

US Patent & Trademark Office

Patent Public Search | Text View

United States Patent	12391737
Kind Code	B2
Date of Patent	August 19, 2025
Inventor(s)	Haebel; Peter Wilhelm et al.

Soluble NPY2 receptor agonists

Abstract

The invention relates to PYY analogues having alanine at position 4, lysine at position 7, QRY as the C-terminal end and a half-life extending group. The analogues of the invention are soluble around pH 6 and 7. The invention also relates to pharmaceutical compositions comprising such PYY analogues, and to the medical use of the analogues.

Inventors: Haebel; Peter Wilhelm (Mittelbiberach, DE), Brennauer; Albert (Biberach an der Riss, DE), Peters; Stefan (Biberach an der Riss, DE), Madsen; Charlotte Stahl (Måløv, DK), Pedersen; Søren Ljungberg (Borup, DK)

Applicant: Boehringer Ingelheim International GmbH (Ingelheim am Rhein, DE)

Family ID: 1000008762432

Assignee: Boehringer Ingelheim International GmbH (Ingelheim am Rhein, DE)

Appl. No.: 17/394522

Filed: August 05, 2021

Prior Publication Data

Document Identifier	Publication Date
US 20220041678 A1	Feb. 10, 2022

Foreign Application Priority Data

EP	20189966	Aug. 07, 2020
----	----------	---------------

Publication Classification

Int. Cl.: C07K14/575 (20060101); A61K38/22 (20060101); A61K45/06 (20060101); A61P3/04 (20060101); A61K38/00 (20060101)

U.S. Cl.:

CPC **C07K14/575** (20130101); **A61K38/22** (20130101); **A61K45/06** (20130101); **A61P3/04** (20180101); A61K38/00 (20130101)

Field of Classification Search

USPC: None

References Cited

U.S. PATENT DOCUMENTS

Patent No.	Issued Date	Patentee Name	U.S. Cl.	CPC
12054525	12/2023	Haebel	N/A	A61K 38/22
2007/0135351	12/2006	Conde-Knape et al.	N/A	N/A
2008/0207512	12/2007	Roth et al.	N/A	N/A
2009/0105122	12/2008	Lumb et al.	N/A	N/A
2010/0323955	12/2009	Roth et al.	N/A	N/A
2013/0281373	12/2012	Klein et al.	N/A	N/A
2015/0152150	12/2014	Oestergaard et al.	N/A	N/A
2018/0155406	12/2017	Bossart et al.	N/A	N/A
2019/0002520	12/2018	Oh et al.	N/A	N/A
2019/0207505	12/2018	Ramadass et al.	N/A	N/A
2019/0231850	12/2018	Acosta et al.	N/A	N/A
2020/0014514	12/2019	Gao et al.	N/A	N/A
2020/0140514	12/2019	Briere et al.	N/A	N/A
2022/0041678	12/2021	Haebel et al.	N/A	N/A
2023/0340039	12/2022	Haebel	N/A	A61K 38/2271

FOREIGN PATENT DOCUMENTS

Patent No.	Application Date	Country	CPC
7500115	12/2015	CO	N/A
2005077072	12/2004	WO	N/A
2005089789	12/2004	WO	N/A
2005077072	12/2004	WO	N/A
2006049681	12/2005	WO	N/A
2006066024	12/2005	WO	N/A
2008152403	12/2007	WO	N/A
2008101017	12/2007	WO	N/A
2008101017	12/2007	WO	N/A
2008152403	12/2007	WO	N/A
2009064298	12/2008	WO	N/A
2009064298	12/2008	WO	N/A
2010007251	12/2009	WO	N/A
2010070251	12/2009	WO	N/A
2010070252	12/2009	WO	N/A
2010070252	12/2009	WO	N/A
2010070253	12/2009	WO	N/A

2010070253	12/2009	WO	N/A
2010070255	12/2009	WO	N/A
2010070255	12/2009	WO	N/A
2011006497	12/2010	WO	N/A
2011006497	12/2010	WO	N/A
2011033068	12/2010	WO	N/A
2011058165	12/2010	WO	N/A
2011060630	12/2010	WO	N/A
2011160630	12/2010	WO	N/A
2011160633	12/2010	WO	N/A
2011160633	12/2010	WO	N/A
2012168430	12/2011	WO	N/A
2012168430	12/2011	WO	N/A
2012168431	12/2011	WO	N/A
2012168432	12/2011	WO	N/A
2012168432	12/2011	WO	N/A
2013092703	12/2012	WO	N/A
2013092703	12/2012	WO	N/A
2013164483	12/2012	WO	N/A
2013164483	12/2012	WO	N/A
2014041195	12/2013	WO	N/A
2015067716	12/2013	WO	N/A
2014178018	12/2013	WO	N/A
2015040182	12/2014	WO	N/A
2015040182	12/2014	WO	N/A
2015055801	12/2014	WO	N/A
2015055802	12/2014	WO	N/A
2015067716	12/2014	WO	N/A
2015071229	12/2014	WO	N/A
2015071229	12/2014	WO	N/A
2015071355	12/2014	WO	N/A
2016146739	12/2015	WO	N/A
2016146739	12/2015	WO	N/A
2016166289	12/2015	WO	N/A
2016198624	12/2015	WO	N/A
2016198624	12/2015	WO	N/A
2016198682	12/2015	WO	N/A
2017116204	12/2015	WO	N/A
2017116205	12/2016	WO	N/A
2017192538	12/2016	WO	N/A
2018046719	12/2017	WO	N/A
2018046719	12/2017	WO	N/A
2018081370	12/2017	WO	N/A
2018081370	12/2017	WO	N/A
2018081375	12/2017	WO	N/A
2018100134	12/2017	WO	N/A
2018100134	12/2017	WO	N/A
2018100135	12/2017	WO	N/A
2018172390	12/2017	WO	N/A
2018224630	12/2017	WO	N/A

2019110982	12/2018	WO	N/A
2019207505	12/2018	WO	N/A
2020092191	12/2019	WO	N/A
2021094259	12/2020	WO	N/A

OTHER PUBLICATIONS

Ahn, Advances in experimental medicine and biology, Amylin Pharma, vol. 611, 2009. cited by applicant

Batterham, Inhibition of food intake, New England J. Med, vol. 349, 2003. cited by applicant

Bak, Physicochemical and Formulation Developability Assessment, The AAPS Journal, vol. 17, 2015. cited by applicant

Roux, Elimination and exchange of trifluoroacetate, J. Pept. Sci. Vol. 14, 2008. cited by applicant

Beck-Sickinger, Complete L-Alanine scan of Neuropeptide Y, Ero. J, Biochem, vol. 225, 1994. cited by applicant

European Search Report for 01-3446-WO-1 mailed Feb. 22, 2021. cited by applicant

Koglin, Novel modified and radiolabelled neuropeptide Y analogies to study Y-receptor subtypes, Science Direct, vol. 38, 2004. cited by applicant

Henry, Vitamin B12 Conjugation, Endocrinology, vol. 156, 2015. cited by applicant

Corrigan, Salt forms, Encyclopedia of Pharma Tech., 2007. cited by applicant

Fields, Principles and Practice of Solid Phase Peptide Synthesis, Advances in Molecular Biology, 2002. cited by applicant

Berge, Pharmaceutical Salts, J. of Pharma Sciences, vol. 66, 1977. cited by applicant

U.S. Appl. No. 18/751,723, filed Jun. 24, 2024, Inventor Peter Haebel (The cited pending U.S. application is stored in the USPTO IFW system (MPEP 609.04(a)(II)(C)). cited by applicant

Ahn, John S. et al. "Synthesis and Biological Evaluation of PYY(3-36) Analogs Substituted with Alanine" (2009), Advances in Experimental Medicine and Biology, vol. 611, 515-516. cited by applicant

Bak, Annette et al. "Physicochemical and Formulation Developability Assessment for Therapeutic Peptide Delivery—A Primer" (2015) The AAPS Journal, vol. 17, No. 1, 144-155. cited by applicant

Batterham, Rachel L. et al. Inhibition of Food Intake in Obese Subjects by Peptide YY3-36, (2003) The New England Journal of Medicine, vol. 349, 10, 941-948. cited by applicant

Beck-Sickinger, Annette G. et al. "Complete L-alanine scan of neuropeptide Y reveals ligands binding to Y1 and Y2 receptors with distinguished conformations" (1994), Eur. J. Biochem, vol. 225, 947-958. cited by applicant

Berge, Stephen, M et al. "Pharmaceutical Salts" (1977) Journal of Pharmaceutical Sciences, vol. 66, No. 1, 1-19. cited by applicant

Bujak, Emil et al. "Reformatting of scFv Antibodies into the scFv-Fc Format and their Downstream Purification", Chapter 20, Monoclonal Antibodies: Methods and Protocols, (2014) vol. 1131, 315-334. cited by applicant

Corrigan, Owen I. "Salt Forms: Pharmaceutical Aspects" (2007) Encyclopedia of Pharmaceutical Technology, 3177-3186. cited by applicant

Fields, Gregg B. et al. "Principles and Practice of Solid-Phase Peptide Synthesis" (2002) Synthetic Peptides, A User's Guide, Second Edition, 93-219. cited by applicant

Gershoni, Jonathan et al. "Epitope Mapping, The First Step in Developing Epitope-Based Vaccines" (2007) Drug Development, vol. 21, 145-156. cited by applicant

Henry, Kelly et al, "Vitamin B12 Conjugation of Peptide YY3-36 Decreases Food Intake, Compared to native Peptide-YY3-36 Upon Subcutaneous Administration in Male Rats" (2015) Endocrinology, vol. 156, 1739-1749. cited by applicant

International Search Report and Written Opinion for application PCT/EP2021/071873, mailed Dec. 20, 2021. cited by applicant

International Search Report for PCT/EP2020/081513 mailed Nov. 9, 2020. cited by applicant
Koglin, Norman et al. "Novel modified and radiolabeled neuropeptide Y analogues to study Y-receptor subtypes" (2004) *Neuropeptides*, vol. 38, No. 4. 153-161. cited by applicant
Merkouris, et al. "Supplemental Appendix, Function-Based Selection of TrkB Activating Antibodies: Characterization of a Full BDNK Agonist Antibody on Human Neurons", *PNAS*, Published Jul. 9, 2018, 10 pgs. cited by applicant
Merkouris, Spyros et al., "Fully Human agonist antibodies to TrkB using autocrine cell-based selection from a combinatorial antibody library", (2018) *PNAS*, vol. 115, No. 30, E7023-E7032. cited by applicant
Roux, Stephane et al. "Elimination and exchange of trifluoroacetate counter-ion from cationic peptides: a critical evaluation of different approaches" (2008), *Journal Peptide Science*, vol. 14, 354-359. cited by applicant
Wang, Shudan et al. "Therapeutic Potential of a TrkB agonistic antibody for Alzheimer's Disease" (2020) *Thernostics*, vol. 10, Issue 15, 6854-6874. cited by applicant

Primary Examiner: Audet; Maury A

Background/Summary

SEQUENCE LISTING

(1) The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on Aug. 4, 2021, is named 01-3446-US-1_SL.txt and is 182,619 bytes in size.

FIELD OF THE INVENTION

(2) 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 related to excess body weight or obesity, e.g. diabetes and cardiovascular diseases.

BACKGROUND INFORMATION

(3) 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. 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.

(4) 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 Europe.

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

(6) 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.

(7) TABLE-US-00001 Sequence of hPYY (3-36): (SEQ ID No: 4) 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

(8) 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 YY.sub.3-36*, N Engl J Med 2003; 349; 941-8).

(9) 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.

(10) 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.

(11) 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.

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

BRIEF SUMMARY OF THE INVENTION

(13) 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 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.

(14) 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) 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.

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

R^{sup.1}—Z—R^{sup.2}, wherein R^{sup.1} is hydrogen, —C(O)C_{sub.1-6} alkyl, —C(O)C_{sub.6H.sub.6}, —C(O)C_{sub.3-6} cycloalkyl, —C(O)C_{sub.1-6} alkyl-C_{sub.3-6} cycloalkyl, C_{sub.1-6} alkyl or C_{sub.1-6} alkyl-C_{sub.3-6} cycloalkyl; R^{sup.2} is OH or NHR^{sup.3}, wherein R^{sup.3} is hydrogen or C_{sub.1-3} alkyl; and Z is a peptide comprising an amino acid sequence of formula Ib:

(16) TABLE-US-00002 (SEQ ID NO: 208) Ala-Pro-X6-Lys-X8-X9-X10-X11-X12-X13-X14-X15-X16-X17-Gln-X19-X20-X21-X22-X23-Leu-Arg-His-X27-X28-X29-X30-Leu-X32-

X33-Gln-Arg-Tyr (Ib) wherein X6 is selected from the group consisting of Ala and Glu; X8 is selected from the group consisting of Ala and Pro; X9 is selected from the group consisting of Glu, Gly and Pro; X10 is selected from the group consisting of Ala and Glu; X11 is selected from the group consisting of Ala, Asp, Glu, Ile, Leu, Pro, Gln and Ser; X12 is selected from the group consisting of Ala, Glu, Leu, Pro, Gln and Ser; X13 is selected from the group consisting of Ala, Glu, Leu, Ser, Gln, Thr and Pro; X14 is selected from the group consisting of Ala, Glu, Leu, Pro, Gln and Ser; X15 is selected from the group consisting of Ala and Glu; X16 is selected from the group consisting of Ala, Glu and Lys; X17 is selected from the group consisting of Ala, Glu, Ile, Leu, Pro, Gln, Ser, Thr and Val; 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; 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; 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.

(17) 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 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.

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

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

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

(21) The invention further provides a composition comprising a PYY analogue as described herein.

(22) 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, diseases, or disorders such as type 2 diabetes, NAFLD or NASH.

(23) 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.

Description

DETAILED DESCRIPTION OF THE INVENTION

Terms, Definitions and Conventions

(1) 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 meaning indicated and the following conventions are adhered to.

(2) 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.

(3) PYY Analogues

(4) 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 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.

(5) The term “PYY analogue” comprises the peptide itself, i.e., in a non-ionized state, as well as the peptide in ionized state (e.g. when one or more side chains of its amino acids are ionized, i.e. (de)protonated). A PYY analogue in a non-ionized state is also referred to herein as a non-salt form of the PYY analogue.

(6) 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 amino acid bears a covalently attached half-life extending group.

(7) 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 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 $N(R^{sup.1})(R^{sup.2})(R^{sup.3})(R^{sup.4})^{sup.+}$, where $R^{sup.1}$, $R^{sup.2}$, $R^{sup.3}$ and $R^{sup.4}$ independently will typically designate hydrogen or optionally substituted $C_{sub.1-6}$ -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).

(8) 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).

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

(10) 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.).

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

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

(13) The term “ $C_{sub.1-n}$ 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 $C_{sub.1-5}$ -alkyl embraces the radicals $H_{sub.3}C-$, $H_{sub.3}C-CH_{sub.2}-$, $H_{sub.3}C-CH_{sub.2}-CH_{sub.2}-$, $H_{sub.3}C-CH(CH_{sub.3})-$, $H_{sub.3}C-CH_{sub.2}-CH_{sub.2}-CH_{sub.2}-$, $H_{sub.3}C-CH_{sub.2}-CH(CH_{sub.3})-$, $H_{sub.3}C-CH(CH_{sub.3})-CH_{sub.2}-$, $H_{sub.3}C-C(CH_{sub.3})_{sub.2}-$, $H_{sub.3}C-CH_{sub.2}-CH_{sub.2}-CH_{sub.2}-CH_{sub.2}-$, $H_{sub.3}C-CH_{sub.2}-CH_{sub.2}-CH(CH_{sub.3})-$, $H_{sub.3}C-CH_{sub.2}-CH(CH_{sub.3})-CH_{sub.2}-$, $H_{sub.3}C-CH(CH_{sub.3})-CH_{sub.2}-CH_{sub.2}-$, $H_{sub.3}C-CH_{sub.2}-C(CH_{sub.3})_{sub.2}-$, $H_{sub.3}C-$

C(CH.sub.3).sub.2—CH.sub.2—, H.sub.3C—CH(CH.sub.3)—CH(CH.sub.3)— and H.sub.3C—CH.sub.2—CH(CH.sub.2CH.sub.3)—.

(14) The term “C.sub.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 C.sub.3-6-cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

(15) “C(O)” or “C(=O)” refers to a carbonyl group.

(16) Nomenclature of Compounds:

(17) As an example,

(18) TABLE-US-00003 (SEQ ID NO: 66) iVal-APAK(C18DA-gGlu-Ahx)PPEDASPEELQRYRYVELRHYYNWLT RQRY-NH₂, wherein iVal represents 3-methylbutanoyl (—C(O)CH.sub.2CH(CH.sub.3).sub.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 carboxy-group to ε-amino-group of lysine (K), completely defines the PYY analogue of the following structure (SEQ ID NO: 66):

(19) ##STR00001##

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

(21) 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).

(22) 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.

(23) 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.

(24) Half-Life Extending Group

(25) 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).

(26) 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.

(27) 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.

(28) 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.

(29) 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.

(30) 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.

