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The use of cetrorelix and other nona- and decapeptides in the preparation of a medicament for combating AIDS and for growth stimulation

Description

Commencing in 1981, a growing incidence of hitherto rare, incurable infections was observed in homosexual men in New York and San Francisco. Severe defects in immune resistance were found in all patients. Soon afterwards, Luc Montagnier at the Institut Pasteur discovered a new virus, (human immunodeficiency virus, HIV).

Currently, only the dideoxynucleoside analog 3'-azido-3'-desoxythymidine (AZT) or Zidovudine (INN) is registered for the treatment of AIDS. It relieves the symptoms and prolongs the mean survival time of AIDS patients (EP-A 206 497). AZT therapy is associated with the development of resistant virus strains and serious bone marrow side effects. Further medicaments are currently undergoing clinical trials. Thus, for example, German published patent 39 35 580 describes the use of 1-octadecyl-2-methyl-glycero-3-phosphocholine for the preparation of medicaments for combating HIV infections. EP-A 493 378 describes the use of 2'-3'-dideoxyguanosin or of mono or triphosphates of 2'-3'-dideoxyguanosin for the same purpose. All these substances are still undergoing clinical trials and are not yet ready to be marketed.

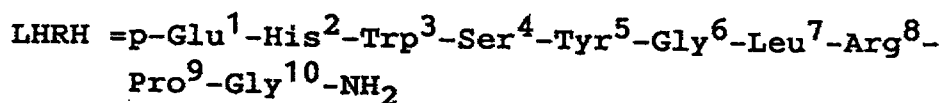
Medicaments currently used as antiviral chemotherapy do not display the desired selectivity. There is consequently a great need for well tolerated, highly effective medicaments which not only delay the course of the illness, but also repress proliferation of the viruses and are, in addition, able to stabilise the weakened immune system of the patients.

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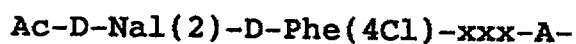
- It has now surprisingly been found in an AIDS screening trial on CEM-IW cells that the LHRH-analog decapeptides of formulae II - VIII display an anti-HIV and a growth stimulating effect on cell cultures.

The object of the invention is the preparation of a medicament based on peptide LHRH antagonists and on bombesin antagonists. The compounds show little toxicity, even in the highest dosages used.

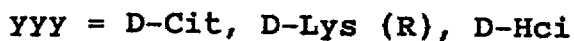
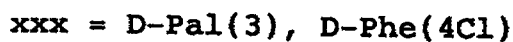
The amino acid sequence of LHRH is:



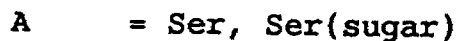
General formula I describes the peptides of the invention:



where:



R may have the meanings (C₁-C₄)-acyl or (C₁-C₁₀)-alkyl.



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sugar can have the meanings glucose, galactose, allose, altrose, mannose, gulose, idose or talose

B = Tyr, Lys(Nic), Mop

Bombesin has the following amino acid sequence:

Bombesin = p-Glu-Gln-Arg-Leu-Gly-Asn⁶-Gln⁷-Trp⁸-Ala⁹-
Val¹⁰-Gly¹¹-His¹²-Leu¹³-Met¹⁴-NH₂

Formula IX

The bombesin-analog peptide according to Formula X has the following structure:

[D-Tpi⁶, Leu-psi-Leu¹³⁻¹⁴]BN(6-14)

Formula X

It is also possible to use bombesin antagonists according to general Formula XI for the treatment of AIDS:

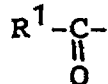
x-A¹-A²-A³-A⁴-A⁵-A⁶-A⁷-A⁸-psi-A⁹-Q Formula XI

where:

Q represents -NH₂ or -OQ¹

where Q¹: hydrogen, (C₁-C₁₀)-alkyl, phenyl or phenyl substituted once or several times by alkyl groups with 7-10 carbon atoms,

X represents: hydrogen or a single bond to the radical A², the acyl radical of an organic acid with 1-6 carbon atoms or a group



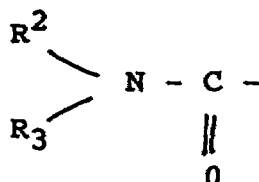
where



1.) R^1 can have the meanings given in connection with Q^1 above or

2.) $R^1 - \underset{\text{O}}{\underset{||}{\text{C}}} -$

may have the meanings



where R^2 and R^3 can be the same or different and represent hydrogen or methyl, in addition R^2 can be an alkyl group with 1-10 carbon atoms, a phenyl group, a phenyl group substituted by one or several alkyl groups with 1-10 carbon atoms, a phenyl group substituted by one or several halogen atoms, for example fluorine, chlorine, bromine or iodine.

