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(54) **Title**: SELECTIVE PYY COMPOUNDS AND USES THEREOF

(57) **Abstract**: The invention relates to PYY compounds having the amino acid in the position corresponding to position 30 of hPYY(1-36) substituted with tryptophan and derivatives thereof with a modifying group attached to the position corresponding to position 10 of hPYY(1-36). The compounds of the invention are selective Y2 receptor agonists. The invention also relates to pharmaceutical compositions comprising such PYY compounds and pharmaceutically acceptable excipients, as well as the medical use of the PYY compounds.

DESCRIPTION

TITLE: SELECTIVE PYY COMPOUNDS AND USES THEREOF

TECHNICAL FIELD

The present invention relates to analogues and/or derivatives of Peptide YY (PYY), and their pharmaceutical use.

INCORPORATION-BY-REFERENCE OF THE SEQUENCE LISTING

The Sequence Listing, entitled "SEQUENCE LISTING", is 6110 bytes, was created on 2 February 2015 and is incorporated herein by reference.

BACKGROUND OF THE INVENTION

PYY is released during a meal from L-cells in the distal small intestine and the colon. PYY is known to have peripheral effects in the gastrointestinal (GI) tract and also act centrally as a satiety signal. PYY is naturally secreted as a 36 amino acid peptide (PYY(1-36)) with a C-terminal amide but is cleaved to PYY(3-36) which constitutes approximately 50% of the circulating PYY. The enzyme responsible for the degradation is dipeptidyl peptidase IV (DPPIV). PYY(3-36) is rapidly eliminated by proteases and other clearance mechanisms. The half-life of PYY(3-36) has been reported to be <30 minutes in pigs. Thus, PYY displays suboptimal pharmacokinetic properties, meaning that the peptide has to be administered at least twice daily.

Whereas PYY(1-36) activates Y1, Y2 and Y5 receptors with very little selectivity and the Y4 receptor slightly less, the DPP IV processed PYY(3-36) displays increased selectivity for the Y2 receptor over Y1, Y4 and Y5 receptors, albeit some Y1 and Y5 affinity is retained. Y2 receptor activation is known to decrease appetite and food intake whereas Y1 and Y5 receptor activation leads to an increase in appetite and food intake. Furthermore, Y1 and Y5 receptor activation may lead to an increase in blood pressure.

PYY(3-36) has been suggested for use in the treatment of obesity and associated diseases based on the demonstrated effects of certain of these peptides in animal models and in man, and on the fact that obese people have low basal levels of PYY as well as lower meal responses of this peptide. Furthermore, Y2 agonists have been demonstrated to have anti-secretory and pro-absorptive effects in the gastro-intestinal (GI) tract. The potential use of Y2 agonists in the treatment of a number of gastro-intestinal disorders has been suggested.

Based on demonstrated effects in e.g. Zucker rats and Diet-Induced Obese (DIO) mice Y2 selective PYY(3-36) analogues have a positive effect on glucose metabolism and are thus suggested to be used for the treatment of diabetes.

WO 2009/138511 relates to long-acting Y2 and/or Y4 receptor agonists. WO 2011/033068 relates to PYY analogues stabilised against C-terminal proteolytic breakdown. WO 2011/058165 relates to Y2 receptor agonists with protracted pharmacokinetic properties.

For the treatment of conditions responsive to Y receptor modulation such as obesity and diabetes it would be attractive to use PYY analogues which are specific for the Y receptor subtype Y2 and importantly also display protracted pharmacokinetic properties and as such can be used in a dosing regimen with lower frequency of administration than PYY or PYY(3-36).

SUMMARY

The invention relates to PYY compounds. The PYY compounds of the present invention have i) tryptophan at the position corresponding to position 30 of hPYY(1-36) (SEQ ID NO:1); ii) N(alpha)-methyl-L-arginine at the position corresponding to position 35 of hPYY(1-36) (SEQ ID NO:1); iii) lysine at the position corresponding to position 10 of hPYY(1-36) (SEQ ID NO:1); and iv) a modifying group attached to the epsilon amino group of the Lysine residue in position 10, and may comprise up to 10 amino acid modifications as compared to human PYY(3-36) (hPYY(3-36), SEQ ID NO:2).In one aspect, the invention also relates to pharmaceutical compositions comprising such PYY compounds and pharmaceutically acceptable excipients, as well as the medical use of the PYY compounds. In another aspect, the PYY compounds of the present invention have i) tryptophan at the position corresponding to position 30 of hPYY(1-36) (SEQ ID NO:1); ii) N(alpha)-methyl-L-arginine at the position corresponding to position 35 of hPYY(1-36) (SEQ ID NO:1); iii) lysine at the position corresponding to position 10 of hPYY(1-36) (SEQ ID NO:1); iv) glutamine at position corresponding to position 18 of hPYY(1-36) (SEQ ID NO:1);and iv) a modifying group attached to the epsilon amino group of the Lysine residue in position 10, and may comprise up to 10 amino acid modifications as compared to human PYY(3-36) (hPYY(3-36), SEQ ID NO:2). The invention also relates to pharmaceutical compositions comprising such PYY compounds and pharmaceutically acceptable excipients, as well as the medical use of the PYY compounds.

Also or alternatively, in one aspect, the invention relates to PYY compounds being Y2 receptor agonists.

Also or alternatively, in one aspect, the invention relates to PYY compounds displaying selectivity towards the Y receptor subtype Y2 as compared to Y receptor subtypes Y1, Y4 and Y5.

Also or alternatively, in one aspect, the invention relates to PYY compounds with longer half-life than the half-life of hPYY(3-36). Also or alternatively, in one aspect, the invention relates to PYY compounds with longer half-life than the half-life of hPYY(1-36).

DESCRIPTION OF THE INVENTION

The invention relates to PYY compounds. The PYY compounds of the present invention have i) tryptophan at the position corresponding to position 30 of hPYY(1-36) (SEQ ID NO:1); ii) a methyl group added to the α-amino group of the arginine residue in the position corresponding to position 35 of hPYY(1-36) (SEQ ID NO:1), meaning that the residue in the position corresponding to position 35 of hPYY(1-36) is thus N(alpha)-methylarginine; iii) lysine at the position corresponding to position 10 of hPYY(1-36) (SEQ ID NO:1); and iv) a modifying group attached to the epsilon amino group of the Lysine residue in position 10. The PYY compounds of the present invention may comprise up to 10 amino acid modifications as compared to human PYY(3-36) (hPYY(3-36), SEQ ID NO:2).

In one aspect, the PYY compounds of the present invention have i) tryptophan at the position corresponding to position 30 of hPYY(1-36) (SEQ ID NO:1); ii) a methyl group added to the α-amino group of the arginine residue in the position corresponding to position 35 of hPYY(1-36) (SEQ ID NO:1), meaning that the residue in the position corresponding to position 35 of hPYY(1-36) is thus N(alpha)-methylarginine; iii) lysine at the position corresponding to position 10 of hPYY(1-36) (SEQ ID NO:1); iv) glutamine at position corresponding to position 18 of hPYY(1-36) (SEQ ID NO:1); and v) a modifying group attached to the epsilon amino group of the Lysine residue in position 10. The PYY compounds of the present invention may comprise up to 10 amino acid modifications as compared to human PYY(3-36) (hPYY(3-36), SEQ ID NO:2).

In one aspect, the invention relates to PYY compounds being Y receptor subtype Y2 agonists.

Also or alternatively, in one aspect, the invention relates to PYY compounds displaying selectivity towards the Y receptor subtype Y2 as compared to Y receptor subtypes Y1, Y4 and Y5.

In one aspect peptides being "selective" for specific receptors over other receptors refers to peptides that display at least 10 fold, such as at least 20 fold, at least

50 fold, or at least 100 fold higher potency for one Y receptor over other Y receptors as measured *in vitro* in an assay for receptor function, such as an Actone functional potency assay, and compared by EC50 values, or a Scintillation Proximity Assay (SPA) measuring receptor binding affinity, and compared by Ki values.

In what follows, Greek letters may be represented by their symbol or the corresponding written name, for example: α = alpha; β = beta; ε = epsilon; γ = gamma; ω = omega; etc.

PYY compounds

The term "hPYY(1-36)" as used herein refers to the human Peptide YY, the sequence of which is included in the sequence listing as SEQ ID NO:1. The peptide having the sequence of SEQ ID NO:1 may also be designated native hPYY.

The term "PYY compound" as used herein refers to a peptide, or a compound, which is a variant of hPYY(1-36). The term "PYY compound" as used herein may also refer to a peptide, or a compound, which is a variant of hPYY(3-36) (SEQ ID NO:2). The term "PYY compound" as used herein may also refer to a peptide, or a compound, which is a variant of hPYY(4-36).

The C-terminal of the PYY compounds of the present invention is an amide, as is the C-terminal of native hPYY(1-36) (SEQ ID NO:1) and hPYY(3-36) (SEQ ID NO:2), respectively.

The PYY compounds of the present invention can be PYY analogues and/or derivatives thereof.

The term "PYY analogue" is used for PYY compounds, where at least one amino acid modification in the backbone is present.

The term "PYY derivative" is used for PYY compounds comprising at least one non-amino acid substituent covalently attached.

A derivative of a PYY analogue is thus a PYY compound comprising at least one amino acid modification and at least one non-amino acid substituent covalently attached.

The PYY compounds of the present invention may comprise up to 10 amino acid modifications as compared to hPYY(3-36) (SEQ ID NO:2).

The PYY compounds of the present invention may comprise up to 9 amino acid modifications as compared to hPYY(3-36) (SEQ ID NO:2).

The PYY compounds of the present invention may comprise up to 8 amino acid modifications as compared to hPYY(3-36) (SEQ ID NO:2).

The PYY compounds of the present invention may comprise up to 7 amino acid

modifications as compared to hPYY(3-36) (SEQ ID NO:2).

The PYY compounds of the present invention may comprise up to 6 amino acid modifications as compared to hPYY(3-36) (SEQ ID NO:2).

The PYY compounds of the present invention may comprise up to 5 amino acid modifications as compared to hPYY(3-36) (SEQ ID NO:2).

The PYY compounds of the present invention may comprise up to 4 amino acid modifications as compared to hPYY(3-36) (SEQ ID NO:2).

The PYY compounds of the present invention may comprise up to 3 amino acid modifications as compared to hPYY(3-36) (SEQ ID NO:2).

The PYY compounds of the present invention may comprise up to 2 amino acid modifications as compared to hPYY(3-36) (SEQ ID NO:2).

The term "amino acid modification" used throughout this application is used in the meaning of a modification to an amino acid as compared to hPYY(3-36). This modification can be the result of a deletion of an amino acid, addition of an amino acid, substitution of one amino acid with another or a substituent covalently attached to an amino acid of the peptide.

The PYY compounds of the invention comprises i) tryptophan at the position corresponding to position 30 of hPYY(1-36), ii) N(alpha)-methyl-L-arginine at the position corresponding to position 35 of hPYY(1-36) (SEQ ID NO:1), and iii) lysine at a position corresponding to position 10 of hPYY(1-36) (SEQ ID NO:1), meaning that the PYY compounds of the invention may comprise up to 7 amino acid modifications as compared to hPYY(3-36) in addition to these modification in the positions corresponding to positions 30, 35 and 10 of hPYY(1-36) (SEQ ID NO:1).

In one aspect, the PYY compounds of the invention comprises i) tryptophan at the position corresponding to position 30 of hPYY(1-36), ii) N(alpha)-methyl-L-arginine at the position corresponding to position 35 of hPYY(1-36) (SEQ ID NO:1), iii) lysine at a position corresponding to position 10 of hPYY(1-36) (SEQ ID NO:1); and (iv) glutamine at the position corresponding to position 18 of hPYY(1-36) (SEQ ID NO:1), meaning that the PYY compounds of the invention may comprise up to 6 amino acid modifications as compared to hPYY(3-36) in addition to these modification in the positions corresponding to positions 18, 30, 35 and 10 of hPYY(1-36) (SEQ ID NO:1).

In one aspect, the PYY compounds of the invention comprises i) tryptophan at the position corresponding to position 30 of hPYY(1-36), ii) N(alpha)-methyl-L-arginine at the position corresponding to position 35 of hPYY(1-36) (SEQ ID NO:1), iii) lysine at a position corresponding to position 10 of hPYY(1-36) (SEQ ID NO:1); and (iv) glutamine at the position corresponding to position 18 of hPYY(1-36) (SEQ ID NO:1), meaning that

the PYY compounds of the invention may comprise up to 5 amino acid modifications as compared to hPYY(3-36) in addition to these modification in the positions corresponding to positions 18, 30, 35 and 10 of hPYY(1-36) (SEQ ID NO:1).

The PYY compounds of the invention comprises i) tryptophan at the position corresponding to position 30 of hPYY(1-36), ii) N(alpha)-methyl-L-arginine at the position corresponding to position 35 of hPYY(1-36) (SEQ ID NO:1), iii) lysine at a position corresponding to position 10 of hPYY(1-36) (SEQ ID NO:1); and (iv) glutamine at the position corresponding to position 18 of hPYY(1-36) (SEQ ID NO:1), meaning that the PYY compounds of the invention may comprise up to 4 amino acid modifications as compared to hPYY(3-36) in addition to these modification in the positions corresponding to positions 18, 30, 35 and 10 of hPYY(1-36) (SEQ ID NO:1).

The PYY compounds of the invention comprises i) tryptophan at the position corresponding to position 30 of hPYY(1-36), ii) N(alpha)-methyl-L-arginine at the position corresponding to position 35 of hPYY(1-36) (SEQ ID NO:1), iii) lysine at a position corresponding to position 10 of hPYY(1-36) (SEQ ID NO:1); and (iv) glutamine at the position corresponding to position 18 of hPYY(1-36) (SEQ ID NO:1), meaning that the PYY compounds of the invention may comprise up to 3 amino acid modifications as compared to hPYY(3-36) in addition to these modification in the positions corresponding to positions 18, 30, 35 and 10 of hPYY(1-36) (SEQ ID NO:1).

The PYY compounds of the invention comprises i) tryptophan at the position corresponding to position 30 of hPYY(1-36), ii) N(alpha)-methyl-L-arginine at the position corresponding to position 35 of hPYY(1-36) (SEQ ID NO:1), iii) lysine at a position corresponding to position 10 of hPYY(1-36) (SEQ ID NO:1); and (iv) glutamine at the position corresponding to position 18 of hPYY(1-36) (SEQ ID NO:1), meaning that the PYY compounds of the invention may comprise up to 2 amino acid modifications as compared to hPYY(3-36) in addition to these modification in the positions corresponding to positions 18, 30, 35 and 10 of hPYY(1-36) (SEQ ID NO:1).

The PYY compounds of the invention comprises i) tryptophan at the position corresponding to position 30 of hPYY(1-36), ii) N(alpha)-methyl-L-arginine at the position corresponding to position 35 of hPYY(1-36) (SEQ ID NO:1), iii) lysine at a position corresponding to position 10 of hPYY(1-36) (SEQ ID NO:1); and (iv) glutamine at the position corresponding to position 18 of hPYY(1-36) (SEQ ID NO:1), meaning that the PYY compounds of the invention may comprise 1 amino acid modification as compared to hPYY(3-36) in addition to these modification in the positions corresponding to positions 18, 30, 35 and 10 of hPYY(1-36) (SEQ ID NO:1).

As an example, [Lys10,Gln18,Trp30,NMeArg35]hPYY(3-36) comprises 4 amino

acid substitutions as compared to hPYY(3-36).

As another example, [Arg4,Lys10,Gln18,Trp30,NMeArg35]hPYY(4-36) comprises 5 amino acid substitutions and 1 deletion as compared to hPYY(3-36), meaning that this compound has 6 amino acid modifications as compared to hPYY(3-36).

In yet another aspect, the PYY peptides of the invention may exhibit at least 70%, 75% or 80% sequence identity to hPYY(3-36). As an example of a method for determination of the sequence identity between two analogues the two peptides [NMeArg35]hPYY(3-36) and hPYY(3-36) are aligned. The sequence identity of the [NMeArg35]hPYY(3-36) analogue relative to hPYY(3-36) is given by the total number of aligned residues minus the number of different residues (i.e. the number of aligned identical residues) divided by the total number of residues in hPYY(3-36). Accordingly, in said example the sequence identity is (34-1)/34, i.e. 97%.

PYY compounds or PYY analogues of the invention may be described by reference to i) the number of the amino acid residue in hPYY(1-36) which corresponds to the amino acid residue which is changed (i.e., the corresponding position in hPYY(1-36), and to ii) the actual change.

The expressions "a position equivalent to" or "corresponding position" are used to characterise the site of change in a variant PYY sequence by reference to hPYY(1-36).

In general throughout the application, when referring to a particular position of a PYY analogue, the position referred to is the position of the PYY analogue corresponding to that particular position of hPYY(1-36).

In the sequence listing, the first amino acid residue of a given sequence is assigned no. 1. This means that e.g. the first amino acid residue of hPYY(3-36), which is isoleucine, is assigned no. 3 in the sequence listings. Throughout this application however, this position is referred to as the position corresponding to position 3 of hPYY(1-36).

The expression used throughout this application, that a PYY compound comprises a particular amino acid at a position corresponding to a certain position of hPYY(1-36), means that the native amino acid in that position has been replaced with that particular amino acid.

The following is a non-limiting example of suitable analogue nomenclature. [NMeArg35]hPYY(3-36) designates an analogue of the human PYY(1-36), wherein the naturally occurring arginine in position 35 has been substituted with N(alpha)-methylarginine (the arginine residue in the position corresponding to position 35 of

hPYY(1-36) has a methyl group added to the alpha-amino group) and the naturally occurring tyrosine and proline in position 1 and 2, respectively, have been deleted.

Likewise, [Trp30]hPYY(3-36) designates an analogue of human PYY(3-36), wherein the naturally occurring leucine in the position of hPYY(3-36) corresponding to position 30 of human PYY(1-36) has been substituted with tryptophan.

The following is a non-limiting example of suitable nomenclature for a derivative of a PYY analogue. N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]-ethoxy]acetyl]-[Lys10,Gln18,Trp30,NMeArg35]hPYY(3-36) designates a derivative of an analogue of hPYY(3-36) (SEQ ID NO:2), wherein [Lys10,Gln18,Trp30,NMeArg35] designate the amino acid changes as compared to human PYY(3-36) with the numbers referring to the corresponding positions of PYY(1-36), and wherein the substituent [2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)-butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]- is attached to the epsilon amino group of the lysine in the position corresponding to position 10 in hPYY(1-36).

Amino acid residues may be identified by their full name, their one-letter code, and/or their three-letter code. These three ways are fully equivalent.

Analogues "comprising" certain specified changes may comprise further changes, when compared to hPYY(1-36). In one aspect, the analogue "has" the specified changes.

PYY analogues

A PYY analogue is a PYY peptide in which a number of amino acid residues have been modified when compared to hPYY(1-36) or hPYY(3-36). These modifications include substitutions, insertions, and/or deletions, alone or in combination.

In a specific aspect, the PYY analogues of the invention include one or more modifications of a "non-essential" amino acid residue. In the context of the invention, a "non-essential" amino acid residue is a residue that can be altered, i.e., deleted or substituted in the human PYY amino acid sequence without abolishing or substantially reducing the activity of the PYY analogue towards the Y2 receptor.

Substitutions. In one aspect amino acids may be substituted by conservative substitution. The term "conservative substitution" as used herein denotes that one or more amino acids are replaced by another, biologically similar residue. Examples include substitution of amino acid residues with similar characteristics, e.g. small amino acids, acidic amino acids, polar amino acids, basic amino acids, hydrophobic amino acids and aromatic amino acids.

In one aspect, the PYY analogues of the invention may comprise substitutions of one or more unnatural and/or non-amino acids, e.g., amino acid mimetics, into the sequence of PYY.

Deletions and Truncations. In one aspect, the PYY analogues of the invention may have one or more amino acid residues deleted from the amino acid sequence of human PYY, alone or in combination with one or more insertions or substitutions.

Insertions. In one aspect, the PYY analogues of the invention may have one or more amino acid residues inserted into the amino acid sequence of human PYY, alone or in combination with one or more deletions and/or substitutions.

In one aspect, the PYY analogues of the invention may include insertions of one or more unnatural amino acids and/or non-amino acids into the sequence of PYY.

The PYY peptide may be derived from vertebrates, such as human, mouse, sheep, goat, cow, or horse. The term "vertebrate" means members of the subphylum Vertebrata, a primary division of the phylum Chordata that includes the fish, amphibians, reptiles, birds, and mammals, all of which are characterized by a segmented spinal column and a distinct well-differentiated head. The term "mammal" means humans as well as all other warm-blooded members of the animal kingdom possessed of a homeostatic mechanism in the class Mammalia, e.g., companion mammals, zoo mammals, and food-source mammals. Some examples of companion mammals are canines (e.g., dogs), felines (e.g., cats) and horses; some examples of food-source mammals are pigs, cattle, sheep, and the like. In one aspect the mammal is a human or a companion mammal. In one aspect the mammal is a human, male or female.

The term “peptide”, as e.g. used in the context of the PYY compounds of the invention, refers to a compound which comprises a series of amino acids interconnected by amide (or peptide) bonds.

The PYY peptides of the invention comprise at least 24 constituent amino acids connected by peptide bonds. In particular embodiments the PYY peptides comprise at least 33 amino acids. In particular embodiments the PYY peptides comprise at least 34 amino acids.

Amino acids are molecules containing an amine group and a carboxylic acid group, and, optionally, one or more additional groups, often referred to as a side chain.

The term "amino acid" includes proteinogenic (or coded or natural) amino acids (amongst the 20 standard amino acids), as well as non-proteinogenic (or non-coded or

non-natural) amino acids. Proteinogenic amino acids are those which are naturally incorporated into proteins. The standard amino acids are those encoded by the genetic code. Non-proteinogenic amino acids are either not found in proteins, or not produced by standard cellular machinery (e.g., they may have been subject to post-translational modification). Non-limiting examples of non-proteinogenic amino acids are Aib (α-aminoisobutyric acid), N(alpha)-methylarginine, as well as the D-isomers of the proteinogenic amino acids. One example of a D-isomer of a proteinogenic amino acid is the D-isomer of aspartic acid, which can also be written as D-Asp.

In what follows, all amino acids of the PYY compound for which the optical isomer is not stated is to be understood to mean the L-isomer (unless otherwise specified).

PYY derivatives

The term "derivative" as used herein in the context of a PYY peptide or analogue means a chemically modified PYY peptide, in which one or more substituents have been covalently attached to the peptide.

In one aspect of the invention, the substituent may be an N-terminal substituent.

Also or alternatively, in one aspect, the substituent may be a modifying group or alternatively, referred to as a protracting moiety.

N-terminal substituent

In one aspect of the invention, the PYY compound comprises a substituent covalently attached to the alpha-amino group in the amino acid residue in the N-terminus of the PYY compound. In one aspect, the amino acid residues in the positions corresponding to positions 1-3 of hPYY(1-36) are absent, and the N-terminal substituent is covalently attached to the amino acid residue in the position corresponding to position 4 of hPYY(1-36).

In one aspect, the N-terminal substituent is an alkoxy group. In one aspect, the N-terminal substituent is an alkoxy group comprising up to 12 carbon atoms. In another aspect, the N-terminal substituent is an alkoxy group comprising up to 6 carbon atoms.

Modifying group / Protracting moiety

In one aspect, the PYY compound comprises a substituent or modifying group covalently attached to the amino acid residue in the position corresponding to position 10 of hPYY(1-36). In one further aspect, the substituent or modifying group is capable of

forming non-covalent conjugates with proteins, thereby promoting the circulation of the derivative with the blood stream, and also having the effect of protracting the time of action of the derivative, due to the fact that the conjugate of the PYY derivative and albumin is only slowly removed by renal clearance. Thus, the substituent, or modifying group, as a whole may also be referred to as a protracting moiety.

The modifying group may be covalently attached to a lysine residue of the PYY peptide by acylation, i.e., via an amide bond formed between a carboxylic acid group of the modifying group and the epsilon amino group of the lysine residue. The amino group of lysine could also be coupled to an aldehyde of the modifying group by reductive amination. In another aspect the thiol group of cysteine could by coupled to a maleiimido group of the modifying group by Michael addition or coupled to the chloro- or iodoacetyl group of the modifying group by nucleophilic substitution.

In one aspect, the modifying group is covalently attached to a lysine residue in a position corresponding to position 10 of hPYY(1-36) by acylation, i.e., via an amide bond formed between a carboxylic acid group of the modifying group and the epsilon amino group of the lysine residue.

The derivatives of the invention may exist in different stereoisomeric forms having the same molecular formula and sequence of bonded atoms, but differing only in the three-dimensional orientation of their atoms in space. The stereoisomerism of the exemplified derivatives of the invention is indicated in the experimental section, in the names as well as the structures, using standard nomenclature. Unless otherwise stated the invention relates to all stereoisomeric forms of the claimed derivative.

Herein, all amino acids of the PYY compound for which the optical isomer is not stated are to be understood to mean the L-isomer (unless otherwise specified).

Pharmaceutically acceptable salts

The PYY compounds of the invention may be in the form of a pharmaceutically acceptable salt.

Salts are e.g. formed by a chemical reaction between a base and an acid, e.g.: $2NH_3 + H_2SO_4 \rightarrow (NH_4)_2SO_4$.

The salt may be a basic salt, an acidic salt, or it may be neither nor (i.e. a neutral salt). Basic salts produce hydroxide ions and acid salts hydronium ions in water.

The salts of the derivatives of the invention may be formed with added cations or anions between anionic or cationic groups, respectively. These groups may be situated in the peptide moiety, and/or in the side chain of the derivatives of the invention.

Non-limiting examples of anionic groups of the derivatives of the invention include free carboxylic groups in the side chain, if any, as well as in the peptide moiety. The peptide moiety often includes free carboxylic groups at internal acid amino acid residues such as Asp and Glu.

Non-limiting examples of cationic groups in the peptide moiety include the free amino group at the N-terminus, if present, as well as any free amino group of internal basic amino acid residues such as His, Arg, and Lys.

FUNCTIONAL PROPERTIES

In a first functional aspect, the PYY compounds of the invention have a good Y2 receptor potency. Also, or alternatively, in a second aspect, they bind very well to the Y2 receptor. Preferably they are full Y2 receptor agonists as is reflected by their ability to bind strongly to the Y2 receptor combined with the capacity to fully activate the receptor compared to hPYY(1-36) and hPYY(3-36).

Also or alternatively, in a second functional aspect, the invention relates to PYY compounds displaying selectivity towards the Y receptor subtype Y2 as compared to Y receptor subtypes Y1, Y4 and Y5.

Also, or alternatively, in a third functional aspect, the PYY compounds of the invention have improved pharmacokinetic properties. Also, or alternatively, in a fourth functional aspect, the PYY compounds of the invention have increased half-life and/or a decreased clearance. Also, or alternatively, in a fifth functional aspect, they have the effect in vivo of decreasing the blood glucose. Also, or alternatively, in a sixth functional aspect, they have the effect in vivo of decreasing food intake. Also, or alternatively, in a seventh functional aspect, they have the effect in vivo of decreasing body weight.

Biological activity – in vitro potency

According to the first functional aspect, the PYY compounds of the invention are biologically active, or potent.

In a particular embodiment, potency and/or activity refers to in vitro potency, i.e. performance in a functional Y2 receptor assay, more in particular to the capability of activating the human Y2 receptor.

The term half maximal effective concentration (EC_{50}) generally refers to the concentration which induces a response halfway between the baseline and maximum, by reference to the dose response curve. EC_{50} is used as a measure of the potency of a compound and represents the concentration where 50% of its maximal effect is observed.

The in vitro potency of the derivatives of the invention may be determined as described in Example 2, and the EC_{50} of the derivative in question determined. The lower the EC_{50} value, the better the potency.

In one aspect of the invention, the derivative of the invention has an in vitro potency determined using the method of Example 2 corresponding to an EC_{50} at or below 50 nM. In one aspect, the derivative of the invention has an in vitro potency determined using the method of Example 2 corresponding to an EC_{50} at or below 30 nM. In one aspect, the derivative of the invention has an in vitro potency determined using the method of Example 2 corresponding to an EC_{50} at or below 15 nM.

Biological activity – in vitro receptor binding

According to the second functional aspect, the PYY compounds of the invention bind very well to the Y2 receptor. This may be determined as described in Example 3.

Generally, the binding to the Y2 receptor should be as good as possible, corresponding to a low Ki value. The Ki value is determined by the Cheng-Prusoff equation Ki=IC50/(1+[L]/Kd), wherein IC50 is the half maximal inhibitory concentration of the agonist, [L] is the concentration of the radioligand and Kd is the dissociation constant for binding.

As an example, in a particular aspect, the Y2 receptor binding affinity (Ki) is below 50 nM. In one aspect of the invention, the Y2 receptor binding affinity (Ki) is below 20 nM. In one aspect of the invention, the Y2 receptor binding affinity (Ki) is below 10 nM.

Biological activity – in vivo pharmacology

In another particular embodiment the PYY compounds of the invention are potent in vivo, which may be determined as is known in the art in any suitable animal model, as well as in clinical trials.

The diabetic db/db mouse is one example of a suitable animal model, and the blood glucose lowering effect may be determined in such mice in vivo, e.g. as described in Example 5.

In addition, inhibition of food intake in the db/db mice is a suitable model for determination of effect on food intake and body weight as also described in Example 5.

Generally, the glucose lowering effect of a 300 nmol/kg dose should be as good as possible corresponding to a low relative % glucose level.

As an example, in a particular aspect of the invention, 16 hours after dosing (300 nmol/kg) the relative % glucose level is below 90%. As an example, in a particular aspect of the invention, 16 hours after dosing (300 nmol/kg) the % relative food intake is

below 30%. As an example, in a particular aspect of the invention, 4 hours after dosing (300 nmol/kg) the relative % glucose level is below 80. As an example, in a particular aspect of the invention, 4 hours after dosing (300 nmol/kg) the % relative food intake is below 20%.

Pharmacokinetics profile

According to the third functional aspect, the PYY compounds of the invention have improved pharmacokinetic properties such as increased terminal half-life and/or decreased clearance.

Increasing terminal half-life and/or decreasing of the clearance means that the compound in question is eliminated slower from the body. For the compounds of the invention this entails an extended duration of pharmacological effect.

The pharmacokinetic properties of the derivatives of the invention may suitably be determined in-vivo in pharmacokinetic (PK) studies. Such studies are conducted to evaluate how pharmaceutical compounds are absorbed, distributed, and eliminated in the body, and how these processes affect the concentration of the compound in the body, over the course of time.

In the discovery and preclinical phase of pharmaceutical drug development, animal models such as the mouse, rat, monkey, dog, or pig, may be used to perform this characterisation. Any of these models can be used to test the pharmacokinetic properties of the derivatives of the invention.

The estimate of terminal half-life and/or clearance is relevant for evaluation of dosing regimens and an important parameter in drug development, in the evaluation of new drug compounds.

Pharmacokinetics profile – half life in vivo in minipigs

According to the third functional aspect, the derivatives of the invention have improved pharmacokinetic properties.

In a particular embodiment, the pharmacokinetic properties may be determined as terminal half-life ($T_{½}$) in vivo in minipigs after i.v. administration, e.g. as described in Example 4 herein.

In one aspect of the invention, the terminal half-life in minipigs is at least 15 hours. In one aspect of the invention, the terminal half-life in minipigs is at least 20 hours. In yet another aspect of the invention, the terminal half-life in minipigs is at least 40 hours.

PRODUCTION OF PYY COMPOUNDS

The production of peptides like the PYY compounds of the present invention is well known in the art.

The PYY moiety of the derivatives of the invention may for instance be produced by classical peptide synthesis, e.g., solid phase peptide synthesis using t-Boc or Fmoc chemistry or other well established techniques, see, e.g., Greene and Wuts, "Protective Groups in Organic Synthesis", John Wiley & Sons, 1999, Florencio Zaragoza Dörwald, "Organic Synthesis on solid Phase", Wiley-VCH Verlag GmbH, 2000, and "Fmoc Solid Phase Peptide Synthesis", Edited by W.C. Chan and P.D. White, Oxford University Press, 2000.

Also, or alternatively, they may be produced by recombinant methods, viz. by culturing a host cell containing a DNA sequence encoding the analogue and capable of expressing the peptide in a suitable nutrient medium under conditions permitting the expression of the peptide. Non-limiting examples of host cells suitable for expression of these peptides are: Escherichia coli, Saccharomyces cerevisiae, as well as mammalian BHK or CHO cell lines.

The PYY compounds of the invention which include non-natural amino acids and/or covalently attached substituents may e.g. be produced as described in the experimental part.

Specific examples of methods of preparing a number of the PYY compounds of the invention are included in the experimental part.

PROTEIN PURIFICATION

The PYY compounds of the present invention may be purified by a variety of procedures known in the art including, but not limited to, chromatography (e.g., ion exchange, affinity, hydrophobic, and reverse-phase high performance liquid chromatography (RP-HPLC)), electrophoretic procedures, or extraction (see, e.g., Protein Purification, J.-C. Janson and Lars Ryden, editors, VCH Publishers, New York, 1989).

MODE OF ADMINISTRATION

The term "treatment" is meant to include both the prevention and minimization of the referenced disease, disorder, or condition (i.e., "treatment" refers to both prophylactic and therapeutic administration of the PYY compounds of the invention or composition comprising the PYY compounds of the invention) unless otherwise indicated or clearly contradicted by context.

The route of administration may be any route which effectively transports a compound of this invention to the desired or appropriate place in the body, such as parenterally, for example, subcutaneously, intramuscularly or intravenously. Alternatively, a compound of this invention can be administered orally, pulmonary, rectally, transdermally, buccally, sublingually, or nasally.

PHARMACEUTICAL COMPOSITIONS

Injectable compositions comprising PYY compounds of the present invention can be prepared using the conventional techniques of the pharmaceutical industry which involve dissolving and mixing the ingredients as appropriate to give the desired end product. Thus, according to one procedure, a PYY compound of this invention is dissolved in a suitable buffer at a suitable pH so precipitation is minimised or avoided. The injectable composition is made sterile, for example, by sterile filtration.

A composition may be a stabilised formulation. The term "stabilised formulation" refers to a formulation with increased physical and/or chemical stability, preferably both. In general, a formulation must be stable during use and storage (in compliance with recommended use and storage conditions) until the expiration date is reached.

The term "physical stability" refers to the tendency of the polypeptide to form biologically inactive and/or insoluble aggregates as a result of exposure to thermo-mechanical stress, and/or interaction with destabilising interfaces and surfaces (such as hydrophobic surfaces). The physical stability of an aqueous polypeptide formulation may be evaluated by means of visual inspection, and/or by turbidity measurements after exposure to mechanical/physical stress (e.g. agitation) at different temperatures for various time periods. Alternatively, the physical stability may be evaluated using a spectroscopic agent or probe of the conformational status of the polypeptide such as e.g. Thioflavin T or "hydrophobic patch" probes.

The term "chemical stability" refers to chemical (in particular covalent) changes in the polypeptide structure leading to formation of chemical degradation products potentially having a reduced biological potency, and/or increased immunogenic effect as compared to the intact polypeptide. The chemical stability can be evaluated by measuring the amount of chemical degradation products at various time-points after exposure to different environmental conditions, e.g. by SEC-HPLC, and/or RP-HPLC.

In one aspect, the invention provides PYY compounds with improved physical stability. In one aspect, the invention provides PYY compounds with improved chemical stability.

COMBINATION TREATMENT

The treatment with a PYY compound according to the present invention may also be combined with one or more additional pharmacologically active substances, e.g. selected from antidiabetic agents, antiobesity agents, appetite regulating agents, antihypertensive agents, agents for the treatment and/or prevention of complications resulting from or associated with diabetes and agents for the treatment and/or prevention of complications and disorders resulting from or associated with obesity.

Examples of these pharmacologically active substances are: GLP-1 receptor agonists, insulin, DPP-IV (dipeptidyl peptidase-IV) inhibitors, amylin agonists and leptin receptor agonists.

In one aspect of the invention, a PYY compound according to the present invention is combined with a GLP-1 agonist. The compounds may be supplied in a single-dosage form wherein the single-dosage form contains both compounds, or in the form of a kit-of-parts comprising a preparation of the PYY compound as a first unit dosage form and a preparation of the GLP-1 agonist as a second unit dosage form.

Non-limiting examples of GLP-1 agonists to be combined with the PYY compounds of the present invention are liraglutide, semaglutide, exenatide, dulaglutide, lixisenatide, taspoglutide, and albiglutide.

Liraglutide, a mono-acylated GLP-1 derivative for once daily administration which is marketed as of 2009 by Novo Nordisk A/S, is disclosed in WO 98/08871.

