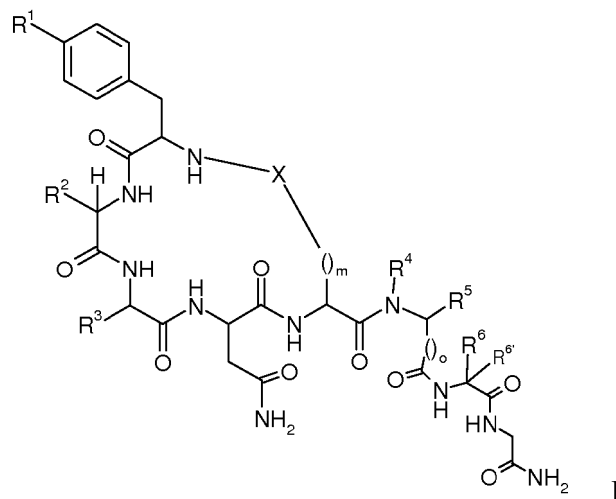


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Peptides as oxytocin agonists

The invention relates to compounds of formula



wherein

R¹ is hydroxy or amino;

5 R² is *sec*-butyl or isobutyl;

R³ is lower alkyl, lower alkyl substituted by hydroxy, $-(CH_2)_2C(O)-NH_2$, $-(CH_2)_3-NH_2$ or $-CH_2$ -five membered aromatic heterocyclic group;

R⁴ is hydrogen or lower alkyl;

R⁵ is hydrogen or lower alkyl; or

10 R⁴ and R⁵ may form together with the N and C atom to which they are attached a pyrrolidine ring, optionally substituted by hydroxy or halogen, a piperidine ring or an azetidine ring;

R⁶ is hydrogen, lower alkyl, lower alkyl substituted by hydroxy, $-(CH_2)_2C(O)OH$, $-(CH_2)_2C(O)NH_2$, benzyl optionally substituted by amino or hydroxy, $-CH_2$ -five membered aromatic heterocyclic group, indolyl, $-CH_2$ -cycloalkyl, cycloalkyl, $-(CH_2)_2-S$ -
 15 lower alkyl or is $-(CH_2)_{1-4}-NH_2$;

R^{6'} is hydrogen or lower alkyl; or

R⁶ and R^{6'} are together cycloalkyl;

X is $-\text{C}(\text{O})-\text{CHR}-\text{NR}'-\text{C}(\text{O})-$;

R/R' are independently from each other hydrogen or lower alkyl;

m is 2;

o is 0 or 1;

- 5 or a to pharmaceutically acceptable acid addition salt, to a racemic mixture or to its corresponding enantiomer and/or optical isomers thereof.

It has been found that the present compounds are oxytocin receptor agonists, which compounds are oxytocin analogs that retain oxytocin bioactivity. Such analog molecules are capable of acting in a manner similar to endogenous oxytocin, including binding the oxytocin
10 receptor. Analogs of oxytocin have completely new molecular structures.

Oxytocin is a nine amino acid cyclic peptide hormone with two cysteine residues that form a disulfide bridge between position 1 and 6. Human oxytocin comprises the sequence Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly.

Peptides have emerged as a commercially relevant class of drugs that offer the advantage
15 of greater specificity and potency and lower toxicity profiles over traditional small molecule pharmaceuticals. They offer promising treatment options for numerous diseases, such as diabetes, HIV, hepatitis, cancer and others, with physicians and patents becoming more accepting of peptide-based medicines. The present invention relates to peptidic oxytocin receptor agonists, which also include the natural hormone oxytocin and carbetocin.

20 Oxytocin is a potent uterotonic agent for the control of uterine atony and excessive bleeding, clinically used to induce labour, and has been shown to enhance the onset and maintenance of lactation (Gimpl et al., *Physiol. Rev.*, 81, (2001), 629 – 683, Ruis et al., *BMJ*, 283, (1981), 340 – 342). Carbetocin (1-deamino-1-carba-2-tyrosine (O-methyl)-oxytocin) is also a potent uterotonic agent clinically used for the control of uterine atony and excessive bleeding.

25 Peptidic oxytocin agonists may be used for the treatment of Prader-Willi Syndrom, which is a rare genetic disorder which affects one child in 25.000.

Further research indicates that oxytocin agonists are useful for the treatment of inflammation and pain, including abdominal and back pain (Yang, *Spine*, 19, 1994, 867-71), sexual dysfunction in both male (Lidberg et al., *Pharmakopsychiat.*, 10, 1977, 21 – 25) and female (Anderson-Hunt, et
30 al., *BMJ*, 309, 1994, 929), irritable bowel syndrome (IBS, Louvel et al., *Gut*, 39, 1996, 741 – 47), constipation and gastrointestinal obstruction (Ohlsson et al., *Neurogastroenterol. Motil.*, 17, 2005,

697 – 704), autism (Hollander et al., Neuropsychopharm., 28, 2008, 193 – 98), stress, including post traumatic stress disorder (PTSD) (Pitman et al., Psychiatry Research, 48, 107 – 117), anxiety, including anxiety disorders and depression (Kirsch et al., J. Neurosci., 25, 49, 11489 – 93, Waldherr et al., PNAS, 104, 2007, 16681 – 84), surgical blood loss or control of post-partum haemorrhage (Fujimoto et al., Acta Obstet. Gynecol., 85, 2006, 1310 -14), labor induction and maintenance (Flamm et al., Obstet. Gynecol., 70, 1987, 70 – 12), wound healing and infection, mastitis and placenta delivery, and osteoporosis. Additionally, oxytocin agonists may be useful for the diagnosis of both cancer and placental insufficiency.

Furthermore, the Articles “Intranasal Oxytocin blocks alcohol withdrawal in human subjects” (Alcohol Clin Exp Res, Vol, No. 2012) and “Breaking the loop: Oxytocin as a potential treatment for drug addiction” (Hormones and Behavior, 61, 2012 , 331- 339) propose to treat alcohol withdrawal and drug addiction with a oxytocin agonist.

Oxytocin and its receptors exists in areas of the brain implicated in the symptoms of schizophrenia, such as the nucleus accumbens and the hippocampus. The oxytocin receptor agonists may be used for the treatment of autism, stress, including post traumatic stress disorder, anxiety, including anxiety disorders and depression, schizophrenia, Alzheimer’s disease, psychiatric disorders, memory loss and metabolic diseases (WO2012/016229).

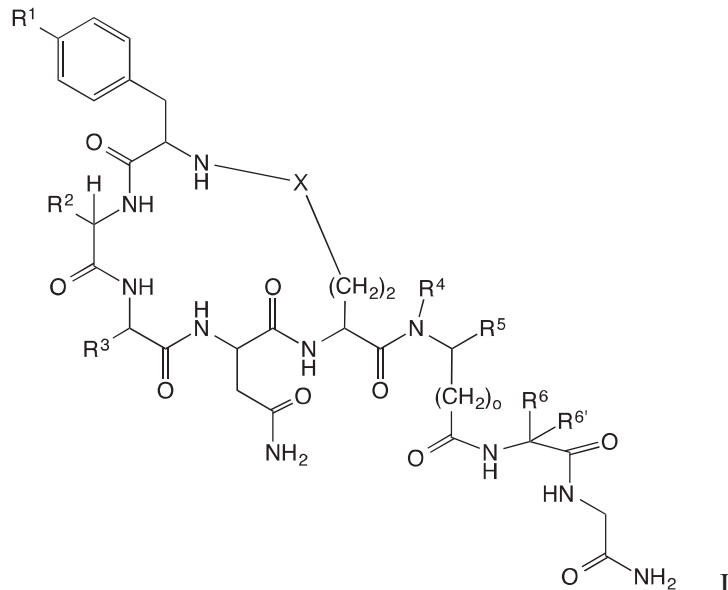
Objects of the embodiments disclosed herein are novel compounds of formula I and the use of compounds of formula I and their pharmaceutically acceptable salts for the treatment of CNS diseases related to the oxytocin receptor, which diseases are autism, stress, including post traumatic stress disorder, anxiety, including anxiety disorders and depression, schizophrenia, psychiatric disorders and memory loss, alcohol withdrawal, drug addiction and for the treatment of Prader-Willi Syndrom.

Further objects are the preparation of novel compounds of formula I and medicaments, containing them.

The present disclosure may provide selective, efficacious compounds, providing alternatives and/or improvements in the treatment of certain CNS diseases including autism, stress, including post traumatic stress disorder, anxiety, including anxiety disorders and depression, schizophrenia, psychiatric disorders and memory loss, alcohol withdrawal, drug addiction and for the treatment of Prader-Willi Syndrom.

SUMMARY

In one aspect, there is provided a compound of formula



wherein

- 5 R¹ is hydroxy or amino;
- R² is *sec*-butyl or isobutyl;
- R³ is C₁₋₇ alkyl, C₁₋₇ alkyl substituted by hydroxy, -(CH₂)₂C(O)-NH₂, -(CH₂)₃-NH₂
or -CH₂-five membered aromatic heterocyclic group;
- R⁴ is hydrogen or C₁₋₇ alkyl;
- 10 R⁵ is hydrogen or C₁₋₇ alkyl; or
- R⁴ and R⁵ may form together with the N and C atom to which they are attached a
pyrrolidine ring, optionally substituted by hydroxy or halogen, a piperidine ring or an azetidine
ring;

R^6 is hydrogen, C_{1-7} alkyl, C_{1-7} alkyl substituted by hydroxy, $-(CH_2)_2C(O)OH$, $-(CH_2)_2C(O)NH_2$, benzyl optionally substituted by amino or hydroxy, $-CH_2$ -five membered aromatic heterocyclic group, indolyl, $-CH_2$ -cycloalkyl, cycloalkyl, $-(CH_2)_2-S-C_{1-7}$ alkyl or is $-(CH_2)_{1-4}-NH_2$;

5 $R^{6'}$ is hydrogen or C_{1-7} alkyl; or

R^6 and $R^{6'}$ are together cycloalkyl;

X is $-C(O)-CHR-NR'-C(O)-$;

R/R' are independently from each other hydrogen or C_{1-7} alkyl;

o is 0 or 1;

10 or a pharmaceutically acceptable acid addition salt, a racemic mixture or its corresponding enantiomer and/or optical isomers thereof.

In another aspect, there is provided a pharmaceutical composition comprising a compound as defined herein and a pharmaceutical acceptable carrier and/or adjuvant.

15 In another aspect, there is provided a compound as defined herein for use as therapeutic active substances.

In another aspect, there is provided use of a compound as defined herein in the preparation of medicaments for the therapeutic and/or prophylactic treatment of autism, stress, including post traumatic stress disorder, anxiety, including anxiety disorders and depression, schizophrenia, psychiatric disorders and memory loss, alcohol withdrawal, drug addiction and
20 for the treatment of Prader-Willi Syndrome.

It has been shown that the present peptides have a very good selectivity to the vasopressin receptors V1a and V2 as shown in the table. This may have a major advantage for use as medicament to avoid side effects. These physiological effects may be considered to be

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undesirable side effects in the case of medicines aimed at treating diseases of the central nervous system. Therefore it is desirable to obtain medicines having selectivity for the oxytocin receptor vs. vasopressin receptor.

As used herein, the term "lower alkyl" denotes a saturated straight- or branched chain group containing from 1 to 7 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, 2-butyl, t-butyl and the like.

The term "lower alkyl substituted by hydroxy" denotes a lower alkyl group as defined above, wherein at least one hydrogen atom is replaced by a hydroxy group.

The term "cycloalkyl" denotes a cyclic alkyl chain, containing from 3 to 6 carbon atoms.

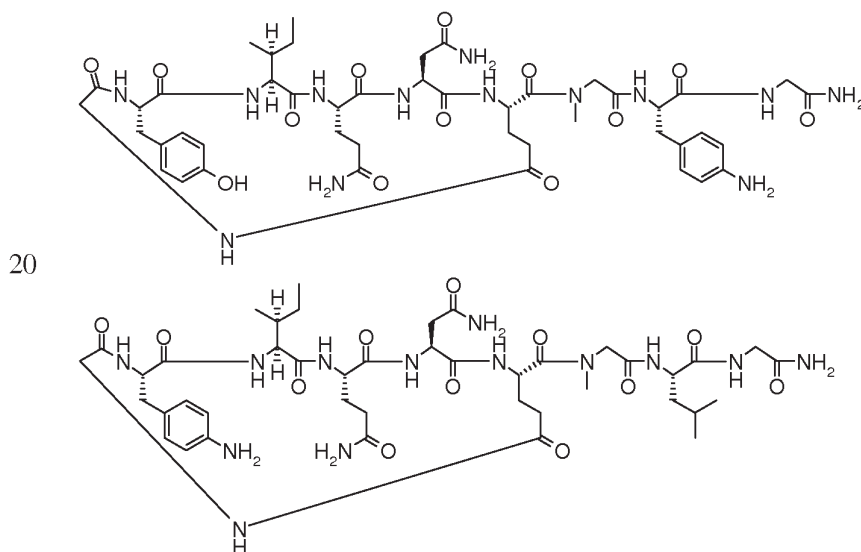
As used herein, the term "five-membered aromatic heterocyclic group" denotes an imidazolyl, thiophenyl, furanyl, pyrrolyl, pyrazolyl, oxazolyl, oxadiazolyl or isoxazolyl group.

The term "pharmaceutically acceptable acid addition salts" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methane-sulfonic acid, p-toluenesulfonic acid and the like.

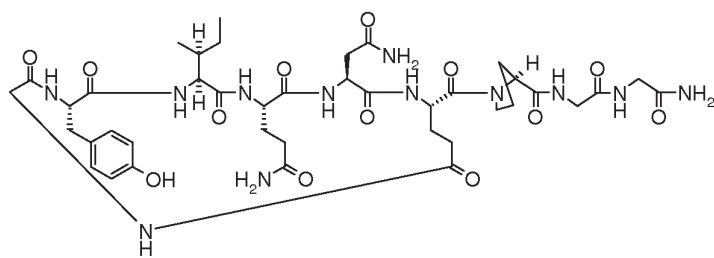
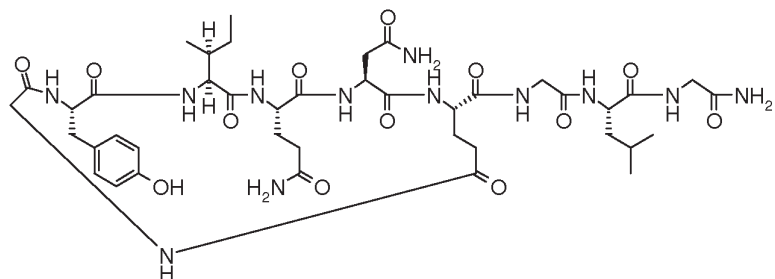
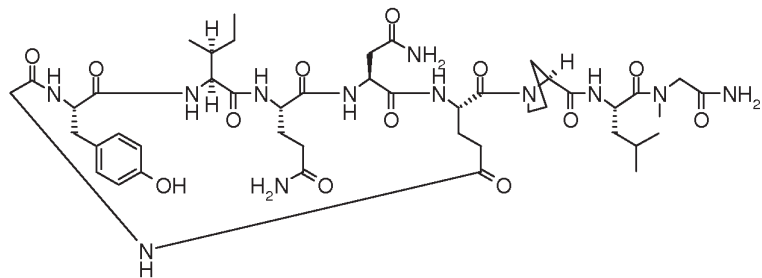
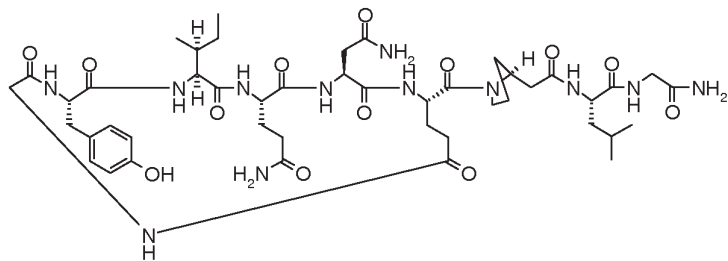
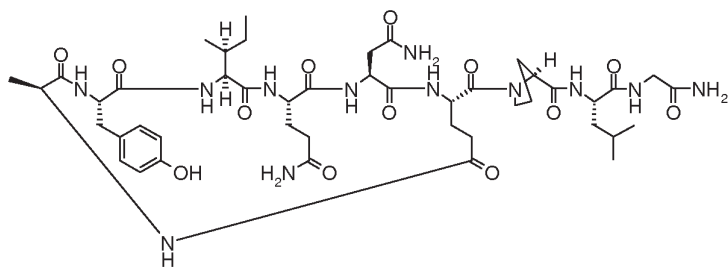
The preferred five-membered heterocyclic ring is an imidazole ring.

