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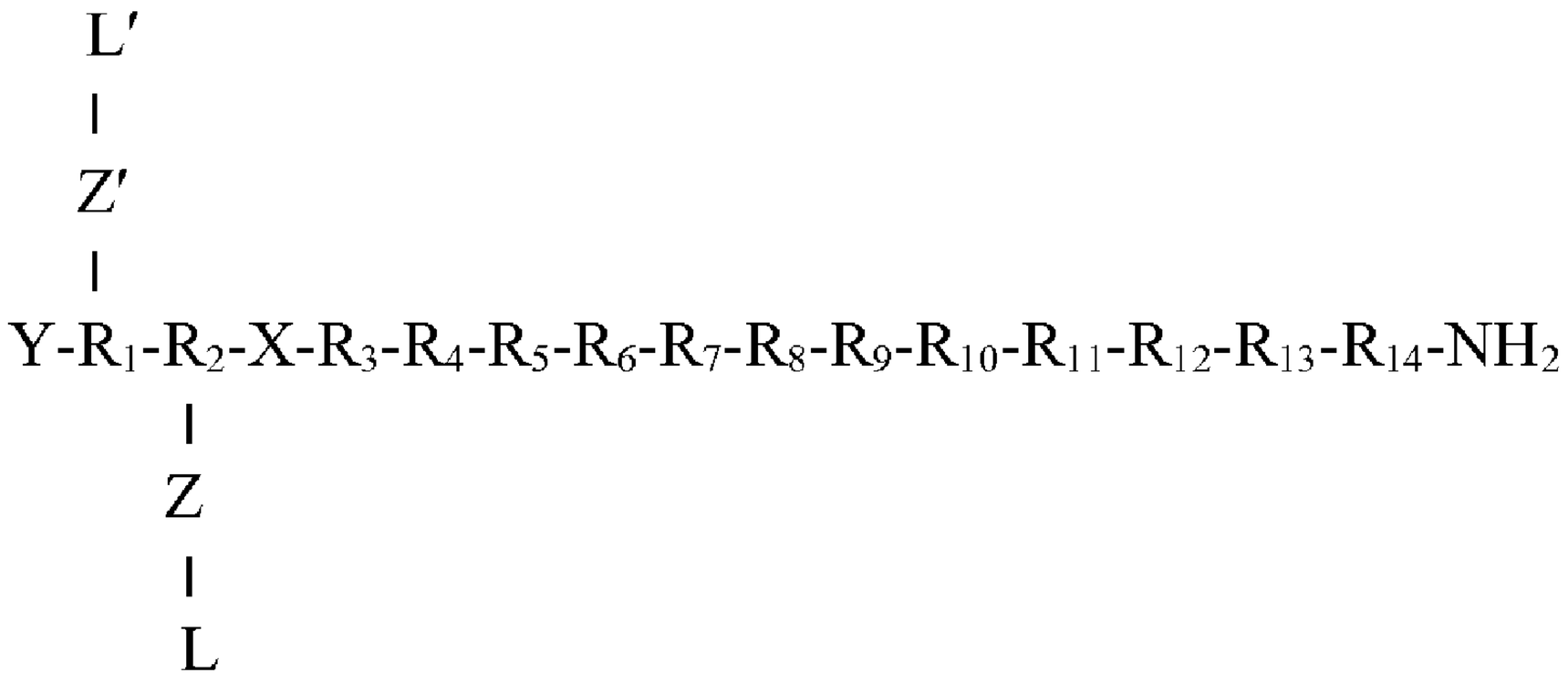
(54) Title: NEUROPEPTIDE-2 RECEPTOR (Y-2R) AGONISTS



(I)

(57) Abrégé/Abstract:
Provided herein are neuropeptide-2 receptor agonists of the formula (I): as well as pharmaceutically acceptable salts, derivatives and fragments thereof, wherein the substituents are as those disclosed in the specification. These compounds, and the pharmaceutical compositions containing them, are useful for the treatment of diseases such as, for example, obesity and diabetes.

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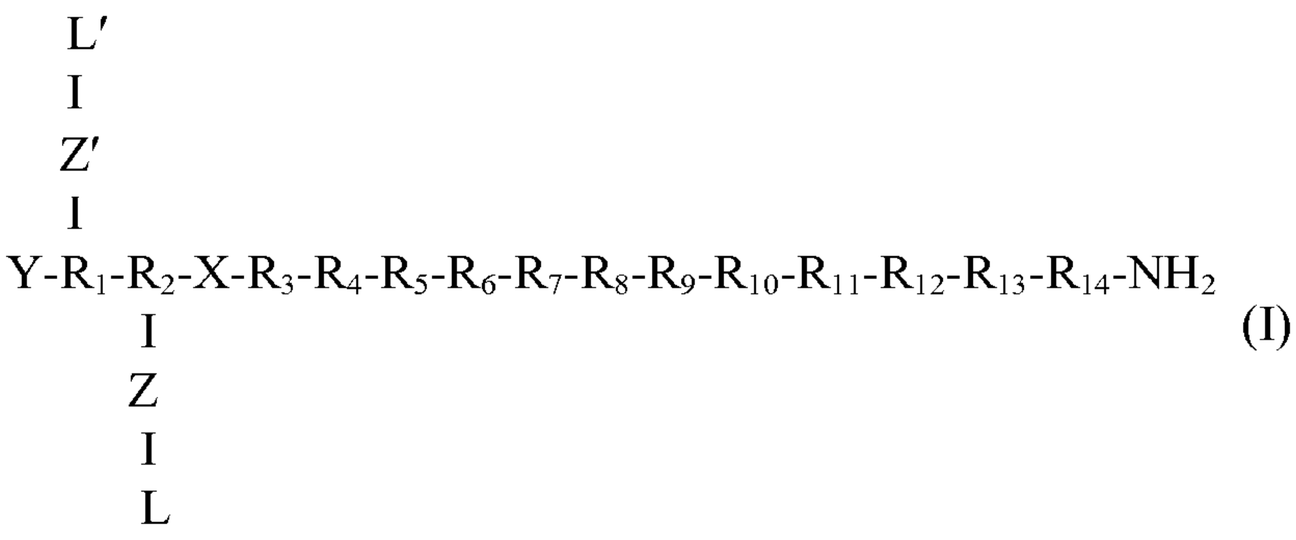

$$Y\text{-}R_1\text{-}R_2\text{-}X\text{-}R_3\text{-}R_4\text{-}R_5\text{-}R_6\text{-}R_7\text{-}R_8\text{-}R_9\text{-}R_{10}\text{-}R_{11}\text{-}R_{12}\text{-}R_{13}\text{-}R_{14}\text{-}NH_2 \quad (I)$$

(57) Abstract: Provided herein are neuropeptide-2 receptor agonists of the formula (I): as well as pharmaceutically acceptable salts, derivatives and fragments thereof, wherein the substituents are as those disclosed in the specification. These compounds, and the pharmaceutical compositions containing them, are useful for the treatment of diseases such as, for example, obesity and diabetes.

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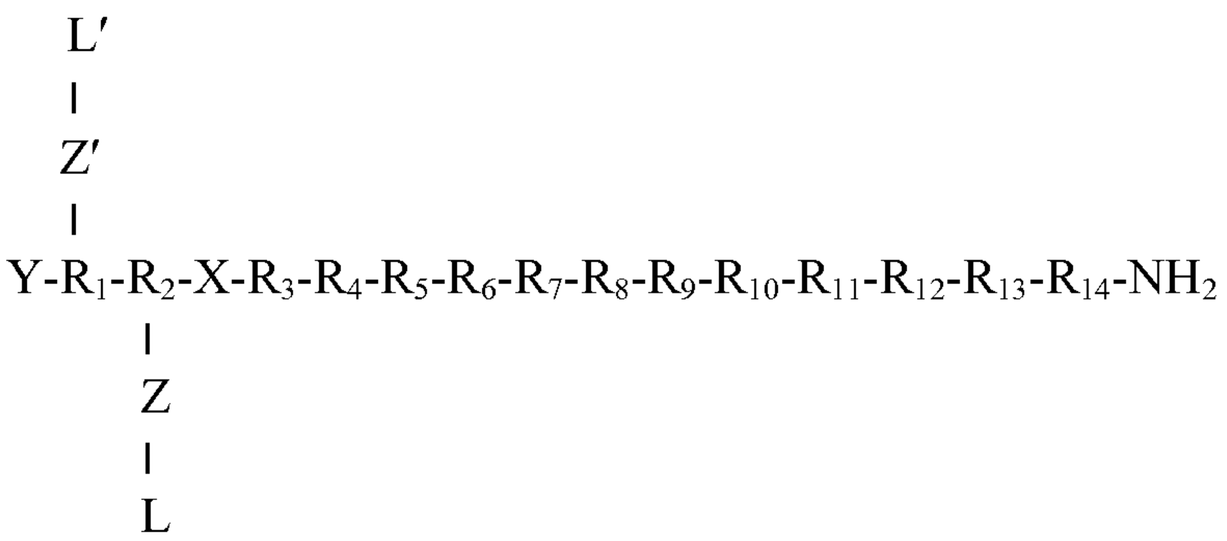
NEUROPEPTIDE-2 RECEPTOR (Y-2R) AGONISTS

The invention provides for truncated, pegylated 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 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.

All documents cited in this document are expressly incorporated herein by reference.

In one embodiment of the present invention, provided is a neuropeptide-2 receptor agonist of the formula (I):



(I),

wherein:
one of L or L′ is a polyethylene glycol (PEG) moiety and the other is a lipid moiety or absent;

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

Y is an acyl moiety or absent;

Z, Z′ is a spacer moiety or absent;

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

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

R_3 is Arg, Cit, 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, His, 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,

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.

Four NPY receptors, the Y1-, Y2-, Y4, and Y5-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 $G\alpha_i$ while displaying low homology with other known NPY receptors. There is a high degree of conservation between rat and human Y2 receptors with 93 % 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 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-pegylated 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;
6Ahx is 6-Aminohexanoic acid;
AOPS is 5-Amino-3-oxa-pentyl-succinamic acid;
Cha is Cyclohexylalanine;
Cit is Citrulline;
Cys(SO_3H) is Cystic acid ;
γGlu is gammaGlu;
(1)Nal is 1-Naphthylalanine;

(2)Nal is 2-Naphthylalanine;

Alloc is Alloxycarbonyl;

Fmoc is 9-Fluorenylmethyloxycarbonyl;

Mtr is 4-Methoxy-2,3,6-trimethyl-benzenesulfonyl;

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;

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-, eicosanoyl-, lauroyl-, myristoyl-, palmitoyl-, 16-bromohexadecanoyl-, 2-hexyldecanoyl-, 15-carboxy-pentadecanoyl, and the like.

As used herein, the term "polyethylene glycol moiety," means a monodispersed structure of Formula (A):

$$CH_3(OCH_2CH_2O)_n(CH_2)_xCO-$$
(A),

or of Formula (B):

$$-NH-CH_2CH_2-(OCH_2CH_2)_n-O-(CH_2)_x-CO-$$
(B),

wherein n is 1 to 30, preferably 1 to 24, and x is 1 to 2. Reagents for the preparation of said polyethylene glycol moieties are commercially available, for example, from Quanta Biodesign, 195 W. Olentangy Street, Suite O, Powell, Ohio 43065. The polyethylene glycol moities of the invention may also be prepared according to the general methods described in GB 779,829; US Patent No. 3,389,170; US Published Application Serial No. 2006/0018874; Miller et al., *Bioconjugate Chem.*, **2006**, *17*, 264-267; and Campbell, et al., *J. Phys. Chem.*, **1991**, *95*, 4647-4651. Examples of preferred polyethylene glycol moities useful for the invention include CH_3-$(OCH_2CH_2)_2$-O-CH_2-CO-, CH_3-$(OCH_2CH_2)_5$-O-CH_2-CO-, CH_3-$(OCH_2CH_2)_7$-O-$(CH_2)_2$-CO-, CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO, -CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO-, and CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO-.

As used herein, the term "spacer moiety" means a chemical group in between said lipid or PEG moiety and the amino acid sequence of said truncated PYY $_{3-36}$ peptide. Examples of spacer moieties include, without limitation, 6Ahx, 6Ahx-6Ahx, Glu-Glu, γGlu- γGlu, AOPSA and Cys(SO_3H)-Cys(SO_3H).

As used herein, the term "acyl" means an optionally substituted alkyl, cycloalkyl, heterocycloalkyl, 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.

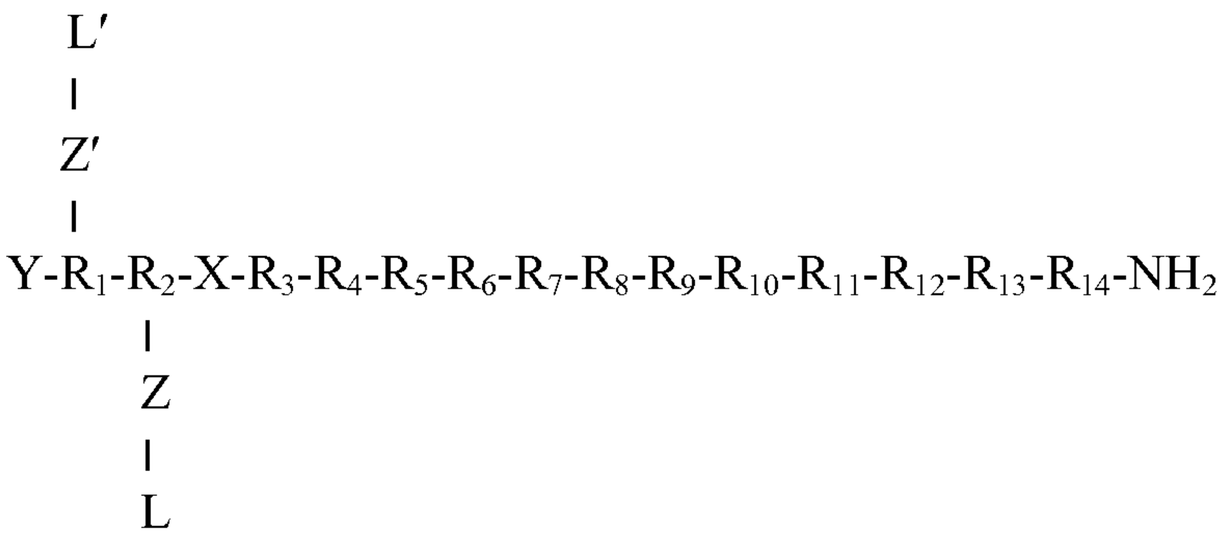
The alkyl, lower alkyl and aryl groups may be substituted or unsubstituted. When substituted, there will generally be, for example, 1 to 4 substituents present, with the understanding that said substituents are not, in turn, substituted further unless indicated otherwise. These substituents may optionally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

In one embodiment of the present invention, provided is a neuropeptide-2 receptor agonist of the formula (I):



(I),

wherein:
one of L or L′ is a polyethylene glycol (PEG) moiety and the other is a lipid moiety or absent;

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

Y is an acyl moiety or absent;

Z, Z′ is a spacer moiety or absent;

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

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

R_3 is Arg, Cit, 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, His, 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,

or a pharmaceutically acceptable salt thereof.

Preferably, said lipid moiety is caproyl, eicosanoyl, lauroyl, myristoyl, palmitoyl, 16-bromohexadecanoyl, 2-hexyldecanoyl or 15-carboxy-pentadecanoyl.

Preferably, said polyethylene glycol moiety is of the formula $CH_3(OCH_2CH_2O)_n(CH_2)_x$ CO-,
wherein n is 1 to 30 and x is 1 or 2. More preferably, n is 1 to 24 and x is 1 or 2.

Preferably, said polyethylene glycol moiety is CH_3-$(OCH_2CH_2)_2$-O-CH_2-CO-, CH_3-$(OCH_2CH_2)_5$-O-CH_2-CO-, CH_3-$(OCH_2CH_2)_7$-O-$(CH_2)_2$-CO-,

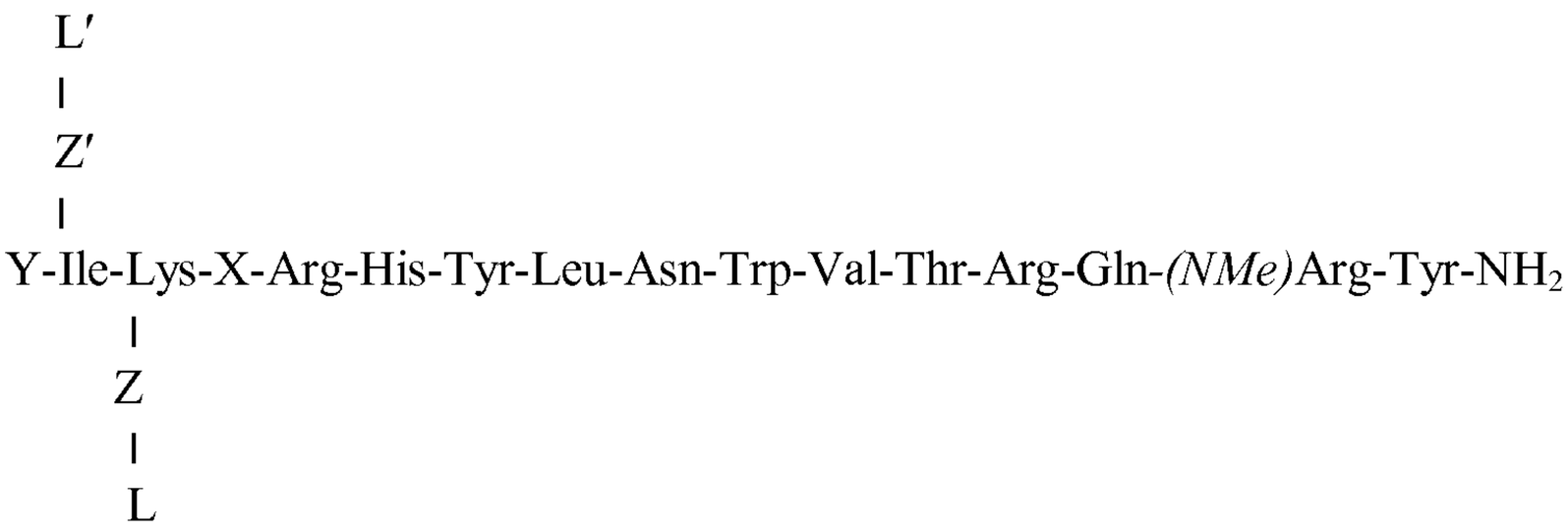
CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO-, CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO-, or CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO-.

Preferably, said spacer moiety is Ahx, Ahx-Ahx, Glu-Glu, γGlu- γGlu, 5AOPS or Cys(SO_3H)-Cys(SO_3H).

In one embodiment, Z is absent. In another embodiment, Z' is absent.

Preferably, said acyl moiety is acetyl.

In a further embodiment, provided is a neuropeptide-2 receptor agonist formula (II):



(II),

wherein:

one of L or L′ is a lipid moiety and the other is a polyethylene glycol (PEG) moiety;

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

Y is an acyl moiety or absent; and

Z, Z′ is Ahx, Ahx-Ahx, Glu-Glu, γGlu- γGlu, 5AOPS or Cys(SO_3H)-Cys(SO_3H),

or a pharmaceutically acceptable salt thereof.

Preferably, said lipid moiety of the neuropeptide-2 receptor agonist of formula (II) is caproyl, eicosanoyl, lauroyl, myristoyl, palmitoyl, 16-bromohexadecanoyl, 2-hexyldecanoyl or 15-carboxy-pentadecanoyl.

Preferably, said polyethylene glycol moiety of the neuropeptide-2 receptor agonist of formula (II) is of the formula $CH_3(OCH_2CH_2O)_n(CH_2)_xCO$-, wherein n is 1 to 30 and x is 1 or 2. Preferably, n is 1 to 24 and x is 1 or 2.

Preferably, said polyethylene glycol moiety of the neuropeptide-2 receptor agonist of formula (II) is CH_3-$(OCH_2CH_2)_2$-O-CH_2-CO-, CH_3-$(OCH_2CH_2)_5$-O-CH_2-CO-, CH_3-$(OCH_2CH_2)_7$-O-$(CH_2)_2$-CO-, CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO-, CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO-, or CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO-.

Preferably, said Z, Z' of the neuropeptide-2 receptor agonist of formula (II) is Ahx, Ahx-Ahx, Glu-Glu, γGlu- γGlu, 5AOPS or Cys(SO_3H)-Cys(SO_3H).

Preferably, said acyl moiety of the neuropeptide-2 receptor agonist of formula (II) is acetyl.

In one embodiment of the neuropeptide-2 receptor agonist of formula (II), Z is absent. In another embodiment of the neuropeptide-2 receptor agonist of formula (II), Z' is absent.

Another embodiment of the present invention is a neuropeptide-2 receptor agonist of formula (III):

(III),

wherein:

one of L or L′ is a lipid moiety and the other is absent;

one of Z or Z′ is a spacer moiety and the other is absent;

one of PEG or PEG' is a polyethelene glycol moiety -NH-CH_2CH_2 -$(OCH_2CH_2)_n$-O-$(CH_2)_x$-CO- and the other is absent, wherein n is 1 to 30 and x is 1 or 2;

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

Y is an acyl moiety or absent,

or a pharmaceutically acceptable salt thereof.

Preferably, in the neuropeptide-2 receptor agonist of formula (III), said lipid moiety is caproyl, eicosanoyl, lauroyl, myristoyl, palmitoyl, 16-bromohexadecanoyl, 2-hexyldecanoyl or 15-carboxy-pentadecanoyl.

Preferably, in the neuropeptide-2 receptor agonist of formula (III), said spacer moiety is Ahx, Ahx-Ahx, Glu-Glu, γGlu- γGlu, 5AOPS or Cys(SO_3H)-Cys(SO_3H).

Preferably, said acyl moiety of the neuropeptide-2 receptor agonist of formula (III) is acetyl.

Preferably, in the neuropeptide-2 receptor agonist of formula (III), n is 1 to 24 and x is 1 or 2.

Preferred neuropeptide-2 receptor agonists of the invention are:

CH_3-$(OCH_2CH_2)_5$-O-CH_2-CO-Ile-Lys(Palmitoyl-6Ahx)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_7$-O-$(CH_2)_2$-CO-Ile-Lys(Palmitoyl-6Ahx)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO-Ile-Lys(Palmitoyl-6Ahx)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO-Ile-Lys(Palmitoyl-6Ahx)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO-Ile-Lys(Palmitoyl-6Ahx)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_5$-O-CH_2-CO-Ile-Lys(Palmitoyl-5AOPS)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO-Ile-Lys(Palmitoyl-5AOPS)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO-Ile-Lys(Palmitoyl-5AOPS)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO-Ile-Lys(Palmitoyl-5AOPS)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO-Ile-Lys(Palmitoyl-5AOPS)-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_7$-O-$(CH_2)_2$-CO-6Ahx-Ile-Lys-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO-6Ahx-Ile-Lys-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO-6Ahx-Ile-Lys-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO-6Ahx-Ile-Lys-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Ac-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_2$-O-CH_2-CO-Ile-Lys(Eicosanoyl-gammaGlu-gammaGlu)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_7$-O-$(CH_2)_2$-CO-Ile-Lys(Eicosanoyl-gammaGlu-gammaGlu)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr -NH_2;

CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO-Ile-Lys(Eicosanoyl-gammaGlu-gammaGlu)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO-Ile-Lys(Eicosanoyl-gammaGlu-gammaGlu)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO-Ile-Lys(Eicosanoyl-gammaGlu-gammaGlu)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO-Ile-Lys(Eicosanoyl-Cys{SO_3}-Cys{SO_3})-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr -NH_2;

CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO-Ile-Lys(Eicosanoyl-Cys{SO_3}-Cys{SO_3})-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO-Ile-Lys(Palmitoyl-Cys{SO_3}-Cys{SO_3})-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Palmitoyl-6Ahx-Ile-Lys[CH_3-$(OCH_2CH_2)_7$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Palmitoyl-6Ahx-Ile-Lys[CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Palmitoyl-6Ahx-Ile-Lys[CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Eicosanoyl-6Ahx-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Palmitoyl-6Ahx-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr -NH_2;

Eicosanoyl-6Ahx-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Lauroyl-6Ahx-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Myristoyl-6Ahx-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Palmitoyl-6Ahx-6Ahx-Ile-Lys[CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Palmitoyl-6Ahx-6Ahx-Ile-Lys[CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Palmitoyl-6Ahx-6Ahx-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Palmitoyl-6Ahx-6Ahx-(D)alloIle-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Eicosanoyl-Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_7$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Eicosanoyl -Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Eicosanoyl -Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Eicosanoyl -Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Eicosanoyl-Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Eicosanoyl -Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Eicosanoyl -Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-C-alphaMeVal-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Eicosanoyl -Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg(CO)-Gln-(NMe)-Arg-Tyr-NH_2;

Eicosanoyl -Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Eicosanoyl -Glu-Glu-(D)alloIle-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

15-Carboxy-pentadecanoyl-Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Eicosanoyl-Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-His-Asn-Trp-Val-Thr-Arg-Gln-Arg-Tyr-NH_2;

Eicosanoyl-Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-His-Asn-Trp-Val-Thr-Arg-Gln-Arg-Tyr-NH_2;

Eicosanoyl -Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-His-Asn-Trp-Val-Thr-Arg-Gln-Arg-Tyr-NH_2;

Eicosanoyl-gammaGlu-gammaGlu-Ile-Lys[CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Eicosanoyl-gammaGlu-gammaGlu-Ile-Lys[CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Eicosanoyl-gammaGlu-gammaGlu-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Eicosanoyl -gammaGlu-gammaGlu-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Eicosanoyl-Cys(SO_3)-Cys(SO_3)-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Palmitoyl-6Ahx-NH-CH_2CH_2-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO-Ile-Lys-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2; and

Ac-Ile-Lys[Palmitoyl-6Ahx-NH-CH_2CH_2-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2,

or pharmaceutically acceptable salts thereof.

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), which are incorporated herein by reference.

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,) 2,24,6,7-Pentamethyldihydro-benzofuran-5-sulfonyl (Pbf), pentamethylchromansulfonyl (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 (CH_2Cl_2), 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), diisopropylethylamine (DIPEA)and propanethiol were 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	CH_2Cl_2	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 $AcOH/H_2O$ 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/CH_3CN) 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.

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, II or III, or a salt thereof, and a pharmaceutically acceptable carrier.

Also an object of the present invention is a neuropeptide-2 receptor agonist, or a salt thereof, according to formula I, II or III, for use as therapeutically active substance.

Also an object of the present invention is the use of a neuropeptide-2 receptor agonist, or a salt thereof, according to formula I, II or III,, for the treatment or prophylaxis of metabolic diseases and disorders.

Also an object of the present invention is the use of a neuropeptide-2 receptor agonist, or a salt thereof, according to formula I, II or III,, for the preparation of a medicament for the treatment or prophylaxis of metabolic diseases and disorders.

A further embodiment of the present invention is a neuropeptide-2 receptor agonist, or a salt thereof, according to formula I, II or III, for the treatment or prophylaxis of metabolic diseases and disorders.

Another embodiment of the present invention is a method for the treatment or prophylaxis of metabolic diseases and disorders, which method comprises administering an effective amount of a neuropeptide-2 receptor agonist, or a salt thereof, according to formula I, II or III,.

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.

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

I. Preparation of Preferred Intermediates

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.

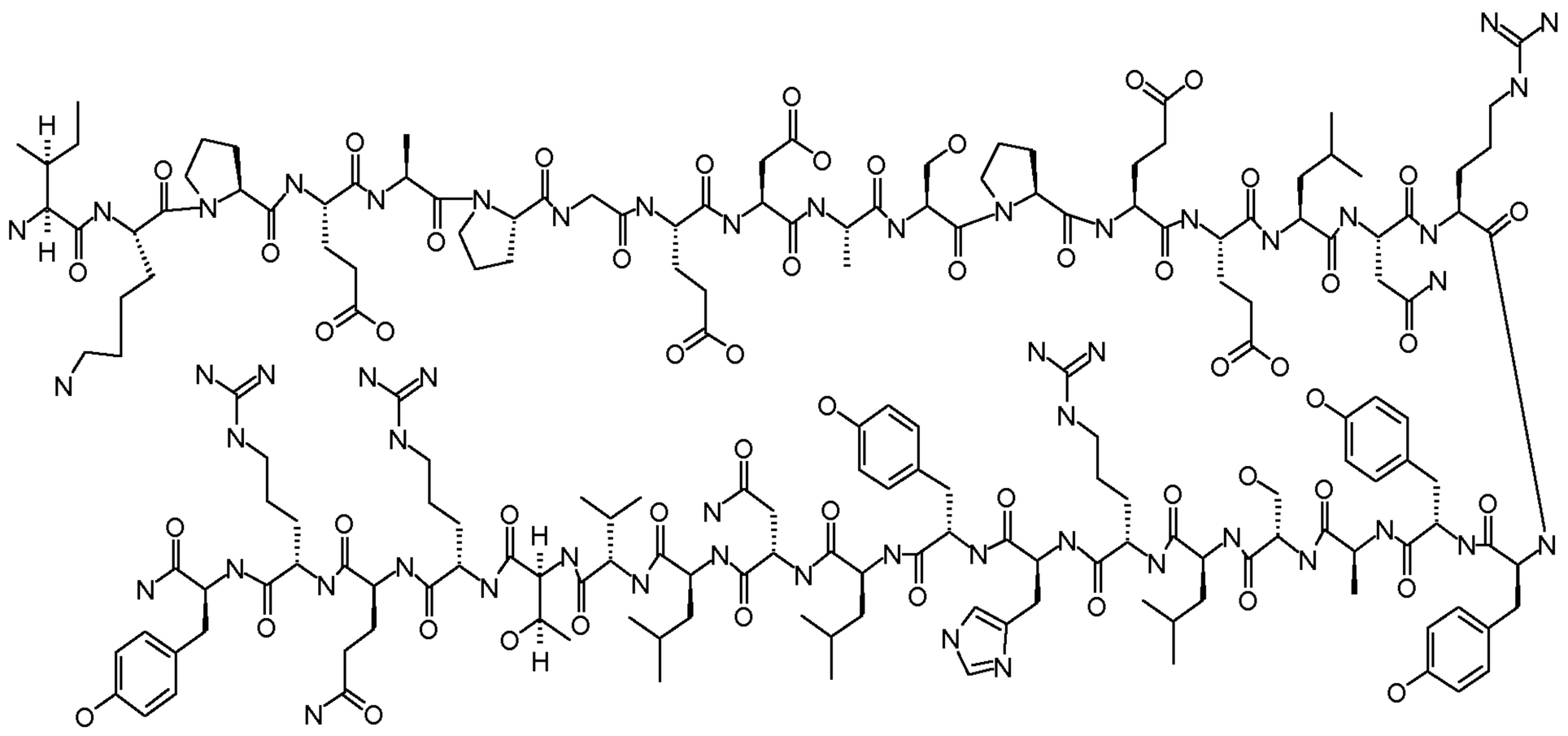
For a 0.25 mmol scale peptide synthesis by Applied Biosystem 433A synthesizer (Foster City, CA), the FastMoc 0.25 mmol cycles were used with either the resin sampling or non resin sampling, 41 mL reaction vessel. The Fmoc-amino acid resin was suspended with 2.1 g NMP, 2g of 0.45M HOBT/HBTU in DMF and 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-Thr-Arg-Gln-Arg-Tyr-NH_2 (PYY_{3-36})

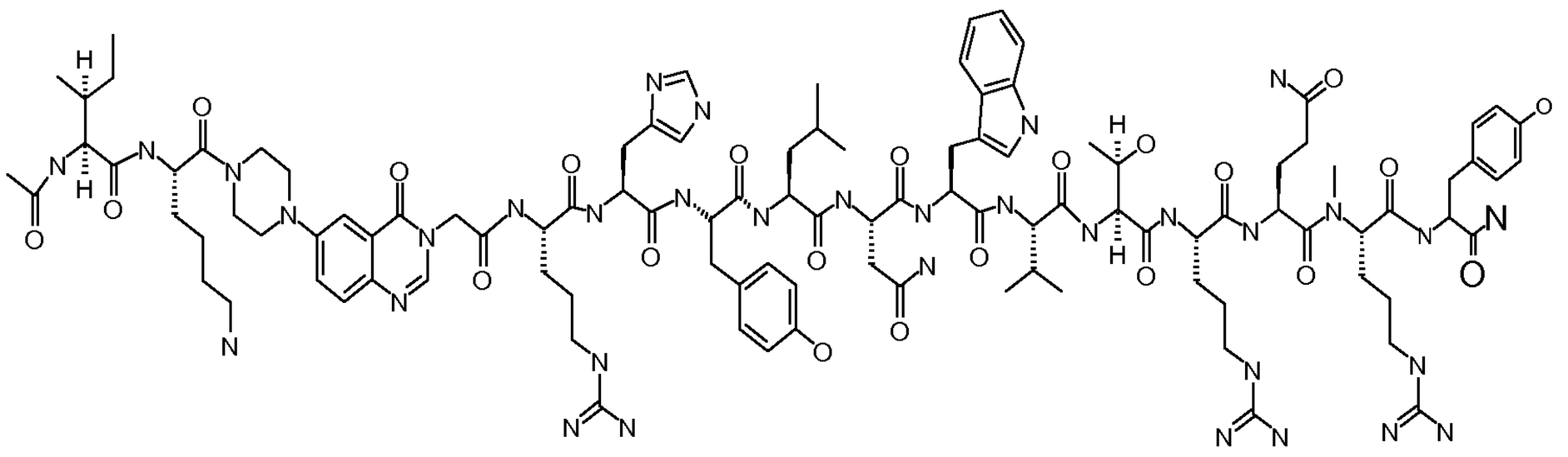


The above peptide was synthesized using Fmoc chemistry on an Applied Biosystem 433A synthesizer. The synthesizer was programmed for double coupling using the modules described in Example 2. The synthesis was carried out on a 0.25 mmol scale using the Fmoc- Linker-BHA resin (450 mg, 0.25 mmol) from Example 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 2-99%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 (18%) of a white amorphous powder. (ES)+-LCMS m/e calculated 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 (15%) of white amorphous powder. (ES)+-LCMS m/e calculated for $C_{106}H_{156}N_{34}O_{22}$ 2257.21 found 2257.19.

