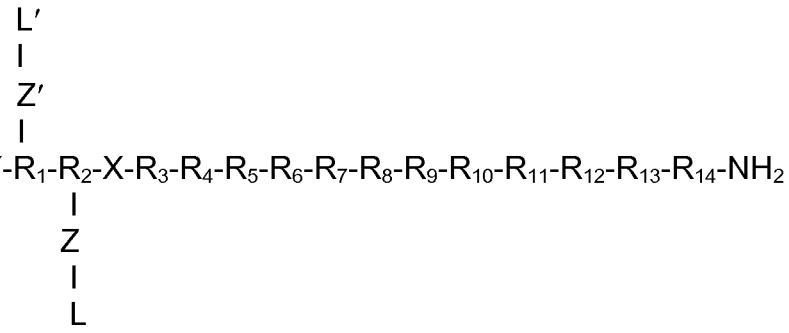
NEUROPEPTIDE-2 RECEPTOR (Y-2R) AGONISTS AND USES THEREOF

The invention provides truncated and lipidated analogs of PYY $_{3-36.}$ The analogs are agonists of the neuropeptide-2 receptor and are useful for the treatment of metabolic diseases and disorders, such as, for example, obesity, type 2 diabetes, metabolic syndrome, insulin resistance and dyslipidemia.

The invention relates in particular to a neuropeptide-2 receptor agonist of formula (I):



(I),

wherein:

L is a lipid moiety;

L′ is a lipid moiety;

X is (4-oxo-6-piperazin-1-yl-4H-quinazolin-3-yl)-acetic acid (Pqa);

Y is H, an acyl moiety or pyro-Glu;

Z is a spacer moiety or absent;

Z′ is a spacer moiety or absent;

R_1 is Ile, Ala, (D)Ile or N-methyl Ile;

R_2 is Lys, Ala, (D)Lys, N-methyl Lys, Nle or (Lys-Gly);

R_3 is Arg, Ala, (D)Arg, N-methyl Arg or Phe;

R_4 is His, Ala, (D)His or N-methyl His;

R_5 is Tyr, Ala, (D)Tyr, N-methyl Tyr or Trp;

R_6 is Leu, Ala, (D)Leu or N-methyl Leu;

R_7 is Asn, Ala or (D)Asn;

R_8 is Leu or Trp;

R_9 is Val, Ala, (D)Val or N-methyl Val;

R_{10} is Thr, Ala or N-methyl Thr;

R_{11} is Arg, (D)Arg or N-methyl Arg;

R_{12} is Gln or Ala;

R_{13} is Arg, (D)Arg or N-methyl Arg; and

R_{14} is Tyr, (D)Tyr, N-methyl Tyr, Phe or Trp; and

wherein moieties L-Z- and L'-Z'- are not both present;

or a pharmaceutically acceptable salt thereof.

Metabolic diseases and disorders are widely recognized as serious health problems for developed countries, having reached epidemic levels in the United States. According to recent studies on obesity, for example, more than 50 % of the U.S. population is considered overweight, with more than 25 % diagnosed as clinically obese and at considerable risk for heart disease, type 2 diabetes and certain cancers. This epidemic presents a significant burden on the health care system as projected obesity treatment costs of more than $70 billion annually are expected in the U.S. alone. Strategies for treating obesity include reduction of food intake and enhancing the expenditure of energy.

Neuropeptide Y (NPY), a 36 amino acid peptide neurotransmitter, is a member of the pancreatic polypeptide class of neurotransmitters/neurohormones which has been shown to be present in both the periphery and central nervous system. NPY is one of the most

potent orexogenic agents known and has been shown to play a major role in the regulation of food intake in animals, including humans.

Six NPY receptors, the Y1-, Y2-, Y3-, Y4, and Y5- and Y6-subtypes, have been cloned, which belong to the rhodopsin-like G-protein-coupled 7-transmembrane spanning receptors (GPCR). The NPY Y2 receptor (Y2R) is a 381 amino-acid receptor which inhibits the activation of adenyl cyclase via G_i while displaying low homology with other known NPY receptors. There is a high degree of conservation between rat and human Y2 receptors with 98 % amino acid identity.

The Y2R receptor is widely distributed within the central nervous system in both rodents and humans. In the hypothalamus, Y2 mRNA is localized in the arcuate nucleus, preoptic nucleus, and dorsomedial nucleus. In the human brain, Y2R is the predominant Y receptor subtype. Within the arcuate nucleus, over 80 % of the NPY neurons co-express Y2R mRNA. Application of a Y2-selective agonist has been shown to reduce the release of NPY from hypothalamic slices in vitro, whereas the Y2 non-peptide antagonist BIIE0246 increases NPY release. These findings support the role of Y2R as a presynaptic autoreceptor that regulates the NPY release and hence may be involved in the regulation of feeding. (Kaga, T. et al., Peptides 22: 501-506 (2001) and King PJ et al., Eur J Pharmacol 396: R1-3 (2000)).

Peptide YY $_{3-36}$ (PYY $_{3-36}$) is a 34 amino acid linear peptide having neuropeptide Y2 agonist activity. It has been demonstrated that Intra-arcuate (IC) or Intra-peritoneal (IP) injection of PYY $_{3-36}$ reduced feeding in rats and, as a chronic treatment, reduced body weight gain. Intra-venous (IV) infusion (0.8 pmol/kg/min) for 90 min of PYY $_{3-36}$ reduced food intake in obese and normal human subjects over 24 hours. These finding suggest that the PYY system may be a therapeutic target for the treatment of obesity. (Batterham RL et al., Nature 418: 650-654 (2002); Batterham RL et al., New Engl J Med 349: 941-948 (2003)). Further, a Cys^2-(D)Cys^{27}-cyclized version of PYY, in which residues 5-24 were replaced by a methylene-chain of 5 to 8 carbons in length, showed activation of the intestinal PYY receptor, as evidenced by reduced current across voltage-clamped mucosal preparations of rat jejunum. (Krstenansky, et al. in Peptides, Proceedings of the Twelfth American Peptide Symposium. J. Smith and J. Rivier Editors, ESCOM. Leiden Page 136-137).

In addition, recent data have shown that Roux-enY gastric bypass patients have an early and exaggerated increase in PYY levels that may be partly responsible for the early glycemic control and long term weight maintenance demonstrating the importance of this peptide in the pathogenesis of metabolic diseases. Other known actions of PYY include: reduced gastric emptying and delayed gastrointestinal transit that is responsible for improved

postprandial glycemic control. Indices of hyperglycaemia such as HbA_{1C} and fructosamine show a dose-dependent reduction after peripheral administration of PYY_{3-36} in animal models of type 2 diabetes. Thus, these results indicate that PYY_{3-36}, or pharmaceutically related agonists, may offer a long term therapeutic approach to glycemic and weight control. (Korner et al., J Clin Endocrinol Metabol 90: 359-365 (2005); Chan JL et al., Obesity 14: 194-198 (2006); Stratis C et al., Obes Surg 16: 752-758 (2006); Borg CM et al., Br J Surg 93: 210-215 (2006); and Pittner RA et al., Int J Obes 28: 963-971 (2004)).

A need exists, therefore, for novel engineered analogs of PYY having lower molecular weight, while possessing equal or better potency and selectivity against Y1, Y4 and Y5 receptors, pharmacokinetic properties and pharmacological properties.

The compounds of the invention are preferably useful for treating metabolic diseases and disorders. Such metabolic diseases and disorders include, for example, obesity, diabetes, preferably type 2 diabetes, metabolic syndrome (also known as Syndrome X), insulin resistance, dyslipidemia, impaired fasting glucose and impaired glucose tolerance.

In a further embodiment of the present invention, provided is a pharmaceutical composition, comprising a therapeutically effective amount of the neuropeptide-2 receptor agonist according to formula I, or a salt thereof, and a pharmaceutically acceptable carrier.

The compounds of the invention are advantageous because, for example, they are truncated versions of the PYY_{3-36}. The shorter peptides, for example, not only facilitate easier synthesis and purification of the compounds, but also improve and reduce manufacturing procedures and expenses. Moreover, the compounds of the invention will preferably interact with Y2-receptors and not with homologous receptors such as NPY Y1, Y4 and Y5. Unwanted agonist or antagonist side reactions are, thereby, minimized. The truncated-lipidated peptides also exhibit longer half-life in vivo and favorable pharmacokinetic properties compared to native peptides while maintaining their biological activity and receptor specificity.

It is to be understood that the invention is not limited to the particular embodiments of the invention described herein, as variations of the particular embodiments may be made and still fall within the scope of the appended claims. It is also to be understood that the terminology employed is for the purpose of describing particular embodiments, and is not intended to be limiting. Instead, the scope of the present invention will be established by the appended claims.

Although any methods, devices and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, the preferred methods, devices and materials are now described.

All peptide sequences mentioned herein are written according to the usual convention whereby the N-terminal amino acid is on the left and the C-terminal amino acid is on the right, unless noted otherwise. A short line between two amino acid residues indicates a peptide bond. Where the amino acid has isomeric forms, it is the L form of the amino acid that is represented unless otherwise expressly indicated. For convenience in describing this invention, the conventional and nonconventional abbreviations for the various amino acids are used. These abbreviations are familiar to those skilled in the art, but for clarity are listed below:
Asp=D=Aspartic Acid; Ala=A=Alanine; Arg=R=Arginine; Asn=N=Asparagine; Gly=G=Glycine; Glu=E=Glutamic Acid; Gln=Q=Glutamine; His=H=Histidine; Ile=I=Isoleucine; Leu=L=Leucine; Lys=K=Lysine; Met=M=Methionine; Phe=F=Phenylalanine; Pro=P=Proline; Ser=S=Serine; Thr=T=Threonine; Trp=W=Tryptophan; Tyr=Y=Tyrosine; Cys =C=Cysteine; and Val=V=Valine.

Also for convenience, the following abbreviations or symbols are used to represent the moieties, reagents and the like used in this invention:

Pqa is (4-oxo-6-piperazin-1-yl-4H-quinazolin-3-yl)-acetic acid;

6-Ahx is 6-Aminohexanoic acid;

Cha is Cyclohexylalanine;

(1)Nal is 1-Naphtylalanine;

(2)Nal is 2-Naphtylalanine;

Nle is Norleucine;

Alloc is Alloxycarbonyl;

Fmoc is 9-Fluorenylmethyloxycarbonyl;

Mtt is 4-Methyltrityl;

Pmc is 2,2,5,7,8-Pentamethylchroman-6-sulfonyl;

Pbf is 2,24,6,7-Pentamethyldihydro-benzofuran-5-sulfonyl

CH_2Cl_2 is Methylene chloride;

Ac_2O is Acetic anhydride;

CH_3CN is Acetonitrile;

DMAc is Dimethylacetamide;

DMF is Dimethylformamide;

DIPEA is N,N-Diisopropylethylamine;

TFA is Trifluoroacetic acid;

iPr_3SiH is Triisopropylsilane;

HOBt is N-Hydroxybenzotriazole;

DIC is N,N'-Diisopropylcarbodiimide;

BOP is Benzotriazol-1-yloxy-tris-(dimethylamino)phosphonium hexafluorophosphate;

HBTU is 2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate;

15-ATOPA is 15-amino-4,7,10,13,-tetraoxapentadecanoic acid;

12-ATODA is 12-amino-4,7,10-trioxadodcadecanoic acid;

8-ADOSA is N-(8-amino-3,6-dioxa-octyl)-succinamic acid;

5-AOPSA is N-(5-amino-3-oxa-pentyl)-succinamic acid;

NMP is 1-methyl 2-pyrolidinone;

FAB-MS is Fast atom bombardment mass spectrometry; and

ES-MS is Electro spray mass spectrometry.

As used herein, the term "lipid moiety" means an optionally substituted linear or branched alkanoyl group of from 4-24 carbon atoms, preferably from 12-20 carbon atoms. The lipid moiety may be naturally-occurring or synthetic. Preferred lipid moieties include, but are not limited to, caproyl-, lauroyl-, myrisoyl-, palmitoyl-, 16-bromohexadecanoyl-, 2-hexyldecanoyl-, eicosanoyl-, and the like.

As used herein, the term "acyl" means an optionally substituted alkyl, cycloalkyl, heterocyclic, aryl or heteroaryl group bound via a carbonyl group and includes groups such as acetyl, propionyl, benzoyl, 3-pyridinylcarbonyl, 2-morpholinocarbonyl, 4-hydroxybutanoyl, 4-fluorobenzoyl, 2-naphthoyl, 2-phenylacetyl, 2-methoxyacetyl and the like.

As used herein, the term "alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of one to twenty carbon atoms, preferably one to sixteen carbon atoms, more preferably one to ten carbon atoms.

The term "cycloalkyl" refers to a, saturated or unsaturated, monovalent mono- or polycarbocyclic radical of three to ten, preferably three to six carbon atoms. This term is further exemplified by radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bornyl, adamantyl, and the like. In a preferred embodiment, the "cycloalkyl" moieties can optionally be substituted with one, two, three or four substituents, with the understanding that said substituents are not, in turn, substituted further unless indicated otherwise. Examples of cycloalkyl moieties include, but are not limited to, optionally substituted cyclopropyl, optionally substituted cyclobutyl, optionally substituted cyclopentyl, optionally substituted cyclopentenyl, optionally substituted cyclohexyl, optionally substituted cyclohexene optionally substituted cycloheptyl, and the like or those which are specifically exemplified herein.

The term "heterocycloalkyl" denotes a mono- or polycyclic alkyl ring, wherein one, two or three of the carbon ring atoms is replaced by a heteroatom such as N, O or S. Examples of heterocycloalkyl groups include, but are not limited to, morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, pyrrolidinyl, tetrahydropyranyl, tetrahydrofuranyl, 1,3-dioxanyl and the like. The heterocycloalkyl groups may be unsubstituted or substituted and attachment may be through their carbon frame or through their heteroatom(s) where appropriate, with the understanding that said substituents are not, in turn, substituted further.

The term "lower alkyl", alone or in combination with other groups, refers to a branched or straight-chain alkyl radical of one to nine carbon atoms, preferably one to six carbon atoms. This term is further exemplified by radicals such as methyl, ethyl, n-propyl, isopropyl, n-butyl, s-butyl, isobutyl, t-butyl, n-pentyl, 3-methylbutyl, n-hexyl, 2-ethylbutyl and the like.

The term “aryl” refers to an aromatic mono- or polycarbocyclic radical of 6 to 12 carbon atoms having at least one aromatic ring. Examples of such groups include, but are not limited to, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthalene, 1,2-dihydronaphthalene, indanyl, 1H-indenyl and the like.

The alkyl, lower alkyl and aryl groups may be substituted or unsubstituted. When substituted, there will generally be, for example, 1 to 4 substituents present, with the understanding that said substituents are not, in turn, substituted further unless indicated otherwise. These substituents may optionally form a ring with the alkyl, loweralkyl or aryl group they are connected with.

The term "heteroaryl," refers to an aromatic mono- or polycyclic radical of 5 to 12 atoms having at least one aromatic ring containing one, two, or three ring heteroatoms selected from N, O, and S, with the remaining ring atoms being C. One or two ring carbon atoms of the heteroaryl group may be replaced with a carbonyl group.

The heteroaryl group described above may be substituted independently with one, two, or three substituents, with the understanding that said substituents are not, in turn, substituted further unless indicated otherwise.

Compounds of formula (I) can have one or more asymmetric carbon atoms and can exist in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates or mixtures of diastereoisomeric racemates. The optically active forms can be obtained for example by resolution of the racemates, by asymmetric synthesis or asymmetric chromatography (chromatography with a chiral adsorbents or eluant). The invention embraces all of these forms as well as all regioisomeric forms.

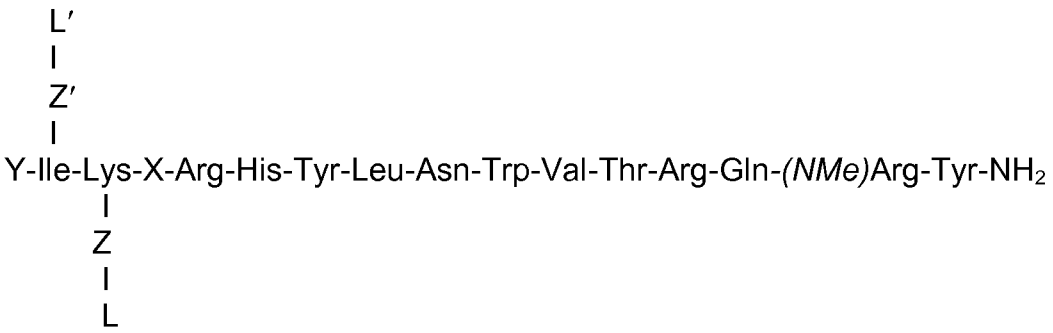
Preferred is a neuropeptide-2 receptor agonist of formula (I) wherein said lipid moiety is carpryloyl, lauroyl, myristoyl, palmitoyl, 16-bromohexadecanoyl, 2-hexyldecanoyl or eicosanoyl.

Further preferred is a neuropeptide-2 receptor agonist of formula (I) wherein said spacer moiety is 6-Ahx, Ala, Glu, Ala-Glu, Glu-Glu, 15-ATOPA, 12-ATODA, 8-ADOSA, 5-AOPSA, Ser-Ser or Thr-Thr.

Also preferred is a neuropeptide-2 receptor agonist of formula (I) wherein Z is absent.

A neuropeptide-2 receptor agonist of formula (I) wherein Z’ is absent is further preferred.

Furthermore, preferred is a neuropeptide-2 receptor agonist of formula (I) having formula (II):



(II);

wherein

L is a lipid moiety;

L′ is a lipid moiety;

X is (4-oxo-6-piperazin-1-yl-4H-quinazolin-3-yl)-acetic acid (Pqa);

Y is H, an acyl moiety or pyro-Glu;

Z is 6-Ahx, Ala, Glu, Ala-Glu, Glu-Glu, 15-ATOPA, 12-ATODA, 8-ADOSA, 5-AOPSA, Ser-Ser, Thr-Thr or absent;

Z′ is 6-Ahx, Ala, Glu, Ala-Glu, Glu-Glu, 15-ATOPA, 12-ATODA, 8-ADOSA, 5-AOPSA, Ser-Ser, Thr-Thr or absent; and

wherein moieties L-Z- and L'-Z'- are not both present.

Further preferred is a neuropeptide-2 receptor agonist of formula (II) wherein said lipid moiety is carpryloyl, lauroyl, myrisoyl, palmitoyl, 16-bromohexadecanoyl, 2-hexyldecanoyl or eicosanoyl.

Also preferred is a neuropeptide-2 receptor agonist of formula (II) wherein one of Z and Z' is Ala, Glu, Ala-Glu, Glu-Glu, Ser-Ser or Thr-Thr.

Also particularly preferred is a neuropeptide-2 receptor agonist according of formula (II) wherein Z is absent.

Further particularly preferred is a neuropeptide-2 receptor agonist of formula (II) wherein Z' is absent.

Preferred is a neuropeptide-2 receptor agonist of formula (I) selected from the group consisting of:

Ac-Ile-Lys(Butyryl)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

Ac-Ile-Lys(Capryloyl)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

Ac-Ile-Lys(Lauroyl)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Lauroyl-6-Ahx)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Lauroyl-beta-Ala)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Lauroyl-Glu)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Myristoyl-6-Ahx)-Pro-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

Ac-Ile-Lys(Palmitoyl)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Palmitoyl)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

Palmitoyl-Ile-Lys-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

Palmitoyl-6-Ahx-Ile-Lys-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

Palmitoyl-6-Ahx-Ile-Lys-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-Arg-Tyr-NH_2;

H-Ile-Lys(Palmitoyl-6-Ahx)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Palmitoyl-6-Ahx)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-Arg-Tyr-NH_2;

H-Ile-Lys(Palmitoyl-beta-Ala)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)Arg-Tyr-NH_2;

H-Ile-Lys(Palmitoyl-Glu)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Palmitoyl- beta-Ala- Glu)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Palmitoyl-Glu-Glu-)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Palmitoyl-gamma-Glu)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2; and

H-Ile-Lys(Palmitoyl-gamma-Glu-gamma-Glu-)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2.

