

TITLE: CNP COMPOUNDS**TECHNICAL FIELD OF INVENTION**

This invention relates to new C-type natriuretic peptide (CNP) compounds,
5 pharmaceutical compositions comprising these compounds, and these compounds for use
as medicaments.

BACKGROUND OF INVENTION

The natriuretic peptides are a family of three structurally related hormones that play
distinctive roles within the cardiovascular system. Atrial natriuretic peptide (ANP) and brain
10 natriuretic peptide (BNP) are expressed in the heart and released in response to a volume-
induced stretch of the atria and ventricles, respectively. Their physiological effects include
regulation of cardiac structure, blood pressure and blood volume.

C-type natriuretic peptide (CNP) is highly expressed in endothelial cells where it is
constitutively released. Other cells within the cardiovascular system, including
15 cardiomyocytes and fibroblasts, also produce CNP, albeit to a lesser extent. CNP has direct
effects on inflammation, fibrosis, cardiac contractility, endothelial function, angiogenesis and
blood pressure.

There are three known receptors for natriuretic peptides. Natriuretic peptide
receptor-1 (NPR1) is a particulate guanylyl cyclase that catalyses the synthesis of cGMP
20 upon binding by ANP or BNP. NPR1 is expressed in kidney, lung, adipose, adrenal, brain,
heart, testis, and vascular smooth muscle tissue. NPR2, which is expressed in bone, brain,
fibroblasts, heart, kidney, liver, lung, uterine, and vascular smooth muscle tissue, is
homologous to NPR1 but is selectively activated by CNP. In contrast, NPR3 only contains a
37-residue intracellular domain and lacks guanylyl cyclase activity. It controls local natriuretic
25 peptide concentrations via receptor-mediated internalization and degradation, but there is
accumulating evidence for a signalling function of NPR3. All three natriuretic peptides bind to
NPR3 with high affinity and this receptor is the most widely and abundantly expressed of the
three receptors. There is also a very high degree of conservation of all three receptors and in
line with CNP, NPR2 is the most highly conserved.

30 Clinical and preclinical data have demonstrated an essential role of CNP and its two
receptors for cardio-renal-metabolic function, and there is also accumulating data supporting
that targeting of this system holds therapeutic potential in a broad range of cardiovascular,
renal, and metabolic diseases (Int. J. Mol. Sci. 2019, 20, 2281; Cardiovasc. Res. 2022, 118,

2085–2102; Cardiovasc. Res. 2022 Aug 25;cvac125)”. Similarly, human genetics, as well as preclinical and clinical data, supports NPR2 and CNP as regulators of bone growth, with therapeutic potential in a broad range of short stature indications that relates to NPR2 and CNP (Lancet, 396:684; J Pharmacol Exp Ther, 370:459; Hisado-Oliva (2018) Genet Med, 20:91, as well as to FGFR3-related skeletal dysplasia (Sabir and Cole Orphanet Journal of Rare Diseases (2019) 14:300; Krakow and Rimoin, Genetics in medicine (2010) 12:6, Decker et al. Human Molecular Genetics (2011), 20:8) and RASopathies (Adv Cancer Res. 153:305). Currently, two CNP compounds are in clinical development for achondroplasia which is a type of Dwarfism (BMN111(Vosoritide) and TransCon CNP). The Mayo clinic has previously explored a CNP compound designed to activate both NPR2 and NPR1 in heart failure (J Am Coll Cardiol. 2008 July 1; 52(1): 60–68).

The clearance of CNP in human plasma is very rapid, with a calculated half-life of minutes. Given this short half-life, it would be beneficial to develop new long acting CNP compounds which can be administered less frequently, while retaining an acceptable clinical profile.

A range of different approaches have been used for modifying the structure of CNP in order to provide a longer acting profile. WO 2013/058833 discloses fusion peptides of CNP and Fc domains. WO 2018/175534 discloses fatty acid modified NPR1 agonists.

SUMMARY OF INVENTION

The invention provides CNP compounds with improved pharmaceutical properties.

In one aspect, the present invention provides a CNP compound comprising a CNP peptide and a modifying group wherein the net charge of the compound at physiological pH is 0 or negative, wherein the CNP peptide comprises an amino acid sequence according to Formula I:

AA₀₁- AA₀₂-AA₀₃-AA₀₄-AA₀₅-AA₀₆-AA₀₇-AA₀₈-AA₀₉-AA₁₀-AA₁₁-AA₁₂-AA₁₃-AA₁₄-
AA₁₅-AA₁₆-AA₁₇-AA₁₈-AA₁₉-AA₂₀-AA₂₁-AA₂₂-AA₂₃-AA₂₄-AA₂₅-AA₂₆-AA₂₇-AA₂₈-AA₂₉-
AA₃₀-AA₃₁-AA₃₂-AA₃₃-AA₃₄-AA₃₅-AA₃₆-AA₃₇

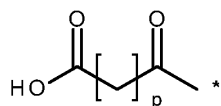
wherein

AA₀₁ is Gln or absent,
AA₀₂ is Glu or absent,
AA₀₃ is His or absent,
AA₀₄ is Pro or absent,
AA₀₅ is Asn or Gln or Glu or absent,

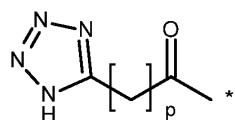
AA₀₆ is Ala or absent,
AA₀₇ is Arg or His or Ala or absent,
AA₀₈ is Lys or Ser or His or absent,
AA₀₉ is Tyr or Glu or absent
5 AA₁₀ is Lys or Glu or Gln or His or absent,
AA₁₁ is Gly,
AA₁₂ is Ala,
AA₁₃ is Gln or Asn or Glu,
AA₁₄ is Lys or His or Glu,
10 AA₁₅ is Lys Ser or Glu or Thr or His,
AA₁₆ is Gly,
AA₁₇ is Leu or Gly or Ser or Val,
AA₁₈ is Ser or His
AA₁₉ is Gln or Ser or Lys or His,
15 AA₂₀ is Gly,
AA₂₁ is Cys,
AA₂₂ is Phe,
AA₂₃ is Gly,
AA₂₄ is Leu,
20 AA₂₅ is Pro or Lys,
AA₂₆ is Leu,
AA₂₇ is Asp or Glu,
AA₂₈ is Arg,
AA₂₉ is Ile,
25 AA₃₀ is Gly,
AA₃₁ is Ser,
AA₃₂ is Leu or Nle or Met,
AA₃₃ is Ser,
AA₃₄ is Gly,
30 AA₃₅ is Leu,
AA₃₆ is Gly, and
AA₃₇ is Cys;

wherein the modifying group comprises Chem. A, Chem. B and Chem. C;

wherein Chem. A is selected from the group consisting of:



(Chem. A1), and



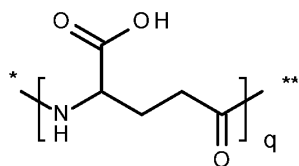
5

(Chem. A2),

wherein p is an integer in the range of 14-20, and

where * denotes an amide bond connecting Chem. A and Chem. B; and

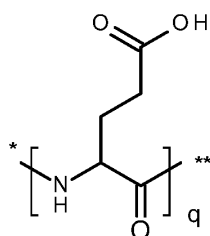
wherein Chem. B is selected from the group consisting of:



10

(Chem. B1)

and



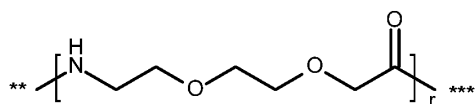
(Chem. B2)

15 wherein q is an integer in the range of 1-8,

wherein * denotes an amide bond connecting Chem. A- and Chem. B-,

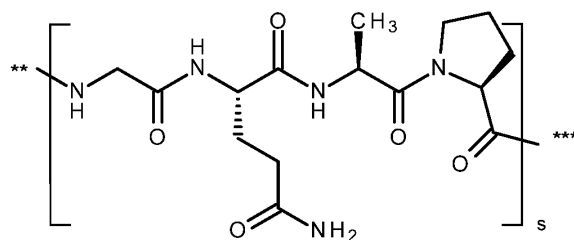
wherein ** denotes an amide bond connecting Chem. B- and Chem. C-; and

wherein Chem. C is selected from the group consisting of:

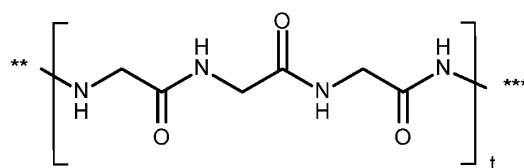


20

(Chem. C1),



(Chem. C2), and



(Chem. C3)

- 5 wherein r is an integer in the range of 0-4,
 wherein s is an integer in the range of 0-3,
 wherein t is an integer in the range of 0-1,
 wherein $**$ denotes an amide bond connecting Chem. B- and Chem. C-,
 wherein $***$ denotes an amide bond connecting Chem. C- and the N-terminal alpha-amine on
 10 the CNP peptide.

In one embodiment, the present invention provides a CNP compound, wherein the CNP peptide has any one of the following amino acid sequences:

- GAQKKGSSQGCFGLPLDRIGSLSGGLGC (SEQ ID NO: 136),
 ARKYKGAQKKGLSQGCFGLPLDRIGSLSGGLGC (SEQ ID NO: 77),
 15 YKGAQKKGSSQGCFGLPLDRIGSLSGGLGC (SEQ ID NO: 88),
 YKGAQKKGLSQGCFGLPLDRIGSLSGGLGC (SEQ ID NO: 103),
 QEHPQARKYKGAQKKGLSSGCFGLPLDRIGSLSGGLGC (SEQ ID NO: 67), and
 QEHPQARKYKGAQKKGLSSGCFGLPLERIGSLSGGLGC (SEQ ID NO: 104).

- In another aspect, the present invention provides a pharmaceutical composition
 20 comprising a compound according to the invention, and one or more pharmaceutically acceptable excipients.

The present invention also in one aspect provides, the use of the compounds of the invention as medicaments for treating or preventing of cardio-renal-metabolic diseases including heart failure, and achondroplasia.

- 25 The short half-life of approximately two minutes of *wf* CNP makes CNP unsuitable for pharmaceutical use. In the present invention, the half-life of CNP is extended by fatty acid

acylation which facilitates albumin binding. However, the combination of the net positively charged CNP peptide (at physiological pH) with a fatty acid albumin binder modification (where the CNP compound is overall positively charged) leads to significant injection site reactions upon subcutaneous injection as well as low bioavailability. This is surprising since a net positively charged CNP peptide without a fatty acid albumin binder attached shows no observable injection site reactions. To solve these problems, amino acid substitutions have been introduced into the CNP peptide and negative charges have been introduced into the modifying group (comprising the fatty acid). The combination of these modifications results in a compound of overall net negative charge at physiological pH which shows good subcutaneous bioavailability and none to mild subcutaneous injection site reactions.

Surprisingly, the addition of negative charges also reduces the *in vitro* and *in vivo* potency of the CNP compounds, in a manner such that higher net negative charge generally correlates with lower *in vivo* potency. To retain sufficient potency of the CNP compounds, only a low number of net negative charges were introduced. However, a low number of net negative charges reduces solubility and biophysical stability of the CNP compounds when formulated for subcutaneous administration at a physiologically relevant pH. The present disclosure strikes a balance with respect to these parameters and, surprisingly, provides CNP compounds with sufficient potency, and also sufficient solubility and biophysical stability for liquid formulation.

Further, *wt* CNP does not show desired chemical stability in liquid formulation needed for convenient pharmaceutical administration. In the present invention, selected amino acid substitutions of the *wt* CNP sequence are introduced to facilitate chemical stability in formulation.

The present disclosure provides CNP compounds with extended half-life and good tolerability for subcutaneous administration while retaining sufficient *in vivo* potency for therapeutic use and high chemical and biophysical stability in liquid formulation.

The invention may also solve further problems that will be apparent from the disclosure of the exemplary embodiments.

DESCRIPTION OF DRAWING

Fig. 1 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 0776 to rats as described in example 11.

Fig. 2 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 0312 to rats as described in example 11.

Fig. 3 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 1225 to rats as described in example 11.

Fig. 4 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 1233 to rats as described in example 11.

5 Fig. 5 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 1227 to rats as described in example 11.

Fig. 6 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 1241 to rats as described in example 11.

10 Fig. 7 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 1351 to rats as described in example 11.

Fig. 8 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 1354 to rats as described in example 11.

Fig. 9 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 1356 to rats as described in example 11.

15 Fig. 10 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 1375 to rats as described in example 11.

Fig. 11 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 1376 to rats as described in example 11.

20 Fig. 12 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 1377 to rats as described in example 11.

Fig. 13 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 1352 to rats as described in example 11.

Fig. 14 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 1379 to rats as described in example 11.

25 Fig. 15 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 1434 to rats as described in example 11.

Fig. 16 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 9384 to rats as described in example 11.

30 Fig. 17 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 9407 to rats as described in example 11.

Fig. 18 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 1420 to rats as described in example 11.

Fig. 19 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 1378 to rats as described in example 11.

Fig. 20 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 1381 to rats as described in example 11.

Fig. 21 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 1386 to rats as described in example 11.

5 Fig. 22 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 1389 to rats as described in example 11.

Fig. 23 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 1392 to rats as described in example 11.

10 Fig. 24 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 1426 to rats as described in example 11.

Fig. 25 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 9435 to rats as described in example 11.

Fig. 26 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 1235 to rats as described in example 11.

15 Fig. 27 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 9482 to rats as described in example 11.

Fig. 28 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 0312 to Göttingen minipigs as described in example 12.

20 Fig. 29 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 0776 to Göttingen minipigs as described in example 12.

Fig. 30 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 9384 to Göttingen minipigs as described in example 12.

Fig. 31 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 9407 to Göttingen minipigs as described in example 12.

25 Fig. 32 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 9435 to Göttingen minipigs as described in example 12.

Fig. 33 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 9480 to Göttingen minipigs as described in example 12.

30 Fig. 34 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 9482 to Göttingen minipigs as described in example 12.

Fig. 35 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 9483 to Göttingen minipigs as described in example 12.

Fig. 36 shows the pharmacodynamic response (cGMP) after s.c. administration of Compound ID 0312 to Göttingen minipigs as described in example 12.

Fig. 37 shows the pharmacodynamic response (cGMP) after s.c. administration of Compound ID 0776 to Göttingen minipigs as described in example 12.

Fig. 38 shows the pharmacodynamic response (cGMP) after s.c. administration of Compound ID 9384 to Göttingen minipigs as described in example 12.

5 Fig. 39 shows the pharmacodynamic response (cGMP) after s.c. administration of Compound ID 9407 to Göttingen minipigs as described in example 12.

Fig. 40 shows the pharmacodynamic response (cGMP) after s.c. administration of Compound ID 9435 to Göttingen minipigs as described in example 12.

10 Fig. 41 shows the pharmacodynamic response (cGMP) after s.c. administration of Compound ID 9480 to Göttingen minipigs as described in example 12.

Fig. 42 shows the pharmacodynamic response (cGMP) after s.c. administration of Compound ID 9482 to Göttingen minipigs as described in example 12.

Fig. 43 shows the pharmacodynamic response (cGMP) after s.c. administration of Compound ID 9483 to Göttingen minipigs as described in example 12.

15 Fig. 44 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 0312 to Domestic LYD pigs as described in example 12.

Fig. 45 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 0776 to Domestic LYD pigs as described in example 12.

20 Fig. 46 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 1225 to Domestic LYD pigs as described in example 12.

Fig. 47 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 1227 to Domestic LYD pigs as described in example 12.

Fig. 48 shows the pharmacodynamic response (cGMP) after i.v. administration of Compound ID 1235 to Domestic LYD pigs as described in example 12.

25 DETAILED DESCRIPTION

The present invention provides CNP compounds with improved pharmaceutical properties. The present invention also provides pharmaceutical compositions and the use of the compounds and compositions of the present invention as medicaments for treating disease.

30 C-type natriuretic peptide

C-type natriuretic peptide (CNP) (GenBank Accession No. NP 077720) is a small, single chain peptide in a family of peptides (ANP, BNP, CNP) having a 17-amino acid residue disulfide ring structure and have important roles in multiple biological processes.

CNP interacts with natriuretic peptide receptor 2 (NPR2, NPR-B, GC-B) to stimulate the generation of cyclic-guanosine monophosphate (cGMP). CNP is expressed more widely, including in the central nervous system, reproductive tract, bone and endothelium of blood vessels. The clearance of CNP in human plasma is rapid, with a half-life of minutes.

5 Natural CNP gene and polypeptide have been previously described. U.S. Patent No. 5,352,770 discloses isolated and purified CNP-22 from porcine brain identical in sequence to human CNP (human wild-type CNP-22: GLSKGCFGLKLDRI GMSGLGC (SEQ ID NO: 01)). U.S. Patent No. 6,034,231 discloses the human gene and polypeptide of pre-pro-CNP (126 amino acids) and the human CNP-53 gene and peptide. Human wild-type CNP-37 has the
10 sequence QEHPNARKYKGANKKGLSKGCFGLKLDRI GMSGLGC (SEQ ID NO: 02).

CNP compound

 In one aspect, the present invention provides a CNP compound comprising a CNP peptide and a modifying group wherein the net charge of the compound at physiological pH is 0 or negative.

15 The CNP compounds as described herein, have been engineered to achieve a compound of overall neutral or net negative charge. This was achieved with introduction of amino acid substitutions of the CNP peptide, and with the introduction of negative charges into the modifying group. It is not trivial to reduce the charge of the CNP compound and still retain biological activity of the CNP compound towards the NPR2 receptor.

20 The term "net charge", as used herein, refers to the sum of all negative and positive charges on the CNP compound at a given pH, where the charges are defined solely by the acid dissociation constant of each ionizable group in the CNP compound.

 In one embodiment, the net charge of the CNP compound at physiological pH is negative determined as described in Example 4.

25 In one embodiment, the net charge of the CNP compound at physiological pH is 0 to -4, determined as described in Example 4.

 The term "physiological pH", as used herein, refers to a pH in the range of 7.35 to 7.45 inclusive, more typically averaging 7.4.

30 In one aspect, the CNP compounds, described herein, have an intramolecular disulfide bridge (disulfide bond between two cysteine residues), resulting in a cyclic structure.

CNP peptide

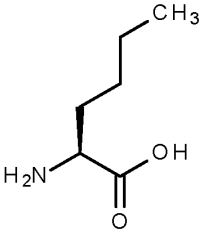
 The term "CNP peptide" as used herein refers to a peptide being 37 to 22 amino acids long comprising the CNP-22 amino acid sequence (SEQ ID NO: 01), and amino acid

sequences thereof including one or more amino acid modifications (e.g. one or more amino acid substitutions, additions, and/or deletions). The term "CNP peptide" as used herein also encompasses CNP variants.

5 The term "CNP variant", as used herein, refers to a CNP peptide, which is an amino acid variant of the CNP-37 sequence (SEQ ID NO:02). In other words, a CNP variant is a CNP peptide including one or more amino acid modifications, i.e. at least one amino acid has been changed compared to SEQ ID NO: 02. These modifications may represent, independently, one or more amino acid substitutions, additions, and/or deletions.

10 A CNP variant may be described by reference to the number of the amino acid residue which is changed (i.e. the corresponding position in the CNP-37 sequence (SEQ ID NO:02)), and the change (e.g. the identity of the amino acid residue in variant at the given position.). That is, numerical references to specific amino acid residues of the CNP peptide, if not stated otherwise, refer to the CNP-37 sequence (SEQ ID NO:2) (i.e., residue 1 is Glutamine (Q1), and residue 37 is Cysteine (C37)). The following is a non-limiting example of
15 suitable variant nomenclature: the des1-4, 5Q, 13Q, 32Nle CNP variant designates a CNP peptide sequence which, when compared to CNP-37, has the following amino acid changes: deletion of the amino acid residues in positions 1-4, as well as substitutions of asparagine (N) at position 5 with Glutamine (Q), of asparagine (N) at position 13 with Glutamine (Q), of Methionine (M) at position 32 with Norleucine.

20 The term "amino acid" refers to any amino acid, naturally occurring (including the 20 standard amino acids which are encoded by the standard genetic code in humans) or not naturally occurring. Amino acid residues may be identified by their full name, their one-letter code, and/or their three-letter code as is usual in the art. These three ways are fully equivalent. The term "non-coded amino acids" refers to all amino acids which aren't among
25 the 20 standard amino acids encoded by the standard genetic code in humans. Non-coded amino acids may exist in nature or be purely synthetic. Non-limiting examples of non-coded amino acids are D-isomers of the coded amino acids, and glycine residues with a side chain attached to the nitrogen atom rather than the alpha-carbon atom. D-isomers of coded amino acids may be referred to as (i) "D-" followed by the full name, followed by the one-letter code, or followed by the three-letter code of the amino acid, or as (ii) the lower case one-letter code
30 of the amino acid. Further abbreviations for non-coded amino acids used in this application are presented below.

Abbreviation	Name of the residue	Chemical structure
Nle (X)	L-Norleucine	 (Chem. D)

In an aspect of the invention, the CNP peptide, comprises an amino acid sequence according to Formula I:

	AA ₀₁ -AA ₀₂ -AA ₀₃ -AA ₀₄ -AA ₀₅ -AA ₀₆ -AA ₀₇ -AA ₀₈ -AA ₀₉ -AA ₁₀ -AA ₁₁ -AA ₁₂ -AA ₁₃ -AA ₁₄ -AA ₁₅ -
5	AA ₁₆ -AA ₁₇ -AA ₁₈ -AA ₁₉ -AA ₂₀ -AA ₂₁ -AA ₂₂ -AA ₂₃ -AA ₂₄ -AA ₂₅ -AA ₂₆ -AA ₂₇ -AA ₂₈ -AA ₂₉ -AA ₃₀ -AA ₃₁ -AA ₃₂ -
	AA ₃₃ -AA ₃₄ -AA ₃₅ -AA ₃₆ -AA ₃₇
	wherein
	AA ₀₁ is Gln or absent,
	AA ₀₂ is Glu or absent,
10	AA ₀₃ is His or absent,
	AA ₀₄ is Pro or absent,
	AA ₀₅ is Asn or Gln or Glu or absent,
	AA ₀₆ is Ala or absent,
	AA ₀₇ is Arg or His or Ala or absent,
15	AA ₀₈ is Lys or Ser or His or absent,
	AA ₀₉ is Tyr or Glu or absent
	AA ₁₀ is Lys or Glu or Gln or His or absent,
	AA ₁₁ is Gly,
	AA ₁₂ is Ala,
20	AA ₁₃ is Gln or Asn or Glu,
	AA ₁₄ is Lys or His or Glu,
	AA ₁₅ is Lys Ser or Glu or Thr or His,
	AA ₁₆ is Gly,
	AA ₁₇ is Leu or Gly or Ser or Val,
25	AA ₁₈ is Ser or His
	AA ₁₉ is Gln or Ser or Lys or His,
	AA ₂₀ is Gly,

AA₂₁ is Cys,
AA₂₂ is Phe,
AA₂₃ is Gly,
AA₂₄ is Leu,
5 AA₂₅ is Pro or Lys,
AA₂₆ is Leu,
AA₂₇ is Asp or Glu,
AA₂₈ is Arg,
AA₂₉ is Ile,
10 AA₃₀ is Gly,
AA₃₁ is Ser,
AA₃₂ is Leu or Nle or Met,
AA₃₃ is Ser,
AA₃₄ is Gly,
15 AA₃₅ is Leu,
AA₃₆ is Gly, and
AA₃₇ is Cys.

In certain embodiments of the invention, amino acid substitutions of the CNP peptide are introduced in order to reduce the positive charges of the CNP peptide. For example Lys₂₅ (AA₂₅) is substituted to Pro and Lys₁₉ (AA₁₉) is substituted to Gln or Ser to remove positive charge.

In certain embodiments of the invention, AA₁₃ of the CNP peptide is Gln; AA₁₉ is Gln or Ser; AA₂₅ is Pro; and AA₃₂ is Leu.

In certain embodiments of the invention, AA₅ of the CNP peptide is Gln; AA₁₃ is Gln; 25 AA₁₉ is Gln or Ser; AA₂₅ is Pro; and AA₃₂ is Leu.

In certain embodiments of the invention, the CNP peptide has any one of the following amino acid sequences:

GAQKKGSSQGCFGLPLDRIGSLSGLC (SEQ ID NO: 136),
ARKYKGAQKKGLSQGCFGLPLDRIGSLSGLC (SEQ ID NO: 77),
30 YKGAQKKGSSQGCFGLPLDRIGSLSGLC (SEQ ID NO: 88),
YKGAQKKGLSQGCFGLPLDRIGSLSGLC (SEQ ID NO: 103),
QEHPQARKYKGAQKKGLSSGCFGLPLDRIGSLSGLC (SEQ ID NO: 67), and
QEHPQARKYKGAQKKGLSSGCFGLPLERIGSLSGLC (SEQ ID NO: 104).

Modifying group

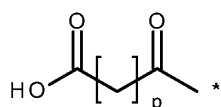
In one aspect of the invention, the CNP compound comprises a modifying group covalently attached to an amino acid residue of the CNP peptide.

In one aspect of the invention, the modifying group is capable of forming non-covalent associations with albumin and thereby promoting the circulation of the CNP compound in the blood stream, this having the effect of protracting plasma exposure and extending plasma half-life of the CNP compound compared to plasma half-life of CNP-22 (SEQ ID NO: 01) and CNP-37 (SEQ ID NO: 02). The modifying group having the effect of extending and protracting the time of action of the CNP compound, thus, may also be referred to as a protracting group.

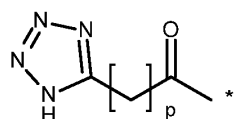
In some embodiments of the invention, the modifying group is covalently attached to the N-terminal amino acid of the CNP peptide.

In some embodiments of the invention, the modifying group is covalently attached to the N-terminal alpha-amine of the CNP peptide.

In an aspect of the invention, the modifying group comprises Chem. A, Chem. B and Chem. C; wherein Chem. A is selected from the group consisting of:



(Chem. A1), and

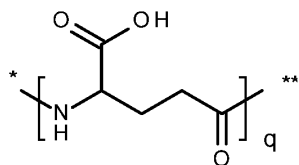


(Chem. A2)

wherein p is an integer in the range of 14-20, and

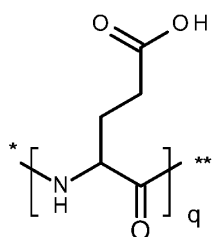
where * denotes an amide bond connecting Chem. A, and Chem. B; and

wherein Chem. B is selected from the group consisting of:



(Chem. B1)

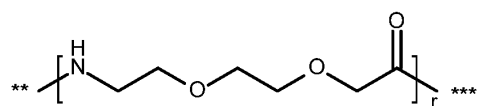
and



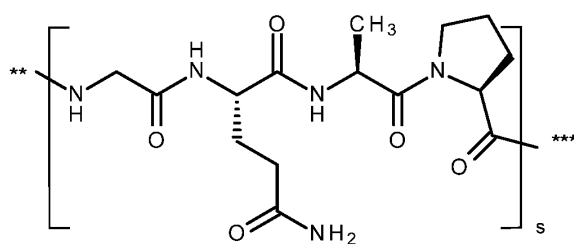
(Chem. B2)

wherein q is an integer in the range of 1-8,wherein $*$ denotes an amide bond connecting Chem. A- and Chem. B-,5 wherein $**$ denotes an amide bond connecting Chem. B- and Chem. C-; and

Wherein Chem. C is selected from the group consisting of:

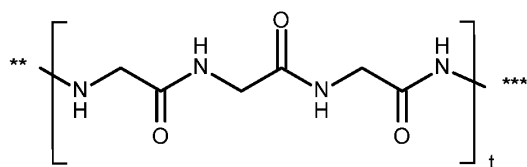


(Chem. C1),

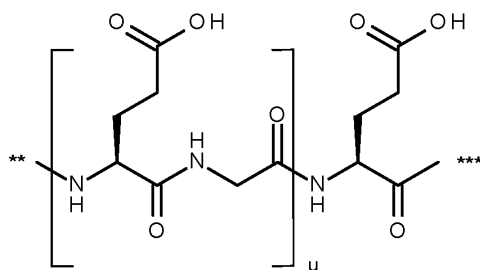


10

(Chem. C2), and



(Chem. C3)



(Chem C4),

wherein r is an integer in the range of 0-4,

wherein s is an integer in the range of 0-3,

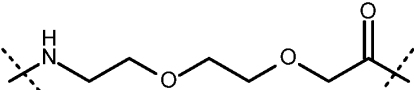
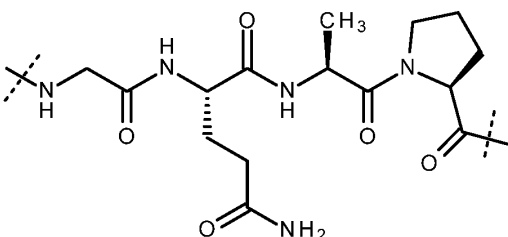
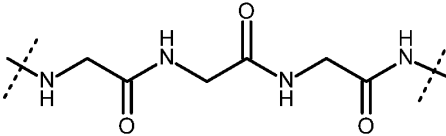
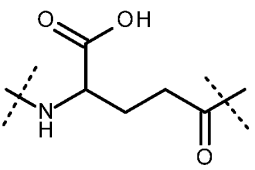
5 wherein t is an integer in the range of 0-1,

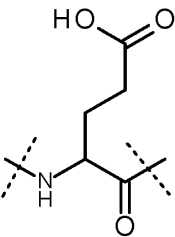
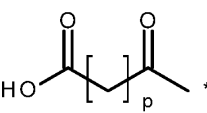
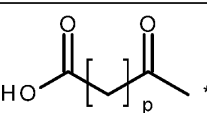
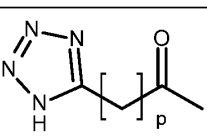
wherein u is an integer in the range of 0-3,

wherein ** denotes an amide bond connecting Chem. B- and Chem. C-,

wherein *** denotes an amide bond connecting Chem. C- and the N-terminal alpha-amine on the CNP peptide.

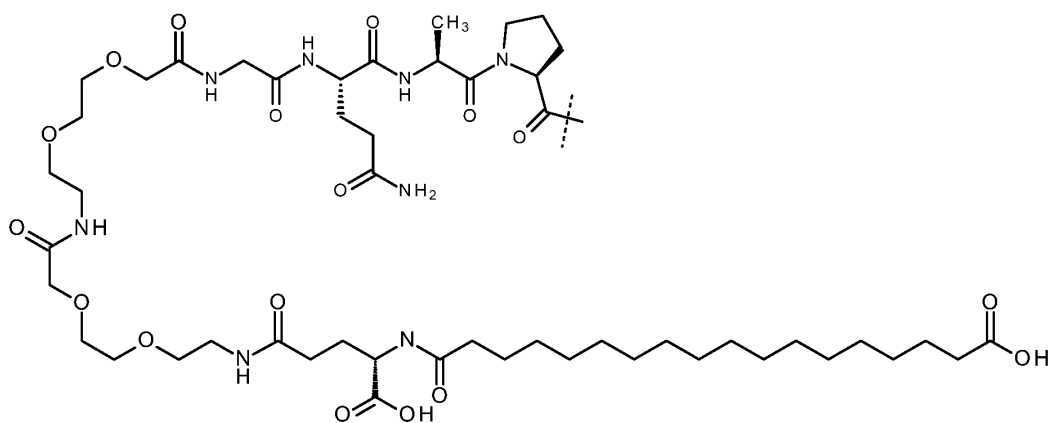
10 Abbreviations for modifying group elements used in this application are presented below:

Abbreviation	Chem. No	Chemical structure
OEG	Chem. C1	
GQAP	Chem. C2	
GGG	Chem. C3	
gGlu,	Chem. B1	

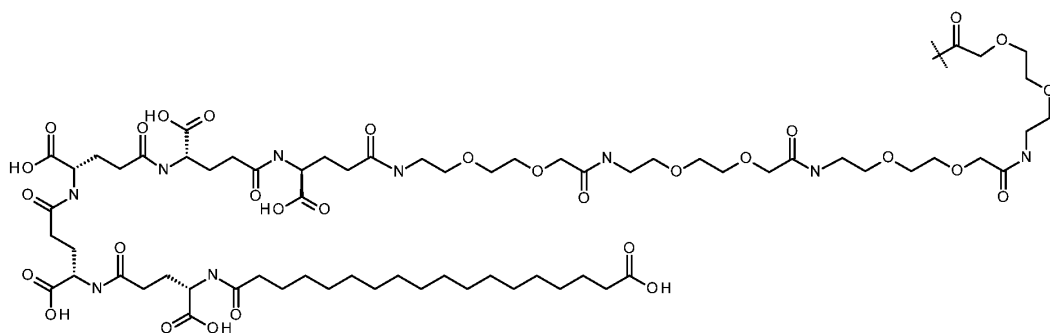
Abbreviation	Chem. No	Chemical structure
Glu	Chem. B2	
C18d	Chem. A1 where p is equal to 16	
C20d	Chem. A1 where p is equal to 18	
Tetrazole-C18	Chem. A2 where p is equal to 16	

In some embodiments of the invention, the modifying group is selected from the following non-limiting examples: Chem. E, Chem. F, Chem. G, Chem. H, Chem. I, and Chem. J (in which the dotted line defines the attachment through an amide bond to the CNP peptide).

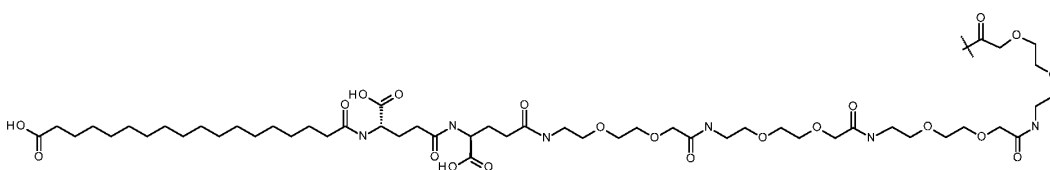
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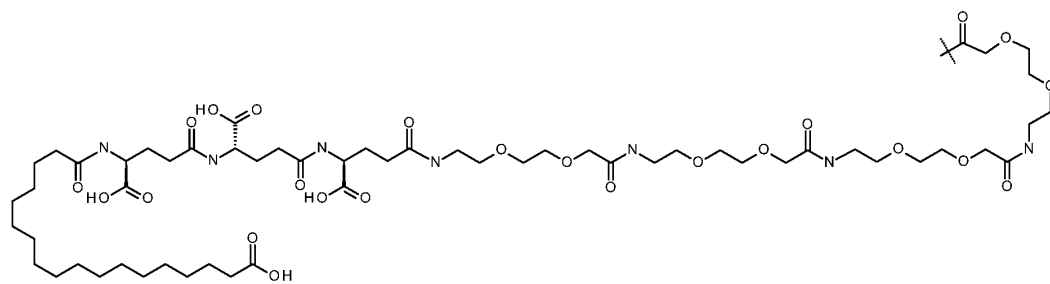
(Chem. E)



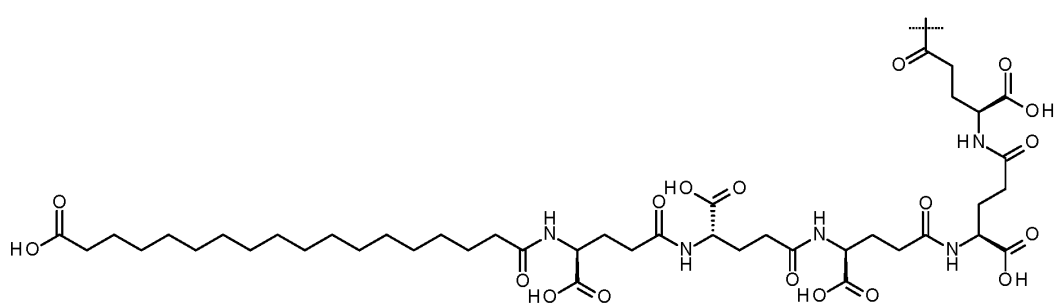
(Chem. F)



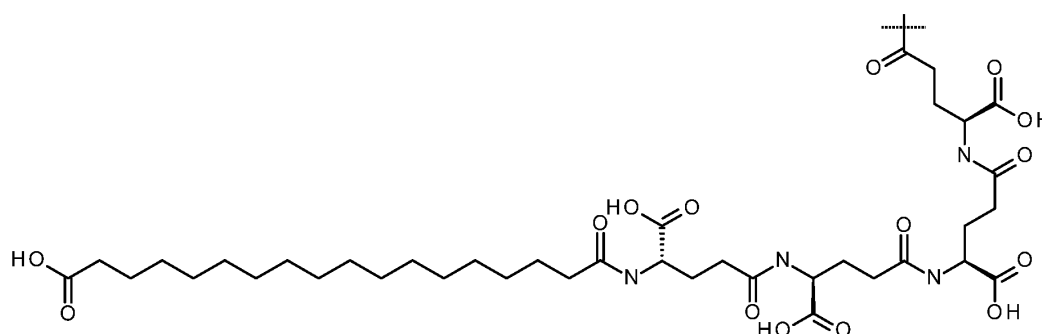
(Chem. G)



(Chem. H)



(Chem. I)



(Chem. J)

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

Functional properties

In some aspects of the invention, the CNP compounds have desirable biophysical properties. The CNP compounds exhibit extended *in vivo* half-life. Also, the CNP compounds of the invention have biological activity. Further, the compounds of the invention have desirable stability. Furthermore, the compounds of the invention have desirable solubility. Furthermore, the compounds of the invention can be dosed subcutaneously without eliciting an undesirable level of local tissue reaction like necrosis.

Biological activity

In one aspect of the invention, the compounds have biological activity *in vitro*, which may be determined as their ability to activate the NPR2 receptor *in vitro* in a cell line expressing the NPR2 receptor which may be determined as their ability to increase the production and concentration of cGMP, representing receptor activation downstream of NPR2, in the cell. Biological activity *in vitro* may be determined e.g. as described in Example 2.

In one aspect of the invention, the compounds have biological activity *in vivo*, which may be determined as their ability to increase the concentration of cGMP in plasma after i.v. or s.c. administration in either rats or Göttingen minipigs or domestic LYD pigs.

The rat is one example of a suitable animal model, and the activity may be determined in such rats *in vivo*, as described in Example 11.

The Göttingen minipigs or domestic LYD pigs is other examples of a suitable animal models, and the activity may be determined in such pigs *in vivo*, as described in Example 12.

5

Plasma half-life

In one aspect of the invention, the CNP compounds have a protracted plasma exposure and have an extended *in vivo* plasma half-life relative to native CNP, which can be determined in a suitable pharmacokinetic *in vivo* study. Extended plasma exposure may be determined as plasma half-life ($T_{1/2}$) after i.v. or s.c. administration to animals such as rats, Göttingen minipigs or domestic LYD pigs.

In some embodiments of the invention, the CNP compounds have a plasma half-life after i.v. administration to rat of at least 4 hours, more preferably at least 8 hours, or most preferably at least 10 hours, determined as described in Example 11.

In some embodiments of the invention, the CNP compounds have an *in vivo* plasma half-life after i.v. or s.c. administration to Göttingen minipigs of at least 10 hours, more preferably at least 40 hours, or most preferably at least 60 hours, determined as described in Example 12.

Bioavailability

In one aspect of the invention, the compounds have suitable bioavailability after subcutaneous injection. Bioavailability (F%) may be determined as is known in the art in any suitable animal model.

The Göttingen minipigs or domestic LYD pigs are examples of a suitable animal models, and the bioavailability may be determined in such Göttingen minipigs or domestic LYD pigs *in vivo*, as described in Example 12.

In some embodiments of the invention, the CNP compounds have a bioavailability after s.c. administration to Göttingen minipigs of at least 40%, 50%, 60% or 70%.

Stability

In one aspect of the invention the compounds have suitable physical and chemical stability. Lack of physical or chemical stability could lead to changes in the compound structure leading to formation of chemical degradation products potentially having a reduced biological activity, decreased solubility, and/or increased immunogenic effect as compared to the intact compound.

The physical stability can be evaluated by measuring the propensity for fibril formation, for example using a ThT assay as described in Example 6.

The chemical stability can be evaluated by measuring the amount of chemical degradation products (like isomers, isoAsp and hydrolysis products) at various time-points after exposure to different conditions like elevated temperature, e.g. as described in Example 8.

Stability could also be evaluated by looking into the molecules ability to form covalent dimers and multimers – referred to as HMWP, e.g. as described in Example 7.

10 Solubility

According to a functional aspect of the invention, the CNP compounds have desirable solubility. Low solubility of CNP may significantly hamper its pharmaceutical formulation properties and therapeutic use, so developing a CNP compound with high solubility in relevant formulations would improve the therapeutic utility.

15 As described herein, solubility is measured as described in Example 5. In certain embodiments, the CNP compounds of the invention have a solubility of at least at least 2000 μ M, 3000 μ M, or 4000 μ M solubility at either pH 4 or pH 6.5.

Pharmaceutical compositions

In one aspect the invention concerns a pharmaceutical composition comprising a compound according to the invention, and pharmaceutically acceptable excipients. The compositions are suited for parenteral administration.

In one embodiment the compound is present in the formulation at a concentration of from about 0.1 mg/ml to about 50 mg/ml. In another aspect, the compound is present in the formulation at a concentration of from about 10 mg/ml to about 30 mg/ml.

25 In another embodiment, the formulation has a pH from 3.0 to 8.0. In another embodiment, the formulation has a pH from 3.5 to 5.5. In a further embodiment, the formulation has a pH from 6.0 to 7.0. Pharmaceutical compositions containing a compound according to the present invention may be prepared by conventional techniques, e.g. as described in Remington's *Pharmaceutical Sciences*, 1985 or in Remington: *The Science and Practice of Pharmacy*, 19th edition, 1995.

30 The formulation may further comprise a buffer system, preservative(s), isotonicity agent(s), chelating agent(s), stabilizers and/or surfactants. The use of such excipients in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to Remington: *The Science and Practice of Pharmacy*, 19th edition, 1995.

In one embodiment the pharmaceutical formulation is an aqueous formulation, i.e. formulation comprising water. Such formulation is typically a solution or a suspension. In a further embodiment of the invention the pharmaceutical formulation is an aqueous solution. The term "aqueous formulation" is defined as a formulation comprising at least 50 %w/w
5 water. Likewise, the term "aqueous solution" is defined as a solution comprising at least 50 %w/w water, and the term "aqueous suspension" is defined as a suspension comprising at least 50 %w/w water.

In another embodiment the pharmaceutical formulation is a freeze-dried formulation, whereto the physician or the patient adds solvents and/or diluents prior to use. In another
10 embodiment the pharmaceutical formulation is a dried formulation (e.g. freeze-dried or spray-dried) ready for use without any prior dissolution. By "dried form" is intended the liquid pharmaceutical composition or formulation is dried either by freeze drying (i.e., lyophilization; see, for example, Williams and Polli (1984) J. Parenteral Sci. Technol. 38:48-59), spray
15 drying (see Masters (1991) in Spray-Drying Handbook (5th ed; Longman Scientific and Technical, Essex, U.K.), pp. 491-676; Broadhead et al. (1992) Drug Devel. Ind. Pharm. 18:1169-1206; and Mumenthaler et al. (1994) Pharm. Res. 11:12-20), or air drying (Carpenter and Crowe (1988) Cryobiology 25:459-470; and Roser (1991) Biopharm. 4:47-53).

In a further embodiment of the invention the buffer(s) are selected from the group
20 consisting of acetate, carbonate, citrate, glycylglycine, histidine, glycine, lysine, arginine, dihydrogen phosphate, hydrogen phosphate, phosphate, and tris(hydroxymethyl)-aminomethan, bicine, tricine, malic acid, lactic acid, succinate, maleic acid, fumaric acid, tartaric acid, aspartic acid or mixtures thereof. Each one of these specific buffers constitutes an alternative embodiment of the invention.

25 In another embodiment of the invention the formulation further comprises a pharmaceutically acceptable preservative. In a further embodiment of the invention the formulation further comprises an isotonic agent, e.g. propylene glycol, mannitol or glycerol. In a further embodiment of the invention the formulation further comprises a chelating agent.

In another embodiment of the invention the formulation further comprises a
30 stabilizer. The use of a stabilizer in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to Remington: *The Science and Practice of Pharmacy*, 19th edition, 1995.

The pharmaceutical compositions of the invention may further comprise an amount
35 of an amino acid base sufficient to decrease aggregate formation by the peptide during storage of the composition.

By "amino acid base" is intended an amino acid or a combination of amino acids, where any given amino acid is present either in its free base form or in its salt form. Where a combination of amino acids is used, all of the amino acids may be present in their free base forms, all may be present in their salt forms, or some may be present in their free base forms while others are present in their salt forms. In one embodiment, amino acids used in preparing the compositions of the invention are those carrying a charged side chain, such as arginine, lysine, aspartic acid, and glutamic acid. Any stereoisomer (i.e., L, D, or a mixture thereof) of a particular amino acid (e.g. methionine, histidine, imidazole, arginine, lysine, isoleucine, aspartic acid, tryptophan, threonine and mixtures thereof) or combinations of these stereoisomers, may be present in the pharmaceutical compositions of the invention so long as the particular amino acid is present either in its free base form or its salt form. In one embodiment the L-stereoisomer is used. Compositions of the invention may also be formulated with derivatives of these amino acids. Suitable arginine derivatives include, for example, aminoguanidine, ornithine and N-monoethyl L-arginine, suitable methionine derivatives include ethionine and buthionine and suitable cysteine derivatives include S-methyl-L cysteine. As with the other amino acids, the amino acid derivatives are incorporated into the compositions in either their free base form or their salt form. In another embodiment of the invention the amino acids or amino acid derivatives thereof are used in a concentration, which is sufficient to prevent or delay aggregation of the protein.

In another embodiment of the invention the formulation further comprises a surfactant. In another embodiment of the invention the formulation further comprises protease inhibitors. The use of a protease inhibitor is particular useful in pharmaceutical compositions comprising zymogens of proteases in order to inhibit autocatalysis.

It is possible that other ingredients may be present in the pharmaceutical formulation of the present invention. Such additional ingredients may include wetting agents, emulsifiers, antioxidants, bulking agents, tonicity modifiers, chelating agents, metal ions, oleaginous vehicles, proteins (e.g., human serum albumin, gelatine or proteins) and a zwitterion (e.g., an amino acid such as betaine, taurine, arginine, glycine, lysine and histidine). Such additional ingredients, of course, should not adversely affect the overall stability of the pharmaceutical formulation of the present invention.

Pharmaceutical compositions according to the present invention may be administered to a patient in need of such treatment at several sites, for example, at topical sites, for example, skin and mucosal sites, at sites which bypass absorption, for example, administration in an artery, in a vein, in the heart, and at sites which involve absorption, for example, administration in the skin, under the skin, in a muscle or in the abdomen.

Administration of pharmaceutical compositions according to the invention may be through several routes of administration, for example, lingual, sublingual, buccal, in the mouth, oral, in the stomach and intestine, nasal, pulmonary, for example, through the bronchioles and alveoli or a combination thereof, epidermal, dermal, transdermal, vaginal, rectal, ocular, for examples through the conjunctiva, uretal, and parenteral to patients in need of such a treatment.

Compositions of the current invention may be administered in several dosage forms, for example, as solutions, suspensions, emulsions, microemulsions, multiple emulsion, foams, salves, pastes, plasters, ointments, tablets, coated tablets, rinses, capsules, for example, hard gelatine capsules and soft gelatine capsules, suppositories, rectal capsules, drops, gels, sprays, powder, aerosols, inhalants, eye drops, ophthalmic ointments, ophthalmic rinses, vaginal pessaries, vaginal rings, vaginal ointments, injection solution, in situ transforming solutions, for example in situ gelling, in situ setting, in situ precipitating, in situ crystallization, infusion solution, and implants.

Compositions of the invention may further be compounded in, or attached to, for example through covalent, hydrophobic and electrostatic interactions, a drug carrier, drug delivery system and advanced drug delivery system in order to further enhance stability of the compound thereof increase bioavailability, increase solubility, decrease adverse effects, achieve chronotherapy well known to those skilled in the art, and increase patient compliance or any combination thereof.

Compositions of the current invention are useful in the formulation of solids, semisolids, powder and solutions for pulmonary administration of the CNP compound of the current invention, using, for example a metered dose inhaler, dry powder inhaler and a nebulizer, all being devices well known to those skilled in the art.

Compositions of the current invention are useful in the formulation of controlled, sustained, protracting, retarded, and slow-release drug delivery systems.

Parenteral administration may be performed by subcutaneous, intramuscular, intraperitoneal or intravenous injection by means of a syringe, optionally a pen-like syringe. Alternatively, parenteral administration can be performed by means of an infusion pump. A further option is a composition which may be a solution or suspension for the administration of the CNP compound of the current invention in the form of a nasal or pulmonal spray. As a still further option, the pharmaceutical compositions containing the peptide of the invention can also be adapted to transdermal administration, e.g. by needle-free injection or from a patch, optionally an iontophoretic patch, or transmucosal, e.g. buccal, administration.

The CNP compound of the current invention can be administered via the pulmonary route in a vehicle, as a solution, suspension or dry powder using any of known types of devices suitable for pulmonary drug delivery. Examples of these comprise of, but are not limited to, the three general types of aerosol-generating for pulmonary drug delivery, and
5 may include jet or ultrasonic nebulizers, metered-dose inhalers, or dry powder inhalers (cf. Yu J, Chien YW. Pulmonary drug delivery: Physiologic and mechanistic aspects. Crit Rev Ther Drug Carr Sys 14(4) (1997) 395-453).

In one embodiment of the invention the pharmaceutical formulation comprising the compound of the invention is stable for more than 6 weeks of usage and for more than 3
10 years of storage. In another embodiment of the invention the pharmaceutical formulation comprising the compound of the invention is stable for more than 2 weeks of usage and for more than two years of storage.

In one aspect a process for preparing a pharmaceutical composition comprising the compound according to the invention comprises mixing a compound according to the
15 invention with at least one pharmaceutically acceptable excipient.

Medical indications

The present invention also relates to a compound for use as a medicament.

The term "treatment", as used herein, refers to the medical treatment of any human subject in need thereof. The timing and purpose of said treatment may vary from one
20 individual to another, according to the status of the subject's health. Said treatment may be prophylactic, palliative, symptomatic and/or curative.

In one aspect, the compound of the invention may be used for treatment of cardio-renal-metabolic diseases. Cardio-renal-metabolic diseases, include, but are not restricted to, the group consisting of hypertension, arteriosclerosis, atherosclerosis, restenosis, acute
25 myocardial infarction, pulmonary hypertension, acute decompensated heart failure, congestive heart failure, cardiac edema, renal edema, hepatic edema*, acute renal insufficiency, chronic renal insufficiency, insulin resistance, and type 2 diabetes.

In one embodiment, the compound of the invention is used for treatment of congestive heart failure.

30 In one embodiment, the compound of the invention is used for treatment of acute decompensated heart failure.

In one aspect, the compound of the invention may be used for treatment of growth disorders including short stature that may relate to FGFR3-related skeletal dysplasia, and related comorbidities.

In some embodiments, the compound of the invention may be used in the treatment of a disease selected from the group consisting of achondroplasia, hypochondroplasia, thanatophoric dysplasia type 1 and type 2, SHOX deficiency, Noonan syndrome, Costello , LEOPARD syndrome, idiopathic short stature, autosomal dominant short stature, growth hormone deficiency, hypophosphatemic rickets, CNP deficiency, Aggrecan deficiency, Heterozygous NPR2 mutation, osteoarthritis, craniosynostosis, (e.g., Muenke syndrome, Crouzon syndrome, Apert syndrome, Jackson- Weiss syndrome, Pfeiffer syndrome, or Crouzonodermoskeletal syndrome), Lacrimo-Auriculo-Dento-Digital syndrome (LADD), Osteoglophonic dysplasia, and SADDAN (severe achondroplasia developmental delay acanthosis nigricans).

In some embodiments, the compound of the invention may be used in the treatment of a disease selected from the group consisting of osteogenesis imperfecta, achondrogenesis, chondrodysplasia punctata, homozygous achondroplasia, rhizomelic type of chondrodysplasia punctata, spondyloepiphyseal dysplasia congenita, congenital short femur, Langer-type mesomelic dysplasia, Neurofibromatosis, Legius syndrome and neurofibromatosis type 1.

In some embodiments, the compound of the invention may be used in the treatment of phenotypes related to growth disorders including short stature that may relate to FGFR3-related skeletal dysplasia, selected from the group consisting of growth retardation, skull deformities, orthodontic defects, cervical cord compression, spinal stenosis, pain in relation to skeletal dysplasia, hydrocephalus, hearing loss due to chronic otitis, cardiovascular disease, neurological disease, and obesity.

Unless otherwise indicated in the specification, terms presented in singular form also may include the plural situation.

List of Embodiments

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

Embodiment 1: a CNP compound comprising a CNP peptide and a modifying group wherein the net charge of the compound at physiological pH is 0 or negative, wherein the CNP peptide comprises an amino acid sequence according to Formula I:

AA01- AA02-AA03-AA04-AA05-AA06-AA07-AA08-AA09-AA10-AA11-AA12-AA13-AA14-
AA15-AA16-AA17-AA18-AA19-AA20-AA21-AA22-AA23-AA24-AA25-AA26-AA27-AA28-AA29-
AA30-AA31-AA32-AA33-AA34-AA35-AA36-AA37

wherein

- AA₀₁ is Gln or absent,
AA₀₂ is Glu or absent,
AA₀₃ is His or absent,
AA₀₄ is Pro or absent,
5 AA₀₅ is Asn or Gln or Glu or absent,
AA₀₆ is Ala or absent,
AA₀₇ is Arg or His or Ala or absent,
AA₀₈ is Lys or Ser or His or absent,
AA₀₉ is Tyr or Glu or absent
10 AA₁₀ is Lys or Glu or Gln or His or absent,
AA₁₁ is Gly,
AA₁₂ is Ala,
AA₁₃ is Gln or Asn or Glu,
AA₁₄ is Lys or His or Glu,
15 AA₁₅ is Lys Ser or Glu or Thr or His,
AA₁₆ is Gly,
AA₁₇ is Leu or Gly or Ser or Val,
AA₁₈ is Ser or His
AA₁₉ is Gln or Ser or Lys or His,
20 AA₂₀ is Gly,
AA₂₁ is Cys,
AA₂₂ is Phe,
AA₂₃ is Gly,
AA₂₄ is Leu,
25 AA₂₅ is Pro or Lys,
AA₂₆ is Leu,
AA₂₇ is Asp or Glu,
AA₂₈ is Arg,
AA₂₉ is Ile,
30 AA₃₀ is Gly,
AA₃₁ is Ser,
AA₃₂ is Leu or Nle or Met,

AA₃₃ is Ser,

AA₃₄ is Gly,

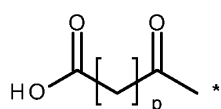
AA₃₅ is Leu,

AA₃₆ is Gly, and

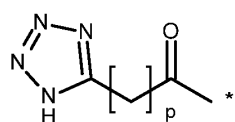
5 AA₃₇ is Cys;

wherein the modifying group comprises Chem. A, Chem. B and Chem. C;

wherein Chem. A is selected from the group consisting of:



(Chem. A1), and



10

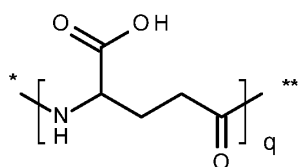
(Chem. A2)

herein p is an integer in the range of 14-20, and

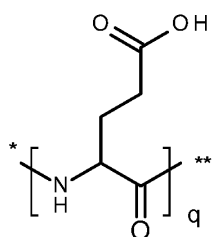
where * denotes an amide bond connecting Chem. A and Chem. B; and

wherein Chem. B is selected from the group consisting of: Chem. B1 and Chem. B2

15



(Chem. B1) and

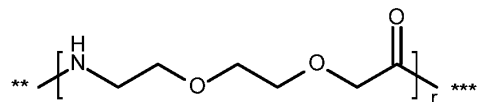


20

(Chem. B2)

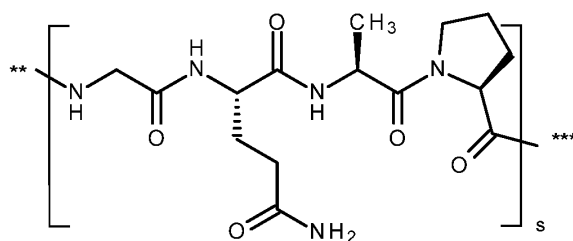
wherein q is an integer in the range of 1-8,

wherein * denotes an amide bond connecting Chem. A- and Chem. B-;
 wherein ** denotes an amide bond connecting Chem. B- and Chem. C-; and
 Wherein Chem. C is selected from the group consisting of:

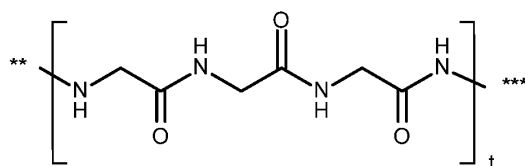


5

(Chem. C1),



(Chem. C2), and



(Chem. C3)

10

wherein r is an integer in the range of 0-4,

wherein s is an integer in the range of 0-3,

wherein t is an integer in the range of 0-1, wherein

** denotes an amide bond connecting Chem. B- and Chem. C-;

wherein *** denotes an amide bond connecting Chem. C- and the N-terminal alpha-amine on the CNP peptide.

15

Embodiment 2: the CNP compound according to embodiment 1, wherein AA₁₃ of the CNP peptide is Gln; AA₁₉ is Gln or Ser; AA₂₅ is Pro; and AA₃₂ is Leu.

20

Embodiment 3: the CNP compound according to embodiment 1, wherein AA₅ of the CNP peptide is Gln; AA₁₃ is Gln; AA₁₉ is Gln or Ser; AA₂₅ is Pro; and AA₃₂ is Leu.

