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CA 2402193 C 2010/05/18

(11)(21) 2 402 193

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 2001/03/12
(87) Date publication PCT/PCT Publication Date: 2001/09/20
(45) Date de délivrance/Issue Date: 2010/05/18
(85) Entrée phase nationale/National Entry: 2002/09/09
(86) N° demande PCT/PCT Application No.: EP 2001/002719
(87) N° publication PCT/PCT Publication No.: 2001/068676
(30) Priorité/Priority: 2000/03/14 (US09/525,007)

(51) Cl.Int./Int.Cl. *C07K 7/00* (2006.01), *C07K 7/23* (2006.01), *A61K 38/00* (2006.01)

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(54) Titre : NOUVEAUX ANTAGONISTES DE LA LHRH, SA PRODUCTION ET SON UTILISATION COMME MEDICAMENT

(54) Title: NOVEL LHRH-ANTAGONISTS, PRODUCTION AND USE THEREOF AS MEDICAMENT

(57) Abrégé/Abstract:
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(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG

(19) Weltorganisation für geistiges Eigentum
Internationales Büro

(43) Internationales Veröffentlichungsdatum
20. September 2001 (20.09.2001)

PCT

(10) Internationale Veröffentlichungsnummer
WO 01/68676 A2

(51) Internationale Patentklassifikation[7]: C07K 7/00

(21) Internationales Aktenzeichen: PCT/EP01/02719

(22) Internationales Anmeldedatum:
12. März 2001 (12.03.2001)

(25) Einreichungssprache: Deutsch

(26) Veröffentlichungssprache: Deutsch

(30) Angaben zur Priorität:
09/525,007 14. März 2000 (14.03.2000) US

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(81) Bestimmungsstaaten *(national)*: AU, BG, BR, BY, CA, CN, CO, CZ, EE, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, UA, US, UZ, YU, ZA.

(84) Bestimmungsstaaten *(regional)*: eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).

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WO 01/68676 A2

(54) **Title:** NOVEL LHRH-ANTAGONISTS, PRODUCTION AND USE THEREOF AS MEDICAMENT

(54) **Bezeichnung:** NEUE LHRH-ANTAGONISTEN, DEREN HERSTELLUNG UND VERWENDUNG ALS ARZNEIMITTEL

(57) **Abstract:** The invention relates to peptides, comprising an N-methylated amino acid component and an improved water solubility. According to the invention, medicaments containing the said peptides can be used for treatment of hormone-dependant tumours and hormone-influenced non-malignant disease states.

(57) **Zusammenfassung:** Die Erfindung betrifft Peptide, die einen N-methylierten Aminosäurebaustein enthalten und eine verbesserte Wasserlöslichkeit aufweisen. Arzneimittel, in denen die erfindungsgemässen Peptide enthalten sind, können zur Behandlung hormonabhängiger Tumore und hormonbeeinflusster nicht-maligner Erkrankungen verwendet werden.

# Novel LHRH-Antagonists, Production And Use Thereof As Medicament

The invention relates to LHRH antagonists having improved solubility properties, processes for the preparation of these compounds, medicaments in which these compounds are contained, and the use of the medicaments for the treatment of hormone-dependent tumours and hormone-influenced non-malignant disorders such as benign prostate hyperplasia (BPH) and endometriosis.

The nomenclature used for the definition of the peptides agrees with that nomenclature explained by the IUPAC-IUB Commission on Biochemical Nomenclature (European J. Biochem. 1984, 138, 9-37), in which, in agreement with the conventional representation, the amino groups at the N terminus appear to the left and the carboxyl group at the C terminus appears to the right. The LH-RH antagonists such as the peptides according to the invention include naturally occurring and synthetic amino acids, the former including Ala, Val, Leu, Ile, Ser, Thr, Lys, Arg, Asp, Asn, Glu, Gln, Cys, Met, Phe, Tyr, Pro, Trp and His. The abbreviations for the individual amino acid residues are based on the trivial names of the amino acids and are Ala=alanine, Arg=arginine, Gly=glycine, Leu=leucine, Lys=lysine, Pal(3)=3-(3-pyridyl)alanine, Nal(2)=3-(2-naphthyl)-alanine, Phe=phenylalanine, Cpa=4-chlorophenylalanine, Pro=proline, Ser=serine, Thr=threonine, Trp=tryptophan, Try=tyrosine and Sar=sarcosine. All amino acids described here originate from the L series, if not mentioned otherwise. For example, D-Nal(2) is the abbreviation for 3-(2-naphthyl)-D-alanine and Ser is the abbreviation for L-serine. Substitutions on the ε amino group in the side chain of lysine are represented by a term placed in brackets behind Lys, if appropriate in the form of an abbreviation.

Other abbreviations used are:

| | |
|---|---|
| Ac | Acetyl |
| B | 4-(4-Amidinophenyl)amino-1,4-dioxobutyl |
| Boc | tert-Butyloxycarbonyl |
| Bop | Benzotriazol-1-oxy-tris(dimethylamino)-phosphonium hexafluorophosphate |
| DCC | Dicyclohexylcarbodiimide |
| DCM | Dichloromethane |
| Ddz | Dimethoxyphenyl-dimethylmethylenoxy-carbonyl (Dimethoxy-dimethyl-Z) |
| DIC | Diisopropylcarbodiimide |
| DIPEA | N,N-Diisopropylethylamine |
| DMF | Dimethylformamide |
| Fmoc | Fluorenylmethyloxycarbonyl |
| HF | Hydrofluoric acid |
| HOBt | 1-Hydroxybenzotriazole |
| HPLC | High-pressure liquid chromatography |
| Me | Methyl |
| TFA | Trifluoroacetic acid |
| Z | Benzyloxycarbonyl |

The peptides according to the invention are analogues of the luteinizing-hormone-releasing hormone (LH-RH), which has the following structure:
p-Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-$NH_2$, [LH-RH, gonadorelin].

For more than 20 years, researchers have sought selective potent antagonists of the LH-RH decapeptide [M. Karten and J.E. Rivier, Endocrine Reviews 7, 44-66 (1986)]. The high interest in such antagonists is based on their usefulness in the field of endocrinology, gynaecology, contraception and cancer. A large number of compounds have been prepared as potential LH-RH antagonists. The most interesting compounds which have been found to date are those compounds whose structures are a modification of the LH-RH structure.