Further preferred is a neuropeptide-2 receptor agonist of formula (I) selected from the group consisting of:

H-Ile-Lys(Palmitoyl-beta-Ala-gamma-Glu-)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(16-Bromohexadecanoyl-gamma-Glu-gamma-Glu-)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

Pyro-Glu-Ile-Lys(Palmitoyl-gamma-Glu- gamma-Glu-)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2

H-Ile-Lys(2-hexyldecanoyl-6-Ahx)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Eicosanoyl-6-Ahx)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Eicosanoyl-gamma-Glu-gamma-Glu-)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Palmitoyl-15-ATOPA)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Eicosanoyl-15-ATOPA)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Palmitoyl-12-ATODA)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Eicosanoyl-12-ATODA)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Palmitoyl-8-ADOSA)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Eicosanoyl-8-ADOSA)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Palmitoyl-5-AOPSA)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr- NH_2;

H-Ile-Lys(Eicosanoyl-5-AOPSA)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Palmitoyl-Ser-Ser)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr- NH_2;

H-Ile-Lys(Eicosanoyl-Ser-Ser)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Palmitoyl-Thr-Thr)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr- NH_2; and

H-Ile-Lys(Eicosanoyl-Thr-Thr)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr- NH_2.

The present representative compounds may be readily synthesized by any known conventional procedure for the formation of a peptide linkage between amino acids. Such conventional procedures include, for example, any solution phase procedure permitting a condensation between the free alpha amino group of an amino acid or residue thereof having its carboxyl group and other reactive groups protected and the free primary

carboxyl group of another amino acid or residue thereof having its amino group or other reactive groups protected.

Such conventional procedures for synthesizing the novel compounds of the present invention include for example any solid phase peptide synthesis method. In such a method the synthesis of the novel compounds can be carried out by sequentially incorporating the desired amino acid residues one at a time into the growing peptide chain according to the general principles of solid phase methods. Such methods are disclosed in, for example, Merrifield, R. B., J. Amer. Chem. Soc. 85, 2149-2154 (1963); Barany *et al.*, The Peptides, Analysis, Synthesis and Biology, Vol. 2, Gross, E. and Meienhofer, J., Eds. Academic Press 1-284 (1980).

Common to chemical syntheses of peptides is the protection of reactive side chain groups of the various amino acid moieties with suitable protecting groups, which will prevent a chemical reaction from occurring at that site until the protecting group is ultimately removed. Usually also common is the protection of the alpha amino group on an amino acid or fragment while that entity reacts at the carboxyl group, followed by the selective removal of the alpha amino protecting group at allow a subsequent reaction to take place at that site. While specific protecting groups have been disclosed in regard to the solid phase synthesis method, it should be noted that each amino acid can be protected by a protective group conventionally used for the respective amino acid in solution phase synthesis.

Alpha amino groups may be protected by a suitable protecting group selected from aromatic urethane-type protecting groups, such as allyloxycarbonyl, benzyloxycarbonyl (Z) and substituted benzyloxycarbonyl, such as p-chlorobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, p-biphenyl-isopropyloxycarbonyl, 9-fluorenylmethyloxycarbonyl (Fmoc) and p-methoxybenzyloxycarbonyl (Moz); aliphatic urethane-type protecting groups, such as t-butyloxycarbonyl (Boc), diisopropylmethyloxycarbonyl, and isopropyloxycarbonyl. Herein, Fmoc is most preferred for alpha amino protection.

Guanidino groups may be protected by a suitable protecting group such as nitro, p-toluenesulfonyl (Tos), (Z,) pentamethylchromanesulfonyl (Pmc), 4-Methoxy-2,3,6,-trimethylbenzenesulfonyl (Mtr), (Pmc), (Mtr) and (Pbf) are most preferred for arginine (Arg).

Epsilon amino groups may be protected by a suitable protecting group such as 2-chloro benzyloxycarbonyl (2-Cl-Z), 2-Bromo benztloxycarbonyl (2-Br-Z)- and t-butyloxycarbonyl (Boc). Boc is the most preferred for (Lys).

Hydroxyl groups (OH) may be protected by a suitable protecting group such as benzyl (Bzl), 2,6-dichlorobenzyl (2,6-diCl-Bzl), and *tert.*-Butyl (t-Bu), (t-Bu) is most preferred for (Tyr), (Ser) and (Thr).

The beta- and gamma- amide groups of Asn and Gln may be protected by a suitable protecting group such as 4-methyltrityl (Mtt), 2,4,6-trimethoxybenzyl (Tmob), 4,4-Dimethoxydityl Bis-(4-methoxyphenyl)-methyl (Dod) and Trityl (Trt). Trt is the most preferred for (Asn) and (Gln).

The indole group may be protected by a suitable protecting group selected from formyl (For), Mesityl-2-sulfonyl (Mts) and t-butyloxycarbonyl (Boc). Boc is the most preferred for (Trp).

The imidazole group may be protected by a suitable protecting group selected from Benzyl (Bzl), t-butyloxycarbonyl (Boc), and Trityl (Trt). Trt is the most preferred for (His).

The synthesis of the amino acid Pqa is described by J. Hutchinson et. al (J .Med. Chem. 1996, 39, 4583-4591). The Fmoc-Pqa derivative was purchased from NeoMPS, Inc. (San Diego CA)

All solvents, isopropanol (iPrOH), methylene chloride (CH2Cl2), dimethylformamide (DMF) and N-methylpyrrolinone (NMP) were purchased from Fisher or Burdick & Jackson and were used without additional treatment. Trifluoroacetic acid was purchased from Halocarbon or Fluka and used without further purification.

Diisopropylcarbodiimide (DIC) and diisopropylethylamine (DIPEA) was purchased from Fluka or Aldrich and used without further purification. Hydroxybenzotriazole (HOBT) dimethylsulfide (DMS) and 1, 2-ethanedithiol (EDT) were purchased from Sigma Chemical Co. and used without further purification. Protected amino acids were generally of the L configuration and were obtained commercially from Bachem, or Neosystem. Purity of these reagents was confirmed by thin layer chromatography, NMR and melting point prior to use. Benzhydrylamine resin (BHA) was a copolymer of styrene - 1% divinylbenzene (100-200 or 200-400 mesh) obtained from Bachem or Advanced Chemtech. Total nitrogen content of these resins were generally between 0.3 - 1.2 meq/g.

In a preferred embodiment, peptides were prepared using solid phase synthesis by the method generally described by Merrifield, (J. Amer. Chem. Soc., 85, 2149 (1963)), although other equivalent chemical synthesis known in the art could be used as previously mentioned. Solid phase synthesis is commenced from the C-terminal end of the peptide by coupling a protected alpha-amino acid to a suitable resin. Such a starting material can be prepared by attaching an alpha-amino-protected amino acid by an ester linkage to a p-benzyloxybenzyl alcohol (Wang) resin, or by an amide bond between an Fmoc-Linker, such as p- ((R, S)-α-(1-(9H-fluoren-9-yl)-methoxyformamido)-2,4-dimethyloxybenzyl)-phenoxyacetic acid (Rink linker) to a benzhydrylamine (BHA) resin. Preparation of the hydroxymethyl resin is well known in the art. Fmoc-Linker-BHA resin supports are commercially available and generally used when the desired peptide being synthesized has an unsubstituted amide at the C-terminus.

Typically, the amino acids or mimetic are coupled onto the Fmoc-Linker-BHA resin using the Fmoc protected form of amino acid or mimetic, with 2 - 5 equivalents of amino acid and a suitable coupling reagent. After couplings, the resin may be washed and dried under vacuum. Loading of the amino acid onto the resin may be determined by amino acid analysis of an aliquot of Fmoc-amino acid resin or by determination of Fmoc groups by UV analysis. Any unreacted amino groups may be capped by reacting the resin with acetic anhydride and diispropylethylamine in methylene chloride.

The alpha amino Fmoc protecting groups are removed under basic conditions. Piperidine, piperazine or morpholine (20-40% v/v) in DMF may be used for this purpose. Preferably 40% piperidine in DMF is utilized.

Following the removal of the alpha amino protecting group, the subsequent protected amino acids are coupled stepwise in the desired order to obtain an intermediate, protected peptide-resin. The activating reagents used for coupling of the amino acids in the solid phase synthesis of the peptides are well known in the art. For example, appropriate reagents for such syntheses are benzotriazol-1-yl-oxy-tri- (dimethylamino) phosphonium hexafluorophosphate (BOP), Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBroP), 2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), and diisopropylcarbodiimide (DIC). Preferred here are HBTU and DIC. Other activating agents are described by Barany and Merrifield (in The Peptides, Vol. 2, J. Meienhofer, ed., Academic Press, 1979, pp 1-284) and may be utilized. Various reagents such as 1-hydroxybenzotriazole (HOBT), N-hydroxysuccinimide (HOSu) and 3, 4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine (HODhBT) may be added to the coupling mixtures in order to optimize the synthetic cycles. Preferred here is HOBt.

For preparation of N-terminal acetyl derivatives, acetylation was carried out by treating the resin bound peptide with 20% acetic anhydride in DMF with 5% DIEA. For other N-terminal acylations, acylation was carried out using the corresponding carboxylic acid activated in-situ with DIC/HOBt for 30 minutes.

The protocol for a typical synthetic cycle is as follows:

Protocol 1

Step	Reagent	Time
1	DMF	2 x 30 sec.
2	20 % piperidine/DMF	1 min.
3	20 % piperidine/DMF	15 min.
4	DMF	2 x 30 sec.
5	iPrOH	2 x 30 sec.
6	DMF	3 x 30 sec.
7	Coupling	60 min - 18 hours.
8	DMF	2 x 30 sec.
9	iPrOH	1 x 30 sec.
10	DMF	1 x 30 sec.
11	CH2Cl2	2 x 30 sec.

Solvents for all washings and couplings were measured to volumes of 10 - 20 mL/g resin. Coupling reactions throughout the synthesis were monitored by the Kaiser Ninhydrin test to determine extent of completion (Kaiser et at. Anal.Biochem.34, 595-598 (1970)). Slow reaction kinetics was observed for Fmoc-Arg (Pmc) and for couplings to secondary amines by sterically hindered acids. Any incomplete coupling reactions were either recoupled with freshly prepared activated amino acid or capped by treating the peptide resin with acetic anhydride as described above. The fully assembled peptide-resins were dried in vacuum for several hours.

For most compounds, the blocking groups were removed and the peptide cleaved from the resin. For example, the peptide-resins were treated with 100 µL ethanedithiol, 100 µl dimethylsulfide, 300 µL anisole, and 9.5 mL trifluoroacetic acid, per gram of resin, at room temperature for 180 min. Or alternately the peptide-resins were treated with 1.0 mL triisopropyl silane and 9.5 mL trifluoroacetic acid, per gram of resin, at room temperature for 180 min. The resin was filtered off and the filtrates were precipitated in chilled ethyl ether. The precipitates were centrifuged and the ether layer was decanted. The residue was washed with two or three volumes of Et_2O and recentrifuged. The crude products were dried under vacuum.

Purification of the crude peptides was preferably performed on Shimadzu LC-8A system by high performance liquid chromatography (HPLC) on a reverse phase C-18 Column (50x250 mm. 300 Å, 10-15 µm). The peptides were injected to the columns in a minimum volume of either 0.1 AcOH/H2O or CH_3CH/H_2O. Gradient elution was generally started at 20% B buffer, 20% -80% B over 70 minutes, (buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH3CN) at a flow rate of 50 mL/min. UV detection was made at 220/280 nm. The fractions containing the products were separated and their purity was judged on Shimadzu LC-10AT analytical system using reverse phase Ace C18 column (4.6 x50mol) at a flow rate of 2 mL/min., gradient (20-80 %) over 10 min.(buffer A: 0.1% TFA/H_2O, buffer B: 0.1% TFA/CH_3CN)). Fractions judged to be of high purity were pooled and lyophilized.

Purity of the final products was checked by analytical HPLC on a reversed phase column as stated above. Purity of all products was judged to be approximately 95 - 99%. All final products were also subjected to fast atom bombardment mass spectrometry (FAB-MS) or electrospray mass spectrometry (ES-MS). All products yielded the expected parent M+H ions within acceptable limits.

The compounds of the present invention can be provided in the form of pharmaceutically acceptable salts. Examples of preferred salts are those formed with pharmaceutically acceptable organic acids, e.g., acetic, lactic, maleic, citric, malic, ascorbic, succinic, benzoic, salicylic, methanesulfonic, toluenesulfonic, trifluoroacetic or pamoic acid, as well as polymeric acids such as tannic acid or carboxymethyl cellulose, and salts with inorganic acids, such as hydrohalic acids (e.g., hydrochloric acid), sulfuric acid, or phosphoric acid and the like. Any procedure for obtaining a pharmaceutically acceptable salt known to a skilled artisan can be used.

The invention also relates to a neuropeptide-2 receptor agonist as described above for use as a therapeutically active substance.

A pharmaceutical composition comprising a neuropeptide-2 receptor agonist as described above and a therapeutically inert carrier is also an object of the present invention.

Furthermore, the invention relates to the use of a neuropeptide-2 receptor agonist as described above for the preparation of medicaments for the treatment or prophylaxis of obesity, type 2 diabetes, metabolic syndrome, insulin resistance or dyslipidemia.

The invention further relates to a method for the treatment or prophylaxis of obesity, type 2 diabetes, metabolic syndrome, insulin resistance or dyslipidemia, which method comprises administering an effective amount of a neuropeptide-2 receptor agonist as described above.

In the practice of the method of the present invention, an effective amount of any one of the peptides of this invention or a combination of any of the peptides of this invention or a pharmaceutically acceptable salt thereof, is administered via any of the usual and acceptable methods known in the art, either singly or in combination. Administration can be, for example, once a day, once every three days or once a week. The compounds or compositions can thus be administered orally (e.g., buccal cavity), sublingually, parenterally (e.g., intramuscularly, intravenously, or subcutaneously), rectally (e.g., by suppositories or washings), transdermally (e.g., skin electroporation) or by inhalation (e.g., by aerosol), and in the form or solid, liquid or gaseous dosages, including tablets and suspensions. The administration can be conducted in a single unit dosage form with continuous therapy or in a single dose therapy ad libitum. The therapeutic composition can also be in the form of an oil emulsion or dispersion in conjunction with a lipophilic salt such as pamoic acid, or in the form of a biodegradable sustained-release composition for subcutaneous or intramuscular administration.

Thus, the method of the present invention is practiced when relief of symptoms is specifically required or perhaps imminent. Alternatively, the method of the present invention is effectively practiced as continuous or prophylactic treatment.

Useful pharmaceutical carriers for the preparation of the compositions hereof, can be solids, liquids or gases; thus, the compositions can take the form of tablets, pills, capsules, suppositories, powders, enterically coated or other protected formulations (e.g. binding on ion-exchange resins or packaging in lipid-protein vesicles), sustained release formulations, solutions, suspensions, elixirs, aerosols, and the like. The carrier can be selected from the various oils including those of petroleum, animal, vegetable or synthetic origin, e.g., peanut oil, soybean oil, mineral oil, sesame oil, and the like. Water, saline, aqueous dextrose, and glycols are preferred liquid carriers, particularly (when isotonic with the

blood) for injectable solutions. For example, formulations for intravenous administration comprise sterile aqueous solutions of the active ingredient(s) which are prepared by dissolving solid active ingredient(s) in water to produce an aqueous solution, and rendering the solution sterile. Suitable pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, talc, gelatin, malt, rice, flour, chalk, silica, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, glycerol, propylene glycol, water, ethanol, and the like. The compositions may be subjected to conventional pharmaceutical additives such as preservatives, stabilizing agents, wetting or emulsifying agents, salts for adjusting osmotic pressure, buffers and the like. Suitable pharmaceutical carriers and their formulation are described in Remington's Pharmaceutical Sciences by E. W. Martin. Such compositions will, in any event, contain an effective amount of the active compound together with a suitable carrier so as to prepare the proper dosage form for proper administration to the recipient.

The dose of a compound of the present invention depends on a number of factors, such as, for example, the manner of administration, the age and the body weight of the subject, and the condition of the subject to be treated, and ultimately will be decided by the attending physician or veterinarian. Such an amount of the active compound as determined by the attending physician or veterinarian is referred to herein, and in the claims, as an "effective amount". For example, the dose for intranasal administration is typically in the range of about 0.001 to about 0.1 mg/kg body weight. In humans, the preferred subcutaneous dose based on peptide content is from about 0.001 mg to about 100 mg; preferably from about 0.1 mg to about 15 mg.

The invention will now be further described in the Examples which follow, which are intended as an illustration only and do not limit the scope of the invention.

Examples

Example 1

Preparation of Fmoc-Linker-BHA Resin

Benzhydrylamine copolystyrene-1% divinylbenzene cross-linked resin (10.0 g, 9.3 mequiv, 100-200 ASTM mesh, Advanced ChemTech) was swelled in 100 mL CH_2Cl_2, filtered and washed successively with 100 mL each of CH_2Cl_2, 6% DIPEA/CH_2Cl_2 (two times), CH_2Cl_2 (two times). The resin was treated with p- ((R, S)-α-(1-(9H-fluoren-9-yl)-methoxyformamido)-2, 4-dimethoxybenzyl)-phenoxyacetic acid (Fmoc-Linker) (7.01 g, 13.0 mmol), N-hydroxybenzotriazole (2.16g, 16.0 mmol), and N,N'-diisopropylcarbodiimide (2.04 mL, 13.0 mmol) in 100 mL 25% DMF/CH_2Cl_2 for 24 hours at room temperature. The resin was filtered and washed successively with 100 mL each of CH_2Cl_2 (two times), isopropanol (two times), DMF, and CH_2Cl_2 (three times). A Kaiser Ninhydrin analysis was negative. The resin was dried under vacuum to yield 16.12 g of Fmoc-Linker-BHA resin. A portion of this resin (3.5 mg) was subjected to Fmoc deprotection and quantitative UV analysis which indicated a loading of 0.56 mmol/g.

Example 2

Protocol for the synthesis of peptides by Applied Biosystem 433A synthesizer using Fluorenylmethyloxycarbonyl (Fmoc) chemistry.

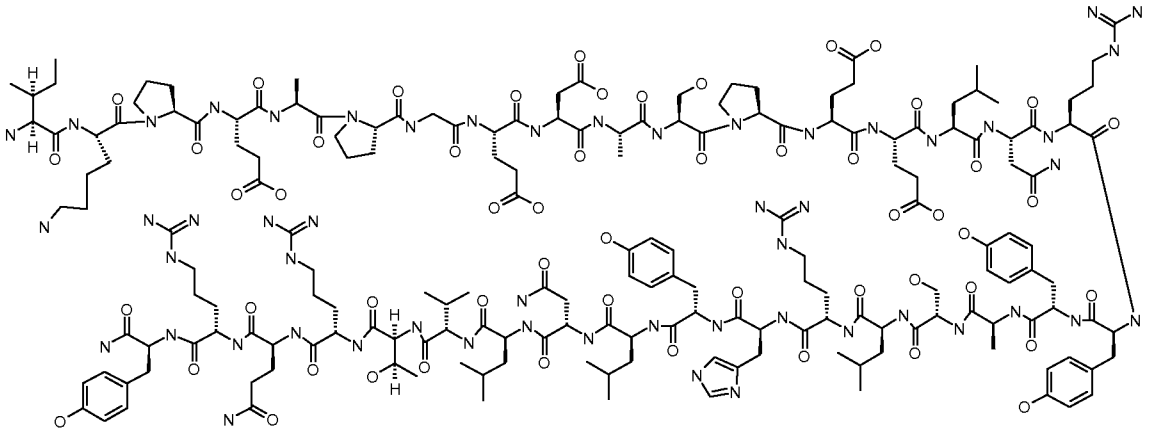
For a 0.25 mmol scale peptide synthesis by Applied Biosystem 433A synthesizer (Foster City, CA), the FastMoc 0.25 mmol cycles were used with either the resin sampling or non resin sampling, 41 mL reaction vessel. The Fmoc-amino acid resin was suspended with 2.1 g NMP, 2g of 0.45M HOBT/HBTU in DMF and 2M DIEA, then transferred to the reaction vessel. The basic FastMoc coupling cycle was represented by "BADEIFD," wherein each letter represents a module (as defined by Applied Biosystems). For example:

B represents the module for Fmoc deprotection using 20% Piperidine/NMP and related washes and readings for 30 min (either UV monitoring or conductivity); A represents the module for activation of amino acid in cartridges with 0.45 M HBTU/HOBt and 2.0 M DIEA and mixing with N_2 bubbling; D represents the module for NMP washing of resin in the reaction vessel; E represents the module for transfer of the activated amino acid to the reaction vessel for coupling; I represents the module for a 10 minute waiting period with vortexing on and off of the reaction vessel; and F represents the module for cleaning the cartridge, coupling for approximately 10 minutes and draining the reaction vessel. Couplings were typically extended by addition of module "I" once or multiple times. For

example, double couplings were run by performing the procedure "BADEIIADEIFD." Other modules were available such as c for methylene chloride washes and "C" for capping with acetic anhydride. Individual modules were also modifiable by, for example, changing the timing of various functions, such as transfer time, in order to alter the amount of solvent or reagents transferred. The cycles above were typically used for coupling one amino acid. For synthesizing tetra peptides, however, the cycles were repeated and strung together. For example, BADEIIADEIFD was used to couple the first amino acid, followed by BADEIIADEIFD to couple the second amino acid, followed by BADEIIADEIFD to couple the third amino acid, followed by BADEIIADEIFD to couple the fourth amino acid, followed by BIDDcc for final deprotection and washing.

