

Our Ref 253676

FORM 1

AUSTRALIA
Patents Act

618335

APPLICATION FOR A STANDARD PATENT

Merck Patent Gesellschaft Mit Beschränkter Haftung, of Frankfurter Strasse
250, D-6100 DARMSTADT, FEDERAL REPUBLIC OF GERMANY

hereby applies for the grant of a standard patent for an invention entitled

Amino acid derivatives

which is described in the accompanying complete specification.

Details of basic application(s):

Basic Application: Country:

Date:

P 38 12 328.2

FEDERAL REPUBLIC OF GERMANY

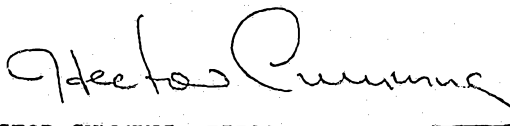
14 April 1988

The address for service is:

ARTHUR S. CAVE & CO.
Patent & Trade Mark Attorneys
Level 10, 10 Barrack Street
SYDNEY NSW 2000

DATED this SIXTH day of APRIL 1989

Merck Patent Gesellschaft Mit
Beschränkter Haftung
By Its Patent Attorneys
ARTHUR S. CAVE & CO.



HECTOR CUMMING, FIPAA

TO:
The Commissioner of Patents
COMMONWEALTH OF AUSTRALIA

FEE: 360.00

5006656 07/04/89

PATENT DECLARATION FORM (CONVENTION)
COMMONWEALTH OF AUSTRALIA
Patents Act 1952

Regulation
12 (2)

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION
FOR A PATENT

To be signed by the applicant(s) or in the case of a body corporate to be
signed by a person authorised by the body corporate.

In support of the Convention application made for a patent for an invention entitled

(a) Insert title
of invention.

(a) AMINO..ACID..DERIVATIVES.....
.....
.....

(b) Insert full
name(s) of
declarant(s).

I/We (b) BRIGITTE NAUMANN and
..... JURGEN HEUMANN

(c) Insert
address(es) of
declarant(s).

of (c) 250 Frankfurter Strasse, D-6100 Darmstadt,
..... Fed..Rep..of..Germany.....
.....

do solemnly and sincerely declare as follows:—

~~1. I am/We are the applicant(s) for the patent~~

(OR, IN THE CASE OF AN APPLICATION BY A BODY CORPORATE,)

1. I am/We are authorised by ...Merck...Patent...Gesellschaft...mit...beschränkter.....
Haftung
..... the applicant for the patent to make this declaration on its behalf.

2. The basic application(s) as defined by Section 141 of the Act was/were made in the following
country or countries on the following date(s) namely:—

(d) Insert
country in
which basic
application(s)
was/were
filed.

in (d) GERMANY on (e) April 14, 1988

(e) Insert date
of basic
application(s).

by (f) on (e)

(f) Insert full
names of basic
applicant(s).

by (f) on (e)

~~3. I am/We are the actual inventor(s) of the invention referred to in the basic application.~~

(OR, WHERE A PERSON OTHER THAN THE INVENTOR IS THE APPLICANT)

(g) Insert full
name(s) of
actual
inventor(s)

3. (g) ...Dr..Peter..Raudatz..Dr..Joachim..Gante..Dr..Johannes..Sombroek.....
.....Dr..Claus..J..Schmitges..Dr..Klaus..Otto..Minck.....

(h) Insert
address(es) of
actual
inventor(s).

of (h) 250..Frankfurter..Strasse..D-6100..Darmstadt.....
..... Fed..Rep..of..Germany.....
.....

is/are the actual inventor(s) of the invention and the facts upon which the applicant(s) is/are entitled to
make the application are as follows:

(i) Set out how
applicant(s)
derive(s) title
from actual
inventor(s)
i.e., assignee of
the invention
from the actual
inventor(s).

(i) The..applicant..is..the..assignee..of..the..invention..from..the..actual.....
.....inventors.....
.....

Attestation or
legalization
not required.

4. The basic application(s) referred to in paragraph 2 of this Declaration was/were the first
application(s) made in a Convention country in respect of the invention the subject of the application.

To:

Declared at Darmstadt this 14th day of February 1989

The Commissioner of Patents

ARTHUR S. CAVE & CO.
PATENT AND TRADE MARK ATTORNEYS
SYDNEY

MERCK PATENT GESELLSCHAFT
MIT BESCHRÄNKTER HAFTUNG
ppa.

Naumann

principal officers

Signature of Declarant(s)
Heumann

(12) PATENT ABRIDGMENT (11) Document No. AU-B-32555/89
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 618335

(54) Title
RENIN INHIBITORS

International Patent Classification(s)

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A61K 031/40	A61K 031/41	A61K 031/47	A61K 031/50
A61K 031/53	A61K 031/54	A61K 037/02	C07C 103/84
C07C 129/12	C07C 143/86	C07C 213/40	C07D 239/42
C07D 241/20	C07D 401/12	C07K 005/08	A61K 031/195
A61K 031/385	A61K 031/405	A61K 031/415	A61K 031/445
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C07C 311/46			

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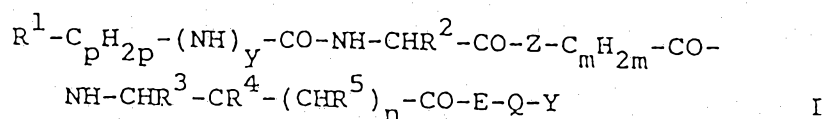
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MERCK PATENT GESELLSCHAFT MIT BESCHRANKTER HAFTUNG

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(57) Claim

1. Amino acid derivatives of the formula I



in which

R^1 is R^6R^7N- , $R^6-NH-C(=NH)-NH-$, $NC-NH-C(=NH)-NH-$, R^6OOC- , R^6O_3S- or $R^6-O-(CH_2CH_2O)_r-$,
 Z is $-O-$, $-CH_2-$, $-CH=CH-$, $-C\equiv C-$, $-NR^8-$, $-CH_2-O-$, $-CH_2-NR^8-$ or $-CH_2-S-$,
 E is 0 to 2 amino acid residues which are linked together in the manner of a peptide and are selected from the group comprising Abu, Ala, Cal, Gly, His, Ile, Leu, Met, Nle, Nva, Phe, Trp, Tyr and Val,
 Q is 0 or NR^{10} ,
 Y is $-C_tH_{2t}-R^{11}$, $-C_tH_{2t}-R^{12}$ or $-C_wH_{2w}-(CR^{13})_s-C_tH_{2t}-R^{11}$,
 R^2 , R^3 and R^{11} are each H, A, Ar, Ar-alkyl, Het,

Het-alkyl, unsubstituted or singly or multiply,
by A, AO and/or Hal, substituted cycloalkyl having
3-7 C atoms, cycloalkylalkyl having 4-11 C atoms,
bicycloalkyl or tricycloalkyl each having 7-14 C
atoms, bicycloalkylalkyl or tricycloalkylalkyl
each having 8-18 C atoms,
 R^4 and R^{13} are each (H, OH), (H, NH_2) or = O,
 R^5 , R^8 and R^{10} are each H or A,
 R^6 and R^7 are each H, A or Ar-alkyl,
 R^7 is also $R^9-O-C_xH_{2x}-CO-$, $R^9-C_xH_{2x}-O-CO-$
or Ac,
 R^9 is A or Ar-alkyl,
 R^6R^7N is also a piperidinyl, morpholinyl, piperazinyl or
pyrrolidinyl group which is unsubstituted or sub-
stituted by A, OH, NH_2 , NHA, NA_2 , NHAc,
 $NH-CO-C_xH_{2x}-O-R^9$, $NH-CO-O-C_xH_{2x}-R^9$, $NH-SO_2-A$,
hydroxyalkyl, COOH, COOA, $CONH_2$, CN, aminoalkyl,
HAN-alkyl, A_2N -alkyl, A_3N^+ alkyl An^- , $NH-CO-NH_2$,
 $NH-CO-NHA$, $NH-CO-NA_2$, guanidinyl or guanidinyl-alkyl,
 R^{12} is $-SO_3H$, $-SO_2NH_2$, $-SO_2NHA$, $-SO_2NA_2$,
 $-NH_2$, $-NHA$, $-NA_2$, $-NH-C(=NH)-NH_2$, $-NH-C(=NH)-$
 $NHCN$, $-NH-CO-NH_2$, $-NH-CO-NHA$, $-NH-CO-NA_2$,
 $-NH-CS-NH_2$, $-NH-CS-NHA$, $-NH-CS-NA_2$, $-COOH$, $-COOA$,
 $-COO$ -alkyl-Ar, $-CONH_2$, $-CONHA$ or $-CONA_2$,
y is 0 or 1,
n and s are each 1 or 2,
m, p, t,
w and x are each 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or
10,
r is 1, 2 or 3,
Ar is phenyl which is unsubstituted or singly or
multiply substituted by A, OA, Hal, CF_3 , OH, NO_2 ,
hydroxyalkyl, NH_2 , NHA, NA_2 , NHAc, SA, $SO-A$, SO_2-
A, SO_2NH_2 , SO_2NHA , COOH, COOA, $CONH_2$, CN, amino-
alkyl, HAN-alkyl, A_2N -alkyl, A_3N^+ alkyl An^- and/or
guanidinyl-alkyl, or is unsubstituted naphthyl,
Het is a saturated or unsaturated 5- or 6-membered
heterocyclic radical which has 1-4 N, O and/or S

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(10) 618335

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atoms and can be fused with a benzene ring and/or can be singly or multiply substituted by A, OA, Hal, CF₃, OH, NO₂, carbonyl oxygen, NH₂, NHA, NA₂, NHAc, SA, SO-A, SO₂-A, SO₂NH₂, SO₂NHA, COOH, COOA, CONH₂, CN, NH-SO₂-A, Ar, Ar-alkyl, Ar-alkenyl, hydroxyalkyl and/or aminoalkyl, and/or whose N and/or S hetero atoms can also be oxidized,

Hal is F, Cl, Br or I,

Ac is H-CO-, A-CO-, CF₃-CO-, Ar-CO-, Ar-alkyl-CO- or A-NH-CO-,

An[⊖] is an anion, which can also be absent if, in its stead, a carboxyl group contained in the compound of the formula I is in the form of a carboxylate anion,

-alkyl- is an alkylene group having 1-8 C atoms, and

A is alkyl having 1-8 C atoms,

in which, furthermore, it is also possible for one or more -NH-CO- groups to be replaced by one or more -NA-CO- groups, as well as the salts thereof.