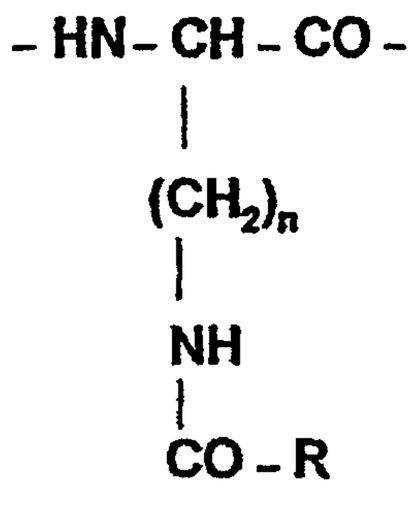
The first series of potent antagonists was obtained by the introduction of aromatic amino acid residues into the positions 1, 2, 3 and 6 or 2, 3 and 6. The customary way of writing the compounds is as follows: the amino acids are first indicated which have taken the place of the amino acids originally present in the peptide chain of LH-RH, the positions in which the exchange took place being marked by superscripted figures. Furthermore, by the notation "LH-RH" placed afterwards it is expressed that these are LH-RH analogues in which the exchange has taken place.

Known antagonists are:
[Ac-D-Cpa$^{1,2}$, D-Trp$^{3,6}$] LH-RH (D.H. Coy et al., In: Gross, E. and Meienhofer, J. (Eds) Peptides; Proceedings of the 6th American Peptide Symposium, pp. 775-779, Pierce Chem. Co., Rockville III. (1979):
[Ac-Pro$^{1}$, D-Cpa$^{2}$, D-Nal(2)$^{3,6}$] LH-RH (US Patent No. 4,419,347) and [Ac-Pro$^{1}$, D-Cpa$^{2}$, D-Trp$^{3,6}$] LH-RH (J.L. Pineda, et al., J. Clin. Endocrinol. Metab. 56, 420, 1983).

In order to improve the action of antagonists, basic amino acids, for example D-Arg, were later introduced into the 6 position. For example [Ac-D-Cpa$^{1.2}$, D-Trp$^{3}$, D-Arg$^{6}$, D-Ala$^{10}$] LH-RH (ORG-30276) (D.H. Coy, et al., Endocrinology 100, 1445, 1982); and
[Ac-D-Nal(2)1, D-Phe(4-F)$^{2}$, D-Trp$^{3}$, D-Arg$^{6}$] LH-RH (ORF 18260) (J.E. Rivier et al., in: Vickery B.H. Nestor, Jr. J.J., Hafez, E.S.E (Eds). LHRH and its Analogs, pp. 11-22 MTP Press, Lancaster, UK 1984).

Further potent LH-RH antagonists are described in WO 92/19651, WO 94/19370, WO 92/17025, WO 94/14841, WO 94/13313, US-A 5,300,492, US-A 5,140,009, EP 0 413 209 A1 and DE 195 44 212 A1.

The latter discloses compounds having a modified ornithine or lysine unit in position 6 and which correspond to the following formula:
Ac-D-Nal(2)$^1$-D-Cpa$^2$-D-Pal(3)$^3$-Ser$^4$-Tyr$^5$-D-Xxx$^6$-Leu$^7$-Arg$^8$-Pro$^9$-D-Ala$^{10}$-$NH_2$,
in which D-Xxx is an amino acid group of the general formula (VI)



Further known LH-RH antagonists are antarelix, ganirelix and cetrorelix.

Antarelix® (INN: teverelix):
Ac-D-Nal(2)$^1$-D-Cpa$^2$-D-Pal(3)$^3$-Ser$^4$-Tyr$^5$-D-Hci$^6$-Leu$^7$-Lys(iPr)$^8$-Pro$^9$-D-Ala$^{10}$-$NH_2$

Ganirelix:
Ac-D-Nal(2)$^1$-D-Cpa$^2$-D-Pal(3)$^3$-Ser$^4$-Tyr$^5$-D-hArg(Et)$_2$$^6$-Leu$^7$-hArg(Et)$_2$$^8$-Pro$^9$-D-Ala$^{10}$-$NH_2$

Cetrorelix:
Ac-D-Nal(2)$^1$-D-Cpa$^2$-D-Pal(3)$^3$-Ser$^4$-Tyr$^5$-D-Cit$^6$-Leu$^7$-Arg$^8$-Pro$^9$-D-Ala$^{10}$-$NH_2$.

The aim of the invention is to create novel LH-RH antagonists which have an increased enzymatic stability and significantly improved water solubility.

This object is achieved by compounds of the following general formula (I)

$A\text{-}Xxx^1\text{-}Xxx^2\text{-}Xxx^3\text{-}Xxx^4\text{-}Xxx^5\text{-}Xxx^6\text{-}Xxx^7\text{-}Xxx^8\text{-}Xxx^9\text{-}Xxx^{10}\text{-}NH_2$
(I)

in which
A is an acetyl group,
$Xxx^1$ is D-Nal(2),
$Xxx^2$ is D-Cpa,
$Xxx^3$ is D-Pal(3),
$Xxx^4$ is Ser,
$Xxx^5$ is N-Me-Tyr,
$Xxx^6$ is D-Cit, D-Hci or D-[•-N'-4-(4-amidinophenyl)-amino-1,4-dioxobutyl]Lys (abbreviation: D-Lys(B)),
$Xxx^7$ is Leu or Nle,
$Xxx^8$ is Arg or Lys(iPr),
$Xxx^9$ is Pro and
$Xxx^{10}$ is D-Ala or Sar,
with the proviso
that if $Xxx^6$ is D-Lys(B), then $Xxx^7$ is Nle,
if $Xxx^6$ is D-Cit, then $Xxx^7$ is Nle and $Xxx^{10}$ is D-Ala, or
if $Xxx^6$ is D-Hci, then $Xxx^7$ is Leu and $Xxx^{10}$ is D-Ala,
and their salts with pharmaceutically acceptable acids, in particular the acetates, embonates and trifluoroacetates.

According to a further aspect of the invention, the following compounds and their salts with pharmaceutically acceptable acids are particularly preferred:

$Ac\text{-}D\text{-}Nal(2)^1\text{-}D\text{-}Cpa^2\text{-}D\text{-}Pal(3)^3\text{-}Ser^4\text{-}N\text{-}Me\text{-}Tyr^5\text{-}D\text{-}Lys(B)^6\text{-}Nle^7\text{-}Arg^8\text{-}Pro^9\text{-}Sar^{10}\text{-}NH_2$

$Ac\text{-}D\text{-}Nal(2)^1\text{-}D\text{-}Cpa^2\text{-}D\text{-}Pal(3)^3\text{-}Ser^4\text{-}N\text{-}Me\text{-}Tyr^5\text{-}D\text{-}Lys(B)^6\text{-}Nle^7\text{-}Arg^8\text{-}Pro^9\text{-}D\text{-}Ala^{10}\text{-}NH_2$,

