type, including, but not limited to, metformin, a sulfonylurea, a glinide, a DPP-IV inhibitor, a glitazone, a GLP-1 receptor agonist (including GLP-1 or a GLP-1 analogue, an exendin-4 or an exendin-4 analogue, any other GLP-1 receptor agonist including Liraglutide (Victoza™), Semaglutide, Dulaglutide, 30 Albiglutide, MK-8521, or a glucagon-GLP-1 dual agonist (e.g. HM-12525, SAR-425899, MEDI-0382, NN-9277 or as described in WO2008/101017, WO2008/152403, WO2010/070252, WO2010/070253, WO2010/070255, WO2010/070251, WO2011/006497, WO2011/160630, WO2011/160633, WO2013/092703,

WO2014/041195, WO2015/055801, WO2015/055802, WO2016/166289), oxyntomodulin, or an oxyntomodulin analog (e.g. TT-401), or a SGLT2 inhibitor (i.e. an inhibitor of sodium-glucose transport, e.g. a gliflozin such as empagliflozin, canagliflozin, dapagliflozin or ipragliflozin), a GPR40 agonist (FFAR1/FFA1 agonist, e.g. fasiglifam), or an insulin or an insulin analogue. Examples of appropriate insulin analogues include, but are not limited to, Lantus™, Novorapid™, Humalog™, Novomix™, Actraphane™ HM, Levemir™ Degludec™ and Apidra™. Other relevant anti-diabetic agents in this connection include GLP-1 receptor agonists, such as exenatide (Byetta™ and Bydureon™ exendin-4) and Byetta LAR™, and lixisenatide (Lyxumia™).

10

According to more specific embodiments, the PYY analogue of the present invention is administered as part of a combination therapy together with

- a GLP-1 receptor agonist selected from the group consisting of Liraglutide, Semaglutide, Dulaglutide and Albiglutide or a glucagon-GLP-1 dual agonist described in WO2011/006497, WO2014/041195, WO2015/055801, WO2015/055802, WO2016/166289 or
- an amylin receptor agonist selected from the group consisting of pramlintide or an amylin analogue disclosed in WO2012/168430, WO2012/168431, WO2012/168432, WO2015/040182, WO2016/146739, or WO2018/046719.

20 A peptide of the invention may further be used in combination with medications targeting cardiovascular diseases treating hypertension, dyslipidemia, inflammation and platelet function. The medication treating hypertension can be selected from the group including, but not limited to, an angiotensin-converting enzyme inhibitor, an angiotensin II receptor blocker, a diuretic, a beta-blocker or a calcium channel blocker.

25 A peptide of the invention may still further be used in combination with an anti-dyslipidemia agent of known type, including, but not limited to, a statin, a fibrate, a niacin, a PCSK9 (Proprotein convertase subtilisin/kexin type 9) inhibitor, or a cholesterol absorption inhibitor.

A peptide of the invention may also be used in combination with a proton pump inhibitor (i.e. a pharmaceutical agent possessing pharmacological activity as an inhibitor of H⁺/K⁺-ATPase) of known type, including, but not limited to, an agent of the benzimidazole derivative type or of the imidazopyridine derivative type, such as Omeprazole™,

30

LansoprazoleTM, DexlansoprazoleTM, EsomeprazoleTM, PantoprazoleTM, RabeprazoleTM, ZolpidemTM, AlpidemTM, SaripidemTM or NecopidemTM.

- In addition, with regard to anti-inflammatory treatment, a peptide of the invention may be beneficial if administered in combination with an anti-inflammatory agent of known type, including, but not limited to:
- steroids and corticosteroids, such as beclomethasone, methylprednisolone, betamethasone, prednisone, dexamethasone, and hydrocortisone;
 - non-steroidal anti-inflammatory agents (NSAIDs), such as propionic acid derivatives (e.g. alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenbufen, fenoprofen, fluprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, pirprofen, pranoprofen, suprofen, tiaprofenic acid and tioxaprofen); acetic acid derivatives (e.g. indomethacin, acemetacin, alclofenac, clidanac, diclofenac, fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac, tolmetin, zidometacin and zomepirac); fenamic acid derivatives (e.g. flufenamic acid, meclofenamic acid, mefenamic acid, niflumic acid and tolfenamic acid); biphenylcarboxylic acid derivatives (e.g. diflunisal and flufenisal); oxicams (e.g. isoxicam, piroxicam, sudoxicam and tenoxicam); salicylates (e.g. acetylsalicylic acid and sulfasalazine); and pyrazolones (e.g. apazone, bezpiperylon, feprazone, mofebutazone, oxyphenbutazone and phenylbutazone);
 - COX II inhibitors, such as rofecoxib and celecoxib; preparations of interferon beta (e.g. interferon beta-1a or interferon beta-1b);
 - and certain other compounds, such as 5-aminosalicylic acid and prodrugs and pharmaceutically acceptable salts thereof.

PREPARATION

General procedure for solid phase synthesis of peptides

All peptides were synthesized by standard Fmoc-based solid phase peptide chemistry on a Tentagel S RAM resin (loading 0.23-0.25 mmol/g, bead size 90 µm) supplied by Iris Biotech GmbH or Rapp Polymere GmbH.

The following protected amino acids were used: Fmoc-Ala-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Asp(tBu)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Glu-OtBu, Fmoc-Gly-OH, Fmoc-His(Trt)-OH, Fmoc-Ile-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Lys(Dde)-OH, Fmoc-Phe-OH, Fmoc-Pro-OH, Fmoc-Ser(tBu)-OH, Fmoc-Thr(tBu)-OH, Fmoc-Trp(Boc)-OH, Fmoc-Tyr(tBu)-OH, Fmoc-Val-OH. The L-form of the amino acid building blocks was utilized if not specified otherwise. The modular half-life extending group was built up by solid-phase peptide synthesis (SPPS) using protected building blocks such as, but not limited to, 18-(tert-butoxy)-18-oxooctadecanoic acid (C18DA(tBu)), 2-[2-[2-[[2-[2-(9H-fluoren-9-ylmethoxycarbonyl-amino)ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetic acid (Fmoc-OEG-OEG-OH), 2-[2-[2-(9H-fluoren-9-ylmethoxycarbonylamino)ethoxy]ethoxy] acetic acid (Fmoc-OEG-OH), 6-[[[(9H-fluoren-9-ylmethoxy)carbonyl]amino]hexanoic acid (Fmoc-Ahx) and Fmoc-Glu-OtBu.

The amino acids, Fmoc-Glu-OtBu, Oxyma and DIC, were purchased from standard suppliers, e.g. Bachem, Novabiochem, ABCR, Iris Biotech GmbH, Sigma-Aldrich. 18-(Tert-butoxy)-18-oxooctadecanoic acid (C18DA(tBu)) was supplied by Cool Pharm Ltd. or AstraTech, 2-[2-[2-[[2-[2-(9H-Fluoren-9-ylmethoxycarbonyl-amino)ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetic acid (Fmoc-OEG-OEG-OH) was supplied by ABCR GmbH & CO. KG or Iris Biotech GmbH, 2-[2-[2-(9H-fluoren-9-ylmethoxycarbonylamino)ethoxy]ethoxy] acetic acid (Fmoc-OEG-OH) was supplied by Combi Blocks Inc., Iris Biotech GmbH or Hangzhou APIChem Technology Co., Ltd. 6-[[[(9H-fluoren-9-ylmethoxy)carbonyl]amino]hexanoic acid (Fmoc-Ahx) was purchased by Activate Scientific GmbH, 3-Methylbutanoic acid was supplied by Sigma-Aldrich GmbH.

Assembly of peptides started from the C-terminus by stepwise chain elongation towards the N-terminus according to the respective sequences until the N-terminal capping group was reached. Deprotection of the side chain of the branching amino acid, e.g. Lys(Dde), was followed by assembly of the half-life extending group.

The PYY analogues were obtained as TFA salts from the cleavage/deprotection or from the HPLC purification. The trifluoroacetate can be exchanged by common procedures, such as resin-ion exchange procedures, e.g. as disclosed in Roux, *St. et al. J. Pept. Sci.* 2008; 14: 354-359.

Synthesis Method 1 (S01)

Peptides were synthesized by microwave-assisted solid-phase peptide synthesis (SPPS) on a CEM Liberty Blue Peptide Synthesizer at 0.25 mmol scale on Tentagel S RAM resin using the Fmoc strategy.

- 5 Standard coupling of amino acids was performed with 4 eq of suitably protected amino acid in DMF (0.2 mol/l, 5 ml) or 4 eq Fmoc-Ahx (0.2 mol/l)/Oxyma (0.2 mol/l) in DMF (5 ml), 4 eq of Oxyma in DMF (1 mol/l, 1 ml) and 8 eq DIC in DMF (1 mol/l, 2 ml) at 90 °C for 4 min. Fmoc-Arg(Pbf)-OH was coupled 2 times at 90 °C for 4 min, Fmoc-His(Trt)-OH was coupled 2 times at 50 °C for 12 min and Fmoc-Glu-OtBu was coupled 4 times at 50
- 10 °C for 12 min. Fmoc-OEG-OH, Fmoc-OEG-OEG-OH, Fmoc-Ahx and C18DA(tBu) were coupled 2 times for 4 min at 90 °C. Capping of the N-terminus was achieved by coupling 3-methylbutanoic acid 3 times at 90 °C for 4 min.

- N^αFmoc deprotection was performed with 20% piperidine/DMF (10 ml) for 1 min at 90 °C. Deprotection of the Lys(Dde)-group was carried out 2 times with 5% hydrazine
- 15 hydrate in DMF (10 ml) for 3 min at 90 °C.

- Raw products were washed on resin with DCM and dried prior to cleavage. Cleavage from resin and deprotection was performed with a mixture of 95% TFA/water (10 ml) and triisopropylsilane (250 µl) for 40 min at 42 °C. Crude peptides were precipitated with cold tert-butyl-methyl ether, dissolved in 50% acetonitrile/water and purified by preparative HPLC
- 20 (P01).

Purification Method 1 (P01)

- Crude peptides were purified by reversed phase chromatography using an Agilent preparative HPLC-MS System with preparative pumps G1361A, a diode array detector
- 25 G1315B, a mass-spectrometer G1956B and a fraction collector CTC PAL IFC. A Waters XSelect CSH Prep C18 column (130 Å, 5 µm, OBD, 30 mm x 150 mm) served as stationary phase. The mobile phase was run with a gradient of buffer A (0.1% TFA in H₂O) and buffer B (0.1% TFA in ACN, gradient: 20-42% over 44 min) at a flow rate of 50 ml/min at 40°C. The relevant fractions were pooled and lyophilized. The final product was
- 30 characterized by analytical HPLC-MS (A01).

Purification Method 2 (P02)

Crude peptides were purified by reversed phase HPLC using a Gilson preparative HPLC System with XSelect CSH Phenyl-Hexyl column (Waters 130 Å, 5µm, 30 mm × 150 mm), preparative pumps (Gilson AP-Mod-250 and Gilson 305), UV/VIS detector (Ecom UV10 DAD 800) and a Gilson fraction collector (GX281). The mobile phase was run with a
 5 gradient of buffer A (0.1% TFA in H₂O) and buffer B (0.1% TFA in ACN, gradient: 22-35% B over 66 min) at a flow rate of 50 ml/min at 40°C. Relevant fractions were analysed, pooled and lyophilized. The final product was characterized by analytical UPLC-MS (A01).

10 Analytical Method 1 (A01)

Peptide purity and mass were determined by analytical HPLC-MS on a Kinetex C8 column (Phenomenex, 100 Å, 2.6 µm, 4.6 mm x 150 mm) using a Waters Acquity HPLC System equipped with 3100 Mass Detector. Analysis was performed by gradient elution with buffer A (0.3% TFA in H₂O) and buffer B (0.24% TFA in ACN) at a temperature of 40 °C.
 15 Details of the gradient and flow rates are summarized in the table below. Retention times and masses were recorded.

Method Name:	A01	Gradient/ Solvent Time [min]	% Sol [Water 0.3% TFA (v/v)]	% Sol [ACN 0.24% TFA (v/v)]	Flow [ml/min]	Temp [°C]
Device description:	Waters Acquity with 3100 MS	0.0	65.0	35.0	0.5	40.0
Column:	Kinetex C8_4.6 x 150 mm_2.6 µm	15.0	45.0	55.0	0.5	40.0
Column producer:	Phenomenex	16.0	10.0	90.0	1.0	40.0
		17.01	65.0	35.0	1.0	40.0
		18.0	65.0	35.0	1.0	40.0

List of abbreviations

ACN: acetonitrile

20 Ahx: 6-aminohexanoic acid

Boc: tert-butyloxycarbonyl

C18DA(tBu): 18-(tert-butoxy)-18-oxooctadecanoic acid

- DPBS: Dulbecco's phosphate-buffered saline
DCM: dichloromethane
DIC: diisopropylcarbodiimide
DIPEA: diisopropylethylamine
5 Dde: (4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl
DMF: N,N-dimethylformamid
DODT: 3,6-dioxa-1,8-octanedithiol
Fmoc: 9H-fluoren-9-ylmethoxycarbonyl
Fmoc-Ahx: 6-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}hexanoic acid
10 Fmoc-OEG-OH: 2-[2-[2-(9H-fluoren-9-ylmethoxycarbonylamino)ethoxy]ethoxy] acetic acid
Fmoc-OEG-OEG-OH: 2-[2-[2-[[2-[2-[2-(9H-fluoren-9-ylmethoxycarbonyl-amino)ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetic acid
HTRF: homogeneous time resolved fluorescence
15 IBMX: 3-isobutyl-1-methylxanthine
iVal: 3-methylbutanoyl (isovalerianoyl)
MRT: mean residence time
NMP: 1-methyl-pyrrolidine-2-one
Oxyma: 2-cyano-2-(hydroxyimino)acetic acid ethyl ester
20 OEG: 2-[2-(2-aminoethoxy)ethoxy]acetic acid
Pbf: 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl
Rt: retention time
RT: room temperature
SPPS: solid-phase peptide synthesis
25 tBu: tert-butyl
Trt: trityl
TES: triethylsilane
TFA: trifluoroacetic acid
30 The following compounds were synthesised. All compounds were obtained as TFA salts:

Compound 1

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,10A,13E,18Q,22I,23A,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEADAEPEELQRYYYIALRHYYNWLTRQRY-NH2
5 MW (calculated): 4792.5 Da
Synthesis and purification methods: S01; P01
LCMS: 010_CA07; Rt: 12.30 min; m/3: 1598.0 m/4: m/5:

Compound 2

10 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,18Q,22I,23A,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDASPEELQRYYYIALRHYYNWLTRQRY-NH2
MW (calculated): 4808.5 Da
15 Synthesis and purification methods: S01; P01
LCMS: 010_CA07; Rt: 13.07 min; m/3: 1603.8 m/4: m/5:

Compound 3

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
20 carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,6A,7K,9E,10A,13E,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)
iVal-APAK(C18DA-gGlu-Ahx)PEADAEPEELQRYYYVALRHYYNWLTRQRY-NH2
MW (calculated): 4720.4 Da
Synthesis and purification methods: S01; P02
25 LCMS: 010_CA07; Rt: 11.00 min; m/3: m/4: 1180.9 m/5:

Compound 4

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
30 [4A,7K,9E,11A,13E,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEAAEPEELQRYYYVSLRHYYNWLTRQRY-NH2
MW (calculated): 4808.5 Da
Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 12.10 min; m/3: 1604.1 m/4: m/5:

Compound 5

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
 5 carboxyheptadecanamido) butanamido]hexanoyl)-
 [4A,6A,7K,9E,18Q,20Q,22V,28Y,30W,31L]-hPYY(4-36)
 iVal-APAK(C18DA-gGlu-Ahx)PEEDASPEELQRQYVSLRHYYNWLTRQRY-NH2
 MW (calculated): 4717.4 Da