4. Process for the preparation of pharmaceutical compositions, characterized in that a compound of the formula I and/or one of the physiologically acceptable salts thereof is converted together with at least one solid, liquid or semi-liquid vehicle or auxiliary and, where appropriate, in combination with one or more other active compound(s) into a suitable dosage form.

Our Ref: 253676

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AUSTRALIA
Patents Act

FORM 10

COMPLETE SPECIFICATION

(ORIGINAL)

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority:
Related Art:

Applicant(s): Merck Patent Gesellschaft Mit Beschränkter Haftung
Frankfurter Strasse 250
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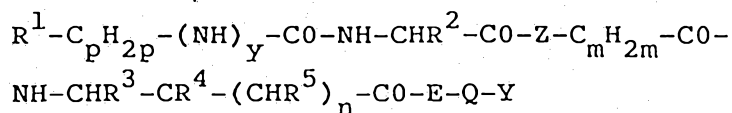
Actual Inventors Dr. Peter Raddatz
Dr. Joachim Gante
Dr. Johannes Sombroek
Dr. Claus J. Schmitges
Dr. Klaus-Otto Minck

Complete specification for the invention entitled "Amino acid derivatives".

The following statement is a full description of this invention, including the best method of performing it known to me:-

Amino acid derivatives

The invention relates to new amino acid derivatives of the formula I



I

in which

R^1 is R^6R^7N- , $R^6-NH-C(=NH)-NH-$, $NC-NH-C(=NH)-NH-$, R^6OOC- , R^6O_3S- or $R^6-O-(CH_2CH_2O)_r-$,
 Z is $-O-$, $-CH_2-$, $-CH=CH-$, $-C\equiv C-$, $-NR^8-$, $-CH_2-O-$, $-CH_2-NR^8-$ or $-CH_2-S-$,
 E is 0 to 2 amino acid residues which are linked together in the manner of a peptide and are selected from the group comprising Abu, Ala, Cal, Gly, His, Ile, Leu, Met, Nle, Nva, Phe, Trp, Tyr and Val,
 Q is 0 or NR^{10} ,
 Y is $-C_{tH_{2t}}-R^{11}$, $-C_{tH_{2t}}R^{12}$ or $-C_{wH_{2w}}-(CR^{13})_s-C_{tH_{2t}}-R^{11}$,

R^2, R^3 and R^{11} are each H, A, Ar, Ar-alkyl, Het, Het-alkyl, unsubstituted or singly or multiply, by A, A0 and/or Hal, substituted cycloalkyl having 3-7 C atoms, cycloalkylalkyl having 4-11 C atoms, bicycloalkyl or tricycloalkyl each having 7-14 C atoms, bicycloalkylalkyl or tricycloalkylalkyl each having 8-18 C atoms,

R^4 and R^{13} are each (H, OH), (H, NH_2) or = 0,

R^5, R^8 and R^{10} are each H or A,

R^6 and R^7 are each H, A or Ar-alkyl,

R^7 is also $R^9-O-C_{xH_{2x}}-CO-$, $R^9-C_{xH_{2x}}-O-CO-$ or Ac,

R^9 is A or Ar-alkyl,

R^6R^7N is also a piperidinyl, morpholinyl, piperazinyl or pyrrolidinyl group which is unsubstituted or substituted by A, OH, NH_2 , NHA, NA_2 , NHAc,

$\text{NH-CO-C}_x\text{H}_{2x}\text{-O-R}^9$, $\text{NH-CO-O-C}_x\text{H}_{2x}\text{-R}^9$,
 $\text{NH-SO}_2\text{-A}$, hydroxyalkyl, COOH , COOA , CONH_2 , CN ,
 aminoalkyl, HAN-alkyl , $\text{A}_2\text{N-alkyl}$, $\text{A}_3\text{N}^{\oplus}\text{alkyl An}^{\ominus}$
 NH-CO-NH_2 , NH-CO-NHA , NH-CO-NA_2 ,
 guanidinyll or guanidinyll-alkyl, is $-\text{SO}_3\text{H}$,
 $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{NHA}$, $-\text{SO}_2\text{NA}_2$, $-\text{NH}_2$, $-\text{NHA}$,
 $-\text{NA}_2$, $-\text{NH-C(=NH)-NH}_2$, $-\text{NH-C(=NH)-NHCN}$,
 $-\text{NH-CO-NH}_2$, $-\text{NH-CO-NHA}$, $-\text{NH-CO-NA}_2$,
 $-\text{NH-CS-NH}_2$, $-\text{NH-CS-NHA}$, $-\text{NH-CS-NA}_2$, $-\text{COOH}$,
 $-\text{COOA}$, $-\text{COO-alkyl-Ar}$, $-\text{CONH}_2$, $-\text{CONHA}$ or $-\text{CONA}_2$,

Y is 0 or 1,

n and s are each 1 or 2,

m, p, t,

w and x are each 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10,

r is 1, 2 or 3,

Ar is phenyl which is unsubstituted or singly or multiply substituted by A, OA, Hal, CF_3 , OH, NO_2 , hydroxyalkyl, NH_2 , NHA, NA_2 , NHAc, SA, SO-A , $\text{SO}_2\text{-A}$, SO_2NH_2 , SO_2NHA , COOH , COOA , CONH_2 , CN , aminoalkyl, HAN-alkyl , $\text{A}_2\text{N-alkyl}$, $\text{A}_3\text{N}^{\oplus}\text{alkyl An}^{\ominus}$ and/or guanidinyll-alkyl, or is unsubstituted naphthyl,

Het is a saturated or unsaturated 5- or 6-membered heterocyclic radical which has 1-4 N, 0 and/or S atoms and can be fused with a benzene ring and/or can be singly or multiply substituted by A, OA, Hal, CF_3 , OH, NO_2 , carbonyl oxygen, NH_2 , NHA, NA_2 , NHAc, SA, SO-A , $\text{SO}_2\text{-A}$, SO_2NH_2 , SO_2NHA , COOH , COOA , CONH_2 , CN , $\text{NH-SO}_2\text{-A}$, Ar, Ar-Alkyl, Ar-alkenyl, hydroxyalkyl and/or aminoalkyl, and/or whose N and/or S hetero atoms can also be oxidized

Hal is F, Cl, Br or I,

Ac is H-CO- , A-CO- , $\text{CF}_3\text{-CO-}$, Ar-CO- , Ar-alkyl-CO- or A-NH-CO- ,

$\text{An}^{\ominus}$ is an anion, which can also be absent if, in its stead, a carboxyl group contained in the compound of the formula I is in the form of a carboxylate

- 2a-

anion,

-alkyl- is an alkylene group having 1-8 C atoms, and

A is alkyl having 1-8 C atoms,

in which, furthermore, it is also possible for one or more

-NH-CO- groups to be replaced by one or more -NA-CO- groups, as well as the salts thereof.

Similar compounds are disclosed in EP-A 249096.

Indicated therein is a formula "I" which also em-
5 braces some of the compounds of the present formula I,
especially some of those compounds of the formula I in
which R^1 is $R^6R^7N-C_pH_{2p}-CO-$, R^6 and R^7 are each H or
alkyl, and p is 0, 1, 2, 3, 4 or 5. Neither the latter
10 group of compounds nor any individual compound covered
thereby is, however, mentioned in EP-A 249096, nor is it
possible to deduce from anywhere in this publication that
particularly this group of compounds has especially
advantageous properties.

The invention had the object of finding new com-
15 pounds with valuable properties, in particular those which
can be used for the preparation of medicaments.

It has been found that the compounds of the
formula I and the salts thereof have very valuable proper-
ties. In particular, they inhibit the activity of human
20 plasma renin. This action can be detected, for example,
by the method of F. Fyhrquist et al., Clin. Chem. 22, 250-
256 (1976). The noteworthy point is that these compounds
are very specific inhibitors of renin; as a rule, the con-
centrations of these compounds necessary for the inhibition
25 of other aspartyl proteinases (for example pepsin and
cathepsin D) are about 100 to 1000 times as high as for
renin inhibition. The actions of the compounds on the
blood pressure and/or on the heart rate, as well as the
inhibition of renin activity in blood plasma can further-
30 more be determined in conscious monkeys, for example fe-
male monkeys (*Macaca fascicularis*); it is possible in
this for the blood pressure and heart rate to be measured
by a modification of the method of M.J. Wood et al., J.
Hypertension 4, 251-254 (1985). In order to stimulate
35 renin activity in this, the animals are preferably pre-
treated with a saluretic. Blood samples for the determin-
ation of the plasma renin activity can be obtained by
puncture of the femoral vein.

The compounds can be used as pharmaceutically

active substances in human and veterinary medicine, in particular for the prophylaxis and for the treatment of diseases of the heart, circulation and vessels, especially of hypertension, cardiac insufficiency and hyperaldosteronism. In addition, the compounds can be used for diagnostic purposes in order to determine, in patients with hypertension or hyperaldosteronism, the possible contribution of the renin activity to maintaining the pathological state. The procedure for such diagnostic tests can be similar to that indicated in EP-A 77 028.