WO 2006/097537 discloses additional GLP-1 derivatives including semaglutide , a mono-acylated GLP-1 derivative for once weekly administration which is under development by Novo Nordisk A/S.

Exenatide is a synthetic version of exendin-4, a hormone found in the saliva of the Gila monster. It displays biological properties similar to GLP-1.

Dulaglutide is a GLP-1-Fc construct (GLP-1 - linker - Fc from IgG4).

Lixisenatide is based on exendin-4(1-39) modified C-terminally with six Lys residues.

Taspoglutide is the 8-(2-methylalanine)-35-(2-methylalanine)-36-L-argininamide derivative of the amino acid sequence 7–36 of human GLP-1.

Albiglutide is a recombinant human serum albumin (HSA)-GLP-1 hybrid protein, likely a GLP-1 dimer fused to HSA. The constituent GLP-1 peptide is an analogue, in which Ala at position 8 has been substituted by Gly.

PHARMACEUTICAL INDICATIONS

The present invention also relates to a PYY compound of the invention for use as

a medicament.

In particular aspects of the invention, the PYY compounds of the invention may be used for the following medical treatments:

(i) prevention and/or treatment of all forms of diabetes, such as hyperglycemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, non-insulin dependent diabetes, MODY (maturity onset diabetes of the young), gestational diabetes, and/or for reduction of HbA1C;

(ii) delaying or preventing diabetic disease progression, such as progression in type 2 diabetes, delaying the progression of impaired glucose tolerance (IGT) to insulin requiring type 2 diabetes, delaying or preventing insulin resistance, and/or delaying the progression of non-insulin requiring type 2 diabetes to insulin requiring type 2 diabetes;

(iii) improving β-cell function, such as decreasing β-cell apoptosis, increasing β-cell function and/or β-cell mass, and/or for restoring glucose sensitivity to β-cells;

(iv) prevention and/or treatment of eating disorders, such as obesity, e.g. by decreasing food intake, reducing body weight, suppressing appetite, inducing satiety; treating or preventing binge eating disorder, bulimia nervosa, and/or obesity induced by administration of an antipsychotic or a steroid; reduction of gastric motility; delaying gastric emptying; increasing physical mobility; and/or prevention and/or treatment of comorbidities to obesity, such as osteoarthritis and/or urine incontinence;

(v) prevention and/or treatment of diabetic complications, such as angiopathy; neuropathy, including peripheral neuropathy; nephropathy; and/or retinopathy;

(vi) improving lipid parameters, such as prevention and/or treatment of dyslipidemia, lowering total serum lipids; increasing HDL; lowering small, dense LDL; lowering VLDL; lowering triglycerides; lowering cholesterol; lowering plasma levels of lipoprotein a (Lp(a)) in a human; inhibiting generation of apolipoprotein a (apo(a)) in vitro and/or in vivo;

(vii) prevention and/or treatment of cardiovascular diseases; and/or

(viii) prevention and/or treatment of sleep apnoea.

The following indications are particularly preferred: Type 2 diabetes, and/or obesity.

In one aspect, a method is disclosed herein for altering energy metabolism in a subject. The method includes administering a therapeutically effective amount of a PYY compound of the invention to the subject, thereby altering energy expenditure. Energy is burned in all physiological processes. The body can alter the rate of energy expenditure

directly, by modulating the efficiency of those processes, or changing the number and nature of processes that are occurring. For example, during digestion the body expends energy moving food through the bowel, and digesting food, and within cells, the efficiency of cellular metabolism can be altered to produce more or less heat.

In one aspect a method is disclosed herein for any and all manipulations of the accurate circuitry described in this application, which alter food intake co-ordinately and reciprocally alter energy expenditure. Energy expenditure is a result of cellular metabolism, protein synthesis, metabolic rate, and calorie utilization. Thus, in this embodiment, peripheral administration results in increased energy expenditure, and decreased efficiency of calorie utilization. In one aspect, a therapeutically effective amount of a PYY compound according to the invention is administered to a subject, thereby increasing energy expenditure.

While "obesity" is generally defined as a body mass index over 30, for purposes of this disclosure, any subject, including those with a body mass index of less than 30, who needs or wishes to reduce body weight is included in the scope of "obese." Without intending to be limited by theory, it is believed that the effects of peripherally administered PYY compounds of the present invention in the reduction of food intake, in the delay of gastric emptying, in the reduction of nutrient availability, and in the causation of weight loss are determined by interactions with one or more unique receptor classes in, or similar to, those in the PP family. More particularly, it appears that a receptor or receptors similar to the PYY-preferring (or Y2) receptors are involved.

PARTICULAR EMBODIMENTS

The invention is further described by the following non-limiting embodiments of the invention:

1. A PYY compound having a maximum of 10 amino acid modifications as compared to hPYY(3-36) (SEQ ID NO:2), wherein the PYY compound comprises

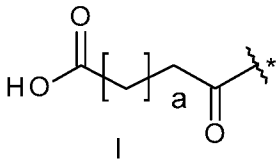
i) tryptophan at the position corresponding to position 30 of hPYY(1-36) (SEQ ID NO:1)

ii) N(alpha)-methyl-L-arginine at the position corresponding to position 35 of hPYY(1-36) (SEQ ID NO:1);

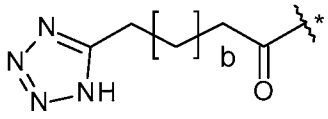
iii) lysine at the position corresponding to position 10 of hPYY(1-36) (SEQ ID NO:1); and

iv) a modifying group attached to the epsilon amino group of the Lysine residue in position 10, wherein said modifying group is defined by **A-B-C-D-E-**, wherein

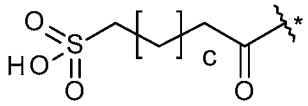
A is selected from



I ,



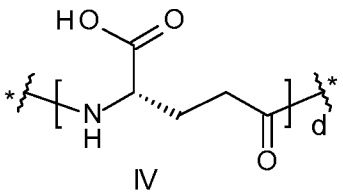
II , and



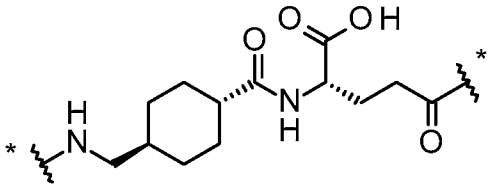
III ,

wherein a is an integer from 12 to 19, b is an integer from 10 to 16, and c is an integer from 10 to 16;

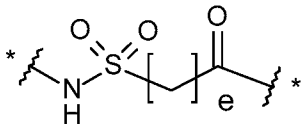
B is selected from



IV ,



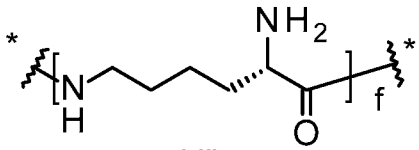
V , and



VI ,

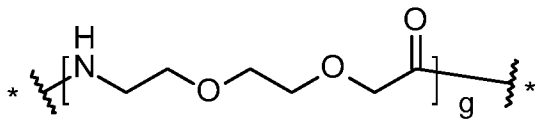
wherein d is 1 or 2; and e is 2, 3 or 4;

C is absent or

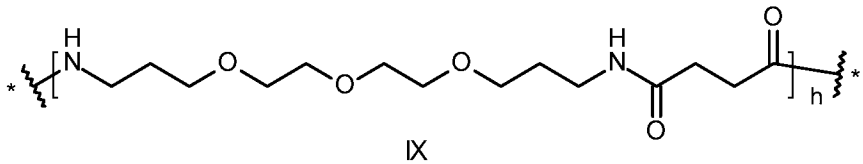


VII , wherein f is 1 or 2;

D is selected from



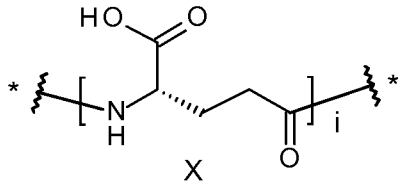
VIII , or



IX ,

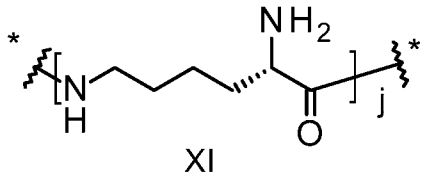
wherein g is 1 or 2, h is 1 or 2; and

E is absent or selected from



X

, and



XI

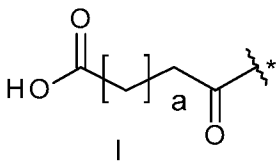
,

wherein i is 1 or 2, and j is 1 or 2; and

wherein * denotes the points of attachment, and wherein A, B, C, D and E are interconnected via amide bonds and in the sequence indicated via said point of attachments.

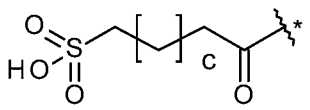
2. A PYY compound according to embodiment 1, wherein a is 13 or 15, b is 14, or c is 13.

3. A PYY compound according to embodiment 1, wherein **A-** is selected from



I

or



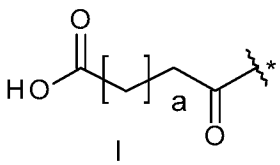
III

,

wherein a is an integer from 12 to 19, and c is an integer from 10 to 16.

4. A PYY compound according to embodiment 3, wherein a is an integer from 13 to 15, and c is 13.

5. A PYY compound according to any one of the preceding embodiments, wherein **A-** is

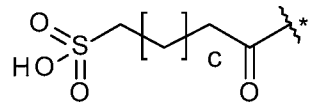


I

, wherein a is an integer from 13 to 15.

6. A PYY compound according to embodiment 5, wherein a is 13 or 15.

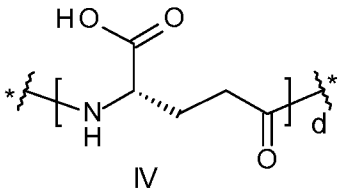
7. A PYY compound according to embodiment 1, wherein **A-** is



III , wherein c is an integer from 10 to 16.

8. A PYY compound according to embodiment 7, wherein c is 13.

9. A PYY compound according to any one of the preceding embodiments, wherein **B-** is



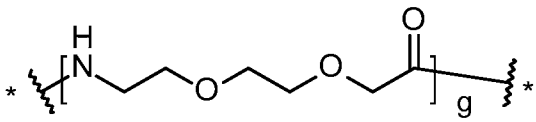
IV , wherein d is 1 or 2.

10. A PYY compound according to embodiment 9, wherein d is 1.

11. A PYY compound according to any one of the preceding embodiments, wherein f is 0.

12. A PYY compound according to any one of the preceding embodiments, wherein C is absent.

13. A PYY compound according to any one of the preceding embodiments, wherein

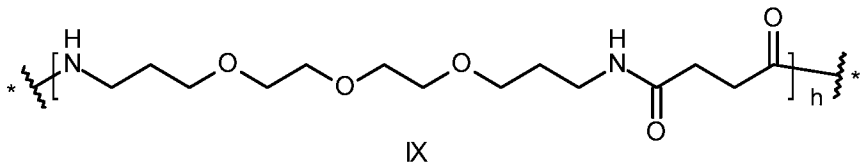


D is VIII ,

wherein g is 1 or 2.

14. A PYY compound according to embodiment 13, wherein g is 2.

15. A PYY compound according to any one of the preceding embodiments, wherein

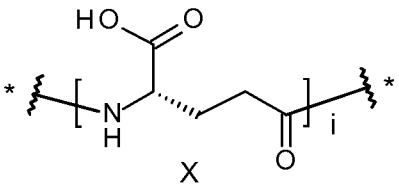


D is IX ,

wherein h is 1 or 2.

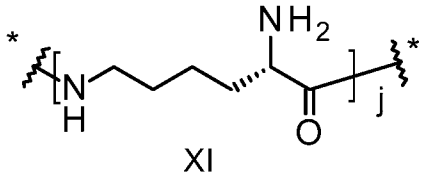
16. A PYY compound according to embodiment 15, wherein h is 2.

17. A PYY compound according to any one of the preceding embodiments, wherein **E** is selected from



X

, and

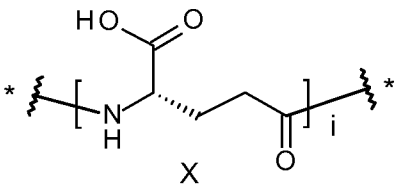


XI ,

wherein i is 1 or 2, and j is 1 or 2.

18. A PYY compound according to embodiment 17, wherein i is 1, and j is 2.

19. A PYY compound according to any one of the preceding embodiments, wherein **E** is

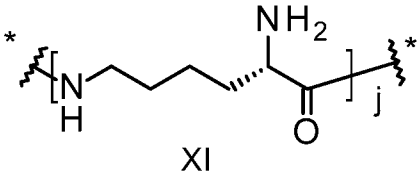


X ,

wherein i is 1 or 2.

20. A PYY compound according to embodiment 19, wherein i is 1.

21. A PYY compound according to any one of the preceding embodiments, wherein



E is XI ,

wherein j is 1 or 2.

22. A PYY compound according to embodiment 21, wherein j is 2.

23. A PYY compound according to any one of the preceding embodiments, wherein **E** is absent.

24. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound comprises glutamine at the position corresponding to position 18 of hPYY(1-36) (SEQ ID NO:1).

25. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound comprises arginine at the position corresponding to position 4 of hPYY(1-36) (SEQ ID NO:1).

26. A PYY compound according to any one of the preceding embodiments, wherein the positions corresponding to positions 1 and 2 of hPYY(1-36) (SEQ ID NO:1) are absent.

27. A PYY compound according to any one of the preceding embodiments, wherein the positions corresponding to positions 1-3 of hPYY(1-36) (SEQ ID NO:1) are absent.

28. A PYY compound according to any one of the preceding embodiments, wherein the positions corresponding to positions 1-3 of hPYY(1-36) (SEQ ID NO:1) are absent, and wherein the PYY compound further comprises an N-terminal substituent, wherein the N-terminal substituent is an alkoxy group comprising up to 12 carbon atoms.

29. A PYY compound according to embodiment 28, wherein the N-terminal substituent is an alkoxy group comprising up to 10 carbon atoms.

30. A PYY compound according to embodiment 28, wherein the N-terminal substituent is an alkoxy group comprising up to 9 carbon atoms.

31. A PYY compound according to embodiment 28, wherein the N-terminal substituent is an alkoxy group comprising up to 8 carbon atoms.

32. A PYY compound according to embodiment 28, wherein the N-terminal substituent is an alkoxy group comprising up to 7 carbon atoms.

33. A PYY compound according to embodiment 28, wherein the N-terminal substituent is an alkoxy group comprising up to 6 carbon atoms.

34. A PYY compound according to embodiment 28, wherein the N-terminal substituent is an alkoxy group comprising 6 carbon atoms.

35. A PYY compound according to embodiment 28, wherein the N-terminal substituent is selected from 3-methylbutanoyl and 3-methylpentanoyl.

36. A PYY compound according to embodiment 28, wherein the N-terminal substituent is 3-methylbutanoyl.

37. A PYY compound according to embodiment 28, wherein the N-terminal substituent is 3-methylpentanoyl.

38. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has a maximum of 9 amino acid modifications as compared to hPYY(3-36).

39. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has a maximum of 8 amino acid modifications as compared to hPYY(3-36).

40. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has a maximum of 7 amino acid modifications as compared to hPYY(3-36).

41. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has a maximum of 6 amino acid modifications as compared to hPYY(3-36).

42. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has a maximum of 5 amino acid modifications as compared to hPYY(3-36).

43. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has a maximum of 4 amino acid modifications as compared to hPYY(3-36).

44. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has a maximum of 3 amino acid modifications as compared to hPYY(3-36).

45. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has a maximum of 2 amino acid modifications as compared to hPYY(3-36).

46. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has a maximum of 1 amino acid modification as compared to hPYY(3-36).

47. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has a minimum of 4 amino acid modifications as compared to hPYY(3-36).

48. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has a minimum of 5 amino acid modifications as compared to hPYY(3-36).

49. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has a minimum of 6 amino acid modifications as compared to hPYY(3-36).

50. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has a minimum of 7 amino acid modifications as compared to hPYY(3-36).

51. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has a minimum of 8 amino acid modifications as compared to hPYY(3-36).

52. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has in the range of 4 to 10 amino acid modifications as compared to hPYY(3-36).

53. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has in the range of 6 to 8 amino acid modifications as compared to hPYY(3-36).

54. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has in the range of 4 to 6 amino acid modifications as compared to hPYY(3-36).

55. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has 4 amino acid modifications as compared to hPYY(3-36).

56. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has 5 amino acid modifications as compared to hPYY(3-36).

57. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has 6 amino acid modifications as compared to hPYY(3-36).

58. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has 7 amino acid modifications as compared to hPYY(3-36).

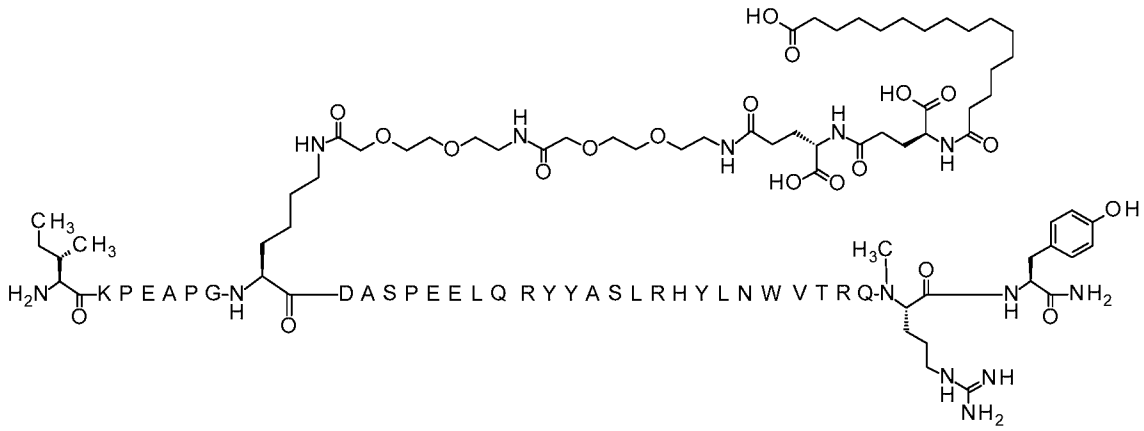
59. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has 8 amino acid modifications as compared to hPYY(3-36).

60. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has 9 amino acid modifications as compared to hPYY(3-36).

61. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has 10 amino acid modifications as compared to hPYY(3-36).

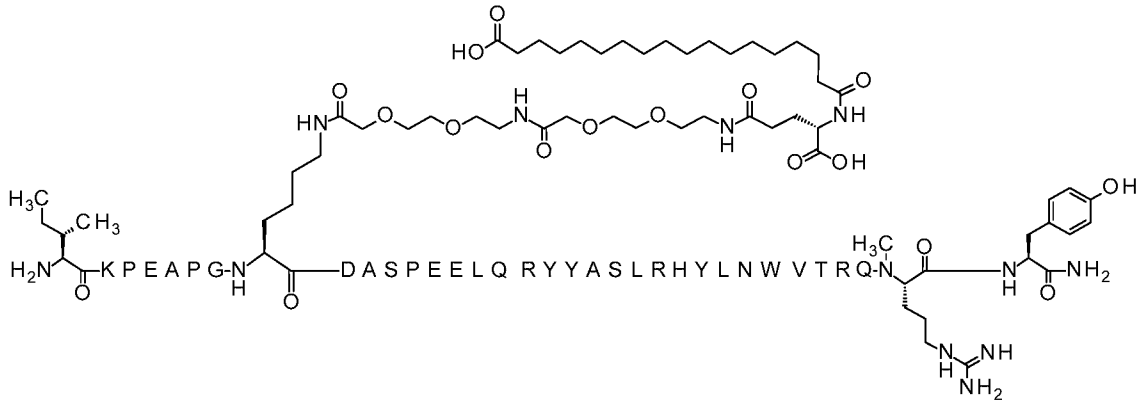
62. A PYY compound according to any one of the preceding embodiments selected from the following:

N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-[[(4S)-4-carboxy-4-(15-carboxypentadecanoylamino)butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]-[Lys10,Gln18,Trp30,NmeArg35]hPYY(3-36) (Compound 4) (1339)



;

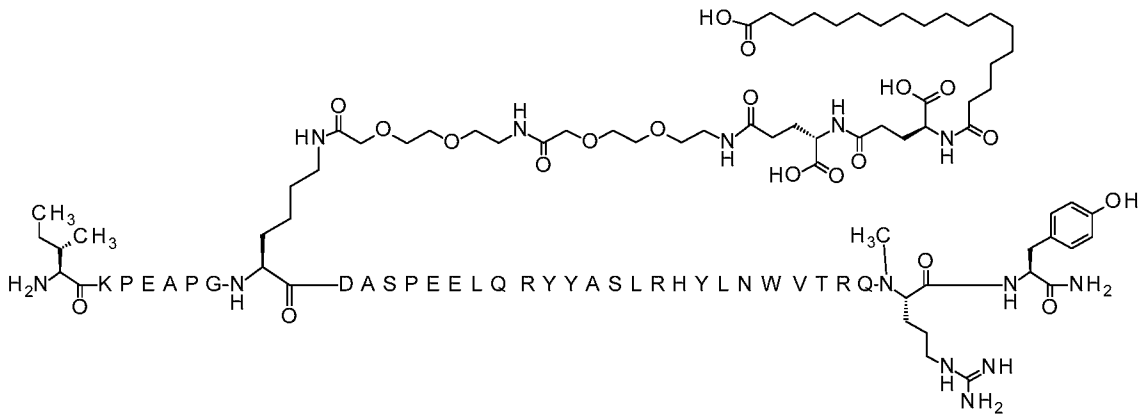
N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)-butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]-ethoxy]acetyl]-[Lys10,Gln18, Trp30,NmeArg35]hPYY(3-36) (Compound 5) (0832)



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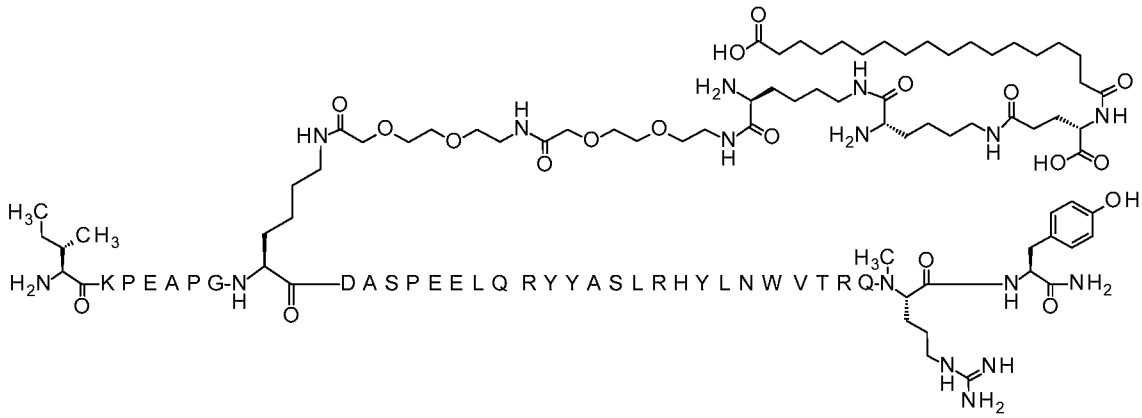
N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]-

acetyl]amino]ethoxy]ethoxy]acetyl]-[Lys10,Gln18,Trp30,NmeArg35]hPYY(3-36) (Compound 6) (0996)



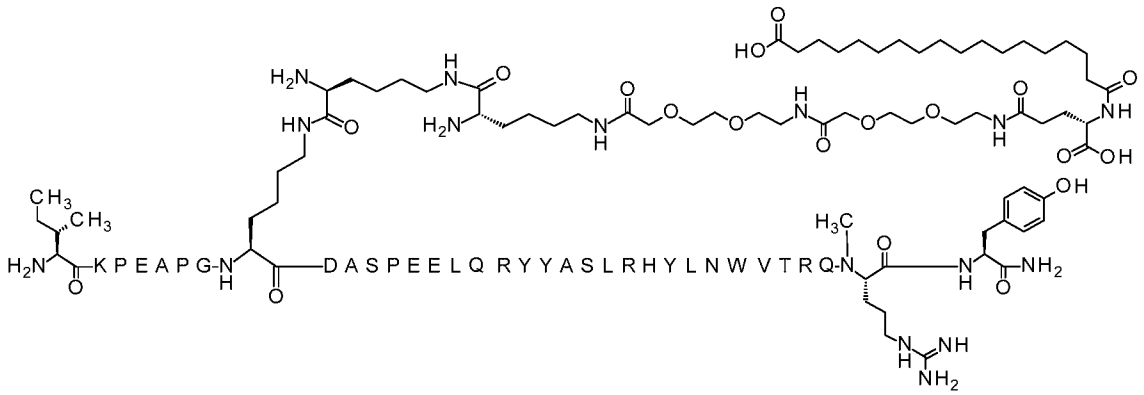
;

N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(2S)-2-amino-6-[[(2S)-2-amino-6-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]hexanoyl]amino]-hexanoyl]amino]-ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]-[Lys10,Gln18,Trp30,NmeArg35]-hPYY(3-36) (Compound 7) (0833)



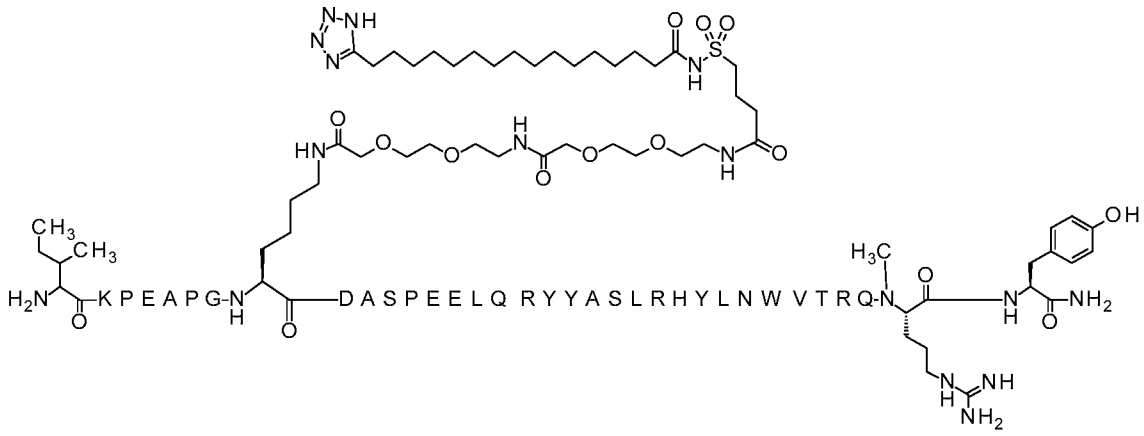
;

N{Epsilon-10}-[(2S)-2-amino-6-[[(2S)-2-amino-6-[[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]-ethoxy]ethoxy]acetyl]amino]hexanoyl]amino]hexanoyl][Lys10,Gln18,Trp30,NmeArg35]-hPYY(3-36) (Compound 8) (1491)



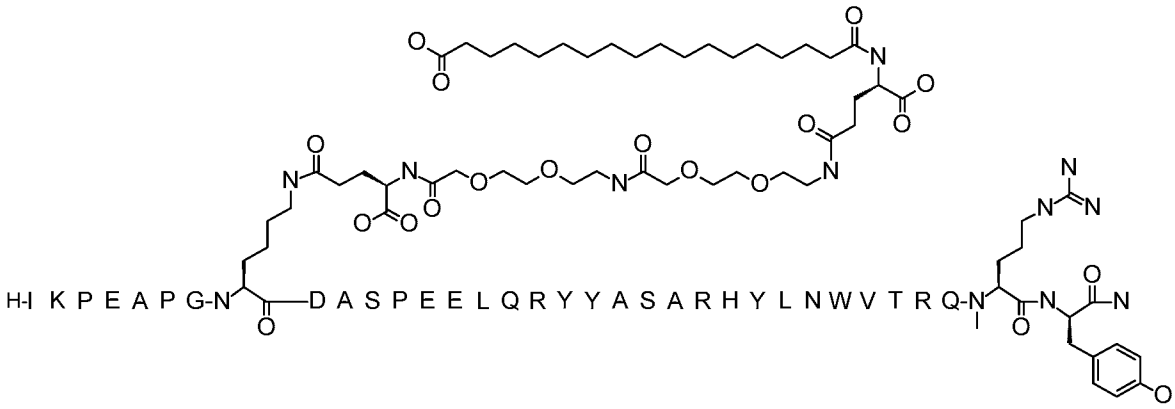
;

N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[4-[16-(1H-tetrazol-5-yl)hexadecanoylsulfamoyl]-butanoylamino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]-[Lys10,Gln18, Trp30,NmeArg35]hPYY(3-36) (Compound 9) (0997)



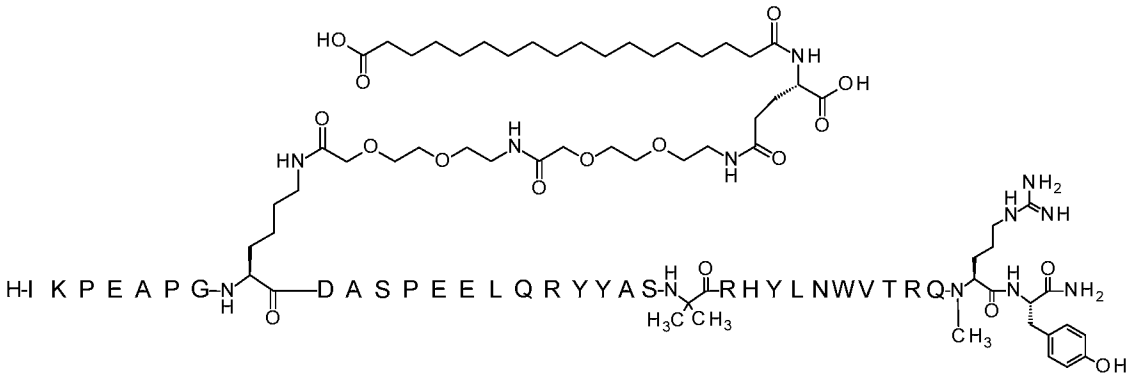
;

N{Epsilon-10}-[(4S)-4-carboxy-4-[[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]-ethoxy]acetyl]amino]butanoyl]-[Lys10,Gln18,Ala24,Trp30,NmeArg35]hPYY(3-36) (Compound 10) (1186)



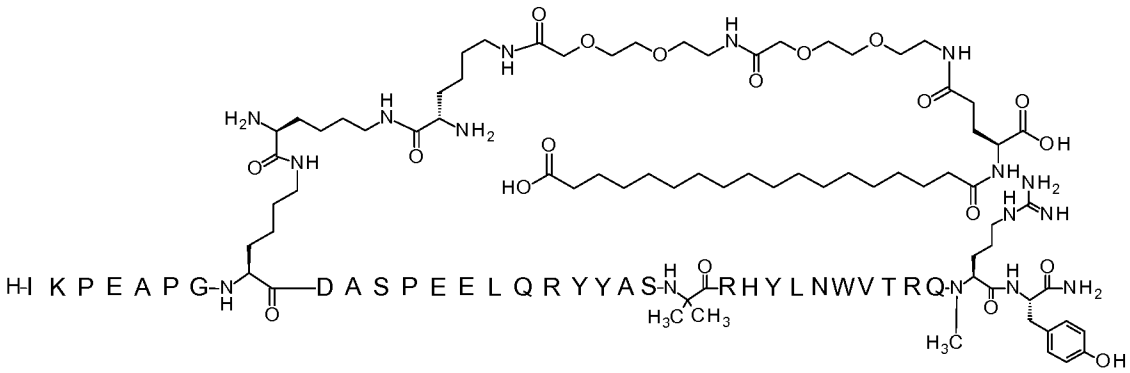
;

N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)-butanoyl]amino]ethoxy]ethoxy]acetyl]-amino]ethoxy]ethoxy]acetyl]-[Lys10,Gln18, Aib24,Trp30,NmeArg35]hPYY(3-36) (Compound 11) (1185)



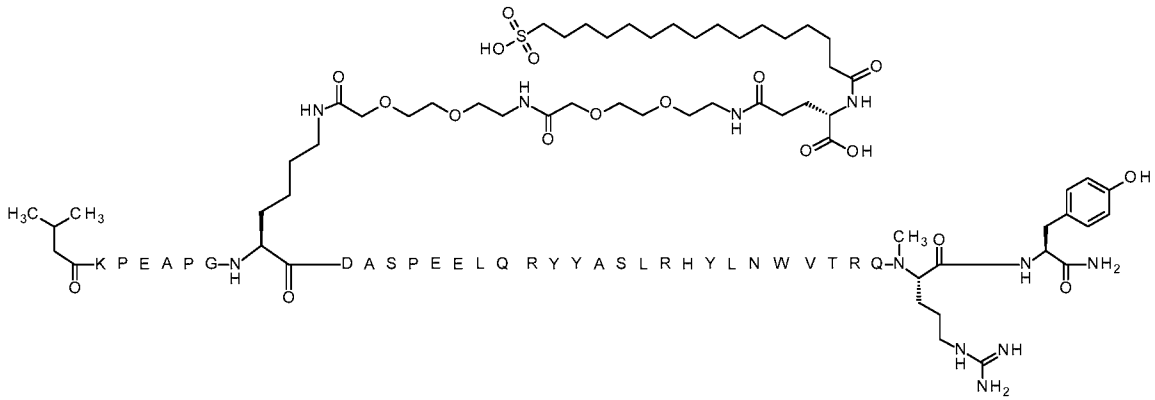
;

N{Epsilon-10}-[(2S)-2-amino-6-[[(2S)-2-amino-6-[[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]-ethoxy]ethoxy]acetyl]amino]hexanoyl]amino]hexanoyl]-[Lys10,Gln18,Aib24, Trp30,NmeArg35]hPYY(3-36) (Compound 12) (1187)



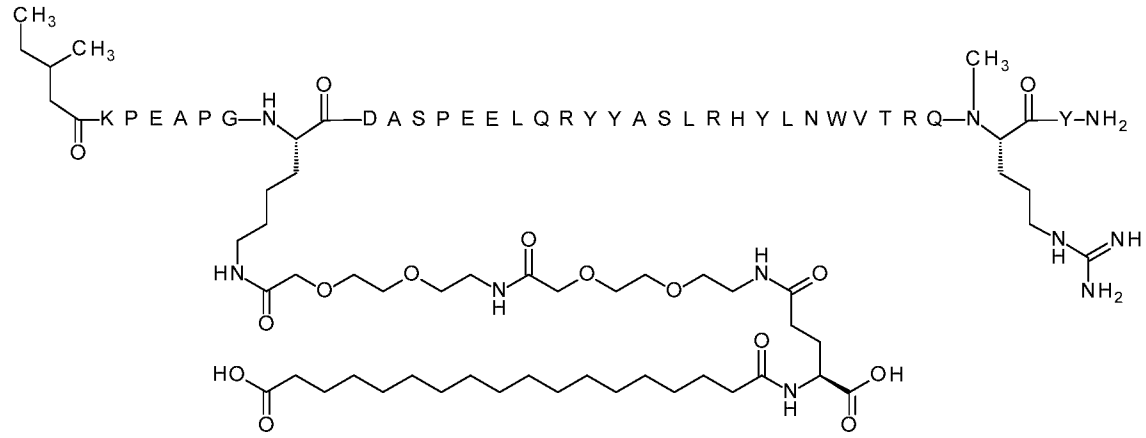
;

N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(16-sulfohexadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]-ethoxy]acetyl]-[Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) (Compound 13) (1640)



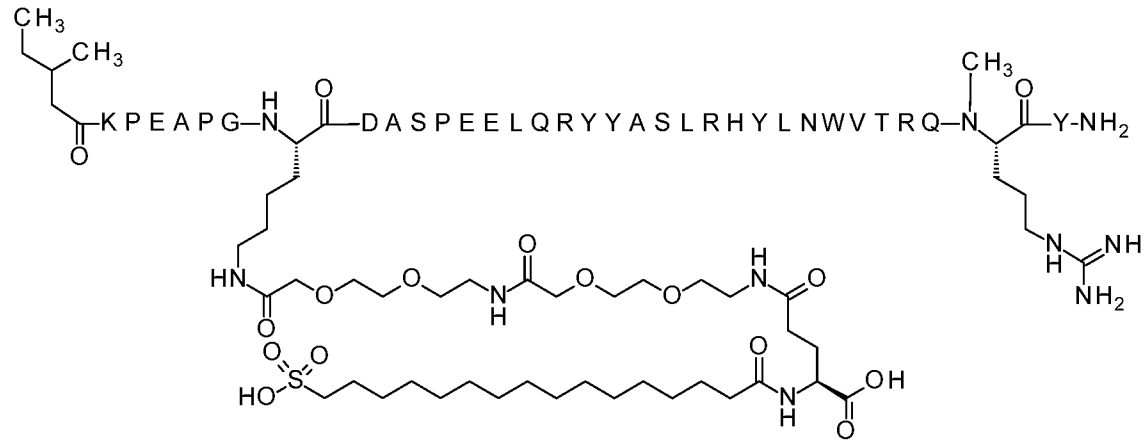
;