EXAMPLE 5

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)-Rink Amide 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. After Fmoc removal and washing, 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 chloranil 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 mmol) 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 600 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 500 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 drying 40.0 g of peptide resin was removed for and saved for analog synthesis. The resin was then washed with CH_2Cl_2, DMF and Fmoc removed and washed again with DMF before 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) .The reaction was complete after 18 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 500 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 500 mL DMF was added. The reaction was complete after 20 hours as determined by chloronil test. After washing and removal of Fmoc, Fmoc-Ile-OH (26.1 g, 73.5 mmol) N-hydroxbenzotriazole (9.95 g, 73.5 mmol) and N,N'-diisopropylcarbodiimide (55.0 mL, 300 mmol) in 500 mL DMF. The reaction was complete after 20 hours. The resin was filtered and washed successively with 600 mL each of CH_2Cl_2 (two times), isopropanol (two times), DMF, and CH_2Cl_2 (three times). After drying under vacuum 210.0 g of peptide resin with a loading of 0.21 mm/g was obtained.

EXAMPLE 6

Preparation of Fmoc-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Rink Amide Resin.

Fmoc-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Rink Amide resin 40.0 grams from Example 5 was washed and swelled with CH_2Cl_2 (three times), and DMF (two times) and Fmoc removed. After washing with DMF (four times), Fmoc-Arg (Pdf) (9.86 g, 14.0 mmol) N-hydroxbenzotriazole (5.95 g, 44.0 mmol) and N,N'-diisopropylcarbodiimide (45.0 mL, 250 mmol) in 300 mL DMF was added. The reaction was complete after 20 hours. After washing and removal of Fmoc, Fmoc-Pqa-OH (4.2 g, 20.5 mmol,) N-hydroxbenzotriazole (2.7 g, 20.5 mmol) and N,N'-diisopropylcarbodiimide (45.0 mL, 250 mmol) in 250 mL DMF was added. After 18 hours the reaction was complete. After washing and removal of the Fmoc, Fmoc-Lys(Alloc)-OH (6.3g, 14.0 mmol), N-hydroxbenzotriazole (5.95 g, 44.0 mmol) and N,N'-diisopropylcarbodiimide (45.0 mL, 250 mmol) was added and the reaction was carried out for 5 hours to completion as judged by a yellow chloronil test. After Fmoc removal and washing, Fmoc-Ile-OH (5.0 g, 14.0 mmol), N-hydroxbenzotriazole (2.7 g, 20.5 mmol) and N,N'-diisopropylcarbodiimide (45.0 mL, 250 mmol) in 250 mL DMF was added. After 18 hours the reaction was complete. The peptide resin was washed successively with 4 times DMF, 3 times with CH_2Cl_2, 3 times with MeOH, 3 times with CH_2Cl_2 and 4 times with MeOH and dried under vacuum to obtain 41.6 grams of protected peptide resin with a loading of 0.22 mm/g.

EXAMPLE 6 A

Preparation of Fmoc-Ile-Lys(Alloc)-Pqa-Cit-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Rink Amide Resin.

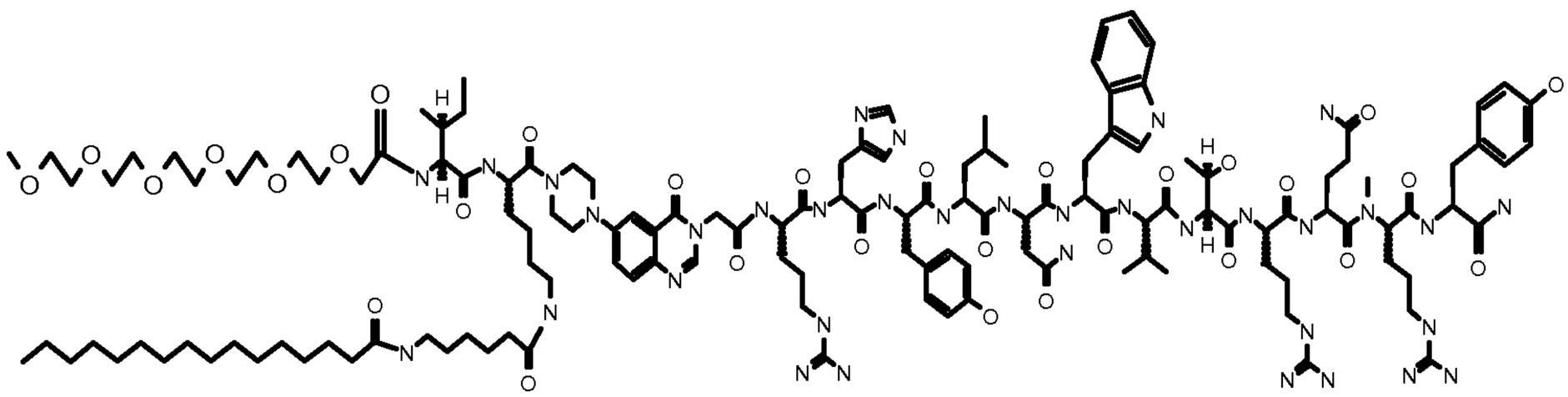
Fmoc-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Rink Amide resin 40.0 grams from Example 5 was washed and swelled with CH_2Cl_2 (three times), and DMF (two times) and Fmoc removed. After washing with DMF (four times), Fmoc-Cit (4.4 g, 14.0 mmol) N-hydroxbenzotriazole (5.95 g, 44.0 mmol) and N,N'-diisopropylcarbodiimide (45.0 mL, 250 mmol) in 300 mL DMF was added. The reaction was complete after 20 hours. After washing and removal of Fmoc, Fmoc-Pqa-OH (4.2 g, 20.5 mmol)

N-hydroxbenzotriazole (2.7 g, 20.5 mmol) and N,N'-diisopropylcarbodiimide (45.0 mL, 250 mmol) in 250 mL DMF was added. After 18 hours the reaction was complete. After washing and removal of the Fmoc, Fmoc-Lys(Alloc)-OH (6.3g, 14.0 mmol), N-hydroxbenzotriazole (5.95 g, 44.0 mmol) and N,N'-diisopropylcarbodiimide (45.0 mL, 250 mmol) was added and the reaction was carried out for 5 hours to completion as judged by a yellow chlorinal test. After Fmoc removal and washing, Fmoc-Ile-OH (5.0 g, 14.0 mmol), N-hydroxbenzotriazole (2.7 g, 20.5 mmol) and N,N'-diisopropylcarbodiimide (45.0 mL, 250 mmol) in 250 mL DMF was added. After 18 hours the reaction was complete. The peptide resin was washed successively with 4 times DMF, 3 times with CH_2Cl_2, 3 times with MeOH, 3 times with CH_2Cl_2 and 4 times with MeOH and dried under vacuum to obtain 41.6 grams of protected peptide resin with a loading of 0.22 mm/g.

II. Preparation of Preferred Embodiments of the Invention

EXAMPLE 7

Preparation of CH_3-$(OCH_2CH_2)_5$-O-CH_2-CO-Ile-Lys(Palmitoyl-6Ahx)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:3 TFA

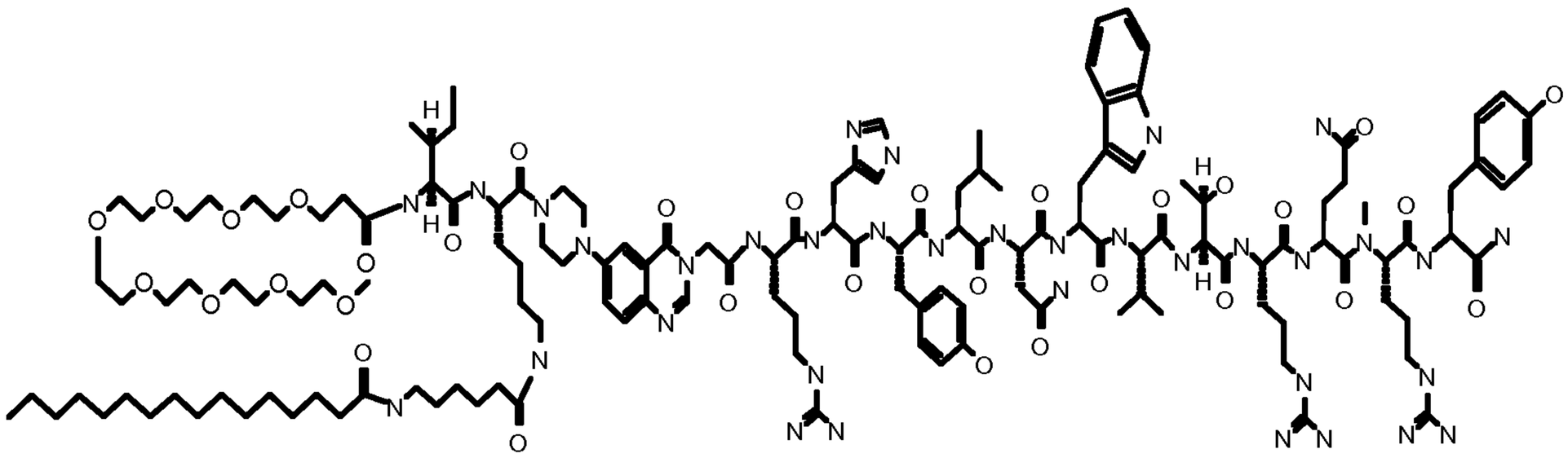


Fmoc-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Rink Amide Resin, 1.0 g (0.22 mmol), obtained from Example 6, was washed with DMF, deprotected and washed and coupled in DMF with [2-(2-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-ethoxy)-ethoxy]-acetic acid m-dPEG n=6 (Quanta Biodesign, 86 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (1.50 ml, 2.0 mmol) were stirred for 18hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL

Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF. Fmoc-6aminohexanoic acid (355.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.110 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in 15 mL DMF was coupled for 18 hr. After Fmoc removal and washing with DMF and CH_2Cl_2, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 mmol) and Palmitoyl 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 was stirred for 18 hr then washed with DMF 2 times and CH_2Cl_2 3 times, before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 70 mg (12%) of white amorphous powder. (ES)+-LCMS m/e calculated 2858.67 $C_{139}H_{219}N_{35}O_{30}$, found 2858.65.

EXAMPLE 8

Preparation of CH_3-$(OCH_2CH_2)_7$-O-$(CH_2)_2$-CO-Ile-Lys(Palmitoyl-6Ahx)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:3 TFA

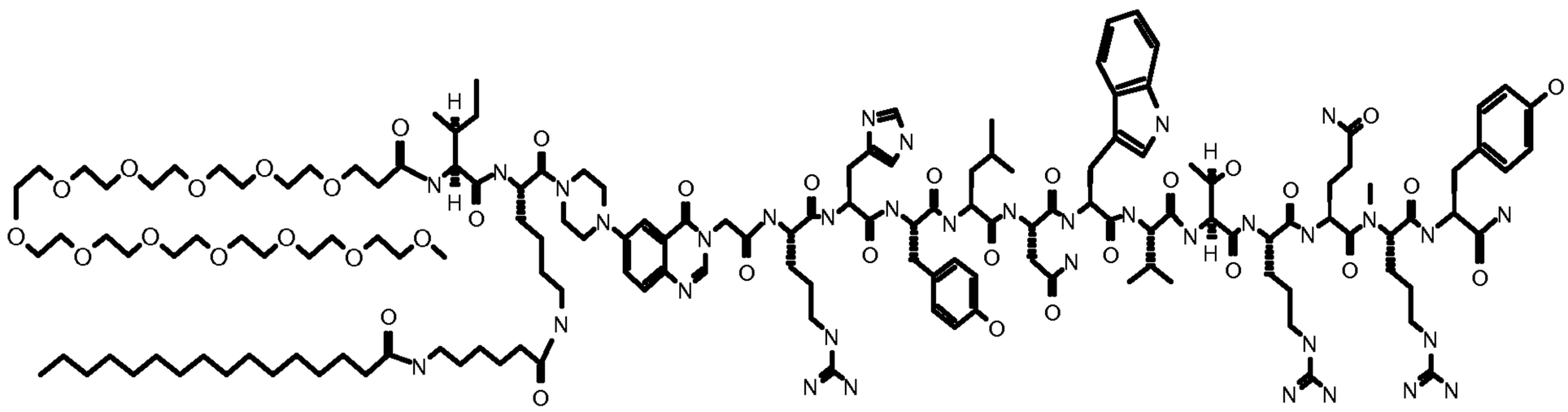


Fmoc-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Rink Amide Resin, 1.0 g (0.22 mmol), obtained from Example 6, was washed with DMF, deprotected, washed and coupled in DMF with m-dPEG n=8 (Quanta Biodesign, 114 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-

carbodiimide (1.50 ml, 2.0 mmol) for 18 hr. After washing with DMF 4 times, the alloc protecting group was removed with 50.0 mg $PdCl_2$(triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF. Fmoc-6aminohexanoic acid (355.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.110 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in 15 mL DMF was coupled for 18 hr. After Fmoc removal and washing with DMF and CH_2Cl_2, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 mmol) and Palmitoyl 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 was stirred for 18 hr and washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 143 mg (24%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{144}H_{229}N_{35}O_{32}$ 2960.74, Found 2960.73.

EXAMPLE 9

Preparation of CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO-Ile-Lys(Palmitoyl-6Ahx)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:3 TFA

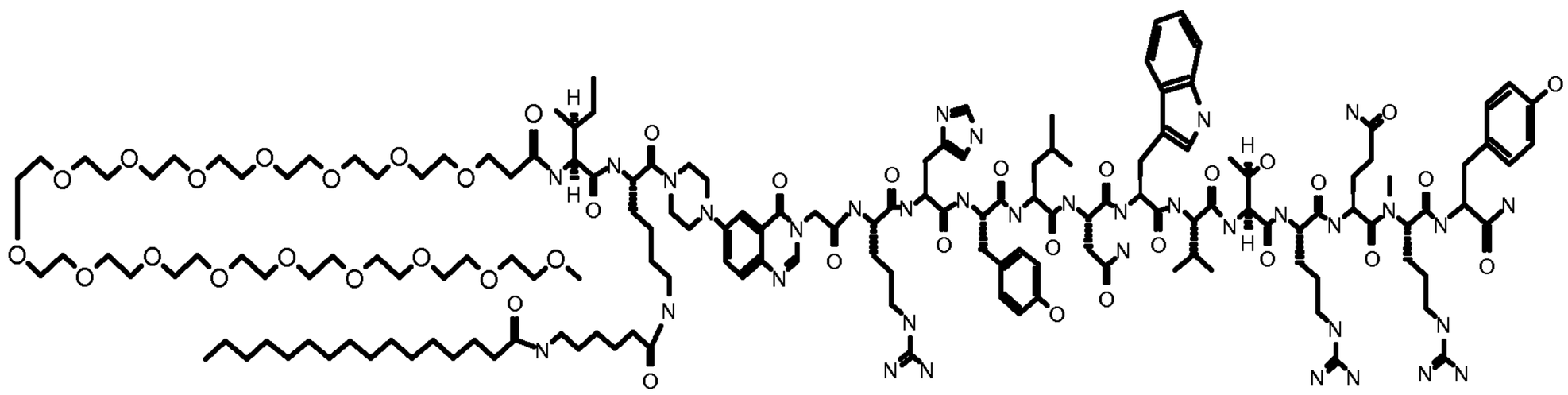


Fmoc-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Rink Amide Resin, 1.0 g (0.22 mmol), obtained from Example 6, was washed with DMF, deprotected, washed and coupled in DMF with m-dPEGn=12 NHS ester (Quanta Biodesign, 189 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and

diisopropyl-carbodiimide (320 μL, 2.0 mmol) for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$(triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF. Fmoc-6aminohexanoic acid (355.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.110 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in 15 mL DMF was coupled for 18 hr. After Fmoc removal and washing with DMF and CH_2Cl_2, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 mmol) and Palmitoyl 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 was stirred for 18 hr and washed with DMF 2 times and CH_2Cl_2l 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 54 mg (9%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{152}H_{245}N_{35}O_{36}$ 3136.84, Found 3136.83.

EXAMPLE 10

Preparation of CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO-Ile-Lys(Palmitoyl-6Ahx)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:3 TFA

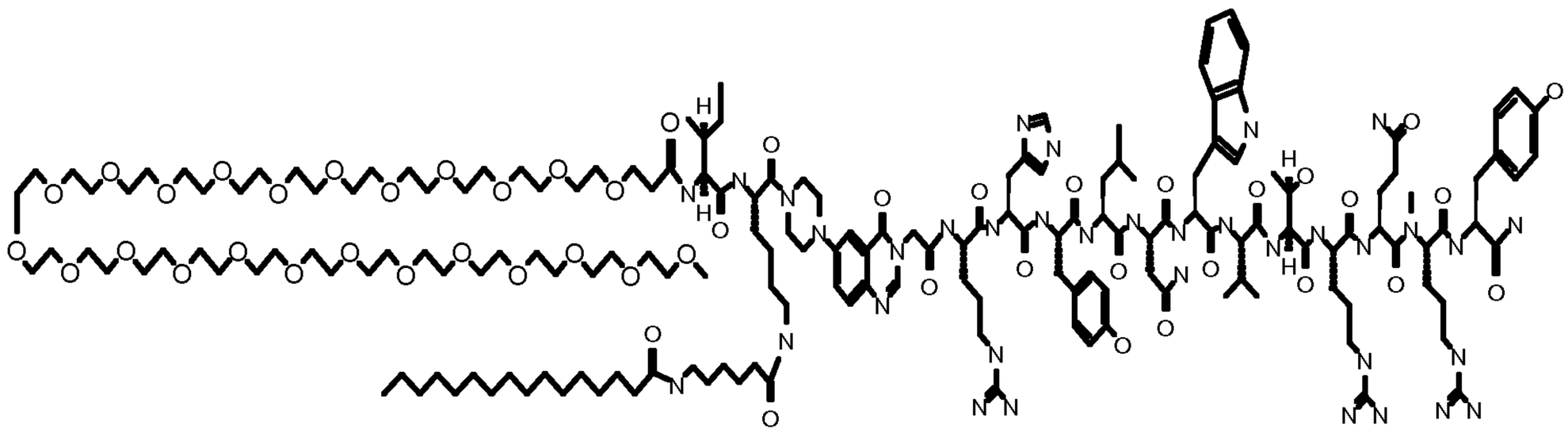


Fmoc-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Rink Amide Resin, 1.0 g (0.22 mmol), obtained from Example 6, was washed with DMF, deprotected and washed and coupled in DMF with m-dPEGn=16 NHS ester (Quanta Biodesign, 238 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and

diisopropyl-carbodiimide (320 µl, 2.0 mmol) for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$(triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF. Fmoc-6aminohexanoic acid (355.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.110 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in 15 mL DMF was coupled for 18 hr. After Fmoc removal and washing with DMF and CH_2Cl_2, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 mmol) and Palmitoyl 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 was stirred for 18 hr and washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 67 mg (10%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{160}H_{261}N_{35}O_{40}$ 3312.95, Found 3312.95.

EXAMPLE 11

Preparation of CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO-Ile-Lys(Palmitoyl-6Ahx)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:3 TFA

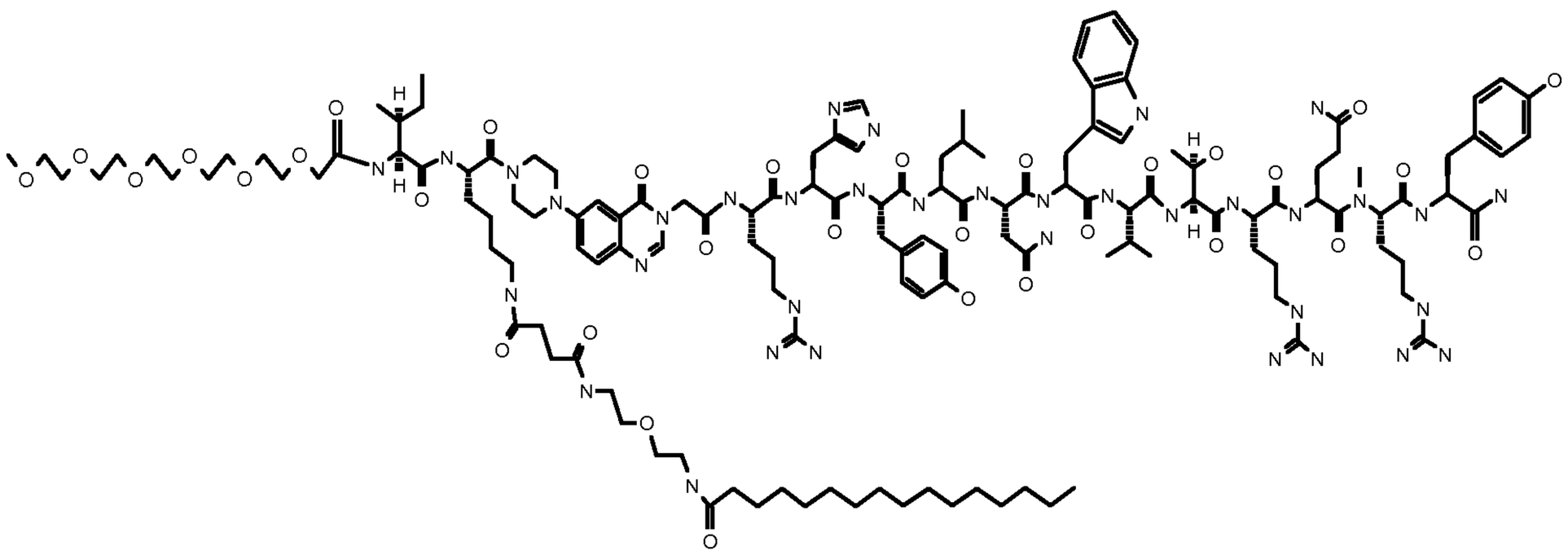


Fmoc-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Rink Amide Resin, 1.0 g (0.22 mmol), obtained from Example 6, was washed with DMF, deprotected, washed and coupled in DMF with m-dPEGn=24 acid (Quanta

Biodesign, 308 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) for 18 hr. After washing with DMF 4 times, the alloc protecting group was removed with 50.0 mg $PdCl_2$(triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF. Fmoc-6aminohexanoic acid (355.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.110 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in 15.0 mL DMF was coupled for 18 hr. After Fmoc removal and washing with DMF and CH_2Cl_2, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 mmol) and Palmitoyl 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 was stirred for 18 hr, washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 40 mg (6%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{176}H_{293}N_{35}O_{48}$ 3665.16, Found 3665.15.

EXAMPLE 12

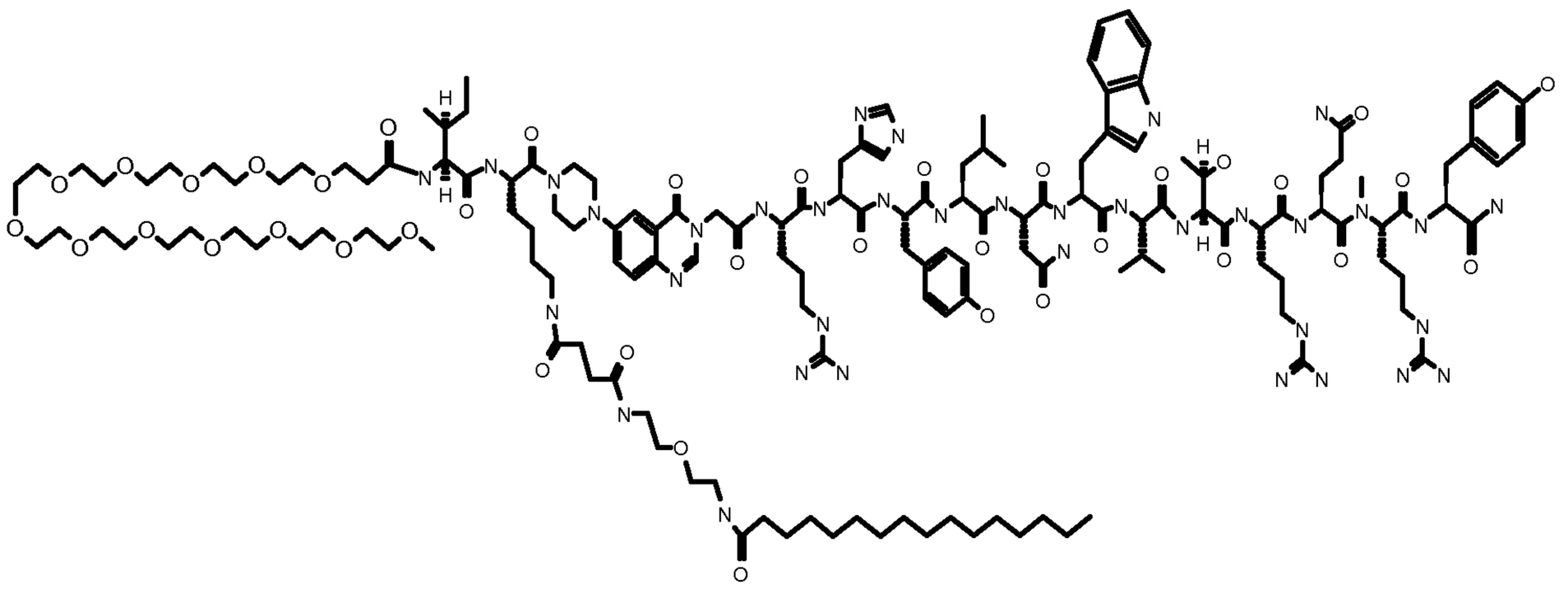
Preparation of CH_3-$(OCH_2CH_2)_5$-O-CH_2-CO-Ile-Lys(Palmitoyl-5AOPS)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:3 TFA



Fmoc-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Rink Amide Resin , 1.0 g (0.22 mmol), obtained from Example 6, was washed with DMF, deprotected, washed and coupled in DMF with [2-(2-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-ethoxy)-ethoxy]-acetic acid (m-dPEGn=6) (Quanta Biodesign, 86 mg, 0.275 mmole); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (1.50 ml, 2.0 mmol) were coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$(triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF. Fmoc-5AOPS (118.0 mg; 0.275 mmol), N-hydroxybenzotriazole (150 mg, 1.110 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled for 18 hr. After Fmoc removal and washing with DMF and CH_2Cl_2, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 mmol) and Palmitoyl 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 was stirred for 18 hr and washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 73mg (13 %) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{141}H_{222}N_{36}O_{32}$ 2931.69, found 2931.70 .

EXAMPLE 13

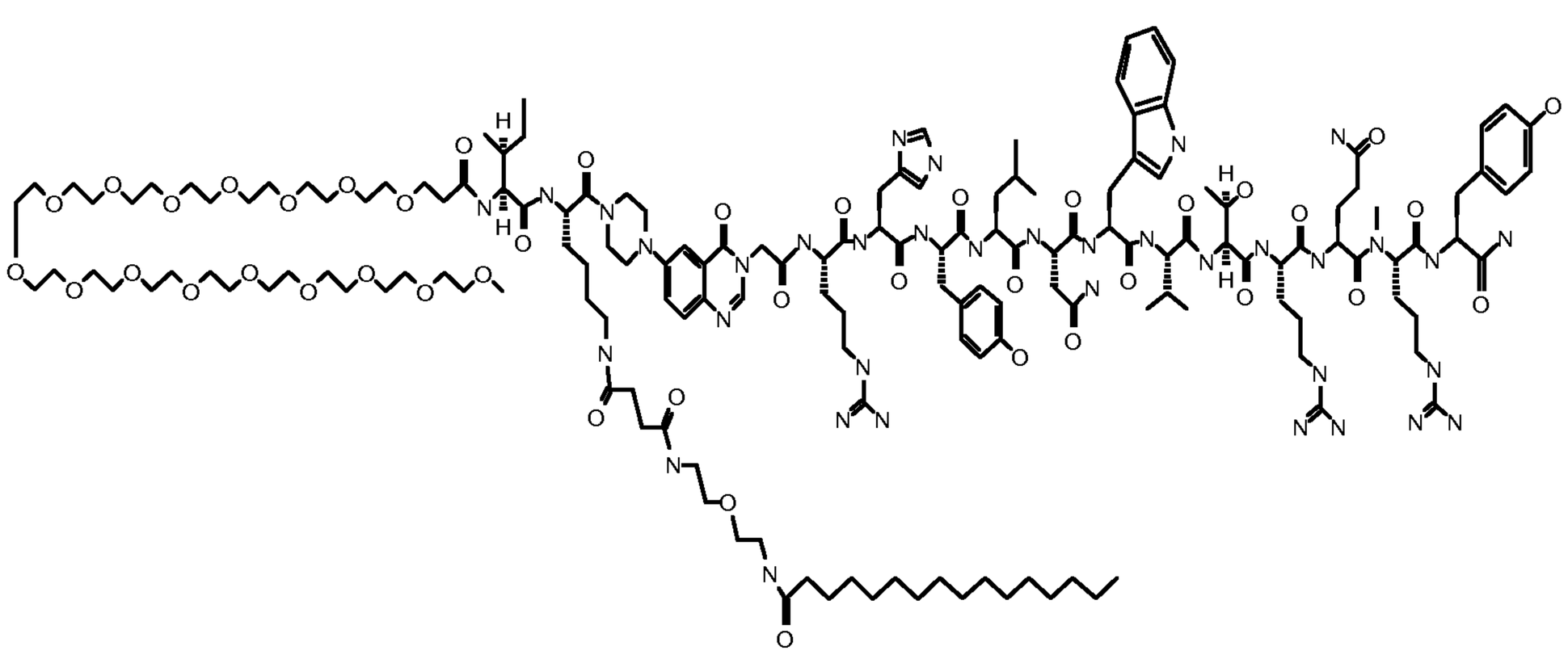
Preparation of CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO-Ile-Lys(Palmitoyl-5AOPS)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:3 TFA



Fmoc-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Rink Amide Resin, 1.0 g (0.22 mmol), obtained from Example 6, was washed with DMF, deprotected and washed and coupled in DMF with m-dPEGn=12 NHS ester (Quanta Biodesign, 189 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (1.50 ml, 2.0 mmol) were coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF. Fmoc-5AOPS (118.0 mg; 0.275 mmol), N-hydroxybenzotriazole (150 mg, 1.110 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled for 18 hr. After Fmoc removal and washing with DMF and CH_2Cl_2, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 mmol) and Palmitoyl 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 was stirred for 18 hr and washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 83 mg (13%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{154}H_{248}N_{36}O_{38}$ 3209.86, found 3209.85.