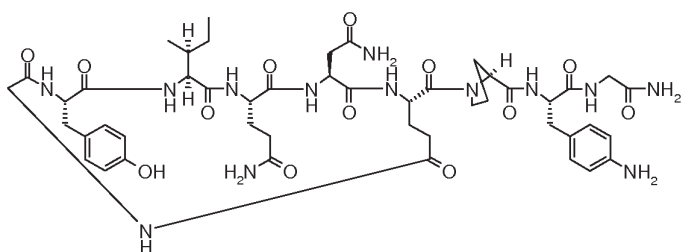
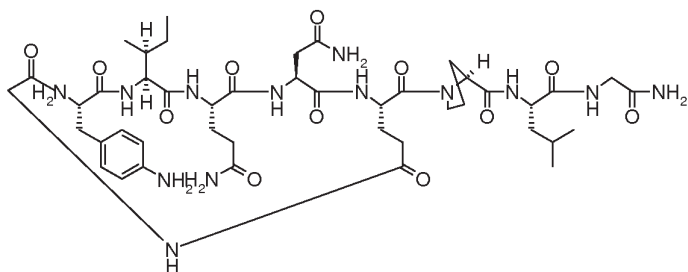
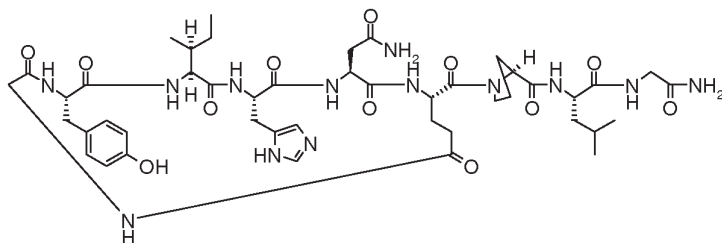
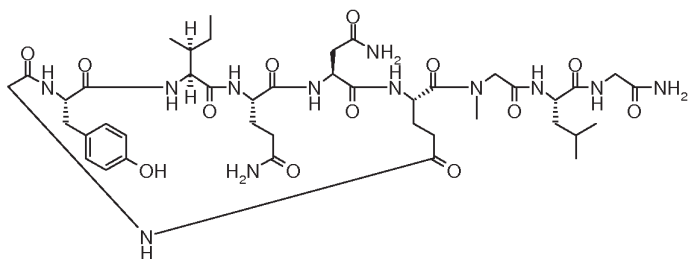
Preferred are compounds of formula I, wherein o is 0 and m is 2.

The following specific compounds have been prepared and tested for their agonistic activity on the oxytocin receptor:

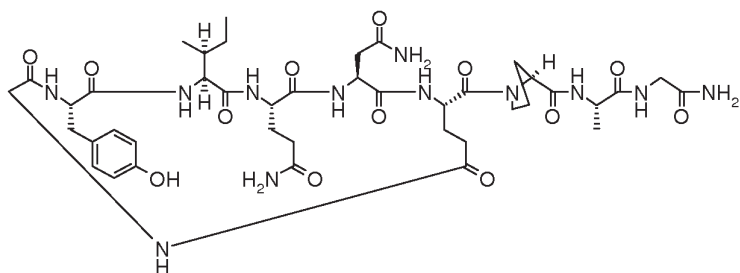
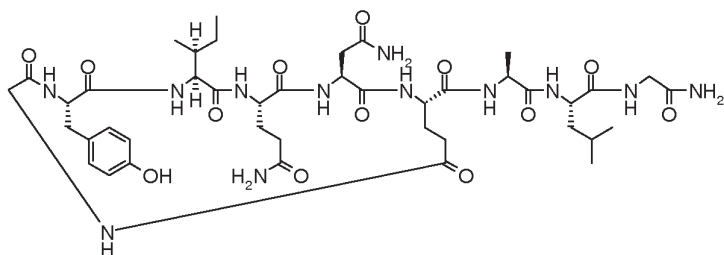
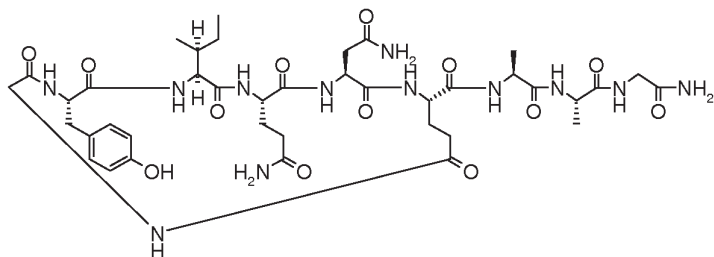
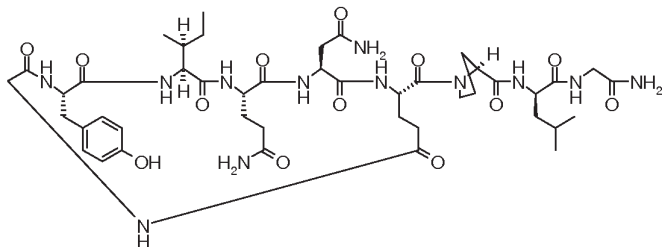
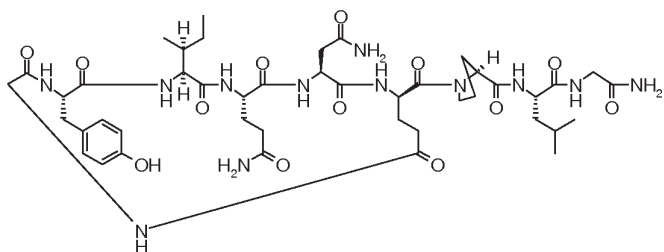


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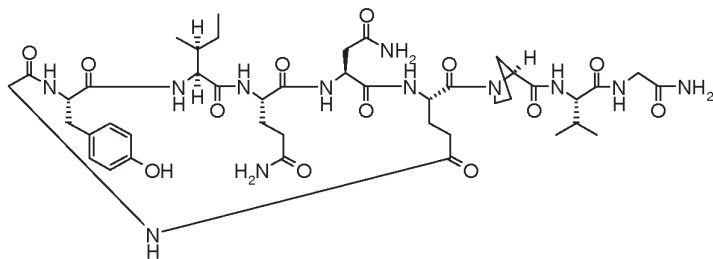


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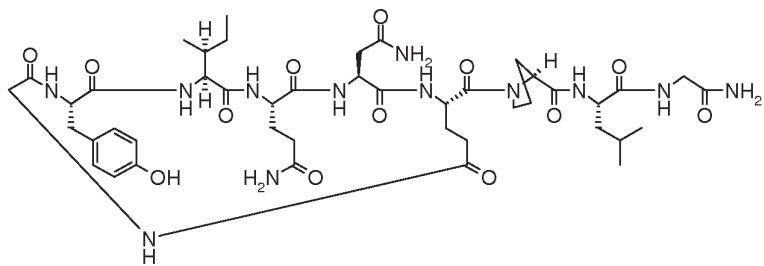
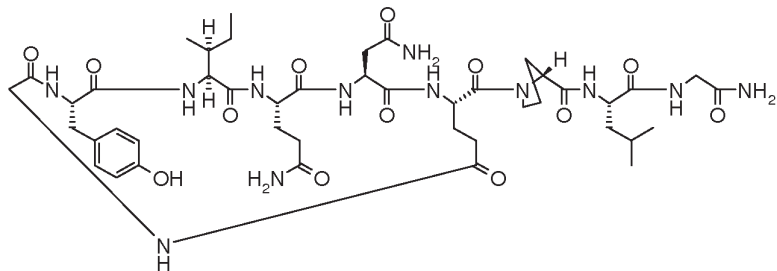
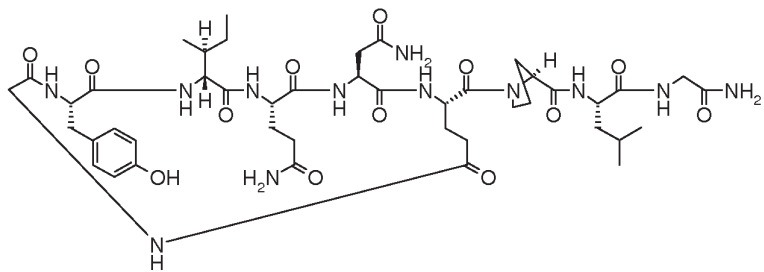
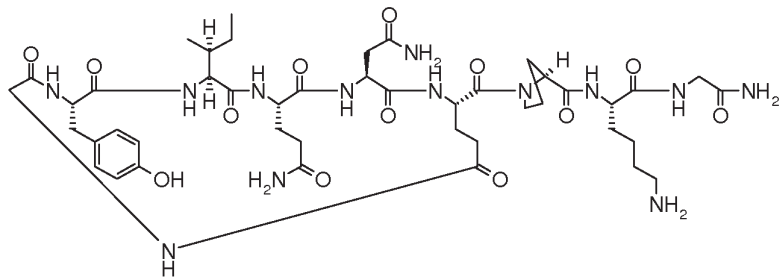
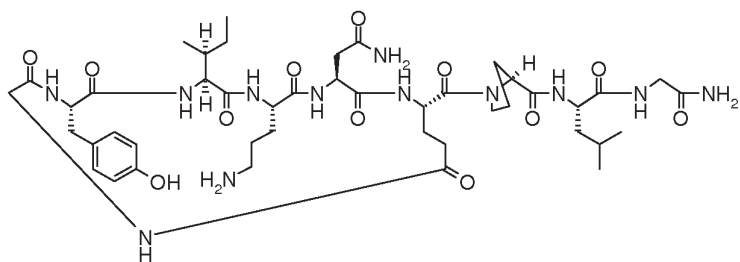
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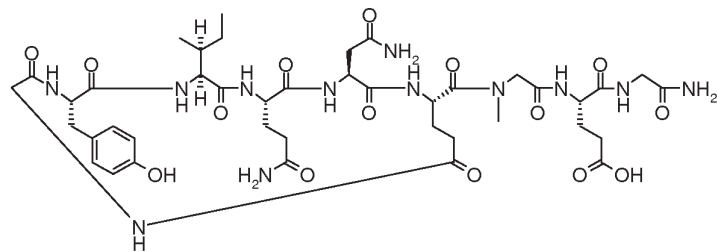
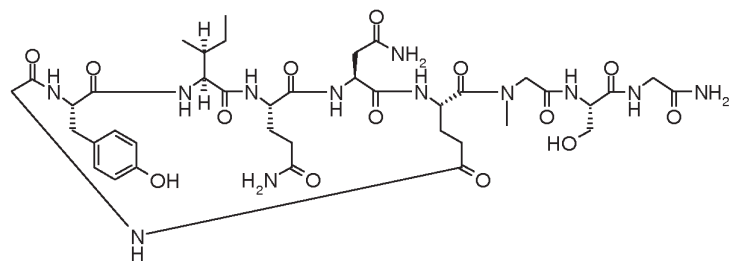
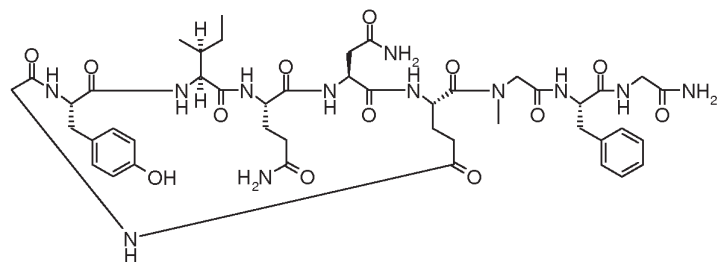
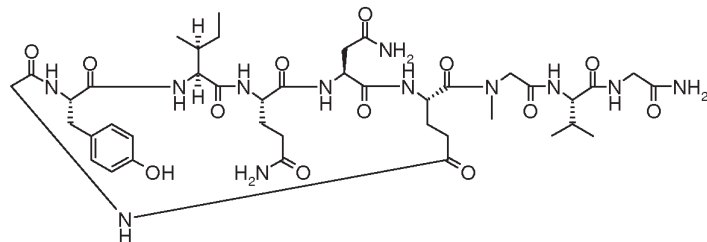