Synthesis and purification methods: S01; P02

10 LCMS: 010_CA07; Rt: 9.77 min; m/3: 1572.4 m/4: 1180.2 m/5:

Compound 6

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
 carboxyheptadecanamido) butanamido]hexanoyl)-
 15 [4A,7K,9E,10A,13E,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)
 iVal-APEK(C18DA-gGlu-Ahx)PEADAEPEELQRYYVALRHYYNWLTRQRY-NH2
 MW (calculated): 4778.5 Da

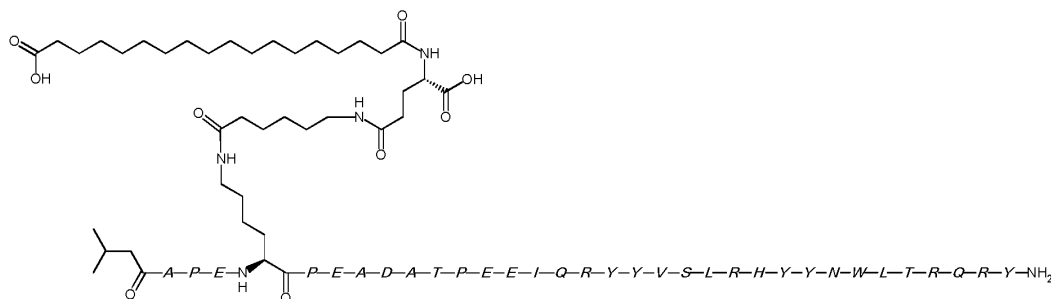
Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 13.50 min; m/3: 1592.9 m/4: m/5:

20

Compound 7

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
 carboxyheptadecanamido) butanamido]hexanoyl)-
 [4A,7K,9E,10A,13T,17I,18Q,22V,28Y,30W,31L]-hPYY(4-36)
 25 iVal-APEK(C18DA-gGlu-Ahx)PEADATPEEIQRYYVSLRHYYNWLTRQRY-NH2



MW (calculated): 4766.4 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 13.50 min; m/3: m/4: 1192.2 m/5:

Compound 8

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
5 carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,12E,13T,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDETPEELQRYYVSLRHYYNWLTRQRY-NH2
MW (calculated): 4882.5 Da
Synthesis and purification methods: S01; P02
10 LCMS: 010_CA07; Rt: 9.94 min; m/3: 1628.0 m/4: 1221.2 m/5:

Compound 9

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
15 [4A,7K,9E,11Q,13T,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEQATPEELQRYYVSLRHYYNWLTRQRY-NH2
MW (calculated): 4837.5 Da
Synthesis and purification methods: S01; P01
LCMS: 010_CA07; Rt: 11.52 min; m/3: 1613.3 m/4: m/5:

20

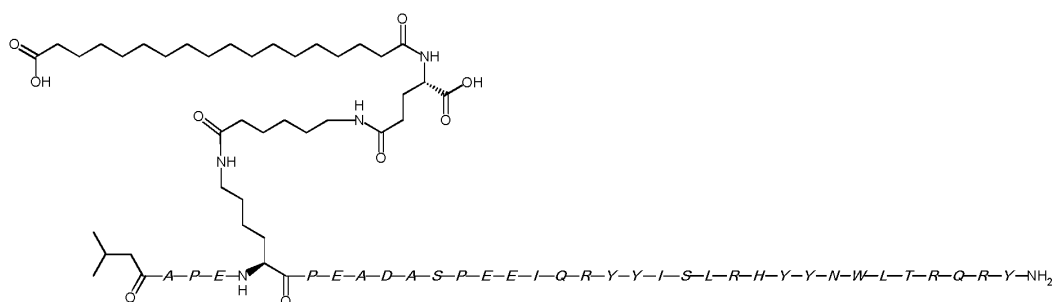
Compound 10

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,6A,7K,9E,10A,11A,13E,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)
25 iVal-APAK(C18DA-gGlu-Ahx)PEAAAEPEELQRYYVALRHYYNWLTRQRY-NH2
MW (calculated): 4676.4 Da
Synthesis and purification methods: S01; P02
LCMS: 010_CA07; Rt: 11.46 min; m/3: 1560.1 m/4: 1170.2 m/5:

30 Compound 11

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,10A,17I,18Q,22I,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEADASPEEIQRYYISLRHYYNWLTRQRY-NH₂



MW (calculated): 4766.4 Da

Synthesis and purification methods: S01; P01

5 LCMS: 010_CA07; Rt: 10.29 min; m/3: 1589.8 m/4: m/5:

Compound 12

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

10 [4A,7K,9E,18Q,19Q,22V,28Y,29H,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEEDASPEELQQYYVSLRHYYHWLTRQRY-NH₂

MW (calculated): 4805.4 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 10.11 min; m/3: 1603.0 m/4: m/5:

15

Compound 13

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,10A,17T,18Q,22V,28Y,30W,31L]-hPYY(4-36)

20 iVal-APEK(C18DA-gGlu-Ahx)PEADASPEETQRYYVSLRHYYNWLTRQRY-NH₂

MW (calculated): 4740.4 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 9.07 min; m/3: 1581.0 m/4: m/5:

25 Compound 14

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,9P,18Q,22V,28Y,30W,31L]-

hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PPEDASPEELQRYYYVSLRHYYNWLTRQRY-NH₂

MW (calculated): 4778.5 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 9.97 min; m/3: m/4: 1195.0 m/5:

5

Compound 15

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,17I,18Q,19Q,22V,28Y,30W,31L]-hPYY(4-36)

10 iVal-APEK(C18DA-gGlu-Ahx)PEEDASPEEIQQYYVSLRHYYNWLTRQRY-NH₂

MW (calculated): 4782.4 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 10.28 min; m/3: 1595.5 m/4: m/5:

15 Compound 16

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,13T,18Q,19K,22V,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQKYYVSLRHYYNWLTRQRY-NH₂

20 MW (calculated): 4796.5 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 10.32 min; m/3: 1600.5 m/4: m/5:

Compound 17

25 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,13T,17I,18Q,22P,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEEIQRYYPSLRHYYNWLTRQRY-NH₂

MW (calculated): 4822.5 Da

30 Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 9.35 min; m/3: 1608.2 m/4: m/5:

Compound 18

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDASPEELQRYYYVALRHYYNWLTRQRY-NH2
5 MW (calculated): 4794.5 Da
Synthesis and purification methods: S01; P01
LCMS: 010_CA07; Rt: 10.50 min; m/3: m/4: 1199.4 m/5:

Compound 19
10 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,13T,14E,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDATEEELQRYYYVSLRHYYNWLTRQRY-NH2
MW (calculated): 4856.5 Da
15 Synthesis and purification methods: S01; P02
LCMS: 010_CA07; Rt: 10.92 min; m/3: 1619.1 m/4: 1214.3 m/5:

Compound 20
N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
20 carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,6A,7K,9E,18Q,21Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APAK(C18DA-gGlu-Ahx)PEEDASPEELQRYQVSLRHYYNWLTRQRY-NH2
MW (calculated): 4717.4 Da
Synthesis and purification methods: S01; P02
25 LCMS: 010_CA07; Rt: 9.67 min; m/3: 1572.9 m/4: 1180.1 m/5:

Compound 21
N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
30 [4A,7K,9E,13E,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDAEPEELQRYYYVALRHYYNWLTRQRY-NH2
MW (calculated): 4836.5 Da
Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 13.50 min; m/3: m/4: 1209.8 m/5:

Compound 22

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
5 carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,12P,13T,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDPTPEELQRYYYVSLRHYYNWLTRQRY-NH2
MW (calculated): 4850.5 Da
Synthesis and purification methods: S01; P02
10 LCMS: 010_CA07; Rt: 9.91 min; m/3: 1616.7 m/4: 1214.2 m/5:

Compound 23

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
15 [4A,7K,9E,11E,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEEASPEELQRYYYVSLRHYYNWLTRQRY-NH2
MW (calculated): 4824.5 Da
Synthesis and purification methods: S01; P01
LCMS: 010_CA07; Rt: 10.29 min; m/3: 1610.2 m/4: m/5:

20

Compound 24

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,12S,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)
25 iVal-APEK(C18DA-gGlu-Ahx)PEEDSSPEELQRYYYVALRHYYNWLTRQRY-NH2
MW (calculated): 4810.5 Da
Synthesis and purification methods: S01; P01
LCMS: 010_CA07; Rt: 10.77 min; m/3: 1603.1 m/4: m/5:

30 Compound 25

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,10A,13T,18Q,22I,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEADATPEELQRYYYISLRHYYNWLTRQRY-NH₂

MW (calculated): 4780.5 Da

Synthesis and purification methods: S01; P02

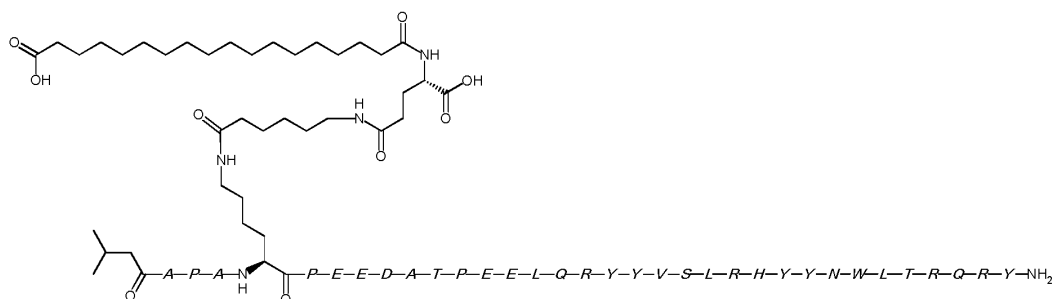
LCMS: 010_CA07; Rt: 10.39 min; m/3: m/4: 1195.1 m/5:

5

Compound 26

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,6A,7K,9E,13T,18Q,22V,28Y,30W,31L]-hPYY(4-36)

10 iVal-APAK(C18DA-gGlu-Ahx)PEEDATPEELQRYVSLRHYYNWLTRQRY-NH₂



MW (calculated): 4766.4 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 10.62 min; m/3: 1590.3 m/4: 1192.1 m/5: 954.2

15

Compound 27

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,13E,17S,18Q,22V,28Y,30W,31L]-hPYY(4-36)

20 iVal-APEK(C18DA-gGlu-Ahx)PEEDAEPEESQRYVSLRHYYNWLTRQRY-NH₂

MW (calculated): 4826.4 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 9.31 min; m/3: 1609.1 m/4: m/5:

25 Compound 28

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9P,13T,17I,18Q,22V,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PPEDATPEEIQRYYVSLRHYYNWLTRQRY-NH₂

MW (calculated): 4792.5 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 9.46 min; m/3: m/4: 1198.6 m/5:

5

Compound 29

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,10A,12S,18Q,22V,28Y,30W,31L]-hPYY(4-36)

10 iVal-APEK(C18DA-gGlu-Ahx)PEADSSPEELQRYYVSLRHYYNWLTRQRY-NH₂

MW (calculated): 4768.4 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 10.22 min; m/3: 1589.1 m/4: m/5:

15 Compound 30

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9P,10A,13T,18Q,22V,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PPADATPEELQRYYVSLRHYYNWLTRQRY-NH₂

20 MW (calculated): 4734.4 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 10.10 min; m/3: m/4: 1184.1 m/5:

Compound 31

25 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,13T,18Q,19P,22V,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQPYYVSLRHYYNWLTRQRY-NH₂

MW (calculated): 4765.4 Da

30 Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 10.82 min; m/3: 1588.5 m/4: m/5:

Compound 32

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,6A,7K,9E,18Q,22V,27Q,28Y,30W,31L]-hPYY(4-36)
iVal-APAK(C18DA-gGlu-Ahx)PEEDASPEELQRYVSLRHQYNWLTRQRY-NH₂

5 MW (calculated): 4717.4 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 9.65 min; m/3: 1573.1 m/4: 1181.1 m/5:

Compound 33

10 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,6A,7K,9E,13E,18Q,22I,28Y,30W,31L]-hPYY(4-36)
iVal-APAK(C18DA-gGlu-Ahx)PEEDAEPEELQRYVSLRHYYNWLTRQRY-NH₂

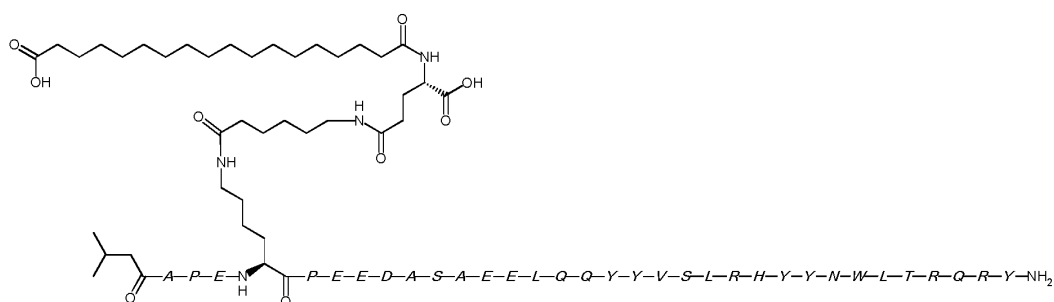
MW (calculated): 4808.5 Da

15 Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 10.55 min; m/3: 1602.9 m/4: m/5:

Compound 34

20 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,14A,18Q,19Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDASAEELQQYYVSLRHYYNWLTRQRY-NH₂



MW (calculated): 4756.4 Da

25 Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 10.86 min; m/3: 1585.9 m/4: 1190.1 m/5:

Compound 35

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,6A,7K,9E,11A,13T,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APAK(C18DA-gGlu-Ahx)PEEAATPEELQRYVSLRHYYNWLTRQRY-NH2
5 MW (calculated): 4722.4 Da
Synthesis and purification methods: S01; P01
LCMS: 010_CA07; Rt: 12.03 min; m/3: m/4: 1181.4 m/5:

Compound 36
10 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,6A,7K,9E,11A,13T,17I,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APAK(C18DA-gGlu-Ahx)PEEAATPEEIQRYYVSLRHYYNWLTRQRY-NH2
MW (calculated): 4722.4 Da
15 Synthesis and purification methods: S01; P02
LCMS: 010_CA07; Rt: 10.66 min; m/3: 1574.8 m/4: 1181.9 m/5:

Compound 37
N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
20 carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,13E,18Q,22T,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDAEPEELQRYTSLRHYYNWLTRQRY-NH2
MW (calculated): 4854.5 Da
Synthesis and purification methods: S01; P01
25 LCMS: 010_CA07; Rt: 11.90 min; m/3: m/4: 1214.4 m/5:

Compound 38
N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
30 [4A,7K,9E,13T,18Q,19E,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQEYYVSLRHYYNWLTRQRY-NH2
MW (calculated): 4797.4 Da
Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 10.38 min; m/3: 1600.9 m/4: m/5:

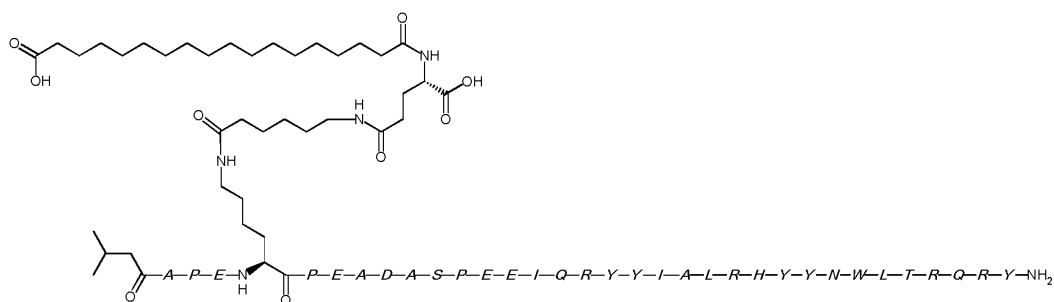
Compound 39

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
 5 carboxyheptadecanamido) butanamido]hexanoyl)-
 [4A,7K,9E,16A,18Q,19E,22V,28Y,30W,31L]-hPYY(4-36)
 iVal-APEK(C18DA-gGlu-Ahx)PEEDASPEALQEYYVSLRHYYNWLTRQRY-NH₂
 MW (calculated): 4725.3 Da