Example 3

Preparation of H-Ile-Lys-Pro-Glu-Ala-Pro-Gly-Glu-Asp-Ala-Ser-Pro-Glu-Glu-Leu-Asn-Arg-Tyr-Tyr-Ala-Ser-Leu-Arg-His-Tyr-Leu-Asn-Leu-Val-The-Arg-Gln-Arg-Tyr-NH_2 (PYY_{3-36})

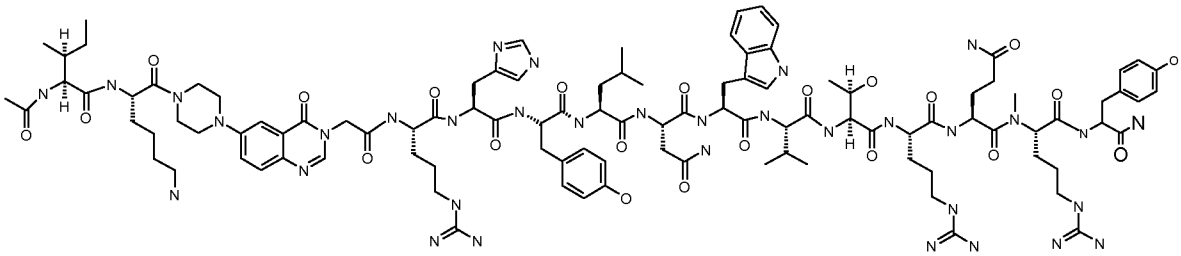


The above peptide was synthesized using Fmoc chemistry on an Applied Biosystem 433A synthesizer. The synthesizer was programmed for double coupling using the modules described in Example 2. The synthesis was carried out on a 0.25 mmol scale using the Fmoc- Linker-BHA resin (450 mg, 0.25 mmol) from Example 1. At the end of the synthesis, the resin was transferred to a reaction vessel on a shaker for cleavage. The peptide was cleaved from the resin using 13.5 mL 97% TFA/ 3%H2O and 1.5mL triisopropylsilane for 180 minutes at room temperature. The deprotection solution was added to 100 mL cold ET_2O, and washed with 1 mL TFA and 30 mL cold Et_2O to precipitate the peptide. The peptide was centrifuged 2x50 mL polypropylene tubes. The precipitates from the individual tubes were combined in a single tube and washed 3 times with cold ET_2O and dried in a desiccator under house vacuum.

The crude material was purified by preparative HPLC on a Pursuit C18-Column (250x50mm, 10µm particle size) and eluted with a linear gradient of 2-70%B (buffer A: 0.1%TFA/H_2O; buffer B: 0.1% TFA/CH_3CN) in 90 min., flow rate 60 mL/min, and detection 220/280 nm. The fractions were collected and were checked by analytical HPLC. Fractions containing pure product were combined and lyophilized to yield 151 mg (15%) of a white amorphous powder. (ES)+-LCMS m/e calculated (calcd) for $C_{180}H_{279}N_{53}O_{54}$ 4049.55 found 4050.20.

Example 4

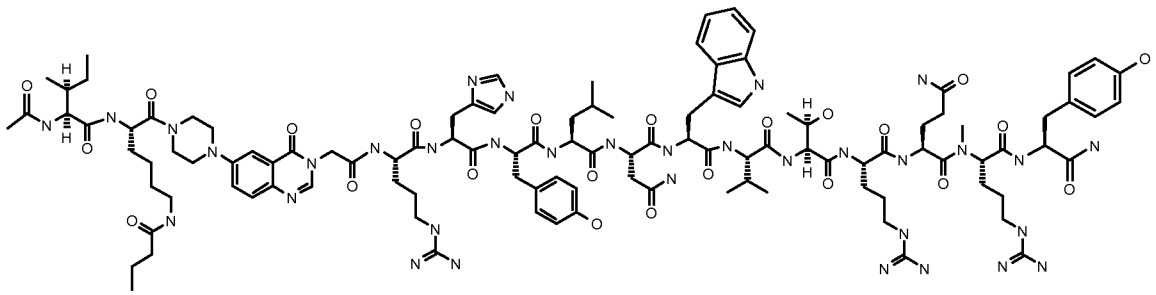
Preparation of Ac-Ile-Lys-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2



Fmoc- Linker-BHA resin (450 mg, 0.25 mmol) from Example 1 was subjected to solid phase synthesis and the crude peptide was purified following the procedure in Example 3 to yield 68 mg (12 %) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) for $C_{106}H_{156}N_{34}O_{22}$ 2257.21 found 2257.19.

Example 5

Preparation of Ac-Ile-Lys(Butyryl)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2

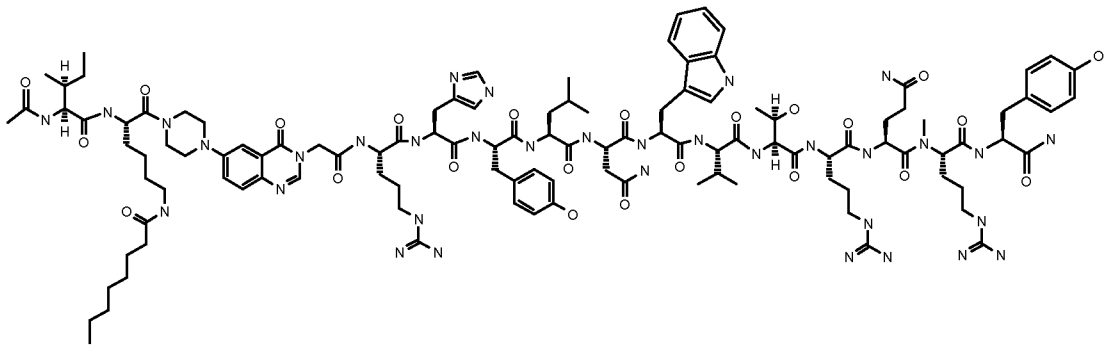


Ac-Ile-Lys-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-Arg-Tyr-NH_2, 200 mg was dissolved in 5.0 mL DMF and 35 uL NMM and 250 uL Butyric anhydride was added. The

solution was stirred for ~16 hr (overnight). 3.0 mL 7 N NH_3 in MeOH was added and stirring continued for ½ hr. The product was then precipitated in 5.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified following the procedure in Example 3 to yield 18 mg (9 %) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) $C_{110}H_{162}N_{34}O_{23}$ 2327.26 found 2327.26.

Example 6

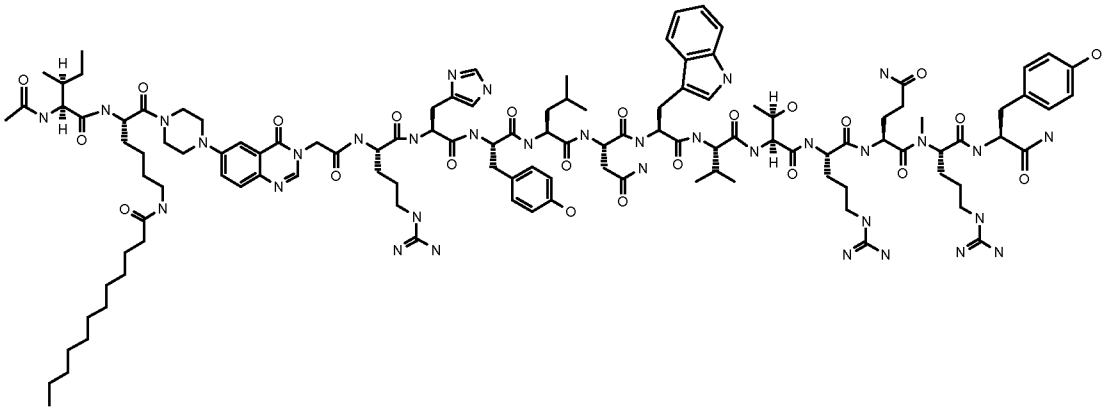
Preparation of Ac-Ile-Lys(Capryloyl)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2



Ac-Ile-Lys-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-Arg-Tyr-NH_2, 200 mg was dissolved in 5.0 mL DMF and N-hydroxybenzotriazole (425 mg, 3.15 mmol), DIEA (500 uL, 3.0 mmol) and capryloyl chloride (2.8 mL, 2.75 mmol) were reacted in 15 mL CH_2Cl_2 for 5 min and added to the peptide resin. The solution was stirred for 16 hr (overnight). 3.0 mL 7 N NH_3 in MeOH was added and stirring continued for ½ hr. The product was then precipitated in 5.0 mL Et_2O, centrifuged, washed and dried in vacuuo. The crude peptide was purified following the procedure in Example 3 to yield 10 mg (5%) of a white amorphous powder. (ES)+-LCMS m/e calculated (calcd) $C_{114}H_{170}N_{34}O_{23}$ 2383.32 found 2383.32.

Example 7

Preparation of Ac-Ile-Lys(Lauroyl)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2



Ac-Ile-Lys-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-Arg-Tyr-NH_2, 200 mg was dissolved in 5.0 mL DMF and N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 m) and lauroyl chloride (2.8 mL, 2.75 m) were reacted in 15 mL CH_2Cl_2 for 5 min and added to the peptide resin.. The solution was stirred for 16 hr (overnight). 3.0 mL 7 N NH_3 in MeOH was added and stirring continued for ½ hr. The product was then precipitated in 5.0 mL Et_2O, centrifuged, washed and dried in vacuuo. The crude material was purified by preparative HPLC on a Pursuit C18-Column (50x250mm, 10µm particle size) and eluted with a linear gradient of 20-90%B (buffer A: 0.1%TFA/H2O; buffer B: 0.1% TFA/CH3CN) in 90 min., flow rate 60mL/min,and detection 220/280 nm. The fractions were collected and were checked by analytical HPLC. Fractions containing pure product were combined and lyophilized to yield 57 mg (26 %) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) $C_{118}H_{178}N_{34}O_{23}$ 2439.38 found 2439.40.

Example 8

Preparation of Boc-Ile-Lys(TFA salt)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Knorr resin.

Benzhydrylamine copolystyrene-1% divinylbenzene cross-linked resin (50.0 g, 55.0 mequiv, 100-200 ASTM mesh, Advanced ChemTech cat #SB5003) was swelled in 400 mL CH2Cl2, filtered and washed successively with 100 mL each of CH_2Cl_2, 6% DIPEA/CH_2Cl_2 (two times), CH_2Cl_2 (two times). The resin was treated with p- [(R, S)-α-[1-(9H-fluoren-9-yl)-methoxyformamido]-2, 4-dimethoxybenzyl]-phenoxyacetic acid (Fmoc-Linker) (37.1 g, 69.0 mmol), N-hydroxybenzotriazole (9.356g, 69.0 mmol), and N,N'-diisopropylcarbodiimide (55.0 mL, 300 mmol) in 400 mL DMF for 24 hours at room temperature.

The resin was filtered and washed successively with 400 mL each of CH_2Cl_2 (two times), isopropanol (two times), DMF, and CH_2Cl_2 (three times). A Kaiser Ninhydrin analysis was

negative. Fmoc-Tyr(But)-OH (41.40 g., 90 mmol, N-hydoxbenzotriazole (12.2g., 90.0 mmol) and N,N'-diisopropylcarbodiimide (55.0 mL, 300 mmol) in 400 mL DMF was added and allowed to react for 24 hours at room temperature. The reaction was not completed and, thus, 25.0 mL DIEA was added and the reaction was allowed to proceed for an additional 1 ½ hr. Coupling was still not complete, therefore acetylation with 25% Ac_2O, 5% DIEA in DMF for ¾ hr. was performed to obtain a negative ninhydrin (complete reaction). After washing and Fmoc removal, Fmoc-NMeArg(Mtr)-OH (43.0 g, 69.0 mmol), N-hydroxybenzotriazole (9.356 g, 69.0 mmol) and N,N'-diisopropylcarbodiimide (110.0 mL, 630 mmol) in 400 mL DMF was added, and allowed to react for 24 hours, whereby the reaction was completed. After washing and Fmoc removal, Fmoc-Gln(Trt)-OH (55.0 g., 90.0 mmol), N-hydroxbenzotriazole (12.2 g , 90.0 mmol) and N,N'-diisopropylcarbodiimide (55.0 mL, 300 mmol) in 400 mL DMF was added and the reaction was allowed to go for 24 h. The reaction was completed as determined by the chlorinal test.

The resin was washed and dried and 25.0 g (18.4%) was saved for different analogs. The remaining 110.0 g resin (44.6 mmol) was carried forward and 1.55 eqv. Fmoc-Arg(Pbf)-OH (45.0 g, 73.5 mmol), N-hydroxbenzotriazole (9.95 g, 73.5 mmol) and N,N'-diisopropylcarbodiimide (55.0 mL, 330 mmol) in 400 mL DMF was added, and the reaction was allowed to go for 24 hours at room temperature at which time, it was completed as judged by the ninhydrin test. After washing and Fmoc removal, Fmoc-Thr(But)-OH (27.40 g ,73.5 mmol), N-hydroxbenzotriazole. (9.95 g, 73.5 mmol) and N,N'-diisopropylcarbodiimide (55 mL, 300 mmole) in 400 mL DMF were added, and the reaction was allowed to go for 24 hours at room temperature at which time, it was completed as determined by the ninhydrin test. After washing and Fmoc removal Fmoc-Val-OH (23.6 g. 73.5 mmol), N-hydroxybenzotriazole (9.95 g, 73.5 mmol) and N,N'-diisopropylcarbodiimide (55.0 mL, 300 mmol) in 400 DMF was added and allowed to react for 6 hours at room temperature at which time, it was completed.

After washing and removal of the Fmoc, Fmoc-Trp-OH (29.5 0 g., 73.5 mmol), N-hydroxbenzotriazole (9.95 g, 73.5 mmol) and N,N'-diisopropylcarbodiimide (55.0 mL, 300 mmol) in 400 mL DMF was added. The reaction was complete after 6 hours. After washing and Fmoc removal, Fmoc-Asn(Trt)-OH (41.4 g, ,73.5 mmol), N-hydroxbenzotriazole (9.95 g, 73.5 mmol) and N,N'-diisopropylcarbodiimide (55 mL, 300 mmol) in 400 mL DMF was added and allowed to react for 18 hours at room temperature at which time, it was completed.

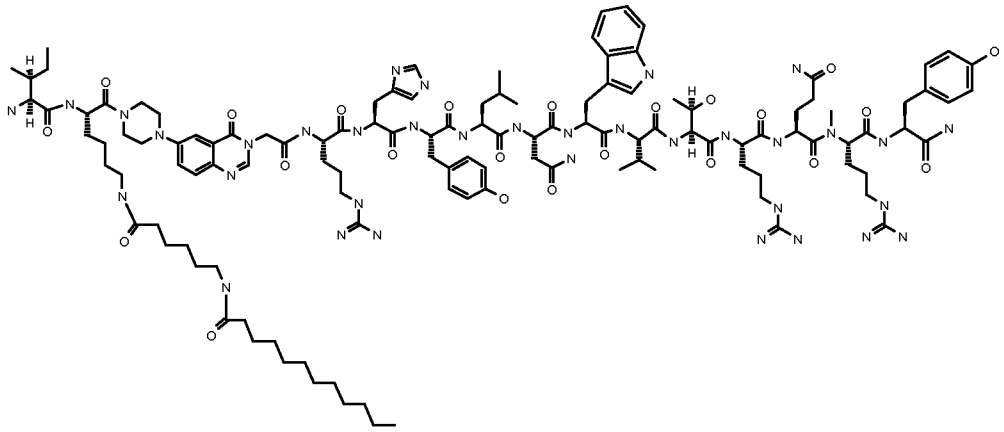
After washing and Fmoc removal, Fmoc-Leu-OH (33.4 g, 73.5 mmol). N-hydroxbenzotriazole (9.95 g, 73.5 mmol) and N,N'-diisopropylcarbodiimide (55.0 mL, 300 mmol) in 400 mL DMF was added and allowed to react 6 hours. After washing and removal of the Fmoc, Fmoc-Tyr(But)-OH (41.4 0 g, 73.5 mmol) , N-hydroxbenzotriazole (9.95 g, 73.5 mmol) and N,N'-diisopropylcarbodiimide (55.0 mL, 300 mmol) in 400 mL DMF was added. The reaction was complete after 18 hours. After washing and Fmoc removal, .Fmoc-His(Trt)-OH (55.5 g, 73.5 mmol), N-hydroxbenzotriazole (9.95 g, 73.5 mmol) and N,N'-diisopropylcarbodiimide (55.0 mL, 300 mmol) in 400 mL DMF was added. The reaction was complete after 20 hours. After washing and Fmoc removal, Fmoc-Arg(Pbf)-OH (58.4 g, 73.5 mmol), N-hydroxbenzotriazole (9.95 g, 73.5 mmol) and N,N'-diisopropylcarbodiimide (55.0 mL, 300 mmol) in 400 mL DMF was added. The reaction was complete after 20 hours.

After washing and removal of Fmoc, Fmoc-Pqa-OH (21.4 g, 73.5 mmol,) N-hydroxbenzotriazole (5.7 g, 42.05 mmol) and N,N'-diisopropylcarbodiimide (55.0 mL, 300 mmol) in 400 mL DMF was added. The reaction was complete after 16 hours. After washing and Fmoc removal, Fmoc-Lys(Alloc)-OH (18.5 g., 73.5 mmol) and N-hydroxbenzotriazole (9.95 g, 73.5 mmol) and N,N'-diisopropylcarbodiimide (55.0 mL, 300 mmol) in 400 mL DMF was added. The reaction was complete after 20 hours as determined by chlorinal test. After washing and drying, a portion was saved for coupling with Fmoc-Ile for N-acetylated analogs. The remaining peptide resin was treated with Boc-Ile-OH (25.0 g, 73.5 mmol) N-hydroxbenzotriazole (9.95 g, 73.5 mmol) and N,N'-diisopropylcarbodiimide (55.0 mL, 300 mmol) in 400 mL DMF for 20 hours at room temperature. The reaction was complete

Removal of the Aloc group from the epsilon-amino group of Lys: Argon was bubbled through a mixture of 1.2 g $PdCl_2$ (triphenylphosphine)$_2$, 5.0 mL morpholine, and 10.0 mL of acetic acid, then 25.0 mL Bu_3SnH was added. Bubbling with Ar was continued until the yellow solution become reddish brown. The reaction mixture was then shaken for ½ hr, and washed 3 times with DMF. The above procedure was repeated a second time (this time the mixture turned dark brown to almost black in color) and shaking was continued for ½ to ¾ hr. The resin was washed 2 times with DMF, 2 times with 5% DIEA/DMF and 3 times with DMF/CH_2Cl_2. The free epsilon-amine of Lysine was converted to the TFA salt by washing with 2.35 mL TFA added to CH_2Cl_2. The resin was then washed 2 times with CH_2Cl_2 and 4 times with MeOH and dried to constant weight under vacuuo.