A^1 represents:

D-, L-, or D,L-p-Glu, Nal, Phe, Thi, Tyr, Hca, Tpi, Hpp, Mpp, Trp or Trp substituted at the benzene ring, where one or several substituents are selected from the group halogen, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{OH}$, C_1 - C_3 -alkyl, C_1 - C_3 -alkoxy and halogen can represent fluorine, chlorine or bromine.

A^2 represents:

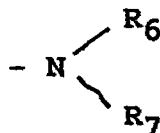
Asp, Dpa, Gln, His, Met His, His (Bz), His (z) or a formula from the group Dpa (x), Asp (y) Glu [-] and Glu [y]

where

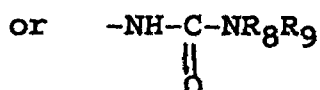
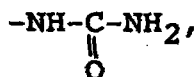
X represents an acyl group, an alkyl group (C₁-C₁₀) or a single bond and

- OR⁵ or

Y have the meaning



where R⁵ and R⁶ can be the same or different and R⁵ represents hydrogen, C₁-C₃-alkyl or phenyl and R⁶ represents hydrogen or C₁-C₃-alkyl or



and [-] is a single bond which combines the carboxyl group with the α-amino group, when X is a single bond
A³ represents Nal, Pal, Tpi, Trp, MeTrp, Trp (For) or Trp with substituted benzene ring, where the benzene ring is substituted by one or several members of the group halogen, NO₂, NH₂, OH, methyl, ethyl or C₁-C₃-alkoxy, where halogen can represent fluorine, chlorine and bromine,

A⁴ represents Ala

A⁵ represents Val or MeVal,

A⁶ represents Gly, Phe, or D-Ala

A⁷ represents His, MeHis, His(Bz), His(Z), Lys(Z) or Pal

A⁸ represents a reduced isostere of Leu or Phe

A⁹ represents Leu, Met, Phe, Tpi or substituted Tpi, where the benzene ring is substituted by the same substituents as in the case of A³ and the benzene radical of Trp is substituted by the same substituents,

and the pharmaceutically acceptable salts of the peptides such as for example hydrochloride, trifluoroacetate, acetate, sulfate, phosphate, mesylate or tosylate.

The appropriate abbreviations for amino acids, peptides and their derivatives are recommended by the IUPAC-IUB Commission for Biochemical Nomenclature.

(European J. Biochem, 1984, 138, 9-37)

Abbreviations for less common amino acids:

Dpa represents 2,3-diaminopropionic acid

Nal represents 3-(2-naphthyl)-alanine,

Thi represents 8-2'-thienylalanine,

Tpi represents 2,3,4,9-tetrahydro-1H-pyrido-
[3,4-b]-indole-3-carboxylic acid

Nic represents Nicotinoyl

Mop represents 4-(morpholinomethyl)-phenylalanine

Particularly preferred compounds according to general Formula I constitute the following amino acid sequences:

Formula II = [Ac-DNal(2)¹, D-Phe(pCl)², D-Pal(3)³,
D-Cit⁶, Nle⁷, D-Ala¹⁰]-LHRH

Formula III = [Ac-DNal(2)¹, D-Phe(pCl)², D-Pal(3)³,
D-Cit⁶, Nva⁷, D-Ala¹⁰]-LHRH

Formula IV = [Ac-DNal(2)¹, D-Phe(pCl)², D-Trp³,
D-Cit⁶, D-Ala¹⁰]-LHRH

Formula V = [Ac-DNal(2)¹, D-Phe(pCl)², D-Pal(3)³,
D-Cit⁶, D-Ala¹⁰]-LHRH

Formula VI = [Ac-DNal(2)¹, D-Phe(pCl)², D-Pal(3)³,
D-HCl⁶, D-Ala¹⁰]-LHRH

Formula VII = [Ac-DNal(2)¹, D-Phe(pCl)², D-Pal³,
D-Cit⁶, t-Leu⁷, D-Ala¹⁰]-LHRH

Formula VIII = [Ac-DNal(2)¹, D-Phe(pCl)², D-Pal(3)³,
D-Cit⁶, Ala⁹, D-Ala¹⁰]-LHRH

The oligopeptides of the invention are synthesised according to conventional processes known from the literature. A summarising description of the appropriate process is, for example, contained in M. Bodanszky, Principles of Peptide Synthesis, Springer-Verlag, Berlin, Heidelberg, New York 1984.