Synthesis and purification methods: S01; P02

10 LCMS: 010_CA07; Rt: 10.52 min; m/3: 1575.9 m/4: m/5:

Compound 40N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
 carboxyheptadecanamido) butanamido]hexanoyl)-
 [4A,7K,9E,10A,17I,18Q,22I,23A,28Y,30W,31L]-hPYY(4-36)
 15 iVal-APEK(C18DA-gGlu-Ahx)PEADASPEEIQRYYIALRHYYNWLTRQRY-NH₂



MW (calculated): 4750.4 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 12.67 min; m/3: 1583.6 m/4: m/5:

20

Compound 41

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
 carboxyheptadecanamido) butanamido]hexanoyl)-
 [4A,7K,9E,13E,18Q,22T,28Y,29Q,30W,31L]-hPYY(4-36)
 25 iVal-APEK(C18DA-gGlu-Ahx)PEEDAEPEELQRYYTSLRHYYQWLTRQRY-NH₂
 MW (calculated): 4868.5 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 9.93 min; m/3: m/4: 1218.3 m/5:

Compound 42

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
 5 [4A,7K,9E,11P,13T,18Q,22V,28Y,30W,31L]-hPYY(4-36)
 iVal-APEK(C18DA-gGlu-Ahx)PEEPATPEELQRYYYVSLRHYYNWLTRQRY-NH2
 MW (calculated): 4806.5 Da
 Synthesis and purification methods: S01; P01
 LCMS: 010_CA07; Rt: 11.57 min; m/3: 1603.0 m/4: m/5:

10

Compound 43

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
 [4A,6A,7K,9E,10A,11A,13E,18Q,22V,28Y,30W,31L]-hPYY(4-36)
 15 iVal-APAK(C18DA-gGlu-Ahx)PEAAAEPEELQRYYYVSLRHYYNWLTRQRY-NH2
 MW (calculated): 4692.4 Da
 Synthesis and purification methods: S01; P02
 LCMS: 010_CA07; Rt: 10.98 min; m/3: 1565.0 m/4: m/5:

20 Compound 44

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
 [4A,7K,9E,13T,18Q,22V,23G,28Y,30W,31L]-hPYY(4-36)
 iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQRYYYVGLRHYYNWLTRQRY-NH2
 25 MW (calculated): 4794.5 Da
 Synthesis and purification methods: S01; P02
 LCMS: 010_CA07; Rt: 10.20 min; m/3: m/4: 1199.3 m/5:

Compound 45

30 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
 [4A,7K,9E,11I,13T,18Q,22V,28Y,30W,31L]-hPYY(4-36)
 iVal-APEK(C18DA-gGlu-Ahx)PEEIATPEELQRYYYVSLRHYYNWLTRQRY-NH2

MW (calculated): 4822.6 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 12.49 min; m/3: 1608.4 m/4: m/5:

5 Compound 46

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,9E,13E,18Q,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEEDAEPEELQRYYYASLRHYYNWLTRQRY-NH2

10 MW (calculated): 4824.4 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 13.52 min; m/3: 1609.4 m/4: 1206.3 m/5:

Compound 47

15 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,9P,17I,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PPEDASPEEIQRYYVALRHYYYNWLTRQRY-NH2

MW (calculated): 4762.5 Da

20 Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 9.44 min; m/3: m/4: 1191.2 m/5:

Compound 48

25 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,6A,7K,9E,11A,13T,18Q,22I,28Y,30W,31L]-hPYY(4-36)

iVal-APAK(C18DA-gGlu-Ahx)PEEAATPEELQRYYYISLRHYYNWLTRQRY-NH2

MW (calculated): 4736.5 Da

Synthesis and purification methods: S01; P01

30 LCMS: 010_CA07; Rt: 12.10 min; m/3: m/4: 1185.0 m/5:

Compound 49

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,13T,18Q,22V,23L,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQRYVLLRHYYNWLTRQRY-NH2
5 MW (calculated): 4850.6 Da
Synthesis and purification methods: S01; P02
LCMS: 010_CA07; Rt: 10.55 min; m/3: m/4: 1213.1 m/5:

Compound 50

10 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,13T,17I,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEEIQRYYVALRHYYNWLTRQRY-NH2
MW (calculated): 4858.1 Da
15 Synthesis and purification methods: S01; P02
LCMS: 010_CA07; Rt: 13.00 min; m/3: m/4: 1215.5 m/5:

Compound 51

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
20 carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,13T,18Q,22V,23Q,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQRYVQLRHYYNWLTRQRY-NH2
MW (calculated): 4865.5 Da
Synthesis and purification methods: S01; P02
25 LCMS: 010_CA07; Rt: 9.86 min; m/3: m/4: 1217.2 m/5:

Compound 52

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
30 [4A,7K,9E,17I,18Q,22V,23E,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDASPEEIQRYYVELRHYYNWLTRQRY-NH2
MW (calculated): 4852.5 Da
Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 10.16 min; m/3: 1619.2 m/4: m/5:

Compound 53

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
5 carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,13E,17V,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDAEPEEVQRYVSLRHYYNWLTRQRY-NH2
MW (calculated): 4838.5 Da
Synthesis and purification methods: S01; P02
10 LCMS: 010_CA07; Rt: 13.20 min; m/3: 1613.2 m/4: 1210.0 m/5:

Compound 54

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
15 [4A,7K,9E,13T,17A,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEEAQRYVSLRHYYNWLTRQRY-NH2
MW (calculated): 4782.4 Da
Synthesis and purification methods: S01; P01
LCMS: 010_CA07; Rt: 9.71 min; m/3: 1594.9 m/4: m/5:

20

Compound 55

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,14E,17I,18Q,22V,28Y,30W,31L]-hPYY(4-36)
25 iVal-APEK(C18DA-gGlu-Ahx)PEEDASEEEIQRYVSLRHYYNWLTRQRY-NH2
MW (calculated): 4842.5 Da
Synthesis and purification methods: S01; P02
LCMS: 010_CA07; Rt: 10.23 min; m/3: 1614.8 m/4: m/5:

30 Compound 56

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,13T,14A,18Q,22V,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEEDATAEELQRYYYVSLRHYYNWLTRQRY-NH₂

MW (calculated): 4798.4 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 11.04 min; m/3: 1600.0 m/4: m/5:

5

Compound 57

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,6A,7K,9E,13T,17A,18Q,22V,28Y,30W,31L]-hPYY(4-36)

10 iVal-APAK(C18DA-gGlu-Ahx)PEEDATPEEAQRYYYVSLRHYYNWLTRQRY-NH₂

MW (calculated): 4724.4 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 11.20 min; m/3: m/4: 1182.0 m/5:

15 Compound 58

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,13T,17V,18Q,22V,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEEVQRYYYVSLRHYYNWLTRQRY-NH₂

20 MW (calculated): 4810.5 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 9.62 min; m/3: m/4: 1203.4 m/5:

Compound 59

25 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,6A,7K,9E,18Q,22V,23Q,28Y,30W,31L]-hPYY(4-36)

iVal-APAK(C18DA-gGlu-Ahx)PEEDASPEELQRYYYVQLRHYYNWLTRQRY-NH₂

MW (calculated): 4793.5 Da

30 Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 9.88 min; m/3: 1598.7 m/4: m/5:

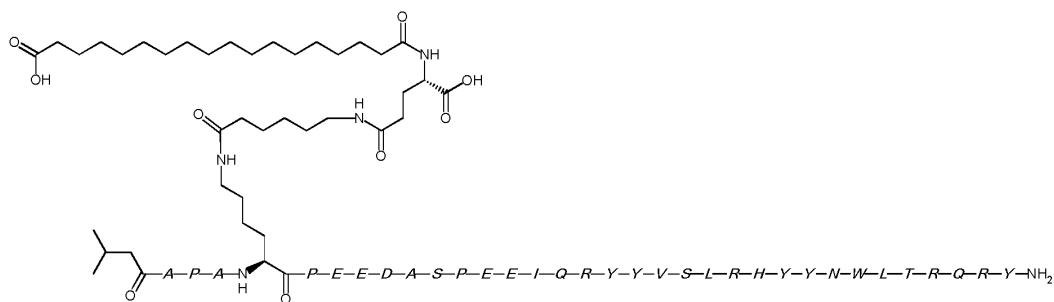
Compound 60

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,18Q,22V,28Y,29Q,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDASPEELQRYYVSLRHYYQWLTRQRY-NH2
5 MW (calculated): 4824.5 Da
Synthesis and purification methods: S01; P02
LCMS: 010_CA07; Rt: 9.59 min; m/3: 1609.4 m/4: m/5:

Compound 61
10 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9P,10A,17I,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PPADASPEEIQRYYVSLRHYYNWLTRQRY-NH2
MW (calculated): 4720.4 Da
15 Synthesis and purification methods: S01; P01
LCMS: 010_CA07; Rt: 9.70 min; m/3: m/4: 1181.5 m/5:

Compound 62
N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
20 carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,6A,7K,9P,18Q,22V,23E,28Y,30W,31L]-hPYY(4-36)
iVal-APAK(C18DA-gGlu-Ahx)PPEDASPEELQRYYVELRHYYNWLTRQRY-NH2
MW (calculated): 4762.5 Da
Synthesis and purification methods: S01; P01
25 LCMS: 010_CA07; Rt: 9.43 min; m/3: 1588.6 m/4: m/5:

Compound 63
N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
30 [4A,6A,7K,9E,17I,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APAK(C18DA-gGlu-Ahx)PEEDASPEEIQRYYVSLRHYYNWLTRQRY-NH2



MW (calculated): 4752.4 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 10.35 min; m/3: 1585.2 m/4: m/5:

5

Compound 64

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9P,13T,17I,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)

10 iVal-APEK(C18DA-gGlu-Ahx)PPEDATPEEIQRYYVALRHYYNWLTRQRY-NH₂

MW (calculated): 4776.5 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 11.50 min; m/3: m/4: 1194.9 m/5:

15 Compound 65

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,6A,7K,9E,17I,18Q,22I,23A,28Y,30W,31L]-hPYY(4-36)

iVal-APAK(C18DA-gGlu-Ahx)PEEDASPEEIQRYYIALRHYYNWLTRQRY-NH₂

20 MW (calculated): 4750.4 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 10.18 min; m/3: m/4: 1187.8 m/5:

Compound 66

25 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,13T,18Q,22I,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQRYYISLRHYYNWLTRQRY-NH₂

MW (calculated): 4838.5 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 13.60 min; m/3: 1613.2 m/4: m/5:

5 Compound 67

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,17T,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEEDASPEETQRYYVALRHYYNWLTRQRY-NH2

10 MW (calculated): 4782.4 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 9.86 min; m/3: 1595.1 m/4: m/5:

Compound 68

15 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,13E,18Q,22V,28Y,29Q,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEEDAEPEELQRYYVSLRHYYQWLTRQRY-NH2

MW (calculated): 4866.5 Da

20 Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 10.02 min; m/3: m/4: 1217.4 m/5:

Compound 69

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

25 [4A,7K,9P,10A,17T,18Q,22V,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PPADASPEETQRYYVSLRHYYNWLTRQRY-NH2

MW (calculated): 4708.4 Da

Synthesis and purification methods: S01; P01

30 LCMS: 010_CA07; Rt: 9.50 min; m/3: m/4: 1178.1 m/5:

Compound 70

- N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,6A,7K,9E,13T,18Q,22I,23A,28Y,30W,31L]-hPYY(4-36)
iVal-APAK(C18DA-gGlu-Ahx)PEEDATPEELQRYYYIALRHYYNWLTRQRY-NH2
5 MW (calculated): 4764.5 Da
Synthesis and purification methods: S01; P02
LCMS: 010_CA07; Rt: 10.55 min; m/3: m/4: 1192.4 m/5:
- Compound 71
10 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,6A,7K,9E,13E,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)
iVal-APAK(C18DA-gGlu-Ahx)PEEDAEPEELQRYYYVALRHYYNWLTRQRY-NH2
MW (calculated): 4778.5 Da
15 Synthesis and purification methods: S01; P02
LCMS: 010_CA07; Rt: 13.10 min; m/3: m/4: 1196.0 m/5:
- Compound 72
N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
20 carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,10A,13E,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEADAEPEELQRYYYVSLRHYYNWLTRQRY-NH2
MW (calculated): 4794.5 Da
Synthesis and purification methods: S01; P01
25 LCMS: 010_CA07; Rt: 10.71 min; m/3: 1598.4 m/4: m/5:
- Compound 73
N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
30 [4A,7K,9E,11A,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEAASPEELQRYYYVALRHYYNWLTRQRY-NH2
MW (calculated): 4750.4 Da
Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 13.24 min; m/3: 1584.1 m/4: m/5:

Compound 74

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
5 carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,13T,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQRYYYVALRHYYNWLTRQRY-NH2
MW (calculated): 4808.5 Da
Synthesis and purification methods: S01; P01
10 LCMS: 010_CA07; Rt: 13.70 min; m/3: m/4: 1203.1 m/5:

Compound 75

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
15 [4A,7K,9E,13P,17I,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDAPPEEIQRYYVSLRHYYNWLTRQRY-NH2
MW (calculated): 4820.5 Da
Synthesis and purification methods: S01; P01
LCMS: 010_CA07; Rt: 10.30 min; m/3: m/4: 1207.1 m/5:

20

Compound 76

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,9E,18Q,22I,28Y,30W,31L]-
hPYY(4-36)
25 iVal-APEK(C18DA-gGlu-Ahx)PEEDASPEELQRYYYISLRHYYNWLTRQRY-NH2
MW (calculated): 4824.5 Da
Synthesis and purification methods: S01; P01
LCMS: U046_001; Rt: 11.60 min; m/3: 1609.0 m/4: m/5:

30 Compound 77

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,6A,7K,9E,18Q,22V,28Q,30W,31L]-hPYY(4-36)

iVal-APAK(C18DA-gGlu-Ahx)PEEDASPEELQRYVSLRHYQNWLTRQRY-NH₂

MW (calculated): 4717.4 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 9.51 min; m/3: 1572.9 m/4: 1180.4 m/5:

5

Compound 78

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,6A,7K,9E,18Q,22V,28Y,29Q,30W,31L]-hPYY(4-36)

10 iVal-APAK(C18DA-gGlu-Ahx)PEEDASPEELQRYVSLRHYQWLTRQRY-NH₂

MW (calculated): 4766.4 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 10.00 min; m/3: 1589.9 m/4: m/5:

15 Compound 79

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,9E,18Q,22V,28Y,30W,31L]-
hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEEDASPEELQRYVSLRHYYNWLTRQRY-NH₂

20 MW (calculated): 4810.5 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 10.11 min; m/3: m/4: 1203.5 m/5:

Compound 80

25 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,14E,15A,18Q,22V,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEEDASEAELQRYVSLRHYYNWLTRQRY-NH₂

MW (calculated): 4784.4 Da

30 Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 10.52 min; m/3: 1594.9 m/4: m/5:

Compound 81

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,13Q,17I,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDAQPPEIQRYVSLRHYYNWLTRQRY-NH2
5 MW (calculated): 4851.5 Da
Synthesis and purification methods: S01; P02
LCMS: 010_CA07; Rt: 9.87 min; m/3: 1618.2 m/4: 1214.5 m/5:

Compound 82

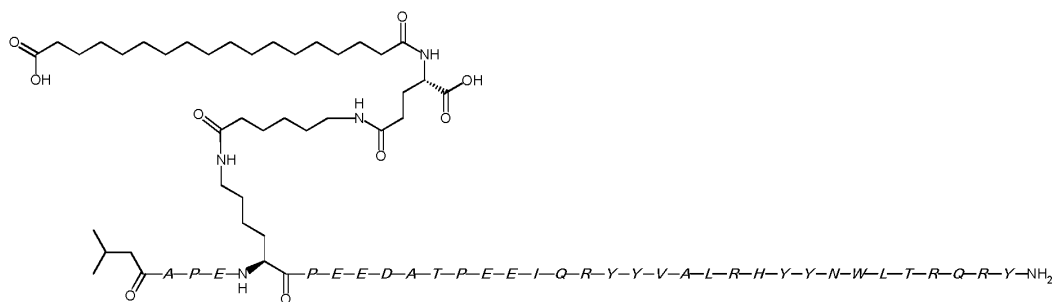
10 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,6A,7K,9P,17I,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APAK(C18DA-gGlu-Ahx)PPEDASPEEQRYVSLRHYYNWLTRQRY-NH2
MW (calculated): 4720.4 Da
15 Synthesis and purification methods: S01; P01
LCMS: 010_CA07; Rt: 9.36 min; m/3: 1574.2 m/4: m/5:

Compound 83

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
20 carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,13T,14S,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDATSEELQRYVSLRHYYNWLTRQRY-NH2
MW (calculated): 4814.4 Da
Synthesis and purification methods: S01; P02
25 LCMS: 010_CA07; Rt: 10.69 min; m/3: 1605.0 m/4: 1204.4 m/5:

Compound 84

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
30 [4A,7K,9E,13T,17I,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEEQRYVALRHYYNWLTRQRY-NH2



MW (calculated): 4808.5 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 13.60 min; m/3: m/4: 1202.9 m/5:

5

Compound 85

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,6A,7K,9E,17T,18Q,22V,28Y,30W,31L]-hPYY(4-36)

10 iVal-APAK(C18DA-gGlu-Ahx)PEEDASPEETQRYVSLRHYYNWLTRQRY-NH₂

MW (calculated): 4740.4 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 9.15 min; m/3: m/4: 1186.2 m/5:

15 Compound 86

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,13T,17I,18Q,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEEIQRYYASLRHYYNWLTRQRY-NH₂

20 MW (calculated): 4796.4 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 9.67 min; m/3: m/4: 1200.1 m/5:

Compound 87

25 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,13T,18Q,22V,23P,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQRYYVPLRHYYNWLTRQRY-NH₂

MW (calculated): 4834.5 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 10.25 min; m/3: m/4: 1209.3 m/5:

5 Compound 88

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,13T,18Q,20Q,22V,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQRQYVSLRHYYNWLTRQRY-NH2

10 MW (calculated): 4789.4 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 9.60 min; m/3: 1596.6 m/4: m/5:

Compound 89

15 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,6A,7K,9P,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)

iVal-APAK(C18DA-gGlu-Ahx)PPEDASPEELQRYYVALRHYYNWLTRQRY-NH2

MW (calculated): 4704.4 Da

20 Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 12.20 min; m/3: 1568.4 m/4: m/5:

Compound 90

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

25 [4A,7K,9E,13T,18Q,22V,23V,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQRYYVVL RHYYNWLTRQRY-NH2

MW (calculated): 4836.5 Da

Synthesis and purification methods: S01; P02

30 LCMS: 010_CA07; Rt: 10.76 min; m/3: m/4: 1209.9 m/5:

Compound 91

- N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,13E,18Q,22T,28Y,29H,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDAEPEELQRYYSLSRHYYHWLTRQRY-NH2
5 MW (calculated): 4877.5 Da
Synthesis and purification methods: S01; P01
LCMS: 010_CA07; Rt: 10.22 min; m/3: 1628.8 m/4: m/5:

Compound 92

- 10 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,18Q,22I,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PGEDASPEELQRYYSLSRHYYNWLTRQRY-NH2
MW (calculated): 4752.4 Da
15 Synthesis and purification methods: S01; P02
LCMS: 010_CA07; Rt: 10.75 min; m/3: 1585.3 m/4: 1188.4 m/5:

Compound 93

- N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
20 [4A,7K,9E,17I,18Q,22V,23Q,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDASPEEIQRYYVQLRHYYNWLTRQRY-NH2
MW (calculated): 4851.5 Da
Synthesis and purification methods: S01; P02
25 LCMS: 010_CA07; Rt: 9.64 min; m/3: m/4: 1213.4 m/5:

Compound 94

- N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
30 [4A,6A,7K,9E,10A,18Q,22V,23E,28Y,30W,31L]-hPYY(4-36)
iVal-APAK(C18DA-gGlu-Ahx)PEADASPEELQRYYSLSRHYYNWLTRQRY-NH2
MW (calculated): 4736.4 Da
Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 10.07 min; m/3: 1578.9 m/4: m/5:

Compound 95

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
5 carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,13T,18Q,19A,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQAYYVSLRHYYNWLTRQRY-NH2
MW (calculated): 4739.4 Da
Synthesis and purification methods: S01; P01
10 LCMS: 010_CA07; Rt: 13.31 min; m/3: 1579.5 m/4: m/5:

Compound 96

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
15 [4A,7K,9E,11S,13T,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEESATPEELQRYVSLRHYYNWLTRQRY-NH2
MW (calculated): 4796.5 Da
Synthesis and purification methods: S01; P01
LCMS: 010_CA07; Rt: 9.90 min; m/3: 1599.4 m/4: m/5:

20

Compound 97

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,13T,17I,18Q,22L,28Y,30W,31L]-hPYY(4-36)
25 iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEEIQRYYLSLRHYYNWLTRQRY-NH2
MW (calculated): 4838.5 Da
Synthesis and purification methods: S01; P02
LCMS: 010_CA07; Rt: 9.88 min; m/3: 1613.3 m/4: m/5:

30 Compound 98

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,10A,13T,17I,18Q,22V,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEADATPEEIQRYYVSLRHYYNWLTRQRY-NH₂

MW (calculated): 4816.1 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 13.35 min; m/3: 1606.6 m/4: m/5:

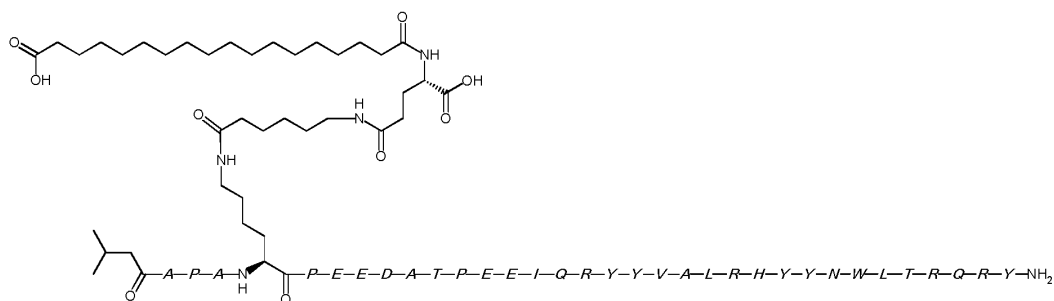
5

Compound 99

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,6A,7K,9E,13T,17I,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)

10 iVal-APAK(C18DA-gGlu-Ahx)PEEDATPEEIQRYYVALRHYYNWLTRQRY-NH₂



MW (calculated): 4750.4 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 11.90 min; m/3: m/4: 1188.5 m/5:

15

Compound 100

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,10A,13T,18Q,22I,23A,28Y,30W,31L]-hPYY(4-36)

20 iVal-APEK(C18DA-gGlu-Ahx)PEADATPEELQRYYIALRHYYNWLTRQRY-NH₂

MW (calculated): 4764.5 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 12.10 min; m/3: m/4: 1192.2 m/5:

25 Compound 101

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,6A,7K,9E,13T,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)

iVal-APAK(C18DA-gGlu-Ahx)PEEDATPEELQRYYYVALRHYYNWLTRQRY-NH₂

MW (calculated): 4750.4 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 12.28 min; m/3: m/4: 1188.8 m/5:

5

Compound 102

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,13T,14L,18Q,22V,28Y,30W,31L]-hPYY(4-36)

10 iVal-APEK(C18DA-gGlu-Ahx)PEEDATLEELQRYYYVSLRHYYNWLTRQRY-NH₂

MW (calculated): 4840.5 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 11.96 min; m/3: 1613.9 m/4: 1210.9 m/5:

15 Compound 103

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,14A,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEEDASAEELQRYYYVALRHYYNWLTRQRY-NH₂

20 MW (calculated): 4768.4 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 10.95 min; m/3: 1590.9 m/4: 1193.5 m/5:

Compound 104

25 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,13E,17A,18Q,22V,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEEDAEPEEAQRYYYVSLRHYYNWLTRQRY-NH₂

MW (calculated): 4882.5 Da

30 Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 12.00 min; m/3: m/4: 1221.8 m/5:

Compound 105

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,13T,14Q,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDATQEELQRYVSLRHYYNWLTRQRY-NH2
5 MW (calculated): 4855.5 Da
Synthesis and purification methods: S01; P02
LCMS: 010_CA07; Rt: 10.63 min; m/3: 1618.4 m/4: 1215.2 m/5:

Compound 106

10 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,6A,7K,9E,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)
iVal-APAK(C18DA-gGlu-Ahx)PEEDASPEELQRYVVALRHYYNWLTRQRY-NH2
MW (calculated): 4736.4 Da
15 Synthesis and purification methods: S01; P01
LCMS: 010_CA07; Rt: 10.50 min; m/3: m/4: 1185.0 m/5:

Compound 107

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
20 carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,13E,17T,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDAEPEETQRYVSLRHYYNWLTRQRY-NH2
MW (calculated): 4840.4 Da
Synthesis and purification methods: S01; P01
25 LCMS: 010_CA07; Rt: 11.30 min; m/3: 1614.3 m/4: m/5:

Compound 108

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
30 [4A,7K,9E,10A,14E,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEADASEEELQRYVSLRHYYNWLTRQRY-NH2
MW (calculated): 4784.4 Da
Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 10.71 min; m/3: 1595.5 m/4: 1196.7 m/5:

Compound 109

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
5 carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,12L,13T,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDLTPEELQRYYVSLRHYYNWLTRQRY-NH2
MW (calculated): 4866.6 Da

Synthesis and purification methods: S01; P02

10 LCMS: 010_CA07; Rt: 10.14 min; m/3: 1623.2 m/4: 1216.9 m/5:

Compound 110

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
15 [4A,7K,9E,13T,18Q,22V,23E,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQRYYVELRHYYNWLTRQRY-NH2
MW (calculated): 4866.5 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 10.31 min; m/3: 1622.9 m/4: m/5:

20

Compound 111

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,6A,7K,9E,10A,11A,13E,17I,18Q,22V,28Y,30W,31L]-hPYY(4-36)
25 iVal-APAK(C18DA-gGlu-Ahx)PEAAAEPEEIQRYYVSLRHYYNWLTRQRY-NH2
MW (calculated): 4692.4 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 11.12 min; m/3: 1564.1 m/4: 1173.3 m/5:

30 Compound 112

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,13E,17I,18Q,22V,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEEDAEPEEIQRYYVSLRHYYNWLTRQRY-NH₂

MW (calculated): 4852.5 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 9.97 min; m/3: m/4: 1214.4 m/5:

5

Compound 113

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,13T,17I,18Q,22V,28Q,30W,31L]-hPYY(4-36)

10 iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEEIQRYYVSLRHYYQNWLTRQRY-NH₂

MW (calculated): 4789.4 Da

Synthesis and purification methods: S01; P01

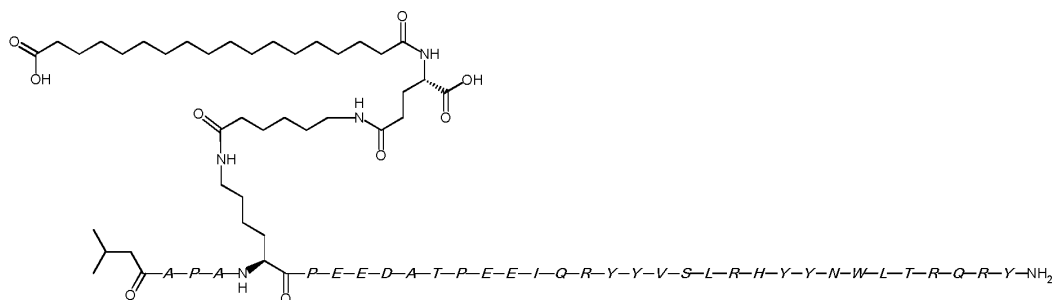
LCMS: 010_CA07; Rt: 9.23 min; m/3: 1596.7 m/4: m/5:

15 Compound 114

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,6A,7K,9E,13T,17I,18Q,22V,28Y,30W,31L]-hPYY(4-36)

iVal-APAK(C18DA-gGlu-Ahx)PEEDATPEEIQRYYVSLRHYYNWLTRQRY-NH₂



20

MW (calculated): 4766.4 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 11.70 min; m/3: m/4: 1192.4 m/5:

25 Compound 115

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,13T,18Q,21Q,22V,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQRYQVSLRHYYNWLTRQRY-NH₂

MW (calculated): 4789.4 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 11.17 min; m/3: 1597.3 m/4: m/5:

5

Compound 116

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,6A,7K,9E,10A,11A,13E,17I,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)

10 iVal-APAK(C18DA-gGlu-Ahx)PEAAAEPEEIQRYYVALRHYYNWLTRQRY-NH₂

MW (calculated): 4676.4 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 11.62 min; m/3: 1559.2 m/4: m/5:

15 Compound 117

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,17A,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEEDASPEEAQRYYVALRHYYNWLTRQRY-NH₂

20 MW (calculated): 4752.4 Da

Synthesis and purification methods: S01; P01

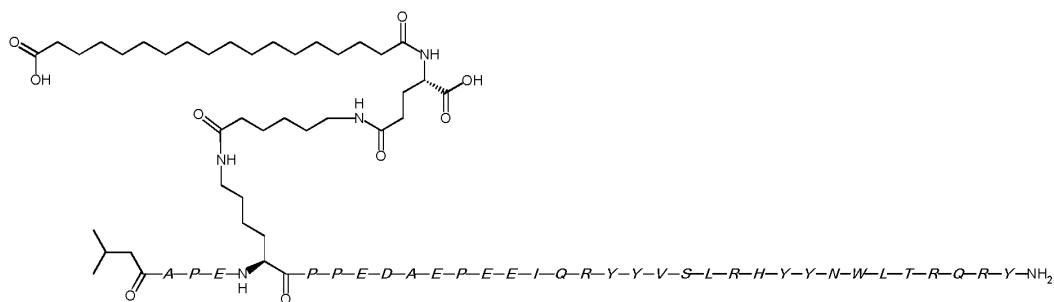
LCMS: 010_CA07; Rt: 12.53 min; m/3: 1584.9 m/4: m/5:

Compound 118

25 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9P,13E,17I,18Q,22V,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PPEDAEPEEIQRYYVSLRHYYNWLTRQRY-NH₂



MW (calculated): 4820.5 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 9.86 min; m/3: 1607.4 m/4: m/5:

5

Compound 119

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,13T,17S,18Q,22V,28Y,30W,31L]-hPYY(4-36)

10 iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEESQRYVSLRHYYNWLTRQRY-NH2

MW (calculated): 4798.4 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 10.92 min; m/3: 1600.3 m/4: m/5:

15 Compound 120

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,6A,7K,9E,11A,13T,17I,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)

iVal-APAK(C18DA-gGlu-Ahx)PEEAATPEEIQRYYVALRHYYNWLTRQRY-NH2

20 MW (calculated): 4706.4 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 11.28 min; m/3: m/4: 1177.1 m/5:

Compound 121

25 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,10A,18Q,22V,23Q,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEADASPEELQRYYVQLRHYYNWLTRQRY-NH2

MW (calculated): 4793.5 Da

Synthesis and purification methods: S01; P02

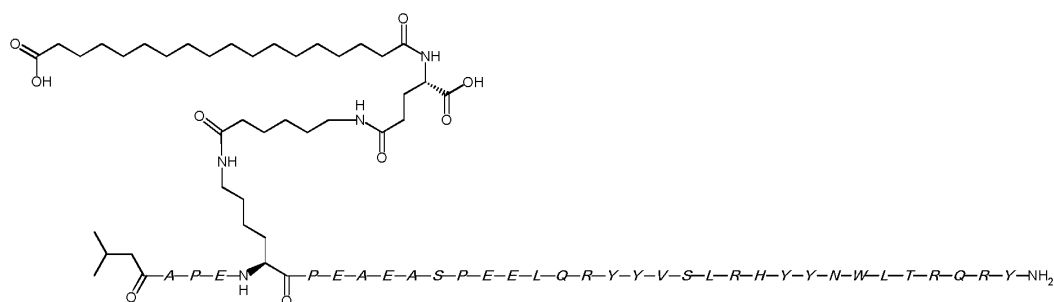
LCMS: 010_CA07; Rt: 9.78 min; m/3: m/4: 1199.3 m/5:

5 Compound 122

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,10A,11E,18Q,22V,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEAEASPEELQRYYYVSLRHYYNWLTRQRY-NH₂



MW (calculated): 4766.4 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 12.40 min; m/3: 1589.2 m/4: m/5:

15 Compound 123

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,13A,18Q,19K,22V,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEEDAPEELQKYYVSLRHYYNWLTRQRY-NH₂

20 MW (calculated): 4766.4 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 10.65 min; m/3: m/4: 1192.1 m/5:

Compound 124

25 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,10A,11A,13E,17I,18Q,22V,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEAAAEPEEIQRYYVSLRHYYNWLTRQRY-NH₂

MW (calculated): 4750.4 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 10.74 min; m/3: 1583.7 m/4: m/5:

5 Compound 125

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,18Q,22V,23E,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEEDASPEELQRYYVELRHYYNWLTRQRY-NH2

10 MW (calculated): 4852.5 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 9.93 min; m/3: 1618.3 m/4: m/5:

Compound 126

15 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,13E,18Q,22V,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEEDAEPEELQRYYVSLRHYYNWLTRQRY-NH2

MW (calculated): 4852.5 Da

20 Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 12.00 min; m/3: 1617.0 m/4: m/5:

Compound 127

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

25 [4A,7K,9E,10A,11A,13E,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEAAAEPEELQRYYVALRHYYNWLTRQRY-NH2

MW (calculated): 4734.4 Da

Synthesis and purification methods: S01; P02

30 LCMS: 010_CA07; Rt: 10.99 min; m/3: m/4: 1184.2 m/5:

Compound 128

- N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,11A,13T,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEAATPEELQRYVSLRHYYNWLTRQRY-NH2
5 MW (calculated): 4780.5 Da
Synthesis and purification methods: S01; P01
LCMS: 010_CA07; Rt: 13.70 min; m/3: 1594.6 m/4: m/5:

Compound 129

- 10 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,14A,17I,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDASAEIQRYYVSLRHYYNWLTRQRY-NH2
MW (calculated): 4784.4 Da
15 Synthesis and purification methods: S01; P02
LCMS: 010_CA07; Rt: 10.37 min; m/3: m/4: 1197.0 m/5:

Compound 130

- N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
20 carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,13T,18Q,19L,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQLYYVSLRHYYNWLTRQRY-NH2
MW (calculated): 4781.5 Da
Synthesis and purification methods: S01; P01
25 LCMS: 010_CA07; Rt: 10.67 min; m/3: 1595.1 m/4: m/5:

Compound 131

- N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
30 [4A,7K,9E,10A,13E,17I,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEADAEPEEIQRYYVALRHYYNWLTRQRY-NH2
MW (calculated): 4778.5 Da
Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 10.83 min; m/3: m/4: 1195.0 m/5:

Compound 132

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
5 carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,10A,13T,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEADATPEELQRYVYVSLRHYYNWLTRQRY-NH2
MW (calculated): 4766.4 Da
Synthesis and purification methods: S01; P02
10 LCMS: 010_CA07; Rt: 9.74 min; m/3: 1589.6 m/4: m/5:

Compound 133

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
15 [4A,6A,7K,9E,13E,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APAK(C18DA-gGlu-Ahx)PEEDAEPEELQRYVYVSLRHYYNWLTRQRY-NH2
MW (calculated): 4794.5 Da
Synthesis and purification methods: S01; P02
LCMS: 010_CA07; Rt: 10.12 min; m/3: 1598.3 m/4: m/5:

20

Compound 134

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,13T,17Q,18Q,22V,28Y,30W,31L]-hPYY(4-36)
25 iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEEQRYVYVSLRHYYNWLTRQRY-NH2
MW (calculated): 4839.5 Da
Synthesis and purification methods: S01; P01
LCMS: 010_CA07; Rt: 9.04 min; m/3: 1613.8 m/4: m/5:

30 Compound 135

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,10A,11A,13E,17I,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEAAAEPEEIQRYYVALRHYYNWLTRQRY-NH₂

MW (calculated): 4734.4 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 11.45 min; m/3: m/4: 1184.2 m/5:

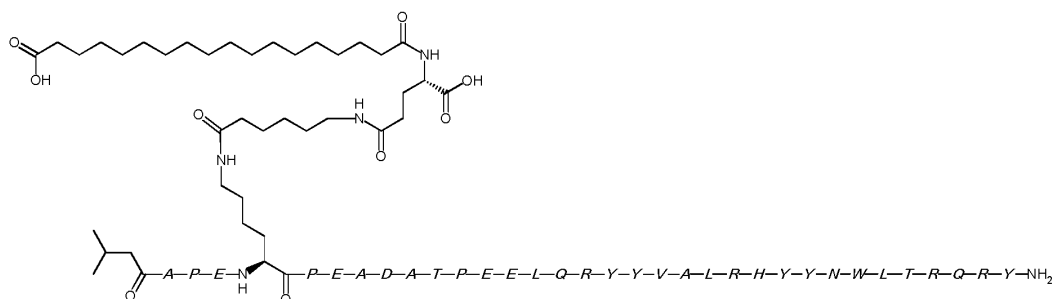
5

Compound 136

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,10A,13T,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)

10 iVal-APEK(C18DA-gGlu-Ahx)PEADATPEELQRYYVALRHYYNWLTRQRY-NH₂



MW (calculated): 4750.4 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 13.80 min; m/3: 1584.4 m/4: m/5:

15

Compound 137

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,13T,18Q,22V,28Y,30W,31L,32L]-hPYY(4-36)

20 iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQRYYVSLRHYYNWLLRQRY-NH₂

MW (calculated): 4836.5 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 11.13 min; m/3: 1558.4 m/4: m/5:

25 Compound 138

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,13E,18Q,19E,22V,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEEDAEPEELQEYYVSLRHYYNWLTRQRY-NH₂

MW (calculated): 4825.4 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 13.90 min; m/3: 1609.1 m/4: 1206.7 m/5:

5

Compound 139

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,11E,15A,18Q,22V,28Y,30W,31L]-hPYY(4-36)

10 iVal-APEK(C18DA-gGlu-Ahx)PEEEASPAELQRYVSLRHYYNWLTRQRY-NH₂

MW (calculated): 4766.4 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 10.01 min; m/3: 1589.4 m/4: 1191.8 m/5:

15 Compound 140

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,10A,17I,18Q,22V,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEADASPEEIQRYYVSLRHYYNWLTRQRY-NH₂

20 MW (calculated): 4752.4 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 10.21 min; m/3: 1585.1 m/4: m/5:

Compound 141

25 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,13T,18Q,19S,22V,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQSYYVSLRHYYNWLTRQRY-NH₂

MW (calculated): 4755.4 Da

30 Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 10.40 min; m/3: 1586.6 m/4: m/5:

Compound 142

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,13L,17I,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDALPEEIQRYYVSLRHYYNWLTRQRY-NH2
5 MW (calculated): 4836.5 Da
Synthesis and purification methods: S01; P02
LCMS: 010_CA07; Rt: 12.05 min; m/3: 1613.6 m/4: 1210.2 m/5:

Compound 143

10 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,12S,13T,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDSTPEELQRYYVSLRHYYNWLTRQRY-NH2
MW (calculated): 4840.5 Da
15 Synthesis and purification methods: S01; P01
LCMS: 010_CA07; Rt: 11.81 min; m/3: 1614.3 m/4: m/5:

Compound 144

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
20 carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,12Q,13T,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDQTPEELQRYYVSLRHYYNWLTRQRY-NH2
MW (calculated): 4881.5 Da
Synthesis and purification methods: S01; P02
25 LCMS: 010_CA07; Rt: 9.95 min; m/3: 1628.4 m/4: 1221.3 m/5:

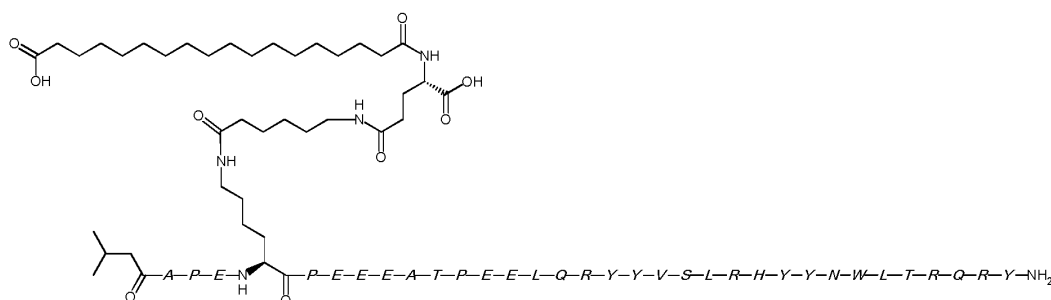
Compound 145

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
30 [4A,6A,7K,9E,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APAK(C18DA-gGlu-Ahx)PEEDASPEELQRYYVSLRHYYNWLTRQRY-NH2
MW (calculated): 4752.4 Da
Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 10.37 min; m/3: 1586.0 m/4: m/5:

Compound 146

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
 5 carboxyheptadecanamido) butanamido]hexanoyl)-
 [4A,7K,9E,11E,13T,18Q,22V,28Y,30W,31L]-hPYY(4-36)
 iVal-APEK(C18DA-gGlu-Ahx)PEEEATPEELQRYYVSLRHYYNWLTRQRY-NH₂



MW (calculated): 4838.5 Da

10 Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 10.57 min; m/3: 1614.2 m/4: m/5:

Compound 147

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
 15 carboxyheptadecanamido) butanamido]hexanoyl)-
 [4A,7K,9E,17I,18Q,22V,28Y,30W,31L]-hPYY(4-36)
 iVal-APEK(C18DA-gGlu-Ahx)PEEDASPEEIQRYYVSLRHYYNWLTRQRY-NH₂

MW (calculated): 4810.5 Da

Synthesis and purification methods: S01; P01

20 LCMS: 010_CA07; Rt: 10.02 min; m/3: 1603.9 m/4: m/5:

Compound 148

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
 carboxyheptadecanamido) butanamido]hexanoyl)-
 25 [4A,7K,9E,13T,18Q,22V,23T,28Y,30W,31L]-hPYY(4-36)
 iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQRYYVTLRHYYNWLTRQRY-NH₂

MW (calculated): 4838.5 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 11.80 min; m/3: m/4: 1210.5 m/5:

Compound 149

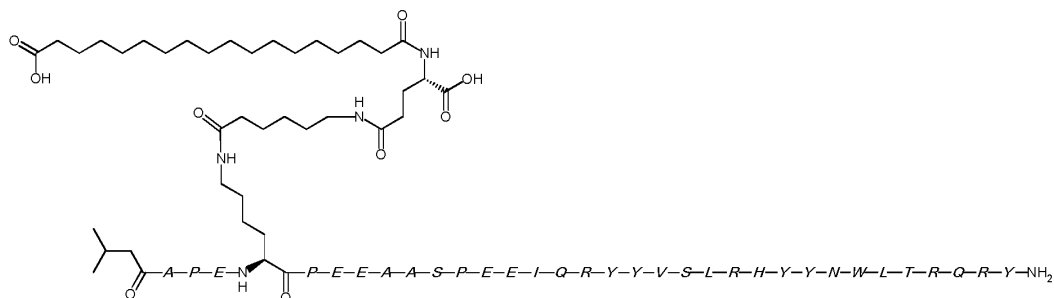
N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
 5 carboxyheptadecanamido) butanamido]hexanoyl)-
 [4A,6A,7K,9E,17S,18Q,22V,28Y,30W,31L]-hPYY(4-36)
 iVal-APAK(C18DA-gGlu-Ahx)PEEDASPEESQRYVSLRHYYNWLTRQRY-NH2
 MW (calculated): 4726.3 Da

Synthesis and purification methods: S01; P02

10 LCMS: 010_CA07; Rt: 9.28 min; m/3: m/4: 1182.3 m/5:

Compound 150

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
 carboxyheptadecanamido) butanamido]hexanoyl)-
 15 [4A,7K,9E,11A,17L,18Q,22V,28Y,30W,31L]-hPYY(4-36)
 iVal-APEK(C18DA-gGlu-Ahx)PEEAASPEEIQRYYVSLRHYYNWLTRQRY-NH2



MW (calculated): 4766.4 Da

Synthesis and purification methods: S01; P01

20 LCMS: 010_CA07; Rt: 12.30 min; m/3: 1590.6 m/4: m/5:

Compound 151

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
 carboxyheptadecanamido) butanamido]hexanoyl)-
 25 [4A,7K,9E,12S,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)
 iVal-APEK(C18DA-gGlu-Ahx)PEEDSSPEELQRYYVALRHYYNWLTRQRY-NH2
 MW (calculated): 4810.5 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 10.05 min; m/3: 1603.5 m/4: m/5:

Compound 152

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
5 carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,13T,17T,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEETQRYYVSLRHYYNWLTRQRY-NH2
MW (calculated): 4812.4 Da
Synthesis and purification methods: S01; P01
10 LCMS: 010_CA07; Rt: 10.96 min; m/3: m/4: 1204.0 m/5:

Compound 153

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
15 [4A,7K,9E,11L,13T,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEELATPEELQRYYVSLRHYYNWLTRQRY-NH2
MW (calculated): 4822.6 Da
Synthesis and purification methods: S01; P01
LCMS: 010_CA07; Rt: 10.90 min; m/3: m/4: 1206.5 m/5:

20

Compound 154

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,11A,13T,17I,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)
25 iVal-APEK(C18DA-gGlu-Ahx)PEEAATPEEIQRYYVALRHYYNWLTRQRY-NH2
MW (calculated): 4764.5 Da
Synthesis and purification methods: S01; P02
LCMS: 010_CA07; Rt: 10.68 min; m/3: 1588.4 m/4: m/5:

30 Compound 155

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,13T,18Q,22V,28Y,30W,31L,32S]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQRYYYVSLRHYYNWLSRQRY-NH₂

MW (calculated): 4810.5 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 11.33 min; m/3: 1604.2 m/4: m/5:

5

Compound 156

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,11A,13E,17I,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)

10 iVal-APEK(C18DA-gGlu-Ahx)PEEAAPEEIQRYYVALRHYYNWLTRQRY-NH₂

MW (calculated): 4792.5 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 10.99 min; m/3: 1598.2 m/4: 1199.1 m/5:

15 Compound 157

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,6A,7K,9E,11A,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)

iVal-APAK(C18DA-gGlu-Ahx)PEEAASPEELQRYYYVALRHYYNWLTRQRY-NH₂

20 MW (calculated): 4692.4 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 13.45 min; m/3: 1564.3 m/4: m/5:

Compound 158

25 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9P,11A,17I,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PPEAASPEEIQRYYVALRHYYNWLTRQRY-NH₂

MW (calculated): 4718.4 Da

30 Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 13.11 min; m/3: 1574.2 m/4: m/5:

Compound 159

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,10A,13E,18Q,22I,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEADAEPEELQRYYYISLRHYYNWLTRQRY-NH2
5 MW (calculated): 4808.5 Da
Synthesis and purification methods: S01; P02
LCMS: 010_CA07; Rt: 10.63 min; m/3: m/4: 1203.2 m/5:

Compound 160

10 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,6A,7K,9E,18Q,22I,23A,28Y,30W,31L]-hPYY(4-36)
iVal-APAK(C18DA-gGlu-Ahx)PEEDASPEELQRYYYIALRHYYYNWLTRQRY-NH2
MW (calculated): 4750.4 Da
15 Synthesis and purification methods: S01; P02
LCMS: 010_CA07; Rt: 13.49 min; m/3: m/4: 1188.2 m/5:

Compound 161

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
20 [4A,6A,7K,9E,11A,13E,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)
iVal-APAK(C18DA-gGlu-Ahx)PEEAAEPEELQRYYYVALRHYYYNWLTRQRY-NH2
MW (calculated): 4734.4 Da
Synthesis and purification methods: S01; P02
25 LCMS: 010_CA07; Rt: 11.00 min; m/3: m/4: 1184.0 m/5:

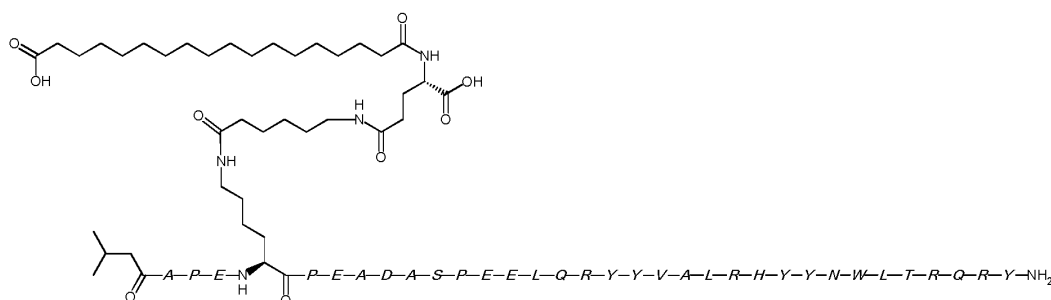
Compound 162

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
30 [4A,7K,9E,13T,17E,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEEEQRYYYVSLRHYYYNWLTRQRY-NH2
MW (calculated): 4840.4 Da
Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 9.20 min; m/3: m/4: 1211.0 m/5:

Compound 163

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
 5 carboxyheptadecanamido) butanamido]hexanoyl)-
 [4A,7K,9E,10A,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)
 iVal-APEK(C18DA-gGlu-Ahx)PEADASPEELQRYYYVALRHYYNWLTRQRY-NH₂



MW (calculated): 4736.4 Da

10 Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 12.30 min; m/3: m/4: 1184.5 m/5:

Compound 164

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
 15 carboxyheptadecanamido) butanamido]hexanoyl)-
 [4A,7K,9E,13T,17I,18Q,22Q,28Y,30W,31L]-hPYY(4-36)
 iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEEIQRYYQSLRHYYNWLTRQRY-NH₂

MW (calculated): 4853.5 Da

Synthesis and purification methods: S01; P01

20 LCMS: 010_CA07; Rt: 11.44 min; m/3: 1618.6 m/4: m/5:

Compound 165

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
 carboxyheptadecanamido) butanamido]hexanoyl)-
 25 [4A,6A,7K,9P,13E,18Q,22V,28Y,30W,31L]-hPYY(4-36)
 iVal-APAK(C18DA-gGlu-Ahx)PPEDAEPEELQRYYYVSLRHYYNWLTRQRY-NH₂

MW (calculated): 4762.5 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 10.11 min; m/3: 1587.7 m/4: m/5:

Compound 166

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
 5 carboxyheptadecanamido) butanamido]hexanoyl)-
 [4A,6A,7K,9E,18Q,22V,23E,28Y,30W,31L]-hPYY(4-36)
 iVal-APAK(C18DA-gGlu-Ahx)PEEDASPEELQRYYYVELRHYYNWLTRQRY-NH2
 MW (calculated): 4794.5 Da
 Synthesis and purification methods: S01; P02
 10 LCMS: 010_CA07; Rt: 9.76 min; m/3: m/4: 1199.2 m/5:

Compound 167

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
 carboxyheptadecanamido) butanamido]hexanoyl)-
 15 [4A,6A,7K,9E,11A,13E,17I,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)
 iVal-APAK(C18DA-gGlu-Ahx)PEEAAEPEEIQRYYVALRHYYNWLTRQRY-NH2
 MW (calculated): 4734.4 Da
 Synthesis and purification methods: S01; P02
 LCMS: 010_CA07; Rt: 11.49 min; m/3: m/4: 1185.0 m/5:

20

Compound 168

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
 carboxyheptadecanamido) butanamido]hexanoyl)-
 [4A,7K,9E,13T,17I,18Q,22S,28Y,30W,31L]-hPYY(4-36)
 25 iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEEIQRYYSSLRHYYNWLTRQRY-NH2
 MW (calculated): 4812.4 Da
 Synthesis and purification methods: S01; P01
 LCMS: 010_CA07; Rt: 9.83 min; m/3: 1605.7 m/4: m/5:

Compound 169

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
 carboxyheptadecanamido) butanamido]hexanoyl)-
 [4A,7K,9E,13E,18Q,19A,22V,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEEDAEPEELQAYYVSLRHYYNWLTRQRY-NH₂

MW (calculated): 4767.4 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 13.90 min; m/3: 1589.0 m/4: 1192.1 m/5:

5

Compound 170

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,13A,17I,18Q,22V,28Y,30W,31L]-hPYY(4-36)

10 iVal-APEK(C18DA-gGlu-Ahx)PEEDAAPEEIQRYYVSLRHYYNWLTRQRY-NH₂

MW (calculated): 4794.5 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 10.60 min; m/3: m/4: 1199.0 m/5:

15 Compound 171

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,10A,18Q,22V,23E,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEADASPEELQRYYVELRHYYNWLTRQRY-NH₂

20 MW (calculated): 4794.5 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 9.57 min; m/3: 1599.2 m/4: m/5:

Compound 172

25 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9P,17I,18Q,22V,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PPEDASPEEIQRYYVSLRHYYNWLTRQRY-NH₂

MW (calculated): 4778.5 Da

30 Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 9.95 min; m/3: 1593.5 m/4: m/5:

Compound 173

- N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,13T,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQRYYYVSLRHYYNWLTRQRY-NH2
5 MW (calculated): 4824.5 Da
Synthesis and purification methods: S01; P01
LCMS: 010_CA07; Rt: 10.50 min; m/3: 1609.0 m/4: m/5:

Compound 174

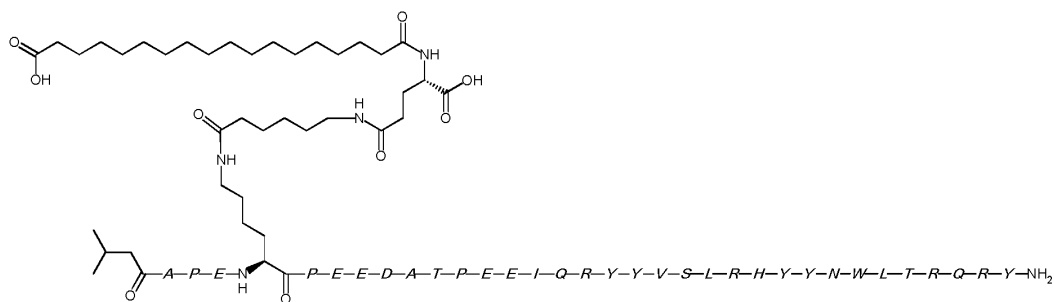
- 10 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,10A,16K,18Q,22V,28Y,29H,30K,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PGADASPEKLQRYYYVSLRHYYHKLTRQRY-NH2
MW (calculated): 4644.4 Da
15 Synthesis and purification methods: S01; P02
LCMS: 010_CA07; Rt: 7.90 min; m/3: 1548.8 m/4: m/5:

Compound 175

- N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
20 carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,6A,7K,9E,13E,18Q,22I,23A,28Y,30W,31L]-hPYY(4-36)
iVal-APAK(C18DA-gGlu-Ahx)PEEDAEPEELQRYYYIALRHYYNWLTRQRY-NH2
MW (calculated): 4792.5 Da
Synthesis and purification methods: S01; P02
25 LCMS: 010_CA07; Rt: 10.86 min; m/3: m/4: 1198.8 m/5:

Compound 176

- N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
30 [4A,7K,9E,13T,17I,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEEIQRYYYVSLRHYYNWLTRQRY-NH2



MW (calculated): 4824.5 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 9.84 min; m/3: 1610.6 m/4: m/5:

5

Compound 177

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,13T,18Q,19Q,22V,28Y,30W,31L]-hPYY(4-36)

10 iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQQYYVSLRHYYNWLTRQRY-NH2

MW (calculated): 4796.4 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 10.00 min; m/3: m/4: 1200.0 m/5:

15 Compound 178

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,10A,11A,13T,17I,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEAAATPEEIQRYYVALRHYYNWLTRQRY-NH2

20 MW (calculated): 4706.4 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 11.21 min; m/3: m/4: 1177.0 m/5:

Compound 179

25 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,10A,17T,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEADASPEETQRYYVALRHYYNWLTRQRY-NH2

MW (calculated): 4724.4 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 12.50 min; m/3: m/4: 1181.4 m/5:

5 Compound 180

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,13T,18Q,22V,28Y,30W,31L,33K]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQRYVSLRHYYNWLTKQRY-NH2

10 MW (calculated): 4796.5 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 9.80 min; m/3: 1600.8 m/4: m/5:

Compound 181

15 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,6A,7K,9E,10A,13E,17I,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)

iVal-APAK(C18DA-gGlu-Ahx)PEADAEPEEIQRYYVALRHYYNWLTRQRY-NH2

MW (calculated): 4720.4 Da

20 Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 11.23 min; m/3: 1574.1 m/4: 1180.8 m/5:

Compound 182

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

25 [4A,6A,7K,9E,17A,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)

iVal-APAK(C18DA-gGlu-Ahx)PEEDASPEEAQRYYVALRHYYNWLTRQRY-NH2

MW (calculated): 4694.3 Da

Synthesis and purification methods: S01; P01

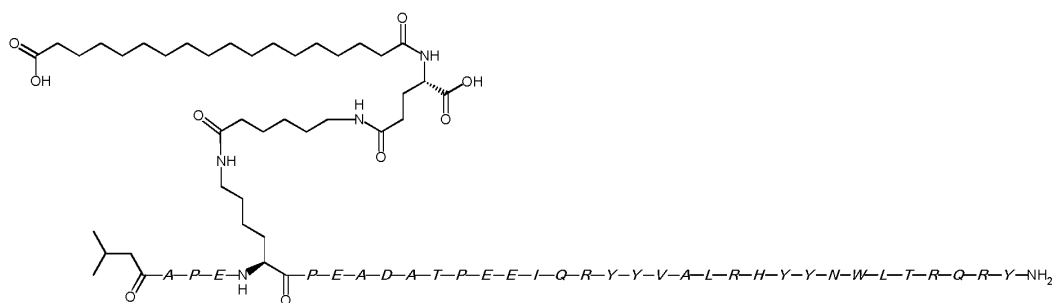
30 LCMS: 010_CA07; Rt: 12.70 min; m/3: 1565.3 m/4: m/5:

Compound 183

- N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
 [4A,7K,8A,9E,17I,18Q,22V,28Y,30W,31L]-hPYY(4-36)
 iVal-APEK(C18DA-gGlu-Ahx)AEEDASPEEIQRYYVSLRHYYNWLTRQRY-NH₂
 5 MW (calculated): 4784.4 Da
 Synthesis and purification methods: S01; P01
 LCMS: 010_CA07; Rt: 10.60 min; m/3: 1595.9 m/4: m/5:

Compound 184

- 10 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
 [4A,7K,9E,10A,13T,17I,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)
 iVal-APEK(C18DA-gGlu-Ahx)PEADATPEEIQRYYVALRHYYNWLTRQRY-NH₂



- 15 MW (calculated): 4750.4 Da
 Synthesis and purification methods: S01; P01
 LCMS: 010_CA07; Rt: 12.00 min; m/3: m/4: 1188.5 m/5:

Compound 185

- 20 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
 [4A,6A,7K,9E,14E,18Q,22V,28Y,30W,31L]-hPYY(4-36)
 iVal-APAK(C18DA-gGlu-Ahx)PEEDASEEELQRYYVSLRHYYNWLTRQRY-NH₂
 MW (calculated): 4784.4 Da

- 25 Synthesis and purification methods: S01; P01
 LCMS: 010_CA07; Rt: 10.80 min; m/3: 1595.2 m/4: m/5:

Compound 186

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,13E,17A,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDAEPEEAQRYYVSLRHYYNWLTRQRY-NH2
5 MW (calculated): 4810.4 Da
Synthesis and purification methods: S01; P01
LCMS: 010_CA07; Rt: 13.20 min; m/3: m/4: 1203.8 m/5:

Compound 187

10 N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,13T,17P,18Q,22V,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEEPQRYYVSLRHYYNWLTRQRY-NH2
MW (calculated): 4808.4 Da
15 Synthesis and purification methods: S01; P01
LCMS: 010_CA07; Rt: 9.38 min; m/3: 1603.3 m/4: m/5:

Compound 188

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
20 carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,13T,18Q,22V,28Y,30W,31L,32Q]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQRYYVSLRHYYNWLQRQRY-NH2
MW (calculated): 4851.5 Da
Synthesis and purification methods: S01; P01
25 LCMS: 010_CA07; Rt: 11.13 min; m/3: 1618.0 m/4: m/5:

Compound 189

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
30 [4A,6A,7K,9E,17T,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)
iVal-APAK(C18DA-gGlu-Ahx)PEEDASPEETQRYYVALRHYYNWLTRQRY-NH2
MW (calculated): 4724.4 Da
Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 11.50 min; m/3: m/4: 1182.1 m/5:

Compound 190

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
5 carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,6A,7K,9E,13T,18Q,22I,28Y,30W,31L]-hPYY(4-36)
iVal-APAK(C18DA-gGlu-Ahx)PEEDATPEELQRYYSISRHYYNWLTRQRY-NH2
MW (calculated): 4780.5 Da
Synthesis and purification methods: S01; P02
10 LCMS: 010_CA07; Rt: 10.28 min; m/3: 1594.5 m/4: m/5:

Compound 191

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
15 [4A,7K,9E,13T,17I,18Q,22E,28Y,30W,31L]-hPYY(4-36)
iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEEIQRYYESLRHYYNWLTRQRY-NH2
MW (calculated): 4854.5 Da
Synthesis and purification methods: S01; P02
LCMS: 010_CA07; Rt: 9.77 min; m/3: 1619.0 m/4: m/5:

20

Compound 192

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,10A,11P,18Q,22V,28Y,30W,31L]-hPYY(4-36)
25 iVal-APEK(C18DA-gGlu-Ahx)PEAPASPEELQRYVSLRHYYNWLTRQRY-NH2
MW (calculated): 4734.4 Da
Synthesis and purification methods: S01; P02
LCMS: 010_CA07; Rt: 10.39 min; m/3: m/4: 1184.5 m/5:

30 Compound 193

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,11E,17I,18Q,22V,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEEEASPEEIQRYYVSLRHYYNWLTRQRY-NH₂

MW (calculated): 4824.5 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 12.20 min; m/3: 1609.1 m/4: m/5:

5

Compound 194

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,6A,7K,9E,13E,17I,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)

10 iVal-APAK(C18DA-gGlu-Ahx)PEEDAEPPEEIQRYYVALRHYYNWLTRQRY-NH₂

MW (calculated): 4778.5 Da

Synthesis and purification methods: S01; P02

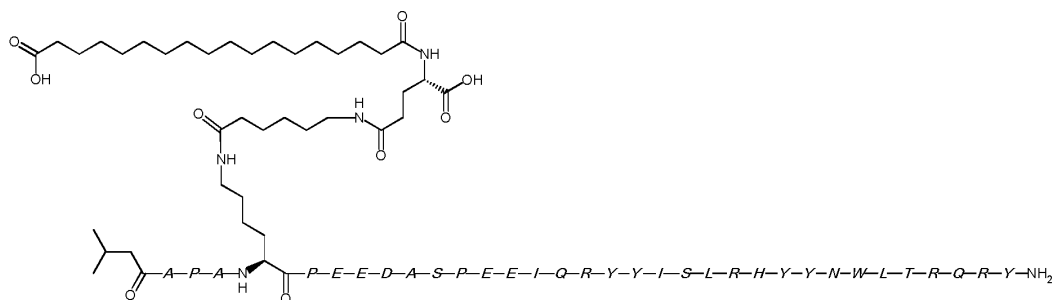
LCMS: 010_CA07; Rt: 10.80 min; m/3: m/4: 1195.1 m/5:

15 Compound 195

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,6A,7K,9E,17I,18Q,22I,28Y,30W,31L]-hPYY(4-36)

iVal-APAK(C18DA-gGlu-Ahx)PEEDASPEEIQRYYISLRHYYNWLTRQRY-NH₂



20

MW (calculated): 4766.4 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 10.02 min; m/3: m/4: 1192.4 m/5:

25 Compound 196

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-

[4A,7K,9E,10A,18Q,22V,28Y,30W,31L]-hPYY(4-36)

iVal-APEK(C18DA-gGlu-Ahx)PEADASPEELQRYYYVSLRHYYNWLTRQRY-NH₂

MW (calculated): 4752.4 Da

Synthesis and purification methods: S01; P01

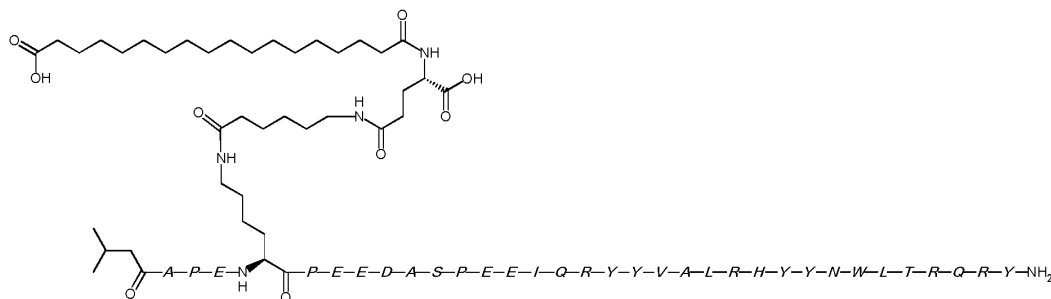
LCMS: 010_CA07; Rt: 10.35 min; m/3: 1584.8 m/4: m/5:

5

Compound 197

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,7K,9E,17I,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)

10 iVal-APEK(C18DA-gGlu-Ahx)PEEDASPEEIQRYYVALRHYYNWLTRQRY-NH₂



MW (calculated): 4794.5 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 10.19 min; m/3: m/4: 1199.4 m/5:

15

Compound 198

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,6A,7K,9E,10A,13E,17I,18Q,22V,28Y,30W,31L]-hPYY(4-36)

20 iVal-APAK(C18DA-gGlu-Ahx)PEADAEPEEIQRYYVSLRHYYNWLTRQRY-NH₂

MW (calculated): 4736.4 Da

Synthesis and purification methods: S01; P02

LCMS: 010_CA07; Rt: 10.70 min; m/3: m/4: 1184.9 m/5:

25 Compound 199

N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,6A,7K,9E,11E,18Q,22V,28Y,30W,31L]-hPYY(4-36)

iVal-APAK(C18DA-gGlu-Ahx)PEEEASPEELQRYYVSLRHYYNWLTRQRY-NH₂

MW (calculated): 4766.4 Da

Synthesis and purification methods: S01; P01

LCMS: 010_CA07; Rt: 10.40 min; m/3: m/4: 1192.0 m/5:

5

The following compound disclosed as Example 32 in WO 2016/198682 A1 was synthesized as reference:

10 Ref. 1

iVal-RPEK(C18DA-gGlu-Ahx)PGEDASPEELQRYYISLRHYYNWLTRQRY-NH₂
(SEQ ID NO: 204)

Further compounds were synthesized as references:

15

Ref. 2

iVal-RPEK(C18DA-gGlu-Ahx) PGEDASPEELQRYYISLRHYYNWLTRQRY-NH₂
(SEQ ID NO: 205)

20 Ref. 3

iVal-RPEK(C18DA-gGlu-Ahx) PGEDASPEELQRYYISLRHYYNWLTAQRY-NH₂
(SEQ ID NO: 206)

Ref. 4

25 iVal-RPEK(C18DA-gGlu-Ahx) PGEDASPEELQRYYISLRHYYNWLTRQAY-NH₂
(SEQ ID NO: 207)

The structure of Ref. 1 is – except for alanine at position 4 – identical to Compound 92.

This R4A mutation leads to a compound that shows much higher solubility at pH 6.2

30 (0.0 mg/ml for Ref. 1 vs. 9.2 mg/ml for Compound 92). At the same time high binding affinity and receptor activity are maintained for Compound 92 (see Table 2). Other arginine to alanine mutations at different positions (R25A in Ref. 2; R33A in Ref. 3; R35A

in Ref. 4) negatively affect binding affinity and receptor activity of the resulting compounds.

Comp.	Seq. mod. vs. Ref. 1	hY2 RLB (nM) (Example 1)	hY2 cAMP (nM) (Example 2)	Sol pH 6 (mg/ml) [final pH] (Example 3)	Sol pH 7 (mg/ml) [final pH] (Example 3)
Ref. 1	-	1.7	0.5	0.0 [6.2]	6.7 [6.8]
Comp. 92	R4A	1.8	0.6	9.2 [6.1]	8.9 [6.7]
Ref. 2	R25A	10.0	3.0	7.0 [6.1]	8.5 [6.7]
Ref. 3	R33A	>316	>10	10.0 [6.1]	10.0 [6.7]
Ref. 4	R35A	>316	>10	10.0 [6.1]	10.0 [6.7]

5 Table 2.

EXAMPLES

The following examples demonstrate certain specific embodiments of the present
 10 invention. The following examples were carried out using standard techniques that are well
 known and routine to those of skill in the art, except where otherwise described in detail.

Example 1: Radioligand binding competition assays (RLB)

15 The filtration RLB assay was carried out in 96-well plates in a final volume of 100 μ l per
 well. Freeze-dried test peptides were dissolved in 100% dimethyl sulfoxide (DMSO) to stock
 solutions of 1mM and serial dilutions were performed in assay buffer (50mM HEPES, 5mM
 MgCl₂, 1mM CaCl₂, pH 7.4) containing 0.2% ovalbumin. 10 μ l/well of the test peptide
 solution was added to the plates to give final concentrations ranging from 1 μ M to 3pM.

Subsequently, 10 μ l of human ^{125} I-PYY(1-36) (Perkin Elmer) in assay buffer containing 0.2% ovalbumin was added to wells to give a final concentration of 0.02nM. Next, 80 μ L membranes (HTS066M, ChemiSCREEN™ Human Neuropeptide Y2 Receptor Membrane Preparation, CHEMICON) were added to each well to give a final protein concentration of 0.5 μ g/well. The plates were sealed and incubated at room temperature for 2 hours in a plate shaker set at 400 rpm. The incubation was stopped by vacuum filtration onto 0.5% polyethylene amine (PEI) presoaked GF/C filters using a 96-well FilterMate™ harvester (Perkin Elmer) followed by four washes with 300 μ l/well ice-cold wash buffer (50mM HEPES, 500mM NaCl, pH7.4). Filter plates were then dried for 60 min at room temperature and the bottom of the plates was sealed with backing tape UniFilter-96. Finally, 50 μ l/well scintillation counter cocktail (Microscint20, Packard) was added and the radioactivity was counted in the Packard TopCount NXT scintillation counter. IC₅₀ values (the half maximal inhibitory concentration of the agonist) were calculated by nonlinear regression analysis of sigmoidal dose-response curves. Ki values for binding affinity were acquired by the Cheng-Prusoff equation ($K_i = IC_{50} / (1 + [L] / K_d)$), where K_d is the previously measured receptor specific dissociation constant (for NPY2R=0.07nM) and [L] is ^{125} I-PYY(1-36) radioligand concentration.

The RLB results are summarized in Table 3, below.

Compound	Ki [nM]		
1	2.05	16	2.81
2	2.40	17	24.63
3	1.57	18	2.48
4	4.65	19	9.63
5	12.71	20	2.41
6	1.42	21	3.38
7	1.04	22	4.98
8	106.17	23	12.59
9	3.32	24	3.39
10	2.46	25	1.55
11	1.40	26	5.64
12	4.16	27	10.47
13	1.53	28	0.49
14	1.28	29	1.36
15	3.98	30	0.30
		31	34.66
		32	13.56

33	2.53
34	3.53
35	1.40
36	1.25
37	3.66
38	12.44
39	2.73
40	0.67
41	19.75
42	1.98
43	2.49
44	5.86
45	6.17
46	5.21
47	0.51
48	1.54
49	11.60
51	2.59
52	2.39
53	3.07
54	8.97
55	2.96
56	4.39
57	2.07
58	3.46
59	1.93
60	6.04
61	0.41
62	1.44
63	0.93
64	0.86
65	0.98
66	2.33
67	2.22
68	9.07
69	0.54
70	2.26
71	1.97
72	2.79

73	2.16
74	3.17
75	1.43
76	2.68
77	9.73
78	1.80
79	1.54
80	4.62
81	2.65
82	0.58
83	6.91
84	1.60
85	1.61
86	4.33
87	22.38
88	16.28
89	1.16
90	8.71
91	4.64
92	1.84
93	1.71
94	0.93
95	2.92
96	3.06
97	4.23
99	0.66
100	1.01
101	1.77
102	7.15
103	1.94
104	14.11
105	5.97
106	2.46
107	5.13
108	2.77
109	13.98
110	6.42
111	2.14
112	4.28

113	3.53
114	0.95
115	2.22
116	2.46
117	3.09
118	1.00
119	5.73
120	1.49
121	1.45
122	2.73
123	3.65
124	3.07
125	3.37
126	4.42
127	3.36
128	2.91
129	1.42
130	9.36
131	1.54
132	2.75
133	4.68
134	2.80
135	3.83
136	1.07
137	49.59
138	12.53
139	3.60
140	1.41
141	8.17
142	3.97
143	3.42
144	9.76
145	5.29
146	8.93
147	5.04
148	2.85
149	3.97
150	2.18
151	1.68

152	1.32
153	6.80
154	3.71
155	7.60
156	4.20
157	1.68
158	0.58
159	2.75
160	1.37
161	4.00
162	14.93
163	0.67
164	2.80
165	1.43
166	2.05
167	4.58
168	3.56
169	5.82
170	2.28
171	2.83
172	0.81
173	4.07
174	0.21
175	3.00
176	1.48
177	8.65
178	3.39
179	0.89
180	15.05
181	1.33
182	2.20
183	18.80
184	0.64
185	2.06
186	7.21
187	15.32
188	5.46
189	0.97
190	1.95

191	8.32	196	3.57
192	0.74	197	2.03
193	3.42	198	1.38
194	26.37	199	2.87
195	0.78		

Table 3

In general, the data from the RLB assay is predictive for the acute food intake inhibition in mice (Experiment 6).

Example 2: HTRF cAMP Gi assay

The Homogenous Time Resolved fluorescence (HTRF) technology optimized for Gi coupled receptors has thoroughly been described in Cisbio cAMP Gi kit manual. Briefly, the production of intracellular cAMP will generate a competition between unlabeled cAMP and exogenously added d2-cAMP for anti-cAMP antibodies conjugated to cryptate. CHO-K1 cells stably expressing the human NPY1, NPY2, NPY4 and NPY5 receptors were used with the cells brought to life from a frozen stock immediately before assay performance. 2000 cells per well were applied for all four NPY receptor subtype assays. A 384-well format was used applying a total volume of 20 μ l using 5 μ l cells, 2.5 μ l peptide agonist, 2.5 μ l forskolin and 5 μ l of each of the fluorophores. Cells were incubated with agonist peptides (11 points concentration response curves) and forskolin (~90% activity level, 3-11 μ M forskolin) for 40 min at 37°C using DPBS containing 0.5 mM IBMX as stimulation buffer. After addition of HTRF® detection reagents and incubation with shaking (2400 rpm) for one hour at room temperature signals at 620 and 665 nm (raw counts: ratio of 665/620) were detected. Concentration-response evaluation of compounds was performed with 11 concentrations of agonist peptides (covering 3 decades). EC50 values were calculated by nonlinear regression using sigmoid concentration-response with variable slope.

The *in vitro* activity results (expressed as EC₅₀ values) are summarized in Table 4, below.

Compound No.	hY2R (nM)	hY1R (nM)	hY4R (nM)	hY5R (nM)
hPYY3-36	0.160	250	>5000	73.2

7	0.143	>5000	>5000	>5000
11	0.136	>5000	>5000	>5000
12	0.250			>5000
14	0.086			>5000
15	0.140			>5000
16	0.310			>5000
23	0.181			>5000
26	0.108			>5000
40	0.122	>5000	>5000	>5000
52	0.176			>5000
53	0.352	>5000	>5000	>5000
55	0.352	>5000	>5000	>5000
63	0.109	>5000	>5000	>5000
67	0.227			>5000
72	0.197			>5000
76	0.172			>5000
79	0.076			>5000
84	0.205	>5000	1000	>5000
91	0.219			5000
99	0.281	>5000	>5000	>5000
106	0.121			>5000
114	0.186	>5000	>5000	>5000
118	0.161	>5000	>5000	>5000
122	0.273	>5000	>5000	>5000
128	0.344	>5000	>5000	>5000
129	0.270	>5000	>5000	>5000
136	0.138	>5000	>5000	>5000
140	0.230			>5000
145	0.118			>5000

146	0.130			>5000
147	0.146			>5000
150	0.243	>5000	>5000	>5000
160	0.230	>5000	>5000	>5000
163	0.130	>5000	>5000	>5000
172	0.079			>5000
176	0.168	>5000	>5000	>5000
183	0.447			>5000
184	0.232	>5000	>5000	>5000
186	0.729	>5000	>5000	>5000
189	0.273	>5000	>5000	>5000
193	0.331	>5000	>5000	>5000
195	0.197	>5000	>5000	>5000
196	0.086			>5000
197	0.156	>5000	>5000	>5000

Table 4

5 Example 3: Solubility determination

Peptides (as TFA salts) were weighed out in a filter unit (Mini-UniPrep Syringeless Filter 0.45 μ m, Whatman), and 0.1 M sodium diphosphate buffer at pH 6.4 or 7.0 was added to achieve 10 mg/ml final concentration. The peptide was dissolved by shaking the filter unit

10 horizontally at 600 rpm for 2 hours at room temperature. The sample was filtered, to remove any insoluble particles and diluted to 1 mg/ml in 50% acetonitrile. The control was prepared by weighing out the corresponding peptide and dissolving it in 50% acetonitrile to final concentration of 1 mg/ml. Both the control and sample were analysed with

15 reversed phase chromatography. The area under the peak of the sample was compared to the control and the solubility was calculated based on that ratio.

The pH was measured and recorded for each sample. Typically, buffer pH dropped by 0.2 to 0.3 pH units due to the TFA content of the peptide.

UPLC method:

System: UltiMate 3000 UPLC, ThermoFisher

5 Mobile phase A: 5% acetonitrile, 95% water, 0.03% trifluoroacetic acid.

Mobile phase B: 95% acetonitrile, 5% water, 0.03% trifluoroacetic acid.

Flow: 1 ml/min

Gradient: 0-100% mobile phase B (2 mins.)

Column: Kinetix, 5 μ m C8, 100 Å, 50 x 2.1 mm

10 Column temperature: 50°C

The results from the solubility determination are summarized in Table 5, below.