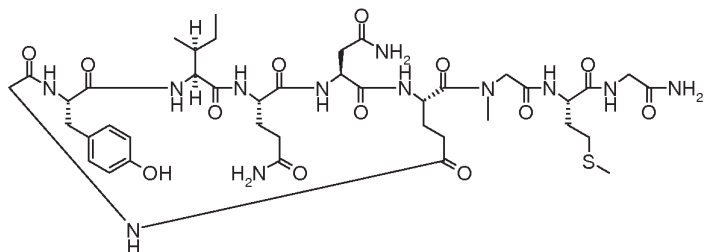
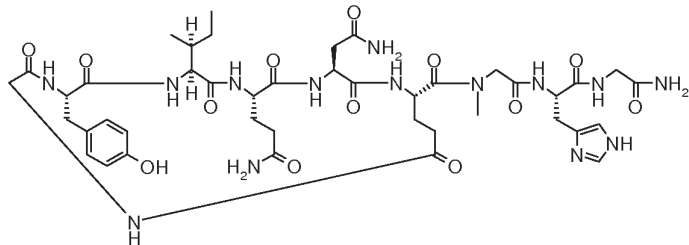
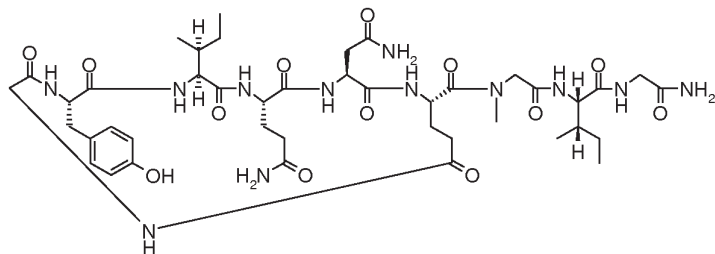
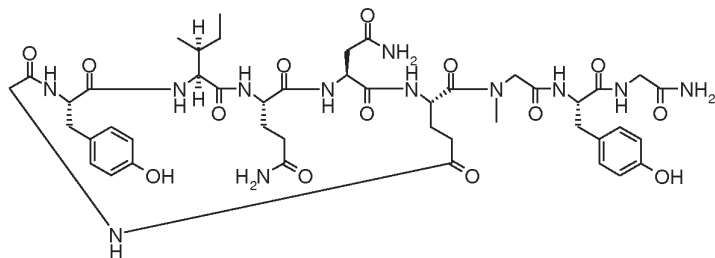
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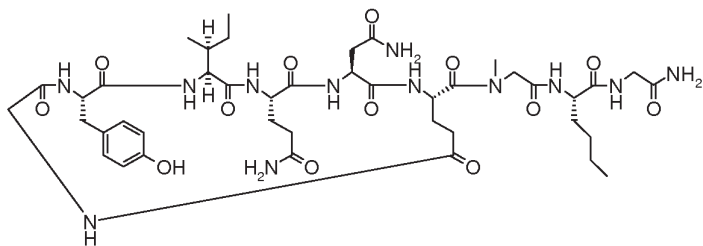
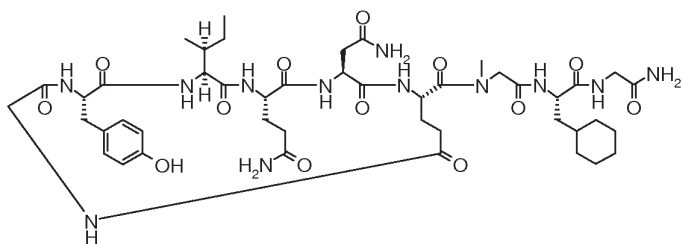
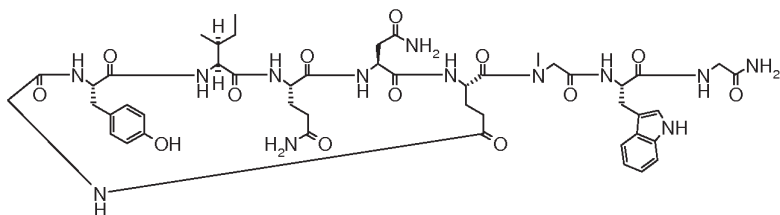
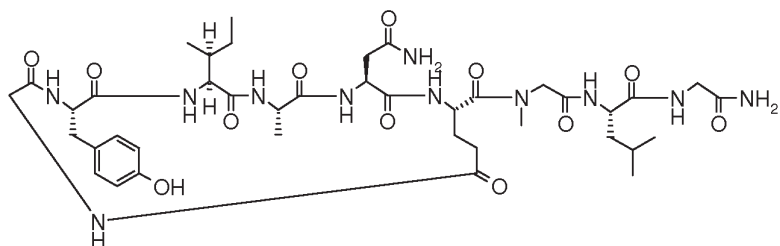
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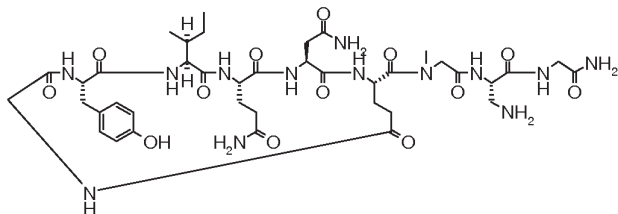
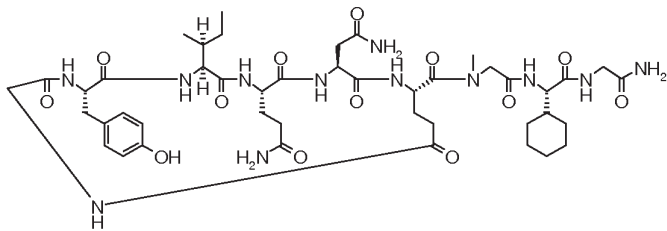
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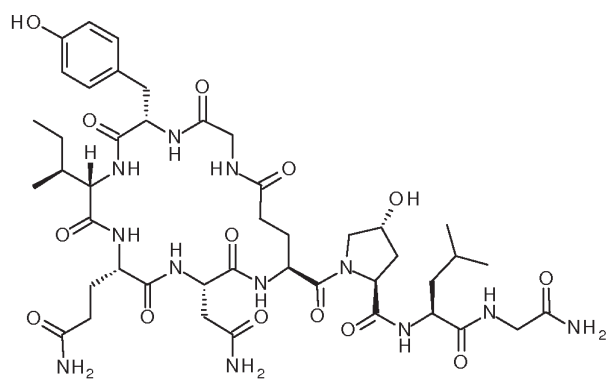
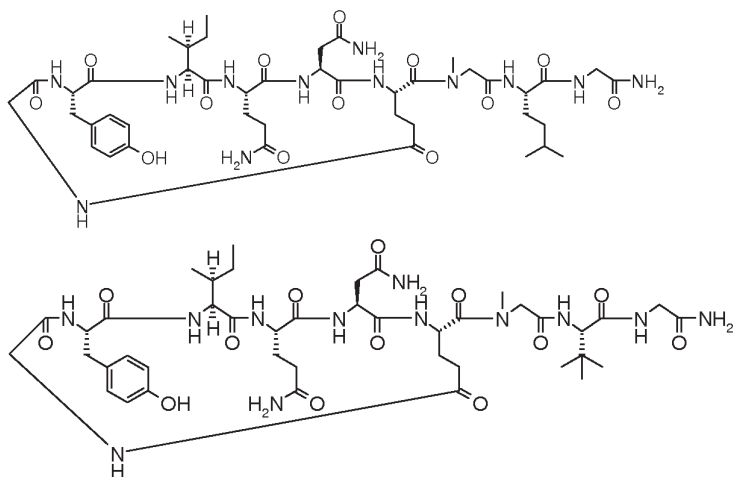
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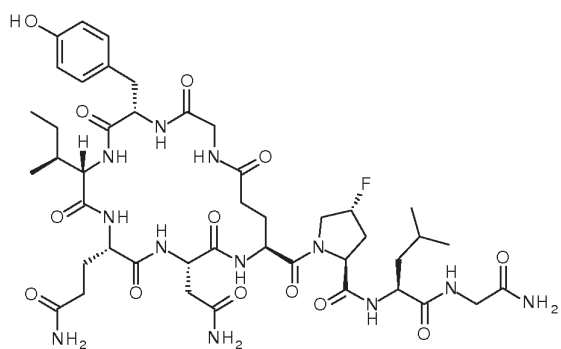
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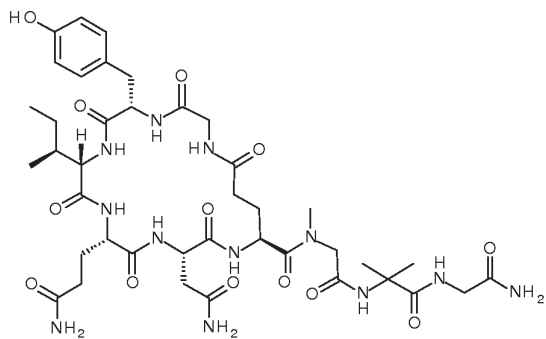
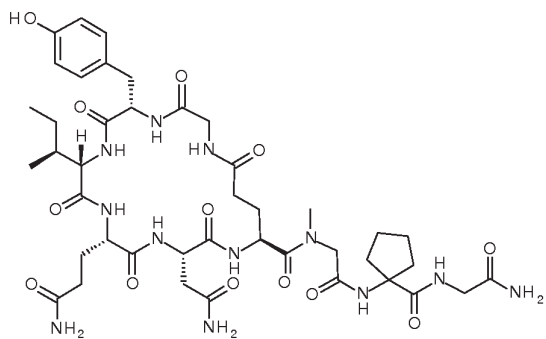
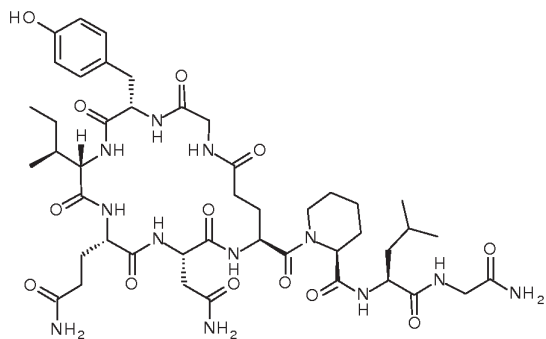


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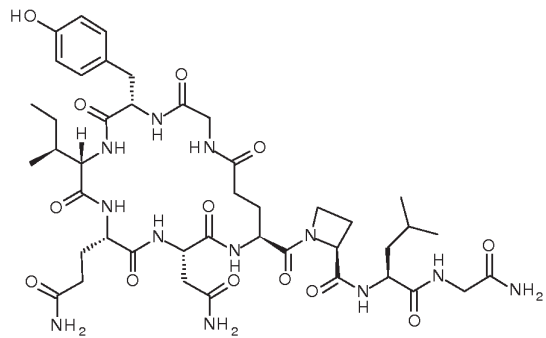


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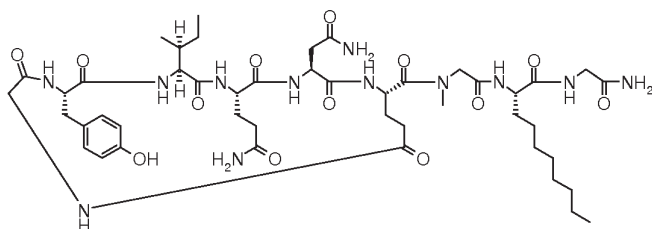
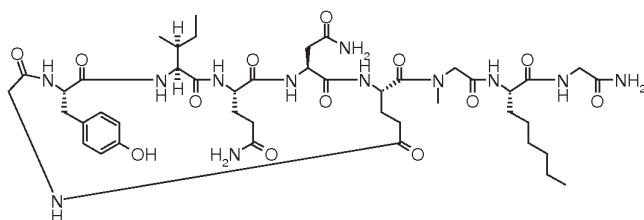
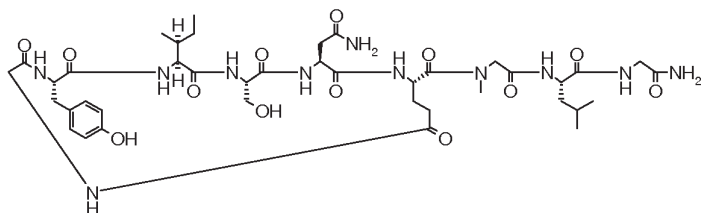
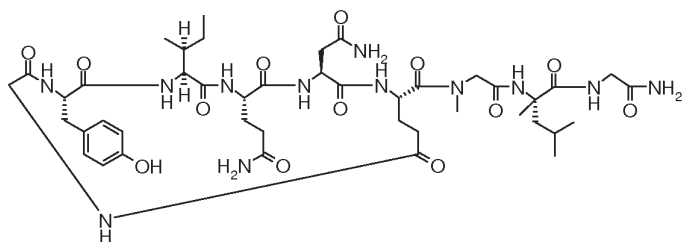




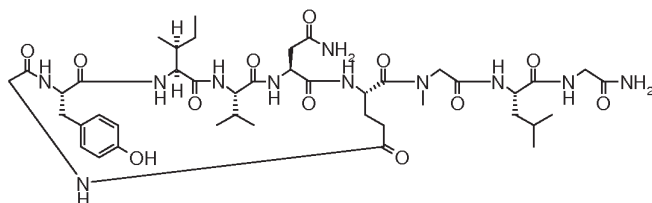
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The preparation of compounds of formula **I** of the present invention may be carried out in sequential or convergent synthetic routes. The skills required for carrying out the reaction and purification of the resulting products are known to those skilled in the art.

The compounds herein were synthesized by standard methods in solid phase peptide chemistry utilizing both Fmoc and Boc methodology. Reactions carried out manually were performed at room temperature, while microwave assisted peptide synthesis was performed at elevated temperature.

General Synthesis Description:

Linear peptides were either synthesized manually or using microwave technology via state-of-the-art solid phase synthesis protocols (Fmoc-chemistry) as referenced by e.g.: Kates and Albericio, Eds., "Solid Phase Synthesis: A practical guide", Marcel Decker, New York, Basel, 2000. As a solid support TentaGel-S-RAM resin (0.24 meq /g) was used. All Fmoc-amino acids were added in a 10-fold excess after activation with HOBt/HBTU 1:1 (0.5 mol/L in DMF) and 4 eq of DIPEA (2 mol/L in NMP). Fmoc-cleavage was achieved with 20 % piperidine in DMF.

Allyl/Aloc-Cleavage & Lactam-Cyclisation:

The resin was treated manually with a solution of 20 eq phenylsilane in DCM and 0.05 eq of tetrakis triphenylphosphine palladium for 30 min at RT. This procedure was repeated. The resin was washed with a solution of 0.5 % sodium dithiocarbamate in DMF. For the on-bead lactam formation, again activation reagent was added to the resin and shaken for additional 8 h at RT. Completion of cyclisation was verified via Ninhydrin-test. Crude peptides were treated with standard peptide activation reagents in DMF. The cyclisation was monitored via HPLC.

Cleavage :

A cleavage-cocktail of trifluoroacetic acid, triisopropylsilane and water (95/2.5/2.5) was added to the resin and shaken for 1 h at RT. Cleaved peptide was precipitated in cold Ether (-18 °C). The peptide was centrifuged and the residue washed twice with cold ether. The residue was dissolved in water/ acetonitrile and lyophilized.

Purification :

Peptides were purified using reversed phase high performance liquid chromatography (RP-HPLC) using a Reprospher 100 C18-T Column (100 x 4.6 mm, 5µ particle size) as a stationary phase and water/acetonitrile as eluent (Gradient 1-50 % MeCN over 30 min). Fractions were collected and analyzed by LC/MS. Pure product samples were combined and lyophilized. All peptides were obtained as white powders with a purity >85 %. Product identification was obtained via mass spectrometry.

All standard amino acids were purchased from CEM. Fmoc-Glu(Allyl)-OH, Fmoc-Phe(4-NHBoc)-OH, Fmoc-DAP(Aloc)-OH, Fmoc-DAB(Aloc)-OH and Fmoc-SAR-OH were purchased from Bachem. Fmoc-β-Homoproline was purchased from Chem-Impax. Fmoc-β-Ala-OH and Mono-tBu-Succinate were purchased from Sigma-Aldrich

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The detailed description for the synthesis of example 6 is provided to further illustrate the synthesis conditions:

Peptide Synthesis:

The peptide was synthesized using CEM Microwave technology with coupling times of 5 minutes per amino acid at elevated temperature (78 °C) and a 0.25mmol scale. The synthesis is carried out using the Tentagel-S RAM resin as a solid support (0.24 meq /g). All amino acids used were dissolved in DMF to 0.2 mol concentration. A mixture of HOBt/HBTU 1:1 (0.5 mol /L) 4 eq. and DIPEA 4eq. was used to activate the amino acids. Fmoc-Cleavage was achieved with Piperidine in DMF (20 %) for 3 min. Fmoc-cleavage was repeated.

10 **Aloc-&Allyl-Cleavage:**

The resin was treated manually with a solution of 20 eq. phenylsilane and 0.05 eq. of tetrakis triphenylphosphine palladium in DCM (5 ml) for 30 min at RT. This procedure was repeated. The resin was washed with a solution of 0.5 % sodium dithiocarbamate in DMF twice. The washing step was repeated with DCM.

15 **On-bead cyclisation:**

Again coupling-reagent (4ml of an 0.5 mol/L solution HOBt/HBTU (1:1) and 1 ml of DIPEA (4 eq.) in DMF was added to the resin. The slurry was shaken for about 8 h at RT. The resin was washed with DMF and DCM twice. Completion of cyclisation was verified via Ninhydrin test.

Cleavage from resin:

20 10 ml of the cleavage-cocktail (TFA; TIS; water (95/2.5/2.5)) was added to the resin and shaken for 1h at RT. Cleaved peptide was precipitated in cold ether (-18 °C). The peptide was centrifuged and the precipitates washed twice with cold ether. The precipitate was dissolved in H₂O/ Acetonitrile and lyophilized to yield 210 mg white powder.

Purification:

25 The crude peptide was purified by preparative HPLC on a Reprospher 100 C18-T Column (100 x 4.6 mm, 5µm particle size). As eluent system a mixture of 0.1 % TFA/water/acetonitrile was used with a gradient of 0-50 % acetonitrile within 0-30 min. The fractions were collected and checked by analytical HPLC. Fractions containing pure product were combined and lyophilized. 7.2 mg of white powder were obtained.

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All other peptides listed below were synthesized accordingly.

Abbreviations:

- Fmoc: 9-Fluorenylmethoxycarbonyl
Gly: Glycine
5 His(Trt): Trityl-protected Histidine
Sar: Sarcosine
Glu: Glutamic Acid
Asn(Trt): Trityl-protected Asparagine
Gln(Trt): Trityl-protected Glutamine
10 Ile: Isoleucine
Tyr: Tyrosine
Leu: Leucine
Pro: Proline
Ala: Alanine
15 Orn: Ornithine
Thr: Threonine
Val: Valine
Dab: Diaminobutyric acid
Dap: Diaminopropionic acid
20 D-Pro: D-Proline
MeLeu: α -Methyl-Leucine
Cha: β -Cyclohexyl-Alanine
Nle: Norleucine
Chg: Cyclohexylglycine
25 HoLeu: Homoleucine
Tle: tert. Butyl-glycine
Hyp: Trans-4-Hydroxy-L-Proline
FluoroPro: Trans-4-Fluoro-L-Proline
Hpr: Homoproline
30 Aib: Aminoisobutyric Acid
Aze: (S)-N-Azetidine-2-Carboxylic Acid
Ser: Serine
2AOC-OH: L-Aminooctanoic Acid

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2ADC-OH: L-Aminodecanoic Acid

cyLeu : Cycloleucine

Aloc: Allyloxycarbonyl

HOBT: N-Hydroxybenzotriazol

5 HBTU: O-Benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluorophosphate

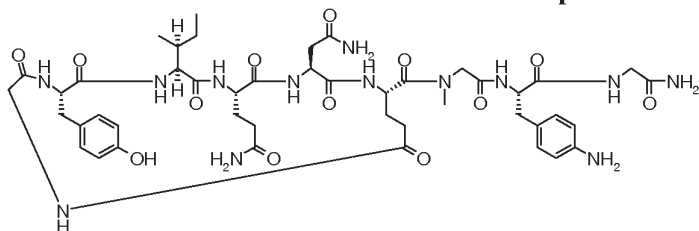
DMF: N,N-Dimethylformamide

NMP: N-Methylpyrrolidone

DIPEA: N,N-Diisopropylamine

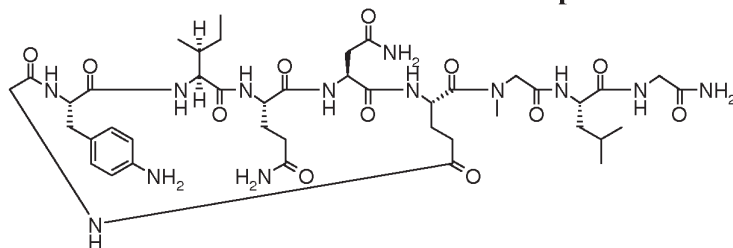
DCM: Dichlormethane

10 MeCN: Acetonitril

Example 1

The following amino acids were used: Fmoc-Gly-OH, FMOC-Phe(4-NHBoc)-OH, Fmoc-SAR-
 15 OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OH