(31) In certain embodiments, the linker moiety U may itself comprise one, two, three or more linked sub-moieties (U.sup.1, U.sup.2, U.sup.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), AEEEE (2-{2-[2-(2-aminoethoxy)ethoxy]ethoxy}acetic acid), H.sub.2N-dPEG(4)-COOH (15-amino-4,7,10,13-tetraoxa-pentadecanoic acid), H.sub.2N-dPEG(6)-COOH (1-amino-3,6,9,12,15,18-hexaoxahenicosan-21-oic acid), H.sub.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}carbonyl)propanoic acid), H-DOOA-DIG-OH (2-[(2-[2-(2-aminoethoxy)ethoxy]ethyl}carbonyl)methoxy]acetic acid), H-TTD-DIG-OH (2-[(3-{2-[2-(3-aminopropoxy)ethoxy]ethoxy}propyl)carbonyl]methoxy}acetic acid), H-TTDS-OH (3-[(3-{2-[2-(3-aminopropoxy)ethoxy]ethoxy}propyl)-carbonyl]propanoic acid), or 8Ado (i.e. 8-amino-

3,6-dioxaoctanoyl also denoted OEG herein).

(32) 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.

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

(34) 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.

(35) Synthesis of PYY Analogues

(36) 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., "Principles and Practice of Solid-Phase Peptide Synthesis" in Synthetic Peptides, Grant G. A. (ed.), Oxford University Press (2.sup.nd edition, 2002).

Embodiments

(37) 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 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.

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

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

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

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

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

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

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

(45) 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.

(46) 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.

(47) 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.

(48) 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) 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.

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

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

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

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

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

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

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

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

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

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

(59) 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.

(60) In some embodiments, the PYY analogue comprises i) alanine at the position corresponding to position 4 of hPYY(3-36) 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) 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) 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) xviii) leucine at the position corresponding to position 31 of hPYY(3-36) xix) the sequence RQRY (SEQ ID NO: 212) 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.

(61) 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.

(62) In some embodiments according to the previous paragraph, the linker U of the half-life extending

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

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

R.sup.1—Z—R.sup.2, wherein R.sup.1 is hydrogen, —C(O)C.sub.1-6 alkyl, —C(O)C.sub.6H.sub.6, —C(O)C.sub.3-6 cycloalkyl, —C(O)C.sub.1-6 alkyl-C.sub.3-6 cycloalkyl, C.sub.1-6 alkyl or C.sub.1-6 alkyl-C.sub.3-6 cycloalkyl; R.sup.2 is OH or NHR.sup.3, wherein R.sup.3 is hydrogen or C.sub.1-3 alkyl; and Z is a peptide comprising an amino acid sequence of formula Ib:

(64) TABLE-US-00004 (SEQ ID NO: 208) Ala-Pro-X6-Lys-X8-X9-X10-X11-X12-X13-X14-X15-X16-X17-Gln-X19-X20-X21-X22-X23-Leu-Arg-His-X27-X28-X29-X30-Leu-X32-X33-Gln-Arg-Tyr (Ib) wherein X6 is selected from the group consisting of Ala and Glu; X8 is selected from the group consisting of Ala and Pro; X9 is selected from the group consisting of Glu, Gly and Pro; X10 is selected from the group consisting of Ala and Glu; X11 is selected from the group consisting of Ala, Asp, Glu, Ile, Leu, Pro, Gln and Ser; X12 is selected from the group consisting of Ala, Glu, Leu, Pro, Gln and Ser; X13 is selected from the group consisting of Ala, Glu, Leu, Ser, Gln, Thr and Pro; X14 is selected from the group consisting of Ala, Glu, Leu, Pro, Gln and Ser; X15 is selected from the group consisting of Ala, and Glu; X16 is selected from the group consisting of Ala, Glu and Lys; X17 is selected from the group consisting of Ala, Glu, Ile, Leu, Pro, Gln, Ser, Thr and Val; 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; 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; X33 is selected from the group consisting of Lys and Arg; wherein one to three amino acids of X6, X8-X19, X21-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.

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

(66) 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.

(67) In a further embodiment R.sup.1 is —C(O)C.sub.1-4 alkyl, —C(O)C.sub.3-5 cycloalkyl, —C(O)C.sub.1-3 alkylC.sub.3-4 cycloalkyl, C.sub.1-4 alkyl or C.sub.1-3 alkyl-C.sub.3-4 cycloalkyl.

(68) In a further embodiment R.sup.1 is —C(O)CH.sub.2CH(CH.sub.3).sub.2, —C(O)CH.sub.2-cyclobutyl, —C(O)CH.sub.2-cyclopropyl.

(69) 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.

(70) Peptide therapeutics are usually provided as pharmaceutical liquid formulation in a prefilled 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.

(71) 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).

(72) A broad pH range, within which a peptide therapeutic is reasonably soluble (solubility 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 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 stability of peptides containing asparagine, aspartate or glutamine, tryptophan, cysteine or methionine is an issue.

(73) Efficacy of obesity therapeutics is limited. However, efficacy might be improved by combining different therapeutic principles. NPY2 receptor agonists seem attractive partners for 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 fixed-dose combination of a PYY analogue with an amylin 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.

(74) 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.

(75) 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).

(76) 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.

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

(78) 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.

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

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

(81) Further, more specific embodiments are defined below:

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

R.sup.1—Z—R.sup.2, wherein R.sup.1 and R.sup.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 sub-moiety is Ahx.

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

R.sup.1—Z—R.sup.2, wherein R.sup.1 is hydrogen, —C(O)C.sub.1-6 alkyl, —C(O)C.sub.6H.sub.6, —C(O)C.sub.3-6 cycloalkyl, —C(O)C.sub.1-6 alkyl-C.sub.3-6 cycloalkyl, or

C.sub.1-6 alkyl or C.sub.1-6 alkyl-C.sub.3-6 cycloalkyl; R.sup.2 is OH or NHR.sup.3, wherein R.sup.3 is hydrogen or C.sub.1-3 alkyl; and Z is an amino acid sequence of formula IIb:

(84) TABLE-US-00005 (SEQ ID NO: 209) Ala-Pro-X6-Lys-X8-X9-X10-X11-Ala-X13-X14-Glu-Glu- X17-Gln-X19-Tyr-Tyr-X22-X23-Leu-Arg-His-Tyr-Tyr- X29-Trp-Leu-Thr-Arg-Gln-Arg-Tyr (IIb) wherein X6 is selected from the group consisting of Ala and Glu; X8 is selected from the group consisting of Ala and Pro; X9 is selected from the group consisting of Glu and Pro; X10 is selected from the group consisting of Ala and Glu; X11 is selected from the group consisting of Ala, Asp and Glu; X13 is selected from the group consisting of Glu, Ser and Thr; X14 is selected from the group consisting of Ala, Glu and Pro; X17 is selected from the group consisting of Ala, Ile, Leu, Ser and Thr; X19 is selected from the group consisting of Arg and Gln; X22 is selected from the group consisting of Ile, Thr and Val; X23 is selected from the group consisting of Ala, Glu, Gln and Ser; X29 is selected from the group consisting of Asn and Gln; and wherein a half-life extending group is attached to the epsilon amino group of the lysine at position 4.

(85) 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.

(86) 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.

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

R.sup.1—Z—R.sup.2, Wherein R.sup.1 and R.sup.2 are as defined above; Z is an amino acid sequence of formula IIb; 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.

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

R.sup.1—Z—R.sup.2, wherein R.sup.1 is hydrogen, —C(O)C.sub.1-6 alkyl, —C(O)C.sub.6H.sub.6, —C(O)C.sub.3-6 cycloalkyl, —C(O)C.sub.1-6 alkyl-C.sub.3-6 cycloalkyl, or C.sub.1-6 alkyl or C.sub.1-6 alkyl-C.sub.3-6 cycloalkyl; R.sup.2 is OH or NHR.sup.3, wherein R.sup.3 is hydrogen or C.sub.1-3 alkyl; and Z is an amino acid sequence of formula IIIb:

(89) TABLE-US-00006 (SEQ ID NO: 210) 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 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; X13 is selected from the group consisting of Ala, Glu, Ser, Thr and Pro; X14 is selected from the group consisting of Ala, Glu and Pro; X15 is selected from the group consisting of Ala and Glu; X16 is selected from the group consisting of Ala and Glu; X17 is selected from the group consisting of Ile, Leu, Thr and Val; X18 is selected from the group consisting of Glu and Gln; X19 is selected from the group consisting of Ala, Glu, Arg, Lys, and Gln; X21 is selected from the group consisting of Glu and Tyr; 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 4.

(90) In a further embodiment Z is an amino acid sequence of formula IVb:

(91) TABLE-US-00007 (SEQ ID NO: 211) Ala-Pro-X6-Lys-Pro-X9-X10-X11-Ala-X13-Pro-Glu-Glu- X17-Gln-Arg-Tyr-Tyr-X22-X23-Leu-Arg-His-Tyr-Tyr- Asn-Trp-Leu-Thr-Arg-Gln-Arg-Tyr (IVb) wherein X6 is selected from the group consisting of Ala and Glu; X9 is selected from the group consisting of Glu and Pro; X10 is selected from the group consisting of Ala and Glu; X11 is

selected from the group consisting of Ala, Asp and Glu; X13 is selected from the group consisting of Glu, Ser and Thr; X17 is selected from the group consisting of Ile and Leu; X22 is selected from the group consisting of Ile and Val; X23 is selected from the group consisting of Ala and Ser; In an embodiment of the present invention, the PYY analogue is a compound having the formula: R.sup.1—Z—R.sup.2, Wherein R.sup.1 and R.sup.2 are as defined above; Z is an amino acid sequence of formula IVb; 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.

(92) 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.

(93) 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.

(94) In further embodiments, R.sup.1 is hydrogen, —C(O)C.sub.1-6 alkyl, —C(O)C.sub.3-6 cycloalkyl, or C.sub.1-6 alkyl.

(95) In further embodiments, R.sup.1 is hydrogen or —C(O)C.sub.1-6 alkyl.

(96) In further embodiments, R.sup.1 is hydrogen or —C(O)C.sub.1-4 alkyl.

(97) In more specific embodiments, R.sup.1 is —C(O)CH.sub.2CH(CH.sub.3).sub.2.

(98) In more specific embodiments, R.sup.2 is NH.sub.2.

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

R.sup.1—Z—R.sup.2, wherein R.sup.1 and R.sup.2 are as defined in any of the definition above; and Z is an amino acid sequence selected from Table 1:

(100) TABLE-US-00008 TABLE 1 cf. compound SEQ ID No Sequence 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

APEKPEEADAEPEELQRYYYVALRHYYNWLTRQRY 25 22

APEKPEEDPTPEELQRYYYVSLRHYYNWLTRQRY 26 23

APEKPEEEASPEELQRYYYVSLRHYYNWLTRQRY 27 24

APEKPEEDSSPEELQRYYYVALRHYYNWLTRQRY 28 25

APEKPEADATPEELQRYYYISLRHYYNWLTRQRY 29 26

APAKPEEDATPEELQRYYYVSLRHYYNWLTRQRY 30 27

APEKPEEDAEPEELQRYYYVSLRHYYNWLTRQRY 31 28
APEKPPEDATPEEIQRYYVSLRHYYNWLTRQRY 32 29
APEKPEADSSPEELQRYYYVSLRHYYNWLTRQRY 33 30
APEKPPADATPEELQRYYYVSLRHYYNWLTRQRY 34 31
APEKPEEDATPEELQPYYVSLRHYYNWLTRQRY 35 32
APAKPEEDASPEELQRYYYVSLRHQYNWLTRQRY 36 33
APAKPEEDAEPEELQRYYISLRHYYNWLTRQRY 37 34
APEKPEEDASAEELQQYYVSLRHYYNWLTRQRY 38 35
APAKPEEAATPEELQRYYYVSLRHYYNWLTRQRY 39 36
APAKPEEAATPEEIQRYYVSLRHYYNWLTRQRY 40 37
APEKPEEDAEPEELQRYYTSLRHYYNWLTRQRY 41 38
APEKPEEDATPEELQEYYVSLRHYYNWLTRQRY 42 39
APEKPEEDASPEALQEYYVSLRHYYNWLTRQRY 43 40
APEKPEADASPEEIQRYYIALRHYYNWLTRQRY 44 41
APEKPEEDAEPEELQRYYTSLRHYYQWLTRQRY 45 42
APEKPEEPATPEELQRYYYVSLRHYYNWLTRQRY 46 43
APAKPEAAAPEELQRYYYVSLRHYYNWLTRQRY 47 44
APEKPEEDATPEELQRYYYVGLRHYYNWLTRQRY 48 45
APEKPEEIATPEELQRYYYVSLRHYYNWLTRQRY 49 46
APEKPEEDAEPEELQRYYASLRHYYNWLTRQRY 50 47
APEKPPEDASPEEIQRYYVALRHYYNWLTRQRY 51 48
APAKPEEAATPEELQRYYISLRHYYNWLTRQRY 52 49
APEKPEEDATPEELQRYYYVLLRHYYNWLTRQRY 53 50
APEKPEEDATPEEIQRYYVALRHYYNWLTRQRY 54 51
APEKPEEDATPEELQRYYYVQLRHYYNWLTRQRY 55 52
APEKPEEDASPEEIQRYYVELRHYYNWLTRQRY 56 53
APEKPEEDAEPEEVQRYYYVSLRHYYNWLTRQRY 57 54
APEKPEEDATPEEAQRYYVSLRHYYNWLTRQRY 58 55
APEKPEEDASEEEIQRYYVSLRHYYNWLTRQRY 59 56
APEKPEEDATAEELQRYYYVSLRHYYNWLTRQRY 60 57
APAKPEEDATPEEAQRYYVSLRHYYNWLTRQRY 61 58
APEKPEEDATPEEVQRYYYVSLRHYYNWLTRQRY 62 59
APAKPEEDASPEELQRYYYVQLRHYYNWLTRQRY 63 60
APEKPEEDASPEELQRYYYVSLRHYYQWLTRQRY 64 61
APEKPPADASPEEIQRYYVSLRHYYNWLTRQRY 65 62
APAKPPEDASPEELQRYYYVELRHYYNWLTRQRY 66 63
APAKPEEDASPEEIQRYYVSLRHYYNWLTRQRY 67 64
APEKPPEDATPEEIQRYYVALRHYYNWLTRQRY 68 65
APAKPEEDASPEEIQRYYIALRHYYNWLTRQRY 69 66
APEKPEEDATPEELQRYYISLRHYYNWLTRQRY 70 67
APEKPEEDASPEETQRYYYVALRHYYNWLTRQRY 71 68
APEKPEEDAEPEELQRYYYVSLRHYYQWLTRQRY 72 69
APEKPPADASPEETQRYYYVSLRHYYNWLTRQRY 73 70
APAKPEEDATPEELQRYYIALRHYYNWLTRQRY 74 71
APAKPEEDAEPEELQRYYYVALRHYYNWLTRQRY 75 72
APEKPEADAPEPEELQRYYYVSLRHYYNWLTRQRY 76 73
APEKPEEAASPEELQRYYYVALRHYYNWLTRQRY 77 74
APEKPEEDATPEELQRYYYVALRHYYNWLTRQRY 78 75
APEKPEEDAPPEEIQRYYVSLRHYYNWLTRQRY 79 76
APEKPEEDASPEELQRYYISLRHYYNWLTRQRY 80 77

APAKPEEDASPEELQRYVSLRHYQNWLTQRQY 81 78
APAKPEEDASPEELQRYVSLRHYYQWLTRQRY 82 79
APEKPEEDASPEELQRYVSLRHYYNWLTRQRY 83 80
APEKPEEDASEAELQRYVSLRHYYNWLTRQRY 84 81
APEKPEEDAQPEEIQRYVSLRHYYNWLTRQRY 85 82
APAKPPEDASPEEIQRYVSLRHYYNWLTRQRY 86 83
APEKPEEDATSEELQRYVSLRHYYNWLTRQRY 87 84
APEKPEEDATPEEIQRYVVALRHYYNWLTRQRY 88 85
APAKPEEDASPEETQRYVSLRHYYNWLTRQRY 89 86
APEKPEEDATPEEIQRYVASLRHYYNWLTRQRY 90 87
APEKPEEDATPEELQRYVPLRHYYNWLTRQRY 91 88
APEKPEEDATPEELQRQYVSLRHYYNWLTRQRY 92 89
APAKPPEDASPEELQRYVVALRHYYNWLTRQRY 93 90
APEKPEEDATPEELQRYVVLRHYYNWLTRQRY 94 91
APEKPEEDAEPeelQRYVTSLRHYHHLTRQRY 95 92
APEKPGEDASPEELQRYVISLRHYYNWLTRQRY 96 93
APEKPEEDASPEEIQRYVQLRHYYNWLTRQRY 97 94
APAKPEADASPEELQRYVVELRHYYNWLTRQRY 98 95
APEKPEEDATPEELQAYYVSLRHYYNWLTRQRY 99 96
APEKPEESATPEELQRYVSLRHYYNWLTRQRY 100 97
APEKPEEDATPEEIQRYVLSLRHYYNWLTRQRY 101 98
APEKPEADATPEEIQRYVSLRHYYNWLTRQRY 102 99
APAKPEEDATPEEIQRYVVALRHYYNWLTRQRY 103 100
APEKPEADATPEELQRYVIALRHYYNWLTRQRY 104 101
APAKPEEDATPEELQRYVVALRHYYNWLTRQRY 105 102
APEKPEEDATLEELQRYVSLRHYYNWLTRQRY 106 103
APEKPEEDASAEELQRYVVALRHYYNWLTRQRY 107 104
APEKPEEDAEPeeAQRYVSLRHYYNWLTRQRY 108 105
APEKPEEDATQEELQRYVSLRHYYNWLTRQRY 109 106
APAKPEEDASPEELQRYVVALRHYYNWLTRQRY 110 107
APEKPEEDAEPETQRYVSLRHYYNWLTRQRY 111 108
APEKPEADASEEELQRYVSLRHYYNWLTRQRY 112 109
APEKPEEDLTPEELQRYVSLRHYYNWLTRQRY 113 110
APEKPEEDATPEELQRYVVELRHYYNWLTRQRY 114 111
APAKPEAAAEPEEIQRYVSLRHYYNWLTRQRY 115 112
APEKPEEDAEPeeIQRYVSLRHYYNWLTRQRY 116 113
APEKPEEDATPEEIQRYVSLRHYQNWLTQRQY 117 114
APAKPEEDATPEEIQRYVSLRHYYNWLTRQRY 118 115
APEKPEEDATPEELQRYQVSLRHYYNWLTRQRY 119 116
APAKPEAAAEPEEIQRYVVALRHYYNWLTRQRY 120 117
APEKPEEDASPEEAQRYVVALRHYYNWLTRQRY 121 118
APEKPPEDAEPeeIQRYVSLRHYYNWLTRQRY 122 119
APEKPEEDATPEESQRYVSLRHYYNWLTRQRY 123 120
APAKPEEAATPEEIQRYVVALRHYYNWLTRQRY 124 121
APEKPEADASPEELQRYVQLRHYYNWLTRQRY 125 122
APEKPEAEASPEELQRYVSLRHYYNWLTRQRY 126 123
APEKPEEDAAPeelQKYYVSLRHYYNWLTRQRY 127 124
APEKPEAAAEPEEIQRYVSLRHYYNWLTRQRY 128 125
APEKPEEDASPEELQRYVVELRHYYNWLTRQRY 129 126
APEKPEEDAEPeelQRYVSLRHYYNWLTRQRY 130 127