$Ac\text{-}D\text{-}Nal(2)^1\text{-}D\text{-}Cpa^2\text{-}D\text{-}Pal(3)^3\text{-}Ser^4\text{-}N\text{-}Me\text{-}Tyr^5\text{-}D\text{-}Lys(B)^6\text{-}Nle^7\text{-}Lys(iPr)^8\text{-}Pro^9\text{-}Sar^{10}\text{-}NH_2$

Ac-D-Nal(2)$^1$-D-Phe(4-Cl)$^2$-D-Pal(3)$^3$-Ser$^4$-N-Me-Tyr$^5$-D-Lys(B)$^6$-Nle$^7$-Lys(iPr)$^8$-Pro$^9$-D-Ala$^{10}$-$NH_2$

Ac-D-Nal(2)$^1$-D-Cpa$^2$-D-Pal(3)$^3$-Ser$^4$-N-Me-Tyr$^5$-D-Cit$^6$-Nle$^7$-Arg$^8$-Pro$^9$-D-Ala$^{10}$-$NH_2$

Ac-D-Nal(2)$^1$-D-Cpa$^2$-D-Pal(3)$^3$-Ser$^4$-N-Me-Tyr$^5$-D-Hci$^6$-Leu$^7$-Arg$^8$-Pro$^9$-D-Ala$^{10}$-$NH_2$

Ac-D-Nal(2)$^1$-D-Cpa$^2$-D-Pal(3)$^3$-Ser$^4$-N-Me-Tyr$^5$-D-Cit$^6$-Nle$^7$-Lys(iPr)$^8$-Pro$^9$-D-Ala$^{10}$-$NH_2$

Ac-D-Nal(2)$^1$-D-Cpa$^2$-D-Pal(3)$^3$-Ser$^4$-N-Me-Tyr$^5$-D-Hci$^6$-Leu$^7$-Lys(iPr)$^8$-Pro$^9$-D-Ala$^{10}$-$NH_2$

According to a further aspect of the invention, the compounds according to the invention are present as an acetate, trifluoroacetate or embonate salt.

According to a further aspect of the invention, the compounds according to the invention can be used as medicaments or pharmaceutical preparations.

According to a further aspect of the invention, pharmaceutical preparations are provided, comprising at least one of the compounds according to the invention and customary vehicles and excipients.

According to a further aspect of the invention, a process for the preparation of the compounds of the general formula I according to the invention is provided, in which fragments from units Xxx$^m$ provided with suitable protective groups, in which m is an integer from 1 to 10 and Xxx$^1$ is acetylated, are synthesized on a solid phase or in solution according to customary processes, then the fragments are bound to a solid phase by segment coupling and after conclusion of the coupling the compounds of the general formula I

are removed from the solid phase using customary processes with amidation on the unit $Xxx^{10}$.

According to a further aspect of the invention, the use of the compounds according to the invention for the production of medicaments for the treatment of hormone-dependent tumours, in particular prostate carcinoma or breast cancer, and for non-malignant indications whose treatment necessitates LH-RH hormone suppression, is provided.

According to a further aspect of the invention, a process for the production of pharmaceutical preparations is provided, where at least one compound according to one of Claims 1 to 10 is mixed with the customary vehicles and excipients and formulated as a pharmaceutical.

According to a further aspect of the invention, a process is provided for the treatment of hormone-dependent tumours, in particular prostate carcinoma, breast cancer or uterine myoma, and for non-malignant indications whose treatment necessitates LH-RH hormone suppression, such as endometriosis, benign prostate hyperplasia (BPH), and in the treatment of fertility disorders of women or of men, in mammals, in particular in humans, by administration of an efficacious dose of at least one compound according to the invention.

The compounds according to the invention can be used for the treatment of hormone-dependent tumours, in particular prostate carcinoma, breast cancer or uterine myoma, and also for non-malignant indications whose treatment necessitates LH-RH hormone suppression, such as endometriosis or benign prostate hyperplasia (BPH). Furthermore, they can be employed for the treatment of fertility disorders in men or in women, for example for controlled ovarian superstimulation in the course of in-vitro fertilization. To this end, they are customarily mixed with conventional vehicles and

excipients and formulated as medicaments according to processes known per se.

The synthesis of compounds according to formula (I) can both be carried out either by classical fragment condensation or by solid-phase synthesis according to Merrifield with synthesis following one another using D-lysine already acylated in the side chain with the carboxylic acid of the general formula $R^1$-COOH or by reaction of a decapeptide unit with the appropriate carboxylic acids by amide linkage in the side chain of D-lysine$^6$. Accordingly, the introduction of the $R^1$-CO- group can be performed in three different positions in the process: before the condensation of the individual units to give the peptide, after the incorporation of lysine or ornithine in the peptide chain, but before the condensation of the next unit or after condensation of all units.

The compounds of the formula (I) are synthesized according to the known methods, such as, for example, by pure solid-phase technique, partly solid-phase technique (so-called fragment condensation) or by the classical solution couplings (see M. Bodanszky, "Principles of Peptide Synthesis", Springer Verlag 1984).

For example, the methods of solid-phase synthesis are described in the textbook "Solid Phase Peptide Synthesis", J.M. Stewart and J.D. Young, Pierce Chem. Company, Rockford, III, 1984, and in G. Barany and R.B. Merrifield "The Peptides", Ch. 1, pp. 1-285, 1979, Academic Press Inc. Classical solution syntheses are described in detail in the treatment "Methoden der Organischen Chemie [Methods of Organic Chemistry] (Houben-Weyl), Synthese von Peptiden" [Synthesis of Peptides] E. Wünsch (Editor) 1974, Georg Thieme Verlag, Stuttgart, FRG.

The stepwise synthesis is carried out, for example, by first covalently bonding the carboxy-terminal amino acid whose α-amino group is protected to an insoluble

support which is customary for this, removing the α-amino protective group of this amino acid, bonding the free amino group thus obtained to the next protected amino acid via its carboxyl group, and in this manner linking the customary amino acids of the peptide to be synthesized in the correct sequence step for step, and after linkage of all amino acids removing the finished peptide from the support and removing any further side function protective groups which may be present. The stepwise condensation is carried out in a conventional manner by synthesis from the corresponding, customarily protected amino acids.

The linkage of the individual amino acids to one another is carried out according to the methods customary for this; those particularly suitable are:

- Symmetrical anhydride method in the presence of dicyclohexylcarbodiimide or diisopropylcarbodiimide (DCC, DIC)
- Carbodiimide method generally
- Carbodiimide/hydroxybenzotriazole method

(see The Peptides, Volume 2, Ed. E. Gross and J. Meienhofer).

In the fragment coupling, the azide coupling, which proceeds without racemization, or the DCC-1-hydroxybenzotriazole or DCC-3-hydroxy-4-oxo-3,4-dihyro-1,2,3-benzotriazine method is preferably used. Activated esters of fragments can also be employed.