EXAMPLE 14

Preparation of CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO-Ile-Lys(Palmitoyl-5AOPS)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:3 TFA

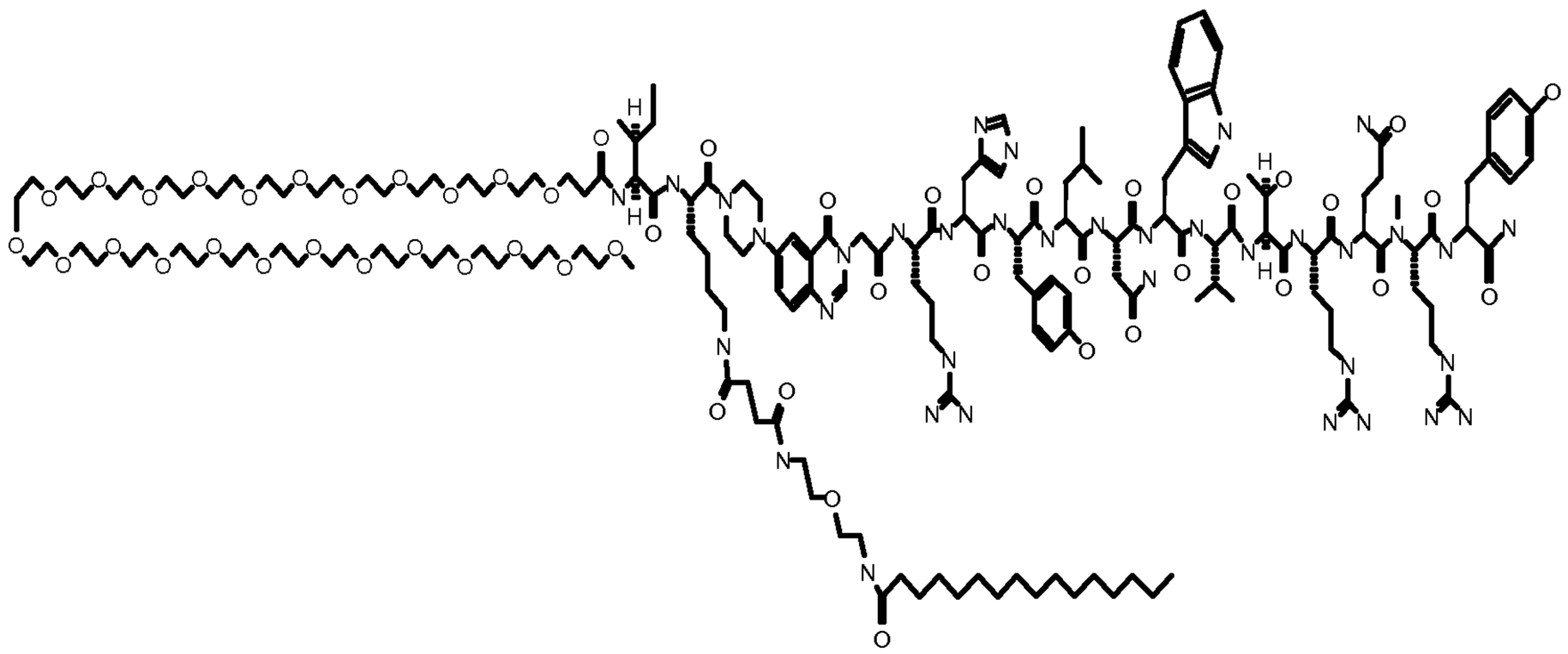


Fmoc-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Rink Amide Resin, 1.0 g (0.22 mmol), obtained from Example 6, was washed with DMF, deprotected and washed and coupled in DMF m-dPEGn=16 NHS ester (Quanta Biodesign, 238 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$ $(triPhenylPhosphine)_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF. Fmoc-5AOPS (118.0 mg; 0.275 mmol), N-hydroxybenzotriazole (150 mg, 1.110 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled for 18 hr. After Fmoc removal and washing with DMF and CH_2Cl_2, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 mmol) and Palmitoyl 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 was stirred for 18 hr and washed with DMF 2 times and CH_2Cl_2 3 times before cleavage

with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 43.5 mg (6 %) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{162}H_{264}N_{36}O_{42}$ 3385.96, found 3385.96.

EXAMPLE 15

Preparation of CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO-Ile-Lys(Palmitoyl-5AOPS)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:3 TFA

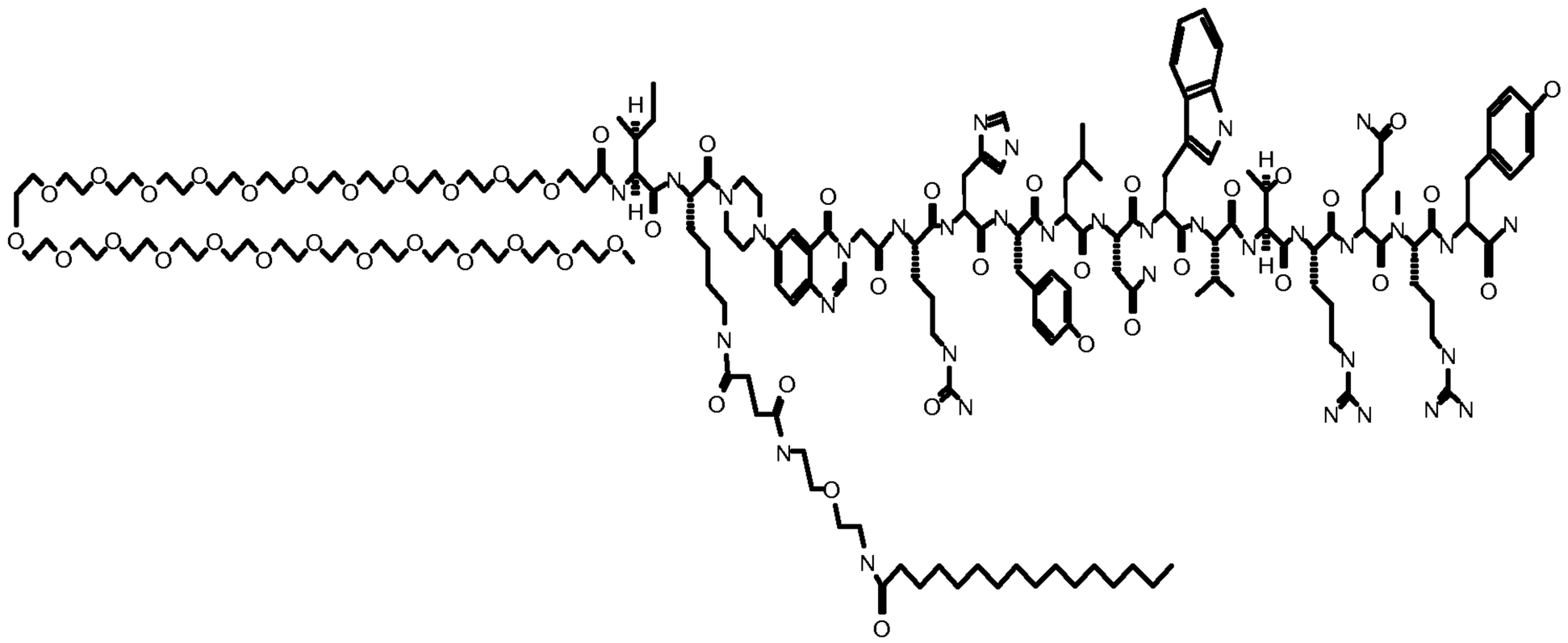


Fmoc-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Rink Amide Resin, 1.0 g (0.22 mmol), obtained from Example 6, was washed with DMF, deprotected and washed and coupled in DMF m-dPEGn=24 acid (Quanta Biodesign, 308 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF. Fmoc-5AOPS (118.0 mg; 0.275 mmol), N-hydroxybenzotriazole (150 mg, 1.110 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in

DMF 15.0 mL was coupled for 18 hr. After Fmoc removal and washing with DMF and CH_2Cl_2, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 mmol) and Palmitoyl 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 was stirred for 18 hr and washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 63 mg (8 %) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{178}H_{296}N_{36}O_{50}$ 3738.17, found 3738.17.

EXAMPLE 16

Preparation of CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO-Ile-Lys(Palmitoyl-5AOPS)-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:2 TFA

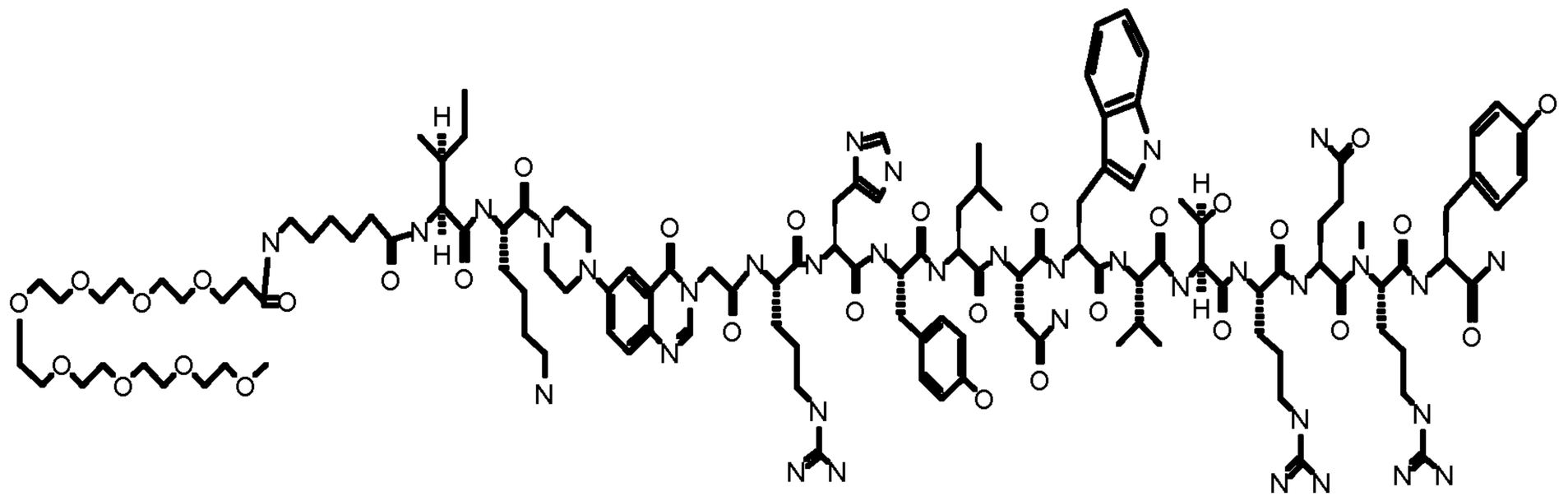


Fmoc-Ile-Lys(Alloc)-Pqa-Cit-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Rink Amide Resin, 1.0 g (0.22 mmol), obtained from Example 6A, was washed with DMF, deprotected and washed and coupled in DMF m-dPEGn=24 acid (Quanta Biodesign, 308 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the

yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF. Fmoc-5AOPS (118.0 mg; 0.275 mmol), N-hydroxybenzotriazole (150 mg, 1.110 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled for 18 hr. After Fmoc removal and washing with DMF and CH_2Cl_2, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 mmol) and Palmitoyl 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 was stirred for 18 hr and washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 76 mg (10%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{178}H_{295}N_{35}O_{51}$ 3739.16, found 3739.16.

EXAMPLE 17

Preparation of CH_3-$(OCH_2CH_2)_7$-O-$(CH_2)_2$-CO-6Ahx-Ile-Lys-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:3 TFA

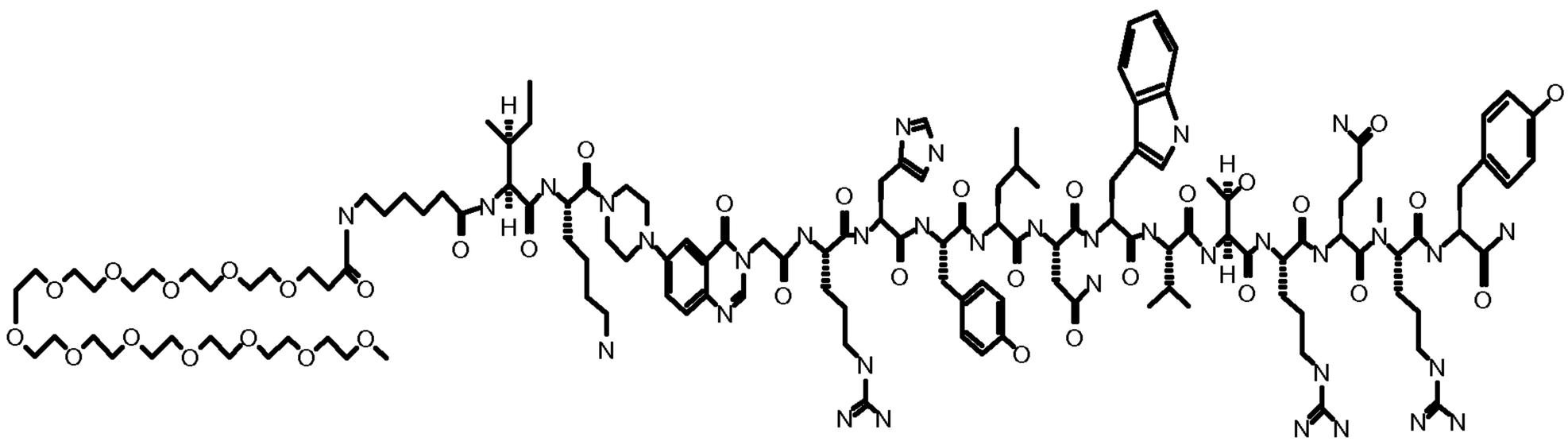


Fmoc-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Rink Amide Resin, 1.0 g (0.22 mmol), obtained from Example 6, was washed with DMF, deprotected and washed and coupled in DMF with Fmoc-6aminohexanoic acid (355.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.110 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in 15 mL DMF was coupled for 18 hr. After Fmoc

removal m-dPEGn=8 (Quanta Biodesign, 114 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and 4 times with CH_2Cl_2 before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 85 mg (16%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{128}H_{199}N_{35}O_{31}$ 2722.51, Found 2722.50.

EXAMPLE 18

Preparation of CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO-6Ahx-Ile-Lys-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:3 TFA

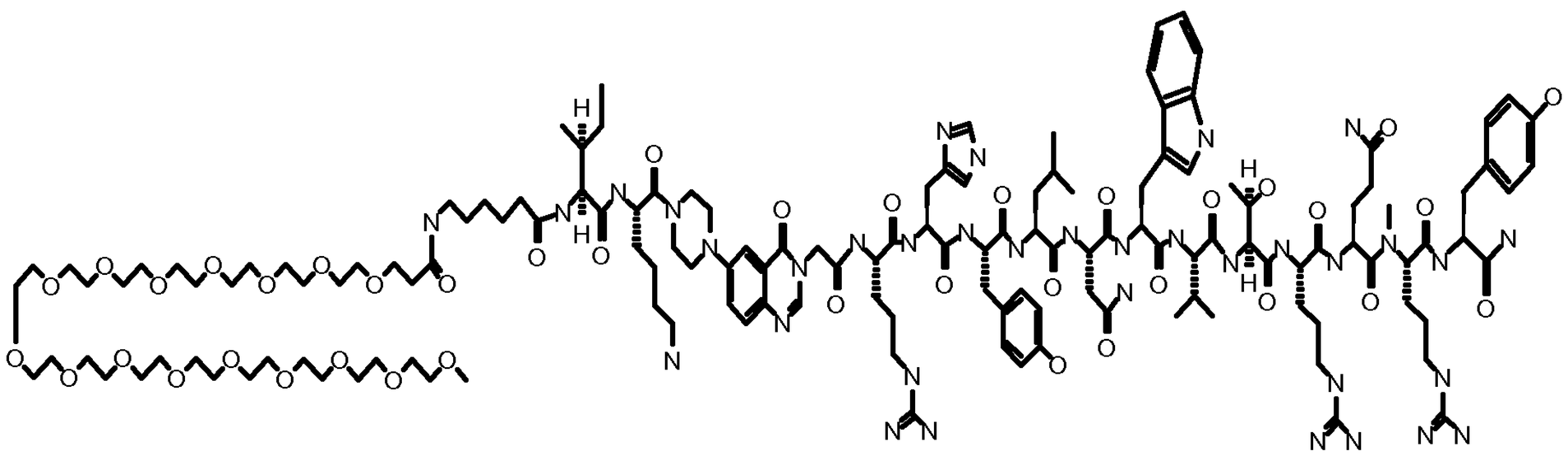


Fmoc-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Rink Amide Resin , 1.0 g (0.22 mmol), obtained from Example 6, was washed with DMF, deprotected and washed and coupled in DMF with Fmoc-6aminohexanoic acid (355.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.110 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in 15 mL DMF was coupled for 18 hr. After Fmoc removal m-dPEGn=12 NHS ester (Quanta Biodesign, 189 mg, 0.275 mmol); N-

hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$(triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and 4 times with CH_2Cl_2 before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 90 mg (16 %) of white amorphous powder. (ES)+- LCMS m/e calculated $C_{136}H_{215}N_{35}O_{35}$ 2898.61, Found 2898.60.

EXAMPLE 19

Preparation of CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO-6Ahx-Ile-Lys-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:3 TFA

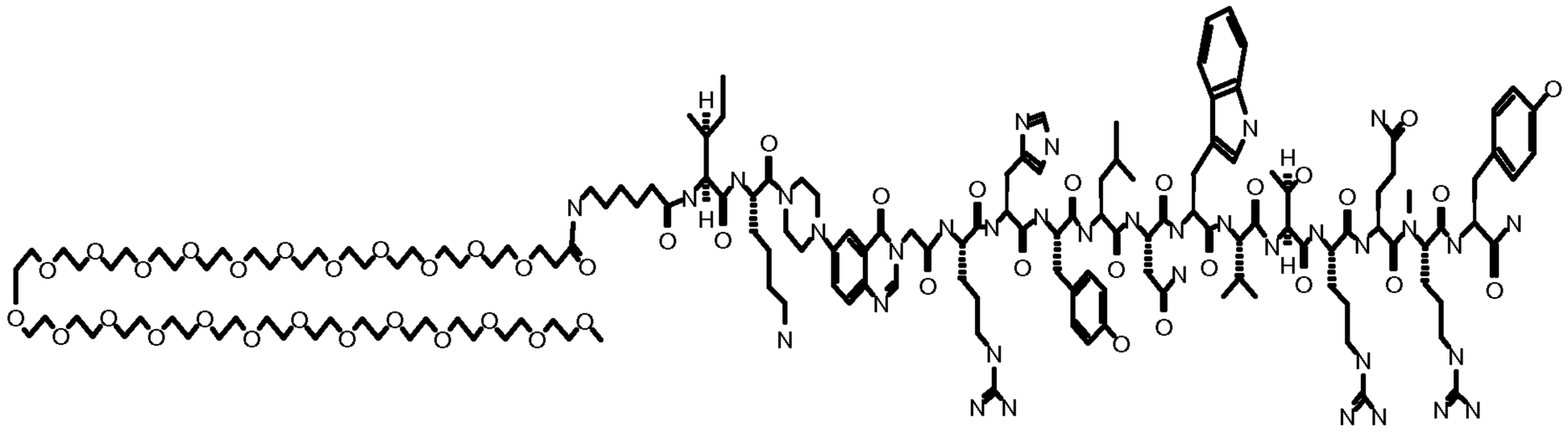


Fmoc-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Rink Amide Resin , 1.0 g (0.22 mmol), obtained from Example 6, was washed with DMF, deprotected and washed and coupled in DMF with Fmoc-6aminohexanoic acid (355.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.110 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in 15 mL DMF was coupled for 18 hr. After Fmoc removal m-dPEGn=16 NHS ester (Quanta Biodesign, 238 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µL 2.0 mmole)

were coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$(triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and 4 times with CH_2Cl_2 before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 92 mg (15%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{144}H_{231}N_{35}O_{39}$ 3074.72, Found 3074.72.

EXAMPLE 20

Preparation of CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO-6Ahx-Ile-Lys-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:3 TFA

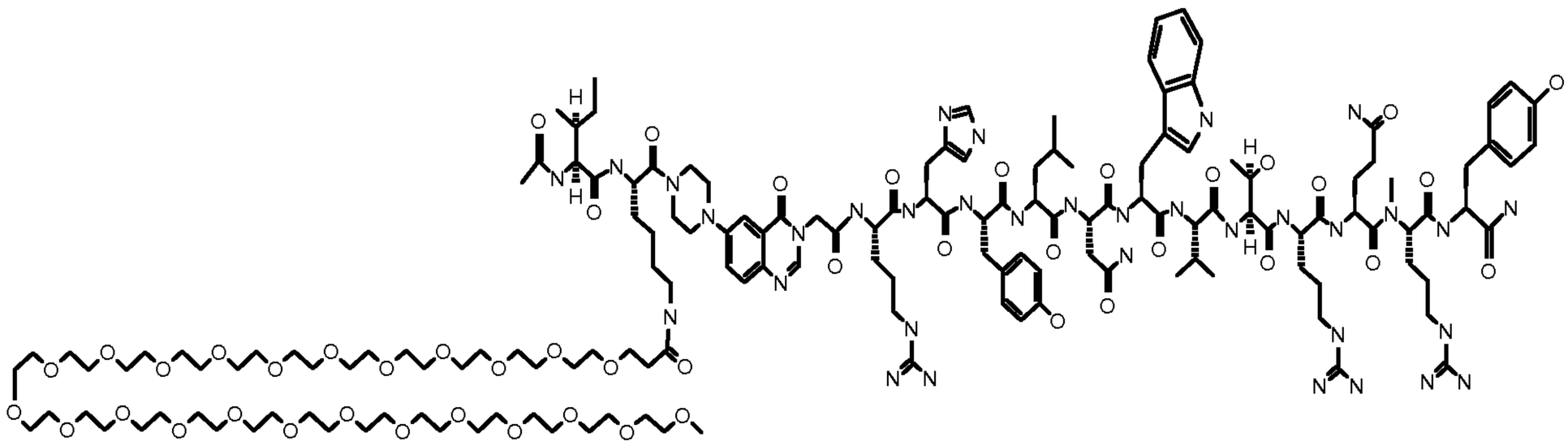


Fmoc-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Amide Rink Resin, 1.0 g (0.22 mmol), obtained from Example 6, was washed with DMF, deprotected and washed and coupled in DMF with Fmoc-6aminohexanoic acid (355.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.110 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in 15 mL DMF was coupled for 18 hr. After Fmoc removal m-dPEGn=24 (Quanta Biodesign, 308 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg

$PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and 4 times with CH_2Cl_2 before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 89 mg (13%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{160}H_{263}N_{35}O_{47}$ 3426.93, Found 3426.93.

EXAMPLE 21

Preparation of Ac-Ile-Lys[CH_3-(OCH_2CH_2)$_{23}$-O-(CH_2)$_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:3 TFA

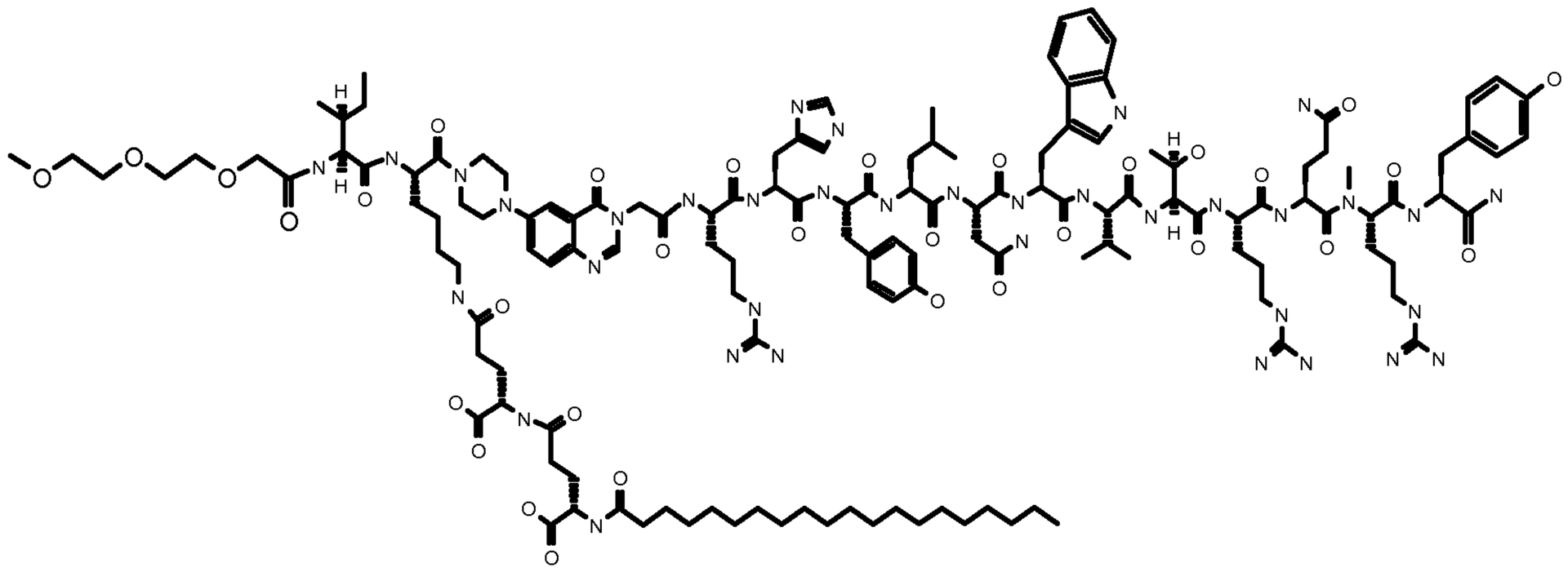


Fmoc-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Rink Amide Resin , 1.0 g (0.22 mmol), obtained from Example 6, was washed with DMF, deprotected and Acetylated. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and m-

dPEGn=24 (Quanta Biodesign, 308 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. The peptide resin was washed 4 times with CH_2Cl_2 before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 66 mg (10%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{156}H_{254}N_{34}O_{47}$ 3355.85, Found 3355.84.

EXAMPLE 22

Preparation of CH_3-$(OCH_2CH_2)_2$-O-CH_2-CO-Ile-Lys(Eicosanoyl-gammaGlu-gammaGlu)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:2 TFA

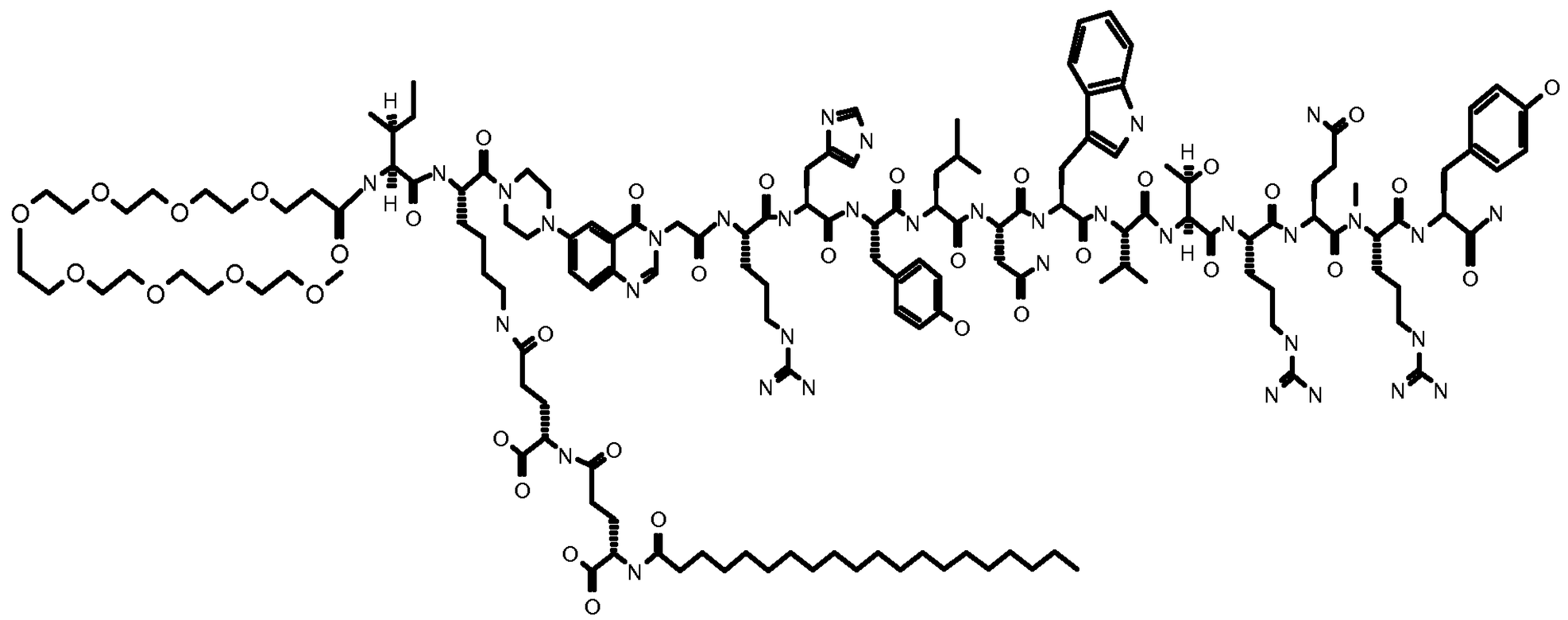


Fmoc-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Rink Amide Resin, 1.0 g (0.22 mmol), obtained from Example 6, was washed with DMF, deprotected and washed and coupled in DMF and 2-[2-(2-Methoxy-ethoxy)-ethoxy]-acetic acid (m-dPEGn=3) (Quanta Biodesign, 178 mg, 1.0 mmol); N-hydroxybenzotriazole (135 mg, 1.00 mmol), and diisopropyl-carbodiimide (3.0 ml, 4.0 mmol) were coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$(triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2

times with DMF, 2 times 5% DIEA/DMF and 4 times DMF. Fmoc-Glu-OtBu (426.0 mg; 01.0 mmol), N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled for 18 hr. After Fmoc removal Fmoc-Glu-OtBu (426.0 mg; 01.0 mmol), N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol)in DMF 15.0 mL was coupled for 18 hr. After Fmoc removal, Eicosanoic acid 313.0 mg (1.0 mmol) N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled for 18 hr. The resin was washed 4 times alternately with MeOH and CH_2Cl_2 and finally 4 times with CH_2Cl_2 before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 31 mg (5%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{141}H_{218}N_{36}O_{32}$ 2927.65, Found 2927.66.