APEKPEAAAEPEELQRYYYVALRHYYNWLTRQRY 131 128
APEKPEEAATPEELQRYYYVSLRHYYNWLTRQRY 132 129
APEKPEEDASAEELQRYYYVSLRHYYNWLTRQRY 133 130
APEKPEEDATPEELQLYYVSLRHYYNWLTRQRY 134 131
APEKPEADAEPEELQRYYYVALRHYYNWLTRQRY 135 132
APEKPEADATPEELQRYYYVSLRHYYNWLTRQRY 136 133
APAKPEEDAEPEELQRYYYVSLRHYYNWLTRQRY 137 134
APEKPEEDATPEEQRYYYVSLRHYYNWLTRQRY 138 135
APEKPEAAAEPEELQRYYYVALRHYYNWLTRQRY 139 136
APEKPEADATPEELQRYYYVALRHYYNWLTRQRY 140 137
APEKPEEDATPEELQRYYYVSLRHYYNWLTRQRY 141 138
APEKPEEDAEPEELQEYYVSLRHYYNWLTRQRY 142 139
APEKPEEEEASPAELQRYYYVSLRHYYNWLTRQRY 143 140
APEKPEADASPEELQRYYYVSLRHYYNWLTRQRY 144 141
APEKPEEDATPEELQSYYYVSLRHYYNWLTRQRY 145 142
APEKPEEDALPEELQRYYYVSLRHYYNWLTRQRY 146 143
APEKPEEDSTPEELQRYYYVSLRHYYNWLTRQRY 147 144
APEKPEEDQTPEELQRYYYVSLRHYYNWLTRQRY 148 145
APAKPEEDASPEELQRYYYVSLRHYYNWLTRQRY 149 146
APEKPEEEEATPEELQRYYYVSLRHYYNWLTRQRY 150 147
APEKPEEDASPEELQRYYYVSLRHYYNWLTRQRY 151 148
APEKPEEDATPEELQRYYYVTLRHYYNWLTRQRY 152 149
APAKPEEDASPEESQRYYYVSLRHYYNWLTRQRY 153 150
APEKPEEAASPEELQRYYYVSLRHYYNWLTRQRY 154 151
APEKPEEDSSPEELQRYYYVALRHYYNWLTRQRY 155 152
APEKPEEDATPEETQRYYYVSLRHYYNWLTRQRY 156 153
APEKPEELATPEELQRYYYVSLRHYYNWLTRQRY 157 154
APEKPEEAATPEELQRYYYVALRHYYNWLTRQRY 158 155
APEKPEEDATPEELQRYYYVSLRHYYNWLTRQRY 159 156
APEKPEEAAAEPEELQRYYYVALRHYYNWLTRQRY 160 157
APAKPEEAASPEELQRYYYVALRHYYNWLTRQRY 161 158
APEKPEEAASPEELQRYYYVALRHYYNWLTRQRY 162 159
APEKPEADAEPEELQRYYYISLRHYYNWLTRQRY 163 160
APAKPEEDASPEELQRYYYIALRHYYNWLTRQRY 164 161
APAKPEEAAAEPEELQRYYYVALRHYYNWLTRQRY 165 162
APEKPEEDATPEEEQRYYYVSLRHYYNWLTRQRY 166 163
APEKPEADASPEELQRYYYVALRHYYNWLTRQRY 167 164
APEKPEEDATPEELQRYYYQSLRHYYNWLTRQRY 168 165
APAKPPEDAEPEELQRYYYVSLRHYYNWLTRQRY 169 166
APAKPEEDASPEELQRYYYVELRHYYNWLTRQRY 170 167
APAKPEEAAAEPEELQRYYYVALRHYYNWLTRQRY 171 168
APEKPEEDATPEELQRYYYSSLRHYYNWLTRQRY 172 169
APEKPEEDAEPEELQAYYYVSLRHYYNWLTRQRY 173 170
APEKPEEDAAPEELQRYYYVSLRHYYNWLTRQRY 174 171
APEKPEADASPEELQRYYYVELRHYYNWLTRQRY 175 172
APEKPPEDASPEELQRYYYVSLRHYYNWLTRQRY 176 173
APEKPEEDATPEELQRYYYVSLRHYYNWLTRQRY 177 174
APEKPGADASPEELQRYYYVSLRHYYHKLTRQRY 178 175
APAKPEEDAEPEELQRYYYIALRHYYNWLTRQRY 179 176
APEKPEEDATPEELQRYYYVSLRHYYNWLTRQRY 180 177

APEKPEEDATPEELQYYYVSLRHYYNWLTRQRY 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
APEKPEEDATPEEPQRYYVSLRHYYNWLTRQRY 191 188
APEKPEEDATPEELQRYYVSLRHYYNWLQRQRY 192 189
APAKPEEDASPEETQRYYVALRHYYNWLTRQRY 193 190
APAKPEEDATPEELQRYYISLRHYYNWLTRQRY 194 191
APEKPEEDATPEEIQRYYESLRHYYNWLTRQRY 195 192
APEKPEAPASPEELQRYYVSLRHYYNWLTRQRY 196 193
APEKPEEEEASPEEIQRYYVSLRHYYNWLTRQRY 197 194
APAKPEEDAEPEEIQRYYVALRHYYNWLTRQRY 198 195
APAKPEEDASPEEIQRYYISLRHYYNWLTRQRY 199 196
APEKPEADASPEELQRYYVSLRHYYNWLTRQRY 200 197
APEKPEEDASPEEIQRYYVALRHYYNWLTRQRY 201 198
APAKPEADAEPEEIQRYYVSLRHYYNWLTRQRY 202 199
APAKPEEEEASPEELQRYYVSLRHYYNWLTRQRY 203

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.

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

R^{sup.1}—Z—R^{sup.2}, Wherein R^{sup.1} and R^{sup.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.

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

(103) In some embodiments the linker U consists of one, two or three sub-moieties (U^{sup.1}, U^{sup.2}, U^{sup.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.

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

(105) 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.

(106) 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-Ahxy-Glu.

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

(108) ##STR00002##

(109) 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.

- (110) In some embodiments, the PYY analogue has a maximum of 15 amino acid modifications as compared to hPYY(3-36).
- (111) In some embodiments, the PYY analogue has a maximum of 14 amino acid modifications as compared to hPYY(3-36).
- (112) In some embodiments, the PYY analogue has a maximum of 13 amino acid modifications as compared to hPYY(3-36).
- (113) In some embodiments, the PYY analogue has a maximum of 12 amino acid modifications as compared to hPYY(3-36).
- (114) In some embodiments, the PYY analogue has a maximum of 11 amino acid modifications as compared to hPYY(3-36).
- (115) 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).
- (116) 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).
- (117) 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).
- (118) 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).
- (119) 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).
- (120) 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).
- (121) 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).
- (122) 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).
- (123) 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).
- (124) 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).
- (125) 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).
- (126) 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).
- (127) 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.
- (128) The PYY analogues of the invention are able to bind to the human NPY2 receptor (hNPY2-R).
- (129) 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.
- (130) 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).
- (131) 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).
- (132) 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).
- (133) 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).
- (134) 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).

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

(136) 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 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 formats, and examples are provided below.

(137) EC.sub.50 values may be used as a numerical measure of agonist potency at a given receptor. An EC.sub.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 Example 2, below.

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

(139) In some embodiments of compounds of the present invention, the EC.sub.50 towards hNPY2 receptor is below 50 nM (e.g. 0.001 to 50 nM).

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

(141) In some embodiments of compounds of the present invention, the EC.sub.50 towards hNPY2 receptor is below 5 nM (e.g. 0.001 to 5 nM).

(142) In some embodiments of compounds of the present invention, the EC.sub.50 towards hNPY2 receptor is below 2 nM (e.g. 0.001 to 2 nM).

(143) 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.

(144) 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).

(145) 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).

(146) 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).

(147) 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).

(148) 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).

(149) 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).

(150) 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).

(151) 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).

(152) 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).

(153) 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).

(154) 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).

(155) 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).

(156) 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).

(157) 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).

(158) 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.

(159) 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.

(160) 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.

(161) Method of Treatment

(162) 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 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).

(163) 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 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. 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 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 independent thereof.

(164) 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 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 comorbid 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 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.

(165) Thus, the invention provides a PYY analogue for use in a method of medical treatment, 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.

(166) 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, 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, dyslipidemia, sleep apnea, cardiovascular disease, cancer, hepatic steatosis, NAFLD and NASH.

(167) 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.

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

(169) 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 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.

(170) In a further aspect the present invention relates to the use of a PYY analogue or a 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.

(171) In a further aspect the present invention relates to methods for the treatment or prevention 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.

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

(173) 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 dosages and in a manner, which allows a pharmaceutically effective amount to be delivered based upon patient's unique condition.

(174) Combination Therapy

(175) 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 or separately, e.g. as constituents in the same pharmaceutical composition or formulation, or as separate formulations.

(176) 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, 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 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).

(177) The anti-obesity agent may be amylin or an amylin analogue, e.g. pramlintide, NN-9838, 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.

(178) Alternatively, the anti-obesity agent may be Orlistat™, Sibutramine™, phentermine, a melanin concentrating hormone receptor 1 antagonist, CCK, leptin analogue, a GOAT 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.

(179) 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, 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™).

(180) 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.

(181) 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.

(182) 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.

(183) 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.sup.+/K.sup.+ 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™, Lansoprazole™, Dexlansoprazole™, Esomeprazole™, Pantoprazole™, Rabeprazole™, Zolpidem™, Alpidem™, Saripidem™ or Necopidem™.

(184) 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, piroprofen, 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

(185) 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.

(186) 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-[2-(9H-fluoren-9-ylmethoxycarbonylamino)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.

(187) 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-[2-(9H-Fluoren-9-ylmethoxycarbonylamino)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-[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.

(188) 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.

(189) 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-exchange procedures, e.g. as disclosed in Roux, St. et al. *J. Pept. Sci.* 2008; 14: 354-359.

(190) Synthesis Method 1 (S01)

(191) 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.

(192) 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° 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.

(193) N.sup.α Fmoc 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 hydrate in DMF (10 ml) for 3 min at 90° C.

(194) 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 tertbutyl-methyl ether, dissolved in 50% acetonitrile/water and purified by preparative HPLC (P01).

(195) Purification Method 1 (P01)

(196) Crude peptides were purified by reversed phase chromatography using an Agilent preparative HPLC-MS System with preparative pumps G1361A, a diode array detector 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×150 mm) served as stationary phase. The mobile phase was run with a gradient of buffer A (0.1% TFA in H.sub.2O) 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 characterized by analytical HPLC-MS (A01).

(197) Purification Method 2 (P02)

(198) Crude peptides were purified by reversed phase HPLC using a Gilson preparative HPLC System with XSelect CSH Phenyl-Hexyl column (Waters 130 Å, 5 µm, 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 gradient of buffer A (0.1% TFA in H.sub.2O) 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).

(199) Analytical Method 1 (A01)

(200) Peptide purity and mass were determined by analytical HPLC-MS on a Kinetex C8 column (Phenomenex, 100 Å, 2.6 µm, 4.6 mm×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 H.sub.2O) and buffer B (0.24% TFA in ACN) at a temperature of 40° C. Details of the gradient and flow rates are summarized in the table below. Retention times and masses were recorded.

(201) TABLE-US-00009 Gradient/ % Sol % Sol Method Solvent [Water 0.3% [ACN 0.24% Flow Temp Name: A01 Time [min] TFA (v/v)] TFA (v/v)] [ml/min] [° C.] Device Waters Acquity 0.0 65.0 35.0 0.5 40.0 description: with 3100 MS Column. Kinetex C8_4.6 × 15.0 45.0 55.0 0.5 40.0

150 mm_2.6 µm Column Phenomenex 16.0 10.0 90.0 1.0 40.0 producer: 17.01 65.0 35.0 1.0 40.0
18.0 65.0 35.0 1.0 40.0

List of Abbreviations

(202) ACN: acetonitrile 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 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 Fmoc-OEG-OH: 2-[2-[2-(9H-fluoren-9-ylmethoxycarbonylamino)ethoxy]ethoxy] acetic acid Fmoc-OEG-OEG-OH: 2-[2-[2-[2-[2-(9H-fluoren-9-ylmethoxycarbonylamino)ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetic acid HTRF: homogeneous time resolved fluorescence 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 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 tBu: tert-butyl Trt: trityl TES: triethylsilane TFA: trifluoroacetic acid

(203) The following compounds were synthesised. All compounds were obtained as TFA salts:

(204) Compound 1

(205) 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)

(206) iVal-APEK(C18DA-gGlu-Ahx)PEADAEPEELQRYYYIALRHYYNWLTRQRY-NH₂ (SEQ ID NO: 5)

(207) MW (calculated): 4792.5 Da

(208) Synthesis and purification methods: S01; P01

(209) LCMS: 010_CA07; Rt: 12.30 min; m/3: 1598.0 m/4: m/5:

(210) Compound 2

(211) 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)

(212) iVal-APEK(C18DA-gGlu-Ahx)PEEDASPEELQRYYYIALRHYYNWLTRQRY-NH₂ (SEQ ID NO: 6)

(213) MW (calculated): 4808.5 Da

(214) Synthesis and purification methods: S01; P01

(215) LCMS: 010_CA07; Rt: 13.07 min; m/3: 1603.8 m/4: m/5:

(216) Compound 3

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

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

(218) iVal-APAK(C18DA-gGlu-Ahx)PEADAEPEELQRYYYVALRHYYNWLTRQRY-NH₂ (SEQ ID NO: 7)

(219) MW (calculated): 4720.4 Da

(220) Synthesis and purification methods: S01; P02

(221) LCMS: 010_CA07; Rt: 11.00 min; m/3: m/4: 1180.9 m/5:

(222) Compound 4

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

(224) iVal-APEK(C18DA-gGlu-Ahx)PEEAAEPEELQRYYYVSLRHYYNWLTRQRY-NH₂ (SEQ

ID NO: 8)
(225) MW (calculated): 4808.5 Da
(226) Synthesis and purification methods: S01; P01
(227) LCMS: 010_CA07; Rt: 12.10 min; m/3: 1604.1 m/4: m/5:
(228) Compound 5
(229) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)[4A,6A,7K,9E,18Q,20Q,22V,28Y,30W,31L]-hPYY(4-36)
(230) iVal-APAK(C18DA-gGlu-Ahx)PEEDASPEELQRQYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 9)
(231) MW (calculated): 4717.4 Da
(232) Synthesis and purification methods: S01; P02
(233) LCMS: 010_CA07; Rt: 9.77 min; m/3: 1572.4 m/4: 1180.2 m/5:
(234) Compound 6
(235) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)
[4A,7K,9E,10A,13E,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)
(236) iVal-APEK(C18DA-gGlu-Ahx)PEADAEPEELQRYYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 10)
(237) MW (calculated): 4778.5 Da
(238) Synthesis and purification methods: S01; P01
(239) LCMS: 010_CA07; Rt: 13.50 min; m/3: 1592.9 m/4: m/5:
(240) Compound 7
(241) 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)
(242) iVal-APEK(C18DA-gGlu-Ahx)PEADATPEEIQRYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 11)
(243) ##STR00003##
(244) MW (calculated): 4766.4 Da
(245) Synthesis and purification methods: S01; P01
(246) LCMS: 010_CA07; Rt: 13.50 min; m/3: m/4: 1192.2 m/5:
(247) Compound 8
(248) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)[4A,7K,9E,12E,13T,18Q,22V,28Y,30W,31L]-hPYY(4-36)
(249) iVal-APEK(C18DA-gGlu-Ahx)PEEDETPEELQRYYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 12)
(250) MW (calculated): 4882.5 Da
(251) Synthesis and purification methods: S01; P02
(252) LCMS: 010_CA07; Rt: 9.94 min; m/3: 1628.0 m/4: 1221.2 m/5:
(253) Compound 9
(254) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)[4A,7K,9E,11Q,13T,18Q,22V,28Y,30W,31L]-hPYY(4-36)
(255) iVal-APEK(C18DA-gGlu-Ahx)PEEQATPEELQRYYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 13)
(256) MW (calculated): 4837.5 Da
(257) Synthesis and purification methods: S01; P01
(258) LCMS: 010_CA07; Rt: 11.52 min; m/3: 1613.3 m/4: m/5:

(259) Compound 10
(260) 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)
(261) iVal-APAK(C18DA-gGlu-Ahx)PEAAAEPEELQRYYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 14)
(262) MW (calculated): 4676.4 Da
(263) Synthesis and purification methods: S01; P02
(264) LCMS: 010_CA07; Rt: 11.46 min; m/3: 1560.1 m/4: 1170.2 m/5:
(265) Compound 11
(266) 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)
(267) iVal-APEK(C18DA-gGlu-Ahx)PEADASPEEIQRYYISLRHYYNWLTRQRY-NH2 (SEQ ID NO: 15)
(268) ##STR00004##
(269) MW (calculated): 4766.4 Da
(270) Synthesis and purification methods: S01; P01
(271) LCMS: 010_CA07; Rt: 10.29 min; m/3: 1589.8 m/4: m/5:
(272) Compound 12
(273) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)[4A,7K,9E,18Q,19Q,22V,28Y,29H,30W,31L]-hPYY(4-36)
(274) iVal-APEK(C18DA-gGlu-Ahx)PEEDASPEELQQYYVSLRHYYHWLTRQRY-NH2 (SEQ ID NO: 16)
(275) MW (calculated): 4805.4 Da
(276) Synthesis and purification methods: S01; P01
(277) LCMS: 010_CA07; Rt: 10.11 min; m/3: 1603.0 m/4: m/5:
(278) Compound 13
(279) 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)
(280) iVal-APEK(C18DA-gGlu-Ahx)PEADASPEETQRYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 17)
(281) MW (calculated): 4740.4 Da
(282) Synthesis and purification methods: S01; P02
(283) LCMS: 010_CA07; Rt: 9.07 min; m/3: 1581.0 m/4: m/5:
(284) Compound 14
(285) 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)
(286) iVal-APEK(C18DA-gGlu-Ahx)PPEDASPEELQRYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 18)
(287) MW (calculated): 4778.5 Da
(288) Synthesis and purification methods: S01; P01
(289) LCMS: 010_CA07; Rt: 9.97 min; m/3: m/4: 1195.0 m/5:
(290) Compound 15
(291) 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)
(292) iVal-APEK(C18DA-gGlu-Ahx)PEEDASPEEIQQYYVSLRHYYNWLTRQRY-NH2 (SEQ

ID NO: 19)
(293) MW (calculated): 4782.4 Da
(294) Synthesis and purification methods: S01; P01
(295) LCMS: 010_CA07; Rt: 10.28 min; m/3: 1595.5 m/4: m/5:
(296) Compound 16
(297) 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)
(298) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQKYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 20)
(299) MW (calculated): 4796.5 Da
(300) Synthesis and purification methods: S01; P01
(301) LCMS: 010_CA07; Rt: 10.32 min; m/3: 1600.5 m/4: m/5:
(302) Compound 17
(303) 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)
(304) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEEIQRYYPSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 21)
(305) MW (calculated): 4822.5 Da
(306) Synthesis and purification methods: S01; P02
(307) LCMS: 010_CA07; Rt: 9.35 min; m/3: 1608.2 m/4: m/5:
(308) Compound 18
(309) 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)
(310) iVal-APEK(C18DA-gGlu-Ahx)PEEDASPEELQRYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 22)
(311) MW (calculated): 4794.5 Da
(312) Synthesis and purification methods: S01; P01
(313) LCMS: 010_CA07; Rt: 10.50 min; m/3: m/4: 1199.4 m/5:
(314) Compound 19
(315) 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)
(316) iVal-APEK(C18DA-gGlu-Ahx)PEEDATEEELQRYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 23)
(317) MW (calculated): 4856.5 Da
(318) Synthesis and purification methods: S01; P02 LCMS: 010_CA07; Rt: 10.92 min; m/3: 1619.1 m/4: 1214.3 m/5:
(319) Compound 20
(320) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)[4A,6A,7K,9E,18Q,21Q,22V,28Y,30W,31L]-hPYY(4-36)
(321) iVal-APAK(C18DA-gGlu-Ahx)PEEDASPEELQRYYQVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 24)
(322) MW (calculated): 4717.4 Da
(323) Synthesis and purification methods: S01; P02
(324) LCMS: 010_CA07; Rt: 9.67 min; m/3: 1572.9 m/4: 1180.1 m/5:
(325) Compound 21

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

(327) iVal-APEK(C18DA-gGlu-Ahx)PEEDAEPEELQRYYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 25)

(328) MW (calculated): 4836.5 Da

(329) Synthesis and purification methods: S01; P01

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

(331) Compound 22

(332) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)[4A,7K,9E,12P,13T,18Q,22V,28Y,30W,31L]-hPYY(4-36)

(333) iVal-APEK(C18DA-gGlu-Ahx)PEEDPTPEELQRYYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 26)

(334) MW (calculated): 4850.5 Da

(335) Synthesis and purification methods: S01; P02

(336) LCMS: 010_CA07; Rt: 9.91 min; m/3: 1616.7 m/4: 1214.2 m/5:

(337) Compound 23

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

(339) iVal-APEK(C18DA-gGlu-Ahx)PEEEASPEELQRYYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 27)

(340) MW (calculated): 4824.5 Da

(341) Synthesis and purification methods: S01; P01

(342) LCMS: 010_CA07; Rt: 10.29 min; m/3: 1610.2 m/4: m/5:

(343) Compound 24

(344) 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)

(345) iVal-APEK(C18DA-gGlu-Ahx)PEEDSSPEELQRYYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 28)

(346) MW (calculated): 4810.5 Da

(347) Synthesis and purification methods: S01; P01

(348) LCMS: 010_CA07; Rt: 10.77 min; m/3: 1603.1 m/4: m/5:

(349) Compound 25

(350) 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)

(351) iVal-APEK(C18DA-gGlu-Ahx)PEADATPEELQRYYYISLRHYYNWLTRQRY-NH2 (SEQ ID NO: 29)

(352) MW (calculated): 4780.5 Da

(353) Synthesis and purification methods: S01; P02

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

(355) Compound 26

(356) 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)

(357) iVal-APAK(C18DA-gGlu-Ahx)PEEDATPEELQRYYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 30)

(358) ##STR00005##
(359) MW (calculated): 4766.4 Da
(360) Synthesis and purification methods: S01; P02
(361) LCMS: 010_CA07; Rt: 10.62 min; m/3: 1590.3 m/4: 1192.1 m/5: 954.2
(362) Compound 27
(363) 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)
(364) iVal-APEK(C18DA-gGlu-Ahx)PEEDAEPEESQRYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 31)
(365) MW (calculated): 4826.4 Da
(366) Synthesis and purification methods: S01; P02
(367) LCMS: 010_CA07; Rt: 9.31 min; m/3: 1609.1 m/4: m/5:
(368) Compound 28
(369) 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)
(370) iVal-APEK(C18DA-gGlu-Ahx)PPEDATPEEIQRYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 32)
(371) MW (calculated): 4792.5 Da
(372) Synthesis and purification methods: S01; P02
(373) LCMS: 010_CA07; Rt: 9.46 min; m/3: m/4: 1198.6 m/5:
(374) Compound 29
(375) 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)
(376) iVal-APEK(C18DA-gGlu-Ahx)PEADSSPEELQRYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 33)
(377) MW (calculated): 4768.4 Da
(378) Synthesis and purification methods: S01; P01
(379) LCMS: 010_CA07; Rt: 10.22 min; m/3: 1589.1 m/4: m/5:
(380) Compound 30
(381) 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)
(382) iVal-APEK(C18DA-gGlu-Ahx)PPADATPEELQRYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 34)
(383) MW (calculated): 4734.4 Da
(384) Synthesis and purification methods: S01; P01
(385) LCMS: 010_CA07; Rt: 10.10 min; m/3: m/4: 1184.1 m/5:
(386) Compound 31
(387) 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)
(388) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQPYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 35)
(389) MW (calculated): 4765.4 Da
(390) Synthesis and purification methods: S01; P01
(391) LCMS: 010_CA07; Rt: 10.82 min; m/3: 1588.5 m/4: m/5:
(392) Compound 32

(393) 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)

(394) iVal-APAK(C18DA-gGlu-Ahx)PEEDASPEELQRYYYVSLRHQYNWLTRQRY-NH2 (SEQ ID NO: 36)

(395) MW (calculated): 4717.4 Da

(396) Synthesis and purification methods: S01; P02

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

(398) Compound 33

(399) 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)

(400) iVal-APAK(C18DA-gGlu-Ahx)PEEDAEPEELQRYYYISLRHYYNWLTRQRY-NH2 (SEQ ID NO: 37)

(401) MW (calculated): 4808.5 Da

(402) Synthesis and purification methods: S01; P02

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

(404) Compound 34

(405) 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)

(406) iVal-APEK(C18DA-gGlu-Ahx)PEEDASAEELQQYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 38)

(407) ##STR00006##

(408) MW (calculated): 4756.4 Da

(409) Synthesis and purification methods: S01; P02

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

(411) Compound 35

(412) 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)

(413) iVal-APAK(C18DA-gGlu-Ahx)PEEAATPEELQRYYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 39)

(414) MW (calculated): 4722.4 Da

(415) Synthesis and purification methods: S01; P01

(416) LCMS: 010_CA07; Rt: 12.03 min; m/3: m/4: 1181.4 m/5:

(417) Compound 36

(418) 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)

(419) iVal-APAK(C18DA-gGlu-Ahx)PEEAATPEEIQRYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 40)

(420) MW (calculated): 4722.4 Da

(421) Synthesis and purification methods: S01; P02

(422) LCMS: 010_CA07; Rt: 10.66 min; m/3: 1574.8 m/4: 1181.9 m/5:

(423) Compound 37

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

(425) iVal-APEK(C18DA-gGlu-Ahx)PEEDAEPEELQRYYTSLRHYYNWLTRQRY-NH2 (SEQ

ID NO: 41)
(426) MW (calculated): 4854.5 Da
(427) Synthesis and purification methods: S01; P01
(428) LCMS: 010_CA07; Rt: 11.90 min; m/3: m/4: 1214.4 m/5:
(429) Compound 38
(430) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)[4A,7K,9E,13T,18Q,19E,22V,28Y,30W,31L]-hPYY(4-36)
(431) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQEYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 42)
(432) MW (calculated): 4797.4 Da
(433) Synthesis and purification methods: S01; P01
(434) LCMS: 010_CA07; Rt: 10.38 min; m/3: 1600.9 m/4: m/5:
(435) Compound 39
(436) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)[4A,7K,9E,16A,18Q,19E,22V,28Y,30W,31L]-hPYY(4-36)
(437) iVal-APEK(C18DA-gGlu-Ahx)PEEDASPEALQEYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 43)
(438) MW (calculated): 4725.3 Da
(439) Synthesis and purification methods: S01; P02
(440) LCMS: 010_CA07; Rt: 10.52 min; m/3: 1575.9 m/4: m/5:
(441) 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)
(442) iVal-APEK(C18DA-gGlu-Ahx)PEADASPEEIQRYYIALRHYYNWLTRQRY-NH2 (SEQ ID NO: 44)
(443) ##STR00007##
(444) MW (calculated): 4750.4 Da
(445) Synthesis and purification methods: S01; P01
(446) LCMS: 010_CA07; Rt: 12.67 min; m/3: 1583.6 m/4: m/5:
(447) Compound 41
(448) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)[4A,7K,9E,13E,18Q,22T,28Y,30W,31L]-hPYY(4-36)
(449) iVal-APEK(C18DA-gGlu-Ahx)PEEDAEPEELQRYYTSLRHYYQWLTRQRY-NH2 (SEQ ID NO: 45)
(450) MW (calculated): 4868.5 Da
(451) Synthesis and purification methods: S01; P02
(452) LCMS: 010_CA07; Rt: 9.93 min; m/3: m/4: 1218.3 m/5:
(453) Compound 42
(454) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)[4A,7K,9E,11P,13T,18Q,22V,28Y,30W,31L]-hPYY(4-36)
(455) iVal-APEK(C18DA-gGlu-Ahx)PEEPATPEELQRYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 46)
(456) MW (calculated): 4806.5 Da
(457) Synthesis and purification methods: S01; P01
(458) LCMS: 010_CA07; Rt: 11.57 min; m/3: 1603.0 m/4: m/5:
(459) Compound 43

(460) 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)

(461) iVal-APAK(C18DA-gGlu-Ahx)PEAAAEPEELQRYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 47)

(462) MW (calculated): 4692.4 Da

(463) Synthesis and purification methods: S01; P02

(464) LCMS: 010_CA07; Rt: 10.98 min; m/3: 1565.0 m/4: m/5:

(465) Compound 44

(466) 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)

(467) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQRYVGLRHYYNWLTRQRY-NH2 (SEQ ID NO: 48)

(468) MW (calculated): 4794.5 Da

(469) Synthesis and purification methods: S01; P02

(470) LCMS: 010_CA07; Rt: 10.20 min; m/3: m/4: 1199.3 m/5:

(471) Compound 45

(472) 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)

(473) iVal-APEK(C18DA-gGlu-Ahx)PEEIATPEELQRYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 49)

(474) MW (calculated): 4822.6 Da

(475) Synthesis and purification methods: S01; P01

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

(477) Compound 46

(478) 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)

(479) iVal-APEK(C18DA-gGlu-Ahx)PEEDAEPEELQRYVASLRHYYNWLTRQRY-NH2 (SEQ ID NO: 50)

(480) MW (calculated): 4824.4 Da

(481) Synthesis and purification methods: S01; P02

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

(483) Compound 47

(484) 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)

(485) iVal-APEK(C18DA-gGlu-Ahx)PPEDASPEEIQRYVVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 51)

(486) MW (calculated): 4762.5 Da

(487) Synthesis and purification methods: S01; P02

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

(489) Compound 48

(490) 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)

(491) iVal-APAK(C18DA-gGlu-Ahx)PEEAATPEELQRYVISLRHYYNWLTRQRY-NH2 (SEQ ID NO: 52)

(492) MW (calculated): 4736.5 Da

(493) Synthesis and purification methods: S01; P01
(494) LCMS: 010_CA07; Rt: 12.10 min; m/3: m/4: 1185.0 m/5:
(495) Compound 49
(496) 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)
(497) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQRYYYVLLRHYYNWLTRQRY-NH2 (SEQ ID NO: 53)
(498) MW (calculated): 4850.6 Da
(499) Synthesis and purification methods: S01; P02
(500) LCMS: 010_CA07; Rt: 10.55 min; m/3: m/4: 1213.1 m/5:
(501) Compound 50
(502) 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)
(503) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEEIQRYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 54)
(504) MW (calculated): 4858.1 Da
(505) Synthesis and purification methods: S01; P02
(506) LCMS: 010_CA07; Rt: 13.00 min; m/3: m/4: 1215.5 m/5:
(507) Compound 51
(508) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,9E,13T,18Q,22V,23Q,28Y,30W,31L]-hPYY(4-36)
(509) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQRYYYVQLRHYYNWLTRQRY-NH2 (SEQ ID NO: 55)
(510) MW (calculated): 4865.5 Da
(511) Synthesis and purification methods: S01; P02
(512) LCMS: 010_CA07; Rt: 9.86 min; m/3: m/4: 1217.2 m/5:
(513) Compound 52
(514) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,9E,17I,18Q,22V,23E,28Y,30W,31L]-hPYY(4-36)
(515) iVal-APEK(C18DA-gGlu-Ahx)PEEDASPEEIQRYYVELRHYYNWLTRQRY-NH2 (SEQ ID NO: 56)
(516) MW (calculated): 4852.5 Da
(517) Synthesis and purification methods: S01; P01
(518) LCMS: 010_CA07; Rt: 10.16 min; m/3: 1619.2 m/4: m/5:
(519) Compound 53
(520) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,9E,13E,17V,18Q,22V,28Y,30W,31L]-hPYY(4-36)
(521) iVal-APEK(C18DA-gGlu-Ahx)PEEDAEPEEVQRYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 57)
(522) MW (calculated): 4838.5 Da
(523) Synthesis and purification methods: S01; P02
(524) LCMS: 010_CA07; Rt: 13.20 min; m/3: 1613.2 m/4: 1210.0 m/5:
(525) Compound 54
(526) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,9E,13T,17A,18Q,22V,28Y,30W,31L]-

hPYY(4-36)
(527) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEEAQRYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 58)
(528) MW (calculated): 4782.4 Da
(529) Synthesis and purification methods: S01; P01
(530) LCMS: 010_CA07; Rt: 9.71 min; m/3: 1594.9 m/4: m/5:
(531) Compound 55
(532) 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)
(533) iVal-APEK(C18DA-gGlu-Ahx)PEEDASEEEIQRYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 59)
(534) MW (calculated): 4842.5 Da
(535) Synthesis and purification methods: S01; P02
(536) LCMS: 010_CA07; Rt: 10.23 min; m/3: 1614.8 m/4: m/5:
(537) Compound 56
(538) 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)
(539) iVal-APEK(C18DA-gGlu-Ahx)PEEDATAEELQRYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 60)
(540) MW (calculated): 4798.4 Da
(541) Synthesis and purification methods: S01; P01
(542) LCMS: 010_CA07; Rt: 11.04 min; m/3: 1600.0 m/4: m/5:
(543) Compound 57
(544) 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)
(545) iVal-APAK(C18DA-gGlu-Ahx)PEEDATPEEAQRYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 61)
(546) MW (calculated): 4724.4 Da
(547) Synthesis and purification methods: S01; P01
(548) LCMS: 010_CA07; Rt: 11.20 min; m/3: m/4: 1182.0 m/5:
(549) Compound 58
(550) 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)
(551) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEEVQRYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 62)
(552) MW (calculated): 4810.5 Da
(553) Synthesis and purification methods: S01; P01
(554) LCMS: 010_CA07; Rt: 9.62 min; m/3: m/4: 1203.4 m/5:
(555) Compound 59
(556) 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)
(557) iVal-APAK(C18DA-gGlu-Ahx)PEEDASPEELQRYVQLRHYYNWLTRQRY-NH2 (SEQ ID NO: 63)
(558) MW (calculated): 4793.5 Da
(559) Synthesis and purification methods: S01; P02