N{Alpha-4}-3-methylpentanoyl)-N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]-ethoxy]acetyl]-[Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) (Compound 14) (1511)



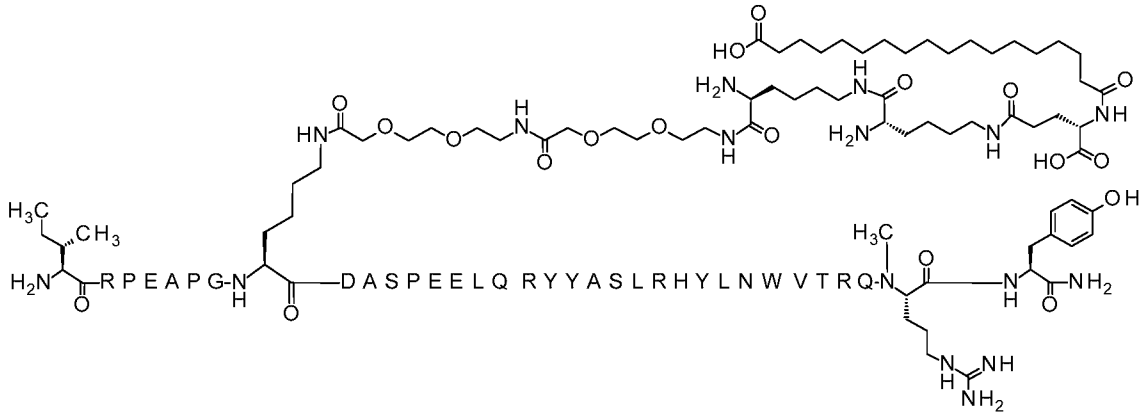
;

N{alpha-4}-(3-Methylpentanoyl)-N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(16-sulfohexadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]-ethoxy]acetyl]-[Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) (Compound 15) (1512)



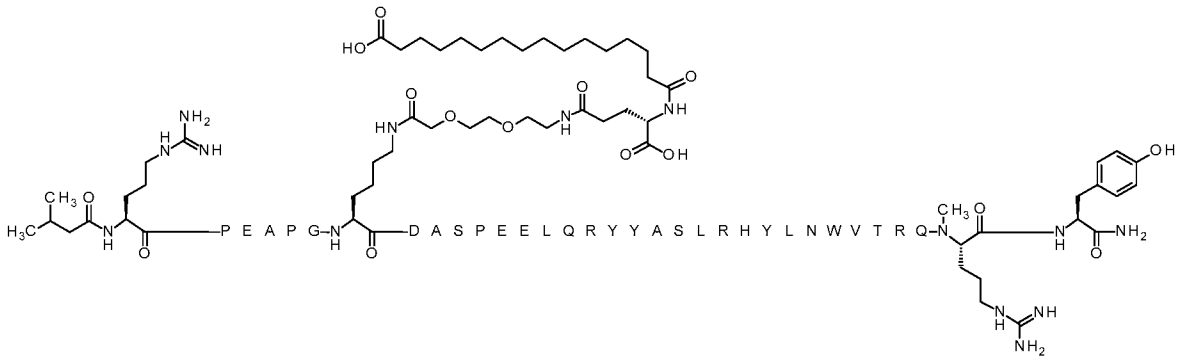
;

N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(2S)-2-amino-6-[[(2S)-2-amino-6-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]hexanoyl]amino]hexanoyl]amino]-ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]-[Arg4,Lys10,Gln18,Trp30, NmeArg35]hPYY(3-36) (Compound 16) (1586)



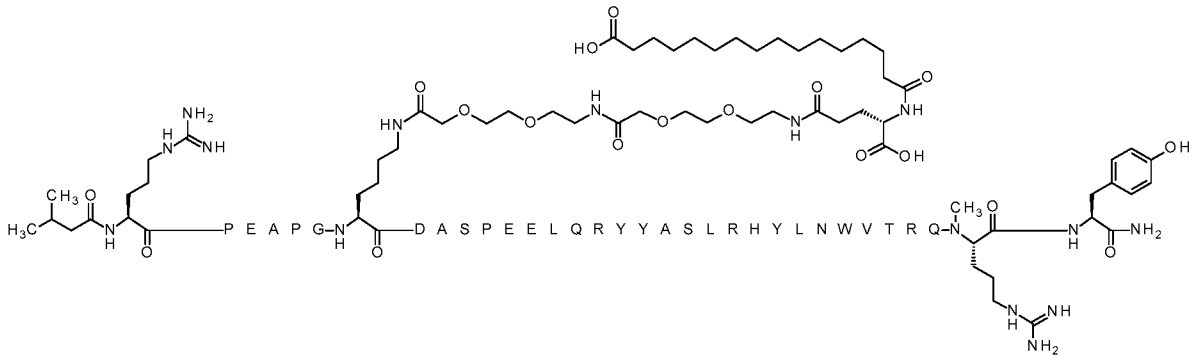
;

N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[2-[2-[2-[[(4S)-4-carboxy-4-(15-carboxypentadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]-[Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) (Compound 17) (1667)



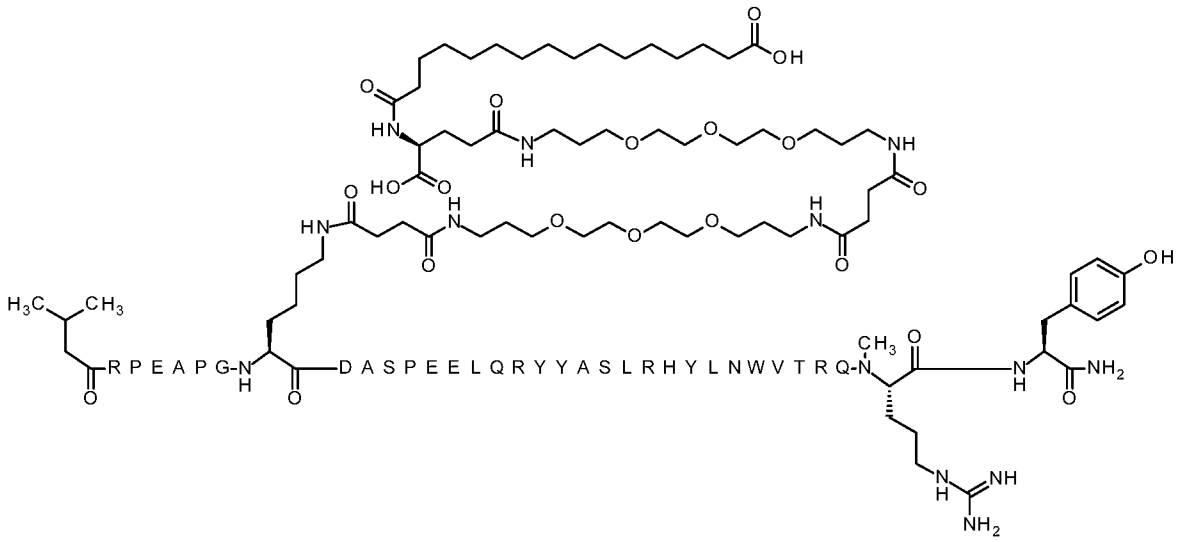
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N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(15-carboxypentadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]-ethoxy]acetyl]-[Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) (Compound 18) (1649)



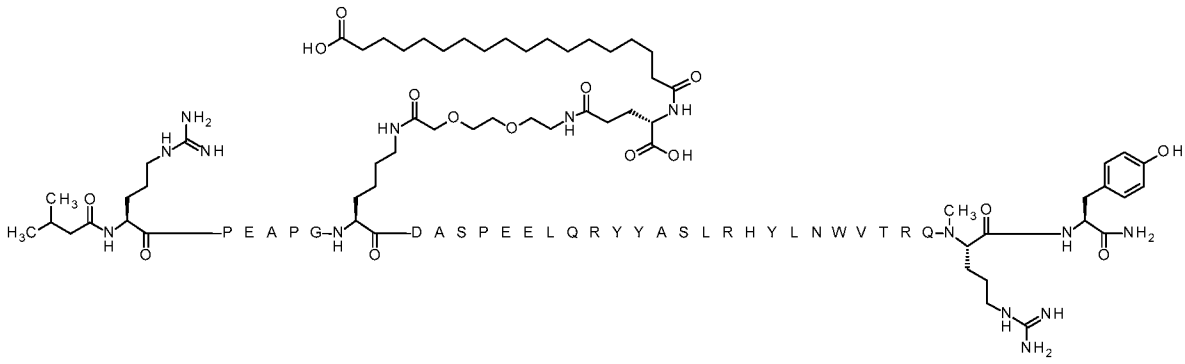
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N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[4-[3-[2-[2-[3-[[4-[3-[2-[2-[3-[[(4S)-4-carboxy-4-(15-carboxypentadecanoylamino)butanoyl]amino]propoxy]ethoxy]ethoxy]-propylamino]-4-oxobutanoyl]amino]propoxy]ethoxy]ethoxy]propylamino]-4-oxobutanoyl]-[Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) (Compound 19) (1639)



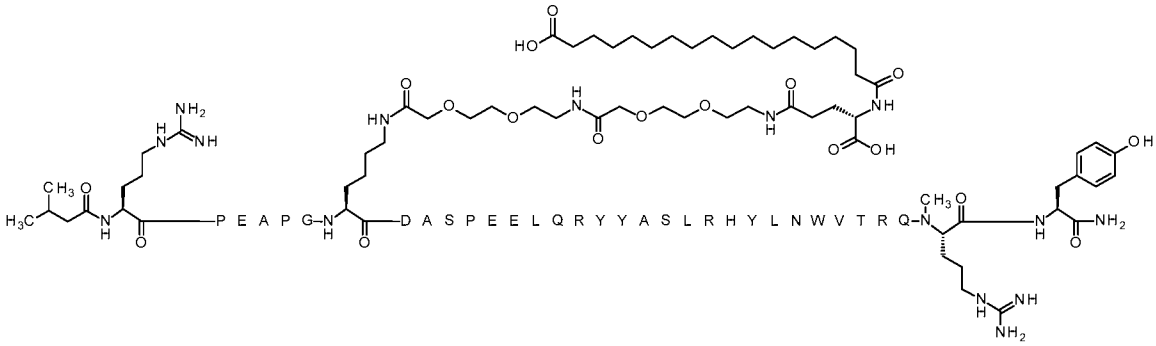
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N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]-[Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) (Compound 20) (1657)



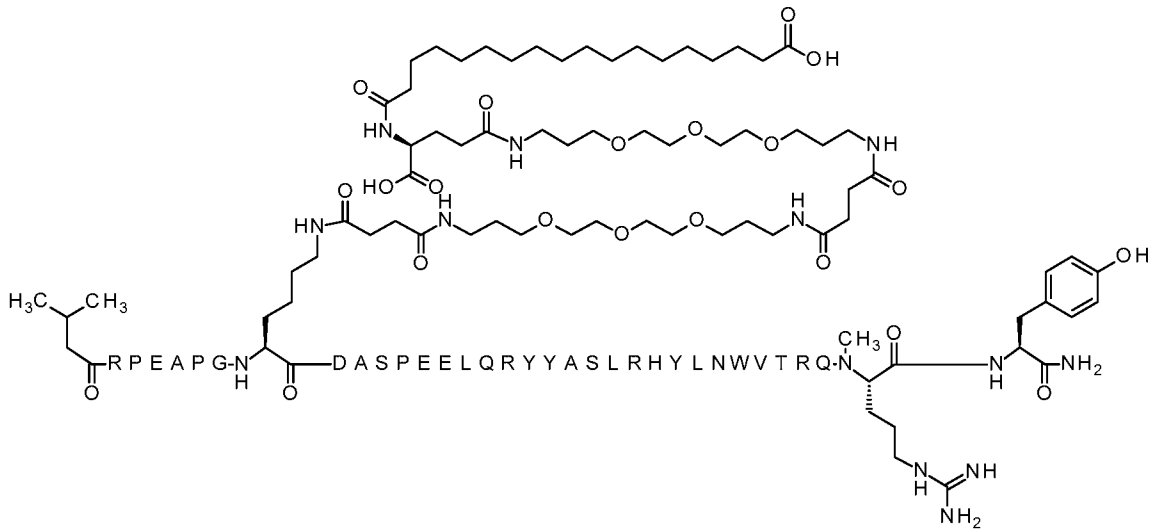
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N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]-ethoxy]acetyl]-[Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) (Compound 21) (1645)



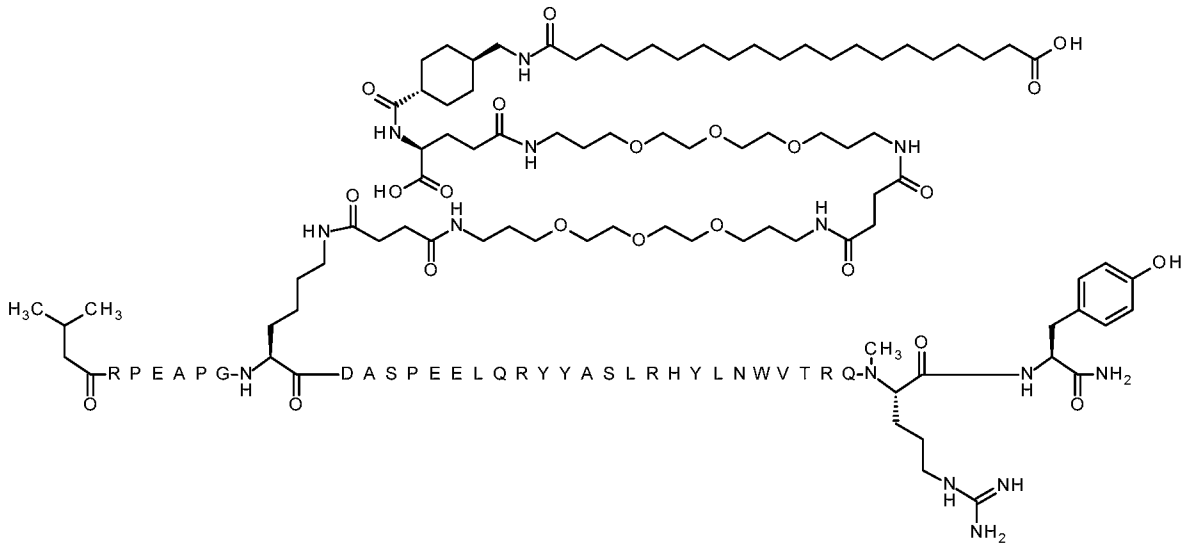
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N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[4-[3-[2-[2-[3-[[4-[3-[2-[2-[3-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]propoxy]ethoxy]-ethoxy]propylamino]-4-oxobutanoyl]amino]propoxy]ethoxy]-ethoxy]propylamino]-4-oxobutanoyl]-[Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) (Compound 22) (1636)



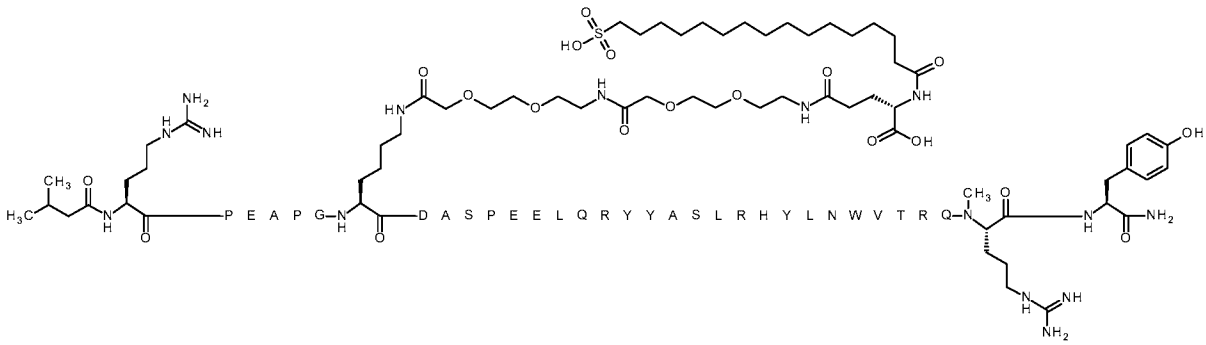
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N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[4-[3-[2-[2-[3-[[4-[3-[2-[2-[3-[[(4S)-4-carboxy-4-[[4-[(19-carboxynonadecanoylamino)methyl]cyclohexanecarbonyl]amino]-butanoyl]amino]propoxy]ethoxy]ethoxy]propylamino]-4-oxobutanoyl]amino]-propoxy]ethoxy]ethoxy]propylamino]-4-oxobutanoyl]-[Arg4,Lys10,Gln18,Trp30, NmeArg35]hPYY(4-36) (Compound 23) (1638)



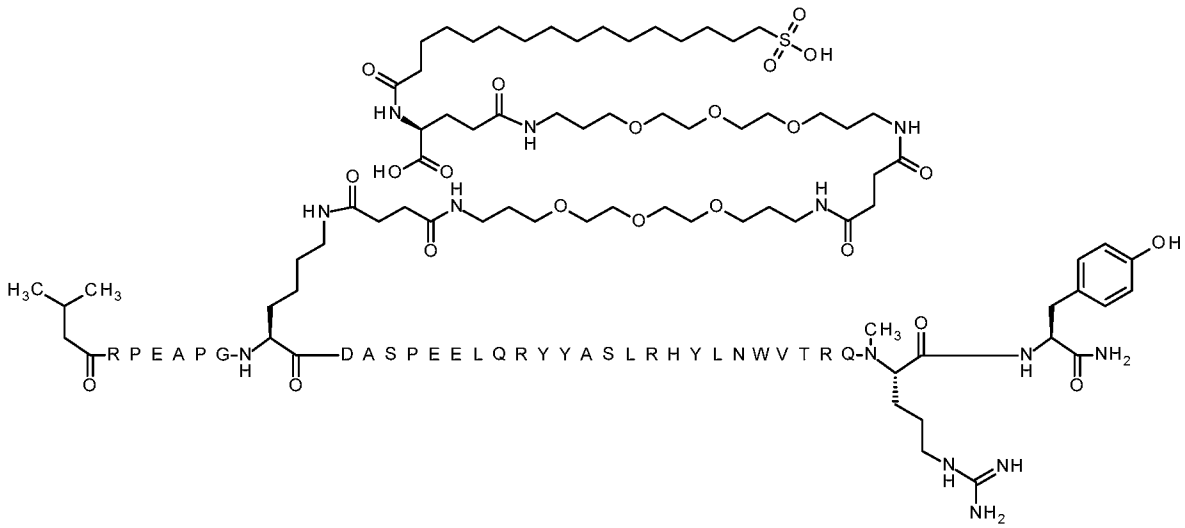
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N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(16-sulfohexadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]-ethoxy]acetyl]-[Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) (Compound 24) (1643)



;

N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[4-[3-[2-[2-[3-[[4-[3-[2-[2-[3-[[(4S)-4-carboxy-4-(16-sulfohexadecanoylamino)butanoyl]amino]-propoxy]ethoxy]ethoxy]-propylamino]-4-oxobutanoyl]amino]propoxy]ethoxy]-ethoxy]propylamino]-4-oxobutanoyl]-[Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) (Compound 25) (1637)



.

63. A PYY compound according to embodiment 1, wherein the PYY compound is compound 4.

64. A PYY compound according to embodiment 1, wherein the PYY compound is compound 5.

65. A PYY compound according to embodiment 1, wherein the PYY compound is compound 6.

66. A PYY compound according to embodiment 1, wherein the PYY compound is compound 7.

67. A PYY compound according to embodiment 1, wherein the PYY compound is compound 8.

68. A PYY compound according to embodiment 1, wherein the PYY compound is compound 9.

69. A PYY compound according to embodiment 1, wherein the PYY compound is compound 10.

70. A PYY compound according to embodiment 1, wherein the PYY compound is compound 11.

71. A PYY compound according to embodiment 1, wherein the PYY compound is compound 12.

72. A PYY compound according to embodiment 1, wherein the PYY compound is compound 13.

73. A PYY compound according to embodiment 1, wherein the PYY compound is compound 14.

74. A PYY compound according to embodiment 1, wherein the PYY compound is compound 15.

75. A PYY compound according to embodiment 1, wherein the PYY compound is compound 16.

76. A PYY compound according to embodiment 1, wherein the PYY compound is compound 17.

77. A PYY compound according to embodiment 1, wherein the PYY compound is compound 18.

78. A PYY compound according to embodiment 1, wherein the PYY compound is compound 19.

79. A PYY compound according to embodiment 1, wherein the PYY compound is compound 20.

80. A PYY compound according to embodiment 1, wherein the PYY compound is compound 21.

81. A PYY compound according to embodiment 1, wherein the PYY compound is compound 22.

82. A PYY compound according to embodiment 1, wherein the PYY compound is compound 23.

83. A PYY compound according to embodiment 1, wherein the PYY compound is compound 24.

84. A PYY compound according to embodiment 1, wherein the PYY compound is compound 25.

85. A PYY compound according to any one of the preceding embodiments which is a human Y2 receptor agonist.

86. A PYY compound according to any one of the preceding embodiments which is a full human Y2 receptor agonist.

87. A PYY compound according to any one of the preceding embodiments which is a selective human Y2 receptor agonist.

88. A PYY compound according to any one of the preceding embodiments which is a selective full human Y2 receptor agonist.

89. A PYY compound according to any one of the preceding embodiments which is capable of activating the human Y2 receptor.

90. A PYY compound according to any one of the preceding embodiments which is capable of activating the human Y2 receptor in an assay with whole cells expressing the human Y2 receptor.

91. A PYY compound according to any one of the preceding embodiments which is capable of activating the human Y2 receptor in the Actone functional potency assay of Example 2.

92. A PYY compound according to any one of the preceding embodiments which is capable of binding to the human Y2 receptor.

93. A PYY compound according to any one of the preceding embodiments which is capable of binding to the human Y2 receptor, wherein the binding to the human Y2 receptor is measured in a competitive binding assay, such as the assay of Example 3.

94. A PYY compound according to any one of the preceding embodiments which has improved pharmacokinetic properties.

95. A PYY compound according to any one of the preceding embodiments which has an increased half-life and/or a decreased clearance.

96. A PYY compound according to any one of the preceding embodiments which has the effect in vivo of decreasing the blood glucose determined in a single-dose study in a db/db mouse model.

97. A PYY compound according to any one of the preceding embodiments which has the effect in vivo of decreasing food intake determined in a single-dose study in a db/db mouse model.

98. A pharmaceutical composition comprising a PYY compound according to any one of embodiments 1-97, and at least one pharmaceutically acceptable excipient.

99. A PYY compound according to any one of embodiments 1-97, for use as a medicament.

100. A PYY compound according to any one of embodiments 1-97, for use in the treatment and/or prevention of all forms of diabetes and related diseases, such as eating disorders, diabetic complications, cardiovascular diseases and/or sleep apnoea; and/or for improving lipid parameters, improving β-cell function, and/or for delaying or preventing diabetic disease progression.

101. A PYY compound according to any one of embodiments 1-97, for use in the treatment and/or prevention of diabetes.

102. A PYY compound according to any one of embodiments 1-97, for use in the treatment and/or prevention of type 2 diabetes.

103. Use of a PYY compound according to any one of embodiments 1-97, for the manufacture of a medicament for the treatment and/or prevention of all forms of diabetes and related diseases, such as eating disorders, diabetic complications, cardiovascular diseases and/or sleep apnoea; and/or for improving lipid parameters, improving β-cell function, and/or for delaying or preventing diabetic disease progression.

104. Use of a PYY compound according to any one of embodiments 1-97, for the manufacture of a medicament for the treatment and/or prevention of diabetes.

105. Use of a PYY compound according to any one of embodiments 1-97, for the manufacture of a medicament for the treatment and/or prevention of type 2 diabetes.

106. A method of treatment and/or prevention of all forms of diabetes and related diseases, such as eating disorders, diabetic complications, cardiovascular diseases and/or sleep apnoea; and/or for improving lipid parameters, improving β-cell function, and/or for delaying or preventing diabetic disease progression by administering a pharmaceutically active amount of a PYY compound according to any one of embodiments 1-97.

107. A method of treatment and/or prevention of diabetes by administering a pharmaceutically active amount of a PYY compound according to any one of embodiments 1-97.

108. A method of treatment and/or prevention of type 2 diabetes by administering a pharmaceutically active amount of a PYY compound according to any one of embodiments 1-97.

109. A PYY compound according to any one of embodiments 1-97, for use in the treatment and/or prevention of eating disorders, such as obesity, e.g. by decreasing food intake, reducing body weight, suppressing appetite, inducing satiety; treating or preventing binge eating disorder, bulimia nervosa, and/or obesity induced by administration of an antipsychotic or a steroid; reduction of gastric motility; delaying gastric emptying; increasing physical mobility; and/or prevention and/or treatment of comorbidities to obesity, such as osteoarthritis and/or urine incontinence.

110. A PYY compound according to any one of embodiments 1-97, for use in the treatment and/or prevention of obesity.

111. Use of a PYY compound according to any one of embodiments 1-97, in the manufacture of a medicament for the treatment and/or prevention of eating disorders, such as obesity, e.g. by decreasing food intake, reducing body weight, suppressing appetite, inducing satiety; treating or preventing binge eating disorder, bulimia nervosa, and/or obesity induced by administration of an antipsychotic or a steroid; reduction of gastric motility; delaying gastric emptying; increasing physical mobility; and/or prevention and/or treatment of comorbidities to obesity, such as osteoarthritis and/or urine incontinence.

112. Use of a PYY compound according to any one of embodiments 1-97, in the manufacture of a medicament for the treatment and/or prevention of obesity.

113. A method of treatment and/or prevention of eating disorders, such as obesity, e.g. by decreasing food intake, reducing body weight, suppressing appetite, inducing satiety; treating or preventing binge eating disorder, bulimia nervosa, and/or obesity induced by administration of an antipsychotic or a steroid; reduction of gastric motility; delaying gastric emptying; increasing physical mobility; and/or prevention and/or treatment of comorbidities to obesity, such as osteoarthritis and/or urine incontinence by administering a pharmaceutically active amount of a PYY compound according to any one of embodiments 1-97.

114. A method of treatment and/or prevention of obesity, by administering a pharmaceutically active amount of a PYY compound according to any one of embodiments 1-97.

The invention is further described by the following non-limiting embodiments of the invention:

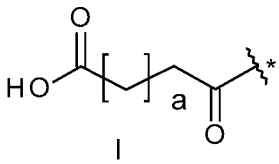
1. A PYY compound having a maximum of 10 amino acid modifications as compared to hPYY(3-36) (SEQ ID NO:2), wherein the PYY compound comprises
i) tryptophan at the position corresponding to position 30 of hPYY(1-36) (SEQ ID NO:1)
ii) N(alpha)-methyl-L-arginine at the position corresponding to position 35 of hPYY(1-36) (SEQ ID NO:1);

iii) lysine at the position corresponding to position 10 of hPYY(1-36) (SEQ ID NO:1);

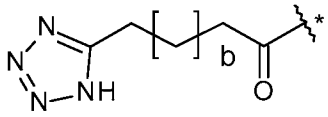
iv) glutamine at the position corresponding to position 18 of hPYY(1-36) (SEQ ID NO:1); and

v) a modifying group attached to the epsilon amino group of the Lysine residue in position 10, wherein said modifying group is defined by **A-B-C-D-E-**, wherein

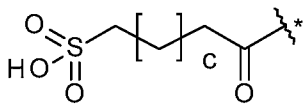
A is selected from



I ,



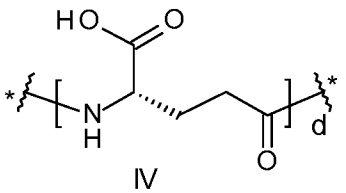
II , and



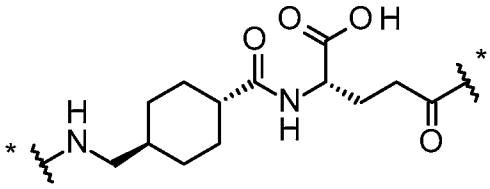
III ,

wherein a is an integer from 12 to 19, b is an integer from 10 to 16, and c is an integer from 10 to 16;

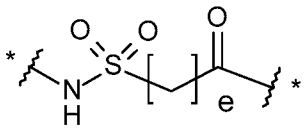
B is selected from



IV ,



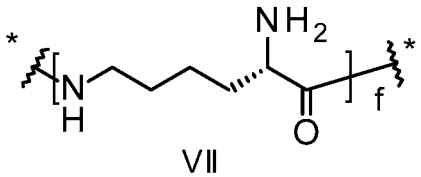
V , and



VI ,

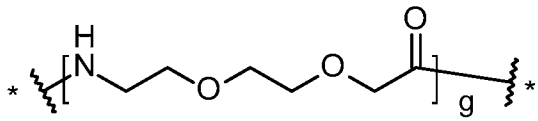
wherein d is 1 or 2; and e is 2, 3 or 4;

C is absent or

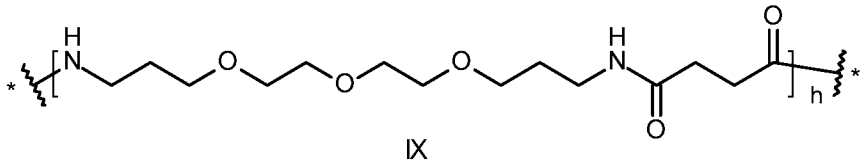


VII , wherein f is 1 or 2;

D is selected from



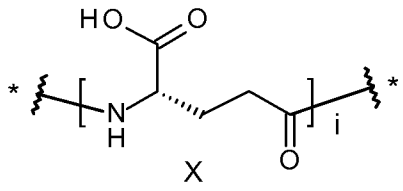
VIII , or



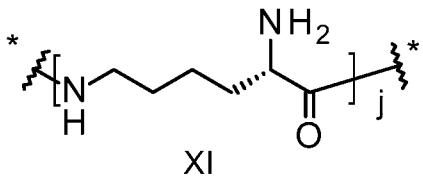
IX ,

wherein g is 1 or 2, h is 1 or 2; and

E is absent or selected from



X , and



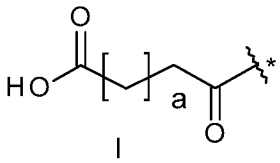
XI ,

wherein i is 1 or 2, and j is 1 or 2; and

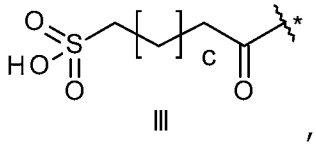
wherein * denotes the points of attachment, and wherein A, B, C, D and E are interconnected via amide bonds and in the sequence indicated via said point of attachments.

2. A PYY compound according to embodiment 1, wherein a is 13 or 15, b is 14, or c is 13.

3. A PYY compound according to embodiment 1, wherein **A-** is selected from



I or

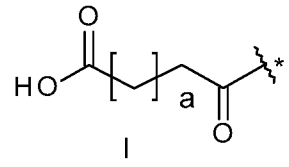


III ,

wherein a is an integer from 12 to 19, and c is an integer from 10 to 16.

4. A PYY compound according to embodiment 3, wherein a is an integer from 13 to 15, and c is 13.

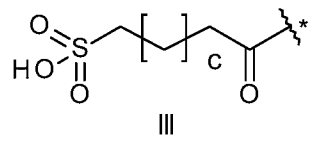
5. A PYY compound according to any one of the preceding embodiments, wherein **A-** is



I , wherein a is an integer from 13 to 15.

6. A PYY compound according to embodiment 5, wherein a is 13 or 15.

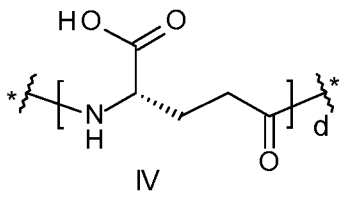
7. A PYY compound according to embodiment 1, wherein **A-** is



III , wherein c is an integer from 10 to 16.

8. A PYY compound according to embodiment 7, wherein c is 13.

9. A PYY compound according to any one of the preceding embodiments, wherein **B-** is



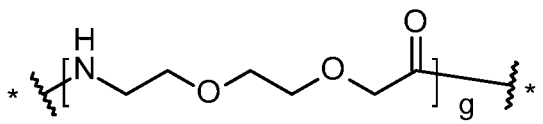
IV , wherein d is 1 or 2.

10. A PYY compound according to embodiment 9, wherein d is 1.

11. A PYY compound according to any one of the preceding embodiments, wherein f is 0.

12. A PYY compound according to any one of the preceding embodiments, wherein C is absent.

13. A PYY compound according to any one of the preceding embodiments, wherein

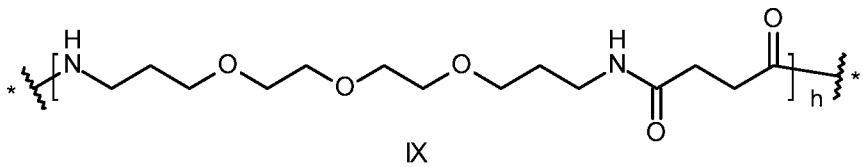


D is VIII ,

wherein g is 1 or 2.

14. A PYY compound according to embodiment 13, wherein g is 2.

15. A PYY compound according to any one of the preceding embodiments, wherein

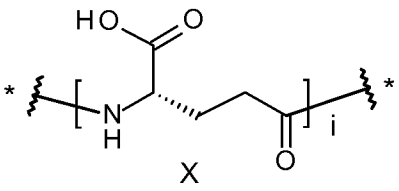


D is IX ,

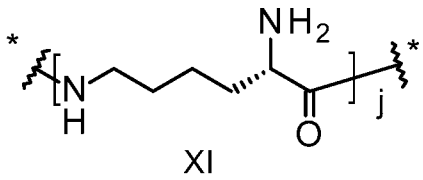
wherein h is 1 or 2.

16. A PYY compound according to embodiment 15, wherein h is 2.

17. A PYY compound according to any one of the preceding embodiments, wherein **E** is selected from



X , and

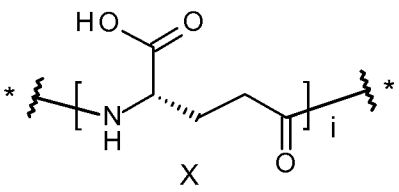


XI ,

wherein i is 1 or 2, and j is 1 or 2.

18. A PYY compound according to embodiment 17, wherein i is 1, and j is 2.

19. A PYY compound according to any one of the preceding embodiments, wherein **E** is

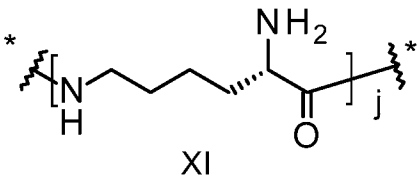


X ,

wherein i is 1 or 2.

20. A PYY compound according to embodiment 19, wherein i is 1.

21. A PYY compound according to any one of the preceding embodiments, wherein



E is XI ,

wherein j is 1 or 2.

22. A PYY compound according to embodiment 21, wherein j is 2.

23. A PYY compound according to any one of the preceding embodiments, wherein **E** is absent.

24. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound comprises arginine at the position corresponding to position 4 of hPYY(1-36) (SEQ ID NO:1).

25. A PYY compound according to any one of the preceding embodiments, wherein the positions corresponding to positions 1 and 2 of hPYY(1-36) (SEQ ID NO:1) are absent.

26. A PYY compound according to any one of the preceding embodiments, wherein the positions corresponding to positions 1-3 of hPYY(1-36) (SEQ ID NO:1) are absent.

27. A PYY compound according to any one of the preceding embodiments, wherein the positions corresponding to positions 1-3 of hPYY(1-36) (SEQ ID NO:1) are absent, and wherein the PYY compound further comprises an N-terminal substituent, wherein the N-terminal substituent is an alkoxy group comprising up to 12 carbon atoms.

28. A PYY compound according to embodiment 27, wherein the N-terminal substituent is an alkoxy group comprising up to 10 carbon atoms.

29. A PYY compound according to embodiment 27, wherein the N-terminal substituent is an alkoxy group comprising up to 9 carbon atoms.