EXAMPLE 23

Preparation of CH_3-$(OCH_2CH_2)_7$-O-$(CH_2)_2$-CO-Ile-Lys(Eicosanoyl-gammaGlu-gammaGlu)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr -NH_2 1:2 TFA

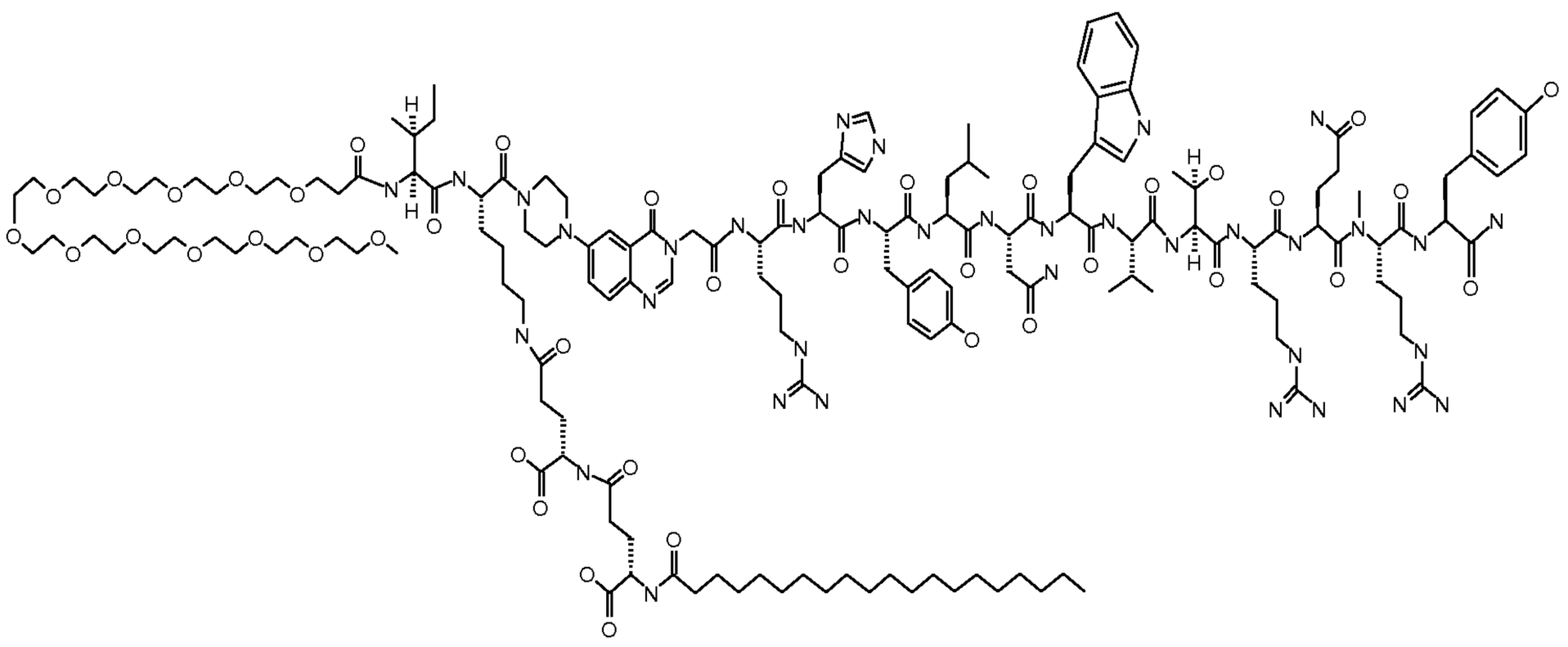


Fmoc-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Rink Amide Resin resin, 1.0 g (0.22 mmol), obtained from Example 6, was washed with DMF, deprotected and washed and coupled in DMF with m-dPEGn=8 (Quanta Biodesign, 114 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr.

After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF. Fmoc-Glu-OtBu (426.0 mg; 01.0 mmol), N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled for 18 hr. After Fmoc removal Fmoc-Glu-OtBu (426.0 mg; 01.0 mmol), N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol)in DMF 15.0 mL was coupled for 18 hr. After Fmoc removal Eicosanoic acid 313.0 mg (1.0 mmol) N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled for 18 hr. The resin was washed 4 times alternately with MeOH and CH_2Cl_2 and finally 4 times with CH_2Cl_2 before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 67 mg (11%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{152}H_{240}N_{36}O_{37}$ 3161.80, Found 3161.79.

EXAMPLE 24

Preparation of CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO-Ile-Lys(Eicosanoyl-gammaGlu-gammaGlu)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:2 TFA

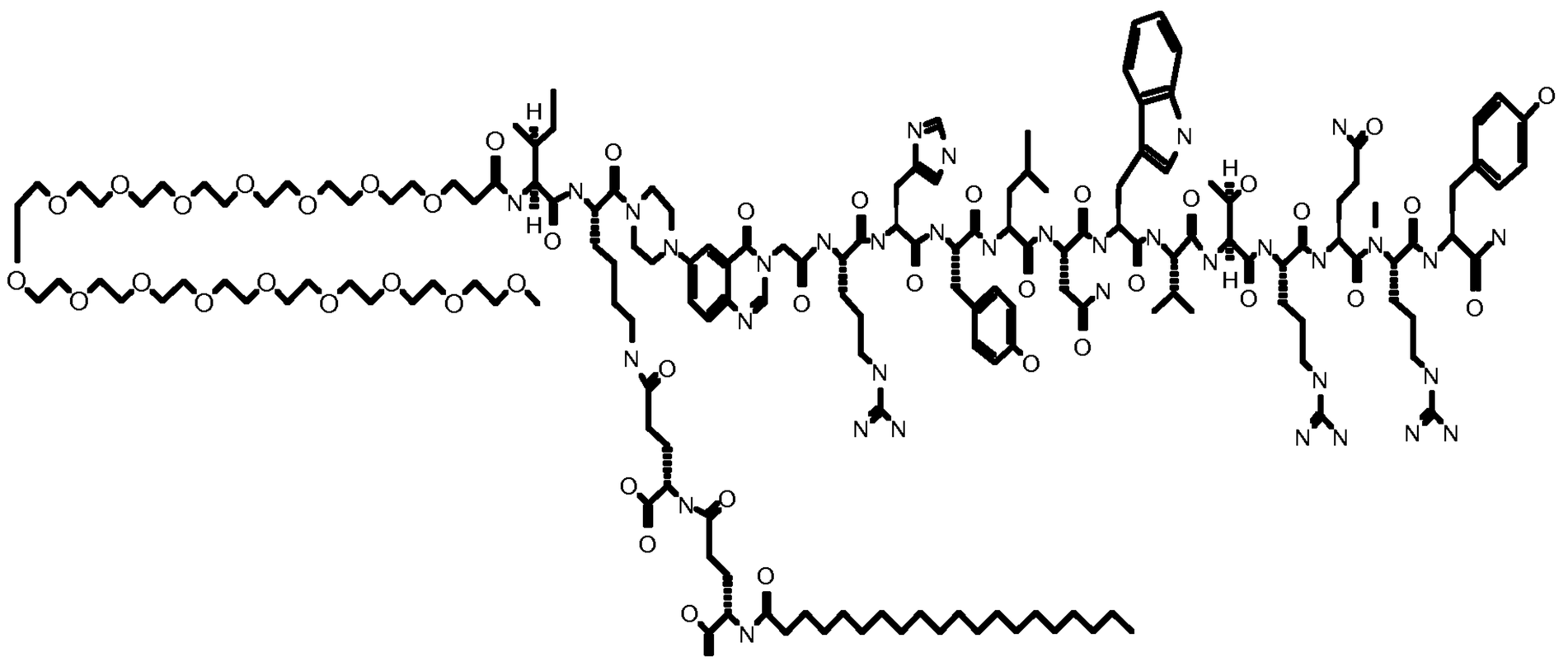


Fmoc-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Amide Rink Resin, 1.0 g (0.22 mmol), obtained from Example 6, was washed with DMF, deprotected and washed and coupled in DMF with m-dPEGn=12 NHS ester (Quanta Biodesign, 189 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 μL, 2.0 mmol) were coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF. Fmoc-Glu-OtBu (426.0 mg; 01.0 mmol), N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled for 18 hr. After Fmoc removal Fmoc-Glu-OtBu (426.0 mg; 01.0 mmol), N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol)in DMF 15.0 mL was coupled for 18 hr. After Fmoc removal Eicosanoic acid 313.0 mg (1.0 mm) N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled for 18 hr. The resin was washed 4 times alternately with MeOH and CH_2Cl_2 and finally 4 times with CH_2Cl_2 before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged,

washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 66 mg (11%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{146}H_{232}N_{36}O_{34}$ 3033.75, Found 3033.76.

EXAMPLE 25

Preparation of CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO-Ile-Lys(Eicosanoyl-gammaGlu-gammaGlu)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:2 TFA

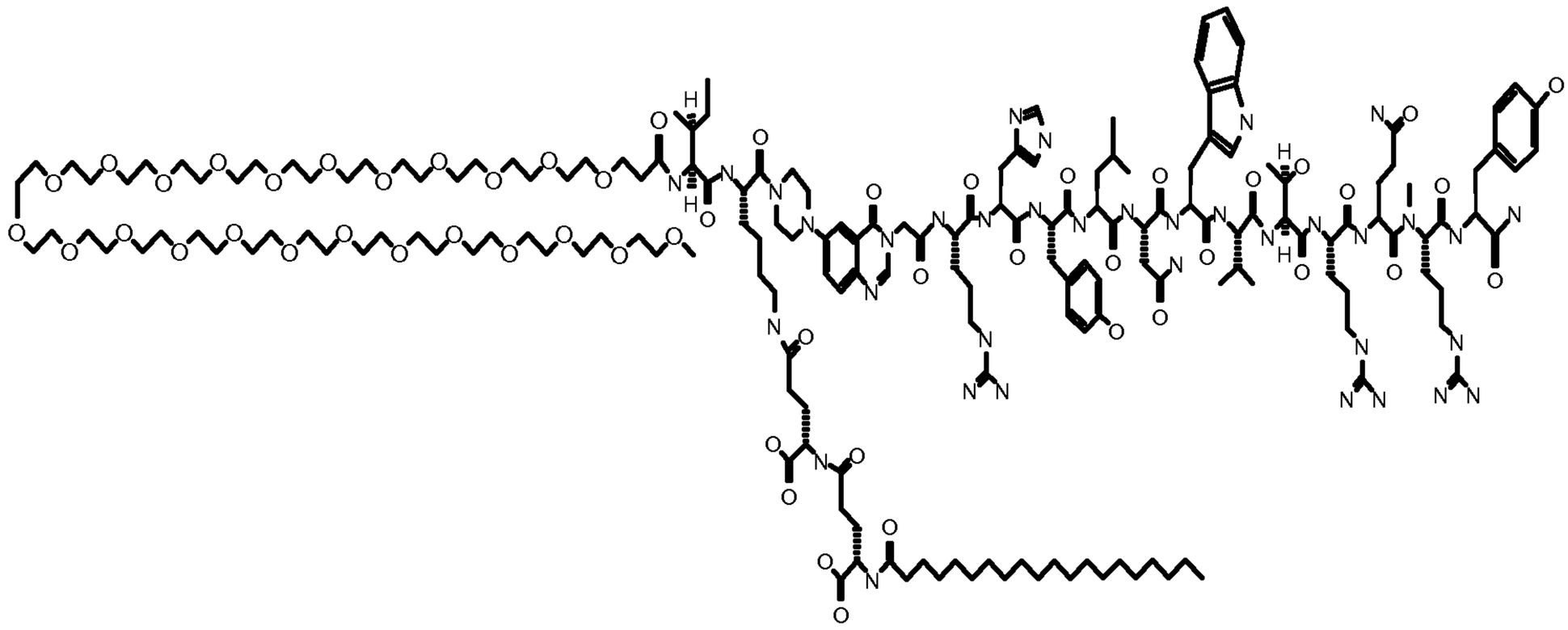


Fmoc-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Rink Amide Resin, 1.0 g (0.22 mmol), obtained from Example 6, was washed with DMF, deprotected and washed and coupled in DMF with m-dPEGn=16 NHS ester (Quanta Biodesign, 238 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µL , 2.0 mmol) were coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF. Fmoc-Glu-OtBu (426.0 mg; 01.0 mmol), N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in

DMF 15.0 mL was coupled for 18 hr. After Fmoc removal Fmoc-Glu-OtBu (426.0 mg; 01.0 mmol), N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled for 18 hr. After Fmoc removal Eicosanoic acid 313.0 mg (1.0 mmol) N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled for 18 hr. The resin was washed 4 times alternately with MeOH and CH_2Cl_2 and finally 4 times with CH_2Cl_2 before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 67 mg (10%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{168}H_{272}N_{36}O_{45}$ 3514.01, Found 3513.99.

EXAMPLE 26

Preparation of CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO-Ile-Lys(Eicosanoyl-gammaGlu-gammaGlu)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:2 TFA

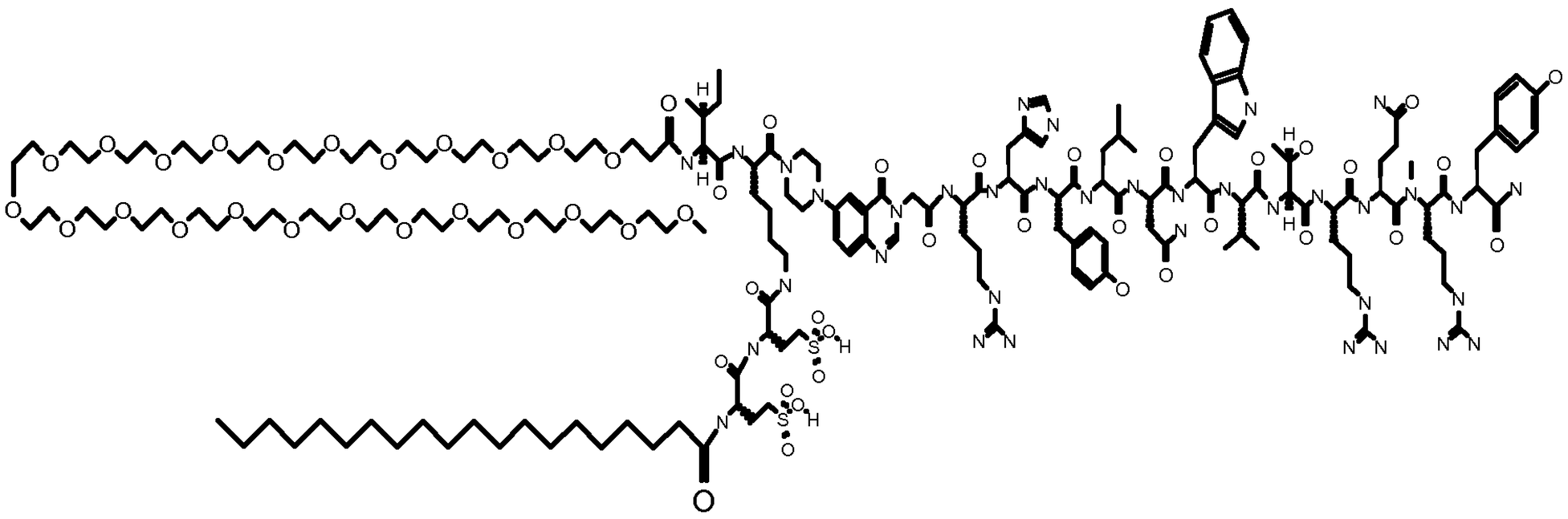


Fmoc-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Rink Amide Resin, 1.0 g (0.22 mmol), obtained from Example 6, was washed with DMF, deprotected and washed and coupled in DMF with m-dPEGn=24 (Quanta Biodesign, 308 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an

atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF. Fmoc-Glu-OtBu (426.0 mg; 01.0 mmol), N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled for 18 hr. After Fmoc removal Fmoc-Glu-OtBu (426.0 mg; 01.0 mmol), N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled for 18 hr. After Fmoc removal Eicosanoic acid 313.0 mg (1.0 mm) N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled for 18 hr. The resin was washed 4 times alternately with MeOH and CH_2Cl_2 and finally 4 times with CH_2Cl_2 before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 34 mg (4.4%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{184}H_{304}N_{36}O_{53}$ 3866.22, Found 3866.21.

EXAMPLE 27

Preparation of CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO-Ile-Lys(Eicosanoyl-Cys{SO_3}-Cys{SO_3})-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr -NH_2 1:3 TFA

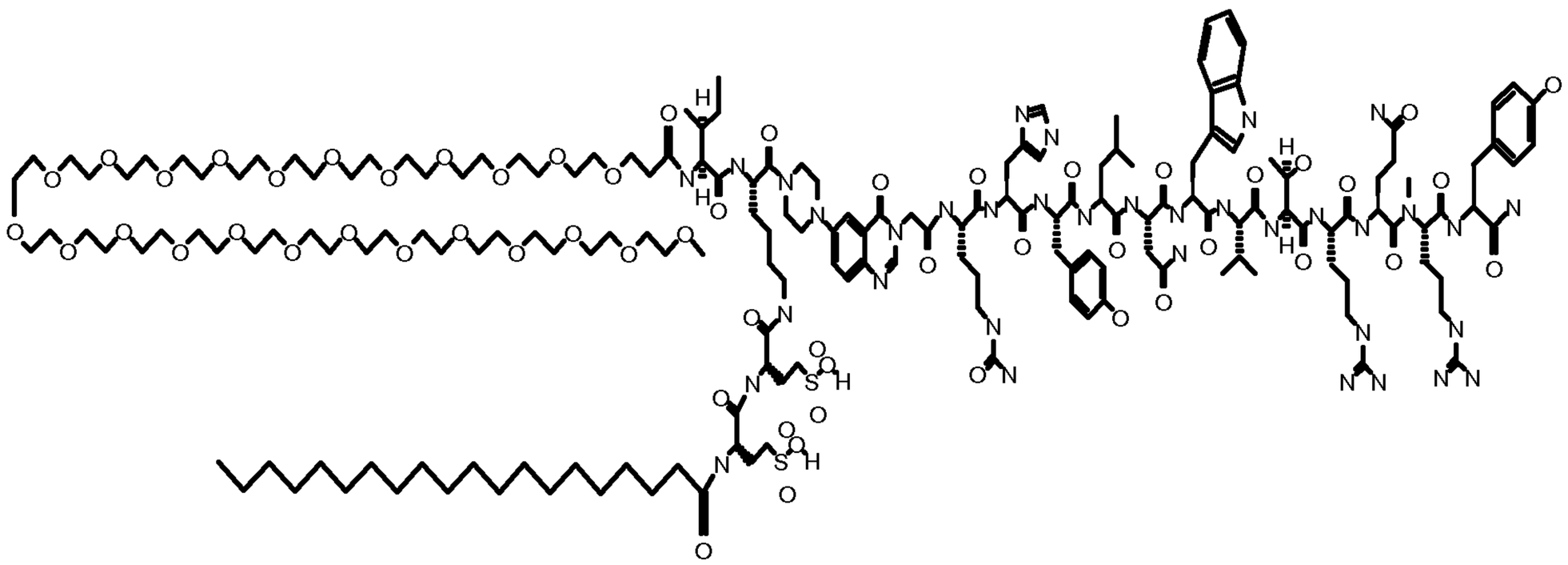


Fmoc-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Rink Amide Resin, 1.0 g (0.22 mmol), obtained from

Example 6, was washed with DMF, deprotected and washed and coupled in DMF with m-dPEGn=24 (Quanta Biodesign, 308 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF. After washing Fmoc-Cys(SO_3)Na_2 (470.0 mg; 01.0 mmol), N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled 18 hr. After Fmoc removal Fmoc-Cys(SO_3)Na_2 (470.0 mg; 01.0 mmol), N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol)in DMF 15.0 mL was coupled 18 hr. The ninhydrin was a reddish-purole and Fmoc-Cys(SO_3)Na_2 (470.0 mg; 01.0 mm;), N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled 6 hf. After Fmoc removal Eicosanoic acid 313.0 mg (1.0 mmol) N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled for 18 hr. The resin was washed 4 times alternately with MeOH and CH_2Cl_2 and finally 4 times with CH_2Cl_2 before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 28.4 mg (4%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{182}H_{304}N_{36}O_{55}S_2$ 3938.15, Found 3938.14.

EXAMPLE 28

Preparation of CH_3-(OCH_2CH_2)$_{23}$-O-(CH_2)$_2$-CO-Ile-Lys(Eicosanoyl-Cys{SO_3}-Cys{SO_3})-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:2 TFA

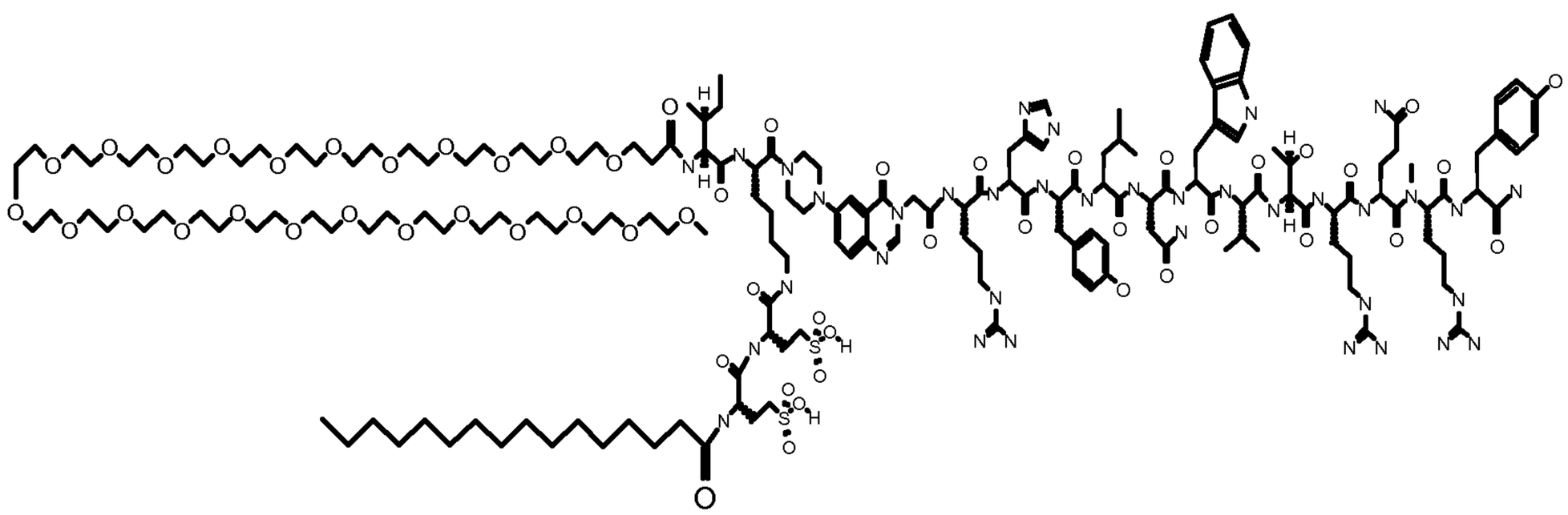


Fmoc-Ile-Lys(Alloc)-Pqa-Cit-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Ring Amide Resin, 1.0 g (0.22 mmol), obtained fro Example 6A, was washed with DMF, deprotected and washed and coupled in DMF with m-dPEGn=24 (Quanta Biodesign, 308 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF. After washing Fmoc-Cys(SO_3)Na_2 (470.0 mg; 01.0 mmol), N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled 18 hr. After Fmoc removal Fmoc-Cys(SO_3)Na_2 (470.0 mg; 01.0 mmol), N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol)in DMF 15.0 mL was coupled 18 hr. The ninhydrin was a reddish-purole and Fmoc-Cys(SO_3)Na_2 (470.0 mg; 01.0 mmol), N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled 6 hf. After Fmoc removal Eicosanoic acid 313.0 mg (1.0 mmol) N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled for 18 hr. The resin

was washed 4 times alternately with MeOH and CH_2Cl_2 and finally 4 times with CH_2Cl_2 before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 51 mg (6 %) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{182}H_{303}N_{35}O_{56}S_2$ 3939.14, Found 3939.14.

EXAMPLE 29

Preparation of CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO-Ile-Lys(Palmitoyl-Cys{SO_3}-Cys{SO_3})-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:3 TFA

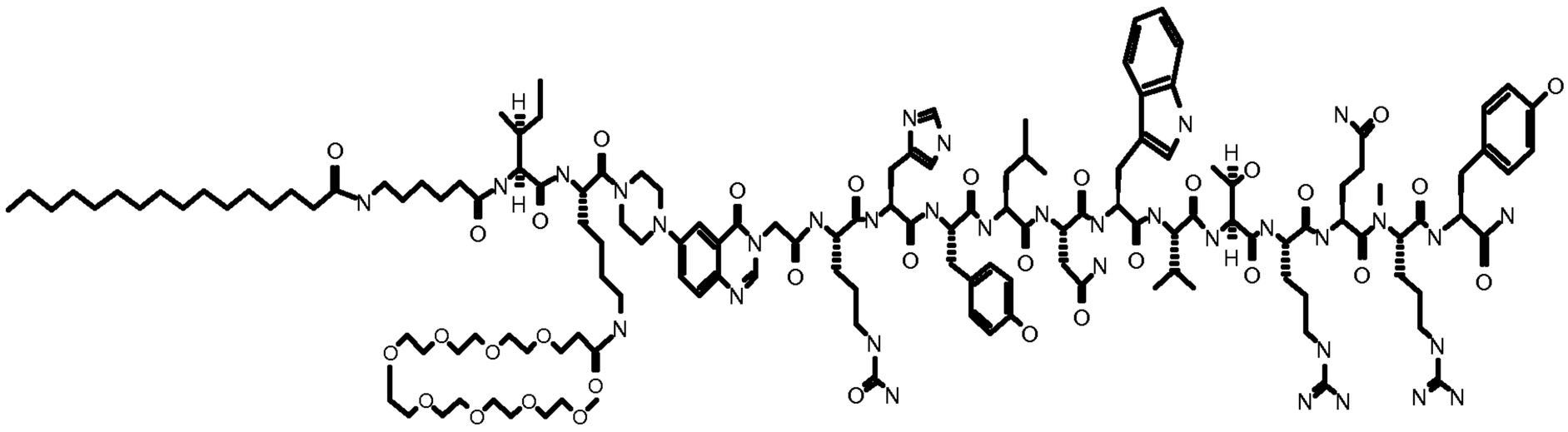


Fmoc-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Rink Amide Resin, 1.0 g (0.22 mmol), obtained fro Example 6, was washed with DMF, deprotected and washed and coupled in DMF with m-dPEGn=24 (Quanta Biodesign, 308 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF. After washing Fmoc-Cys(SO_3)Na_2 (470.0 mg; 01.0 mmol), N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0

mmol) in DMF 15.0 mL was coupled 18 hr. After Fmoc removal Fmoc-Cys(SO_3)Na_2 (470.0 mg; 01.0 mmol), N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled 18 hr. The ninhydrin was a reddish-purole and Fmoc-Cys(SO_3)Na_2 (470.0 mg; 01.0 mmol), N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled 6 hf. After Fmoc removal, washing with DMF and CH_2Cl_2, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 mmol) and Palmitoyl 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 was stirred for 18 hr and washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 44 mg (6%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{178}H_{296}N_{36}O_{55}S_2$ 3882.0, Found 3881.98.

EXAMPLE 30

Preparation of Palmitoyl-6Ahx-Ile-Lys[CH_3-$(OCH_2CH_2)_7$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:2 TFA

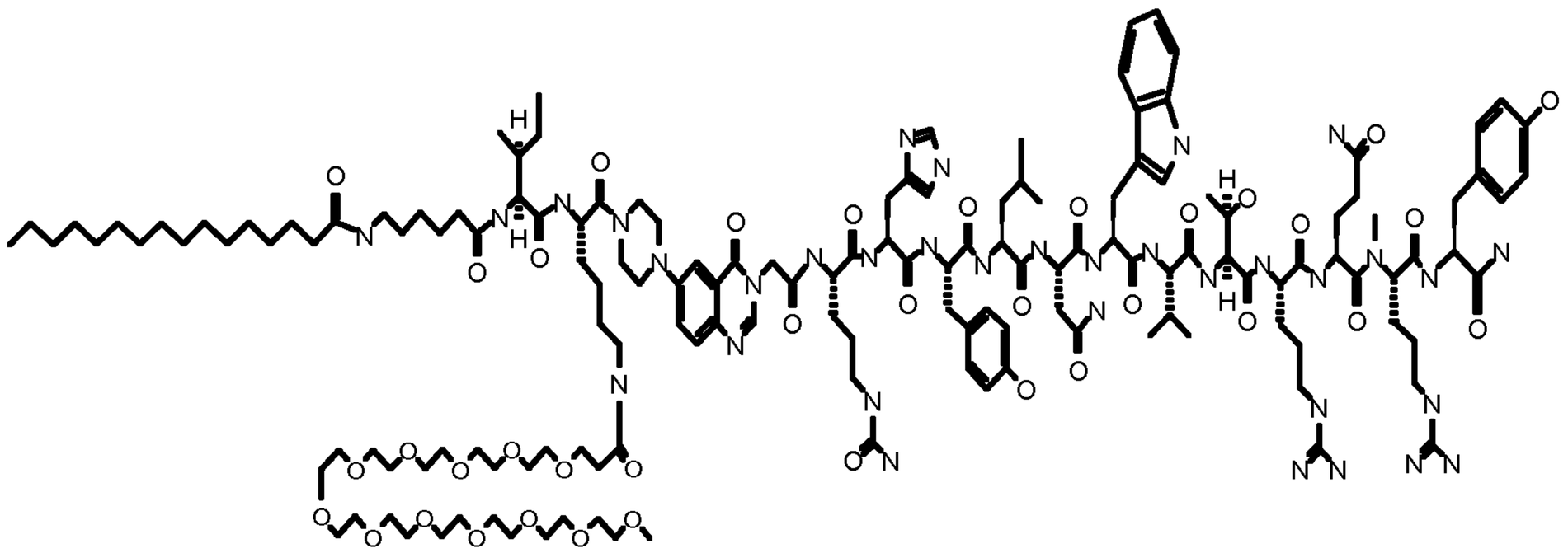


Fmoc-Ile-Lys(Alloc)-Pqa-Cit-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Rink Amide Resin , 1.0 g (0.22 mmol) , obtained from Example 6A, was washed with DMF, deprotected and washed and coupled in DMF with Fmoc-6aminohexanoic acid (355.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.110 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in 15 mL DMF was coupled for 18 hr. After Fmoc removal and washing with DMF and CH_2Cl_2, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 mmol) and Palmitoyl 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 was stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and coupled in DMF with m-dPEGn=12 NHS ester (Quanta Biodesign, 189 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (1.50 ml, 2.0 mmol) were coupled and stirred for 18 hr. The resin was washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 73 mg (12%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{144}H_{228}N_{34}O_{33}$ 2961.72, Found 2961.70.

EXAMPLE 31

Preparation of Palmitoyl-6Ahx-Ile-Lys[CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:2 TFA

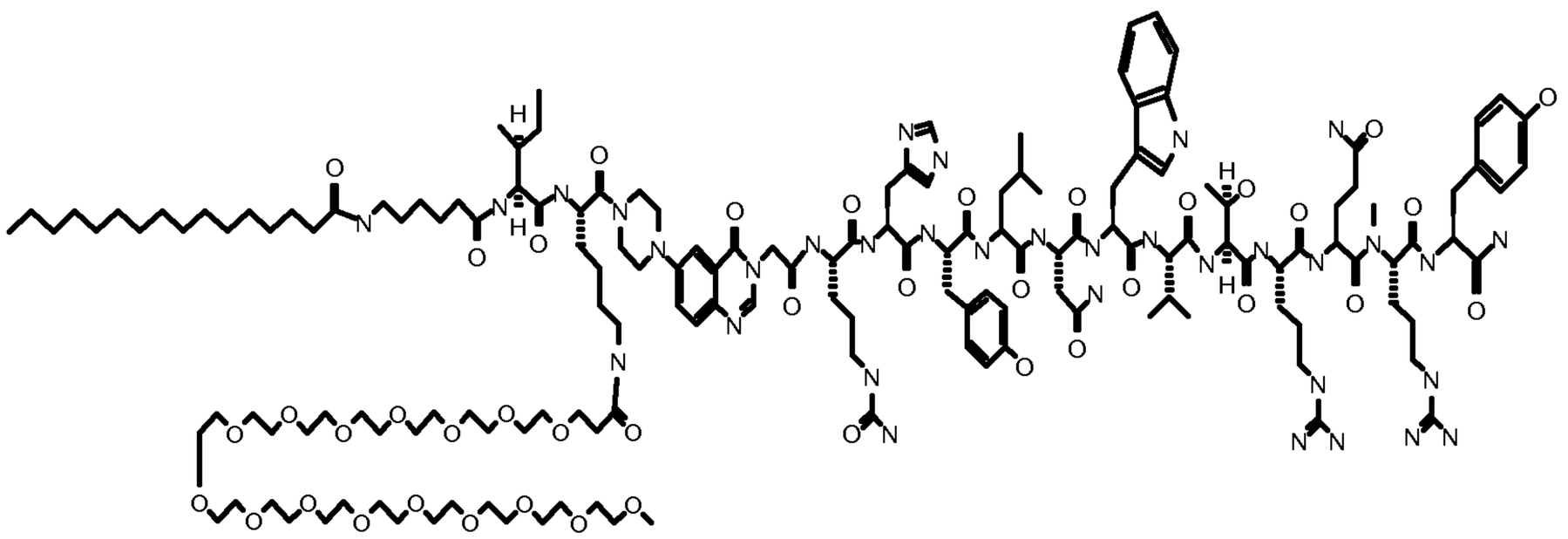


Fmoc-Ile-Lys(Alloc)-Pqa-Cit-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Rink Amide Resin, 1.0 g (0.22 mmol), obtained from Example 6A, was washed with DMF, deprotected and washed and coupled in DMF with Fmoc-

6aminohexanoic acid (355.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.110 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in 15 mL DMF was coupled for 18 hr. After Fmoc removal and washing with DMF and CH_2Cl_2, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 mmol) and Palmitoyl 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 was stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and coupled in DMF with m-dPEGn=12 NHS ester (Quanta Biodesign, 189 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (1.50 ml, 2.0 mmol) were coupled and stirred for 18 hr. The resin was washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 46 mg (16%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{152}H_{244}N_{34}O_{37}$ 3137.83 Found 3137.83.