Embodiment 4: the CNP compound according to embodiment 1, wherein the CNP peptide comprises one of the following amino acid sequences:

YKGANKKGLSKGCFGLKLDRIGSXSLGC	SEQ ID NO: 6
NARKYKGANKSGLSSGCFGLKLDRIGSXSLGC	SEQ ID NO: 7
GANKKGLSKGCFGLKLDRIGSXSLGC	SEQ ID NO: 8
GAQKKGLSKGCFGLKLDRIGSXSLGC	SEQ ID NO: 9
YEGAQKKGLSKGCFGLKLDRIGSLSLGC	SEQ ID NO: 10
EEGAQKKGLSKGCFGLKLDRIGSLSLGC	SEQ ID NO: 11
YEGAQEKGLSKGCFGLKLDRIGSLSLGC	SEQ ID NO: 12
YEGAQKKGLSSGCFGLKLDRIGSLSLGC	SEQ ID NO: 13
YEGAQKKGLSKGCFGLPLDRIGSLSLGC	SEQ ID NO: 14
YEGAQEKGLSKGCFGLPLDRIGSLSLGC	SEQ ID NO: 15
YEGAQKKGLSSGCFGLPLDRIGSLSLGC	SEQ ID NO: 16
YEGAQEKGLSSGCFGLPLDRIGSLSLGC	SEQ ID NO: 17
EKGAQEKGLSKGCFGLKLDRIGSLSLGC	SEQ ID NO: 18
EKGAQEKGLSSGCFGLKLDRIGSLSLGC	SEQ ID NO: 19
EQGAQEKGLSKGCFGLKLDRIGSLSLGC	SEQ ID NO: 20
YKGAQEKGLSKGCFGLKLDRIGSLSLGC	SEQ ID NO: 21
YKGAQKKGLSSGCFGLPLDRIGSLSLGC	SEQ ID NO: 22
EHGAQEKGLSKGCFGLKLDRIGSLSLGC	SEQ ID NO: 23
YHGAQEKGLSKGCFGLKLDRIGSLSLGC	SEQ ID NO: 24
YHGAQEKGLSKGCFGLPLDRIGSLSLGC	SEQ ID NO: 25
YHGAQKKGLSSGCFGLPLDRIGSLSLGC	SEQ ID NO: 26
YHGAQEKGLSSGCFGLPLDRIGSLSLGC	SEQ ID NO: 27
YEGAEKKGLSQGCFGLPLDRIGSLSLGC	SEQ ID NO: 28
EGAQEKGLSSGCFGLPLDRIGSLSLGC	SEQ ID NO: 29
EGAQKEGLSSGCFGLPLDRIGSLSLGC	SEQ ID NO: 30
YEGAQKEGLSSGCFGLPLDRIGSLSLGC	SEQ ID NO: 31
YHGAQKTGLSSGCFGLPLDRIGSLSLGC	SEQ ID NO: 32
YHGAQKTGVSSGCFGLPLDRIGSLSLGC	SEQ ID NO: 33
YHGAQHTGLSSGCFGLPLDRIGSLSLGC	SEQ ID NO: 34
YKGAQHTGLSSGCFGLPLDRIGSLSLGC	SEQ ID NO: 35
EHGAQKKGLSKGCFGLPLDRIGSLSLGC	SEQ ID NO: 36
EHGAQKKGLSSGCFGLPLDRIGSLSLGC	SEQ ID NO: 37
EHGAQKKGVSSGCFGLPLDRIGSLSLGC	SEQ ID NO: 38
EHGAQKTGVSSGCFGLPLDRIGSLSLGC	SEQ ID NO: 39
YHGAQHHGLSKGCFGLKLERIGSLSLGC	SEQ ID NO: 40
YKGAQHHGLSQGCFGLKLERIGSLSLGC	SEQ ID NO: 41
YEGAQKKGLSSGCFGLPLERIGSLSLGC	SEQ ID NO: 42
EGAQKKGLSSGCFGLPLDRIGSLSLGC	SEQ ID NO: 43
YKGAQHHGLSQGCFGLKLDRIGSLSLGC	SEQ ID NO: 44
YKGAQHHGLSQGCFGLPLDRIGSLSLGC	SEQ ID NO: 45
YHGAQHHGLSKGCFGLKLDRIGSLSLGC	SEQ ID NO: 46
YHGAQHHGLSKGCFGLPLDRIGSLSLGC	SEQ ID NO: 47
GAQKKGLSHGCFGLPLDRIGSLSLGC	SEQ ID NO: 48
GAQKKGLHSGCFGLPLDRIGSLSLGC	SEQ ID NO: 49

ARKYHGAQHTGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 50
ARKYHGAQHTGVSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 51
ARKYHGAQKTGVSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 52
ARKEHGAQKTGVSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 53
ARKEHGAQHTGVSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 54
YEGAQKKGGSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 55
QEHPQARSYEGAQKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 57
QEHPQRSYEGAQKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 58
QEHPQAHKYHGAQHGGSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 59
QEHPQAHKYKGAQKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 60
QEHPQAHKYHGAQKHGSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 61
ARKYEGAQKKGLSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 63
ARKYKGAQKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 64
QEHPQARKYKGAQKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 67
QEHPQARKYEGAQKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 68
YEGAQKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 69
QEHPQARKYEGAQKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 70
QEHPQAAKYEGAQKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 71
QEHPQARHYKGAQKKGSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 72
QEHPQAHKYKGAQKKGSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 73
QEHPQARKYKGAQKKGLSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 74
QEHPQARKYKGAQKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 75
QEHPQARKYKGAQKKGSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 76
ARKYKGAQKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 77
ARKYHGAQHTGVSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 78
ARKYKGAQKTGVSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 79
ARKYHGAQKKGVSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 80
ARKYHGAQKTGVSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 81
ARKYKGAQKTGVSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 82
YHGAQKTGVSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 83
ARKYHGAQKSGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 84
YEGAQKKGGSHGCFGLPLDRIGSLSGLC	SEQ ID NO: 85
ARKYEGAQHKGSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 86
YHGAQKKGSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 87
YKGAQKKGSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 88
YKGAQKKGVSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 89
YHGAQKKGVSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 90
QEHPQARKYEGAQKKGLSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 91
ARKYHGAQKKGVSSGCFGLPLERIGSLSGLC	SEQ ID NO: 92
ARKYKGAQKKGLSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 96
YHGAQKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 97
ARKYKGAQKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 98
ARKYKGANKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 99
ARKYKGAQKKGLSQGCFGLPLDRIGSMSGLGC	SEQ ID NO: 100

QEHPQARKYKGAQKKGLSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 101
ARKYKGAQKKGLSQGCFGLPLERIGSLSGLC	SEQ ID NO: 102
YKGAQKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 103
QEHPQARKYKGAQKKGLSSGCFGLPLERIGSLSGLC	SEQ ID NO: 104
YKGAQKKGGSQGCFGLPLERIGSLSGLC	SEQ ID NO: 108
YKGAQKKGLSQGCFGLPLERIGSLSGLC	SEQ ID NO: 109
GAQKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 112
GAQKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 113
GAQKKGGSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 114
GAQKKGSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 115
GAQKKGLSQGCFGLKLDIGSLSGLC	SEQ ID NO: 116
GAQKKGLSSGCFGLKLDIGSLSGLC	SEQ ID NO: 117
GAQKKGGSQGCFGLKLDIGSLSGLC	SEQ ID NO: 118
GAQKKGSSGCFGLKLDIGSLSGLC	SEQ ID NO: 119
GANKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 120
GANKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 121
GANKKGGSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 122
GANKKGSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 123
GAQKKGLSQGCFGLPLDRIGMSGSLGC	SEQ ID NO: 124
GAQKKGLSSGCFGLPLDRIGMSGSLGC	SEQ ID NO: 125
GAQKKGGSQGCFGLPLDRIGMSGSLGC	SEQ ID NO: 126
GAQKKGSSGCFGLPLDRIGMSGSLGC	SEQ ID NO: 127
GAQKKGLSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 128
GAQKKGGSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 129
GAQKKGLSQGCFGLPLERIGSLSGLC	SEQ ID NO: 130
GAQKKGLSSGCFGLPLERIGSLSGLC	SEQ ID NO: 131
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GANKKGLSSGCFGLPLERIGMSGSLGC	SEQ ID NO: 135
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GAQKKGSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 137
GAQKKGSSQGCFGLKLDIGSLSGLC	SEQ ID NO: 138
GAQKKGSSGCFGLKLDIGSLSGLC	SEQ ID NO: 139
GANKKGSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 140
GANKKGSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 141
GAQKKGSSQGCFGLPLDRIGMSGSLGC	SEQ ID NO: 142
GAQKKGSSGCFGLPLDRIGMSGSLGC	SEQ ID NO: 143
GAQKKGSSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 144
YKGAQKKGSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 145
YKGAQKKGLSQGCFGLKLDIGSLSGLC	SEQ ID NO: 146
YKGAQKKGLSSGCFGLKLDIGSLSGLC	SEQ ID NO: 147
YKGAQKKGGSQGCFGLKLDIGSLSGLC	SEQ ID NO: 148
YKGAQKKGSSGCFGLKLDIGSLSGLC	SEQ ID NO: 149

YKGANKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 150
YKGANKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 151
YKGANKKGGSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 152
YKGANKKGGSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 153
YKGAQKKGLSQGCFGLPLDRIGSMSGLGC	SEQ ID NO: 154
YKGAQKKGLSSGCFGLPLDRIGSMSGLGC	SEQ ID NO: 155
YKGAQKKGGSQGCFGLPLDRIGSMSGLGC	SEQ ID NO: 156
YKGAQKKGGSSGCFGLPLDRIGSMSGLGC	SEQ ID NO: 157
YKGAQKKGLSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 158
YKGAQKKGGSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 159
YKGAQKKGLSQGCFGLPLERIGSLSGLC	SEQ ID NO: 160
YKGAQKKGLSSGCFGLPLERIGSLSGLC	SEQ ID NO: 161
YKGANKKGLSQGCFGLPLDRIGSMSGLGC	SEQ ID NO: 162
YKGANKKGLSSGCFGLPLDRIGSMSGLGC	SEQ ID NO: 163
YKGANKKGLSQGCFGLPLERIGSMSGLGC	SEQ ID NO: 164
YKGANKKGLSSGCFGLPLERIGSMSGLGC	SEQ ID NO: 165
YKGAQKKGGSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 166
YKGAQKKGGSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 167
YKGAQKKGGSQGCFGLKLDIGSLSGLC	SEQ ID NO: 168
YKGAQKKGGSSGCFGLKLDIGSLSGLC	SEQ ID NO: 169
YKGANKKGGSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 170
YKGANKKGGSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 171
YKGAQKKGGSQGCFGLPLDRIGSMSGLGC	SEQ ID NO: 172
YKGAQKKGGSSGCFGLPLDRIGSMSGLGC	SEQ ID NO: 173
YKGAQKKGGSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 174
ARKYKGAQKKGGSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 175
ARKYKGAQKKGGSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 176
ARKYKGAQKKGLSSGCFGLKLDIGSLSGLC	SEQ ID NO: 177
ARKYKGAQKKGGSQGCFGLKLDIGSLSGLC	SEQ ID NO: 178
ARKYKGAQKKGGSSGCFGLKLDIGSLSGLC	SEQ ID NO: 179
ARKYKGANKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 180
ARKYKGANKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 181
ARKYKGANKKGGSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 182
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ARKYKGAQKKGLSQGCFGLPLDRIGSMSGLGC	SEQ ID NO: 184
ARKYKGAQKKGLSSGCFGLPLDRIGSMSGLGC	SEQ ID NO: 185
ARKYKGAQKKGGSQGCFGLPLDRIGSMSGLGC	SEQ ID NO: 186
ARKYKGAQKKGGSSGCFGLPLDRIGSMSGLGC	SEQ ID NO: 187
ARKYKGAQKKGGSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 188
ARKYKGAQKKGLSQGCFGLPLERIGSLSGLC	SEQ ID NO: 189
ARKYKGAQKKGLSSGCFGLPLERIGSLSGLC	SEQ ID NO: 190
ARKYKGANKKGLSQGCFGLPLDRIGSMSGLGC	SEQ ID NO: 191
ARKYKGANKKGLSSGCFGLPLDRIGSMSGLGC	SEQ ID NO: 192
ARKYKGANKKGLSQGCFGLPLERIGSMSGLGC	SEQ ID NO: 193

ARKYKGANKKGLSSGCFGLPLERIGSMSGLGC	SEQ ID NO: 194
ARKYKGAQKKGSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 195
ARKYKGAQKKGSSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 196
ARKYKGAQKKGSSQGCFGLKLDIGSLSGLC	SEQ ID NO: 197
ARKYKGAQKKGSSSGCFGLKLDIGSLSGLC	SEQ ID NO: 198
ARKYKGANKKGSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 199
ARKYKGANKKGSSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 200
ARKYKGAQKKGSSQGCFGLPLDRIGSMSGLGC	SEQ ID NO: 201
ARKYKGAQKKGSSSGCFGLPLDRIGSMSGLGC	SEQ ID NO: 202
ARKYKGAQKKGSSKGCFLPLDRIGSLSGLC	SEQ ID NO: 203
GAQKKGSSQGCFGLPLERIGSLSGLC	SEQ ID NO: 232

Embodiment 5: the CNP compound according to embodiment 1, wherein the CNP peptide has any one of the following amino acid sequences:

YKGANKKGLSKGCFGLKLDIGSXSLGC	SEQ ID NO: 6
NARKYKGANKSGLSSGCFGLKLDIGSXSLGC	SEQ ID NO: 7
GANKKGLSKGCFGLKLDIGSXSLGC	SEQ ID NO: 8
GAQKKGLSKGCFGLKLDIGSXSLGC	SEQ ID NO: 9
YEGAQKKGLSKGCFGLKLDIGSLSGLC	SEQ ID NO: 10
EEGAQKKGLSKGCFGLKLDIGSLSGLC	SEQ ID NO: 11
YEGAQEKGLSKGCFGLKLDIGSLSGLC	SEQ ID NO: 12
YEGAQKKGLSSGCFGLKLDIGSLSGLC	SEQ ID NO: 13
YEGAQKKGLSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 14
YEGAQEKGLSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 15
YEGAQKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 16
YEGAQEKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 17
EKGAQEKGLSKGCFGLKLDIGSLSGLC	SEQ ID NO: 18
EKGAQEKGLSSGCFGLKLDIGSLSGLC	SEQ ID NO: 19
EQGAQEKGLSKGCFGLKLDIGSLSGLC	SEQ ID NO: 20
YKGAQEKGLSKGCFGLKLDIGSLSGLC	SEQ ID NO: 21
YKGAQKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 22
EHGAQEKGLSKGCFGLKLDIGSLSGLC	SEQ ID NO: 23
YHGAQEKGLSKGCFGLKLDIGSLSGLC	SEQ ID NO: 24
YHGAQEKGLSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 25
YHGAQKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 26
YHGAQEKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 27
YEGAEEKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 28
EGAQEKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 29
EGAQKEGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 30
YEGAQKEGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 31
YHGAQKTGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 32
YHGAQKTGVSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 33
YHGAQHTGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 34

YKGAQHTGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 35
EHGAQKKGLSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 36
EHGAQKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 37
EHGAQKKGVSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 38
EHGAQKTGVSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 39
YHGAQHHGLSKGCFGLKLERIGSLSGLC	SEQ ID NO: 40
YKGAQHHGLSQGCFGLKLERIGSLSGLC	SEQ ID NO: 41
YEGAQKKGLSSGCFGLPLERIGSLSGLC	SEQ ID NO: 42
EGAQKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 43
YKGAQHHGLSQGCFGLKLDIGSLSGLC	SEQ ID NO: 44
YKGAQHHGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 45
YHGAQHHGLSKGCFGLKLDIGSLSGLC	SEQ ID NO: 46
YHGAQHHGLSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 47
GAQKKGLSHGCFGLPLDRIGSLSGLC	SEQ ID NO: 48
GAQKKGLHSGCFGLPLDRIGSLSGLC	SEQ ID NO: 49
ARKYHGAQHTGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 50
ARKYHGAQHTGVSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 51
ARKYHGAQKTGVSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 52
ARKEHGAQKTGVSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 53
ARKEHGAQHTGVSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 54
YEGAQKKGGSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 55
QEHPQARSYEGAQKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 57
QEHPQRSYEGAQKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 58
QEHPQAHKYHGAQHHGSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 59
QEHPQAHKYKGAQKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 60
QEHPQAHKYHGAQKHGSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 61
ARKYEGAQKKGLSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 63
ARKYKGAQKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 64
QEHPQARKYKGAQKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 67
QEHPQARKYEGAQKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 68
YEGAQKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 69
QEHPQARKYEGAQKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 70
QEHPQAAKYEGAQKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 71
QEHPQARHYKGAQKKGSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 72
QEHPQAHKYKGAQKKGSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 73
QEHPQARKYKGAQKKGLSKGCFGLKLDIGSLSGLC	SEQ ID NO: 74
QEHPQARKYKGAQKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 75
QEHPQARKYKGAQKKGSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 76
ARKYKGAQKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 77
ARKYHGAQHTGVSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 78
ARKYKGAQKTGVSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 79
ARKYHGAQKKGVSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 80
ARKYHGAQKTGVSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 81
ARKYKGAQKTGVSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 82

YHGAQKTGVSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 83
ARKYHGAQKSGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 84
YEGAQKKGGSHGCFGLPLDRIGSLSGLC	SEQ ID NO: 85
ARKYEGAQHKGGSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 86
YHGAQKKGGSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 87
YKGAQKKGGSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 88
YKGAQKKGVSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 89
YHGAQKKGVSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 90
QEHPQARKYEGAQKKGLSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 91
ARKYHGAQKKGVSSGCFGLPLERIGSLSGLC	SEQ ID NO: 92
YHGAQKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 97
ARKYKGAQKKGLSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 96
ARKYKGAQKKGLSQGCFGLKLDIGSLSGLC	SEQ ID NO: 98
ARKYKGANKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 99
ARKYKGAQKKGLSQGCFGLPLDRIGSMGLGC	SEQ ID NO: 100
QEHPQARKYKGAQKKGLSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 101
ARKYKGAQKKGLSQGCFGLPLERIGSLSGLC	SEQ ID NO: 102
YKGAQKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 103
QEHPQARKYKGAQKKGLSSGCFGLPLERIGSLSGLC	SEQ ID NO: 104
YKGAQKKGGSQGCFGLPLERIGSLSGLC	SEQ ID NO: 108
YKGAQKKGLSQGCFGLPLERIGSLSGLC	SEQ ID NO: 109
GAQKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 112
GAQKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 113
GAQKKGGSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 114
GAQKKGSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 115
GAQKKGLSQGCFGLKLDIGSLSGLC	SEQ ID NO: 116
GAQKKGLSSGCFGLKLDIGSLSGLC	SEQ ID NO: 117
GAQKKGGSQGCFGLKLDIGSLSGLC	SEQ ID NO: 118
GAQKKGSSGCFGLKLDIGSLSGLC	SEQ ID NO: 119
GANKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 120
GANKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 121
GANKKGGSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 122
GANKKGSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 123
GAQKKGLSQGCFGLPLDRIGSMGLGC	SEQ ID NO: 124
GAQKKGLSSGCFGLPLDRIGSMGLGC	SEQ ID NO: 125
GAQKKGGSQGCFGLPLDRIGSMGLGC	SEQ ID NO: 126
GAQKKGSSGCFGLPLDRIGSMGLGC	SEQ ID NO: 127
GAQKKGLSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 128
GAQKKGGSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 129
GAQKKGLSQGCFGLPLERIGSLSGLC	SEQ ID NO: 130
GAQKKGLSSGCFGLPLERIGSLSGLC	SEQ ID NO: 131
GANKKGLSQGCFGLPLDRIGSMGLGC	SEQ ID NO: 132
GANKKGLSSGCFGLPLDRIGSMGLGC	SEQ ID NO: 133
GANKKGLSQGCFGLPLERIGSMGLGC	SEQ ID NO: 134

GANKKGLSSGCFGLPLERIGMSGSLGC	SEQ ID NO: 135
GAQKKGSSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 136
GAQKKGSSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 137
GAQKKGSSSQGCFGLKLDRIIGSLSGLC	SEQ ID NO: 138
GAQKKGSSSGCFGLKLDRIIGSLSGLC	SEQ ID NO: 139
GANKKGSSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 140
GANKKGSSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 141
GAQKKGSSSQGCFGLPLDRIGMSGSLGC	SEQ ID NO: 142
GAQKKGSSSGCFGLPLDRIGMSGSLGC	SEQ ID NO: 143
GAQKKGSSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 144
YKGAQKKGSSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 145
YKGAQKKGLSQGCFGLKLDRIIGSLSGLC	SEQ ID NO: 146
YKGAQKKGLSSGCFGLKLDRIIGSLSGLC	SEQ ID NO: 147
YKGAQKKGSSSQGCFGLKLDRIIGSLSGLC	SEQ ID NO: 148
YKGAQKKGSSSGCFGLKLDRIIGSLSGLC	SEQ ID NO: 149
YKGANKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 150
YKGANKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 151
YKGANKKGSSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 152
YKGANKKGSSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 153
YKGAQKKGLSQGCFGLPLDRIGMSGSLGC	SEQ ID NO: 154
YKGAQKKGLSSGCFGLPLDRIGMSGSLGC	SEQ ID NO: 155
YKGAQKKGSSSQGCFGLPLDRIGMSGSLGC	SEQ ID NO: 156
YKGAQKKGSSSGCFGLPLDRIGMSGSLGC	SEQ ID NO: 157
YKGAQKKGLSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 158
YKGAQKKGSSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 159
YKGAQKKGLSQGCFGLPLERIGSLSGLC	SEQ ID NO: 160
YKGAQKKGLSSGCFGLPLERIGSLSGLC	SEQ ID NO: 161
YKGANKKGLSQGCFGLPLDRIGMSGSLGC	SEQ ID NO: 162
YKGANKKGLSSGCFGLPLDRIGMSGSLGC	SEQ ID NO: 163
YKGANKKGLSQGCFGLPLERIGMSGSLGC	SEQ ID NO: 164
YKGANKKGLSSGCFGLPLERIGMSGSLGC	SEQ ID NO: 165
YKGAQKKGSSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 166
YKGAQKKGSSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 167
YKGAQKKGSSSQGCFGLKLDRIIGSLSGLC	SEQ ID NO: 168
YKGAQKKGSSSGCFGLKLDRIIGSLSGLC	SEQ ID NO: 169
YKGANKKGSSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 170
YKGANKKGSSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 171
YKGAQKKGSSSQGCFGLPLDRIGMSGSLGC	SEQ ID NO: 172
YKGAQKKGSSSGCFGLPLDRIGMSGSLGC	SEQ ID NO: 173
YKGAQKKGSSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 174
ARKYKGAQKKGSSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 175
ARKYKGAQKKGSSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 176
ARKYKGAQKKGLSSGCFGLKLDRIIGSLSGLC	SEQ ID NO: 177
ARKYKGAQKKGSSSQGCFGLKLDRIIGSLSGLC	SEQ ID NO: 178

ARKYKGAQKKGGSSGCFGLKLDRIGSLSGLC	SEQ ID NO: 179
ARKYKGANKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 180
ARKYKGANKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 181
ARKYKGANKKGGSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 182
ARKYKGANKKGGSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 183
ARKYKGAQKKGLSQGCFGLPLDRIGSMSGLGC	SEQ ID NO: 184
ARKYKGAQKKGLSSGCFGLPLDRIGSMSGLGC	SEQ ID NO: 185
ARKYKGAQKKGGSSQGCFGLPLDRIGSMSGLGC	SEQ ID NO: 186
ARKYKGAQKKGGSSGCFGLPLDRIGSMSGLGC	SEQ ID NO: 187
ARKYKGAQKKGGSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 188
ARKYKGAQKKGLSQGCFGLPLERIGSLSGLC	SEQ ID NO: 189
ARKYKGAQKKGLSSGCFGLPLERIGSLSGLC	SEQ ID NO: 190
ARKYKGANKKGLSQGCFGLPLDRIGSMSGLGC	SEQ ID NO: 191
ARKYKGANKKGLSSGCFGLPLDRIGSMSGLGC	SEQ ID NO: 192
ARKYKGANKKGLSQGCFGLPLERIGSMSGLGC	SEQ ID NO: 193
ARKYKGANKKGLSSGCFGLPLERIGSMSGLGC	SEQ ID NO: 194
ARKYKGAQKKGGSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 195
ARKYKGAQKKGGSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 196
ARKYKGAQKKGGSSQGCFGLKLDRIGSLSGLC	SEQ ID NO: 197
ARKYKGAQKKGGSSGCFGLKLDRIGSLSGLC	SEQ ID NO: 198
ARKYKGANKKGGSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 199
ARKYKGANKKGGSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 200
ARKYKGAQKKGGSSQGCFGLPLDRIGSMSGLGC	SEQ ID NO: 201
ARKYKGAQKKGGSSGCFGLPLDRIGSMSGLGC	SEQ ID NO: 202
ARKYKGAQKKGGSSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 203
QEHPQARKYKGAQKKGGSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 204
QEHPQARKYKGAQKKGLSQGCFGLKLDRIGSLSGLC	SEQ ID NO: 205
QEHPQARKYKGAQKKGLSSGCFGLKLDRIGSLSGLC	SEQ ID NO: 206
QEHPQARKYKGAQKKGGSSQGCFGLKLDRIGSLSGLC	SEQ ID NO: 207
QEHPQARKYKGAQKKGGSSGCFGLKLDRIGSLSGLC	SEQ ID NO: 208
QEHPNARKYKGANKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 209
QEHPNARKYKGANKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 210
QEHPNARKYKGANKKGGSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 211
QEHPNARKYKGANKKGGSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 212
QEHPQARKYKGAQKKGLSQGCFGLPLDRIGSMSGLGC	SEQ ID NO: 213
QEHPQARKYKGAQKKGLSSGCFGLPLDRIGSMSGLGC	SEQ ID NO: 214
QEHPQARKYKGAQKKGGSSQGCFGLPLDRIGSMSGLGC	SEQ ID NO: 215
QEHPQARKYKGAQKKGGSSGCFGLPLDRIGSMSGLGC	SEQ ID NO: 216
QEHPQARKYKGAQKKGGSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 217
QEHPQARKYKGAQKKGLSQGCFGLPLERIGSLSGLC	SEQ ID NO: 218
QEHPNARKYKGANKKGLSQGCFGLPLDRIGSMSGLGC	SEQ ID NO: 219
QEHPNARKYKGANKKGLSSGCFGLPLDRIGSMSGLGC	SEQ ID NO: 220
QEHPNARKYKGANKKGLSQGCFGLPLERIGSMSGLGC	SEQ ID NO: 221
QEHPNARKYKGANKKGLSSGCFGLPLERIGSMSGLGC	SEQ ID NO: 222

QEHPQARKYKGAQKKGSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 223
QEHPQARKYKGAQKKGSSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 224
QEHPQARKYKGAQKKGSSQGCFGLKLDIGSLSGLC	SEQ ID NO: 225
QEHPQARKYKGAQKKGSSSGCFGLKLDIGSLSGLC	SEQ ID NO: 226
QEHPNARKYKGANKKGSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 227
QEHPNARKYKGANKKGSSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 228
QEHPQARKYKGAQKKGSSQGCFGLPLDRIGSMGLGC	SEQ ID NO: 229
QEHPQARKYKGAQKKGSSSGCFGLPLDRIGSMGLGC	SEQ ID NO: 230
QEHPQARKYKGAQKKGSSKGCFLPLDRIGSLSGLC	SEQ ID NO: 231
GAQKKGSSQGCFGLPLERIGSLSGLC	SEQ ID NO: 232

Embodiment 6: the CNP compound according to embodiment 1, wherein the CNP peptide has any one of the following amino acid sequences:

- 5 GAQKKGSSQGCFGLPLDRIGSLSGLC (SEQ ID NO: 136),
 ARKYKGAQKKGLSQGCFGLPLDRIGSLSGLC (SEQ ID NO: 77),
 YKGAQKKGSSQGCFGLPLDRIGSLSGLC (SEQ ID NO: 88),
 YKGAQKKGLSQGCFGLPLDRIGSLSGLC (SEQ ID NO: 103),
 QEHPQARKYKGAQKKGLSSGCFGLPLDRIGSLSGLC (SEQ ID NO: 67), and
 10 QEHPQARKYKGAQKKGLSSGCFGLPLERIGSLSGLC (SEQ ID NO: 104).

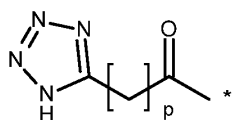
Embodiment 7: the CNP compound according to embodiment 1, wherein the CNP peptide has the following amino acid sequence:

QEHPQARKYKGAQKKGLSSGCFGLPLDRIGSLSGLC (SEQ ID NO: 67).

- 15 Embodiment 8: the CNP compound according to any one of the preceding embodiments, wherein the modifying group is covalently attached to the N-terminal alpha-amine of the CNP peptide.

- 20 Embodiment 9: the CNP compound according to any one of the preceding embodiments, wherein Chem. A of the modifying group has a p of 16.

Embodiment 10: the CNP compound according to embodiments 1-8, wherein Chem. A of the modifying group is Chem. A2



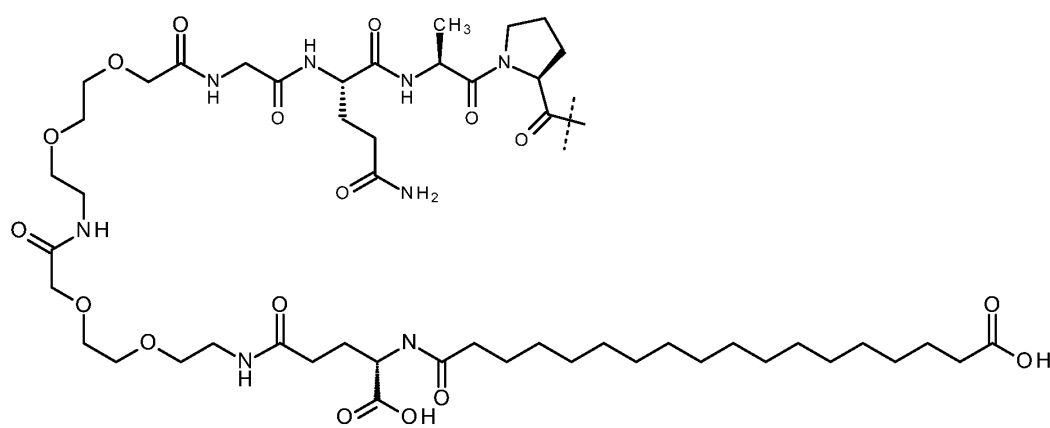
- 25 (Chem. A2)

wherein p is 16.

Embodiment 11: the CNP compound according to any one of the preceding embodiments, wherein Chem. B of the modifying group has a q of 1-5.

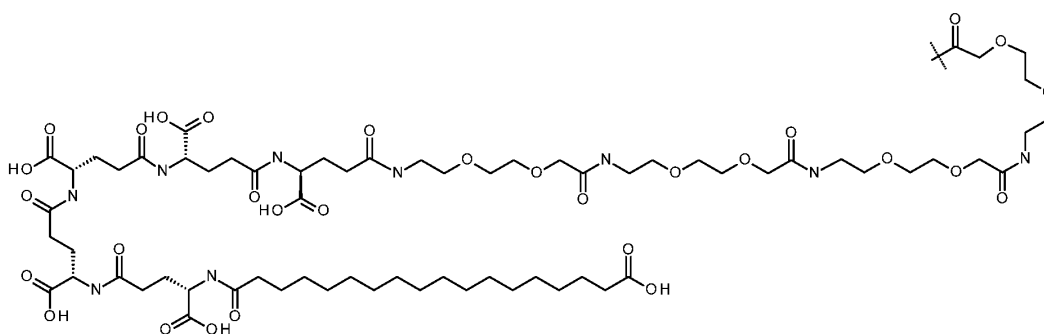
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Embodiment 12: the CNP compound according to any one of the preceding embodiments, wherein the modifying group is selected from the following non-limiting examples Chem. E, Chem. F, Chem. G, Chem. H, Chem. I, and Chem. J (in which the dotted line defines the attachment through an amide bond to the CNP peptide)

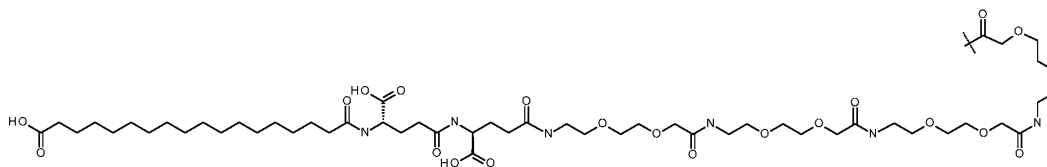


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(Chem. E)

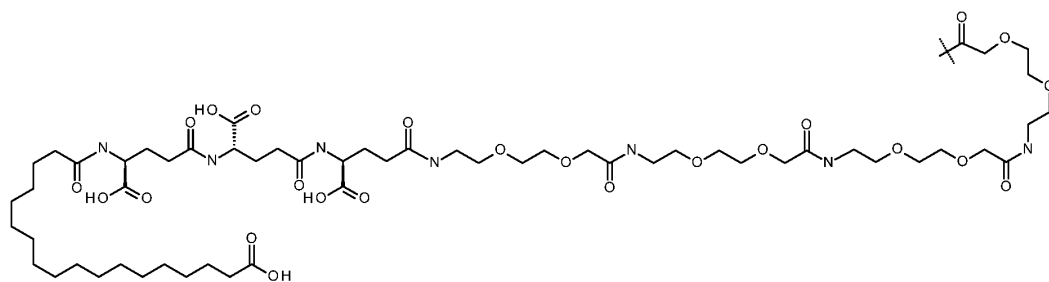


(Chem. F)

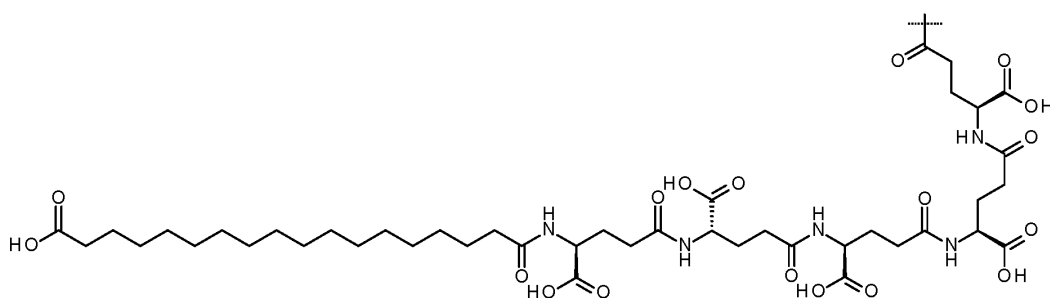


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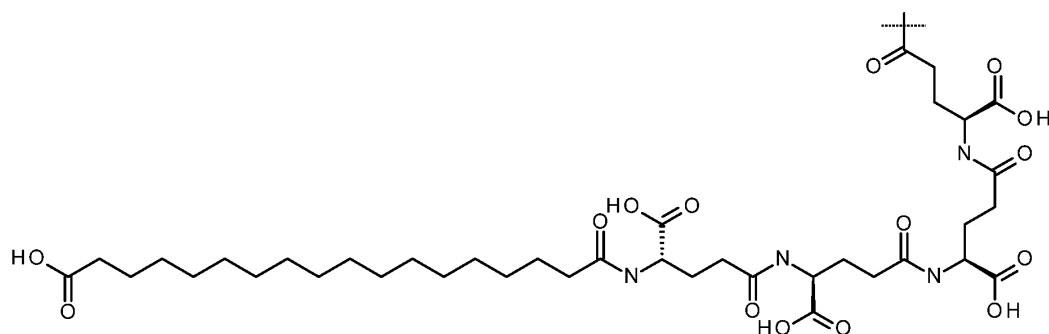
(Chem. G)



(Chem. H)



(Chem. I)



(Chem. J).

Embodiment 13: the CNP compound according to any one of the preceding
embodiments, wherein the modifying group is Chem. I.

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Embodiment 14: a CNP compound comprising a CNP peptide and a modifying
group comprising a Chem. A, a Chem. B and a Chem. C, wherein the compound is
according to any one of the compounds disclosed in Table 1 (see below).

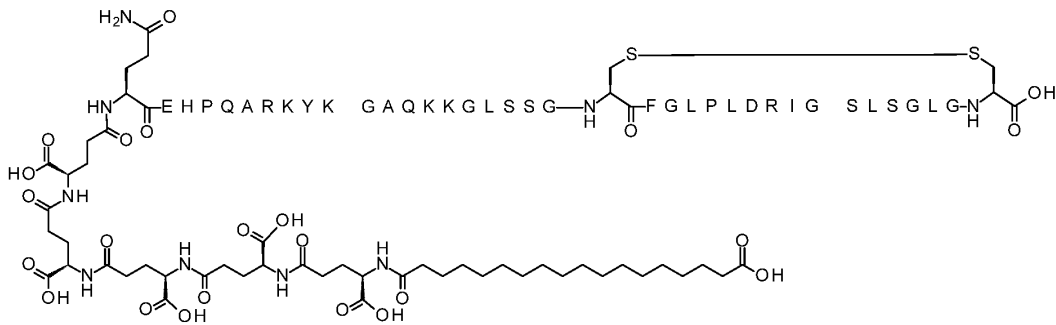
Embodiment 15: a CNP compound comprising a CNP peptide and a modifying group wherein the compound is according to any one of the compounds disclosed in Table 1a.

Table 1a:

Compound ID	Modifying group	CNP peptide - with sequence modifications vis-a-vis CNP37	SEQ ID NO
9384	C18d	gGlu-2xOEG-1xGQAP des1-10, 13Q, 17S, 19Q, 25P, 32L	62
9407	C18d	5xgGlu-4xOEG des1-5, 13Q, 19Q, 25P, 32L	77
9435	C18d	2xgGlu-4xOEG des1-8, 13Q, 17G, 19Q, 25P, 32L	88
9480	C18d	3xgGlu-4xOEG des1-8, 13Q, 19Q, 25P, 32L	103
9482	C18d	5xgGlu 5Q, 13Q, 19S, 25P, 32L	67
9483	C18d	4xgGlu 5Q, 13Q, 19S, 25P, 27E, 32L	104

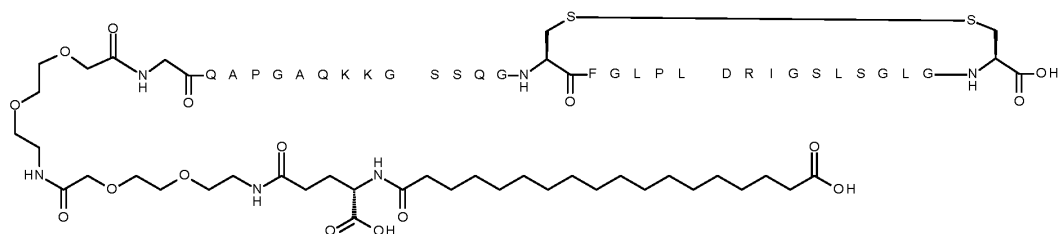
Embodiment 16: a CNP compound comprising a CNP peptide and a modifying group, wherein the CNP peptide has the following amino acid sequence, QEHPQARKYKGAQKKGLSSGCFGLPLDRIGSLSGLG (SEQ ID NO: 67), and wherein the modifying group is Chem. I.

Embodiment 17: a CNP compound according to Formula II:

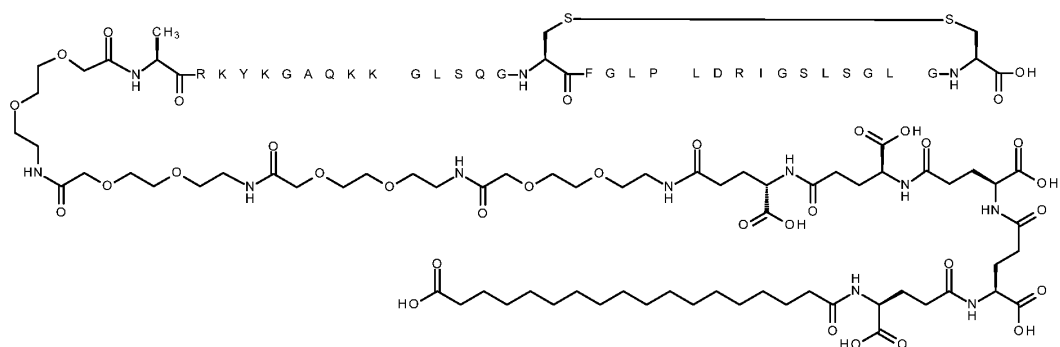


(Formula II).

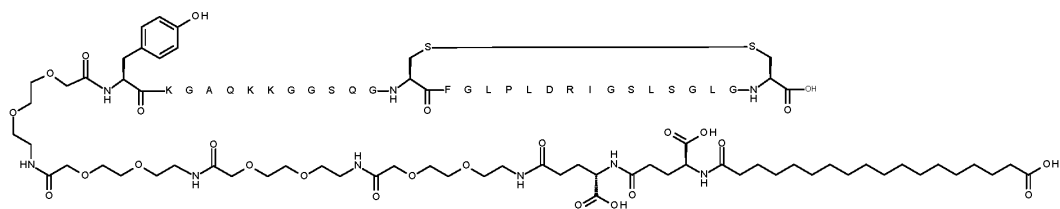
Embodiment 18: a CNP compound according to any one of Formula II, III, IV, V, VI, and VII:



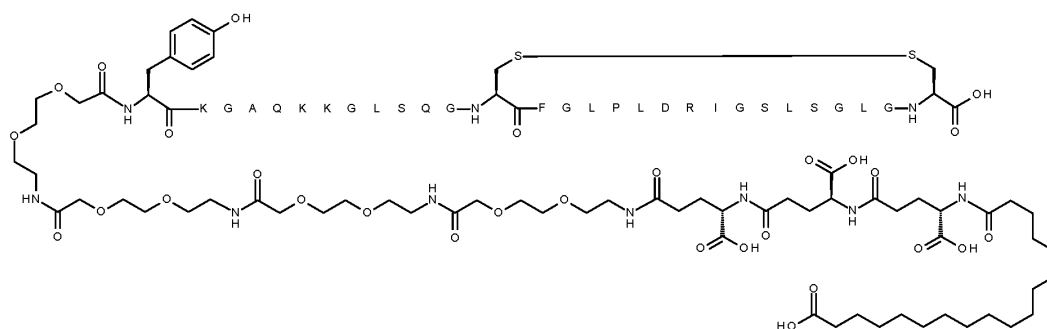
(Formula III)



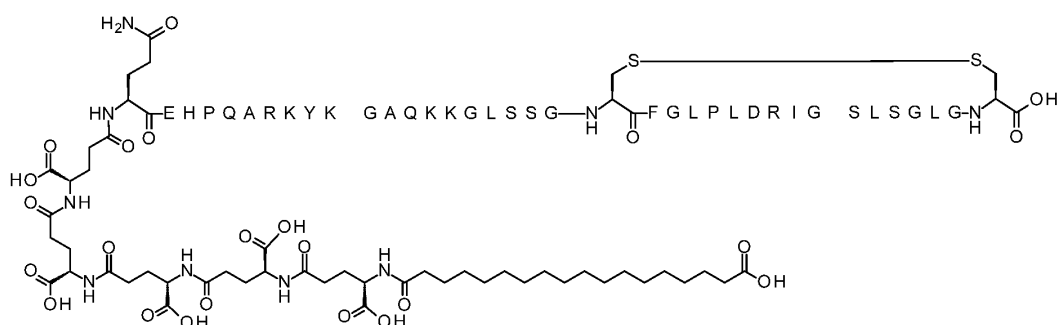
(Formula IV)



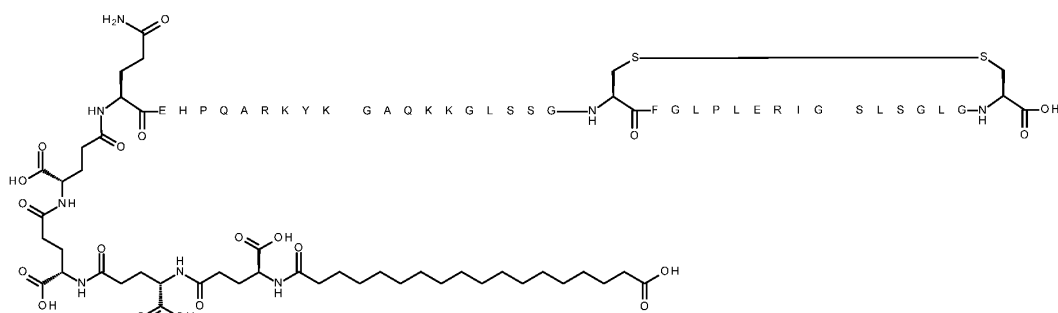
(Formula V)



(Formula VI)



(Formula II)



(Formula VII)

Embodiment 19: the compound according to any one of the embodiments 1-18 wherein the net charge of the CNP compound at physiological pH is 0 to -4, determined as described in Example 4.

Embodiment 20: the compound according to any one of the embodiments 1-18 wherein the compound has a *in vivo* half-life after s.c. administration to Göttingen minipigs of at least 10 hours, determined as described in Example 12.

Embodiment 21: the compound according to any one of the embodiments 1-18 wherein the compound has a *in vivo* half-life after s.c. administration to Göttingen minipigs of at least 20 hours, determined as described in Example 12.

20 Embodiment 22: the compound according to any one of the embodiments 1-18
wherein the compound has a *in vivo* half-life after s.c. administration to Göttingen minipigs of
at least 30 hours, determined as described in Example 12.

Embodiment 23: the compound according to any one of the embodiments 1-18 wherein the compound has a *in vivo* half-life after s.c. administration to Göttingen minipigs of at least 40 hours, determined as described in Example 12.

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Embodiment 24: the compound according to any one of the embodiments 1-18 wherein the compound has a *in vivo* half-life after s.c. administration to Göttingen minipigs of at least 50 hours, determined as described in Example 12.

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Embodiment 25: the compound according to any one of the embodiments 1-18 wherein the compound has a bioavailability after s.c. administration to Göttingen minipigs of at least 40%, determined as described in Example 12.

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Embodiment 26: the compound according to any one of the embodiments 1-18 wherein the compound has a bioavailability after s.c. administration to Göttingen minipigs of at least 50%, determined as described in Example 12.

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Embodiment 27: the compound according to any one of the embodiments 1-18 wherein the compound has a bioavailability after s.c. administration to Göttingen minipigs of at least 60%, determined as described in Example 12.

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Embodiment 28: the compound according to any one of the embodiments 1-18 wherein the compound has a bioavailability after s.c. administration to Göttingen minipigs of at least 70%, determined as described in Example 12.

Embodiment 29: the compound according to any one of the embodiments 1-18 wherein the compound has a solubility of at least at least 2000 μ M at either pH 4 or pH 6.5 measured as described in Example 5.

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Embodiment 30: the compound according to any one of the embodiments 1-18 wherein the compound has a solubility of at least at least 3000 μ M at either pH 4 or pH 6.5 measured as described in Example 5.

Embodiment 31: the compound according to any one of the embodiments 1-18 wherein the compound has a solubility of at least at least 4000 μ M at either pH 4 or pH 6.5 measured as described in Example 5.

5 Embodiment 32: the compound according to any one of the embodiments 1-31 wherein the compound comprises an intramolecular disulfide bridge resulting in a cyclic structure.

 Embodiment 33: a pharmaceutical composition comprising a compound according
10 to any one of embodiments 1-32, and one or more pharmaceutically acceptable excipients.

 Embodiment 34: the compound according to any one of the embodiments 1-32, or a composition according to embodiment 33, for the use in the treatment or prevention of cardio-renal-metabolic diseases.

15 Embodiment 35: the compound according to any one of the embodiments 1-32, or a composition according to embodiment 33, for the use in the treatment or prevention of cardio-renal-metabolic diseases, including the group consisting of hypertension, arteriosclerosis, atherosclerosis, restenosis, acute myocardial infarction, pulmonary
20 hypertension, acute decompensated heart failure, congestive heart failure, cardiac edema, renal edema, hepatic edema*, acute renal insufficiency, chronic renal insufficiency, insulin resistance, and type 2 diabetes.

 Embodiment 36: the compound according to any one of the embodiments 1-32, or a
25 composition according to embodiment 33, for the use in the treatment or prevention of congestive heart failure.

 Embodiment 37: the compound according to any one of the embodiments 1-32, or a composition according to embodiment 33, for the use in the treatment or prevention of
30 decompensated heart failure.

 Embodiment 38: the compound according to any one of the embodiments 1-32, or a composition according to embodiment 33, for the use in the treatment or prevention of growth disorders including short stature that may relate to FGFR3-related skeletal dysplasia,
35 and related comorbidities.

Embodiment 39: the compound according to any one of the embodiments 1-32, or a composition according to embodiment 33, for the use in the treatment or prevention of achondroplasia, hypochondroplasia, thanatophoric dysplasia type 1 and type 2, SHOX deficiency, Noonan syndrome, Costello, LEOPARD syndrome, idiopathic short stature, autosomal dominant short stature, growth hormone deficiency, hypophosphatemic rickets, CNP deficiency, Aggrecan deficiency, Heterozygous NPR2 mutation, osteoarthritis, craniosynostosis, (e.g., Muenke syndrome, Crouzon syndrome, Apert syndrome, Jackson-Weiss syndrome, Pfeiffer syndrome, or Crouzonodermoskeletal syndrome), Lacrimo-Auriculo-Dento-Digital syndrome (LADD), Osteoglophonic dysplasia, and SADDAN (severe achondroplasia developmental delay acanthosis nigricans).

Embodiment 40: the compound according to any one of the embodiments 1-32, or a composition according to embodiment 33, for the use in the treatment or prevention of osteogenesis imperfecta, achondrogenesis, chondrodysplasia punctata, homozygous achondroplasia, rhizomelic type of chondrodysplasia punctata, spondyloepiphyseal dysplasia congenita, congenital short femur, Langer-type mesomelic dysplasia, Neurofibromatosis, Legius syndrome and neurofibromatosis type 1.

Embodiment 41: the compound according to any one of the embodiments 1-32, or a composition according to embodiment 33, for the use in the treatment or prevention of phenotypes related to growth disorders including short stature that may relate to FGFR3-related skeletal dysplasia, selected from the group consisting of growth retardation, skull deformities, orthodontic defects, cervical cord compression, spinal stenosis, pain in relation to skeletal dysplasia, hydrocephalus, hearing loss due to chronic otitis, cardiovascular disease, neurological disease, and obesity.

Embodiment 42: a method of treating or preventing cardio-renal-metabolic diseases, comprising administering to a patient in need thereof an effective amount of the compound according to any one of the embodiments 1-32, or a composition according to embodiment 33.

Embodiment 43: a method of treating or preventing cardio-renal-metabolic diseases, including the group consisting of hypertension, arteriosclerosis, atherosclerosis, restenosis, acute myocardial infarction, pulmonary hypertension, acute decompensated heart failure,

congestive heart failure, cardiac edema, renal edema, hepatic edema*, acute renal insufficiency, chronic renal insufficiency, insulin resistance, and type 2 diabetes, comprising administering to a patient in need thereof an effective amount of the compound according to any one of the embodiments 1-32, or a composition according to embodiment 33.

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Embodiment 44: a method of treating or preventing growth disorders including short stature that may relate to FGFR3-related skeletal dysplasia, and related comorbidities, comprising administering to a patient in need thereof an effective amount of the compound according to any one of the embodiments 1-32, or a composition according to embodiment

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33.

Embodiment 45: a method of treating or preventing achondroplasia, hypochondroplasia, thanatophoric dysplasia type 1 and type 2, SHOX deficiency, Noonan syndrome, Costello , LEOPARD syndrome, idiopathic short stature, autosomal dominant short stature, growth hormone deficiency, hypophosphatemic rickets, CNP deficiency, Aggrecan deficiency, Heterozygous NPR2 mutation, osteoarthritis, craniosynostosis, (e.g., Muenke syndrome, Crouzon syndrome, Apert syndrome, Jackson- Weiss syndrome, Pfeiffer syndrome, or Crouzonodermoskeletal syndrome), Lacrimo-Auriculo-Dento-Digital syndrome (LADD), Osteoglophonic dysplasia, and SADDAN (severe achondroplasia developmental delay acanthosis nigricans), comprising administering to a patient in need thereof an effective amount of the compound according to any one of the embodiments 1-32, or a composition according to embodiment 33.

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Embodiment 46: a method of treating or preventing osteogenesis imperfecta, achondrogenesis, chondrodysplasia punctata, homozygous achondroplasia, rhizomelic type of chondrodysplasia punctata, spondyloepiphyseal dysplasia congenita, congenital short femur, Langer-type mesomelic dysplasia, Neurofibromatosis, Legius syndrome and neurofibromatosis type 1, comprising administering to a patient in need thereof an effective amount of the compound according to any one of the embodiments 1-32, or a composition according to embodiment 33.

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Embodiment 47: a method of treating or preventing phenotypes related to growth disorders including short stature that may relate to FGFR3-related skeletal dysplasia, selected from the group consisting of growth retardation, skull deformities, orthodontic defects, cervical cord compression, spinal stenosis, pain in relation to skeletal dysplasia,

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hydrocephalus, hearing loss due to chronic otitis, cardiovascular disease, neurological disease, and obesity, comprising administering to a patient in need thereof an effective amount of the compound according to any one of the embodiments 1-32, or a composition according to embodiment 33.

5 EXAMPLES

Materials and Methods

List of Abbreviations

10	2-CITrt	2-Chlorotrityl resin
	Aldrithiol-4	4,4'-Dipyridyl disulfide
	AUC	Area under the curve
	BEH	Ethylene Bridged Hybrid
	Boc	tert-Butyloxycarbonyl
15	C18d	Octadecanedioic acid
	C20d	Eicosanedioic acid
	CAD	Charged aerosol detector
	cGMP	Cyclic guanosine monophosphate
	CL	Clearance
20	CSH	Charged Surface Hybrid
	DCM	Dichloromethane
	DgGlu	D-configuration gamma-glutamoyl
	DIC	N,N'-Diisopropylcarbodiimide
	DMEM	Dulbecco's Modified Eagle Medium
25	DMF	Dimethylformamide
	DMSO	Dimethyl sulfoxide
	DTT	Dithiothreitol
	EDTA	Ethylenediaminetetraacetic acid
	ESI	Electrospray ionisation
30	F%	Bioavailability
	Fd	Faraday
	Fmoc	Fluorenylmethyloxycarbonyl
	FPLC	Fast protein liquid chromatography
	gGlu	Gamma-glutamoyl

	HEPES	2-[4-(2-Hydroxyethyl)piperazin-1-yl]ethane-1-sulfonic acid
	HFIP	Hexafluoro-2-propanol
	HMWP	High molecular weight protein
	HSA	Human serum albumin
5	i.v.	Intravenous
	IPA	Isopropanol
	LCMS	Liquid chromatography–mass spectrometry
	LLOQ	Lower limit of quantitation
	LYD	Landrace, Yorkshire & Duroc
10	MeCN	Acetonitrile
	MMPX	8-Methoxymethyl-3-isobutyl 1-methylxanthine
	MS	Mass spectrometry
	NAD	No abnormalities detected
	NCA	Non-compartmental analysis
15	n.d.	not detected
	Nle (X)	Norleucine
	NMP	N-Methyl-2-pyrrolidone
	OEG	Oligoethylene glycol
	Oxyma Pure	Ethyl cyanohydroxyiminoacetate
20	Pbf	2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl
	PBS	Phosphate buffered saline
	PD	Pharmacodynamics
	PDA	Photodiode-array detection
	PK	Pharmacokinetics
25	QC	Quality control
	RP	Reversed phase
	RPM	Rounds per minute
	s.c.	Subcutaneous
	SEC	Size-exclusion chromatography
30	SIL	Stable isotope labelled
	SPPS	Solid-phase peptide synthesis
	T _{1/2}	Half-life
	tBu	tert-Butyl
	Tetrazole-C18	17-(2H-Tetrazol-5-yl)heptadecanoic acid
35	TF	Time-of-flight

	TFA	Trifluoroacetic acid
	ThT	Thioflavin T
	TIPS	Triisopropyl silane
	Tris	2-Amino-2-(hydroxymethyl)propane-1,3-diol
5	Trt	Trityl
	TUV	Tunable UV
	UPLC	Ultra-performance liquid chromatography
	UV	Ultraviolet

10 General Methods of Preparation

Method A – Solid-phase peptide synthesis

Peptides can be synthesized by solid-phase peptide synthesis which is well known in the art, below is described methods used to synthesize the exemplified compounds of the present invention.

Synthesis of compounds was performed on a SymphonyX Solid Phase Peptide Synthesizer (GYROS Protein Technologies AB, Tucson, AZ).

Typically synthesis was performed using 450 µmol resin, but syntheses using 150 or 300 µmol resin were also used. In a typical synthesis, the resin was washed in DMF. After washing with DMF, the resin was incubated with Fmoc-protected amino acid (5 eq., 0.3 M in 0.3 M Oxyma Pure in DMF, 7.5 mL), DIC (5 eq., 0.75 M in DMF, 3.0 mL), and collidine (5 eq., 0.75 M in DMF, 3.0 mL) for 30 min. Additional DIC (5 eq., 0.75 M in DMF, 3.0 mL) was then added and the resin incubated for 90 min. After each coupling, the resin was capped by treatment with acetic anhydride (1 M, 7.5 mL) and collidine (0.75 M, 3.0 mL) in DMF for 20 min. Fatty acids were coupled using fatty acid mono-tert-butyl ester (5 eq., 0.3 M in 0.3 M Oxyma Pure, 7.5 mL), DIC (5 eq., 0.75 M in DMF, 3.0 mL), and collidine (5 eq., 0.75 M in DMF, 3.0 mL) for 6 h.

The Fmoc-protected amino acids used were the standard recommended: Fmoc-Ala-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Asp(OtBu)-OH, Fmoc-Cys(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Glu(OtBu)-OH, Fmoc-Gly-OH, Fmoc-His(Trt)-OH, Fmoc-Ile-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Met-OH, Fmoc-Phe-OH, Fmoc-Pro-OH, Fmoc-Ser(tBu)-OH, Fmoc-Thr(tBu)-OH, Fmoc-Trp(Boc)-OH, Fmoc-Tyr(tBu)-OH, Fmoc-Val-OH and Fmoc-Nle-OH, supplied from e.g. Anaspec, Bachem, Iris Biotech or NovabioChem. Where nothing else is specified the naturally occurring L-form of the amino acids were used.

In cases where a serine or a threonine is present in the peptide, pseudoproline di-peptides may be used (see also W.R. Sampson et al., J. Pept. Sci. 1999, 5, 403-409).

For peptides acylated at any position during SPPS the following suitably protected building blocks such as, but not limited to, Fmoc-8-amino-3,6-dioxaoctanoic acid and Boc-Glu(Fmoc)-OH were supplied from e.g. Anaspec, Bachem, Iris Biotech, or Novabiochem.

Octadecanedioic acid mono-tert-butyl-ester and eicosanedioic acid mono-tert-butyl ester was prepared as is known in the art, e.g. as described in WO 2010102886 A1.

17-(2H-tetrazol-5-yl)heptadecanoic acid (Tetrazole-C18) was incorporated by coupling the protected building block (S)-4-(17-(1H-tetrazol-5-yl)heptadecanamido)-5-(tert-butoxy)-5-oxopentanoic acid which was synthesized according to the following procedure: 5-Chloro-1-((dimethylamino)(dimethyliminio)methyl)-1H-benzo[d][1,2,3]triazole 3-oxide tetrafluoroborate (TCTU, 5.87 g, 16.5 mmol) and N-methylmorpholine (NMM, 8.00 mL, 72.8 mmol) were sequentially added to a stirred suspension of 17-(1H-tetrazol-5-yl)heptadecanoic acid (5.10 g, 15.0 mmol) in dry DMF (70 mL). The mixture was stirred at room temperature for 30 minutes. H-L-Glu-OtBu (L-glutamic acid 1-tert-butyl ester, 4.58 g, 22.5 mmol) was added in one portion. The suspension turned into yellow solution in 5 minutes. It was allowed to stand at room temperature for 4 hours and then poured into an ice cooled stirred solution of hydrochloric acid (35%, 20 mL) in water (1 L). The crude product was filtered off and washed with water (3 x 100 mL) and shortly dried on a glass sintered frit by suction and redissolved in DMF (70 mL). This solution was poured into water (1 L), the resulting suspension stirred for 5 minutes and the solid was filtered off, washed with water (3 x 100 mL) and dried in vacuo. Crude product was dissolved in ethyl acetate (400 mL) and filtered through a silica gel (Silicagel 60, 0.040-0.063 mm) column (100 g) and the column was washed by ethyl acetate (600 mL). Ethyl acetate was removed in vacuo. Solid residue was boiled in 1,2-dichloroethane (200 mL) with vigorous stirring for 5 minutes, then the emulsion was allowed to cool to room temperature in 5 minutes and allowed to crystallize at the same temperature overnight. The waxy crystals were filtered off and washed by 1,2-dichloromethane (50 mL) and n-heptane (100 mL) and dried on air. This purification step was repeated one more time. Finally the compound was dissolved in 1,4-dioxane (50 mL) and freeze dried to afford (S)-4-(17-(1H-tetrazol-5-yl)heptadecanamido)-5-(tert-butoxy)-5-oxopentanoic acid as off-white powder.