(560) LCMS: 010_CA07; Rt: 9.88 min; m/3: 1598.7 m/4: m/5:
(561) Compound 60
(562) 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)
(563) iVal-APEK(C18DA-gGlu-Ahx)PEEDASPEELQRYYYVSLRHYYQWLTRQRY-NH2 (SEQ ID NO: 64)
(564) MW (calculated): 4824.5 Da
(565) Synthesis and purification methods: S01; P02
(566) LCMS: 010_CA07; Rt: 9.59 min; m/3: 1609.4 m/4: m/5:
(567) Compound 61
(568) 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)
(569) iVal-APEK(C18DA-gGlu-Ahx)PPADASPEEIQRYYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 65)
(570) MW (calculated): 4720.4 Da
(571) Synthesis and purification methods: S01; P01
(572) LCMS: 010_CA07; Rt: 9.70 min; m/3: m/4: 1181.5 m/5:
(573) Compound 62
(574) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,6A,7K,9P,18Q,22V,23E,28Y,30W,31L]-hPYY(4-36)
(575) iVal-APAK(C18DA-gGlu-Ahx)PPEDASPEELQRYYYVELRHYYNWLTRQRY-NH2 (SEQ ID NO: 66)
(576) MW (calculated): 4762.5 Da
(577) Synthesis and purification methods: S01; P01
(578) LCMS: 010_CA07; Rt: 9.43 min; m/3: 1588.6 m/4: m/5:
(579) Compound 63
(580) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,6A,7K,9E,17I,18Q,22V,28Y,30W,31L]-hPYY(4-36)
(581) iVal-APAK(C18DA-gGlu-Ahx)PEEDASPEEIQRYYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 67)
(582) ##STR00008##
(583) MW (calculated): 4752.4 Da
(584) Synthesis and purification methods: S01; P01
(585) LCMS: 010_CA07; Rt: 10.35 min; m/3: 1585.2 m/4: m/5:
(586) Compound 64
(587) 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)
(588) iVal-APEK(C18DA-gGlu-Ahx)PPEDATPEEIQRYYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 68)
(589) MW (calculated): 4776.5 Da
(590) Synthesis and purification methods: S01; P01
(591) LCMS: 010_CA07; Rt: 11.50 min; m/3: m/4: 1194.9 m/5:
(592) Compound 65
(593) 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)
(594) iVal-APAK(C18DA-gGlu-Ahx)PEEDASPEEIQRYYIALRHYYNWLTRQRY-NH2 (SEQ ID NO: 69)
(595) MW (calculated): 4750.4 Da
(596) Synthesis and purification methods: S01; P02
(597) LCMS: 010_CA07; Rt: 10.18 min; m/3: m/4: 1187.8 m/5:
(598) Compound 66
(599) 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)
(600) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQRYYISLRHYYNWLTRQRY-NH2 (SEQ ID NO: 70)
(601) MW (calculated): 4838.5 Da
(602) Synthesis and purification methods: S01; P01
(603) LCMS: 010_CA07; Rt: 13.60 min; m/3: 1613.2 m/4: m/5:
(604) Compound 67
(605) 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)
(606) iVal-APEK(C18DA-gGlu-Ahx)PEEDASPEETQRYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 71)
(607) MW (calculated): 4782.4 Da
(608) Synthesis and purification methods: S01; P01
(609) LCMS: 010_CA07; Rt: 9.86 min; m/3: 1595.1 m/4: m/5:
(610) Compound 68
(611) 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)
(612) iVal-APEK(C18DA-gGlu-Ahx)PEEDAEPEELQRYYVSLRHYYQWLTRQRY-NH2 (SEQ ID NO: 72)
(613) MW (calculated): 4866.5 Da
(614) Synthesis and purification methods: S01; P02
(615) LCMS: 010_CA07; Rt: 10.02 min; m/3: m/4: 1217.4 m/5:
(616) Compound 69
(617) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,9P,10A,17T,18Q,22V,28Y,30W,31L]-hPYY(4-36)
(618) iVal-APEK(C18DA-gGlu-Ahx)PPADASPEETQRYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 73)
(619) MW (calculated): 4708.4 Da
(620) Synthesis and purification methods: S01; P01
(621) LCMS: 010_CA07; Rt: 9.50 min; m/3: m/4: 1178.1 m/5:
(622) Compound 70
(623) 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)
(624) iVal-APAK(C18DA-gGlu-Ahx)PEEDATPEELQRYYIALRHYYNWLTRQRY-NH2 (SEQ ID NO: 74)
(625) MW (calculated): 4764.5 Da
(626) Synthesis and purification methods: S01; P02

(627) LCMS: 010_CA07; Rt: 10.55 min; m/3: m/4: 1192.4 m/5:
(628) Compound 71
(629) 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)
(630) iVal-APAK(C18DA-gGlu-Ahx)PEEDAEPEELQRYYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 75)
(631) MW (calculated): 4778.5 Da
(632) Synthesis and purification methods: S01; P02
(633) LCMS: 010_CA07; Rt: 13.10 min; m/3: m/4: 1196.0 m/5:
(634) Compound 72
(635) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,9E,10A,13E,18Q,22V,28Y,30W,31L]-hPYY(4-36)
(636) iVal-APEK(C18DA-gGlu-Ahx)PEADAEPEELQRYYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 76)
(637) MW (calculated): 4794.5 Da
(638) Synthesis and purification methods: S01; P01
(639) LCMS: 010_CA07; Rt: 10.71 min; m/3: 1598.4 m/4: m/5:
(640) Compound 73
(641) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,9E,11A,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)
(642) iVal-APEK(C18DA-gGlu-Ahx)PEEAASPEELQRYYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 77)
(643) MW (calculated): 4750.4 Da
(644) Synthesis and purification methods: S01; P01
(645) LCMS: 010_CA07; Rt: 13.24 min; m/3: 1584.1 m/4: m/5:
(646) Compound 74
(647) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,9E,13T,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)
(648) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQRYYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 78)
(649) MW (calculated): 4808.5 Da
(650) Synthesis and purification methods: S01; P01
(651) LCMS: 010_CA07; Rt: 13.70 min; m/3: m/4: 1203.1 m/5:
(652) Compound 75
(653) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,9E,13P,17I,18Q,22V,28Y,30W,31L]-hPYY(4-36)
(654) iVal-APEK(C18DA-gGlu-Ahx)PEEDAPPEEIQRYYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 79)
(655) MW (calculated): 4820.5 Da
(656) Synthesis and purification methods: S01; P01
(657) LCMS: 010_CA07; Rt: 10.30 min; m/3: m/4: 1207.1 m/5:
(658) Compound 76
(659) 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)
(660) iVal-APEK(C18DA-gGlu-Ahx)PEEDASPEELQRYYYISLRHYYNWLTRQRY-NH2 (SEQ ID

NO: 80)

(661) MW (calculated): 4824.5 Da

(662) Synthesis and purification methods: S01; P01

(663) LCMS: U046_001; Rt: 11.60 min; m/3: 1609.0 m/4: m/5:

(664) Compound 77

(665) 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)

(666) iVal-APAK(C18DA-gGlu-Ahx)PEEDASPEELQRYYYVSLRHYQNLTRQRY-NH2 (SEQ ID NO: 81)

(667) MW (calculated): 4717.4 Da

(668) Synthesis and purification methods: S01; P02

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

(670) Compound 78

(671) 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)

(672) iVal-APAK(C18DA-gGlu-Ahx)PEEDASPEELQRYYYVSLRHYQWLTRQRY-NH2 (SEQ ID NO: 82)

(673) MW (calculated): 4766.4 Da

(674) Synthesis and purification methods: S01; P01

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

(676) Compound 79

(677) 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)

(678) iVal-APEK(C18DA-gGlu-Ahx)PEEDASPEELQRYYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 83)

(679) MW (calculated): 4810.5 Da

(680) Synthesis and purification methods: S01; P02

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

(682) Compound 80

(683) 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)

(684) iVal-APEK(C18DA-gGlu-Ahx)PEEDASEAELQRYYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 84)

(685) MW (calculated): 4784.4 Da

(686) Synthesis and purification methods: S01; P02

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

(688) Compound 81

(689) 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)

(690) iVal-APEK(C18DA-gGlu-Ahx)PEEDAQP EEIQRYYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 85)

(691) MW (calculated): 4851.5 Da

(692) Synthesis and purification methods: S01; P02

(693) LCMS: 010_CA07; Rt: 9.87 min; m/3: 1618.2 m/4: 1214.5 m/5:

(694) Compound 82

(695) 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)

(696) iVal-APAK(C18DA-gGlu-Ahx)PPEDASPEEIQRYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 86)

(697) MW (calculated): 4720.4 Da

(698) Synthesis and purification methods: S01; P01

(699) LCMS: 010_CA07; Rt: 9.36 min; m/3: 1574.2 m/4: m/5:

(700) Compound 83

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

(702) iVal-APEK(C18DA-gGlu-Ahx)PEEDATSEELQRYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 87)

(703) MW (calculated): 4814.4 Da

(704) Synthesis and purification methods: S01; P02

(705) LCMS: 010_CA07; Rt: 10.69 min; m/3: 1605.0 m/4: 1204.4 m/5:

(706) Compound 84

(707) 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)

(708) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEEIQRYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 88)

(709) ##STR00009##

(710) MW (calculated): 4808.5 Da

(711) Synthesis and purification methods: S01; P01

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

(713) Compound 85

(714) 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)

(715) iVal-APAK(C18DA-gGlu-Ahx)PEEDASPEETQRYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 89)

(716) MW (calculated): 4740.4 Da

(717) Synthesis and purification methods: S01; P02

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

(719) Compound 86

(720) 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)

(721) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEEIQRYYASLRHYYNWLTRQRY-NH2 (SEQ ID NO: 90)

(722) MW (calculated): 4796.4 Da

(723) Synthesis and purification methods: S01; P02

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

(725) Compound 87

(726) 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)

(727) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQRYYVPLRHYYNWLTRQRY-NH2 (SEQ ID NO: 91)

(728) MW (calculated): 4834.5 Da
(729) Synthesis and purification methods: S01; P02
(730) LCMS: 010_CA07; Rt: 10.25 min; m/3: m/4: 1209.3 m/5:
(731) Compound 88
(732) 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)
(733) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQRQYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 92)
(734) MW (calculated): 4789.4 Da
(735) Synthesis and purification methods: S01; P01
(736) LCMS: 010_CA07; Rt: 9.60 min; m/3: 1596.6 m/4: m/5:
(737) Compound 89
(738) 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)
(739) iVal-APAK(C18DA-gGlu-Ahx)PPEDASPEELQRYYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 93)
(740) MW (calculated): 4704.4 Da
(741) Synthesis and purification methods: S01; P01
(742) LCMS: 010_CA07; Rt: 12.20 min; m/3: 1568.4 m/4: m/5:
(743) Compound 90
(744) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,9E,13T,18Q,22V,23V,28Y,30W,31L]-hPYY(4-36)
(745) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQRYYYVVL RHYYNWLTRQRY-NH2 (SEQ ID NO: 94)
(746) MW (calculated): 4836.5 Da
(747) Synthesis and purification methods: S01; P02
(748) LCMS: 010_CA07; Rt: 10.76 min; m/3: m/4: 1209.9 m/5:
(749) Compound 91
(750) 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)
(751) iVal-APEK(C18DA-gGlu-Ahx)PEEDAEPEELQRYYTSLRHYYHWLTRQRY-NH2 (SEQ ID NO: 95)
(752) MW (calculated): 4877.5 Da
(753) Synthesis and purification methods: S01; P01
(754) LCMS: 010_CA07; Rt: 10.22 min; m/3: 1628.8 m/4: m/5:
(755) Compound 92
(756) 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)
(757) iVal-APEK(C18DA-gGlu-Ahx)PGEDASPEELQRYYISLRHYYNWLTRQRY-NH2 (SEQ ID NO: 96)
(758) MW (calculated): 4752.4 Da
(759) Synthesis and purification methods: S01; P02
(760) LCMS: 010_CA07; Rt: 10.75 min; m/3: 1585.3 m/4: 1188.4 m/5:
(761) Compound 93
(762) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,9E,17I,18Q,22V,23Q,28Y,30W,31L]-

hPYY(4-36)
(763) iVal-APEK(C18DA-gGlu-Ahx)PEEDASPEEIQRYYVQLRHYYNWLTRQRY-NH2 (SEQ ID NO: 97)
(764) MW (calculated): 4851.5 Da
(765) Synthesis and purification methods: S01; P02
(766) LCMS: 010_CA07; Rt: 9.64 min; m/3: m/4: 1213.4 m/5:
(767) Compound 94
(768) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,6A,7K,9E,10A,18Q,22V,23E,28Y,30W,31L]-hPYY(4-36)
(769) iVal-APAK(C18DA-gGlu-Ahx)PEADASPEELQRYYVELRHYYNWLTRQRY-NH2 (SEQ ID NO: 98)
(770) MW (calculated): 4736.4 Da
(771) Synthesis and purification methods: S01; P01
(772) LCMS: 010_CA07; Rt: 10.07 min; m/3: 1578.9 m/4: m/5:
(773) Compound 95
(774) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,9E,13T,18Q,19A,22V,28Y,30W,31L]-hPYY(4-36)
(775) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQAYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 99)
(776) MW (calculated): 4739.4 Da
(777) Synthesis and purification methods: S01; P01
(778) LCMS: 010_CA07; Rt: 13.31 min; m/3: 1579.5 m/4: m/5:
(779) Compound 96
(780) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,9E,11S,13T,18Q,22V,28Y,30W,31L]-hPYY(4-36)
(781) iVal-APEK(C18DA-gGlu-Ahx)PEESATPEELQRYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 100)
(782) MW (calculated): 4796.5 Da
(783) Synthesis and purification methods: S01; P01
(784) LCMS: 010_CA07; Rt: 9.90 min; m/3: 1599.4 m/4: m/5:
(785) Compound 97
(786) 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)
(787) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEEIQRYYLSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 101)
(788) MW (calculated): 4838.5 Da
(789) Synthesis and purification methods: S01; P02
(790) LCMS: 010_CA07; Rt: 9.88 min; m/3: 1613.3 m/4: m/5:
(791) Compound 98
(792) 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)
(793) iVal-APEK(C18DA-gGlu-Ahx)PEADATPEEIQRYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 102)
(794) MW (calculated): 4816.1 Da
(795) Synthesis and purification methods: S01; P02