MS ($M+H^+$): expected 994.1; observed 994.9

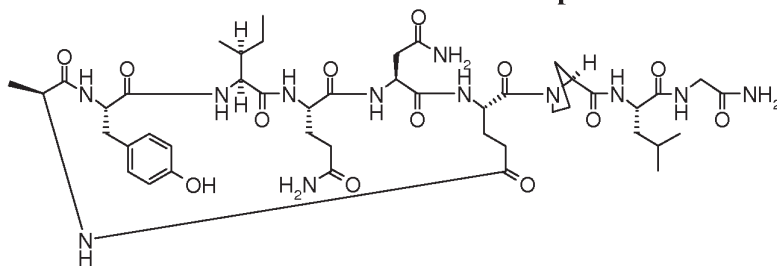
Example 2

20 The following amino acids were used: Fmoc-Gly-OH, Fmoc-Leu-OH, Fmoc-SAR-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, FMOC-Phe(4-NHBoc)-OH

MS ($M+H^+$): expected 944.1; observed 944.4

25

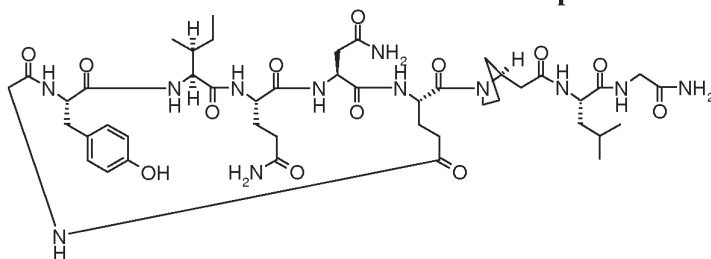
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Example 3

The following amino acids were used: Fmoc-Gly-OH, Fmoc-Leu-OH, Fmoc-Pro-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OH,

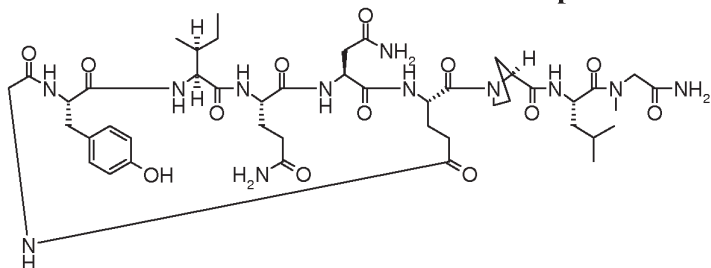
5 Fmoc-Ala-OH

MS ($M+H^+$): expected 985.1; observed 986.3

Example 4

10 The following amino acids were used: Fmoc-Gly-OH, Fmoc-Leu-OH, Fmoc-β-Pro-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OH

MS ($M+H^+$): expected 984.5; observed 984.9

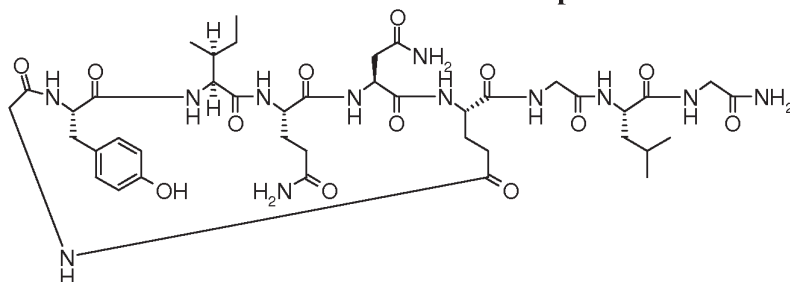
Example 5

15 The following amino acids were used: Fmoc-SAR-OH, Fmoc-Leu-OH, Fmoc-Pro-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OH, Fmoc-Gly-OH

MS ($M+H^+$): expected 984.5; observed 984.9

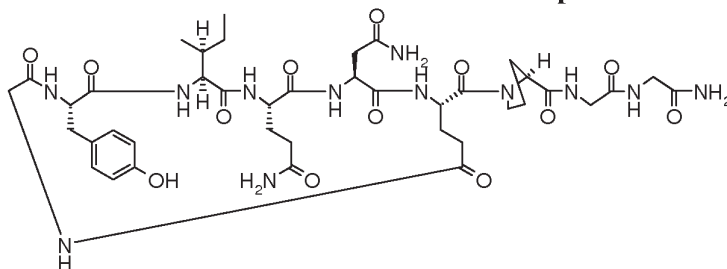
20

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Example 6

The following amino acids were used: Fmoc-Gly-OH, Fmoc-Leu-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OH

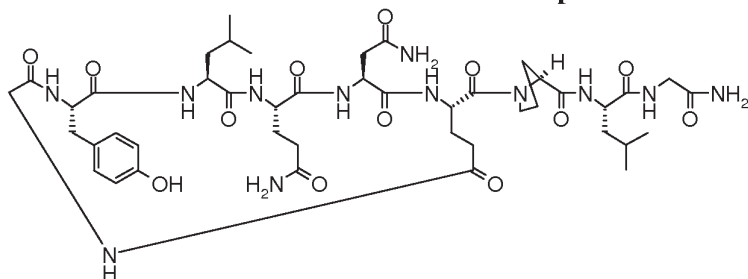
5 MS ($M+H^+$): expected 931.0; observed 932.0

Example 7

The following amino acids were used: Fmoc-Gly-OH, Fmoc-Pro-OH, Fmoc-Glu(Allyl)-OH,

10 Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OH

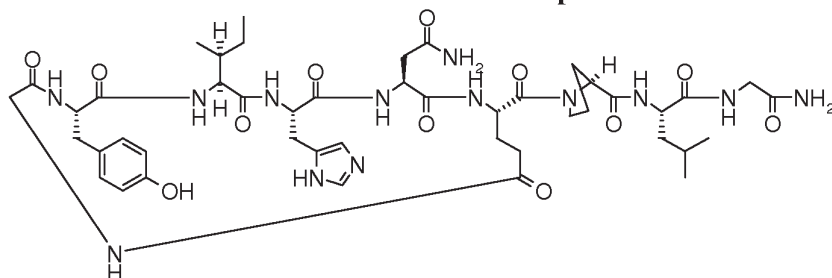
MS ($M+H^+$): expected 914.9; observed 915.9

Example 8

15 The following amino acids were used: Fmoc-Gly-OH, Fmoc-Leu, Fmoc-Pro-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Tyr(tBu)-OH

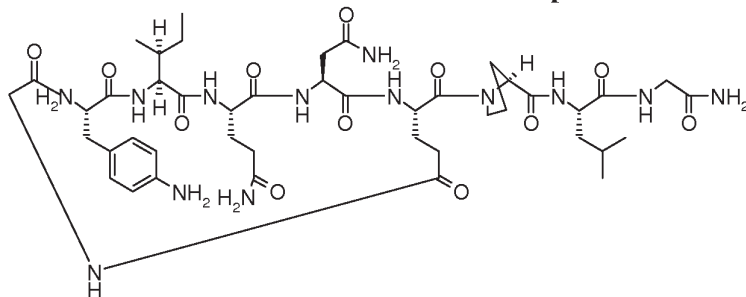
MS ($M+H^+$): expected 971.1; observed 971.5

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Example 9

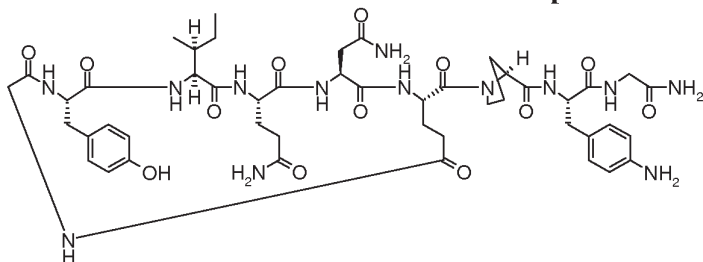
The following amino acids were used: Fmoc-Gly-OH, Fmoc-Leu, Fmoc-Pro-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-His(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OH

5 MS ($M+H^+$): expected 980.1; observed 981.5

Example 10

The following amino acids were used: Fmoc-Gly-OH, Fmoc-Leu, Fmoc-Pro-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, FMOC-Phe(4-NHBoc)-OH

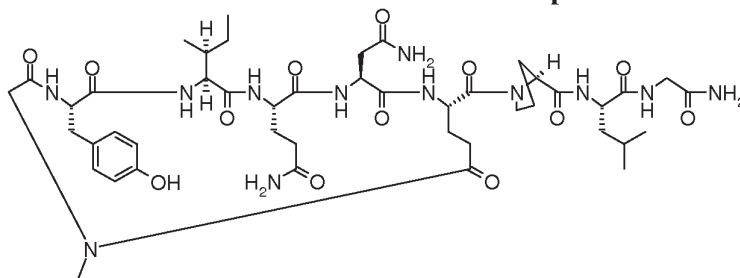
10 MS ($M+H^+$): expected 970.1; observed 970.8

Example 11

15 The following amino acids were used: FMOC-Phe(4-NHBoc)-OH, Fmoc-Pro-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OH

MS ($M+H^+$): expected 1020.0; observed 1021.0

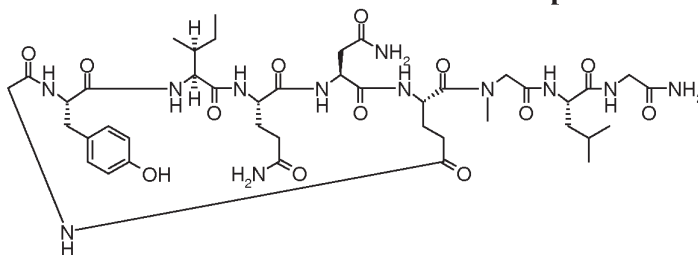
-22-

Example 12

The following amino acids were used: Fmoc-Gly-OH, Fmoc-Leu-OH, Fmoc-Pro-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OH,

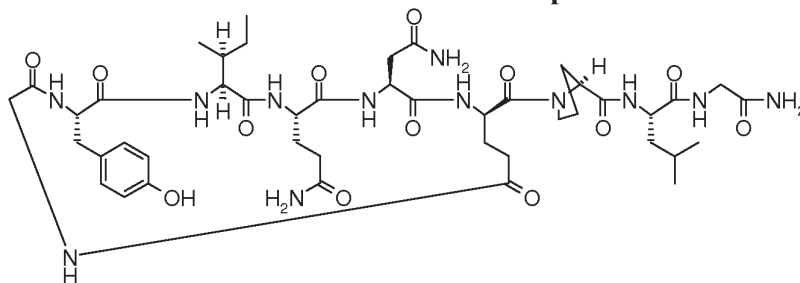
5 Fmoc-SAR-OH

MS ($M+H^+$): expected 985.1; observed 985.4

Example 13

10 The following amino acids were used: Fmoc-Gly-OH, Fmoc-Leu-OH, Fmoc-SAR-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OH

MS ($M+H^+$): expected 945.1; observed 945.4

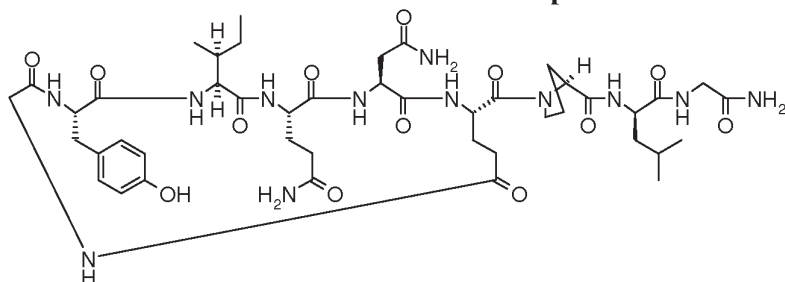
Example 14

15 The following amino acids were used: Fmoc-Gly-OH, Fmoc-Leu-OH, Fmoc-Pro-OH, Fmoc-D-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OH

MS ($M+H^+$): expected 971.1; observed 971.5

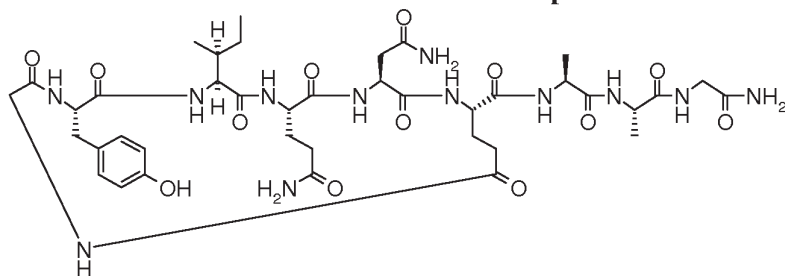
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Example 15

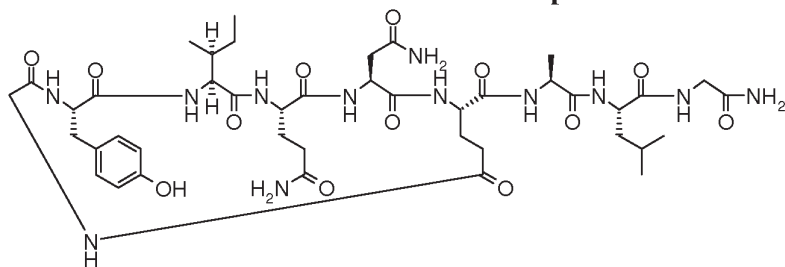
The following amino acids were used: Fmoc-Gly-OH, Fmoc-D-Leu-OH, Fmoc-Pro-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OH

5 MS ($M+H^+$): expected 971.1; observed 971.3

Example 16

The following amino acids were used: Fmoc-Gly-OH, Fmoc-Ala-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OH

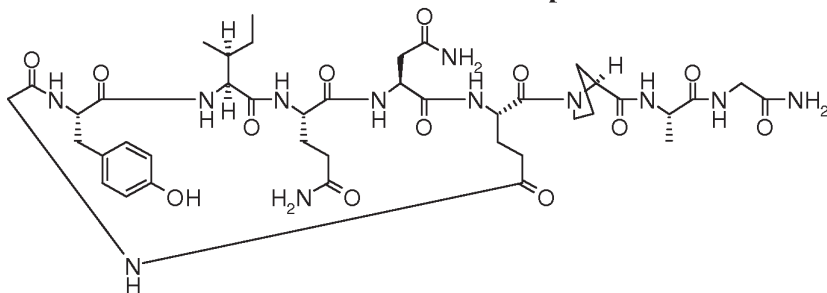
10 MS ($M+H^+$): expected 902.9; observed 903.8

Example 17

15 The following amino acids were used: Fmoc-Gly-OH, Fmoc-Leu-OH, Fmoc-Ala-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OH

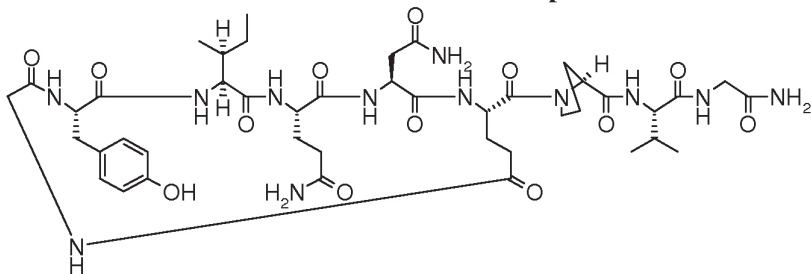
MS ($M+H^+$): expected 944.5; observed 945.0

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Example 18

The following amino acids were used: Fmoc-Gly-OH, Fmoc-Ala-OH, Fmoc-Pro-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OH

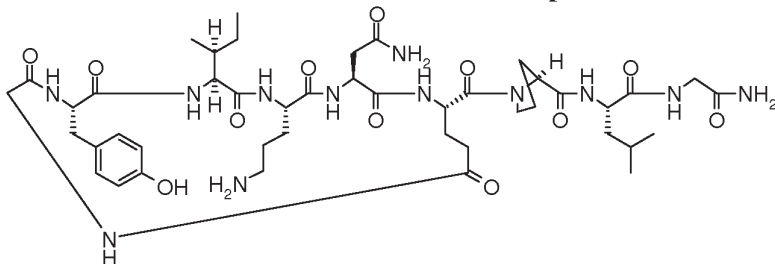
5 MS ($M+H^+$): expected 928.9; observed 929.7

Example 19

The following amino acids were used: Fmoc-Gly-OH, Fmoc-Val-OH, Fmoc-Pro-OH, Fmoc-

10 Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OH

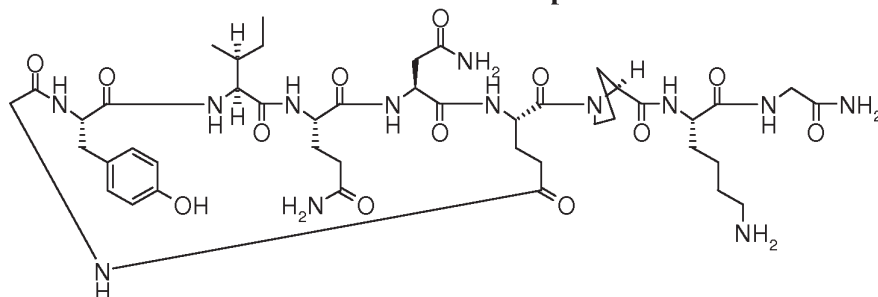
MS ($M+H^+$): expected 957.1; observed 957.8