Example 9

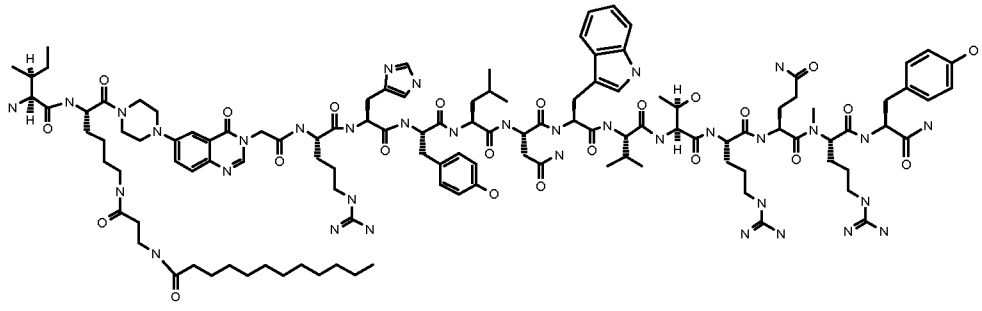
Preparation of H-Ile-Lys(Lauroyl-6-Ahx)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2



Boc-Ile-Lys(TFA salt)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Knorr resin 1.0 g was washed with 5% DIEA in DMF and coupled with Fmoc-6-aminohexanoic acid (355.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) overnight. After Fmoc removal and washing with DMF N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 m) and Lauroyl chloride (2.8 mL, 2.75 m) were reacted in 15 mL CH_2Cl_2 for 5 min and added to the peptide resin. The reaction mixture was stirred over night and washed with DMF 2 times and CH_2Cl_2 3 times before cleavage was effected with TFA, 17 mL, 400 uL iPrSiH and 800 uL propanethiol for 6 hr. The product was precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuuo. The crude peptide was purified following the procedure in Example 7 to yield 30 mg (7 %) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) $C_{122}H_{187}N_{35}O_{23}$ 2510.45 found 2510.44.

Example 10

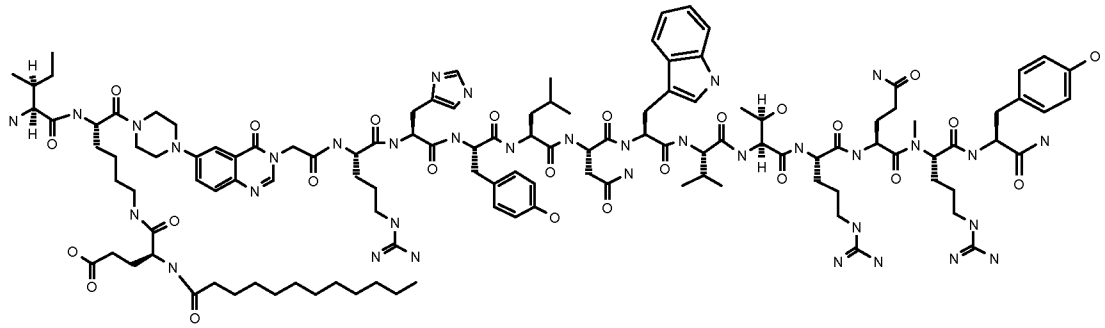
Preparation of H-Ile-Lys(Lauroyl-beta-Ala)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2



Boc-Ile-Lys (epsilon TFA salt)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Knorr resin 1.0 g was washed with 5% DIEA in DMF and coupled with Fmoc-betaAla (325.0 mg; 1.0 mmmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) overnight. After Fmoc removal and washing with DMF, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 m) and lauroyl chloride (2.8 mL, 2.75 mmol) were reacted in 15 mL CH_2Cl_2 for 5 min and added to the peptide resin. The reaction mixture was stirred over night and washed with DMF 2 times and CH_2Cl_2 3 times before cleavage was effected with TFA, 17 mL, 400 uL iPrSiH and 800 uL propanethiol for 6 hr. The product was precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuuo. The crude peptide was purified following the procedure in Example 7 to yield 20 mg (4 %) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) $C_{119}H_{181}N_{35}O_{23}$ 2468.41, found 2468.6.

Example 11

Preparation of H-Ile-Lys(Lauroyl-Glu)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2

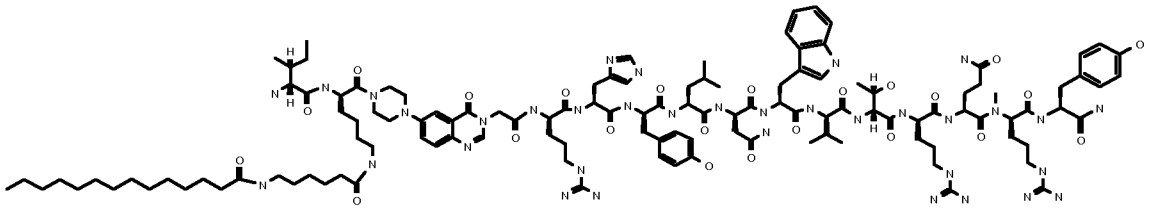


Boc-Ile-Lys(epsilon-TFA salt)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Knorr resin 1.0 g was washed with 5% DIEA in DMF and coupled with Fmoc-Glu(Bu^t) (325.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) was carried out overnight. After Fmoc removal and washing with DMF, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 mmol) and lauroyl chloride (2.8 mL, 2.75 mmol) were reacted in 15 mL CH_2Cl_2 for 5 min and added to the peptide resin. The reaction mixture was stirred over night and washed with DMF 2 times and CH_2Cl_2 3 times before cleavage was effected with TFA, 17 mL, 400 uL iPrSiH and 800 uL propanethiol for 6 hr. The product was precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuuo. The crude peptide was purified following the procedure in

Example 7 to yield 30 mg (7 %) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) $C_{121}H_{183}N_{35}O_{25}$ 2526.41, found 2526.40.

Example 12

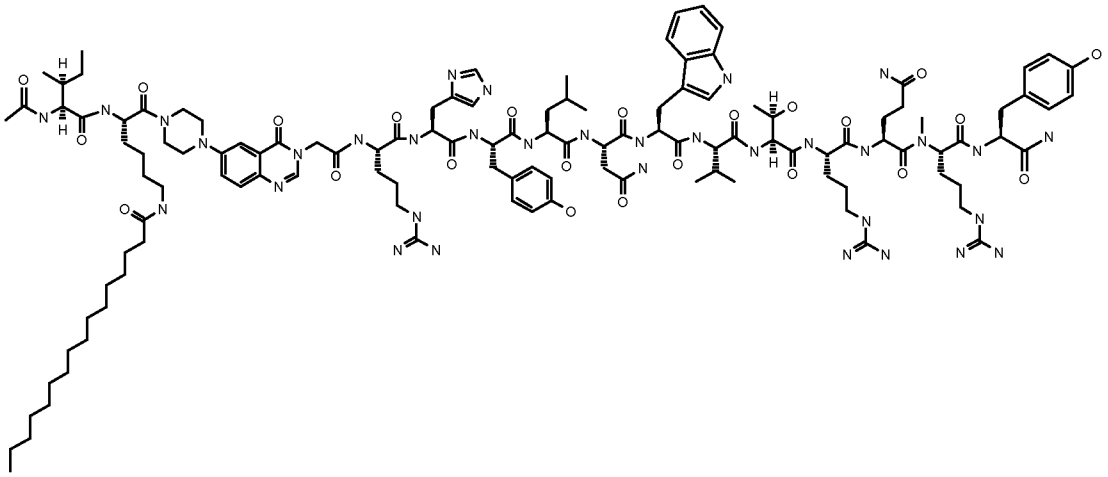
Preparation of H-Ile-Lys(Myristoyl-6Ahx)-Pro-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2



Boc-Ile-Lys(epsilonTFA salt)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Knorr resin 1.0 g was washed with 5% DIEA in DMF and coupled with Fmoc-6-aminohexanoic acid (355 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) overnight. After Fmoc removal and washing with DMF, myristric acid (230 mg, 1 mmol); N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) were coupled and stirred over night. After washing with DMF 2 times and CH_2Cl_2 3 times, cleavage was effected with TFA, 17 mL 400 uL iPrSiH and 800 uL propanethiol for 6 hr. The product was precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuuo. The crude peptide was purified following the procedure in Example 7 to yield 66 mg (13 %) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) $C_{124}H_{191}N_{35}O_{23}$ 2538.49, found 2538.47.

Example 13

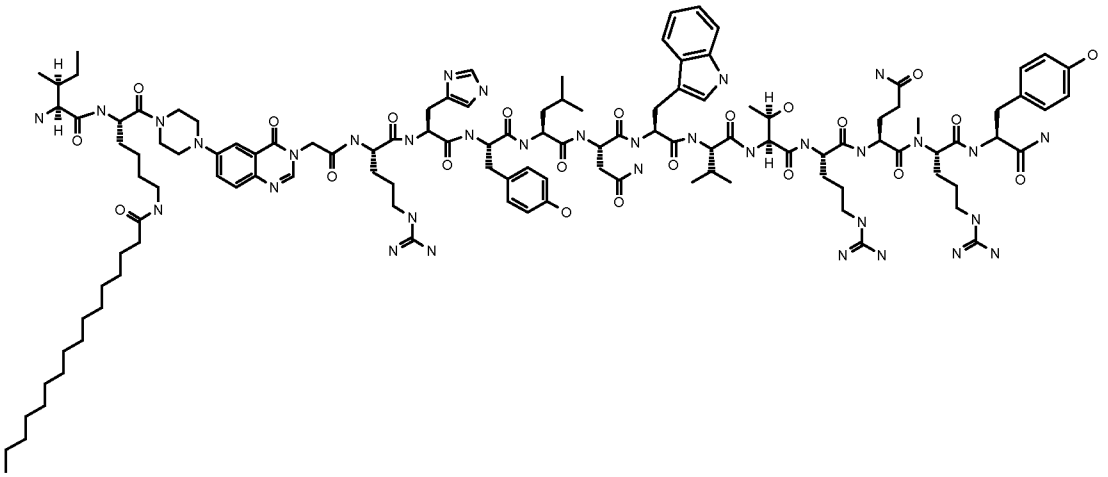
Preparation of Ac-Ile-Lys(Palmitoyl)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2



Ac-Ile-Lys-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-Arg-Tyr-NH_2, 200 mg was dissolved in 5.0 mL DMF and N-hydroxybenzotriazole (425 mg, 3.15 mmol), DIEA (500 uL, 3.0 mmol) and palmitoyl chloride (2.8 mL, 2.8 mmol) were reacted in 15 mL of CH_2Cl_2 for 5 min. and added to the peptide resin. The solution was stirred for ~16 hr (overnight). 3.0 mL 7 N NH_3 in MeOH was added and stirring continued for ½ hr. The product was then precipitated in 5.0 mL Et_2O, centrifuged, washed and dried in vacuuo. The crude peptide was purified following the procedure in Example 7 to yield 42 mg (19 %) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) $C_{122}H_{186}N_{34}O_{23}$ 2495.44, found 2495.43.

Example 14

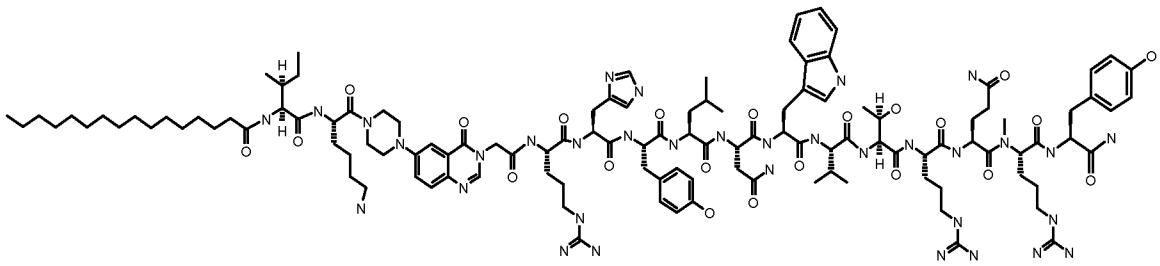
Preparation of H-Ile-Lys(Palmitoyl)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2



Boc-Ile-Lys(TFA epsilon salt)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Knorr resin 1.0 g was washed with 5% DIEA in DMF and coupled with Fmoc-6-aminohexanoic acid (355.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) overnight. After Fmoc removal and washing with DMF, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 mmol) and palmitoyl chloride (2.8 mL, 2.8 mmol) were reacted in 15 mL CH_2Cl_2 for 5 min and added to the peptide resin. The reaction mixture was stirred over night and washed with DMF 2 times and CH_2Cl_2 3 times before cleavage was effected with TFA, 17 mL, 400 uL iPrSiH and 800 uL propanethiol for 6 hr. The product was precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuuo. The crude peptide was purified following the procedure in Example 7 to yield 46 mg (10%) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) $C_{120}H_{184}N_{34}O_{22}$ 2453.43, found 2453.41.

Example 15

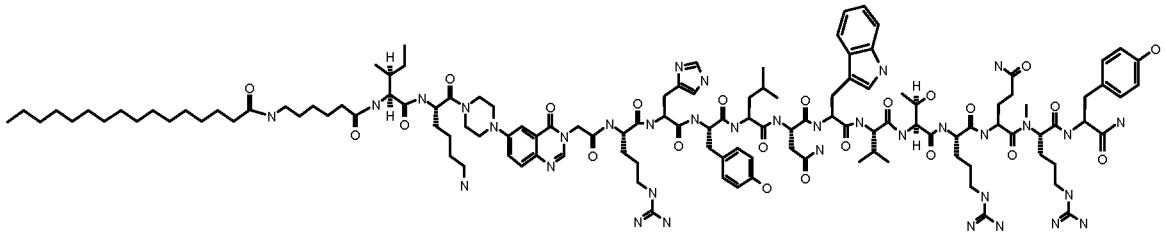
Preparation of Palmitoyl-Ile-Lys-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2



Fmoc- Linker-BHA resin (450 mg, 0.25 mmol) from Example 1 was subjected to solid phase synthesis. Synthesis was carried out according to the general procedure described in example 4 as far as the N-terminal deprotected 15-mer and acylated manually with palmitoyl chloride (288 uL, 1.0 mmol) and DIEA (200 uL, 1.15 mmol) in CH_2Cl_2 for ½ hr. The resin was cleaved and the product purified by following the procedure in Example 7 to yield 55 mg (9 %) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) for $C_{120}H_{184}N_{34}O_{22}$ 2453.43, found 2453.41.

Example 16

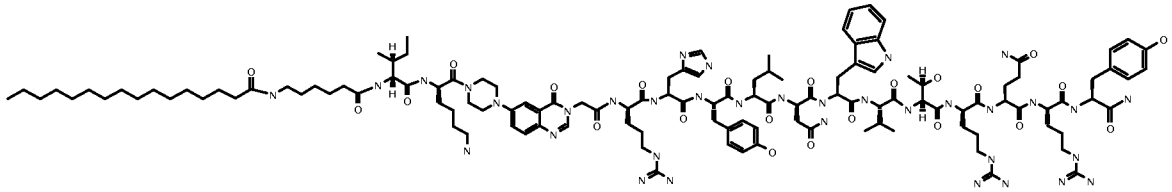
Preparation of Palmitoyl-6-Ahx-Ile-Lys-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2



Fmoc- Linker-BHA resin (450 mg, 0.25 mmol) from Example 1 was subjected to solid phase synthesis. Synthesis was carried out as generally described in Example 4 as far as the deprotected 15 mer and coupled manually with Fmoc-6-aminohexanoic acid (355.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) were added and the reaction was allowed to proceed overnight. After Fmoc removal, the resin bound peptide was acylated with palmitoyl chloride (288 uL 1.0 mmol) , DIEA (200 uL, 1.15 mmol) in CH_2Cl_2 for ½ hr. The resin was cleaved and the crude peptide was purified following the procedure in Example 7 to yield 45 mg (7%) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) for $C_{126}H_{195}N_{35}O_{23}$ 2566.52, found 2566.51.

Example 17

Preparation of Palmitoyl-6-Ahx-Ile-Lys-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-Arg-Tyr-NH_2

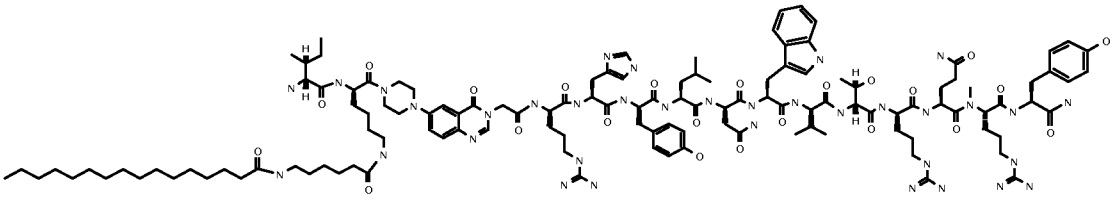


Fmoc- Linker-BHA resin (450 mg, 0.25 mmol) from Example 1 was subjected to solid phase synthesis. Synthesis was carried out according to the general procedure described in Example 4 as far as the deprotected 15-mer and coupled manually with Fmoc-6-aminohexanoic acid (355.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) overnight. After Fmoc removal the resin bound peptide was acylated with palmitoyl chloride (288 uL, 1.0 mmol) and DIEA (200 uL, 1.15mol) in CH_2Cl_2 for ½ hr. The resin was cleaved and the crude peptide was purified following the procedure in Example 7 to yield 77 mg (12%) of white

amorphous powder. (ES)+-LCMS m/e calculated (calcd) for $C_{125}H_{193}N_{35}O_{23}$ 2552.50 found 2552.49.

Example 18

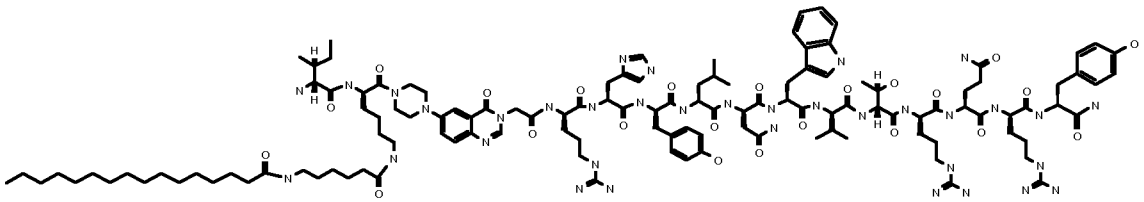
Preparation of H-Ile-Lys(Palmitoyl-6-Ahx)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2



Boc-Ile-Lys(epsilon TFA salt)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Knorr resin 1.0 g was washed with 5% DIEA in DMF and coupled with Fmoc-6-aminohexanoic acid (355.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) overnight. After Fmoc removal and washing with DMF, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 m) and palmitoyl chloride (2.8 mL, 2.75 m) were reacted in 15 mL CH_2Cl_2 for 5 min and added to the peptide resin. The reaction mixture was stirred over night and washed with DMF 2 times and CH_2Cl_2 3 times before cleavage was effected with TFA, 17 mL, 400 uL iPrSiH and 800 uL propanethiol for 6 hr. The product was precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuuo. The crude peptide was purified following the procedure in Example 7 to yield 14 mg (3 %) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) $C_{126}H_{195}N_{35}O_{23}$ 2566.51 found 2566.50.

Example 19

Preparation of H-Ile-Lys(Palmitoyl-6Ahx)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln--Arg-Tyr-NH_2

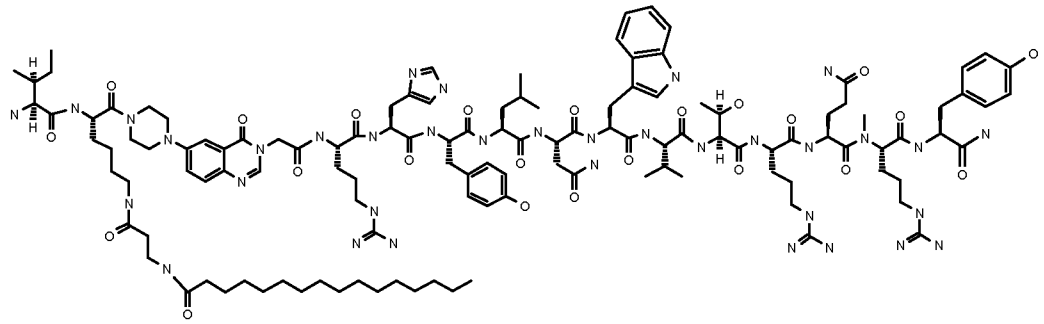


Boc-Ile-Lys(alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-Arg-Tyr(tBu)-Knorr resin (prepared as in Example 14) was washed

with 5% DIEA in DMF and coupled with Fmoc-6-aminohexanoic acid (355.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) overnight. After Fmoc removal and washing with DMF, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 m) and Palmitoyl chloride (2.8 mL, 2.75 m) were reacted in 15 mL CH_2Cl_2 for 5 min and added to the peptide resin. The reaction mixture was stirred over night and washed with DMF 2 times and CH_2Cl_2 3 times before cleavage was effected with TFA, 17 mL, 400 uL iPrSiH and 800 uL propanethiol for 6 hr. The product was precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuuo. The crude peptide was purified following the procedure in Example 7 to yield 52 mg (15%) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) $C_{125}H_{193}N_{35}O_{23}$ 2552.50 found 2552.49.