For peptides featuring a C-terminal cysteine the resin was a pre-loaded H-Cys(Trt)-2-CITrt (e.g. from Bachem or Novabiochem).

Method B – Peptide cleavage from the resin.

After synthesis the resin was washed with DCM, and the peptide cleaved from the resin by a 2-3 hours treatment with TFA/TIPS/water/DTT (e.g. in the ratios 90:5:2.5:2.5 or 92.5:2.5:2.5:5) followed by precipitation with diethyl ether. The precipitate was centrifuged and washed several times with diethyl ether.

Method C – Disulfide bridge formation

Native CNP contains a disulfide bridge which, if reduced, abolishes binding to the NPR2 receptor. Methods for disulfide bridge formation for synthetic peptides are well known in the art, below is described three methods used to prepare the exemplified compounds of the present invention.

Folding using Aldrithiol-4

The crude precipitated peptide from a 150 µmol synthesis was dissolved in 10 ml DMSO, followed by addition of water to 700 mL and additional addition of 100 mL MeCN. Finally, 2 mL of 0.5M NaOAc buffer pH 5.0 was added to the peptide solution. The pH was adjusted with 1M NaOH to pH 5-6.5 until the solution was clear. The amount of peptide in solution was quantified using CAD and a fresh stock solution of Aldrithiol-4 (2 mg/ml in MeOH) was prepared. 1.0 equiv of Aldrithiol-4 in MeOH compared to peptide content was added over 5-10 min. under vigorous stirring. The solution was stirred for 10 min and additional 0.5 or 1.0 equiv of Aldrithiol-4 stock solution added. The reaction was quenched with 2 mL TFA once complete as determined by LCMS. The peptide was purified by RP-HPLC as described below.

Folding using DMSO

The crude peptide precipitate from a 450 µmol synthesis was dissolved in MeCN/water 1:1 (50 mL), and added to a 500 mM Tris-HCl pH 8.0 buffer (1 L) and diluted with water (1.4 L) and DMSO (600 mL). The solution was left with gentle stirring for 16-24 h at RT. The reaction was quenched by addition of 5.0 equiv. of iodoacetamide (50 mM in water), then acidified after 10 min with TFA to pH 2 and diluted to 5 L with water. The peptide was purified by RP-HPLC as described below.

Folding using cysteine/cystine or cysteamine/cystamine redox buffer

The crude peptide precipitate from a 150 µmol synthesis was dissolved in DMSO (20 mL) and added to a buffer of 50 mM Tris-HCl, 3 mM cysteine, 0.3 mM cystine pH 8.2

(800 mL) or a buffer of 50 mM Tris-HCl, 3 mM cysteamine, 0.3 mM cystamine pH 8.2. The solution was left with gentle stirring for 16-24 h at RT. The reaction was quenched by addition of 3 mL TFA, diluted with 100 mL MeCN and purified by RP-HPLC as described below.

5

Method D – Purification

Methods of peptide purification are well known in the art, below is described two methods used to purify the exemplified compounds of the present invention.

Reverse phase preparative HPLC using acidic eluents

10 Crude folded peptides were purified by preparative reverse phase HPLC on a Waters Delta Prep 4000 or a Gilson Model 322 H2 system fitted with a C18 column, e.g. a Waters Xbridge Prep C18 OBD, 5 µm, 250 x 50 mm or a Phenomenex Gemini Axia NX C18, 5 µm, 250 x 30 mm. The peptide was eluted from the column using a linear gradient of eluents A (0.1% TFA in water) and B (0.1% TFA in acetonitrile), e.g. from 27-42% eluent B
15 over 30 min at a constant flowrate of 25 mL/min (Ø30 mm column) or from 30-40% eluent B over 10 min at 120 mL/min (Ø50 mm column). The peptide fractions with acceptable purity were collected, pooled and lyophilised to yield the peptide TFA salt as a colourless powder.

Reverse phase preparative HPLC using near neutral eluents

If further purification was required the lyophilised peptide TFA salt was purified on a
20 similar preparative HPLC system in a neutral or near-neutral pH eluent, e.g. eluent A: 100 mM NaOAc pH 6.5, 5% MeCN; eluent B: MeCN. The peptide was eluted from the column using a linear gradient of eluents A and B, e.g. from 25-55% eluent B over 30 min at a constant flowrate of 60 mL/min (Ø50 mm column). The peptide fractions with acceptable purity were collected, pooled and desalted using either of the methods described below.

25

Method E – Resalting and desalting

In some instances, it was desirable to change the counter ion to sodium to ease formulation at pH 6.5. Methods for exchanging peptide counter ions are well known in the art, below is described a method used to change counter ion for some of the exemplified
30 compounds of the present invention.

Size exclusion desalting

- The counter-ion was exchanged by solubilising the peptide TFA salt in 400 mM NaOAc pH 6.5 and 20% MeCN at 2-3 mg/mL. The dissolved peptide was then desalted on an Äkta Purifier FPLC system using a HiPrep 26/10 desalting column. The column was pre-equilibrated with 20% MeCN and the peptide was injected and eluted over 1.5 CV of isocratic 20% MeCN at 6 mL/min. The peptide was collected, quantified by CAD analysis and lyophilised to yield the peptide sodium salt as a colourless powder.

General Methods of Detection and Characterisation:

- In order to confirm the identity, to measure the purity and to quantify the amount of a prepared synthetic peptide, the peptide is characterised using methods such as LCMS and reverse-phase UPLC that are well known in the art. Below is described methods used to characterise the exemplified compounds of the present invention.

Method F – Analytical chromatography methods

The prepared CNP compounds were characterised by RP-UPLC and LCMS and the amount prepared quantified by RP-UPLC/CAD.

LCMS34

- LCMS was performed on a setup consisting of a Waters ACQUITY UPLC system and a Xevo G2-XS QTOF mass spectrometer. The system was fitted with a Waters ACQUITY UPLC BEH C18 Column, 1.7 µm, 2.1 mm x 50 mm, column temperature 60 °C. UV-detection was at 214 nm. MS ionisation mode was ESI+.

- Eluent A: 0.1% formic acid in water; eluent B: 0.1% formic acid in acetonitrile. The analysis was performed by injecting an appropriate volume of the sample (preferably 1-10 µL) onto the column which was eluted with a linear gradient of eluents A and B from 5-95% eluent B over 4.0 min at a constant flowrate of 0.4 mL/min.

RP-UPLC107:

- Alternatively, LCMS was performed on a setup consisting of a Waters ACQUITY UPLC system and a Waters QDA mass detector. The system was fitted with a Waters ACQUITY UPLC BEH C18 Column, 1.7 µm, 2.1 mm x 50 mm, column temperature 40 °C. UV-detection was at 214 nm.

Eluent A: 0.05% TFA in water; eluent B: 0.05% TFA in acetonitrile. The analysis was performed by injecting an appropriate volume of the sample (preferably 1-10 µL) onto the

column which was eluted with a linear gradient of eluents A and B from 5-60% eluent B over 1.6 min at a constant flowrate of 0.9 mL/min.

RP-UPLC02:

RP-UPLC02 was performed on a Waters ACQUITY UPLC system with a TUV or
5 PDA detector. The system was fitted with a Waters ACQUITY UPLC BEH C18 column, 1.7 μ m, 2.1 mm x 150 mm, column temperature 40 °C. UV-detection was at 214 nm. Eluent A: 0.05% TFA in water; eluent B: 0.05% TFA in acetonitrile.

The analysis was performed by injecting an appropriate volume of the sample (preferably 1-10 μ L) onto the column which was eluted with a linear gradient of eluents A and B from 5-
10 95% eluent B over 16.0 min at a constant flowrate of 0.4 mL/min.

RP-UPLC61:

RP-UPLC61 was performed on a Waters ACQUITY UPLC system with a TUV or
PDA detector. The system was fitted with a Waters ACQUITY UPLC BEH Shield C18
column, 1.7 μ m, 2.1 mm x 150 mm, column temperature 60 °C. UV-detection was at 214 nm.
15 Eluent A: 20 mM Na₂SO₄, 2 mM Na₂HPO₄, 2 mM NaH₂PO₄ in water/MeCN 9:1, pH 7.2;
eluent B: MeCN/water 7:3. The analysis was performed by injecting an appropriate volume of
the sample (preferably 1-10 μ L) onto the column which was eluted with a linear gradient of
eluents A and B from 5-20% B over 3 min, then 20-80% B over 17 min, then 80-90% B over
1 min at a constant flowrate of 0.4 mL/min.

CAD02 peptide quantification:

CAD was performed on a Thermo Scientific Vanquish UPLC system with a UV-DAD
and CAD (Charged Aerosol Detector). The system was fitted with a Waters ACQUITY UPLC
CSH C18 column, 1.7 μ m, 2.1 mm x 50 mm, column temperature 40 °C. UV-detection was at
214 nm. Eluent A: 0.1% v/v TFA in water; eluent B: 0.1% v/v TFA in MeCN. The analysis was
25 performed by injecting an appropriate volume of the sample onto the column which was
eluted with a linear gradient of eluents A and B from 0-95% B over 4 min at a constant
flowrate of 0.45 mL/min. Calibration was performed using a standard curve generated by
injecting an external standard of Insulin Aspart, 3.55 mg/mL.

Method G – Preparation of CNP compound formulations for *in vivo* experiments

Formulations for *in vivo* studies were prepared according to the principles outlined
below.

Procedure: The formulations used for the *in-vivo* studies were prepared by dissolving the lyophilized peptide in formulation buffers with compositions identical to the final formulations (final formulation composition are specified in Example 9 to Example 15). The following final formulation compositions have been used:

- 5 • pH 4.0: 5 mM sodium acetate, 250 mM glycerol, pH 4.0
- pH 4.0: 5 mM sodium acetate, 240 mM propylene glycol, pH 4.0
- pH 4.0: 5 mM sodium acetate, 250 mM glycerol, 0.007% polysorbate 20, pH 4.0
- pH 6.0: 20 mM sodium phosphate, 223 mM propylene glycol, pH 6.0
- pH 6.5: 8 mM sodium phosphate, 250 mM glycerol, pH 6.5
- 10 • pH 7.4: 8 mM sodium phosphate, 250 mM glycerol, pH 7.4
- pH 7.4: 8 mM sodium phosphate, 250 mM glycerol, 0.007% polysorbate 20, pH 7.4
- pH 7.5: 8 mM sodium phosphate, 250 mM glycerol, pH 7.5
- pH 5.5: 1.33 mM citric acid monohydrate; 3.67 mM citrate, trisodium; 52 mg/ml trehalose; 15 mg/ml D-mannose; 0.73 mg/ml L-methionine; 0.05 mg/ml polysorbate
- 15 80, pH 5.5

The formulation procedure was for practical reasons slightly different for pH 6.5 formulations compared to formulations of other pH targets.

20 Formulations at pH 6.5: The lyophilized peptide was dissolved in a pH 7.4 buffer (8 mM sodium phosphate, 250 mM glycerol, pH 7.4) to a nominal concentration of 20-50% above the target peptide concentration and pH was adjusted to pH 6.5 using 0.2N NaOH, or 0.2N HCl. The actual peptide concentration was determined using CAD (Method F, CAD02) and a volume of a pH 6.5 buffer (8 mM sodium phosphate, 250 mM glycerol, pH 6.5) was

25 added to reach a nominal concentration corresponding to the target peptide concentration and pH was adjusted to pH 6.5 using 0.2N NaOH, or 0.2N HCl. The actual peptide concentration was determined using CAD (Method F, CAD02). The formulation was sterile filtered (0.22µm), the final peptide concentration was determined using CAD (Method F, CAD02) and the formulation was filled into sterile containers.

30 Formulations at pH 4.0, pH 6.0, pH 7.4 and pH 7.5: The lyophilized peptide was dissolved in a formulation buffer with a composition corresponding to the composition of the final formulation (specified in Example 9 to Example 15) to a nominal concentration of 20-50% above the target peptide concentration and pH was adjusted to target using 0.2 N NaOH, or 0.2 N HCl. The actual peptide concentration was determined using CAD (Method

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F, CAD02) and a volume of the same formulation buffer was added to reach a nominal concentration corresponding to the target peptide concentration and pH was adjusted to target using 0.2 N NaOH, or 0.2 N HCl. The actual peptide concentration was determined using CAD (Method F, CAD02). The formulation was sterile filtered (0.22µm), the final peptide concentration was determined using CAD (Method F, CAD02) and the formulation was filled into sterile containers.

Example 1 – Synthesis of CNP compounds

CNP compounds were synthesized and characterized according to the general methods of preparation described above. The exemplified CNP compounds and their constituents are summarised in Table 1. The protractor and linker elements, of Table 1, together form up the modifying group of the CNP compounds.

Table 1: Summary of exemplified compounds Chem. 1-148

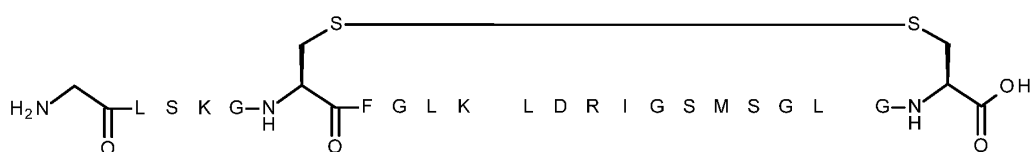
Chem. No.	Compound ID	Protractor (Chem A)	Linker (Chem B-C)	CNP37 sequence modifications	SEQ ID
1	0065			des1-15 (CNP22)	1
2	1510			(CNP37)	2
3	0312	C18d	gGlu-2xOEG	des1-4, 5Q, 13Q, 32Nle	3
4	0776	C18d	gGlu-2xOEG	des1-5, 13Q, 27E, 32L	4
5	1235	C18d	gGlu-2xOEG	des1-8, 9E, 10H, 13Q, 32L	5
6	0262	C18d	6xgGlu	des1-8, 32Nle	6
7	0296	C18d	6xgGlu	des1-4, 15S, 19S, 32Nle	7
8	0313	C18d	5xgGlu	des1-10, 32Nle	8
9	0334	C18d	5xgGlu	des1-10, 13Q, 32Nle	9
10	1221	C18d	gGlu-2xOEG	des1-8, 10E, 13Q, 32L	10
11	1222	C18d	gGlu-2xOEG	des1-8, 9E, 10E, 13Q, 32L	11
12	1223	C18d	gGlu-2xOEG	des1-8, 10E, 13Q, 14E, 32L	12
13	1224	C18d	gGlu-2xOEG	des1-8, 10E, 13Q, 19S, 32L	13
14	1225	C18d	gGlu-2xOEG	des1-8, 10E, 13Q, 25P, 32L	14
15	1226	C18d	gGlu-2xOEG	des1-8, 10E, 13Q, 14E, 25P, 32L	15
16	1227	C18d	gGlu-2xOEG	des1-8, 10E, 13Q, 19S, 25P, 32L	16
17	1228	C18d	gGlu-2xOEG	des1-8, 10E, 13Q, 14E, 19S, 25P, 32L	17
18	1229	C18d	gGlu-2xOEG	des1-8, 9E, 13Q, 14E, 32L	18
19	1230	C18d	gGlu-2xOEG	des1-8, 9E, 13Q, 14E, 19S, 32L	19
20	1231	C18d	gGlu-2xOEG	des1-8, 9E, 10Q, 13Q, 14E, 32L	20
21	1232	C18d	gGlu-2xOEG	des1-8, 13Q, 14E, 32L	21
22	1233	C18d	gGlu-2xOEG	des1-8, 13Q, 19S, 25P, 32L	22
23	1236	C18d	gGlu-2xOEG	des1-8, 9E, 10H, 13Q, 14E, 32L	23
24	1237	C18d	gGlu-2xOEG	des1-8, 10H, 13Q, 14E, 32L	24

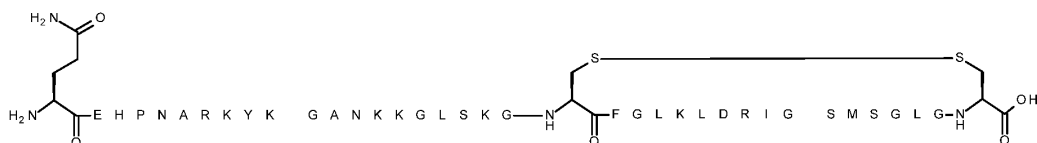
25	1240	C18d	gGlu-2xOEG	des1-8, 10H, 13Q, 14E, 25P, 32L	25
26	1241	C18d	gGlu-2xOEG	des1-8, 10H, 13Q, 19S, 25P, 32L	26
27	1242	C18d	gGlu-2xOEG	des1-8, 10H, 13Q, 14E, 19S, 25P, 32L	27
28	1274	C18d	gGlu-2xOEG	des1-8, 10E, 13E, 19Q, 25P, 32L	28
29	1287	C18d	gGlu-2xOEG	des1-9, 10E, 13Q, 14E, 19S, 25P, 32L	29
30	1288	C18d	gGlu-2xOEG	des1-9, 10E, 13Q, 15E, 19S, 25P, 32L	30
31	1289	C18d	gGlu-2xOEG	des1-8, 10E, 13Q, 15E, 19S, 25P, 32L	31
32	1290	C18d	2xgGlu-2xOEG	des1-8, 10E, 13Q, 19S, 25P, 32L	16
33	1302	C18d	gGlu-2xOEG	des1-8, 10H, 13Q, 15T, 19S, 25P, 32L	32
34	1303	C18d	gGlu-2xOEG	des1-8, 10H, 13Q, 15T, 17V, 19S, 25P, 32L	33
35	1304	C18d	gGlu-2xOEG	des1-8, 10H, 13Q, 14H, 15T, 19S, 25P, 32L	34
36	1305	C18d	gGlu-2xOEG	des1-8, 13Q, 14H, 15T, 19S, 25P, 32L	35
37	1309	C18d	gGlu-2xOEG	des1-8, 9E, 10H, 13Q, 25P, 32L	36
38	1310	C18d	gGlu-2xOEG	des1-8, 9E, 10H, 13Q, 19S, 25P, 32L	37
39	1311	C18d	gGlu-2xOEG	des1-8, 9E, 10H, 13Q, 17V, 19S, 25P, 32L	38
40	1312	C18d	gGlu-2xOEG	des1-8, 9E, 10H, 13Q, 15T, 17V, 19S, 25P, 32L	39
41	1322	C18d	gGlu-2xOEG	des1-8, 10H, 13Q, 14H, 15H, 27E, 32L	40
42	1323	C18d	2xgGlu-2xOEG	des1-8, 10H, 13Q, 14H, 15H, 27E, 32L	40
43	1324	C18d	2xgGlu-2xOEG	des1-8, 13Q, 14H, 15H, 19Q, 27E, 32L	41
44	1338	C18d	gGlu-2xOEG	des1-8, 10E, 13Q, 19S, 25P, 27E, 32L	42
45	1339	C18d	gGlu-2xOEG	des1-9, 10E, 13Q, 19S, 25P, 32L	43
46	1340	C18d	gGlu-2xOEG	des1-8, 13Q, 14H, 15H, 19Q, 32L	44
47	1341	C18d	gGlu-2xOEG	des1-8, 13Q, 14H, 15H, 19Q, 25P, 32L	45
48	1345	C18d	gGlu-2xOEG	des1-8, 10H, 13Q, 14H, 15H, 32L	46
49	1346	C18d	gGlu-2xOEG	des1-8, 10H, 13Q, 14H, 15H, 25P, 32L	47
50	1347	C18d	gGlu-2xOEG	des1-10, 13Q, 19H, 25P, 32L	48
51	1348	C18d	gGlu-2xOEG	des1-10, 13Q, 18H, 19S, 25P, 32L	49
52	1350	C18d	gGlu-2xOEG	des1-5, 10H, 13Q, 14H, 15T, 19S, 25P, 32L	50
53	1351	C18d	gGlu-2xOEG	des1-5, 10H, 13Q, 14H, 15T, 17V, 19S, 25P, 32L	51
54	1352	C18d	gGlu-3xOEG	des1-8, 10H, 13Q, 15T, 17V, 19S, 25P, 32L	33
55	1353	C18d	gGlu-3xOEG	des1-8, 9E, 10H, 13Q, 25P, 32L	36
56	1354	C18d	2xgGlu-2xOEG	des1-5, 10H, 13Q, 15T, 17V, 19S, 25P, 32L	52
57	1355	C18d	gGlu-3xOEG	des1-8, 13Q, 19S, 25P, 32L	22

58	1356	C18d	2xgGlu-3xOEG	des1-8, 13Q, 19S, 25P, 32L	22
59	1357	C18d	2xgGlu-3xOEG	des1-8, 9E, 10H, 13Q, 32L	5
60	1359	C18d	gGlu-2xOEG	des1-5, 9E, 10H, 13Q, 15T, 17V, 19S, 25P, 32L	53
61	1360	C18d	gGlu-2xOEG	des1-5, 9E, 10H, 13Q, 14H, 15T, 17V, 19S, 25P, 32L	54
62	1375	C18d	gGlu-4xOEG	des1-8, 10E, 13Q, 25P, 32L	14
63	1376	C20d	gGlu-2xOEG	des1-8, 10E, 13Q, 25P, 32L	14
64	1377	C18d	gGlu-2xOEG	des1-8, 10E, 13Q, 17G, 25P, 32L	55
65	1378	C18d	gGlu-2xOEG-GGG	des1-8, 10E, 13Q, 19S, 25P, 32L	56
66	1379	C18d	gGlu-2xOEG	5Q, 8S, 10E, 13Q, 19S, 25P, 32L	57
67	1380	C18d	gGlu-2xOEG	5E, 8S, 10E, 13Q, 19S, 25P, 32L	58
68	1381	C18d	gGlu-2xOEG	5Q, 7H, 10H, 13Q, 14H, 15H, 17S, 19Q, 25P, 32L	59
69	1382	C18d	3xgGlu-2xOEG	5Q, 7H, 13Q, 19Q, 25P, 32L	60
70	1383	C18d	2xgGlu-2xOEG	5Q, 7H, 10H, 13Q, 15H, 17S, 19Q, 25P, 32L	61
71	9384	C18d	gGlu-2xOEG-GQAP	des1-10, 13Q, 17S, 19Q, 25P, 32L	62
72	1385	C18d	4xgGlu	des1-5, 10E, 13Q, 25P, 32L	63
73	1386	C18d	4xgGlu	des1-5, 13Q, 19S, 25P, 32L	64
74	1387	C18d	4xgGlu-GGG	des1-8, 13Q, 19S, 25P, 32L	65
75	1388	C18d	4xgGlu-GGG	des1-8, 13Q, 25P, 32L	66
76	1389	C18d	4xgGlu	5Q, 13Q, 19S, 25P, 32L	67
77	1390	C18d	4xgGlu	5Q, 10E, 13Q, 19S, 25P, 32L	68
78	1391	C18d	gGlu-4xOEG	des1-8, 10E, 13Q, 17G, 25P, 32L	55
79	1392	C18d	gGlu-4xOEG	des1-8, 10E, 13Q, 19S, 25P, 32L	16
80	1393	C18d	gGlu-4xOEG	des1-8, 10E, 13Q, 19Q, 25P, 32L	69
81	1394	C18d	gGlu-2xOEG	5Q, 10E, 13Q, 19Q, 25P, 32L	70
82	1395	C18d	gGlu-2xOEG	5Q, 7A, 10E, 13Q, 19Q, 25P, 32L	71
83	1396	C18d	2xgGlu-2xOEG	5Q, 10E, 13Q, 19Q, 25P, 32L	70
84	1398	C18d	4xgGlu-2xOEG	5Q, 8H, 13Q, 17S, 19Q, 25P, 32L	72
85	1399	C20d	4xgGlu-2xOEG	5Q, 8H, 13Q, 17S, 19Q, 25P, 32L	72
86	1400	C18d	4xgGlu-2xOEG	5Q, 7H, 13Q, 17G, 19Q, 25P, 32L	73
87	1401	C18d	8xgGlu-2xOEG	5Q, 13Q, 32L	74
88	1402	C18d	6xgGlu-2xOEG	5Q, 13Q, 19Q, 25P, 32L	75
89	1403	C18d	6xgGlu-2xOEG	5Q, 13Q, 17G, 19Q, 25P, 32L	76
90	1404	C18d	6xgGlu-4xOEG	5Q, 13Q, 19Q, 25P, 32L	75
91	1405	C20d	6xgGlu-2xOEG	5Q, 13Q, 19Q, 25P, 32L	75
92	1406	C18d	5xgGlu-4xOEG	5Q, 13Q, 19Q, 25P, 32L	75
93	9407	C18d	5xgGlu-4xOEG	des1-5, 13Q, 19Q, 25P, 32L	77
94	1419	C18d	2xgGlu-2xOEG	des1-5, 10H, 13Q, 14H, 15T, 17V, 19S, 25P, 32L	51
95	1420	C18d	3xgGlu-2xOEG	des1-5, 10H, 13Q, 14H, 15T, 17V, 25P, 32L	78
96	1421	C18d	3xgGlu-2xOEG	des1-5, 13Q, 15T, 17V, 19S, 25P, 32L	79

97	1422	C18d	3xgGlu-2xOEG	des1-5, 10H, 13Q, 17V, 19S, 25P, 32L	80
98	1423	C18d	3xgGlu-2xOEG	des1-5, 10H, 13Q, 15T, 17V, 25P, 32L	81
99	1424	C18d	4xgGlu-2xOEG	des1-5, 13Q, 15T, 17V, 25P, 32L	82
100	1425	C18d	2xgGlu-4xOEG	des1-8, 10H, 13Q, 15T, 17V, 25P, 32L	83
101	1426	Tetrazole-C18	2xgGlu-2xOEG	des1-5, 10H, 13Q, 15S, 19Q, 25P, 32L	84
102	1431	C18d	gGlu-4xOEG	des1-8, 10E, 13Q, 17G, 19H, 25P, 32L	85
103	1432	C18d	2xgGlu-4xOEG	des1-5, 10E, 13Q, 14H, 17G, 19Q, 25P, 32L	86
104	1434	C18d	2xgGlu-4xOEG	des1-8, 10H, 13Q, 17G, 19Q, 25P, 32L	87
105	9435	C18d	2xgGlu-4xOEG	des1-8, 13Q, 17G, 19Q, 25P, 32L	88
106	1436	C18d	2xgGlu-4xOEG	des1-8, 13Q, 17V, 19Q, 25P, 32L	89
107	1437	C18d	2xgGlu-4xOEG	des1-8, 10H, 13Q, 17V, 19Q, 25P, 32L	90
108	1448	C18d	4xgGlu	5Q, 10E, 13Q, 25P, 32L	91
109	1449	C18d	3xgGlu-2xOEG	des1-5, 10H, 13Q, 14H, 15T, 17V, 19S, 25P, 32L	51
110	1450	C18d	3xgGlu-2xOEG	des1-5, 10H, 13Q, 15T, 17V, 19S, 25P, 32L	52
111	1451	C18d	3xgGlu-2xOEG	des1-5, 10H, 13Q, 17V, 19S, 25P, 27E, 32L	92
112	1452	C18d	5xgGlu-3xOEG	des1-5, 13Q, 19Q, 25P, 32L	77
113	1453	C18d	5xgGlu-2xOEG	des1-5, 13Q, 19Q, 25P, 32L	77
114	1454	C18d	4xgGlu-4xOEG	des1-5, 13Q, 19Q, 25P, 32L	77
115	1455	C18d	4xgGlu-3xOEG	des1-5, 13Q, 19Q, 25P, 32L	77
116	1456	C18d	4xgGlu-2xOEG	des1-5, 13Q, 19Q, 25P, 32L	77
117	1457	C18d	gGlu-2xOEG-3xGQAP	des1-10, 13Q, 19Q, 25P, 32L	93
118	1458	C18d	gGlu-2xOEG-2xGQAP	des1-10, 13Q, 17S, 19Q, 25P, 32L	94
119	1459	C18d	4xgGlu-2xOEG-GQAP	des1-5, 13Q, 17S, 19Q, 25P, 32L	95
120	1460	C18d	6xgGlu-2xOEG	des1-5, 13Q, 25P, 32L	96
121	1461	C18d	2xgGlu-4xOEG	des1-8, 10H, 13Q, 19Q, 25P, 32L	97
122	1462	C18d	5xgGlu-4xOEG	des1-5, 13Q, 25P, 32L	96
123	1463	C18d	5xgGlu-4xOEG	des1-5, 13Q, 19Q, 32L	98
124	1464	C18d	5xgGlu-4xOEG	des1-5, 19Q, 25P, 32L	99
125	1465	C18d	5xgGlu-4xOEG	des1-5, 13Q, 19Q, 25P	100
126	1470	C18d	5xgGlu-2xOEG	des1-5, 13Q, 25P, 32L	96
127	1471	C18d	5xgGlu-2xOEG	5Q, 13Q, 19Q, 25P, 32L	75
128	1472	C18d	4xgGlu-2xOEG	5Q, 13Q, 19Q, 25P, 32L	75
129	1473	C18d	4xgGlu-2xOEG	5Q, 13Q, 19S, 25P, 32L	67
130	1474	C18d	5xgGlu-2xOEG	5Q, 13Q, 25P, 32L	101
131	1475	C18d	5xGlu-4xOEG	des1-5, 13Q, 19Q, 25P, 32L	77
132	1476	C18d	4x(Glu-Gly)-Glu-2xOEG	des1-5, 13Q, 19Q, 25P, 32L	77

133	1477	C18d	5xgGlu-4xOEG	des1-5, 13Q, 19Q, 25P, 27E, 32L	102
134	1478	C18d	2xgGlu-4xOEG	des1-8, 13Q, 19Q, 25P, 32L	103
135	9480	C18d	3xgGlu-4xOEG	des1-8, 13Q, 19Q, 25P, 32L	103
136	1481	C18d	3xGlu-4xOEG	des1-8, 13Q, 19Q, 25P, 32L	103
137	9482	C18d	5xgGlu	5Q, 13Q, 19S, 25P, 32L	67
138	9483	C18d	4xgGlu	5Q, 13Q, 19S, 25P, 27E, 32L	104
139	1484	C18d	gGlu-2xOEG-GQAP	des1-10, 13Q, 19Q, 25P, 32L	105
140	1486	C18d	gGlu-2xOEG-GQAP	des1-10, 13Q, 17S, 19Q, 25P, 27E, 32L	106
141	1487	C18d	gGlu-2xOEG-3xGQAP	des1-10, 13Q, 19Q, 25P, 32L	107
142	1488	C18d	gGlu-3xGQAP	des1-10, 13Q, 19Q, 25P, 32L	107
143	1489	C18d	2xgGlu-4xOEG	des1-8, 13Q, 17G, 19Q, 25P, 27E, 32L	108
144	1493	C18d	2xgGlu-4xOEG	des1-8, 13Q, 19Q, 25P, 27E, 32L	109
145	1511	C18d	Glu-2xOEG-GQAP	des1-10, 13Q, 17S, 19Q, 25P, 32L	62
146	1512	C18d	2xGlu-4xOEG	des1-8, 13Q, 17G, 19Q, 25P, 32L	88
147	1513	C18d	5xGlu	5Q, 13Q, 19S, 25P, 32L	110
148	1514	C18d	4xGlu	5Q, 13Q, 19S, 25P, 27E, 32L	111
149	1265	C18d	DgGlu-2xOEG	des1-5, 6a, 7r, 8k, 9y, 10k, 12a, 13q, 14k, 15k, 17l, 18s, 19k, 21c, 22f, 24l, 25k, 26l, 27e, 28r, 29i, 31s, 32l, 33s, 35l, 37c	233
150	0106			-2P, -1G	234
151	0089	C18d	gGlu-2xOEG	des1-15	1
152	0230	C18d	gGlu-2xOEG-5xGQAP	des1-15	235
153	0231	C18d	gGlu-8xOEG	des1-15	1

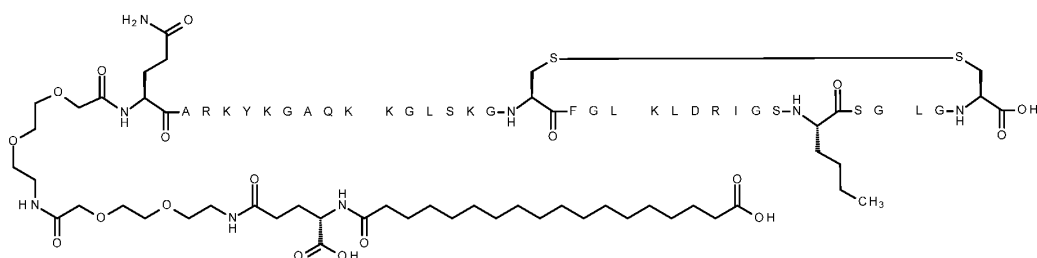
Chem. 1; Compound ID 0065; SEQ ID NO: 1
hCNP22



Molecular weight: 3948.5589. UPLC107UPLC107: m/z calcd: 1317.1863

Chem. 3; Compound ID 0312; SEQ ID NO: 3

5 [N-terminal([2-[2-[2-[[2-[2-[2-[(4S)-4-carboxy-4-(17-
carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acet
yl)], des1-4, 5Q, 13Q, 32Nle)-hCNP37

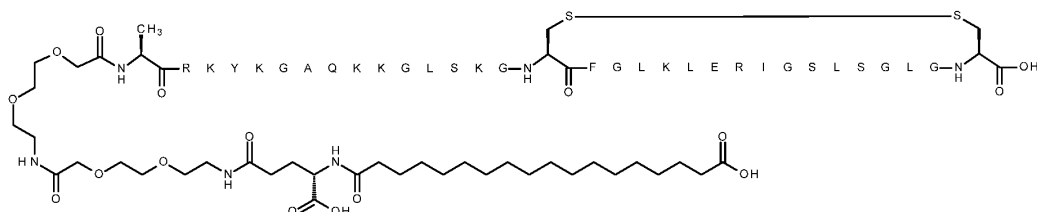


Molecular weight: 4182.9477. LCMS34LCMS34: m/3 calcd: 1395.3159; m/3 found:

10 1395.1200; m/4 calcd: 1046.7369; m/4 found: 1046.600

Chem. 4; Compound ID 0776; SEQ ID NO: 4

[N-terminal([2-[2-[2-[[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-5, 13Q, 27E, 32L)-hCNP37

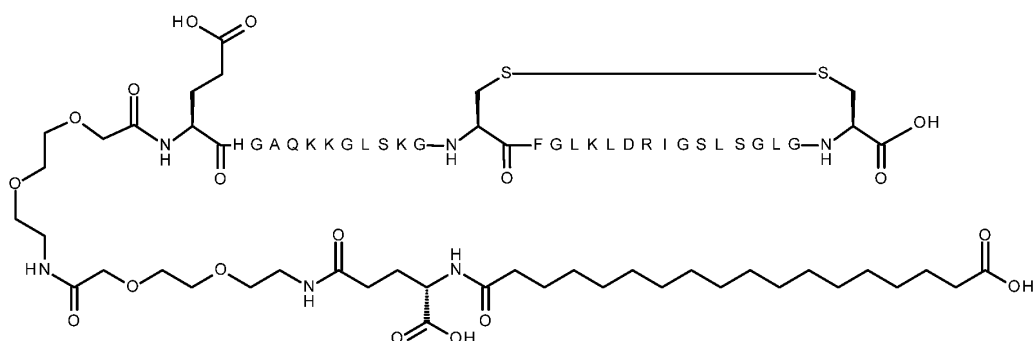


Molecular weight: 4068.8451. LCMS34LCMS34: m/z calcd: 1357.2817; m/z found:

1357.2694; m/z calcd: 1018.2113; m/z found: 1018.2089

20 Chem. 5; Compound ID 1235; SEQ ID NO: 5

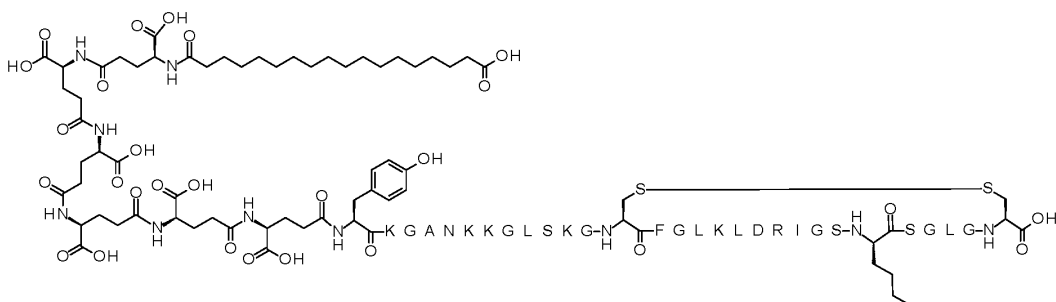
[N-terminal([2-[2-[2-[2-[2-[2-[[[4S]-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 9E, 10H, 13Q, 32L]-hCNP37



Molecular weight: 3674.2904. UPLC107: m/3 calcd: 1225.7635; m/3 found: 1225.5700

Chem. 6; Compound ID 0262; SEQ ID NO: 6

- 5 [N-terminal([(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl)], des1-8, 32Nle]-hCNP37

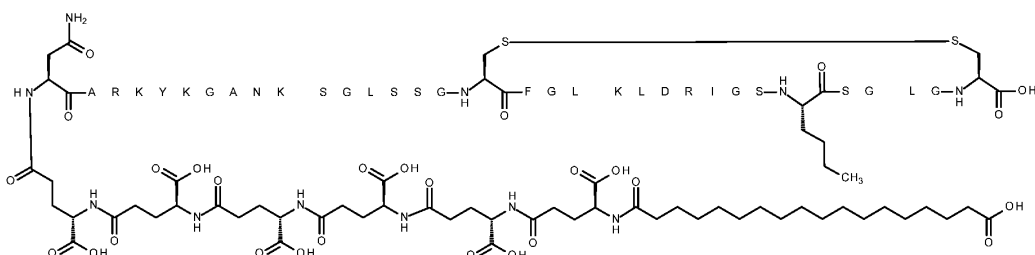


10

Molecular weight: 4040.6131. LCMS34LCMS34: m/3 calcd: 1347.8710; m/3 found: 1347.7200; m/4 calcd: 1011.1533; m/4 found: 1010.7900

Chem. 7; Compound ID 0296; SEQ ID NO: 7

- 15 [N-terminal([(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl)], des1-4, 15S, 19S, 32Nle]-hCNP37

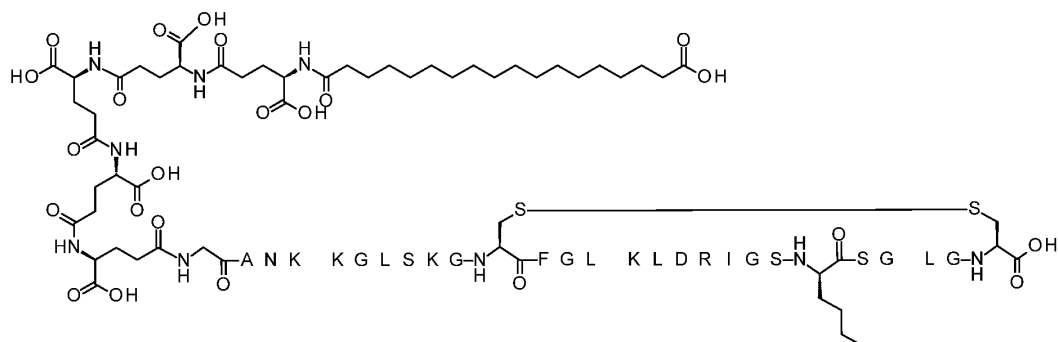


20

Molecular weight: 4427.9616. LCMS34LCMS34: m/3 calcd: 1476.9872; m/3 found: 1476.9200; m/4 calcd: 1107.9904; m/4 found: 1108.1700

Chem. 8; Compound ID 0313; SEQ ID NO: 8

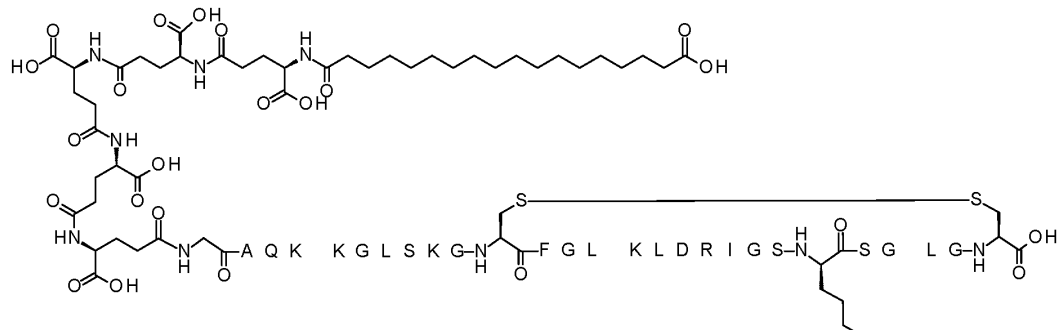
[N-terminal([(4S)-4-carboxy-4-([(4S)-4-carboxy-4-([(4S)-4-carboxy-4-([(4S)-4-carboxy-4-([(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino)butanoyl]amino)butanoyl]amino)butanoyl]amino)butanoyl]amino)butanoyl)], des1-10, 32Nle)-hCNP37



Molecular weight: 3620.1536. LCMS34: m/3 calcd: 1207.7179; m/3 found: 1207.6400; m/4 calcd: 906.0384; m/4 found: 905.9900

Chem. 9; Compound ID 0334; SEQ ID NO: 9

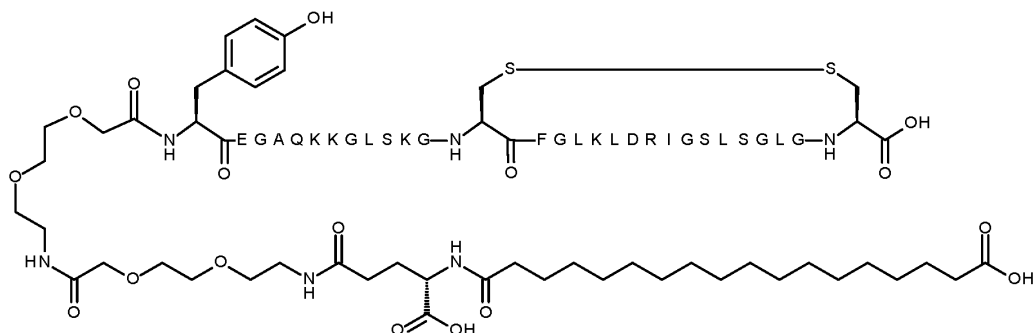
[N-terminal(((4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl)], des1-10, 13Q, 32Nle)-hCNP37



Molecular weight: 3634.1801. LCMS34: m/3 calcd: 1212.3934; m/3 found: 1212.3100; m/4 calcd: 909.5450; m/4 found: 909.2400

Chem. 10; Compound ID 1221; SEQ ID NO: 10

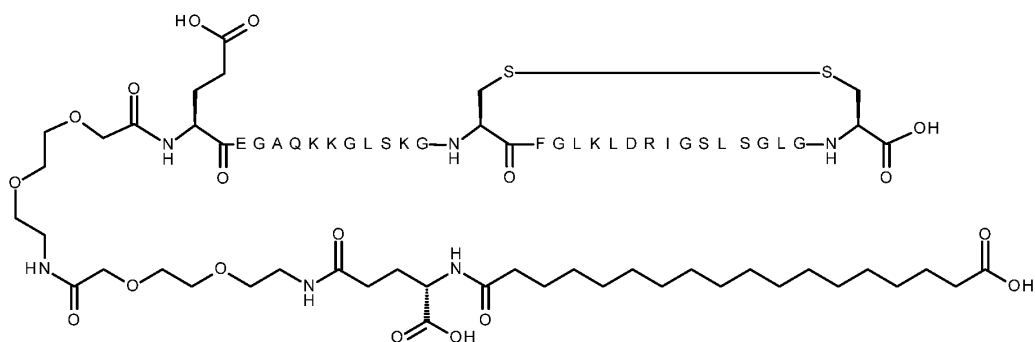
[N-terminal([2-[2-[2-[2-[2-[2-[[[4S]-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 10E, 13Q, 32L]-hCNP37



Molecular weight: 3700.3243. UPLC107: m/3 calcd: 1234.4414; m/3 found: 1234.2700

Chem. 11; Compound ID 1222; SEQ ID NO: 11

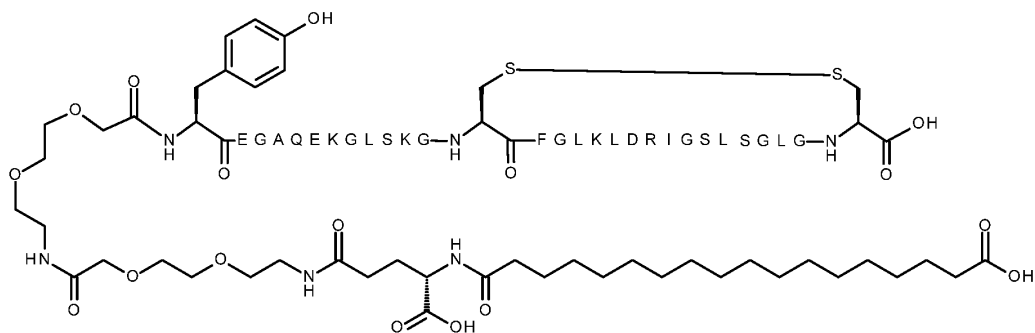
- 5 [N-terminal([2-[2-[2-[[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 9E, 10E, 13Q, 32L]-hCNP37



Molecular weight: 3666.2651. LCMS34: m/3 calcd: 1223.0884; m/3 found: 1222.9000; ;

Chem. 12; Compound ID 1223; SEQ ID NO: 12

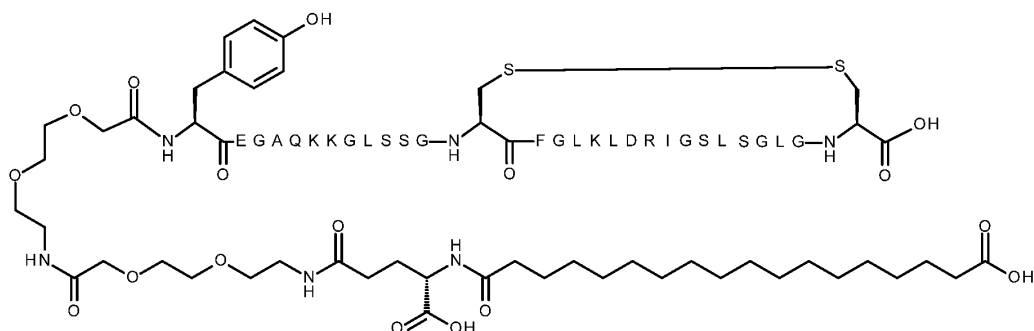
- 10 [N-terminal([2-[2-[2-[[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 10E, 13Q, 14E, 32L]-hCNP37



Molecular weight: 3701.266. LCMS34: m/3 calcd: 1234.7553; m/3 found: 1234.5800; ;

Chem. 13; Compound ID 1224; SEQ ID NO: 13

[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 10E, 13Q, 19S, 32L]-hCNP37

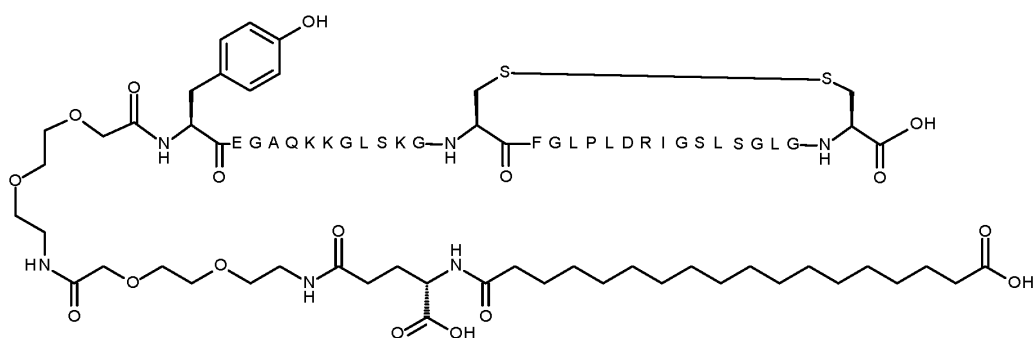


5

Molecular weight: 3659.2294. LCMS34: m/3 calcd: 1220.7431; m/3 found: 1220.3212; m/4 calcd: 915.8074; m/4 found: 915.7400

Chem. 14; Compound ID 1225; SEQ ID NO: 14

10 [N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 10E, 13Q, 25P, 32L]-hCNP37

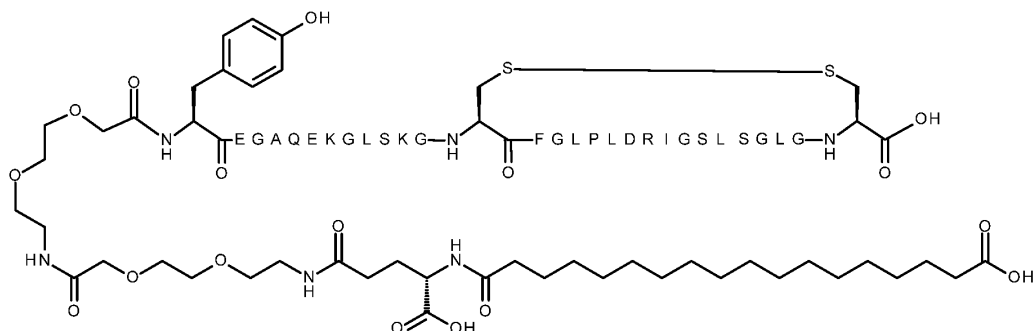


15

Molecular weight: 3669.2672. UPLC107: m/3 calcd: 1224.0891; m/3 found: 1223.9400

Chem. 15; Compound ID 1226; SEQ ID NO: 15

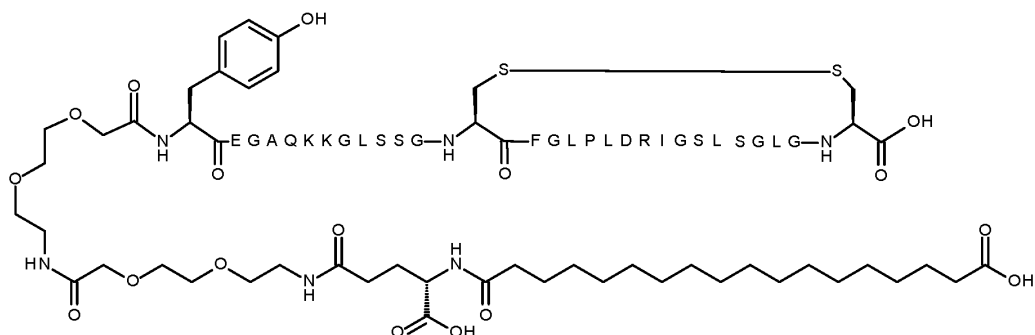
[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 10E, 13Q, 14E, 25P, 32L]-hCNP37



Molecular weight: 3670.2089. UPLC107: m/3 calcd: 1224.4030; m/3 found: 1224.2000

Chem. 16; Compound ID 1227; SEQ ID NO: 16

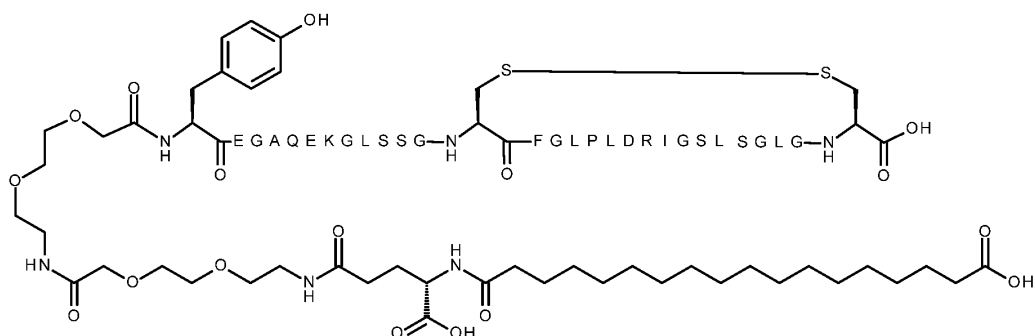
- 5 [N-terminal([2-[2-[2-[[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 10E, 13Q, 19S, 25P, 32L]-hCNP37



- 10 Molecular weight: 3628.1723. LCMS34: m/3 calcd: 1210.3908; m/3 found: 1210.4200; m/4 calcd: 908.0431; m/4 found: 908.0900

Chem. 17; Compound ID 1228; SEQ ID NO: 17

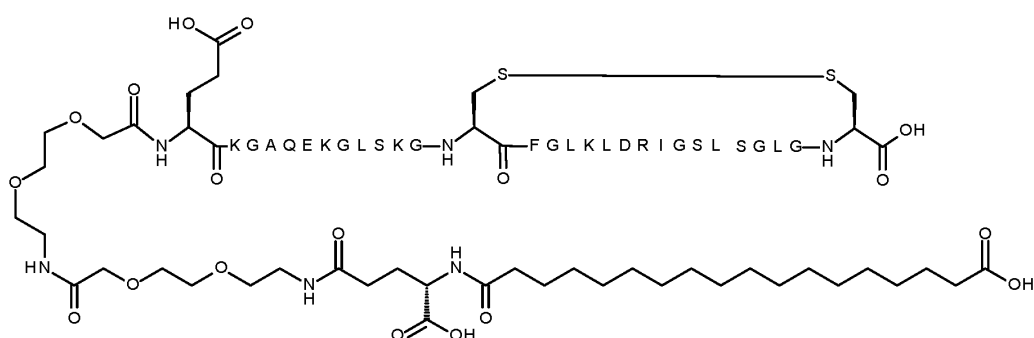
- 15 [N-terminal([2-[2-[2-[[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 10E, 13Q, 14E, 19S, 25P, 32L]-hCNP37



Molecular weight: 3629.114. LCMS34: m/3 calcd: 1210.7047; m/3 found: 1210.5790; m/4 calcd: 908.2785; m/4 found: 908.1400

Chem. 18; Compound ID 1229; SEQ ID NO: 18

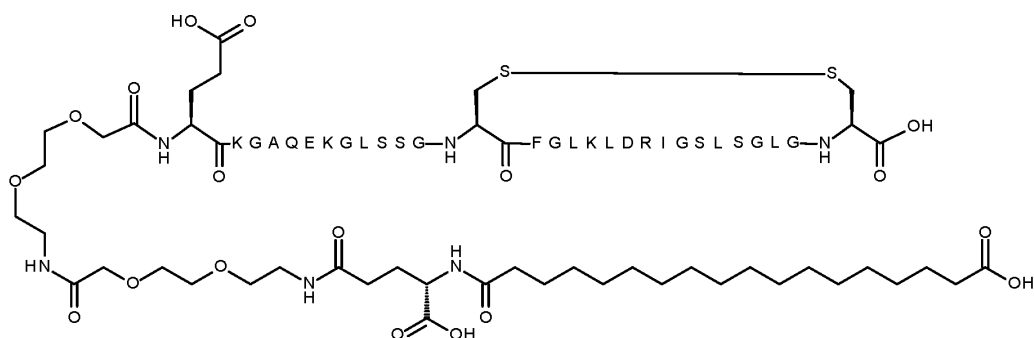
- 5 [N-terminal([2-[2-[2-[[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 9E, 13Q, 14E, 32L]-hCNP37



Molecular weight: 3666.2651. UPLC107: m/3 calcd: 1223.0884; m/3 found: 1222.9300

Chem. 19; Compound ID 1230; SEQ ID NO: 19

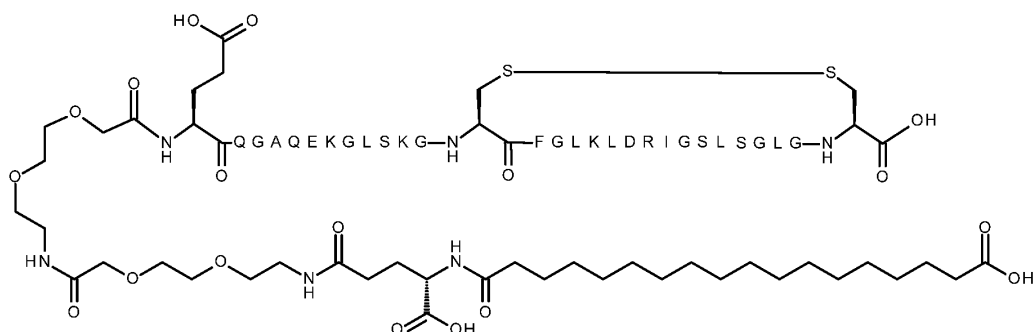
- 10 [N-terminal([2-[2-[2-[[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 9E, 13Q, 14E, 19S, 32L]-hCNP37



Molecular weight: 3625.1701. UPLC107: m/3 calcd: 1209.3900; m/3 found: 1209.2800

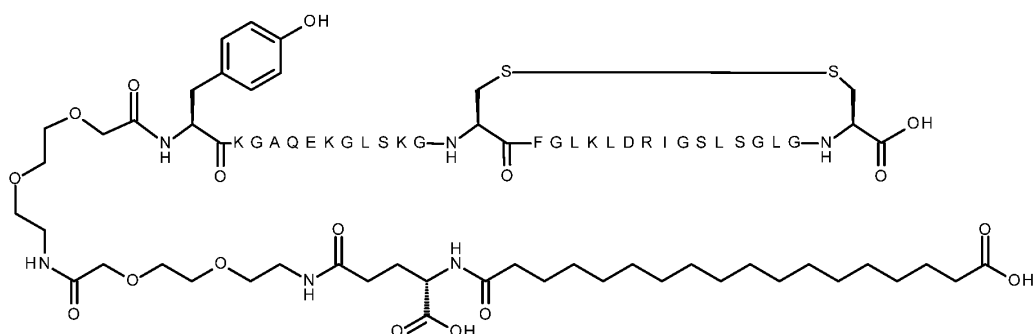
Chem. 20; Compound ID 1231; SEQ ID NO: 20

- 20 [N-terminal([2-[2-[2-[[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 9E, 10Q, 13Q, 14E, 32L]-hCNP37



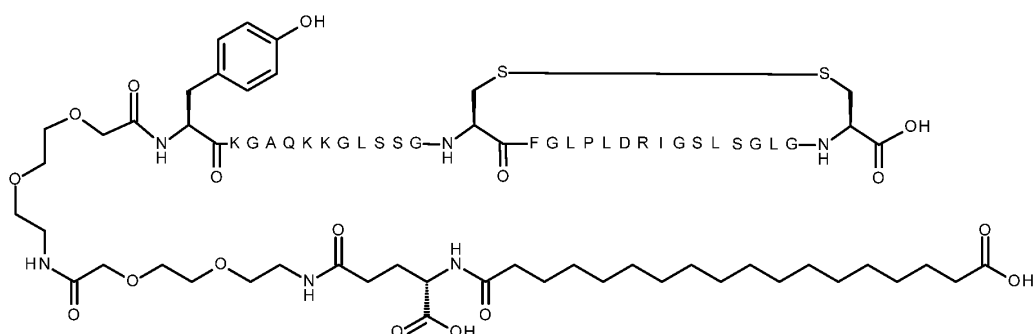
Molecular weight: 3666.222. UPLC107: m/3 calcd: 1223.0740; m/3 found: 1222.9700