Example 20

15 The following amino acids were used: Fmoc-Gly-OH, Fmoc-Leu-OH, Fmoc-Pro-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Orn(Boc)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OH

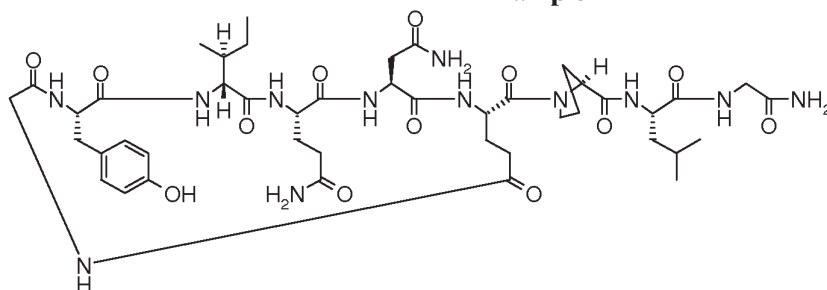
MS ($M+H^+$): expected 957.1; observed 957.9

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Example 21

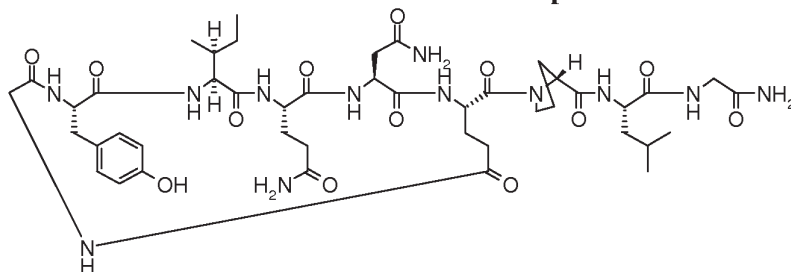
The following amino acids were used: Fmoc-Gly-OH, Fmoc-Lys(Boc)-OH, Fmoc-Pro-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OH

MS ($M+H^+$): expected 986.1; observed 986.9

Example 22

The following amino acids were used: Fmoc-Gly-OH, Fmoc-Leu-OH, Fmoc-Pro-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-D-Ile-OH, Fmoc-Tyr(tBu)-OH

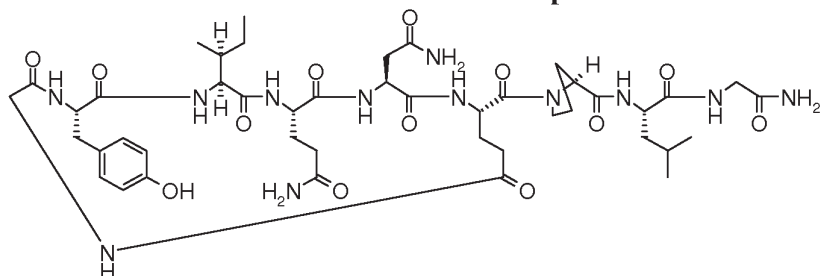
MS ($M+H^+$): expected 971.1; observed 971.5

Example 23

The following amino acids were used: Fmoc-Gly-OH, Fmoc-Leu-OH, Fmoc-D-Pro-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OH

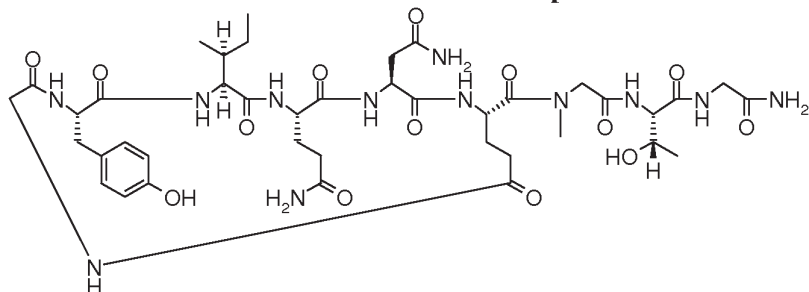
MS ($M+H^+$): expected 971.1; observed 971.5

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Example 24

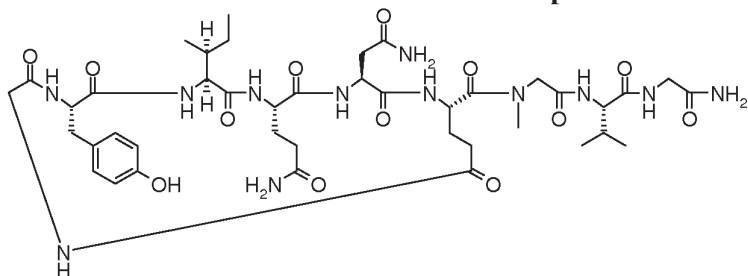
The following amino acids were used: Fmoc-Gly-OH, Fmoc-Leu-OH, Fmoc-Pro-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OH

5 MS ($M+H^+$): expected 971.1; observed 971.8

Example 25

The following amino acids were used: Fmoc-Gly-OH, Fmoc-Thr(tBu)-OH, Fmoc-Sar-OH,
10 Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OH

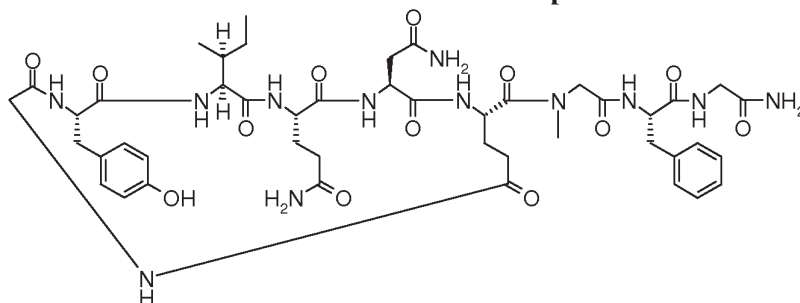
MS ($M+H^+$): expected 932.9 ; observed 933.6

Example 26

15 The following amino acids were used: Fmoc-Gly-OH, Fmoc-Val-OH, Fmoc-Sar-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OH

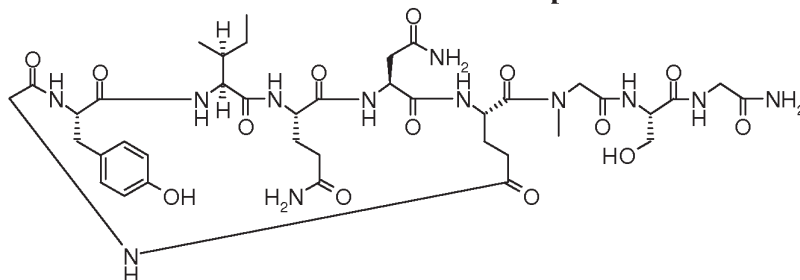
MS ($M+H^+$): expected 931.0; observed 931.6.

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Example 27

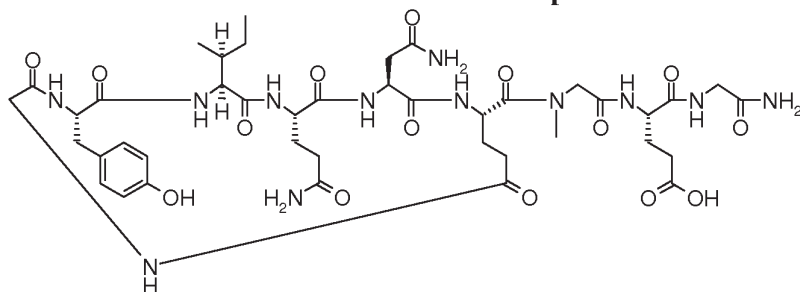
The following amino acids were used: Fmoc-Gly-OH, Fmoc-Phe-OH, Fmoc-Sar-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OH

5 MS ($M+H^+$): expected 979.0; observed 979.5

Example 28

The following amino acids were used: Fmoc-Gly-OH, Fmoc-Ser(tBu)-OH, Fmoc-Sar-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OH

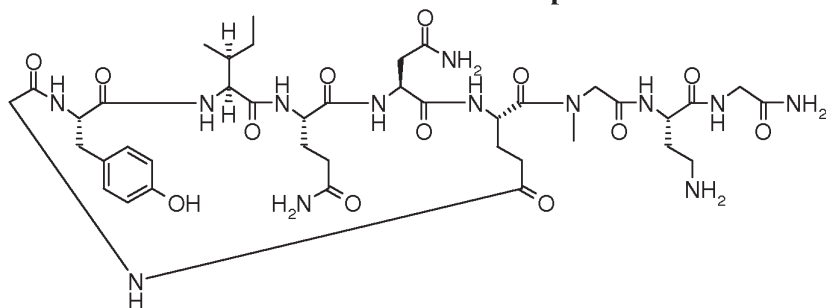
10 MS ($M+H^+$): expected 918.9; observed 919.7

Example 29

15 The following amino acids were used: Fmoc-Gly-OH, Fmoc-Glu(tBu)-OH, Fmoc-Sar-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OH

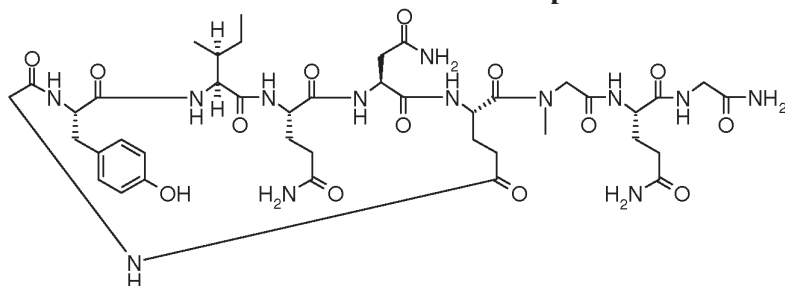
MS ($M+H^+$): expected 960.9; observed 962.1

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Example 30

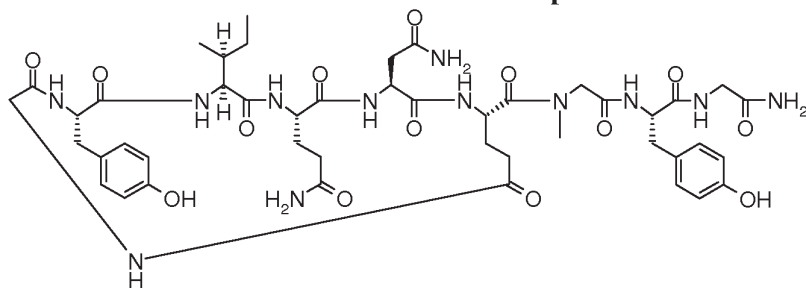
The following amino acids were used: Fmoc-Gly-OH, Fmoc-Dab(Boc)-OH, Fmoc-Sar-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-

5 OHMS ($M+H^+$): expected 932.0; observed 932.6

Example 31

The following amino acids were used: Fmoc-Gly-OH, Fmoc-Sar-OH, Fmoc-Glu(Allyl)-OH,

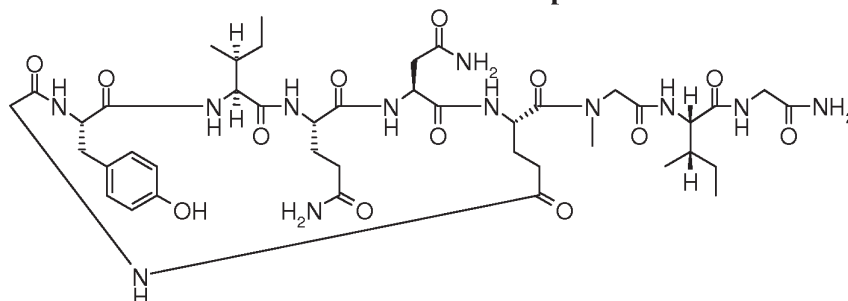
10 Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OHMS ($M+H^+$):
expected 960.0; observed 960.9

Example 32

15 The following amino acids were used: Fmoc-Gly-OH, Fmoc-Sar-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OH

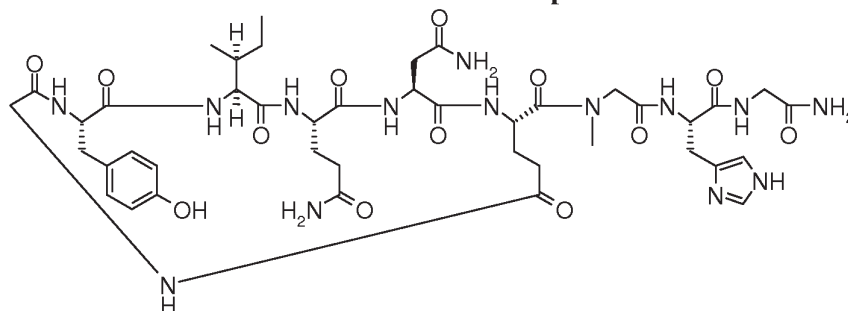
MS ($M+H^+$): expected 995.0; observed 996.0

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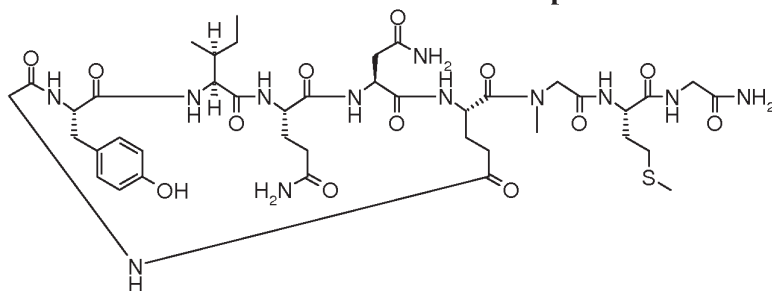
Example 33

The following amino acids were used: Fmoc-Gly-OH, Fmoc-Sar-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OH

5 MS ($M+H^+$): expected 945.0; observed 945.0

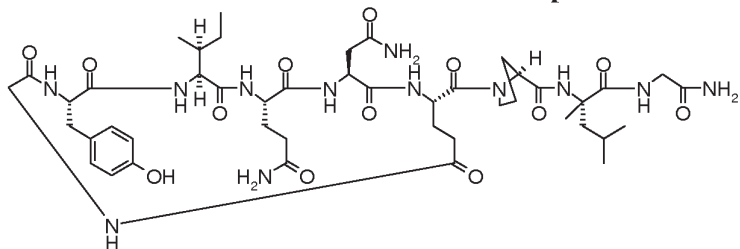
Example 34

The following amino acids were used: Fmoc-Gly-OH, Fmoc-His(Trt)-OH, Fmoc-Sar-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OHMS
 10 ($M+H^+$): expected 969.0; observed 969.7

Example 35

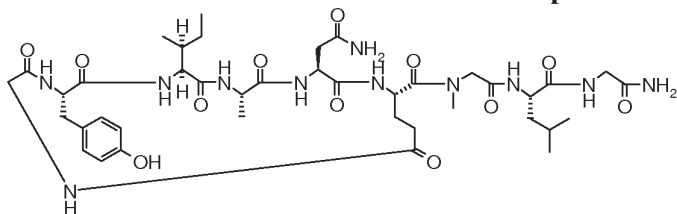
15 The following amino acids were used: Fmoc-Gly-OH, Fmoc-Met-OH, Fmoc-Sar-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OHMS
 ($M+H^+$): expected 995.0; observed 996.0

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Example 36

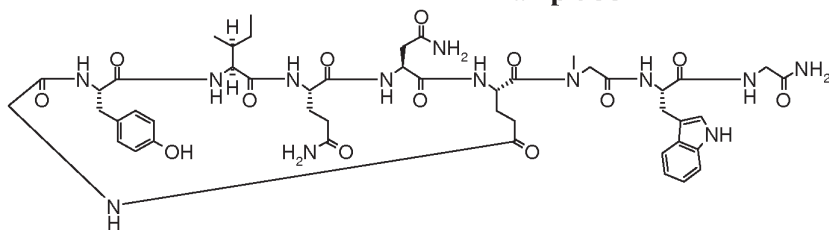
The following amino acids were used: Fmoc-Gly-OH, Fmoc-MeLeu-OH, Fmoc-Pro-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OHMS

5 (M+H⁺): expected 955.1; observed 985.1

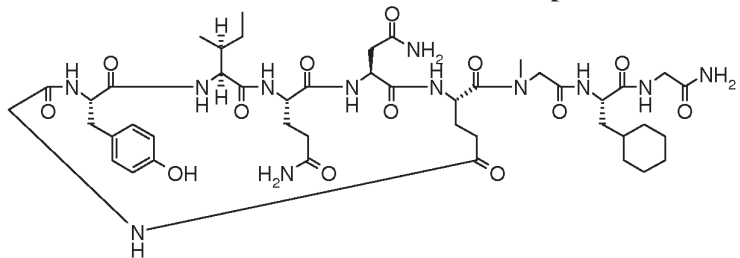
Example 37

The following amino acids were used: Fmoc-Gly-OH, Fmoc-Leu-OH, Fmoc-Sar-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Ala-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OHMS