The abbreviations quoted hereinbefore and hereinafter for amino acid residues represent the radicals $-NR'-R''-CO-$, as a rule $-NH-CHR-CO-$ (in which R, R' and R'' have the specific meaning known for each amino acid), of the following amino acids:

Abu	2-Aminobutyric acid
AHCH	4S-Amino-3S-hydroxy-6-cyclohexyl-hexanoic acid
AHCP	4S-Amino-3S-hydroxy-5-cyclohexyl-pentanoic acid
AHPP	4S-Amino-3S-hydroxy-5-phenyl-pentanoic acid
Ala	Alanine
BAla	β -Alanine
Cal	3-Cyclohexylalanine
DACH	3S,4S-Diamino-6-cyclohexyl-hexanoic acid
DACP	3S,4S-Diamino-5-cyclohexyl-pentanoic acid
DAMH	3S,4S-Diamino-6-methyl-heptanoic acid
DAPP	3S,4S-Diamino-5-phenyl-pentanoic acid
Gly	Glycine
His	Histidine
Ile	Isoleucine
Leu	Leucine
Mal	3-(p-Methoxyphenyl)-alanine
Met	Methionine
α Nal	3-(α -Naphthyl)-alanine
β Nal	3-(β -Naphthyl)-alanine
NLe	Norleucine
N-Me-His	N-Methyl-histidine
N-Me-Phe	N-Methyl-phenylalanine
Nva	Norvaline
Phe	Phenylalanine

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	Pia	3-(Piperidyl)-alanine [e.g. 2-pia = 3-(2-piperidyl)-alanine]
	Pya	3-(Pyridyl)-alanine [e.g. 3-pya = 3-(3-pyridyl)-alanine]
5	Sta	Statine
	Tia	3-(Thienyl)-alanine [e.g. 2-tia = 3-(2-thienyl)-alanine]
	Trp	Tryptophan
	Tyr	Tyrosine
10	Val	Valine.
		Further meanings hereinafter are:
	ADPA	N-2-Amino-5,6-dimethyl-3-pyrazinylmethyl-amide
	AMPA	N-4-Amino-2-methyl-5-pyrimidinylmethyl-amide
	BOC	tert.-Butoxycarbonyl
15	BOM	Benzyloxymethyl
	imi-BOM	Benzyloxymethyl in the 1 position of the imidazole ring
	CBZ	Benzyloxycarbonyl
	DCCI	Dicyclohexylcarbodiimide
20	DMF	Dimethylformamide
	DNP	2,4-Dinitrophenyl
	imi-DNP	2,4-Dinitrophenyl in the 1 position of the imidazole ring
	ETOC	Ethoxycarbonyl
25	FMOC	9-Fluorenylmethoxycarbonyl
	HOBt	1-Hydroxybenzotriazole
	IPOC	Isopropoxycarbonyl
	OMe	Methyl ester
	OEt	Ethyl ester
30	POA	Phenoxyacetyl
	THF	Tetrahydrofuran.

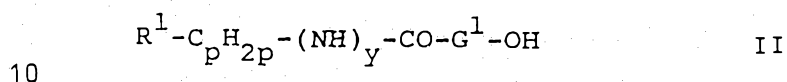
If the abovementioned amino acids can occur in more than one enantiomeric form, then all these forms, as well as mixtures thereof (for example the DL forms), are included hereinbefore and hereinafter, for example as constituent of the compounds of the formula I. The L forms are preferred. Where individual compounds are mentioned hereinafter, then the abbreviations of these amino acids each relate to the L form unless expressly indicated

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otherwise.

The invention furthermore relates to a process for the preparation of an amino acid derivative of the formula I, and of the salts thereof, characterized in that it is
5 liberated from one of its functional derivatives by treatment with a solvolyzing or hydrogenolyzing agent, or in that a carboxylic acid of the formula II



in which G^1 is (a) absent,

- (b) $-NH-CHR^2-CO-$,
- (c) $-NH-CHR^2-CO-Z-C_mH_{2m}-CO-$,
- 15 (d) $-NH-CHR^2-CO-Z-C_mH_{2m}-CO-W-$,
- (e) $-NH-CHR^2-CO-Z-C_mH_{2m}-CO-W-E^1-$,
- (f) $-NH-CHR^2-CO-Z-C_mH_{2m}-CO-W-E-$ and
W is $-NH-CHR^3-CR^4-(CHR^5)_n-CO-$

or one of the reactive derivatives thereof, is reacted
20 with an amino compound of the formula III



in which G^2 is (a) $-NH-CHR^2-CO-Z-C_mH_{2m}-CO-W-E-Q-Y$,

- (b) $-Z-C_mH_{2m}-CO-W-E-Q-Y$,
- 25 (c) $-W-E-Q-Y$,
- (d) $-E-Q-Y$,
- (e) $-E^2-Q-Y$,
- (f) $-NR^{10}-Y$ and

$E^1 + E^2$ are together E,

30 and in that a functionally modified amino and/or hydroxyl group in a compound of the formula I is liberated where appropriate by treatment with solvolyzing or hydrogenolyzing agents, and/or for the preparation of a compound of the formula I, $R^4 = (H, OH)$ or (H, NH_2) , an amino keto
35 acid derivative of the formula I, $R^4 = O$, is reduced or reductively aminated, and/or one radical R^1 is converted to another radical R^1 and/or a compound of the formula I is converted by treatment with an acid into one of the salts thereof.

Hereinbefore and hereinafter the radicals and
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parameters R^1 to R^{13} , Z, E, Q, Y, m, n, p, r, s, t, w, x, y, Ar, Het, Hal, Ac, An, A, G^1 , G^2 , E^1 , E^2 and W have the meanings indicated for the formulae I, II or III unless expressly indicated otherwise.

5 A in the formulae mentioned hereinbefore has 1-8, preferably 1, 2, 3 or 4, C atoms. A is preferably methyl, furthermore ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl or tert.-butyl, as well as pentyl, 1-, 2- or 3-methylbutyl, 1,1-, 1,2- or 2,2-dimethylpropyl, 1-ethyl-
10 propyl, hexyl, 1-, 2-, 3- or 4-methylpentyl, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-dimethylbutyl, 1- or 2-ethyl-butyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, 1,1,2- or 1,2,2-trimethylpropyl, heptyl or octyl.

 Cycloalkyl is preferably cyclopropyl, cyclobutyl,
15 cyclopentyl, cyclohexyl or cycloheptyl, but is also, for example, 1-, 2- or 3-methylcyclopentyl, or 1-, 2-, 3- or 4-methylcyclohexyl.

 Correspondingly, cycloalkylalkyl is preferably cyclopropylmethyl, 2-cyclopropylethyl, cyclobutylmethyl,
20 2-cyclobutylethyl, cyclopentylmethyl, 2-cyclopentylethyl, cyclohexylmethyl, 2-cyclohexylethyl, but is also, for example, 1-, 2- or 3-methylcyclopentylmethyl, or 1-, 2-, 3- or 4-methylcyclohexylmethyl.

 Bicycloalkyl is preferably 1- or 2-decalyl, 2-bi-
25 cyclo[2.2.1]heptyl or 6,6-dimethyl-2-bicyclo[3.1.1]heptyl.

 Tricycloalkyl is preferably 1-adamantyl.

 Hal is preferably F, Cl or Br, but is also I.

 Ac is preferably A-CO-, such as acetyl, propionyl or butyryl, Ar-CO- such as benzoyl, o-, m- or p-methoxy-
30 benzoyl or 3,4-dimethoxybenzoyl, or A-NH-CO- such as N-methyl- or N-ethylcarbamoyl.

 Ar is preferably phenyl and is furthermore preferably o-, m- or p-tolyl, o-, m- or p-ethylphenyl, o-, m- or p-methoxyphenyl, o-, m- or p-fluorophenyl, o-, m- or p-chlorophenyl, o-, m- or p-bromophenyl, o-, m- or p-
35 iodophenyl, o-, m- or p-trifluoromethylphenyl, o-, m- or p-hydroxyphenyl, o-, m- or p-sulfamoylphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dimethoxyphenyl, 3,4,5-trimethoxyphenyl, o-, m- or p-aminophenyl, o-, m- or

p-aminomethylphenyl, o-, m- or p-dimethylaminomethylphenyl, o-, m- or p-guanidinomethylphenyl, or 1- or 2-naphthyl.

Correspondingly, Ar-alkyl is preferably benzyl, 1- or 2-phenylethyl, o-, m- or p-methylbenzyl, 1- or 2-o-, -m- or -p-tolyethyl, o-, m- or p-ethylbenzyl, 1- or 2-o-, -m- or -p-ethylphenylethyl, o-, m- or p-methoxybenzyl, 1- or 2-o-, -m- or -p-methoxy-phenylethyl, o-, m- or p-fluorobenzyl, 1- or 2-o-, -m- or -p-fluorophenylethyl, o-, m- or p-chlorobenzyl, 1- or 2-o-, -m- or -p-chlorophenylethyl, o-, m- or p-bromobenzyl, 1- or 2-o-, -m- or -p-bromophenylethyl, o-, m- or p-iodobenzyl, 1- or 2-o-, -m- or -p-iodophenylethyl, o-, m- or p-trifluoromethylbenzyl, o-, m- or p-hydroxybenzyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dimethoxybenzyl, 3,4,5-trimethoxybenzyl, o-, m- or p-aminobenzyl, o- m- or p-aminomethylbenzyl, o-, m- or p-dimethylaminomethylbenzyl, o-, m- or p-guanidinomethylbenzyl, or 1- or 2-naphthylmethyl.