30. A PYY compound according to embodiment 27, wherein the N-terminal substituent is an alkoxy group comprising up to 8 carbon atoms.

31. A PYY compound according to embodiment 27, wherein the N-terminal substituent is an alkoxy group comprising up to 7 carbon atoms.

32. A PYY compound according to embodiment 27, wherein the N-terminal substituent is an alkoxy group comprising up to 6 carbon atoms.

33. A PYY compound according to embodiment 27, wherein the N-terminal substituent is an alkoxy group comprising 6 carbon atoms.

34. A PYY compound according to embodiment 27, wherein the N-terminal substituent is selected from 3-methylbutanoyl and 3-methylpentanoyl.

35. A PYY compound according to embodiment 27, wherein the N-terminal substituent is 3-methylbutanoyl.

36. A PYY compound according to embodiment 27, wherein the N-terminal substituent is 3-methylpentanoyl.

37. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has a maximum of 9 amino acid modifications as compared to hPYY(3-36).

38. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has a maximum of 8 amino acid modifications as compared to hPYY(3-36).

39. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has a maximum of 7 amino acid modifications as compared to hPYY(3-36).

40. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has a maximum of 6 amino acid modifications as compared to hPYY(3-36).

41. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has a maximum of 5 amino acid modifications as compared to hPYY(3-36).

42. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has a maximum of 4 amino acid modifications as compared to hPYY(3-36).

43. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has a maximum of 3 amino acid modifications as compared to hPYY(3-36).

44. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has a maximum of 2 amino acid modifications as compared to hPYY(3-36).

45. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has a maximum of 1 amino acid modification as compared to hPYY(3-36).

46. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has a minimum of 4 amino acid modifications as compared to hPYY(3-36).

47. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has a minimum of 5 amino acid modifications as compared to hPYY(3-36).

48. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has a minimum of 6 amino acid modifications as compared to hPYY(3-36).

49. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has a minimum of 7 amino acid modifications as compared to hPYY(3-36).

50. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has a minimum of 8 amino acid modifications as compared to hPYY(3-36).

51. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has in the range of 4 to 10 amino acid modifications as compared to hPYY(3-36).

52. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has in the range of 6 to 8 amino acid modifications as compared to hPYY(3-36).

53. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has in the range of 4 to 6 amino acid modifications as compared to hPYY(3-36).

54. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has 4 amino acid modifications as compared to hPYY(3-36).

55. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has 5 amino acid modifications as compared to hPYY(3-36).

56. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has 6 amino acid modifications as compared to hPYY(3-36).

57. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has 7 amino acid modifications as compared to hPYY(3-36).

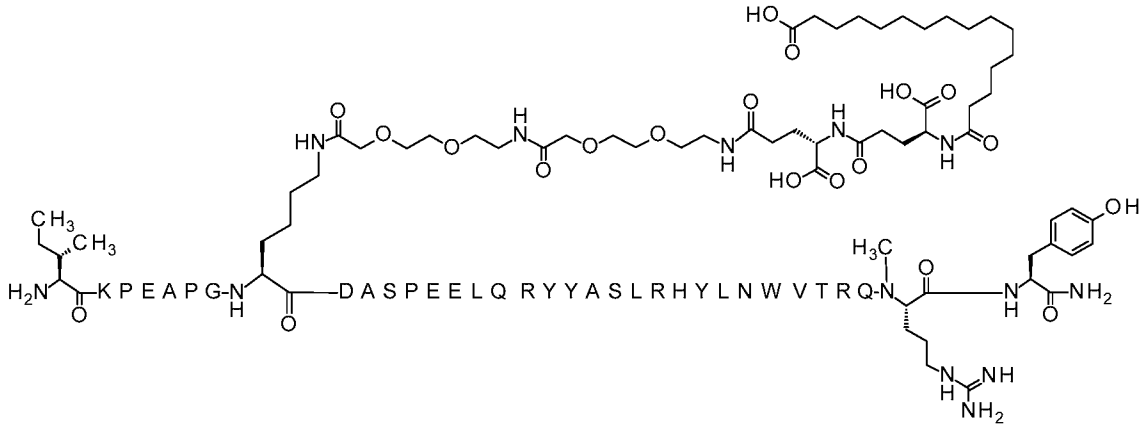
58. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has 8 amino acid modifications as compared to hPYY(3-36).

59. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has 9 amino acid modifications as compared to hPYY(3-36).

60. A PYY compound according to any one of the preceding embodiments, wherein the PYY compound has 9 amino acid modifications as compared to hPYY(3-36).

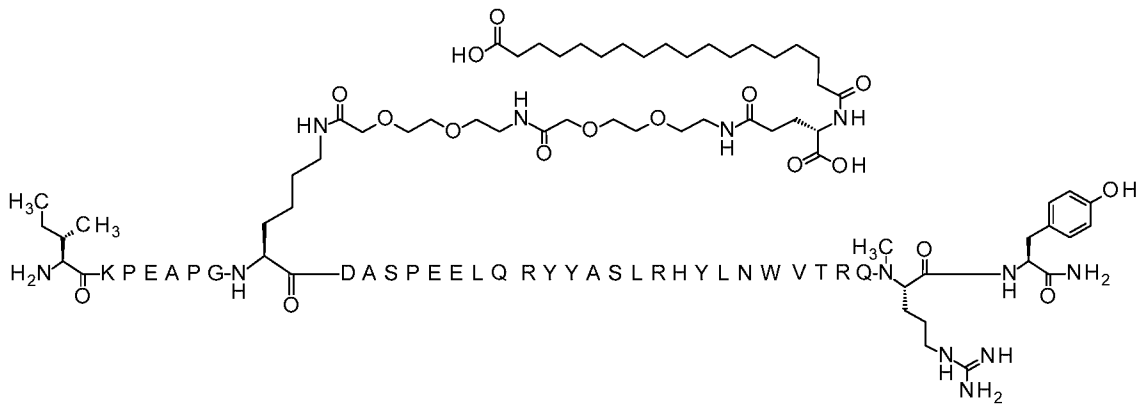
61. A PYY compound according to any one of the preceding embodiments selected from the following:

N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-[[(4S)-4-carboxy-4-(15-carboxypentadecanoylamino)butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]-[Lys10,Gln18,Trp30,NmeArg35]hPYY(3-36) (Compound 4) (1339)



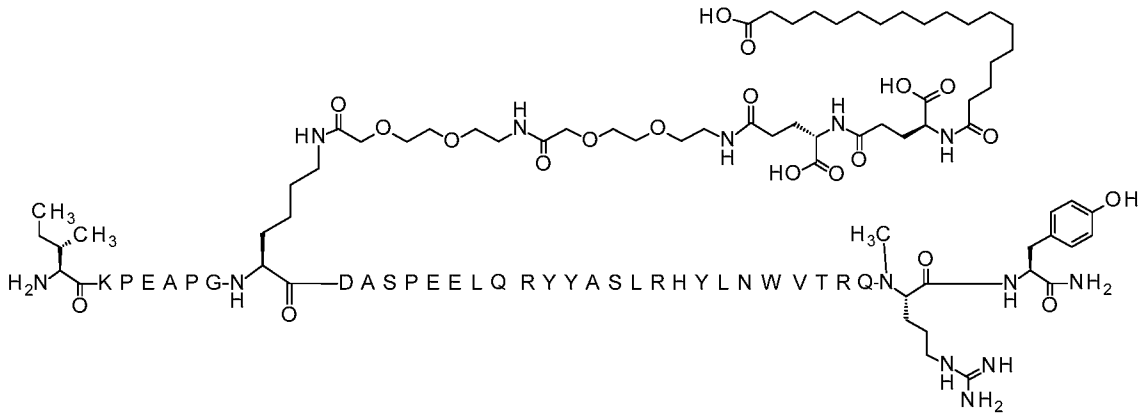
;

N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)-butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]-ethoxy]acetyl]-[Lys10,Gln18, Trp30,NmeArg35]hPYY(3-36) (Compound 5) (0832)



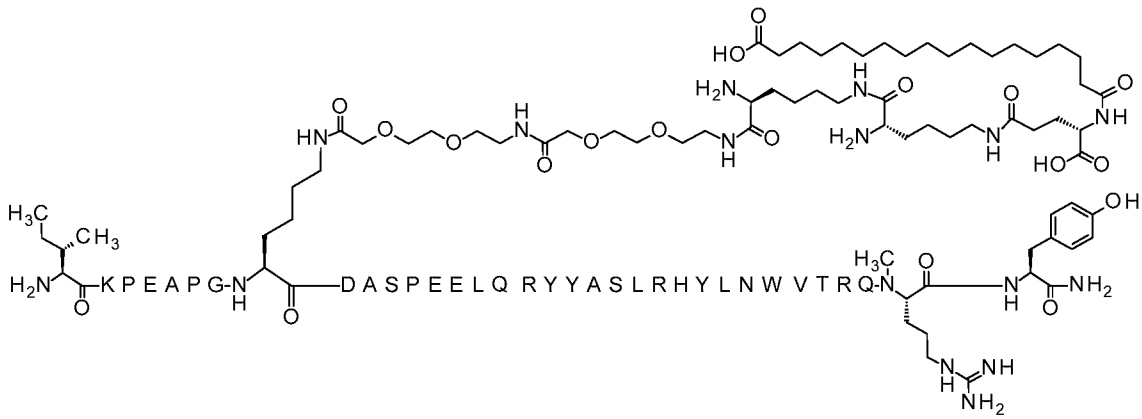
;

N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]-acetyl]amino]ethoxy]ethoxy]acetyl]-[Lys10,Gln18,Trp30,NmeArg35]hPYY(3-36) (Compound 6) (0996)



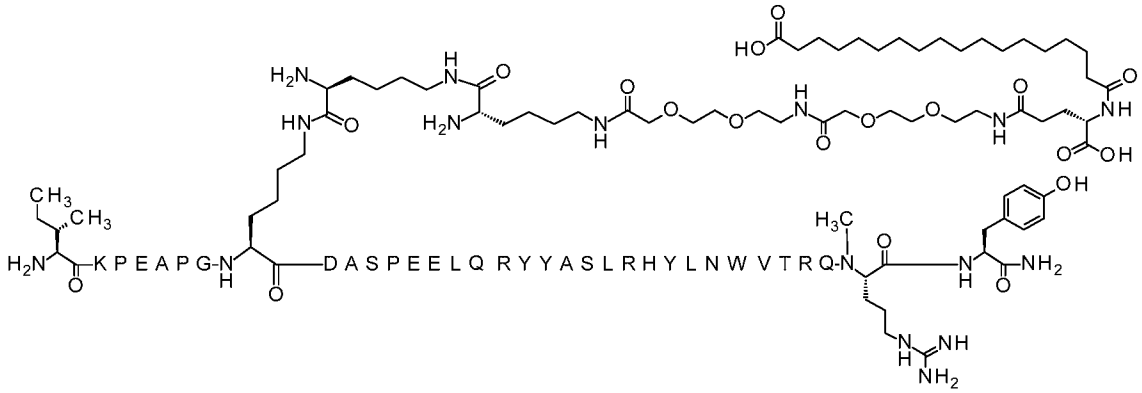
;

N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(2S)-2-amino-6-[[(2S)-2-amino-6-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]hexanoyl]amino]-hexanoyl]amino]-ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]-[Lys10,Gln18,Trp30,NmeArg35]-hPYY(3-36) (Compound 7) (0833)



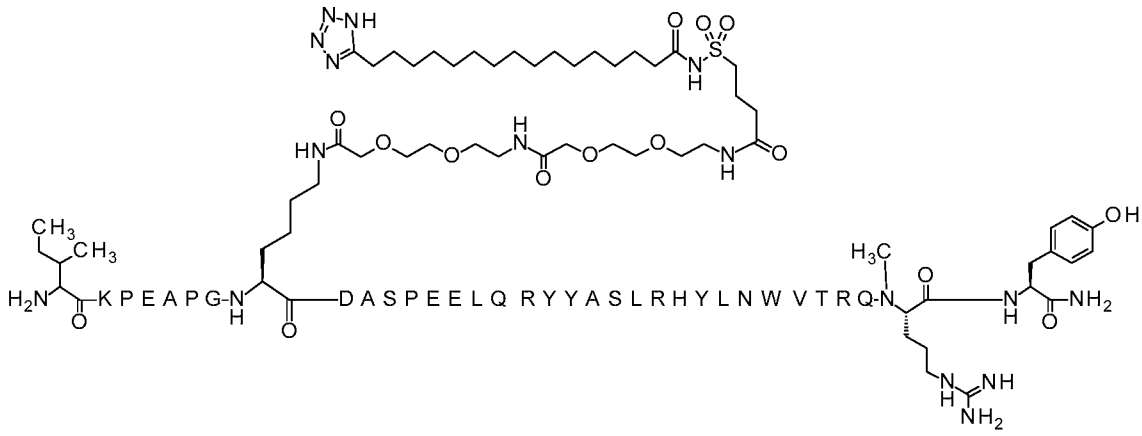
;

N{Epsilon-10}-[(2S)-2-amino-6-[[(2S)-2-amino-6-[[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]-ethoxy]ethoxy]acetyl]amino]hexanoyl]amino]hexanoyl][Lys10,Gln18,Trp30,NmeArg35]-hPYY(3-36) (Compound 8) (1491)



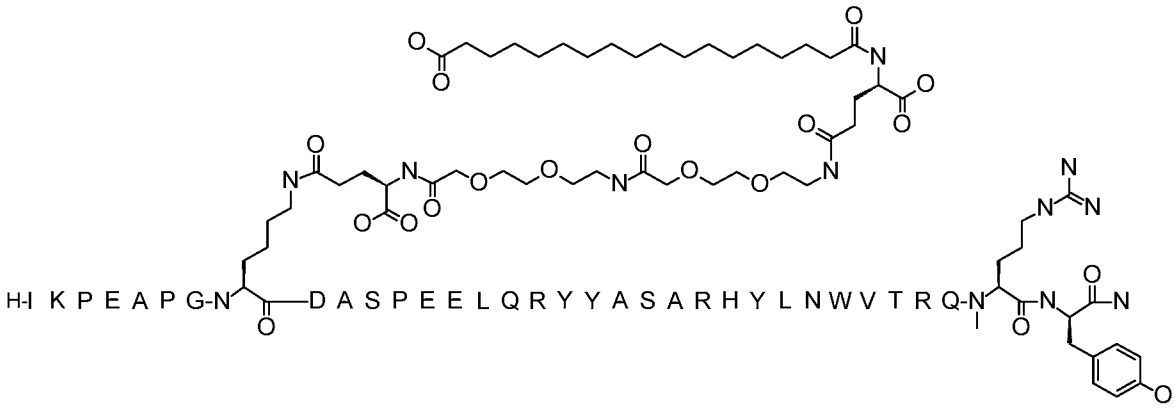
;

N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[4-[16-(1H-tetrazol-5-yl)hexadecanoylsulfamoyl]-butanoylamino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]-[Lys10,Gln18, Trp30,NmeArg35]hPYY(3-36) (Compound 9) (0997)



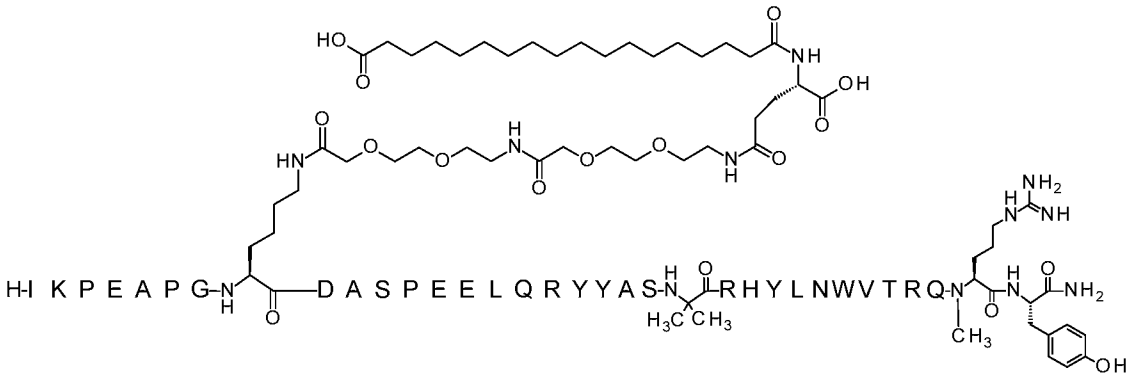
;

N{Epsilon-10}-[(4S)-4-carboxy-4-[[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]-ethoxy]acetyl]amino]butanoyl]-[Lys10,Gln18,Ala24,Trp30,NmeArg35]hPYY(3-36) (Compound 10) (1186)



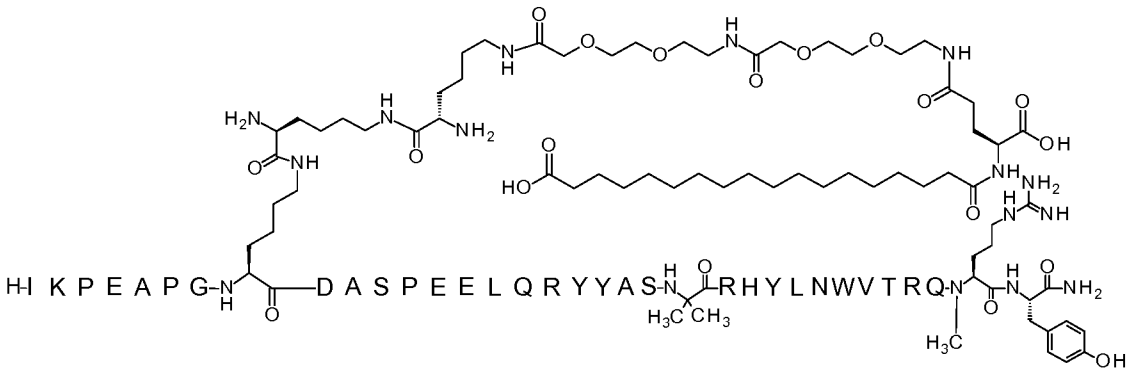
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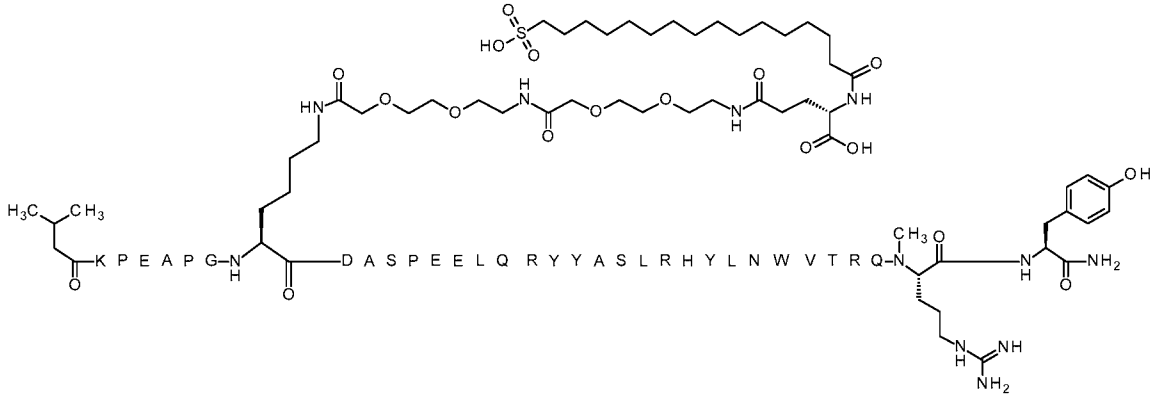
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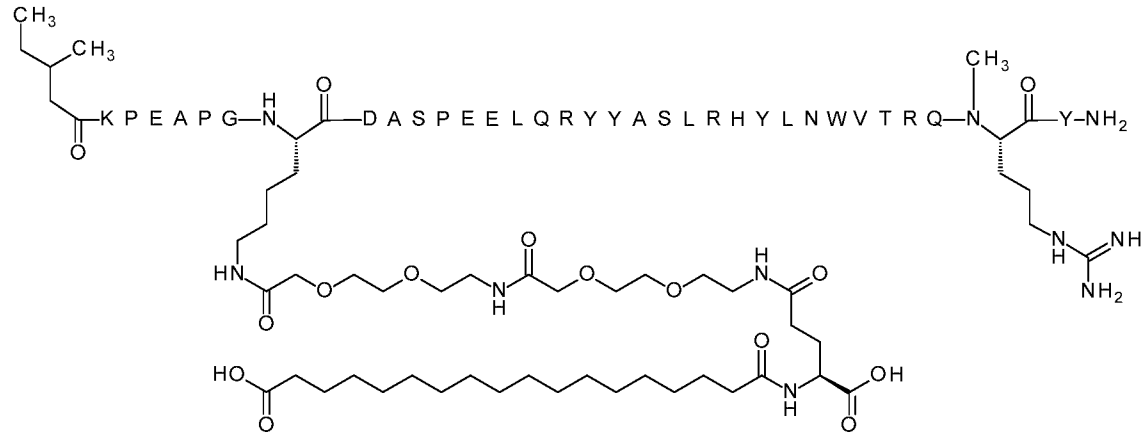
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N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(16-sulfohexadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]-ethoxy]acetyl]-[Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) (Compound 13) (1640)



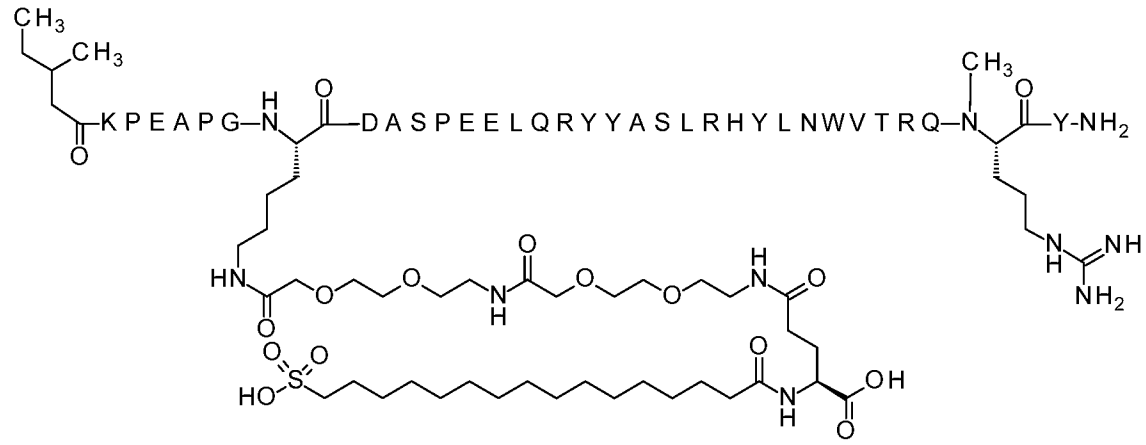
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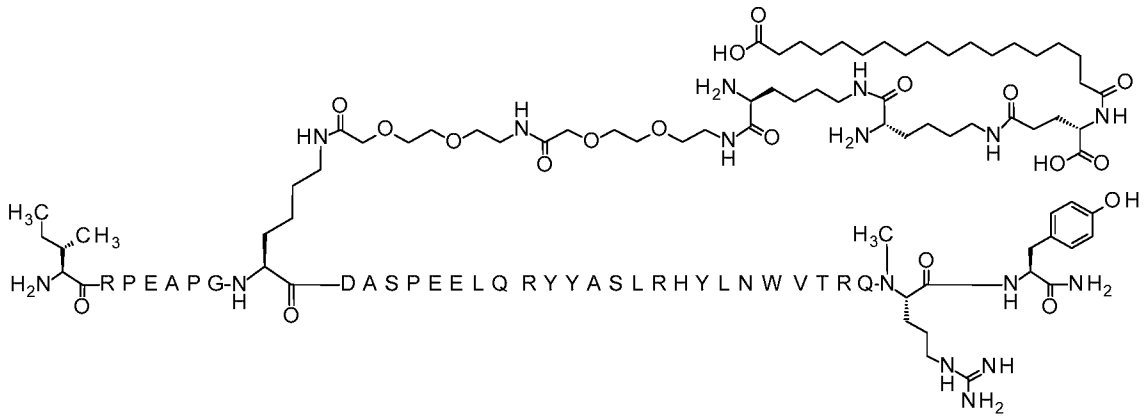
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N{alpha-4}-(3-Methylpentanoyl)-N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(16-sulfohexadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]-ethoxy]acetyl]-[Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) (Compound 15) (1512)



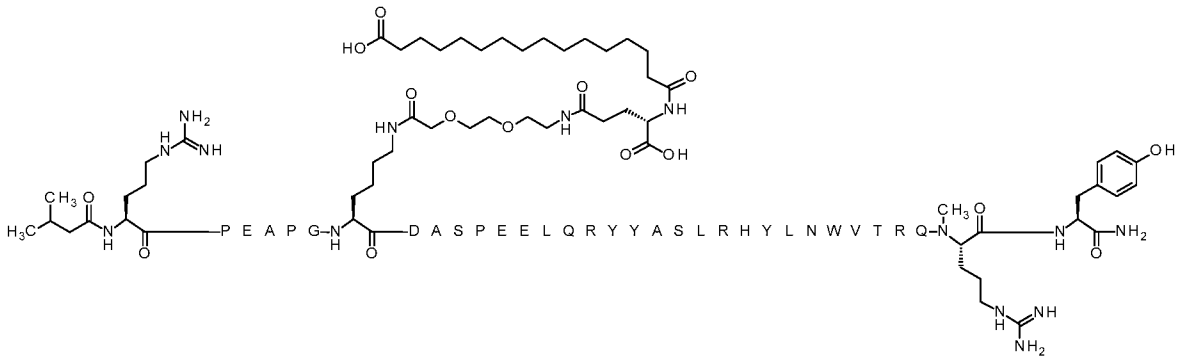
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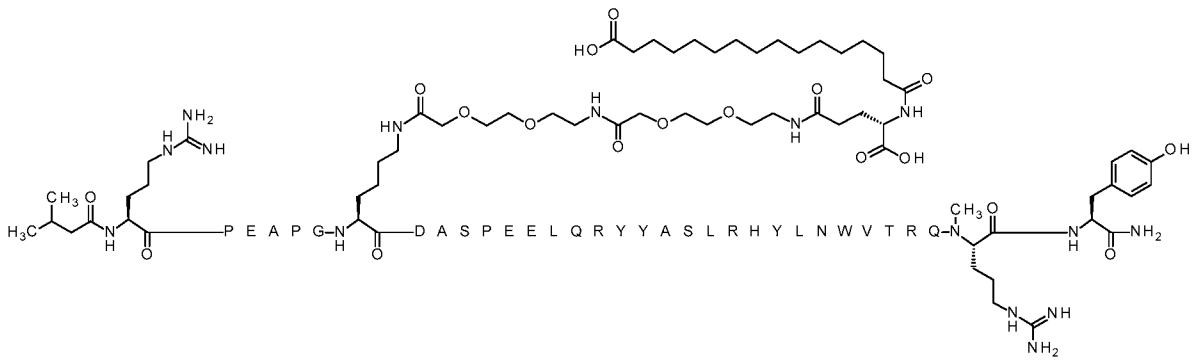
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N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[2-[2-[2-[[(4S)-4-carboxy-4-(15-carboxypentadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]-[Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) (Compound 17) (1667)



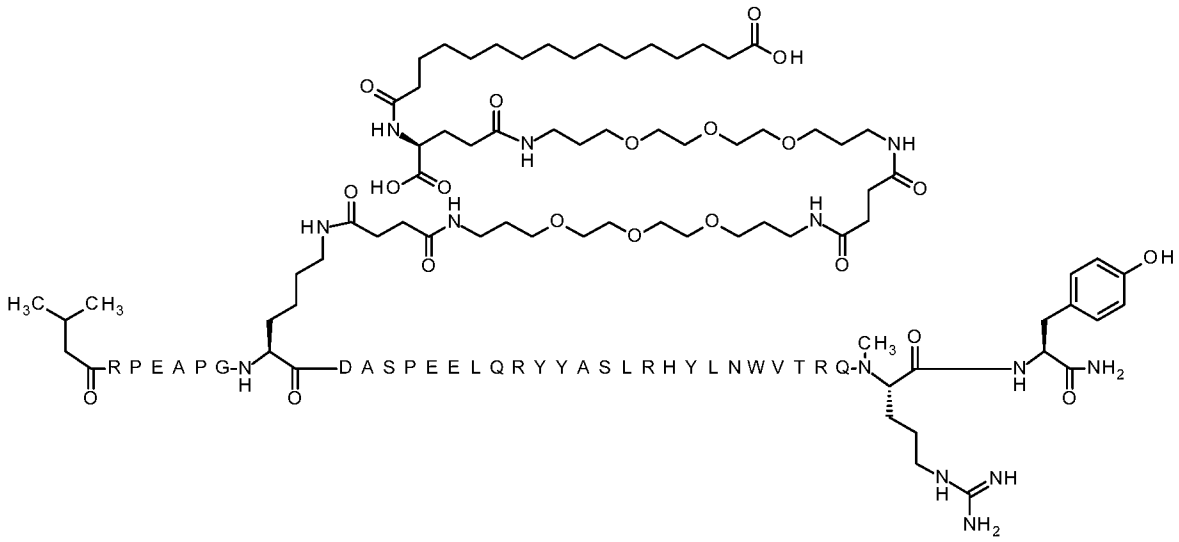
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N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(15-carboxypentadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]-ethoxy]acetyl]-[Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) (Compound 18) (1649)



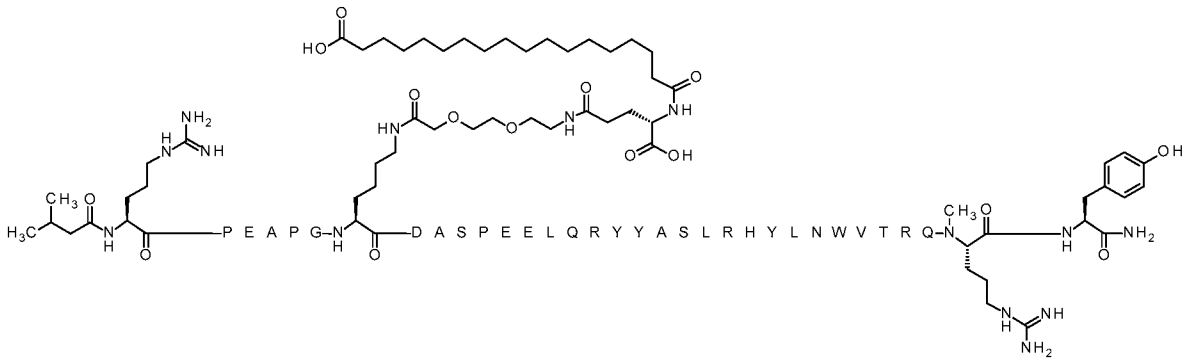
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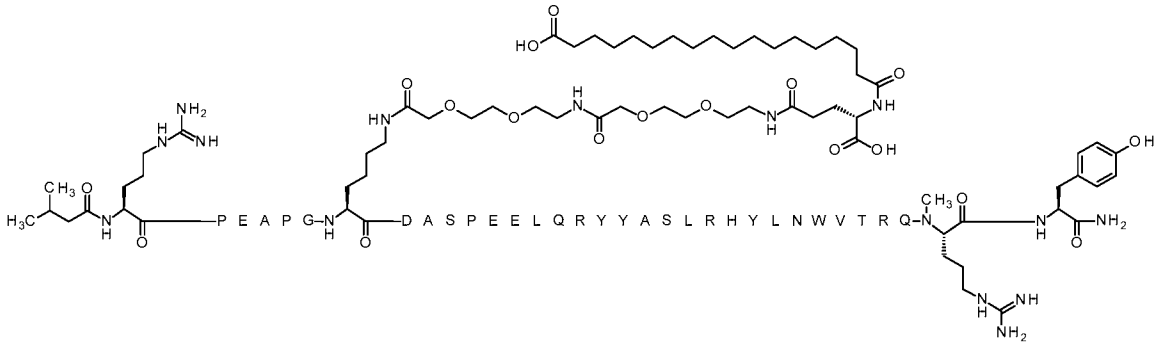
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N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]-[Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) (Compound 20) (1657)



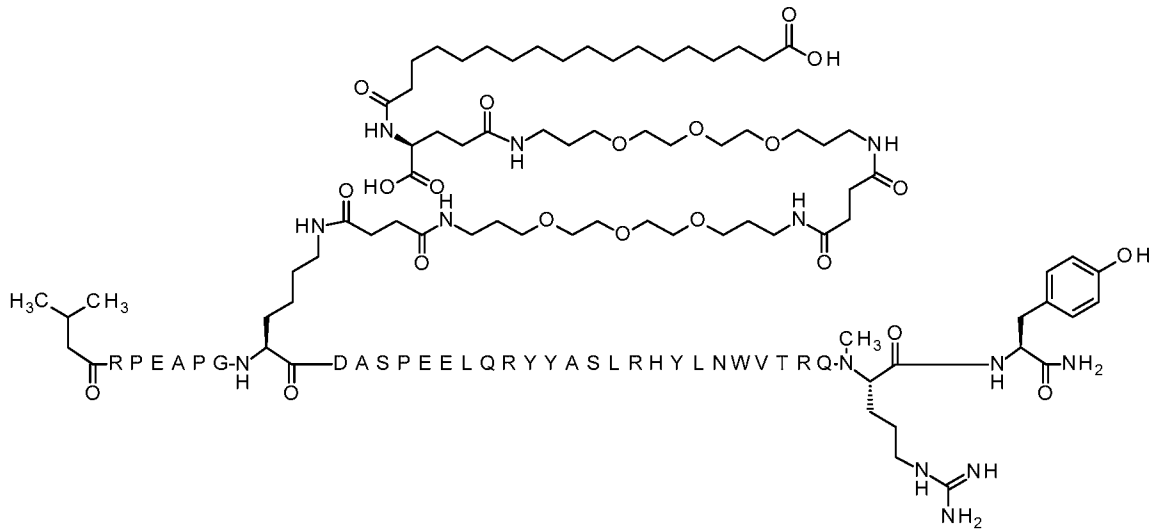
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N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]-ethoxy]acetyl]-[Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) (Compound 21) (1645)



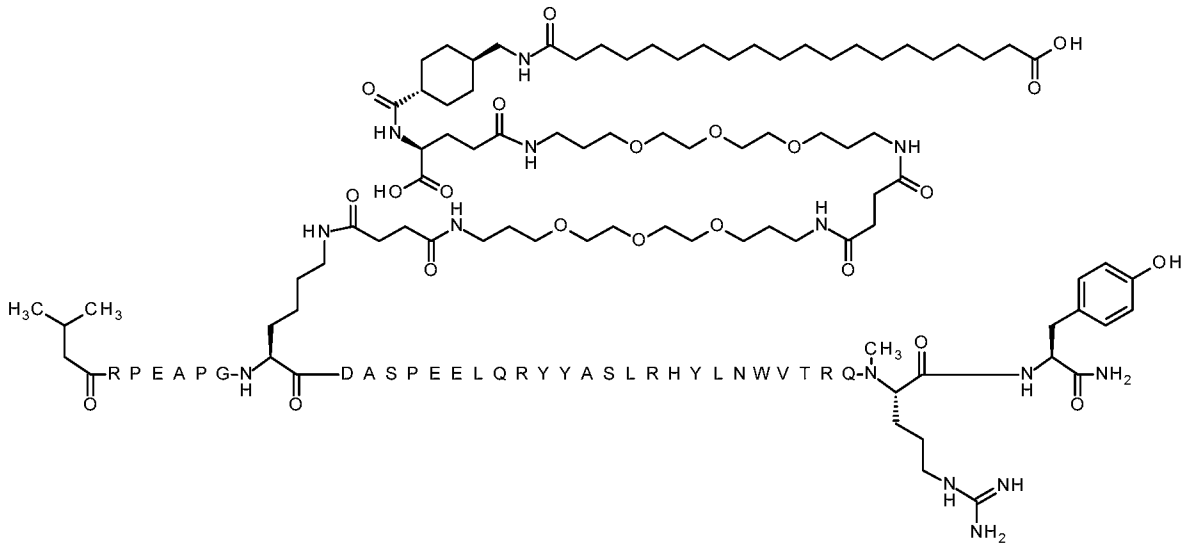
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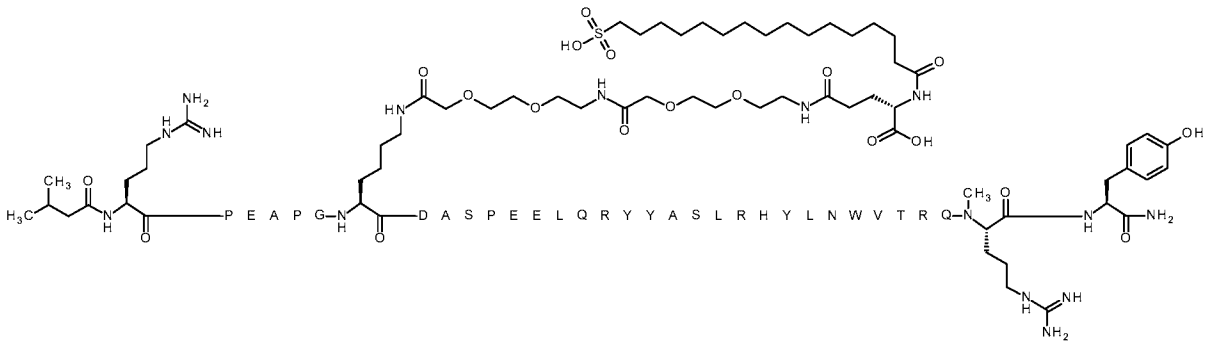
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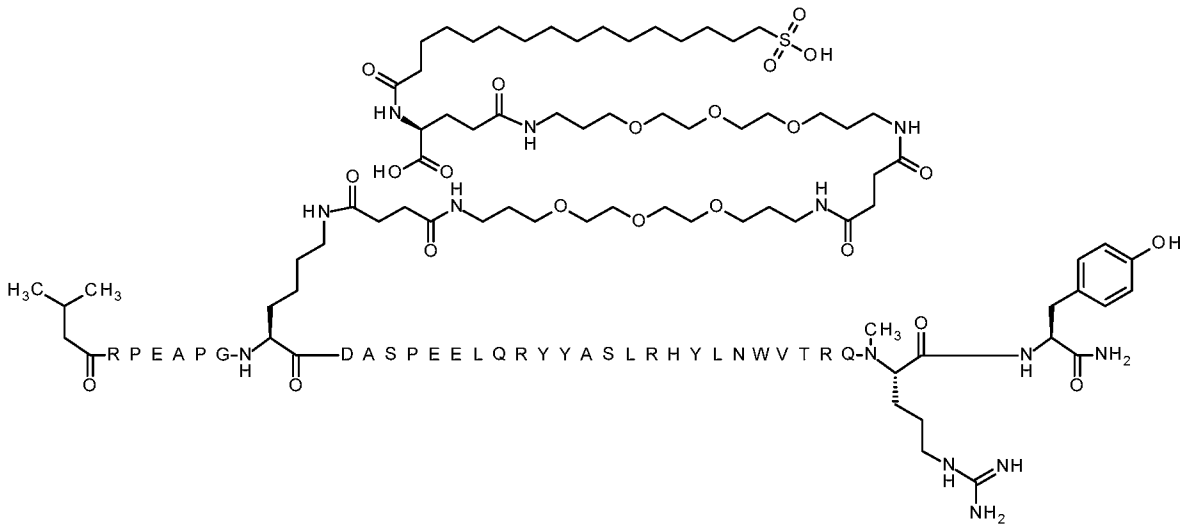
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N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(16-sulfohexadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]-ethoxy]acetyl]-[Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) (Compound 24) (1643)



;

N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[4-[3-[2-[2-[3-[[4-[3-[2-[2-[3-[[(4S)-4-carboxy-4-(16-sulfohexadecanoylamino)butanoyl]amino]-propoxy]ethoxy]ethoxy]-propylamino]-4-oxobutanoyl]amino]propoxy]ethoxy]-ethoxy]propylamino]-4-oxobutanoyl]-[Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) (Compound 25) (1637)



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62. A PYY compound according to embodiment 1, wherein the PYY compound is compound 4.