- 5 Chem. 21; Compound ID 1232; SEQ ID NO: 21
[N-terminal([2-[2-[2-[[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 13Q, 14E, 32L]-hCNP37



Molecular weight: 3700.3243. UPLC107: m/3 calcd: 1234.4414; m/3 found: 1234.2100

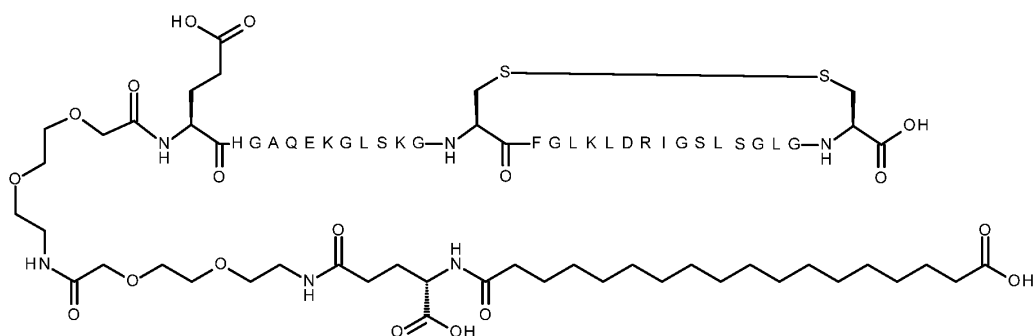
- 10 Chem. 22; Compound ID 1233; SEQ ID NO: 22
[N-terminal([2-[2-[2-[[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 13Q, 19S, 25P, 32L]-hCNP37



- 15 Molecular weight: 3627.2306. UPLC107: m/3 calcd: 1210.0769; m/3 found: 1209.9600

Chem. 23; Compound ID 1236; SEQ ID NO: 23

[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 9E, 10H, 13Q, 14E, 32L]-hCNP37

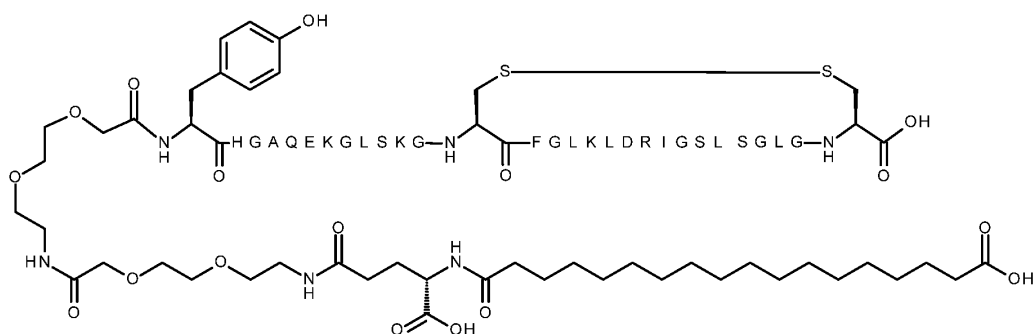


5

Molecular weight: 3675.2321. LCMS34: m/3 calcd: 1226.0774; m/3 found: 1225.8900; ;

Chem. 24; Compound ID 1237; SEQ ID NO: 24

10 [N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 10H, 13Q, 14E, 32L]-hCNP37

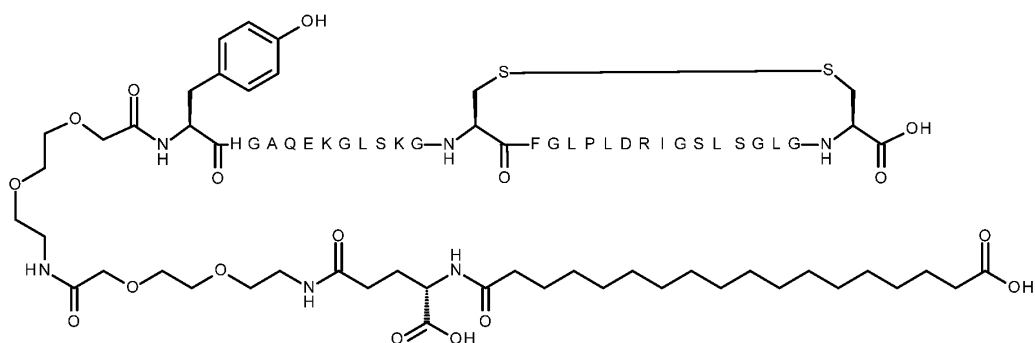


Molecular weight: 3709.2913. UPLC107: m/3 calcd: 1237.4304; m/3 found: 1237.3400

15

Chem. 25; Compound ID 1240; SEQ ID NO: 25

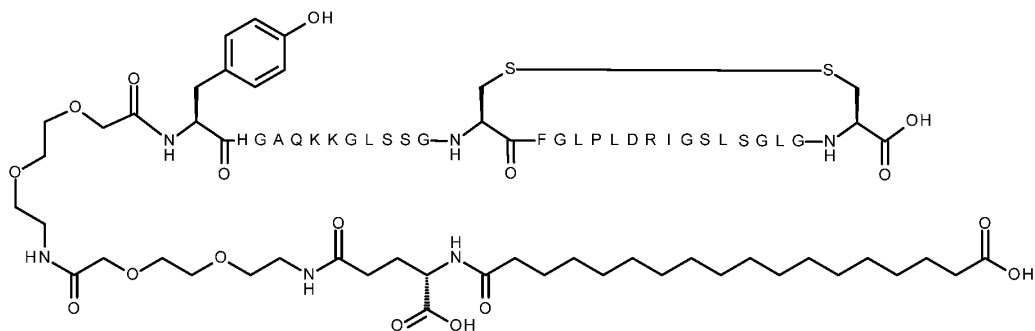
[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 10H, 13Q, 14E, 25P, 32L]-hCNP37



Molecular weight: 3678.2342. UPLC107: m/3 calcd: 1227.0781; m/3 found: 1226.9500

Chem. 26; Compound ID 1241; SEQ ID NO: 26

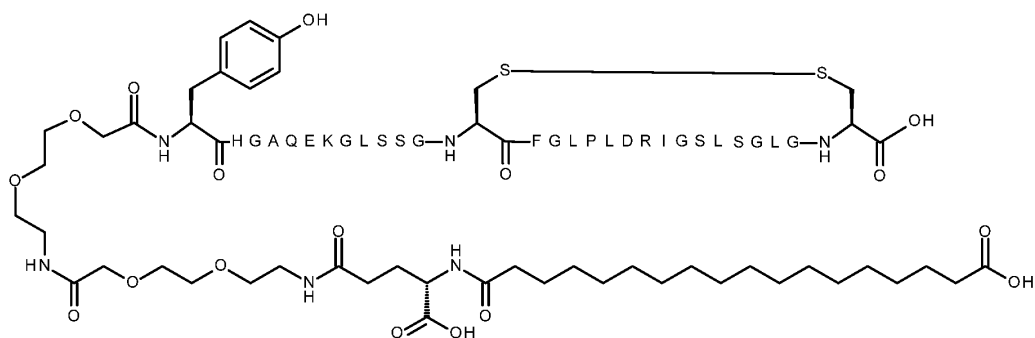
- 5 [N-terminal([2-[2-[2-[[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 10H, 13Q, 19S, 25P, 32L]-hCNP37



10 Molecular weight: 3636.1976. LCMS34: m/3 calcd: 1213.0659; m/3 found: 1213.1011; m/4 calcd: 910.0494; m/4 found: 910.0900

Chem. 27; Compound ID 1242; SEQ ID NO: 27

- 15 [N-terminal([2-[2-[2-[[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 10H, 13Q, 14E, 19S, 25P, 32L]-hCNP37

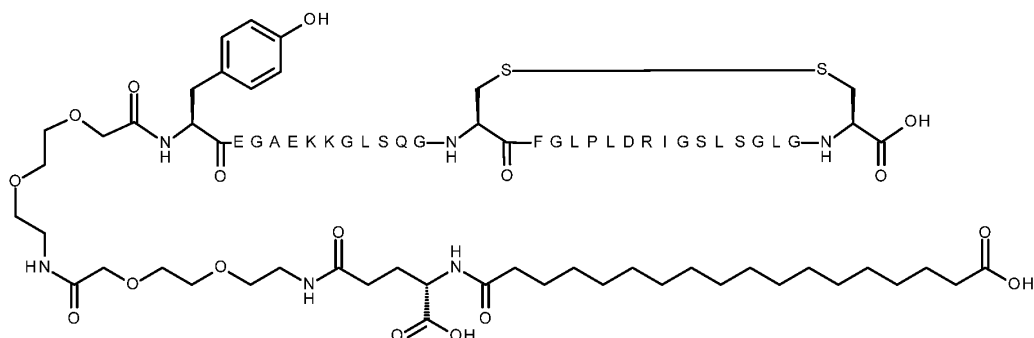


Molecular weight: 3637.1393. UPLC107: m/3 calcd: 1213.3798; m/3 found: 1213.2100

Chem. 28; Compound ID 1274; SEQ ID NO: 28

[N-terminal([2-[2-[2-[[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 10E, 13E, 19Q, 25P, 32L]-hCNP37

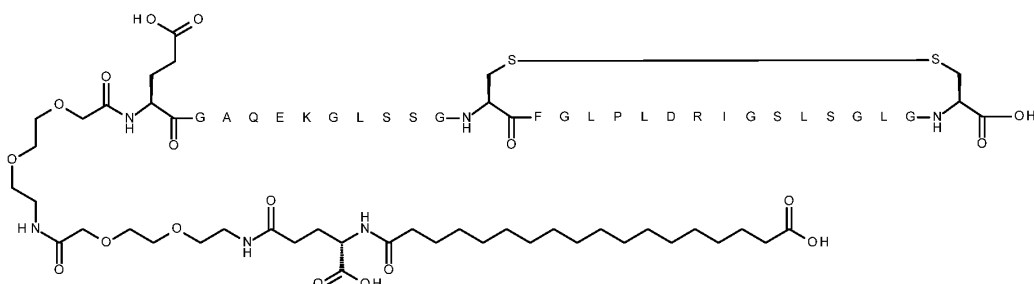
5



Molecular weight: 3670.2089. LCMS34: m/3 calcd: 1224.4030; m/3 found: 1224.3150; m/4 calcd: 918.5522; m/4 found: 918.4840

10 Chem. 29; Compound ID 1287; SEQ ID NO: 29

[N-terminal([2-[2-[2-[[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-9, 10E, 13Q, 14E, 19S, 25P, 32L]-hCNP37

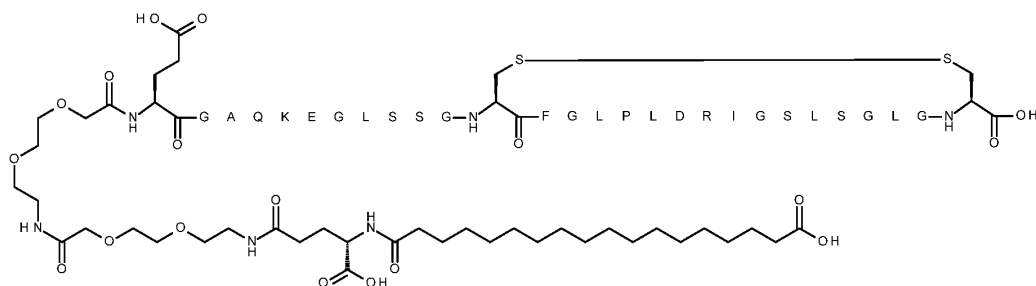


15 Molecular weight: 3465.9407. LCMS34: m/3 calcd: 1156.3136; m/3 found: 1156.5100; m/4 calcd: 867.4852; m/4 found: 867.3800

Chem. 30; Compound ID 1288; SEQ ID NO: 30

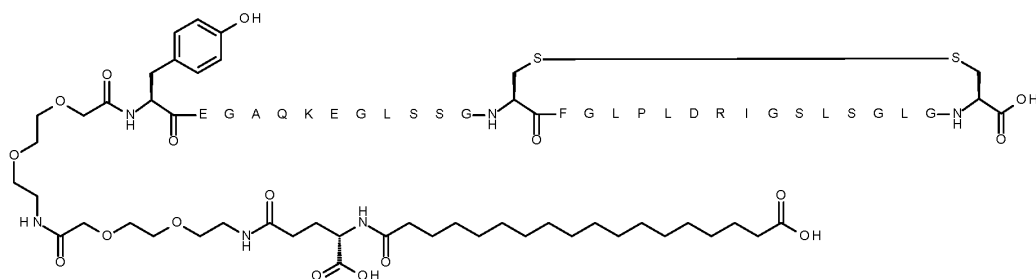
[N-terminal([2-[2-[2-[[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-9, 10E, 13Q, 15E, 19S, 25P, 32L]-hCNP37

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Molecular weight: 3465.9407. LCMS34: m/3 calcd: 1156.3136; m/3 found: 1155.8400; m/4 calcd: 867.4852; m/4 found: 867.3800

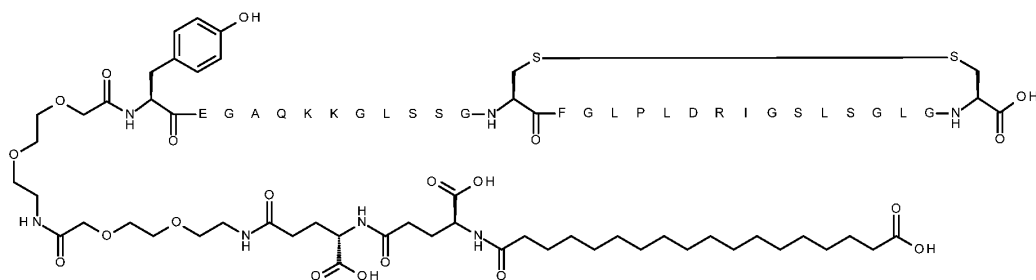
- 5 Chem. 31; Compound ID 1289; SEQ ID NO: 31
[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 10E, 13Q, 15E, 19S, 25P, 32L]-hCNP37



- 10 Molecular weight: 3629.114. LCMS34: m/3 calcd: 1210.7047; m/3 found: 1210.5500; m/4 calcd: 908.2785; m/4 found: 908.1600

Chem. 32; Compound ID 1290; SEQ ID NO: 16

- 15 [N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 10E, 13Q, 19S, 25P, 32L]-hCNP37

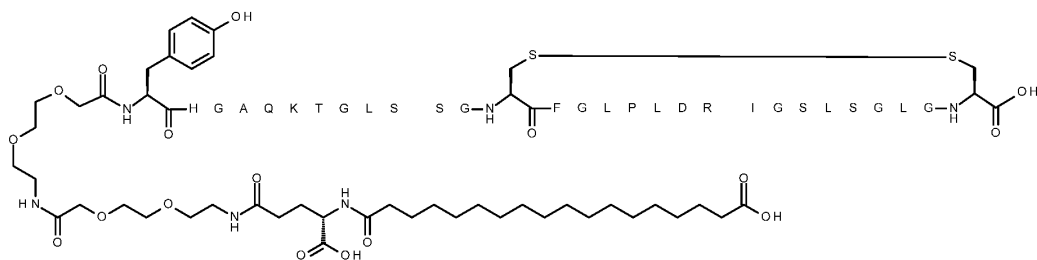


Molecular weight: 3757.2862. LCMS34: m/3 calcd: 1253.4287; m/3 found: 1253.5700; m/4 calcd: 940.3216; m/4 found: 940.1700

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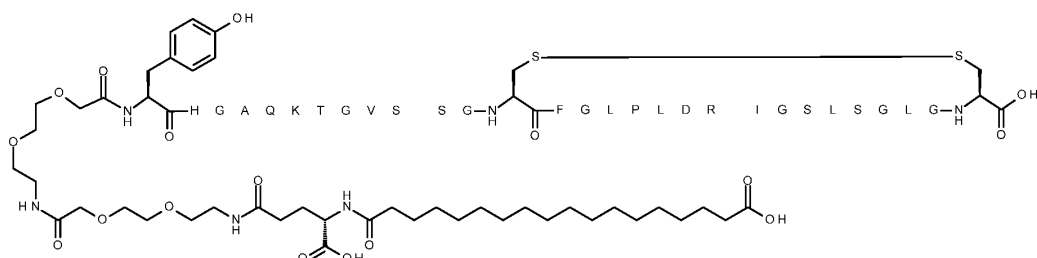
Chem. 33; Compound ID 1302; SEQ ID NO: 32

[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 10H, 13Q, 15T, 19S, 25P, 32L]-hCNP37



Molecular weight: 3609.1292. LCMS34: m/3 calcd: 1204.0431; m/3 found: 1203.7523; m/4 calcd: 903.2823; m/4 found: 903.3355

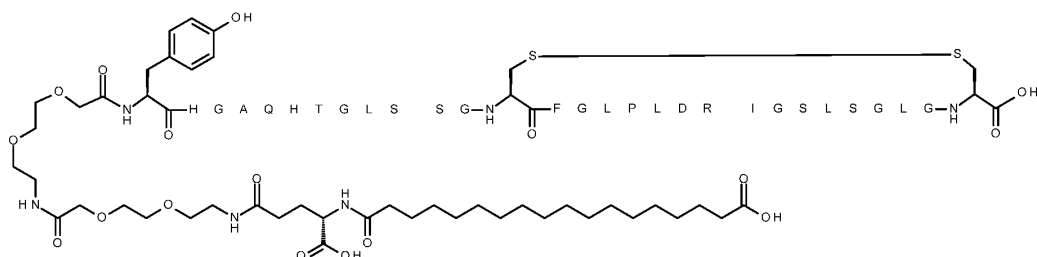
- 5 Chem. 34; Compound ID 1303; SEQ ID NO: 33
[N-terminal([2-[2-[2-[[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 10H, 13Q, 15T, 17V, 19S, 25P, 32L]-hCNP37



- 10 Molecular weight: 3595.1026. LCMS34: m/3 calcd: 1199.3675; m/3 found: 1199.3210; m/4 calcd: 899.7757; m/4 found: 899.7320

Chem. 35; Compound ID 1304; SEQ ID NO: 34

- 15 [N-terminal([2-[2-[2-[[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 10H, 13Q, 14H, 15T, 19S, 25P, 32L]-hCNP37

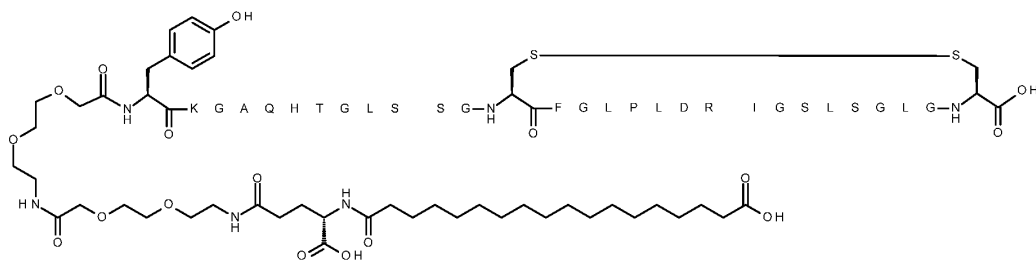


Molecular weight: 3618.0962. LCMS34: m/3 calcd: 1207.0321; m/3 found: 1206.7366; m/4 calcd: 905.5241; m/4 found: 905.5760

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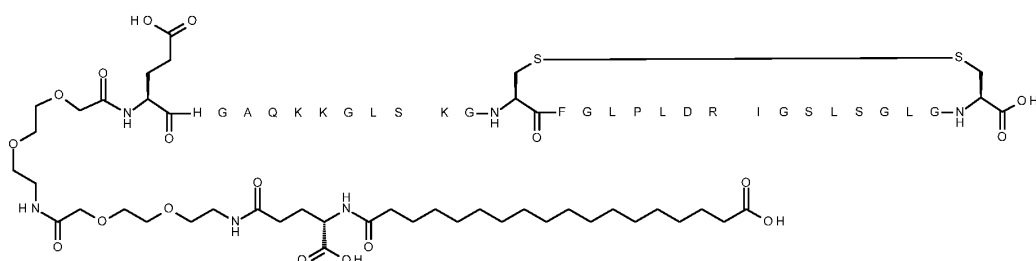
Chem. 36; Compound ID 1305; SEQ ID NO: 35

- [N-terminal([2-[2-[2-[[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 13Q, 14H, 15T, 19S, 25P, 32L]-hCNP37



Molecular weight: 3609.1292. LCMS34: m/3 calcd: 1204.0431; m/3 found: 1204.0040; m/4 calcd: 903.2823; m/4 found: 903.2470

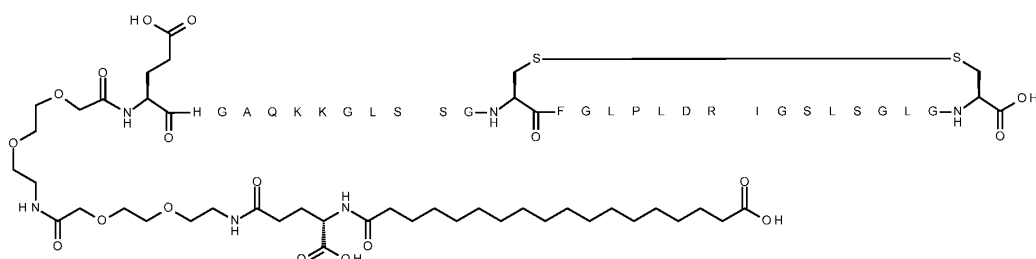
- 5 Chem. 37; Compound ID 1309; SEQ ID NO: 36
[N-terminal([2-[2-[2-[2-[2-[2-[[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 9E, 10H, 13Q, 25P, 32L]-hCNP37



- 10 Molecular weight: 3643.2333. LCMS34: m/3 calcd: 1215.4111; m/3 found: 1215.4546; m/4 calcd: 911.8083; m/4 found: 911.8567

Chem. 38; Compound ID 1310; SEQ ID NO: 37

- 15 [N-terminal([2-[2-[2-[2-[2-[2-[[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 9E, 10H, 13Q, 19S, 25P, 32L]-hCNP37

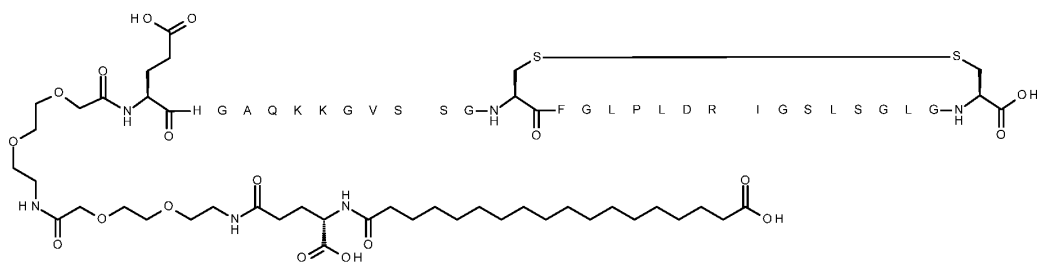


Molecular weight: 3602.1383. LCMS34: m/3 calcd: 1201.7128; m/3 found: 1201.7507; m/4 calcd: 901.5346; m/4 found: 901.5770

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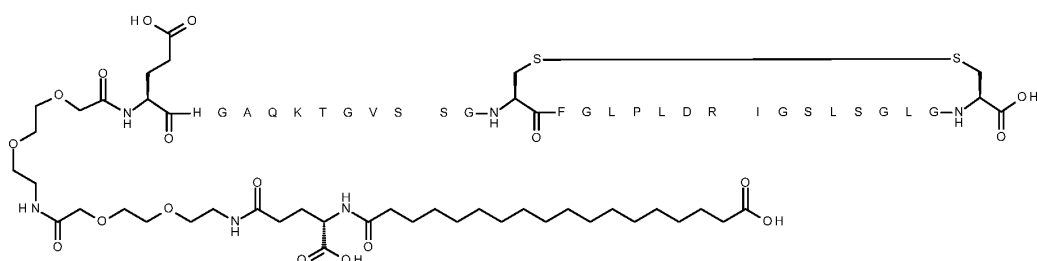
Chem. 39; Compound ID 1311; SEQ ID NO: 38

- [N-terminal([2-[2-[2-[2-[2-[2-[[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 9E, 10H, 13Q, 17V, 19S, 25P, 32L]-hCNP37



Molecular weight: 3588.1117. LCMS34: m/3 calcd: 1197.0372; m/3 found: 1197.0725; m/4 calcd: 898.0279; m/4 found: 898.0776

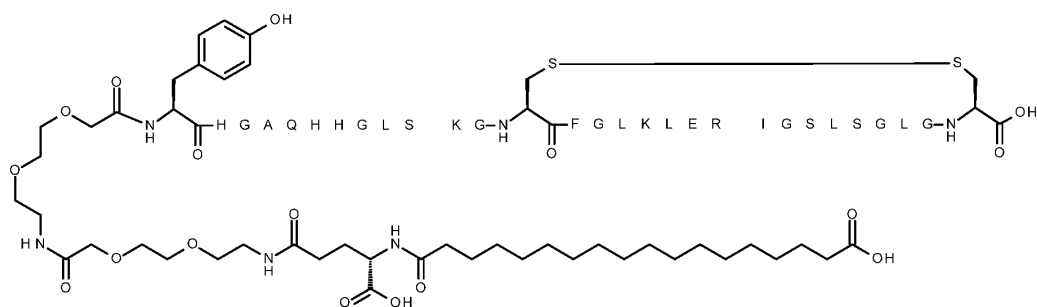
- 5 Chem. 40; Compound ID 1312; SEQ ID NO: 39
[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 9E, 10H, 13Q, 15T, 17V, 19S, 25P, 32L]-hCNP37



- 10 Molecular weight: 3561.0433. LCMS34: m/3 calcd: 1188.0144; m/3 found: 1187.9800; m/4 calcd: 891.2608; m/4 found: 891.2320

Chem. 41; Compound ID 1322; SEQ ID NO: 40

- 15 [N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 10H, 13Q, 14H, 15H, 27E, 32L]-hCNP37

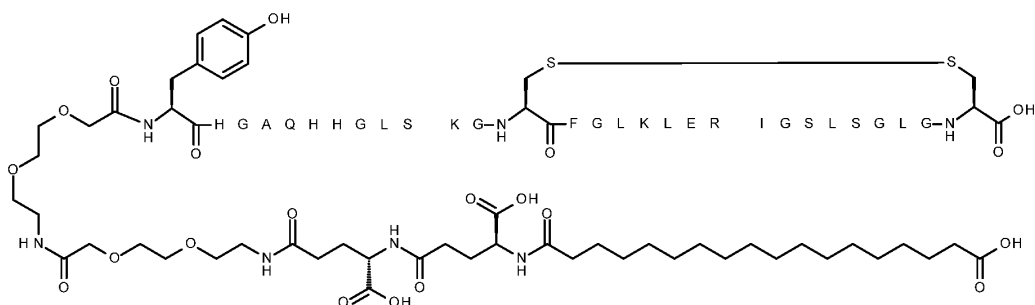


Molecular weight: 3740.3102. LCMS34: m/3 calcd: 1247.7701; m/3 found: 1247.6970; m/4 calcd: 936.0776; m/4 found: 936.0280

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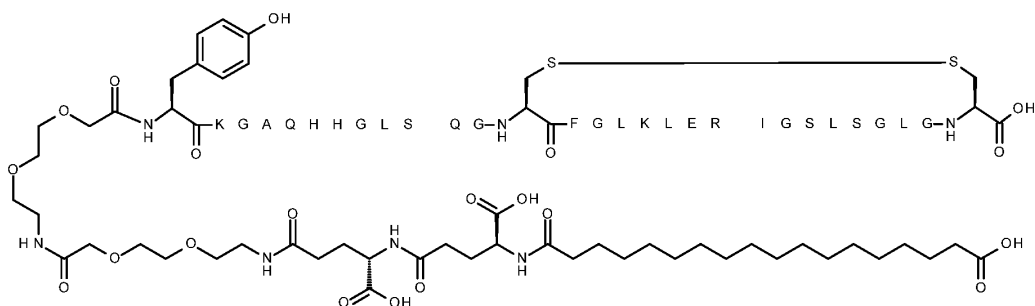
Chem. 42; Compound ID 1323; SEQ ID NO: 40

[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 10H, 13Q, 14H, 15H, 27E, 32L]-hCNP37



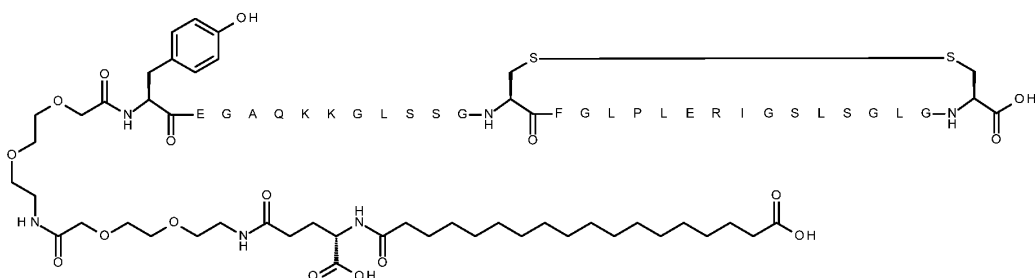
Molecular weight: 3869.4242. LCMS34: m/3 calcd: 1290.8081; m/3 found: 1290.7130; m/4 calcd: 968.3561; m/4 found: 968.2840

- 5 Chem. 43; Compound ID 1324; SEQ ID NO: 41
[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 13Q, 14H, 15H, 19Q, 27E, 32L]-hCNP37



- 10 Molecular weight: 3860.4141. LCMS34: m/3 calcd: 1287.8047; m/3 found: 1287.7150; m/4 calcd: 966.1035; m/4 found: 966.0310

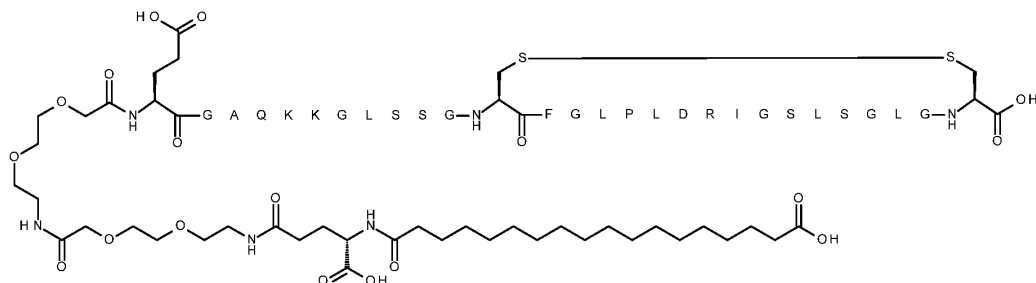
- Chem. 44; Compound ID 1338; SEQ ID NO: 42
15 [N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 10E, 13Q, 19S, 25P, 27E, 32L]-hCNP37



Molecular weight: 3642.1988. LCMS34: m/3 calcd: 1215.0663; m/3 found: 1214.9827; m/4 calcd: 911.5497; m/4 found: 911.2273

- 20 Chem. 45; Compound ID 1339; SEQ ID NO: 43

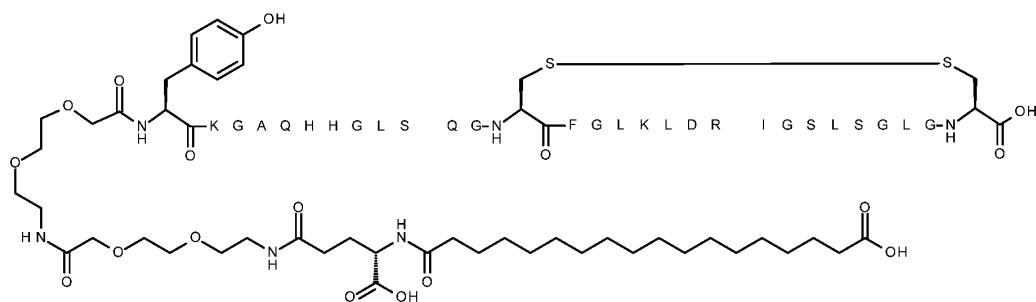
[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-9, 10E, 13Q, 19S, 25P, 32L]-hCNP37



- 5 Molecular weight: 3464.999. LCMS34: m/3 calcd: 1155.9997; m/3 found: 1155.9600; m/4 calcd: 867.2498; m/4 found: 866.9667

Chem. 46; Compound ID 1340; SEQ ID NO: 44

- 10 [N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 13Q, 14H, 15H, 19Q, 32L]-hCNP37

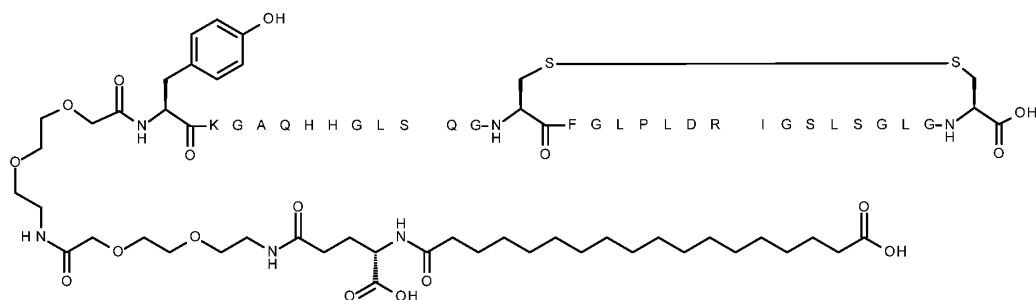


Molecular weight: 3717.2736. LCMS34: m/3 calcd: 1240.0912; m/3 found: 1240.0320; m/4 calcd: 930.3184; m/4 found: 930.2630

15

Chem. 47; Compound ID 1341; SEQ ID NO: 45

[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 13Q, 14H, 15H, 19Q, 25P, 32L]-hCNP37



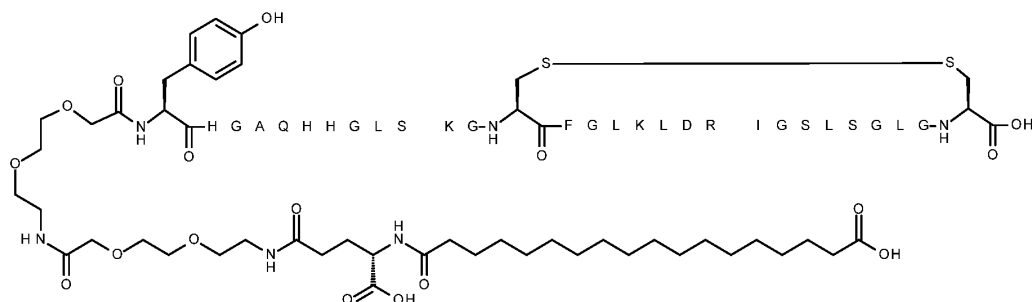
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Molecular weight: 3686.2165. LCMS34: m/3 calcd: 1229.7388; m/3 found: 1229.6760; m/4 calcd: 922.5541; m/4 found: 922.5020

Chem. 48; Compound ID 1345; SEQ ID NO: 46

[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 10H, 13Q, 14H, 15H, 32L]-hCNP37

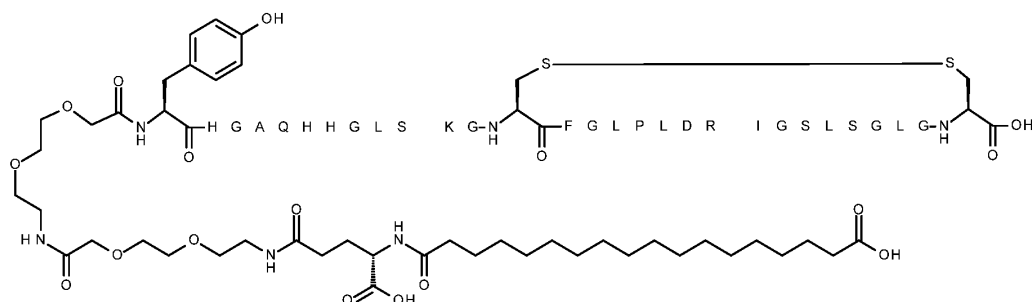
5



Molecular weight: 3726.2836. LCMS34: m/3 calcd: 1243.0945; m/3 found: 1243.0310; m/4 calcd: 932.5709; m/4 found: 932.5240

10 Chem. 49; Compound ID 1346; SEQ ID NO: 47

[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 10H, 13Q, 14H, 15H, 25P, 32L]-hCNP37

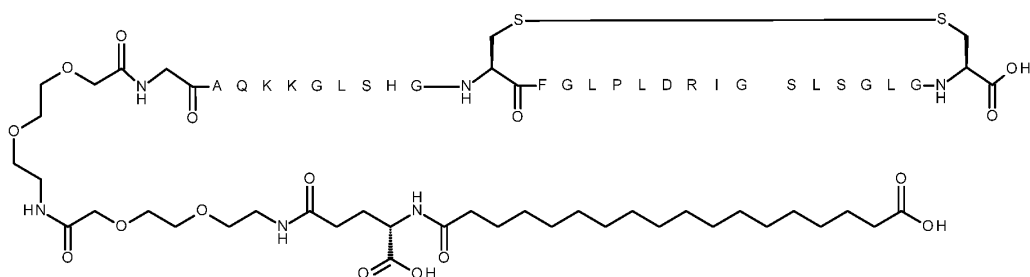


15 Molecular weight: 3695.2265. LCMS34: m/3 calcd: 1232.7422; m/3 found: 1232.6930; m/4 calcd: 924.8066; m/4 found: 924.7340

Chem. 50; Compound ID 1347; SEQ ID NO: 48

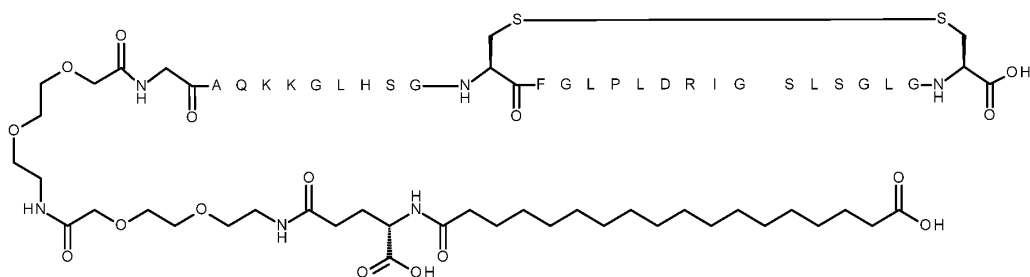
[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-10, 13Q, 19H, 25P, 32L]-hCNP37

20



Molecular weight: 3385.947. LCMS34: m/3 calcd: 1129.6490; m/3 found: 1129.2775; m/4 calcd: 847.4868; m/4 found: 847.2063

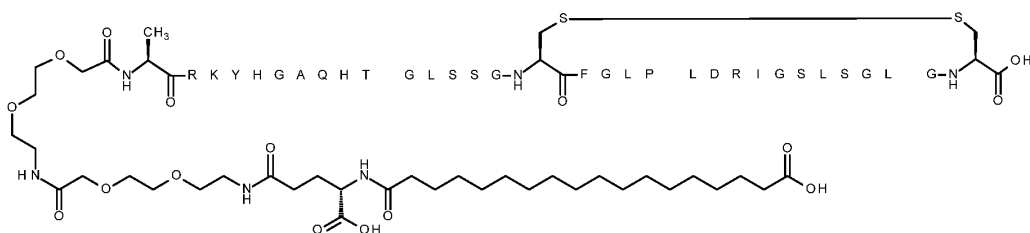
- 5 Chem. 51; Compound ID 1348; SEQ ID NO: 49
[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-10, 13Q, 18H, 19S, 25P, 32L]-hCNP37



- 10 Molecular weight: 3385.947. LCMS34: m/3 calcd: 1129.6490; m/3 found: 1129.2775; m/4 calcd: 847.4868; m/4 found: 847.4684

Chem. 52; Compound ID 1350; SEQ ID NO: 50

- 15 [N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-5, 10H, 13Q, 14H, 15T, 19S, 25P, 32L]-hCNP37

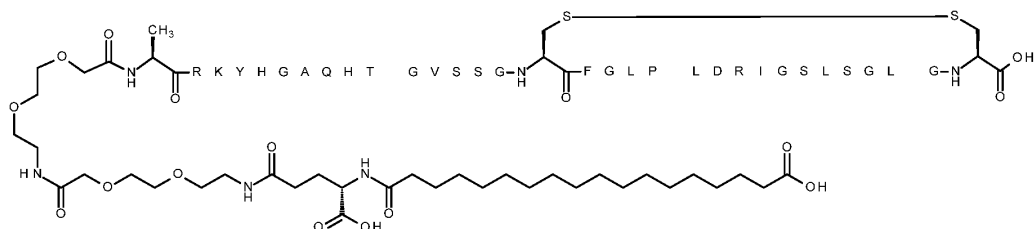


Molecular weight: 3973.532. LCMS34: m/3 calcd: 1325.5107; m/3 found: 1325.3463; m/4 calcd: 994.3830; m/4 found: 994.2843

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Chem. 53; Compound ID 1351; SEQ ID NO: 51

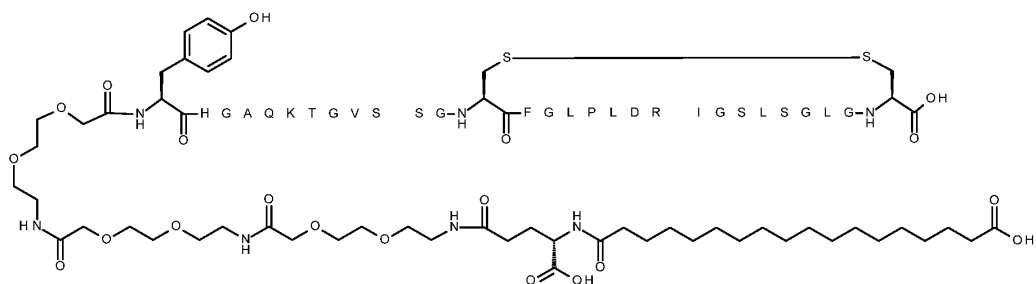
[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-5, 10H, 13Q, 14H, 15T, 17V, 19S, 25P, 32L]-hCNP37



- 5 Molecular weight: 3959.5054. LCMS34: m/3 calcd: 1320.8351; m/3 found: 1320.6271; m/4 calcd: 990.8764; m/4 found: 990.7383

Chem. 54; Compound ID 1352; SEQ ID NO: 33

- 10 [N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 10H, 13Q, 15T, 17V, 19S, 25P, 32L]-hCNP37

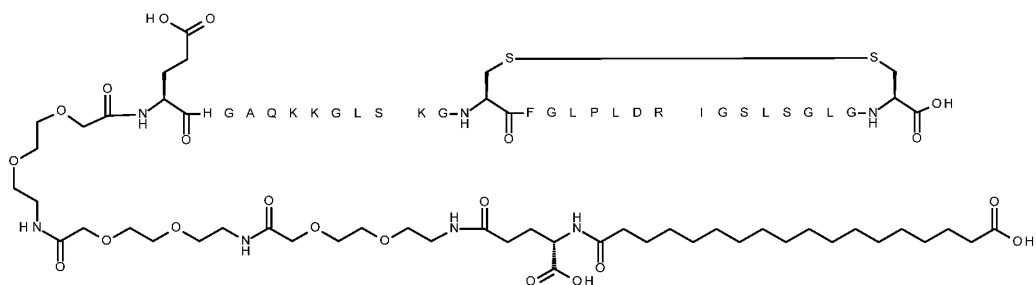


Molecular weight: 3740.259. LCMS34: m/3 calcd: 1247.7530; m/3 found: 1247.3048; m/4 calcd: 936.0648; m/4 found: 935.9911

15

Chem. 55; Compound ID 1353; SEQ ID NO: 36

[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 9E, 10H, 13Q, 25P, 32L]-hCNP37

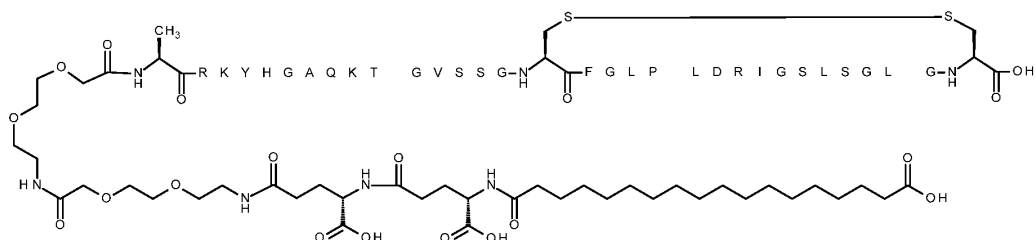


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Molecular weight: 3788.3897. LCMS34: m/3 calcd: 1263.7966; m/3 found: 1263.6780; m/4 calcd: 948.0974; m/4 found: 947.7735

Chem. 56; Compound ID 1354; SEQ ID NO: 52

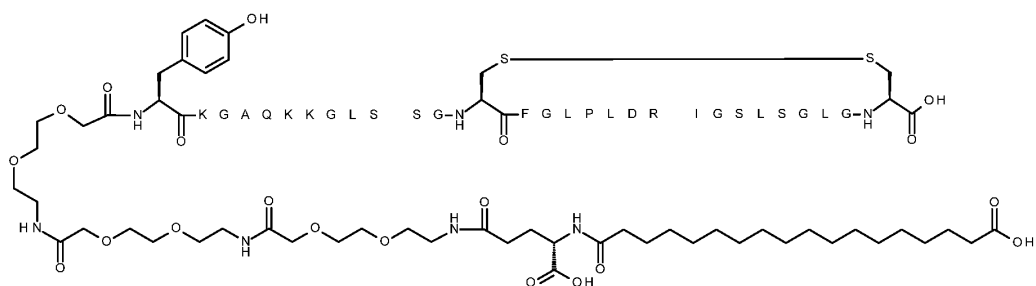
[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-5, 10H, 13Q, 15T, 17V, 19S, 25P, 32L]-hCNP37



- 5 Molecular weight: 4079.6524. LCMS34: m/3 calcd: 1360.8841; m/3 found: 1360.7530; m/4 calcd: 1020.9131; m/4 found: 1020.8160

Chem. 57; Compound ID 1355; SEQ ID NO: 22

- 10 [N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 13Q, 19S, 25P, 32L]-hCNP37

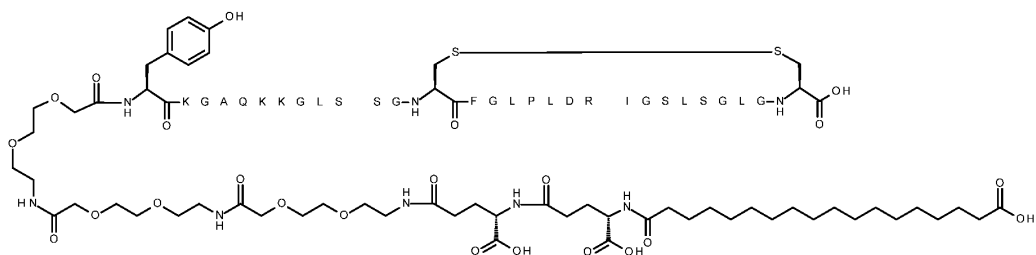


Molecular weight: 3772.387. LCMS34: m/3 calcd: 1258.4623; m/3 found: 1258.3439; m/4 calcd: 944.0968; m/4 found: 944.0223

15

Chem. 58; Compound ID 1356; SEQ ID NO: 22

[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 13Q, 19S, 25P, 32L]-hCNP37

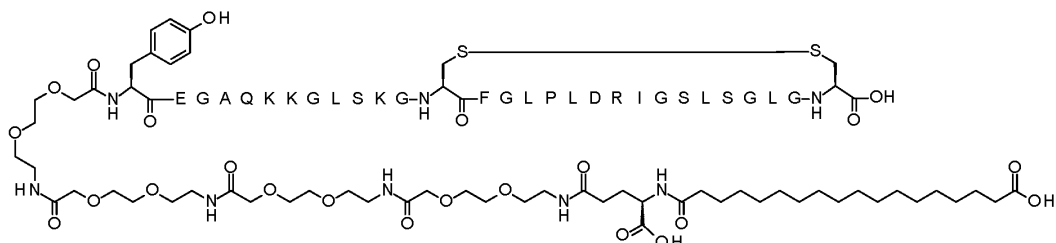


20

Molecular weight: 3901.501. LCMS34: m/3 calcd: 1301.5003; m/3 found: 1301.3470; m/4 calcd: 976.3753; m/4 found: 976.2725

Chem. 59; Compound ID 1357; SEQ ID NO: 5

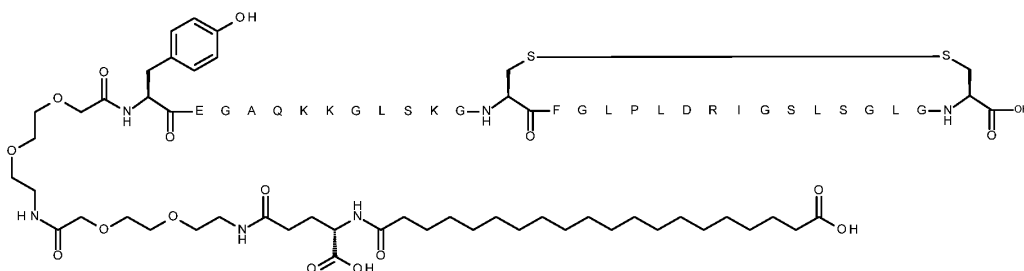
[N-terminal([2-[2-[2-[2-[2-[2-[2-[[[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des-1-8, 10E, 13Q, 25P, 32L]-hCNP37



5 Molecular weight: 3959.5801. LCMS34: m/z calcd: 1320.8600; m/z found: 1320.7200; m/z calcd: 990.8950; m/z found: 990.5400

Chem. 63; Compound ID 1376; SEQ ID NO: 14

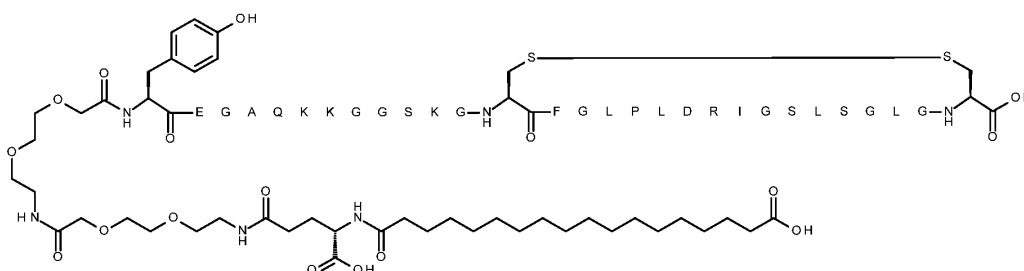
10 [N-terminal([2-[2-[2-[2-[2-[2-[[[4S]-4-carboxy-4-(19-carboxynonadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 10E, 13Q, 25P, 32L)-hCNP37



15 Molecular weight: 3697.3204. LCMS34: m/3 calcd: 1233.4401; m/3 found: 1233.3500; m/4 calcd: 925.3301; m/4 found: 925.2600

Chem. 64; Compound ID 1377; SEQ ID NO: 55

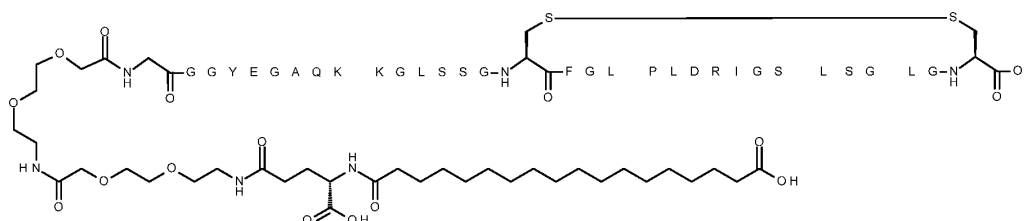
20 [N-terminal([2-[2-[2-[[2-[2-[[[4S]-4-carboxy-4-(17-
carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acet
yl)], des1-8, 10E, 13Q, 17G, 25P, 32L)-hCNP37



Molecular weight: 3613.1609. LCMS34: m/z calcd: 1205.3870; m/z found: 1205.3100; m/z calcd: 904.2902; m/z found: 903.9800

25 Chem. 65; Compound ID 1378; SEQ ID NO: 56

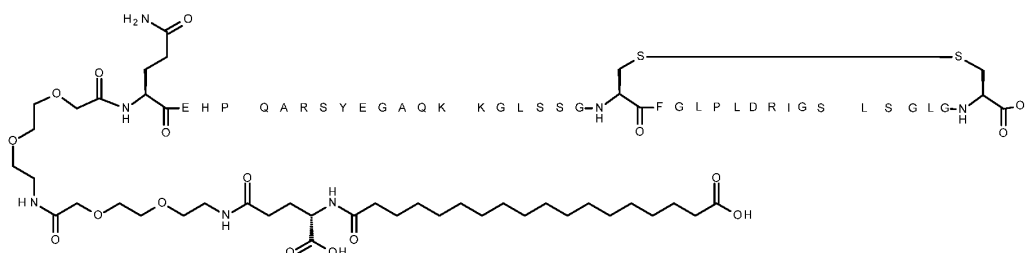
[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-5, 6G, 7G, 8G, 10E, 13Q, 19S, 25P, 32L]-hCNP37



- 5 Molecular weight: 3799.3262. LCMS34: m/3 calcd: 1267.4421; m/3 found: 1267.3470; m/4 calcd: 950.8316; m/4 found: 950.7240

Chem. 66; Compound ID 1379; SEQ ID NO: 57

- 10 [N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], 5Q, 8S, 10E, 13Q, 19S, 25P, 32L]-hCNP37

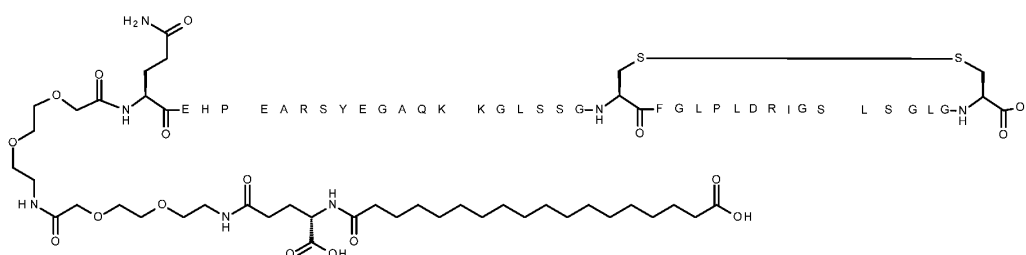


Molecular weight: 4562.14. LCMS34: m/3 calcd: 1521.7133; m/3 found: 1521.3220; m/4 calcd: 1141.5350; m/4 found: 1141.2370

15

Chem. 67; Compound ID 1380; SEQ ID NO: 58

[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], 5E, 8S, 10E, 13Q, 19S, 25P, 32L]-hCNP37

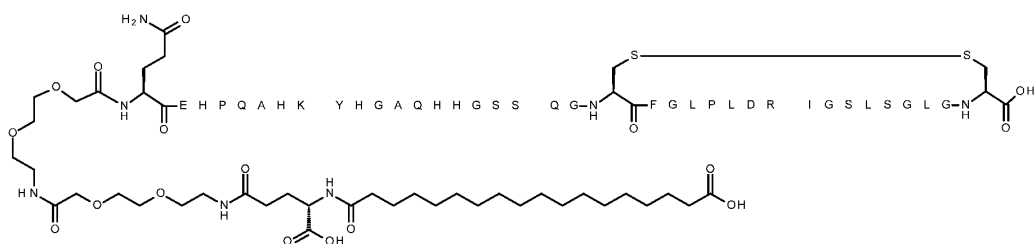


20

Molecular weight: 4563.1248. LCMS34: m/3 calcd: 1522.0416; m/3 found: 1521.8490; m/4 calcd: 1141.7812; m/4 found: 1141.6240

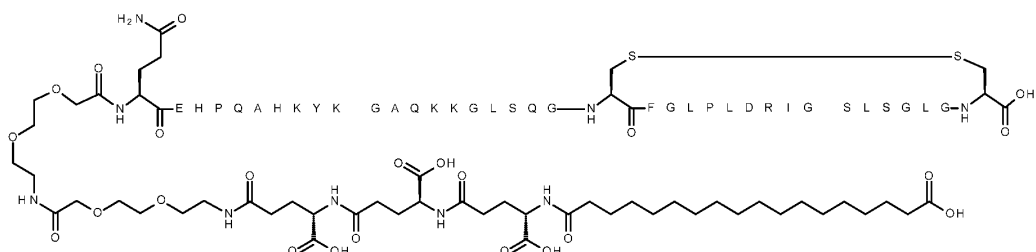
Chem. 68; Compound ID 1381; SEQ ID NO: 59

- 25 [N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], 5Q, 7H, 10H, 13Q, 14H, 15H, 17S, 19Q, 25P, 32L]-hCNP37



Molecular weight: 4625.1195. LCMS34: m/3 calcd: 1542.7065; m/3 found: 1542.3070; m/4 calcd: 1157.2799; m/4 found: 1156.9700

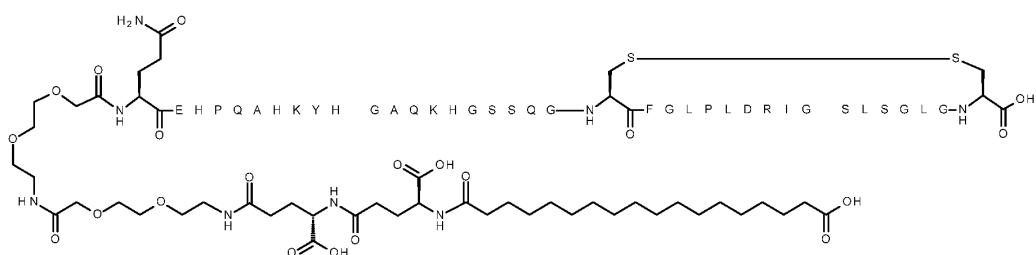
- 5 Chem. 69; Compound ID 1382; SEQ ID NO: 60
[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], 5Q, 7H, 13Q, 19Q, 25P, 32L]-hCNP37



- 10 Molecular weight: 4882.5268. LCMS34: m/3 calcd: 1628.5089; m/3 found: 1628.2280; m/4 calcd: 1221.6317; m/4 found: 1221.2810