(796) LCMS: 010_CA07; Rt: 13.35 min; m/3: 1606.6 m/4: m/5:
(797) Compound 99
(798) 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)
(799) iVal-APAK(C18DA-gGlu-Ahx)PEEDATPEEIQRYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 103)
(800) ##STR00010##
(801) MW (calculated): 4750.4 Da
(802) Synthesis and purification methods: S01; P01
(803) LCMS: 010_CA07; Rt: 11.90 min; m/3: m/4: 1188.5 m/5:
(804) Compound 100
(805) 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)
(806) iVal-APEK(C18DA-gGlu-Ahx)PEADATPEELQRYYIALRHYYNWLTRQRY-NH2 (SEQ ID NO: 104)
(807) MW (calculated): 4764.5 Da
(808) Synthesis and purification methods: S01; P01
(809) LCMS: 010_CA07; Rt: 12.10 min; m/3: m/4: 1192.2 m/5:
(810) Compound 101
(811) 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)
(812) iVal-APAK(C18DA-gGlu-Ahx)PEEDATPEELQRYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 105)
(813) MW (calculated): 4750.4 Da
(814) Synthesis and purification methods: S01; P02
(815) LCMS: 010_CA07; Rt: 12.28 min; m/3: m/4: 1188.8 m/5:
(816) Compound 102
(817) 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)
(818) iVal-APEK(C18DA-gGlu-Ahx)PEEDATLEELQRYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 106)
(819) MW (calculated): 4840.5 Da
(820) Synthesis and purification methods: S01; P02
(821) LCMS: 010_CA07; Rt: 11.96 min; m/3: 1613.9 m/4: 1210.9 m/5:
(822) Compound 103
(823) 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)
(824) iVal-APEK(C18DA-gGlu-Ahx)PEEDASAEELQRYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 107)
(825) MW (calculated): 4768.4 Da
(826) Synthesis and purification methods: S01; P02
(827) LCMS: 010_CA07; Rt: 10.95 min; m/3: 1590.9 m/4: 1193.5 m/5:
(828) Compound 104
(829) 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)
(830) iVal-APEK(C18DA-gGlu-Ahx)PEEDAEPEEAQRYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 108)
(831) MW (calculated): 4882.5 Da
(832) Synthesis and purification methods: S01; P01
(833) LCMS: 010_CA07; Rt: 12.00 min; m/3: m/4: 1221.8 m/5:
(834) Compound 105
(835) 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)
(836) iVal-APEK(C18DA-gGlu-Ahx)PEEDATQEELQRYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 109)
(837) MW (calculated): 4855.5 Da
(838) Synthesis and purification methods: S01; P02
(839) LCMS: 010_CA07; Rt: 10.63 min; m/3: 1618.4 m/4: 1215.2 m/5:
(840) Compound 106
(841) 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)
(842) iVal-APAK(C18DA-gGlu-Ahx)PEEDASPEELQRYVVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 110)
(843) MW (calculated): 4736.4 Da
(844) Synthesis and purification methods: S01; P01
(845) LCMS: 010_CA07; Rt: 10.50 min; m/3: m/4: 1185.0 m/5:
(846) Compound 107
(847) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,9E,13E,17T,18Q,22V,28Y,30W,31L]-hPYY(4-36)
(848) iVal-APEK(C18DA-gGlu-Ahx)PEEDAEPEETQRYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 111)
(849) MW (calculated): 4840.4 Da
(850) Synthesis and purification methods: S01; P01
(851) LCMS: 010_CA07; Rt: 11.30 min; m/3: 1614.3 m/4: m/5:
(852) Compound 108
(853) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,9E,10A,14E,18Q,22V,28Y,30W,31L]-hPYY(4-36)
(854) iVal-APEK(C18DA-gGlu-Ahx)PEADASEEELQRYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 112)
(855) MW (calculated): 4784.4 Da
(856) Synthesis and purification methods: S01; P02
(857) LCMS: 010_CA07; Rt: 10.71 min; m/3: 1595.5 m/4: 1196.7 m/5:
(858) Compound 109
(859) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,9E,12L,13T,18Q,22V,28Y,30W,31L]-hPYY(4-36)
(860) iVal-APEK(C18DA-gGlu-Ahx)PEEDLTPEELQRYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 113)
(861) MW (calculated): 4866.6 Da
(862) Synthesis and purification methods: 501; P02

(863) LCMS: 010_CA07; Rt: 10.14 min; m/3: 1623.2 m/4: 1216.9 m/5:
(864) Compound 110
(865) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,9E,13T,18Q,22V,23E,28Y,30W,31L]-hPYY(4-36)
(866) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQRYYYVELRHYYNWLTRQRY-NH2 (SEQ ID NO: 114)
(867) MW (calculated): 4866.5 Da
(868) Synthesis and purification methods: S01; P02
(869) LCMS: 010_CA07; Rt: 10.31 min; m/3: 1622.9 m/4: m/5:
(870) Compound 111
(871) 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)
(872) iVal-APAK(C18DA-gGlu-Ahx)PEAAAEPEEIQRYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 115)
(873) MW (calculated): 4692.4 Da
(874) Synthesis and purification methods: S01; P02
(875) LCMS: 010_CA07; Rt: 11.12 min; m/3: 1564.1 m/4: 1173.3 m/5:
(876) Compound 112
(877) 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)
(878) iVal-APEK(C18DA-gGlu-Ahx)PEEDAEPEEIQRYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 116)
(879) MW (calculated): 4852.5 Da
(880) Synthesis and purification methods: S01; P02
(881) LCMS: 010_CA07; Rt: 9.97 min; m/3: m/4: 1214.4 m/5:
(882) Compound 113
(883) 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)
(884) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEEIQRYYVSLRHYYQNLTRQRY-NH2 (SEQ ID NO: 117)
(885) MW (calculated): 4789.4 Da
(886) Synthesis and purification methods: S01; P01
(887) LCMS: 010_CA07; Rt: 9.23 min; m/3: 1596.7 m/4: m/5:
(888) Compound 114
(889) 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)
(890) iVal-APAK(C18DA-gGlu-Ahx)PEEDATPEEIQRYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 118)
(891) ##STR00011##
(892) MW (calculated): 4766.4 Da
(893) Synthesis and purification methods: S01; P01
(894) LCMS: 010_CA07; Rt: 11.70 min; m/3: m/4: 1192.4 m/5:
(895) Compound 115
(896) 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)
(897) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQRYQVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 119)
(898) MW (calculated): 4789.4 Da
(899) Synthesis and purification methods: S01; P01
(900) LCMS: 010_CA07; Rt: 11.17 min; m/3: 1597.3 m/4: m/5:
(901) Compound 116
(902) 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)
(903) iVal-APAK(C18DA-gGlu-Ahx)PEAAAEPEEIQRYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 120)
(904) MW (calculated): 4676.4 Da
(905) Synthesis and purification methods: S01; P02
(906) LCMS: 010_CA07; Rt: 11.62 min; m/3: 1559.2 m/4: m/5:
(907) Compound 117
(908) 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)
(909) iVal-APEK(C18DA-gGlu-Ahx)PEEDASPEEAQRYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 121)
(910) MW (calculated): 4752.4 Da
(911) Synthesis and purification methods: S01; P01
(912) LCMS: 010_CA07; Rt: 12.53 min; m/3: 1584.9 m/4: m/5:
(913) Compound 118
(914) 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)
(915) iVal-APEK(C18DA-gGlu-Ahx)PPEDAEPEEIQRYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 122)
(916) ##STR00012##
(917) MW (calculated): 4820.5 Da
(918) Synthesis and purification methods: S01; P02
(919) LCMS: 010_CA07; Rt: 9.86 min; m/3: 1607.4 m/4: m/5:
(920) Compound 119
(921) 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)
(922) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEESQRYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 123)
(923) MW (calculated): 4798.4 Da
(924) Synthesis and purification methods: S01; P01
(925) LCMS: 010_CA07; Rt: 10.92 min; m/3: 1600.3 m/4: m/5:
(926) Compound 120
(927) 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)
(928) iVal-APAK(C18DA-gGlu-Ahx)PEEAATPEEIQRYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 124)
(929) MW (calculated): 4706.4 Da

(930) Synthesis and purification methods: S01; P02
(931) LCMS: 010_CA07; Rt: 11.28 min; m/3: m/4: 1177.1 m/5:
(932) Compound 121
(933) 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)
(934) iVal-APEK(C18DA-gGlu-Ahx)PEADASPEELQRYYYVQLRHYYNWLTRQRY-NH2 (SEQ ID NO: 125)
(935) MW (calculated): 4793.5 Da
(936) Synthesis and purification methods: S01; P02
(937) LCMS: 010_CA07; Rt: 9.78 min; m/3: m/4: 1199.3 m/5:
(938) Compound 122
(939) 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)
(940) iVal-APEK(C18DA-gGlu-Ahx)PEAEASPEELQRYYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 126)
(941) ##STR00013##
(942) MW (calculated): 4766.4 Da
(943) Synthesis and purification methods: S01; P01
(944) LCMS: 010_CA07; Rt: 12.40 min; m/3: 1589.2 m/4: m/5:
(945) Compound 123
(946) 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)
(947) iVal-APEK(C18DA-gGlu-Ahx)PEEDAAPEELQKYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 127)
(948) MW (calculated): 4766.4 Da
(949) Synthesis and purification methods: S01; P02
(950) LCMS: 010_CA07; Rt: 10.65 min; m/3: m/4: 1192.1 m/5:
(951) Compound 124
(952) 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)
(953) iVal-APEK(C18DA-gGlu-Ahx)PEAAAPEEIQRYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 128)
(954) MW (calculated): 4750.4 Da
(955) Synthesis and purification methods: S01; P02
(956) LCMS: 010_CA07; Rt: 10.74 min; m/3: 1583.7 m/4: m/5:
(957) Compound 125
(958) 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)
(959) iVal-APEK(C18DA-gGlu-Ahx)PEEDASPEELQRYYYVELRHYYNWLTRQRY-NH2 (SEQ ID NO: 129)
(960) MW (calculated): 4852.5 Da
(961) Synthesis and purification methods: S01; P01
(962) LCMS: 010_CA07; Rt: 9.93 min; m/3: 1618.3 m/4: m/5:
(963) Compound 126
(964) 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)

(965) iVal-APEK(C18DA-gGlu-Ahx)PEEDAEPEELQRYYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 130)

(966) MW (calculated): 4852.5 Da

(967) Synthesis and purification methods: S01; P01

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

(969) Compound 127

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

(971) iVal-APEK(C18DA-gGlu-Ahx)PEAAAEPEELQRYYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 131)

(972) MW (calculated): 4734.4 Da

(973) Synthesis and purification methods: 501; P02

(974) LCMS: 010_CA07; Rt: 10.99 min; m/3: m/4: 1184.2 m/5:

(975) Compound 128

(976) 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)

(977) iVal-APEK(C18DA-gGlu-Ahx)PEEAATPEELQRYYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 132)

(978) MW (calculated): 4780.5 Da

(979) Synthesis and purification methods: S01; P01

(980) LCMS: 010_CA07; Rt: 13.70 min; m/3: 1594.6 m/4: m/5:

(981) Compound 129

(982) 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)

(983) iVal-APEK(C18DA-gGlu-Ahx)PEEDASAEIQRYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 133)

(984) MW (calculated): 4784.4 Da

(985) Synthesis and purification methods: S01; P02

(986) LCMS: 010_CA07; Rt: 10.37 min; m/3: m/4: 1197.0 m/5:

(987) Compound 130

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

(989) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQLYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 134)

(990) MW (calculated): 4781.5 Da

(991) Synthesis and purification methods: S01; P01

(992) LCMS: 010_CA07; Rt: 10.67 min; m/3: 1595.1 m/4: m/5:

(993) Compound 131

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

(995) iVal-APEK(C18DA-gGlu-Ahx)PEADAPEEIQRYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 135)

(996) MW (calculated): 4778.5 Da

(997) Synthesis and purification methods: S01; P02
(998) LCMS: 010_CA07; Rt: 10.83 min; m/3: m/4: 1195.0 m/5:
(999) Compound 132
(1000) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,9E,10A,13T,18Q,22V,28Y,30W,31L]-hPYY(4-36)
(1001) iVal-APEK(C18DA-gGlu-Ahx)PEADATPEELQRYYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 136)
(1002) MW (calculated): 4766.4 Da
(1003) Synthesis and purification methods: S01; P02
(1004) LCMS: 010_CA07; Rt: 9.74 min; m/3: 1589.6 m/4: m/5:
(1005) Compound 133
(1006) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,6A,7K,9E,13E,18Q,22V,28Y,30W,31L]-hPYY(4-36)
(1007) iVal-APAK(C18DA-gGlu-Ahx)PEEDAEPEELQRYYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 137)
(1008) MW (calculated): 4794.5 Da
(1009) Synthesis and purification methods: 501; P02
(1010) LCMS: 010_CA07; Rt: 10.12 min; m/3: 1598.3 m/4: m/5:
(1011) Compound 134
(1012) 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)
(1013) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEEQRYYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 138)
(1014) MW (calculated): 4839.5 Da
(1015) Synthesis and purification methods: S01; P01
(1016) LCMS: 010_CA07; Rt: 9.04 min; m/3: 1613.8 m/4: m/5:
(1017) Compound 135
(1018) 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)
(1019) iVal-APEK(C18DA-gGlu-Ahx)PEAAAEPEEIQRYYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 139)
(1020) MW (calculated): 4734.4 Da
(1021) Synthesis and purification methods: S01; P02
(1022) LCMS: 010_CA07; Rt: 11.45 min; m/3: m/4: 1184.2 m/5:
(1023) Compound 136
(1024) 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)
(1025) iVal-APEK(C18DA-gGlu-Ahx)PEADATPEELQRYYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 140)
(1026) ##STR00014##
(1027) MW (calculated): 4750.4 Da
(1028) Synthesis and purification methods: 501; P01
(1029) LCMS: 010_CA07; Rt: 13.80 min; m/3: 1584.4 m/4: m/5:
(1030) Compound 137
(1031) 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)

(1032) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQRYYYVSLRHYYNWLLRQRY-NH2 (SEQ ID NO: 141)

(1033) MW (calculated): 4836.5 Da

(1034) Synthesis and purification methods: S01; P01

(1035) LCMS: 010_CA07; Rt: 11.13 min; m/3: 1558.4 m/4: m/5:

(1036) Compound 138

(1037) 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)

(1038) iVal-APEK(C18DA-gGlu-Ahx)PEEDAEPEELQEYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 142)

(1039) MW (calculated): 4825.4 Da

(1040) Synthesis and purification methods: S01; P02

(1041) LCMS: 010_CA07; Rt: 13.90 min; m/3: 1609.1 m/4: 1206.7 m/5:

(1042) Compound 139

(1043) 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)

(1044) iVal-APEK(C18DA-gGlu-Ahx)PEEEASPAELQRYYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 143)

(1045) MW (calculated): 4766.4 Da

(1046) Synthesis and purification methods: S01; P02

(1047) LCMS: 010_CA07; Rt: 10.01 min; m/3: 1589.4 m/4: 1191.8 m/5:

(1048) Compound 140

(1049) 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)

(1050) iVal-APEK(C18DA-gGlu-Ahx)PEADASPEEIQRYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 144)

(1051) MW (calculated): 4752.4 Da

(1052) Synthesis and purification methods: S01; P01

(1053) LCMS: 010_CA07; Rt: 10.21 min; m/3: 1585.1 m/4: m/5:

(1054) Compound 141

(1055) 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)

(1056) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQSYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 145)

(1057) MW (calculated): 4755.4 Da

(1058) Synthesis and purification methods: S01; P01

(1059) LCMS: 010_CA07; Rt: 10.40 min; m/3: 1586.6 m/4: m/5:

(1060) Compound 142

(1061) 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)

(1062) iVal-APEK(C18DA-gGlu-Ahx)PEEDALPEEIQRYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 146)

(1063) MW (calculated): 4836.5 Da

(1064) Synthesis and purification methods: S01; P02
(1065) LCMS: 010_CA07; Rt: 12.05 min; m/3: 1613.6 m/4: 1210.2 m/5:
(1066) Compound 143
(1067) 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)
(1068) iVal-APEK(C18DA-gGlu-Ahx)PEEDSTPEELQRYYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 147)
(1069) MW (calculated): 4840.5 Da
(1070) Synthesis and purification methods: S01; P01
(1071) LCMS: 010_CA07; Rt: 11.81 min; m/3: 1614.3 m/4: m/5:
(1072) Compound 144
(1073) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,9E,12Q,13T,18Q,22V,28Y,30W,31L]-hPYY(4-36)
(1074) iVal-APEK(C18DA-gGlu-Ahx)PEEDQTPEELQRYYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 148)
(1075) MW (calculated): 4881.5 Da
(1076) Synthesis and purification methods: S01; P02
(1077) LCMS: 010_CA07; Rt: 9.95 min; m/3: 1628.4 m/4: 1221.3 m/5:
(1078) Compound 145
(1079) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,6A,7K,9E,18Q,22V,28Y,30W,31L]-hPYY(4-36)
(1080) iVal-APAK(C18DA-gGlu-Ahx)PEEDASPEELQRYYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 149)
(1081) MW (calculated): 4752.4 Da
(1082) Synthesis and purification methods: S01; P02
(1083) LCMS: 010_CA07; Rt: 10.37 min; m/3: 1586.0 m/4: m/5:
(1084) Compound 146
(1085) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,9E,11E,13T,18Q,22V,28Y,30W,31L]-hPYY(4-36)
(1086) iVal-APEK(C18DA-gGlu-Ahx)PEEEATPEELQRYYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 150)
(1087) ##STR00015##
(1088) MW (calculated): 4838.5 Da
(1089) Synthesis and purification methods: S01; P01
(1090) LCMS: 010_CA07; Rt: 10.57 min; m/3: 1614.2 m/4: m/5:
(1091) Compound 147
(1092) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,9E,17I,18Q,22V,28Y,30W,31L]-hPYY(4-36)
(1093) iVal-APEK(C18DA-gGlu-Ahx)PEEDASPEEIQRYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 151)
(1094) MW (calculated): 4810.5 Da
(1095) Synthesis and purification methods: S01; P01
(1096) LCMS: 010_CA07; Rt: 10.02 min; m/3: 1603.9 m/4: m/5:
(1097) Compound 148
(1098) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-

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

(1099) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQRYYYVTLRHYYNWLTRQRY-NH2 (SEQ ID NO: 152)