Esters of N-protected amino acids, such as, for example, N-hydroxysuccinimide esters or 2,4,5-trichlorophenyl esters, are particularly highly suitable for the stepwise condensation of amino acids. The aminolysis can be very well catalysed by N-hydroxy compounds which have approximately the acidity of acetic acid, such as, for example, 1-hydroxybenzotriazole.

Intermediate amino protective groups which present themselves are groups which are removed by hydrogenation, such as, for example, the benzyloxycarbonyl radical (= Z radical) or groups which can be removed by weak acid. Suitable protective groups for the α-amino groups are, for example: tertiary butyloxycarbonyl groups, fluorenylmethyl-oxycarbonyl groups, carbobenzoxy groups or carbobenzothio groups (if appropriate in each case having a p-bromo- [sic] or p-nitrobenzyl radical), the trifluoroacetyl group, the phthalyl radical, the o-nitrophenoxyacetyl group, the trityl group, the p-toluenesulphonyl group, the benzyl group, benzyl radicals substituted in the benzene nucleus (p-bromo- or p-nitrobenzyl radical) and the α-phenylethyl radical. Reference is also made here to P. Greenstein and Milton Winitz, Chemistry of Amino Acids, New York 1961, John Wiley and Sons, Inc., Volume 2, for example page 883 et seq., "Principles of Peptide Synthesis", Springer Verlag 1984, "Solid Phase Peptide Synthesis", J.M. Stewart and J.D. Young, Pierce Chem. Company, Rockford, III, 1984, G. Barany and R.B. Merrifield "The Peptides", Ch. 1, pp. 1-285, 1979, Academic Press Inc., and also The Peptides, Volume 2, Ed. E. Gross and J. Maienhofer, Academic Press, New York. These protective groups are fundamentally also suitable for the protection of further functional side groups (OH groups, $NH_2$ groups) of the corresponding amino acids.

Hydroxyl groups present (serine, threonine) are preferably protected by benzyl groups and similar groups. Further amino groups not in the α-position (for example amino groups in the ω-position, guanidino group of arginine) are preferably orthogonally protected.

The individual amino acid units, excluding lysine [lacuna] modified by the $R^1$-CO-group, are commercially obtainable.

A possible course of the process for the preparation of lysine modified by $R^1$-CO-group is as follows:

1. The α-carboxylic acid group is suitably protected, for example by esterification.
2. The ε-amino group is protected, for example by the Z group.
3. The α-amino group is protected (e.g. Boc group) in such a way that a selectivity with respect to the later removal of the amino protective groups results.
4. The Z group on the ε-amino group is removed.
5. The desired group $R^1$-CO- is introduced on the ε-amino group.
6. The protective group on the α-amino group is removed.
7. The α-amino group is optionally reversibly derivatized, e.g. with the Z group.

For the introduction of the $R^1$-CO-group by reaction of the amino group of the lysine with the appropriate carboxylic acid or carboxylic acid derivative, suitable processes are fundamentally the same processes as described above for the linkage of the amino acids. However, condensation using carbodiimide, for example 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, and 1-hydroxybenzotriazole is particularly preferred.

The reaction for the linkage of the amino acids takes place in an inert solvent or suspending agent which is customary for this (for example dichloromethane), it being possible to add dimethylformamide, if necessary, to improve the solubility.

Suitable synthetic supports are insoluble polymers, for example polystyrene resin in bead form, which can be swollen in organic solvents (for example a copolymer of polystyrene and 1% divinylbenzene). The synthesis of a protected decapeptide amide on a methylbenzhydrylamine resin (MBHA resin, i.e. polystyrene resin provided with methylbenzhydrylamine groups), which affords the desired C-terminal amide function of the peptide after HF cleavage from the support, can be carried out according to the following flow diagram:

Flow diagram

Peptide synthesis protocol using Boc-protected amino acids

| Stage | Function | Solvent/Reagent (v/v) | Time |
|---|---|---|---|
| 1 | Washing | Methanol | 2 × 2 min |
| 2 | Washing | DCM | 3 × 3 min |
| 3 | Removal | DCM/TFA (1:1) | 1 × 30 min |
| 4 | Washing | Isopropanol | 2 × 2 min |
| 5 | Washing | Methanol | 2 × 2 min |
| 6 | Washing | DCM | 2 × 3 min |
| 7 | Neutralization | DCM/DIPEA (9:1) | 3 × 5 min |
| 8 | Washing | Methanol | 2 × 2 min |
| 9 | Washing | DCM | 3 × 3 min |
| 10 | STOP | Addition of the Boc-As in DCM + DIC + HOBt | |
| 11 | Coupling | DCM, optionally DCM/DCF | approx. 90 min |
| 12 | Washing | Methanol | 3 × 2 min |
| 13 | Washing | DCM | 2 × 3 min |

The Nα-Boc-protected amino acids are customarily coupled in a three fold molar excess in the presence of diisopropylcarbodiimide (DIC) and 1-hydroxybenzotriazole (HOBt) in $CH_2Cl_2$/DMF in the course of 90 min, and the Boc-protected group is removed by action of 50% trifluoroacetic acid (TFA) in $CH_2Cl_2$ for half an hour.

To check for complete conversion, the chloranil test according to Christensen and the Kaiser's ninhydrin test can be used. Radicals of free amino functions are blocked by acetylation in a five fold excess of acetylimidazole in $CH_2Cl_2$. The sequence of the reaction steps of the peptide synthesis on the resin follows from the flow diagram. For the removal of the resin-bound peptides, the respective final product of the solid phase synthesis is dried in vacuo over $P_2O_5$ and treated at 0°C for 60 min in a 500-fold excess of HF/anisole 10:1/v:v.

After distilling of HF and anisole in vacuo, the peptide amides are obtained as white solids by washing with anhydrous ethyl ether with stirring, and the removal of polymeric support additionally obtained is carried out by washing with 50% strength aqueous acetic acid. By careful concentration of the acetic acid solutions in vacuo, the respective peptides can be obtained as highly viscous oils, which are converted into white solids after addition of abs. ether in the cold.

Further purification is carried out by routine methods of preparative high-pressure liquid chromatography (HPLC).

The conversion of the peptides into their acid addition salts can be effected in a manner known per se by reaction thereof with acids. Conversely, free peptides can be obtained by reaction of their acid addition salts with bases. Peptide embonates can be prepared by reaction of trifluoroacetic acid salts (TFA salts) of the peptide with free embonic acid (pamoic acid) or the corresponding disodium salt of embonic acid. For this, the peptide TFA salt is treated in aqueous solution with the solution of disodium embonate in polar aprotic

medium, preferably dimethylacetamide, and the pale yellow precipitate formed is isolated.