The principles of the solid phase synthesis of polypeptides are for example set out in the textbook by J.M. Stewart and J.D. Young, Solid Phase Peptide Synthesis, Pierce Chem. Co., Rockford, Il, 1984 (2nd edition) and in the survey by L. Barany et al., Int.J. Peptide Protein Res. 30, 705-739 (1987).

The syntheses of the peptides according to formulae II - VIII occur according to the block diagram on methyl-benzhydryl amine resin (hydrochloride commercial form) of Advanced Chem. Tech/Louisville (Kentucky), USA, which was converted into the free base in each case before binding of the C-terminal Boc-D-alanine by 10% triethylamine in dichloromethane (V/V).

All the following N α -Boc-protected amino acids were coupled in threefold molar excess in the presence of diisopropyl carbodiimide (DIC) and 1-hydroxybenzotriazole (HOBt) in CH₂Cl₂/DMF within 90 minutes, in dichloromethane/dimethyl-formamide mixtures of the composition 80/20 (V/V) and the Boc protecting group by reaction of 50 % trifluoroacetic acid (TFA) in dichloromethane for half an hour. Remains of free amino functions are blocked by acetylation in fivefold excess of acetylimidazole in dichloromethane. The sequence of the

reaction steps in the resin-supported peptide synthesis is shown in the block diagram. To split the resin-bound peptides, the end product of the solid phase synthesis was in each case dried in a vacuum and treated in 500fold excess on HF/anisol 10 : 1 (V/V) for 45 to 60 minutes at 0°C.

After distillation of HF and anisol in a vacuum, all raw peptide amides accumulated as white solids by stirring out with anhydrous ethyl ether, the separation of also accumulating polymer carriers occurred by washing out with 50% (V/V) aqueous acetic acid. Cautious concentration of the acetate solutions in a vacuum yielded the corresponding peptides as highly viscous oils which gradually changed into white solids after the addition of absolute ether in the cold. The raw peptides were isolated, washed on a frit with absolute ether and dried in a vacuum.

Preparative cleaning was carried out using high pressure liquid chromatography (HPLC) under the conditions cited:

Parameters for preparative HPLC

Apparatus:	Shimadzu LC-8A pump Shimadzu SPD-6A detector Shimadzu C-R4A integrator Shimadzu SCL-6A controller
Reagents:	Acetonitrile Lichrosolv Merck Art. 30 Trifluoroacetic acid Fluka No. 91700 Purest water (Seralpur installation)
Mobile phase A:	970 ml water (VE water purest) + 30 ml acetonitrile + 1 ml trifluoroacetic acid

Mobile phase B: 300 ml water (VE water, purest)
 + 700 ml acetonitrile
 + 1 ml trifluoroacetic acid

Flow rate: 40 ml/min

Pressure: 14 bar

Average time of flow of a preparative passage: approx. 30 to 40 min.

The correct identity of all peptides synthesized was demonstrated after HPLC purification by means of amino acid analysis, mass spectrometry and ^1H -NMR-spectroscopy.

Block diagram for the solid phase synthesis of the LH-RH peptides: the repeated working steps of the solid phase synthesis are summarised in the following diagram; steps 1 to 17 describe the requisite sequence of operating steps for attaching one amino acid in each case:

Step	Reagents and Operations	Time [min]
1	Boc-amino acid, DIC, HOBT 1 : 1 : 1	90
2	Colour test for total reaction, if positive: repeat 1 and 2	
3	MeOH, washing	1
4	DIPEA, 10 % in CH ₂ Cl ₂ ; neutralisation	2
5	MeOH; washing	1
6	CH ₂ Cl ₂ ; washing, 3-times	2
7	(CH ₃ CO) ₂ O, imidazole, 1 : 1, acetylation	30
8	MeOH; washing, twice	1
9	CH ₂ Cl ₂ ; washing, 3-times	2
10	TFA, 50% in CH ₂ Cl ₂ , splitting Boc	1
11	TFA, 50% in CH ₂ Cl ₂ , splitting Boc	30
12	Isopropanol; washing and decolorisation	2
13	DIPEA, 10% in CH ₂ Cl ₂ ; neutralisation	3
14	MeOH; washing	1
15	DIPEA, 10% in CH ₂ Cl ₂ ; neutralisation	3
16	MeOH; washing	1
17	CH ₂ Cl ₂ ; washing, twice	2

Synthesis product according to the above block diagram:

Ac-D-Nal(2)-D-Phe(4Cl)-Xxx-A-B-Yyy-Zzz-Arg-Pro-D-Ala-NH₂
(according to Formula I)

The completeness of the synthesis was checked using the chloranil test after Th. Christensen; Acta Chem. Scand, B 33, 763 (1979) and using Kaiser's ninhydrin test after Stewart, Young.

The invention relates to a process for the preparation of a medicament for the treatment of viral infections, preferably for the treatment of AIDS. Novel peptides and their syntheses are also described which can be used for antiviral treatment. The peptides are of low toxicity, even at the highest dosage used. Compared to the reference compound azidothymidine tested at the same time, the EC50 values of the peptides tested were between 5.9×10^{-7} mol/litre and 2.0×10^{-5} mol/litre in the NCI experiment.

The reference compound AZT (azidothymidine) tested at the same time had, for example, an EC50 value of 3.10×10^{-9} mol/l. All compounds were dosed in the range of 10^{-4} to 10^{-8} mol/l. The conventionally stated IC50 value (inhibitory concentration in which 50% of cells die in the non-infected culture) is therefore higher than the highest dosage.

The infected culture treated has an EC50 value of 4.5×10^{-5} mol/l. Since the values for the treated, non-infected culture do not fall to an IC50 value, only the value for the highest dosage can be given for the IC50 value, that is $IC50 = >3.3 \times 10^{-5}$ mol/l. The therapeutic index ($TI\ 50 = IC50/EC50$) is then greater than 7.30.

Description of the screening method for anti-HIV activity

The process is suitable for locating active substances which are effective in all phases of the virus proliferation cycle. The test principle is based on the destruction of the T4 lymphocytes by the HIV virus.

Small amounts of HIV virus are added to the cell cultures. At least two complete viral reproduction cycles are needed to destroy the T4 lymphocytes and to be able to evaluate the results.

Active substances that react with virions (virus-like particles), cells or with products of the viral genes in order to interact with viral activities and thus block proliferation of the viruses will protect the cells from destruction and lysis.

The test system is automated to permit examination of a large number of cells infected with viruses. Compounds which degenerate, denaturise or that are rapidly metabolised cannot, however, be reliably discovered using the test procedure.

AZT (azidothymidine) and DDC serve as positive controls for the test.

Test procedure

1. T4 lymphocytes (CEM cell line) are mixed with virus in the ratio of virus : cell of ca. 1 : 0.05 in microtiter plates.
2. Unless otherwise stated, the substance to be tested is dissolved in dimethylsulfoxide (DMSO) and diluted in a ratio of 1 : 200 (parts by weight).
Other dilutions are prepared in semilogarithmic steps with DMSO and then added to infected and non-infected cell cultures.
3. The cultures are incubated for 6-7 days at 37°C in a 5% CO₂ atmosphere.
4. The tetrazolium salt XTT is added to the cell cultures and the cell cultures are further incubated to run the formazan colour reaction by coupling with phenazine methosulfonate (PMS) through surviving cells.

5. The individual cell cultures are analysed spectrophotometrically and examined microscopically to detect surviving cells in order to confirm the protective effect.
6. Treated, virus-infected cells are compared with treated, non-infected cells. Other comparisons (untreated, infected cells and untreated, uninfected cells, active substance-containing, cell-free depressions) are carried out on the same plate.
7. The activity of the tested compound is determined.

The remaining experimental details can be taken from Weislow, J.Nat. Canc. Inst. 81 (8), page 577 (1989).

The peptides according to the invention are thus suitable for the preparation of medicaments for combating AIDS and for combating diseases that are associated with infection with the immune deficiency virus (AIDS-related complex, ARC).