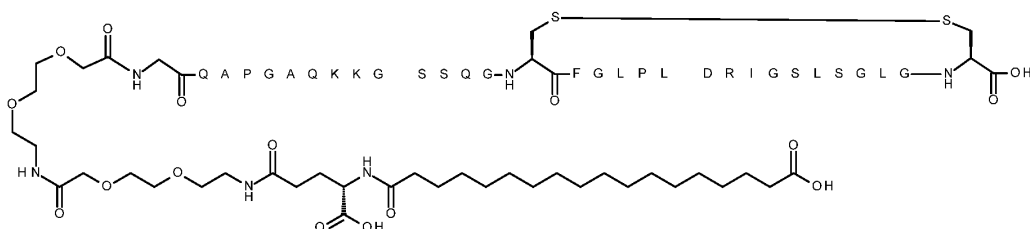
Chem. 70; Compound ID 1383; SEQ ID NO: 61

- 15 [N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], 5Q, 7H, 10H, 13Q, 15H, 17S, 19Q, 25P, 32L]-hCNP37



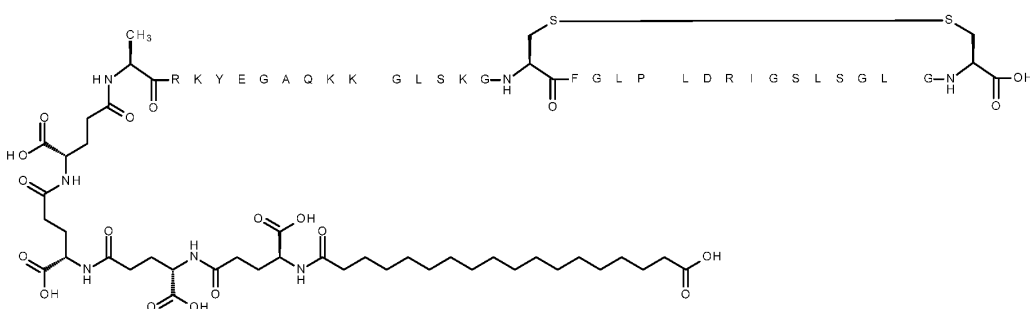
Molecular weight: 4745.2665. LCMS34: m/3 calcd: 1582.7555; m/3 found: 1582.5080; m/4 calcd: 1187.3166; m/4 found: 1186.9970

- 20 Chem. 71; Compound ID 9384; SEQ ID NO: 62
[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-6, 7G, 8Q, 9A, 10P, 13Q, 17S, 19Q, 25P, 32L]-hCNP37



Molecular weight: 3704.2302. LCMS34: m/3 calcd: 1235.7434; m/3 found: 1235.5400; m/4 calcd: 927.0576; m/4 found: 926.9010

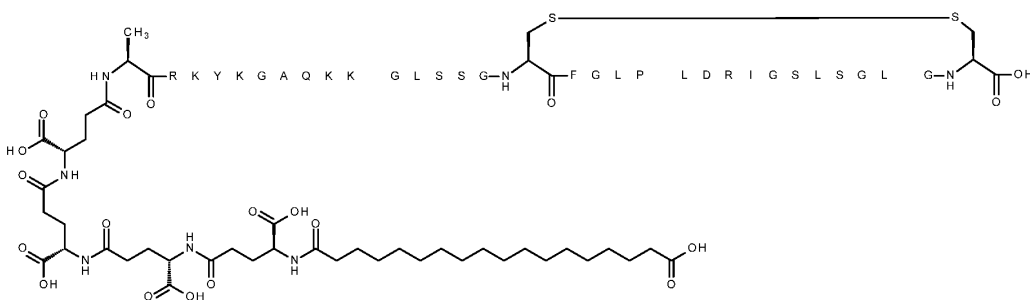
- 5 Chem. 72; Compound ID 1385; SEQ ID NO: 63
[N-terminal([(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(17-
carboxyheptadecanoylamino)butanoyl]amino)butanoyl]amino)butanoyl]amino)butanoyl)],
des1-5, 10E, 13Q, 25P, 32L)-hCNP37



- 10 Molecular weight: 4121.7322. LCMS34: m/3 calcd: 1374.9107; m/3 found: 1374.6120; m/4 calcd: 1031.4331; m/4 found: 1031.2130

Chem. 73; Compound ID 1386; SEQ ID NO: 64

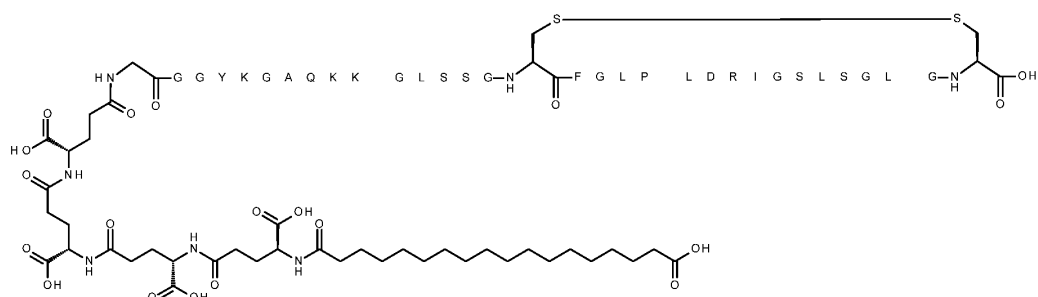
- 15 [N-terminal([(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl)], des1-5, 13Q, 19S, 25P, 32L]-hCNP37



Molecular weight: 4079.6955. LCMS34: m/3 calcd: 1360.8985; m/3 found: 1360.7680; m/4 calcd: 1020.9239; m/4 found: 1020.8160

Chem. 74; Compound ID 1387; SEQ ID NO: 65

[N-terminal([(4S)-4-carboxy-4-([(4S)-4-carboxy-4-([(4S)-4-carboxy-4-([(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino)butanoyl]amino)butanoyl]amino)butanoyl]amino)butanoyl)], des1-5, 6G, 7G, 8G, 13Q, 19S, 25P, 32L]-hCNP37

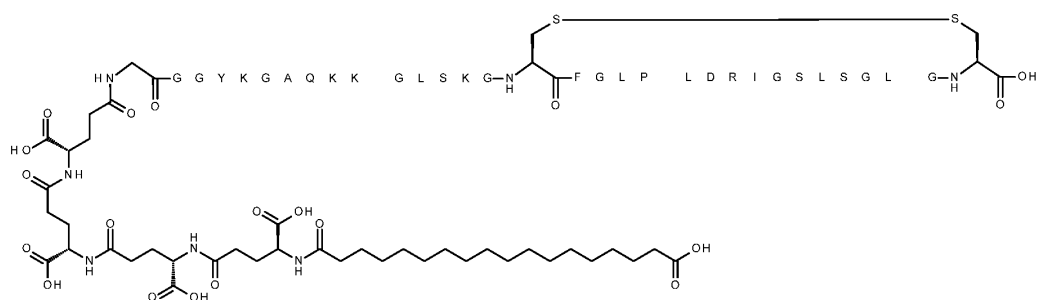


5

Molecular weight: 3895.4136. LCMS34: m/3 calcd: 1299.4712; m/3 found: 1299.3300; m/4 calcd: 974.8534; m/4 found: 974.7500

Chem. 75; Compound ID 1388; SEQ ID NO: 66

10 [N-terminal([(4S)-4-carboxy-4-([(4S)-4-carboxy-4-([(4S)-4-carboxy-4-([(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino)butanoyl]amino)butanoyl]amino)butanoyl]amino)butanoyl)], des1-5, 6G, 7G, 8G, 13Q, 25P, 32L]-hCNP37

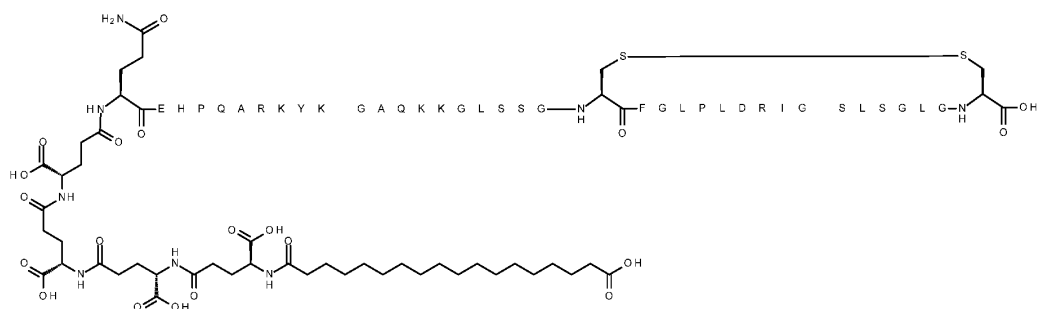


15

Molecular weight: 3936.5086. LCMS34: m/3 calcd: 1313.1695; m/3 found: 1313.0250; m/4 calcd: 985.1272; m/4 found: 985.2870

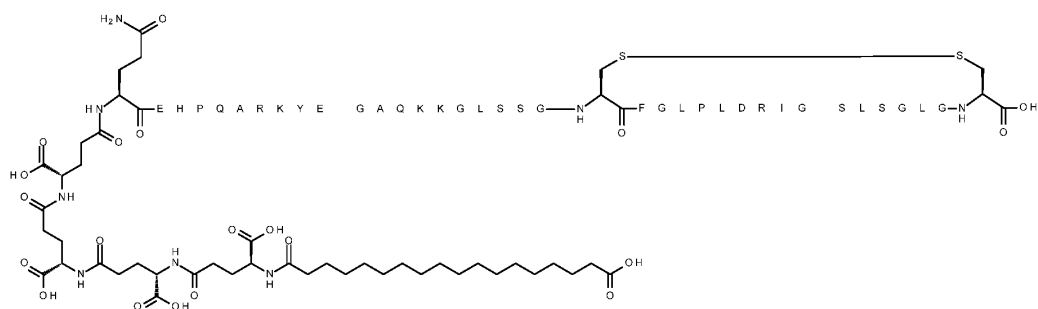
Chem. 76; Compound ID 1389; SEQ ID NO: 67

20 [N-terminal([(4S)-4-carboxy-4-([(4S)-4-carboxy-4-([(4S)-4-carboxy-4-([(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino)butanoyl]amino)butanoyl]amino)butanoyl]amino)butanoyl)], 5Q, 13Q, 19S, 25P, 32L]-hCNP37



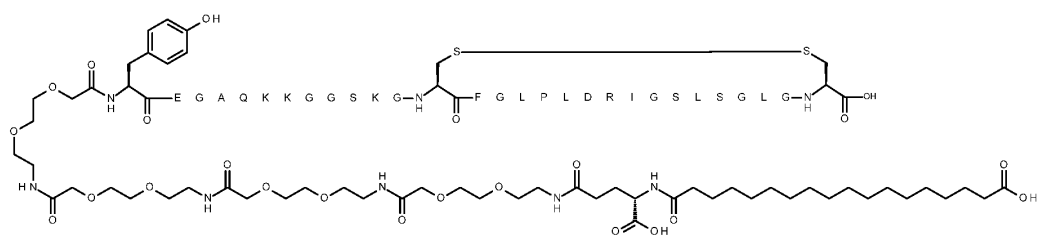
Molecular weight: 4699.3224. LCMS34: m/3 calcd: 1567.4408; m/3 found: 1567.4835; m/4 calcd: 1175.8306; m/4 found: 1176.1075

- 5 Chem. 77; Compound ID 1390; SEQ ID NO: 68
[N-terminal([(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl)], 5Q, 10E, 13Q, 19S, 25P, 32L]-hCNP37



- 10 Molecular weight: 4700.2641. LCMS34: m/3 calcd: 1567.7547; m/3 found: 1567.5480; m/4 calcd: 1176.0660; m/4 found: 1175.8970

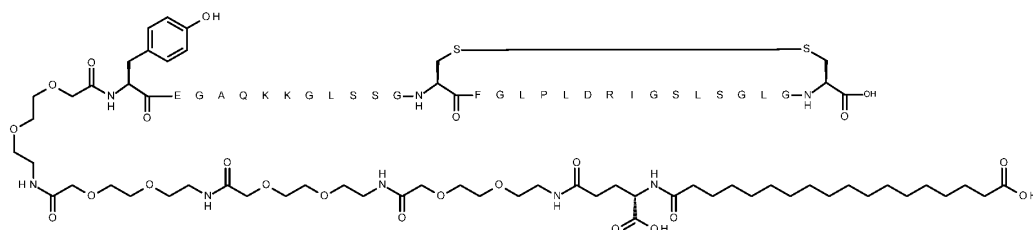
- Chem. 78; Compound ID 1391; SEQ ID NO: 55
15 [N-terminal([2-[2-[2-[2-[2-[2-[2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 10E, 13Q, 17G, 25P, 32L]-hCNP37



- 20 Molecular weight: 3903.4738. LCMS34: m/3 calcd: 1302.1579; m/3 found: 1302.0100; m/4 calcd: 976.8685; m/4 found: 976.5200

Chem. 79; Compound ID 1392; SEQ ID NO: 16
[N-terminal([2-[2-[2-[2-[2-[2-[2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]

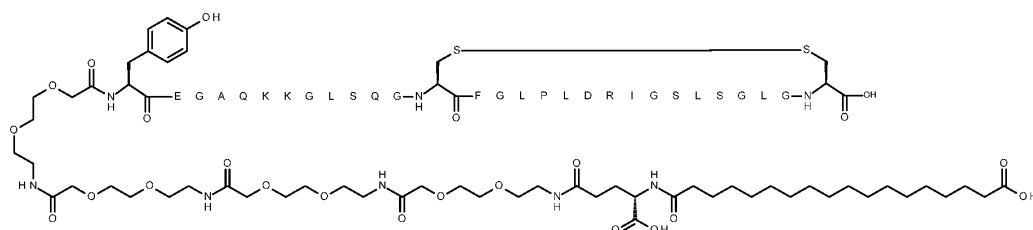
yl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 10E, 13Q, 19S, 25P, 32L]-hCNP37



5 Molecular weight: 3918.4851. LCMS34: m/3 calcd: 1307.1617; m/3 found: 1307.3500; m/4 calcd: 980.6213; m/4 found: 980.5300

Chem. 80; Compound ID 1393; SEQ ID NO: 69

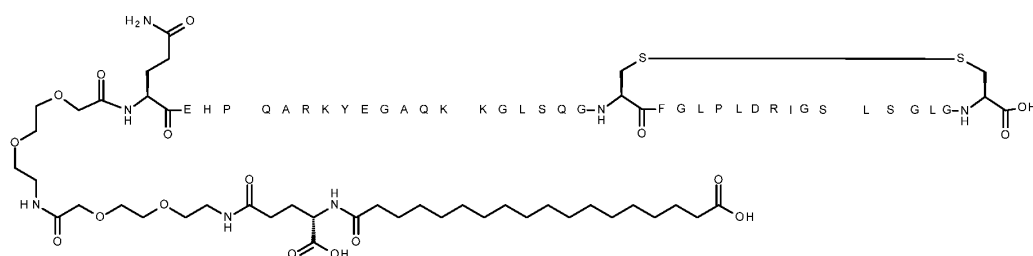
10 [N-terminal([2-[2-[2-[[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 10E, 13Q, 19Q, 25P, 32L]-hCNP37



15 Molecular weight: 3959.5371. LCMS34: m/3 calcd: 1320.8457; m/3 found: 1321.0300; m/4 calcd: 990.8843; m/4 found: 990.7800

Chem. 81; Compound ID 1394; SEQ ID NO: 70

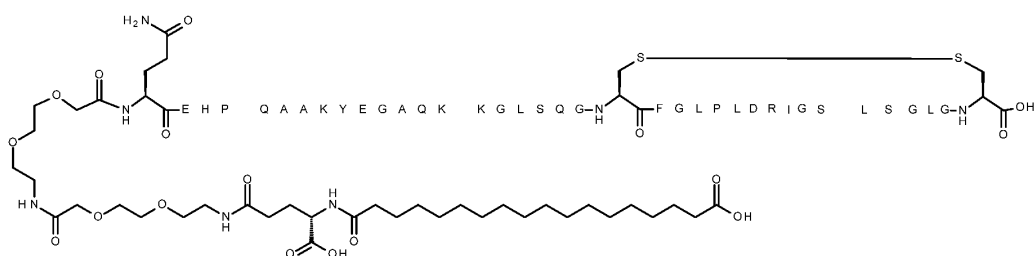
[N-terminal([2-[2-[2-[[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], 5Q, 10E, 13Q, 19Q, 25P, 32L]-hCNP37



20 Molecular weight: 4644.2869. LCMS34: m/3 calcd: 1549.0956; m/3 found: 1548.7900; m/4 calcd: 1162.0717; m/4 found: 1161.8500

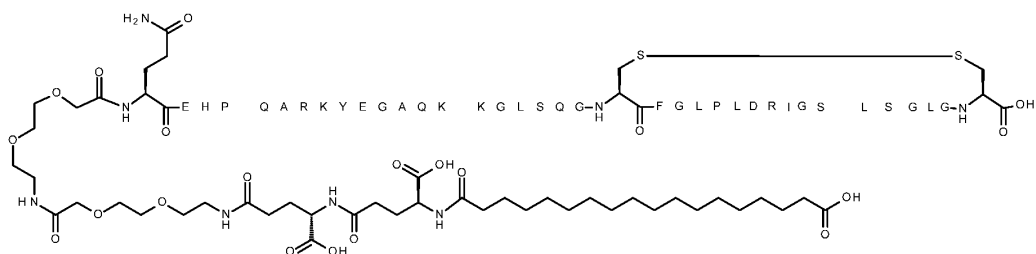
Chem. 82; Compound ID 1395; SEQ ID NO: 71

25 [N-terminal([2-[2-[2-[[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], 5Q, 7A, 10E, 13Q, 19Q, 25P, 32L]-hCNP37



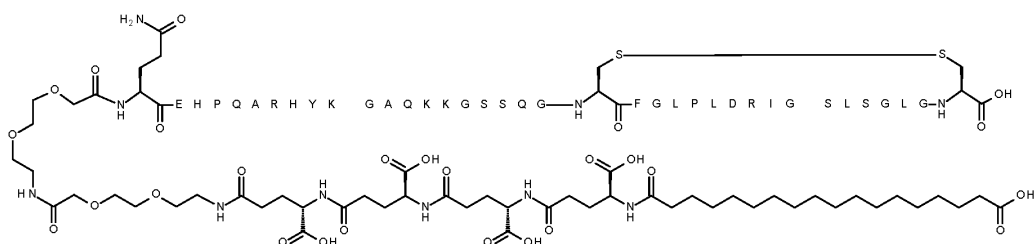
Molecular weight: 4559.1791. LCMS34: m/3 calcd: 1520.7264; m/3 found: 1520.4600; m/4 calcd: 1140.7948; m/4 found: 1140.600

- 5 Chem. 83; Compound ID 1396; SEQ ID NO: 70
[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], 5Q, 10E, 13Q, 19Q, 25P, 32L]-hCNP37



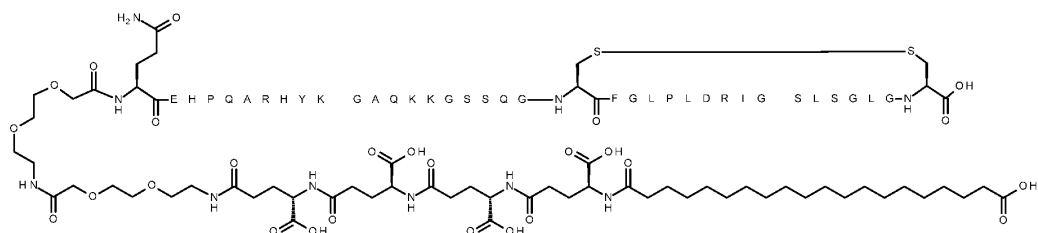
- 10 Molecular weight: 4773.4009. LCMS34: m/3 calcd: 1592.1336; m/3 found: 1592.1600; m/4 calcd: 1194.3502; m/4 found: 1194.3700

- Chem. 84; Compound ID 1398; SEQ ID NO: 72
15 [N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], 5Q, 8H, 13Q, 17S, 19Q, 25P, 32L]-hCNP37



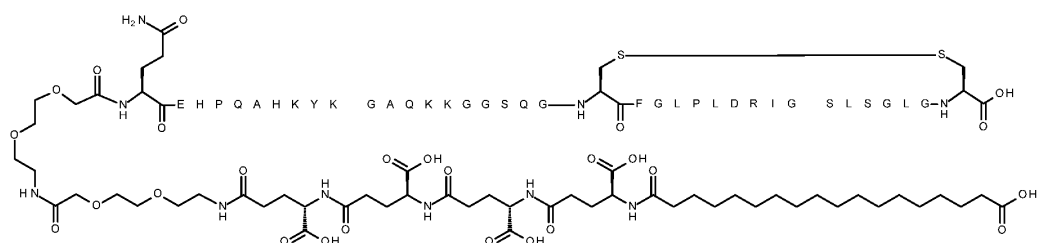
- 20 Molecular weight: 5013.5738. LCMS34: m/3 calcd: 1672.1913; m/3 found: 1672.1528; m/4 calcd: 1254.3935; m/4 found: 1254.1224

- Chem. 85; Compound ID 1399; SEQ ID NO: 72
25 [N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(19-carboxynonadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], 5Q, 8H, 13Q, 17S, 19Q, 25P, 32L]-hCNP37



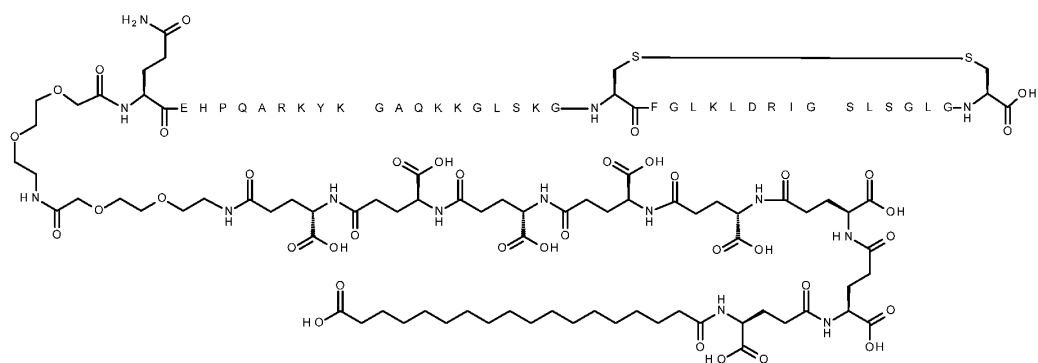
Molecular weight: 5041.627. LCMS34: m/3 calcd: 1681.5423; m/3 found: 1681.5050; m/4 calcd: 1261.4068; m/4 found: 1261.1331

- 5 Chem. 86; Compound ID 1400; SEQ ID NO: 73
[N-terminal([2-[2-[2-[[2-[2-[2-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-[[[(4S)-
4-carboxy-4-(17-
carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino
10]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], 5Q, 7H, 13Q, 17G, 19Q, 25P, 32L]-
hCNP37



Molecular weight: 4955.5344. LCMS34: m/3 calcd: 1652.8448; m/3 found: 1652.8279; m/4 calcd: 1239.8836; m/4 found: 1239.8716

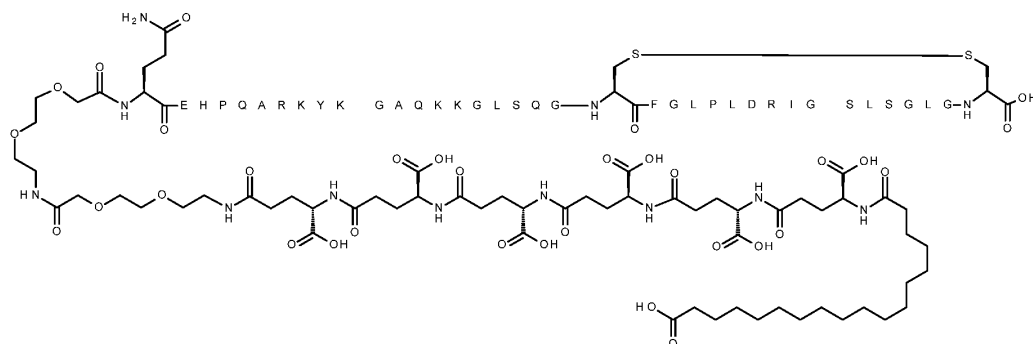
- 15 Chem. 87; Compound ID 1401; SEQ ID NO: 74
[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-
4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(17-
carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]
20 ethoxy]ethoxy]acetyl)], 5Q, 13Q, 32L]-hCNP37



Molecular weight: 5578.2432. LCMS34: m/3 calcd: 1860.4144; m/3 found: 1860.2654; m/4 calcd: 1395.5608; m/4 found: 1395.4623

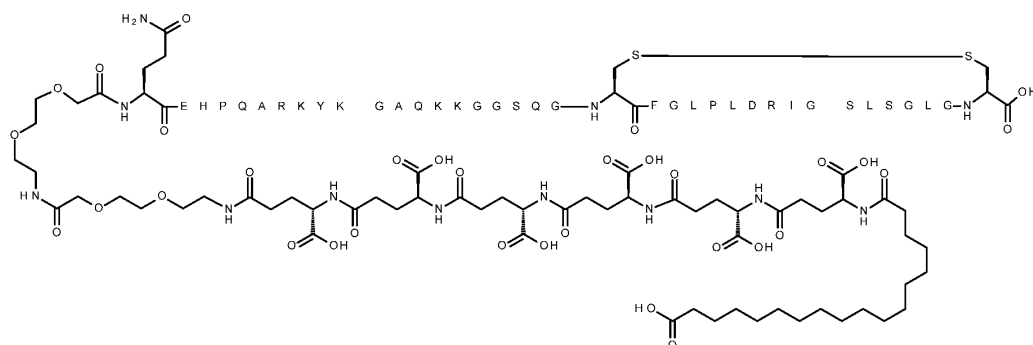
- 25 Chem. 88; Compound ID 1402; SEQ ID NO: 75

- 5 [N-terminal([2-[2-[2-[2-[2-[2-[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], 5Q, 13Q, 19Q, 25P, 32L]-hCNP37



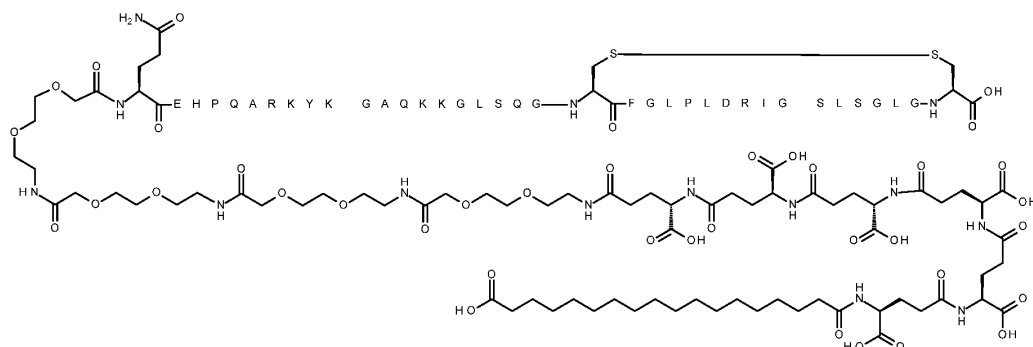
Molecular weight: 5288.9151. LCMS34: m/3 calcd: 1763.9717; m/3 found: 1763.8729; m/4 calcd: 1323.2288; m/4 found: 1323.1718

- 10 Chem. 89; Compound ID 1403; SEQ ID NO: 76
[N-terminal([2-[2-[2-[2-[2-[2-[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], 5Q, 13Q, 17G, 19Q, 25P, 32L]-hCNP37



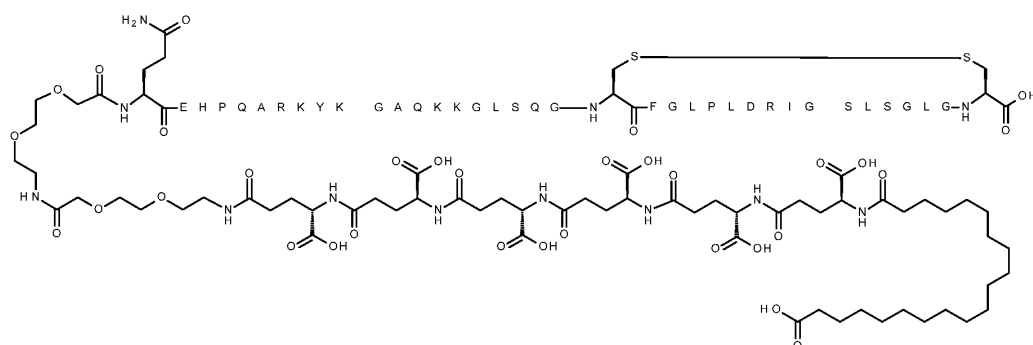
Molecular weight: 5232.8088. LCMS34: m/3 calcd: 1745.2696; m/3 found: 1744.8611; m/4 calcd: 1309.2022; m/4 found: 1309.1547

- 20 Chem. 90; Compound ID 1404; SEQ ID NO: 75
[N-terminal([2-[2-[2-[2-[2-[2-[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], 5Q, 13Q, 19Q, 25P, 32L]-hCNP37



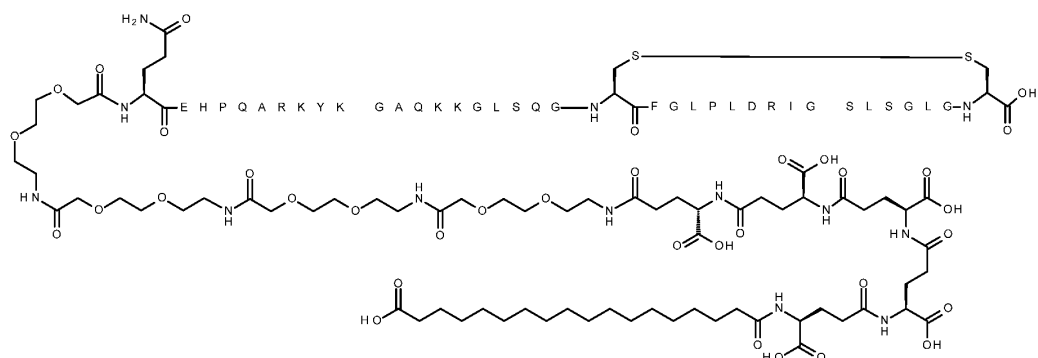
Molecular weight: 5579.228. LCMS34: m/3 calcd: 1860.7427; m/3 found: 1860.6008; m/4 calcd: 1395.8070; m/4 found: 1395.7069

- 5 Chem. 91; Compound ID 1405; SEQ ID NO: 75
[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(19-carboxynonadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], 5Q, 13Q, 19Q, 25P, 32L]-hCNP37



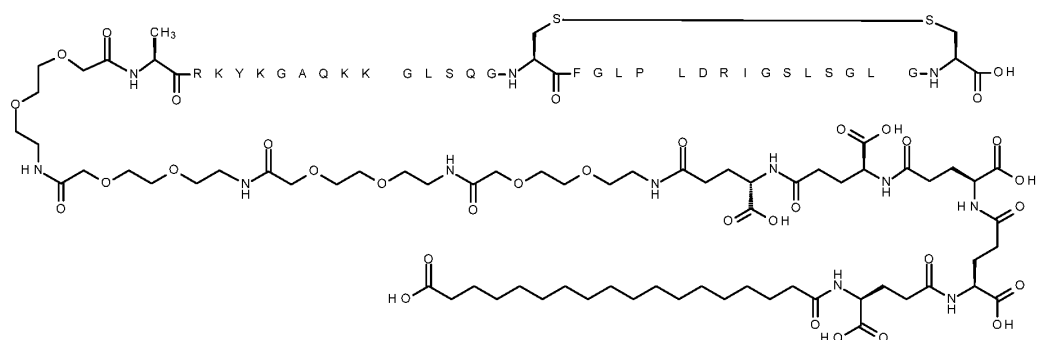
Molecular weight: 5316.9683. LCMS34: m/3 calcd: 1773.3228; m/3 found: 1773.2192; m/4 calcd: 1330.2421; m/4 found: 1330.1785

- 15 Chem. 92; Compound ID 1406; SEQ ID NO: 75
[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], 5Q, 13Q, 19Q, 25P, 32L]-hCNP37



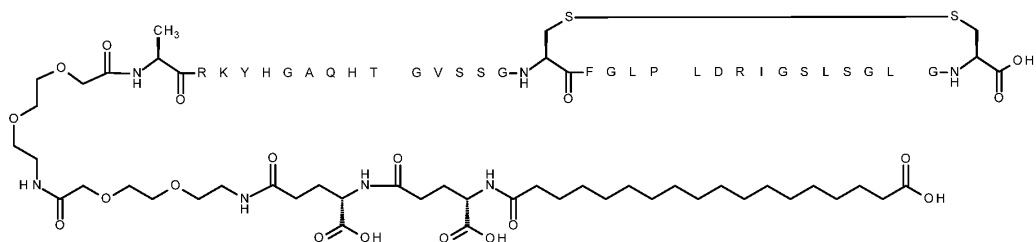
Molecular weight: 5450.114. LCMS34: m/3 calcd: 1817.7047; m/3 found: 1817.5808; m/4 calcd: 1363.5285; m/4 found: 1363.4484

- 5 Chem. 93; Compound ID 9407; SEQ ID NO: 77
[N-terminal([2-[2-[2-[2-[2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-
carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(17-
carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino
]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl
10]amino]ethoxy]ethoxy]acetyl)], des1-5, 13Q, 19Q, 25P, 32L]-hCNP37



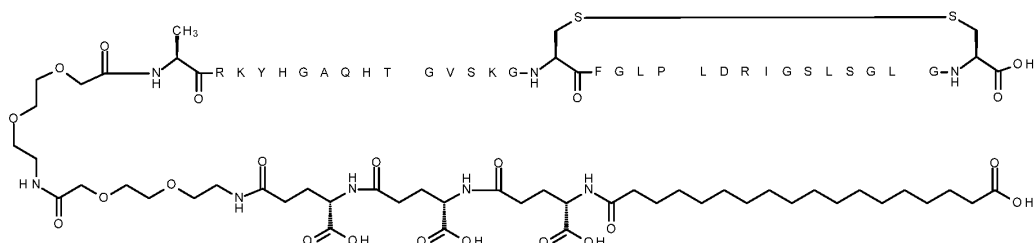
Molecular weight: 4830.4871. LCMS34: m/3 calcd: 1611.1624; m/3 found: 1610.8330; m/4 calcd: 1208.6218; m/4 found: 1208.3823

- 15 Chem. 94; Compound ID 1419; SEQ ID NO: 51
[N-terminal([2-[2-[2-[2-[2-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(17-
carboxyheptadecanoylamino]butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]eth
oxy]ethoxy]acetyl)), des1-5, 10H, 13Q, 14H, 15T, 17V, 19S, 25P, 32L]-hCNP37



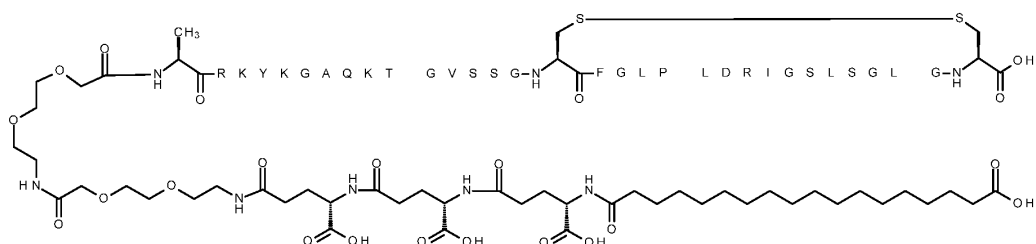
Molecular weight: 4088.6194. LCMS34: m/3 calcd: 1363.8731; m/3 found: 1363.6902; m/4 calcd: 1023.1549; m/4 found: 1023.0371

- 5 Chem. 95; Compound ID 1420; SEQ ID NO: 78
[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-5, 10H, 13Q, 14H, 15T, 17V, 25P, 32L]-hCNP37



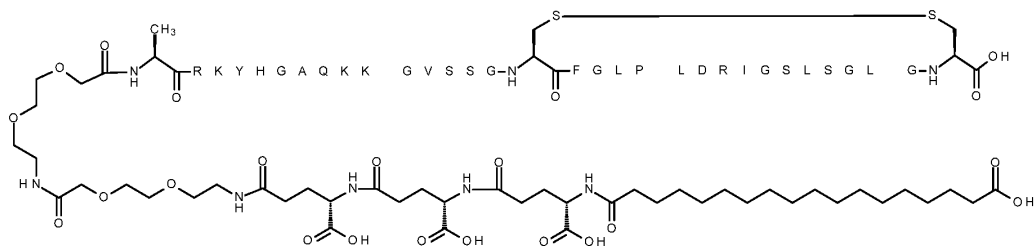
- 10 Molecular weight: 4258.8284. LCMS34: m/3 calcd: 1420.6095; m/3 found: 1420.3875; m/4 calcd: 1065.7071; m/4 found: 1065.5448

- Chem. 96; Compound ID 1421; SEQ ID NO: 79
15 [N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-5, 13Q, 15T, 17V, 19S, 25P, 32L]-hCNP37



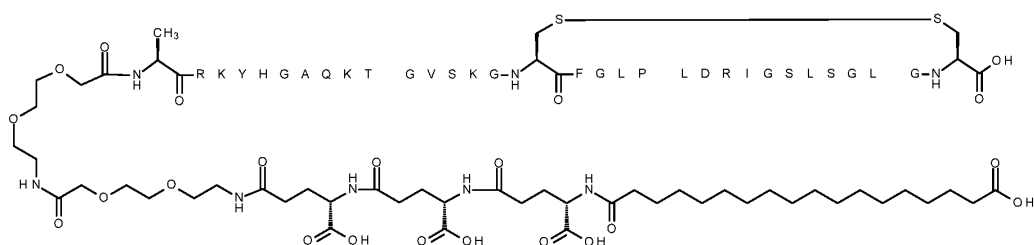
- 20 Molecular weight: 4199.7994. LCMS34: m/3 calcd: 1400.9331; m/3 found: 1400.7268; m/4 calcd: 1050.9499; m/4 found: 1050.8062

- Chem. 97; Compound ID 1422; SEQ ID NO: 80
[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-5, 10H, 13Q, 17V, 19S, 25P, 32L]-hCNP37



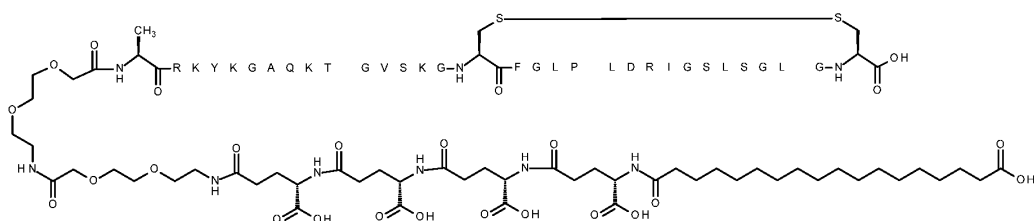
Molecular weight: 4235.8348. LCMS34: m/3 calcd: 1412.9449; m/3 found: 1412.7313; m/4 calcd: 1059.9587; m/4 found: 1059.8075

- 5 Chem. 98; Compound ID 1423; SEQ ID NO: 81
[N-terminal([2-[2-[2-[2-[2-[2-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-5, 10H, 13Q, 15T, 17V, 25P, 32L]-hCNP37



- 10 Molecular weight: 4249.8614. LCMS34: m/3 calcd: 1417.6205; m/3 found: 1417.3965; m/4 calcd: 1063.4654; m/4 found: 1063.3148

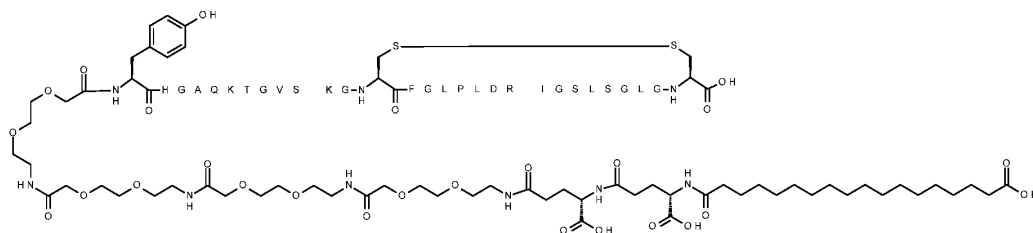
Chem. 99; Compound ID 1424; SEQ ID NO: 82
15 [N-terminal([2-[2-[2-[2-[2-[2-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-5, 13Q, 15T, 17V, 25P, 32L]-hCNP37



- 20 Molecular weight: 4370.0084. LCMS34: m/3 calcd: 1457.6695; m/3 found: 1457.4309; m/4 calcd: 1093.5021; m/4 found: 1093.5833

Chem. 100; Compound ID 1425; SEQ ID NO: 83
25 [N-terminal([2-[2-[2-[2-[2-[2-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]

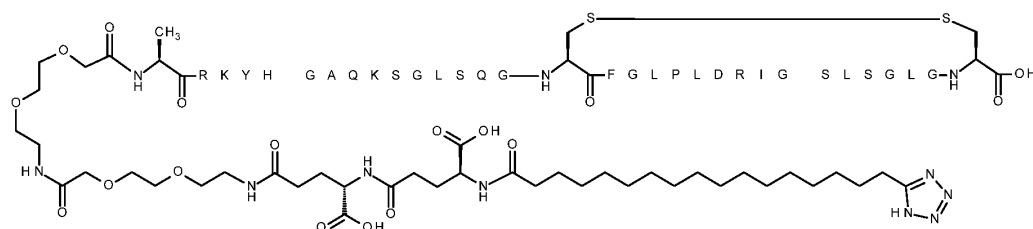
oxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)), des1-8, 10H, 13Q, 15T, 17V, 25P, 32L]-hCNP37



5 Molecular weight: 4055.6244. LCMS34: m/3 calcd: 1352.8748; m/3 found: 1352.6941; m/4 calcd: 1014.9061; m/4 found: 1014.5325

Chem. 101; Compound ID 1426; SEQ ID NO: 84

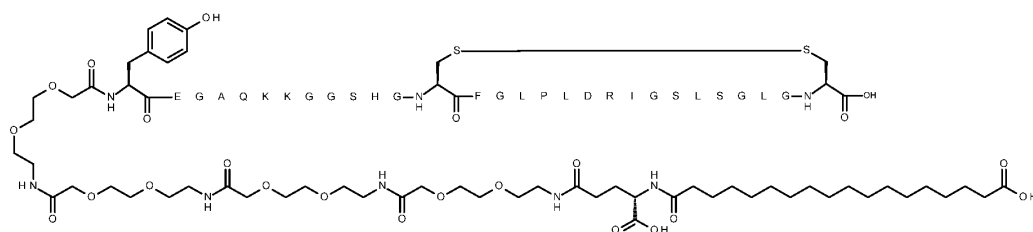
10 [N-terminal([2-[2-[2-[[2-[2-[2-[[4S)-4-carboxy-4-[[4S)-4-carboxy-4-[17-(1H-tetrazol-5-yl)heptadecanoylamino]butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)), des1-5, 10H, 13Q, 15S, 19Q, 25P, 32L]-hCNP37



Molecular weight: 4144.7323. LCMS34: m/3 calcd: 1382.5774; m/3 found: 1382.3732; m/4 calcd: 1037.1831; m/4 found: 1037.0341

15 Chem. 102; Compound ID 1431; SEQ ID NO: 85

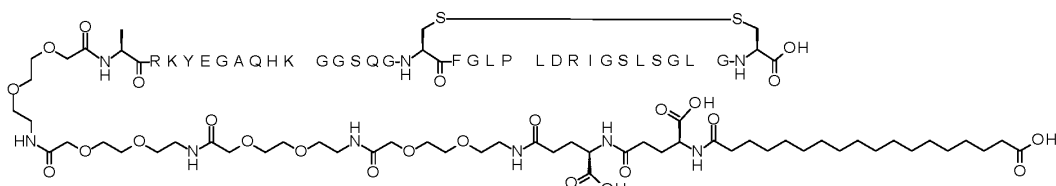
[N-terminal([2-[2-[2-[[2-[2-[2-[[2-[2-[2-[[4S)-4-carboxy-4-(17-carboxyheptadecanoylamino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)), des1-8, 10E, 13Q, 17G, 19H, 25P, 32L]-hCNP37



20 Molecular weight: 3912.4408. LCMS34: m/3 calcd: 1305.1469; m/3 found: 1304.9080; m/4 calcd: 979.1102; m/4 found: 978.9250

Chem. 103; Compound ID 1432; SEQ ID NO: 86

25 [N-terminal([2-[2-[2-[[2-[2-[2-[[2-[2-[2-[[4S)-4-carboxy-4-[[4S)-4-carboxy-4-(17-carboxyheptadecanoylamino]butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)), des1-5, 10E, 13Q, 14H, 17G, 19Q, 25P, 32L]-hCNP37



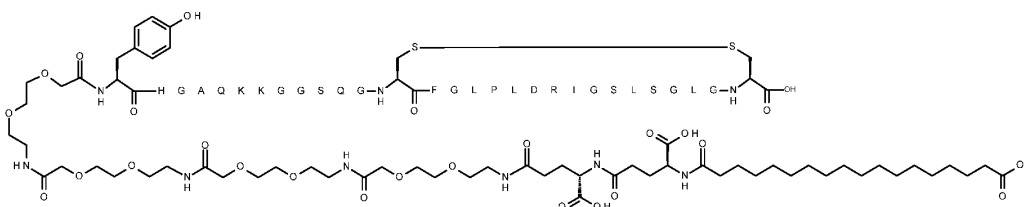
Molecular weight: 4396.9476. LCMS34: m/z calcd: 1466.6492; m/z found: 1466.3500; m/z calcd: 1100.2369; m/z found: 1100.0354

5

Chem. 104; Compound ID 1434; SEQ ID NO: 87

[N-terminal]([2-[2-[2-[2-[2-[2-[2-[[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]), des-1-8, 10H, 13Q, 17G, 19Q, 25P, 32L]-hCNP37

10

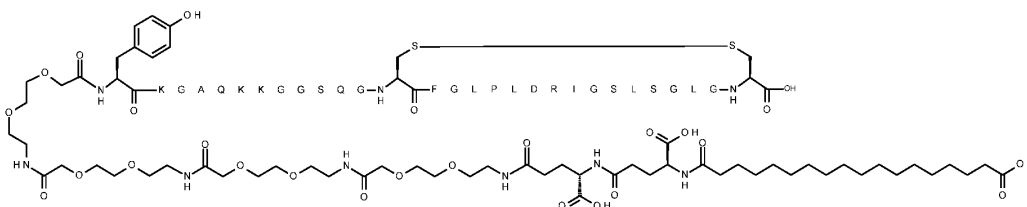


Molecular weight: 4040.57. LCMS34: m/3 calcd: 1347.8567; m/3 found: 1347.9714; m/4 calcd: 1011.1425; m/4 found: 1011.2499

15

Chem. 105; Compound ID 9435; SEQ ID NO: 88

[N-terminal]([2-[2-[2-[2-[2-[2-[2-[2-[2-[[[4S]-4-carboxy-4-[[[4S]-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]), des-1-8, 13Q, 17G, 19Q, 25P, 32L]-hCNP37



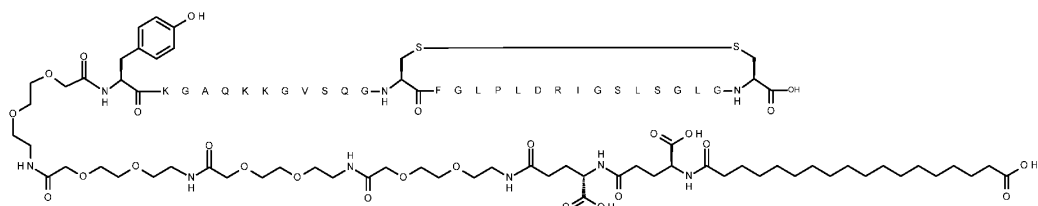
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Molecular weight: 4031.603. LCMS34: m/3 calcd: 1344.8677; m/3 found: 1344.7600; m/4 calcd: 1008.9008; m/4 found: 1008.8210

Chem. 106; Compound ID 1436; SEQ ID NO: 89

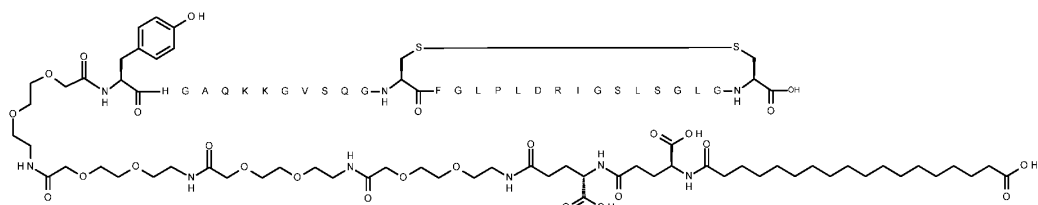
25

[N-terminal]([2-[2-[2-[[[2-[2-[2-[[[2-[2-[2-[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]), des1-8, 13Q, 17V, 19Q, 25P, 32L]-hCNP37



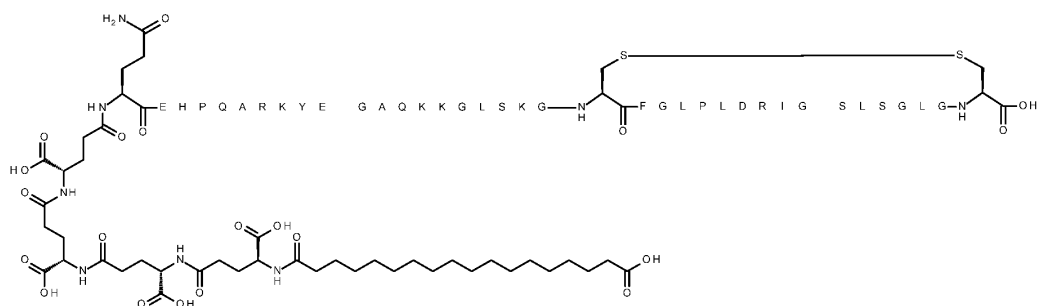
Molecular weight: 4073.6828. LCMS34: m/z calcd: 1358.8943; m/z found: 1358.6617; m/z calcd: 1019.4207; m/z found: 1019.2703

- 5 Chem. 107; Compound ID 1437; SEQ ID NO: 90
[N-terminal([2-[2-[2-[[2-[2-[2-[[2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-(17-
carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]eth
oxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 10H,
13Q, 17V, 19Q, 25P, 32L)-hCNP37



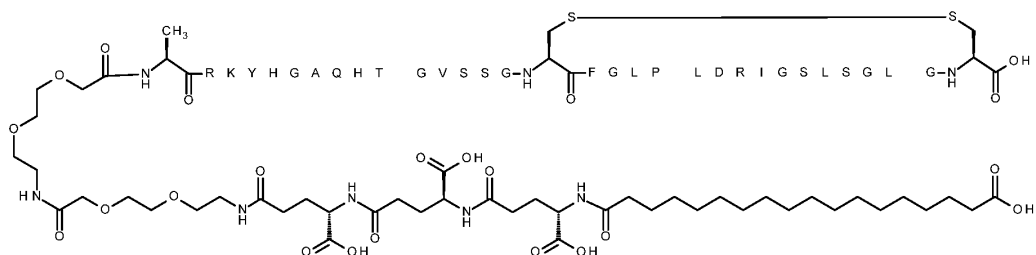
Molecular weight: 4082.6498. LCMS34: m/z calcd: 1361.8833; m/z found: 1361.7580; m/z calcd: 1021.6625; m/z found: 1021.5750

- Chem. 108; Compound ID 1448; SEQ ID NO: 91
- 15 [N-terminal([(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl)], 5Q, 10E, 13Q, 25P, 32L]-hCNP37



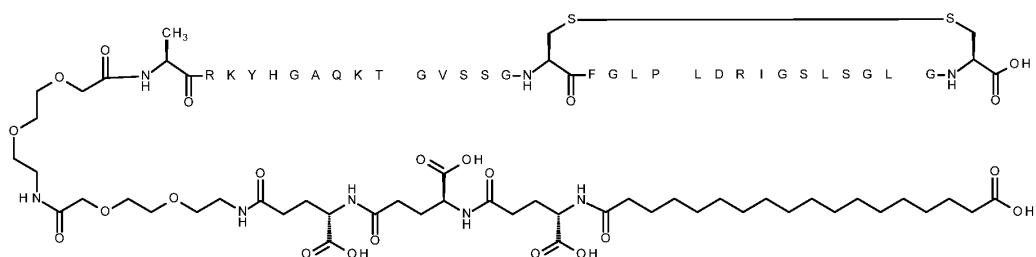
Molecular weight: 4741.359. LCMS34: m/3 calcd: 1581.4530; m/3 found: 1581.2060; m/4 calcd: 1186.3398; m/4 found: 1186.0240

- Chem. 109; Compound ID 1449; SEQ ID NO: 51
[N-terminal([2-[2-[2-[2-[2-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-(17-
carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]
25 acetyl]amino]ethoxy]ethoxy]acetyl)], des1-5, 10H, 13Q, 14H, 15T, 17V, 19S, 25P, 32L]-
hCNP37



Molecular weight: 4217.7334. LCMS34: m/3 calcd: 1406.9111; m/3 found: 9407.0500; m/4 calcd: 1055.4334; m/4 found: 1055.300

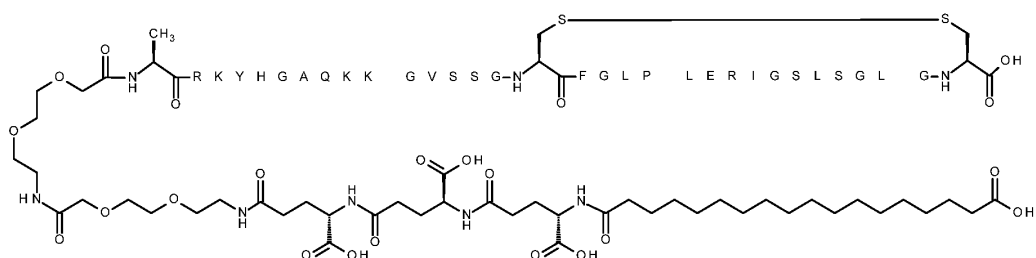
- 5 Chem. 110; Compound ID 1450; SEQ ID NO: 52
[N-terminal([2-[2-[2-[[[2-[2-[2-[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-(17-
carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]
acetyl]amino]ethoxy]ethoxy]acetyl)], des1-5, 10H, 13Q, 15T, 17V, 19S, 25P, 32L]-hCNP37



- 10 Molecular weight: 4208.7664. LCMS34: m/3 calcd: 1403.9221; m/3 found: 1403.7330; m/4 calcd: 1053.1916; m/4 found: 1053.0130

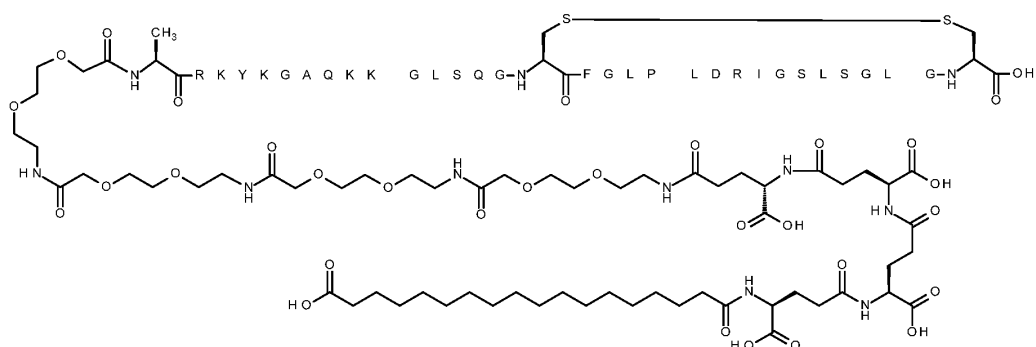
Chem. 111; Compound ID 1451; SEQ ID NO: 92

- 15 [N-terminal([2-[2-[2-[[[2-[2-[2-[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-5, 10H, 13Q, 17V, 19S, 25P, 27E, 32L)-hCNP37



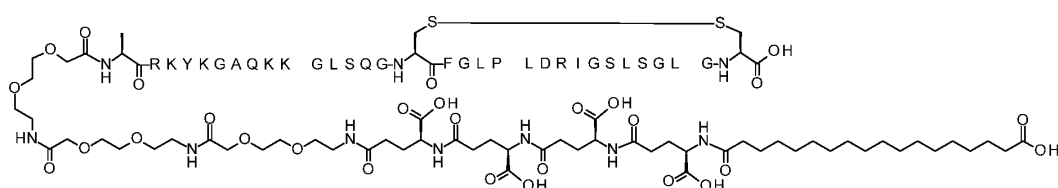
Molecular weight: 4249.8614. LCMS34: m/3 calcd: 1417.6205; m/3 found: 1417.4290; m/4 calcd: 1063.4654; m/4 found: 1063.3310

- Chem. 112; Compound ID 1452; SEQ ID NO: 77



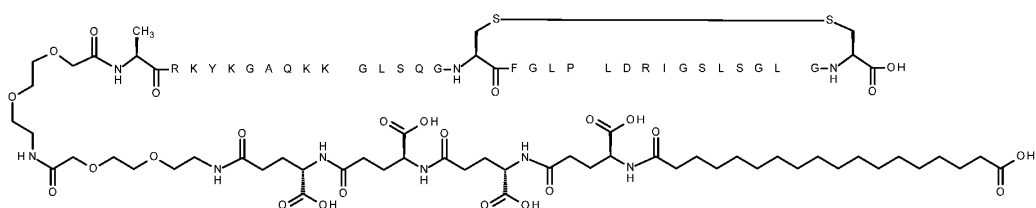
Molecular weight: 4701.3732. LCMS34: m/3 calcd: 1568.1244; m/3 found: 1567.7415; m/4 calcd: 1176.3433; m/4 found: 1176.0765

- 5 Chem. 115; Compound ID 1455; SEQ ID NO: 77
[N-terminal([2-[2-[2-[[2-[2-[2-[[2-[2-[2-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-5, 13Q, 19Q, 25P, 32L]-hCNP37



Molecular weight: 4556.2167. LCMS34: m/3 calcd: 1519.7389; m/3 found: 1519.3893; m/4 calcd: 1140.0542; m/4 found: 1139.8102

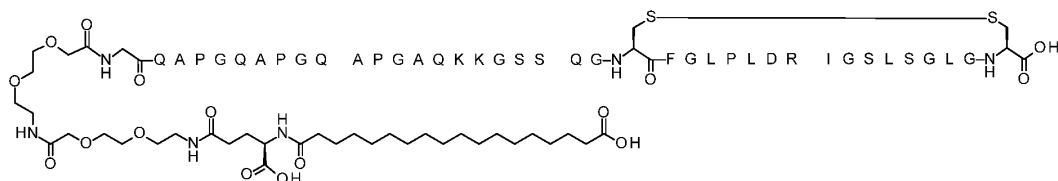
- 15 Chem. 116; Compound ID 1456; SEQ ID NO: 77
[N-terminal([2-[2-[2-[[2-[2-[2-[[2-[2-[2-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-5, 13Q, 19Q, 25P, 32L]-hCNP37



Molecular weight: 4411.0603. LCMS34: m/3 calcd: 1471.3534; m/3 found: 1471.0409; m/4 calcd: 1103.7651; m/4 found: 1103.5541