The following examples serve to illustrate the invention without restricting it.

Example 1 (D-68968):

Ac-D-Nal(2)$^{1}$-D-Cpa$^{2}$-D-Pal(3)$^{3}$-Ser$^{4}$-N-Me-Tyr$^{5}$-D-Lys(B)$^{6}$-Nle$^{7}$-Arg$^{8}$-Pro$^{9}$-Sar$^{10}$-$NH_2$

The synthesis of the decapeptide was carried out on a polymeric support having a loading density of 0.55 mmol/g (aminomethyl-substituted resin, Fmoc protection, type D-1675, Bachem). Lysine was coupled as Fmoc-D-Lys(Boc)-OH and the Fmoc protective groups were removed using 20% piperidine/DMF. After simultaneous removal of all side-chain protective groups and detachment from the polymeric support, the isolated crude peptide was purified by means of preparative HPLC. After freeze-drying, 98.5% strength decapeptide was obtained.

The substitution on the •-nitrogen of D-lysine with 4-(4-aminophenyl)amino-1,4-dioxobutyric acid was carried out using PyBop in DMF with the addition of DIPEA. The purification of the isolated crude peptide was carried out by means of preparative HPLC. The subsequent freeze drying afforded about 99% strength product (trifluoroacetate) of the empirical formula $C_{82}H_{106}ClN_{19}O_{15}$ with correct FAB-MS 1633 (M+H) (calc. 1631.78096)

Example 2 (D-68969):

Ac-D-Nal(2)$^{1}$-D-Cpa$^{2}$-D-Pal(3)$^{3}$-Ser$^{4}$-N-Me-Tyr$^{5}$-D-Lys(B)$^{6}$-Nle$^{7}$-Arg$^{8}$-Pro$^{9}$-D-Ala$^{10}$-$NH_2$

The synthesis of the decapeptide was carried out on a polymeric support having a loading density of 0.55 mmol/g (aminomethyl-substituted resin, Fmoc protection, type D-1675, Bachem). Lysine was coupled as Fmoc-D-Lys(Boc)-OH and the Fmoc protective groups were removed using 20% piperidine/DMF. After simultaneous removal of all side-chain protective groups and detachment from the polymeric support, the isolated crude peptide having a content of about 71% (HPLC) was reacted further without purification.

The side-chain substitution of D-lysine with 4-(4-aminophenyl)amino-1,4-dioxobutyric acid was carried out using PyBop in DMF with the addition of DIPEA. The isolated crude peptide was purified by means of preparative HPLC. After subsequent freeze drying, a 98.8% strength product (trifluoroacetate) of the empirical formula $C_{82}H_{106}ClN_{19}O_{15}$ was obtained with correct FAB-MS 1633 (M+H) (calc. 1631.78096)

Example 3 (D-68971):

Ac-D-Nal(2)$^{1}$-D-Cpa$^{2}$-D-Pal(3)$^{3}$-Ser$^{4}$-N-Me-Tyr$^{5}$-D-Lys(B)$^{6}$-Nle$^{7}$-Lys(iPr)$^{8}$-Pro$^{9}$-Sar$^{10}$-$NH_2$

The synthesis of the decapeptide was carried out on a polymeric support having a loading density of 0.55 mmol/g (aminomethyl-substituted resin, Fmoc protection, type D-1675, Bachem). Lysine was coupled as Fmoc-D-Lys(Boc)-OH and the Fmoc protective groups were removed using 20% piperidine/DMF. After simultaneous removal of all side-chain protective groups and detachment from the polymeric support, the isolated crude peptide (content about 59%, HPLC) was purified by means of preparative HPLC. After freeze drying, 95% strength decapeptide was obtained.

The side-chain substitution of D-lysine with 4-(4-aminophenyl)amino-1,4-dioxobutyric acid was

carried out using PyBop in DMF with the addition of DIPEA. The isolated crude peptide was purified by means of preparative HPLC. After subsequent freeze drying, a 96.6% strength product (trifluoroacetate) of the empirical formula $C_{85}H_{112}ClN_{17}O_{15}$ ws obtained with correct FAB-MS 1648 (M+H) (calc. 1645.8218)

Example 4 (D-68987)

Ac-D-Nal(2)$^{1}$-D-Phe(4-Cl)$^{2}$-D-Pal(3)$^{3}$-Ser$^{4}$-N-Me-Tyr$^{5}$-D-Lys(B)$^{6}$-Nle$^{7}$-Lys(iPr)$^{8}$-Pro$^{9}$-D-Ala$^{10}$-$NH_2$

The synthesis of the D-Lys-6-unsubstituted decapeptide was carried out on 9.09 g of polymeric support having a loading density of 0.55 mmol/g, lysine$^{6}$ was coupled as Fmoc-D-Lys(Boc)-OH.

After removal from the resin, 8.15 g of crude peptide were isolated. The purification of the crude peptide was carried out by means of preparative HPLC.
The side-chain substitution of D-lysine with 4-(4-aminophenyl)amino-1,4-dioxobutyric acid was carried out using PyBop in DMF, with addition of DIPEA. The isolated crude peptide was purified by means of preparative HPLC. After subsequent freeze drying, a 94.6% strength product (trifluoroacetate) of the empirical formula $C_{85}H_{112}ClN_{17}O_{15}$ was obtained with corresponding FAB-MS 1646.8 (M+H; calculated 1645.82)

Example 5:

Ac-D-Nal(2)$^{1}$-D-Cpa$^{2}$-D-Pal(3)$^{3}$-Ser$^{4}$-N-Me-Tyr$^{5}$-D-Cit$^{6}$-Nle$^{7}$-Arg$^{8}$-Pro$^{9}$-D-Ala$^{10}$-$NH_2$

Example 6:

Ac-D-Nal(2)$^1$-D-Cpa$^2$-D-Pal(3)$^3$-Ser$^4$-N-Me-Tyr$^5$-D-Hci$^6$-Leu$^7$-Arg$^8$-Pro$^9$-D-Ala$^{10}$-$NH_2$

Example 7:

Ac-D-Nal(2)$^1$-D-Cpa$^2$-D-Pal(3)$^3$-Ser$^4$-N-Me-Tyr$^5$-D-Cit$^6$-Nle$^7$-Lys(iPr)$^8$-Pro$^9$-D-Ala$^{10}$-$NH_2$

Example 8:

Ac-D-Nal(2)$^1$-D-Cpa$^2$-D-Pal(3)$^3$-Ser$^4$-N-Me-Tyr$^5$-D-Hci$^6$-Leu$^7$-Lys(iPr)$^8$-Pro$^9$-D-Ala$^{10}$-$NH_2$

General working procedures for the preparation of the peptides according to Examples 5 to 8:

The decapeptides can be prepared both by the Merrifield solid-phase synthesis (SPPS) [sic] and by classical fragment condensation in solution. The synthesis of the peptide sequence on the polymeric support is to be preferred for economic reasons and can in principle be carried out alternatively according to (1)*Boc or* (2) *Fmoc* strategy; correspondingly, in each case either a methylbenzhydrylamine resin (for 1) or an Fmoc-2,4-dimethoxy-4'-(carboxymethyloxy)benzhydrylamine resin (for 2) can be employed for the C-terminal bonding of D-alanine.