Compound	Sol6 (mg/ml)	Sol6 pH	Sol7 (mg/ml)	Sol7 pH
1	10.0	6.1	7.6	6.8
2	9.5	6.1	9.5	6.8
3	10.0	6.3	10.0	6.8
4	10.0	6.1	10.0	6.8
5	3.6	6.2	8.8	6.8
6	9.6	6.1	10.0	6.8
7	8.9	6.1	9.2	6.9
8	9.7	6.0	9.6	6.7
9	9.7	6.1	9.9	6.7
10	0.0	6.2	0.0	6.7
11	8.9	6.1	8.7	6.8
12	9.4	6.0	9.8	6.7
13	10.0	6.1	10.0	6.7
14	9.3	6.2	8.4	6.8
15	9.3	6.2	9.2	6.8
16	10.0	6.1	8.3	6.8
17	10.0	6.0	10.0	6.7
18	9.3	6.0	9.5	6.7
19	10.0	6.0	9.2	6.7
20	>10.0	6.1	10.0	6.8
21	10.0	6.1	10.0	6.8
22	9.7	6.0	9.8	6.7
23	9.8	6.2	10.0	6.8
24	9.8	6.1	10.0	6.8
25	9.3	6.2	9.3	6.8
26	9.2	6.2	9.1	6.8

27	9.1	6.1	9.4	6.8
28	>10.0	6.1	>10.0	6.7
29	9.9	6.2	10.0	6.8
30	0.1	6.2	9.4	6.8
31	>10.0	6.1	10.0	6.8
32	8.2	6.2	9.3	6.8
33	7.2	6.2	8.3	6.8
34	9.2	6.1	9.1	6.8
35	0.0	6.2	2.4	6.8
36	0.0	6.3	0.4	6.8
37	10.0	6.1	10.0	6.8
38	10.0	6.1	10.0	6.8
39	10.0	6.1	10.0	6.8
40	8.5	6.1	8.2	6.8
41	9.8	6.0	10.0	6.7
42	9.8	6.0	9.9	6.7
43	0.0	6.3	0.0	6.8
44	9.7	6.2	10.0	6.8
45	>10.0	6.1	>10.0	6.7
46	10.0	6.1	10.0	6.8
47	9.4	6.1	9.9	6.7
48	0.0	6.1	0.3	6.7
49	>10.0	6.1	>10.0	6.7
51	9.6	6.0	9.7	6.7
52	9.5	6.0	9.5	6.7
53	8.7	6.1	9.6	6.8
54	10.0	6.0	10.0	6.7
55	>10.0	6.0	>10.0	6.7
56	9.0	6.1	9.2	6.7
57	8.3	6.1	9.6	6.7
58	8.6	6.0	8.8	6.7
59	9.7	6.0	9.6	6.7
60	>10.0	6.1	10.0	6.7
61	0.1	6.1	8.9	6.8
62	8.8	6.1	9.3	6.7
63	10.0	6.1	>10.0	6.8
64	9.8	6.1	9.6	6.7
65	7.9	6.2	9.0	6.8
66	9.2	6.1	9.2	6.8
67	9.3	6.1	7.9	6.8
68	9.9	6.0	10.0	6.7
69	0.1	6.2	9.5	6.8
70	9.2	6.2	9.5	6.8
71	>10.0	6.1	>10.0	6.8
72	9.0	6.1	9.2	6.7

73	8.6	6.1	8.2	6.8
74	8.4	6.2	9.2	6.8
75	>10.0	6.0	>10.0	6.6
76	10.0	6.2	10.0	6.8
77	>10.0	6.1	9.0	6.9
78	8.1	6.2	7.6	6.8
79	10.0	6.1	10.0	6.7
80	8.1	6.1	8.2	6.8
81	8.9	6.0	8.9	6.7
82	0.0	6.2	9.0	6.9
83	10.0	6.1	10.0	6.7
84	9.3	6.2	9.3	6.8
85	8.6	6.2	9.1	6.8
86	>10.0	6.0	>10.0	6.7
87	9.7	6.1	9.7	6.7
88	8.7	6.0	8.9	6.6
89	0.1	6.2	8.0	6.8
90	9.6	6.1	10.0	6.8
91	8.9	6.0	9.4	6.7
92	9.2	6.1	8.9	6.7
93	9.4	6.1	9.7	6.7
94	8.4	6.1	8.9	6.8
95	8.9	6.1	7.9	6.8
96	8.8	6.1	8.7	6.7
97	>10.0	6.1	>10.0	6.7
99	9.4	6.1	9.3	6.8
100	9.8	6.2	5.7	6.8
101	9.1	6.2	9.2	6.8
102	10.0	6.1	9.7	6.7
103	8.0	6.1	7.8	6.8
104	9.6	6.1	8.6	6.8
105	>10.0	6.1	9.9	6.7
106	9.4	6.2	7.4	6.8
107	11.0	6.1	11.0	6.8
108	8.6	6.2	8.0	6.8
109	10.0	6.0	8.5	6.7
110	10.0	6.1	>10.0	6.7
111	0.0	6.2	0.0	6.8
112	9.9	6.0	10.0	6.7
113	>10.0	6.0	10.0	6.7
114	8.5	6.1	9.2	6.8
115	9.0	6.0	8.5	6.8
116	0.0	6.3	0.0	6.8
117	9.8	6.1	9.4	6.8
118	10.0	6.0	9.5	6.7

119	9.3	6.0	9.1	6.7
120	0.0	6.3	0.2	6.8
121	9.1	6.1	8.9	6.7
122	9.8	6.2	9.9	6.8
123	9.1	6.1	8.7	6.8
124	9.7	6.2	>10.0	6.8
125	9.7	6.1	10.0	6.8
126	9.6	6.1	8.8	6.8
127	6.5	6.2	>10.0	6.8
128	10.0	6.2	>10.0	6.9
129	10.0	6.0	10.0	6.7
130	9.9	6.0	10.0	6.6
131	10.0	6.1	>10.0	6.7
132	8.7	6.2	9.3	6.8
133	9.6	6.1	9.7	6.7
134	10.0	6.0	10.0	6.7
135	0.2	6.2	>10.0	6.8
136	9.6	6.2	10.0	6.8
137	>10.0	6.2	>10.0	6.8
138	9.9	6.0	9.5	6.8
139	7.3	6.1	8.8	6.8
140	9.9	6.1	9.3	6.8
141	9.6	6.2	9.7	6.8
142	>10.0	6.1	>10.0	6.7
143	10.0	6.0	>10.0	6.7
144	9.7	6.0	9.6	6.7
145	7.2	6.2	9.0	6.8
146	9.8	6.1	9.6	6.8
147	9.4	6.1	9.2	6.8
148	9.7	6.1	10.0	6.7
149	8.7	6.2	10.0	6.8
150	9.7	6.2	10.0	6.8
151	8.2	6.1	9.7	6.8
152	8.8	6.0	8.8	6.7
153	6.0	6.0	9.5	6.7
154	8.3	6.2	>10.0	6.8
155	>10.0	6.2	>10.0	6.8
156	9.8	6.1	9.6	6.8
157	0.0	6.2	0.3	6.8
158	0.0	6.2	0.4	6.9
159	>10.0	6.1	10.0	6.8
160	10.0	6.2	9.7	6.9
161	0.2	6.2	>10.0	6.8
162	9.0	6.0	9.3	6.7
163	8.9	6.2	9.2	6.8

164	9.3	6.1	9.2	6.7
165	8.8	6.1	9.1	6.7
166	9.2	6.1	9.7	6.7
167	0.0	6.2	9.5	6.9
168	8.8	6.2	9.1	6.8
169	9.7	6.1	9.8	6.8
170	>10.0	6.0	10.0	6.7
171	10.0	6.1	10.0	6.8
172	10.0	6.2	>10.0	6.8
173	9.2	6.0	9.6	6.7
174	3.1	6.1	1.2	6.7
175	10.0	6.1	10.0	6.8
176	9.4	6.2	9.3	6.8
177	>10.0	6.0	10.0	6.7
178	0.0	6.3	0.4	6.9
179	8.1	6.2	8.3	6.8
180	9.9	6.2	10.0	6.8
181	9.5	6.2	9.3	6.9
182	6.9	6.1	8.4	6.8
183	8.4	6.2	8.7	6.8
184	9.1	6.1	9.1	6.8
185	8.7	6.1	8.9	6.8
186	9.0	6.1	10.0	6.8
187	7.8	6.1	>10.0	6.7
188	9.5	6.2	9.8	6.8
189	9.4	6.2	9.8	6.8
190	8.4	6.2	8.4	6.8
191	>10.0	6.0	>10.0	6.7
192	0.0	6.2	9.0	6.8
193	8.9	6.2	9.1	6.8
194	>10.0	6.2	10.0	6.8
195	8.2	6.2	8.2	6.8
196	8.4	6.2	9.8	6.8
197	8.9	6.1	10.0	6.8
198	>10.0	6.3	>10.0	6.8
199	9.0	6.2	9.1	6.8
Ref 1.	0.0	6.2	6.7	6.8

Table 5

Example 4: DLS studies

Aggregation combined with particle growth in peptide solutions was detected by dynamic light scattering (DLS). Test peptides (5 mg/ml) were dissolved in 50 mM phosphate buffer with EDTA (0.05 mg/ml) which is adjusted to a final pH of 7.2. Solutions were filtered through a 0.2 µm filter and shaken with a lab shaker at approx. 150 rpm at room temperature for 5 to 7 days. Samples were analyzed with a particle size analyzer (DLS, Horiba Nano Particle Analyzer SZ-100) at day 0 and at the end of the study. Formation of aggregates was detected by an increase in particle size over time and rated as OK, indicating no increase in particle size, and NOK, indicating an increase in particle size.

The results from the DLS studies are summarized in Table 6.

Example	DLS
7	OK
11	OK
26	OK
40	OK
63	OK
84	OK
92	NOK
99	OK
114	OK
118	OK
122	OK
129	NOK
136	OK
146	OK
150	OK
160	NOK
163	OK
176	OK
184	OK
195	OK
197	OK

Table 6

Example 5: Mouse PK

Pharmacokinetic parameters of the test compounds were determined after intravenous
5 administration to NMRI mice.

Male NMRI mice were obtained either from Charles River (Germany) or from Janvier
(France) weighing approximately 30 to 40 g. Mice were housed in standard cages with
light cycle of 12-hour dark and 12-hour light. Standardized food and water were offered ad
libitum to the animals during the whole experimental period.

10 The respective peptide was dissolved in 50 mM phosphate buffer (pH 7.0) containing 5%
mannitol. Intravenous doses of 30 nmol/kg were given via a tail vein.

Serial blood samples were collected from the vena saphena into tubes containing EDTA as
anticoagulant at different time points up to 48h post dosing. After centrifugation for
approximately 5 minutes, plasma samples were transferred to 96-well PCR plates,
15 immediately frozen and kept at approximately -20°C until analyzed for plasma
concentration by liquid chromatography mass spectrometry (LC-MS/MS). Individual
plasma concentration-time profiles were analyzed by a non-compartmental approach, and
the resulting pharmacokinetic parameters were determined.

Compound	Mouse MRT (h)	Terminal half-life (h)
Ref. 1	13.0	9.0

20

Mouse MRT of the PYY analogues according to the invention that have been measured
were comparable to Ref. 1 and show very long half-lives as compared to the half-life of
hPYY(3-36).

25

Example 6: Effect on acute food intake in normal NMRI mice

Male NMRI mice were obtained from Charles River (Charles River, Research Models &
Services Germany GmbH) or from JanVier (JanVier Labs, France) at 5 weeks of age. The
30 animals were group housed 4 mice pr. cage under a 12/12 h dark-light cycle, light off at 3

PM. Room temperature was controlled to $21\text{ }^{\circ}\text{C} \pm 1\text{ }^{\circ}\text{C}$, with $60\% \pm 20\%$ humidity.

Animals had ad libitum access to regular rodent chow (KLIBA Nafag 3430 or Altromin 1324, Brogaarden, Denmark) and tap water.

Animals were transferred 5-7 days before the start of the study to a real-time food intake monitoring system, HM-2 system (MBRose, Denmark), to allow acclimatization to experimental conditions. As the animals were uniquely identified with microchips, each individual animal was identified by its microchip upon entry and exit from the food channel. Randomization of the mice for each study group ($n=7-8$) was based on body weight measured the day before the start of the study. A vehicle-treated (50mM phosphate buffer pH7 with 5% Mannitol) group was included in each experiment. Six hours before the start of the night phase animals were fasted. One hour before the dark phase animals were dosed once subcutaneously (5 nmol/kg) with test peptide. Food intake was reported hourly for a period of 24h. The food intake of the treated groups was normalized (in %) to the average food intake of the group receiving vehicle (Table 7). Statistical significance was evaluated using One-way analysis of variance with Turkey's multiple comparison test. $P < 0.05$ was considered statistically significant.

Compound	Acute Food Intake 24h [%vehicle]		
7	38	114	65
26	53	136	64
40	41	146	50
63	62	163	46
84	57	176	44
		197	57
		Ref. 1	49

Table 7

20

Example 7: Activity after incubation in solutions at different pH values

Peptides (as TFA salts) were weighed out in a filter unit (Mini-UniPrep Syringeless Filter 0.45 μm , Whatman), and 0.1 M sodium diphosphate buffer at pH 6.4 or 7.4, respectively, or 0.2 M TRIS buffer at pH 8.3 was added to achieve 10 mg/ml final concentration. The

25

peptide was (partially) dissolved by shaking the filter unit horizontally at approx. 400 rpm for 2 hours at room temperature. The sample was filtered to remove any insoluble particles. The filtrate was subsequently subjected to the binding assay as described in Example 1. The apparent binding affinity (K_i) reported in Table 8 is calculated based on an assumed concentration of 10 mg/ml.

Compounds of the invention are active in the binding assay after incubation in solutions at different pH values, including pH 6. This demonstrates the fundamental feasibility of a liquid formulation of the compounds according to the invention at ~pH 6 (in the pH range from ~6 to ~8).

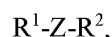
Contrary hereto, after incubation at ~pH 6, solutions of Ref. 1 (after filtration) show a weak response in the binding assay (apparent significant (>45x) affinity loss due to low solubility of Ref. 1 in buffered media at pH 6). Therefore, the low intrinsic solubility of Ref. 1 at ~pH 6 limits the formulation space in the physiological pH range of 6-8 of a liquid formulation of Ref. 1.

Com- pound	hY2R RLB K _i (nM) DMSO	RLB 6 (pH6.1 – 6.2) (nM)	RLB 7 (pH7.1 – 7.2) (nM)	RLB 8 (pH8.1 – 8.2) (nM)	RLB ratio (RLB6 /RLB7)	RLB ratio (RLB8 /RLB7)
Ref. 1	9.3	>316	7.1	4.6	>45	0.7
176	8.7	3.9	4.0	5.7	1.0	1.4
7	4.6	4.7	4.5	3.1	1.1	0.7
84	4.8	7.5	5.5	5.4	1.3	1.0
40	5.6	4.6	7.3	3.8	0.6	0.5
163	7.6	6.8	7.1	4.9	1.0	0.7
63	6.6	5.6	5.4	4.7	1.0	0.9

Table 8

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)

15

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;

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

5 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;

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

10 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 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).

20

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

Ala-Pro-X6-Lys-X8-X9-X10-X11-Ala-X13-X14-Glu-Glu-X17-Gln-X19-Tyr-Tyr-
25 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;

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

30 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;
X19 is selected from the group consisting of Arg and Gln;
X22 is selected from the group consisting of Ile, Thr and Val;
5 X23 is selected from the group consisting of Ala, Glu, Gln and Ser;
X29 is selected from the group consisting of Asn and Gln.

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

10 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)

wherein

15 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;
X11 is selected from the group consisting of Ala, Asp, Glu and Pro;
X12 is selected from the group consisting of Ala and Ser;
20 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;
25 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;
X22 is selected from the group consisting of Ile and Val;
X23 is selected from the group consisting of Ala, Glu, Ser and Thr.

- 30 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

- 5 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;
10 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,
15 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).
20
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
25 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.
30
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.

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,
5 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.
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
10 compound 199.
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.
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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
20 solubility of the PYY analogue is greater than 1.0 mg/ml at pH 6.
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.
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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 treatment of a condition or disease related or caused by excess body weight or excess body weight gain.
- 30 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.

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.
- 5 20. A 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 administered as part of a combination therapy together with an agent for treatment of diabetes, obesity, dyslipidemia or hypertension.
- 10 21. A 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 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
- 15 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.