- 25 Chem. 117; Compound ID 1457; SEQ ID NO: 93

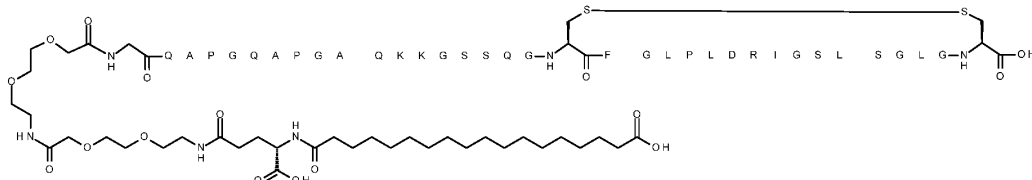
[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], -2G, -1Q, 2P, 3G, 4Q, 5A, 6P, 7G, 8Q, 9A, 10P, 13Q, 19Q, 25P, 32L]-hCNP37



Molecular weight: 4410.9775. LCMS34: m/3 calcd: 1471.3258; m/3 found: 1471.0251; m/4 calcd: 1103.7444; m/4 found: 1103.7853

Chem. 118; Compound ID 1458; SEQ ID NO: 94

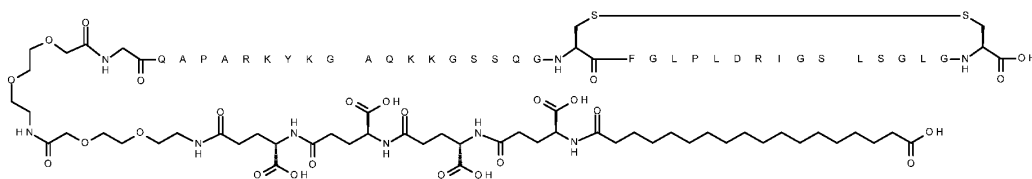
[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-2, 3G, 4Q, 5A, 6P, 7G, 8Q, 9A, 10P, 13Q, 17S, 19Q, 25P, 32L]-hCNP37



Molecular weight: 4057.6038. LCMS34: m/3 calcd: 1353.5346; m/3 found: 1353.3113; m/4 calcd: 1015.4010; m/4 found: 1015.2496

Chem. 119; Compound ID 1459; SEQ ID NO: 95

[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl)], des1, 2G, 3Q, 4A, 5P, 13Q, 17S, 19Q, 25P, 32L]-hCNP37

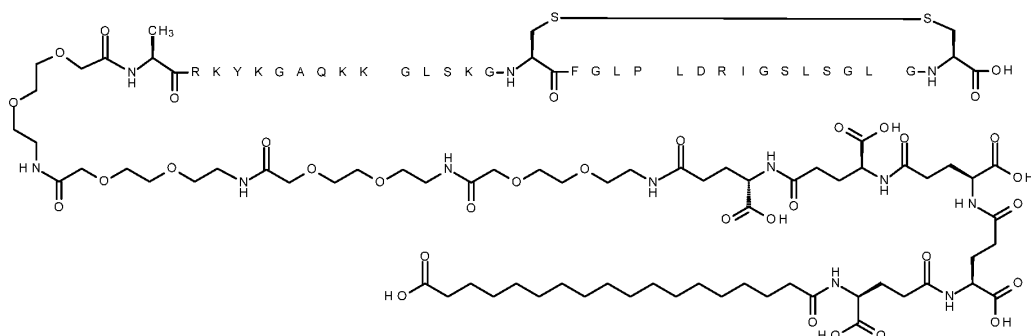


Molecular weight: 4738.3536. LCMS34: m/3 calcd: 1580.4512; m/3 found: 1580.0658; m/4 calcd: 1185.5884; m/4 found: 1185.5701

Chem. 120; Compound ID 1460; SEQ ID NO: 96

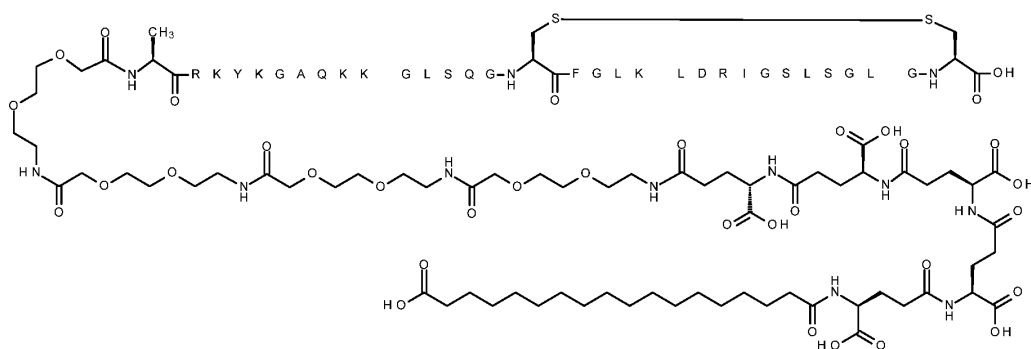
[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl)], des1-5, 13Q, 25P, 32L]-hCNP37





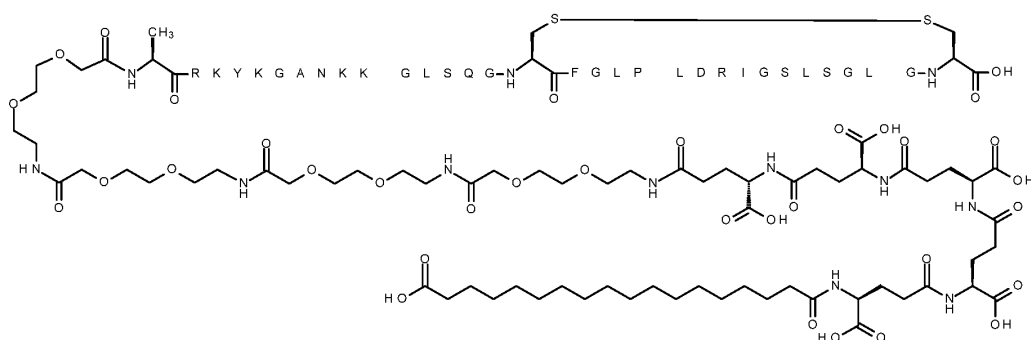
Molecular weight: 4830.5302. LCMS34: m/3 calcd: 1611.1767; m/3 found: 1611.1900; m/4 calcd: 1208.6326; m/4 found: 1208.6500

- 5 Chem. 123; Compound ID 1463; SEQ ID NO: 98
[N-terminal([2-[2-[2-[[2-[2-[2-[2-[2-[2-[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-[[[(4S)-4-
carboxy-4-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-(17-
carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino
]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl
10]amino]ethoxy]ethoxy]acetyl)], des1-5, 13Q, 19Q, 32L]-hCNP37



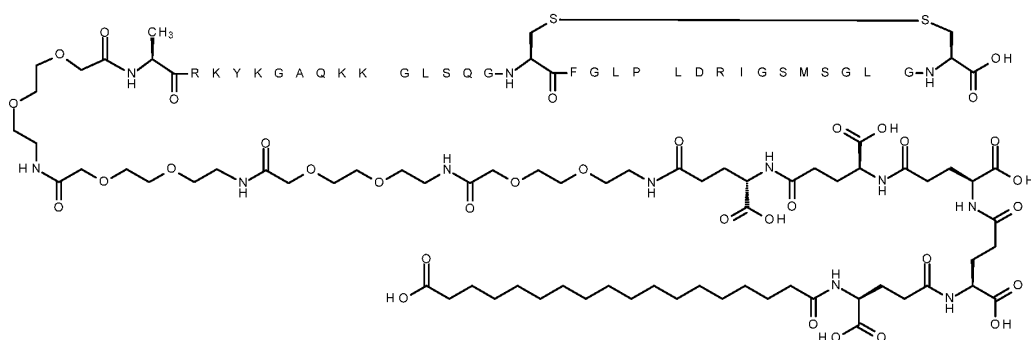
Molecular weight: 4861.5442. LCMS34: m/3 calcd: 1621.5147; m/3 found: 1621.1760; m/4 calcd: 1216.3861; m/4 found: 1216.1420

- 15 Chem. 124; Compound ID 1464; SEQ ID NO: 99
[N-terminal([2-[2-[2-[2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-
carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(17-
carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino
]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl
20]amino]ethoxy]ethoxy]acetyl)], des1-5, 19Q, 25P, 32L]-hCNP37



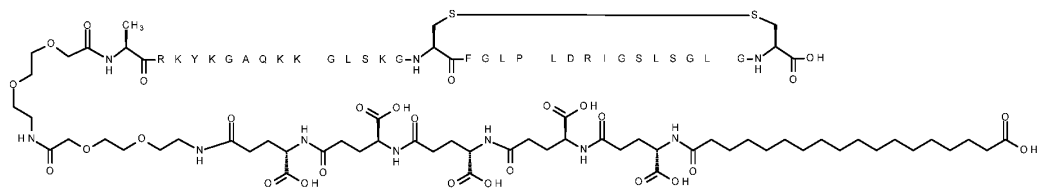
Molecular weight: 4816.4606. LCMS34: m/3 calcd: 1606.4869; m/3 found: 1606.1700; m/4 calcd: 1205.1152; m/4 found: 1204.8820

- 5 Chem. 125; Compound ID 1465; SEQ ID NO: 100
[N-terminal([2-[2-[2-[2-[2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-5, 13Q, 19Q, 25P]-hCNP37



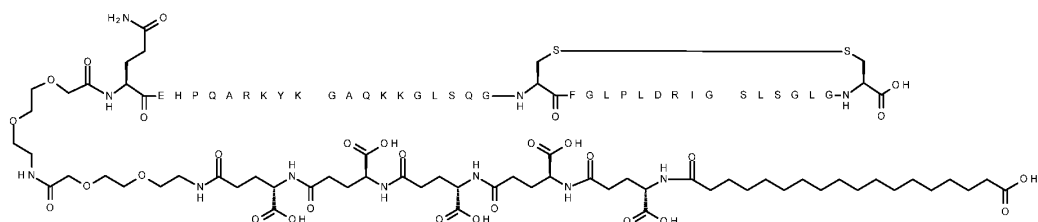
Molecular weight: 4848.5256. LCMS34: m/3 calcd: 1617.1752; m/3 found: 1616.8130; m/4 calcd: 1213.1314; m/4 found: 1212.8620

- 15 Chem. 126; Compound ID 1470; SEQ ID NO: 96
[N-terminal([2-[2-[2-[2-[2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-5, 13Q, 25P, 32L]-hCNP37



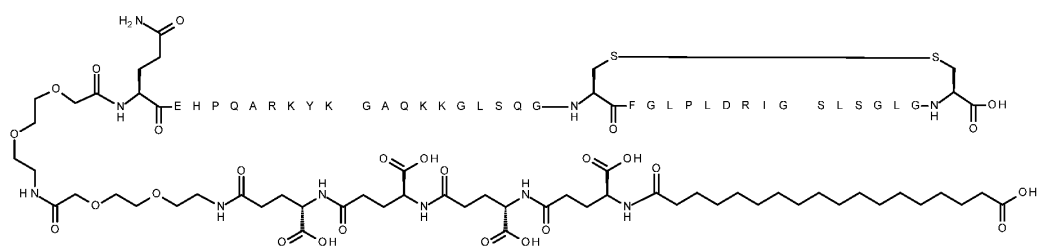
Molecular weight: 4540.2173. LCMS34: m/3 calcd: 1514.4058; m/3 found: 1514.1500; m/4 calcd: 1136.0543; m/4 found: 1135.8500

- 5 Chem. 127; Compound ID 1471; SEQ ID NO: 75
[N-terminal([2-[2-[2-[2-[2-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], 5Q, 13Q, 19Q, 25P, 32L]-hCNP37



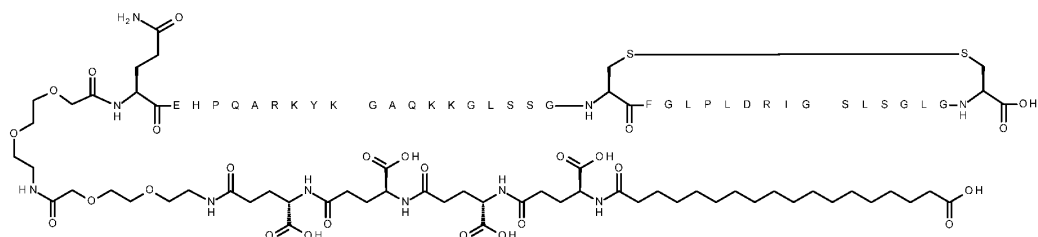
Molecular weight: 5159.8011. LCMS34: m/3 calcd: 1720.9337; m/3 found: 1720.8900; m/4 calcd: 1290.9503; m/4 found: 1290.9200

- 15 Chem. 128; Compound ID 1472; SEQ ID NO: 75
[N-terminal([2-[2-[2-[2-[2-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], 5Q, 13Q, 19Q, 25P, 32L]-hCNP37



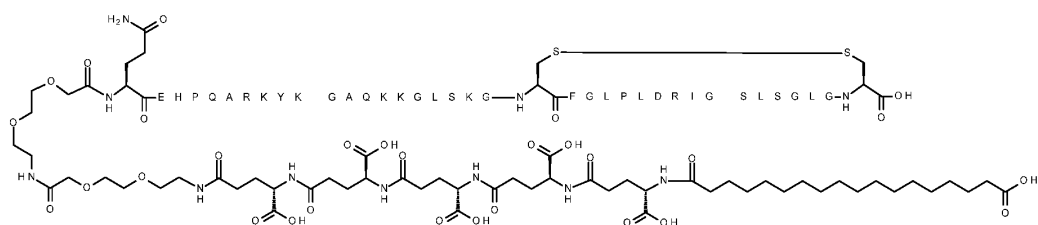
- 20 Molecular weight: 5030.6872. LCMS34: m/3 calcd: 1677.8957; m/3 found: 1677.8700; m/4 calcd: 1258.6718; m/4 found: 1258.6600

- 25 Chem. 129; Compound ID 1473; SEQ ID NO: 67
[N-terminal([2-[2-[2-[2-[2-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], 5Q, 13Q, 19S, 25P, 32L]-hCNP37



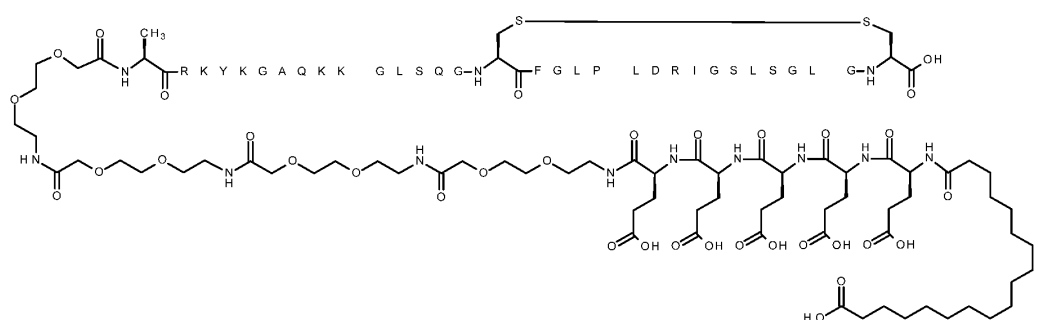
Molecular weight: 4989.6352. LCMS34: m/3 calcd: 1664.2117; m/3 found: 1664.2000; m/4 calcd: 1248.4088; m/4 found: 1248.400

- 5 Chem. 130; Compound ID 1474; SEQ ID NO: 101
[N-terminal([2-[2-[2-[2-[2-[2-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], 5Q, 13Q, 25P, 32L]-hCNP37



Molecular weight: 5159.8442. LCMS34: m/3 calcd: 1720.9481; m/3 found: 1720.8900; m/4 calcd: 1290.9611; m/4 found: 1290.9200

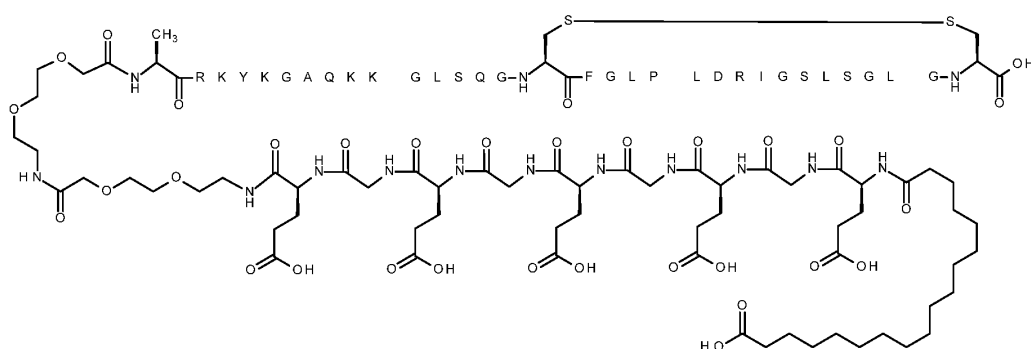
- 15 Chem. 131; Compound ID 1475; SEQ ID NO: 77
[N-terminal([2-[2-[2-[2-[2-[2-[[[(2S)-4-carboxy-2-[[[(2S)-4-carboxy-2-[[[(2S)-4-carboxy-2-[[[(2S)-4-carboxy-2-[[[(2S)-4-carboxy-2-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-5, 13Q, 19Q, 25P, 32L]-hCNP37



Molecular weight: 4830.4871. LCMS34: m/3 calcd: 1611.1624; m/3 found: 1610.7510; m/4 calcd: 1208.6218; m/4 found: 1208.5814

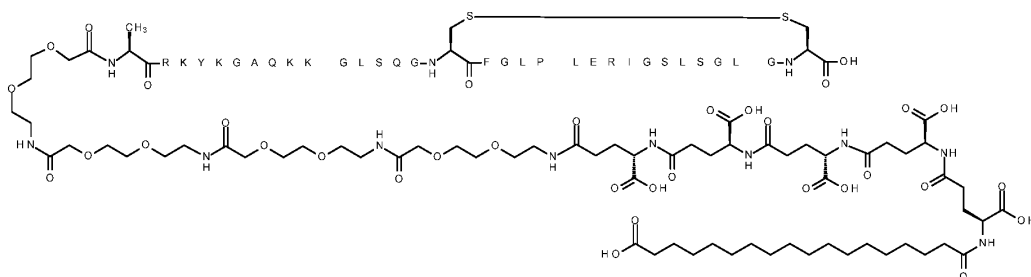
- 25 Chem. 132; Compound ID 1476; SEQ ID NO: 77

- 5 [N-terminal([2-[2-[2-[2-[2-[2-[(2S)-4-carboxy-2-[[2-[(2S)-4-carboxy-2-[[2-[(2S)-4-carboxy-2-[[2-[(2S)-4-carboxy-2-(17-carboxyheptadecanoylamino)butanoyl]amino]acetyl]amino]butanoyl]amino]acetyl]amino]butanoyl]amino]acetyl]amino]butanoyl]amino]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-5, 13Q, 19Q, 25P, 32L]-hCNP37



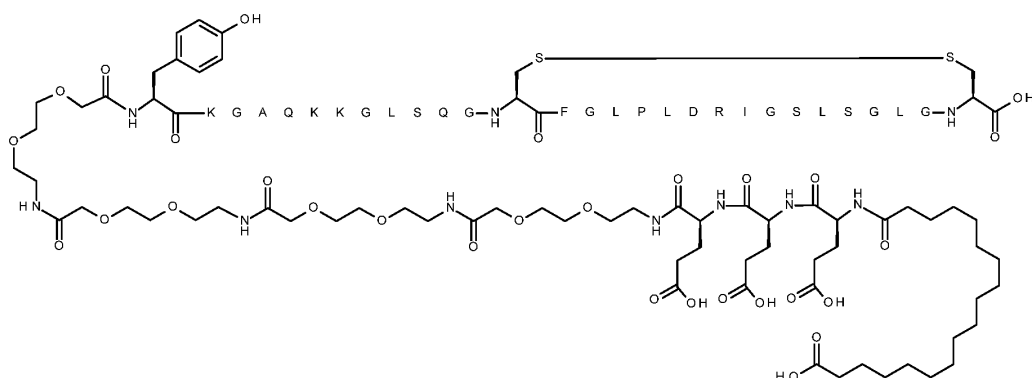
Molecular weight: 4768.3795. LCMS34: m/3 calcd: 1590.4598; m/3 found: 1590.4137; m/4 calcd: 1193.0949; m/4 found: 1193.0793

- 10 Chem. 133; Compound ID 1477; SEQ ID NO: 102
[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-[[4S)-4-carboxy-4-[[4S)-4-carboxy-4-[[4S)-4-carboxy-4-[[4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-5, 13Q, 19Q, 25P, 27E, 32L]-hCNP37



Molecular weight: 4844.5137. LCMS34: m/3 calcd: 1615.8379; m/3 found: 1615.4194; m/4 calcd: 1212.1284; m/4 found: 1212.0844

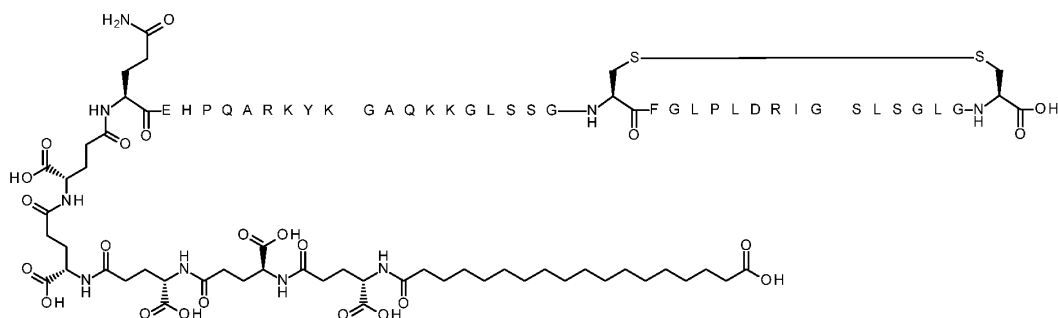
- 20 Chem. 134; Compound ID 1478; SEQ ID NO: 103
[N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-[[4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 13Q, 19Q, 25P, 32L]-hCNP37



Molecular weight: 4216.8233. LCMS34: m/3 calcd: 1406.6078; m/3 found: 1406.3542; m/4 calcd: 1055.2058; m/4 found: 1055.0295

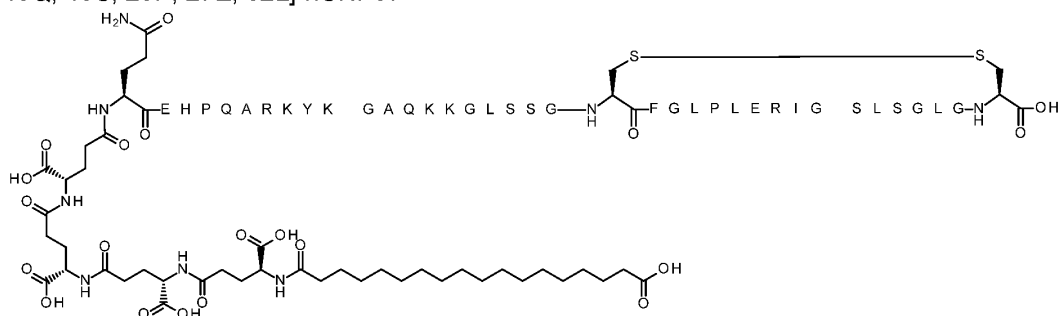
- 5 Chem. 137; Compound ID 9482; SEQ ID NO: 67
[N-terminal([(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-
[(4S)-4-carboxy-4-(17-
carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl]amino
]butanoyl)], 5Q, 13Q, 19S, 25P, 32L]-hCNP37

10



Molecular weight: 4828.4363. LCMS34: m/3 calcd: 1610.4788; m/3 found: 1610.4060; m/4 calcd: 1208.1091; m/4 found: 1207.8275

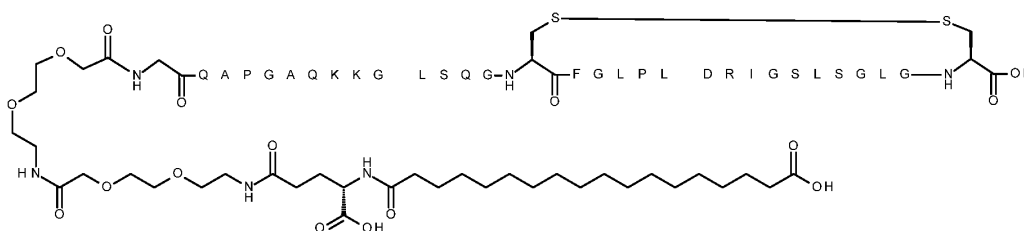
- 15 Chem. 138; Compound ID 9483; SEQ ID NO: 104
[N-terminal([(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-[(4S)-4-carboxy-4-(17-
carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]butanoyl]amino]butanoyl)], 5Q,
13Q, 19S, 25P, 27E, 32L]-hCNP37



Molecular weight: 4713.3489. LCMS34: m/3 calcd: 1572.1163; m/3 found: 1572.1500; m/4 calcd: 1179.3372; m/4 found: 1179.1200

Chem. 139; Compound ID 1484; SEQ ID NO: 105

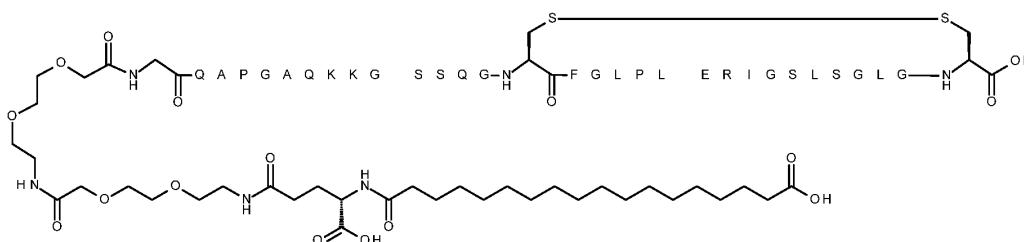
- 5 [N-terminal([2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-6, 7G, 8Q, 9A, 10P, 13Q, 19Q, 25P, 32L]-hCNP37



10 Molecular weight: 3730.3106. LCMS34: m/3 calcd: 1244.4369; m/3 found: 1244.7042; m/4 calcd: 933.5777; m/4 found: 933.5259

Chem. 140; Compound ID 1486; SEQ ID NO: 106

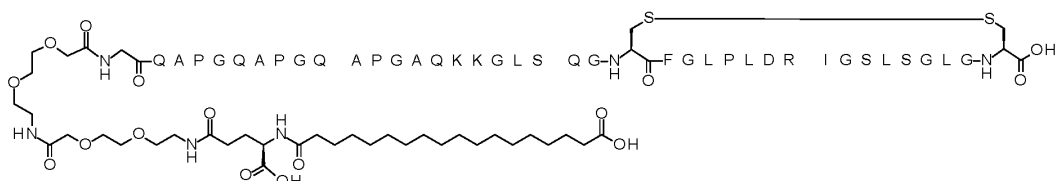
- 15 [N-terminal([2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-6, 7G, 8Q, 9A, 10P, 13Q, 17S, 19Q, 25P, 27E, 32L]-hCNP37



Molecular weight: 3718.2568. LCMS34: m/3 calcd: 1240.4189; m/3 found: 1240.3220; m/4 calcd: 930.5642; m/4 found: 930.4920

- 20 Chem. 141; Compound ID 1487; SEQ ID NO: 107

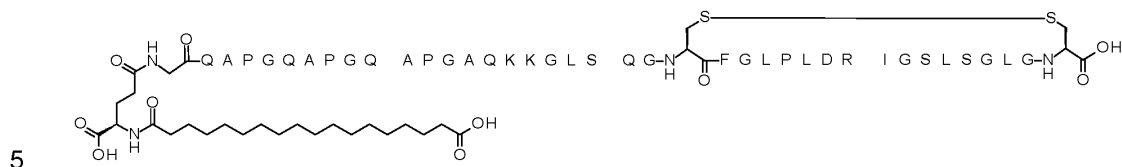
[N-terminal([2-[2-[2-[[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], -2G, -1Q, 2P, 3G, 4Q, 5A, 6P, 7G, 8Q, 9A, 10P, 13Q, 19Q, 25P, 32L]-hCNP37



25 Molecular weight: 4437.0578. LCMS34: m/3 calcd: 9480.0193; m/3 found: 1479.8291; m/4 calcd: 1110.2645; m/4 found: 1110.3766

Chem. 142; Compound ID 1488; SEQ ID NO: 107

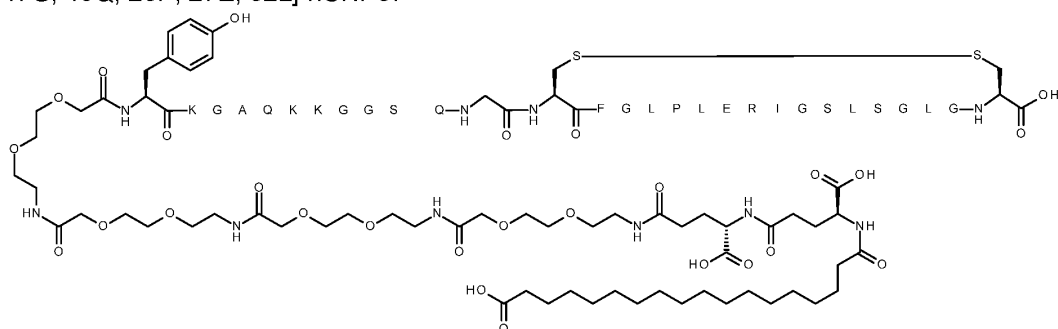
[N-terminal]([(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]), -2G, -1Q, 2P, 3G, 4Q, 5A, 6P, 7G, 8Q, 9A, 10P, 13Q, 19Q, 25P, 32L]-hCNP37



Molecular weight: 4146.7449. LCMS34: m/3 calcd: 1383.2483; m/3 found: 1383.4402; m/4 calcd: 1037.6862; m/4 found: 1037.5803

Chem. 143; Compound ID 1489; SEQ ID NO: 108

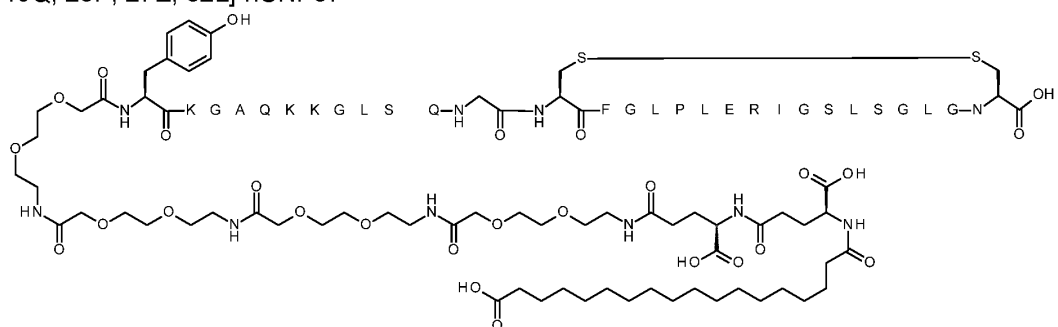
10 [N-terminal]([2-[2-[[[2-[2-[[[2-[2-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]), des1-8, 13Q, 17G, 19Q, 25P, 27E, 32L]-hCNP37



15 Molecular weight: 4045.6296. LCMS34: m/3 calcd: 1349.5432; m/3 found: 1349.3710; m/4 calcd: 1012.4074; m/4 found: 1012.2860

Chem. 144; Compound ID 1493; SEQ ID NO: 109

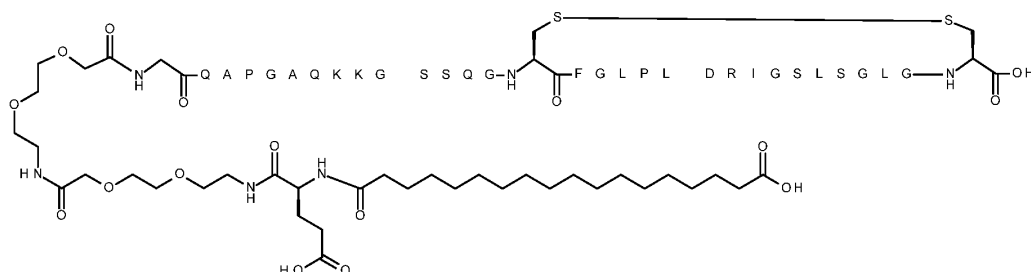
[N-terminal([2-[2-[2-[2-[2-[2-[2-[[[2-[2-[2-[[[(4S)-4-carboxy-4-[[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 13Q, 19Q, 25P, 27E, 32L]-hCNP37



25 Molecular weight: 4101.7359. LCMS34: m/3 calcd: 1368.2453; m/3 found: 1368.0680; m/4 calcd: 1026.4340; m/4 found: 1026.3130

Chem. 145; Compound ID 1511; SEQ ID NO: 62

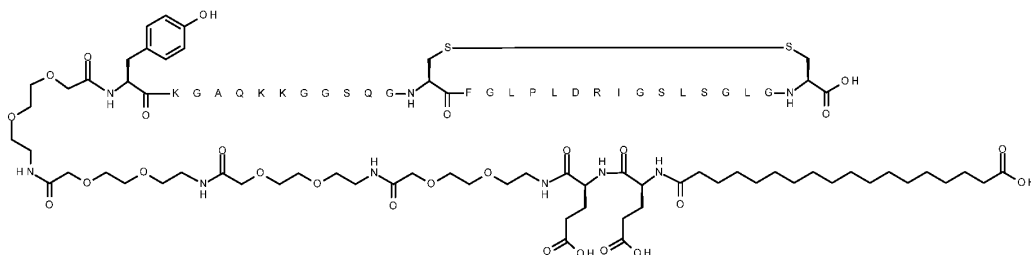
[N-terminal([2-[2-[2-[2-[2-[2-[[[(2S)-4-carboxy-2-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-6, 7G, 8Q, 9A, 10P, 13Q, 17S, 19Q, 25P, 32L]-hCNP37



- 5 Molecular weight: 3704.2302. LCMS34: m/3 calcd: 1235.7434; m/3 found: 1235.6700; m/4 calcd: 927.0576; m/4 found: 927.0010

Chem. 146; Compound ID 1512; SEQ ID NO: 88

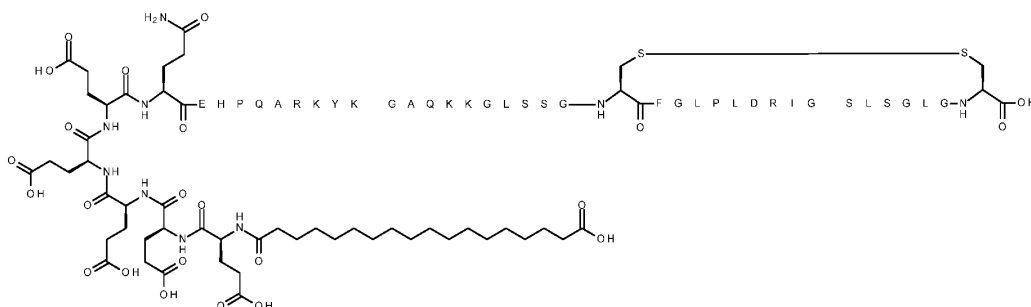
- 10 [N-terminal([2-[2-[2-[2-[2-[2-[[[(2S)-4-carboxy-2-(17-carboxyheptadecanoylamino)butanoyl]amino]butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-8, 13Q, 17G, 19Q, 25P, 32L]-hCNP37



- 15 Molecular weight: 4031.603. LCMS34: m/3 calcd: 1344.8677; m/3 found: 1344.7600; m/4 calcd: 1008.9008; m/4 found: 1008.8080

Chem. 147; Compound ID 1513; SEQ ID NO: 110

[N-terminal(17-carboxyheptadecanoyl), -5E, -4E, -3E, -2E, -1E, 5Q, 13Q, 19S, 25P, 32L]-hCNP37

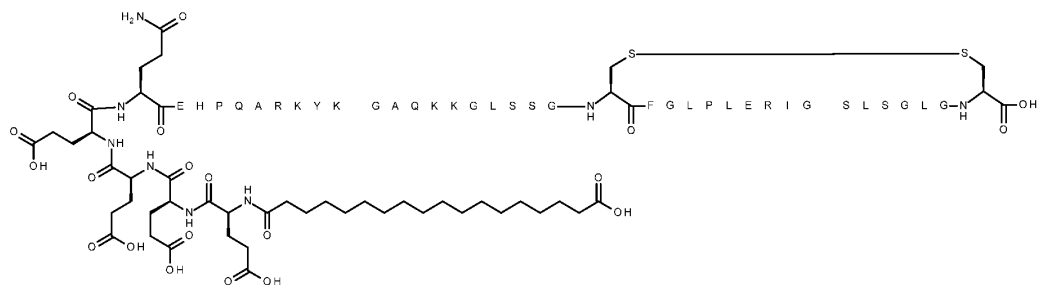


20

Molecular weight: 4828.4363. LCMS34: m/3 calcd: 1610.4788; m/3 found: 1610.2260; m/4 calcd: 1208.1091; m/4 found: 1207.9160

Chem. 148; Compound ID 1514; SEQ ID NO: 111

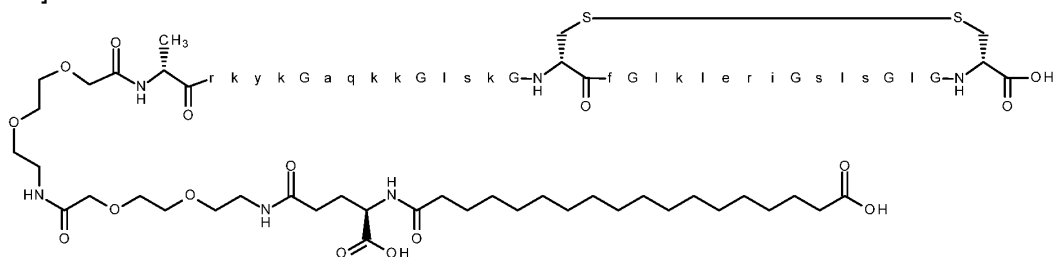
[N-terminal(17-carboxyheptadecanoyl), -4E, -3E, -2E, -1E, 5Q, 13Q, 19S, 25P, 27E, 32L]-hCNP37



- 5 Molecular weight: 4713.3489. LCMS34: m/3 calcd: 1572.1163; m/3 found: 1571.8940; m/4 calcd: 1179.3372; m/4 found: 1179.1550

Chem. 149; Compound ID 1265; SEQ ID NO: 233

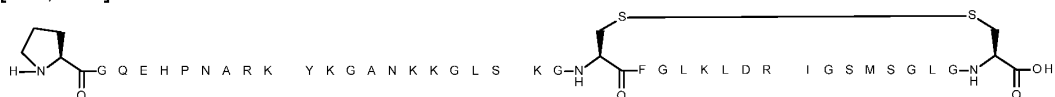
- 10 [N-terminal([2-[2-[2-[2-[2-[2-[(4R)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-5, 6a, 7r, 8k, 9y, 10k, 12a, 13q, 14k, 15k, 17l, 18s, 19k, 21c, 22f, 24l, 25k, 26l, 27e, 28r, 29i, 31s, 32l, 33s, 35l, 37c]-hCNP37



- 15 Molecular weight: 4068.8451. LCMS34: m/4 calcd: 1018.2113; m/4 found: 1018.1958

Chem. 150; Compound ID 0106; SEQ ID NO: 234

[-2P, -1G]-hCNP37



- 20 Molecular weight: 4102.7254. LCMS34: m/3 calcd: 1368.5751; m/3 found: 1368.362; m/4 calcd: 1026.6814; m/4 found: 1026.529

Chem. 151; Compound ID 0089; SEQ ID NO: 1

- 25 [N-terminal([2-[2-[2-[2-[2-[2-[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]amino]ethoxy]ethoxy]acetyl)], des1-5, 6a, 7r, 8k, 9y, 10k, 12a, 13q, 14k, 15k, 17l, 18s, 19k, 21c, 22f, 24l, 25k, 26l, 27e, 28r, 29i, 31s, 32l, 33s, 35l, 37c]-hCNP22

Example 2 - *In vitro* hNPR2 activity assay

To evaluate the *in vitro* activity of CNP22 (0065; Chem. 1) and CNP compounds of the invention, they were tested for their ability to induce production of cyclic guanosine monophosphate (cGMP) in reporter cells expressing the human natriuretic peptide receptor 2 (hNPR2).

Cell culture: To produce the reporter cell line, HEK293 (ATCC® CRL-1573™) cells were stably transfected with the pGloSensor-42F reporter plasmid (GloSensor cGMP reporter - luciferase, Promega) and an expression plasmid encoding the hNPR2 receptor. A single cell clone was isolated for the reporter cell line. When reporter cells are exposed to an hNPR2 activating compound, hNPR2 cause production of cGMP. GloSensor luciferase, produced from the pGloSensor-42F plasmid, binds cGMP and this binding induces a conformational shift of the GloSensor luciferase, activating the otherwise inactive enzyme. Active GloSensor luciferase is able to convert luciferin to oxyluciferin, a process that produces bioluminescence. Upon cell lysis and supply of luciferase substrate, luciferase activity can be quantified by detection of luminescence. Therefore, addition of an hNPR2 activating compound and subsequent addition of detection reagent to reporter cells causes generation of luminescence in a dose dependent manner. By testing a number of different concentrations of hNPR2 activating compound, a half maximal effective concentration (EC50) can be determined. This measure, also referred to as *in vitro* potency, is reported for all compounds tested. In all the *in vitro* activity experiments, CNP22 was used as a positive in-plate control for hNPR2 activation. To reduce inter-assay variation, we also report the potency of each compound relative to the potency of the CNP22 control on each plate.

Procedure: HEK293-hNPR2/GloSensor clone 35 cells were continuously cultured in selection medium (DMEM containing 10% FCS, 1% P/S, 200 µg/mL G418 and 100 µg/mL hygromycin). To perform the assay, cells were detached with TrypLE Express (Gibco #12604013), put through a 70 µm cell strainer, counted and seeded in 30 µL/well assay medium (DMEM without phenol red and with 1% P/S) at 10,000 cells/well in white 384-well plates (Perkin Elmer #6007680) overnight. The following day, test compounds were serially diluted in dilution medium (DMEM without phenol red containing 1% OVA (Sigma #A5505 lot 04M7001V), 0.01% Tween20 (Roche #33766700) and 1% P/S) and 10 µL/well of diluted test compounds were subsequently added to the cells. For each compound, ten different concentrations in the range 0.25 pM – 10 µM were tested. After 30 min of incubation at 37 °C and 5% CO₂, 40 µL/well Bright-Glo detection reagent (Promega # E2650) was added. Immediately thereafter or after 15 min, luminescence was detected by an EnVision Multimode Plate Reader (PerkinElmer). To determine the *in vitro* potency or EC50 of each

test compound, a four parameter logistic regression was done on the raw data for each test compound using the Python package SciPy optimize. The average EC50 values are listed as “hNPR2 0% HSA. [EC50 (nM)]” in Table 2. A relative potency was calculated by the following expression: $EC50 \text{ (CNP22 in-plate control)} / EC50 \text{ (test compound)} * 100$, shown as “hNPR2 0% HSA. [EC50 % rel CNP]” in Table 2. A minimum of two replicates was measured for each test compound. The reported values are averages of the replicates and listed in Table 2.

Table 2 – *In vitro* human NPR2 potencies of CNP compounds:

Compound ID (Chem ref.)	hNPR2 0% HSA. [EC50 (nM)]	hNPR2 0% HSA. [EC50 % rel CNP]
0065 (CNP22, chem. 1)	0.28	100.0
1510	0.05	139.2
0312	0.47	80.0
0776	0.58	33.2
1235	1.17	27.2
0262	15.44	1.8
0296	5.50	3.6
0313	48.37	0.7
0334	124.43	2.0
1221	1.17	35.9
1222	2.94	14.3
1223	1.05	6.77
1224	0.86	16.9
1225	2.23	29.4
1226	2.95	7.5
1227	1.01	38.2
1228	11.03	12.3
1229	4.44	5.3
1230	6.98	4.2
1231	5.62	4.1
1232	1.63	16.0
1233	0.81	49.7
1236	3.40	6.1
1237	1.95	11.8
1240	4.01	11.2
1241	1.35	30.5
1242	6.58	5.4
1274	7.66	13.2
1287	12.78	2.9

1288	12.42	3.0
1289	12.97	2.9
1290	5.30	7.0
1302	2.80	26.5
1303	1.48	25.5
1304	2.91	20.7
1305	6.98	8.7
1309	1.35	33.3
1310	6.88	10.4
1311	6.79	12.7
1312	7.82	9.0
1322	4.73	1.9
1323	11.24	0.8
1324	5.51	1.6
1338	6.77	1.3
1339	1.03	15.5
1340	0.18	44.4
1341	0.48	16.7
1345	0.38	21.1
1346	0.47	17.0
1347	0.52	15.4
1348	0.35	31.4
1350	0.39	41.0
1351	0.29	55.2
1352	0.39	38.6
1353	1.22	9.0
1354	0.40	27.5
1355	0.39	28.2
1356	0.49	22.4
1357	2.53	4.3
1359	0.39	28.2
1360	0.73	15.1
1375	0.68	16.2
1376	0.12	91.7
1377	0.39	28.2
1378	0.33	28.6
1379	0.35	33.5
1380	0.72	15.7
1381	0.25	38.7
1382	0.23	43.8
1383	0.25	43.1
9384	0.10	53.7
1385	0.35	30.7

1386	0.29	36.9
1387	0.46	20.6
1388	0.41	23.5
1389	0.13	52.3
1390	0.33	84.6
1391	0.35	37.9
1392	0.45	29.5
1393	0.42	27.8
1394	0.21	93.9
1395	0.04	60.2
1396	0.07	43.1
1398	0.14	55.6
1399	0.13	137.0
1400	0.26	85.3
1401	0.56	19.7
1402	0.24	57.6
1403	0.25	87.1
1404	0.31	81.3
1405	0.31	62.3
1406	0.28	59.1
9407	0.16	38.6
1419	0.33	37.2
1420	0.08	87.5
1421	0.14	50.0
1422	0.28	75.3
1423	0.31	37.7
1424	0.19	36.2
1425	0.25	26.4
1426	0.19	76.2
1431	1.11	14.3
1432	0.43	26.0
1434	0.46	29.0
9435	0.07	73.6
1436	0.23	30.2
1437	0.35	19.9
1448	0.24	33.3
1449	0.16	110.0
1450	0.24	84.2
1451	0.72	47.5
1452	0.03	57.6
1453	0.04	33.5
1454	0.02	63.6
1455	0.03	43.4

1456	0.03	50.4
1457	0.02	79.4
1458	0.02	93.6
1459	0.02	76.1
1460	0.04	32.4
1461	0.20	28.9
1462	0.01	106.6
1463	0.30	20.0
1464	0.12	48.8
1465	0.25	24.0
1470	0.06	23.9
1471	0.03	40.2
1472	0.03	52.0
1473	0.01	107.7
1474	0.03	62.5
1475	0.13	46.5
1476	0.12	48.4
1477	0.13	10.3
1478	0.05	26.6
9480	0.05	45.2
1481	0.02	35.1
9482	0.06	39.4
9483	0.30	10.2
1484	0.03	27.9
1486	0.14	6.0
1487	0.04	22.0
1488	0.03	29.3
1489	0.22	3.7
1493	0.80	11.5
1265	>1000	N/A
0106	0.18	201.1
0089	12.25	3.1
0230	29.23	0.4
0231	14.53	0.8

These data demonstrate that the tested CNP compounds span a broad range of NPR2 *in vitro* activation levels and that negatively charged CNP compounds commonly show reduced *in vitro* NPR2 potency relative to positively charged CNP compounds.

5 **Example 3 - *In vitro* neprilysin stability of CNP-compounds**

It has been reported that native CNP can be metabolised by neprilysin (neutral endopeptidase, NEP), which is a protease that is widely present in the body. Therefore, an *in*

vitro neprilysin stability assay was set up to test the neprilysin mediated degradation of selected CNP compounds.

Procedure: In short, the assay buffer consisted of PBS-buffer (pH 7.4, ThermoFisher Scientific) with a final concentration of 0.005% v/v tween 20 (Sigma-Aldrich). Recombinant human neprilysin (rhNEP; R&D Systems) and the CNP compounds were dissolved in assay buffer. Native CNP22 (0065, Chem. 1) was included as positive control on each day of incubation. Initially, the CNP compound (the final concentration was 1000 nM) was pre-incubated in assay buffer for 10 min at 37 °C. The assay was started by adding either rhNEP (final concentration was 2 µg protein per mL) or assay buffer (adsorption experiment) and the incubation was conducted at 37 °C. The reaction was terminated at selected time points (0.5; 5; 15; 30; 60; 90 and 120 min) by adding one volume of incubation mixture to three volumes of ethanol (containing 1% v/v of formic acid). The mixture was centrifuged at 13000 rpm at 4 °C for 20 minutes. After centrifugation, one volume of supernatant was mixed with one volume of Milli-Q water.

Analysis by LCMS: The mixture was analysed by LCMS using an Acquity UPLC Peptide CSH C18 analytical column from Waters (130Å, 1.7µm, 1*50mm) operated at 60°C. A gradient elution was conducted with a Nexera UHPLC system (Shimadzu) using mobile phase A (consisting of Milli-Q water with 0.1% formic acid) and mobile phase B (consisting of acetonitrile with 0.1% formic acid). The flow was 0.3 ml/min. A zenoTOF 7600 mass spectrometer (Sciex) was used as detector and operated in positive electrospray ionisation mode. Data was recorded in full scan mode (m/z 300-1700).

Calibration curves were prepared in assay buffer and treated as study samples. These samples were used for calculating the concentration of the relevant CNP compound in the *in vitro* samples. Quality control samples were included. For at least 75% of the standards and QCs, the deviation between nominal and calculated concentration was below 20%.

All incubations were conducted in duplicate. Data was reported as percent remaining at 90 min (based on calculated concentrations) compared to the average concentration in the 0.5-minute time point samples. An example of seven compounds and CNP22 (0065, Chem. 1) is shown in Table 3.

Table 3 - Percent remaining of CNP-compounds upon incubation with rhNEP for 90 minutes

Compound	Remaining of parent after 90 min (%)
0065* (CNP22)	1.7
0106	95.1

9384	87.8
9407	96.6
9435	93.2
9480	98.3
9482	96.3
9483	105.6

*: Run as positive control within each experiment

These data demonstrate that the CNP compounds of the present invention are substantially stable in the presence of recombinant human neprilysin in comparison to
5 CNP22 which is rapidly degraded.

Example 4 – Peptide net charge calculation

The charge of an ionizable group in a peptide at a given pH can be calculated using the Henderson-Hasselbalch equation using empirically determined acid dissociation
10 constants (pKa) for each amino acid residue or modifying group as is well known in the art, for example as by the method described by B. Skoog and A. Wichman (Trends in Analytical Chemistry, 1986, vol. 5, pp. 82-83.) and L. Kozłowski (Biology Direct, 2016, 11:55). This is shown for negatively charged amino acids or modifying groups in Equation 1 and for
15 positively charged amino acids and modifying groups in Equation 2, in which pK_n is the pKa of the negatively charged group and pK_p is the pKa of the positively charged group and where pH in the equation is the pH of interest. The net charge of a peptide at a given pH is then the sum of the negative and positive charges of all the ionizable groups in the peptide.

Equation 1:

20
$$\sum_{i=1}^n \frac{-1}{1 + 10^{pK_n - pH}}$$

Equation 2:

$$\sum_{i=1}^n \frac{1}{1 + 10^{pH - pK_p}}$$

For natural amino acid residues, tabulated pKa constants are used for free terminals and ionizable sites in side chains. pKa-values for modified amino acid and modifying groups were estimated by the ACD/Labs ver. 12 package and also shown in Table 4.

As an example, to calculate the net charge of compound 9482 at pH 7.4 the sum of negative charges carried by positions Cys37 (C-terminal acid), Asp27, Glu2, gGlu (1), gGlu (2), gGlu (3), gGlu (4), gGlu (5) and C18d fatty acid is minus 8.995 Fd when using the pKa values shown in Table 4. The sum of positive charges carried by positions Arg28, Lys15, Lys14, Lys10, Lys8, Arg7 and His3 is 6.162 Fd. The net charge is then the sum of the above which is minus 2.833.

Calculated charge values for selected pH (pH 7.4 and pH 6.5) using the above principle for CNP compounds of the present invention are shown in Table 5.

Table 4 - pKa values for termini, sidechains of amino acids and modifying groups used when calculating pI and net charge of CNP compounds

Residue	N-terminal	C-terminal	Side chain
Ala	7.8	3.7	N/A
Arg	7.4	3.6	13.3
Asn	6.1	3.5	N/A
Asp	7.4	3.5	4.2
Cys	6.1	3.3	9.1
Gln	6.9	3.5	N/A
Glu	8.4	3.5	4.4
Gly	7.3	3.7	N/A
His	6.1	3.1	6.7
Ile	7.9	3.7	N/A
Leu	7.9	3.7	N/A
Lys	7.2	3.6	10.4
Met	6.9	3.5	N/A
Phe	7.0	3.6	N/A
Pro	8.9	3.4	N/A
Ser	6.3	3.3	N/A
Thr	6.3	3.3	N/A
Trp	7.7	3.7	N/A
Tyr	7.3	3.7	9.8
Val	7.9	3.7	N/A
Cys in disulfide	6.1	3.3	N/A
C18d	N/A	N/A	4.8
C20d	N/A	N/A	4.8
Tetrazole-C18	N/A	N/A	5.1

gGlu	N/A	N/A	3.5
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Table 5 – Calculated values of net charge (Q) at pH 7.4 and net charge at 6.5 for CNP compounds

Chem No	Compound ID	Q (pH=7.4)	Q (pH=6.5)
1	0065	1.4	1.9
2	1510	5.4	6.4
3	0312	4.0	4.0
4	0776	4.0	4.0
5	1235	0.2	0.6
6	0262	-3.0	-3.0
7	0296	-3.0	-3.0
8	0313	-3.0	-3.0
9	0334	-3.0	-3.0
10	1221	0.0	0.0
11	1222	-1.0	-1.0
12	1223	-2.0	-2.0
13	1224	-1.0	-1.0
14	1225	-1.0	-1.0
15	1226	-3.0	-3.0
16	1227	-2.0	-2.0
17	1228	-4.0	-4.0
18	1229	-1.0	-1.0
19	1230	-2.0	-2.0
20	1231	-2.0	-2.0
21	1232	0.0	0.0
22	1233	0.0	0.0
23	1236	-1.8	-1.4
24	1237	-0.8	-0.4
25	1240	-1.8	-1.4
26	1241	-0.8	-0.4
27	1242	-2.8	-2.4

28	1274	-3.0	-3.0
29	1287	-4.0	-4.0
30	1288	-4.0	-4.0
31	1289	-4.0	-4.0
32	1290	-3.0	-3.0
33	1302	-1.8	-1.4
34	1303	-1.8	-1.4
35	1304	-2.7	-1.8
36	1305	-1.8	-1.4
37	1309	-0.8	-0.4
38	1310	-1.8	-1.4
39	1311	-1.8	-1.4
40	1312	-2.8	-2.4
41	1322	-0.5	0.9
42	1323	-1.5	-0.2
43	1324	-1.7	-0.8
44	1338	-2.0	-2.0
45	1339	-2.0	-2.0
46	1340	-0.7	0.2
47	1341	-1.7	-0.8
48	1345	-0.5	0.9
49	1346	-1.5	-0.2
50	1347	-0.8	-0.4
51	1348	-0.8	-0.4
52	1350	-0.7	0.2
53	1351	-0.7	0.2
54	1352	-1.8	-1.4
55	1353	-0.8	-0.4
56	1354	-0.8	-0.4
57	1355	0.0	0.0
58	1356	-1.0	-1.0
59	1357	-0.8	-0.4
60	1359	-0.8	-0.4
61	1360	-1.7	-0.8

62	1375	-1.0	-1.0
63	1376	-1.0	-1.0
64	1377	-1.0	-1.0
65	1378	-2.0	-2.0
66	1379	-1.8	-1.4
67	1380	-2.8	-2.3
68	1381	-2.2	0.1
69	1382	-1.7	-0.8
70	1383	-2.4	-0.5
71	9384	-1.0	-1.0
72	1385	-2.0	-2.0
73	1386	-1.0	-1.0
74	1387	-3.0	-3.0
75	1388	-2.0	-2.0
76	1389	-1.8	-1.4
77	1390	-3.8	-3.4
78	1391	-1.0	-1.0
79	1392	-2.0	-2.0
80	1393	-2.0	-2.0
81	1394	-0.8	-0.4
82	1395	-1.8	-1.4
83	1396	-1.8	-1.4
84	1398	-2.7	-1.8
85	1399	-2.7	-1.8
86	1400	-2.7	-1.8
87	1401	-3.8	-3.4
88	1402	-3.8	-3.4
89	1403	-3.8	-3.4
90	1404	-3.8	-3.4
91	1405	-3.8	-3.4
92	1406	-2.8	-2.4
93	9407	-2.0	-2.0
94	1419	-1.7	-0.8
95	1420	-1.7	-0.8

96	1421	-1.0	-1.0
97	1422	-0.8	-0.4
98	1423	-0.8	-0.4
99	1424	-1.0	-1.0
100	1425	-1.8	-1.4
101	1426	-0.8	-0.4
102	1431	-1.8	-1.4
103	1432	-1.8	-1.4
104	1434	-1.8	-1.4
105	9435	-1.0	-1.0
106	1436	-1.0	-1.0
107	1437	-1.8	-1.4
108	1448	-2.8	-2.4
109	1449	-2.7	-1.8
110	1450	-1.8	-1.4
111	1451	-0.8	-0.4
112	1452	-2.0	-2.0
113	1453	-2.0	-2.0
114	1454	-1.0	-1.0
115	1455	-1.0	-1.0
116	1456	-1.0	-1.0
117	1457	-1.0	-1.0
118	1458	-1.0	-1.0
119	1459	-1.0	-1.0
120	1460	-2.0	-2.0
121	1461	-1.8	-1.4
122	1462	-1.0	-1.0
123	1463	-1.0	-1.0
124	1464	-2.0	-2.0
125	1465	-2.0	-2.0
126	1470	-1.0	-1.0
127	1471	-2.8	-2.4
128	1472	-1.8	-1.4
129	1473	-1.8	-1.4

130	1474	-1.8	-1.4
131	1475	-2.0	-1.9
132	1476	-2.0	-1.9
133	1477	-2.0	-2.0
134	1478	-1.0	-1.0
135	9480	-2.0	-2.0
136	1481	-2.0	-2.0
137	9482	-2.8	-2.4
138	9483	-1.8	-1.4
139	1484	-1.0	-1.0
140	1486	-1.0	-1.0
141	1487	-1.0	-1.0
142	1488	-1.0	-1.0
143	1489	-1.0	-1.0
144	1493	-1.0	-1.0
145	1511	-1.0	-1.0
146	1512	-1.0	-1.0
147	1513	-2.8	-2.3
148	1514	-1.8	-1.3
149	1265	4.0	4.0
150	0106	6.1	6.6
151	0089	-1.0	-1.0
152	0230	-1.0	-1.0
153	0231	-1.0	-1.0

Example 5 – Solubility of CNP compounds

In order to assess the suitability of CNP compounds for a soluble liquid formulation, the solubility of CNP compounds in pharmaceutically relevant buffers were measured.