Solid-phase synthesis, Merrifield process:

The decapeptides are synthesized according to *Fmoc* strategy under standardized reaction conditions (flow scheme, Table I) for a solid-phase synthesis, using 5 grams of the polymeric support Fmoc-2,4-dimethoxy-4'-(carboxymethyloxy)benzhydrylamine resin, Bachem™ D1675, loading density about 0.55 mmol/gram, grain size 200-400 mesh.

The stepwise synthesis of the sequence on the resin is carried out with the aid of N•-*Fmoc*-protected amino acids, according to the following flow scheme:

Table I:

| Step | Function | Solvent | Time | Repetitions |
|---|---|---|---|---|
| 1 | Washing | DMF | 2 min | 2 x |
| 2 | Removal | 20% piperidine in DMF | 5 min | 2 x |
| 3 | Washing | DMF | 2 min | 2 x |
| 4 | Washing | Isopropanol | 2 min | 1 x |
| 5 | Washing | DMF | 2 min | 2 x |
| 6 | Washing | Isopropanol | 2 min | 1 x |
| 7 | Washing | DMF | 2 min | 2 x |
| 8 | Coupling | Boc-AS-OH, HOBT, DIC in DMF | 90 min | 1 x |
| 9 | Washing | DMF | 2 min | 1 x |
| 10 | Washing | Isopropanol | 2 min | 1 x |
| 11 | Washing | DMF | 2 min | 1 x |
| 12 | Washing | Isopropanol | 2 min | 1 x |
| 13 | Washing | DMF | 2 min | 1 x |
| 14 | Washing | Isopropanol | 2 min | 1 x |
| 15 | Checking | Chloranil colour test* | | |

(*according to T. Christensen, *Acta Chem. Scand. B 33, 763-766, 1979)*

Process-typical (repetitive) reaction parameters of the solid-phase synthesis of the decapeptides according to the above scheme:

-Removal of the Fmoc protective group using 20% piperidine in DMF, 2 x 5 min at RT (Step 2).

-Couplings each in a threefold molar excess of Fmoc-amino acids with diisopropylcarbodiimide (DIC) in the presence of hydroxybenzotriazole (HOBt) (Step 8).
-C-terminal removal from the polymeric support including removal of the amino acid side-chain protective groups using trifluoroacetic acid (TFA).

After removal from the polymeric support, when using 5 grams of resin about 5-6 grams of crude peptide mixture having a content of about 70-80% of desired component are formed; this is recovered by subsequent preparative HPLC chromatography.

Preparative HPLC purification of the decapeptides; chromatography conditions:

Prep. HPLC, Shimadzu, Dynamax column RP18, 12 µm, 300 Å, L = 250 mm, ID = 41.4 mm
Gradient system with time programme, 40% B • 90% B, 50 min
Eluent A: 970 ml of $H_2O$ + 30 ml of $CH_3CN$ + 1 ml of $CF_3COOH$
Eluent B: 300 ml of $H_2O$ + 700 ml of $CH_3CN$ + 1 ml of $CF_3COOH$
UV detection, • = 220 nm, flow rate 60 ml/min

The fractions obtained are concentrated in vacuo and lyophilized. The decapeptides are formed as a light colourless material.
A double decomposition into the *acetate salt form* desired for pharmacological development is then carried out by chromatographic ion-exchange.

Investigations of the biological action:

The compounds according to formula I according to the invention are investigated for their receptor binding. The process closely follows the process described in

Beckers et al., Eur. J. Biochem. 231, 535-543 (1995). Cetrorelix obtained according to the synthesis disclosed above is iodinated with [$^{125}$I] (Amersham; specific activity 80.5 Bq/fmol) using the IodoGen™ reagent (Pierce). The reaction mixture is purified by reverse-phase high-performance liquid chromatography, monoiodinated cetrorelix being obtained without unlabelled peptide. In each case, about 80% of the [$^{125}$I]-cetrorelix and the unlabelled compound according to the invention are suitable for the specific receptor association.

The compounds according to the invention can be tested for their in-vitro action using the following Methods 1 and 2, the binding affinities in the binding assay being determined with [$^{125}$I]-cetrorelix (Method 1) and the functional activities being determined with triptorelin as an agonist stimulus (Method 2).

Method 1 (determination of $K_D$ using the example of cetrorelix):

Receptor binding assay according to Beckers, T., Marheineke, K., Reiländer, H., Hilgard P. (1995) "Selection and characterization of mammalian cell lines with stable overexpression of human pituitary receptors for gonadoliberin (GnRH)" Eur. J. Biochem. 231, 535-543.

For investigation of the receptor binding, cetrorelix is iodinated using the IodoGen reagent (Pierce) with [$^{125}$I] (Amersham; 80.5 Bq/fmol specific activity). The reaction mixture is purified by high-performance liquid chromatography with exchanged phases, monoiodinated cetrorelix being obtained without unlabelled peptide. About 80% of the [$^{125}$I] cetrorelix was capable of specific receptor association.

The receptor binding assay is carried out under physiological conditions as described (Beckers et al., 1995) using intact cells. Subconfluent cultures of stably transfected $LTK^-$ cells, which express the human LHRH receptor, are separated off by incubation in $NaCl/P_i$ (137 mM NaCl, 2.7 mM KCl, 8.1 mM $Na_2HPO_4$, 11.47 mM $KH_2PO_4$)/1 mM EDTA and collected by centrifugation. The cell pellet is resuspended in binding buffer (DMEM without $H_2CO_3$, with 4.5 g/l of glucose, 10 mM Hepes pH 7.5, 0.5% (mass/volume) BSA, 1 g/l bacitracin, 0.1 g/l SBTI, 0.1% (mass/volume) $NaN_3$). For displacement assays, $0.25 \times 10^6$ cells/100 µl are incubated with approximately 225 pM of the [$^{125}$I]-cetrorelix (specific activity 5-10 $\times 10^5$ dpm/pmol) and various concentrations of unlabelled compound according to the invention as competitor. The cell suspension in 100 µl of binding medium is layered in 400 µl assay tubes over 200 µl of 84% by volume silicone oil (Merck Type 550)/16% by volume paraffin oil. After incubation for 1 h at 37°C with slow, continuous shaking, the cells are separated from the incubation medium by centrifugation for 2 min at 9000 rpm (rotor type HTA13.8; Heraeus Sepatec, Osterode/Germany). The tips of the tubes which contained the cell pellet are cut off. Cell pellet and supernatants are then analysed by counting the γ radiation. The amount of non-specifically bound material is determined at a final concentration of 1 µM with inclusion of unlabelled cetrorelix and is typically ≤ 10% of the total bound material. The analysis of the binding data is carried out using the EBDA/ligand analysis programme (Biosoft V3.0).