EXAMPLE 32

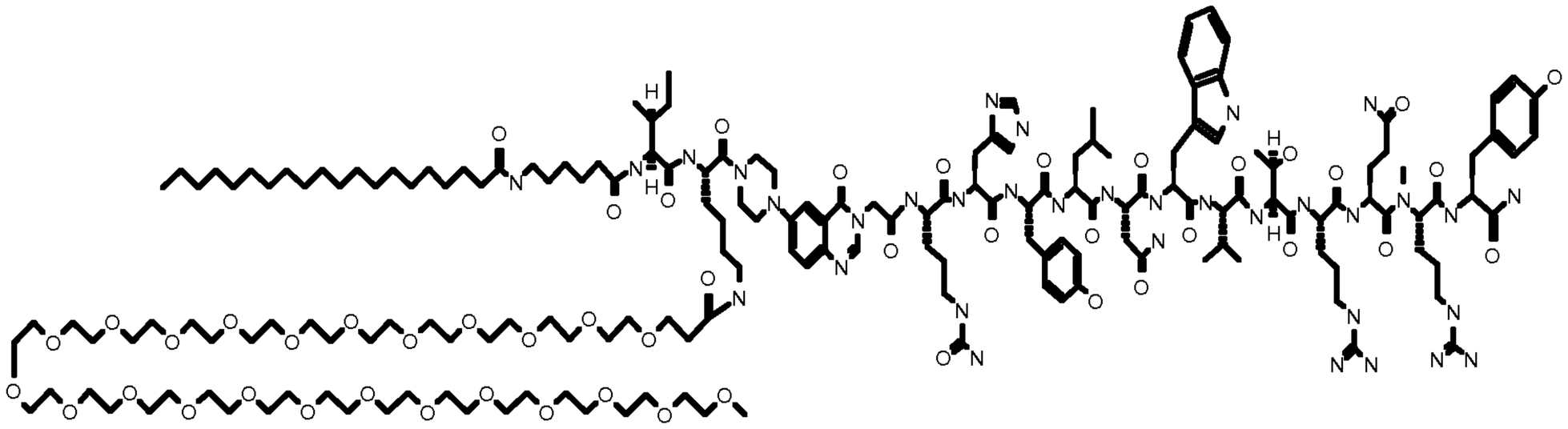
Preparation of Palmitoyl-6Ahx-Ile-Lys[CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:2 TFA



Fmoc-Ile-Lys(Alloc)-Pqa-Cit-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Rink Amide Resin resin, 1.0 g (0.22 mmol), obtained from Example 6A, was washed with DMF, deprotected and washed and coupled in DMF with Fmoc-6aminohexanoic acid (355.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.110 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in 15 mL DMF was coupled for 18 hr. After Fmoc removal and washing with DMF and CH_2Cl_2, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 mmol) and Palmitoyl 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 was stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and coupled in DMF with m-dPEGn=16 NHS ester (Quanta Biodesign, 238 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. The resin was washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 32 mg (5%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{160}H_{260}N_{34}O_4$ 3313.93, Found 3313.93.

EXAMPLE 33

Preparation of Eicosanoyl-6Ahx-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:2 TFA

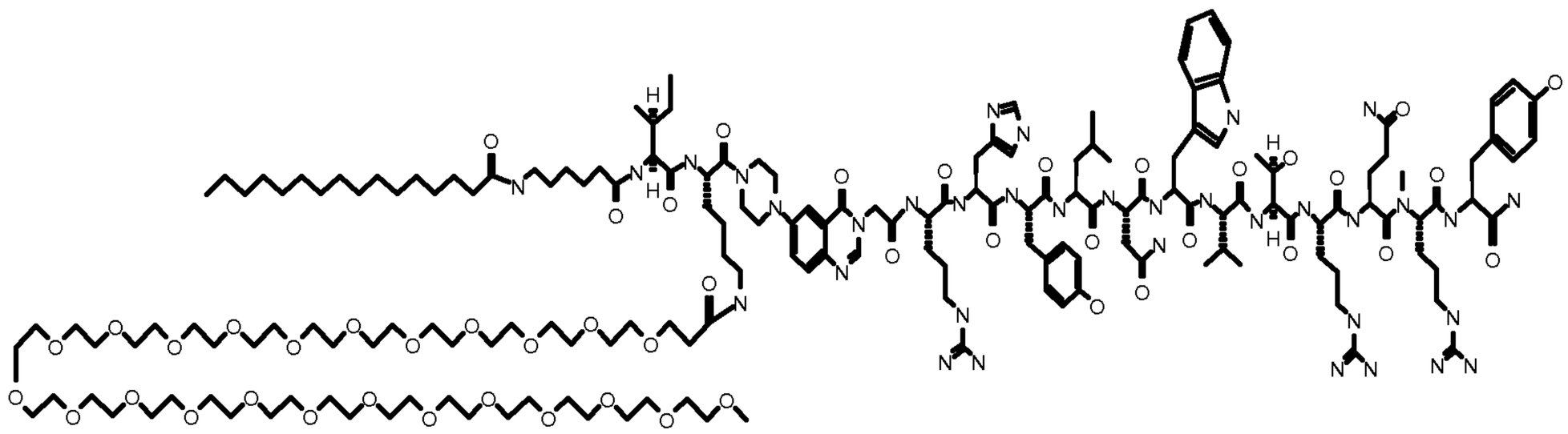


Fmoc-Ile-Lys(Alloc)-Pqa-Cit-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Amide Resin, 1.0 g (0.22 mmol), obtained from Example 6A, was washed with DMF, deprotected and washed and coupled in DMF with Fmoc-6aminohexanoic acid (355.0 mg; 1.0 mmol;), N-hydroxybenzotriazole (150 mg, 1.110 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in 15 mL DMF was coupled for 18 hr. After Fmoc removal Eicosanoic acid 313.0 mg (1.0 mmol) N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and coupled in DMF with m-dPEGn=24 (Quanta Biodesign, 308 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. The resin was washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo.

The crude peptide was purified by following the procedure in Example 3 to yield 64 mg (9%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{180}H_{300}N_{34}O_{49}$ 3722.20, Found 3722.19.

EXAMPLE 34

Preparation of Palmitoyl-6Ahx-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr -NH_2 1:3 TFA

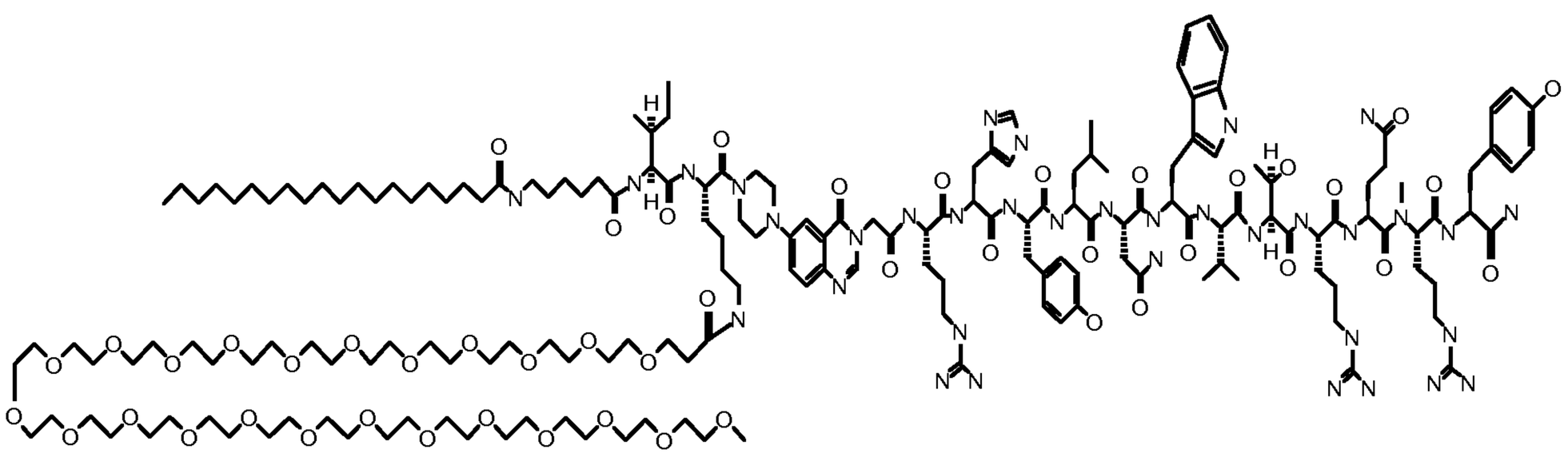


Fmoc-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Ring Amide Resin, 1.0 g (0.22 mmol), obtained from Example 6, was washed with DMF, deprotected and washed and coupled in DMF with Fmoc-6aminohexanoic acid (355.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.110 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in 15 mL DMF was coupled for 18 hr. After Fmoc removal and washing with DMF and CH_2Cl_2, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 mmol) and Palmitoyl 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 was stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and coupled in DMF with m-dPEGn=24 (Quanta Biodesign, 308 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-

carbodiimide (320 μL, 2.0 mmol) were coupled and stirred for 18 hr. The resin was washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 66 mg (9%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{176}H_{293}N_{35}O_{48}$ 3665.16, Found 3665.15.

EXAMPLE 35

Preparation of Eicosanoyl-6Ahx-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:3 TFA

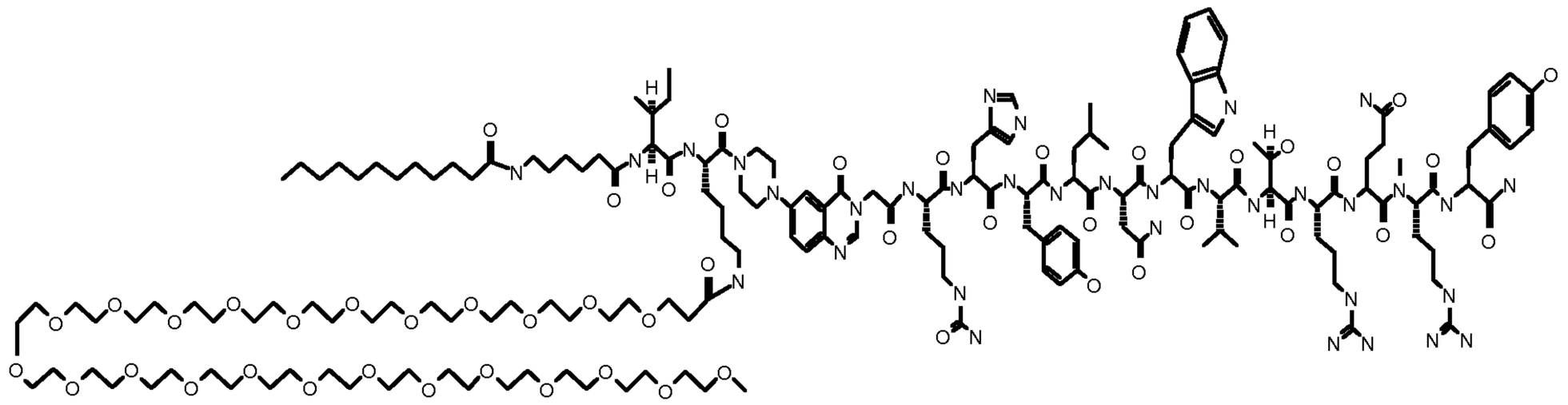


Fmoc-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Ring Amide Resin, 1.0 g (0.22 mmol), obtained from Example 6, was washed with DMF, deprotected and washed and coupled in DMF with Fmoc-6aminohexanoic acid (355.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.110 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in 15 mL DMF was coupled for 18 hr. After Fmoc removal Eicosanoic acid 313.0 mg (1.0 mmol) N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2

times 5% DIEA/DMF and 4 times DMF and coupled in DMF with m-dPEGn=24 (Quanta Biodesign, 308 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. The resin was washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 86 mg (12 %) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{180}H_{301}N_{35}O_{48}$ 3721.22, Found 3721.21.

EXAMPLE 36

Preparation of Lauroyl-6Ahx-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:2 TFA

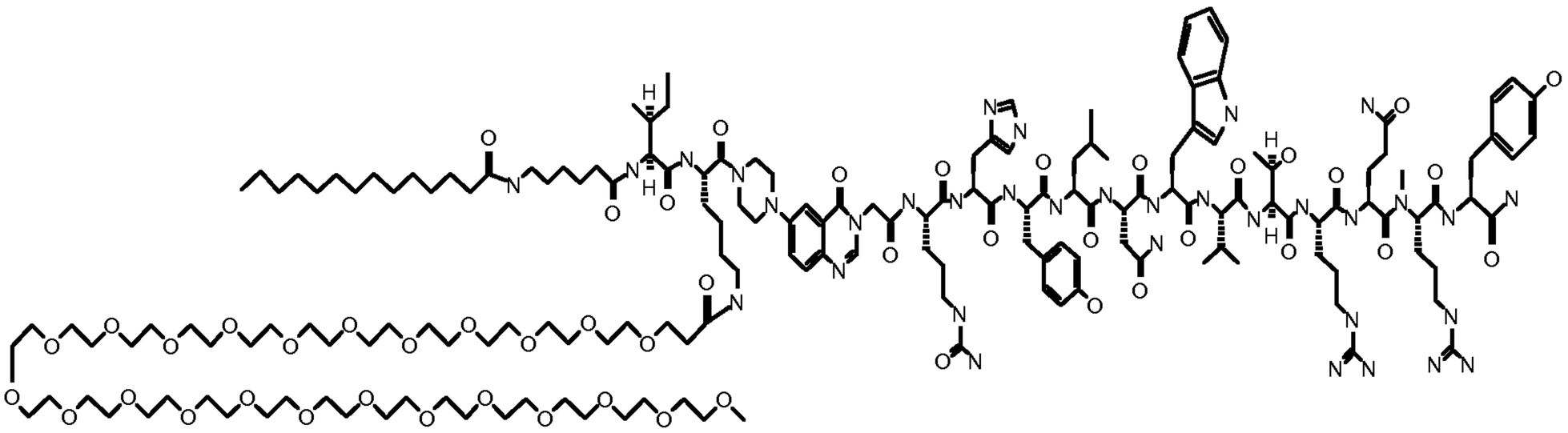


Fmoc-Ile-Lys(Alloc)-Pqa-Cit-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Ring Amide Resin, 1.0 g (0.22 mmol), obtained from Example 6A, was washed with DMF, deprotected and washed and coupled in DMF with Fmoc-6aminohexanoic acid (355.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.110 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in 15 mL DMF was coupled for 18 hr. After Fmoc removal Lauric acid 220.0 mg (1.0 mmol;) N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3

times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and coupled in DMF with m-dPEGn=24 (Quanta Biodesign, 308 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. The resin was washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 63 mg (9%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{172}H_{284}N_{34}O_{49}$ 3610.08, Found 3610.07.

EXAMPLE 37

Preparation of Myristoyl-6Ahx-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:2 TFA

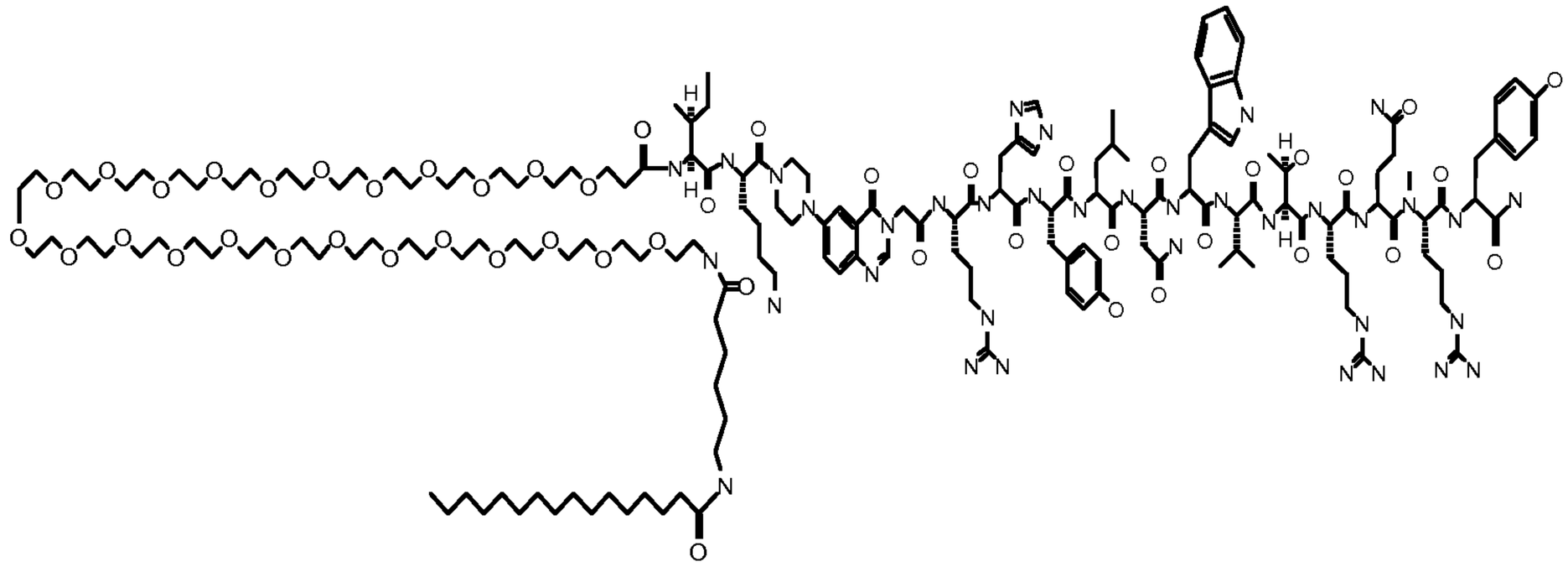


Fmoc-Ile-Lys(Alloc)-Pqa-Cit-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Ring Amide Resin, 1.0 g (0.22 mmol), obtained from Example 6A, was washed with DMF, deprotected and washed and coupled in DMF with Fmoc-6aminohexanoic acid (355.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.110 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in 15 mL DMF was coupled for 18 hr. After Fmoc removal Myristic acid 2520.0 mg (1.0 mmol) N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an

atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and coupled in DMF with m-dPEGn=24 (Quanta Biodesign, 308 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. The resin was washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 43 mg (6%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{174}H_{288}N_{34}O_{49}$ 3638.11, Found 3638.10.

EXAMPLE 38

Preparation of Palmitoyl-6Ahx-NH-CH_2CH_2-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO-Ile-Lys-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:3 TFA



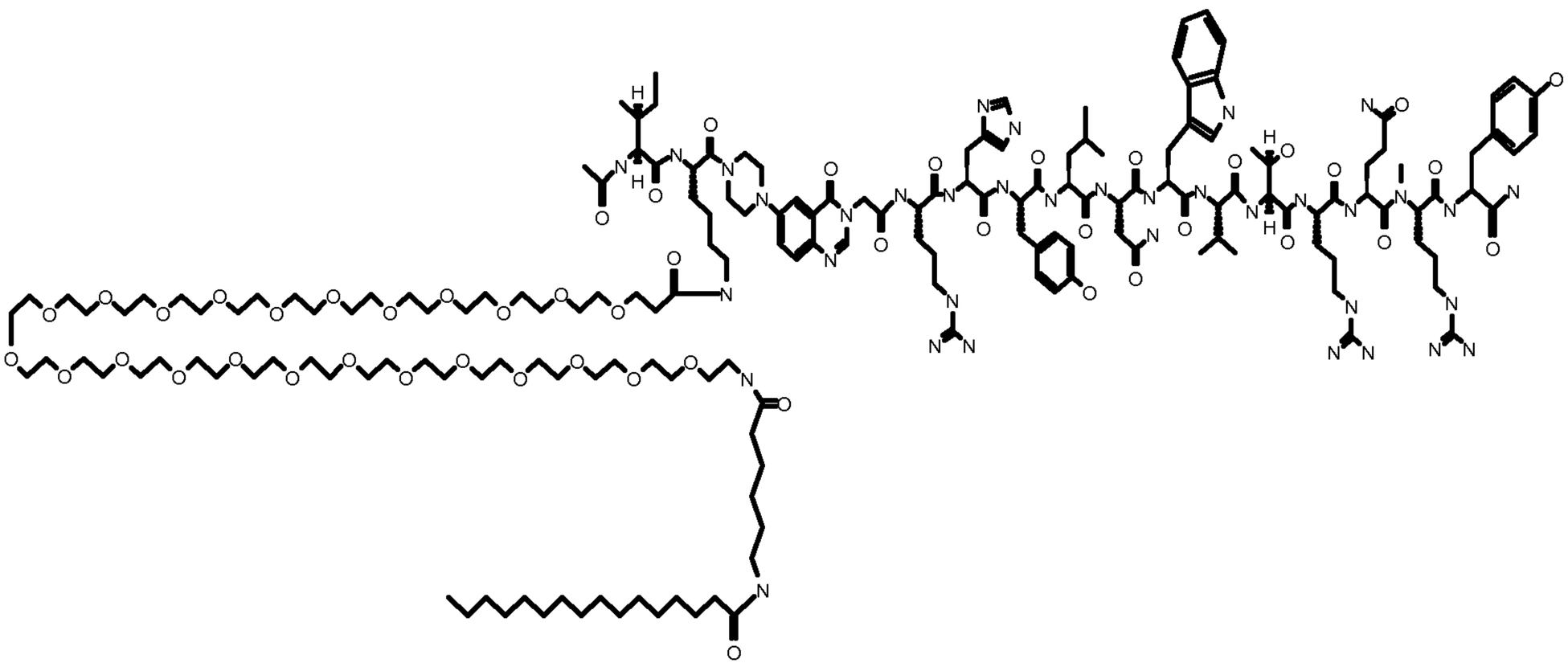
Fmoc-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Ring Amide Resin, 1.0 g (0.22 mmol), obtained from Example 6, was washed with DMF, deprotected and washed and coupled in DMF with Fmoc-N-dPeg(n=24) (Quanta Biodesign, 333 mg, 0.90 mmol), N-hydroxybenzotriazole (150 mg, 1.110 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in 15 mL DMF was coupled for 18 hr. After Fmoc removal and washing with DMF. Fmoc-6aminohexanoic acid (355.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.110 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol)

in 15 mL DMF was coupled for 18 hr. After Fmoc removal and washing with DMF and CH_2Cl_2, 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 was stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and coupled in DMF with m-dPEGn=24 (Quanta Biodesign, 308 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr.

The resin was washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 55 mg (7%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{177}H_{296}N_{36}O_{48}$ 3694.18 , Found 3694.19.

EXAMPLE 39

Preparation of Ac-Ile-Lys[Palmitoyl-6Ahx-NH-CH_2CH_2-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:3 TFA

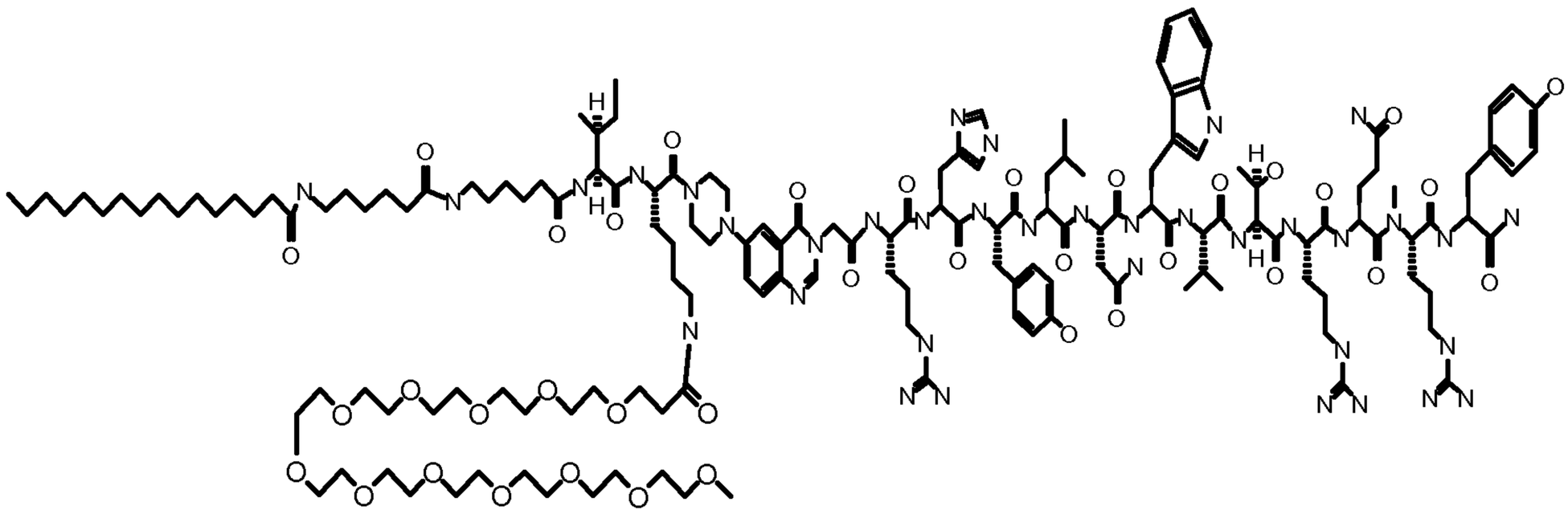


Fmoc-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Ring Amide Resin, 1.0 g (0.22 mmol), obtained from Example 6, was washed with DMF, deprotected and Acetylated. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$(triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and coupled in DMF with m-dPEGn=24 (Quanta Biodesign, 308 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. washed with DMF, deprotected and washed and coupled in DMF with Fmoc-N-dPeg(n=24) (Quanta Biodesign, 333 mg, 0.90 mmol), N-hydroxybenzotriazole (150 mg, 1.110 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmole) in 15 mL DMF was coupled for 18 hr. After Fmoc removal and washing with DMF Fmoc-6aminohexanoic acid (355.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.110 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in 15 mL DMF was coupled for 18 hr. After Fmoc removal and washing with DMF and CH_2Cl_2, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 mmol) and Palmitoyl 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 was stirred for 18 hr. The resin was

washed with CH_2Cl_2 4 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 58 mg (8%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{179}H_{298}N_{36}O_{49}$ 3736.19 Found 3736.20.

EXAMPLE 40

Preparation of Palmitoyl-6Ahx-6Ahx-Ile-Lys[CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:3 TFA

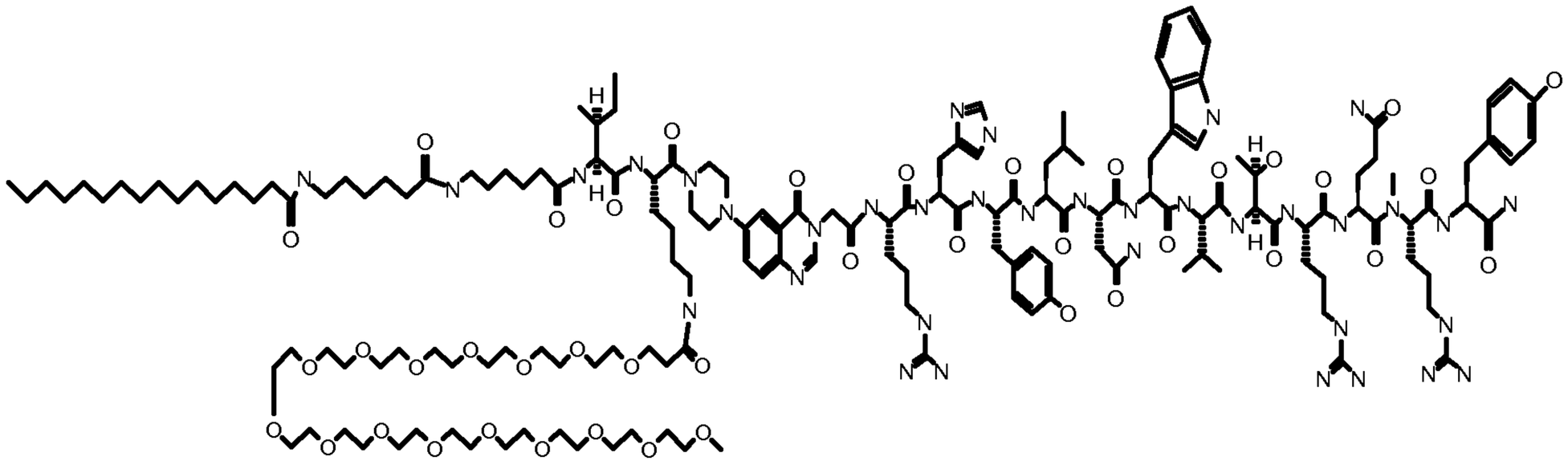


Fmoc-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Ring Amide Resin, 1.0 g (0.22 mmol), obtained from Example 6, was washed with DMF, deprotected and washed and coupled in DMF with Fmoc-6aminohexanoic acid (355.0 mg; 1.0 mmol, HCTU (413.7; 1.0 mmol) and NMM (250 ul; 2.27 mmol) for 7 hr. After Fmoc deprotections and washing with DMF, Fmoc-6-aminohexanoic acid (355.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.110 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in 15 mL DMF was coupled for 18 hr. After Fmoc removal and washing with DMF and CH_2Cl_2, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 mmol) and Palmitoyl 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 was stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$(triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was

repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and coupled in DMF with m-dPEGn=12 NHS ester (Quanta Biodesign, 189 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmole) were coupled and stirred for 18 hr. The resin was washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 100 mg (15%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{158}H_{256}N_{36}O_{37}$ 3249.93, Found 3249.92.

EXAMPLE 41

Preparation of Palmitoyl-6Ahx-6Ahx-Ile-Lys[CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:3 TFA

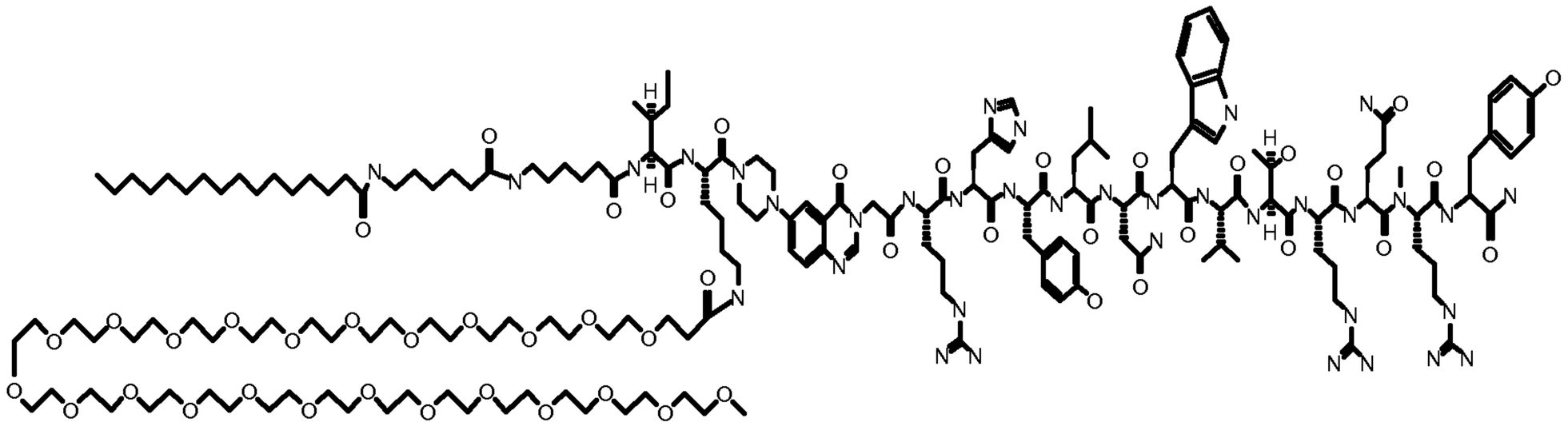


Fmoc-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Ring Amide Resin, 1.0 g (0.22 mmol), obtained from Example 6, was washed with DMF, deprotected and washed and coupled in DMF with Fmoc-6aminohexanoic acid (355.0 mg; 1.0 mmol, HCTU (413.7; 1.0 mmol) and NMM (250 ul; 2.27 mmol) for 7 hr. After Fmoc deprotections and washing with DMF, Fmoc-6-aminohexanoic acid (355.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.110 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in 15 mL DMF was coupled for 18 hr. After Fmoc removal and washing with DMF and CH_2Cl_2, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 mmol) and Palmitoyl 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 was stirred for 18 hr. After washing with DMF 4

times the alloc protecting group was removed with 50.0 mg $PdCl_2$(triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and coupled in DMF with m-dPEGn=16 NHS ester (Quanta Biodesign, 238 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. The resin was washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 54 mg (8%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{166}H_{272}N_{36}O_{41}$ 3426.03, Found 3426.02.