63. A PYY compound according to embodiment 1, wherein the PYY compound is compound 5.

64. A PYY compound according to embodiment 1, wherein the PYY compound is compound 6.

65. A PYY compound according to embodiment 1, wherein the PYY compound is compound 7.

66. A PYY compound according to embodiment 1, wherein the PYY compound is compound 8.

67. A PYY compound according to embodiment 1, wherein the PYY compound is compound 9.

68. A PYY compound according to embodiment 1, wherein the PYY compound is compound 10.

69. A PYY compound according to embodiment 1, wherein the PYY compound is compound 11.

70. A PYY compound according to embodiment 1, wherein the PYY compound is compound 12.

71. A PYY compound according to embodiment 1, wherein the PYY compound is compound 13.

72. A PYY compound according to embodiment 1, wherein the PYY compound is compound 14.

73. A PYY compound according to embodiment 1, wherein the PYY compound is compound 15.

74. A PYY compound according to embodiment 1, wherein the PYY compound is compound 16.

75. A PYY compound according to embodiment 1, wherein the PYY compound is compound 17.

76. A PYY compound according to embodiment 1, wherein the PYY compound is compound 18.

77. A PYY compound according to embodiment 1, wherein the PYY compound is compound 19.

78. A PYY compound according to embodiment 1, wherein the PYY compound is compound 20.

79. A PYY compound according to embodiment 1, wherein the PYY compound is compound 21.

80. A PYY compound according to embodiment 1, wherein the PYY compound is compound 22.

81. A PYY compound according to embodiment 1, wherein the PYY compound is compound 23.

82. A PYY compound according to embodiment 1, wherein the PYY compound is compound 24.

83. A PYY compound according to embodiment 1, wherein the PYY compound is compound 25.

84. A PYY compound according to any one of the preceding embodiments which is a human Y2 receptor agonist.

85. A PYY compound according to any one of the preceding embodiments which is a full human Y2 receptor agonist.

86. A PYY compound according to any one of the preceding embodiments which is a selective human Y2 receptor agonist.

87. A PYY compound according to any one of the preceding embodiments which is a selective full human Y2 receptor agonist.

88. A PYY compound according to any one of the preceding embodiments which is capable of activating the human Y2 receptor.

89. A PYY compound according to any one of the preceding embodiments which is capable of activating the human Y2 receptor in an assay with whole cells expressing the human Y2 receptor.

90. A PYY compound according to any one of the preceding embodiments which is capable of activating the human Y2 receptor in the Actone functional potency assay of Example 2.

91. A PYY compound according to any one of the preceding embodiments which is capable of binding to the human Y2 receptor.

92. A PYY compound according to any one of the preceding embodiments which is capable of binding to the human Y2 receptor, wherein the binding to the human Y2 receptor is measured in a competitive binding assay, such as the assay of Example 3.

93. A PYY compound according to any one of the preceding embodiments which has improved pharmacokinetic properties.

94. A PYY compound according to any one of the preceding embodiments which has an increased half-life and/or a decreased clearance.

95. A PYY compound according to any one of the preceding embodiments which has the effect in vivo of decreasing the blood glucose determined in a single-dose study in a db/db mouse model.

96. A PYY compound according to any one of the preceding embodiments which has the effect in vivo of decreasing food intake determined in a single-dose study in a db/db mouse model.

97. A pharmaceutical composition comprising a PYY compound according to any one of embodiments 1-96, and at least one pharmaceutically acceptable excipient.

98. A PYY compound according to any one of embodiments 1-96, for use as a medicament.

99. A PYY compound according to any one of embodiments 1-96, for use in the treatment and/or prevention of all forms of diabetes and related diseases, such as eating disorders, diabetic complications, cardiovascular diseases and/or sleep apnoea; and/or for improving lipid parameters, improving β-cell function, and/or for delaying or preventing diabetic disease progression.

100. A PYY compound according to any one of embodiments 1-96, for use in the treatment and/or prevention of diabetes.

101. A PYY compound according to any one of embodiments 1-96, for use in the treatment and/or prevention of type 2 diabetes.

102. Use of a PYY compound according to any one of embodiments 1-96, for the manufacture of a medicament for the treatment and/or prevention of all forms of diabetes and related diseases, such as eating disorders, diabetic complications, cardiovascular diseases and/or sleep apnoea; and/or for improving lipid parameters, improving β-cell function, and/or for delaying or preventing diabetic disease progression.

103. Use of a PYY compound according to any one of embodiments 1-96, for the manufacture of a medicament for the treatment and/or prevention of diabetes.

104. Use of a PYY compound according to any one of embodiments 1-96, for the manufacture of a medicament for the treatment and/or prevention of type 2 diabetes.

105. A method of treatment and/or prevention of all forms of diabetes and related diseases, such as eating disorders, diabetic complications, cardiovascular diseases and/or sleep apnoea; and/or for improving lipid parameters, improving β-cell function, and/or for delaying or preventing diabetic disease progression by administering a pharmaceutically active amount of a PYY compound according to any one of embodiments 1-96.

106. A method of treatment and/or prevention of diabetes by administering a pharmaceutically active amount of a PYY compound according to any one of embodiments 1-96.

107. A method of treatment and/or prevention of type 2 diabetes by administering a pharmaceutically active amount of a PYY compound according to any one of embodiments 1-96.

108. A PYY compound according to any one of embodiments 1-96, for use in the treatment and/or prevention of eating disorders, such as obesity, e.g. by decreasing food intake, reducing body weight, suppressing appetite, inducing satiety; treating or preventing binge eating disorder, bulimia nervosa, and/or obesity induced by administration of an antipsychotic or a steroid; reduction of gastric motility; delaying gastric emptying; increasing physical mobility; and/or prevention and/or treatment of comorbidities to obesity, such as osteoarthritis and/or urine incontinence.

109. A PYY compound according to any one of embodiments 1-96, for use in the treatment and/or prevention of obesity.

110. Use of a PYY compound according to any one of embodiments 1-96, in the manufacture of a medicament for the treatment and/or prevention of eating disorders, such as obesity, e.g. by decreasing food intake, reducing body weight, suppressing appetite, inducing satiety; treating or preventing binge eating disorder, bulimia nervosa, and/or obesity induced by administration of an antipsychotic or a steroid; reduction of gastric motility; delaying gastric emptying; increasing physical mobility; and/or prevention and/or treatment of comorbidities to obesity, such as osteoarthritis and/or urine incontinence.

111. Use of a PYY compound according to any one of embodiments 1-96, in the manufacture of a medicament for the treatment and/or prevention of obesity.

112. A method of treatment and/or prevention of eating disorders, such as obesity, e.g. by decreasing food intake, reducing body weight, suppressing appetite, inducing satiety; treating or preventing binge eating disorder, bulimia nervosa, and/or obesity induced by administration of an antipsychotic or a steroid; reduction of gastric motility; delaying gastric emptying; increasing physical mobility; and/or prevention and/or treatment of comorbidities to obesity, such as osteoarthritis and/or urine incontinence by administering a pharmaceutically active amount of a PYY compound according to any one of embodiments 1-96.

113. A method of treatment and/or prevention of obesity, by administering a pharmaceutically active amount of a PYY compound according to any one of embodiments 1-96.

EXAMPLES

This experimental part starts with a list of abbreviations, and is followed by a section including general methods for synthesising and characterising compounds of the invention. Then follows a number of Examples which relate to the preparation of specific PYY compounds, and at the end a number of examples have been included relating to the activity and properties of these compounds (section headed pharmacological methods).

The examples serve to illustrate the invention.

List of Abbreviations

ACN: acetonitrile

Aib: α-aminoisobutanoic acid

Boc: tert butyloxycarbonyl

CH_3CN: acetonitrile

cpm: counts per minute

DCM: dichloromethane

DIC: Diisopropylcarbodiimide

DIPEA: diisopropylethylamine

DMF: N,N-dimethylformamide

Et2O: diethyl ether

Fmoc: 9 H-fluoren-9-ylmethoxycarbonyl

HFIP: Hexafluoroisopropanol

HMWP: High molecular weight proteins

h: hours

H_2O: water

HOAc: acetic acid

HOAt: 1-Hydroxy-7-azabenzotriazole

HOBt: 1-Hydroxybenzotriazole

Min: minutes

Mtt: 4-methyltrityl

MW: Molecular weight

NMeArg: N(alpha)-methyl-L-arginine

NMF: 1-Methyl-formamide

NMP: 1-Methyl-pyrrolidin-2-one

OtBu: tert butyl ester

Pbf: 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl

PyBOP: benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate

rpm: rounds per minute

r.t: Room temperature

tBu: tert butyl

TFA: trifluoroacetic acid

TIPS: triisopropylsilane

Trt: triphenylmethyl

Materials and Methods

General Methods of Preparation

This section relates to methods for solid phase synthesis of peptide backbone and synthesis of side chain attached to backbone (SPPS methods, including methods for the coupling of amino acids, the de-protection of Fmoc-amino acids, methods for cleaving the peptide from the resin, and for its purification).

1. Synthesis of resin bound protected peptide backbone

Procedure for the automatic step-wise assembly of peptide backbone. The protected peptidyl resin was synthesized according to the Fmoc strategy on a solid phase peptide synthesiser Prelude (Protein Technologies, Tucson, USA) either 0.25 mmol scale or 0.4 mmol scale using the manufacturer supplied machine protocols. The Fmoc-protected amino acid derivatives used were the standard recommended: Fmoc-Ala-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Asp(OtBu)-OH, Fmoc-Cys(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Glu(OtBu)-OH, Fmoc-Glu-Otbu, Fmoc-Gly-OH, Fmoc-His(Trt)-OH, Fmoc-Ile-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Lys(Mtt)-OH, Fmoc-Met-OH, Fmoc-Phe-OH, Fmoc-Pro-OH, Fmoc-Ser(tBu)-OH, Fmoc-Thr(tBu)-OH, Fmoc-Trp(Boc)-OH, Fmoc-Tyr(tBu)-OH, or, Fmoc-Val-OH etc. supplied from e.g., Bachem, Iris Biotech, Protein Technologies or Novabiochem. Fmoc-8-amino-3,6-dioxaoctanoic acid was purchased from Polypeptides, and [N1-(9-Fluorenylmethoxycarbonyl)-1,13-diamino-4,7,10-trioxatridecan-succinamic (Fmoc-TTDS-OH) was purchased from IRIS Biotech. If nothing else is specified the natural L-form of the amino acids are used. Coupling was done by the use of DIC (dicyclohexylcarbodiimide) and Ozyma Pure (ethyl 2-cyano-2-(hydroxyimino)-acetate, Merck, Novabiochem, Switzerland) mediated couplings in NMP (N-methyl pyrrolidone). The coupling of the Fmoc-amino acid was done as described above using 4-8 time excess of amino acid relative to resin substitution (4-8 eq). Coupling time ranged from 1 hour up to 4 hours. The Fmoc-Arg(pbf)-OH was coupled using a double coupling procedure (1 hour + 1 hour). The resin used for the synthesis of the peptide amides can be Tentagel RAM (Rapp Polymere, Germany), Rink amid ChemMatrix resin (Matrix Innovation, Canada) Rink-Amide resin (Merck/Novabiochem). The protected amino acid derivatives used were standard Fmoc-amino acids (supplied from e.g. Protein Technologies, or Novabiochem. The epsilon amino group of lysine to be derivatised was protected with Mtt. The N-terminal amino acid or building was coupled as a Boc-protected amino acid, e.g., Boc-Ile. Alternatively isovaleric acid was coupled according to the above described coupling procedure for the Fmoc-amino acids. The step-

wise solid phase assembly on the Prelude was done using the following steps: 1) deprotection (removal of Fmoc) by the use of 25% piperidine in NMP for 2x4 min., step 2) Wash (removal of piperidine) with NMP and DCM, step 3) Coupling of Fmoc-amino acid (0.3M Fmoc-amino acid in 0.3M Oxyma Pure in NMP) 4-8 eq excess for 1-4 hours coupling initiated by adding 1/10 volume of 3M DIC in NMP and 1/10 volume collidine in NMP. Mixing was done by occasional bubbling with nitrogen, step 4) Wash (removal of excess amino acid and reagents by the use of NMP and DCM). Last step included washing with DCM which made the resin ready for attachment of a modifying group on lysine side chain.

2. Attachment of modifying groups to resin bound protected peptide backbone

Procedure for manual removal of Mtt-protection (lysine(Mtt)): Before synthesis of the modifying group, the Mtt group on the site of attachment (lysine) must be removed. The resin was placed in a syringe or reaction flask and treated with 75% hexafluroisopropanol (HFIP) + 25% DCM for 2 X 30 minutes to remove the Mtt group. The resin was then washed with DCM and NMP as described above and neutralized with 5% DIPEA (neutralisation step) in NMP or 25% piperidine in NMP followed by NMP washing before coupling the modifying group. Alternatively, the neutralisation step was omitted.

Procedure for Prelude removal of Mtt-protection (Lysine(Mtt)): On the Prelude the resin was treated with 75% hexafluoroisopropanol (HFIP) + 25% DCM for 2 x 2 minutes followed 2 X 30 minutes to remove the Mtt group on the lysine. The resin was then washed with DCM and NMP followed by a neutralisation step using 25% piperidine in NMP by 4 minutes, and was then ready for the synthesis of the modifying group.

Procedure for manual synthesis of modifying groups onto a lysine residue:

The building blocks Fmoc-8-amino-3,6-dioxaoctanoic acid (CAS No. 166108-71-0), Fmoc-TTDS-OH (CAS No. 172089-14-4, IRIS Biotech GmbH), Fmoc-L-Glu-OtBu (84793-07-7), and eicosanedioic acid mono-tert-butyl ester (CAS No. 843666-40-0) were coupled using DIC and Oxyma Pure in 4-8 eq relative to resin substitution. The coupling time was 2-16 hours usually followed by a capping step using 1 M acetic anhydride for 15-60 min. The Fmoc-group was removed by 25% piperidine in NMP for 10-30 min. followed by washing.

The 16-sulfonic hexadecanoic acid was solubilised in NMP or N-methylformamid (NMF) at 60 degree Celsius or above and activated by PyBOP 1 eq relative to the sulfonic hexadecanoic acid and 2eq of diisopropylethylamine (DIPEA) relative to sulfonic

hexadecanoic acid was also added. The peptidyl resin was washed with hot NMP or NMF just prior to the addition of activated sulfonic hexadecanoic acid. An excess of 3-4 of the sulfonic building block was used and coupling allowed to proceed > 16 hours.

Procedure for automated synthesis of modifying groups onto a lysine residue:
For the synthesis of the modifying groups the following building blocks were used: Fmoc-8-amino-3,6-dioxaoctanoic acid, Fmoc-TTDS-OH, Fmoc-Glu-OtBu, and eicosanedioic acid mono-tert-butyl ester (CAS No. 843666-40-0). Modifying groups were coupled using DIC and Oxyma Pure in 4-8 eq relative to resin substitution. The coupling time was 2-16 hours usually followed by a capping step using 1 M acetic anhydride for 20 min. The Fmoc-group was removed by 25% piperidine in NMP for 2x4 min. followed by washing as described in the SPPS of the peptide backbone. All other synthesis steps were also the same as described above with the backbone synthesis. The coupling of 16-sulfonic hexadecanoic acid was done by the manual procedure as described above using pyBOP as coupling reagent.

3. Cleavage of resin bound peptide with or without attached modifying groups and purification

Prior to TFA deprotection the peptidyl resin was washed with DCM or diethyl ether and dried. The peptide and side chain protection groups were removed by addition of 20-40 ml (0.25 mmol scale) 30-60 (0.4 mmol scale) ml 92% TFA, 5% TIPS and 3% H_2O for 2-4 hours. Then TFA was filtered and in some cases concentrated by a stream of argon and diethyl ether was added to precipitate the peptide. The peptide was washed three-five times with diethyl ether and dried.

General Methods of Detection and Characterisation

This section relates to methods for detection and characterisation of the resulting peptides, including LCMS, MALDI and UPLC methods.

1. LC-MS method (LCMS1)

Agilent Technologies LC/MSD TOF (G1969A) mass spectrometer was used to identify the molecular weight of the peptide after elution from an Agilent 1200 series HPLC system. The de-convolution of the mass data was calculated using the Agilents software.
Eluents:
Buffer A: 0.1% TFA in water
Buffer B: 0.1% TFA in CH_3CN

LC-MS Waters Acquity (LCMS2)
LC-system: Waters Acquity UPLC
Column: Waters Acquity UPLC BEH, C-18, 1.7µm, 2.1mm x 50mm
Detector: Waters (Micromass) LCT Premier XE
Linear gradient: 5 % to 95 % B
Gradient run-time: 4.0 minutes
Total run-time: 7.0 minutes
Flow rate: 0.4 ml/minutes
Column temperature: 40°C
Solvent A: 99.90 % MQ-water, 0.1% formic acid
Solvent B: 99.90 % acetonitrile, 0.1 % formic acid

2. UPLC methods

Method UPLC29v01
Buffer A: 0.05% TFA
Buffer B CH3CN + 0.05% TFA
Flow: 0.45 ml/min
Gradient: 15-35% Buffer B (0,5 – 4 min.)
Column: Acquity UPLC BEH C18 1.7um, 2.1 x 50 mm
Column temperature: 40 °C

Method UPLC30v01
Buffer A: 0.05% TFA
Buffer B: CH3CN + 0.05% TFA
Flow: 0.45 ml/min
Gradient: 20-40% Buffer B (0.5 – 4 min.)
Column: Acquity UPLC BEH C18 1.7um, 2.1 x 50 mm
Column temperature: 40 °C

Method UPLC31v01
Buffer A: 0.05% TFA
Buffer B: CH3CN + 0.05% TFA
Flow: 0.45 ml/min
Gradient: 25-45% Buffer B (0.5 – 4 min.)
Column: Acquity UPLC BEH C18 1.7um, 2.1 x 50 mm

Column temperature: 40 °C

Method UPLC02v01

System: Waters Acquity UPLC system

Buffer A: 0.05% TFA in H_2O

Buffer B: CH3CN + 0.05% TFA

Flow: 0.40 ml/min

Gradient: 5-95 % Buffer B (16 min.)

Column: Acquity UPLC BEH C18 1.7um, 2.1 x 150 mm

Column temperature: 40 °C

Method UPLC16v01

System: Waters Acquity UPLC system

Buffer A: 0.2 M Sodium Sulfate, 0.02 M di-Sodium Hydrogen Phosphate, 0.02 M Sodium di-Hydrogen Phosphate, 90% Water and 10% Acetonitrile, pH 7.2

Buffer B: 70% Acetonitrile, 30% Water

Flow: 0.40 ml/min

Gradient: 20-50 % Buffer B (3-20 min.)

Column: ACQUITY UPLC BEH Shield RP18, 1.7um, 2.1 mm x 150 mm column

Column temperature: 60 °C

Method UPLC17

System: Waters Acquity UPLC system

Buffer A: 0.2 M Sodium Sulfate, 0.02 M di-Sodium Hydrogen Phosphate, 0.02 M Sodium di-Hydrogen Phosphate, 90% Water and 10% Acetonitrile, pH 7.2

Buffer B: 70% Acetonitrile, 30% Water

Flow: 0.40 ml/min

Step gradient: 10-20% B over 3 minutes, then 20-80% B over 17 minutes, then 80-90% B over 1 minute

Column: ACQUITY UPLC BEH Shield RP18, 1.7um, 2.1 mm x 150 mm column

Column temperature: 60 °C

Method UPLC61

System: Waters Acquity UPLC system

Buffer A: 0.02 M Sodium Sulfate, 0.02 M di-Sodium Hydrogen Phosphate, 0.02 M Sodium di-Hydrogen Phosphate, 90% Water and 10% Acetonitrile, pH 7.2

Buffer B: 70% Acetonitrile, 30% Water
Flow: 0.40 ml/min
Gradient: 10-20% buffer B (0-3 min) 20-80 % Buffer B (3-20 min.)
Column: ACQUITY UPLC BEH Shield RP18, 1.7um, 2.1 mm x 150 mm column
Column temperature: 60 °C

Method UPLC- AP-01
Buffer A: 0,1% TFA in H_2O
Buffer B: CH3CN + 0,1% TFA
Flow: 0,40 ml/min
Gradient: 5-95 % Buffer B (16 min.)
Column; Acquity UPLC BEH130; 150x 2.1; 1.7um
Column temperature: 40 °C

3. MALDI-MS method

Molecular weights of the peptides were determined using matrix-assisted laser desorption time of flight mass spectroscopy (MALDI-MS), recorded on a Microflex (Bruker). A matrix of alpha-cyano-4-hydroxy cinnamic acid was used. The molecular weight of the product was calculated based on the result of MALDI-MS analysis using the software supplied from the manufacturer.

Synthesis of Intermediates

Synthesis of 16-sulfo-hexadecanoic acid

16-Hexadecanolide (997 g, 3.92 mol) was dissolved in methanol (15.1 L) and toluene-4-sulfonic acid monohydrate (90.0 g, 0.473 mol) was added. Reaction mixture was heated in 50 L reactor at 55 °C for 16 hours. After cooling down sodium hydrogen carbonate (56.0 g, 0.67 mol) was added and the reaction mixture was stirred for 15 min. Solvent was evaporated on Heidolph 20 L rotary evaporator. Ethyl acetate (12 L) was added and the mixture was extracted with 5% solution of sodium hydrogen carbonate (10 L). Organic layer was separated; emulsion layer was extracted with ethyl acetate (3 x 3 L), white insoluble muddy material was separated and ethyl acetate layer was washed again with 5% solution of sodium hydrogen carbonate (5 L).Organic layers were combined and washed with saturated solution of sodium hydrogen carbonate (5 L) and brine (10 L). Solvent was evaporated on Heidolph 20 L rotary evaporator. Crude product was crystallized from hexanes (8 L). Hot solution in hexanes was decanted and then let

to crystallize in ice bath. The material was filtered on large frit and washed with cold hexanes (2 L). Pure material was dried in *vacuo*.

Yield: 1062.2 g (95%). R_F (SiO_2, dichloromethane/methanol 95:5): 0.65.

^1H NMR spectrum (300 MHz, $CDCl_3$, δ_H): 3.67 (s, 3 H); 3.67-3.60 (m, 2 H); 2.30 (t, J=7.5 Hz, 2 H); 1.67-1.53 (m, 4 H); 1.25 (s, 22 H).

The above ester (957 g, 3.34 mol) was dissolved in dichloromethane (7 L) on Heidolph 20 L rotary evaporator. Triethylamine (695 mL, 4.98 mol) was added, reaction mixture was cooled to 0 °C (by putting ice into evaporator bath) and methanesulfonyl chloride (325 mL, 4.19 mol) in dichloromethane (200 mL) was added slowly during 10 minutes by external tubing using small *vacuum*. Then the reaction mixture was heated to 35 °C for 1 hour. NMR analysis showed complete conversion. Water was added (690 mL) and solvents were evaporated. Ethyl acetate (8 L) was added and the mixture was washed with 1 M hydrochloric acid (4 L) and 5% solution of sodium carbonate (4 L). Since sodium carbonate extraction formed an emulsion this layer was extracted with ethyl acetate (4 L) and added to main portion. Combined ethyl acetate layer was washed with brine (4 L), dried over anhydrous sodium sulfate and filtered. Solvent was evaporated giving 16-methanesulfonyloxy-hexadecanoic acid methyl ester as white solid.

Yield: 1225.4 g (100%).

^1H NMR spectrum (300 MHz, $CDCl_3$, δ_H): 4.22 (t, J=6.6 Hz, 2 H); 3.66 (s, 3 H); 3.00 (s, 3 H); 2.30 (t, J=7.5 Hz, 2 H) 1.82-1.67 (m, 2 H); 1.68-1.54 (m, 2 H); 1.36-1.17 (m, 22 H).

The above mesylate (1.23 kg, 3.34 mol) was dissolved in acetone (8 L) and lithium bromide (585 g, 6.73 mol) was added and the reaction mixture was heated on Heidolph 20 L rotary evaporator at 50 °C for 12 hours. After cooling down solvent was evaporated, ethyl acetate (10 L) was added and the mixture was washed with 5% solution of sodium hydrogencarbonate (3 x 15 L) and brine (8 L). Solvent was evaporated to dryness to yield 16-bromo-hexadecanoic acid methyl ester as pale yellow oil which started to crystallize.

Yield: 1219 g (105%); contains acetone and product of acetone aldolization.

R_F (SiO_2, hexanes/ethyl acetate 9:1): 0.90.

^1H NMR spectrum (300 MHz, $CDCl_3$, δ_H): 3.65 (s, 3 H); 3.42 (t, J=6.9 Hz, 2 H); 2.32 (t, J=7.5 Hz, 2 H); 1.92-1.77 (m, 2 H) 1.69-1.53 (m, 2 H); 1.50-1.35 (m, 2 H); 1.25 (bs, 10 H).

Solutions of sodium sulfite (327 g, 2.60 mol) in water (1.26 L) and 16-bromo-hexadecanoic acid methyl ester (728 g, 2.00 mol, 96% purity) in 1-propanol (945 mL)

and methanol (420 mL) were heated to reflux in 6 L reactor equipped with mechanical stirrer for 48 hours. The reaction mixture was cooled to 27 °C and diluted with tetrahydrofuran (2 L). Reaction mixture was filtered and solid material was washed with tetrahydrofuran (3 x 700 mL). Filtrate was cooled to 0 °C and another portion of material was precipitated. This precipitate was filtered and washed with tetrahydrofuran (2 x 200 mL). Solids were combined and mixed with water (8.4 L) in 20 L pot. Solution of sodium hydroxide (120 g, 3.00 mol) was added. The mixture was heated to boiling for about 5 hours. Solution of sulfuric acid (430 mL, 8.00 mol) in water (500 mL) was slowly added into the reaction mixture (sulfur dioxide is formed). Reaction mixture was heated to boiling for 10 minutes and then let to cool to 15 °C (ice bath). The mixture was filtered on Büchner funnel through filter paper Seitz (several layers filter) applying *vacuo*. This procedure was very slow and took two days. Solid material was several times washed with distilled water until pH of filtrate was between 2 and 3. This procedure took about three days. Muddy white material was dried in oven at 80 °C giving desired product.

Yield: 510 g (76%).

^{1}H NMR spectrum (300 MHz, DMSO-d_6, δ_H): 2.45-2.33 (m, 2 H); 2.18 (t, J=7.3 Hz, 2 H); 1.60-1.40 (m, 4 H); 1.24 (s, 22 H).

MS-ESI (neg, sample in H_2O/MeCN + $NaHCO_3$; m/z) : 335.5 $(M-H)^-$, 357.5 $(M-2H+Na)^-$, 167.3 $(M-2H)^{2-}$

Example 1: Synthesis of compounds of the invention

The compounds of the invention was synthesised according to the general methods of preparation as described above.

Example 1.1: hPYY(3-36)

IKPEAPGEDASPEELNRYYASLRHYLNLVTRQRY-NH_2

SEQ ID NO:2

Retention time HPLC method *UPLC16v01*: 3.37 minutes (91.4%)

Retention time HPLC method *UPLC29v01*: 10.07 minutes (85.6%)

MW calculated: 4049.6 g/mol

MALDI MS: 4048.2 g/mol

Example 1.2: Compound 1 (0165-0131)

[NMeArg35]hPYY(3-36)

SEQ ID NO:3



Example 1.3: Compound 2

[Trp30]hPYY(3-36)

SEQ ID NO:4



Retention time HPLC method *UPLC- AP-01*: (96.6%)

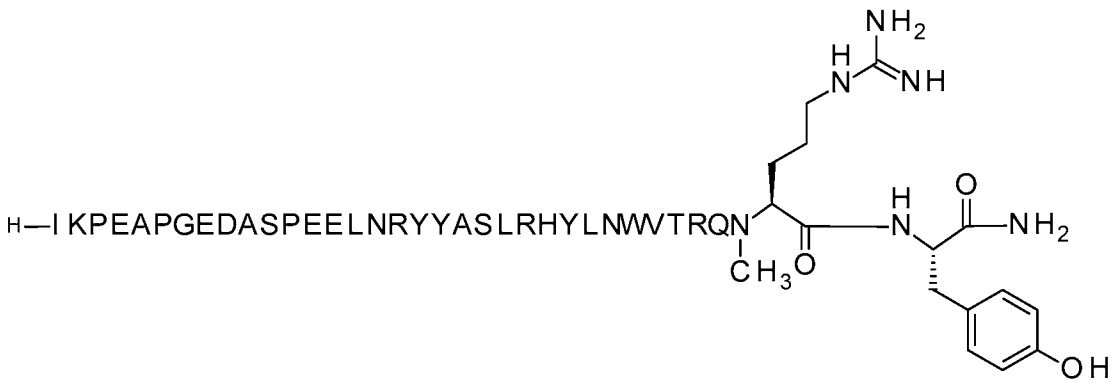
MW calculated: 4123.6 g/mol

LCMS1: ((M/3)+3) 1374,8; ((M/4)+4) 1031,3

Example 1.4: Compound 3

[Trp30,NMeArg35]hPYY(3-36)

SEQ ID NO:5



Retention time UPLC29v01: 3.43 minutes (100%)

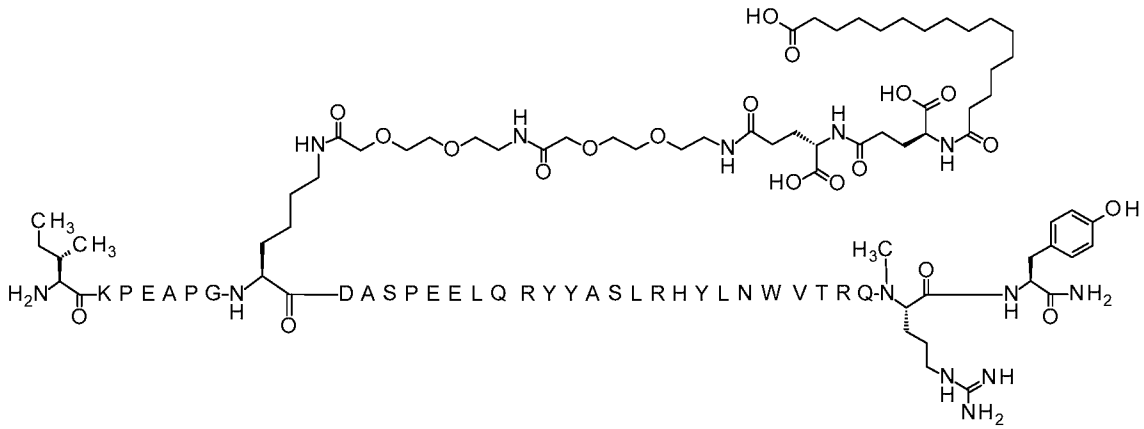
Retention time UPLC16v01: 10.93 (90.9%)

MW calculated: 4136,6 g/mol

LCMS2: ((M/1)+1) 4136.03; ((M/2)+2) 2069,02 ((M/3)+3) 1379,68; ((M/4)+4) 1035,02

Example 1.5: Compound 4

N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-[[(4S)-4-carboxy-4-(15-carboxypentadecanoylamino)butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]-[Lys10,Gln18,Trp30,NmeArg35]hPYY(3-36)

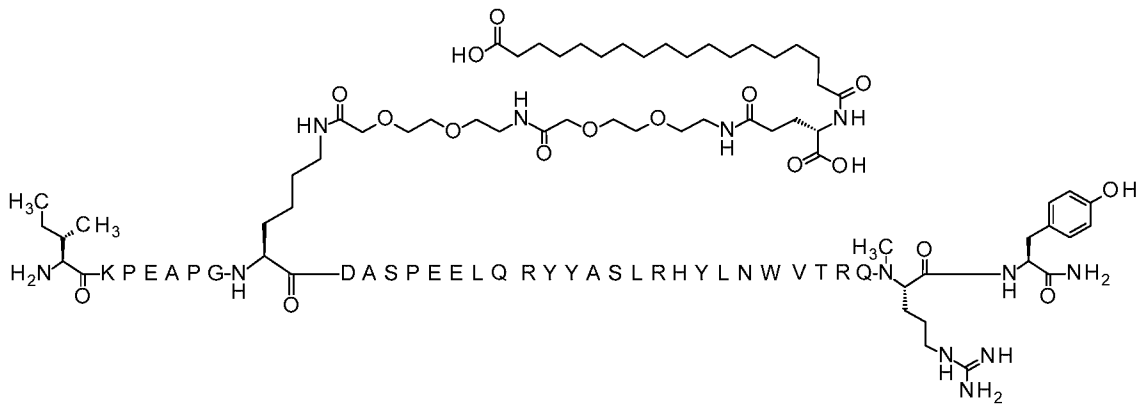


The amino acid sequence of [Lys10,Gln18,Trp30,NmeArg35]hPYY(3-36) is given in SEQ ID NO:6.