Cetrorelix has a $K_D$ value of 170 picomol per litre (pM) (number of experiments carried out independently: 21).

Method 2 (functional assay for the determination of the antagonistic activity ($IC_{50}$ value)):

The assay is carried out, provided with the modifications mentioned below, as described in Beckers, T., Reiländer, H., Hilgard, P. (1997) "Characterization of gonadotropin-releasing hormone analogs based on a sensitive cellular luciferase reporter gene assay", Analyt. Biochem. 251, 17-23 (Beckers et al., 1997). 10,000 cells per well, which express the human LHRH receptor and a luciferase reporter gene, are cultured for 24 h in microtitre plates using DMEM with additives and 1% (v:v) $FCS_i$. The cells are then stimulated with 1 nM [D-Trp$^6$] LHRH for 6 h. Antagonistic compounds according to the invention are added before the stimulation and the cells are lysed at the end for the quantification of the cellular Luc activity. The calculation of the $IC_{50}$ values from dose-effect curves is carried out by non-linear regression analysis using the Hill model (Programme EDX 2.0 from C. Grunwald, Arzneimittelwerk Dresden).

The quantification of the Luc activity is carried out in duplicate essentially as described (Promega Technical Bulletins #101/161) using the respective luciferase assay system (Promega E4030). Owing to addition of coenzyme A (CoA), an oxidation of luciferyl-CoA takes place with advantageous kinetics. After the removal of the culture medium from the microtitre plate, the cells are lysed by addition of 100 µl of lysis buffer (25 mM tris-phosphate pH 7.8, 2 mM dithiothreitol, 2 mM 1,2-diaminocyclohexane-N,N,N',N'-tetraacetic acid (CDTA), 10% (v:v) glycerol, 1% (v:v) Triton™ X-100). After incubation at room temperature for 15 min, 10 µl of cell lysate are transferred into a white microtitre plate suitable for luminometric detection (Dynatech). The enzymatic reaction is initiated by addition of 50 µl of assay buffer (20 mM tricine pH 7.8, 1.07 mM $(MgCO_3)_4Mg(OH)_2$, 2.67 mM $MgSO_4$, 0.1 mM ethylenediaminetetraacetic acid

(EDTA), 33.3 mM dithiothreitol, 270 µM coenzyme A, 470 µM glow-worm (Photinus pyralis) luciferin, 530 µM rATPNa$_2$). After one minute, the luminescence is determined for a total time of one second with a signal half-life of five minutes using the EG&G Berthold MicroLumat LB 96 P.

Physicochemical and in-vitro data of the compounds according to the invention are summarized in Table 2. $IC_{50}$ stands for the functional activity and pM denotes picomoles per litre. The water solubility was determined according to the process described under Note 2):

Table 2:

| Compound | Water solubility[2] [mg/ml] | $IC_{50}$ [pM] |
|---|---|---|
| Cetrorelix | 0.002 | 198(5)[1] |
| Example 1 (D-68968) | 1.03 | 1300(1)[1] |
| Example 2 (D-68969) | 1.11 | 1400(1)[1] |
| Example 3 (D-68971) | 1.36 | 4700(1)[1] |
| Example 4 (D-68987) | 1.18 | 700(1)[1] |

Notes:

1) the number in brackets indicates the number of experiments independent of one another

2) the water solubility was determined according to the method described below:

**Solubility according to the official gazette method in Ringer's solution:**

For the determination of the solubility according to the official gazette method, the test substance is mixed in an excess with an inert carrier material such as, for example, sand and packed into a glass column (volume size about 10 ml). A sieve of cotton wool and a glass fibre filter had been incorporated into the column bottom beforehand. The substance-sand mixture is allowed to swell for 1 hour in 1.0 ml of solvent in

which the solubility is to be determined. 10 ml of the solvent are then poured into the glass column. The solution is recycled by means of a peristaltic pump. This determination is carried out at room temperature (about 20°C). The solubility is determined when the mass concentration of successive fractions withdrawn is constant.

The determination of the mass concentration is determined [sic] by means of the HPLC method described below.

**HPLC method:**

Equipment

HPLC system: Hewlett Packard 1100; detector: Hewlett Packard DAD series 1100

| | | |
|---|---|---|
| Column: | column material: | Nucleosil® 120-3 $C_{18}$ |
| | particle size: | 3 µm |
| | column size: | 125 x 4 mm |
| | manufacturer: | Macherey & Nagel |
| Equipment parameters: | injection volume: | 15 µl |
| | flow: | 1.0 ml/min |
| | oven temperature: | 45°C |
| | wavelength: | 226 nm |
| | stop time: | 15 min |

55% mobile phase A: 970 ml of Milli-Q-H2O™, 30 ml of acetonitrile and 1 ml of trifluoroacetic acid are mixed. The resulting pH is about 1.9.

45% mobile phase B: 300 ml of Milli-Q-H2O, 700 ml of acetonitrile and 1 ml of trifluoroacetic acid are mixed. The resulting pH is about 1.8.

The administration of the compounds according to the invention can be carried out in different forms suitable for peptide active compounds. Suitable administrations are well known to the person skilled in the art. Administration can be carried out, for example, by injection. Administration can be carried out, for example, parenterally. Subcutaneous (s.c.),

intra-muscular (i.m.), intravenous (i.v.), buccal (e.g. sublingual) or rectal administration are preferred here. I.s. and i.m. Administration are particularly preferred.

The compounds according to the invention are suitable for the preparation of different administration forms, for example for lyophilizates, solutions or suspensions. Suitable administration forms and their preparation are known to the person skilled in the art. Suitable excipients and bulking agents are, for example, hexitols, such as mannitol, in particular D-mannitol, L-mannitol or D,L-mannitol, sorbitol, such as D-sorbitol, D- or L-altritol, iditol, glucitol and dulcitol. Preparation is carried out according to procedures known per se, for example by mixing, suspending or lyophilizing.

Example A: Lyophilizate for the preparation of an s.c. injection solution

1 mg of compound according to Example 1 (corresponding to 0.26-0.27 mg of acetate salt); 0-16.9 parts by weight of D-mannitol, preferably 0.1-7 parts by weight, in each case based on Example 1, and water for injection (for the preparation of the injection solution from the lyophilizate).