Example 20

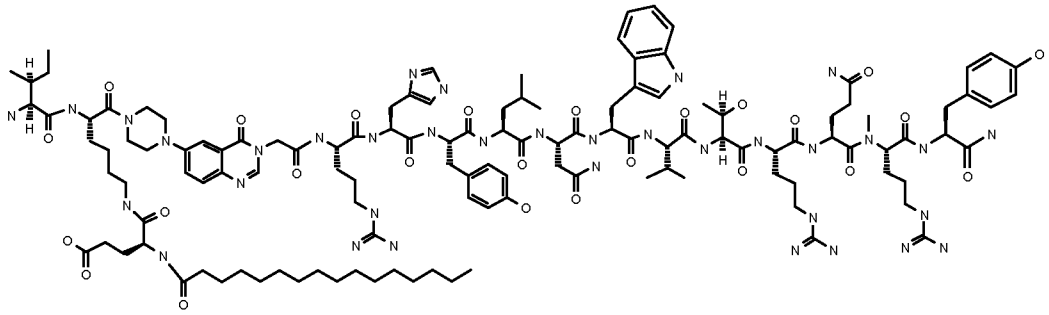
Prepa*ration of H*-Ile-Lys(Palmitoyl-beta-Ala)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)Arg-Tyr-NH_2



Boc-Ile-Lys(epsilon TFA salt)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Knorr resin 1.0 g was washed with 5% DIEA in DMF and coupled with Fmoc-beta-Ala (312.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) overnight. After Fmoc removal and washing with DMF, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 m) and palmitoyl chloride (2.8 mL, 2.75 m) were reacted in 15 mL CH_2Cl_2 for 5 min and added to the peptide resin. The reaction mixture was stirred over night and washed with DMF 2 times and CH_2Cl2 3 times before cleavage was effected with TFA, 17 mL, 400 uL iPrSiH and 800 uL propanethiol for 6 hr. The product was precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuuo. The crude peptide was purified following the procedure in Example 7 to yield 20 mg (4.4 %) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) $C_{123}H_{189}N_{35}O_{23}$ 2524.476, found 2524.47.

Example 21

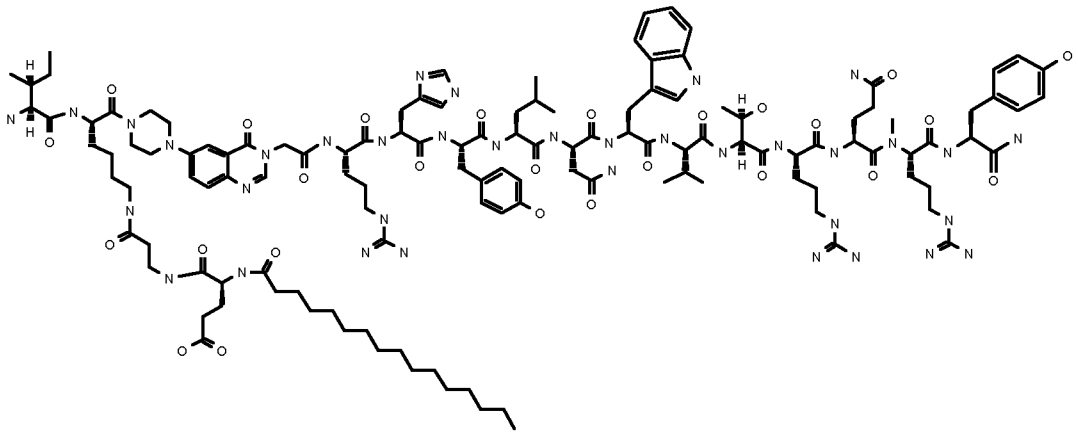
Preparation of H-Ile-Lys(Palmitoyl-Glu)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2



Boc-Ile-Lys(epsilon TFA salt)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Knorr resin 1.0 g was washed with 5% DIEA in DMF and coupled with Fmoc-Glu(Bu^t) (312.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) overnight. After Fmoc removal and washing with DMF, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 m) and palmitoyl chloride (2.8 mL, 2.75 m) were reacted in 15 mL CH_2Cl_2 for 5 min and added to the peptide resin. The reaction mixture was stirred over night and washed with DMF 2 times and CH_2Cl2 3 times before cleavage was effected with TFA, 17 mL, 400 uL iPrSiH and 800 uL propanethiol for 6 hr. The product was precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuuo. The crude peptide was purified following the procedure in Example 7 to yield 14 mg (3%) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) $C_{125}H_{191}N_{35}O_{25}$ 2582.48, found 2582.48.

Example 22

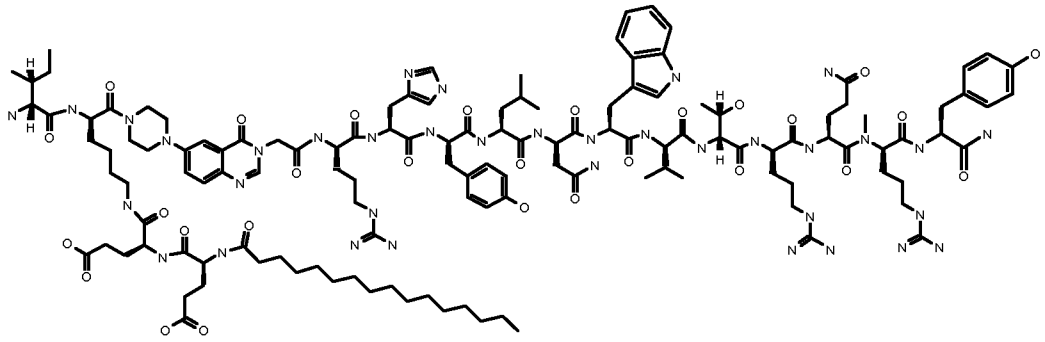
Preparation of H-Ile-Lys(Palmitoyl- beta-Ala-Glu)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2



Boc-Ile-Lys(epsilon TFA salt)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Knorr resin 1.0 g was washed with 5% DIEA in DMF and coupled with Fmoc-beta-Ala (312.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) overnight. After Fmoc removal and washing with DMF, Fmoc-Glu(Bu^t) (312.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) were added and the reaction was allowed to procede overnight. After Fmoc removal and washing with DMF, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 m) and palmitoyl chloride (2.8 mL, 2.75 m) were reacted in 15 mL CH_2Cl_2 for 5 min and added to the peptide resin. The reaction mixture was stirred over night and washed with DMF 2 times and CH_2Cl_2 3 times before cleavage was effected with TFA, 17 mL, 400 uL iPrSiH and 800 uL propanethiol for 6 hr. The product was precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuuo. The crude peptide was purified following the procedure in Example 7 to yield 29 mg (6%) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) $C_{128}H_{196}N_{36}O_{26}$ 2653.51, found 2653.50.

Example 23

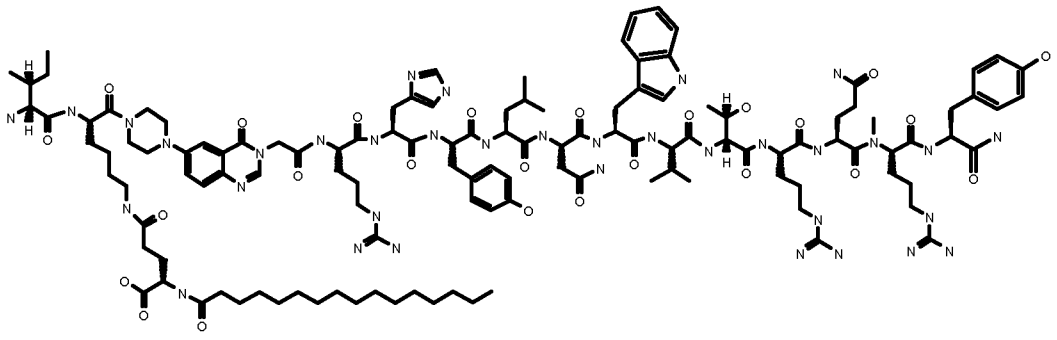
Preparation of H-Ile-Lys(Palmitoyl-Glu-Glu-)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2



Boc-Ile-Lys(epsilon TFA salt)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Knorr resin 1.0 g was washed with 5% DIEA in DMF and coupled with Fmoc-Glu(Bu^t) 426.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) overnight. After Fmoc removal and washing with DMF coupling was effected with Fmoc-Glu(Bu^t) (426.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) overnight. After Fmoc removal and washing with DMF, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 m) and palmitoyl chloride (2.8 mL, 2.75 m) were reacted in 15 mL CH_2Cl_2 for 5 min and added to the peptide resin. The reaction mixture was stirred over night and washed with DMF 2 times and CH_2Cl_2 3 times before cleavage was effected with TFA, 17 mL, 400 uL iPrSiH and 800 uL propanethiol for 6 hr. The product was precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuuo. The crude peptide was purified following the procedure in Example 7 to yield 25 mg (5%) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) $C_{130}H_{198}N_{36}O_{28}$ 2711.52, found 2711.51.

Example 24

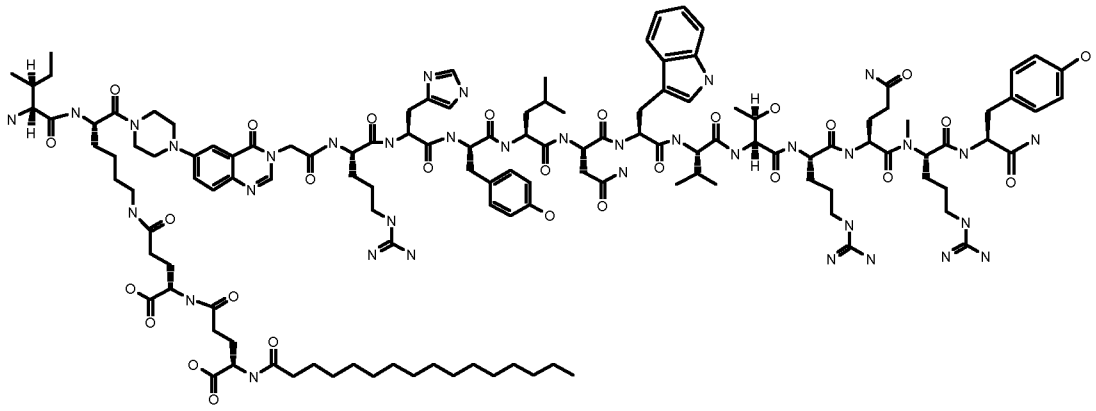
Preparation of H-Ile-Lys(Palmitoyl-gamma-Glu)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2



Boc-Ile-Lys(epsilon TFA salt)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Knorr resin 1.0 g was washed with 5% DIEA in DMF and coupled with Fmoc-gamma-Glu-alpha OBu^t (426.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) overnight. After Fmoc removal and washing with DMF, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 m) and palmitoyl chloride (2.8 mL, 2.75 m) were reacted in 15 mL CH_2Cl_2 for 5 min and added to the peptide resin. The reaction mixture was stirred over night and washed with DMF 2 times and CH_2Cl_2 3 times before cleavage was effected with TFA, 17 mL, 400 uL iPrSiH and 800 uL propanethiol for 6 hr. The product was precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuuo. The crude peptide was purified following the procedure in Example 7 to yield 28 mg (6%) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) $C_{125}H_{191}N_{35}O_{25}$ 2582.48 , found 2582.47.

Example 25

Preparation of H-Ile-Lys(Palmitoyl-gamma-Glu-gamma-Glu-)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2

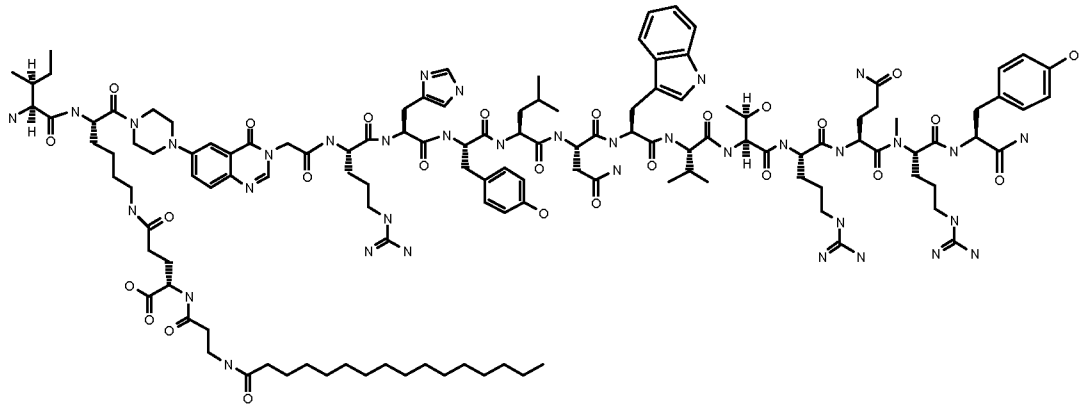


Boc-Ile-Lys(epsilon TFA salt)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Knorr resin 1.0 g was washed with 5% DIEA in DMF and coupled with Fmoc- Glu-alpha-OBu^t (426.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) overnight. After Fmoc removal and washing with DMF, Fmoc-Glu-alphaOBu^t (426.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) were added and the reaction was allowed to proceed overnight. After Fmoc removal and washing with DMF, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 m) and palmitoyl chloride (2.8 mL, 2.75 m) were reacted in 15 mL CH_2Cl_2 for 5 min and added to the peptide resin. The reaction

mixture was stirred over night and washed with DMF 2 times and CH_2Cl_2 times before cleavage with TFA 17 mL, 400 uL iPrSiH and 800 uL propanethiol for 6 hr. The product was precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuuo. The crude peptide was purified following the procedure in Example 7 to yield 40 mg (8%) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) $C_{130}H_{198}N_{36}O_{28}$ 2711.52, found 2711.50.

Example 26

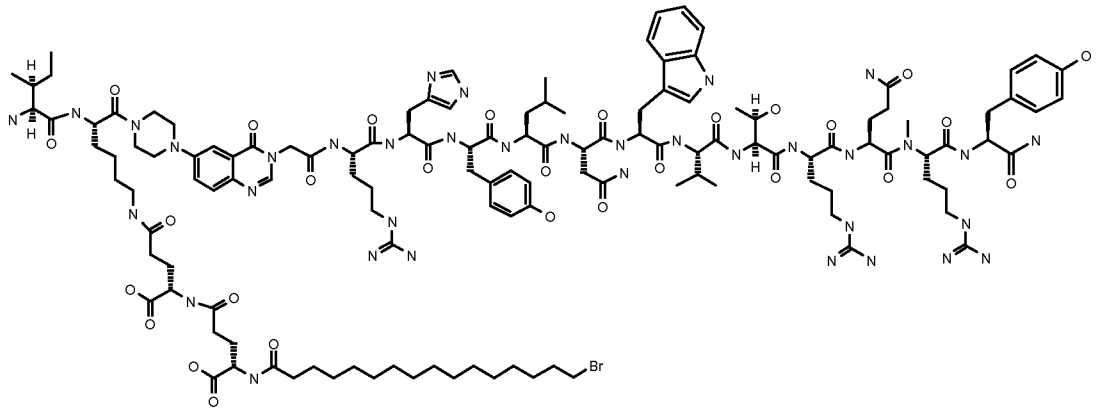
Preparation of H-Ile-Lys(Palmitoyl-beta-Ala-gamma-Glu-)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2



Boc-Ile-Lys(epsilon TFA salt)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Knorr resin 1.0 g was washed with 5% DIEA in DMF and coupled with Fmoc-–Glu-alphaOBu^t (426.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) overnight. After Fmoc removal and washing with DMF, Fmoc-beta-Ala (312.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) were added and the reaction was allowed to proceed overnight. After Fmoc removal and washing with DMF, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 m) and palmitoyl chloride (2.8 mL, 2.75 m) were reacted in 15 mL CH_2Cl_2 for 5 min and added to the peptide resin. The reaction mixture was stirred over night and washed with DMF 2 times and CH_2Cl_2 3 times before cleavage was effected with TFA, 17 mL, 400 uL iPrSiH and 800 uL propanethiol for 6 hr. The product was precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuuo. The crude peptide was purified following the procedure in Example 7 to yield 34 mg (7%) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) $C_{128}H_{196}N_{36}O_{26}$ 2653.51, found 2653.50.

Example 27

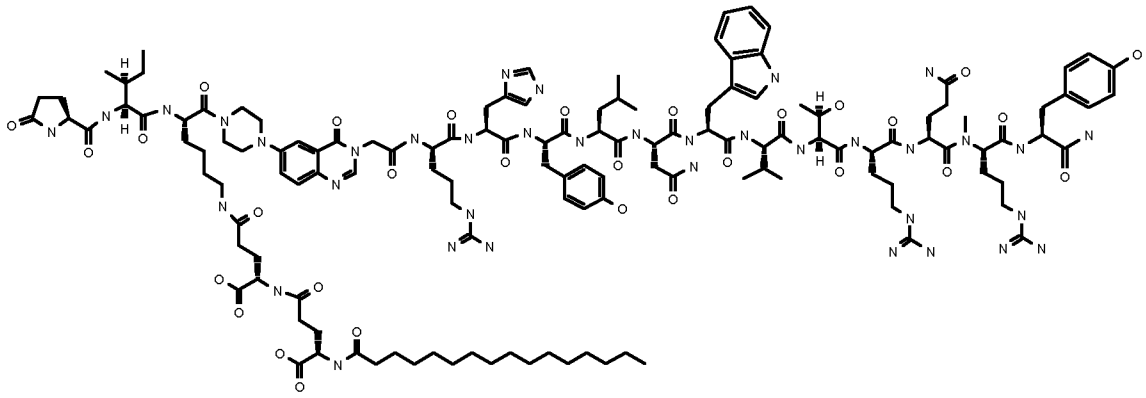
Preparation of H-Ile-Lys(16-Bromohexadecanoyl-gamma-Glu-gamma-Glu-)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2



Boc-Ile-Lys(epsilon TFA salt)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Knorr resin 1.0 g was washed with 5% DIEA in DMF and coupled with Fmoc-Glu-alphaOBut (426.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) overnight. After Fmoc removal and washing with DMF, Fmoc-Glu-alphaOBut (426.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) were added and the reaction was allowed to proceed overnight. After Fmoc removal and washing with DMF, N-hydroxybenzotriazole (150 mg, 1.15 mmol), N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) and 16-bromohexadecanoic acid (336 mg, 1.0 mmol)l were coupled overnight. After washing with DMF 2 times and CH_2Cl_2 3 times, cleavage was effected with TFA, 17 mL, 400 uL iPrSiH and 800 uL propanethiol for 6 hr. The product was precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuuo. The crude peptide was purified following the procedure in Example 7 to yield 61 mg (11%) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) $C_{130}H_{197}BrN_{36}O_{28}$ 2789.43, found 2789.41.

Example 28

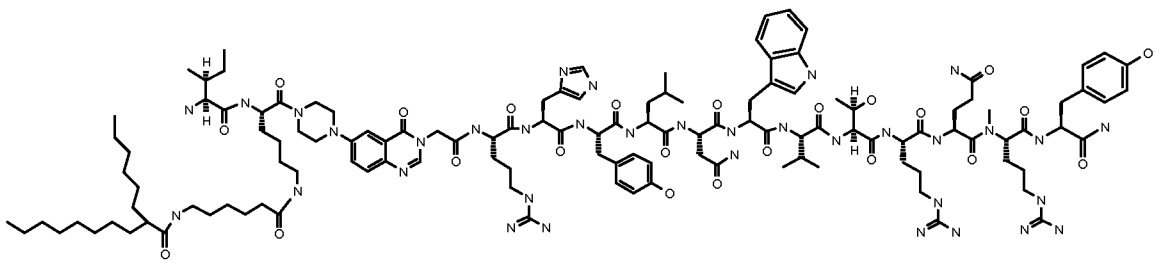
Preparation of Pyro-Glu-Ile-Lys(Palmitoyl-gamma-Glu- gamma-Glu-)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2



Fmoc- Linker-BHA resin (450 mg, 0.25 mmol) from Example 1 was subjected to solid phase synthesis with amine terminal Boc-Ile and Lys(alloc) in position for appropriate side chain modification. After palladium catalyzed deprotection as described in Example 8 and neutralization Fmoc-Glu-alphaOBut (426.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) were coupled overnight. After Fmoc removal and washing with DMF, Fmoc-Glu-alphaOBut (426.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) were coupled overnight. After Fmoc removal and washing with DMF, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 m) and palmitoyl chloride (2.8 mL, 2.75 m) were reacted in 15 mL CH_2Cl_2 for 5 min and added to the peptide resin. The reaction mixture was stirred over night and washed with DMF 2 times and CH_2Cl_2 3 times before cleavage was effected with TFA, 17 mL, 400 uL iPrSiH and 800 uL propanethiol for 6 hr. The product was precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuuo. The crude peptide was purified following the procedure in Example 7 to yield 58 mg (8.3 %) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) $C_{135}H_{203}N_{37}O_{30}$ 2822.55, found 2822.55.