Dosage information:

The dosage of the medicament of the invention is between 0.01 mg and 10 mg in the case of daily administration.

Example 1

Peptide according to formula II:

Mass spectrum: $[M+H^+]= 1431$

^1H -NMR-spectrum (DMSO- d_6 , 250 MHz) δ in ppm:

8.65-7.1; many multiplets, aromatic and NH signals; 7.0 and 6.6, 2.1, 4H, aromatic H Tyr; 5.95 m, NHCONH_2 Cit; 4.8 - 4.1, several multiplets, C_αH ; 3.75 and 3.5, 2 multiplets; aliphatic H; 3.2-2.65, several multiplets, CBH aliphatic and aromatic amino acids; 2.1-1.3, several multiplets, residual aliphatic H; 1.780, d, 3H, CH_3CO^- ; 1.20, d, 3H, CBHAla; 0.80, m, Nle.

Example 2

Peptide according to formula III:

^1H -NMR-spectrum (DMSO- d_6 , 250 MHz) δ in ppm:

8.65-7.1; many multiplets, aromatic and NH signals; 7.0 and 6.6 2d, 4H, aromatic H Tyr; 5.9 m, NHCONH_2 , Cit; 4.8 - 4.1, several multiplets, C_2H ; 3.75 and 3.5, 2 multiplets; aliphatic H; 3.2-2.65, several multiplets, CBH aliphatic and aromatic amino acids; 2.1-1.25, several multiplets, residual aliphatic H; 1.70, 5, 3H, CH_3CO^- ; 1.20, d, 3 H, CBH, Ala; 0.85, m, 3H, Nva.

Mass spectrum: $[M+H^+]= 1417$

Example 3

Peptide according to formula IV:

Mass spectrum: $[M+H^+]= 1469$

^1H -NMR-spectrum (DMSO- d_6 , 250 MHz) δ in ppm:

8.2-6.5, many multiplets, aromatic and NH signals; 5.8 and 5.4, 2 m 3 H, NH-CO-NH₂ citrollia, 4.5, 4.3, 4.2 and 4.0, multiplets C₆H, 3.8 - 2.6, several multiplets; aliphatic and aromatic C₈H; 2.0-1.9, several multiplets, residual aliphatic protons; 1,6,5,3 H, CH₃CO⁻; 1.1, d, 2H, C₈H Ala; 0.7, d, 6 H C H leu

Example 4

Peptide according to formula V, INN: cetorelix

Mass spectrum: $[M+H^+]= 1431$

^1H -NMR-spectrum (DMSO- d_6 , 250 MHz) δ in ppm:

8.7-7.2, many multiplets, aromatic and NH signals; 7.05 and 6.65, 2d, 4H, aromatic H Tyr; 5.85, m NHCONH₂, Cit; 4.8-4.1, several multiplets; C₆H; 3.8 and 3.55, 2 m, aliphatic H; 3.3 - 2.7 C₈H aliphatic and aromatic amino acids; 2.1-1.3, several multiplets, residual aliphatic signals; 1,7,5,3 H, CH₃CO⁻; 1.2, d, 3 H, C₈H Ala; 0.85 2d, 6H, C₈H leu

Example 5

Peptide according to formula VI:

Mass spectrum: $[M+H^+]= 1444$

^1H -NMR-spectrum (DMSO- d_6 , 250 MHz) δ in ppm:

8.6-7.1, many multiplets, aromatic and NH signals; 7.0 and 6.6, 2 d, 4 H, aromatic H Tyr; 4.8-4.0, several multiplets; CoH; 3.7 and 3.5, 2 m 4 H; 3.2-2.7, several multiplets, C β H aromatic and aliphatic amino acids; 2.0-1.0, several multiplets, residual aliphatic signals; 1.7, 5, 3H, CH₃CO; 1.2, d, 3H, C β H Ala; 0.8, dd, 6H, C β H leu

Example 6

Peptide according to formula VII:

Mass spectrum: $[M+H^+]= 1431$

^1H -NMR-spectrum (DMSO- d_6 , 250 MHz) δ in ppm:

8.6-7.1, many multiplets, aromatic and NH signals; 7.0 and 6.6, 2d, 4H, aromatic H Tyr; 5.9 m NHCONH₂, Cit; 4.8-4.0, several multiplets; CoH; 3.85 and 3.5, 2 multiplets, aliphatic H; 3.1-2.7 several multiplets C β H aliphatic and aromatic amino acids; 2.1-1.3, several multiplets, residual aliphatic H; 1.7, 5, 3 H, CH₃CO⁻; 1.20, d, 3H, C β H Ala; 0.85, 5, 9H, t-butyl, Tle

Example 7

Peptide according to formula VIII:

Mass spectrum: $[M+H^+]= 1405$

^1H -NMR-spectrum (DMSO- d_6 , 500 MHz) δ in ppm:

9.1-7.3, many multiplets, aromat. and NH signals; 7.21, dd, 4H, aromatic H p-cl-Phe; 7.0 and 6.6, 2d, 4 H, aromatic H Tyr; 5.9 and 5.4, 2m, 3H, NHCONH_2 Cit; 4.7-4.1, several multiplets, C α H; 3.55-2.8, several multiplets, C β H aliphatic and aromatic amino acids; 1.70, 5, 3H, CH_3CO^- ; 1.55 and 1.45, 2 m aliphatic signals Arg and Leu; 0.80, dd, 6H, C β H Leu



Claims

1. A medicament containing at least one compound of Formula I or of Formula XI

Formula I:

Ac-D-Nal(2)-D-Phe(4Cl)-xxx-A-

-B-yyy-zzz-Arg-Pro-D-Ala-NH₂

where:

xxx = D-Pal(3), D-Phe(4Cl)

yyy = D-Cit, D-Lys (R), D-Arg, D-Hci

R may have the meanings (C₁-C₄)-acyl or (C₁-C₁₀)-alkyl.

zzz = L-Leu, NLe, Nva, t-Leu

A = Ser, Ser(sugar)

sugar can have the meanings glucose, galactose, allose, altrose, mannose, gulose, idose or talose

B = Tyr, Lys(Nic), Mop

Formula XI:

x-A¹-A²-A³-A⁴-A⁵-A⁶-A⁷-A⁸-psi A⁹-Q.

where:

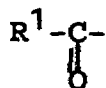
Q represents -NH₂ or -OQ¹





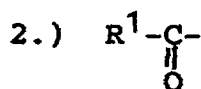
where Q^1 : hydrogen, (C1-C10)-alkyl, phenyl or phenyl substituted once or several times by alkyl groups with 7-10 carbon atoms,

X represents: hydrogen or a single bond for the radical A^2 , the acyl radical of an organic acid with 1-6 carbon atoms or a group

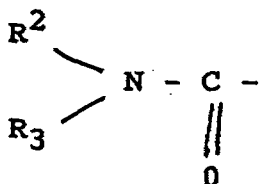


where

1.) R^1 can have the meanings given in connection with Q^1 above or



may have the meanings



where R^2 and R^3 can be the same or different and represent hydrogen or methyl, in addition R^2 can be an alkyl group with 1-10 carbon atoms, a phenyl group, a phenyl group substituted by one or several alkyl groups with 1-10 carbon atoms, a phenyl group substituted by one or several halogen atoms, for example fluorine, chlorine, bromine or iodine.

A^1 represents:

D-, L-, or D,L-p-Glu, Nal, Phe, Thi, Tyr, Hca, Tpi, Hpp, Mpp, Trp or Trp substituted at the benzene ring, where one or several substituents are selected from the





group halogen, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{OH}$, $\text{C}_1\text{-C}_3\text{-alkyl}$,
 $\text{C}_1\text{-C}_3\text{-alkoxy}$ and halogen can represent fluorine,
chlorine or bromine.

A^2 represents:

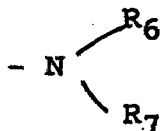
Asp, Dpa, Gln, His, Met His, His (Bz), His (z) or a
formula from the group Dpa (x), Asp (y) Glu [-] and Glu
[y]

where

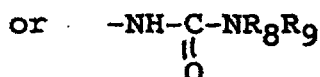
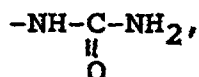
X represents an acyl group, an alkyl group ($\text{C}_1\text{-C}_{10}$)
or a single bond and