Retention time UPLC30v01: 3.5 min. (92.9%)
Retention time UPLC16v01: 12.0 min. (94.8%)
MW calculated: 4966.56 g/mol
MALDI-MS: 4966.6

Example 1.6: Compound 5

N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)-butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]-ethoxy]acetyl]-[Lys10,Gln18, Trp30,NmeArg35]hPYY(3-36)

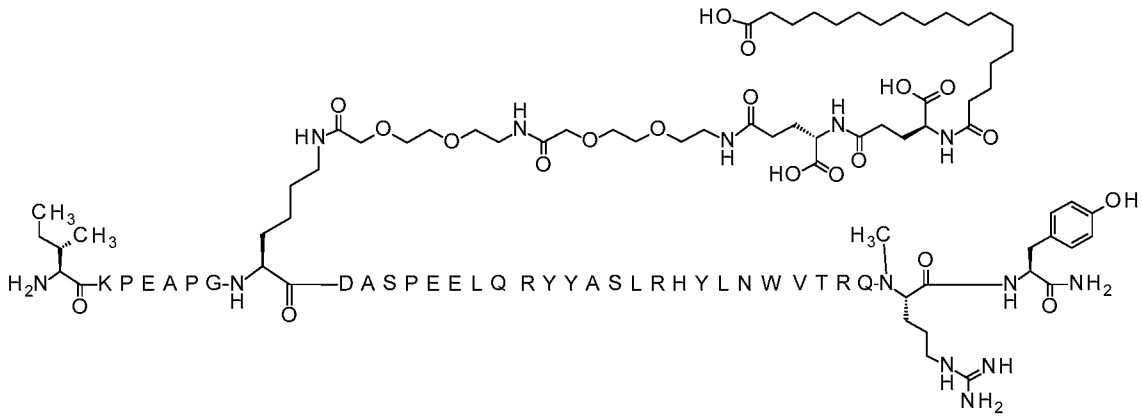


The amino acid sequence of [Lys10,Gln18,Trp30,NmeArg35]hPYY(3-36) is given in SEQ ID NO:6.

Retention time UPLC AP-01: 7.41 minutes (96.3%)
MW calculated: 4865.5 g/mol
LCMS2: ((M/3)+3) 1622.6; ((M/4)+4) 1217.2; ((M/5)+5) 974.0

Example 1.7: Compound 6

N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]-acetyl]amino]ethoxy]ethoxy]acetyl]-[Lys10,Gln18,Trp30,NmeArg35]hPYY(3-36)

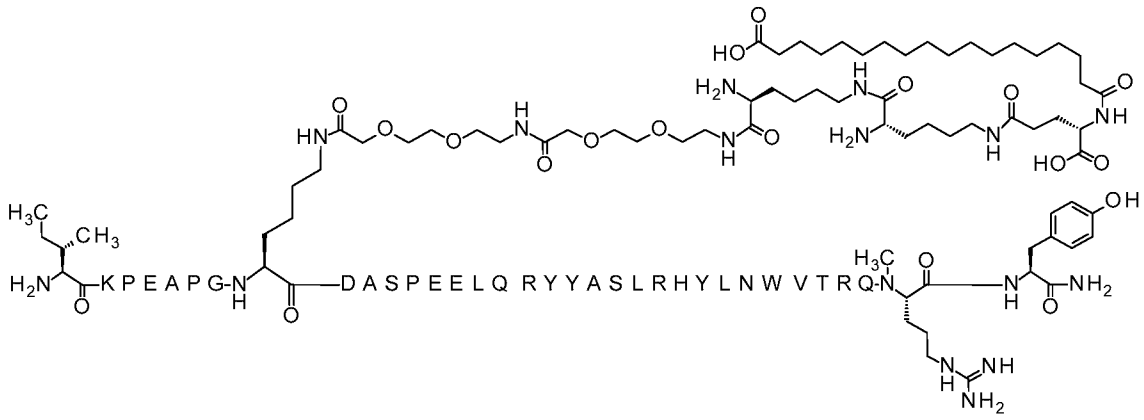


The amino acid sequence of [Lys10,Gln18,Trp30,NmeArg35]hPYY(3-36) is given in SEQ ID NO:6.

Retention time UPLC31v01: 3.1 min. (96.7%)
Retention time UPLC16v01: 13.5 min. (97.2%)
MW calculated: 4994.73 g/mol
LCMS2: ((M/3)+3) 1666.2; ((M/4)+4) 1249.9; ((M/6)+6) 833.7

Example 1.8: Compound 7

N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(2S)-2-amino-6-[[(2S)-2-amino-6-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]hexanoyl]amino]-hexanoyl]-amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]-[Lys10,Gln18,Trp30, NmeArg35]hPYY(3-36)

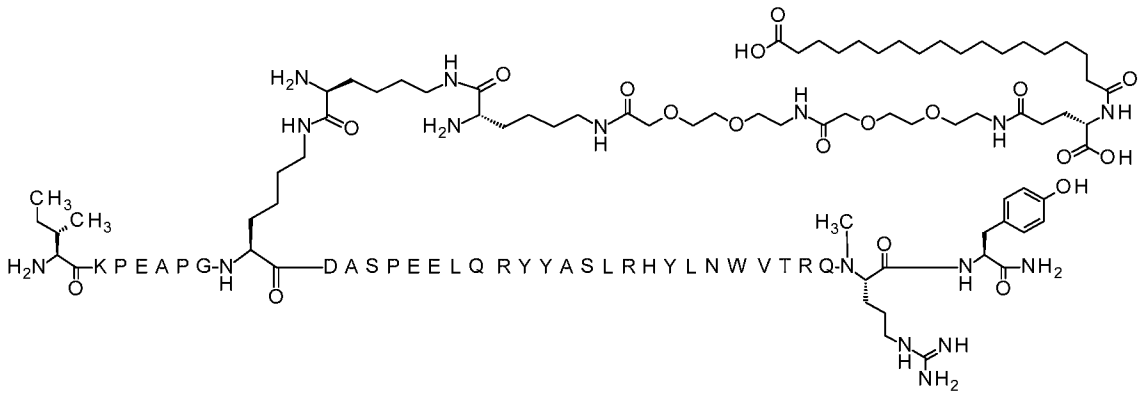


The amino acid sequence of [Lys10,Gln18,Trp30,NmeArg35]hPYY(3-36) is given in SEQ ID NO:6.

Retention time UPLC31v01: 2.7 min. (100%)
Retention time UPLC16v01: 13.3 min. (90.9%)
MW calculated: 5121.8 g/mol
LCMS2: ((M/3)+3) 1708.3; ((M/4)+4) 1281.5; ((M/7)+7) 732.7

Example 1.9: Compound 8

N{Epsilon-10}-[(2S)-2-amino-6-[[(2S)-2-amino-6-[[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]-ethoxy]ethoxy]acetyl]amino]hexanoyl]amino]hexanoyl]-[Lys10,Gln18,Trp30, NmeArg35]hPYY(3-36)

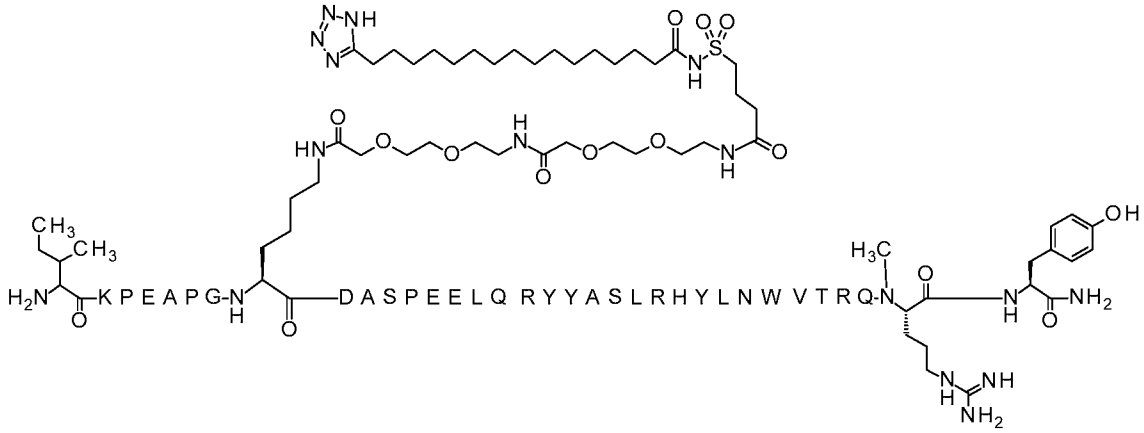


The amino acid sequence of [Lys10,Gln18,Trp30,NmeArg35]hPYY(3-36) is given in SEQ ID NO:6.

Retention time UPLC21v01: 7.6 min. (92.7%)
Retention time UPLC16v01: 12.4 min. (90.6%)
MW calculated: 5121.84 g/mol
LCMS2: ((M/5)+5) 1025.16;

Example 1.10: Compound 9

N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[4-[16-(1H-tetrazol-5-yl)hexadecanoylsulfamoyl]-butanoylamino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]-[Lys10,Gln18, Trp30,NmeArg35]hPYY(3-36)

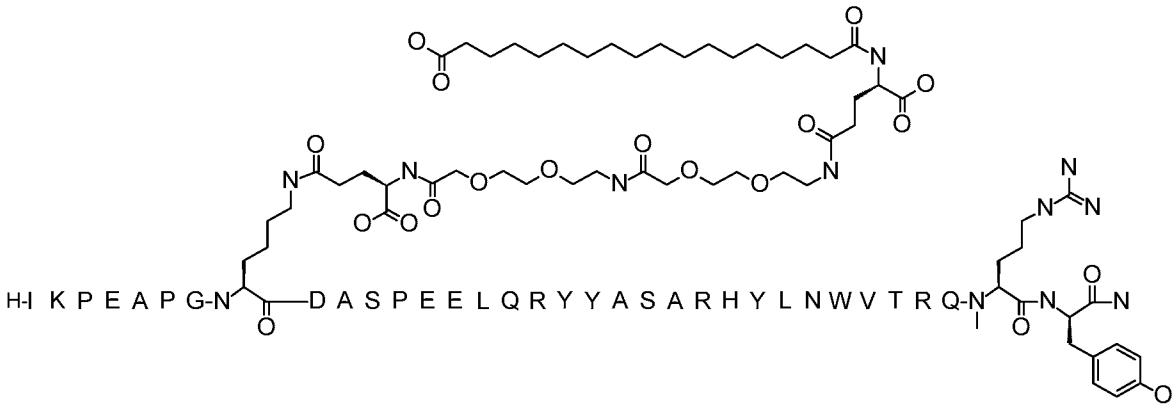


The amino acid sequence of [Lys10,Gln18,Trp30,NmeArg35]hPYY(3-36) is given in SEQ ID NO:6.

Retention time UPLC31v01: 3.0 min. (96.4%)
Retention time UPLC16v01: 14.4 min. (99.4%)
MW calculated: 4895.6 g/mol
LCMS2: ((M/3)+3) 1633.15; ((M/4)+4) 1224.90; ((M/6)+6) 817.17

Example 1.11: Compound 10

N{Epsilon-10}-[(4S)-4-carboxy-4-[[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]-ethoxy]acetyl]amino]butanoyl]-[Lys10,Gln18,Ala24,Trp30,NmeArg35]hPYY(3-36)

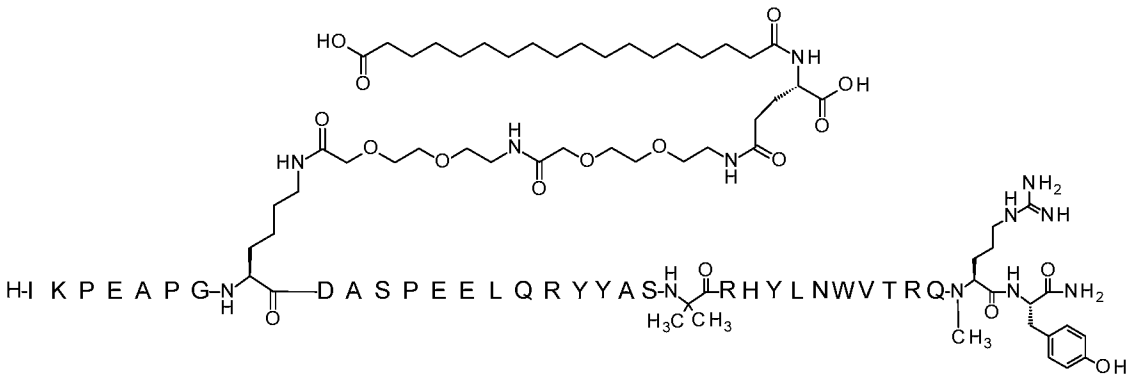


The amino acid sequence of [Lys10,Gln18,Ala24,Trp30,NmeArg35]hPYY(3-36) is given in SEQ ID NO:7.

Retention time UPLC30v01: 3.5 min. (93.1%)
Retention time UPLC16v01: 10.7 min. (91.4%)
MW calculated: 4952.53 g/mol
LCMS2: ((M/3)+3) 1651.5; ((M/4)+4) 1239.2; ((M/6)+6) 826.5

Example 1.12 Compound 11

N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)-butanoyl]amino]ethoxy]ethoxy]acetyl]-amino]ethoxy]ethoxy]acetyl]-[Lys10,Gln18, Aib24,Trp30,NmeArg35]hPYY(3-36)



The amino acid sequence of [Lys10,Gln18,Aib24,Trp30,NmeArg35]hPYY(3-36) is given in SEQ ID NO:8.

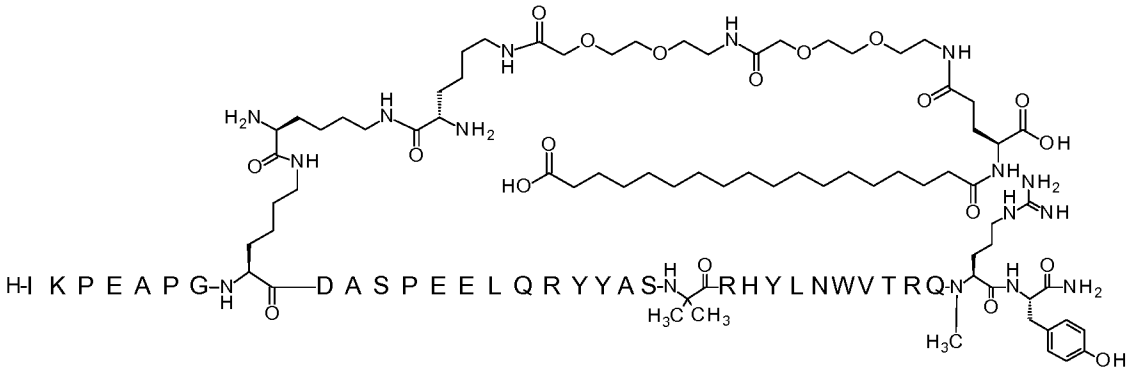
Retention time UPLC30v01: 3.6 min. (95.2%)
Retention time UPLC16v01: 11.9 min. (95.3%)

MW calculated: 4837.44 g/mol

LCMS2: ((M/3)+3) 1613.6; ((M/4)+4) 1210.2; ((M/6)+6) 807.3

Example 1.13: Compound 12

N{Epsilon-10}-[(2S)-2-amino-6-[[(2S)-2-amino-6-[[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]-ethoxy]ethoxy]acetyl]amino]hexanoyl]amino]hexanoyl]-[Lys10,Gln18,Aib24,Trp30, NmeArg35]hPYY(3-36)



The amino acid sequence of [Lys10,Gln18,Aib24,Trp30,NmeArg35]hPYY(3-36) is given in SEQ ID NO:8.

Retention time UPLC30v01: 3.2 min. (94.6%)

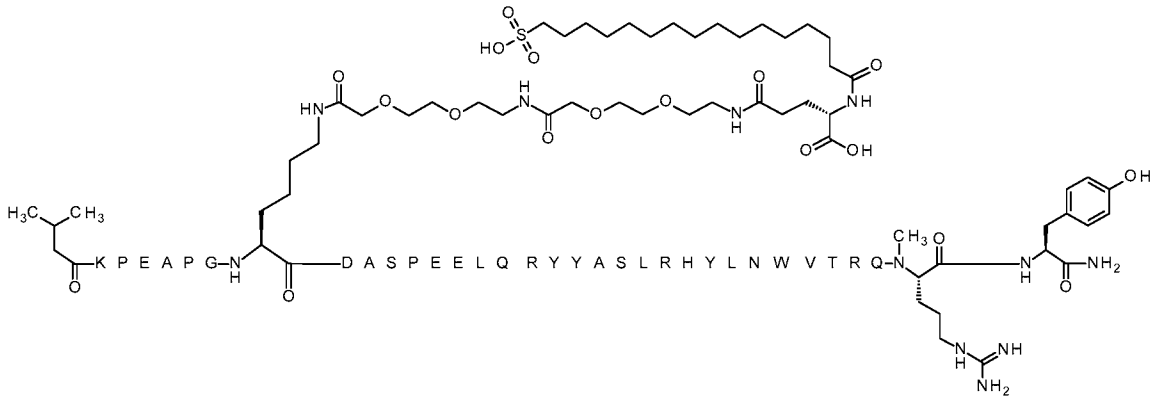
Retention time UPLC16v01: 11.6 min. (91.8%)

MW calculated: 5093.79 g/mol

LCMS2: ((M/3)+3) 1698.9; ((M/4)+4) 1274.4; ((M/7)+7) 728.7

Example 1.14: Compound 13

N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(16-sulfohexadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]-ethoxy]acetyl]-[Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36)

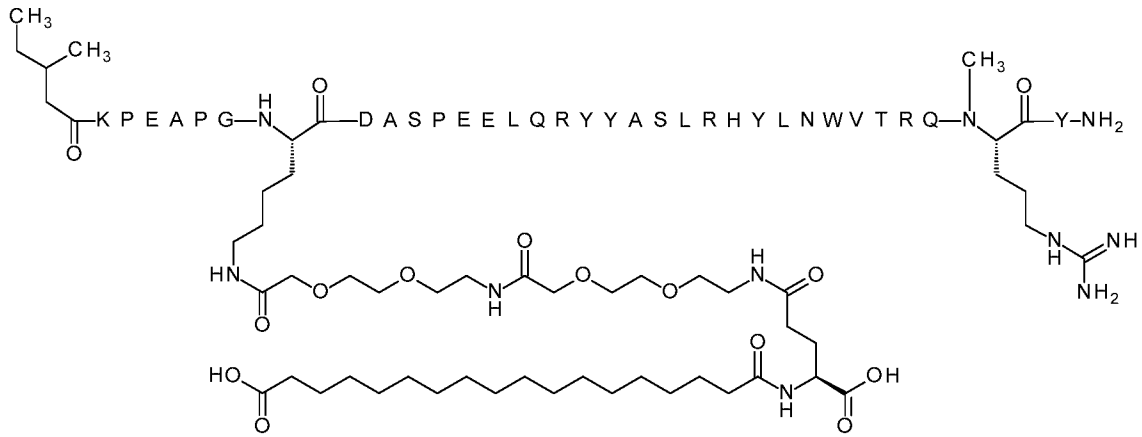


The amino acid sequence of [Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) is given in SEQ ID NO:9.

Retention time UPLC30: 3.6 min. (97.9%)
Retention time UPLC17: 9.6 min. (90.4%)
MW calculated: 4858.49 g/mol
MALDI-MS (found): 4856

Example 1.15: Compound 14

N{Alpha-4}-3-methylpentanoyl)-N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]-ethoxy]ethoxy]acetyl]-[Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36)

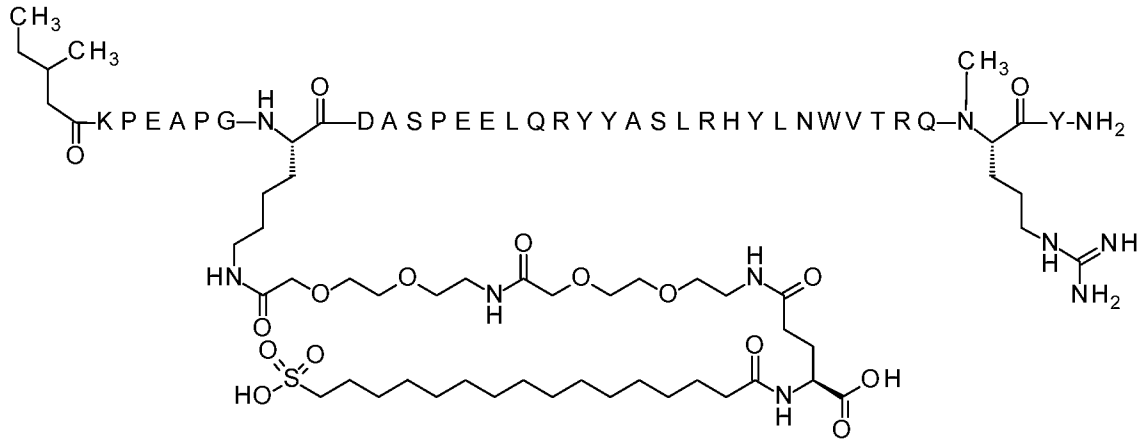


The amino acid sequence of [Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) is given in SEQ ID NO:9.

Retention time UPLC02v01: 7.7 min. (98.8%)
Retention time UPLC16v01: 8.9 min. (82.9%)
MW calculated: 4850.48 g/mol
LCMS2: ((M/4)+4) 1213.7

Example 1.16: Compound 15

N{alpha-4}-(3-Methylpentanoyl)-N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(16-sulfohexadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]-ethoxy]acetyl]-[Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36)

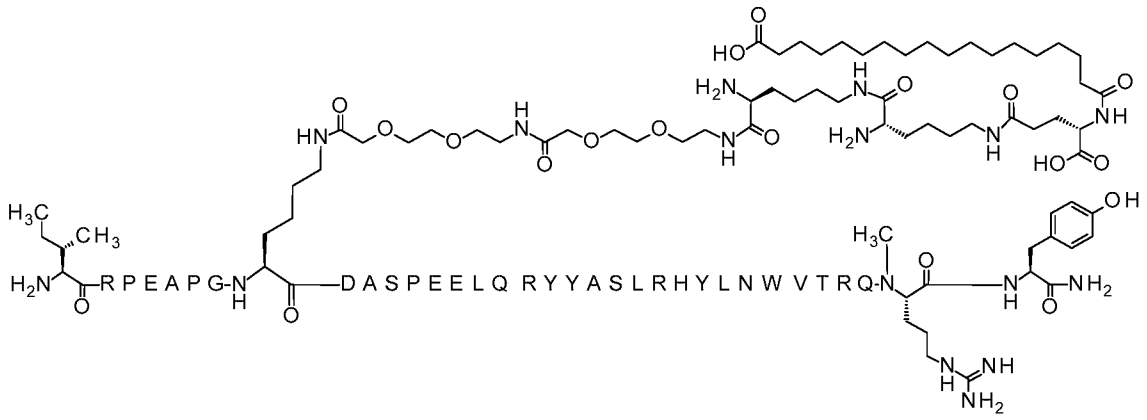


The amino acid sequence of [Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) is given in SEQ ID NO:9.

Retention time UPLC02v01: 6.9 min. (99.0%)
Retention time UPLC16v01: 12.9 min. (86.6%)
MW calculated: 4872.5 g/mol
LCMS2: ((M/4)+4) 1218.79

Example 1.17: Compound 16

N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(2S)-2-amino-6-[[(2S)-2-amino-6-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]hexanoyl]amino]hexanoyl]amino]-ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]-[Arg4,Lys10,Gln18,Trp30, NmeArg35]hPYY(3-36)

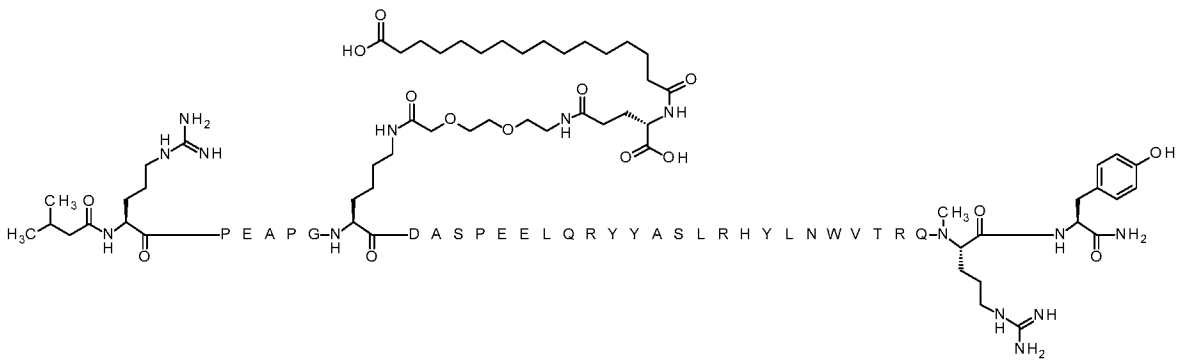


The amino acid sequence of [Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(3-36) is given in SEQ ID NO:10.

Retention time UPLC AP-01: 6.94 min. (95.4%)
MW calculated: 4865.5 g/mol
LCMS1: ((M/3)+3) 1717.5; ((M/4)+4) 1288.3; ((M/5)+5) 1031.5

Example 1.18: Compound 17

N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[2-[2-[2-[[(4S)-4-carboxy-4-(15-carboxypentadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]-[Arg4,Lys10,Gln18, Trp30,NmeArg35]hPYY(4-36)



The amino acid sequence of [Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) is given in SEQ ID NO:11.

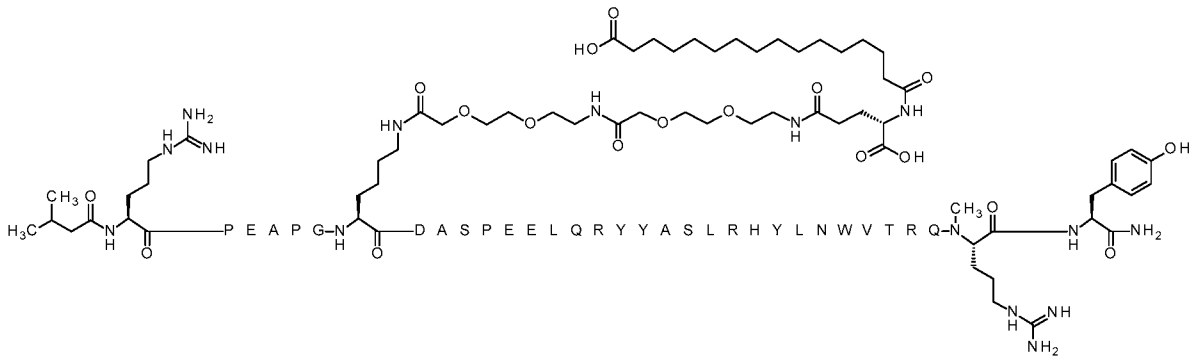
Retention time UPLC31: 3.1 min. (89.8%)
Retention time UPLC17: 8.7 min. (91.2%)

MW calculated: 4691.26 g/mol

LCMS1: ((M/3)+3) 1564.8; ((M/4)+4) 1173.8

Example 1.19: Compound 18

N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(15-carboxypentadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]-ethoxy]acetyl]-[Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36)



The amino acid sequence of [Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) is given in SEQ ID NO:11.

Retention time UPLC31: 6.1 min. (96.8%)

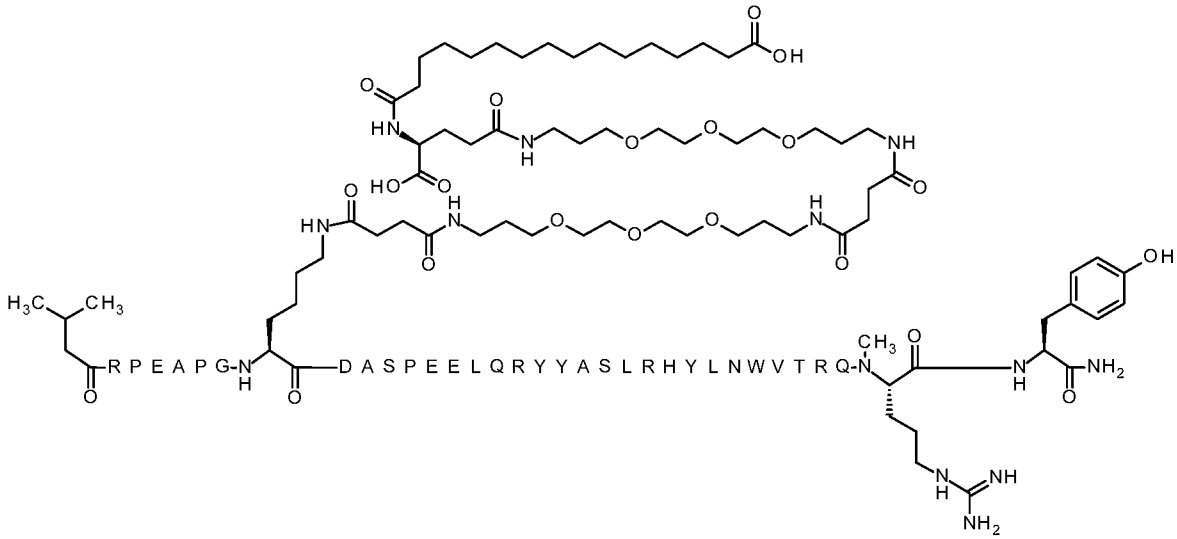
Retention time UPLC17: 9.2 min. (88.0%)

MW calculated: 4836.52 g/mol

LCMS1: ((M/4)+4) 1210.1 ; ((M/5)+5) 968.28

Example 1.20: Compound 19

N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[4-[3-[2-[2-[3-[[4-[3-[2-[2-[3-[[(4S)-4-carboxy-4-(15-carboxypentadecanoylamino)butanoyl]amino]propoxy]ethoxy]ethoxy]-propylamino]-4-oxobutanoyl]amino]propoxy]ethoxy]ethoxy]propylamino]-4-oxobutanoyl]-[Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36)

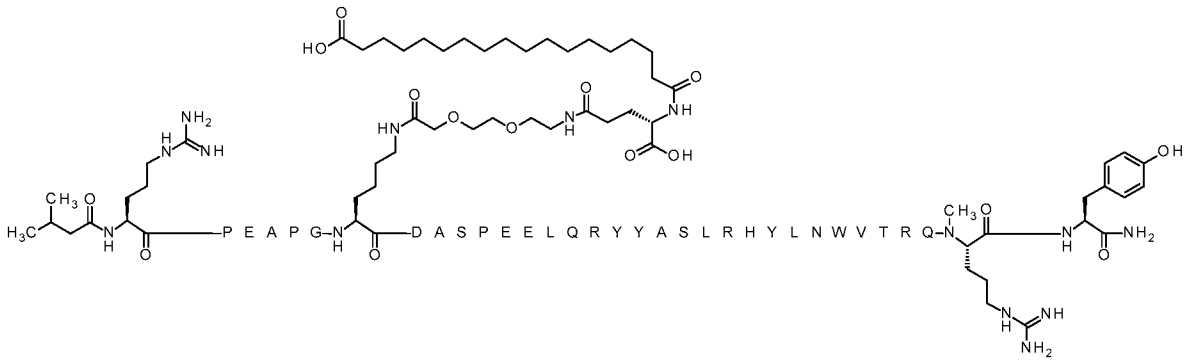


The amino acid sequence of [Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) is given in SEQ ID NO:11.

Retention time UPLC31: 3.1 min. (97.8%)
Retention time UPLC16: 12.0 min. (90.2%)
MW calculated: 5150.96 g/mol
LCMS1: ((M/4)+4) 1288.7; ((M/5)+5) 1031.95

Example 1.21: Compound 20

N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]-[Arg4,Lys10, Gln18,Trp30,NmeArg35]hPYY(4-36)



The amino acid sequence of [Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) is given in SEQ ID NO:11.

Retention time UPLC31: 3.6 min. (89.3%)

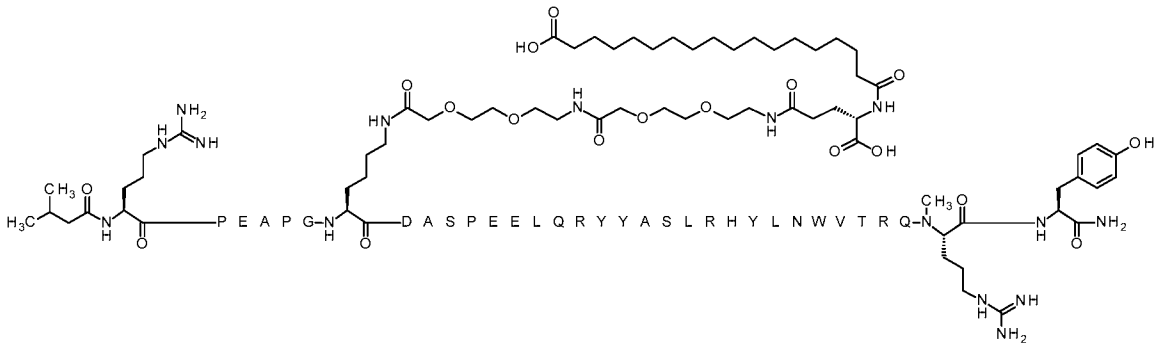
Retention time UPLC17: 9.3 min. (91.8%)

MW calculated: 4719.31 g/mol

LCMS1: ((M/3)+3) 1574.4; ((M/4)+4) 1180.85

Example 1.22: Compound 21

N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]-ethoxy]acetyl]-[Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36)



The amino acid sequence of [Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) is given in SEQ ID NO:11.

Retention time UPLC02: 7.8 min. (92.5%)

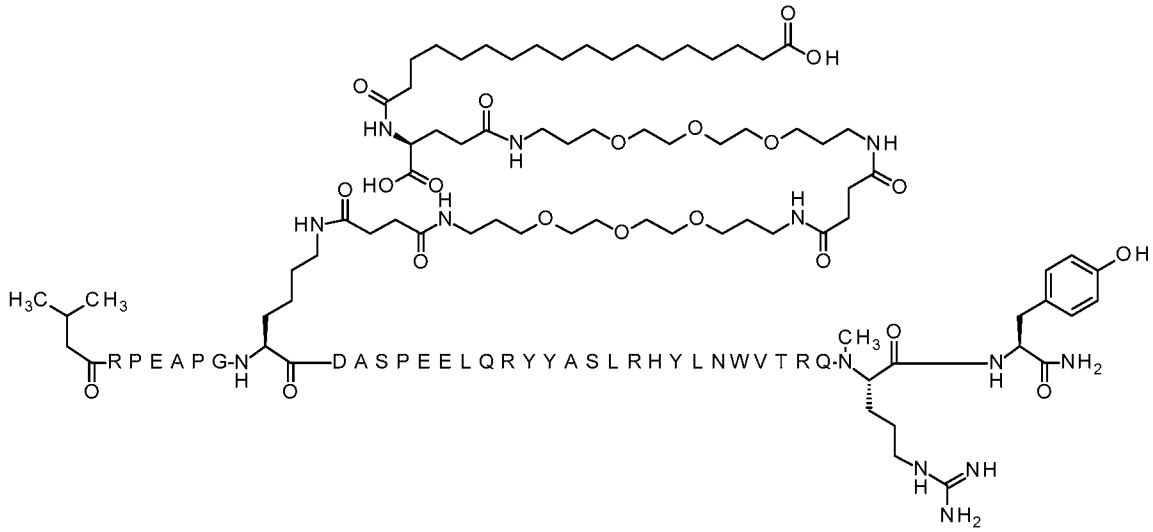
Retention time UPLC17: 10.4 min. (93.4%)

MW calculated: 4864.58 g/mol

LCMS1: ((M/4)+4) 1217.1 ; ((M/5)+5) 973.9

Example 1.23: Compound 22

N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[4-[3-[2-[2-[3-[[4-[3-[2-[2-[3-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]propoxy]ethoxy]ethoxy]-propylamino]-4-oxobutanoyl]amino]propoxy]ethoxy]-ethoxy]propylamino]-4-oxobutanoyl]-[Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36)

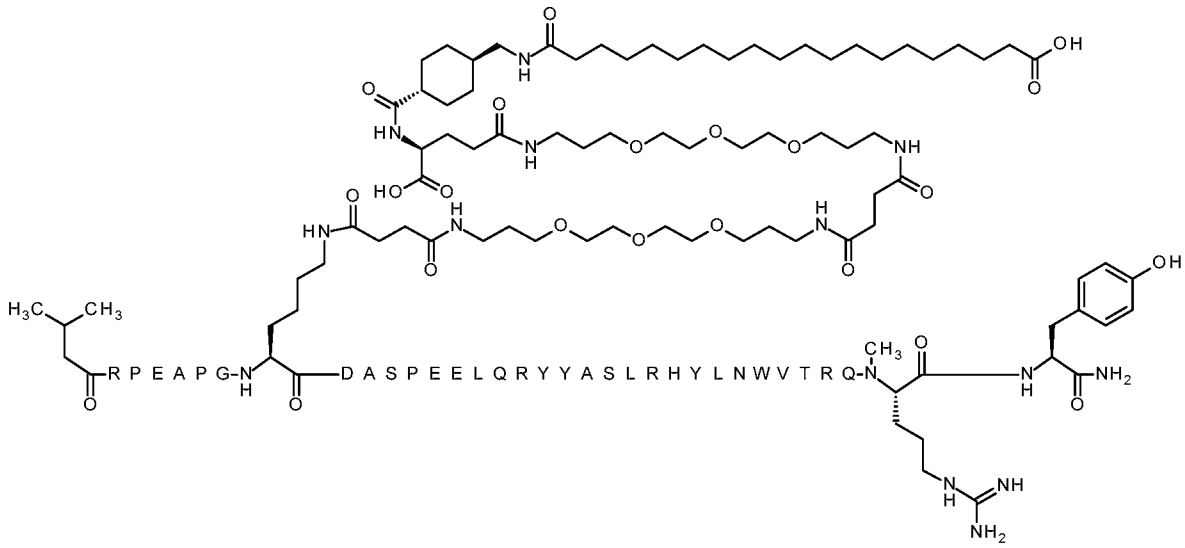


The amino acid sequence of [Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) is given in SEQ ID NO:11.