(1100) MW (calculated): 4838.5 Da

(1101) Synthesis and purification methods: S01; P01

(1102) LCMS: 010_CA07; Rt: 11.80 min; m/3: m/4: 1210.5 m/5:

(1103) Compound 149

(1104) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,6A,7K,9E,17S,18Q,22V,28Y,30W,31L]-hPYY(4-36)

(1105) iVal-APAK(C18DA-gGlu-Ahx)PEEDASPEESQRYYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 153)

(1106) MW (calculated): 4726.3 Da

(1107) Synthesis and purification methods: S01; P02

(1108) LCMS: 010_CA07; Rt: 9.28 min; m/3: m/4: 1182.3 m/5:

(1109) Compound 150

(1110) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,9E,11A,17I,18Q,22V,28Y,30W,31L]-hPYY(4-36)

(1111) iVal-APEK(C18DA-gGlu-Ahx)PEEAASPEEIQRYYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 154)

(1112) ##STR00016##

(1113) MW (calculated): 4766.4 Da

(1114) Synthesis and purification methods: S01; P01

(1115) LCMS: 010_CA07; Rt: 12.30 min; m/3: 1590.6 m/4: m/5:

(1116) Compound 151

(1117) 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)

(1118) iVal-APEK(C18DA-gGlu-Ahx)PEEDSSPEELQRYYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 155)

(1119) MW (calculated): 4810.5 Da

(1120) Synthesis and purification methods: S01; P01

(1121) LCMS: 010_CA07; Rt: 10.05 min; m/3: 1603.5 m/4: m/5:

(1122) Compound 152

(1123) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,9E,13T,17T,18Q,22V,28Y,30W,31L]-hPYY(4-36)

(1124) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEETQRYYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 156)

(1125) MW (calculated): 4812.4 Da

(1126) Synthesis and purification methods: S01; P01

(1127) LCMS: 010_CA07; Rt: 10.96 min; m/3: m/4: 1204.0 m/5:

(1128) Compound 153

(1129) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,9E,11L,13T,18Q,22V,28Y,30W,31L]-hPYY(4-36)

(1130) iVal-APEK(C18DA-gGlu-Ahx)PEELATPEELQRYYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 157)

(1131) MW (calculated): 4822.6 Da
(1132) Synthesis and purification methods: S01; P01
(1133) LCMS: 010_CA07; Rt: 10.90 min; m/3: m/4: 1206.5 m/5:
(1134) Compound 154
(1135) 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)
(1136) iVal-APEK(C18DA-gGlu-Ahx)PEEAATPEEIQRYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 158)
(1137) MW (calculated): 4764.5 Da
(1138) Synthesis and purification methods: S01; P02
(1139) LCMS: 010_CA07; Rt: 10.68 min; m/3: 1588.4 m/4: m/5:
(1140) Compound 155
(1141) 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)
(1142) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQRYYVSLRHYYNWL SRQRY-NH2 (SEQ ID NO: 159)
(1143) MW (calculated): 4810.5 Da
(1144) Synthesis and purification methods: S01; P01
(1145) LCMS: 010_CA07; Rt: 11.33 min; m/3: 1604.2 m/4: m/5:
(1146) Compound 156
(1147) 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)
(1148) iVal-APEK(C18DA-gGlu-Ahx)PEEAAEPEEIQRYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 160)
(1149) MW (calculated): 4792.5 Da
(1150) Synthesis and purification methods: S01; P02
(1151) LCMS: 010_CA07; Rt: 10.99 min; m/3: 1598.2 m/4: 1199.1 m/5:
(1152) Compound 157
(1153) 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)
(1154) iVal-APAK(C18DA-gGlu-Ahx)PEEAA SPEELQRYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 161)
(1155) MW (calculated): 4692.4 Da
(1156) Synthesis and purification methods: S01; P01
(1157) LCMS: 010_CA07; Rt: 13.45 min; m/3: 1564.3 m/4: m/5:
(1158) Compound 158
(1159) 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)
(1160) iVal-APEK(C18DA-gGlu-Ahx)PPEAASPEEIQRYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 162)
(1161) MW (calculated): 4718.4 Da
(1162) Synthesis and purification methods: S01; P01
(1163) LCMS: 010_CA07; Rt: 13.11 min; m/3: 1574.2 m/4: m/5:
(1164) Compound 159
(1165) 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)

(1166) iVal-APEK(C18DA-gGlu-Ahx)PEADAEPEELQRYYYISLRHYYNWLTRQRY-NH2 (SEQ ID NO: 163)

(1167) MW (calculated): 4808.5 Da

(1168) Synthesis and purification methods: S01; P02

(1169) LCMS: 010_CA07; Rt: 10.63 min; m/3: m/4: 1203.2 m/5:

(1170) Compound 160

(1171) 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)

(1172) iVal-APAK(C18DA-gGlu-Ahx)PEEDASPEELQRYYYIALRHYYNWLTRQRY-NH2 (SEQ ID NO: 164)

(1173) MW (calculated): 4750.4 Da

(1174) Synthesis and purification methods: 501; P02

(1175) LCMS: 010_CA07; Rt: 13.49 min; m/3: m/4: 1188.2 m/5:

(1176) Compound 161

(1177) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,6A,7K,9E,11A,13E,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)

(1178) iVal-APAK(C18DA-gGlu-Ahx)PEEAAEPEELQRYYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 165)

(1179) MW (calculated): 4734.4 Da

(1180) Synthesis and purification methods: S01; P02

(1181) LCMS: 010_CA07; Rt: 11.00 min; m/3: m/4: 1184.0 m/5:

(1182) Compound 162

(1183) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,9E,13T,17E,18Q,22V,28Y,30W,31L]-hPYY(4-36)

(1184) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEEEQRYYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 166)

(1185) MW (calculated): 4840.4 Da

(1186) Synthesis and purification methods: S01; P02

(1187) LCMS: 010_CA07; Rt: 9.20 min; m/3: m/4: 1211.0 m/5:

(1188) Compound 163

(1189) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,9E,10A,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)

(1190) iVal-APEK(C18DA-gGlu-Ahx)PEADASPEELQRYYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 167)

(1191) ##STR00017##

(1192) MW (calculated): 4736.4 Da

(1193) Synthesis and purification methods: 501; P01

(1194) LCMS: 010_CA07; Rt: 12.30 min; m/3: m/4: 1184.5 m/5:

(1195) Compound 164

(1196) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,9E,13T,17I,18Q,22Q,28Y,30W,31L]-hPYY(4-36)

(1197) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEEIQRYYYQSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 168)

(1198) MW (calculated): 4853.5 Da
(1199) Synthesis and purification methods: S01; P01
(1200) LCMS: 010_CA07; Rt: 11.44 min; m/3: 1618.6 m/4: m/5:
(1201) Compound 165
(1202) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,6A,7K,9P,13E,18Q,22V,28Y,30W,31L]-hPYY(4-36)
(1203) iVal-APAK(C18DA-gGlu-Ahx)PPEDAEPEELQRYYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 169)
(1204) MW (calculated): 4762.5 Da
(1205) Synthesis and purification methods: S01; P01
(1206) LCMS: 010_CA07; Rt: 10.11 min; m/3: 1587.7 m/4: m/5:
(1207) Compound 166
(1208) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,6A,7K,9E,18Q,22V,23E,28Y,30W,31L]-hPYY(4-36)
(1209) iVal-APAK(C18DA-gGlu-Ahx)PEEDASPEELQRYYYVELRHYYNWLTRQRY-NH2 (SEQ ID NO: 170)
(1210) MW (calculated): 4794.5 Da
(1211) Synthesis and purification methods: S01; P02
(1212) LCMS: 010_CA07; Rt: 9.76 min; m/3: m/4: 1199.2 m/5:
(1213) Compound 167
(1214) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,6A,7K,9E,11A,13E,17I,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)
(1215) iVal-APAK(C18DA-gGlu-Ahx)PEEAAEPEEIQRYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 171)
(1216) MW (calculated): 4734.4 Da
(1217) Synthesis and purification methods: S01; P02
(1218) LCMS: 010_CA07; Rt: 11.49 min; m/3: m/4: 1185.0 m/5:
(1219) Compound 168
(1220) 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)
(1221) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEEIQRYYSSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 172)
(1222) MW (calculated): 4812.4 Da
(1223) Synthesis and purification methods: S01; P01
(1224) LCMS: 010_CA07; Rt: 9.83 min; m/3: 1605.7 m/4: m/5:
(1225) Compound 169
(1226) 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)
(1227) iVal-APEK(C18DA-gGlu-Ahx)PEEDAEPEELQAYYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 173)
(1228) MW (calculated): 4767.4 Da
(1229) Synthesis and purification methods: S01; P02
(1230) LCMS: 010_CA07; Rt: 13.90 min; m/3: 1589.0 m/4: 1192.1 m/5:
(1231) Compound 170
(1232) 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)

(1233) iVal-APEK(C18DA-gGlu-Ahx)PEEDAAPEEIQRYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 174)

(1234) MW (calculated): 4794.5 Da

(1235) Synthesis and purification methods: S01; P01

(1236) LCMS: 010_CA07; Rt: 10.60 min; m/3: m/4: 1199.0 m/5:

(1237) Compound 171

(1238) 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)

(1239) iVal-APEK(C18DA-gGlu-Ahx)PEADASPEELQRYYVELRHYYNWLTRQRY-NH2 (SEQ ID NO: 175)

(1240) MW (calculated): 4794.5 Da

(1241) Synthesis and purification methods: S01; P01

(1242) LCMS: 010_CA07; Rt: 9.57 min; m/3: 1599.2 m/4: m/5:

(1243) Compound 172

(1244) 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)

(1245) iVal-APEK(C18DA-gGlu-Ahx)PPEDASPEEIQRYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 176)

(1246) MW (calculated): 4778.5 Da

(1247) Synthesis and purification methods: S01; P01

(1248) LCMS: 010_CA07; Rt: 9.95 min; m/3: 1593.5 m/4: m/5:

(1249) Compound 173

(1250) 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)

(1251) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQRYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 177)

(1252) MW (calculated): 4824.5 Da

(1253) Synthesis and purification methods: S01; P01

(1254) LCMS: 010_CA07; Rt: 10.50 min; m/3: 1609.0 m/4: m/5:

(1255) Compound 174

(1256) 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)

(1257) iVal-APEK(C18DA-gGlu-Ahx)PGADASPEKLQRYYVSLRHYYHKLTRQRY-NH2 (SEQ ID NO: 178)

(1258) MW (calculated): 4644.4 Da

(1259) Synthesis and purification methods: S01; P02

(1260) LCMS: 010_CA07; Rt: 7.90 min; m/3: 1548.8 m/4: m/5:

(1261) Compound 175

(1262) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,6A,7K,9E,13E,18Q,22I,23A,28Y,30W,31L]-hPYY(4-36)

(1263) iVal-APAK(C18DA-gGlu-Ahx)PEEDAEPEELQRYYIALRHYYNWLTRQRY-NH2 (SEQ ID NO: 179)

(1264) MW (calculated): 4792.5 Da

(1265) Synthesis and purification methods: S01; P02
(1266) LCMS: 010_CA07; Rt: 10.86 min; m/3: m/4: 1198.8 m/5:
(1267) Compound 176
(1268) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,9E,13T,17I,18Q,22V,28Y,30W,31L]-hPYY(4-36)
(1269) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEEIQRYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 180)
(1270) ##STR00018##
(1271) MW (calculated): 4824.5 Da
(1272) Synthesis and purification methods: S01; P01
(1273) LCMS: 010_CA07; Rt: 9.84 min; m/3: 1610.6 m/4: m/5:
(1274) Compound 177
(1275) 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)
(1276) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQQYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 181)
(1277) MW (calculated): 4796.4 Da
(1278) Synthesis and purification methods: S01; P02
(1279) LCMS: 010_CA07; Rt: 10.00 min; m/3: m/4: 1200.0 m/5:
(1280) Compound 178
(1281) 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)
(1282) iVal-APEK(C18DA-gGlu-Ahx)PEAAATPEEIQRYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 182)
(1283) MW (calculated): 4706.4 Da
(1284) Synthesis and purification methods: 501; P02
(1285) LCMS: 010_CA07; Rt: 11.21 min; m/3: m/4: 1177.0 m/5:
(1286) Compound 179
(1287) 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)
(1288) iVal-APEK(C18DA-gGlu-Ahx)PEADASPEETQRYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 183)
(1289) MW (calculated): 4724.4 Da
(1290) Synthesis and purification methods: S01; P01
(1291) LCMS: 010_CA07; Rt: 12.50 min; m/3: m/4: 1181.4 m/5:
(1292) Compound 180
(1293) 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)
(1294) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQRYYVSLRHYYNWLTKQRY-NH2 (SEQ ID NO: 184)
(1295) MW (calculated): 4796.5 Da
(1296) Synthesis and purification methods: S01; P02
(1297) LCMS: 010_CA07; Rt: 9.80 min; m/3: 1600.8 m/4: m/5:
(1298) Compound 181
(1299) 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)
(1300) iVal-APAK(C18DA-gGlu-Ahx)PEADAEPEEIQRYYVALRHYYNWLTRQRY-NH2 (SEQ
ID NO: 185)
(1301) MW (calculated): 4720.4 Da
(1302) Synthesis and purification methods: 501; P02
(1303) LCMS: 010_CA07; Rt: 11.23 min; m/3: 1574.1 m/4: 1180.8 m/5:
(1304) Compound 182
(1305) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-
carboxyheptadecanamido) butanamido]hexanoyl)-
[4A,6A,7K,9E,17A,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)
(1306) iVal-APAK(C18DA-gGlu-Ahx)PEEDASPEEAQRYYVALRHYYNWLTRQRY-NH2 (SEQ
ID NO: 186)
(1307) MW (calculated): 4694.3 Da
(1308) Synthesis and purification methods: S01; P01
(1309) LCMS: 010_CA07; Rt: 12.70 min; m/3: 1565.3 m/4: m/5:
(1310) Compound 183
(1311) 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)
(1312) iVal-APEK(C18DA-gGlu-Ahx)AEEDASPEEIQRYYVSLRHYYNWLTRQRY-NH2 (SEQ
ID NO: 187)
(1313) MW (calculated): 4784.4 Da
(1314) Synthesis and purification methods: S01; P01
(1315) LCMS: 010_CA07; Rt: 10.60 min; m/3: 1595.9 m/4: m/5:
(1316) Compound 184
(1317) 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)
(1318) iVal-APEK(C18DA-gGlu-Ahx)PEADATPEEIQRYYVALRHYYNWLTRQRY-NH2 (SEQ
ID NO: 188)
(1319) ##STR00019##
(1320) MW (calculated): 4750.4 Da
(1321) Synthesis and purification methods: 501; P01
(1322) LCMS: 010_CA07; Rt: 12.00 min; m/3: m/4: 1188.5 m/5:
(1323) Compound 185
(1324) 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)
(1325) iVal-APAK(C18DA-gGlu-Ahx)PEEDASEEELQRYYVSLRHYYNWLTRQRY-NH2 (SEQ
ID NO: 189)
(1326) MW (calculated): 4784.4 Da
(1327) Synthesis and purification methods: S01; P01
(1328) LCMS: 010_CA07; Rt: 10.80 min; m/3: 1595.2 m/4: m/5:
(1329) Compound 186
(1330) 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)
(1331) iVal-APEK(C18DA-gGlu-Ahx)PEADAEPEEAQRYYVSLRHYYNWLTRQRY-NH2 (SEQ
ID NO: 190)

(1332) MW (calculated): 4810.4 Da
(1333) Synthesis and purification methods: S01; P01
(1334) LCMS: 010_CA07; Rt: 13.20 min; m/3: m/4: 1203.8 m/5:
(1335) Compound 187
(1336) 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)
(1337) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEEPQRYYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 191)
(1338) MW (calculated): 4808.4 Da
(1339) Synthesis and purification methods: S01; P01
(1340) LCMS: 010_CA07; Rt: 9.38 min; m/3: 1603.3 m/4: m/5:
(1341) Compound 188
(1342) 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,32Q]-hPYY(4-36)
(1343) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEELQRYYYVSLRHYYNWLQRQRY-NH2 (SEQ ID NO: 192)
(1344) MW (calculated): 4851.5 Da
(1345) Synthesis and purification methods: S01; P01
(1346) LCMS: 010_CA07; Rt: 11.13 min; m/3: 1618.0 m/4: m/5:
(1347) Compound 189
(1348) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,6A,7K,9E,17T,18Q,22V,23A,28Y,30W,31L]-hPYY(4-36)
(1349) iVal-APAK(C18DA-gGlu-Ahx)PEEDASPEETQRYYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 193)
(1350) MW (calculated): 4724.4 Da
(1351) Synthesis and purification methods: S01; P02
(1352) LCMS: 010_CA07; Rt: 11.50 min; m/3: m/4: 1182.1 m/5:
(1353) Compound 190
(1354) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,6A,7K,9E,13T,18Q,22I,28Y,30W,31L]-hPYY(4-36)
(1355) iVal-APAK(C18DA-gGlu-Ahx)PEEDATPEELQRYYYISLRHYYNWLTRQRY-NH2 (SEQ ID NO: 194)
(1356) MW (calculated): 4780.5 Da
(1357) Synthesis and purification methods: S01; P02
(1358) LCMS: 010_CA07; Rt: 10.28 min; m/3: 1594.5 m/4: m/5:
(1359) Compound 191
(1360) N{alpha-4}-(3-methylbutanoyl)-N{epsilon-7}-(6-[(4S)-4-carboxy-4-(17-carboxyheptadecanamido) butanamido]hexanoyl)-[4A,7K,9E,13T,17I,18Q,22E,28Y,30W,31L]-hPYY(4-36)
(1361) iVal-APEK(C18DA-gGlu-Ahx)PEEDATPEEIQRYYESLRHYYNWLTRQRY-NH2 (SEQ ID NO: 195)
(1362) MW (calculated): 4854.5 Da
(1363) Synthesis and purification methods: S01; P02
(1364) LCMS: 010_CA07; Rt: 9.77 min; m/3: 1619.0 m/4: m/5:
(1365) Compound 192
(1366) 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)