$-\text{OR}^5$ or

Y have the meaning



where R^5 and R^6 can be the same or different and R^5
represents hydrogen, $\text{C}_1\text{-C}_3\text{-alkyl}$ or phenyl and R^6
represents hydrogen or $\text{C}_1\text{-C}_3\text{-alkyl}$ or



and [-] is a single bond which combines the carboxyl
group with the α -amino group, when X is a single bond
 A^3 represents Nal, Pal, Tpi, Trp, MeTrp, Trp (For) or Trp
with substituted benzene ring, where the benzene ring
is substituted by one or several members of the group
halogen, NO_2 , NH_2 , OH , methyl, ethyl or
 $\text{C}_1\text{-C}_3\text{-alkoxy}$, where halogen can represent fluorine,
chlorine and bromine,

A^4 represents Ala

A^5 represents Val or MeVal,

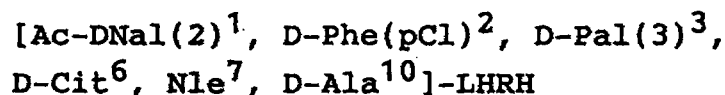
A^6 represents Gly, Phe, or D-Ala



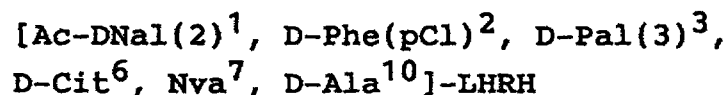


A⁷ represents His, MeHis, His(Bz), His(Z), Lys(Z) or Pal
A⁸ represents a reduced isostere of Leu or Phe
A⁹ represents Leu, Met, Phe, Tpi or substituted Tpi, where the benzene ring is substituted by the same substituents as in the case of A³ and the benzene radical of Trp is substituted by the same substituents, and the pharmaceutically acceptable salts of the peptides such as for example hydrochloride, trifluoroacetate, acetate, sulfate, phosphate, mesylate or tosylate.

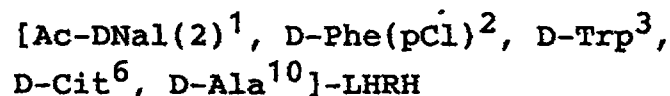
2. A peptide or pharmaceutically acceptable salt according to Formula II with the amino acid sequence:



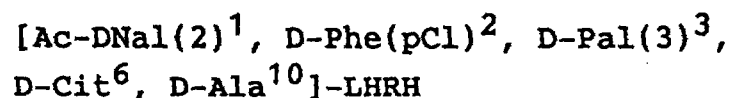
3. A peptide or pharmaceutically acceptable salt with the amino acid sequence according to Formula III



4. A peptide or pharmaceutically acceptable salt with the amino acid sequence according to Formula IV

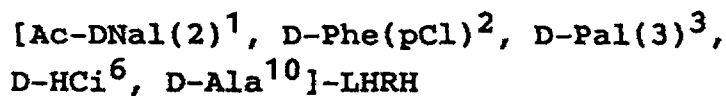


5. A peptide or pharmaceutically acceptable salt with the amino acid sequence according to Formula V

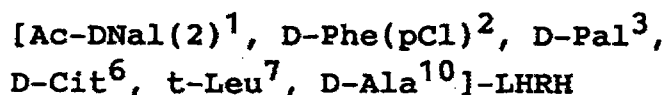




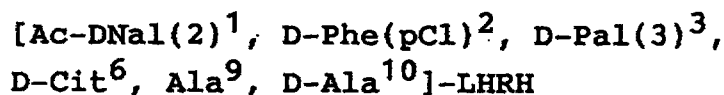
6. A peptide or pharmaceutically acceptable salt with the amino acid sequence according to Formula VI



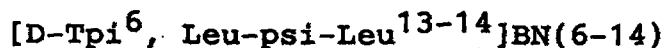
7. A peptide or pharmaceutically acceptable salt with the amino acid sequence according to Formula VII



8. A peptide or pharmaceutically acceptable salt with the amino acid sequence according to Formula VIII



9. A peptide or pharmaceutically acceptable salt with the following amino acid sequence according to Formula X



10. The use of the peptides according to Claims 1-9 for the preparation of medicaments for combating AIDS and ARC.

11. The use of the peptides according to Claims 1-9 for the preparation of medicaments for immune stimulation.

12. A process for the preparation of a medicament for combating AIDS and ARC, characterised in that a peptide according to Claims 1 - 9 is mixed with conventional carriers, diluents and auxiliary substances and manufactured as a medicament.