Retention time UPLC31: 3.6 min. (97.0%)
Retention time UPLC17: 10.4 min. (90.9%)
MW calculated: 5179.01 g/mol
MALDI-MS (found): 5178.8

Example 1.24: Compound 23

N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[4-[3-[2-[2-[3-[[4-[3-[2-[2-[3-[[(4S)-4-carboxy-4-[[4-[(19-carboxynonadecanoylamino)methyl]cyclohexanecarbonyl]amino]-butanoyl]amino]propoxy]ethoxy]ethoxy]propylamino]-4-oxobutanoyl]amino]-propoxy]ethoxy]ethoxy]propylamino]-4-oxobutanoyl]-[Arg4,Lys10,Gln18,Trp30, NmeArg35]hPYY(4-36)

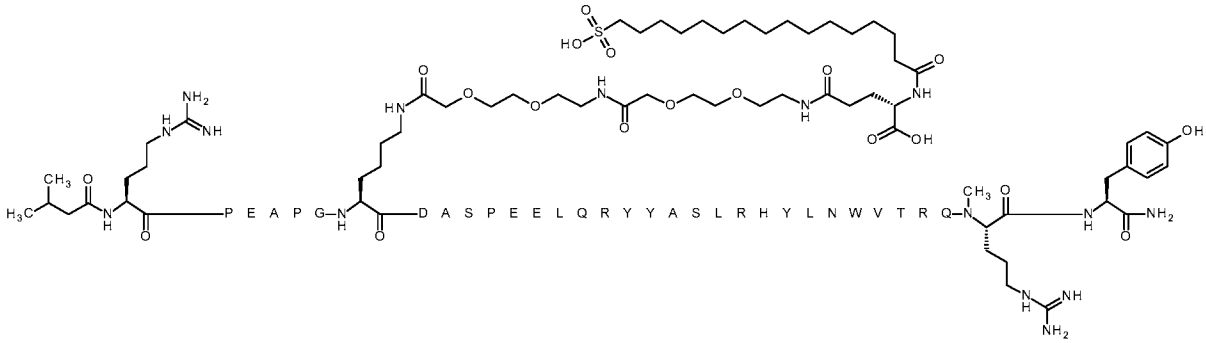


The amino acid sequence of [Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) is given in SEQ ID NO:11.

Retention time UPLC30: 3.4 min. (90.2%)
Retention time UPLC17: 11.4 min. (86.3%)
MW calculated: 5346.26 g/mol
MALDI-MS (found): 5201

Example 1.25: Compound 24

N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(16-sulfohexadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]-ethoxy]acetyl]-[Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36)



The amino acid sequence of [Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) is given in SEQ ID NO:11.

Retention time UPLC30: 3.7 min. (98.2%)

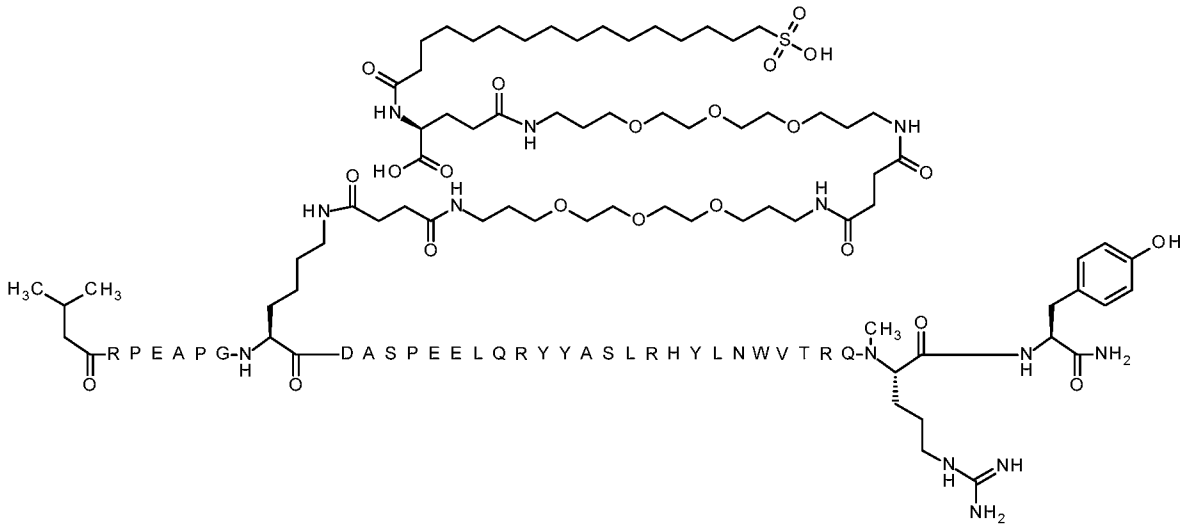
Retention time UPLC17: 8.8 min. (90.1%)

MW calculated: 4886.54 g/mol

LCMS1: ((M/4)+4) 1222.6; ((M/5)+5) 978.1

Example 1.26: Compound 25

N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[4-[3-[2-[2-[3-[[4-[3-[2-[2-[3-[[(4S)-4-carboxy-4-(16-sulfohexadecanoylamino)butanoyl]amino]-propoxy]ethoxy]-ethoxy]propylamino]-4-oxobutanoyl]amino]propoxy]ethoxy]-ethoxy]propylamino]-4-oxobutanoyl]-[Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36)



The amino acid sequence of [Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) is given in SEQ ID NO:11.

Retention time UPLC30: 3.7 min. (98.1%)

Retention time UPLC17: 9.6 min. (84.7%)

MW calculated: 5201.04 g/mol

MALDI-MS (found): 5201

Pharmacological methods

The utility of PYY peptide derivatives or analogues thereof of the present invention as pharmaceutically active agents in the reduction of weight gain and treatment of obesity in mammals (such as humans), and for treatment of diabetes may be demonstrated by

the activity of the agonists in conventional assays and in the *in vitro* and *in vivo* assays described below.

Such assays also provide a means whereby the activities of the PYY compounds of this invention can be compared with the activities of known compounds.

Example 2: Receptor potency of PYY compounds

The purpose of this example is to test the activity, or potency, of the PYY compounds in vitro. The in vitro potency is the measure of the activation of the human Y1, Y2, Y4 and Y5 receptor subtypes, respectively, in a whole cell assay.

The potencies of the PYY compounds of example 1 were determined using the Actone functional potency assay as described below. hPYY(3-36) (Example 1.1, SEQ ID NO:2) was included as a reference.

Actone functional potency assay

The Neuropeptide Y (NPY) receptors are G_i-coupled seven trans-membrane receptors that mainly signal through the cAMP dependent pathway by inhibiting adenylate cyclase activity which results in a decrease of cAMP production from ATP. The Actone assay is based on a modified calcium channel that has a selective binding for cAMP, resulting in cellular calcium influx, detected by a calcium responsive dye. In order to measure decreased levels of cAMP, as result of NPY receptor activation, the β1/β2-adrenoreceptor agonist, isoproterenol, is added to activate adenylate cyclase and increases cAMP levels in the cell. Decreased cellular calcium concentrations, reflecting a decrease of cAMP levels due to NPY receptor activation, is detected as a decrease in fluorescence from the calcium sensitive dye.

HEK-293 cells expressing the cAMP sensitive calcium channel and one of the human NPY receptors Y1, Y2, Y4 or Y5 (CodexBiosolution, Gaithersburg, MD, USA) were seeded into poly lysine coated 384 well plates at a density of 14.000 cells/well (28.000cells/well for Y2 cells) in a volume of 25 µl in DMEM medium containing 10% heat inactivated fetal calf serum (FCS), 1% Penicillin-Streptomycin, 250 µg/ml aminoglycoside antibiotic G418 and 1 µg/ml aminonucleoside antibiotic puromycin and 0.1 mM (4S)-4-carboxy-4-[[(4S)-4-carboxy-4-(19-carboxynonadecanoylamino)butanoyl]amino]butanoic acid (or another fatty acid derived compound that binds to albumin's fatty acid binding sites having no affinity to the Y receptors) for saturation of albumin. The cells were incubated over night at +37 °C in a humidified milieu in 5% CO_2 followed by addition of 25 µl calcium dye buffer containing: 1 vial Calcium 5 dye (Molecular Devices, Sunnyvale, CA, USA) solved in 100 ml HBSS buffer containing 20 mM Hepes, 0.1% Ovalbumin,

0.005% Tween 20, 1.5 mM probenecid, 250 µM PDE-inhibitor 4-(3-Butoxy-4-methoxybenzyl)imidazolidin-2-one and 8 mM $CaCl_2$ and pH was adjusted to 7.40. Cells were incubated for 1 hour with the calcium dye buffer and then placed in a FLIPR Tetra System (Molecular Devices) where the liquid handling system added PYY compound (ranging from 1000-1 nM final concentrations in the Y1, Y4 and Y5 assays and 30-0.03 nM in the Y2 assay) and isoproterenol (0.05 µM final concentration) simultaneously directly followed by fluorescence signal measurement (Ex540/Em590) for 360 seconds with 30 seconds intervals. All measurements were performed in duplicates and EC_{50} values were calculated by nonlinear regression analysis of sigmoidal dose response curves using the GraphPad Prism v 5.02 (Graph Pad software, La Jolla, CA, USA). The EC50 values are shown in table 1.

Table 1. In vitro potency

Compound	**Y2 EC50 (nM)**	**Y1 EC50 (nM)**	**Y4 EC50(nM)**	**Y5 EC50 (nM)**
hPYY(1-36)	0.60	0.06	2.2	4.4
hPYY(3-36)	0.87	7.0	8.8	651
1	4.5	111	228	955
2	0.57	335	16	403
3	0.64	>1000	201.4	>1000
4	13.6	542	529	>1000
5	2.5	>1000	209	554
6	2.1	>1000	250	427
7	1.9	939	257	101
8	1.1	>1000	105	>1000
9	1.5	500		225
10	13.5	>1000	849	1000.0
11	10.0	933	616	803
12	7.6	>1000	547	434
13	1.0	>1000	>1000	>1000
14	1.2	>1000	200	>1000
15	1.9	>1000	316	>1000
16	1.4	>1000	156	>1000
17	2.6	>1000	643	>1000
18	2.4	>1000	607	>1000

19	2.3	>1000	463	>1000
20	3.5	>1000	856	>1000
21	2.2	>1000	690	>1000
22	3.4	>1000	>1000	>1000
23	2.8	>1000	>1000	>1000
24	1.8	>1000	848	>1000
25	1.1	>1000	>1000	>1000

The PYY compounds of the inventions all display good Y2 potency, whereas the potency on the receptors Y1, Y4 and Y5 is strongly reduced.

Example 3: Y1, Y2, Y4 and Y5 receptor subtype binding

The purpose of this example is to test the in vitro binding of the PYY compounds to the Y1, Y2, Y4 and Y5 receptor subtypes, respectively. The receptor binding affinity is a measure of affinity of a compound for the human Y1, Y2, Y4 and Y5 receptor subtypes, respectively.

The in vitro binding of the PYY compounds of example 1 were determined in a scintillation proximity assay (SPA) as described below. hPYY(3-36) (Example 1.1, SEQ ID NO:2) was included as a reference.

Scintillation Proximity Assay (SPA)

NPY-receptor expressing cell lines. All cells were cultured at +37 °C in a humidified atmosphere with 5% CO_2. BHK-21 clone 6-482-8 cells with inducible expression of the human Y1 receptor (P25929, NPY1R_HUMAN, Uniprot) were cultured in Dulbecco's Modified Eagle Medium (DMEM) with 10% heat inactivated fetal bovine serum (FBS), 1% Penicillin-Streptomycin (P/S), 1 mg/ml G418 antibiotic, 1mg/ml Hygromycin B antibiotic and 1% Non-essential amino acids. 1 mM Isopropyl β-D-1-thiogalactopyranoside (IPTG) was added 24 hours prior to harvesting cells for induction of NPY-Y1 receptor expression. CHO-K1 cells stably expressing the human Y2 receptor (P49146, NPY2R_HUMAN, Uniprot) were cultured in DMEM F-12 with 10% FBS, 1% P/S, 150 µg/ml Hygromycin B and 10 µg/ml Puromycin antibiotic. CHO-K1 cells stably expressing the human Y4 receptor (P50391, NPY4R_HUMAN, Uniprot) were cultured in DMEM F-12 with 10% FBS, 1% P/S, 10 µg/ml Puromycin. HEK-293 cells stably expressing the human Y5 receptor (Q15761, NPY5R_HUMAN, Uniprot) were cultured in DMEM F-12 medium containing 10% FBS, 1% Penicillin-Streptomycin, 250 µg/ml G418 and 1 µg/ml puromycin.

Membrane preparation. Cultured cells were detached mechanically by scraping and washed in ice cold PBS (137 mM NaCl, 2.7 mM KCl, 4.3 mM Na_2HPO_4,1.47 mM KH_2PO_4 pH adjusted to 7.4) and transferred to tubes and centrifuged for 5 minutes at 1000 g at +4 °C. Pellets were resuspended in ice cold homogenization buffer; Y1: 20 mM Hepes, 10mM EDTA, with 2 complete EDTA-free protease inhibitor cocktail tablets/50 ml (Roche, Mannheim, Germany) pH 7.4); Y2, Y4: 20 mM Hepes, 5mM $MgCl_2$, 1 mg/ml Bacitracin, pH 7.1; Y5: 10 mM NaCl, 20 mM Hepes, 0.22 mM KH_2PO_4, 1.26 mM $CaCl_2$, 0.81 mM $MgSO_4$, pH 7.4 and then homogenized for 30 seconds using a tissue homogenizer at medium speed. The homogenate was centrifuged at 35000g using an ultracentrifuge for 10 minutes at +4°C and the supernatant was discarded and fresh homogenization buffer added. Homogenization of the pellet was repeated a total of three times. The final pellet was resuspended in a few millilitres of homogenization buffer and protein concentration was determined using the Bradford method and measured at 595 nm in a microplate reader. Protein concentration were adjusted to 1mg/ml and transferred to cryotubes and stored at -80°C. 250 mM sucrose was added to Y5 membranes prior to freezing.

Assay. Human Y receptor SPA binding assay were performed in white 96-well plates in a total volume of 200 µl per well. Wheat germ agglutinin coated beads containing scintillation liquid (PerkinElmer, Waltham, MA, USA) were reconstituted in binding buffer; Y1, Y2: 50 mM Hepes, 1 mM $CaCl_2$, 5 mM $MgCl_2$, 0.02% tween 20, 0.25% ovalbumin pH 7.4; Y4, Y5: 20 mM Hepes, 10 mM NaCl, 0.22 mM KH_2PO_4, 1.26 mM $CaCl_2$, 0.81mM $MgSO_4$, 0.1% bacitracin and 0.25% ovalbumin pH 7.4 and mixed with membrane preparation to give final concentration of 0.5 mg beads/well and 3 µg of Y1 membranes/well, 3 µg of Y2 membranes/well, 1µg of Y4 membranes/well or 20 µg of Y5 membranes/well. 50000 cpm per well of radio ligand human [^{125}I]-PYY(1-36) was added corresponding to a concentration of 100 pM in Y1, Y2 and Y5 binding assays. 50000 cpm per well of radio ligand human [^{125}I]-Pancreatic Polypeptide (PP) corresponding to a concentration of 100 pM was used in Y4 binding assay.

Freeze dried analogues were dissolved in 80% dimethyl sulfoxide (DMSO), 19% H_2O and 1% acetic acid (CH_3COOH) to stock solutions of 2000 µM (Y1,Y4 and Y5) and 200 µM (Y2) and serial dilutions (1:10) were performed in binding buffer to final concentrations ranging from 10000 nM to 1 pM in the Y1, Y4 and Y5 assays and 1000 nM to 0.1 pM in the Y2 assay. Plates were sealed and incubated at +25 °C for 2 hours in a plate shaker set at 400 rpm and thereafter centrifuged at 1500 rpm for 10 minutes prior

to reading of luminescence on a microplate scintillation and luminescence counter. Y1 SPA plates were let to stand in room temperature for 16 hours prior to reading. Displacement of radioligand was measured as reduction in luminescence and IC_{50} values were calculated by nonlinear regression analysis of sigmoidal dose-response curves. Ki values for binding affinity were acquired by the Cheng-Prusoff equation (Ki=IC50/(1+[L]/Kd) including receptor specific Kd values (Y1=0.556 nM; Y2=0.275 nM; Y4=0.111 nM; Y5=0.345 nM), radioligand concentration and IC50 values.

Table 2: Y receptor binding affinity

Compound no.	**Y2 Ki (nM)**	**Y1 Ki (nM)**	**Y4 Ki (nM)**	**Y5 Ki (nM)**
hPYY(1-36)	0.30	0.19	0.68	5.13
hPYY(3-36)	0.38	44	4.2	38
1	1.8	418	151	657
2	0.21	443	10	3.5
5	0.9	>10000	314	2758
6	1.9	>10000	856	6669
7	1.4	8450	198	2854
8	0.4	>10000	318	2019
11	3.6	698	750	>10000
12	1.0	>10000	111	>10000
13	0.9	>10000	1193	4648
14	0.7	8258	206	1738
15	3.2	>10000	720	6128
16	0.7	8835	183	2188
17	1.2	>10000	1026	3473
18	2.0	>10000	828	4234
19	2.3	>10000	1290	3848
20	2.4	>10000	2210	4490
21	2.7	>10000	1257	3661
22	3.0	>10000	1238	7013
23	5.0	>10000	2479	7965
24	1.9	>10000	1085	3430
25	3.7	4000	900	1000

The PYY compounds of the invention all display good Y2 binding while the binding affinity on the receptors Y1, Y4 and Y5 is strongly reduced.

Example 4: Pharmacokinetic study in minipigs

The purpose of this study is to determine the half-life in vivo of the PYY compounds after i.v. administration to minipigs, i.e. the prolongation of their time in the body and thereby their time of action. This is done in a pharmacokinetic (PK) study, where the terminal half-life of the derivative in question is determined. By terminal half-life is generally meant the period of time it takes to halve a certain plasma concentration, measured after the initial distribution phase.

In vivo studies on pharmacokinetic evaluation in Göttingen minipigs after intravenous administration.

Animals. Göttingen minipigs female, 15-25 kg, purchased from Ellegaard Minipigs, Denmark. The animals were housed in the Animal Unit, Novo Nordisk A/S and were kept and handled according to normal procedure in the Animal Unit. After minimum 2 weeks of acclimatization two permanent central venous catheters were implemented in vena cava caudalis in each animal. After surgery the animals were in their normal individual pens during the pharmacokinetic experiments.

Body Weight. The animals were weighed weekly. The animals were fasted on the morning prior to dosing but had ad libitum access to water; food was supplied during dosing.

Administration of peptides and dosing solutions. Intravenous injections were given through the central short catheter, which was flushed with minimum 10 ml of sterile saline post administration. The test substance was dosed at 15 nmol/kg, n = 3, in a volume of 0.05 ml/kg. Buffer: 50 mM sodium phosphate, 70 mM sodium chloride, 0.05% tween 80, pH 7.4 or 20 mM HEPES, 2.2% glycerol, 0.05% Polysorbate 80, pH 6.5.

Blood samples and analysis. Blood samples were taken through the central catheter according to the following schedule: Predose, 5, 15, 30, 45 min, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h, 24 h, 48 h, 72 h, 96 h, 120 h, 168 h, 192 h, 216 h, 240 h, 264 h and 288 h. On day 1 the catheters are coupled to extension tubes, which will be removed at the end of day 1. Samples (0.8 ml) were taken through the catheter. Blood was collected in test tubes containing EDTA buffer (8 mM) and 50 µl Val-Pyr buffer (Stabilization buffer containing 3.097g K3EDTA dissolved in 50 ml Trasylol and 0.5 ml 20 mM Val-Pyr was added. The pH was regulated to 7.4). After each blood sample the catheter was flushed with minimum 5 ml of sterile 0.9 % NaCl and 10 IE/ml heparin. Aseptic technique was demanded to avoid bacterial growth in the catheter that increases

the risk of clot formation in the catheter. Samples were kept on wet ice until centrifugation (10 min, 4 °C, 1942 g). Afterwards, plasma (min. 200 µl) was transferred immediately to Micronic tubes and kept at -20 °C until analysis. The plasma samples were analysed by LC/MS as described below.

Data and results. Plasma concentration-time profiles was analysed by a non-compartmental pharmacokinetics analysis using Phoenix (Pharsight Inc., Mountain View, CA, USA). Calculations were performed using individual concentration-time values from each animal.

Sample analysis

Quantitative Assay for Plasma Samples. The test substances were assayed in plasma by Turbulent Flow Chromatography coupled to Liquid Chromatography with subsequent Mass Spectrometric Detection (TFC/LC/MS). The selectivity of the method allowed various compounds to be quantitated in one sample, e.g. cassette dosing of four compounds per animal. The concentrations of the test substance in unknown samples were calculated using the peak area as a function of amount. Calibration graphs based on plasma samples spiked with the analyte were constructed by regression analysis. Typical dynamic range for the assay was 1 – 2,000 nmol/l. The method performance was assured by co-assaying quality control (QC) samples in duplicate at three concentration levels. Stock and working solutions of analytes were prepared in plasma and incubated by 37 °C for 1 hour.

Sample Preparation. 40.0 µl EDTA-plasma was added 160 µl 50% methanol, 1% formic acid, then vortexed and centrifuged at 14300 rpm (16457 g) at 4 °C for 20 minutes. The supernatant was transferred to a 96 well plate, (the plates have been preincubated with 0.4% BSA, 37 °C for ½ hour). Injection volume was 25 µl.

For sample clean up a TurboFlow Cyclone column (0.5 x 50 mm) both from Thermo Scientific, Franklin, MA, USA, was used and the LC separation was done either on an Onyx C18 column (2.0 x 50 mm) from Phenomenex, Torrance, CA, USA. Eluents were isocratic and gradient combinations of methanol, acetonitril, Milli-Q water and formic acid. Selective detection was done by mass spectrometry operated in positive mode ionisation.

Data handling. Plasma concentration-time profiles was analysed by a non-compartmental pharmacokinetics analysis using Phoenix (Pharsight Inc., Mountain View, CA, USA). Calculations were performed using individual concentration-time values from each animal.

Table 3: Half-life (t½)

Compound no.	**t½ (hours)**
hPYY(3-36)	0.33
4	16
5	53
6	54
7	43
9	58
10	71
11	58
12	60
13	68
15	70
16	41
17	32
19	24
21	83
22	76
23	56
25	66

The tested PYY compounds of the invention have very long half-lives as compared to the half-life of hPYY(3-36).

Example 5: Pharmacodynamic studies in db/db mice

In order to determine the in vivo effects of the PYY compounds on blood glucose and food intake in a diabetic setting, the compounds were tested in an obese, diabetic mouse model (db/db mice) as described below.

Male db/db mice are housed in a normal daily rhythm (6 pm to 6 am dark cycle) and provided ad libitum access to Altromin diet. At 11-13 weeks of age the mice are matched for blood glucose as well as body weight and divided into matching groups of 9 mice and housed 3 per cage. Mice are dosed subcutaneously with the indicated compound or vehicle (50 mM Na2HPO4, pH 7,4, 70 mM NaCl, 0.05% Tween 80) at a volume of 2.5 ml/kg at the indicated doses at 4 pm (time =0) and in some experiments a

second injection was given at time=23 hours. Blood glucose and food intake are measured at the indicated time points post injection, e.g at 4 hours (4 h), 16 hours (16 h), 23 hours (23 h) and 40 hours (40 h) post injection. Blood samples for blood glucose are taken from the tail vein, into a 5 µl heparin coated capillary tube which is placed in an eppendorf tube with Biosen® system solution (250 µl). The samples are analysed on a Biosen® instrument immediately.

Blood glucose (BG) measurements are reported as mean ± SEM of vehicle adjusted % BG relative to pre-treatment and calculated as follows:

100-[%BG(vehicle,average)-%BG] where,

%BG=100*[BG(time=t)/BG(pre-treatment)]

and %BG(vehicle,average)=average of %BG values for the vehicle group at time=t relative to vehicle pre-treatment.

Food intake is reported as mean ± SEM food intake per cage as a percentage of average food intake of the vehicle group for the indicated interval.

Table 4: Effect on blood glucose in db/db mice. Blood glucose (BG) measurements are reported as mean ± SEM of vehicle adjusted % BG relative to pre-treatment

Compound no.	**Dose (nmol/kg)**	**% relative change in blood glucose**			
		4 h	**16 h**	**23 h**	**40 h**
7	300	70	84	87	80
13	300	47	53	38	56

Table 5: Effect on food intake in db/db mice. Food intake is reported as mean ± SEM food intake per cage as a percentage of average food intake of the vehicle group for the indicated interval.

Compound no.	**Dose (nmol/kg)**	**% relative food intake**			
		4 h	**16 h**	**23 h**	**40 h**
7	300	17	27	36	32
13	300	8	8	15	13

These data strongly support the blood glucose lowering effect and the inhibition of food intake of the PYY compounds of the invention.

While certain features of the invention have been illustrated and described herein, many modifications, substitutions, changes, and equivalents will now occur to those of ordinary skill in the art. It is, therefore, to be understood that the appended claims are intended to cover all such modifications and changes as fall within the true spirit of the invention.

CLAIMS

1. A PYY compound having a maximum of 10 amino acid modifications as compared to hPYY(3-36) (SEQ ID NO:2), wherein the PYY compound comprises

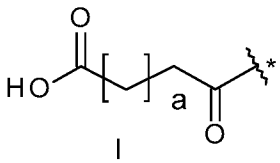
i) tryptophan at the position corresponding to position 30 of hPYY(1-36) (SEQ ID NO:1);

ii) N(alpha)-methyl-L-arginine at the position corresponding to position 35 of hPYY(1-36) (SEQ ID NO:1);

iii) lysine at the position corresponding to position 10 of hPYY(1-36) (SEQ ID NO:1); and

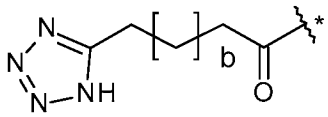
iv) a modifying group attached to the epsilon amino group of the Lysine residue in position 10, wherein said modifying group is defined by **A-B-C-D-E-**, wherein

A is selected from



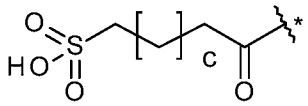
I

,



II

, and

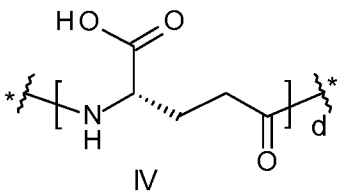


III

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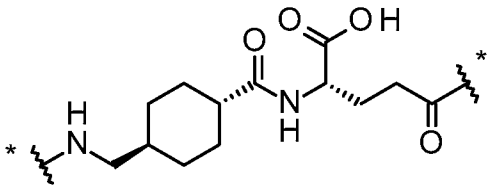
wherein a is an integer from 12 to 19, b is an integer from 10 to 16, and c is an integer from 10 to 16;

B is selected from



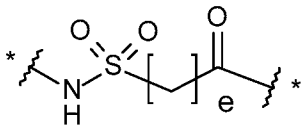
IV

,



V

, and

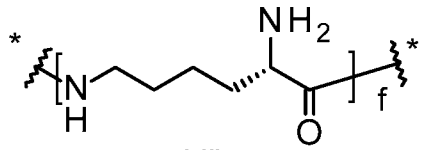


VI

,

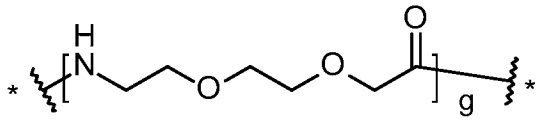
wherein d is 1 or 2; and e is 2, 3 or 4;

C is absent or

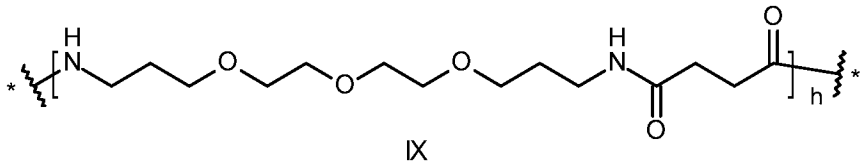


VII , wherein f is 1 or 2;

D is selected from



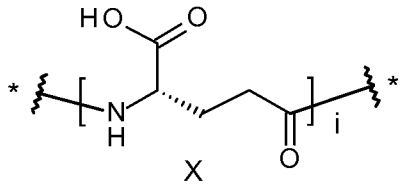
VIII , or



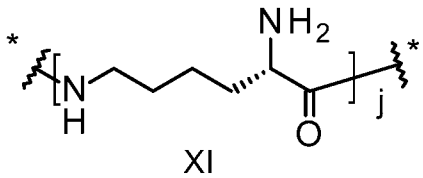
IX ,

wherein g is 1 or 2, h is 1 or 2; and

E is absent or selected from



X , and

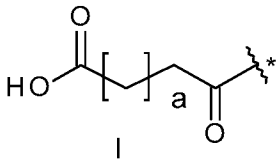


XI ,

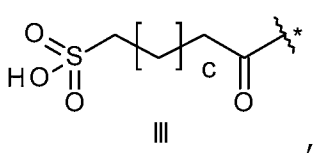
wherein i is 1 or 2, and j is 1 or 2; and

wherein * denotes the points of attachment, and wherein A, B, C, D and E are interconnected via amide bonds and in the sequence indicated via said point of attachments.

2. A PYY compound according to claim 1, wherein **A-** is selected from



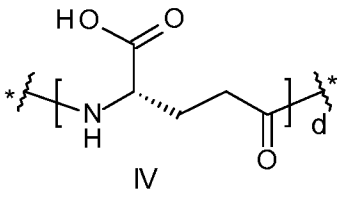
I or



III ,

wherein a is an integer from 12 to 19, and c is an integer from 10 to 16.

3. A PYY compound according to any one of the preceding claims, wherein **B-** is



IV , wherein d is 1 or 2.

4. A PYY compound according to claim 3, wherein d is 1.

5. A PYY compound according to any one of the preceding claims, wherein f is 0.

6. A PYY compound according to any one of the preceding claims, wherein C is absent.

7. A PYY compound according to any one of the preceding claims, wherein the PYY compound comprises glutamine at the position corresponding to position 18 of hPYY(1-36) (SEQ ID NO:1).

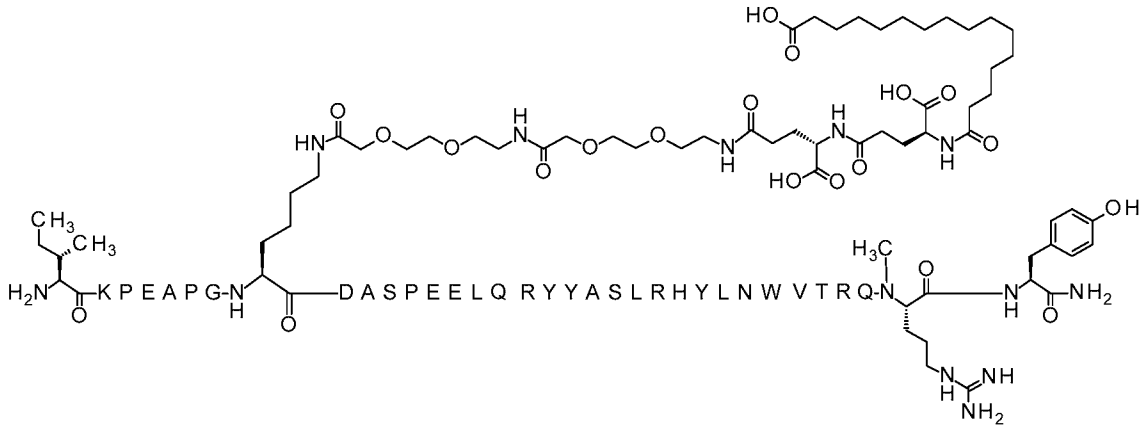
8. A PYY compound according to any one of the preceding claims, wherein the positions corresponding to positions 1 and 2 of hPYY(1-36) (SEQ ID NO:1) are absent.

9. A PYY compound according to any one of the preceding claims, wherein the positions corresponding to positions 1-3 of hPYY(1-36) (SEQ ID NO:1) are absent.

10. A PYY compound according to any one of the preceding claims, wherein the positions corresponding to positions 1-3 of hPYY(1-36) (SEQ ID NO:1) are absent, and wherein the PYY compound further comprises an N-terminal substituent, wherein the N-terminal substituent is an alkoxy group comprising up to 12 carbon atoms.