EXAMPLE 42

Preparation of Palmitoyl-6Ahx-6Ahx-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:3 TFA

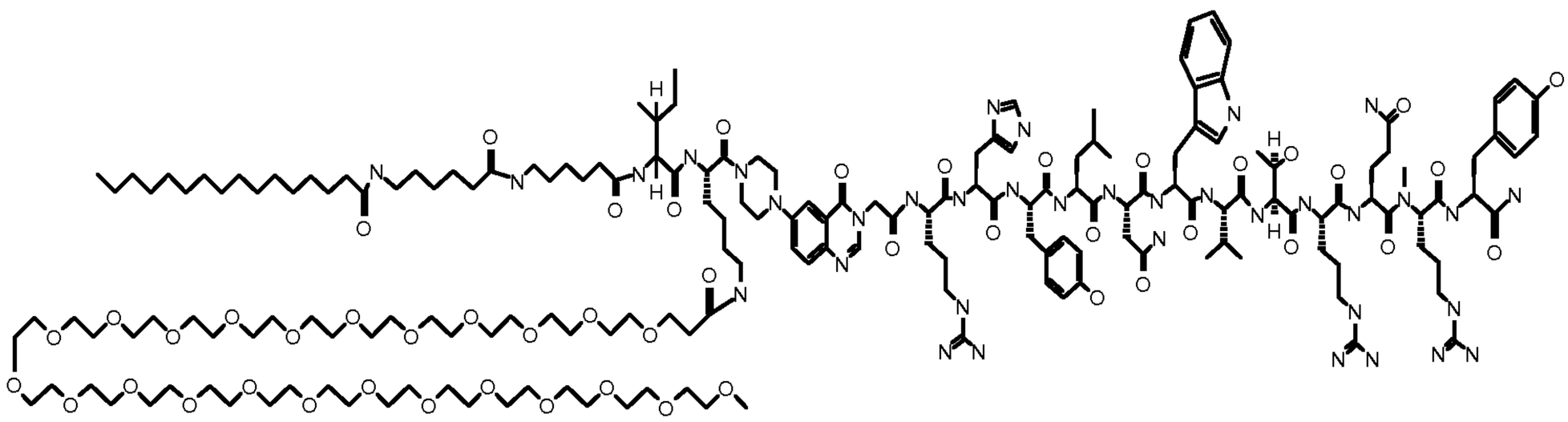


Fmoc-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Ring Amide Resin, 1.0 g (0.22 mmol), obtained from Example 6, was washed with DMF, deprotected and washed and coupled in DMF with Fmoc-6aminohexanoic acid (355.0 mg; 1.0 mmol, HCTU (413.7; 1.0 mmol) and NMM (250 ul; 2.27 mmol) for 7 hr. After Fmoc deprotections and washing with DMF, Fmoc-6-aminohexanoic acid (355.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.110 mmol), and diisopropyl-

carbodiimide (875 ul, 5.0 mmol) in 15 mL DMF was coupled for 18 hr. After Fmoc removal and washing with DMF and CH_2Cl_2, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 mmol) and Palmitoyl 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 was stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$(triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and coupled in DMF with m-dPEGn=24 (Quanta Biodesign, 308 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. The resin was washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 56 mg (7%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{182}H_{304}N_{36}O_{49}$ 3778.24, Found 3778.25.

EXAMPLE 43

Preparation of Palmitoyl-6Ahx-6Ahx-(D)alloIle-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:3 TFA

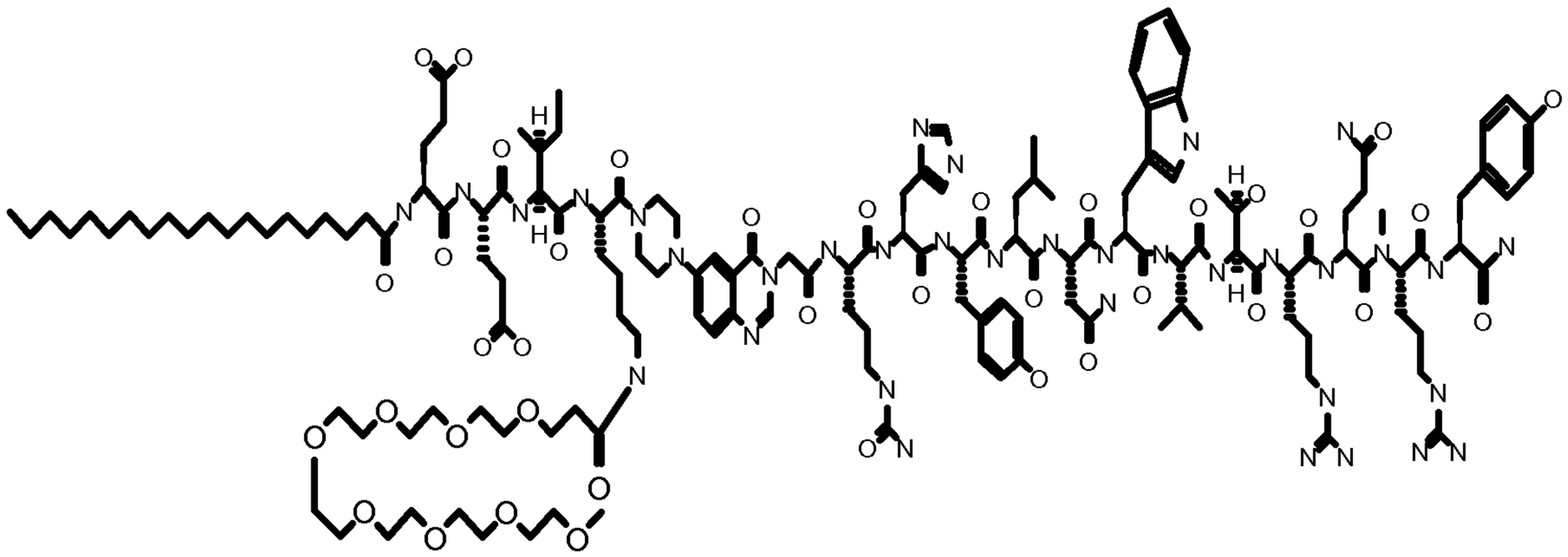


Fmoc-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Ring Amide Resin, 1.0 g (0.22 mmol), obtained from

Example 6, was washed with DMF, deprotected and washed and coupled in DMF with Fmoc-(D)alloIle (110 mg. 0.302 mmol) ; N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (1.50 ml, 2.0 mmol) were coupled and stirred for 18 hr. After washing, Fmoc deprotections and washing with DMF 4 times Fmoc-6aminohexanoic acid (355.0 mg; 1.0 mmol), HCTU (413.7; 1.0 mmol) and NMM (250 ul; 2.27 mmol) were coupled in DMF for 7 hr. After Fmoc deprotections and washing with DMF, Fmoc-6aminohexanoic acid (355.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.110 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in 15 mL DMF was coupled for 18 hr. After Fmoc removal and washing with DMF and CH_2Cl_2, N-hydroxybenzotriazole (425 mg, 3.150 mmol), DIEA (500 uL, 3.0 mmol) and Palmitoyl 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 was stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$(triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and coupled in DMF with m-dPEGn=24 (Quanta Biodesign, 308 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. The resin was washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 85 mg (11%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{182}H_{304}N_{36}O_{49}$ 3778.24, Found 3778.23.

EXAMPLE 44

Preparation of Eicosanoyl-Glu-Glu-Ile-Lys[CH_3-(OCH_2CH_2)$_7$-O-(CH_2)$_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:2 TFA

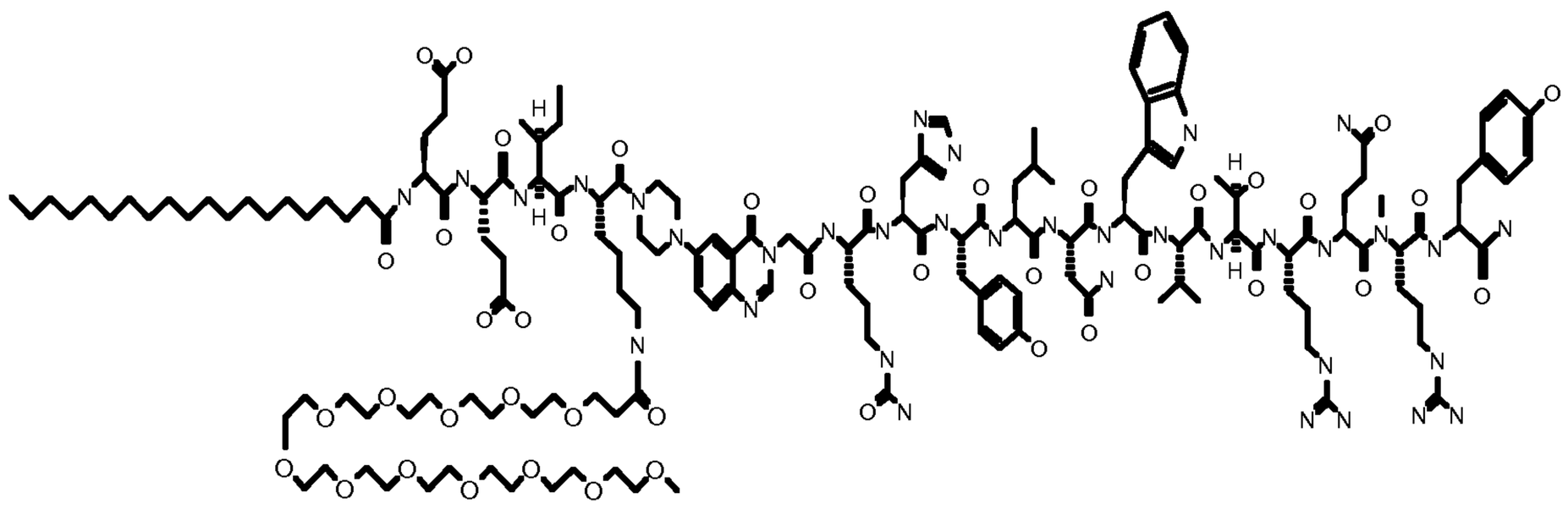


Fmoc-Ile-Lys(Alloc)-Pqa-Cit-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Amide Ring Resin, 1.0 g (0.22 mmol), obtained from Example 6A, was washed with DMF, deprotected and washed and coupled in DMF with Fmoc-Glu(OBut)-OH (426.0 mg; 1.0 mmol), HCTU (413.7; 1.0 mmol) and NMM (250 ul; 2.27 mmol) were coupled in DMF for 7 hr. After washing, Fmoc deprotections and washing with DMF 4 times, Fmoc-Glu(OBut)-OH (426.0 mg; 1.0 mmol), 1.0 mm) N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled and stirred for 18 hr. After Fmoc removal and washing, Eicosanoic acid 313.0 mg (1.0 mmol) N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol)in DMF 15.0 mL was coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$(triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and coupled in DMF with m-dPEGn=8 (Quanta Biodesign, 115 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. The resin was washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O,

centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 53 mg (8%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{152}H_{239}N_{35}O_{38}$ 3162.78, Found 3162.77.

EXAMPLE 45

Preparation of Eicosanoyl -Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:2 TFA

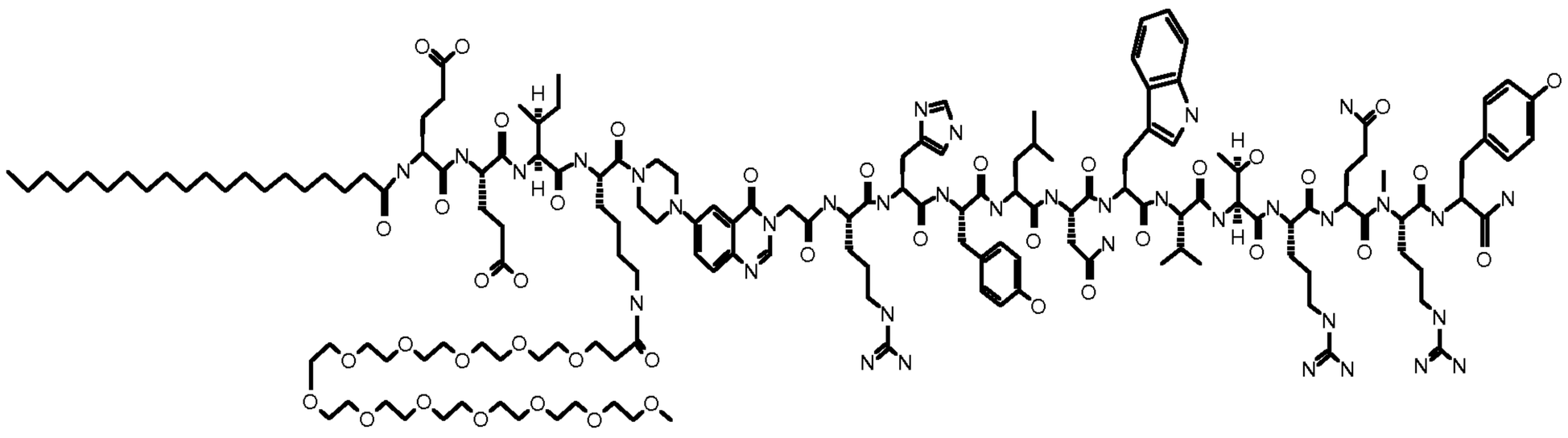


Fmoc-Ile-Lys(Alloc)-Pqa-Cit-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Ring Amide Resin, 1.0 g (0.22 mmol), obtained from Example 6A, was washed with DMF, deprotected and washed and coupled in DMF with Fmoc-Glu(OBut)-OH (426.0 mg; 1.0 mm), HCTU (413.7; 1.0 mmol) and NMM (250 ul; 2.27 mmol) were coupled in DMF for 7 hr. After Fmoc removal and washing with DMF, Fmoc-Glu(OBut)-OH (426.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled and stirred for 18 hr. After Fmoc removal and washing, Eicosanoic acid 313.0 mg (1.0 mmol) N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF,

2 times 5% DIEA/DMF and 4 times DMF and coupled in DMF with m-dPEGn=12 NHS ester (Quanta Biodesign, 189 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. The resin was washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 32 mg (5%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{160}H_{255}N_{35}O_{42}$ 3338.89, Found 3338.90.

EXAMPLE 46

Preparation of Eicosanoyl -Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:3 TFA

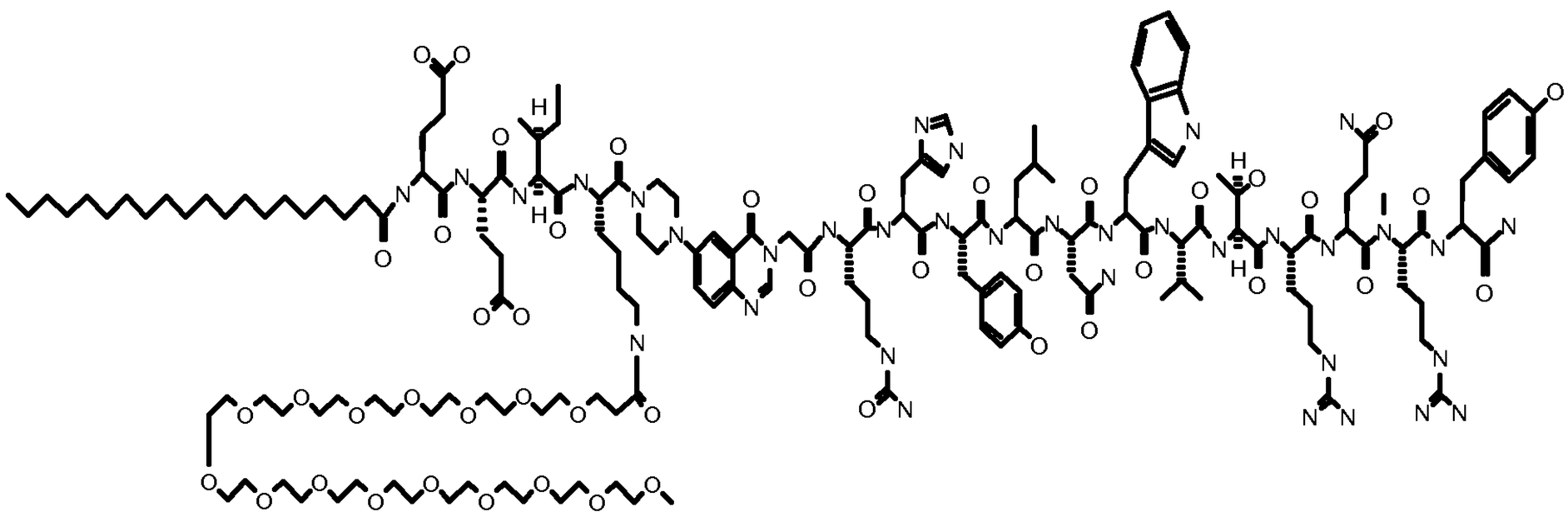


Fmoc-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Ring Amide Resin, 1.0 g (0.22 mmol), obtained fro Example 6, was washed with DMF, deprotected and washed and coupled in DMF with Fmoc-Glu(OBut)-OH (426.0 mg; 1.0 mmol), HCTU (413.7; 1.0 mmol) and NMM (250 ul; 2.27 mmol) were coupled in DMF for 7 hr. After Fmoc removal and washing with DMF, Fmoc-Glu(OBut)-OH (426.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled and stirred for 18 hr. After Fmoc removal and washing, Eicosanoic acid 313.0 mg (1.0 mmol) N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF

under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and coupled in DMF with m-dPEGn=12 NHS ester (Quanta Biodesign, 189 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. The resin was washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 18 mg (3 %) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{160}H_{256}N_{36}O_{41}$ 3337.91, Found 3337.89.

EXAMPLE 47

Preparation of Eicosanoyl -Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:2 TFA

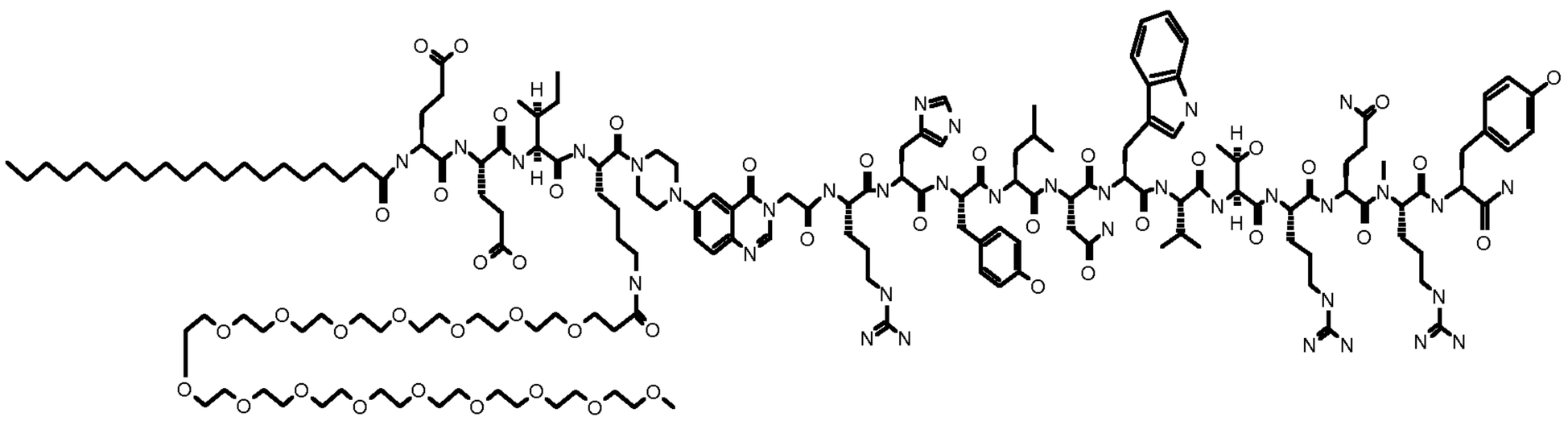


Fmoc-Ile-Lys(Alloc)-Pqa-Cit-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Ring Amide Resin, 1.0 g (0.22 mmol), obtained from Example 6A , was washed with DMF, deprotected and washed and coupled in DMF with Fmoc-Glu(OBut)-OH (426.0 mg; 1.0 mmol), HCTU (413.7; 1.0 mmol) and NMM (250 ul; 2.27 mmol) were coupled in DMF for 7 hr. After Fmoc removal and washing with DMF, Fmoc-Glu(OBut)-OH (426.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-

carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled and stirred for 18 hr. After Fmoc removal and washing, Eicosanoic acid 313.0 mg (1.0 mmol) N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and coupled in DMF m-dPEGn=16 NHS ester (238 mg, 0.275 mmol); N-hydroxybenzotriazole (Quanta Biodesign, 40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. The resin was washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 32 mg (5%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{168}H_{271}N_{35}O_{46}$ 3514.99, Found 3514.97.

EXAMPLE 48

Preparation of Eicosanoyl-Glu-Glu-Ile-Lys[CH_3-(OCH_2CH_2)$_{15}$-O-(CH_2)$_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:3 TFA

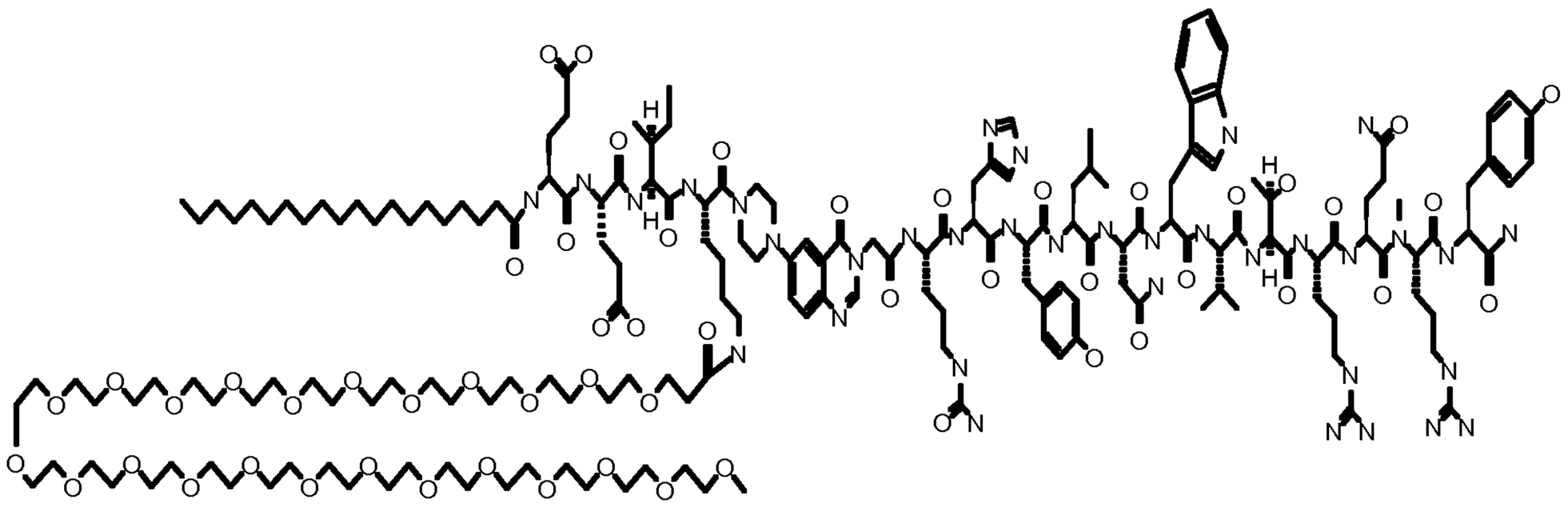


Fmoc-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Ring Amide Resin, 1.0 g (0.22 mmol), obtained from

Example 6, was washed with DMF, deprotected and washed and coupled in DMF with Fmoc-Glu(OBut)-OH (426.0 mg; 1.0 mmol), HCTU (413.7; 1.0 mmol) and NMM (250 ul; 2.27 mmol) were coupled in DMF for 7 hr. After Fmoc removal and washing with DMF, Fmoc-Glu(OBut)-OH (426.0 mg; 1.0 mmol), 1N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled and stirred for 18 hr. After Fmoc removal and washing, Eicosanoic acid 313.0 mg (1.0 mmol) N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmole)in DMF 15.0 mL was coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and coupled in DMF m-dPEGn=16 NHS ester (Quanta Biodesign, 238 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. The resin was washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 17 mg (2 %) of white amorphous powder. (ES)+-LCMS m/e calculated ("calcd") $C_{168}H_{272}N_{36}O_{45}$ 3514.01, Found 3513.99.

EXAMPLE 49

Preparation of Eicosanoyl -Glu-Glu-Ile-Lys[CH_3-(OCH_2CH_2)$_{23}$-O-(CH_2)$_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:2 TFA

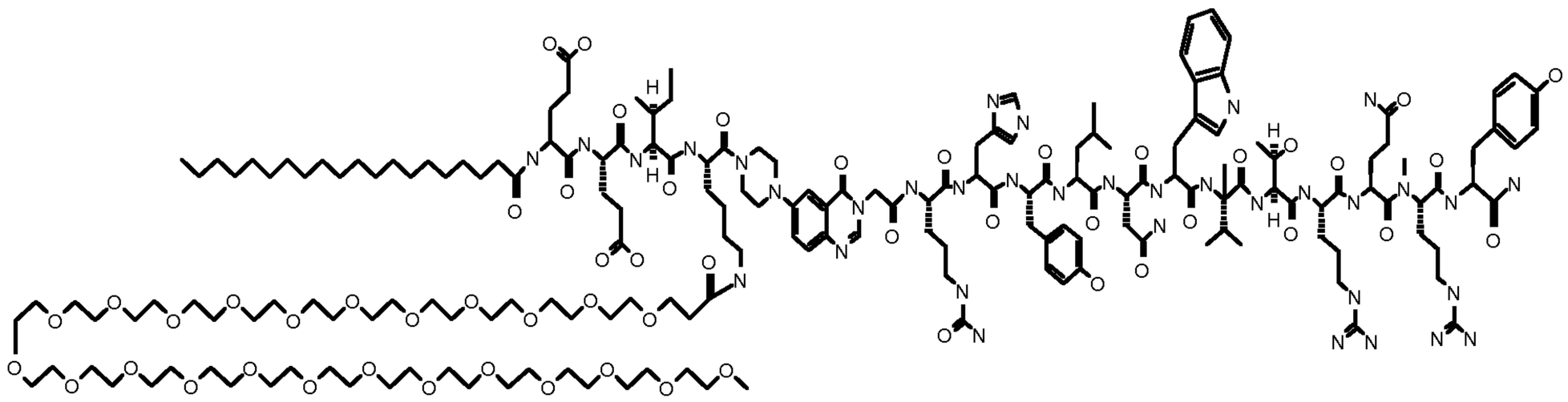


Fmoc-Ile-Lys(Alloc)-Pqa-Cit-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Ring Amide Resin, 1.0 g (0.22 mmol), obtained from Example 6A, was washed with DMF, deprotected and washed and coupled in DMF with Fmoc-Glu(OBut)-OH (426.0 mg; 1.0 mmol), HCTU (413.7; 1.0 mmol) and NMM (250 ul; 2.27 mmol) were coupled in DMF for 7 hr. After Fmoc removal and washing with DMF, Fmoc-Glu(OBut)-OH (426.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled and stirred for 18 hr. After Fmoc removal and washing, Eicosanoic acid 313.0 mg (1.0 mmol) N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and coupled in m-dPEGn=24 (Quanta Biodesign, 308 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. The resin was washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 49 mg (6%) of

white amorphous powder. (ES)+-LCMS m/e calculated $C_{184}H_{303}N_{35}O_{54}$ 3867.20, Found 3867.19.

EXAMPLE 50

Preparation of Eicosanoyl -Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-C-alphaMeVal-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:2 TFA

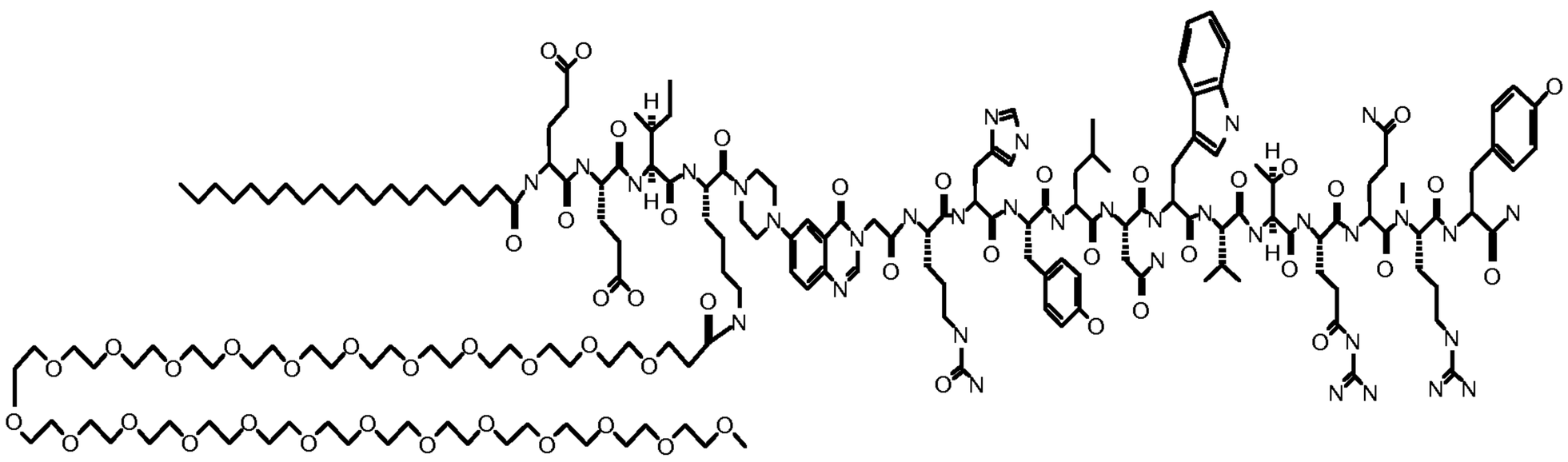


Fmoc-Glu(OBut)-Glu(OBut)-Ile-Lys(Alloc)-Pqa-Cit-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-C-alpha-MeVal-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Ring Amide Resin, was synthesized on the ABI synthesizer from 555 mg (0.25 mmol) resin according to the standard protocol. The resin was washed, and Eicosanoic acid 313.0 mg (1.0 mmol) N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$(triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and coupled in m-dPEGn=24 (Quanta Biodesign, 308 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. The resin was washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in

Example 3 to yield 70 mg (9%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{185}H_{305}N_{35}O_{54}$ 3881.22, Found 3881.20.