(1367) iVal-APEK(C18DA-gGlu-Ahx)PEAPASPEELQRYYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 196)

(1368) MW (calculated): 4734.4 Da

(1369) Synthesis and purification methods: S01; P02

(1370) LCMS: 010_CA07; Rt: 10.39 min; m/3: m/4: 1184.5 m/5:

(1371) Compound 193

(1372) 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)

(1373) iVal-APEK(C18DA-gGlu-Ahx)PEEEASPEEIQRYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 197)

(1374) MW (calculated): 4824.5 Da

(1375) Synthesis and purification methods: S01; P01

(1376) LCMS: 010_CA07; Rt: 12.20 min; m/3: 1609.1 m/4: m/5:

(1377) Compound 194

(1378) 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)

(1379) iVal-APAK(C18DA-gGlu-Ahx)PEEDAEPEEIQRYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 198)

(1380) MW (calculated): 4778.5 Da

(1381) Synthesis and purification methods: S01; P02

(1382) LCMS: 010_CA07; Rt: 10.80 min; m/3: m/4: 1195.1 m/5:

(1383) Compound 195

(1384) 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)

(1385) iVal-APAK(C18DA-gGlu-Ahx)PEEDASPEEIQRYYISLRHYYNWLTRQRY-NH2 (SEQ ID NO: 199)

(1386) ##STR00020##

(1387) MW (calculated): 4766.4 Da

(1388) Synthesis and purification methods: S01; P02

(1389) LCMS: 010_CA07; Rt: 10.02 min; m/3: m/4: 1192.4 m/5:

(1390) Compound 196

(1391) 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)

(1392) iVal-APEK(C18DA-gGlu-Ahx)PEADASPEELQRYYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 200)

(1393) MW (calculated): 4752.4 Da

(1394) Synthesis and purification methods: 501; P01

(1395) LCMS: 010_CA07; Rt: 10.35 min; m/3: 1584.8 m/4: m/5:

(1396) Compound 197

(1397) 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)

(1398) iVal-APEK(C18DA-gGlu-Ahx)PEEDASPEEIQRYYVALRHYYNWLTRQRY-NH2 (SEQ ID NO: 201)

(1399) ##STR00021##
 (1400) MW (calculated): 4794.5 Da
 (1401) Synthesis and purification methods: S01; P01
 (1402) LCMS: 010_CA07; Rt: 10.19 min; m/3: m/4: 1199.4 m/5:
 (1403) Compound 198
 (1404) 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)
 (1405) iVal-APAK(C18DA-gGlu-Ahx)PEADAEPEEIQRYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 202)
 (1406) MW (calculated): 4736.4 Da
 (1407) Synthesis and purification methods: S01; P02
 (1408) LCMS: 010_CA07; Rt: 10.70 min; m/3: m/4: 1184.9 m/5:
 (1409) Compound 199
 (1410) 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)
 (1411) iVal-APAK(C18DA-gGlu-Ahx)PEEEASPEELQRYYVSLRHYYNWLTRQRY-NH2 (SEQ ID NO: 203)
 (1412) MW (calculated): 4766.4 Da
 (1413) Synthesis and purification methods: S01; P01
 (1414) LCMS: 010_CA07; Rt: 10.40 min; m/3: m/4: 1192.0 m/5:
 (1415) The following compound disclosed as Example 32 in WO 2016/198682 A1 was synthesized as reference:
 (1416) TABLE-US-00010 Ref. 1 (SEQ ID NO: 204) iVal-RPEK(C18DA-gGlu-Ahx)PGEDASPEELQRYYISLRHYYNWL TRQRY-NH2
 (1417) Further compounds were synthesized as references:
 (1418) TABLE-US-00011 Ref. 2 (SEQ ID NO: 205) iVal-RPEK(C18DA-gGlu-Ahx) PGEDASPEELQRYYISLAHYYNWL TRQRY-NH2 Ref. 3 (SEQ ID NO: 206) iVal-RPEK(C18DA-gGlu-Ahx) PGEDASPEELQRYYISLRHYYNWL TAQRY-NH2 Ref. 4 (SEQ ID NO: 207) iVal-RPEK(C18DA-gGlu-Ahx) PGEDASPEELQRYYISLRHYYNWL TRQAY-NH2
 (1419) 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 (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.
 (1420) TABLE-US-00012 TABLE 2 hY2 RLB hY2 cAMP SoL pH 6 Sol pH 7 Seq. (nM) (nM) (mg/mL) (mg/mL) mod. vs. (Example (Example [final pH] [final pH] Comp. Ref. 1 1) 2) (Example 3) (Example 3) Ref. 1 — 1.7 0.5 0.0 6.7 [6.2] [6.8] Comp. 92 R4A 1.8 0.6 9.2 8.9 [6.1] [6.7] Ref. 2 R25A 10.0 3.0 7.0 8.5 [6.1] [6.7] Ref. 3 R33A >316 >10 10.0 10.0 [6.1] [6.7] Ref. 4 R35A >316 >10 10.0 10.0 [6.1] [6.7].

EXAMPLES

(1421) The following examples demonstrate certain specific embodiments of the present 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)

(1422) The filtration RLB assay was carried out in 96-well plates in a final volume of 100 µl per well. Freeze-dried test peptides were dissolved in 100% dimethyl sulfoxide (DMSO) to stock

solutions of 1 mM and serial dilutions were performed in assay buffer (50 mM HEPES, 5 mM MgCl.sub.2, 1 mM CaCl.sub.2, pH 7.4) containing 0.2% ovalbumin. 10 µl/well of the test peptide solution was added to the plates to give final concentrations ranging from 1 µM to 3 pM. Subsequently, 10 µl of human .sup.125I-PYY(1-36) (Perkin Elmer) in assay buffer containing 0.2% ovalbumin was added to wells to give a final concentration of 0.02 nM. Next, 80 µL membranes (HTS066M, ChemiSCREEN™ Human Neuropeptide Y2 Receptor Membrane Preparation, CHEMICON) were added to each well to give a final protein concentration of 0.5 µg/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 (PE) presoaked GF/C filters using a 96-well FilterMate™ harvester (Perkin Elmer) followed by four washes with 300 µl/well ice-cold wash buffer (50 mM HEPES, 500 mM 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 µl/well scintillation counter cocktail (Microscint20, Packard) was added and the radioactivity was counted in the Packard TopCount NXT scintillation counter. IC.sub.50 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 Kd is the previously measured receptor specific dissociation constant (for NPY2R=0.07 nM) and [L] is .sup.125I-PYY(1-36) radioligand concentration.

(1423) The RLB results are summarized in Table 3, below.

(1424) TABLE-US-00013

TABLE 3	Compound	Ki [nM]
1	2.05	2
2	2.40	3
3	1.57	4
4	4.65	5
5	12.71	6
6	1.42	7
7	1.04	8
8	106.17	9
9	3.32	10
10	2.46	11
11	1.40	12
12	4.16	13
13	1.53	14
14	1.28	15
15	3.98	16
16	2.81	17
17	24.63	18
18	2.48	19
19	9.63	20
20	2.41	21
21	3.38	22
22	4.98	23
23	12.59	24
24	3.39	25
25	1.55	26
26	5.64	27
27	10.47	28
28	0.49	29
29	1.36	30
30	0.30	31
31	34.66	32
32	13.56	33
33	2.53	34
34	3.53	35
35	1.40	36
36	1.25	37
37	3.66	38
38	12.44	39
39	2.73	40
40	0.67	41
41	19.75	42
42	1.98	43
43	2.49	44
44	5.86	45
45	6.17	46
46	5.21	47
47	0.51	48
48	1.54	49
49	11.60	50
50	2.59	51
51	2.39	52
52	3.07	53
53	8.97	54
54	8.97	55
55	2.96	56
56	4.39	57
57	2.07	58
58	3.46	59
59	1.93	60
60	6.04	61
61	0.41	62
62	1.44	63
63	0.93	64
64	0.86	65
65	0.98	66
66	2.33	67
67	2.22	68
68	9.07	69
69	0.54	70
70	2.26	71
71	1.97	72
72	2.79	73
73	2.16	74
74	3.17	75
75	1.43	76
76	2.68	77
77	9.73	78
78	1.80	79
79	1.54	80
80	4.62	81
81	2.65	82
82	0.58	83
83	6.91	84
84	1.60	85
85	1.61	86
86	4.33	87
87	22.38	88
88	16.28	89
89	1.16	90
90	8.71	91
91	4.64	92
92	1.84	93
93	1.71	94
94	0.93	95
95	2.92	96
96	3.06	97
97	4.23	98
98	0.66	99
99	1.01	100
100	1.77	101
101	7.15	102
102	7.15	103
103	1.94	104
104	14.11	105
105	5.97	106
106	2.46	107
107	5.13	108
108	2.77	109
109	13.98	110
110	6.42	111
111	2.14	112
112	4.28	113
113	3.53	114
114	0.95	115
115	2.22	116
116	2.46	117
117	3.09	118
118	1.00	119
119	5.73	120
120	1.49	121
121	1.45	122
122	2.73	123
123	3.65	124
124	3.07	125
125	3.37	126
126	4.42	127
127	3.36	128
128	2.91	129
129	1.42	130
130	9.36	131
131	1.54	132
132	2.75	133
133	4.68	134
134	2.80	135
135	3.83	136
136	1.07	137
137	49.59	138
138	12.53	139
139	3.60	140
140	1.41	141
141	8.17	142
142	3.97	143
143	3.42	144
144	9.76	145
145	5.29	146
146	8.93	147
147	5.04	148
148	2.85	149
149	3.97	150
150	2.18	151
151	1.68	152
152	1.32	153
153	6.80	154
154	3.71	155
155	7.60	156
156	4.20	157
157	1.68	158
158	0.58	159
159	2.75	160
160	1.37	161
161	4.00	162
162	14.93	163
163	0.67	164
164	2.80	165
165	1.43	166
166	2.05	167
167	4.58	168
168	3.56	169
169	5.82	170
170	2.28	171
171	2.83	172
172	0.81	173
173	4.07	174
174	0.21	175
175	3.00	176
176	1.48	177
177	8.65	178
178	3.39	179
179	0.89	180
180	15.05	181
181	1.33	182
182	2.20	183
183	18.80	184
184	0.64	185
185	2.06	186
186	7.21	187
187	15.32	188
188	5.46	189
189	0.97	190
190	1.95	191
191	8.32	192
192	0.74	193
193	3.42	194
194	26.37	195
195	0.78	196
196	3.57	197
197	2.03	198
198	1.38	199
199	2.87	

(1425) 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

(1426) 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 µl using 5 µl cells, 2.5 µl peptide agonist, 2.5 µl forskolin and 5 µl 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.

(1427) The in vitro activity results (expressed as EC.sub.50 values) are summarized in Table 4, below.

(1428) TABLE-US-00014 TABLE 4 hY2R hY1R hY4R hY5R Compound No. (nM) (nM) (nM) (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

Example 3: Solubility Determination

(1429) 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 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 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.

(1430) 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.

(1431) UPLC Method:

(1432) System: UltiMate 3000 UPLC, ThermoFisher

(1433) Mobile phase A: 5% acetonitrile, 95% water, 0.03% trifluoroacetic acid.

(1434) Mobile phase B: 95% acetonitrile, 5% water, 0.03% trifluoroacetic acid.

(1435) Flow: 1 ml/min

(1436) Gradient: 0-100% mobile phase B (2 mins.)

(1437) Column: Kinetix, 5 μ m C8, 100 Å, 50×2.1 mm

(1438) Column temperature: 50° C.

(1439) The results from the solubility determination are summarized in Table 5, below.

(1440) TABLE-US-00015 TABLE 5 Sol6 Sol6 Sol7 Sol7 Compound (mg/ml) pH (mg/ml) pH 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

Example 4: DLS Studies

(1441) 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 μ m 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.

(1442) The results from the DLS studies are summarized in Table 6.

(1443) TABLE-US-00016 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

Example 5: Mouse PK

(1444) Pharmacokinetic parameters of the test compounds were determined after intravenous administration to NMRI mice.

(1445) 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.

(1446) 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.

(1447) Serial blood samples were collected from the vena sephena into tubes containing EDTA as anticoagulant at different time points up to 48 h post dosing. After centrifugation for approximately 5 minutes, plasma samples were transferred to 96-well PCR plates, 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.

(1448) TABLE-US-00017 Compound Mouse MRT (h) Terminal half-life (h) Ref. 1 13.0 9.0

(1449) 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).

Example 6: Effect on Acute Food Intake in Normal NMRI Mice

(1450) 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 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 $21^{\circ}\text{C} \pm 1^{\circ}\text{C}$., with $60\% \pm 20\%$ humidity.

(1451) Animals had ad libitum access to regular rodent chow (KLIBA Nafag 3430 or Altromin 1324, Brogaarden, Denmark) and tap water.

(1452) 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 (50 mM 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 24 h. 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.

(1453) TABLE-US-00018 TABLE 7 Acute Food Intake 24 h Compound [% vehicle] 7 38 26 53 40 41 63 62 84 57 114 65 136 64 146 50 163 46 176 44 197 57 Ref. 1 49

Example 7: Activity after Incubation in Solutions at Different pH Values

(1454) 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 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.

(1455) 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 $\sim\text{pH } 6$ (in the pH range from ~ 6 to ~ 8).

(1456) Contrary hereto, after incubation at $\sim\text{pH } 6$, solutions of Ref. 1 (after filtration) show a weak response in the binding assay (apparent significant ($>45\times$) 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.
 (1457) TABLE-US-00019 TABLE 8 hY2R RLB 6 RLB 7 RLB 8 RLB RLB RLB (pH6.1- (pH7.1- (pH8.1- ratio ratio Com- Ki (nM) 6.2) 7.2) 8.2) (RLB6/ (RLB8/ pound DMSO (nM) (nM) (nM) RLB7) 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

Claims

1. A PYY analogue comprising: ##STR00022## or a pharmaceutically acceptable salt thereof.
2. A PYY analogue, wherein the PYY analogue is: ##STR00023## or a pharmaceutically acceptable salt thereof.
3. A PYY analogue comprising: ##STR00024##
4. A PYY analogue, wherein the PYY analog is: ##STR00025##
5. A PYY analogue comprising: ##STR00026## wherein the PYY analogue is in the form of a pharmaceutically acceptable salt.
6. A PYY analogue, wherein the PYY analog is: ##STR00027## wherein the PYY analogue is in the form of a pharmaceutically acceptable salt.
7. A pharmaceutical composition comprising the PYY analogue or pharmaceutically acceptable salt thereof according to claim 1, and one or more pharmaceutically acceptable excipients.
8. A pharmaceutical composition comprising the PYY analogue or pharmaceutically acceptable salt thereof according to claim 2, and one or more pharmaceutically acceptable excipients.
9. A pharmaceutical composition comprising the PYY analogue according to claim 3, and one or more pharmaceutically acceptable excipients.
10. A pharmaceutical composition comprising the PYY analogue according to claim 4, and one or more pharmaceutically acceptable excipients.
11. A pharmaceutical composition comprising the PYY analogue according to claim 5, and one or more pharmaceutically acceptable excipients.
12. A pharmaceutical composition comprising the PYY analogue according to claim 6, and one or more pharmaceutically acceptable excipients.
13. A method for treating a condition or disease related or caused by excess body weight or excess body weight gain, the method comprising administering to a patient in need thereof a pharmaceutically effective amount of a PYY analogue according to claim 1, or a pharmaceutically acceptable salt thereof.
14. A method for treating obesity or an obesity-related condition or disease, the method comprising administering to a patient in need thereof a pharmaceutically effective amount of a PYY analogue according to claim 1, or a pharmaceutically acceptable salt thereof, wherein the obesity or the obesity-related condition or disease is selected from the group consisting of type 2 diabetes, hypertension, dyslipidemia, sleep apnea and cardiovascular disease.
15. A method for treating atherogenic dyslipidemia, hepatic steatosis, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), kidney failure or atherosclerosis, the method comprising administering to a patient in need thereof a pharmaceutically effective amount of a PYY analogue according to claim 1, or a pharmaceutically acceptable salt thereof.
16. The method according to claim 13, wherein the PYY analogue is administered as part of a combination therapy together with an agent for treatment of diabetes, obesity, dyslipidemia or hypertension.
17. The method according to claim 14, wherein the PYY analogue is administered as part of a combination therapy together with an agent for treatment of diabetes, obesity, dyslipidemia or hypertension.

18. The method according to claim 15, wherein the PYY analogue is administered as part of a combination therapy together with an agent for treatment of diabetes, obesity, dyslipidemia or hypertension.