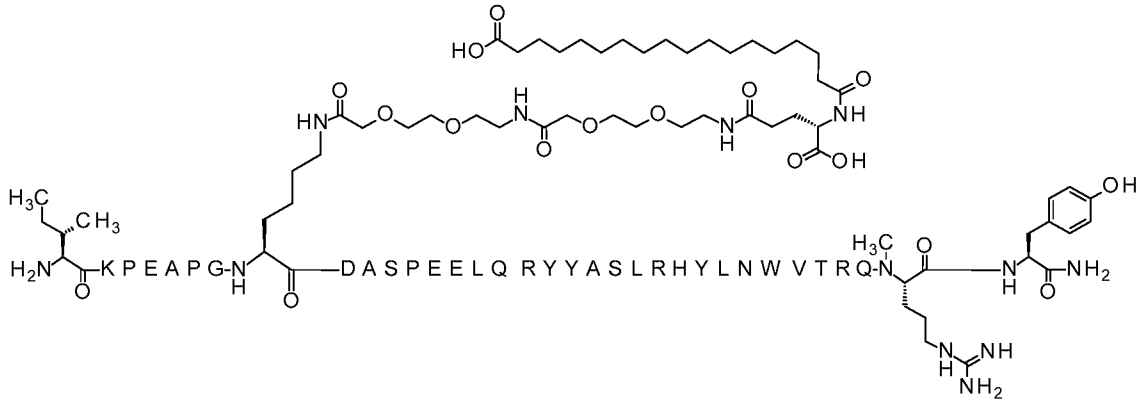
11. A PYY compound according to any one of the preceding claims selected from the following:

N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-[[(4S)-4-carboxy-4-(15-carboxypentadecanoylamino)butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]-[Lys10,Gln18,Trp30,NmeArg35]hPYY(3-36) (Compound 4) (1339)



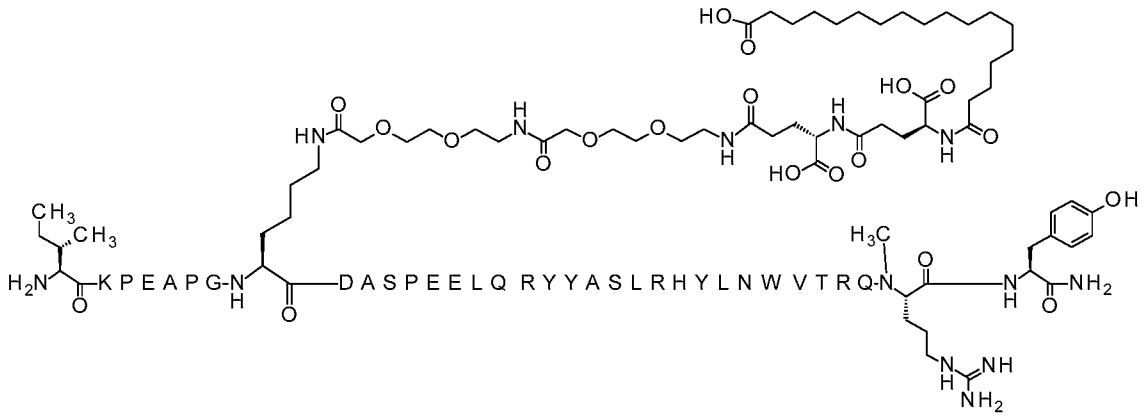
;

N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)-butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]-ethoxy]acetyl]-[Lys10,Gln18, Trp30,NmeArg35]hPYY(3-36) (Compound 5) (0832)



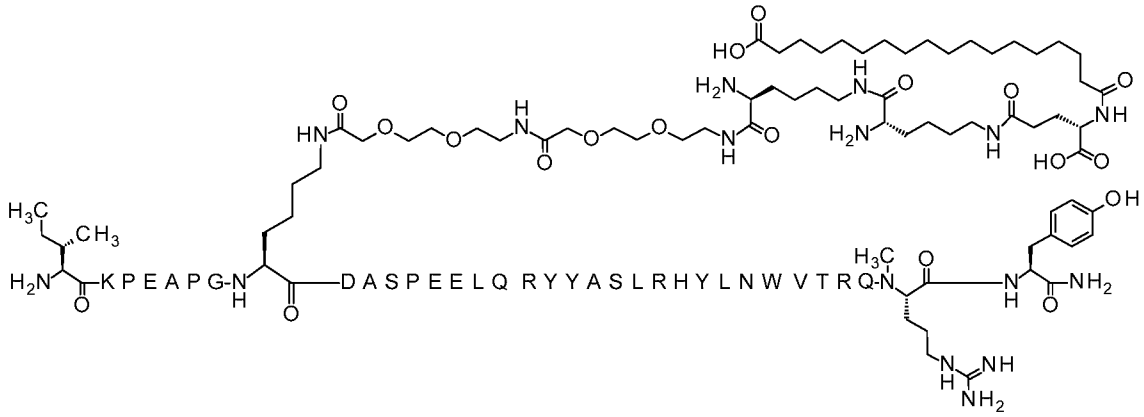
;

N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]-acetyl]amino]ethoxy]ethoxy]acetyl]-[Lys10,Gln18,Trp30,NmeArg35]hPYY(3-36) (Compound 6) (0996)



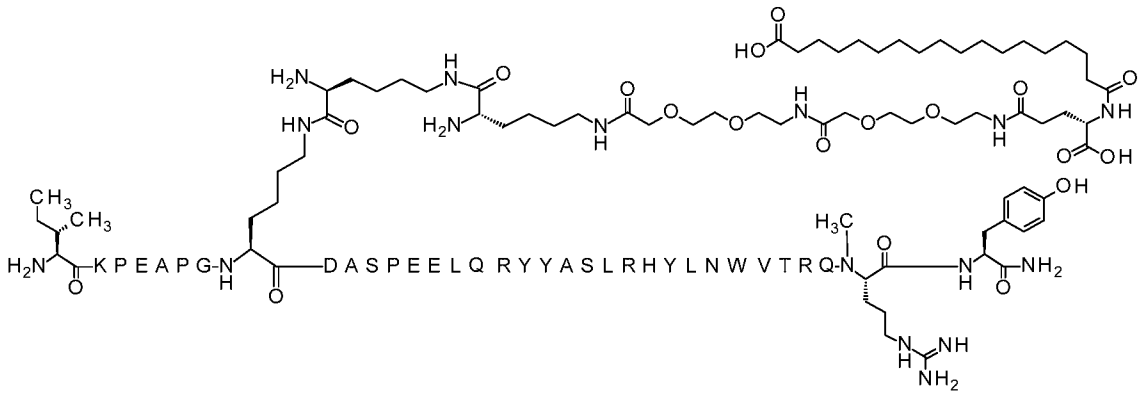
;

N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(2S)-2-amino-6-[[(2S)-2-amino-6-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]hexanoyl]amino]-hexanoyl]amino]-ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]-[Lys10,Gln18,Trp30,NmeArg35]-hPYY(3-36) (Compound 7) (0833)



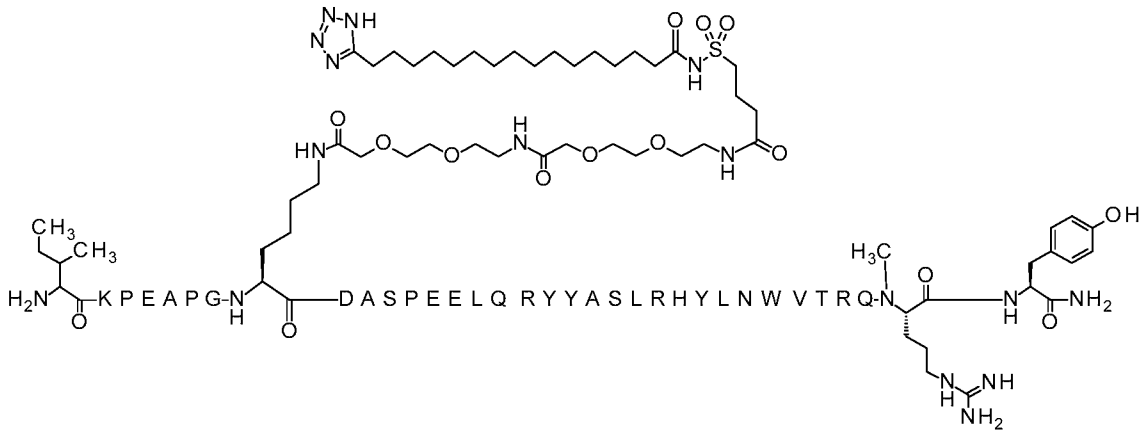
;

N{Epsilon-10}-[(2S)-2-amino-6-[[(2S)-2-amino-6-[[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]-ethoxy]ethoxy]acetyl]amino]hexanoyl]amino]hexanoyl][Lys10,Gln18,Trp30,NmeArg35]-hPYY(3-36) (Compound 8) (1491)



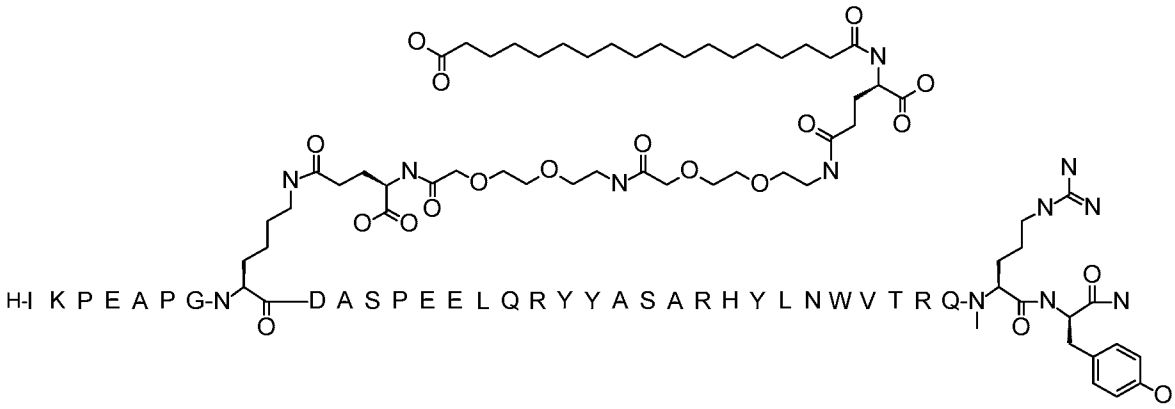
;

N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[4-[16-(1H-tetrazol-5-yl)hexadecanoylsulfamoyl]-butanoylamino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]-[Lys10,Gln18, Trp30,NmeArg35]hPYY(3-36) (Compound 9) (0997)



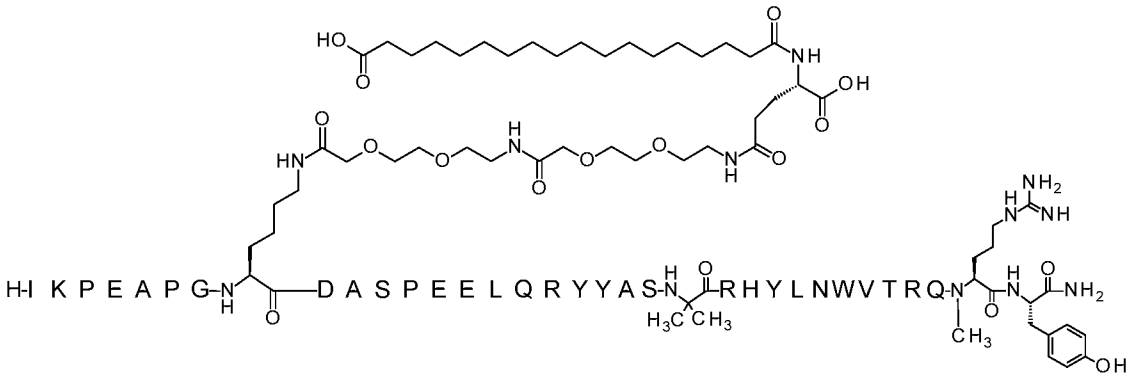
;

N{Epsilon-10}-[(4S)-4-carboxy-4-[[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]-ethoxy]acetyl]amino]butanoyl]-[Lys10,Gln18,Ala24,Trp30,NmeArg35]hPYY(3-36) (Compound 10) (1186)



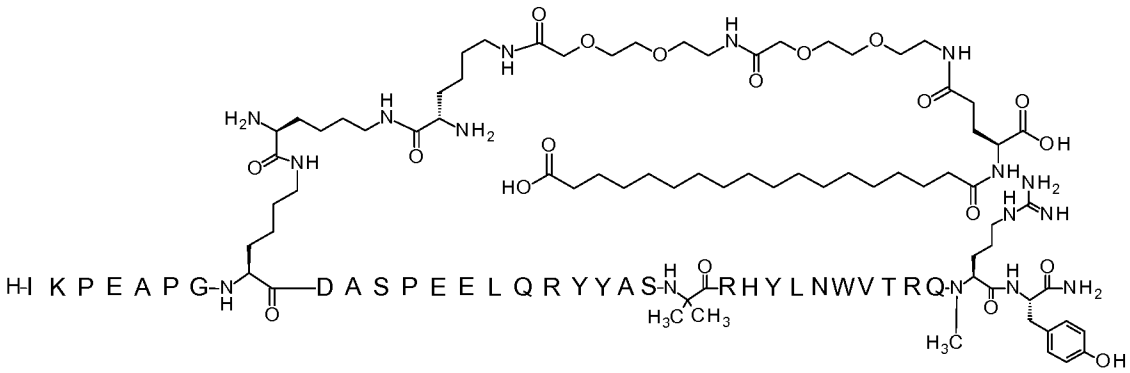
;

N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)-butanoyl]amino]ethoxy]ethoxy]acetyl]-amino]ethoxy]ethoxy]acetyl]-[Lys10,Gln18, Aib24,Trp30,NmeArg35]hPYY(3-36) (Compound 11) (1185)



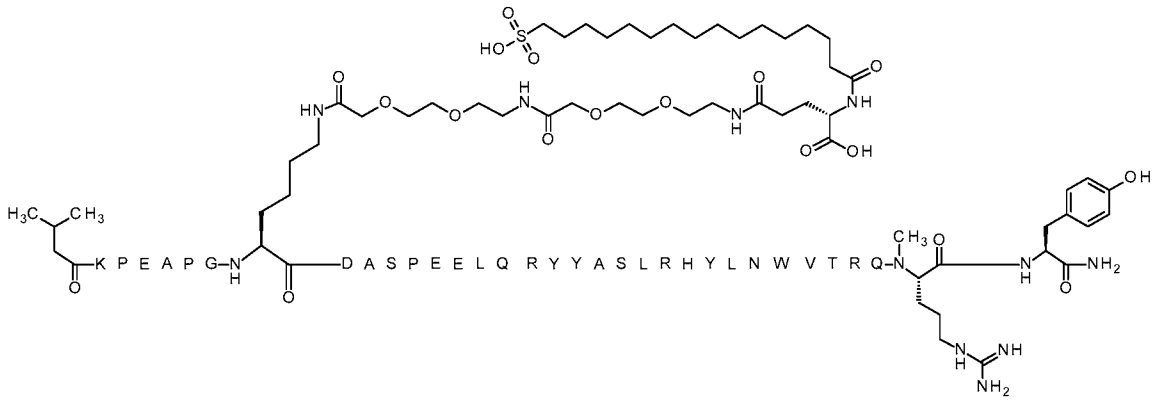
;

N{Epsilon-10}-[(2S)-2-amino-6-[[(2S)-2-amino-6-[[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]-ethoxy]ethoxy]acetyl]amino]hexanoyl]amino]hexanoyl]-[Lys10,Gln18,Aib24, Trp30,NmeArg35]hPYY(3-36) (Compound 12) (1187)



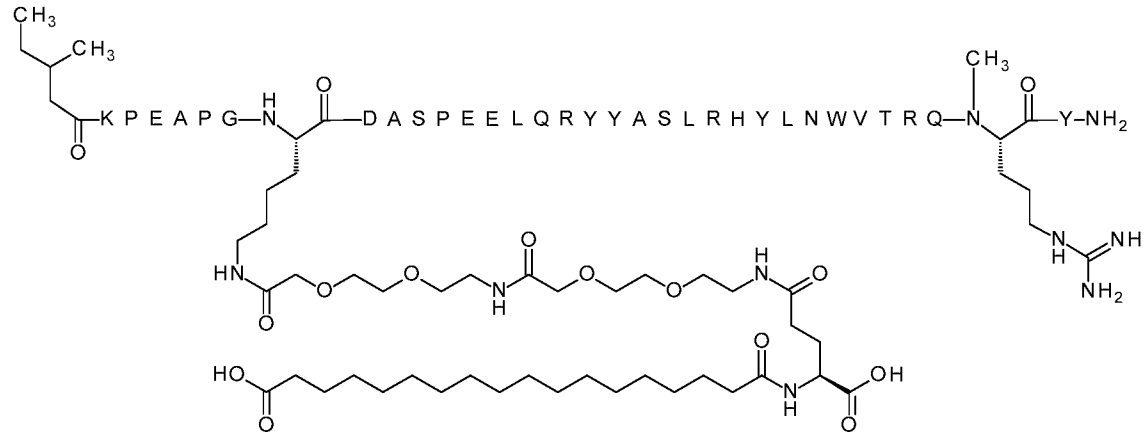
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N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(16-sulfohexadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]-ethoxy]acetyl]-[Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) (Compound 13) (1640)



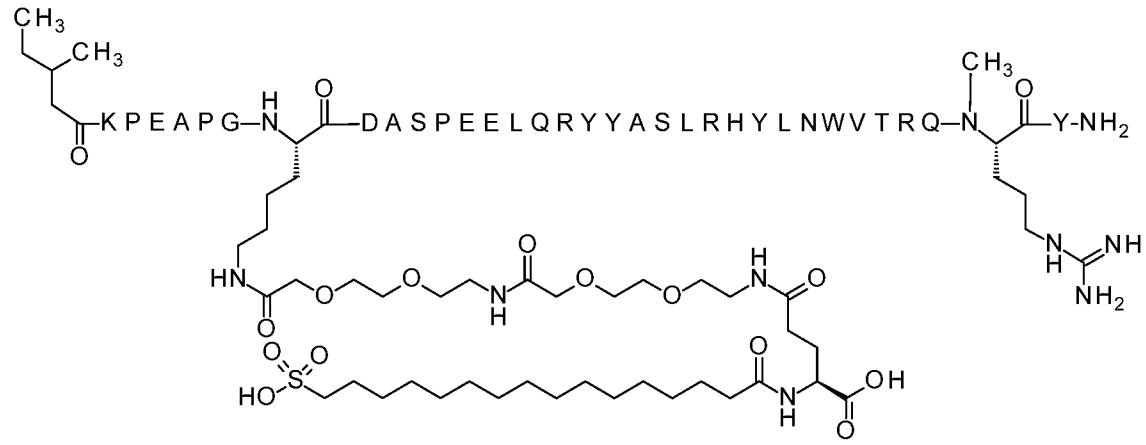
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N{Alpha-4}-3-methylpentanoyl)-N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]-ethoxy]acetyl]-[Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) (Compound 14) (1511)



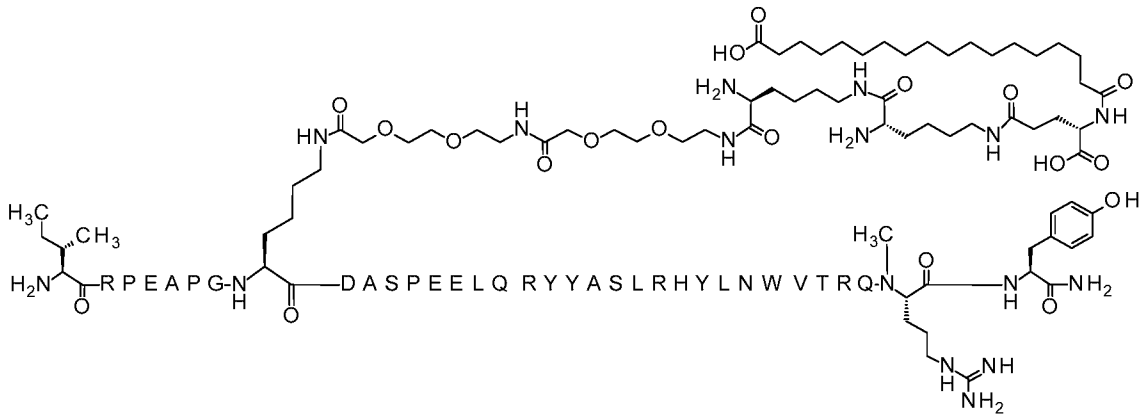
;

N{alpha-4}-(3-Methylpentanoyl)-N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(16-sulfohexadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]-ethoxy]acetyl]-[Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) (Compound 15) (1512)



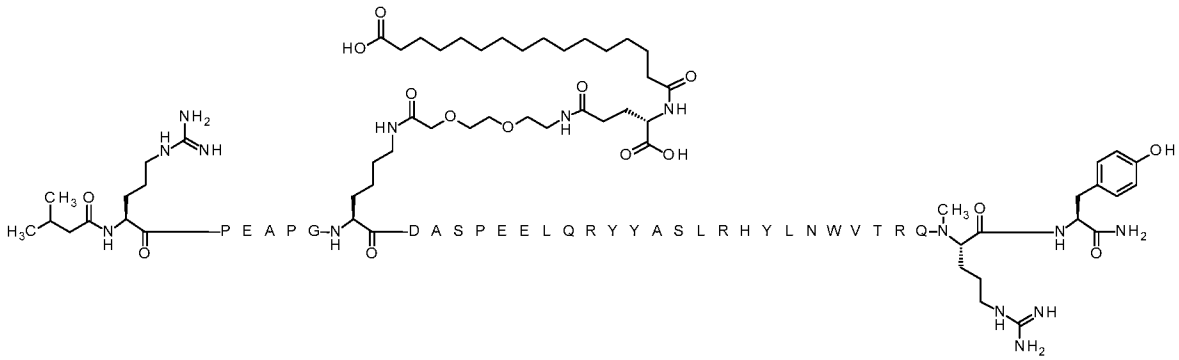
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N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(2S)-2-amino-6-[[(2S)-2-amino-6-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]hexanoyl]amino]hexanoyl]amino]-ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]-[Arg4,Lys10,Gln18,Trp30, NmeArg35]hPYY(3-36) (Compound 16) (1586)



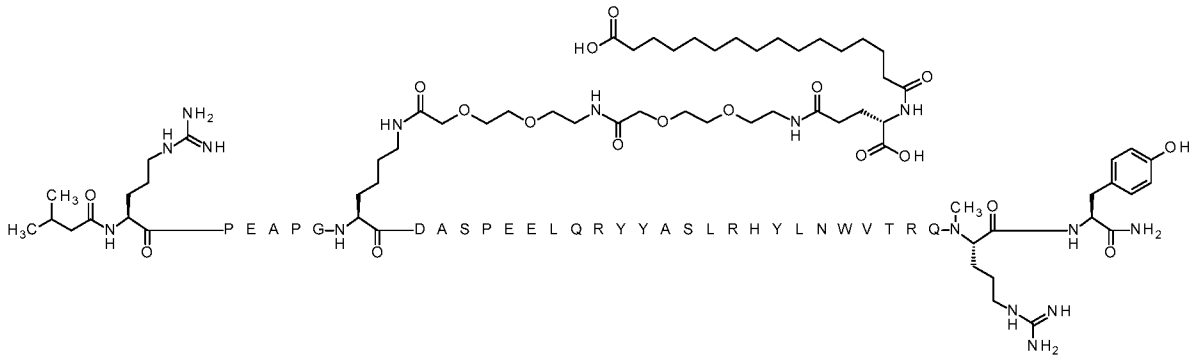
;

N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[2-[2-[2-[[(4S)-4-carboxy-4-(15-carboxypentadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]-[Arg4,Lys10, Gln18,Trp30,NmeArg35]hPYY(4-36) (Compound 17) (1667)



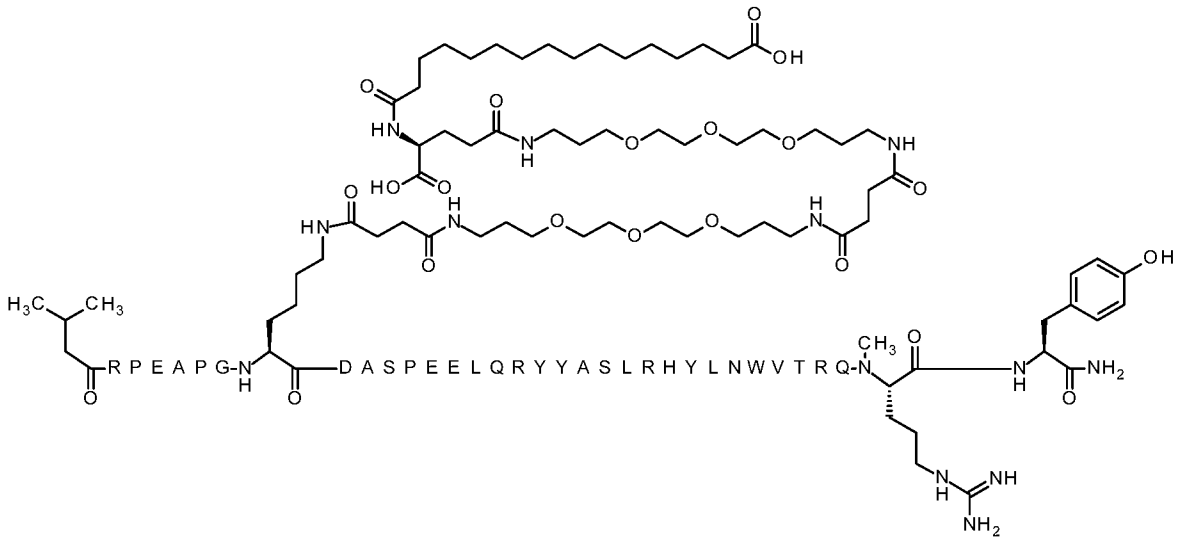
;

N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(15-carboxypentadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]-ethoxy]acetyl]-[Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) (Compound 18) (1649)



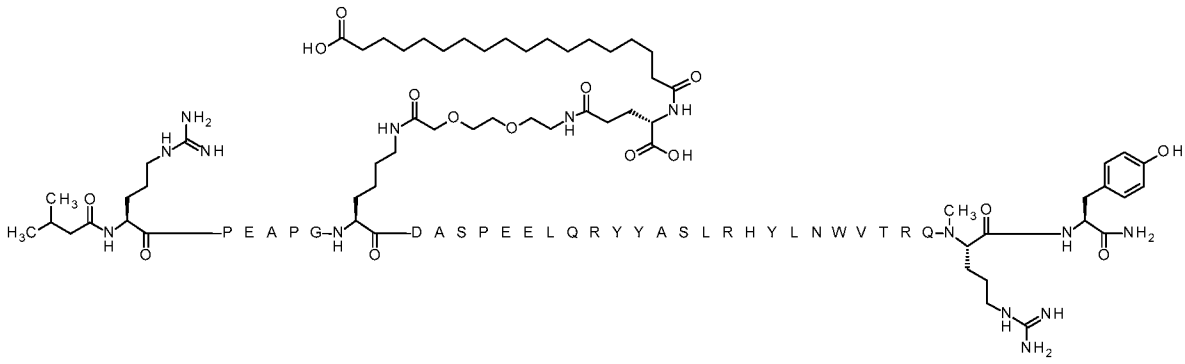
;

N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[4-[3-[2-[2-[3-[[4-[3-[2-[2-[3-[[(4S)-4-carboxy-4-(15-carboxypentadecanoylamino)butanoyl]amino]propoxy]ethoxy]ethoxy]-propylamino]-4-oxobutanoyl]amino]propoxy]ethoxy]ethoxy]propylamino]-4-oxobutanoyl]-[Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) (Compound 19) (1639)



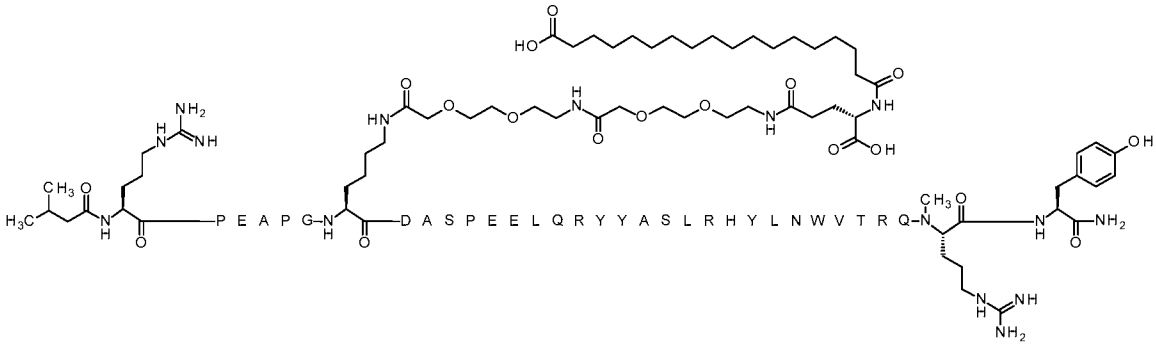
;

N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]-[Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) (Compound 20) (1657)



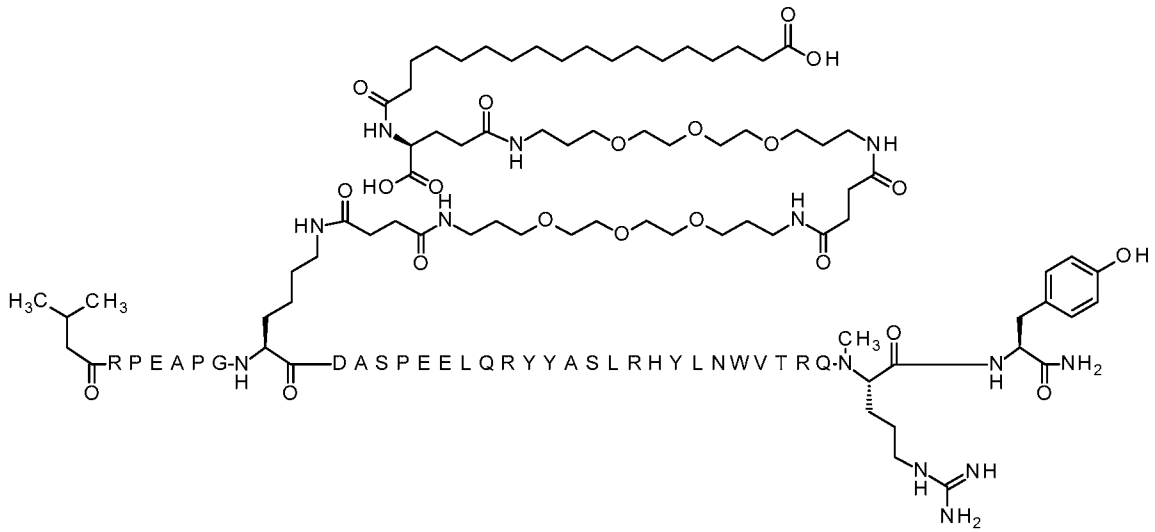
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N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]-ethoxy]acetyl]-[Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) (Compound 21) (1645)



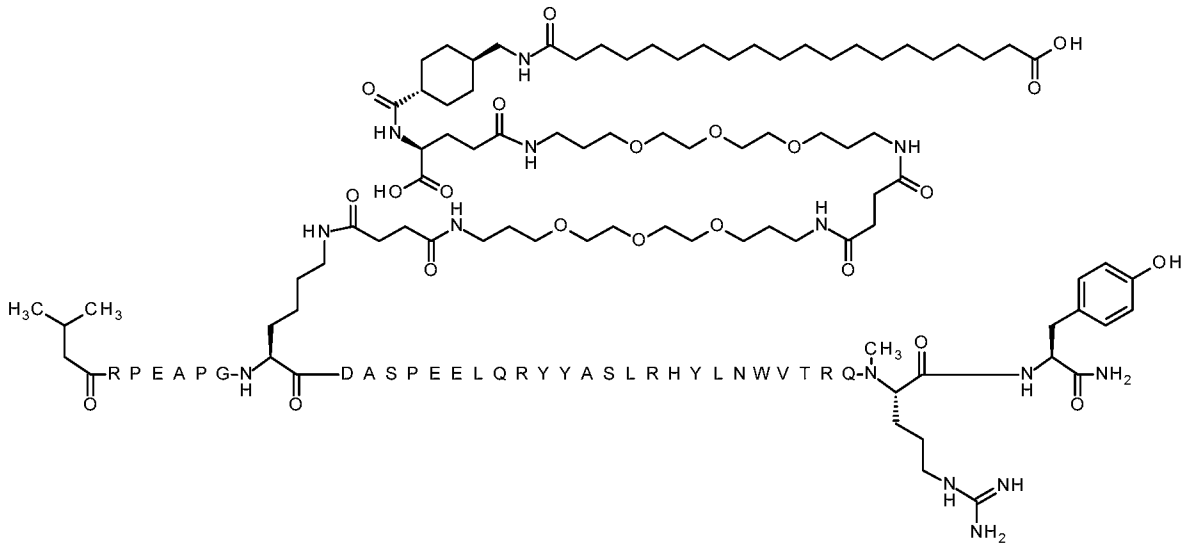
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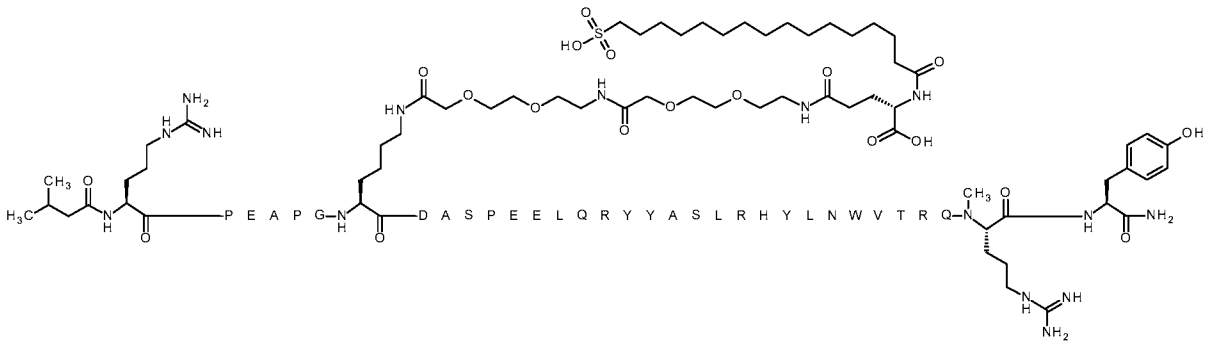
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N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[4-[3-[2-[2-[3-[[4-[3-[2-[2-[3-[[(4S)-4-carboxy-4-[[4-[(19-carboxynonadecanoylamino)methyl]cyclohexanecarbonyl]amino]-butanoyl]amino]propoxy]ethoxy]ethoxy]propylamino]-4-oxobutanoyl]amino]-propoxy]ethoxy]ethoxy]propylamino]-4-oxobutanoyl]-[Arg4,Lys10,Gln18,Trp30, NmeArg35]hPYY(4-36) (Compound 23) (1638)



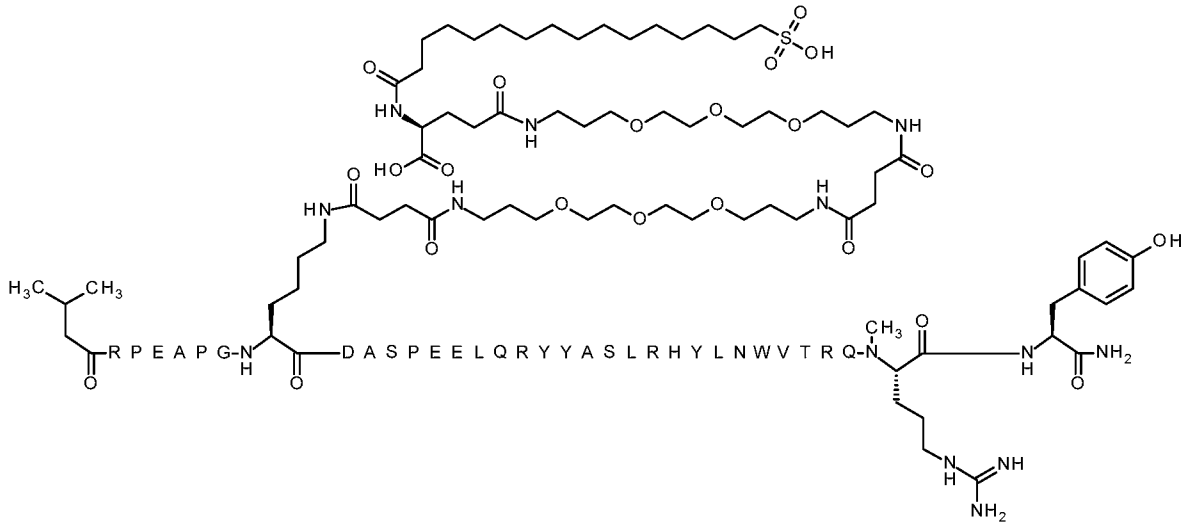
;

N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(16-sulfohexadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]-ethoxy]acetyl]-[Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) (Compound 24) (1643)



;

N{alpha-4}-(3-Methylbutanoyl)-N{Epsilon-10}-[4-[3-[2-[2-[3-[[4-[3-[2-[2-[3-[[(4S)-4-carboxy-4-(16-sulfohexadecanoylamino)butanoyl]amino]-propoxy]ethoxy]ethoxy]-propylamino]-4-oxobutanoyl]amino]propoxy]ethoxy]-ethoxy]propylamino]-4-oxobutanoyl]-[Arg4,Lys10,Gln18,Trp30,NmeArg35]hPYY(4-36) (Compound 25) (1637)



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12. A pharmaceutical composition comprising a PYY compound according to any one of claims 1-11, and at least one pharmaceutically acceptable excipient.

13. A PYY compound according to any one of claims 1-11, for use as a medicament.

14. A PYY compound according to any one of claims 1-11, for use in the treatment and/or prevention of all forms of diabetes and related diseases, such as eating disorders, diabetic complications, cardiovascular diseases and/or sleep apnoea; and/or for improving lipid parameters, improving β-cell function, and/or for delaying or preventing diabetic disease progression.

15. A PYY compound according to any one of claims 1-11, for use in the treatment and/or prevention of eating disorders, such as obesity, e.g. by decreasing food intake, reducing body weight, suppressing appetite, inducing satiety; treating or preventing binge eating disorder, bulimia nervosa, and/or obesity induced by administration of an antipsychotic or a steroid; reduction of gastric motility; delaying gastric emptying; increasing physical mobility; and/or prevention and/or treatment of comorbidities to obesity, such as osteoarthritis and/or urine incontinence.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2016/052371

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

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      ☒ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/052371

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K14/575
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	WO 2011/058165 A1 (NOVO NORDISK AS [DK]; KOFOED JACOB [DK]; YNDDAL LARS [DK]; OESTERGAARD) 19 May 2011 (2011-05-19) cited in the application page 112 - page 120; sequence 36	1-15
Y	WO 2011/033068 A1 (NOVO NORDISK AS [DK]; KOFOED JACOB [DK]; OLSEN JOERGEN [DK]; OESTERGAA) 24 March 2011 (2011-03-24) cited in the application page 27 - page 40; example 3; sequence 35	1-15

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 April 2016	25/04/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Pinheiro Vieira, E

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/052371

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2016/052371

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