- 5 Solubility at two different pH-levels (pH 4.0 and pH 6.5) was examined as pH is expected to affect solubility.

Preparation of pH 4.0 samples: The pH 4.0 samples of the CNP compounds were prepared by mixing freeze dried peptide with a pH 4.0 5 mM sodium acetate, 250 mM glycerol buffer at room temperature to a nominal concentration of at least 4000-5000

nmol/mL. The pH of the samples was measured and adjusted to pH 4.0 and the samples were allowed to equilibrate at room temperature until next day if not fully dissolved.

Preparation of pH 6.5 samples: The pH 6.5 samples of the CNP compounds were prepared by dissolving the freeze dried peptide in water. While stirring, a part of the peptide solution was transferred to a buffer consisting of 41 mM sodium phosphate and 118 mg/mL glycerol, pH 7.5-8.0, followed by addition of diluted sodium hydroxide followed by another part of the peptide solution and further addition of diluted sodium hydroxide. This procedure was repeated until all of the peptide solution had been added where a nominal concentration of at least 4000-5000 nmol/mL had been reached and the buffer composition was 8 mM sodium phosphate, 23 mg/mL glycerol. The pH of the samples was measured and adjusted to pH 6.5 and the samples were allowed to equilibrate at room temperature until next day if not fully dissolved.

Procedure: Samples at pH 4.0 were prepared as described above and the compound concentration in the supernatant was determined using CAD (Method F, CAD02). The compound concentration at pH 4.0 represents the solubility at pH 4.0 and the measured values are given in Table 6.

Table 6 – Solubility of CNP compounds formulated at pH 4.0

Compound ID (chem. ref.)	Solubility at pH 4.0 (µM)
1351	6168
1381	8995
1389	8896
1422	8286
1426	11242
9435	7416
1470	6476
1473	5832
1474	6376
1478	6507
9480	23
9482	99
9483	4964
1484	0
1489	5932

Samples at pH 6.5 were prepared as described above and peptide concentration in the supernatant was determined by CAD (Method F, CAD02). The peptide concentration at pH 6.5 represents the solubility at pH 6.5 and the measured values are given in Table 7.

Table 7 – Solubility of CNP compound formulations at pH 6.5

Compound ID	Solubility at pH 6.5 (µM)
0745	872
1218	2160
1303	4840
1304	6661
1310	7610
1318	6100
1352	7727
1354	440
1375	3131
1377	443
1378	8923
1379	2674
1382	3175
9384	7559
1386	490
1389	426
1392	9877
1402	10021
1404	6883
1406	5670
9407	6687
1411	3296 (at pH 5.5)
1417	1928
1419	318
1420	1409
1421	857
1432	9825
1434	8514

9435	2356
1453	7885
1457	8955
1470	595
1473	1764
1474	969
1477	5346
1478	2177
9480	6166
9482	5323
1484	2332

As a rule of thumb, only samples containing more than 4000 μM were subjected to further testing as described below.

- These results demonstrate the CNP compounds of the present invention can be
- 5 formulated in pharmaceutically relevant buffers at concentrations suitable for s.c. administration.

Example 6 – Thioflavin T (ThT) assay

- The ThT assay was used to evaluate physical stability of the CNP compounds and
- 10 their suitability for liquid formulation. Low physical stability of peptides may lead to amyloid fibril formation, which is observed as well-ordered, thread-like macromolecular structures in the sample eventually resulting in gel formation. This has traditionally been tested by visual inspection of the sample. However, that kind of measurement is very subjective and
- 15 depending on the observer. Therefore, the application of a small molecule indicator probe is much more advantageous. Thioflavin T (ThT) is such a probe and has a distinct fluorescence signature when binding to fibrils [Naiki et al. (1989) Anal. Biochem. 177, 244-249; LeVine (1999) Methods. Enzymol. 09, 274-284].

- Procedure: Thioflavin T was added to the supernatant samples from Example 5 (pH 4.0 and 6.5) using an aqueous ThT stock solution to a final concentration of about 1 μM in
- 20 the samples. Sample aliquots of 150 μL were placed in a 96 well microtiter plate (Packard OptiPlate™-96, white polystyrene). Usually, two to three replicas of each sample were applied to the plate. The plate was sealed and placed in a fluorescence plate reader (Fluoroskan Ascent FL) and incubated at 37 °C with orbital shaking (960 rpm; 1 mm amplitude). Fluorescence measurements were performed every 20 minutes using excitation

through a 444 nm filter and measurement of emission through a 485 nm filter. Between each measurement, the plate was shaken and heated as described above and the assay was terminated after 45 hours. Fluorescence measurements for each microtiter plate well were plotted against time and the lag-time (time until an increase in ThT fluorescence was observed) was estimated.

To assess loss of dissolved peptide following 45h incubation, peptide recovery was measured as the ratio between total peak area after incubation vs. before incubation using the RP-UPLC method described below.

Measurement of LagTime and Peptide recovery % using RP-UPLC: RP-UPLC was conducted using an Acquity UPLC BEH C18 1.7 μ m (2.1 x 30 mm) Waters column (Eluent A: 0.1 %v/v% TFA in water; Eluent B: 0.1 %v/v TFA in acetonitrile/water 4:1) with gradient elution (0 min: 95% A; 2 min: 20% A; 2.3 min: 20% A; 2.4 min: 95% A; 9 min: 95% A) in a flow rate of 0.9 mL/min and a column temperature of 30 °C. UV-detection at 215 nm was used to assess the total peptide area.

Samples at pH 4.0 were prepared as described in Example 5 and subjected to the ThT assay as described above. LagTime and Peptide recovery values are given in Table 8.

Table 8 – ThT assay lagtime and peptide recovery of CNP compounds at pH 4.0

Compound ID	LagTime (h) at pH 4.0	Peptide Recovery (%) at pH 4.0
1351	45	110
1381	45	112
1422	45	99
1426	0.33	0
1389	45	117
9435	45	111
1473	45	118
1470	45	121
1474	45	161
1478	0.33	3
9483	45	74
1489	45	99

Samples at pH 6.5 were prepared as described in Example 5 and subjected to the ThT assay as described above. LagTime and Peptide recovery values are given in Table 9.

Table 9 – ThT assay lagtime and peptide recovery of CNP compounds at pH 6.5

Compound ID	LagTime (h) at pH 6.5	Peptide Recovery (%) at pH 6.5
1318	45	105
1218	45	89
1303	5	16
1310	45	117
1375	45	88
1304	45	141
1352	23	0
9384	45	135
9407	45	128
1411	45	112
1417	45	119
1382	45	157
1432	45	188
1434	45	127
1378	2.5	23
1392	45	118
9435	45	99
1402	45	123
1404	45	148
1406	45	120
1453	45	109
1457	45	109
1477	23	16
1478	45	99
9480	45	104
9482	45	93
1484	4	98

In conclusion this experiment demonstrates that most CNP compounds of the invention can be formulated in pharmaceutically relevant buffers with low propensity towards
5 fibril formation.

Example 7 – Measurement of High-Molecular-Weight-Protein (HMWP)

In order to assess the propensity of CNP compounds to form covalent dimers or oligomers when formulated the High-Molecular-Weight-Protein content of CNP compound formulations at pH 4.0 and 6.5 were determined.

Procedure: The relative amount of covalent HMWP was assessed using SEC-UPLC. SEC-UPLC was conducted using a Waters UPLC Protein BEH SEC column, 125Å, 4.6 x 150 mm, 1.7 µm, with isocratic elution (0.3 M NaCl, 10 mM NaH₂PO₄ and 5 mM H₃PO₄, 50% (v/v) isopropanol, pH 2.4) with a flow rate of 0.3 mL/min, a column temperature at 50 °C with UV-detection at 215 nm. The total area of peaks eluting prior to the monomeric main peak was termed HMWP and given on a percentage scale relative to the total peptide peak area.

Results: HMWP Formation Following 2-Weeks Quiescent Incubation at 37 °C: Samples at pH 4.0 were prepared as described in Example 5 and the amount of HMWP was determined as described above. Samples were incubated for two weeks at 37 °C and the amount of HMWP was determined again. The increase in HMWP over two weeks incubation at 37 °C are reported in Table 10 (in case the incubation period deviated from two weeks the increase in HMWP was normalized to two weeks assuming a constant formation rate).

Table 10 – 2-Week HMWP formation at pH 4.0 (%)

Compound ID	% relative to total peak area
1351	1.94
1381	0.84
1422	36
1389	1.43
9435	1.07
1473	0.9
1470	1.75
1473	1.26
1474	1.6
1478	1.98
9483	3.0
1489	2.12

Samples at pH 6.5 were prepared as described in Example 5 and the amount of HMWP was determined as described above. Samples were incubated for two weeks at 37 °C and the amount of HMWP was determined again. The increase in HMWP over two weeks incubation at 37 °C are reported in Table 11 (in case the incubation period deviated from two weeks the increase in HMWP was normalized to two weeks assuming a constant formation rate).

Table 11 - 2-Week HMWP formation at pH 6.5 (%)

Compound ID	% relative to total peak area
1318	1.18
1218	0.43
1310	0.87
1304	1.55
1352	0.82
9384	1.5
9407	12
1411	0.62
1417	3.19
1382	0
1432	2.89
1434	3.2
1378	6.67
1392	0.33
9435	1.93
1402	2.19
1404	1.8
1406	2.77
1453	3.94
1457	3.24
1477	1.83
9480	2.65
9482	1.96

In conclusion, this experiment demonstrates that CNP compounds of the invention can be formulated in pharmaceutically relevant buffers with low propensity towards HMWP formation.

5 **Example 8 – Accelerated chemical stability of CNP compounds**

 In order to determine the chemical stability of CNP compounds in formulation, samples of CNP compounds in buffer were exposed to accelerated chemical degradation by heating. The stability of a given peptide was assessed by measuring recovery of intact peptide by quantification by RP-UPLC. To assess the chemical degradation pattern samples
10 were also analysed by LC-MS.

Sample preparation: Samples for the 2 week study were prepared according to the principles described in Example 5.

 Samples for the 6 week study were prepared by dissolving lyophilized peptide in buffer (8 mM phosphate, 250 mM glycerol, pH 7.4) to a nominal peptide concentration of
15 5000 nmol/ml followed by pH adjustment with 0.1N HCl to pH 6.5.

Incubation: For the 2 week study a time-zero (TZ) sample was pulled and stored at -18 °C and the remaining volume was incubated at 37 °C. Samples were pulled and stored at -18 °C after 2 weeks of incubation. Frozen samples were thawed, diluted to about 200 nmol/mL and the extent of chemical degradation was determined using LCMS as described.

20 For the 6 week study a time-zero (TZ) sample was pulled and stored at -18 °C and the remaining volume was incubated at 37 °C. Samples were pulled on a weekly basis and stored at -18 °C until the last sampling time point at 6 weeks. Frozen samples were thawed, diluted to about 200 nmol/mL and the extent of chemical degradation was determined using RP-UPLC and LCMS as described.

25 Analysis of peptide recovery by RP-UPLC: The RP-UPLC method was performed on a Waters ACQUITY H-CLASS UPLC system fitted with a PDA detector. Separation was carried out on an ACQUITY UPLC BEH C8 Column (130Å, 1.7 µm, 2.1 mm X 150 mm) operating at a column temperature of 50 °C with eluent A (19.59 mM NH₄H₂PO₄ 41.71 mM (NH₄)₂HPO₄, pH 6.5 and MeCN 9:1 v:v) and eluent B (80 % MeCN in water). UV-detection
30 was carried out at 214 nm. The analysis was performed by injection of 3 µL of sample onto the column which was eluted with a 1-step linear gradient of eluents A and B from 27 to 30% B over 20 minutes followed by a wash at 95% B over 2 minutes followed by a re-equilibration phase for 7 minutes at a constant flow rate of 0.3 mL/min. This yielded an analysis time of 30 minutes per sample. The area of the peak corresponding to intact CNP compound was given
35 on a percentage scale relative to the total peptide peak area.

Analysis of chemical degradation patterns by LCMS: Samples were analysed on a VANQUISH UPLC from Thermo Scientific, using a Waters Acquity C18 reversed-phase column, 300Å, 1.7 µM particles 1 mm x 150 mm. The compounds were separated by a linear gradient of solvent B from 5% to 55% over 48 minutes, using solvent A: water, 0.1% formic acid with 0.02% TFA and solvent B: acetonitrile, 0.1% formic acid with 0.02% TFA. Mass spectra were acquired by a Q Exactive Plus hybrid Quadrupole-Orbitrap mass spectrometer, BioPharma option (Thermo Scientific) interfaced with H-ESI II ion source. Data acquisitions were performed with a m/z 500 to 2000 scan range and a resolution of 30000.

The data list was aggregated into a summed table of the compounds. The table headers were defined as follows:

“Recovery”: The compound peak (i.e. the main peak intensity at time zero possessing the compounds monoisotopic mass) recovery’s are normalized to the compound peak at a given time point; “Isomers”: as the summed intensity of peaks with isobaric masses to the main compound, which segregate in the RT dimension; “Loss of 18 amu”: i.e., the summed intensity of peaks with masses 18 amu lower than the CNP compound peak, which segregate in the RT dimension; Fragments: the summed intensity of peaks with a mass 50 amu lower than the compound peak and peaks with a mass 18 amu higher than the compound mass, which segregate in the RT dimension and develop over time and assumed to be derived from hydrolytic peptide backbone cleavage; and finally “Others”: contains the sum intensities of peaks with a 32 amu addition or dimers of the main peak, which develop over time.

Results: The results from LCMS analysis of a 2 week accelerated degradation study on several CNP compounds of the present invention are summarised in Table 12. The results from RP-UPLC and LCMS analysis of a 6 week accelerated degradation study on CNP compound 9482 (Chem. 137) is summarised in Table 13 and Table 14 respectively.

Table 12 – Recovery and chemical degradation pattern of CNP compounds after 2 weeks incubation at 37 °C:

Compound	Buffer	Recovery		Isomers		Loss of 18 amu		Fragments		Others	
		TZ	2W	TZ	2W	TZ	2W	TZ	2W	TZ	2W
9407	8 mM sodium phosphate, 250 mM	100	98.5	0	1.1	0	0	0	0.7	0.1	0.3

	glycerol pH 6.5										
9435	5 mM sodium acetate, 250 mM glycerol, pH 4	100	92.9	0	0.6	0	4.1	0	0	0.0	0.0
9480	8 mM sodium phosphate, 250 mM glycerol, pH 6.5	100	100.5	0	0	0	0	0	0	0.0	0.6
9482	8 mM sodium phosphate, 250 mM glycerol, pH 6.5	100	99.6	0	0	0	0	0	0	0.0	0.3
9483	5 mM sodium acetate, 250 mM glycerol, pH 4	100	96.2	0	0	0	0	0	0	0.2	0.6

Table 13 – RP-UPLC analysis of peptide recovery of CNP compound [9482] over 6 weeks:

Compound	% relative to total peak area						
	TZ	1 Week	2 Week	3 Week	4 Week	5 Week	6 Week
9482 (Chem. 137)	90.6	89.1	89.1	86.9	85.5	83.5	81.8

Table 14 – LCMS analysis of recovery and chemical degradation pattern of CNP compound 9482 (Chem. 137) over 6 weeks:

Compound no.	Time						
9482	TZ	1W	2W	3W	4W	5W	6W
Recovery	100.00	100.10	99.50	98.90	95.10	94.70	92.30
Isomers	0.00	0.00	0.60	1.20	1.70	2.40	3.90
Loss of 18 amu	0.00	0.00	0.10	0.10	0.20	0.20	0.30

Fragments	0.00	0.20	0.30	0.50	0.90	0.80	1.20
Others	0.20	0.30	0.30	0.30	0.50	0.40	0.50

These data show that a CNP compound according to the present invention display substantial chemical stability in formulation.

5 **Example 9 - Local tolerance of CNP compounds in rats**

The purpose of this study was to evaluate the local tissue reaction to subcutaneous injection of CNP compounds in rats.

10 Procedure: The CNP compounds were formulated according to the principles described in General Methods of Preparation - Method G. Each Sprague Dawley rat (male, 10-11 weeks of age at arrival, Janvier, France) was dosed s.c. with 250 or 350 μ L of the same compound (formulation concentration of 1000 nmol/mL) 120 h prior to tissue collection resulting in a total of two injections for each animal (Table 15). Injection site (flank or neck) was alternated across animals within each group and time point.

Table 15 - Experimental timeline for local tolerance study in rats

Time point	Study activity
Day 0	Shaving (e.g. neck) followed by 1 st dose into shaved area
Day 3	Shaving (e.g. flank)
Day 4	2 nd dose into shaved area (e.g. flank)
Day 5	Observation of skin, tissue collection and termination

15

Animals had access to tap water and food (Altromin 1324) ad libitum. Group size was $n = 3$ for vehicles and positive control, and $n = 4$ for test compounds. Vehicles and compounds were formulated in either 5 mM sodium acetate, 250 mM glycerol, pH 4.0 or 8 mM sodium phosphate, 250 mM glycerol, pH 7.4 as shown in Table 16.

20 The animals were anesthetized with isoflurane. Via an electric shaving machine, a squared area of fur (2 cm x 2 cm) was removed either from the rats' neck or flank area). For dosing, a new injection needle (25G canula, 1 ml syringe) was placed in the middle of the square border closest to the animal's head and the needle was inserted into the skin from the border towards the center of the square. Hence, the needle tip was located in the center of the square, the location was marked with a permanent pen and the formulation was inserted
25 in the center of the square. On the day of tissue collection, the rats were deeply anaesthetized with isoflurane and euthanized by exsanguination. The injection sites were

inspected and scored with regards to pathological lesions. The injection sites were evaluated, and any changes were noted (location, colour, shape and size), and sampled for histology preparation.

- 5 The injection sites were removed and fixed in 4% phosphate buffered neutral formaldehyde in sealed plastic containers.

- Each injection site was subsequently cut into three sections 0.8 cm, 1.0 cm and 1.2 cm from the square border where the injection needle was placed, and, respectively, these sections represented the injection sites and the adjacent tissue. The tissue was processed, embedded in paraffin and cut in 2-4 μ m thin sections, stained with the haematoxylin and eosin (H&E), and evaluated microscopically with a light microscope. Histopathological changes were graded on a 5-level scale (Minimal (Min), Mild (Mil), Moderate (Mod), Marked (Mar) and Severe (Sev)). The studies are summarised in Table 16.

Table 16 - Overview of compound, timepoint for sampling, and formulations

Compound ID	Dosing volume	Timepoint for sampling (days post injection)	Formulations
1351	350 μ l	5	pH=4.01; 947 nmol/ml compound 1351; 8 mM phosphate; 250 mM glycerol
9384	350 μ l	5	pH=7.39; 1032 nmol/ml 9384; 8 mM phosphate; 250 mM glycerol
9407	350 μ l	5	pH=7.40; 1046 nmol/ml 9407; 8 mM phosphate; 250 mM glycerol
1420	350 μ l	5	pH=3.98; 1021 nmol/ml compound 1420; 5 mM acetate; 250 mM glycerol
Inactive control: 1265	350 μ L	5	pH=4; 1042 nmol/ml 1265; 5 mM acetate; 250 mM glycerol

Positive net charge control: 0776	250 µl	5	pH=4.02; 4417 nmol/ml 0776; 5 mM acetate; 240 mM propylene glycol
	350 µl	5	pH=4.02; 1019 nmol/ml compound 0776; 5 mM acetate; 250 mM glycerol

Results: The results from the local tolerance study are summarised in Table 17.

Table 17 - Severity and incidence of local subcutaneous reactions* 4 or 5 days after injection of different compounds in rats.

Compound ID	Number of injection sites evaluated	Number of injections by severity of necrosis					
		NAD **	Min.	Mil.	Mod.	Mar.	Sev.
1351	4	4					
9384	4	4					
9407	4	4					
1420	4	3		1			
1265	2					2	
Positive net charge control: 0776	3					3	
	3				1	2	

5

* Necrosis was used as a marker for local subcutaneous reactions; **NAD = No Abnormalities Detected

Conclusions: The positive net charge control 0776 showed moderate to marked local subcutaneous necrosis 5 days after subcutaneous injections in the rat.

- 10 In comparison the compounds 1351, 9384, 9407 and 1420 showed no or mild local subcutaneous necrosis 5 days after subcutaneous injections in the rat and were all assessed as acceptable for human subcutaneous administration.

Example 10 - CNP local tolerance study in LYD pigs

The purpose of this study was to evaluate the local tissue reaction response to subcutaneous injection of CNP compounds in pigs.

- 5 Procedure: In domestic pigs, the injection site was subjected to histopathologic examination after subcutaneous dosing. Injections were placed mid-back between the shoulder and hip on both sides of the dorsal midline, and one or two days before injection sites of 2x2 cm were shaved and marked by permanent ink under light anaesthesia.

- Each injection consisted of 100 or 200 µl formulation with a concentration of approx.
10 4400 µM. CNP compound formulations were prepared according to the principles in General Methods of Preparation - Method G, and were either A) 8 mM sodium phosphate, 250 mM glycerol, pH 6.5, B) 5 mM sodium acetate, 250 mM glycerol, pH 4.0 or C) 5 mM sodium acetate, 240 mM propylene glycol, pH 4.0 and physiological saline was included as negative control.

- 15 On Day 1 the pigs were lightly anaesthetised. An insulin pen (NovoPen 4) and insulin needle (NovoTwist 32G/5mm) were used for accurate deposition of the CNP formulations in the subcutaneous fat tissue with the needle perpendicular to the skin. On Day 5 (4 days post injection) or 6 (5 days post injection), the pigs were euthanised, and the injection sites were removed and fixed in 4% phosphate buffered neutral formaldehyde in
20 sealed plastic containers. The tissue blocks were prefixed for 2-4 hours in 10% buffered formalin, cut into 2 mm thick slabs with a multi knife, examined for macroscopic changes and finally fixed overnight in cassettes. Two slabs of tissue were selected for light microscopic evaluation where the tissue reaction was maximal or alternatively in the central part of the injection site. Three to four 2-4 µm sections were cut from three levels at 100 µm distance,
25 stained with haematoxylin and eosin (H&E) and evaluated in a light microscope. Histopathological changes were graded on a 5-level scale ((Minimal (Min), Mild (Mil), Moderate (Mod), Marked (Mar) and Severe (Sev)). The studies are summarised in Table 18.

Table 18 - Overview of compound, timepoint for sampling and formulations:

Compound ID	Timepoint for sampling (days post injection)	Formulations
9384	5	pH=6.57; 3988 µM compound 9384; 8 mM phosphate; 250 mM glycerol (A)

9407	5	pH=6.50; 4343 µM compound 9407; 8 mM phosphate; 250 mM glycerol (A)
9435	5	pH=4.00; 4362 µM compound 9435; 5 mM acetate; 250 mM glycerol (B)
9480	4	pH=6.46; 4362 µM compound 9480; 8 mM phosphate; 250 mM glycerol (A)
9482	4	pH=6.49; 4383 µM compound 9482; 8 mM phosphate; 250 mM glycerol (A)
9483	4	pH=3.96; 4385 µM compound 9483; 5 mM acetate; 250 mM glycerol (B)
0106	5	pH=5.5; 4321 µM compound 0106; 1.33 mM citric acid monohydrate; 3.67 mM citrate, trisodium; 52 mg/ml trehalose; 15 mg/ml D-mannose; 0.73 mg/ml L-methionine; 0.05 mg/ml polysorbate 80
Positive net charge control: 0776	5	pH=4.02; 4157 µM compound 0776; 5 mM acetate; 240 mM propylene glycol (C)
Positive net charge control: 1235	5	pH=4.05; 4528 µM compound 1235; 5 mM acetate; 250 mM glycerol (B)

Results: The results are summarised in Table 19. * Necrosis was used as a marker for local subcutaneous reactions; **NAD: No Abnormalities Detected

Table 19 - Severity and incidence of local subcutaneous reactions 4 or 5 days after injection of different compounds in pigs:

5

Compound ID	Number of injection sites evaluated	Number of injections by severity of necrosis

Severity grade		NAD *	Min.	Mild	Mod.	Mar.	Sev.
9384	4	3	1				
9407	4	3	1				
9435	4		3	1			
9480	4	4					
9482	4	4					
9483	4	2		1	1		
0106	4	4					
Positive net charge control: 0776	4				1	3	
Weakly positive net charge control: 1235	4		2	2			

In conclusion the positive net charge control compound 0776 showed moderate to marked local subcutaneous necrosis 5 days after subcutaneous injections in the pig, whereas the net positively charged CNP peptide 0106 without a fatty acid albumin binder attached shows no observable injection site reactions.

In comparison the compounds 9480 and 9482 showed no local subcutaneous necrosis 5 days after subcutaneous injections in the pig; compounds 9384 and compounds 9407 showed no to minimal local subcutaneous necrosis 5 days after subcutaneous injections in the pig; compounds 9435 and 1235 showed minimal to mild local subcutaneous necrosis 5 days after subcutaneous injections in the pig and compound 9483 showed no to moderate local subcutaneous necrosis 5 days after subcutaneous injections in the pig. The compounds 9384, 9407, 9435, 9480 and 9482 were all assessed as acceptable for human subcutaneous administration.

Example 11 – PK/PD of CNP compounds after i.v. and s.c. administration to rats

In order to assess the i.v. and s.c. PK/PD profile of CNP compounds of the present invention, formulations of CNP compounds were administered to rats, blood samples taken and exposure and cGMP response measured.

- 5 cGMP biomarker assay: The biological activity of CNP compounds *in vivo* was assessed by measuring cGMP in plasma samples by plasma protein precipitation followed by quantification with LC-MS/MS.

To evaluate the cyclic guanosine monophosphate (cGMP) biomarker response in biological samples, after administration of CNP compounds to study animals, a plasma
10 protein precipitation procedure was applied, followed by liquid chromatography with tandem mass spectrometric (LC-MS/MS) analysis. In principle, the concentration of cGMP in study plasma samples, was determined using a standard curve prepared with a stable isotope labelled (SIL) surrogate analyte ($^{13}\text{C}_{10}$ $^{15}\text{N}_5$ cGMP) as a reference. The surrogate analyte was spiked in pooled authentic blank matrix to cover an analytical range of 5 nM – 2000 nM. 8-
15 Methoxymethyl-3-isobutyl 1-methylxanthine (MMPX) was used as an internal standard. The plasma protein precipitation procedure was conducted using an organic solvent to precipitate the plasma protein, leaving a supernatant that contained the cGMP molecules which would then be analysed on the LC-MS/MS instrument.

To prepare the standard samples, frozen authentic blank plasma matrix was thawed
20 and subsequently centrifuged for 5 min at 4000 RPM, at 4 °C. A stock solution of SIL-cGMP was used to prepare a standard of 2000 nM in blank plasma, which is then transferred to a 1 mL Eppendorf 96-well plate (Pat. 8,636,965). This was placed in a liquid handler (TECAN Fluent 78) to prepare standards and QCs (5, 10, 20, 50, 100, 200, 500, 1000, 2000 nM) by serial dilution in blank plasma in a 96-well microplate (Chimney Well 651201). Blank plasma
25 samples were prepared in the same plate. Study samples were thawed by ventilation for 10 min at ambient temperature, shaken on a table shaker for 5 min at ambient temperature, and subsequently centrifuged for 5 min at 4000 RPM at 4 °C. The samples were then placed in the liquid handler to perform the plasma protein precipitation procedure. A volume of Standards, QCs, Zero, and study samples were precipitated with 4 volumes of acetonitrile
30 (OPTIMA® LC/MS Grade) containing 30 nM of MMPX (Sigma #M2547). The samples were then shaken on a table shaker for 4 min at ambient temperature, and subsequently, centrifuged for 30 min, at 4000 RPM at 4 °C, whereafter the supernatant was transferred to a new 96-well microplate. The plates were subsequently evaporated using an Eppendorf concentrator plus™ for 60 min at 30 °C. Residues were reconstituted in a volume of 5%
35 acetonitrile and 0.1% formic acid (RATHBURN LC/MS Grade), shaken on a table shaker for

2 min at ambient temperature and centrifuged for 10 min at 4 °C. The prepared samples were then analysed on a LC-MS/MS instrument (Sciex ExionLC™ coupled to a Sciex 6500+ Triple quadrupole). Gradient elution was applied on the reverse-phase LC, using 0.1% formic acid as mobile phase A and 95% acetonitrile and 0.1 % formic acid as mobile phase B. A

- 5 Waters Acquity UPLC® CSH™ Fluoro-Phenyl 1.7 µm, 2.1x100mm column, was used as a stationary phase and thermoregulated at 60 °C. SIL-cGMP, endogenous cGMP, and MMPX were detected in the MS/MS in positive ion mode by selective reaction monitoring.

- Acceptance criteria for the analytical run: The SIL-cGMP standard curve was established with a 1/x² weighting and was evaluated in terms of linearity, precision, and
10 accuracy. At least 75% of the calibration standards had to meet the following criteria when back calculated: Calibration standards had to fall within ± 15% of the nominal concentration of the respective calibration standards, except for LLOQ that had to fall within ± 20% of the nominal concentration of the LLOQ standards. Values falling outside these limits must be discarded provided they did not change the established model. If discarding one calibration
15 standard resulted in another calibration standard being outside the boundaries, then this calibration standard was also discarded.

- At least two-thirds of the QC samples had to be within 15% of their respective nominal values. One-third of the QC samples could be outside 15% of their respective nominal value, but never more than 50% of the QC samples at the same nominal
20 concentration.

- Quantitative plasma analysis of CNP-compounds: Plasma concentrations of CNP compounds were assayed by plasma protein precipitation and analysed by turboflow liquid chromatography mass spectrometry (TF-LC-MS). Calibrators were prepared by spiking either blank rat or minipig plasma with the relevant CNP compound in the range from 0.5 to 2000
25 nM. Calibrators, plasma blanks or study samples were prepared for TF-LC-MS by protein precipitation by adding three or four volumes of either ethanol or methanol containing 20 nM of internal standard to one volume of sample. For some compounds, formic acid was added to the precipitation reagent (the final concentration was 1% v/v). After the addition of the precipitation reagent, the mixture was centrifuged at 6200 rpm at 4 °C for 30 minutes. After
30 centrifugation, one volume of supernatant was mixed with two volumes of water (with 1% v/v formic acid). The mixture was analysed by TF-LC-MS using a Cyclone turboflow column (0.5 x 50 mm, ThermoFisher Scientific) and either a XBridge Protein BEH C4 3.5 µm 300Å or a XBridge Protein BEH C18 3.5 µm 130Å analytical column (both were 50 x 2.1 mm and obtained from Waters). A gradient elution was conducted using mobile phase A (consisting of
35 milli-Q water with 1% formic acid and 5% methanol/acetonitrile (50/50)) and mobile phase B

(consisting of methanol/acetonitrile (50/50) with 1% formic acid and 5% milli-Q water). The mass spectrometer was operated in positive ionisation mode. A TSQ Altis mass spectrometer (ThermoFisher Scientific) was used as detector in selected reaction monitoring mode (specific transition were optimised for each CNP compound). Linear calibration curves (weighed 1/x²) were used for calculating the concentration in the plasma samples. Quality control samples were included. The deviation between nominal and calculated concentration in the calibrators and quality control samples were below 15%.

Animals and dosing: Groups of 4-6 rats (male, Sprague Dawley, 350 g at arrival, Janvier, France) per compound and route of administration were dosed with a CNP compound formulated either in A) 8mM sodium phosphate, 250 mM glycerol, 0.007% polysorbate 20, pH 7.4 or B) 5 mM sodium acetate, 250 mM glycerol, 0.007% polysorbate 20, pH 4.0 depending on the respective compound. S.c. dose was 300 nmol/kg, at a concentration of 1000 nmol/L resulting in a dosing volume of 0.3 mL/kg, whereas i.v. dose was 100 nmol/kg, at a concentration of 100 nmol/L resulting in a dosing volume of 1 mL/kg.

Sampling: Sublingual blood samples of 250 μ L were collected from unanaesthetised rats in EDTA-coated vials (Microvette 600K3E ref # 15.1673.100 Sarstedt) at baseline (-1 h before dosing) as well as 5 min (only i.v. dosed groups), 2 h, 6 h, 24 h, 48 h and 72 h (only for exposure analysis) post-dosing. The blood samples were quickly stored on ice and centrifuged (4 °C, 8000 RPM, 5 min) within 10 min of collection. Plasma samples of 50 μ L were transferred to each micronic tube for either exposure or cGMP analysis, kept on dry ice and stored in a freezer (-20 °C). Rats had access to food (Altromin) and tap water ad libitum.

Analysis: PK parameters were calculated by non-compartment analysis (NCA) using software Phoenix WinNonlin (ver. 8.1 or later, Certara) for each animal. Clearance (Cl) was calculated as: Dose / AUC_{inf} (linear up, log down). Half-life ($t_{1/2}$) was calculated as $\ln(2) / \lambda$ where λ is estimated by linear regression of time vs. log concentration, typically in a time range between 2 to 48 hours (e.g. from 6 to 48 hours). Bioavailability was calculated as dose normalized AUC's: (AUC(sc) / Dose(sc)) / (AUC(iv) / Dose(iv)). Values in the table are means from individual animals (n = 4-6 individual animals). The subsequent plots for cGMP plasma concentration versus time are (Y-axis) mean cGMP concentration (n= 4-6 individual animals) after IV dosing and (X-axis) nominal plasma sampling time.

Results: The PK data with clearance (CL), half-life $T_{1/2}$ and bioavailability (F%) are summarised in Table 20. Plasma cGMP concentrations after i.v. dosing of CNP compounds

are shown in Figures 1-27, the dose is shown in Table 20. Plasma cGMP are reported as the mean.

Table 20 – Pharmacokinetic profile of CNP compounds dosed i.v. or s.c. in rats

	i.v. administration			s.c. administration		
Compound ID	Dose (nmol/kg)	Cl (L/hr/kg)	T _{1/2} (hr)	Dose (nmol/kg)	T _{1/2} (hr)	F (%)
1225	91	0.0103	5.03	286	5.1	61.2
1227	102	0.0168	3.56	n.d.	n.d.	n.d.
1233	101	0.0246	1.42	287	3.57	33.8
1241	92	0.0164	2.78	n.d.	n.d.	n.d.
1351	102	0.0093	6.07	n.d.	n.d.	n.d.
1352	102	0.0102	6.34	n.d.	n.d.	n.d.
1354	100	0.00652	7.56	n.d.	n.d.	n.d.
1356	102	0.0141	3.47	n.d.	n.d.	n.d.
1375	100	0.0057	9.66	n.d.	n.d.	n.d.
1376	103	0.00418	9.55	n.d.	n.d.	n.d.
1377	94	0.00747	6.29	n.d.	n.d.	n.d.
1378	100	0.00926	5.29	n.d.	n.d.	n.d.
1379	90	0.0051	9.8	n.d.	n.d.	n.d.
1381	94	0.00382	15.2	n.d.	n.d.	n.d.
9384	99	0.00493	9.15	306	9.47	49.7
1386	91	0.00605	8.16	n.d.	n.d.	n.d.
1389	95	0.00415	14.6	n.d.	n.d.	n.d.
1392	95	0.00799	5.72	n.d.	n.d.	n.d.
9407	94.2	0.00515	15.2	309	14.9	37.2
1420	100	0.00764	8.34	306	9.47	49.7
1426	94	0.00348	9.96	n.d.	n.d.	n.d.
1434	100	0.00764	8.34	n.d.	n.d.	n.d.
9435	93	0.00458	10.4	n.d.	n.d.	n.d.
9482	102	0.00549	14.5	323	18.6	71.5
0312	99.8	0.00738	9.4	300	8.24	20.2
0776	100	0.00613	10.7	267	5.63	7.35

1235	93.9	0.0115	6.2	329	6.28	65.8
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In conclusion this experiment shows that the CNP compounds of the present invention show prolonged half-lives and reduced clearance in a *in vivo* rat model. Furthermore, the experiment shows that the CNP compounds are biologically active based on their ability to elicit a cGMP response in the dosed animals (Figure 1-27).

Example 12- PK/PD of CNP compounds after i.v. and s.c. administration to minipigs and LYD pigs

The purpose of this study was to investigate pharmacokinetic and pharmacodynamic properties after intravenous (i.v.) and subcutaneous (s.c.) administration to Göttingen Minipig and domestic LYD pig, and to estimate bioavailability after s.c. dosing. Quantitative plasma analysis of CNP and cGMP levels were performed as described in Example 11.

Animals and dosing: The pharmacokinetic and pharmacodynamic studies in Göttingen Minipig or domestic LYD pig were conducted at CRO Minerva Imaging or Novo Nordisk A/S, respectively. CNP compounds were dosed to normal female 1) Göttingen minipigs 6-12 months of age with an average weight of 22 kg or 2) domestic LYD pigs 4-5 months of age with an average weight of 80 kg. At least one week prior to dosing, permanent central venous catheters were implanted for blood sampling and intravenous (i.v.) dosing. For subcutaneous (s.c.) dosing, the pigs were ultrasound scanned and the optimal injection area laterally on the neck marked by a permanent tattoo. An insulin pen (NovoPen Echo or NovoPen 4) and insulin needle (NovoFine 32G/4mm or NovoTwist 32G/5mm) were used for accurate deposition of the CNP formulations in the subcutaneous fat tissue with the needle perpendicular to the skin.

CNP compounds were formulated according to the principles in General Methods of Preparation - Method G and were either A) 8 mM sodium phosphate, 250 mM glycerol, pH 6.5, B) 5 mM sodium acetate, 250 mM glycerol, pH 4.0, C) 5 mM sodium acetate, 240 mM propylene glycol, pH=4.0, D) 8 mM sodium phosphate, 250 mM glycerol, pH 7.5 or E) 20 mM sodium phosphate, 223 mM propylene glycol, pH 6.0.

Intravenously, the CNP compounds were dosed at 30-60 nmol/kg to Minipig and 15-43 nmol/kg to domestic pig using formulations A-E. Subcutaneously, the CNP compounds were dosed at 55-62 nmol/kg to Minipig and 20-30 nmol/kg to domestic pig using formulations A-D.

Sampling: Blood samples of approximately 1 mL were collected pre dose and up to 14 days post dose into EDTA-coated tubes (8 mM) for cGMP and CNP compound analysis by LC-MS. In few instances, cGMP was only analysed up to 48 hours post dose after intravenous dosing in domestic LYD pig. The blood samples were kept on wet ice for maximum 30 minutes until centrifugation for 10 minutes at 4 °C and minimum 1500G, and the plasma samples were stored at -20 °C until analysis.

Plasma concentration–time profiles were analyzed by non-compartmental PK analysis using Phoenix WinNonlin 8.1, Pharsight Inc., Mountain View, CA, USA. Calculation of the area under the plasma concentration–time curve (AUC) was based on the “linear up log down” method, and uniform weighting was used for estimation of the terminal rate constant (λ_z). S.c. bioavailability (F) was calculated as the dose-normalized AUC (AUC/dose) after s.c. administration divided by the AUC/dose after i.v. administration.

Results: The PK data with clearance (CL), half-life $T_{1/2}$ and bioavailability (F%) in minipig are summarised in Table 21. The PK data with clearance (CL), half-life $T_{1/2}$ and bioavailability (F%) in LYD domestic pig are summarised in Table 22. Plasma cGMP concentrations after i.v. or s.c. dosing of CNP compounds in minipigs and domestic pigs are shown in Figures 28-48 the dose is shown in Tables 21 and 22. Plasma cGMP are reported as the mean of n=2-4 for 14 days in minipigs and the mean of n=2-4 for 2 days in domestic LYD pigs.

Table 21. Pharmacokinetic parameters after i.v. and s.c. administration of CNP compounds to Göttingen Minipig:

Compound ID	Göttingen Minipig							
	Intravenous PK				Subcutaneous PK			
	Dose (nmol/kg)	n	CL (ml/hr/kg)	$T_{1/2,iv}$ (h)	Dose (nmol/kg)	n	$T_{1/2,sc}$ (h)	F (%)
9384	60	3	1.53	61	60	3	61	78
9407	62	3	1.20	82	60	3	92	86
9435	55	4	1.02	77	60	4	82	77
9480	60	3	1.13	74	45	3	67	87
9482	60	4	1.07	89	45	3	84	89
9483	60	3	1.04	88	60	3	75	44
0312	30	3	0.927	71	60	3	36	10

0776	30	3	0.841	60	60	3	56	13
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Table 22 - Pharmacokinetic parameters after i.v. and s.c. administration of CNP compounds to domestic LYD pig:

Compound ID	Domestic LYD pig							
	Intravenous PK				Subcutaneous PK			
	Dose (nmol/kg)	n	CL (ml/hr/kg)	T _{1/2,iv} (h)	Dose (nmol/kg)	n	T _{1/2,sc} (h)	F (%)
1225	43	2	3.23	15				
1227	43	2	5.54	11	20	3	9	55
0312	15	3	1.60	32	30	3	29	11
0776	15	4	1.34	29	30	3	41	7
1235	43	2	3.28	20	20	2	29	25

Half-life (T_{1/2}) and s.c. bioavailability (F) given as mean in Table 21 and 22.

5

Conclusion: this experiment shows that the CNP compounds of the present invention show prolonged half-lives and reduced clearance in both minipig and domestic LYD pig. Furthermore, the experiment shows that the CNP compounds are biologically active based on their ability to elicit a cGMP response in the dosed animals (Figure 28-48).

10 Furthermore, the experiment shows subcutaneous bioavailabilities (F) (Table 21 and 22) above 40% for the compounds of the invention. Whereas the non-working positively charged examples (Compound ID 0776 and 0312) show low subcutaneous bioavailabilities (7-13%). The non-working example (Compound ID 1235) with around neutral charge shows medium subcutaneous bioavailability of 25%.

15

Example 13 - Telemetry measurement of heart rate and blood pressure

The purpose of the study was to investigate the effect of acute dosing with the CNP compound 9482 (Chem. 137) on mean blood pressure (MAP) and heart rate (HR) in awake rats.

20

Procedure: The transducers are implanted in Sprague Dawley rats (Charles River) and the rats are allowed a 2–3-week period for recovery. Before surgery, the devices are registered in the software by placing them on a receiver plate and powered on. Sterile saline

is added to the transducer catheter before surgery start, and the transmitter is then powered on. The transmitters are placed in the abdomen with the sensor in aorta abdominalis.

Isoflurane is used as anaesthetic, and during and after surgery, the rats receive Temgesic (0.05 mg/kg s.c.), Norodyl (5 mg/kg s.c.), and Baytril (10 mg/kg s.c.) as pain relief and to

5 prevent bacterial infection.

Study design: Rats are housed 2/cage (1 with device and 1 as social partner). All animals will have free access to water and food (altromin) throughout the entire study. The rats will be housed in light cycles with light from 6 AM to 6 PM and dark from 6 PM to 6 AM. Eight rats are divided into 2 groups according to a crossover study design.

10 Telemetry: Each rat is equipped with a transducer (HD-S10 from DSI) capable of measuring blood pressure, heart rate, and activity using Ponemah software with a 100 Hz frequency. During measurements, there should be no disturbances in the room that the rats are housed in to minimize variability in the data. A 4-hour baseline recording will be taken prior to start of the study to capture mean arterial pressure (MAP) and heart rate (HR)

15 patterns in untreated, undisturbed rats. The recording period after drug administration was 24 hours.

Dosing scheme: Rats are dosed in a crossover study design with 4 rats in each group. Each rat is given a washout period of 1 week prior to the next dosing event. Dosing will be intravenous (IV) in the tail vein. Dosing of 9482 was tested in 30, 100, and 300

20 nmol/kg i.v. in separate experiments. The vehicle consists of 8 mM phosphate, 250 mM glycerol, pH 7.4.

Data analysis and statistics was conducted in Ponemah software and Graphpad prism. For statistics, a paired t test was applied with a confidence level of 95% and $P < 0.05$ denoting statistical significance.

25 Results: Within the first 30 min after dosing, no difference in MAP and HR was observed with 30, 100, or 300 nmol/kg of CNP compound 9482 compared to vehicle (Table 23 and Table 25). An average of the first 12 h resulted in no differences in MAP between vehicle and the three tested doses of 9482 (Table 24). An increase ($P < 0.05$) of $8.8 \pm 10.1\%$ and $6.4 \pm 6.6\%$ in HR was detected in the same period with 100 and 300 nmol/kg (Table 26).

30 No change in HR was observed with a dose of 30 nmol/kg (Table 26).

Table 23 – Mean arterial pressure: 30 min

	Vehicle		9482		
Dose (nmol/kg)	Mean (mmHg)	SD	Mean (mmHg)	SD	<i>P</i>

30	117	13	116	15	ns
100	113	7	114	6	ns
300	111	8	111	8	ns

Table 24 – Mean arterial pressure: 12 h

	Vehicle		9482		
Dose (nmol/kg)	Mean (mmHg)	SD	Mean (mmHg)	SD	<i>P</i>
30	108	14	106	10	ns
100	104	7	104	7	ns
300	103	5	102	6	ns

Table 25 – Heart rate: 30 min

	Vehicle		9482		
Dose (nmol/kg)	Mean (bpm)	SD	Mean (bpm)	SD	<i>P</i>
30	366	26	356	24	ns
100	382	19	388	12	ns
300	379	18	370	18	ns

Table 26 – Heart rate: 12 h

	Vehicle		9482		
Dose (nmol/kg)	Mean (bpm)	SD	Mean (bpm)	SD	<i>P</i>
30	311	13	332	27	ns
100	335	15	364	28	0.04
300	334	15	355	15	0.03

5

Conclusion: Acute IV infusion of CNP compound 9482 was not associated with any major hemodynamic changes over a 12 h period as evidenced by unaltered MAP and only minor increases in HR at the two highest doses.

Example 14 - Mouse metatarsal bone dissection and culture:

The purpose of this study was to evaluate bone growth after administration of CNP compounds in an ex vivo mouse model.

Procedure: One-day old mouse pups (NMRI, Javier Labs France) were euthanised prior to dissection. All applicable international and internal Novo Nordisk guidelines for care and use of animals were followed. The three middle metatarsal bones were dissected out from each hind paw. The dissected bones were placed in 24-well cell culture plates and cultured in 400 µl α-Minimum Essential Media supplemented with 0.2% BSA, 1% Pen/Strep at 37 °C and 5% CO₂. The bones from all animals were randomised into a control group and six CNP compound-treated groups (100 nM; n=8). The medium was changed every 2-3 days. All compounds were formulated according to the principles described in General Methods of Preparation - Method G. Compounds 9435 and 9483 were formulated in A) 5 mM sodium acetate, 250 mM glycerol, pH 4.0 while compounds 9384, 9407, 9480 and 9482 were formulated in B) 8 mM sodium phosphate, 250 mM glycerol, pH 7.4. Vehicle alone did not affect bone growth compared to media alone. Digital pictures were captured on day 0, 4, 7, 11, and 14 using a digital camera attached to a Nikon microscope. The length of each metatarsal bone was measured using ImageJ software and increase in bone length was expressed as percentage change from the length measured at the day of dissection (Mean (SD)).

Results: All CNP compounds significantly increased bone length compared to control group after 11 days of treatment (p<0.05; two-way ANOVA). Total increases in bone length were 28-48% higher after treatment with CNP compounds compared to the control group after 14 days in culture. The results from the study are summarised in Table 27.

Table 27 - Increase in bone length after administration of CNP compounds (100 nM):

Com- pound	control		9384			9407			9435		
Day	mean (%)	SD	mean (%)	SD	p<	mean (%)	SD	p<	mean (%)	SD	p<
4	25.3	4.1	33.6	8.3	ns	35.1	4.1	ns	36.2	3.8	ns
7	32.9	4.9	42.6	7.0	0.05	45.4	4.5	0.001	47.3	2.5	0.001
11	36.8	3.1	50.1	7.2	0.01	53.2	6.4	0.001	53.9	4.8	0.001
14	40.1	3.7	54.4	7.9	0.01	55.8	8.2	0.01	59.2	3.5	0.001

Com- pound	control		9480			9482			9483		
Day	mean (%)	SD	mean (%)	SD	p<	mean (%)	SD	p<	mean (%)	SD	p<
4	25.3	4.1	33.1	5.2	ns	37.7	10.9	ns	30.2	4.6	ns
7	32.9	4.9	43.9	4.9	0.01	47.1	10.3	0.05	39.5	8.8	ns
11	36.8	3.1	49.2	5.2	0.001	54.4	13.1	0.05	49.7	6.0	0.001
14	40.1	3.7	52.1	5.2	0.001	57.5	12.0	0.05	51.5	5.1	0.001

In Table 27, metatarsal bones were isolated from mice and cultured for up to 14 days. Length was measured every 3-4 days throughout the study and expressed as percentage change from day 0 (Mean (SD)). Statistically significant differences are indicated compared to control group (two-way ANOVA).

Conclusion: This experiment demonstrates that the CNP compounds of the current invention are able to significantly increase bone length in an *ex vivo* mouse model.

Example 15 - Mouse growth study

The purpose of this study was to evaluate growth in mice after treatment with two doses of CNP compound.

Procedure: Mice (C57BL/6J, male, age 4 weeks; n=10) received daily subcutaneous injections of compound 9482 or vehicle for 35 days. Formulations were prepared according to the principles described in General Methods of Preparation - Method G (30 and 70 nmol/kg, 10 mL/kg; Formulation buffer 8 mM sodium phosphate, 250 mM glycerol, 0.007% polysorbate 20, pH 7.4). Body weight and tail and body length were measured weekly throughout the study. The increase in growth was expressed as percentage change from day 0 (mean (SD)).

Results: Both 30 and 70 nmol/kg doses of CNP compound 9482 significantly increased tail and body length after 7 and 18 days, respectively, ($p < 0.05$, two-way ANOVA) compared to control. After 35 days, the change in tail length (from day 0) was increased by 45 and 83%, respectively, after treatment with 30 and 70 nmol/kg CNP compound compared to control animals. Body length was 30 and 67% higher, respectively, compared to control group after treatment with 30 and 70 nmol/kg CNP compound for 35 days. The results from the study are summarised in Tables 28 and Table 29.

Table 28 - Tail length of mice treated with daily injections of CNP compound for 35 days

	Vehicle		9482 30 nmol/kg			9482 70 nmol/kg		
Day	Mean (%)	SD	Mean (%)	SD	p<	Mean (%)	SD	p<
7	7.7	2.3	11.8	3.0	0.05	14.3	3.2	0.001
14	10.8	3.0	16.0	3.9	0.01	20.3	5.0	0.001
21	18.1	3.2	24.1	3.8	0.01	29.0	5.0	0.001
28	17.3	2.7	25.6	4.0	0.001	32.0	4.8	0.001
35	19.5	3.2	28.5	4.7	0.001	35.7	4.6	0.001

In Table 28, increase in tail length is expressed as percentage change from day 0 (mean (SD)). Statistically significant differences are indicated compared to control group (two-way ANOVA).

Table 29 - Body length of mice treated with daily injections of CNP compound for 35 days

	Vehicle		9482 30 nmol/kg			9482 70 nmol/kg		
Day	Mean (%)	SD	Mean (%)	SD	p<	Mean (%)	SD	p<
8	9.4	2.2	10.2	2.3	ns	12.8	2.4	0.01
18	14.1	2.9	17.5	2.0	0.05	21.5	4.0	0.001
25	16.5	3.4	22.5	3.4	0.01	29.0	4.5	0.001
35	21.1	3.3	27.4	3.2	0.001	35.3	4.6	0.001

In Table 29, increase in body length is expressed as percentage change from day 0 (mean (SD)). Statistically significant differences are indicated compared to control group (two-way ANOVA).

Conclusion: This experiment shows that CNP compounds of the present invention increase tail and body length of mice to a significant degree when administered subcutaneously in a pharmaceutically relevant formulation.

CLAIMS

1. A CNP compound comprising a CNP peptide and a modifying group wherein the net charge of the compound at physiological pH is 0 or negative, wherein the CNP peptide
- 5 comprises an amino acid sequence according to Formula I:

AA₀₁- AA₀₂-AA₀₃-AA₀₄-AA₀₅-AA₀₆-AA₀₇-AA₀₈-AA₀₉-AA₁₀-AA₁₁-AA₁₂-AA₁₃-AA₁₄-
AA₁₅-AA₁₆-AA₁₇-AA₁₈-AA₁₉-AA₂₀-AA₂₁-AA₂₂-AA₂₃-AA₂₄-AA₂₅-AA₂₆-AA₂₇-AA₂₈-AA₂₉-
AA₃₀-AA₃₁-AA₃₂-AA₃₃-AA₃₄-AA₃₅-AA₃₆-AA₃₇

wherein

- 10 AA₀₁ is Gln or absent,
AA₀₂ is Glu or absent,
AA₀₃ is His or absent,
AA₀₄ is Pro or absent,
AA₀₅ is Asn or Gln or Glu or absent,
15 AA₀₆ is Ala or absent,
AA₀₇ is Arg or His or Ala or absent,
AA₀₈ is Lys or Ser or His or absent,
AA₀₉ is Tyr or Glu or absent,
AA₁₀ is Lys or Glu or Gln or His or absent,
20 AA₁₁ is Gly,
AA₁₂ is Ala,
AA₁₃ is Gln or Asn or Glu,
AA₁₄ is Lys or His or Glu,
AA₁₅ is Lys or Ser or Glu or Thr or His,
25 AA₁₆ is Gly,
AA₁₇ is Leu or Gly or Ser or Val,
AA₁₈ is Ser or His,
AA₁₉ is Gln or Ser or Lys or His,
AA₂₀ is Gly,
30 AA₂₁ is Cys,
AA₂₂ is Phe,
AA₂₃ is Gly,
AA₂₄ is Leu,

AA₂₅ is Pro or Lys,

AA₂₆ is Leu,

AA₂₇ is Asp or Glu,

AA₂₈ is Arg,

5 AA₂₉ is Ile,

AA₃₀ is Gly,

AA₃₁ is Ser,

AA₃₂ is Leu or Nle or Met,

AA₃₃ is Ser,

10 AA₃₄ is Gly,

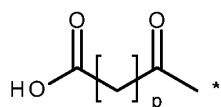
AA₃₅ is Leu,

AA₃₆ is Gly, and

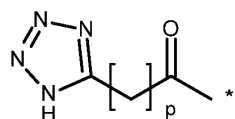
AA₃₇ is Cys;

wherein the modifying group comprises Chem. A, Chem. B and Chem. C;

15 wherein Chem. A is selected from the group consisting of:



(Chem. A1), and

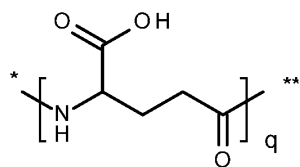


(Chem. A2)

20 wherein p is an integer in the range of 14-20, and

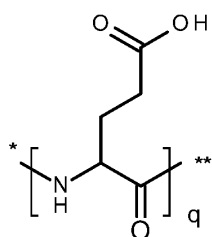
where * denotes an amide bond connecting Chem. A and Chem. B; and

wherein Chem. B is selected from the group consisting of:



(Chem. B1)

25 and

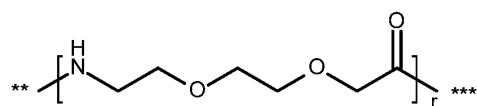


(Chem. B2)

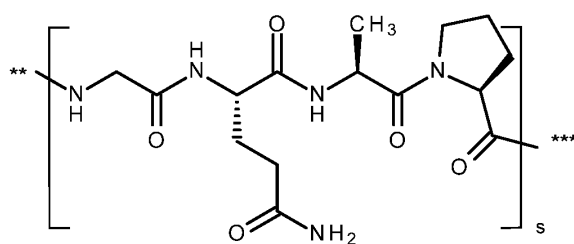
wherein q is an integer in the range of 1-8,

wherein * denotes an amide bond connecting Chem. A- and Chem. B-,

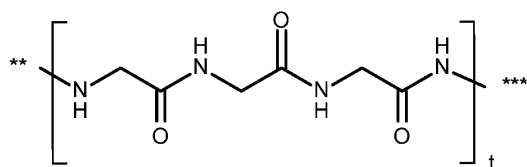
5 wherein ** denotes an amide bond connecting Chem. B- and Chem. C-; and
wherein Chem. C is selected from the group consisting of:



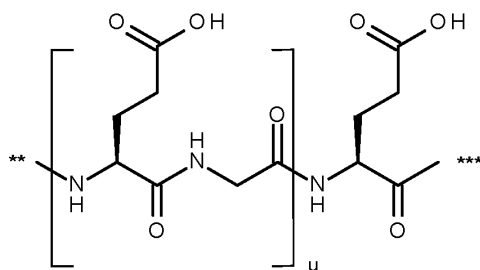
(Chem. C1),



10 (Chem. C2), and



(Chem. C3)



(Chem C4),

wherein r is an integer in the range of 0-4,

wherein s is an integer in the range of 0-3,

5 wherein t is an integer in the range of 0-1,

wherein u is an integer in the range of 0-3,

wherein ** denotes an amide bond connecting Chem. B- and Chem. C-,

wherein *** denotes an amide bond connecting Chem. C- and the N-terminal alpha-amine on the CNP peptide.

10

2. The CNP compound according to claim 1, wherein AA₁₃ of the CNP peptide is Gln; AA₁₉ is Gln or Ser; AA₂₅ is Pro; and AA₃₂ is Leu.

3. The CNP compound according to claim 1, wherein AA₅ of the CNP peptide is Gln;
15 AA₁₃ is Gln; AA₁₉ is Gln or Ser; AA₂₅ is Pro; and AA₃₂ is Leu.