Example 29

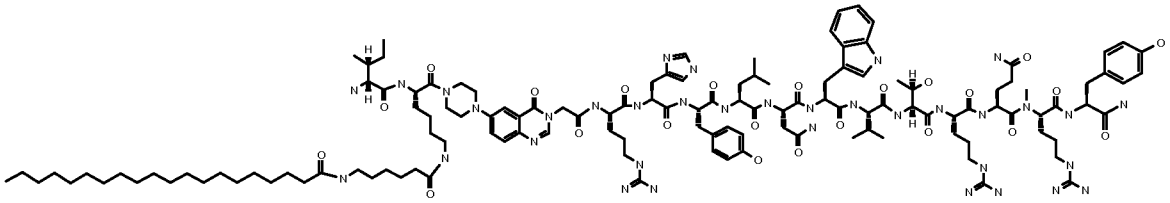
Preparation of H-Ile-Lys(2-Hexadecanoyl-6Ahx)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2



Boc-Ile-Lys(epsilon TFA salt)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Knorr resin 1.0 g was washed with 5% DIEA in DMF and coupled with Fmoc-6-aminohexanoic acid (355.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) overnight. After Fmoc removal and washing with DMF, N-hydroxybenzotriazole (150 mg, 1.15 mmol), N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) and 2-hexyldecanoic acid (286 mg, 1.0 mmole) were coupled overnight. After washing with DMF 2 times and CH_2Cl_2 3 times, cleavage was effected with TFA 17 mL, 400 uL iPrSiH and 800 uL propanethiol for 6 hr. The product was precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuuo. The crude peptide was purified following the procedure in Example 7 to yield 94 mg (18 %) of white amorphous powder. (ES)+-LCMS m/e calculated ("calcd) $C_{126}H_{195}N_{35}O_{23}$ 2566.52, found 2566.51.

Example 30

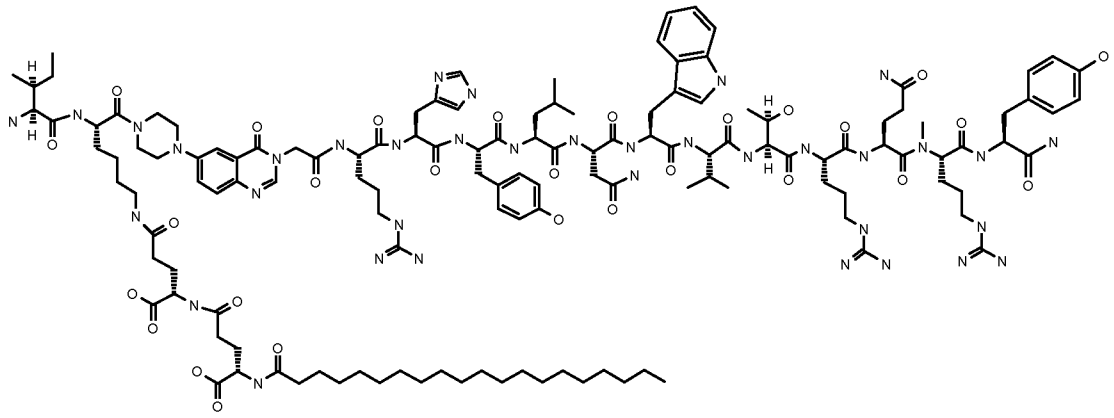
Preparation of H-Ile-Lys(Eicosanoyl-6Ahx)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2



Boc-Ile-Lys(epsilon TFA salt)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Knorr resin 1.0 g was washed with 5% DIEA in DMF and coupled with Fmoc-6-aminohexanoic acid (355.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) overnight. After Fmoc removal and washing with DMF, eicosanoic acid (315 mg, 1 mmol); N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) were coupled and stirred over night. After washing with DMF 2 times and CH_2Cl_2 3 times cleavage with TFA 17 mL, 400 uL iPrSiH and 800 uL propanethiol for 6 hr. The product was precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuuo. The crude peptide was purified following the procedure in Example 7 to yield 75 mg (14 %) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) $C_{130}H_{203}N_{35}O_{23}$ 2622.58 , found 2622.57.

Example 31

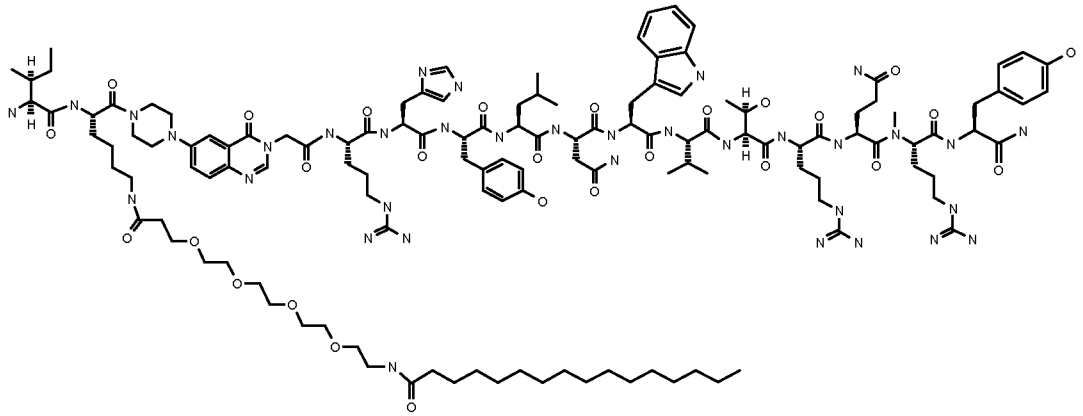
Preparation of H-Ile-Lys(Eicosanoyl-gamma-Glu-gamma-Glu-)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2



Boc-Ile-Lys(epsilonTFA salt)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Knorr resin 1.0 g was washed with 5% DIEA in DMF and coupled with Fmoc-Glu-alphaOBut (426.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) overnight. After Fmoc removal and washing with DMF, Fmoc-Glu-alpha OBu^t (426.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) were added and the reaction allowed to proceed overnight. After Fmoc removal and washing with DMF, eicosanoic acid (315 mg, 1 mol); N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) were added to the resin bound peptide and the mixture was stirred over night. After washing with DMF 2 times and CH_2Cl_2 3 times cleavage was effected with TFA 17 mL, 400 uL iPrSiH and 800 uL propanethiol for 6 hr. The product was precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuuo. The crude peptide was purified following the procedure in Example 7 to yield 66 mg (12%) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) $C_{134}H_{206}N_{36}O_{28}$ 2767.58, found 2767.58.

Example 32

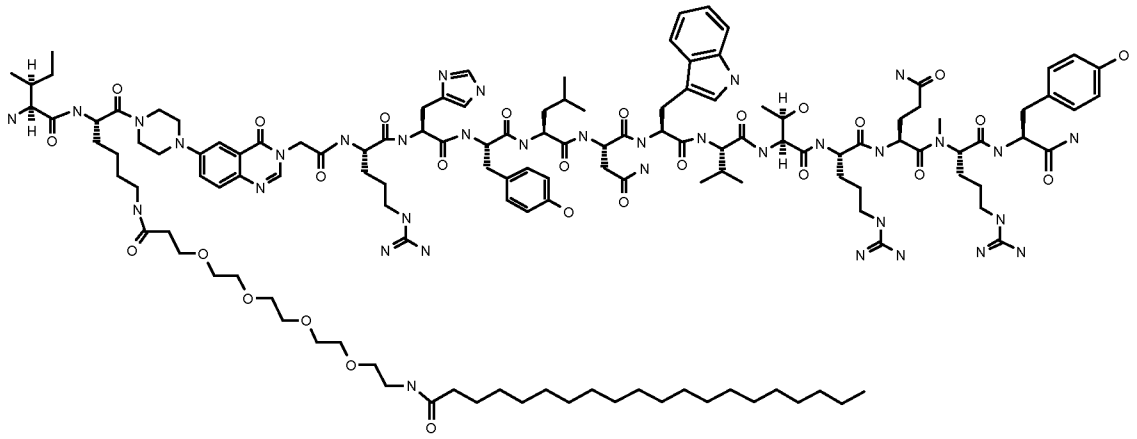
Preparation of H-Ile-Lys(Palmitoyl-15-ATOPA)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2



Fmoc- Linker-BHA resin (450 mg, 0.25 mmol) from Example 1 was subjected to solid phase synthesis with amine terminal Boc-Ile and Lys(alloc) in position for appropriate side chain modification. After palladium catalyzed deprotection as described in example 8 and neutralization, coupling with Fmoc-15-amino-4,7,10,13-tetraoxapentadecanoic acid (488 mg; 1.0 mm;), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) was carried out overnight. After Fmoc removal and washing with DMF, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 m) and palmitoyl chloride (2.8 mL, 2.75 m) were reacted in 15 mL CH_2Cl_2 for 5 min and added to the peptide resin. The reaction mixture was stirred over night and washed with DMF 2 times and CH_2Cl_2 3 times before cleavage was effected with TFA, 17 mL, 400 uL iPrSiH and 800 uL propanethiol for 6 hr. The product was precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuuo. The crude peptide was purified following the procedure in Example 7 to yield 95 mg (14%) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) $C_{131}H_{205}N_{35}O_{27}$ 2700.57, found 2700.56.

Example 33

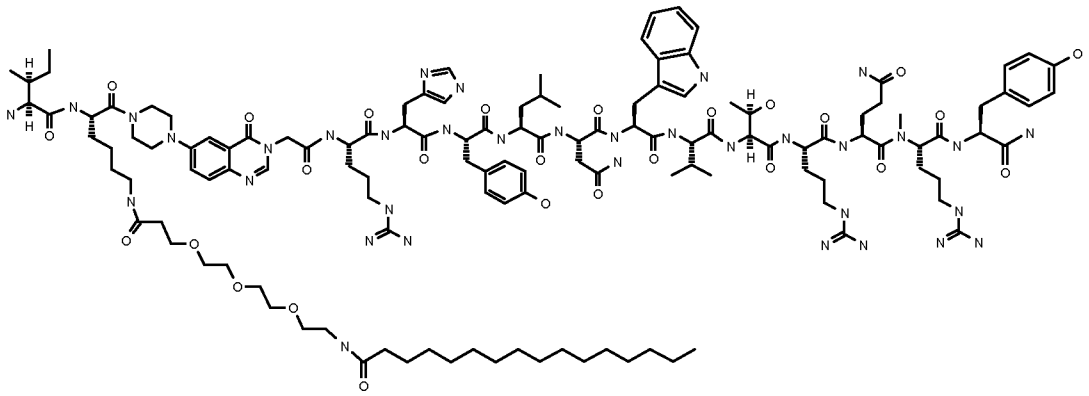
Preparation of H-Ile-Lys(Eicosanoyl-15-ATOPA)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2



Fmoc- Linker-BHA resin (450 mg, 0.25 mmol) from Example 1 was subjected to solid phase synthesis with amine terminal Boc-Ile and Lys(alloc) in position for appropriate side chain modification. After palladium catalyzed deprotection as described in Example 8 and neutralization, coupling with Fmoc-15-amino-4,7,10,13-tetraoxapentadecanoic acid (488 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) was carried out overnight. After Fmoc removal and washing with DMF, eicosanoic acid (315 mg, 1 mmol); N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) were coupled and stirred over night. After washing with DMF 2 times and CH_2Cl_2 3 times cleavage was effected with TFA 17 mL, 400 uL iPrSiH and 800 uL propanethiol for 6 hr. The product was precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuuo. The crude peptide was purified following the procedure in Example 7 to yield 140 mg (20%) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) $C_{135}H_{213}N_{35}O_{27}$ 2756.64, found 2756.62.

Example 34

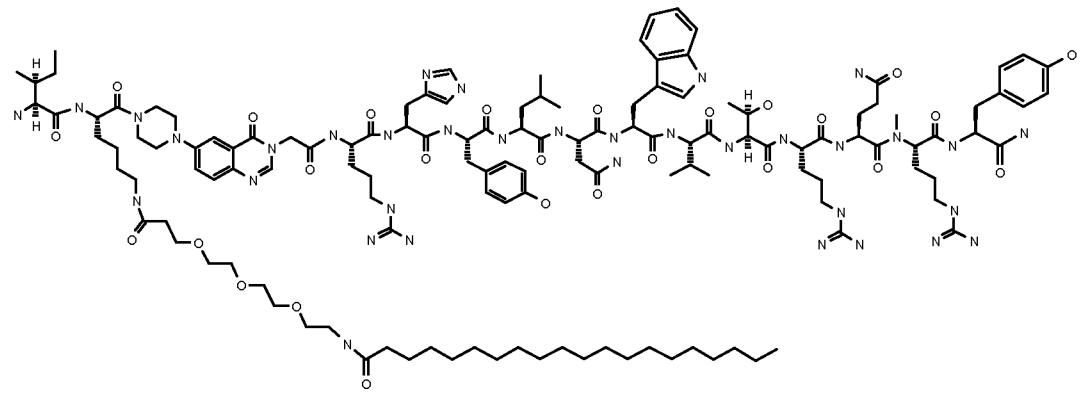
Preparation of H-Ile-Lys(Palmitoyl-12-ATODA)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2



Fmoc- Linker-BHA resin (450 mg, 0.25 mmol) from Example 1 was subjected to solid phase synthesis with amine terminal Boc-Ile and Lys(alloc) in position for appropriate side chain modification. After palladium catalyzed deprotection as described in example 8 and neutralization, coupling with Fmoc-12-amino-4,7,10 -trioxadodecanoic acid (488.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) was carried out overnight. After Fmoc removal and washing with DMF, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 m) and palmitoyl chloride (2.8 mL, 2.75 m) were reacted in 15 mL CH_2Cl_2 for 5 min and added to the peptide resin. The reaction mixture was stirred over night and washed with DMF 2 times and CH_2Cl_2 3 times before cleavage was effected with TFA, 17 mL, 400 uL iPrSiH and 800 uL propanethiol for 6 hr. The product was precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuuo. The crude peptide was purified following the procedure in Example 7 to yield 134 mg (20%) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) $C_{129}H_{201}N_{35}O_{26}$ 2656.55, found 2656.54.

Example 35

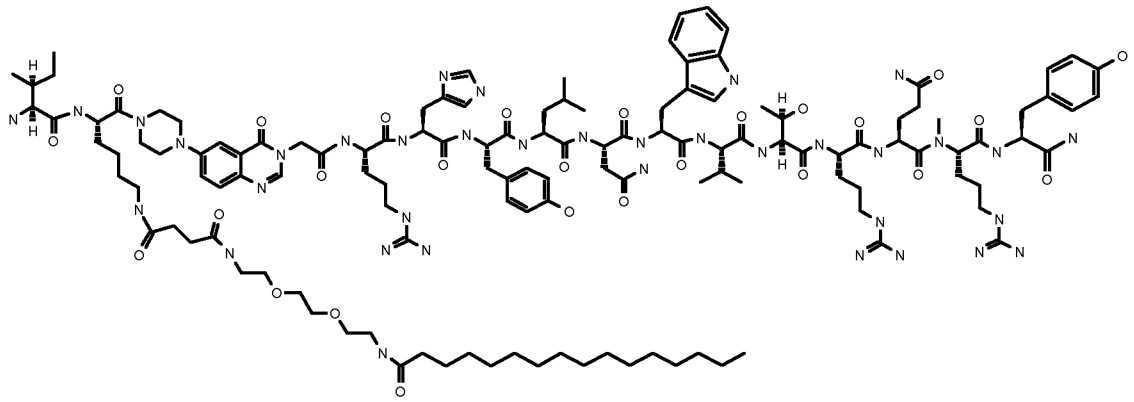
Preparation of H-Ile-Lys(Eicosanoyl-12-ATODA)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2



Fmoc- Linker-BHA resin (450 mg, 0.25 mmol) from Example 1 was subjected to solid phase synthesis with amine terminal Boc-Ile and Lys(alloc) in position for appropriate side chain modification. After palladium catalyzed deprotection as described in Example 8 and neutralization, coupling with Fmoc-12-Amino-4,7,10 -trioxadodecanoic acid (488.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) was carried out overnight. After Fmoc removal and washing with DMF, eicosanoic acid (315 mg, 1 mmol); N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) were coupled and stirred over night. After washing with DMF 2 times and CH_2Cl_2 3 times, cleavage was effected with TFA 17 mL, 400 uL iPrSiH and 800 uL propanethiol for 6 hr. The product was precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuuo. The crude peptide was purified following the procedure in Example 7 to yield 128 mg (19 %) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) $C_{133}H_{209}N_{35}O_{26}$ 2712.61, found 2712.59 .

Example 36

Preparation of H-Ile-Lys(Palmitoyl-8-ADOSA)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2

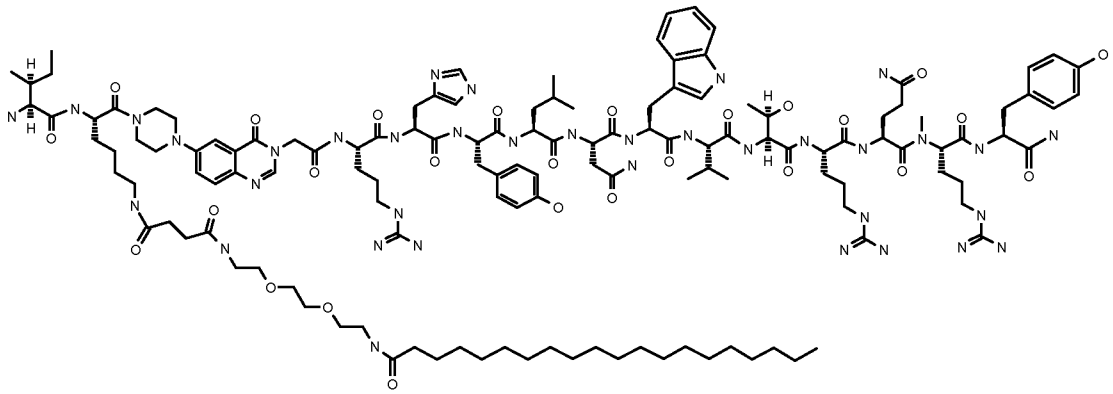


Fmoc- Linker-BHA resin (450 mg, 0.25 mmol) from Example 1 was subjected to solid phase synthesis with amine terminal Boc-Ile and Lys(alloc) in position for appropriate side chain modification. After palladium catalyzed deprotection and neutralization, coupling with Fmoc-(8-Amino-3,6-dioxa-octyl)succinic acid (488.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) was carried out overnight. After Fmoc removal and washing with DMF, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 m) and palmitoyl chloride (2.8 mL, 2.75 m) were reacted in 15 mL CH_2Cl_2 for 5 min and added to the peptide resin. The reaction mixture was stirred over night and washed with DMF 2 times

and CH_2Cl_2 3 times before cleavage was effected with TFA, 17 mL, 400 uL iPrSiH and 800 uL propanethiol for 6 hr. The product was precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuuo. The crude peptide was purified following the procedure in Example 7 to yield 114 mg (17%) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) $C_{130}H_{202}N_{36}O_{26}$ 2683.56 found 2683.55.