EXAMPLE 51

Preparation of Eicosanoyl -Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg(CO)-Gln-(NMe)-Arg-Tyr-NH_2 1:2 TFA

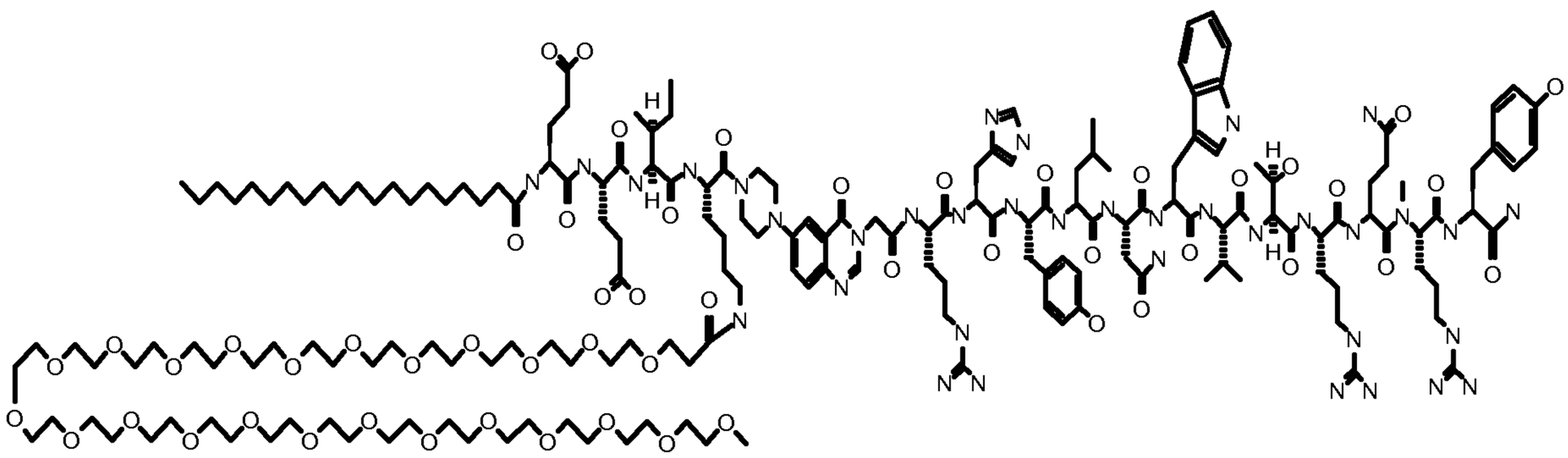


Fmoc-Glu(OBut)-Glu(OBut)-Ile-Lys(Alloc)-Pqa-Cit-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Glu(2Pip)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Rink Amide Resin, was synthesized on the ABI synthesizer from 555 mg (0.25 mmol) resin according to the standard protocol. The resin was washed, and Eicosanoic acid 313.0 mg (1.0 mmol) N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol)in DMF 15.0 mL was coupled and stirred for 18 hr. After washing with DMF 4 times and CH_2Cl_2 4 times the 2 Pip was removed with 2% TFA in CH_2Cl 5 times for 2 minutes. The resin was then was with DMF 2 times and CH_2Cl_2 2 times, neutralize with 2 X 5% DIEA in DMF and finally washed with DMF 4 times. Boc-Guandine (CAS 219511-71-4) (1.5g, 0.94 mmol), HATU (1.4g, 3.6 mmol) and NMM (1.5 mL, 13.6 mmol) were coupled in DMF for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and coupled in m-

dPEGn=24 (Quanta Biodesign, 308 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. The resin was washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 54 mg (7%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{185}H_{305}N_{35}O_{54}$ 3881.22, Found 3881.20.

EXAMPLE 52

Preparation of Eicosanoyl -Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:3 TFA

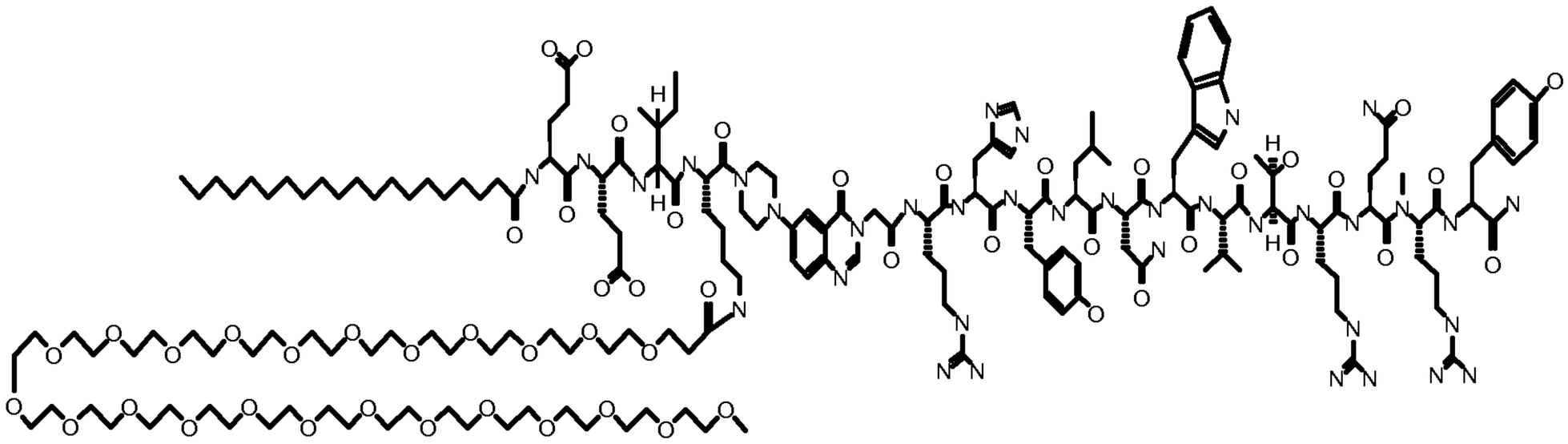


Fmoc-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Rink Amide Resin, 1.0 g (0.22 mmol), obtained from Example 6), was washed with DMF, deprotected and washed and coupled in DMF with Fmoc-Glu(OBut)-OH (426.0 mg; 1.0 mmol), HCTU (413.7; 1.0 mmol) and NMM (250 ul; 2.27 mmol) were coupled in DMF for 7 hr. After Fmoc removal and washing with DMF, Fmoc-Glu(OBut)-OH (426.0 mg; 1.0 mmol) N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled and stirred for 18 hr. After Fmoc removal and washing, Eicosanoic acid 313.0 mg (1.0 mmol) N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$(triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued

until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and coupled in m-dPEGn=24 (Quanta Biodesign, 308 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. The resin was washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 53 mg (7%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{184}H_{301}N_{35}O_{55}$ 3881.18, found 3881.19.

EXAMPLE 53

Preparation of Eicosanoyl -Glu-Glu-(D)alloIle-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:3 TFA

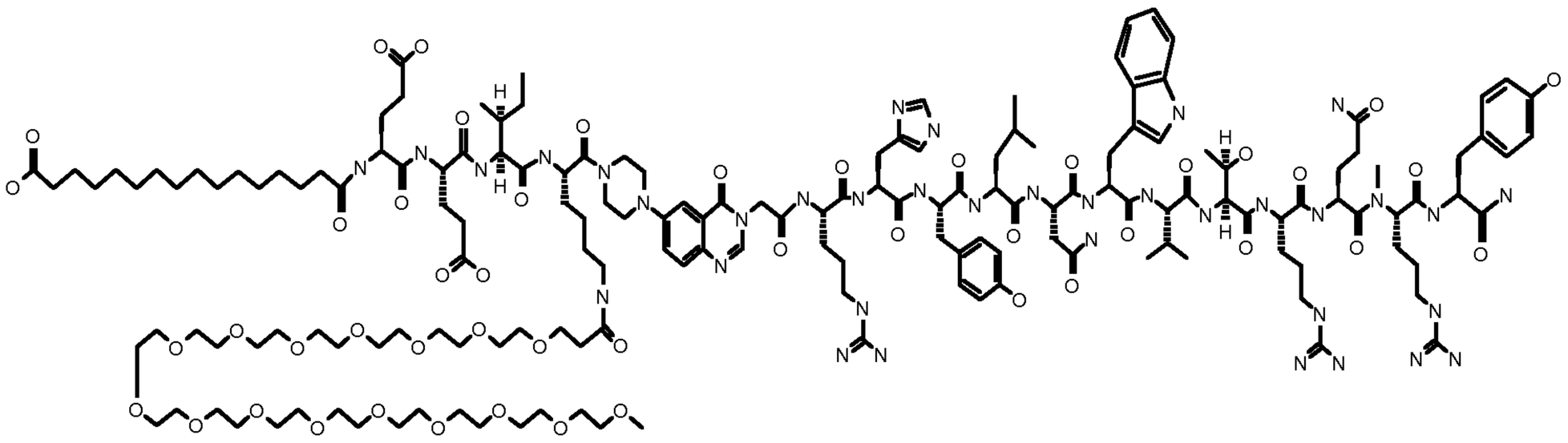


Fmoc-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Ring Amide Resin , 1.0 g (0.22 mmol), obtained from Example 6, was washed with DMF, deprotected and washed and coupled in DMF with Fmoc-(D)alloIle (110 mg. 0.302 mmol) ; N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. After deprotections and washing, Fmoc-Glu(OBut)-OH (426.0 mg; 1.0 mmol), HCTU (413.7; 1.0 mmol) and NMM (250 ul; 2.27 mmol) were coupled in DMF for 7 hr. After washing and deprotection Fmoc-Glu(OBut)-OH (426.0 mg; 1.0 mmol) N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled and

stirred for 18 hr. After Fmoc removal and washing, Eicosanoic acid 313.0 mg (1.0 mmol) N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmole) in DMF 15.0 mL was coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$(triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and coupled inDMF with m-dPEGn=24 (Quanta Biodesign, 308 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) with stirring for 18 hr. The resin was washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 90 mg (12%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{184}H_{304}N_{36}O_{53}$ 3866.22, Found 3866.22.

EXAMPLE 54

Preparation of 15-Carboxy-pentadecanoyl-Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:3 TFA

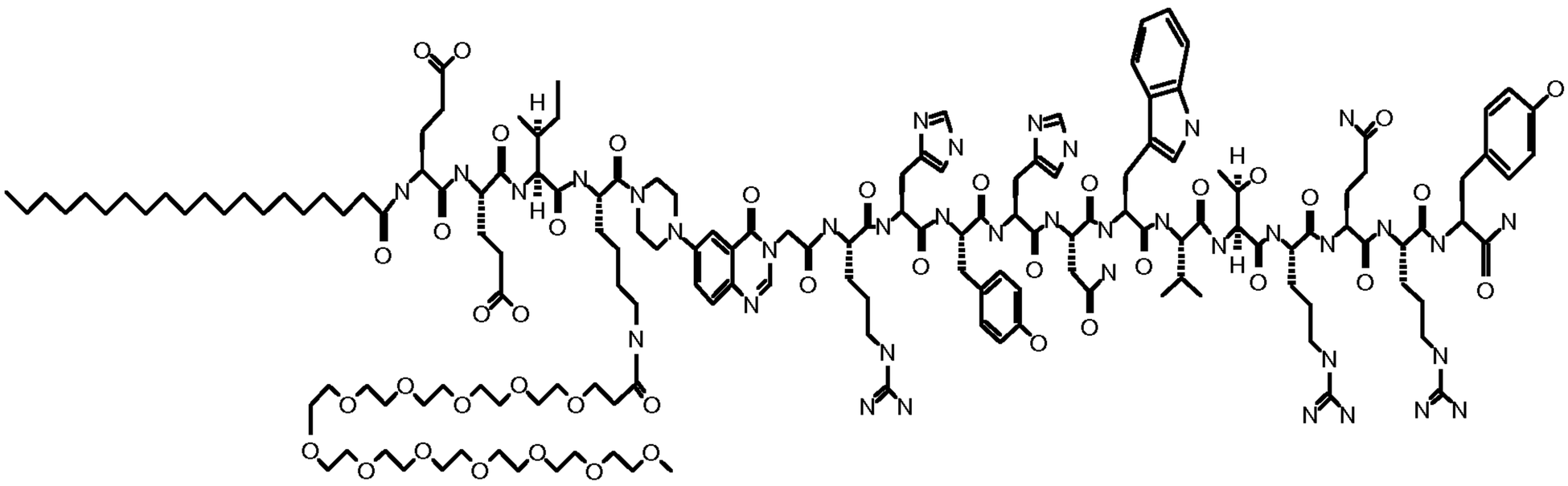


Fmoc-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Ring Amide Resin, 1.0 g (0.22 mmol), obtained from Example 6, was washed with DMF, deprotected and washed and coupled with Hexadecandioic

acid (290.0 mg, 1.0 mmol), HATU (570.0 mg, 1.5 mmol), and DIEA (950 uL, 5.4 mmol) in Pyridine (15.0 mL) for 6 hr. After washing with DMF, $LiOH{\cdot}H_2O$ (100 uL, 3.7 mmol), 5.0 mL H_2O and 16.0 mL 1,4-Dioxane and 4.0 mL DMF were stirred for 24 hr. After washing with DMF 4 times, the alloc protecting group was removed with 50.0 mg $PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and coupled in DMF with m-dPEGn=16 NHS ester (Quanta Biodesign, 238 mg, 0.275 mmol), N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) with stirring for 18 hr.. The resin was washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 43 mg (6%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{164}H_{262}N_{36}O_{47}$ 3487.92, found 3487.91.

EXAMPLE 55

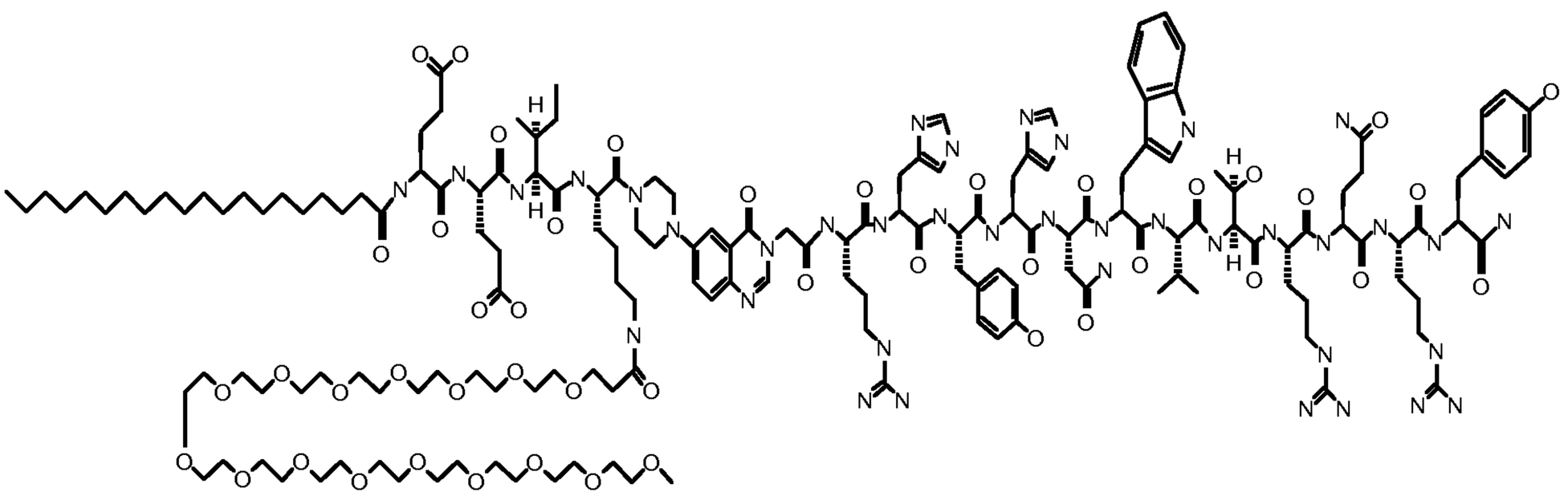
Preparation of Eicosanoyl-Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-His-Asn-Trp-Val-Thr-Arg-Gln-Arg-Tyr-NH_2 1:3 TFA



Fmoc-Glu(OBut)-Glu(OBut)-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-His(Trt)-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)- Arg(Pbf)-Tyr(tBu)-Rink Amide Resin, was synthesized on the ABI synthesizer from 555 mg (0.25 mmol) resin according to the standard protocol. The resin was washed, and Eicosanoic acid 313.0 mg (1.0 mmol) N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and coupled in DMF with m-dPEGn=12 NHS ester (Quanta Biodesign, 189 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. The resin was washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 283 mg (43 %) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{159}H_{250}N_{38}O_{41}$ 3347.86, Found 3347.85.

EXAMPLE 56

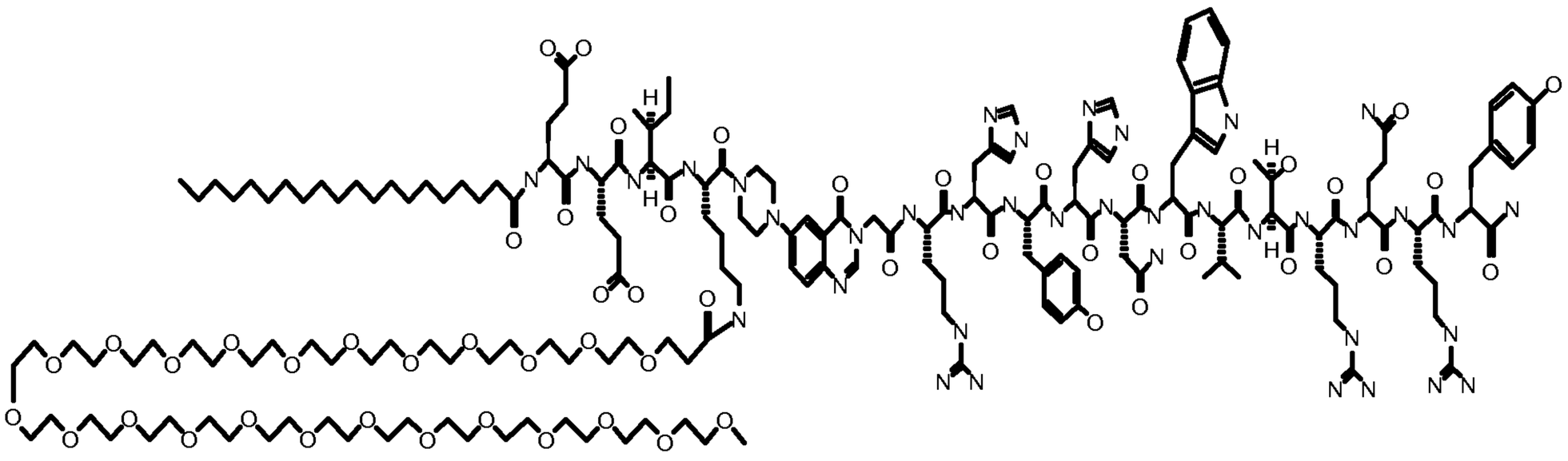
Preparation of Eicosanoyl-Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-His-Asn-Trp-Val-Thr-Arg-Gln-Arg-Tyr-NH_2 1:3 TFA



Fmoc-Glu(OBut)-Glu(OBut)-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-His(Trt)-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-Arg(Pbf)-Tyr(tBu)-Ring Amide Resin , was synthesized on the ABI synthesizer from 555 mg (0.25 mmol) resin according to the standard protocol. The resin was washed, and Eicosanoic acid 313.0 mg (1.0 mmol) N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and coupled in DMF with m-dPEGn=16 NHS ester (238 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. The resin was washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 340 mg (49%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{167}H_{266}N_{38}O_{45}$ 3523.97, Found 3523.96.

EXAMPLE 57

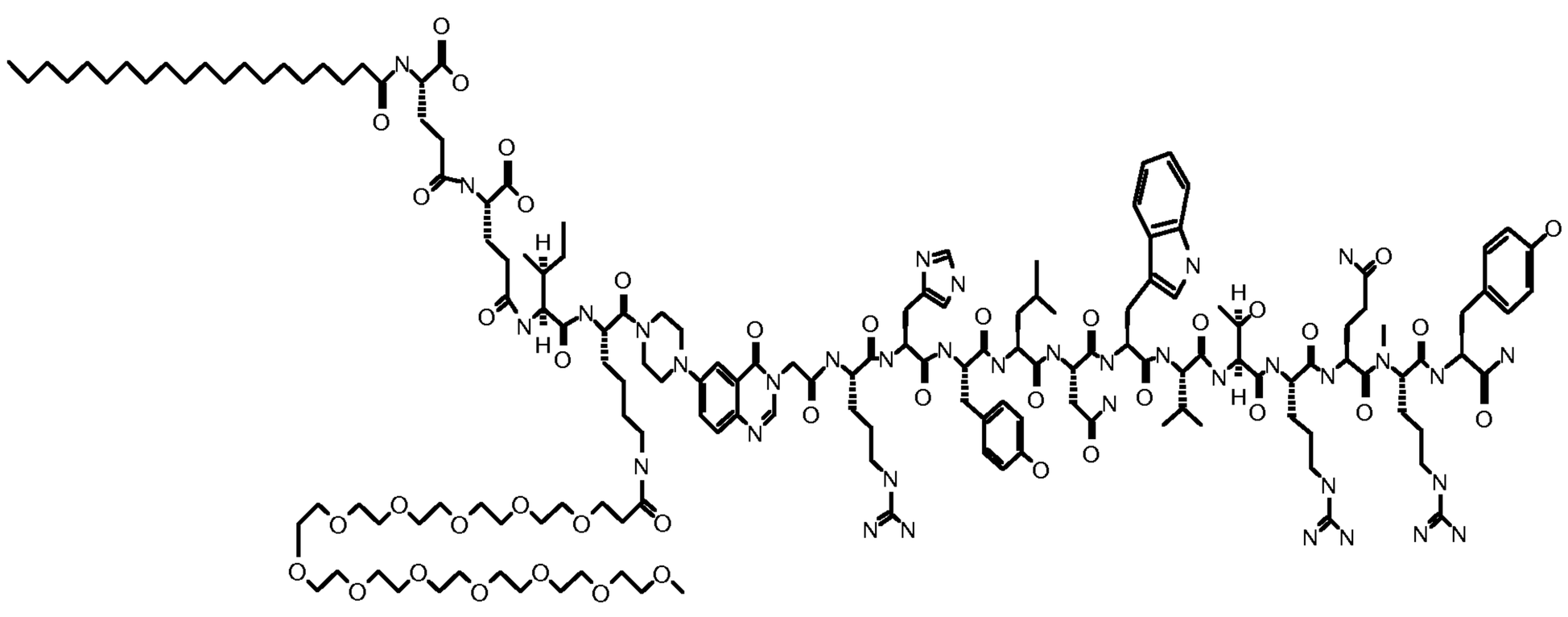
Preparation of Eicosanoyl -Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-His-Asn-Trp-Val-Thr-Arg-Gln-Arg-Tyr-NH_2 1:3 TFA



Fmoc-Glu(OBut)-Glu(OBut)-Ile-Lys(Alloc)-Pqa-Arg(Pbf)-His(Trt)-Tyr(tBu)-His(Trt)-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-Arg(Pbf)-Tyr(tBu)-Ring Amide Resin, was synthesized on the ABI synthesizer from 555 mg (0.25 mmol) resin according to the standard protocol. The resin was washed, and Eicosanoic acid 313.0 mg (1.0 mmol) N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and couple in DMF with m-dPEGn=24 (308 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. The resin was washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 490 mg (70%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{183}H_{298}N_{38}O_{53}$ 3876.18, Found 3877.2.

EXAMPLE 58

Preparation of Eicosanoyl-gammaGlu-gammaGlu-Ile-Lys[CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:3 TFA

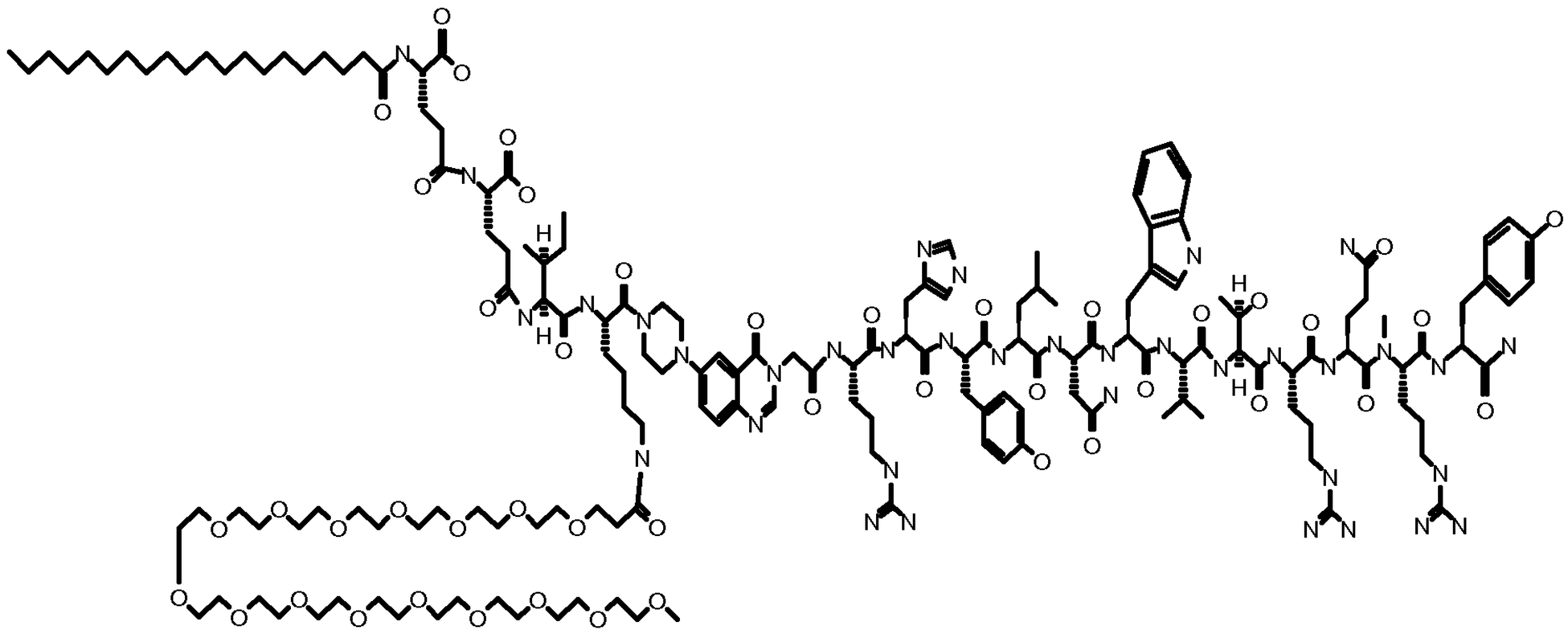


Fmoc-Ile-Lys(Alloc)-Pqa-Arg-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Ring Amide Resin, 1.0 g (0.22 mmol), obtained fro Example 6, was washed with DMF, deprotected and washed and coupled in DMF with Fmoc-Glu-OBut-OH (426.0 mg; 1.0 mmol), HCTU (413.7; 1.0 mmol) and NMM (250 ul; 2.27 mmol) were coupled in DMF for 7 hr. After Fmoc removal and washing with DMF, Fmoc-Glu-OBut-OH (426.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled and stirred for 18 hr. After Fmoc removal and washing, Eicosanoic acid 313.0 mg (1.0 mmol) N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and coupled in DMF m-dPEGn=12 NHS ester (189 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. The resin was washed with DMF 2 times

and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 86 mg (13%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{160}H_{256}N_{36}O_{41}$, 3337.91, Found 3337.90

EXAMPLE 59

Preparation of Eicosanoyl-gammaGlu-gammaGlu-Ile-Lys[CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:3 TFA

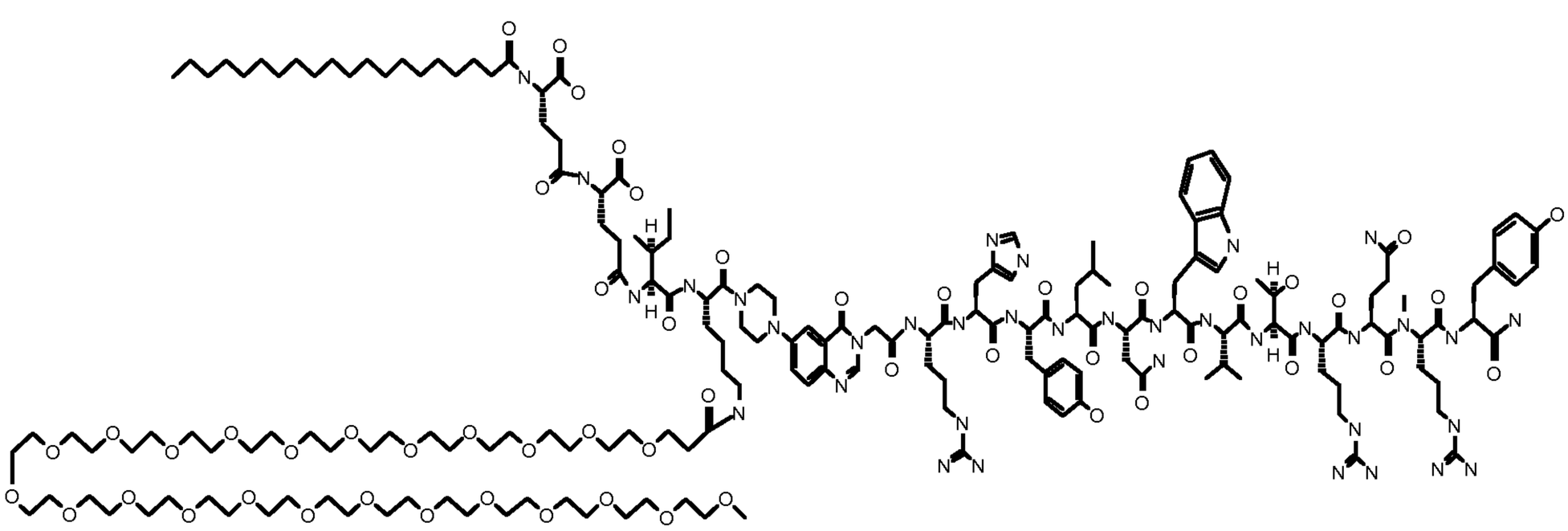


Fmoc-Ile-Lys(Alloc)-Pqa-Arg-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Ring Amide Resin, 1.0 g (0.22 mmol), obtained from Example 6, was washed with DMF, deprotected and washed and coupled in DMF with Fmoc-Glu-OBut-OH (426.0 mg; 1.0 mmol), HCTU (413.7; 1.0 mmol) and NMM (250 ul; 2.27 mmol) were coupled in DMF for 7 hr. After Fmoc removal and washing with DMF, Fmoc-Glu-OBut-OH (426.0 mg; 1.0 mmol), 1.0 mm) N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled and stirred for 18 hr. After Fmoc removal and washing, Eicosanoic acid 313.0 mg (1.0 mmol) N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$ (triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF

under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and coupled in DMF m-dPEGn=16 NHS ester (238 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. The resin was washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 42mg (6%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{168}H_{272}N_{36}O_{45}$ 3514.01, Found 3513.98.