10 (M+H⁺): expected 888.0; observed 888.6

Example 38

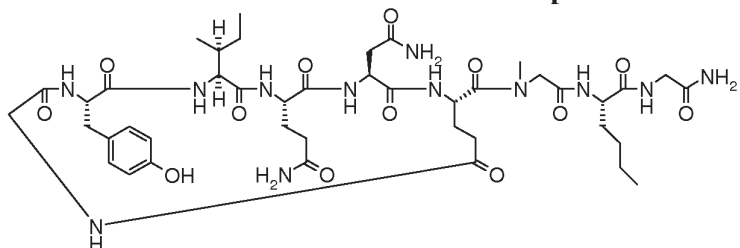
15 The following amino acids were used: Fmoc-Gly-OH, Fmoc-Trp-OH, Fmoc-Sar-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OHMS
(M+H⁺): expected 1018.1; observed 1018.8

Example 39

-31-

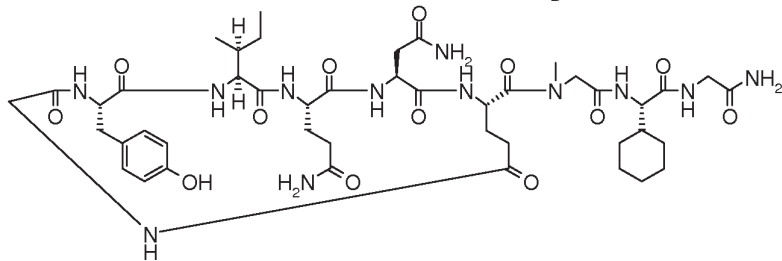
The following amino acids were used: Fmoc-Gly-OH, Fmoc-Cha-OH, Fmoc-Sar-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OHMS ($M+H^+$): expected 985.1; observed 985.6

5

Example 40

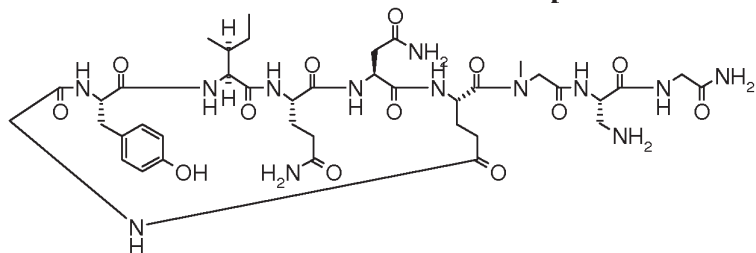
The following amino acids were used: Fmoc-Gly-OH, Fmoc-Nle-OH, Fmoc-Sar-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OHMS ($M+H^+$): expected 945.0; observed 945.5

10

Example 41

The following amino acids were used: Fmoc-Gly-OH, Fmoc-Chg-OH, Fmoc-Sar-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OHMS ($M+H^+$): expected 971.1; observed 971.9

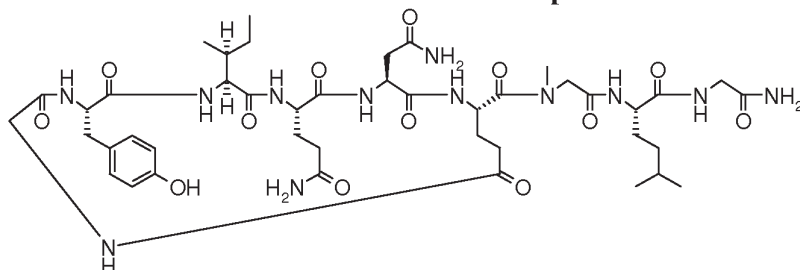
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Example 42

The following amino acids were used: Fmoc-Gly-OH, Fmoc-Dap-OH, Fmoc-Sar-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OHMS ($M+H^+$): expected 918.0; observed 918.7

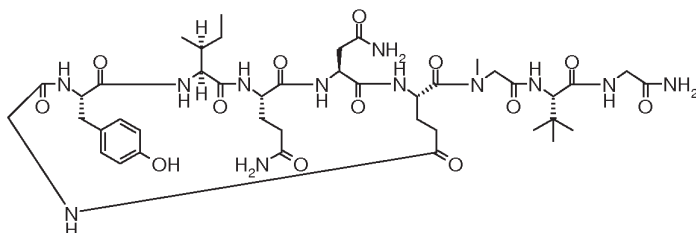
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-32-

Example 43

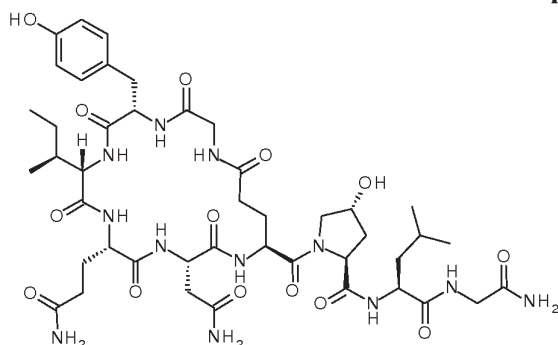
The following amino acids were used: Fmoc-Gly-OH, Fmoc-HoLeu-OH, Fmoc-Sar-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OHMS

5 (M+H⁺): expected 959.1; observed 959.9

Example 44

The following amino acids were used: Fmoc-Gly-OH, Fmoc-Tle-OH, Fmoc-Sar-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OHMS

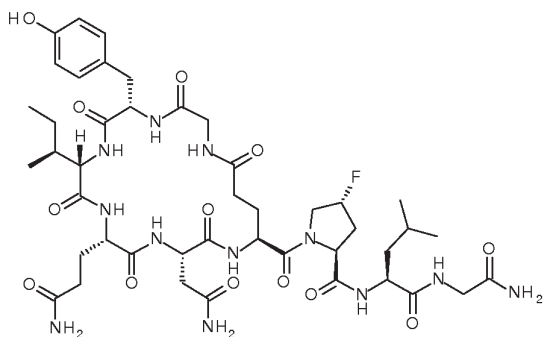
10 (M+H⁺): expected 945.0; observed 944.7

Example 45

The following amino acids were used: Fmoc-Gly-OH, Fmoc-Leu-OH, Fmoc-Hyp-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OHMS

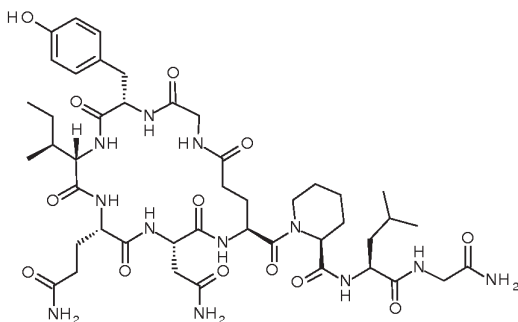
15 (M+H⁺): expected 987.1; observed 988.0

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Example 46

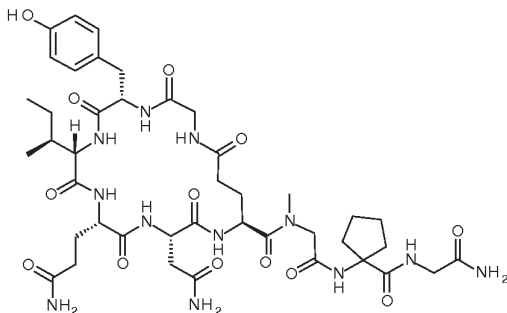
The following amino acids were used: Fmoc-Gly-OH, Fmoc-Leu-OH, Fmoc-FluoroPro-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-

5 OHMS ($M+H^+$): expected 989.1; observed 989.3

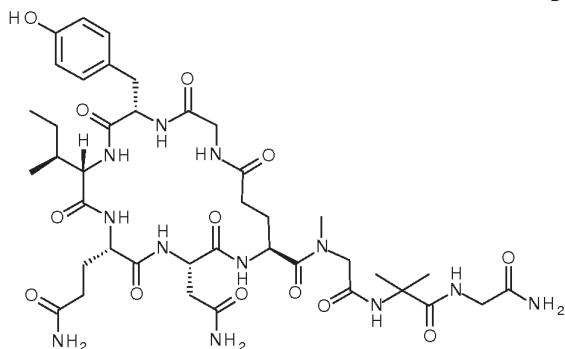
Example 47

The following amino acids were used: Fmoc-Gly-OH, Fmoc-Leu-OH, Fmoc-Hpr-OH, Fmoc-

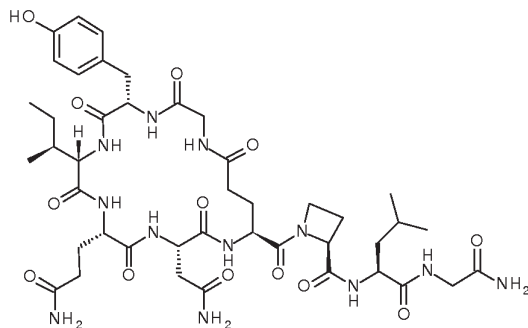
10 Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OHMS ($M+H^+$): expected 985.1; observed 985.1

Example 48

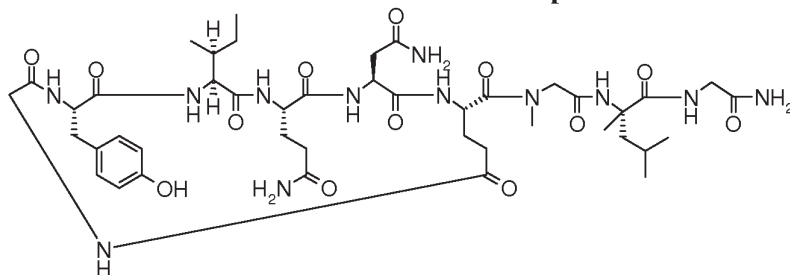
15 The following amino acids were used: Fmoc-Gly-OH, Fmoc-cyLeu-OH, Fmoc-Sar-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OHMS ($M+H^+$): expected 943.0; observed 943.1

Example 49

- The following amino acids were used: Fmoc-Gly-OH, Fmoc-Aib-OH, Fmoc-Sar-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OHMS
 5 (M+H⁺): expected 917.0; observed 917.8

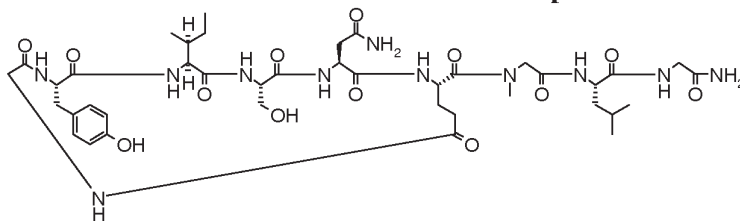
Example 50

- The following amino acids were used: Fmoc-Gly-OH, Fmoc-Leu-OH, Fmoc-Aze-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OHMS
 10 (M+H⁺): expected 957.0; observed 957.1

Example 51

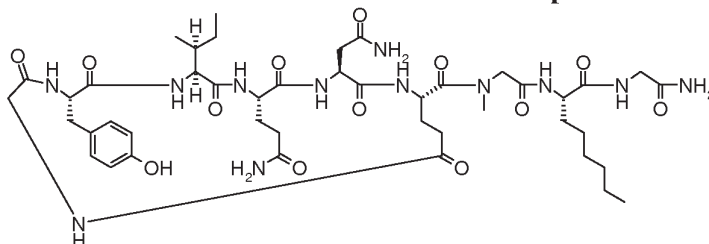
- The following amino acids were used: Fmoc-Gly-OH, Fmoc-MeLeu-OH, Fmoc-Sar-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OHMS
 15 (M+H⁺): expected 959.1; observed 959.7

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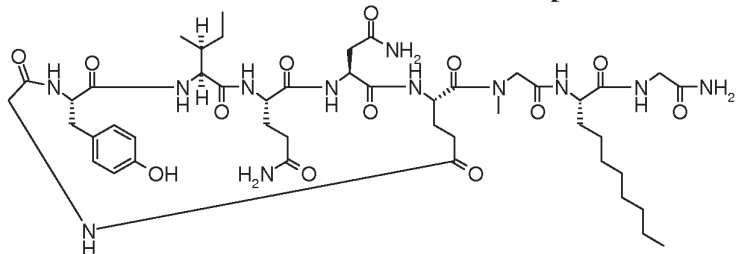
Example 52

The following amino acids were used: Fmoc-Gly-OH, Fmoc-MeLeu-OH, Fmoc-Sar-OH, Fmoc-

- 5 Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OHMS ($M+H^+$): expected 903.0; observed 903.2

Example 53

- 10 The following amino acids were used: Fmoc-Gly-OH, Fmoc-2AOC-OH, Fmoc-Sar-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OHMS ($M+H^+$): expected 973.0; observed 973.5

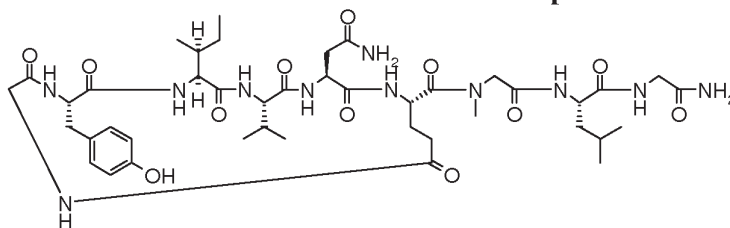
Example 54

- 15 The following amino acids were used: Fmoc-Gly-OH, Fmoc-2ADC-OH, Fmoc-Sar-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OHMS ($M+H^+$): expected 1001.1; observed 1000.5

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Example 55

The following amino acids were used: Fmoc-Gly-OH, Fmoc-Leu, Fmoc-Sar-OH, Fmoc-Glu(Allyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Val-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OHMS

5 (M+H⁺): expected 916.0; observed 917.2

Material and Methodes**Cell culture and stable clone production**

Chines Hamster Ovary (CHO) cells were transfected with expression plasmids encoding either
 10 the human V1a, the human Oxytocin (OTR) or the humanV2 receptor, the later in combination
 with the chimeric Gqs5 G protein to redirect the signal to Calcium flux. Stable cells were cloned
 by limiting dilution to yield monoclonal cell lines expressing either human V1a, human
 V2+Gqs5 or human OTR receptors and selected based on functional responses detected on a
 fluorometric imaging plate reader (FLIPR) detecting Calcium flux in the cell after receptor
 15 activation. The stable cell lines were grown in F-12 K Nutrient Mixture (Kaighns Modification),
 containing 10 % foetal bovine serum (FBS), 1 % penicillin-streptomycin, 1 % L-glutamate, 200
 ug/ml Geneticin at 37 °C in a 10 % CO₂ incubator at 95 % humidity.

Calcium flux assays using fluorescent imaging (Fluorometric Imaging Plate Reader, FLIPR)

20 On the afternoon before the assay, cells were plated at a density of 50,000 cells/well into black
 96 well plates with clear bottoms to allow cell inspection and fluorescence measurements from
 the bottom of each well. The density of cells was sufficient to yield a confluent monolayer the
 next day. Hanks balanced salt solution, without phenol red, containing 20 mM HEPES (pH 7.3)
 and 2.5 mM probenecid (assay buffer) was prepared fresh for each experiment. Compound
 25 dilutions were made using a Beckman Biomek 2000 laboratory automation workstation, in assay
 buffer containing 1 % DMSO. The dye-loading buffer consisted of a final concentration of 2
 µM Fluo-4-AM (dissolved in DMSO and pluronic acid) in assay buffer. The existing culture
 media was removed from the wells and 100 µl of the dye-loading buffer was added to each well
 and incubated for approximately 60 min at 37 °C in a 5 % CO₂ incubator at 95 % humidity. Once

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dye-loaded, the cells were washed thoroughly on an Embla cell washer with the assay buffer to remove any unincorporated dye. Exactly 100 µl assay buffer was left in each well.

Each 96 well plate containing dye-loaded cells was placed into the FLIPR machine and the laser intensity set to a suitable level to detect low basal fluorescence. To test compounds as agonists,

- 5 25 µl diluted compound was added to the plate 10 seconds into the fluorescent measurements and fluorescent response was recorded for 5 minutes. The fluorescence data was normalized to the endogenous full agonist dose-response set at 100 % for the maximum response and 0 % for the minimum. Each agonist concentration-response curve was constructed using a four parameter logistic equation with Microsoft Excel XLFit as follows: $Y = \text{Minimum} + ((\text{Maximum} -$
 10 $\text{Minimum}) / (1 + 10^{(\text{LogEC}_{50}-X)nH}))$, where y is the % normalized fluorescence, minimum is the minimum y, maximum is the maximum y, logEC_{50} is the log_{10} concentration which produces 50 % of the maximum induced fluorescence, x is the log_{10} of the concentration of the agonist compound and H is the slope of the curve (the Hill Coefficient). The maximum value gives the efficacy of the agonist test compound in percentage. The concentration of agonist that produced
 15 a half-maximal response is represented by the EC_{50} value, the logarithm of which yielded the pEC_{50} value.