Example 37

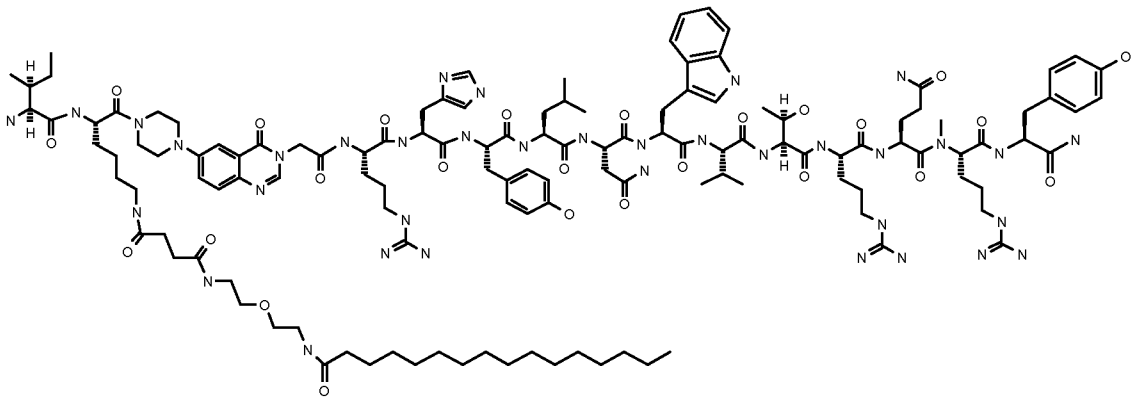
Preparation of H-Ile-Lys(Eicosanoyl-8-ADOSA)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2



Fmoc- Linker-BHA resin (450 mg, 0.25 mmol) from Example 1 was subjected to solid phase synthesis with amine terminal Boc-Ile and Lys(alloc) in position for appropriate side chain modification. After palladium deprotection and neutralization, coupling with Fmoc-N-(8-amino-3,6-dioxa-octyl)succinamic acid (488.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) was carried out overnight. After Fmoc removal and washing with DMF, eicosanoic acid (315 mg, 1 mmol); N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) were coupled and stirred over night. After washing with DMF 2 times and CH_2Cl_2 3 times, cleavage was effected with TFA 17 mL, 400 uL iPrSiH and 800 uL propanethiol for 6 hr. The product was precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuuo. The crude peptide was purified following the procedure in Example 7 to yield 110 mg (16%) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) $C_{134}H_{210}N_{36}O_{26}$ 2739.62, found 2739.60.

Example 38

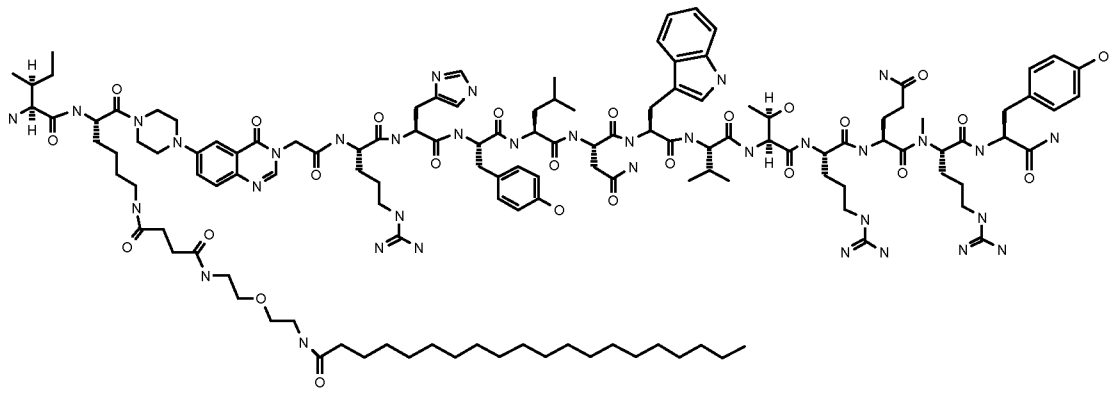
Preparation of H-Ile-Lys(Palmitoyl-5-AOPSA)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr- NH_2



Fmoc- Linker-BHA resin (450 mg, 0.25 mmol) from Example 1 was subjected to solid phase synthesis with amine terminal Boc-Ile and Lys(alloc) in position for appropriate side chain modification. After palladium catalyzed deprotection as described in example 8 and neutralization, coupling was effected with N-Fmoc-(5-amino-3-oxa-pentyl)succinamic acid (427.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) was carried out overnight. After Fmoc removal and washing with DMF, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 m) and palmitoyl chloride (2.8 mL, 2.75 m) were reacted in 15 mL CH_2Cl_2 for 5 min and added to the peptide resin. The reaction mixture was stirred over night and washed with DMF 2 times and CH_2Cl_2 3 times before cleavage was effected with TFA, 17 mL, 400 uL iPrSiH and 800 uL propanethiol for 6 hr. The product was precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuuo. The crude peptide was purified following the procedure in Example 7 to yield 158 mg (24%) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) $C_{128}H_{198}N_{36}O_{25}$ 2639.53, found 2639.50.

Example 39

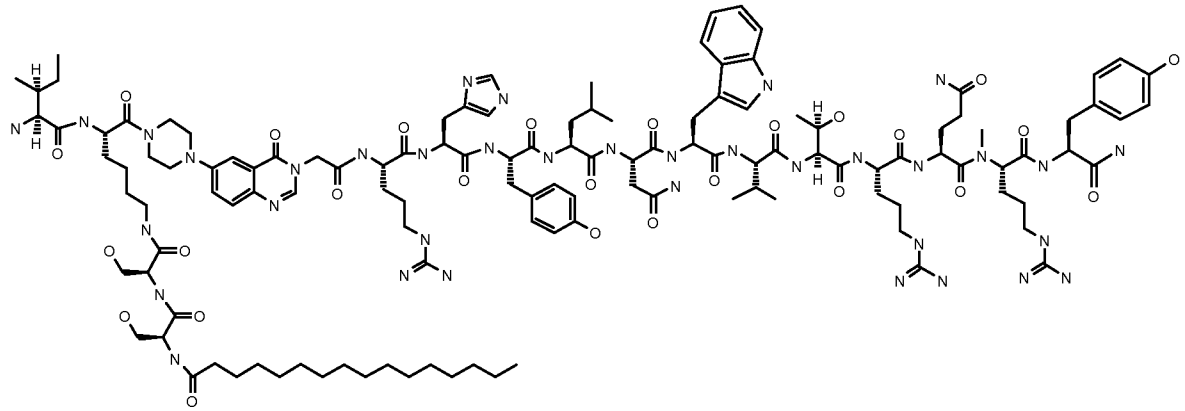
Preparation of H-Ile-Lys(Eicosanoyl-5-AOPSA)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2



Fmoc- Linker-BHA resin (450 mg, 0.25 mmol) from Example 1 was subjected to solid phase synthesis with amine terminal Boc-Ile and Lys(alloc) in position for appropriate side chain modification. After palladium catalyzed deprotection as described in example 8 and neutralization, coupling with Fmoc-(5-amino-3-oxa-pentyl)succinamic acid (427.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) was carried out overnight. After Fmoc removal and washing with DMF, eicosanoic acid (315 mg, 1 mol); N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) were added and the mixture was stirred over night. After washing with DMF 2 times and CH_2Cl_2 3 times, cleavage was effected with TFA 17 mL, 400 uL iPrSiH and 800 uL propanethiol for 6 hr, the product was precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuuo. The crude peptide was purified following the procedure in Example 7 to yield 128 mg (19%) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) $C_{132}H_{206}N_{36}O_{25}$ 2695.60, found 2695.59.

Example 40

Preparation of H-Ile-Lys(Palmitoyl-Ser-Ser)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr- NH_2

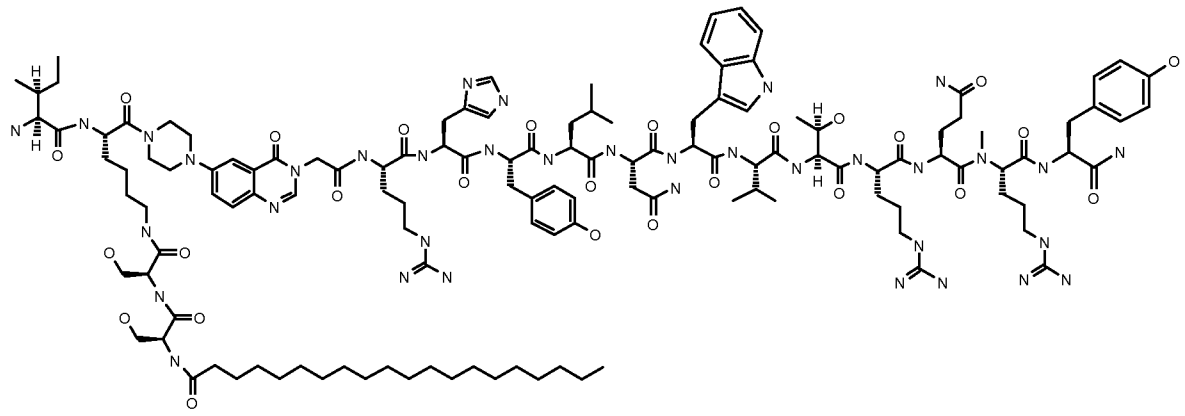


Fmoc- Linker-BHA resin (450 mg, 0.25 mmol) from Example 1 was subjected to solid phase synthesis with amine terminal Boc-Ile and Lys(alloc) in position for appropriate side chain modification. After palladium catalyzed deprotection and neutralization, coupling with Fmoc-Ser(Bu^t) (384.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) was carried out overnight. After Fmoc removal and washing with DMF the resin bound peptide was again coupled with Fmoc-Ser(Bu^t) (384.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) overnight. After Fmoc removal and

washing with DMF, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 m) and palmitoyl chloride (2.8 mL, 2.75 m) were reacted in 15 mL CH_2Cl_2 for 5 min and added to the peptide resin. The reaction mixture was stirred over night and washed with DMF 2 times and CH_2Cl_2 3 times before cleavage was effected with TFA, 17 mL, 400 uL iPrSiH and 800 uL propanethiol for 6 hr. The product was precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuuo. The crude peptide was purified following the procedure in Example 7 to yield 98 mg (15%) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) $C_{126}H_{194}N_{36}O_{26}$ 2627.50, found 2627.49.

Example 41

Preparation of H-Ile-Lys(Eicosanoyl-Ser-Ser)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2

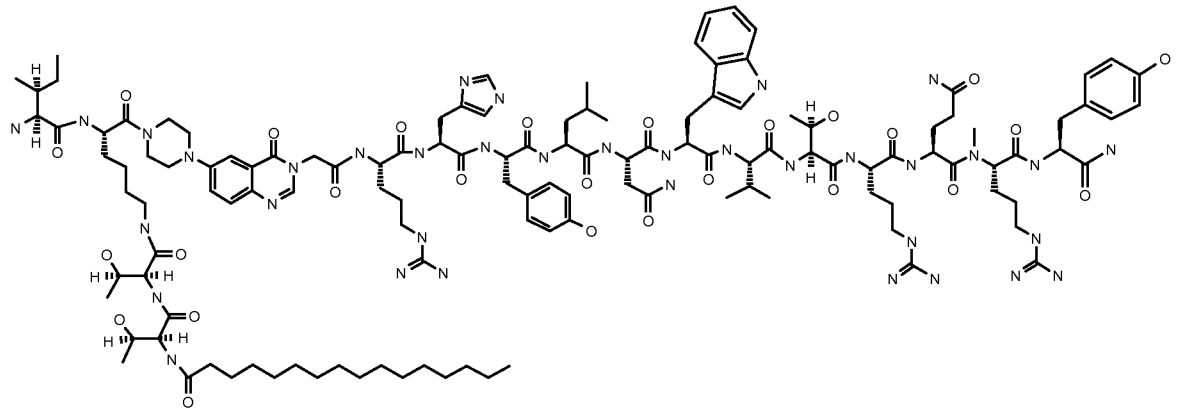


Fmoc- Linker-BHA resin (450 mg, 0.25 mmol) from Example 1 was subjected to solid phase synthesis with amine terminal Boc-Ile and Lys(alloc) in position for appropriate side chain modification. After palladium catalyzed deprotection as described in Example 8 and neutralization, coupling with Fmoc-Ser(Bu^t) (384.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) was carried out overnight. After Fmoc removal and washing with DMF the resin was again coupled with Fmoc-Ser(Bu^t) (384.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) overnight. Eicosanoic acid (315 mg, 1 mol); N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) were coupled to the resin bound peptide overnight. After washing with DMF 2 times and CH_2Cl_2 3 times, cleavage was effected with TFA 17 mL, 400 uL iPrSiH and 800 uL propanethiol for 6 hr. The product was precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuuo. The crude peptide was purified following the procedure in Example 7 to yield 107 mg

(16%) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) $C_{130}H_{202}N_{36}O_{26}$ 2683.56, found 2683.55.

Example 42

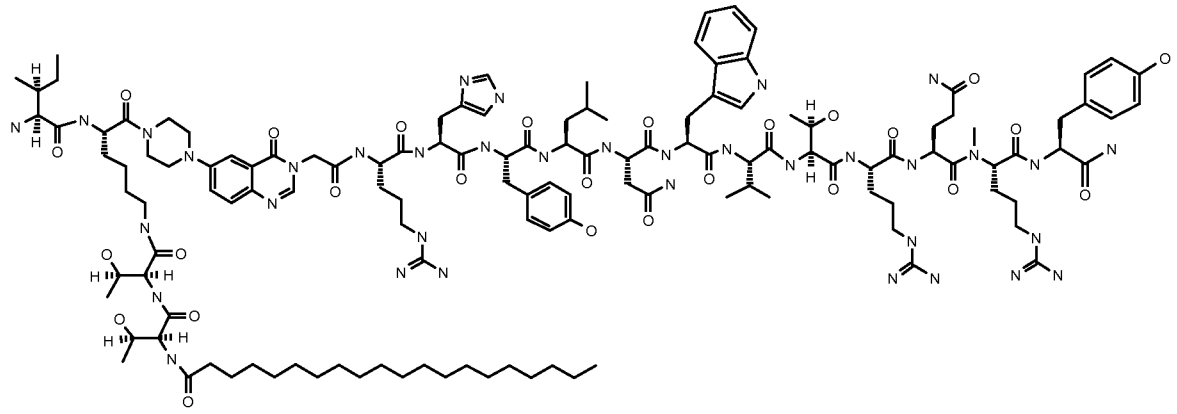
Preparation of H-Ile-Lys(Palmitoyl-Thr-Thr)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr- NH_2



Fmoc- Linker-BHA resin (450 mg, 0.25 mmol) from Example 1 was subjected to solid phase synthesis with amine terminal Boc-Ile and Lys(alloc) in position for appropriate side chain modification. After palladium catalyzed deprotection as described in Example 8 and neutralization, coupling with Fmoc-Thr(Bu^t) (398.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) was carried out overnight. After Fmoc removal and washing with DMF the resin was again coupled with Fmoc-Thr(Bu^t) (398.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) overnight. After Fmoc removal and washing with DMF, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 m) and palmitoyl chloride (2.8 mL, 2.75 m) were reacted in 15 mL CH_2Cl_2 for 5 min and added to the peptide resin. The reaction mixture was stirred over night and washed with DMF 2 times and CH_2Cl_2 3 times before cleavage was effected with TFA, 17 mL, 400 uL iPrSiH and 800 uL propanethiol for 6 hr. The product was precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuuo. The crude peptide was purified following the procedure in Example 7 to yield 73 mg (11%) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) $C_{128}H_{198}N_{36}O_{26}$ 2655.53, found 2655.51.

Example 43

Preparation of H-Ile-Lys(Eicosanoyl-Thr-Thr)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr- NH_2



Fmoc- Linker-BHA resin (450 mg, 0.25 mmol) from Example 1 was subjected to solid phase synthesis with amine terminal Boc-Ile and Lys(alloc) in position for appropriate side chain modification. After palladium catalyzed deprotection as described in Example 8 and neutralization, coupling with Fmoc-Thr(Bu^t) (398.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) was carried out overnight. After Fmoc removal and washing with DMF the resin was again coupled with Fmoc-Thr(Bu^t) (398.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) was carried out overnight. Eicosanoic acid (315 mg, 1 mmol); N-hydroxybenzotriazole (150 mg, 1.11 mmol), and N,N'-diisopropylcarbodiimide (1.50 mL, 2.0 mmol) were added and the mixture was stirred over night. After washing with DMF 2 times and CH_2Cl_2 3 times cleavage was effected with TFA 17 mL, 400 uL iPrSiH and 800 uL propanethiol for 6 hr. The product was precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuuo. The crude peptide was purified following the procedure in Example 7 to yield 69 mg (10%) of white amorphous powder. (ES)+-LCMS m/e calculated (calcd) $C_{132}H_{206}N_{36}O_{26}$ 2711.59, found 2711.57

Example 44

cAMP agonist assay

In this example, the following materials were used: 384-well plate; Tropix cAMP-Screen Kit; cAMP ELISA System (Applied Biosystems, cat. #T1505; CS 20000); Forskolin (Calbiochem cat. # 344270); cells: HEK293/hNPY2R; growth medium: Dulbecco's modified eagle medium (D-MEM, Gibco); 10% Fetal bovine serum (FBS, Gibco), heat-

inactivated; 1% Penicillin/Streptomycin (Pen 10000 unit/mL: Strep 10000 mg/mL, Gibco); 500 mg/mL G418 (Geneticin, Gibco cat. # 11811-031); and plating medium: DMEM/F12 w/o phenol red (Gibco); 10% FBS (Gibco, cat. # 10082-147), heat-inactivated; 1% Penicillin/Streptomycin (Gibco, cat. # 15140-122); 500 mg/mL G418 (Geneticin, Gibco, cat. # 11811-031).

On the first day, medium was discarded, and the monolayer cells were washed with 10 mL PBS per flask (T225). After decanting with PBS, 5 mL VERSENE (Gibco, cat#1504006) was used to dislodge the cells (5min @37C). The flask was gently tapped and the cell suspension was pooled. Each flask was rinsed with 10 mL plating medium and centrifuged at 1000rpm for 5 min. The suspension was pooled and counted. The suspension was resuspended in plating medium at a density of 2.0 X 10^5 cells/mL for HEK293/hNPY2R. 50 microliters of cells (HEK293/hNPY2R – 10,000cells/well) were transferred into the 384-well plate using Multi-drop dispenser. The plates were incubated at 37°C overnight. On the second day, the cells were checked for 75-85% confluence. The media and reagents were allowed to come to room temperature. Before the dilutions were prepared, the stock solution of stimulating compound in dimethyl sulphoxide (DMSO, Sigma, cat#D2650) was allowed to warm up to 32C for 5-10 min. The dilutions were prepared in DMEM/F12 with 0.5mM 3-Isobutyl-1-methylxanthine (IBMX, Calbiochem, cat#410957) and 0.5mg/mL BSA. The final DMSO concentration in the stimulation medium was 1.1% with Forskolin concentration of 5μM. The cell medium was tapped off with a gentle inversion of the cell plate on a paper towel. 50μL of stimulation medium was placed per well (each concentration done in four replicates). The plates were incubated at room temperature for 30 min, and the cells were checked under a microscope for toxicity. After 30 minutes of treatment, the stimulation media was discarded and 50mL/well of Assay Lysis Buffer (provided in the Tropix kit) was added. The plates were incubated for 45 min@ 37°C. 20μL of the lysate was transferred from stimulation plates into the pre-coated antibody plates (384-well) from the Tropix kit. 10 μL of AP conjugate and 20μL of anti-cAMP antibody was added. The plates were incubated at room temperature while shaking for 1 hour. The plates were then washed 5 times with Wash Buffer, 70 μL per well for each wash. The plates were tapped to dry. 30 μL /well of CSPD/Saphire-II RTU substrate/enhancer solution was added and incubated for 45 min @ RT (shake). Signal for 1 sec/well in a Luminometer. (VICTOR-V) was measured.

Example 45

CaFlux Assay

Hek-293 cells were stably transfected with the G protein chimera Gaqi9 and the hygromycin-B resistance gene were further transfected with the human NPY2 receptor and G418 antibiotic selection. Following selection in both hygromycin-B and G418, individual clones were assayed for their response to PYY. The transfected cells were cultured in DMEM medium supplemented with 10% fetal bovine serum, 50µg/mL hygromycin-B 2mM glutamine, 100U/mL penicillin, 100µg/mL streptomycin and 250µg/mL G418. Cells are harvested with trypsin-EDTA and counted using ViaCount reagent. The cell suspension volume is adjusted to $4.8x10^5$ cells /mL with complete growth media. Aliquots of 25µL are dispensed into 384 well Poly-D Lysine coated black/clear microplates (Falcon) and the microplates were placed in a 37°C CO_2 incubator overnight. Loading Buffer (Calcium-3 Assay Kit, Molecular Devices) was prepared by dissolving the contents of one vial (Express Kit) into 1000 mL Hank's Balanced Salt Solution containing 20mM HEPES and 5mM probenecid. Aliquots of 25µL of diluted dye were dispensed into the cell plates and the plates are then incubated for 1 hour at 37°C. During the incubation, test compounds were prepared at 3.5X the desired concentration in HBSS(20mM HEPES)/0.05%BSA/1%DMSO and transferred to a 384 well plate for use on FLIPR. After incubation, both the cell and compound plates were brought to the FLIPR and 20µL of the diluted compounds were transferred to the cell plates by the FLIPR. During the assay, fluorescence readings were taken simultaneously from all 384 wells of the cell plate every 1.5 seconds. Five readings were taken to establish a stable baseline, and then 20µL of sample was rapidly (30µL/sec) and simultaneously added to each well of the cell plate. The fluorescence was continuously monitored before, during and after sample addition for a total elapsed time of 100 seconds. Responses (increase in peak fluorescence) in each well following addition were determined. The initial fluorescence reading from each well, prior to ligand stimulation, was used as a zero baseline value for the data from that well. The responses are expressed as % of maximal response of the positive control.