Het is preferably 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, furthermore preferably 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or -5-yl, 1- or 5-tetrazolyl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 2,1,5-thiadiazol-3- or -4-yl, 2-, 3-, 4-, 5- or 6-2H-thiopyranyl, 2-, 3- or 4-4H-thiopyranyl, 3- or 4-pyridazinyl, pyrazinyl, 2-, 3-, 4-, 5-, 6- or 7-benzofuryl, 2-, 3-, 4-, 5-, 6- or 7-benzothienyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-isoindolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzothiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 4-, 5-, 6- or 7-benz-2,1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl, 1-,

- 8a-

2-, 3-, 4- or 9-carbazolyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-,
8- or 9-acridinyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolyl, 2-,

4-, 5-, 6-, 7- or 8-quinazolyl. The heterocyclic radicals can also be partially or completely hydrogenated. Thus, Het can also be, for example, 2,3-dihydro-2-, -3-, -4- or -5-furyl, 2,5-dihydro-2-, -3-, -4- or -5-furyl, tetrahydro-2- or -3-furyl, tetrahydro-2- or -3-thienyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 2,5-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 1-, 2- or 3-pyrrolidinyl, tetrahydro-1-, -2- or -4-imidazolyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrazolyl, tetrahydro-1-, -3- or -4-pyrazolyl, 1,4-dihydro-1-, -2-, -3- or -4-pyridyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5- or -6-pyridyl, 1,2,3,6-tetrahydro-1-, -2-, -3-, -4-, -5- or -6-pyridyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, tetrahydro-2-, -3- or -4-pyranyl, 1,4-dioxanyl, 1,3-dioxan-2-, -4- or -5-yl, hexahydro-1-, -3- or -4-pyridazinyl, hexahydro-1-, -2-, -4- or -5-pyrimidinyl, 1-, 2- or 3-piperazinyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-quinolyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-isoquinolyl.

The heterocyclic radicals can also be substituted as indicated. Het can also preferably be, for example, 2-amino-4-thiazolyl, 4-carboxy-2-thiazolyl, 4-carbamoyl-2-thiazolyl, 4-(2-aminoethyl)-2-thiazolyl, 4-amino-2-methyl-5-pyrimidinyl, 2-amino-5,6-dimethyl-3-pyrazinyl, 4-carbamoyl-piperidino, furthermore, for example, 3-, 4- or 5-methyl-2-furyl, 2-, 4- or 5-methyl-3-furyl, 2,4-dimethyl-3-furyl, 5-nitro-2-furyl, 5-styryl-2-furyl, 3-, 4- or 5-methyl-2-thienyl, 2-, 4- or 5-methyl-3-thienyl, 3-methyl-5-tert.-butyl-2-thienyl, 5-chloro-2-thienyl, 5-phenyl-2- or -3-thienyl, 1-, 3-, 4- or 5-methyl-2-pyrrolyl, 1-methyl-4- or -5-nitro-2-pyrrolyl, 3,5-dimethyl-4-ethyl-2-pyrrolyl, 4-methyl-5-pyrazolyl, 5-methyl-3-isoxazolyl, 3,4-dimethyl-5-isoxazolyl, 4- or 5-methyl-2-thiazolyl, 2- or 5-methyl-4-thiazolyl, 2- or 4-methyl-5-thiazolyl, 2,4-dimethyl-5-thiazolyl, 3-, 4-, 5- or 6-methyl-2-pyridyl, 2-, 4-, 5- or 6-methyl-3-pyridyl, 2- or 3-methyl-4-pyridyl, 3-, 4-, 5- or 6-chloro-2-pyridyl, 2-, 4-, 5- or 6-chloro-3-pyridyl, 2- or 3-chloro-4-pyridyl, 2,6-dichloropyridyl, 2-hydroxy-3-, -4-, -5- or -6-pyridyl (= 1H-2-pyridon-3-, -4-, -5- or

6-yl), 5-phenyl-1H-2-pyridon-3-yl, 5-p-methoxyphenyl-1H-2-pyridon-3-yl, 2-methyl-3-hydroxy-4-hydroxymethyl-5-pyridyl, 2-hydroxy-4-amino-6-methyl-3-pyridyl, 3-N'-methylureido-1H-4-pyridon-5-yl, 4-methyl-2-pyrimidinyl, 4,6-dimethyl-2-pyrimidinyl, 2-, 5- or 6-methyl-4-pyrimidinyl, 2,6-dimethyl-4-pyrimidinyl, 2,6-dihydroxy-4-pyrimidinyl, 5-chloro-2-methyl-4-pyrimidinyl, 3-methyl-2-benzofuryl, 2-ethyl-3-benzofuryl, 7-methyl-2-benzothienyl, 1-, 2-, 4-, 5-, 6- or 7-methyl-3-indolyl, 1-methyl-5- or -6-benzimidazolyl, 1-ethyl-5- or -6-benzimidazolyl, 3-, 4-, 5-, 6-, 7- or 8-hydroxy-2-quinolyl, 2-oxo-pyrrolidino, 2-oxo-piperidino, 2,5-dioxopyrrolidino or 3-benzyl-2,5-dioxopyrrolidino.

R^1 is preferably R^6R^7N or R^6OOC .

Z is preferably $-NR^8-$, in particular $-NH-$ or $-N(CH_3)-$, furthermore preferably $-CH_2-$, $-CH_2-O-$, $-CH_2-NR^3-$ (in particular $-CH_2-NH-$) or $-CH_2-S-$. Correspondingly, $-Z-C_mH_{2m}-CO-$ is preferably Gly or BAla, furthermore preferably $-CH_2CH_2-CO-$, $-CH_2CH_2CH_2-CO-$ or $-CH_2-S-CH_2-CO-$.

The parameter y is preferably 0; n and s are preferably each 1; m is preferably 1 or 2, furthermore preferably 0; p is preferably 1, 2, 3, 4 or 5, furthermore 6 or 7; r is preferably 1 or 2. The groups C_mH_{2m} and C_pH_{2p} are preferably $-(CH_2)_m-$, in particular $-CH_2-$, or $-(CH_2)_p-$, in particular $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_4-$ or $-(CH_2)_5-$. The groups C_tH_{2t} and C_wH_{2w} are preferably each $-CH_2-$, $-(CH_2)_2-$, $-CH(CH_3)-$, $-CH(isobutyl)-$ or $-CH(sec.-butyl)-$; it is also possible and preferable for the group C_tH_{2t} to be absent ($t = 0$). The parameter x is preferably 1, furthermore 0 or 2.

R^2 is preferably Ar-alkyl, in particular benzyl, 1- or 2-naphthylmethyl, furthermore preferably cycloalkyl-alkyl, in particular cyclohexylmethyl, as well as Het-alkyl, in particular 2-, 3- or 4-piperidylmethyl, 2-, 3- or 4-pyridylmethyl, 2- or 3-thienylmethyl. Accordingly, the group $-NH-CHR^2-CO-$ is preferably Phe, and is furthermore preferably Mal, α Nal, β Nal, Cal, Pia, Pya or Tia.

R^3 is preferably cyclohexylmethyl, furthermore preferably A, in particular methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, pentyl, isopentyl,

(3-methylbutyl) or 2-methylbutyl, phenyl, benzyl, p-chloro-benzyl, 2-cyclohexylethyl, bicyclo[2.2.1]heptyl-2-methyl or 6,6-dimethylbicyclo[3.1.1]heptyl-2-methyl.

R^4 and R^{13} are each preferably (H, OH).

5 R^5 , R^6 , R^7 , R^8 and R^{10} are each preferably H or methyl, furthermore ethyl, propyl, isopropyl, butyl or isobutyl, and R^7 is also preferably benzyl, alkoxycarbonyl such as ETOC, IPOC or BOC or Ar-alkoxycarbonyl such as CBZ, and R^6R^7N is also preferably pyrrolidino, piperidino
10 or 4-methylpiperidino.