The following EC_{50} (nM), and efficacy (%) for the specific peptides may be provided, together with comparative data for hV1a and hV2:

Expl.	hOT $\text{EC}_{50}(\text{nM})$ / efficacy (%)	hV1a EC_{50} (nM)	hV2 EC_{50} (nM)/ efficacy (%)	Expl.	hOT $\text{EC}_{50}(\text{nM})$ / efficacy (%)	hV1a EC_{50} (nM)/ efficacy (%)	hV2 EC_{50} (nM) efficacy (%)
1	10/111	>27000	4800/107	29	32/130	>10000	10682/39
2	9/112	>27000	7906/74	30	6/119	>10000	142/104
3	4/94			31	9/131	>10000	2708/91
4	31/102			32	4/119	>10000	1985/106
5	181/108			33	2/119	>27000	3821/101
6	11/95	>27000		34	10/136	>10000	145/120
7	124/87			35	3/111	>10000	1672/104
8	100/92			36	41/138		

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9	118/93			37	4/137		
10	17/91	>2700		38	1/126		
11	11/94	>27000		39	0.4/122	>27000	3707/111
12	48/82			40	0.4/124	>27000	2194/117
13	0.2/111	>27000	5110/97	41	69/117		
14	250/92			42	1/119		
15	52/102	>12000		43	26/124		
16	30/105	>12000		44	0.5/117	>27000	1230/112
17	45/92	>12000		45	0.6/113	>27000	3806/91
18	24/91	>12000		46	10/104		
19	1.5/122	127/33		47	1.5/111		
20	40	>12000		48	3.6/108		
21	12/105	32/55		49	5.9/97		
22	98/116			50	3.6/99	>27000	
23	88/64			51	13/97	>27000	
24	2.2/152	>27000	2505/98	52	4.3/121		
25	3/125	>10000	3823/103	53	1.1/127		
26	2/124	>10000	2624/102	54	0.8/134		
27	5/128	>10000	1498/101	55	20/104		
28	5/122	>10000	4173/87				

The compounds of formula I and the pharmaceutically acceptable salts of the compounds of formula I can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered preferably transdermal, intranasal,

5 subcutaneous or intra venous (iv).

Transdermal is a route of administration wherein active ingredients are delivered across the skin for systematic distribution. Examples include transdermal patches used for medicine delivery, and transdermal implants used for medical or aesthetic purposes.

Nasal administration can be used to deliver drugs for either local or systemic effects, nasal sprays for local effect are quite common. Peptide drugs may be administered as nasal sprays to avoid drug degradation after oral administration.

Subcutaneous injections are also common for the administration of peptide drugs. An
5 intramuscular injection is the injection of a substance directly into the muscle. It is one of several alternative methods for the administration of medications. It is often used for particular forms of medication that are administered in small amounts. The injections should be given under the skin.

The intravenous route is the infusion of liquid substances directly into a vein. Compared
10 with other routes of administration, the intravenous route is the fastest way to deliver fluids and medications throughout the body.

The pharmaceutical preparations can, moreover, contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

15 Medicaments containing a compound of formula I or a pharmaceutically acceptable salt thereof and a therapeutically inert carrier are also an object of the present invention, as is a process for their production, which comprises bringing one or more compounds of formula I and/or pharmaceutically acceptable acid addition salts and, if desired, one or more other therapeutically valuable substances into a galenical administration form together with one or
20 more therapeutically inert carriers.

The most preferred indications in accordance with the present invention are those which include disorders of the central nervous system, for example the treatment or prevention of autism, stress, including post traumatic stress disorder, anxiety, including anxiety disorders and depression, schizophrenia, psychiatric disorders and memory, loss alcohol withdrawel, drug addiction and
25 for the treatment of Prader-Willi Syndrom. .

The dosage can vary within wide limits and will, of course, have to be adjusted to the individual requirements in each particular case. The dosage for adults can vary from about 0.01 mg to about 1000 mg per day of a compound of general formula I or of the corresponding amount of a pharmaceutically acceptable salt thereof. The daily dosage may be administered as
30 single dose or in divided doses and, in addition, the upper limit can also be exceeded when this is found to be indicated.

Claims

The chemical structure is a complex molecule featuring several amide and urea linkages. It includes a benzene ring with a substituent R¹. The molecule is connected via a chain containing a urea group, a cyclic urea (6-membered ring), and another urea group. Substituents R², R³, R⁴, R⁵, R⁶, and R^{6'} are attached to various parts of the structure. A linker X connects the nitrogen of the first urea group to a (CH₂)₂ chain. A (CH₂)₀ group indicates a direct connection between the nitrogen of the second urea group and the R⁵ substituent. The structure also includes a terminal amide group and a terminal urea group.

5 R¹ is hydroxy or amino;

 R² is *sec*-butyl or isobutyl;

 R³ is C₁₋₇ alkyl, C₁₋₇ alkyl substituted by hydroxy, -(CH₂)₂C(O)-NH₂, -(CH₂)₃-NH₂ or -CH₂-
five membered aromatic heterocyclic group;

 R⁴ is hydrogen or C₁₋₇ alkyl;

R^5 is hydrogen or C_{1-7} alkyl; or

R^4 and R^5 may form together with the N and C atom to which they are attached a pyrrolidine ring, optionally substituted by hydroxy or halogen, a piperidine ring or an azetidine ring;

5 R^6 is hydrogen, C_{1-7} alkyl, C_{1-7} alkyl substituted by hydroxy, $-(CH_2)_2C(O)OH$, $-(CH_2)_2C(O)NH_2$, benzyl optionally substituted by amino or hydroxy, $-CH_2$ -five membered aromatic heterocyclic group, indolyl, $-CH_2$ -cycloalkyl, cycloalkyl, $-(CH_2)_2-S-C_{1-7}$ alkyl or is $-(CH_2)_{1-4}-NH_2$;

$R^{6'}$ is hydrogen or C_{1-7} alkyl; or

R^6 and $R^{6'}$ are together cycloalkyl;

10 X is $-C(O)-CHR-NR'-C(O)-$;

R/R' are independently from each other hydrogen or C₁₋₇alkyl;

o is 0 or 1;

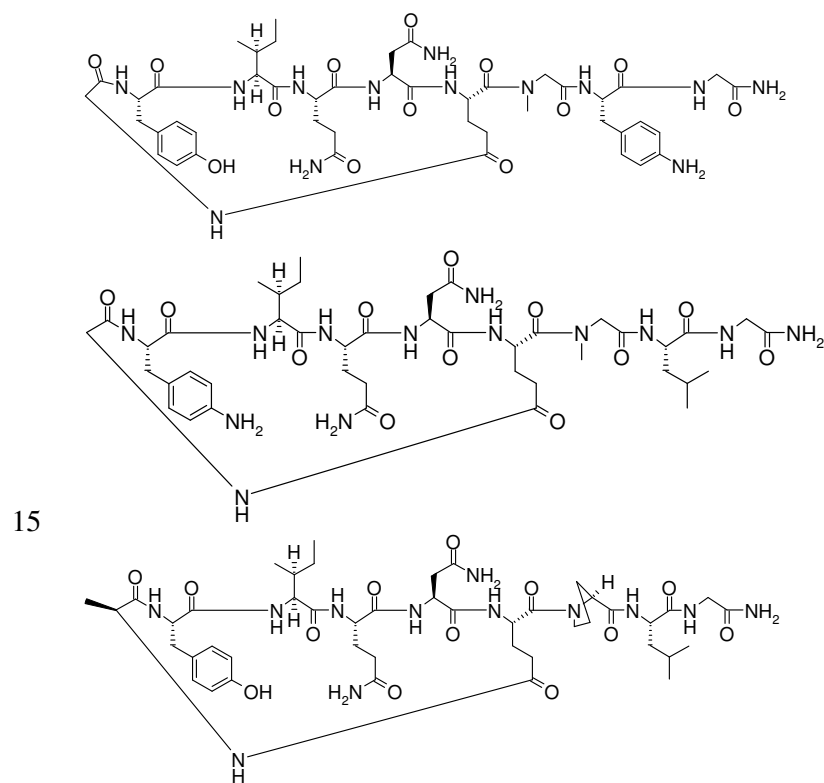
or a pharmaceutically acceptable acid addition salt, a racemic mixture or its corresponding enantiomer and/or optical isomers thereof.

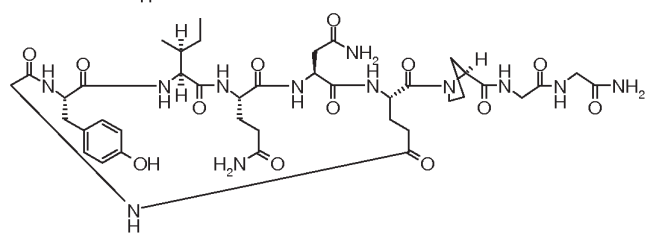
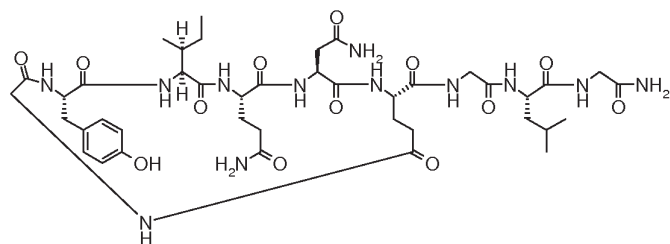
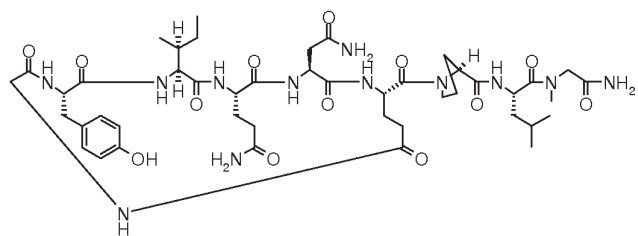
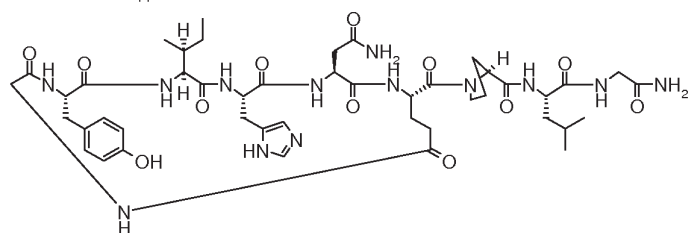
5 2. A compound of formula I according to claim 1, wherein R² is *sec*-butyl.

3. A compound of formula I according to claim 1, wherein the five-membered heterocyclic ring is an imidazole ring.

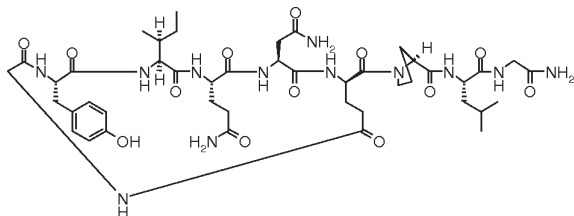
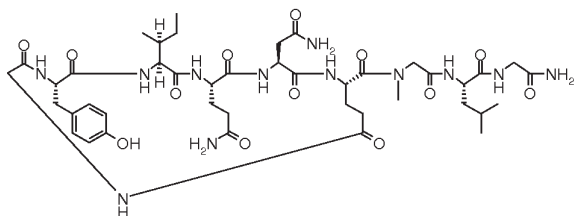
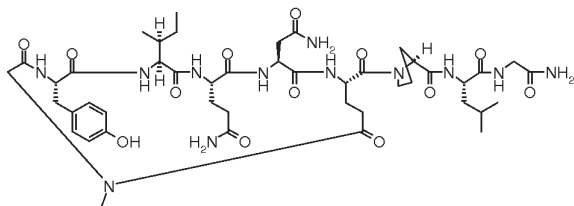
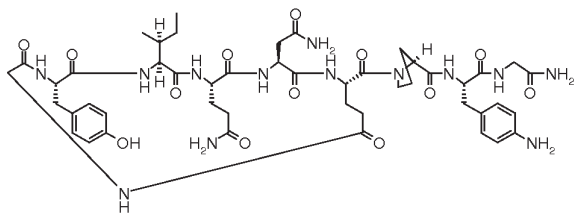
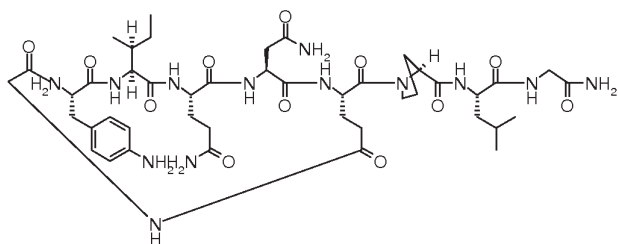
10 4. A compound of formula I according to claim 1, wherein o is 0.

5. A compound of formula I according to claim 1, wherein the compounds are

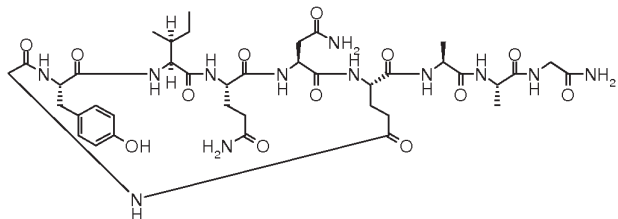
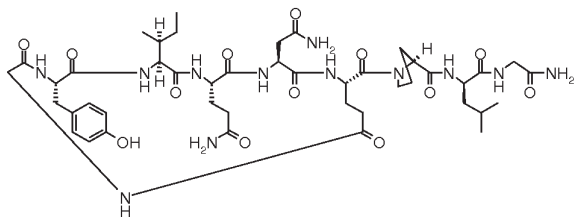


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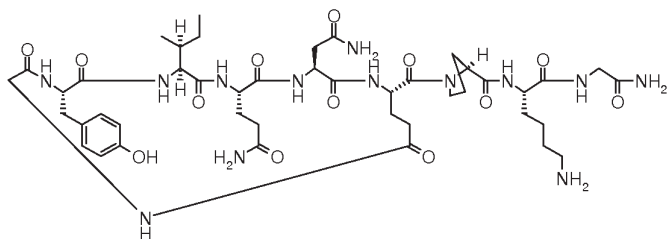
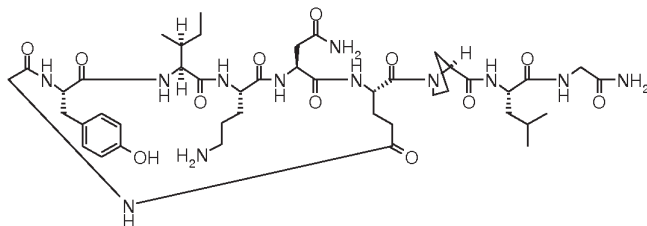
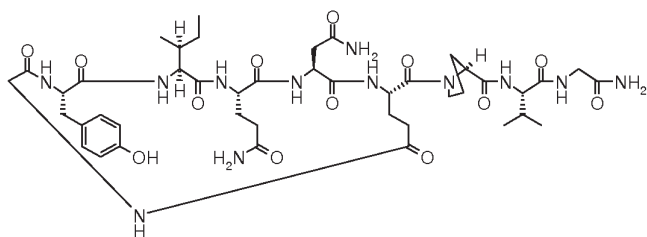
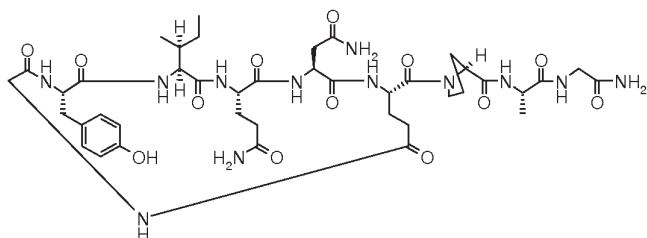
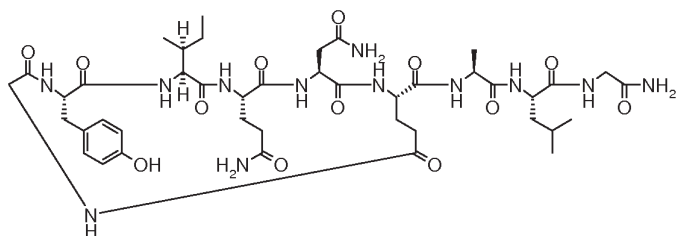
-43-