The compounds of the present invention exhibited selective Neuropeptide -2 receptor activity in vitro, as demonstrated in the cAMP assay and CaFlux Assay (FLIPR). Summary of the in vitro results, IC50 and EC50 for representative compounds of the invention, are illustrated in Table 1 below:

Table 1

		Y2R	Y2R	Y1R	Y4R	Y5R
Example	Sequence	EC50 (nM)	EC50 (nM)	EC50 (nM)	EC50 (nM)	EC_{50} (nM)
		FLIRR	cAMP	FLIPR	FLIPR	FLIPR
1	Fmoc-linker-BHA-Resin					
2	ABI-protocol					

3	IKPEAPGEDASPEELNRYYASLRHYLNLVTRQR Y (PYY 3-36)	0.013	0.038	356	1187	121
4	Ac-IK-Pqa-RHYLNWVTRQ(N-methyl)RY	0.21	0.34	>5000	>5000	>5000
5	Ac-IK(Butyryl)-Pqa-RHYLNWVTRQ(N-methyl)RY	0.18	0.39	>5000	31633	24896
6	Ac-IK(Capryloyl)-Pqa-RHYLNWVTRQ(N-methyl)RY	1.45	1.7	5200	2467	99894
7	Ac-IK(Lauroyl)-Pqa-RHYLNWVTRQ(N-methyl)RY	4.7	5.4	6433	14467	12845
8	Protected Peptide Resin					
9	IK(Lauroyl-6Ahx)-Pqa-RHYLNWVTRQ(N-methyl)RY	0.031	3.5	>5000	2449	3793
10	IK(Lauroyl-beta-Ala)-Pqa-RHYLNWVTRQ(N-methyl)RY	0.016	5.2	>5000	3507	4743
11	IK(Lauroyl-Glu)-Pqa-RHYLNWVTRQ(N-methyl)RY	0.026	3.6	>5000	2427	3554
12	IK(Myrisoyl-6Ahx)-Pqa-RHYLNWVTRQ(N-methyl)RY	0.14	0.16	>5000	>5000	1422
13	Ac-IK(Palmitoyl)-Pqa-RHYLNWVTRQ(N-methyl)RY	1.31	1.2	29233	32167	9379
14	IK(Palmitoyl)-Pqa-RHYLNWVTRQ(N-methyl)RY	0.73	1	>5000	>5000	12666
15	Palmitoyl-IK-Pqa-RHYLNWVTRQ(N-methyl)RY	1.03	0.97	>5000	1355	>5000
16	Palmitoyl- 6Ahx-IK-Pqa-RHYLNWVTRQ(N-methyl)RY	0.18	0.23	>5000	13700	544
17	Palmitoyl- 6Ahx-IK-Pqa-RHYLNWVTRQRY	0.09	0.25	>5000	14500	27
18	IK(Palmitoyl-6Ahx)-Pqa-RHYLNWVTRQ(N-methyl)RY	0.012	0.18	>5000	>5000	1185
19	IK(Palmitoyl-6Ahx)-Pqa-RHYLNWVTRQRY	0.004	0.15	>5000	>5000	45
20	IK(Palmitoyl-beta Ala)-Pqa-RHYLNWVTRQ(N-methyl)RY	0.015	0.26	>5000	>5000	1878
21	IK(Palmitoyl-Glu)-Pqa-RHYLNWVTRQ(N-methyl)RY	0.43	1	>5000	>5000	4185
22	IK(Palmitoyl-beta Ala-Glu)-Pqa-RHYLNWVTRQ(N-methyl)RY	0.048	0.15	>5000	>5000	227 (70%)
23	IK(Palmitoyl-Glu-Glu)-Pqa-RHYLNWVTRQ(N-methyl)RY	0.033	0.29	>5000	>5000	459 (70%)
24	IK(Palmitoyl-gamaGlu)-Pqa-RHYLNWVTRQ(N-methyl)RY	0.039	0.21	>5000	>5000	168 (70%)
25	IK(Palmitoyl-gamaGlu-gamaGlu)-Pqa-RHYLNWVTRQ(N-methyl)RY	0.08	0.22	>5000	>5000	443 (70%)
26	IK(Palmitoyl-beta Ala-gamaGlu)-Pqa-RHYLNWVTRQ(N-methyl)RY	0.045	0.15	>5000	>5000	129 (70%)
27	IK(16-Bromohexadecanoyl-gamaGlu-gamaGlu)-Pqa-RHYLNWVTRQ(N-methyl)RY	0,23	0.4	>5000	>5000	2536
28	PyroGlu-IK(Palmitoyl-gamaGlu-gamaGlu)-Pqa-RHYLNWVTRQ(N-methyl)RY	0.176	0.21	>5000	>5000	2062
29	IK(2-hexyldecanoyl-6Ahx)-Pqa-RHYLNWVTRQ(N-methyl)RY	0.361	2.8	>5000	>5000	>5000
30	IK(Eicosanoyl-6Ahx)-Pqa-RHYLNWVTRQ(N-methyl)RY	0.96	0.14	>5000	>5000	306 (28%)
31	IK(Eicosanoyl-gamaGlu-gamaGlu)-Pqa-RHYLNWVTRQ(N-methyl)RY	0.091	0.07	>5000	>5000	634 (60%)
32	IK(Palmitoyl-15-ATOPA)-Pqa-RHYLNWVTRQ(N-methyl)RY	0.26	0.19	>5000	>5000	973 (28%)

33	IK(Eicosanoyl-15-ATOPA)-Pqa-RHYLNWVTRQ(N-methyl)RY	1.08	0.13	>5000	>5000	241 (53%)
34	IK(Palmitoyl-12-ATODA)-Pqa-RHYLNWVTRQ(N-methyl)RY	0.003	0.1	>5000	>5000	2337 (80%)
35	IK(Eicosanoyl-12-ATODA)-Pqa-RHYLNWVTRQ(N-methyl)RY	1.02	0.11	>5000	>5000	501 (65 %)
36	IK(Palmitoyl-8-ADOSA)-Pqa-RHYLNWVTRQ(N-methyl)RY	0.138	0.15	>5000	>5000	481 (73%)
37	IK(Eicosanoyl-8-ADOSA)-Pqa-RHYLNWVTRQ(N-methyl)RY	0.367	0.13	>5000	>5000	77.9 (48%)
38	IK(Palmitoyl-5-APOSA)-Pqa-RHYLNWVTRQ(N-methyl)RY	0.003	0.17	>5000	>5000	644 (83%)
39	IK(Eicosanyl-5-APOSA)-Pqa-RHYLNWVTRQ(N-methyl)RY	0.073	0.21	>5000	>5000	285 (50%)
40	IK(Palmitoyl-Ser-Ser)-Pqa-RHYLNWVTRQ(N-methyl)RY	0.36	0.18	>5000	>5000	602 (85%)
41	IK(Eicosanoyl-Ser-Ser)-Pqa-RHYLNWVTRQ(N-methyl)RY	0.165	0.11	>5000	>5000	1833 (37%)
42	IK(Palmitoyl-Thr-Thr)-Pqa-RHYLNWVTRQ(N-methyl)RY	0.018	0.14	>5000	>5000	193 (46%)
43	IK(Eicosanoyl-Thr-Thr)-Pqa-RHYLNWVTRQ(N-methyl)RY	0.074	0.26	>5000	>5000	243 (23%)

The compounds according to formula (I) have an activity in one of the above assay s (Y2R EC50), of 0.001 nM to 10 nM. The most preferred compounds of formula (I) have an activity of 0.001 nM to 5 nM in one of the above assay s (Y2R EC50), preferably of 0.001 nM to 1 nM.

Example A

Film coated tablets containing the following ingredients can be manufactured in a conventional manner:

Ingredients	*Per tablet*	
Kernel:		
Compound of formula (I)	10.0 mg	200.0 mg
Microcrystalline cellulose	23.5 mg	43.5 mg
Lactose hydrous	60.0 mg	70.0 mg
Povidone K30	12.5 mg	15.0 mg
Sodium starch glycolate	12.5 mg	17.0 mg
Magnesium stearate	1.5 mg	4.5 mg
(Kernel Weight)	120.0 mg	350.0 mg
Film Coat:		
Hydroxypropyl methyl cellulose	3.5 mg	7.0 mg

Polyethylene glycol 6000	0.8 mg	1.6 mg
Talc	1.3 mg	2.6 mg
Iron oxyde (yellow)	0.8 mg	1.6 mg
Titan dioxide	0.8 mg	1.6 mg

The active ingredient is sieved and mixed with microcristalline cellulose and the mixture is granulated with a solution of polyvinylpyrrolidon in water. The granulate is mixed with sodium starch glycolate and magesiumstearate and compressed to yield kernels of 120 or 350 mg respectively. The kernels are lacquered with an aqueous solution / suspension of the above mentioned film coat.

Example B

Capsules containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per capsule
Compound of formula (I)	25.0 mg
Lactose	150.0 mg
Maize starch	20.0 mg
Talc	5.0 mg

The components are sieved and mixed and filled into capsules of size 2.

Example C

Injection solutions can have the following composition:

Compound of formula (I)	3.0 mg
Polyethylene Glycol 400	150.0 mg
Acetic Acid	q.s. ad pH 5.0
Water for injection solutions	ad 1.0 ml

The active ingredient is dissolved in a mixture of Polyethylene Glycol 400 and water for injection (part). The pH is adjusted to 5.0 by Acetic Acid. The volume is adjusted to 1.0 ml

by addition of the residual amount of water. The solution is filtered, filled into vials using an appropriate overage and sterilized.

Example D

Soft gelatin capsules containing the following ingredients can be manufactured in a conventional manner:

Capsule contents	
Compound of formula (I)	5.0 mg
Yellow wax	8.0 mg
Hydrogenated Soya bean oil	8.0 mg
Partially hydrogenated plant oils	34.0 mg
Soya bean oil	110.0 mg
Weight of capsule contents	165.0 mg
Gelatin capsule	
Gelatin	75.0 mg
Glycerol 85 %	32.0 mg
Karion 83	8.0 mg (dry matter)
Titan dioxide	0.4 mg
Iron oxide yellow	1.1 mg

The active ingredient is dissolved in a warm melting of the other ingredients and the mixture is filled into soft gelatin capsules of appropriate size. The filled soft gelatin capsules are treated according to the usual procedures.

Example E

Sachets containing the following ingredients can be manufactured in a conventional manner:

Compound of formula (I)	50.0 mg
Lactose, fine powder	1015.0 mg
Microcristalline cellulose (AVICEL PH 102)	1400.0 mg
Sodium carboxymethyl cellulose	14.0 mg

Polyvinylpyrrolidon K 30	10.0 mg
Magnesiumstearate	10.0 mg
Flavoring additives	1.0 mg

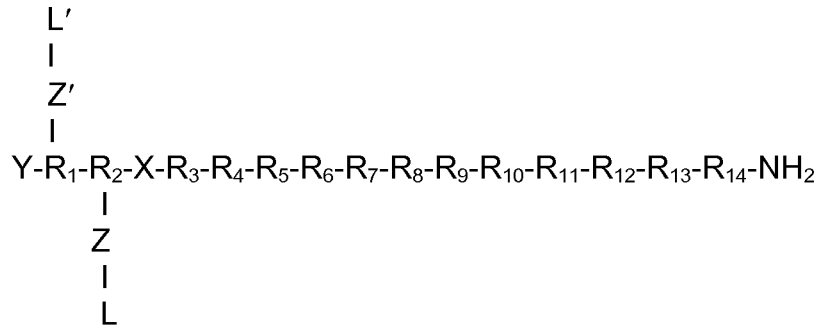
The active ingredient is mixed with lactose, microcristalline cellulose and sodium carboxymethyl cellulose and granulated with a mixture of polyvinylpyrrolidon in water.

The granulate is mixed with magnesiumstearate and the flavouring additives and filled into sachets.

It is to be understood that the invention is not limited to the particular embodiments of the invention described above, as variations of the particular embodiments may be made and still fall within the scope of the appended claims.

Claims

1. A neuropeptide-2 receptor agonist of formula (I):



(I),

wherein:

L is a lipid moiety;

L′ is a lipid moiety;

X is (4-oxo-6-piperazin-1-yl-4H-quinazolin-3-yl)-acetic acid;

Y is H, an acyl moiety or pyro-Glu;

Z is a spacer moiety or absent;

Z′ is a spacer moiety or absent;

R_1 is Ile, Ala, (D)Ile or N-methyl Ile;

R_2 is Lys, Ala, (D)Lys, N-methyl Lys, Nle or (Lys-Gly);

R_3 is Arg, Ala, (D)Arg, N-methyl Arg or Phe;

R_4 is His, Ala, (D)His or N-methyl His;

R_5 is Tyr, Ala, (D)Tyr , N-methyl Tyr or Trp;

R_6 is Leu, Ala, (D)Leu or N-methyl Leu;

R_7 is Asn, Ala or (D)Asn;

R_8 is Leu or Trp;

R_9 is Val, Ala, (D)Val or N-methyl Val;

R_{10} is Thr, Ala or N-methyl Thr;

R_{11} is Arg, (D)Arg or N-methyl Arg;

R_{12} is Gln or Ala;

R_{13} is Arg, (D)Arg or N-methyl Arg; and

R_{14} is Tyr, (D)Tyr, N-methyl Tyr, Phe or Trp; and

wherein moieties L-Z- and L'-Z'- are not both present;

or a pharmaceutically acceptable salt thereof.

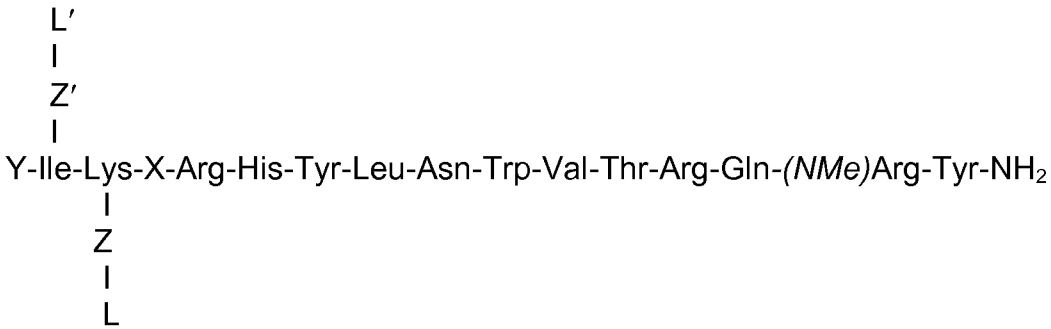
2. The neuropeptide-2 receptor agonist according to claim 1, wherein said lipid moiety is carpryloyl, lauroyl, myristoyl, palmitoyl, 16-bromohexadecanoyl, 2-hexyldecanoyl or eicosanoyl.

3. The neuropeptide-2 receptor agonist according to claim 1 or 2, wherein said spacer moiety is 6-Ahx, Ala, Glu, Ala-Glu, Glu-Glu, 15-ATOPA, 12-ATODA, 8-ADOSA, 5-AOPSA, Ser-Ser or Thr-Thr.

4. The neuropeptide-2 receptor agonist according to claim 1 or 2, wherein Z is absent.

5. The neuropeptide-2 receptor agonist according to claim 1 or 2, wherein Z' is absent.

6. The neuropeptide-2 receptor agonist according to any one of claims 1 to 5, having formula (II):



(II);

wherein

L is a lipid moiety;

L′ is a lipid moiety;

X is (4-oxo-6-piperazin-1-yl-4H-quinazolin-3-yl)-acetic acid;

Y is H, an acyl moiety or pyro-Glu;

Z is 6-Ahx, Ala, Glu, Ala-Glu, Glu-Glu, 15-ATOPA, 12-ATODA, 8-ADOSA, 5-AOPSA, Ser-Ser, Thr-Thr or absent;

Z′ is 6-Ahx, Ala, Glu, Ala-Glu, Glu-Glu, 15-ATOPA, 12-ATODA, 8-ADOSA, 5-AOPSA, Ser-Ser, Thr-Thr or absent; and

wherein moieties L-Z- and L'-Z'- are not both present.

7. The neuropeptide-2 receptor agonist according to claim 6, wherein said lipid moiety is carpryloyl, lauroyl, myrisoyl, palmitoyl, 16-bromohexadecanoyl, 2-hexyldecanoyl or eicosanoyl.

8. The neuropeptide-2 receptor agonist according to claim 6 or 7, wherein one of Z and Z' is Ala, Glu, Ala-Glu, Glu-Glu, Ser-Ser or Thr-Thr.

9. The neuropeptide-2 receptor agonist according to claim 6 or 7, wherein Z is absent.

10. The neuropeptide-2 receptor agonist according to claim 6 or 7, wherein Z' is absent.

11. The neuropeptide-2 receptor agonist according to any one of claims 1 to 10, selected from the group consisting of:

Ac-Ile-Lys(Butyryl)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

Ac-Ile-Lys(Capryloyl)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

Ac-Ile-Lys(Lauroyl)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Lauroyl-6-Ahx)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Lauroyl-beta-Ala)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Lauroyl-Glu)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Myristoyl-6-Ahx)-Pro-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

Ac-Ile-Lys(Palmitoyl)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Palmitoyl)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

Palmitoyl-Ile-Lys-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

Palmitoyl-6-Ahx-Ile-Lys-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

Palmitoyl-6-Ahx-Ile-Lys-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-Arg-Tyr-NH_2;

H-Ile-Lys(Palmitoyl-6-Ahx)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Palmitoyl-6-Ahx)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-Arg-Tyr-NH_2;

H-Ile-Lys(Palmitoyl-beta-Ala)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)Arg-Tyr-NH_2;

H-Ile-Lys(Palmitoyl-Glu)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Palmitoyl- beta-Ala- Glu)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Palmitoyl-Glu-Glu-)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Palmitoyl-gamma-Glu)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2; and

H-Ile-Lys(Palmitoyl-gamma-Glu-gamma-Glu-)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2.

12. The neuropeptide-2 receptor agonist according to any one of claims 1 to 11, selected from the group consisting of:

H-Ile-Lys(Palmitoyl-beta-Ala-gamma-Glu-)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(16-Bromohexadecanoyl-gamma-Glu-gamma-Glu-)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

Pyro-Glu-Ile-Lys(Palmitoyl-gamma-Glu- gamma-Glu-)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2

H-Ile-Lys(2-hexyldecanoyl-6-Ahx)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Eicosanoyl-6-Ahx)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Eicosanoyl-gamma-Glu-gamma-Glu-)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Palmitoyl-15-ATOPA)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Eicosanoyl-15-ATOPA)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Palmitoyl-12-ATODA)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Eicosanoyl-12-ATODA)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Palmitoyl-8-ADOSA)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Eicosanoyl-8-ADOSA)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Palmitoyl-5-AOPSA)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Eicosanoyl-5-AOPSA)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Palmitoyl-Ser-Ser)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Eicosanoyl-Ser-Ser)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2;

H-Ile-Lys(Palmitoyl-Thr-Thr)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2; and

H-Ile-Lys(Eicosanoyl-Thr-Thr)-*Pqa*-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-*(NMe)*Arg-Tyr-NH_2.

13. A neuropeptide-2 receptor agonist according to any one of claims 1 to 12 for use as a therapeutically active substance.

14. A pharmaceutical composition comprising a neuropeptide-2 receptor agonist in accordance with any one of claims 1 to 12 and a therapeutically inert carrier.

15. The use of a neuropeptide-2 receptor agonist according to any one of claims 1 to 12 for the preparation of medicaments for the treatment or prophylaxis of obesity, type 2 diabetes, metabolic syndrome, insulin resistance or dyslipidemia.

16. A method for the treatment or prophylaxis of obesity, type 2 diabetes, metabolic syndrome, insulin resistance or dyslipidemia, which method comprises administering an effective amount of a neuropeptide-2 receptor agonist as defined in any one of claims 1 to 12.

17. The invention as hereinbefore described.

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