Accordingly, the group $R^1-C_pH_{2p}-(NH)_y-CO-$ is preferably $R^1-C_pH_{2p}-CO-$, in particular $R^1(CH_2)_p-CO-$, specifically and in particular $R^6R^7N-C_pH_{2p}-CO-$, preferably $R^6R^7N-(CH_2)_p-CO-$, especially $H_2N-C_pH_{2p}-CO-$, such as aminocar-
15 bonyl, aminoacetyl (H-Gly-), 3-aminopropionyl (H-BAla-), 4-amino-butyryl, 5-aminopentanoyl, 6-aminohexanoyl, 7-aminoheptanoyl, 8-amino-octanoyl, 9-aminononanoyl, 10-aminodecanoyl, 11-aminoundecanoyl, but also, for example, 2-amino-propionyl (Ala), 2-amino-2-methylpropionyl; $ANH-$
20 $C_pH_{2p}-CO-$ such as methylaminocarbonyl, methylaminoacetyl (sarcosyl), 3-methylaminopropionyl, 4-methylaminobutyryl, 5-methylaminopentanoyl, 6-methylaminohexanoyl, 6-ethyl-aminohexanoyl, 7-methylaminoheptanoyl, 8-methylaminooctanoyl, 9-methylaminononanoyl, 10-methylaminodecanoyl, 11-methyl-
25 aminoundecanoyl; $A_2N-C_pH_{2p}-CO-$ such as dimethylamino-carbonyl, dimethylaminoacetyl, 3-dimethylaminopropionyl, 4-dimethylaminobutyryl, 5-dimethylaminopentanoyl, 6-dimethylaminohexanoyl, 6-diethylaminohexanoyl, 7-dimethyl-aminoheptanoyl, 8-dimethylaminooctanoyl, 9-dimethylamino-
30 nonanoyl, 10-dimethylaminodecanoyl, 11-dimethylaminounde-canoyl; $A-O-CO-NH-C_pH_{2p}-CO-$ such as BOC-Gly, ETOC-Gly-, IPOC-Gly, BOC-BAla, ETOC-BAla, IPOC-BAla-, 4-BOC-amino-butyryl, 5-BOC-amino-pentanoyl, 6-BOC-amino-hexanoyl, 7-BOC-amino-heptanoyl, 8-BOC-amino-octanoyl, 9-BOC-amino-
35 nonanoyl, 10-BOC-amino-decanoyl, 11-BOC-amino-undecanoyl; $ArCH_2-O-CO-NH-C_pH_{2p}-CO-$ such as CBZ-Gly-, CBZ-BAla, 4-CBZ-amino-butyryl, 5-CBZ-amino-hexanoyl, 7-CBZ-amino-heptanoyl, 8-CBZ-amino-octanoyl, 9-CBZ-amino-nonanoyl, 10-CBZ-amino-decanoyl, 11-CBZ-amino-undecanoyl; Pyrrolidino- $C_pH_{2p}-CO-$
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such as pyrrolidinocarbonyl, pyrrolidino-acetyl, 3-pyrrolidino-propionyl, 4-pyrrolidino-butyryl, 5-pyrrolidino-pentanoyl, 6-pyrrolidino-hexanoyl, 4-pyrrolidino-heptanoyl, 8-pyrrolidino-octanoyl, 9-pyrrolidino-nonanoyl, 10-pyrrolidino-decanoyl; piperidino-C₆H₂p-CO- such as piperidinocarbonyl, piperidinoacetyl, 3-piperidino-propionyl, 4-piperidino-butyryl, 5-piperidino-pentanoyl, 6-piperidino-hexanoyl, 7-piperidinoheptanoyl, 8-piperidino-octanoyl, 9-piperidino-nonanoyl, 10-piperidino-decanoyl; morpholino-C₆H₂p-CO- such as morpholinocarbonyl, morpholinoacetyl, 3-morpholino-propionyl, 4-morpholino-butyryl, 5-morpholino-pentanoyl, 6-morpholino-hexanoyl, 7-morpholino-heptanoyl, 8-morpholino-octanoyl, 9-morpholino-nonanoyl, 10-morpholino-decanoyl; 4-amino-piperidino-C₆H₂p-CO- such as 4-amino-piperidino-carbonyl, 4-amino-piperidino-acetyl, 3-(4-amino-piperidino)-propionyl, 4-(4-amino-piperidino)-butyryl, 5-(4-amino-piperidino)-pentanoyl, 6-(4-amino-piperidino)-hexanoyl, 7-(4-amino-piperidino)-heptanoyl, 8-(4-amino-piperidino)-octanoyl, 9-(4-amino-piperidino)-nonanoyl, 10-(4-amino-piperidino)-decanoyl; 4-dialkylamino-piperidino-C₆H₂p-CO- such as 4-dimethylamino-piperidinocarbonyl, 4-dimethylaminopiperidino-acetyl; 4-guanidino-piperidino-C₆H₂p-CO- such as 4-guanidino-piperidino-carbonyl, 4-guanidino-piperidino-acetyl; 4-carboxy-piperidino-C₆H₂p-CO- such as 4-carboxy-piperidino-carbonyl, 4-carboxy-piperidino-acetyl; 4-alkoxycarbonyl-piperidino-C₆H₂p-CO- such as 4-methoxycarbonyl-piperidino-carbonyl, 4-ethoxycarbonyl-piperidino-carbonyl, 4-methoxycarbonyl-piperidino-acetyl, 4-ethoxycarbonylpiperidino-acetyl; 4-AcNH-piperidino-C₆H₂p-CO- such as 4-acetamido-piperidino-carbonyl, 4-acetamido-piperidino-acetyl; H₂N-C(=NH)-NH-C₆H₂p-CO- such as guanidinoacetyl, 3-guanidinopropionyl, 4-guanidino-butyryl, 5-guanidino-pentanoyl, 6-guanidino-hexanoyl, 7-guanidino-heptanoyl, 8-guanidino-octanoyl; NC-NH-C(=NH)-NH-C₆H₂p-CO- such as N'-cyanoguanidino-acetyl, 3-(N'-cyanoguanidino)-propionyl, 4-(N'-cyanoguanidino)-butyryl; 5-(N'-cyanoguanidino)-pentanoyl, 6-(N'-cyanoguanidino)-hexanoyl, 7-(N'-cyanoguanidino)-heptanoyl, 8-(N'-cyanoguanidino)-

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octanoyl; $\text{HOOC-C}_p\text{H}_{2p}\text{-CO-}$ such as malonyl, succinyl, glutaryl, adipyl, 6-carboxyhexanoyl, 7-carboxyheptanoyl, 8-carboxyoctanoyl, 9-carboxynonanoyl, 10-carboxy-decanoyl, 11-carboxyundecanoyl; $\text{AOCO-C}_p\text{H}_{2p}\text{-CO-}$ such as methoxycarbonyl-acetyl, 3-methoxycarbonyl-propionyl, 4-methoxycarbonyl-butyryl, 5-methoxycarbonyl-pentanoyl, 6-methoxycarbonyl-hexanoyl, 7-methoxycarbonyl-heptanoyl, 8-methoxycarbonyl-octanoyl, 9-methoxycarbonyl-nonanoyl, 10-methoxycarbonyl-decanoyl, ethoxycarbonyl-acetyl, 3-ethoxycarbonyl-propionyl, 4-ethoxycarbonyl-butyryl, 5-ethoxycarbonyl-pentanoyl, 6-ethoxycarbonyl-hexanoyl, 7-ethoxycarbonyl-heptanoyl, 8-ethoxycarbonyl-octanoyl, 9-ethoxycarbonyl-nonanoyl, 10-ethoxycarbonyl-decanoyl; $\text{H-SO}_3\text{-C}_p\text{H}_{2p}\text{-CO-}$ such as sulfo-acetyl, 3-sulfo-propionyl, 4-sulfo-butyryl, 5-sulfo-pentanoyl, 6-sulfo-hexanoyl, 7-sulfo-heptanoyl, 8-sulfo-octanoyl, 9-sulfo-nonanoyl, 10-sulfo-decanoyl; $\text{A-SO}_3\text{-C}_p\text{H}_{2p}\text{-CO-}$ such as methoxysulfonyl-acetyl, 3-methoxysulfonyl-propionyl, 4-methoxysulfonyl-butyryl, 5-methoxysulfonyl-pentanoyl, 6-methoxysulfonyl-hexanoyl, 7-methoxysulfonyl-heptanoyl, 8-methoxysulfonyl-octanoyl, 9-methoxysulfonyl-nonanoyl, 10-methoxysulfonyl-decanoyl, ethoxysulfonyl-acetyl, 3-ethoxysulfonyl-propionyl, 4-ethoxysulfonyl-butyryl, 5-ethoxysulfonyl-pentanoyl, 6-ethoxysulfonyl-hexanoyl, 7-ethoxysulfonyl-heptanoyl, 8-ethoxysulfonyl-octanoyl, 9-ethoxysulfonyl-nonanoyl, 10-ethoxysulfonyl-decanoyl; $\text{A-O-(CH}_2\text{CH}_2\text{O)}_r\text{-C}_p\text{H}_{2p}\text{-CO-}$ such as 3,6-dioxa-heptanoyl, 3,6- or 4,7-dioxa-octanoyl, 3,6-, 4,7- or 5,8-dioxa-nonanoyl, 3,6,9-trioxa-decanoyl, 3,6,9- or 4,7,10-trioxa-undecanoyl, 3,6,9-, 4,7,10- or 5,8,11-trioxa-dodecanoyl.

If n is 2, the two radicals R^5 can be identical to or different from one another; in the latter case, preferably one radical R^5 is H and the other is A, in particular isopropyl, and the group $\text{-(CHR}^5\text{)}_n\text{-}$ is preferably $\text{-CH}_2\text{-CH}_2\text{-}$, in particular $\text{-CH}_2\text{-CH(isopropyl)-}$.

R^9 is preferably methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, tert.-butyl or benzyl.

The group W is preferably $\text{-NH-CHR}^3\text{-CHOH-CH}_2\text{-CO-}$, in particular AHCP, AHCH, Sta or AHPP. The group W is

furthermore preferably $\text{-NH-CHR}^3\text{-CH(NH}_2\text{)-CH}_2\text{-CO-}$, in particular DACP, DACH, DAMH or DAPP.

The group W has at least one chiral centre.

Further chiral centres may be present in the groups R^1 to R^5 , C_pH_{2p} , C_mH_{2m} , Z, E, Q and Y. The compounds of the formula I can therefore occur in various, optically inactive or optically active, forms. The formula I embraces all these forms. If W is $\text{-NH-CHR}^3\text{-CR}^4\text{-CH}_2\text{-CO-}$ with R^4 being (H, OH) or (H, NH_2), the 3S-hydroxy-4S-amino enantiomers and 3S,4S-diamino enantiomers are preferred. The abbreviations AHCP, AHCH, Sta, AHPP, DACP, DACH, DAMH and DAPP always relate to the 3S,4S forms.

The abovementioned cycloalkyl and phenyl groups are preferably unsubstituted or preferably have 1 to 3, in particular 1 or 2, substituents.

E is preferably one of the said amino acid residues, in particular Ile or Leu; furthermore, E is preferably absent or is preferably Abu, Cal, Met, Nle, Nva, Phe or Val.

Q is preferably NR^{10} , in particular NH or $\text{N(CH}_3\text{)}$.

Y is preferably $\text{-C}_t\text{H}_{2t}\text{-R}^{11}$ or $\text{-C}_t\text{H}_{2t}\text{-R}^{12}$, in particular $\text{-CH}_2\text{R}^{11}$, $\text{-CH}_2\text{R}^{12}$ or $\text{-CH}_2\text{CH}_2\text{R}^{12}$. In these, R^{11} is preferably H, A, Ar or Het, specifically and preferably H, alkyl having 3-5 C atoms, phenyl, o-, m- or p-amino-methylphenyl, o-, m- or p-guanidinomethylphenyl, o-, m- or p-dialkylaminomethylphenyl, such as o-, m- or p-dimethylaminomethylphenyl, 2-, 3- or 4-pyridyl, 2-hydroxy-4,6-dimethyl-3-pyridyl, 4-amino-2-methyl-5-pyrimidinyl or 2-amino-5,6-dimethyl-3-pyrazinyl. R^{12} is preferably $\text{-SO}_3\text{H}$, $\text{-SO}_2\text{NH}_2$, -NA_2 , $\text{-NA}_3^+\text{An}^-$, -NH-C(=NH)-NH_2 , -NH-CO-NHA or -NH-CS-NHA , wherein A is preferably CH_3 .