4. The CNP compound according to claim 1, wherein the CNP peptide comprises one of the following amino acid sequences:

YKGANKKGLSKGCFGLKLDRIGSXSGGLGC	SEQ ID NO: 6
NARKYKGANKSGLSSGCFGLKLDRIGSXSGGLGC	SEQ ID NO: 7
GANKKGLSKGCFGLKLDRIGSXSGGLGC	SEQ ID NO: 8
GAQKKGLSKGCFGLKLDRIGSXSGGLGC	SEQ ID NO: 9
YEGAQKKGLSKGCFGLKLDRIGSLSGGLGC	SEQ ID NO: 10
EEGAQKKGLSKGCFGLKLDRIGSLSGGLGC	SEQ ID NO: 11
YEGAQEKGLSKGCFGLKLDRIGSLSGGLGC	SEQ ID NO: 12
YEGAQKKGLSSGCFGLKLDRIGSLSGGLGC	SEQ ID NO: 13
YEGAQKKGLSKGCFGLPLDRIGSLSGGLGC	SEQ ID NO: 14
YEGAQEKGLSKGCFGLPLDRIGSLSGGLGC	SEQ ID NO: 15
YEGAQKKGLSSGCFGLPLDRIGSLSGGLGC	SEQ ID NO: 16
YEGAQEKGLSSGCFGLPLDRIGSLSGGLGC	SEQ ID NO: 17
EKGAQEKGLSKGCFGLKLDRIGSLSGGLGC	SEQ ID NO: 18
EKGAQEKGLSSGCFGLKLDRIGSLSGGLGC	SEQ ID NO: 19
EQGAQEKGLSKGCFGLKLDRIGSLSGGLGC	SEQ ID NO: 20
YKGAQEKGLSKGCFGLKLDRIGSLSGGLGC	SEQ ID NO: 21
YKGAQKKGLSSGCFGLPLDRIGSLSGGLGC	SEQ ID NO: 22
EHGAQEKGLSKGCFGLKLDRIGSLSGGLGC	SEQ ID NO: 23
YHGAQEKGLSKGCFGLKLDRIGSLSGGLGC	SEQ ID NO: 24
YHGAQEKGLSKGCFGLPLDRIGSLSGGLGC	SEQ ID NO: 25
YHGAQKKGLSSGCFGLPLDRIGSLSGGLGC	SEQ ID NO: 26

YHGAQEKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 27
YEGAEKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 28
EGAQEKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 29
EGAQKEGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 30
YEGAQKEGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 31
YHGAQKTGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 32
YHGAQKTGVSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 33
YHGAQHTGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 34
YKGAQHTGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 35
EHGAQKKGLSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 36
EHGAQKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 37
EHGAQKKGVSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 38
EHGAQKTGVSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 39
YHGAQHHGLSKGCFGLKLERIGSLSGLC	SEQ ID NO: 40
YKGAQHHGLSQGCFGLKLERIGSLSGLC	SEQ ID NO: 41
YEGAQKKGLSSGCFGLPLERIGSLSGLC	SEQ ID NO: 42
EGAQKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 43
YKGAQHHGLSQGCFGLKLDIGSLSGLC	SEQ ID NO: 44
YKGAQHHGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 45
YHGAQHHGLSKGCFGLKLDIGSLSGLC	SEQ ID NO: 46
YHGAQHHGLSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 47
GAQKKGLSHGCFGLPLDRIGSLSGLC	SEQ ID NO: 48
GAQKKGLHSGCFGLPLDRIGSLSGLC	SEQ ID NO: 49
ARKYHGAQHTGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 50
ARKYHGAQHTGVSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 51
ARKYHGAQKTGVSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 52
ARKEHGAQKTGVSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 53
ARKEHGAQHTGVSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 54
YEGAQKKGGSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 55
QEHPQARSYEGAQKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 57
QEHPQRSYEGAQKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 58
QEHPQAHKYHGAQHHGSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 59
QEHPQAHKYKGAQKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 60
QEHPQAHKYHGAQKHGSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 61
ARKYEGAQKKGLSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 63
ARKYKGAQKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 64
QEHPQARKYKGAQKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 67
QEHPQARKYEGAQKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 68
YEGAQKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 69
QEHPQARKYEGAQKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 70
QEHPQAAKYEGAQKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 71
QEHPQARHYKGAQKKGSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 72
QEHPQAHKYKGAQKKGSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 73
QEHPQARKYKGAQKKGLSKGCFGLKLDIGSLSGLC	SEQ ID NO: 74

QEHPQARKYKGAQKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 75
QEHPQARKYKGAQKKGGSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 76
ARKYKGAQKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 77
ARKYHGAQHTGVSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 78
ARKYKGAQKTGVSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 79
ARKYHGAQKKGVSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 80
ARKYHGAQKTGVSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 81
ARKYKGAQKTGVSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 82
YHGAQKTGVSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 83
ARKYHGAQKSGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 84
YEGAQKKGGSHGCFGLPLDRIGSLSGLC	SEQ ID NO: 85
ARKYEGAQHKGGSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 86
YHGAQKKGGSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 87
YKGAQKKGGSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 88
YKGAQKKGVSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 89
YHGAQKKGVSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 90
QEHPQARKYEGAQKKGLSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 91
ARKYHGAQKKGVSSGCFGLPLERIGSLSGLC	SEQ ID NO: 92
ARKYKGAQKKGLSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 96
YHGAQKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 97
ARKYKGAQKKGLSQGCFGLKLDRIGSLSGLC	SEQ ID NO: 98
ARKYKGANKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 99
ARKYKGAQKKGLSQGCFGLPLDRIGSMSGLGC	SEQ ID NO: 100
QEHPQARKYKGAQKKGLSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 101
ARKYKGAQKKGLSQGCFGLPLERIGSLSGLC	SEQ ID NO: 102
YKGAQKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 103
QEHPQARKYKGAQKKGLSSGCFGLPLERIGSLSGLC	SEQ ID NO: 104
YKGAQKKGGSQGCFGLPLERIGSLSGLC	SEQ ID NO: 108
YKGAQKKGLSQGCFGLPLERIGSLSGLC	SEQ ID NO: 109
GAQKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 112
GAQKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 113
GAQKKGGSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 114
GAQKKGSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 115
GAQKKGLSQGCFGLKLDRIGSLSGLC	SEQ ID NO: 116
GAQKKGLSSGCFGLKLDRIGSLSGLC	SEQ ID NO: 117
GAQKKGGSQGCFGLKLDRIGSLSGLC	SEQ ID NO: 118
GAQKKGSSGCFGLKLDRIGSLSGLC	SEQ ID NO: 119
GANKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 120
GANKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 121
GANKKGGSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 122
GANKKGSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 123
GAQKKGLSQGCFGLPLDRIGSMSGLGC	SEQ ID NO: 124
GAQKKGLSSGCFGLPLDRIGSMSGLGC	SEQ ID NO: 125
GAQKKGGSQGCFGLPLDRIGSMSGLGC	SEQ ID NO: 126

GAQKKGGSSGCFGLPLDRIGSMSGLGC	SEQ ID NO: 127
GAQKKGLSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 128
GAQKKGGSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 129
GAQKKGLSQGCFGLPLERIGSLSGLC	SEQ ID NO: 130
GAQKKGLSSGCFGLPLERIGSLSGLC	SEQ ID NO: 131
GANKKGLSQGCFGLPLDRIGSMSGLGC	SEQ ID NO: 132
GANKKGLSSGCFGLPLDRIGSMSGLGC	SEQ ID NO: 133
GANKKGLSQGCFGLPLERIGSMSGLGC	SEQ ID NO: 134
GANKKGLSSGCFGLPLERIGSMSGLGC	SEQ ID NO: 135
GAQKKGSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 136
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GANKKGSSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 141
GAQKKGSSQGCFGLPLDRIGSMSGLGC	SEQ ID NO: 142
GAQKKGSSSGCFGLPLDRIGSMSGLGC	SEQ ID NO: 143
GAQKKGSSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 144
YKGAQKKGGSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 145
YKGAQKKGLSQGCFGLKLDRIGSLSGLC	SEQ ID NO: 146
YKGAQKKGLSSGCFGLKLDRIGSLSGLC	SEQ ID NO: 147
YKGAQKKGGSQGCFGLKLDRIGSLSGLC	SEQ ID NO: 148
YKGAQKKGGSSGCFGLKLDRIGSLSGLC	SEQ ID NO: 149
YKGANKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 150
YKGANKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 151
YKGANKKGGSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 152
YKGANKKGGSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 153
YKGAQKKGLSQGCFGLPLDRIGSMSGLGC	SEQ ID NO: 154
YKGAQKKGLSSGCFGLPLDRIGSMSGLGC	SEQ ID NO: 155
YKGAQKKGGSQGCFGLPLDRIGSMSGLGC	SEQ ID NO: 156
YKGAQKKGGSSGCFGLPLDRIGSMSGLGC	SEQ ID NO: 157
YKGAQKKGLSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 158
YKGAQKKGGSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 159
YKGAQKKGLSQGCFGLPLERIGSLSGLC	SEQ ID NO: 160
YKGAQKKGLSSGCFGLPLERIGSLSGLC	SEQ ID NO: 161
YKGANKKGLSQGCFGLPLDRIGSMSGLGC	SEQ ID NO: 162
YKGANKKGLSSGCFGLPLDRIGSMSGLGC	SEQ ID NO: 163
YKGANKKGLSQGCFGLPLERIGSMSGLGC	SEQ ID NO: 164
YKGANKKGLSSGCFGLPLERIGSMSGLGC	SEQ ID NO: 165
YKGAQKKGSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 166
YKGAQKKGSSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 167
YKGAQKKGSSQGCFGLKLDRIGSLSGLC	SEQ ID NO: 168
YKGAQKKGSSSGCFGLKLDRIGSLSGLC	SEQ ID NO: 169
YKGANKKGSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 170

YKGANKKGSSSGCFGLPLDRIGSLSGLGC	SEQ ID NO: 171
YKGAQKKGSSQGCFLPLDRIGSMSGLGC	SEQ ID NO: 172
YKGAQKKGSSSGCFGLPLDRIGSMSGLGC	SEQ ID NO: 173
YKGAQKKGSSKGCFLPLDRIGSLSGLGC	SEQ ID NO: 174
ARKYKGAQKKGSSQGCFLPLDRIGSLSGLGC	SEQ ID NO: 175
ARKYKGAQKKGSSSGCFGLPLDRIGSLSGLGC	SEQ ID NO: 176
ARKYKGAQKKGLSSGCFGLKLDRIGSLSGLGC	SEQ ID NO: 177
ARKYKGAQKKGSSQGCFLKLDRIGSLSGLGC	SEQ ID NO: 178
ARKYKGAQKKGSSSGCFGLKLDRIGSLSGLGC	SEQ ID NO: 179
ARKYKGANKKGLSQGCFGLPLDRIGSLSGLGC	SEQ ID NO: 180
ARKYKGANKKGLSSGCFGLPLDRIGSLSGLGC	SEQ ID NO: 181
ARKYKGANKKGSSQGCFLPLDRIGSLSGLGC	SEQ ID NO: 182
ARKYKGANKKGSSSGCFGLPLDRIGSLSGLGC	SEQ ID NO: 183
ARKYKGAQKKGLSQGCFGLPLDRIGSMSGLGC	SEQ ID NO: 184
ARKYKGAQKKGLSSGCFGLPLDRIGSMSGLGC	SEQ ID NO: 185
ARKYKGAQKKGSSQGCFLPLDRIGSMSGLGC	SEQ ID NO: 186
ARKYKGAQKKGSSSGCFGLPLDRIGSMSGLGC	SEQ ID NO: 187
ARKYKGAQKKGSSKGCFLPLDRIGSLSGLGC	SEQ ID NO: 188
ARKYKGAQKKGLSQGCFGLPLERIGSLSGLGC	SEQ ID NO: 189
ARKYKGAQKKGLSSGCFGLPLERIGSLSGLGC	SEQ ID NO: 190
ARKYKGANKKGLSQGCFGLPLDRIGSMSGLGC	SEQ ID NO: 191
ARKYKGANKKGLSSGCFGLPLDRIGSMSGLGC	SEQ ID NO: 192
ARKYKGANKKGLSQGCFGLPLERIGSMSGLGC	SEQ ID NO: 193
ARKYKGANKKGLSSGCFGLPLERIGSMSGLGC	SEQ ID NO: 194
ARKYKGAQKKGSSQGCFLPLDRIGSLSGLGC	SEQ ID NO: 195
ARKYKGAQKKGSSSGCFGLPLDRIGSLSGLGC	SEQ ID NO: 196
ARKYKGAQKKGSSQGCFLKLDRIGSLSGLGC	SEQ ID NO: 197
ARKYKGAQKKGSSSGCFGLKLDRIGSLSGLGC	SEQ ID NO: 198
ARKYKGANKKGSSQGCFLPLDRIGSLSGLGC	SEQ ID NO: 199
ARKYKGANKKGSSSGCFGLPLDRIGSLSGLGC	SEQ ID NO: 200
ARKYKGAQKKGSSQGCFLPLDRIGSMSGLGC	SEQ ID NO: 201
ARKYKGAQKKGSSSGCFGLPLDRIGSMSGLGC	SEQ ID NO: 202
ARKYKGAQKKGSSKGCFLPLDRIGSLSGLGC	SEQ ID NO: 203
GAQKKGSSQGCFLPLERIGSLSGLGC	SEQ ID NO: 232

5. The CNP compound according to claim 1, wherein the CNP peptide has any one of the following amino acid sequences:

YKGANKKGLSKGCFGLKLDRIGSXSLGC	SEQ ID NO: 6
NARKYKGANKSGLSSGCFGLKLDRIGSXSLGC	SEQ ID NO: 7
GANKKGLSKGCFGLKLDRIGSXSLGC	SEQ ID NO: 8
GAQKKGLSKGCFGLKLDRIGSXSLGC	SEQ ID NO: 9
YEGAQKKGLSKGCFGLKLDRIGSLSGLGC	SEQ ID NO: 10
EEGAQKKGLSKGCFGLKLDRIGSLSGLGC	SEQ ID NO: 11

YEGAQEKGLSKGCFGLKLDRIIGLSLGLGC	SEQ ID NO: 12
YEGAQKKGLSSGCFGLKLDRIIGLSLGLGC	SEQ ID NO: 13
YEGAQKKGLSKGCFGLPLDRIIGLSLGLGC	SEQ ID NO: 14
YEGAQEKGLSKGCFGLPLDRIIGLSLGLGC	SEQ ID NO: 15
YEGAQKKGLSSGCFGLPLDRIIGLSLGLGC	SEQ ID NO: 16
YEGAQEKGLSSGCFGLPLDRIIGLSLGLGC	SEQ ID NO: 17
EKGAQEKGLSKGCFGLKLDRIIGLSLGLGC	SEQ ID NO: 18
EKGAQEKGLSSGCFGLKLDRIIGLSLGLGC	SEQ ID NO: 19
EQGAQEKGLSKGCFGLKLDRIIGLSLGLGC	SEQ ID NO: 20
YKGAQEKGLSKGCFGLKLDRIIGLSLGLGC	SEQ ID NO: 21
YKGAQKKGLSSGCFGLPLDRIIGLSLGLGC	SEQ ID NO: 22
EHGAQEKGLSKGCFGLKLDRIIGLSLGLGC	SEQ ID NO: 23
YHGAQEKGLSKGCFGLKLDRIIGLSLGLGC	SEQ ID NO: 24
YHGAQEKGLSKGCFGLPLDRIIGLSLGLGC	SEQ ID NO: 25
YHGAQKKGLSSGCFGLPLDRIIGLSLGLGC	SEQ ID NO: 26
YHGAQEKGLSSGCFGLPLDRIIGLSLGLGC	SEQ ID NO: 27
YEGAQKKGLSQGCFGLPLDRIIGLSLGLGC	SEQ ID NO: 28
EGAQEKGLSSGCFGLPLDRIIGLSLGLGC	SEQ ID NO: 29
EGAQKEGLSSGCFGLPLDRIIGLSLGLGC	SEQ ID NO: 30
YEGAQKEGLSSGCFGLPLDRIIGLSLGLGC	SEQ ID NO: 31
YHGAQKTGLSSGCFGLPLDRIIGLSLGLGC	SEQ ID NO: 32
YHGAQKTGVSSGCFGLPLDRIIGLSLGLGC	SEQ ID NO: 33
YHGAQHTGLSSGCFGLPLDRIIGLSLGLGC	SEQ ID NO: 34
YKGAQHTGLSSGCFGLPLDRIIGLSLGLGC	SEQ ID NO: 35
EHGAQKKGLSKGCFGLPLDRIIGLSLGLGC	SEQ ID NO: 36
EHGAQKKGLSSGCFGLPLDRIIGLSLGLGC	SEQ ID NO: 37
EHGAQKKGVSSGCFGLPLDRIIGLSLGLGC	SEQ ID NO: 38
EHGAQKTGVSSGCFGLPLDRIIGLSLGLGC	SEQ ID NO: 39
YHGAQHHGLSKGCFGLKLERIGLSLGLGC	SEQ ID NO: 40
YKGAQHHGLSQGCFGLKLERIGLSLGLGC	SEQ ID NO: 41
YEGAQKKGLSSGCFGLPLERIGLSLGLGC	SEQ ID NO: 42
EGAQKKGLSSGCFGLPLDRIIGLSLGLGC	SEQ ID NO: 43
YKGAQHHGLSQGCFGLKLDRIIGLSLGLGC	SEQ ID NO: 44
YKGAQHHGLSQGCFGLPLDRIIGLSLGLGC	SEQ ID NO: 45
YHGAQHHGLSKGCFGLKLDRIIGLSLGLGC	SEQ ID NO: 46
YHGAQHHGLSKGCFGLPLDRIIGLSLGLGC	SEQ ID NO: 47
GAQKKGLSHGCFGLPLDRIIGLSLGLGC	SEQ ID NO: 48
GAQKKGLHSGCFGLPLDRIIGLSLGLGC	SEQ ID NO: 49
ARKYHGAQHTGLSSGCFGLPLDRIIGLSLGLGC	SEQ ID NO: 50
ARKYHGAQHTGVSSGCFGLPLDRIIGLSLGLGC	SEQ ID NO: 51
ARKYHGAQKTGVSSGCFGLPLDRIIGLSLGLGC	SEQ ID NO: 52
ARKEHGAQKTGVSSGCFGLPLDRIIGLSLGLGC	SEQ ID NO: 53
ARKEHGAQHTGVSSGCFGLPLDRIIGLSLGLGC	SEQ ID NO: 54
YEGAQKKGGSKGCFGLPLDRIIGLSLGLGC	SEQ ID NO: 55

QEHQPARSYEGAQKKGLSSGCFGLPLDRIGSLSGLGC	SEQ ID NO: 57
QEHPEARSYEGAQKKGLSSGCFGLPLDRIGSLSGLGC	SEQ ID NO: 58
QEHPPAHKYHGAQHGGSSQGCFGLPLDRIGSLSGLGC	SEQ ID NO: 59
QEHPPAHKYKGAQKKGLSQGCFGLPLDRIGSLSGLGC	SEQ ID NO: 60
QEHPPAHKYHGAQKHGSSQGCFGLPLDRIGSLSGLGC	SEQ ID NO: 61
ARKYEGAQKKGLSKGCFGLPLDRIGSLSGLGC	SEQ ID NO: 63
ARKYKGAQKKGLSSGCFGLPLDRIGSLSGLGC	SEQ ID NO: 64
QEHPPARKYKGAQKKGLSSGCFGLPLDRIGSLSGLGC	SEQ ID NO: 67
QEHPPARKYEGAQKKGLSSGCFGLPLDRIGSLSGLGC	SEQ ID NO: 68
YEGAQKKGLSQGCFGLPLDRIGSLSGLGC	SEQ ID NO: 69
QEHPPARKYEGAQKKGLSQGCFGLPLDRIGSLSGLGC	SEQ ID NO: 70
QEHPPAAKYEGAQKKGLSQGCFGLPLDRIGSLSGLGC	SEQ ID NO: 71
QEHPPARHYKGAQKKGSSQGCFGLPLDRIGSLSGLGC	SEQ ID NO: 72
QEHPPAHKYKGAQKKGSSQGCFGLPLDRIGSLSGLGC	SEQ ID NO: 73
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QEHPPARKYKGAQKKGLSQGCFGLPLDRIGSLSGLGC	SEQ ID NO: 75
QEHPPARKYKGAQKKGSSQGCFGLPLDRIGSLSGLGC	SEQ ID NO: 76
ARKYKGAQKKGLSQGCFGLPLDRIGSLSGLGC	SEQ ID NO: 77
ARKYHGAQHTGVSKGCFGLPLDRIGSLSGLGC	SEQ ID NO: 78
ARKYKGAQKTGVSSGCFGLPLDRIGSLSGLGC	SEQ ID NO: 79
ARKYHGAQKKGVSSGCFGLPLDRIGSLSGLGC	SEQ ID NO: 80
ARKYHGAQKTGVSKGCFGLPLDRIGSLSGLGC	SEQ ID NO: 81
ARKYKGAQKTGVSKGCFGLPLDRIGSLSGLGC	SEQ ID NO: 82
YHGAQKTGVSKGCFGLPLDRIGSLSGLGC	SEQ ID NO: 83
ARKYHGAQKSGLSQGCFGLPLDRIGSLSGLGC	SEQ ID NO: 84
YEGAQKKGGSHGCFGLPLDRIGSLSGLGC	SEQ ID NO: 85
ARKYEGAQHKGSSQGCFGLPLDRIGSLSGLGC	SEQ ID NO: 86
YHGAQKKGGSSQGCFGLPLDRIGSLSGLGC	SEQ ID NO: 87
YKGAQKKGGSSQGCFGLPLDRIGSLSGLGC	SEQ ID NO: 88
YKGAQKKGVSSQGCFGLPLDRIGSLSGLGC	SEQ ID NO: 89
YHGAQKKGVSSQGCFGLPLDRIGSLSGLGC	SEQ ID NO: 90
QEHPPARKYEGAQKKGLSKGCFGLPLDRIGSLSGLGC	SEQ ID NO: 91
ARKYHGAQKKGVSSGCFGLPLERIGSLSGLGC	SEQ ID NO: 92
ARKYKGAQKKGLSKGCFGLPLDRIGSLSGLGC	SEQ ID NO: 96
YHGAQKKGLSQGCFGLPLDRIGSLSGLGC	SEQ ID NO: 97
ARKYKGAQKKGLSQGCFGLKLDIGSLSGLGC	SEQ ID NO: 98
ARKYKGANKKGLSQGCFGLPLDRIGSLSGLGC	SEQ ID NO: 99
ARKYKGAQKKGLSQGCFGLPLDRIGSMISGLGC	SEQ ID NO: 100
QEHPPARKYKGAQKKGLSKGCFGLPLDRIGSLSGLGC	SEQ ID NO: 101
ARKYKGAQKKGLSQGCFGLPLERIGSLSGLGC	SEQ ID NO: 102
YKGAQKKGLSQGCFGLPLDRIGSLSGLGC	SEQ ID NO: 103
QEHPPARKYKGAQKKGLSSGCFGLPLERIGSLSGLGC	SEQ ID NO: 104
YKGAQKKGGSSQGCFGLPLERIGSLSGLGC	SEQ ID NO: 108
YKGAQKKGLSQGCFGLPLERIGSLSGLGC	SEQ ID NO: 109

GAQKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 112
GAQKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 113
GAQKKGGSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 114
GAQKKGSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 115
GAQKKGLSQGCFGLKLDRIKSLSGLC	SEQ ID NO: 116
GAQKKGLSSGCFGLKLDRIKSLSGLC	SEQ ID NO: 117
GAQKKGGSQGCFGLKLDRIKSLSGLC	SEQ ID NO: 118
GAQKKGSSGCFGLKLDRIKSLSGLC	SEQ ID NO: 119
GANKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 120
GANKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 121
GANKKGGSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 122
GANKKGSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 123
GAQKKGLSQGCFGLPLDRIGMSGSLGC	SEQ ID NO: 124
GAQKKGLSSGCFGLPLDRIGMSGSLGC	SEQ ID NO: 125
GAQKKGGSQGCFGLPLDRIGMSGSLGC	SEQ ID NO: 126
GAQKKGSSGCFGLPLDRIGMSGSLGC	SEQ ID NO: 127
GAQKKGLSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 128
GAQKKGSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 129
GAQKKGLSQGCFGLPLERIGSLSGLC	SEQ ID NO: 130
GAQKKGLSSGCFGLPLERIGSLSGLC	SEQ ID NO: 131
GANKKGLSQGCFGLPLDRIGMSGSLGC	SEQ ID NO: 132
GANKKGLSSGCFGLPLDRIGMSGSLGC	SEQ ID NO: 133
GANKKGLSQGCFGLPLERIGMSGSLGC	SEQ ID NO: 134
GANKKGLSSGCFGLPLERIGMSGSLGC	SEQ ID NO: 135
GAQKKGSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 136
GAQKKGSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 137
GAQKKGSSQGCFGLKLDRIKSLSGLC	SEQ ID NO: 138
GAQKKGSSGCFGLKLDRIKSLSGLC	SEQ ID NO: 139
GANKKGSSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 140
GANKKGSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 141
GAQKKGSSQGCFGLPLDRIGMSGSLGC	SEQ ID NO: 142
GAQKKGSSGCFGLPLDRIGMSGSLGC	SEQ ID NO: 143
GAQKKGSSKGCFGLPLDRIGSLSGLC	SEQ ID NO: 144
YKGAQKKGSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 145
YKGAQKKGLSQGCFGLKLDRIKSLSGLC	SEQ ID NO: 146
YKGAQKKGLSSGCFGLKLDRIKSLSGLC	SEQ ID NO: 147
YKGAQKKGGSQGCFGLKLDRIKSLSGLC	SEQ ID NO: 148
YKGAQKKGSSGCFGLKLDRIKSLSGLC	SEQ ID NO: 149
YKGANKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 150
YKGANKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 151
YKGANKKGGSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 152
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QEHPQARKYKGAQKKGGSSSGCFGLKLDIGSLSGLC	SEQ ID NO: 208
QEHPNARKYKGANKKGLSQGCFGLPLDRIGSLSGLC	SEQ ID NO: 209
QEHPNARKYKGANKKGLSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 210
QEHPNARKYKGANKKGGSSQGCFLPLDRIGSLSGLC	SEQ ID NO: 211
QEHPNARKYKGANKKGGSSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 212
QEHPQARKYKGAQKKGLSQGCFGLPLDRIGMSGSLGC	SEQ ID NO: 213
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QEHPQARKYKGAQKKGGSSKGCFLPLDRIGSLSGLC	SEQ ID NO: 217
QEHPQARKYKGAQKKGLSQGCFGLPLERIGSLSGLC	SEQ ID NO: 218
QEHPNARKYKGANKKGLSQGCFGLPLDRIGMSGSLGC	SEQ ID NO: 219
QEHPNARKYKGANKKGLSSGCFGLPLDRIGMSGSLGC	SEQ ID NO: 220
QEHPNARKYKGANKKGLSQGCFGLPLERIGMSGSLGC	SEQ ID NO: 221
QEHPNARKYKGANKKGLSSGCFGLPLERIGMSGSLGC	SEQ ID NO: 222
QEHPQARKYKGAQKKGGSSQGCFLPLDRIGSLSGLC	SEQ ID NO: 223
QEHPQARKYKGAQKKGGSSSGCFGLPLDRIGSLSGLC	SEQ ID NO: 224
QEHPQARKYKGAQKKGGSSQGCFLKLDIGSLSGLC	SEQ ID NO: 225
QEHPQARKYKGAQKKGGSSSGCFGLKLDIGSLSGLC	SEQ ID NO: 226
QEHPNARKYKGANKKGGSSQGCFLPLDRIGSLSGLC	SEQ ID NO: 227
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QEHPQARKYKGAQKKGGSSQGCFLPLDRIGMSGSLGC	SEQ ID NO: 229
QEHPQARKYKGAQKKGGSSSGCFGLPLDRIGMSGSLGC	SEQ ID NO: 230
QEHPQARKYKGAQKKGGSSKGCFLPLDRIGSLSGLC	SEQ ID NO: 231
GAQKKGGSSQGCFLPLERIGSLSGLC	SEQ ID NO: 232

6. The CNP compound according to claim 1, wherein the CNP peptide has any one of the following amino acid sequences:

- 5 GAQKKGGSSQGCFLPLDRIGSLSGLC (SEQ ID NO: 136),
ARKYKGAQKKGLSQGCFGLPLDRIGSLSGLC (SEQ ID NO: 77),
YKGAQKKGGSSQGCFLPLDRIGSLSGLC (SEQ ID NO: 88),
YKGAQKKGLSQGCFGLPLDRIGSLSGLC (SEQ ID NO: 103),
QEHPQARKYKGAQKKGLSSGCFGLPLDRIGSLSGLC (SEQ ID NO: 67), and
QEHPQARKYKGAQKKGLSSGCFGLPLERIGSLSGLC (SEQ ID NO: 104).

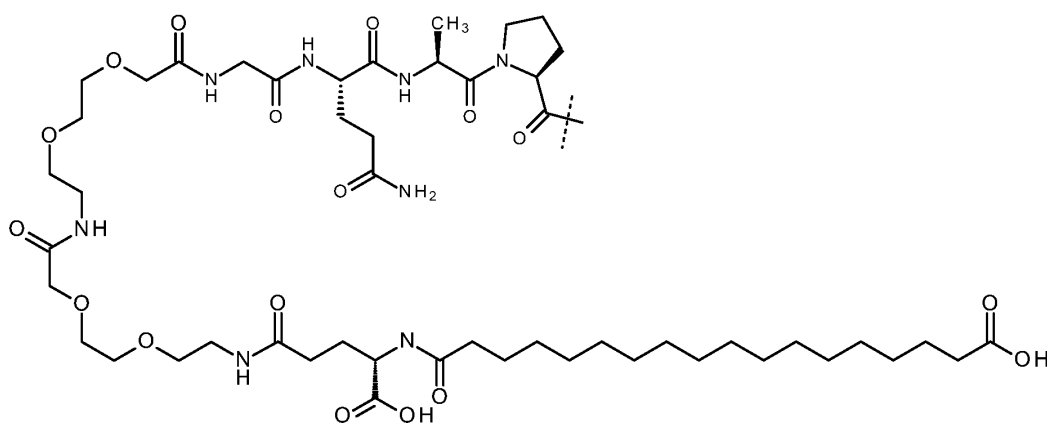
7. The CNP compound according to claim 1, wherein the CNP peptide has the following amino acid sequence:

QEHPQARKYKGAQKKGLSSGCFGLPLDRIGSLSGLG (SEQ ID NO: 67).

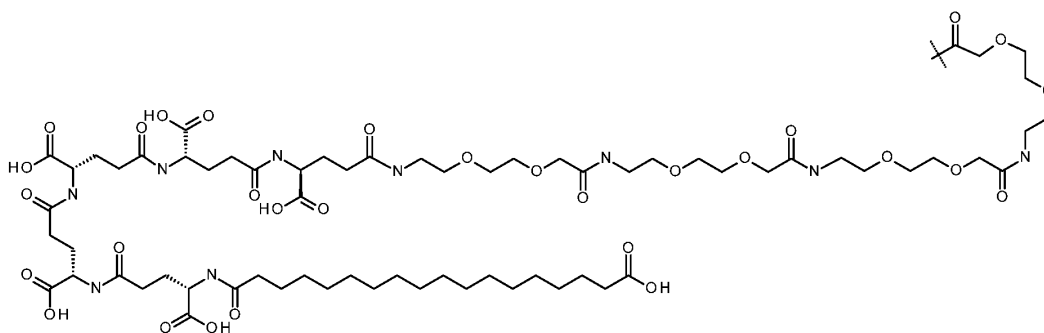
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8. The CNP compound according to any one of the preceding claims, wherein Chem. B of the modifying group has a q of 1-5.

9. The CNP compound according to any one of the preceding claims, wherein the
10 modifying group is selected from the following: Chem. E, Chem. F, Chem. G, Chem. H, Chem. I, and Chem. J (in which the dotted line defines the attachment through an amide bond to the N-terminal alpha-amine of the CNP peptide)

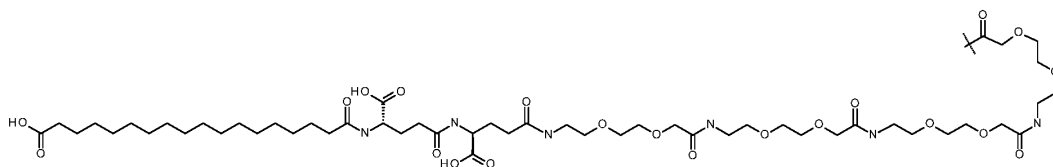


(Chem. E)

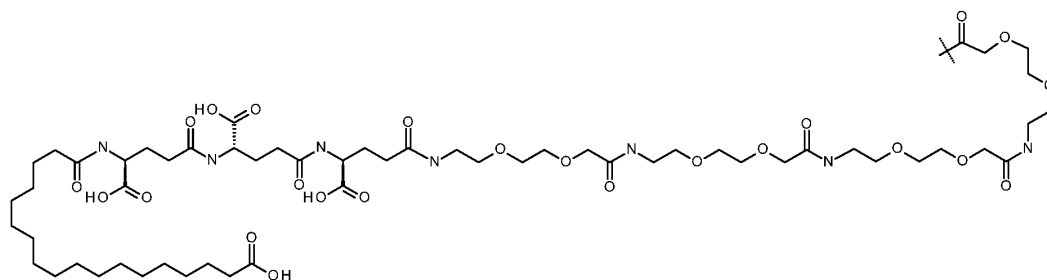


(Chem. F)

15

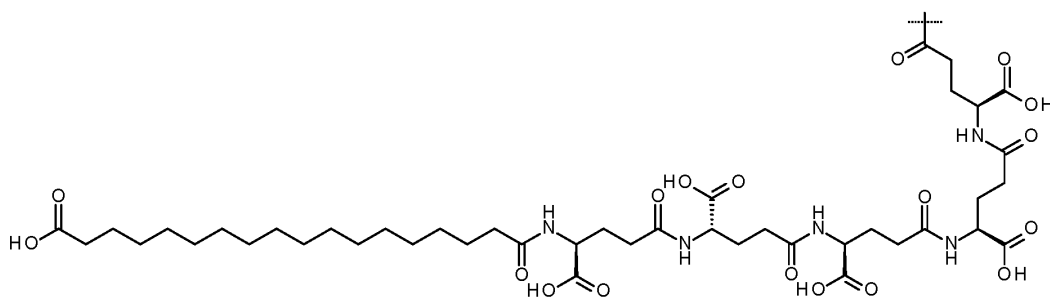


(Chem. G)

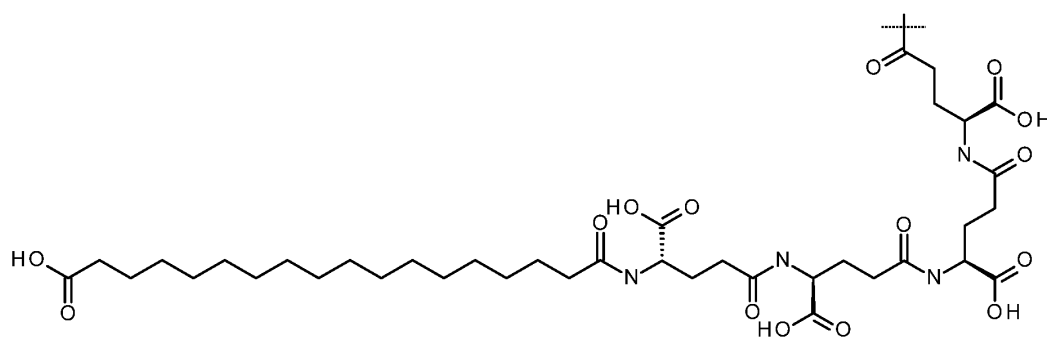


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(Chem. H)



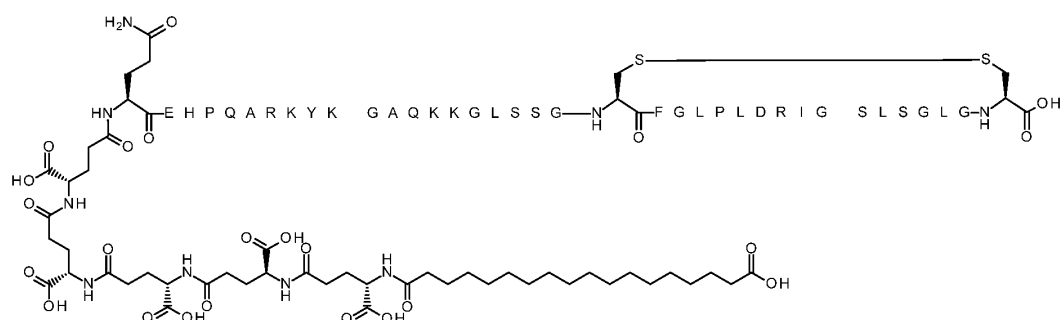
(Chem. I)



(Chem. J).

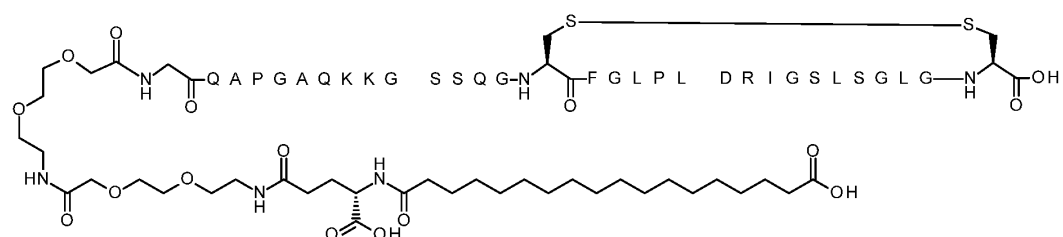
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10. A CNP compound according to Formula II:

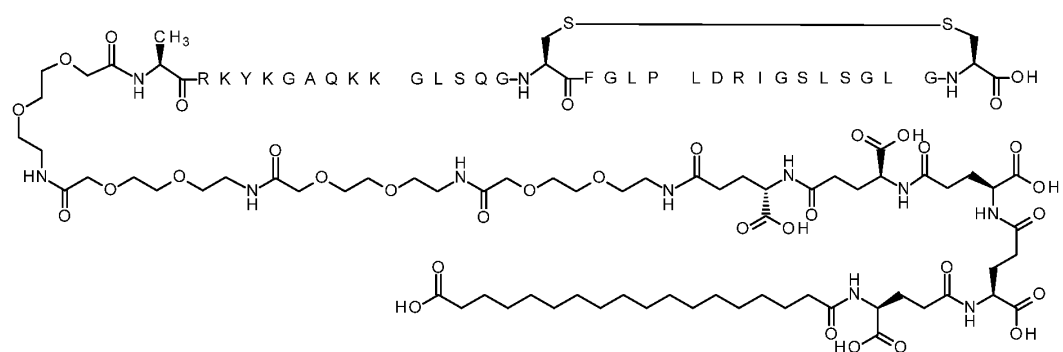


(Formula II).

5 11. A CNP compound according to any one of Formula II, III, IV, V, VI, and VII:

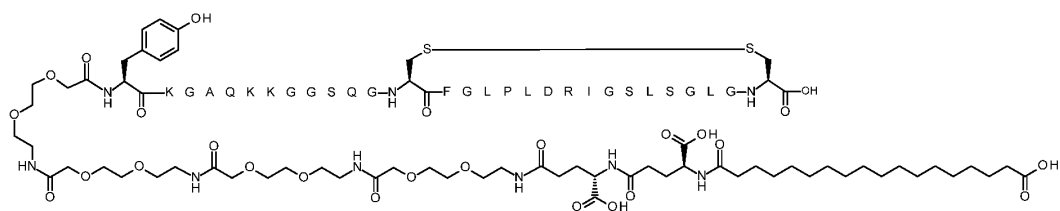


(Formula III)

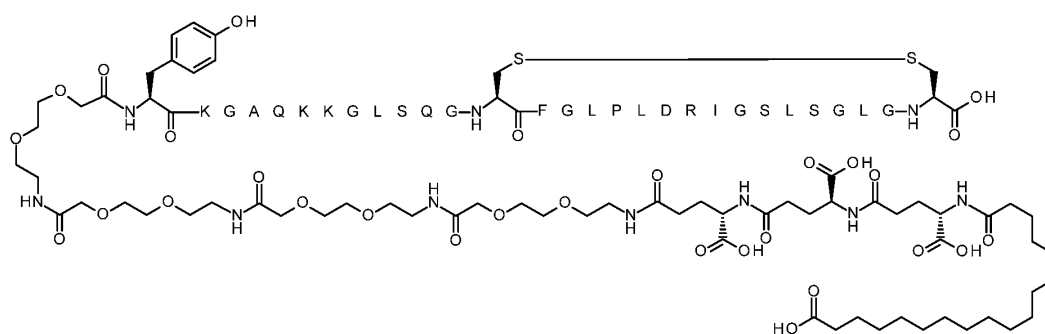


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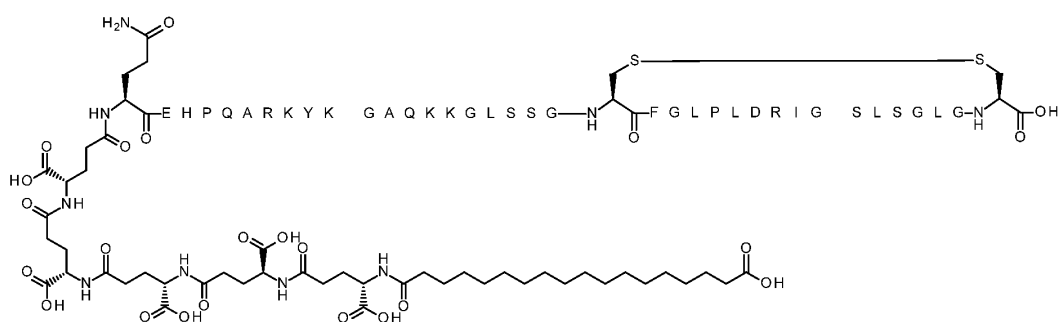
(Formula IV)



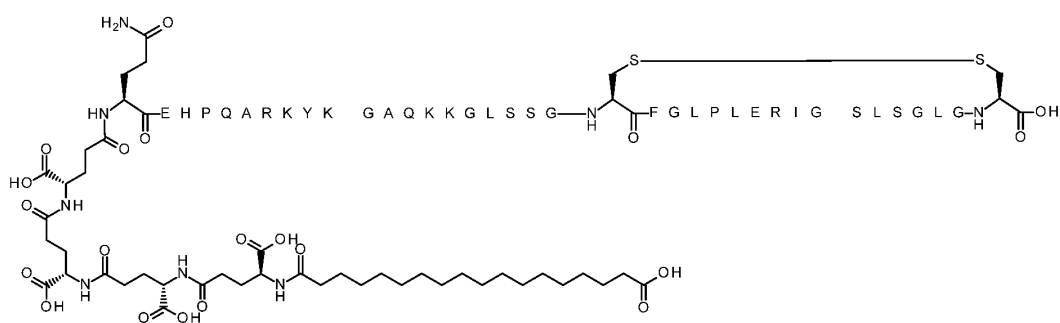
(Formula V)



5 (Formula VI)



(Formula II)



10

(Formula VII).

12. A CNP compound comprising a CNP peptide and a modifying group, wherein the compound is any one of the compounds disclosed in Table 1:

5 Table 1: Summary of compounds Chem. 6-148

Chem. No.	Compound ID	Protractor (Chem A)	Linker (Chem B-C)	CNP37 and sequence modifications	SEQ ID
6	0262	C18d	6xgGlu	des1-8, 32Nle	6
7	0296	C18d	6xgGlu	des1-4, 15S, 19S, 32Nle	7
8	0313	C18d	5xgGlu	des1-10, 32Nle	8
9	0334	C18d	5xgGlu	des1-10, 13Q, 32Nle	9
10	1221	C18d	gGlu-2xOEG	des1-8, 10E, 13Q, 32L	10
11	1222	C18d	gGlu-2xOEG	des1-8, 9E, 10E, 13Q, 32L	11
12	1223	C18d	gGlu-2xOEG	des1-8, 10E, 13Q, 14E, 32L	12
13	1224	C18d	gGlu-2xOEG	des1-8, 10E, 13Q, 19S, 32L	13
14	1225	C18d	gGlu-2xOEG	des1-8, 10E, 13Q, 25P, 32L	14
15	1226	C18d	gGlu-2xOEG	des1-8, 10E, 13Q, 14E, 25P, 32L	15
16	1227	C18d	gGlu-2xOEG	des1-8, 10E, 13Q, 19S, 25P, 32L	16
17	1228	C18d	gGlu-2xOEG	des1-8, 10E, 13Q, 14E, 19S, 25P, 32L	17
18	1229	C18d	gGlu-2xOEG	des1-8, 9E, 13Q, 14E, 32L	18
19	1230	C18d	gGlu-2xOEG	des1-8, 9E, 13Q, 14E, 19S, 32L	19
20	1231	C18d	gGlu-2xOEG	des1-8, 9E, 10Q, 13Q, 14E, 32L	20
21	1232	C18d	gGlu-2xOEG	des1-8, 13Q, 14E, 32L	21
22	1233	C18d	gGlu-2xOEG	des1-8, 13Q, 19S, 25P, 32L	22
23	1236	C18d	gGlu-2xOEG	des1-8, 9E, 10H, 13Q, 14E, 32L	23
24	1237	C18d	gGlu-2xOEG	des1-8, 10H, 13Q, 14E, 32L	24
25	1240	C18d	gGlu-2xOEG	des1-8, 10H, 13Q, 14E, 25P, 32L	25
26	1241	C18d	gGlu-2xOEG	des1-8, 10H, 13Q, 19S, 25P, 32L	26
27	1242	C18d	gGlu-2xOEG	des1-8, 10H, 13Q, 14E, 19S, 25P, 32L	27
28	1274	C18d	gGlu-2xOEG	des1-8, 10E, 13E, 19Q, 25P, 32L	28
29	1287	C18d	gGlu-2xOEG	des1-9, 10E, 13Q, 14E, 19S, 25P, 32L	29
30	1288	C18d	gGlu-2xOEG	des1-9, 10E, 13Q, 15E, 19S, 25P, 32L	30
31	1289	C18d	gGlu-2xOEG	des1-8, 10E, 13Q, 15E, 19S, 25P, 32L	31
32	1290	C18d	2xgGlu-2xOEG	des1-8, 10E, 13Q, 19S, 25P, 32L	16
33	1302	C18d	gGlu-2xOEG	des1-8, 10H, 13Q, 15T, 19S, 25P, 32L	32
34	1303	C18d	gGlu-2xOEG	des1-8, 10H, 13Q, 15T, 17V, 19S, 25P, 32L	33
35	1304	C18d	gGlu-2xOEG	des1-8, 10H, 13Q, 14H, 15T, 19S, 25P, 32L	34

36	1305	C18d	gGlu-2xOEG	des1-8, 13Q, 14H, 15T, 19S, 25P, 32L	35
37	1309	C18d	gGlu-2xOEG	des1-8, 9E, 10H, 13Q, 25P, 32L	36
38	1310	C18d	gGlu-2xOEG	des1-8, 9E, 10H, 13Q, 19S, 25P, 32L	37
39	1311	C18d	gGlu-2xOEG	des1-8, 9E, 10H, 13Q, 17V, 19S, 25P, 32L	38
40	1312	C18d	gGlu-2xOEG	des1-8, 9E, 10H, 13Q, 15T, 17V, 19S, 25P, 32L	39
41	1322	C18d	gGlu-2xOEG	des1-8, 10H, 13Q, 14H, 15H, 27E, 32L	40
42	1323	C18d	2xgGlu-2xOEG	des1-8, 10H, 13Q, 14H, 15H, 27E, 32L	40
43	1324	C18d	2xgGlu-2xOEG	des1-8, 13Q, 14H, 15H, 19Q, 27E, 32L	41
44	1338	C18d	gGlu-2xOEG	des1-8, 10E, 13Q, 19S, 25P, 27E, 32L	42
45	1339	C18d	gGlu-2xOEG	des1-9, 10E, 13Q, 19S, 25P, 32L	43
46	1340	C18d	gGlu-2xOEG	des1-8, 13Q, 14H, 15H, 19Q, 32L	44
47	1341	C18d	gGlu-2xOEG	des1-8, 13Q, 14H, 15H, 19Q, 25P, 32L	45
48	1345	C18d	gGlu-2xOEG	des1-8, 10H, 13Q, 14H, 15H, 32L	46
49	1346	C18d	gGlu-2xOEG	des1-8, 10H, 13Q, 14H, 15H, 25P, 32L	47
50	1347	C18d	gGlu-2xOEG	des1-10, 13Q, 19H, 25P, 32L	48
51	1348	C18d	gGlu-2xOEG	des1-10, 13Q, 18H, 19S, 25P, 32L	49
52	1350	C18d	gGlu-2xOEG	des1-5, 10H, 13Q, 14H, 15T, 19S, 25P, 32L	50
53	1351	C18d	gGlu-2xOEG	des1-5, 10H, 13Q, 14H, 15T, 17V, 19S, 25P, 32L	51
54	1352	C18d	gGlu-3xOEG	des1-8, 10H, 13Q, 15T, 17V, 19S, 25P, 32L	33
55	1353	C18d	gGlu-3xOEG	des1-8, 9E, 10H, 13Q, 25P, 32L	36
56	1354	C18d	2xgGlu-2xOEG	des1-5, 10H, 13Q, 15T, 17V, 19S, 25P, 32L	52
57	1355	C18d	gGlu-3xOEG	des1-8, 13Q, 19S, 25P, 32L	22
58	1356	C18d	2xgGlu-3xOEG	des1-8, 13Q, 19S, 25P, 32L	22
59	1357	C18d	2xgGlu-3xOEG	des1-8, 9E, 10H, 13Q, 32L	5
60	1359	C18d	gGlu-2xOEG	des1-5, 9E, 10H, 13Q, 15T, 17V, 19S, 25P, 32L	53
61	1360	C18d	gGlu-2xOEG	des1-5, 9E, 10H, 13Q, 14H, 15T, 17V, 19S, 25P, 32L	54
62	1375	C18d	gGlu-4xOEG	des1-8, 10E, 13Q, 25P, 32L	14
63	1376	C20d	gGlu-2xOEG	des1-8, 10E, 13Q, 25P, 32L	14
64	1377	C18d	gGlu-2xOEG	des1-8, 10E, 13Q, 17G, 25P, 32L	55
65	1378	C18d	gGlu-2xOEG-GGG	des1-8, 10E, 13Q, 19S, 25P, 32L	56
66	1379	C18d	gGlu-2xOEG	5Q, 8S, 10E, 13Q, 19S, 25P, 32L	57
67	1380	C18d	gGlu-2xOEG	5E, 8S, 10E, 13Q, 19S, 25P, 32L	58
68	1381	C18d	gGlu-2xOEG	5Q, 7H, 10H, 13Q, 14H, 15H, 17S, 19Q, 25P, 32L	59

69	1382	C18d	3xgGlu-2xOEG	5Q, 7H, 13Q, 19Q, 25P, 32L	60
70	1383	C18d	2xgGlu-2xOEG	5Q, 7H, 10H, 13Q, 15H, 17S, 19Q, 25P, 32L	61
71	9384	C18d	gGlu-2xOEG-GQAP	des1-10, 13Q, 17S, 19Q, 25P, 32L	62
72	1385	C18d	4xgGlu	des1-5, 10E, 13Q, 25P, 32L	63
73	1386	C18d	4xgGlu	des1-5, 13Q, 19S, 25P, 32L	64
74	1387	C18d	4xgGlu-GGG	des1-8, 13Q, 19S, 25P, 32L	65
75	1388	C18d	4xgGlu-GGG	des1-8, 13Q, 25P, 32L	66
76	1389	C18d	4xgGlu	5Q, 13Q, 19S, 25P, 32L	67
77	1390	C18d	4xgGlu	5Q, 10E, 13Q, 19S, 25P, 32L	68
78	1391	C18d	gGlu-4xOEG	des1-8, 10E, 13Q, 17G, 25P, 32L	55
79	1392	C18d	gGlu-4xOEG	des1-8, 10E, 13Q, 19S, 25P, 32L	16
80	1393	C18d	gGlu-4xOEG	des1-8, 10E, 13Q, 19Q, 25P, 32L	69
81	1394	C18d	gGlu-2xOEG	5Q, 10E, 13Q, 19Q, 25P, 32L	70
82	1395	C18d	gGlu-2xOEG	5Q, 7A, 10E, 13Q, 19Q, 25P, 32L	71
83	1396	C18d	2xgGlu-2xOEG	5Q, 10E, 13Q, 19Q, 25P, 32L	70
84	1398	C18d	4xgGlu-2xOEG	5Q, 8H, 13Q, 17S, 19Q, 25P, 32L	72
85	1399	C20d	4xgGlu-2xOEG	5Q, 8H, 13Q, 17S, 19Q, 25P, 32L	72
86	1400	C18d	4xgGlu-2xOEG	5Q, 7H, 13Q, 17G, 19Q, 25P, 32L	73
87	1401	C18d	8xgGlu-2xOEG	5Q, 13Q, 32L	74
88	1402	C18d	6xgGlu-2xOEG	5Q, 13Q, 19Q, 25P, 32L	75
89	1403	C18d	6xgGlu-2xOEG	5Q, 13Q, 17G, 19Q, 25P, 32L	76
90	1404	C18d	6xgGlu-4xOEG	5Q, 13Q, 19Q, 25P, 32L	75
91	1405	C20d	6xgGlu-2xOEG	5Q, 13Q, 19Q, 25P, 32L	75
92	1406	C18d	5xgGlu-4xOEG	5Q, 13Q, 19Q, 25P, 32L	75
93	9407	C18d	5xgGlu-4xOEG	des1-5, 13Q, 19Q, 25P, 32L	77
94	1419	C18d	2xgGlu-2xOEG	des1-5, 10H, 13Q, 14H, 15T, 17V, 19S, 25P, 32L	51
95	1420	C18d	3xgGlu-2xOEG	des1-5, 10H, 13Q, 14H, 15T, 17V, 25P, 32L	78
96	1421	C18d	3xgGlu-2xOEG	des1-5, 13Q, 15T, 17V, 19S, 25P, 32L	79
97	1422	C18d	3xgGlu-2xOEG	des1-5, 10H, 13Q, 17V, 19S, 25P, 32L	80
98	1423	C18d	3xgGlu-2xOEG	des1-5, 10H, 13Q, 15T, 17V, 25P, 32L	81
99	1424	C18d	4xgGlu-2xOEG	des1-5, 13Q, 15T, 17V, 25P, 32L	82
100	1425	C18d	2xgGlu-4xOEG	des1-8, 10H, 13Q, 15T, 17V, 25P, 32L	83
101	1426	Tetrazole-C18	2xgGlu-2xOEG	des1-5, 10H, 13Q, 15S, 19Q, 25P, 32L	84
102	1431	C18d	gGlu-4xOEG	des1-8, 10E, 13Q, 17G, 19H, 25P, 32L	85
103	1432	C18d	2xgGlu-4xOEG	des1-5, 10E, 13Q, 14H, 17G, 19Q, 25P, 32L	86
104	1434	C18d	2xgGlu-4xOEG	des1-8, 10H, 13Q, 17G, 19Q, 25P, 32L	87

105	9435	C18d	2xgGlu-4xOEG	des1-8, 13Q, 17G, 19Q, 25P, 32L	88
106	1436	C18d	2xgGlu-4xOEG	des1-8, 13Q, 17V, 19Q, 25P, 32L	89
107	1437	C18d	2xgGlu-4xOEG	des1-8, 10H, 13Q, 17V, 19Q, 25P, 32L	90
108	1448	C18d	4xgGlu	5Q, 10E, 13Q, 25P, 32L	91
109	1449	C18d	3xgGlu-2xOEG	des1-5, 10H, 13Q, 14H, 15T, 17V, 19S, 25P, 32L	51
110	1450	C18d	3xgGlu-2xOEG	des1-5, 10H, 13Q, 15T, 17V, 19S, 25P, 32L	52
111	1451	C18d	3xgGlu-2xOEG	des1-5, 10H, 13Q, 17V, 19S, 25P, 27E, 32L	92
112	1452	C18d	5xgGlu-3xOEG	des1-5, 13Q, 19Q, 25P, 32L	77
113	1453	C18d	5xgGlu-2xOEG	des1-5, 13Q, 19Q, 25P, 32L	77
114	1454	C18d	4xgGlu-4xOEG	des1-5, 13Q, 19Q, 25P, 32L	77
115	1455	C18d	4xgGlu-3xOEG	des1-5, 13Q, 19Q, 25P, 32L	77
116	1456	C18d	4xgGlu-2xOEG	des1-5, 13Q, 19Q, 25P, 32L	77
117	1457	C18d	gGlu-2xOEG-3xGQAP	des1-10, 13Q, 19Q, 25P, 32L	93
118	1458	C18d	gGlu-2xOEG-2xGQAP	des1-10, 13Q, 17S, 19Q, 25P, 32L	94
119	1459	C18d	4xgGlu-2xOEG-GQAP	des1-5, 13Q, 17S, 19Q, 25P, 32L	95
120	1460	C18d	6xgGlu-2xOEG	des1-5, 13Q, 25P, 32L	96
121	1461	C18d	2xgGlu-4xOEG	des1-8, 10H, 13Q, 19Q, 25P, 32L	97
122	1462	C18d	5xgGlu-4xOEG	des1-5, 13Q, 25P, 32L	96
123	1463	C18d	5xgGlu-4xOEG	des1-5, 13Q, 19Q, 32L	98
124	1464	C18d	5xgGlu-4xOEG	des1-5, 19Q, 25P, 32L	99
125	1465	C18d	5xgGlu-4xOEG	des1-5, 13Q, 19Q, 25P	100
126	1470	C18d	5xgGlu-2xOEG	des1-5, 13Q, 25P, 32L	96
127	1471	C18d	5xgGlu-2xOEG	5Q, 13Q, 19Q, 25P, 32L	75
128	1472	C18d	4xgGlu-2xOEG	5Q, 13Q, 19Q, 25P, 32L	75
129	1473	C18d	4xgGlu-2xOEG	5Q, 13Q, 19S, 25P, 32L	67
130	1474	C18d	5xgGlu-2xOEG	5Q, 13Q, 25P, 32L	101
131	1475	C18d	5xGlu-4xOEG	des1-5, 13Q, 19Q, 25P, 32L	77
132	1476	C18d	4x(Glu-Gly)-Glu-2xOEG	des1-5, 13Q, 19Q, 25P, 32L	77
133	1477	C18d	5xgGlu-4xOEG	des1-5, 13Q, 19Q, 25P, 27E, 32L	102
134	1478	C18d	2xgGlu-4xOEG	des1-8, 13Q, 19Q, 25P, 32L	103
135	9480	C18d	3xgGlu-4xOEG	des1-8, 13Q, 19Q, 25P, 32L	103
136	1481	C18d	3xGlu-4xOEG	des1-8, 13Q, 19Q, 25P, 32L	103
137	9482	C18d	5xgGlu	5Q, 13Q, 19S, 25P, 32L	67
138	9483	C18d	4xgGlu	5Q, 13Q, 19S, 25P, 27E, 32L	104
139	1484	C18d	gGlu-2xOEG-GQAP	des1-10, 13Q, 19Q, 25P, 32L	105
140	1486	C18d	gGlu-2xOEG-GQAP	des1-10, 13Q, 17S, 19Q, 25P, 27E, 32L	106
141	1487	C18d	gGlu-2xOEG-3xGQAP	des1-10, 13Q, 19Q, 25P, 32L	107

142	1488	C18d	gGlu-3xGQAP	des1-10, 13Q, 19Q, 25P, 32L	107
143	1489	C18d	2xgGlu-4xOEG	des1-8, 13Q, 17G, 19Q, 25P, 27E, 32L	108
144	1493	C18d	2xgGlu-4xOEG	des1-8, 13Q, 19Q, 25P, 27E, 32L	109
145	1511	C18d	Glu-2xOEG-GQAP	des1-10, 13Q, 17S, 19Q, 25P, 32L	62
146	1512	C18d	2xGlu-4xOEG	des1-8, 13Q, 17G, 19Q, 25P, 32L	88
147	1513	C18d	5xGlu	5Q, 13Q, 19S, 25P, 32L	110
148	1514	C18d	4xGlu	5Q, 13Q, 19S, 25P, 27E, 32L	111

13. A pharmaceutical composition comprising a compound according to any one of claims 1-12, and one or more pharmaceutically acceptable excipients.

5 14. The compound according to any one of claims 1-12, or a composition according to claim 13, for use in the treatment or prevention of cardio-renal-metabolic diseases including heart failure, and growth disorders including achondroplasia.

10 15. A method of treating or preventing heart failure, comprising administering to a patient in need thereof an effective amount of the compound according to any one of the claims 1-12, optionally in combination with one or more additional therapeutically active compounds.