EXAMPLE 60

Preparation of Eicosanoyl-gammaGlu-gammaGlu-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:3 TFA

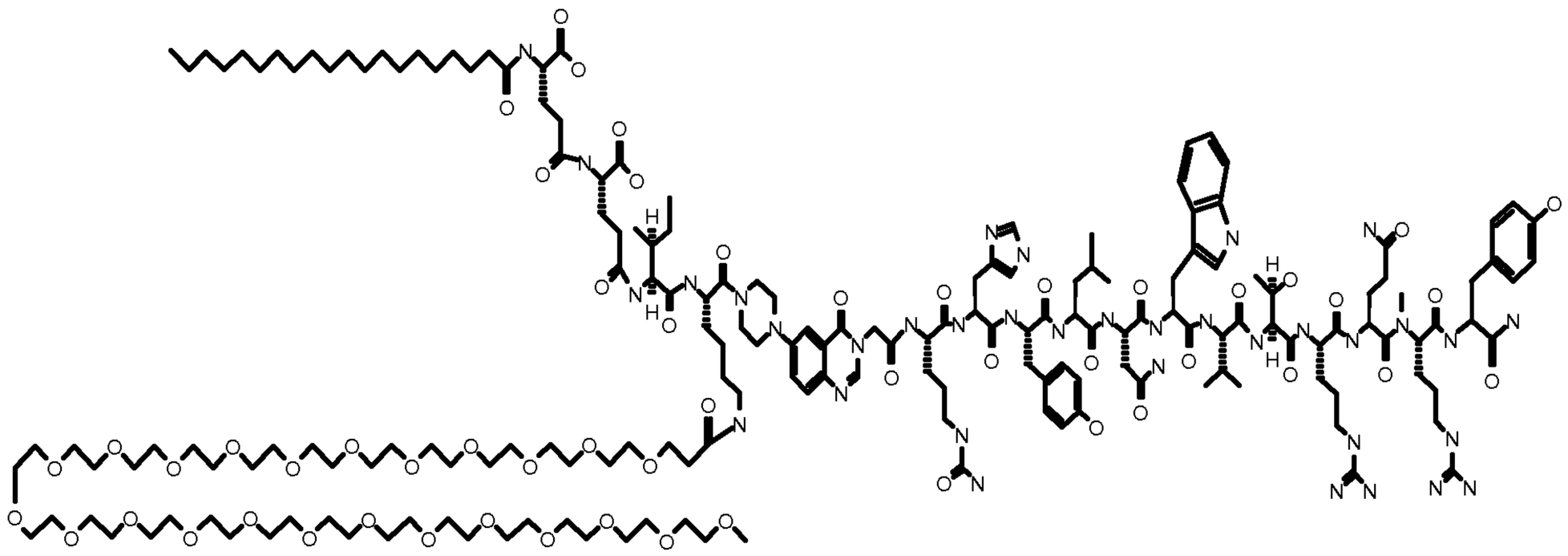


Fmoc-Ile-Lys(Alloc)-Pqa-Arg-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Ring Amide Resin, 1.0 g (0.22 mmol), obtained from Example 6, was washed with DMF, deprotected and washed and coupled in DMF with Fmoc-Glu-OBut-OH (426.0 mg; 1.0 mmol), HCTU (413.7; 1.0 mmol) and NMM (250 ul; 2.27 mmol) were coupled in DMF for 7 hr. After Fmoc removal and washing with DMF, Fmoc-Glu-OBut-OH (426.0 mg; 1.0 mmol), N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled and stirred for 18 hr. After Fmoc

removal and washing, Eicosanoic acid 313.0 mg (1.0 mmol) N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$(triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and coupled in DMF m-dPEGn=24 (308 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. The resin was washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 33 mg (4%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{184}H_{304}N_{36}O_{53}$ 3866.22, Found 3866.21.

EXAMPLE 61

Preparation of Eicosanoyl -gammaGlu-gammaGlu-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:2 TFA

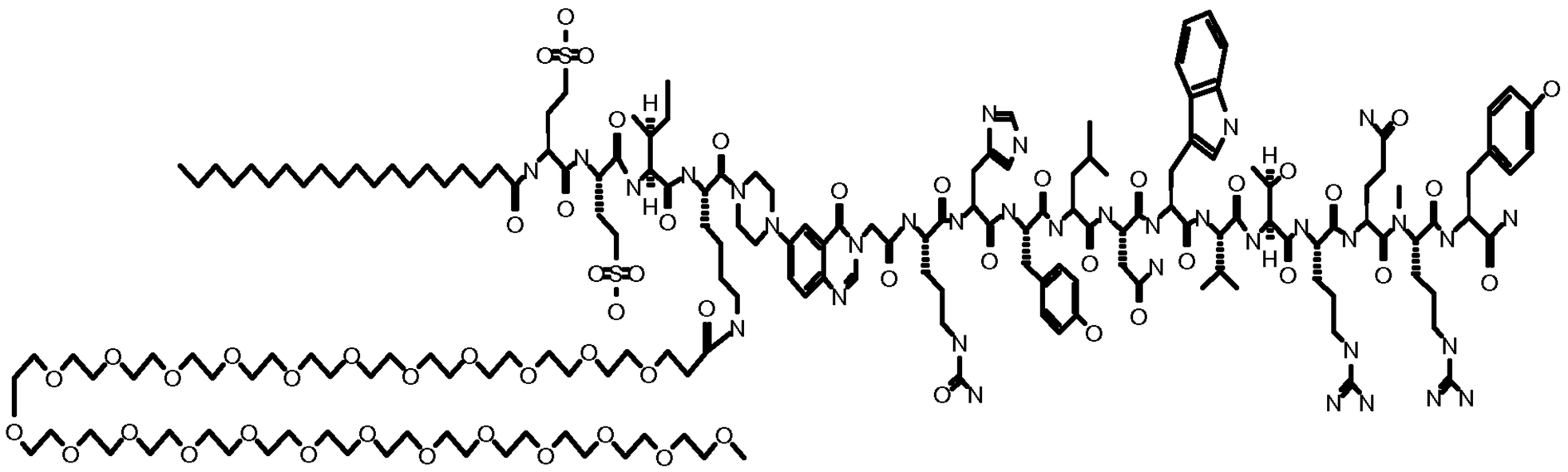


Fmoc-Ile-Lys(Alloc)-Pqa-Cit-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Ring Amide Resin, 1.0 g (0.22 mmol), obtained from Example 6A, was washed with DMF, deprotected and washed and coupled in DMF with Fmoc-

Glu(OBut)-OH (426.0 mg; 1.0 mmol), HCTU (413.7; 1.0 mmol) and NMM (250 ul; 2.27 mmol) were coupled in DMF for 7 hr. Fmoc-Glu-OBut-OH (426.0 mg; 1.0 mmol), HCTU (413.7; 1.0 mmol) and NMM (250 ul; 2.27 mmol) were coupled in DMF for 7 hr. After washing Fmoc-gammaGlu-OBut-OH (426.0 mg; 1.0 mmol), 1.0 mmol) N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled and stirred for 18 hr. After Fmoc removal and washing, Eicosanoic acid 313.0 mg (1.0 mmol) N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$(triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and coupled in m-dPEGn=24 (308 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. The resin was washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield 81 mg (11%) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{184}H_{303}N_{35}O_{54}$ 3867.20, Found 3867.19.

EXAMPLE 62

Preparation of Eicosanoyl-Cys(SO_3)-Cys(SO_3)-Glu-Ile-Lys[CH_3-(OCH_2CH_2)$_{23}$-O-(CH_2)$_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2 1:3 TFA



Fmoc-Ile-Lys(Alloc)-Pqa-Cit-His(Trt)-Tyr(tBu)-Leu-Asn(Trt)-Trp-Val-Thr(tBu)-Arg(Pbf)-Gln(Trt)-NMe-Arg(Mtr)-Tyr(tBu)-Ring Amide Resin, 1.0 g (0.22 mmol), obtained from Example 6A, was washed with DMF, deprotected and washed and coupled in DMF with Fmoc-Cys(SO_3)Na_2 (470.0 mg; 01.0 mmol), N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled 18 hr. After Fmoc removal Fmoc-Cys(SO_3)Na_2 (470.0 mg; 01.0 mmol), N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled 18 hr. The ninhydrin was a reddish-purple and Fmoc-Cys(SO_3)Na_2 (470.0 mg; 01.0 mmol), N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled 6 hr. After Fmoc removal and washing, Eicosanoic acid 313.0 mg (1.0 mmol) N-hydroxybenzotriazole (150 mg, 1.10 mmol), and diisopropyl-carbodiimide (875 ul, 5.0 mmol) in DMF 15.0 mL was coupled and stirred for 18 hr. After washing with DMF 4 times the alloc protecting group was removed with 50.0 mg $PdCl_2$(triPhenylPhosphine)$_2$, 50 uL Morpholine, 100 uL Acetic acid in 15 mL DMF under an atmosphere of Ar, and then 500 uL Bu_3SnH was added. Bubbling with Ar continued until the yellow solution become reddish brown. The reaction was then mixed for 1/4 hr and washed 3 times with DMF. The above procedure was repeated a second time (this time yielding a dark brown to almost black color) for 1/4 to 1/2 hr. The product was washed 2 times with DMF, 2 times 5% DIEA/DMF and 4 times DMF and coupled in m-dPEGn=24 (308 mg, 0.275 mmol); N-hydroxybenzotriazole (40 mg, 0.30 mmol), and diisopropyl-carbodiimide (320 µl, 2.0 mmol) were coupled and stirred for 18 hr. The resin was washed with DMF 2 times and CH_2Cl_2 3 times before cleavage with TFA 17 mL and 400 uL iPrSiH and 800 uL propanethiol for 6 hr, precipitated in 100.0 mL Et_2O, centrifuged, washed and dried in vacuo. The crude peptide was purified by following the procedure in Example 3 to yield

37 mg (4 %) of white amorphous powder. (ES)+-LCMS m/e calculated $C_{182}H_{303}N_{35}O_{56}S_2$ 3939.14, Found 3939.13.

EXAMPLE 63

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 64

CaFlux Assay

HEK-293 cells were stably transfected with the G protein chimera Gαqi9 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, 50 µg/mL hygromycin-B, 2 mM glutamine, 100 U/mL penicillin, 100 µg/mL streptomycin and 250 µg/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 25 µL 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 20 mM HEPES and 5 mM probenecid. Aliquots of 25 µL 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 3.5× the desired concentration in HBSS (20 mM 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 20 µL 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 20 µL of sample was rapidly (30 µL/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, EC50 values for representative compounds of the invention, are illustrated in Table 1 below:

Table 1

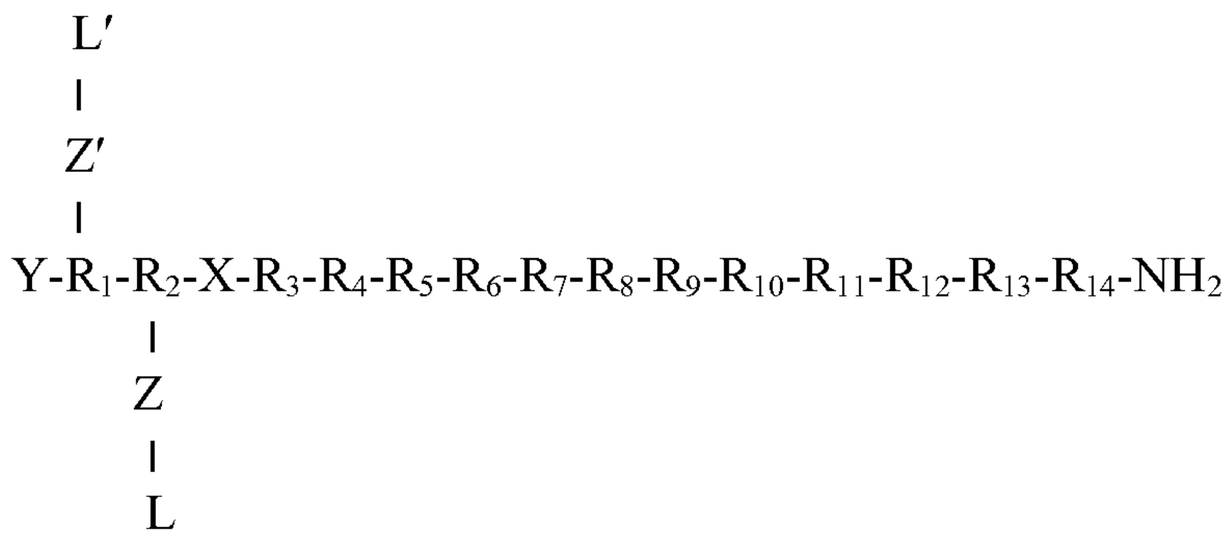
Example	Y2R EC_{50} (nM) FLIPR	Y2R EC_{50} (nM) cAMP	Y1R EC_{50} (nM) FLIPR	Y4R EC_{50} (nM) FLIPR	Y5R EC_{50} (nM) FLIPR
7	0.044	0.16	>5000	>5000	1132
8	0.033	0.17	>5000	>5000	1763
9	0.025	0.08	>5000	>5000	1032
10	0.04	0.13	>5000	>5000	816
11	0.058	0.08	>5000	>5000	915
12	0.097	0.09	>5000	>5000	527
13	0.055	0.15	>5000	>5000	401
14	0.032	0.08	>5000	>5000	370 (P.A)
15	0.084	0.06	>5000	>5000	248 (P.A)
16	0.059	0.09	>5000	>5000	1360
17	0.479	1.4	>6000	>6000	>6000
18	0.357	0.9	>6000	>6000	>6000
19	0.424	0.26	>6000	>6000	>6000
20	0.488	0.89	>6000	>6000	>6000
21	0.139	1.29	>6000	>6000	>6000
22	0.298	0.065	>6000	>6000	1513
23	0.295	0.05	>9000	>9000	2215
24	0.064	0.09	>9000	>9000	265 (P.A)
25	0.14	0.09	>9000	>9000	2582 (P.A)
26	0.01	0.1	>9000	>9000	1918 (P.A)
27	9.6	2.3	>6000	>6000	>6000

28	11.12	1.8	>6000	>6000	1318
29	0.156	0.14	>6000	>6000	>6000
30	0.143	0.47	>6000	>6000	5687
31	0.111	0.37	>6000	>6000	3515
32	0.15	0.23	>6000	>6000	4756
33	0.127	0.13	>6000	>6000	4287
34	0.068	0.18	>5000	>5000	988
35	0.097	0.17	>6000	>6000	1007
36	0.388	12.7	>6000	>6000	>6000
37	0.158	2.8	>6000	>6000	4256
38	0.1	0.07	>6000	>6000	1375.67
39	0.038	0.07	>6000	>6000	1949
40	0.058	0.11	>6000	>6000	820
41	0.04	0.17	>6000	>6000	1316
42	0.069	0.13	>6000	>6000	814.7
43	0.1	0.1	>6000	>6000	316
44	0.313	0.43	>6000	>6000	>6000
45	0.158	0.3	>6000	>6000	>6000
46	0.214	0.29	>9000	>9000	4580
47	0.158	0.23	>6000	>6000	>6000
48	0.388	0.52	>9000	>9000	4322
49	0.098	0.25	>9000	>9000	518 (P.A)
50	1.8	25	262(PA)	>6000	>6000
51	9.405	5.5	>6000	>6000	>6000
52	0.147	0.2	>9000	>9000	4264
53	0.66	0.56	>6000	>6000	>6000
54	292	36	>6000	>6000	>6000
55	0.027	0.014	>6000	>6000	8.665
56	0.098	0.013	>6000	>6000	8.735
57	0.016	0.011	>6000	>6000	5.665
58	0.114	0.21	>9000	>9000	4184
59	0.285	0.29	>9000	>9000	3884
60	0.18	0.29	>9000	>9000	2597
61	0.243	0.28	>6000	>6000	>6000
62	9.26	6.5	>6000	>6000	>6000

P.A. = partial agonist

Claims

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



(I),

wherein:

one of L or L′ is a polyethylene glycol (PEG) moiety and the other is a lipid moiety or absent;

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

Y is an acyl moiety or absent;

Z, Z′ is a spacer moiety or absent;

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

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

R_3 is Arg, Cit, 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, His, 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,

or a pharmaceutically acceptable salt thereof.

2. The neuropeptide-2 receptor agonist according to claim 1, wherein said lipid moiety is caproyl, eicosanoyl, lauroyl, myristoyl, palmitoyl, 16-bromohexadecanoyl, 2-hexyldecanoyl or 15-carboxy-pentadecanoyl.

3. The neuropeptide-2 receptor agonist according to claim 1 or 2, wherein said polyethylene glycol moiety is of the formula:

$$CH_3(OCH_2CH_2O)_n(CH_2)_xCO\text{-},$$

wherein n is 1 to 30 and x is 1 or 2.

4. The neuropeptide-2 receptor agonsist according to claim 3, wherein n is 1 to 24 and x is 1 or 2.

5. The neuropeptide-2 receptor agonist according to any one of claims 1 to 4, wherein said polyethylene glycol moiety is CH_3-$(OCH_2CH_2)_2$-O-CH_2-CO-, CH_3-$(OCH_2CH_2)_5$-O-CH_2-CO-, CH_3-$(OCH_2CH_2)_7$-O-$(CH_2)_2$-CO-, CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO- CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO-, or CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO-.

.

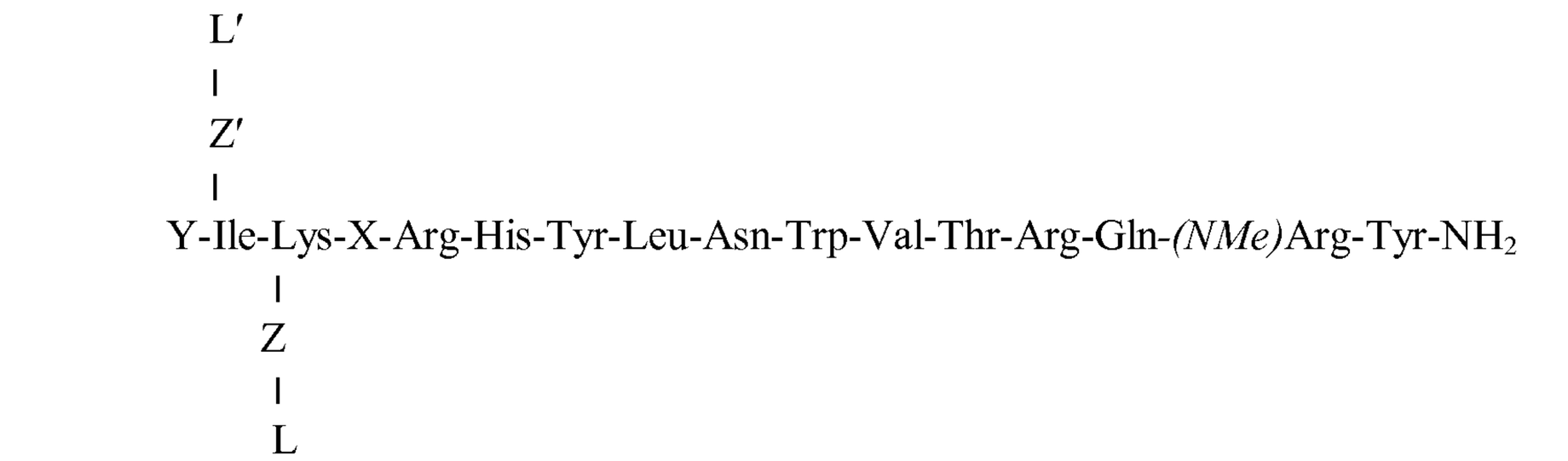
6. The neuropeptide-2 receptor agonist according to any one of claims 1 to 5, wherein said spacer moiety is Ahx, Ahx-Ahx, Glu-Glu, γGlu- γGlu, 5AOPS or Cys(SO_3H)-Cys(SO_3H).

7. The neuropeptide-2 receptor agonist according to any one of claims 1 to 6, wherein said acyl moiety is acetyl.

8. The neuropeptide-2 receptor agonist according to any one of claims 1 to 7, wherein Z is absent.

9. The neuropeptide-2 receptor agonist according to any one of claims 1 to 8, wherein Z' is absent.

10. The neuropeptide-2 receptor agonist according to claim 1, having formula (II):



(II),

wherein:

one of L or L′ is a lipid moiety and the other is a polyethylene glycol (PEG) moiety;

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

Y is an acyl moiety or absent; and

Z, Z′ is Ahx, Ahx-Ahx, Glu-Glu, γGlu- γGlu, 5AOPS or Cys(SO_3H)-Cys(SO_3H).

11. The neuropeptide-2 receptor agonist according to claim 10, wherein said lipid moiety is caproyl, eicosanoyl, lauroyl, myristoyl, palmitoyl, 16-bromohexadecanoyl, 2-hexyldecanoyl or 15-carboxy-pentadecanoyl.

12. The neuropeptide-2 receptor agonist according to claim 10 or 11, wherein said polyethylene glycol moiety is of the formula:

$$CH_3(OCH_2CH_2O)_n(CH_2)_xCO\text{-},$$

wherein n is 1 to 30 and x is 1 or 2.

13. The neuropeptide-2 receptor agonsist according to any one of claims 10 to 13, wherein n is 1 to 24 and x is 1 or 2.

14. The neuropeptide-2 receptor agonist according to claim 10, wherein said polyethylene glycol moiety is CH_3-$(OCH_2CH_2)_2$-O-CH_2-CO-, CH_3-$(OCH_2CH_2)_5$-O-CH_2-CO-, CH_3-$(OCH_2CH_2)_7$-O-$(CH_2)_2$-CO-, CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO-

CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO-, or CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO-.

15. The neuropeptide-2 receptor agonist according to any one of claims 10 to 14, wherein Z, Z' is Ahx, Ahx-Ahx, Glu-Glu, γGlu- γGlu, 5AOPS or Cys(SO_3H)-Cys(SO_3H).

16. The neuropeptide-2 receptor agonist according to claim 1, wherein said acyl moiety is acetyl.

17. The neuropeptide-2 receptor agonist according to any one of claims 10 to 15, wherein Z is absent.

18. The neuropeptide-2 receptor agonist according to any one of claims 10 to 16, wherein Z' is absent.

19. The neuropeptide-2 receptor agonist according to claim 1, selected from the group consisting of:

CH_3-$(OCH_2CH_2)_5$-O-CH_2-CO-Ile-Lys(Palmitoyl-6Ahx)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_7$-O-$(CH_2)_2$-CO-Ile-Lys(Palmitoyl-6Ahx)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO-Ile-Lys(Palmitoyl-6Ahx)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO-Ile-Lys(Palmitoyl-6Ahx)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO-Ile-Lys(Palmitoyl-6Ahx)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_5$-O-CH_2-CO-Ile-Lys(Palmitoyl-5AOPS)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO-Ile-Lys(Palmitoyl-5AOPS)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO-Ile-Lys(Palmitoyl-5AOPS)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO-Ile-Lys(Palmitoyl-5AOPS)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO-Ile-Lys(Palmitoyl-5AOPS)-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_7$-O-$(CH_2)_2$-CO-6Ahx-Ile-Lys-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO-6Ahx-Ile-Lys-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO-6Ahx-Ile-Lys-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO-6Ahx-Ile-Lys-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Ac-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_2$-O-CH_2-CO-Ile-Lys(Eicosanoyl-gammaGlu-gammaGlu)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_7$-O-$(CH_2)_2$-CO-Ile-Lys(Eicosanoyl-gammaGlu-gammaGlu)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr -NH_2;

CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO-Ile-Lys(Eicosanoyl-gammaGlu-gammaGlu)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO-Ile-Lys(Eicosanoyl-gammaGlu-gammaGlu)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO-Ile-Lys(Eicosanoyl-gammaGlu-gammaGlu)-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO-Ile-Lys(Eicosanoyl-Cys{SO_3}-Cys{SO_3})-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr -NH_2;

CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO-Ile-Lys(Eicosanoyl-Cys{SO_3}-Cys{SO_3})-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2; and

CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO-Ile-Lys(Palmitoyl-Cys{SO_3}-Cys{SO_3})-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2,
or a pharmaceutically acceptable salt thereof.

20. The neuropeptide-2 receptor agonist according to claim 1, selected from the group consisting of:
Palmitoyl-6Ahx-Ile-Lys[CH_3-$(OCH_2CH_2)_7$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;
Palmitoyl-6Ahx-Ile-Lys[CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;
Palmitoyl-6Ahx-Ile-Lys[CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;
Eicosanoyl-6Ahx-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;
Palmitoyl-6Ahx-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr -NH_2;
Eicosanoyl-6Ahx-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;
Lauroyl-6Ahx-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;
Myristoyl-6Ahx-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;
Palmitoyl-6Ahx-6Ahx-Ile-Lys[CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;
Palmitoyl-6Ahx-6Ahx-Ile-Lys[CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;
Palmitoyl-6Ahx-6Ahx-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;
Palmitoyl-6Ahx-6Ahx-(D)alloIle-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Eicosanoyl-Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_7$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Eicosanoyl -Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Eicosanoyl -Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Eicosanoyl -Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Eicosanoyl-Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Eicosanoyl -Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Eicosanoyl -Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-C-alphaMeVal-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Eicosanoyl -Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg(CO)-Gln-(NMe)-Arg-Tyr-NH_2;

Eicosanoyl -Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Eicosanoyl -Glu-Glu-(D)alloIle-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

15-Carboxy-pentadecanoyl-Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Eicosanoyl-Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-His-Asn-Trp-Val-Thr-Arg-Gln-Arg-Tyr-NH_2;

Eicosanoyl-Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-His-Asn-Trp-Val-Thr-Arg-Gln-Arg-Tyr-NH_2;

Eicosanoyl -Glu-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-His-Asn-Trp-Val-Thr-Arg-Gln-Arg-Tyr-NH_2;

Eicosanoyl-gammaGlu-gammaGlu-Ile-Lys[CH_3-$(OCH_2CH_2)_{11}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Eicosanoyl-gammaGlu-gammaGlu-Ile-Lys[CH_3-$(OCH_2CH_2)_{15}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

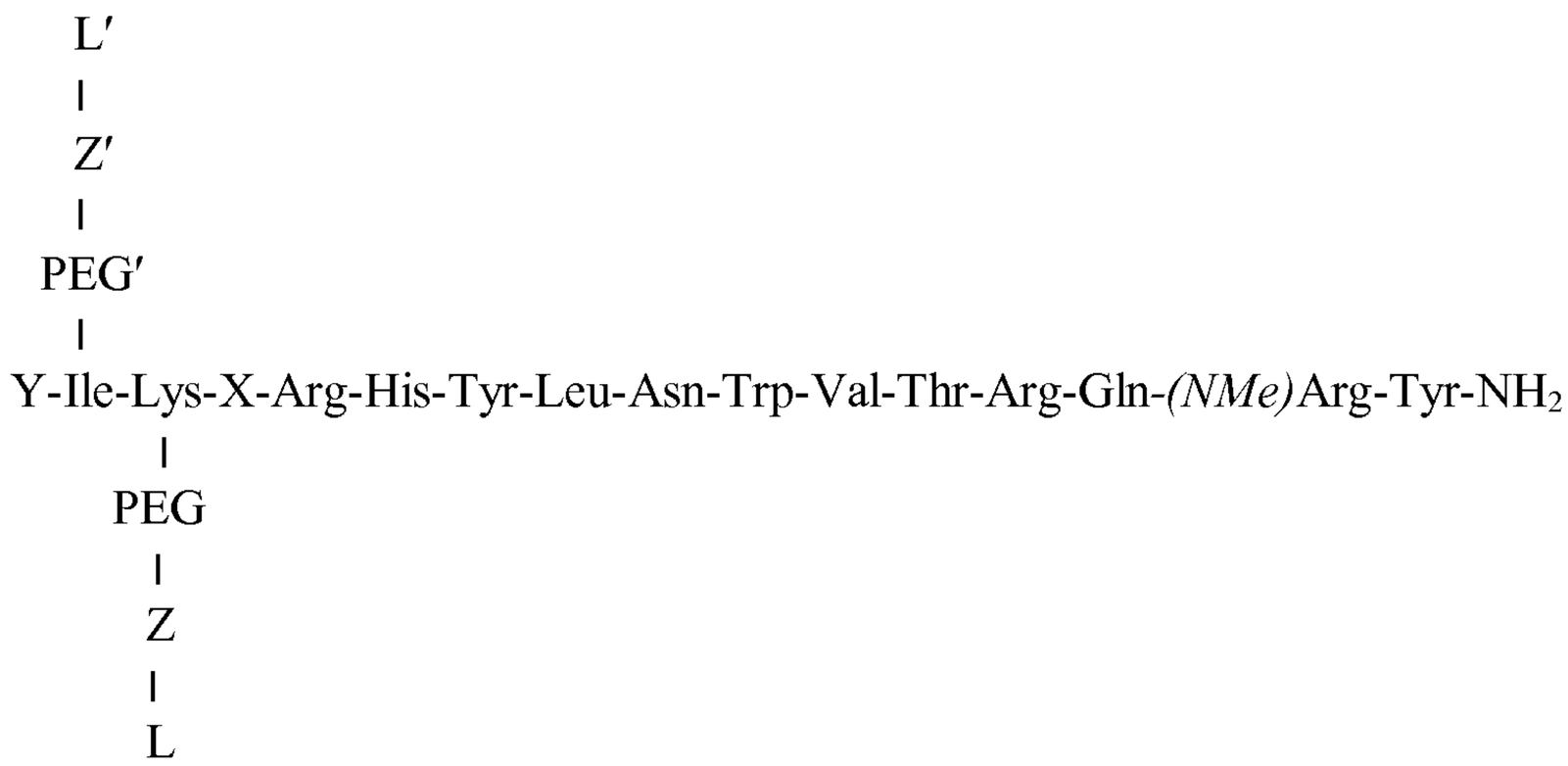
Eicosanoyl-gammaGlu-gammaGlu-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2;

Eicosanoyl -gammaGlu-gammaGlu-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2; and

Eicosanoyl-Cys(SO_3)-Cys(SO_3)-Glu-Ile-Lys[CH_3-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Cit-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2,

or pharmaceutically acceptable salts thereof.

21. A neuropeptide-2 receptor agonist of formula (III):



(III),

wherein:

one of L or L′ is a lipid moiety and the other is absent;

one of Z or Z′ is a spacer moiety and the other is absent;

one of PEG or PEG' is a polyethelene glycol moiety -NH-CH_2CH_2 -$(OCH_2CH_2)_n$-O-$(CH_2)_x$-CO- and the other is absent, wherein n is 1 to 30 and x is 1 or 2;

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

Y is an acyl moiety or absent,

or a pharmaceutically acceptable salt thereof.

22. The neuropeptide-2 receptor agonist according to claim 21, wherein said lipid moiety is caproyl, eicosanoyl, lauroyl, myristoyl, palmitoyl, 16-bromohexadecanoyl, 2-hexyldecanoyl or 15-carboxy-pentadecanoyl.

23. The neuropeptide-2 receptor agonist according to claim 21 or 22, wherein said spacer moiety is Ahx, Ahx-Ahx, Glu-Glu, γGlu- γGlu, 5AOPS or Cys(SO_3H)-Cys(SO_3H).

24. The neuropeptide-2 receptor agonsist according to any one of claims 21 to 23, wherein n is 1 to 24 and x is 1 or 2.

25. The neuropeptide-2 receptor agonist according to any one of claims 21 to 24, wherein said polyethylene glycol moiety is NH-CH_2CH_2-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO.

26. The neuropeptide-2 receptor agonist according to any one of claims 21 to 25, wherein said acyl moiety is acetyl.

27. The neuropeptide-2 receptor agonist according to claim 21, selected from the group consisting of:
Palmitoyl-6Ahx-NH-CH_2CH_2-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO-Ile-Lys-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2; and
Ac-Ile-Lys[Palmitoyl-6Ahx-NH-CH_2CH_2-$(OCH_2CH_2)_{23}$-O-$(CH_2)_2$-CO]-Pqa-Arg-His-Tyr-Leu-Asn-Trp-Val-Thr-Arg-Gln-(NMe)-Arg-Tyr-NH_2,
or a pharmaceutically acceptable salt thereof.

28. A pharmaceutical composition, comprising a therapeutically effective amount of the neuropeptide-2 receptor agonist according to any one of claims 1 to 20, or a salt thereof, and a pharmaceutically acceptable carrier.

29. A pharmaceutical composition, comprising a therapeutically effective amount of the neuropeptide-2 receptor agonist according to any one of claims 21 to 27, or a salt thereof, and a pharmaceutically acceptable carrier.

30. A neuropeptide-2 receptor agonist, or a salt thereof, according any one of claims 1 to 27 for use as therapeutically active substance.

31. The use of a compound according to any one of claims 1 to 27 for the treatment or prophylaxis of metabolic diseases and disorders.

32. The use of a compound according to any one of claims 1 to 27 for the preparation of a medicament for the treatment or prophylaxis of metabolic diseases and disorders.

33. A neuropeptide-2 receptor agonist, or a salt thereof, according any one of claims 1 to 27 for the treatment or prophylaxis of metabolic diseases and disorders.

34. A method for the treatment or prophylaxis of metabolic diseases and disorders, which method comprises administering an effective amount of a neuropeptide-2 receptor agonist, or a salt thereof, according any one of claims 1 to 27.

35. The invention as hereinbefore described.