Some particularly preferred meanings of the group Q-Y are $\text{-NH-CH}_2\text{-(4-amino-2-methyl-5-pyrimidinyl)}$ ("AMPA"), $\text{-NH-CH}_2\text{-(2-amino-5,6-dimethyl-3-pyrazinyl)}$ ("ADPA") and $\text{-NH-CH}_2\text{-(3-pyridyl)}$, furthermore -NH-A .

Accordingly, the invention particularly relates to those compounds of the formula I in which at least one of the said radicals has one of the preferred meanings indicated hereinbefore. Some preferred groups of compounds can be represented by the following part-formulae Ia to

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Ii, which correspond to the formula I but in which

- in Ia R^1 is R^6R^7N- ;
 in Ib R^1 is $R^6-NH-C(=NH)-NH$ or $NC-NH-C(=NH)-NH$;
 in Ic R^1 is R^6OOC- ;
 5 in Id R^1 is R^6O_3S- ;
 in Ie R^1 is $R^6-O-(CH_2CH_2O)_r-$;
 in If R^1 is R^6R^7N- ,
 R^6 is H or A,
 R^7 is H, A, BOC or CBZ,
 10 R^6R^7N is also 4-aminopiperidino,
 y is 0 and
 p is 0, 1, 2, 3, 4, 5, 6 or 7;
 in Ig R^1 is R^6OOC ,
 R^6 is H or A and
 15 y is 0;
 in Ih R^1 is R^6O_3S ,
 R^6 is H or A and
 y is 0;
 in Ii R^6R^7N is 4-aminopiperidino and
 20 y and p are each 0.

Particularly preferred compounds are those of the part-formulae:

- (a) Iaa to Iia, which correspond to the formulae Ia to Ii but in which additionally
 25 R^2 is phenyl or p-methoxyphenyl;
 (b) Iab to Iib as well as Iaab to Iiab, which correspond to the formulae Ia to Ii and Iaa to Iia but in which additionally $-Z-C_mH_{2m}-$ is $-NH-CH_2-$ or $-NH-CH_2CH_2-$;
 30 (c) Iac to Iic, Iaac to Iiac, Iabc to Iibc and Iaabc to Iiabc, which correspond to the formulae Ia to Ii, Iaa to Iia, Iab to Iib and Iaab to Iiab but in which additionally $-NH-CHR^3-CR^4-(CHR^5)_n-CO-$ ($=W$) is AHCP;
 35 (d) Iad to Iid, Iaad to Iiad, Iabd to Iibd, Iacd to Iicd, Iaabd to Iiabd, Iaacd to Iiacd, Iabcd to Iibcd and Iaabcd to Iiabcd, which correspond to the formulae Ia to Ii, Iaa to Iia, Iab to Iib, Iac to Iic, Iaab to Iiab, Iaac to Iiac, Iabc to Iibc and Iaabc to Iiabc but in which additionally

E is Ile or Leu;

Particularly preferred compounds are those of the part-formulae:

I* and Ia* to Ii*, which correspond to the formulae I and
5 Ia to Ii, as well as those compounds which correspond to the other abovementioned part-formulae but in which additionally

Q is NH,

Y is H, A or $-\text{CH}_2\text{R}^{11}$ and

10 R^{11} is o-, m- or p-aminomethylbenzyl, o-, m- or p-guanidinomethylbenzyl, 3-pyridyl, 4-amino-2-methyl-5-pyrimidinyl or 2-amino-5,6-dimethyl-3-pyrazinyl;

I' and Ia' to Ii', which correspond to the formulae I and Ia to Ii, as well as those compounds which correspond to
15 the other abovementioned part-formulae but in which additionally

Q is NH and

Y is H, A, 4-amino-2-methyl-5-pyrimidinylmethyl or 2-amino-5,6-dimethyl-3-pyrazinylmethyl.

20 The compounds of the formula I, as well as the starting materials for the preparation thereof, are furthermore prepared by methods which are known per se and as are described in the literature (for example in the standard works such as Houben-Weyl), Methoden der organischen Chemie,
25 (Methods of Organic Chemistry), published by Georg Thieme, Stuttgart; as well as EP-A 45665, EP-A 77028, EP-A 77029, EP-A 81783, EP-A 249096) specifically under reaction conditions which are known and suitable for the said reactions. In this connection it is also possible to make use of
30 variants which are known per se and which are not mentioned in detail herein.

It is also possible, if desired, to form the starting materials in situ so that they are not isolated from the reaction mixture but are immediately reacted further
35 to give the compounds of the formula I.

The compounds of the formula I can be obtained by liberating them from their functional derivatives by solvolysis, in particular hydrolysis, or by hydrogenolysis.

Preferred starting materials for the solvolysis

or hydrogenolysis are those which correspond to the formula I apart from containing, in place of one or more free amino and/or hydroxyl groups, corresponding protected amino and/or hydroxyl groups, preferably those which carry
5 an amino protective group in place of an H atom bonded to an N atom, for example those which correspond to the formula I but contain in place of a His group an N(im)-R'-His group (in which R' is an amino protective group, for example BOM or DNP), or those of the formula $R^1-C_pH_{2p}-(NH)_y-CO-NH-CHR^2-CO-Z-C_mH_{2m}-CO-NH-CHR^3-CH(NHR')-(CHR^5)_n-CO-E-Q-Y$.
10

Further preferred starting materials are those which carry, in place of the H atom of a hydroxyl group, a hydroxyl protective group, for example those of the
15 formula $R^1-C_pH_{2p}-(NH)_y-CO-NH-CHR^2-CO-Z-C_mH_{2m}-CO-NH-CHR^3-CHOR''-(CHR^5)_n-CO-E-Q-Y$, in which R'' is a hydroxyl protective group.

It is also possible for more than one - identical or different - protected amino and/or hydroxyl groups to
20 be present in the molecule of the starting material. If the protective groups which are present differ from one another it is possible in many cases to eliminate them selectively.

The term "amino protective group" is generally
25 known and relates to groups which are suitable for protecting (blocking) an amino group from chemical reactions but which can easily be removed after the desired chemical reaction has been carried out elsewhere in the molecule. Typical of such groups are, in particular, unsubstituted
30 or substituted acyl, aryl (for example DNP), aralkoxy-methyl (for example BOM) or aralkyl groups (for example benzyl, 4-nitrobenzyl, triphenylmethyl). Since the amino protective groups are removed after the desired reaction (or reaction sequence), their nature and size are not
35 otherwise critical; however, those which are preferred have 1-20, in particular 1-8, C atoms. The term "acyl group" in connection with the present process is to be interpreted in the widest sense. It embraces acyl groups derived from aliphatic, araliphatic, aromatic or
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heterocyclic carboxylic acids or sulfonic acids, as well as, in particular, alkoxycarbonyl, aryloxy carbonyl and, especially, aralkoxycarbonyl groups. Examples of such acyl groups are alkanoyl such as acetyl, propionyl,

5 butyryl; aralkanoyl such as phenylacetyl; aroyl such as benzoyl or toluyyl; aryloxyalkanoyl such as POA; alkoxy carbonyl such as methoxycarbonyl, ETOC, 2,2,2-trichloroethoxycarbonyl, IPOC, BOC, 2-iodoethoxycarbonyl; aralkyloxy carbonyl such as CBZ, 4-methoxybenzyloxycarbonyl,
10 FMOC. Preferred amino protective groups are BOC, DNP and BOM, as well as CBZ, FMOC, benzyl and acetyl.

The term "hydroxyl protective group" is likewise generally known and relates to groups which are suitable for protecting a hydroxyl group from chemical reactions
15 but which can easily be removed after the desired chemical reaction has been carried out elsewhere in the molecule. Typical of such groups are the abovementioned unsubstituted or substituted aryl, aralkyl or acyl groups, as well as alkyl groups. The nature and size of the hydroxyl protective groups are not critical because they are removed
20 again after the desired chemical reaction or reaction sequence; preferred groups have 1-20, in particular 1-10, C atoms. Examples of hydroxyl protective groups are, inter alia, tert.-butyl, benzyl, p-nitrobenzoyl, p-toluene-
25 sulphonyl and acetyl, with benzyl and acetyl being particularly preferred.

The functional derivatives of the compounds of the formula I which are to be used as starting materials can be prepared by customary methods of amino acid and peptide
30 synthesis as are described, for example, in the said standard works and patent applications, for example also by the solid-phase method of Merrifield.

The liberation of the compounds of the formula I from their functional derivatives is effected - depending
35 on the protective group used - for example with strong acids, preferably with trifluoroacetic acid or perchloric acid, but also with other strong inorganic acids such as hydrochloric acid or sulfuric acid, strong organic carboxylic acids such as trichloroacetic acid or sulfonic

acids such as benzene- or p-toluenesulfonic acid. The presence of an additional inert solvent is possible but not always necessary. Suitable and preferred inert solvents are organic, for example carboxylic acids such as acetic acid, ethers such as tetrahydrofuran or dioxane, amides such as dimethylformamide (DMF), halogenated hydrocarbons such as dichloromethane, as well as alcohols such as methanol, ethanol or isopropanol, and water. Furthermore suitable are mixtures of the abovementioned solvents. Trifluoroacetic acid is preferably used in excess without the addition of another solvent, and perchloric acid in the form of a mixture of acetic acid and 70 % perchloric acid in the ratio 9:1. The reaction temperatures for the cleavage are preferably between about 0 and about 50°, preferably between 15 and 30° (room temperature).

The BOC group can be eliminated, for example, preferably with 40 % trifluoroacetic acid in dichloromethane or with about 3 to 5 N HCl in dioxane at 15-30°, and the FMOC group with an approximately 5-20 % solution of dimethylamine, diethylamine or piperidine in DMF at 15-30°. Elimination of the DNP group is effected, for example, also with an approximately 3-10 % solution of 2-mercaptoethanol in DMF/water at 15-30°.