Preparation: Dissolve 1.62 g of Example 1 in 30% strength acetic acid (about 1.5 litres of water for injection and 91.17 g of acetic acid). Dilute the solution with 1.5 litres of water. Add 82.2 g of mannitol, sterile filter, dispense into sterile 2 ml injection vials under aseptic conditions and freeze dry. 1 mg of lyophilizate of the compound according to Example 1 is obtained.

The compounds according to the invention are suitable, for example, for the treatment of malignant or non-malignant hormone-dependent disorders, such as, for example, for the treatment of breast carcinoma, of prostate carcinoma, of endometriosis, of uterine myoma,

benign prostate hyperplasia (BPH) and in the treatment of female or male fertility disorders, for example for the prevention of premature ovulation in patients who are subjected to controlled ovarian stimulation followed by egg cell removal and techniques of assisted reproduction. The treatments mentioned can be carried out in mammals, in particular in humans.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A compound of the general formula I:

$A\text{-}Xxx^{1}\text{-}Xxx^{2}\text{-}Xxx^{3}\text{-}Xxx^{4}\text{-}Xxx^{5}\text{-}Xxx^{6}\text{-}Xxx^{7}\text{-}Xxx^{8}\text{-}Xxx^{9}\text{-}Xxx^{10}\text{-}NH_2$ (I)

in which:

A is an acetyl group;

$Xxx^{1}$ is D-Nal(2);

$Xxx^{2}$ is D-Cpa;

$Xxx^{3}$ is D-Pal(3);

$Xxx^{4}$ is Ser;

$Xxx^{5}$ is N-Me-Tyr;

$Xxx^{6}$ is D-Cit or D-[•-N'-4-(4-amidinophenyl)-amino-1,4-dioxobutyl]Lys (abbreviation: D-Lys(B));

$Xxx^{7}$ is Leu or Nle;

$Xxx^{8}$ is Arg or Lys(iPr);

$Xxx^{9}$ is Pro; and

$Xxx^{10}$ is D-Ala or Sar;

with the proviso:

that if $Xxx^{6}$ is D-Lys(B), then $Xxx^{7}$ is Nle; and if $Xxx^{6}$ is D-Cit, then $Xxx^{7}$ is Nle and $Xxx^{10}$ is D-Ala;

or a pharmaceutically acceptable salt acid thereof.

2. A compound according to claim 1, which is:

$Ac\text{-}D\text{-}Nal(2)^{1}\text{-}D\text{-}Cpa^{2}\text{-}D\text{-}Pal(3)^{3}\text{-}Ser^{4}\text{-}N\text{-}Me\text{-}Tyr^{5}\text{-}D\text{-}Lys(B)^{6}\text{-}Nle^{7}\text{-}Arg^{8}\text{-}Pro^{9}\text{-}Sar^{10}\text{-}NH_2$

or a pharmaceutically acceptable salt acid thereof.

3. A compound according to claim 1, which is:

Ac-D-Nal(2)$^{1}$-D-Cpa$^{2}$-D-Pal(3)$^{3}$-Ser$^{4}$-N-Me-Tyr$^{5}$-D-Lys(B)$^{6}$-Nle$^{7}$-Arg$^{8}$-Pro$^{9}$-D-Ala$^{10}$-$NH_2$

or a pharmaceutically acceptable salt acid thereof.

4. A compound according to claim 1, which is:

Ac-D-Nal(2)$^{1}$-D-Cpa$^{2}$-D-Pal(3)$^{3}$-Ser$^{4}$-N-Me-Tyr$^{5}$-D-Lys(B)$^{6}$-Nle$^{7}$-Lys(iPr)$^{8}$-Pro$^{9}$-Sar$^{10}$-$NH_2$

or a pharmaceutically acceptable salt acid thereof.

5. A compound according to claim 1, which is:

Ac-D-Nal(2)$^{1}$-D-Cpa$^{2}$-D-Pal(3)$^{3}$-Ser$^{4}$-N-Me-Tyr$^{5}$-D-Lys(B)$^{6}$-Nle$^{7}$-Lys(iPr)$^{8}$-Pro$^{9}$-D-Ala$^{10}$-$NH_2$

or a pharmaceutically acceptable salt acid thereof.

6. A compound according to claim 1, which is:

Ac-D-Nal(2)$^{1}$-D-Cpa$^{2}$-D-Pal(3)$^{3}$-Ser$^{4}$-N-Me-Tyr$^{5}$-D-Cit$^{6}$-Nle$^{7}$-Arg$^{8}$-Pro$^{9}$-D-Ala$^{10}$-$NH_2$

or a pharmaceutically acceptable salt acid thereof.

7. A compound according to claim 1, which is:

Ac-D-Nal(2)$^{1}$-D-Cpa$^{2}$-D-Pal(3)$^{3}$-Ser$^{4}$-N-Me-Tyr$^{5}$-D-Cit$^{6}$-Nle$^{7}$-Lys(iPr)$^{8}$-Pro$^{9}$-D-Ala$^{10}$-$NH_2$

or a pharmaceutically acceptable salt acid thereof.

8. A compound according to any one of claims 1 to 7, in which the salt is an acetate, trifluoroacetate or embonate.

9. A compound according to any one of claims 1 to 8 for use as a medicament.

10. A pharmaceutical preparation, comprising at least one compound as defined in any one of claims 1 to 8, and a pharmaceutically acceptable carrier or excipient.

11. A process for the preparation of a compound of the general formula I as defined in claim 1 or any one of claims 2 to 7, in which fragments from units $Xxx^m$ provided with protective groups, in which m is an integer from 1 to 10 and $Xxx^1$ is acetylated, are synthesized on a solid phase or in solution, then the fragments are linked to a solid phase by segment coupling and after conclusion of the coupling the compounds of the general formula I are removed from the solid phase with amidation on the unit $Xxx^{10}$.

12. Use of a compound as defined in any one of claims 1 to 8 for the production of a medicament for the treatment of a hormone-dependent tumor or a non-malignant indication whose treatment necessitates LH-RH hormone suppression, or for the treatment of a female or male fertility disorder, in a mammal.

13. Use according to claim 12, wherein the hormone-dependent tumour is prostate carcinoma, breast cancer or uterine myoma.

14. Use according to claim 12, wherein the non-malignant indication is endometriosis or benign prostate hyperplasia (BPH).

15. Use according to claim 12, 13 or 14, wherein the mammal is a human.

16. A process for the production of pharmaceutical preparation as defined in claim 10, wherein at least one compound as defined in any one of claims 1 to 10 is mixed with the pharmaceutically acceptable carrier or excipient and formulated as a medicament.