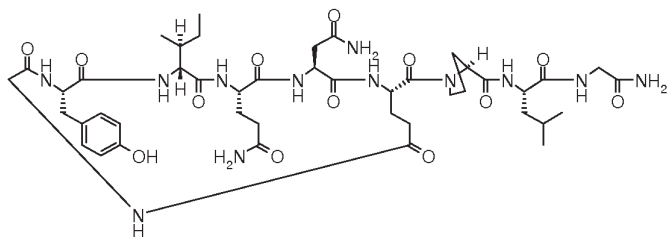
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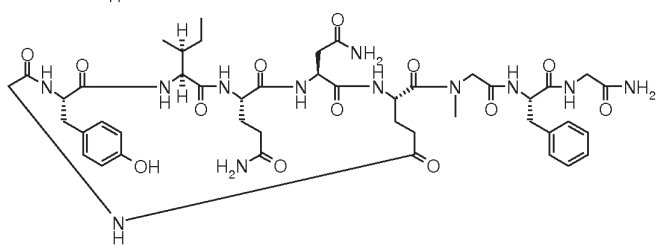
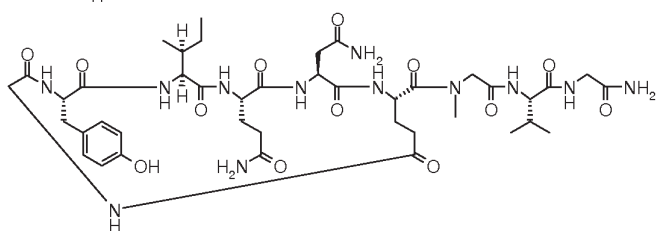
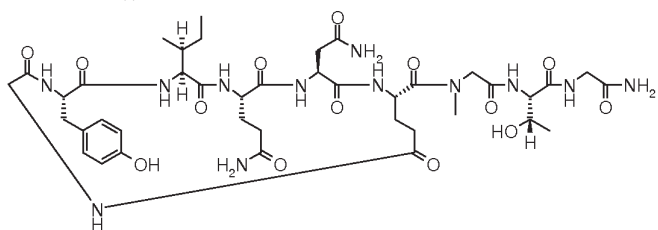
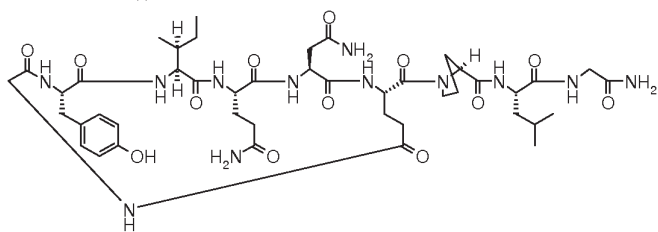


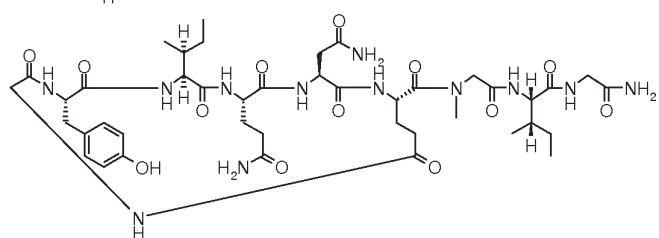
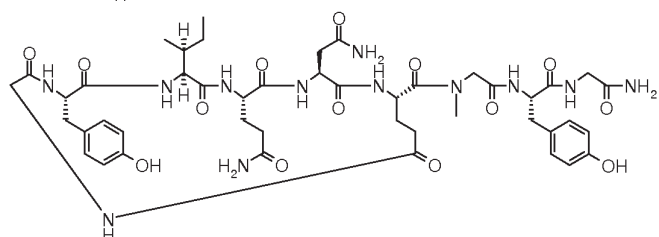
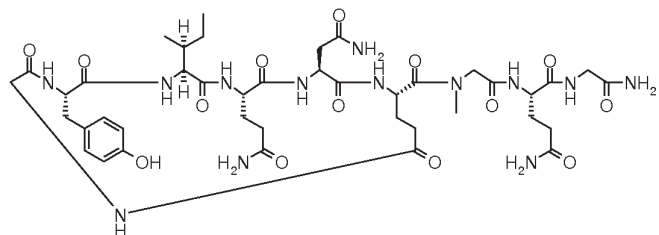
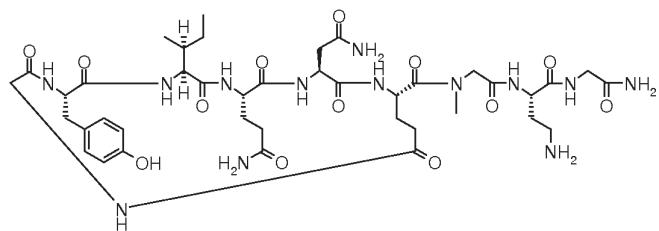
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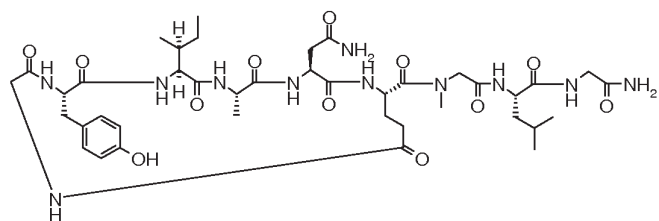
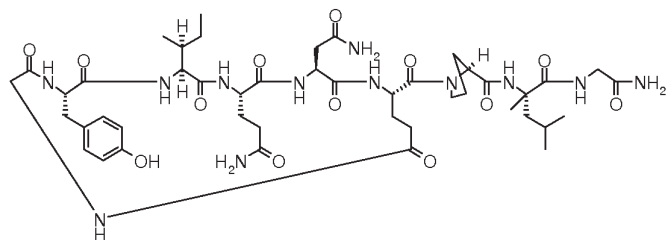
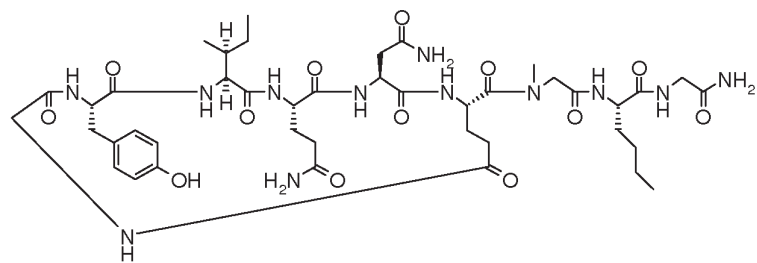
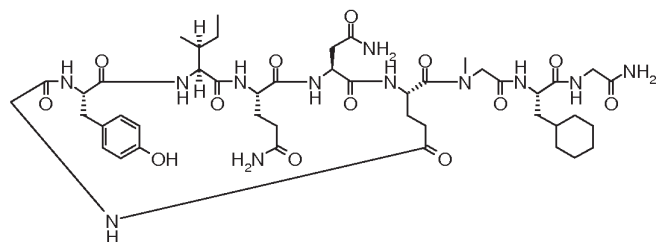


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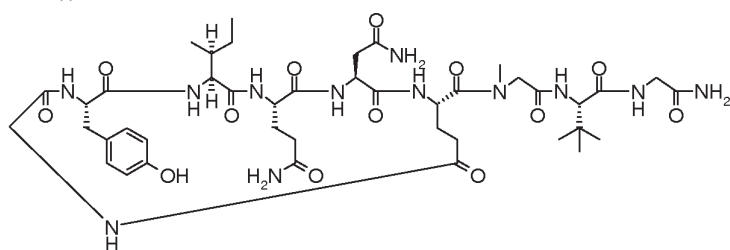
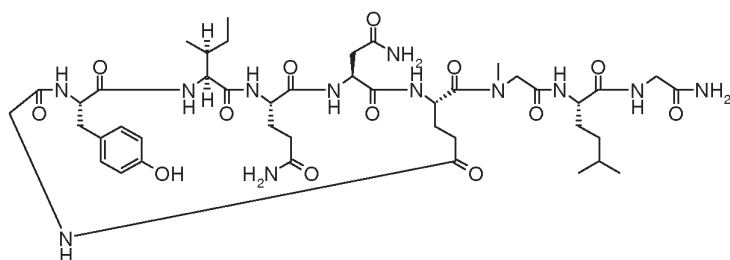
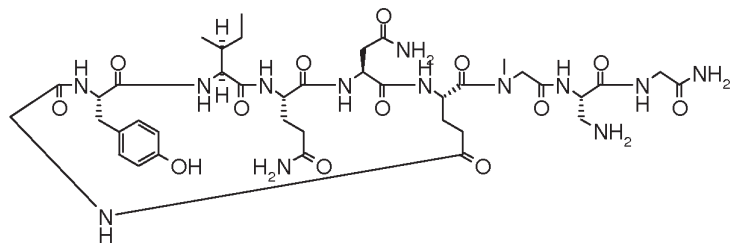
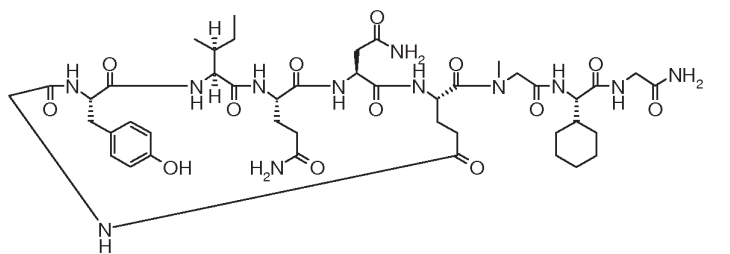


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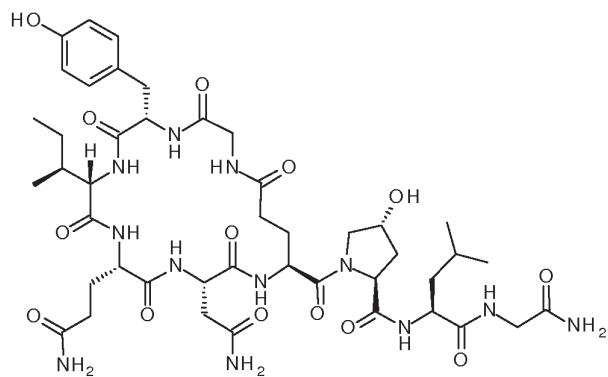
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NC(=O)NCC(=O)N[C@@H](Cc1c[nH]c2ccccc12)C(=O)NCC(=O)N[C@@H](Cc1ccc(O)cc1)C(=O)N[C@@H](C)C(=O)N[C@@H](C(=O)N)C(=O)NCC(=O)N

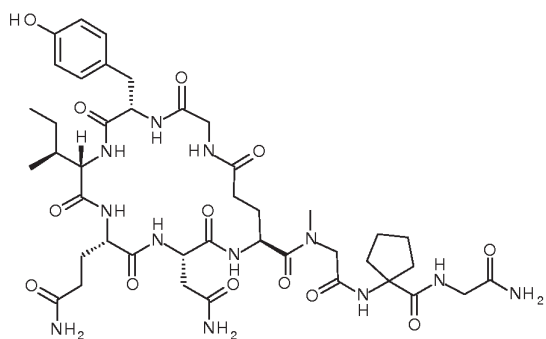
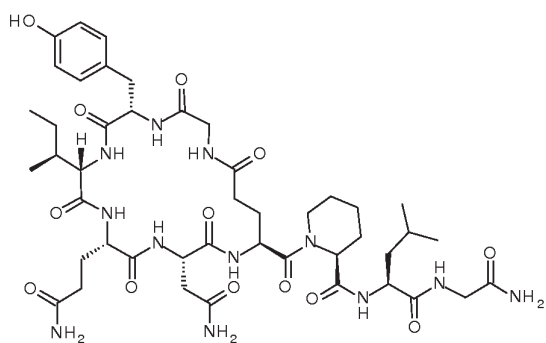
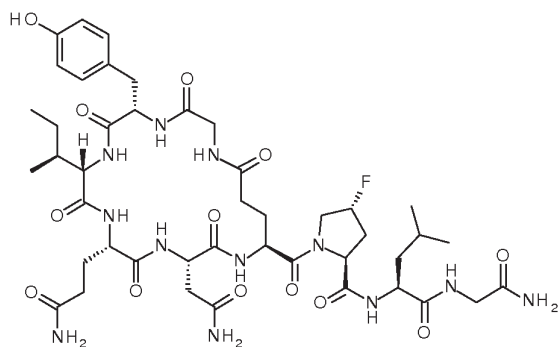
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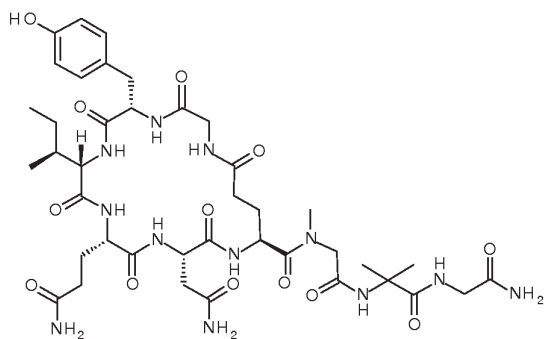
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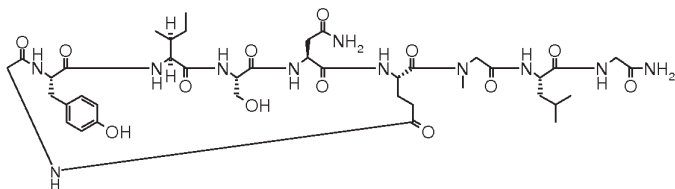
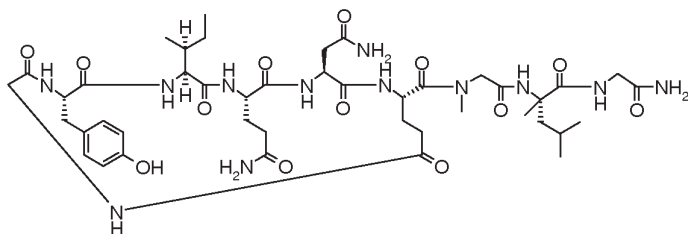
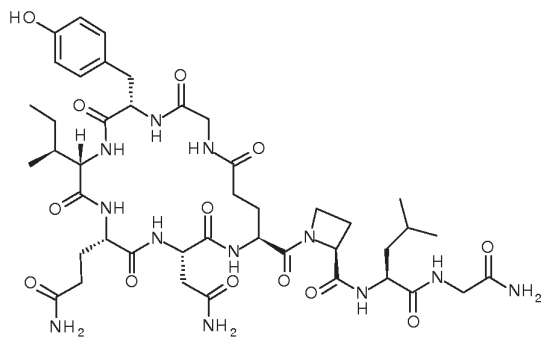
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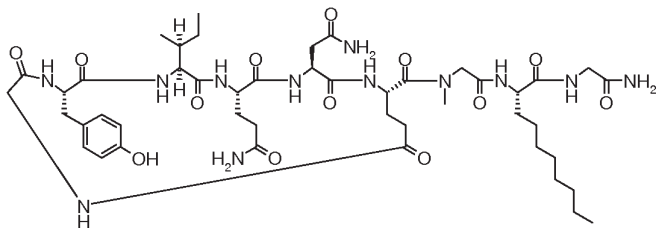
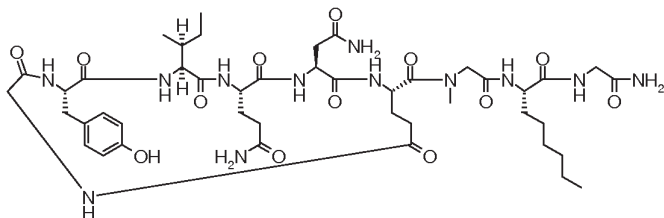
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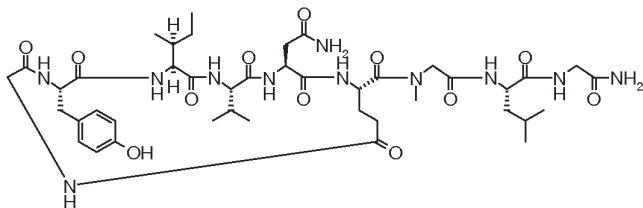
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6. A pharmaceutical composition comprising a compound according to any one of claims 1 –5 and a pharmaceutical acceptable carrier and/or adjuvant.
- 5 7. A compound according to any one of claims 1–5 for use as therapeutic active substances.
8. The use of a compound according to any one of claims 1–5 in the preparation of medicaments for the therapeutic and/or prophylactic treatment of autism, stress, including post traumatic stress disorder, anxiety, including anxiety disorders and depression,
- 10 schizophrenia, psychiatric disorders and memory loss, alcohol withdrawal, drug addiction and for the treatment of Prader-Willi Syndrome.