Protective groups which can be removed by hydrogenolysis (for example BOM, CBZ or benzyl) can be eliminated, for example by treatment with hydrogen in the presence of a catalyst (for example a noble metal catalyst such as palladium, preferably on a support such as carbon). Solvents suitable for this are those mentioned above, in particular, for example, alcohols such as methanol or ethanol or amides such as DMF. Hydrogenolysis is, as a rule, carried out at temperatures between about 0 and 100° under pressures between about 1 and 200 bar, preferably at 20-30° and under 1-10 bar. Hydrogenolysis of the CBZ group is effected satisfactorily, for example, on 5-10 % Pd-C in methanol at 20-30°.

Compounds of the formula I can also be obtained by direct peptide synthesis from a carboxylic acid component (formula II) and an amine component (formula III).

Examples of suitable carboxylic acid components are those of the part-formulae (a) $R^1-C_pH_{2p}-(NH)_y-COOH$, (b) $R^1-C_pH_{2p}-(NH)_y-CO-NH-CHR^2-COOH$, (c) $R^1-C_pH_{2p}-(NH)_y-CO-NH-CHR^2-CO-Z-C_mH_{2m}-COOH$, (d) $R^1-C_pH_{2p}-(NH)_y-CO-NH-CHR^2-CO-Z-C_mH_{2m}-CO-W-OH$ or (f) $R^1-C_pH_{2p}-(NH)_y-CO-NH-CHR^2-CO-Z-C_mH_{2m}-CO-W-E-OH$, and of amine components are those of the part-formulae (a) $H_2N-CHR^2-CO-Z-C_mH_{2m}-CO-W-E-Q-Y$, (b) $H-Z-C_mH_{2m}-CO-W-E-Q-Y$, (c) $H-W-E-Q-Y$, (d) $H-E-Q-Y$ or (f) $H-NR^{10}-Y$. The peptide linkage can, however, also be formed within the group E; this entails a carboxylic acid of the formula (e) $R^1-C_pH_{2p}-(NH)_y-CO-NH-CHR^2-CO-Z-C_mH_{2m}-CO-W-E^1-OH$ being reacted with an amino compound of the formula $H-E^2-Q-Y$, where $E^1 + E^2 = E$. The methods preferably used for this are those customary in peptide synthesis, as are described, for example, in Houben-Weyl, l. c., Volume 15/II, pages 1-806 (1974).

The reaction is preferably effected in the presence of a dehydrating agent, for example a carbodiimide such as DCCI or dimethylaminopropylethyl-carbodiimide, or else propanephosphonic anhydride (compare Angew. Chem. 92, 129 (1980)), diphenylphosphoryl azide or 2-ethoxy-N-ethoxycarbonyl-1,2-dihydroquinoline, in an inert solvent, for example a halogenated hydrocarbon such as dichloromethane, an ether such as tetrahydrofuran or dioxane, an amide such as DMF or dimethylacetamide, or a nitrile such as acetonitrile, at temperatures between about -10 and 40, preferably between 0 and 30°.

It is also possible, in place of II or III, to use suitable reactive derivatives of these substances in the reaction, for example those in which reactive groups have undergone intermediate blocking with protective groups. The acid derivatives II can be used, for example, in the form of their activated esters which are preferably formed in situ, for example by addition of HOBT or N-hydroxysuccinimide.

Urea derivatives of the formula I ($y = 1$) can be obtained, for example, by reacting an isocyanate of the formula $R^1-C_pH_{2p}-NCO$ (can be prepared from an amine of the formula $R^1-C_pH_{2p}-NH_2$ and phosgene) with an amine of the

formula $\text{H}_2\text{N}-\text{CHR}^2-\text{CO}-\text{Z}-\text{C}_m\text{H}_{2m}-\text{CO}-\text{W}-\text{E}-\text{Q}-\text{Y}$ (IIa), preferably in an inert solvent such as THF, at temperatures between about -10 and 40° , preferably between 10 and 30° .

The starting materials of formulae II and III are mostly known. Those which are unknown can be prepared by known methods, for example the abovementioned methods of peptide synthesis and of elimination of protective groups.

If desired, it is possible for a functionally modified amino and/or hydroxyl group in a compound of the formula I to be liberated by solvolysis or hydrogenolysis by one of the methods described above.

Thus, for example, a compound of the formula I which contains an $\text{R}^9-\text{C}_x\text{H}_{2x}-\text{O}-\text{CO}-\text{NH}-$, an $\text{AcNH}-$, an $\text{ArCH}_2-\text{SO}_3-$ or an $\text{AOCO}-$ group can be converted into the corresponding compound of the formula I which contains in its stead an $\text{H}_2\text{N}-$, an HSO_3- or an $\text{HOOC}-$ group, preferably by selective solvolysis by one of the methods indicated above. $\text{AOCO}-$ groups can, for example, be hydrolyzed with NaOH or KOH in water/dioxane at temperatures between 0 and 40° , preferably 10 and 30° .

Furthermore, for example, keto compounds of the formula I ($\text{R}^4 = \text{O}$) can be reduced to compounds of the formula I ($\text{R}^4 = (\text{H}, \text{OH})$), for example with a complex metal hydride such as NaBH_4 which does not simultaneously reduce the peptide carbonyl groups, in an inert solvent such as methanol at temperatures between about -10 and $+30^\circ$.

Keto compounds of the formula I ($\text{R}^4 = \text{O}$) can also be converted into compounds of the formula I ($\text{R}^4 = \text{H}, \text{NH}_2$) by reductive amination. The reductive amination can be carried out in one or more stages. Thus, for example, the keto compound can be treated with ammonium salts, for example ammonium acetate and NaCNBH_3 , preferably in an inert solvent, for example an alcohol such as methanol, at temperatures between about 0 and 50° , in particular between 15 and 30° . It is furthermore possible initially to convert the keto compound into the oxime, using hydroxylamine in a customary manner, and to reduce the oxime to the amine, for example by catalytic hydrogenation on Raney

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nickel.

A base of the formula I can be converted into the relevant acid addition salt using an acid. Particularly suitable acids for this reaction are those which provide physiologically acceptable salts. Thus, it is possible to use inorganic acids, for example sulfuric acid, nitric acid, hydrohalic acids such as hydrochloric acid or hydrobromic acid, phosphoric acids such as orthophosphoric acid, sulfamic acid, as well as organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic mono- or polybasic carboxylic, sulfonic or sulfuric acids, for example formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethanesulfonic acid, ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalene-mono- and -disulfonic acids and lauryl sulfuric acid. Salts with physiologically unacceptable acids, for example picrates, can be used to isolate and/or purify the compounds of the formula I.

The new compounds of the formula I and the physiologically acceptable salts thereof can be used to prepare pharmaceutical products by converting them, together with at least one vehicle or auxiliary and, if desired, together with one or more other active substance(s), into a suitable dosage form. The compositions obtained in this way can be used as medicaments in human or veterinary medicine. Suitable vehicles are organic or inorganic substances which are suitable for enteral (for example oral or rectal) or parenteral administration or for administration in the form of a spray for inhalation and which do not react with the new compounds, for example water, vegetable oils, benzyl alcohols, polyethylene glycols, glycerol triacetate and other fatty acid glycerides, gelatin, soya lecithin, carbohydrates such as lactose or starch, magnesium stearate, talc and cellulose. Used orally are, in

particular, tablets, coated tablets, capsules, syrups, elixirs or drops; specifically of interest are lacquered tablets and capsules with enteric coatings or capsule shells. Used rectally are suppositories, and for parenteral administration are solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions or implants. For administration by spray for inhalation, it is possible to use sprays which contain the active substance either dissolved or suspended in a propellant gas mixture (for example fluorochlorohydrocarbons). The active substance is preferably used for this in micronized form, with one or more additional physiologically tolerated solvents possibly being present, for example ethanol. Solutions for inhalation can be administered with the aid of customary inhalers. The new compounds can also be freeze-dried and the resulting lyophilisates used, for example, to prepare products for injection. The stated compositions can be sterilized and/or contain auxiliaries such as preservatives, stabilizers and/or wetting agents, emulsifiers, salts to influence the osmotic pressure, buffer substances, colorants and/or flavourings. They can, if desired, also contain one or more other active substances, for example one or more vitamins.

The substances according to the invention are, as a rule, administered in analogy to other known, commercially available peptides, but especially in analogy to the compounds described in EP-A 249096, preferably in dosages between about 10 mg and 1 g, in particular between 50 mg and 500 mg, per dosage unit. The daily dosage is preferably between about 0.2 and 20 mg/kg, in particular 1 and 10 mg/kg, of bodyweight. The specific dose for each particular patient depends, however, on a wide variety of factors, for example on the activity of the specific compound used, on the age, body weight, general state of health and sex, on the diet, on the time and route of administration and on the rate of excretion, medicinal substance combination and severity of the particular disease for which the therapy is applied. Parenteral administration is preferred.

Renin-dependent hypertension and hyperaldosteronism can be effectively treated by administration of dosages between, in particular, about 1 and 300, preferably between 5 and 50, mg/kg of body weight. For diagnostic purposes,
5 it is possible and preferable for the new compounds to be administered in single doses, particularly in about 0.1 and 10 mg/kg of body weight.

All temperatures stated hereinbefore and hereinafter are in °C. In the examples which follow, "usual working up" means: if necessary, water is added, the pH is
10 adjusted to between 2 and 8, depending on the constitution of the final product, extraction is carried out with ethyl acetate or dichloromethane, the organic phase is separated off, dried over sodium sulfate, filtered and concentrated,
15 and purification is carried out by chromatography on silica gel and/or crystallization.

Example 1

A mixture of 890 mg of 3S-hydroxy-4S-(4-dimethylaminobutyryl-L-phenylalanyl-glycyl-amino)-5-cyclohexyl-pentanoyl-N-imino-(2,4-dinitrophenyl)-L-histidine N-butylamide ["4-dimethylaminobutyryl-Phe-Gly-AHCP-(imi-DNP-His) N-butylamide"; obtainable by reaction of 4-dimethylaminobutyric acid with H-Phe-Gly-AHCP-(imi-DNP-His) N-butylamide],
20 2 g of 2-mercaptoethanol, 20 ml of DMF and 20 ml of water is adjusted to pH 8 with aqueous Na₂CO₃ solution while
25 stirring at 20° and is stirred at 20° for 2 hours. The usual working up results in 4-dimethylaminobutyryl-Phe-Gly-AHCP-His N-butylamide.

Example 2

30 10 g of 3S-CBZ-amino-4S-(4-dimethylamino-butyryl-Phe-Gly-amino)-5-cyclohexyl-pentanoyl-Ile AMPA (obtainable by reaction of 4-dimethylaminobutyryl-Phe-OH with 3S-CBZ-amino-4S-Gly-amino-5-cyclohexyl-pentanoyl-Ile AMPA) are dissolved in 150 ml of ethanol and hydrogenated on 5 g of
35 10 % Pd-C at 20° and under 1 bar until H₂ uptake ceases, the mixture is filtered, the filtrate is evaporated, and purification by chromatography results in 3S-amino-4S-(4-dimethylamino-butyryl-Phe-Gly-amino)-5-cyclohexyl-pentanoyl-Ile AMPA ("4-dimethylaminobutyryl-Phe-Gly-DACP-Ile
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AMPA").

The following are obtained analogously from the corresponding CBZ derivatives:

- 5 4-Morpholino-butyryl-Phe-Gly-DACH-Ile-OMe
- 4-Pyrrolidino-butyryl-Phe-Gly-DAMH-Ile-NH₂
- 4-Piperidino-butyryl-Phe-Gly-DAPP-Ile-OEt.

- 4-BOC-amino-piperidinocarbonyl-Phe-Gly-AHCP-His-NH₂
- 10 is obtained analogously by hydrogenolysis of 4-BOC-amino-piperidinocarbonyl-Phe-Gly-AHCP-(imi-BOM-His) amide.

Example 3

- A solution of 1 g of the di-BOC derivative of 4-guanidino-piperidinocarbonyl-Phe-βAla-AHCP-Ile AMPA [obtainable by reaction of N,N'-di-BOC-S-methyl-isothiourea (m.p. 121°) with 4-aminopiperidinocarbonyl-Phe benzyl ester to give 4-(N,N'-di-BOC-guanidino)-piperidinocarbonyl-Phe benzyl ester, hydrogenolysis to give 4-(N,N'-di-BOC-guanidino)-piperidinocarbonyl-Phe-OH and condensation with
- 20 H-βAla-AHCP-Ile AMPA] in 20 ml of 4 N HCl in dioxane is stirred at 20° for 30 min and then evaporated. 4-Guanidino-piperidinocarbonyl-Phe-βAla-AHCP-Ile AMPA is obtained in the form of the dihydrochloride.

- The following are obtained analogously from the corresponding di-BOC or tri-BOC derivatives:
- 25

- 4-Guanidino-piperidinocarbonyl-Phe-Gly-AHCP-Ile AMPA
 - 4-Guanidino-piperidinocarbonyl-Phe-Gly-AHCP-Ile ADPA
 - 4-Guanidino-piperidinocarbonyl-Phe-Gly-AHCP-Leu AMPA
 - 30 4-Guanidino-piperidinocarbonyl-Phe-Gly-AHCP-Leu ADPA
 - 4-Guanidino-piperidinocarbonyl-Phe-βAla-AHCP-Ile ADPA
 - 4-Guanidino-piperidinocarbonyl-Phe-βAla-AHCP-Leu AMPA
 - 4-Guanidino-piperidinocarbonyl-Phe-βAla-AHCP-Leu ADPA
 - 35 6-Guanidino-hexanoyl-Phe-Gly-AHCP-Ile AMPA
 - 6-Guanidino-hexanoyl-Phe-Gly-AHCP-Ile ADPA
 - 6-Guanidino-hexanoyl-Phe-Gly-AHCP-Leu AMPA
 - 6-Guanidino-hexanoyl-Phe-Gly-AHCP-Leu ADPA
 - 6-Guanidino-hexanoyl-Phe-βAla-AHCP-Ile AMPA
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- 6-Guanidino-hexanoyl-Phe- β Ala-AHCP-Ile ADPA
6-Guanidino-hexanoyl-Phe- β Ala-AHCP-Leu AMPA
6-Guanidino-hexanoyl-Phe- β Ala-AHCP-Leu ADPA
6-Guanidino-hexanoyl-Mal-Gly-AHCP-Ile AMPA
5 6-Guanidino-hexanoyl-Mal-Gly-AHCP-Ile ADPA
6-Guanidino-hexanoyl-Mal- β Ala-AHCP-Ile AMPA
6-Guanidino-hexanoyl-Mal- β Ala-AHCP-Ile ADPA.
- 6-Amino-hexanoyl-Phe-Gly-AHCP-Ile N-6-aminohexyl-amide
10 6-Amino-hexanoyl-Phe- β Ala-AHCP-Ile N-6-aminohexyl-amide
6-Amino-hexanoyl-Phe-Gly-AHCP-Ile N-6-guanidinohexyl-amide
6-Amino-hexanoyl-Phe- β Ala-AHCP-Ile N-6-guanidinohexyl-amide.

Example 4

- 15 1.01 g of N-methylmorpholine are added to a solution of 6.52 g of H-Phe-Gly-AHCP-Ile AMPA (obtainable by condensation of BOC-Phe-Gly-AHCP-Ile-OH with 4-amino-5-aminomethyl-2-methyl-pyrimidine to give BOC-Phe-Gly-AHCP-Ile AMPA and subsequent elimination of the BOC group) in
20 160 ml of DMF. While stirring, 2.31 g of 6-BOC-amino-hexanoic acid, 1.35 g of HOBT and a solution of 2.06 g of DCCI in 50 ml of CH_2Cl_2 are added, the mixture is stirred at 4° for 12 hours, the precipitated dicyclohexylurea is filtered off, and the filtrate is evaporated.
25 The usual working up results in 6-BOC-aminohexanoyl-Phe-Gly-AHCP-Ile AMPA, m.p. 114° .

The following are obtained analogously:

- BOC- β Ala-Phe-Gly-AHCP-Ile-NH₂
30 BOC- β Ala-Phe-Gly-AHCP-Ile N-butylamide
BOC- β Ala-Phe-Gly-AHCP-Ile N-pentylamide
BOC- β Ala-Phe-Gly-AHCP-Ile N,N-diethylamide
- BOC- β Ala-Phe-Gly-AHCP-Ile AMPA
35 BOC- β Ala-Phe-Gly-AHCP-Ile ADPA
BOC- β Ala-Phe-Gly-AHCP-Leu AMPA
BOC- β Ala-Phe-Gly-AHCP-Leu ADPA

BOC- β Ala-Phe- β Ala-AHCP-Ile AMPA

BOC- β Ala-Phe- β Ala-AHCP-Ile ADPA

BOC- β Ala-Phe- β Ala-AHCP-Leu AMPA

BOC- β Ala-Phe- β Ala-AHCP-Leu ADPA

- 5 4-BOC-aminobutyryl-Phe-Gly-AHCP-Ile AMPA
4-BOC-aminobutyryl-Phe-Gly-AHCP-Ile ADPA
4-BOC-aminobutyryl-Phe-Gly-AHCP-Leu AMPA
4-BOC-aminobutyryl-Phe-Gly-AHCP-Leu ADPA
4-BOC-aminobutyryl-Phe- β Ala-AHCP-Ile AMPA
10 4-BOC-aminobutyryl-Phe- β Ala-AHCP-Ile ADPA
4-BOC-aminobutyryl-Phe- β Ala-AHCP-Leu AMPA
4-BOC-aminobutyryl-Phe- β Ala-AHCP-Leu ADPA

4-BOC-aminobutyryl-Mal-Gly-AHCP-Ile AMPA
15 4-BOC-aminobutyryl-Mal-Gly-AHCP-Ile ADPA
4-BOC-aminobutyryl-Mal- β Ala-AHCP-Ile AMPA
4-BOC-aminobutyryl-Mal- β Ala-AHCP-Ile ADPA

5-BOC-aminopentanoyl-Phe-Gly-AHCP-Ile AMPA
20 5-BOC-aminopentanoyl-Phe-Gly-AHCP-Ile ADPA
5-BOC-aminopentanoyl-Phe- β Ala-AHCP-Ile AMPA
5-BOC-aminopentanoyl-Phe- β Ala-AHCP-Ile ADPA

6-BOC-aminohexanoyl-Phe-Gly-AHCP-Ile amide
25 6-BOC-aminohexanoyl- β Ala-Gly-AHCP-Ile amide
6-BOC-aminohexanoyl-Phe-Gly-AHCP-Ile ADPA, m.p. 170-171°
6-BOC-aminohexanoyl-Phe-Gly-AHCP-Leu AMPA
6-BOC-aminohexanoyl-Phe-Gly-AHCP-Leu ADPA
6-BOC-aminohexanoyl-Phe- β Ala-AHCP-Ile AMPA
30 6-BOC-aminohexanoyl-Phe- β Ala-AHCP-Ile ADPA
6-BOC-aminohexanoyl-Phe- β Ala-AHCP-Leu AMPA
6-BOC-aminohexanoyl-Phe- β Ala-AHCP-Leu ADPA

6-BOC-aminohexanoyl-Mal-Gly-AHCP-Ile AMPA
35 6-BOC-aminohexanoyl-Mal-Gly-AHCP-Ile ADPA
6-BOC-aminohexanoyl-Mal- β Ala-AHCP-Ile AMPA
6-BOC-aminohexanoyl-Mal- β Ala-AHCP-Ile ADPA
6-BOC-aminohexanoyl-Phe-Gly-AHCP-Ile N-3-pyridylmethyl-
amide, m.p. 167 - 168°
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- 6-BOC-aminohexanoyl-Phe-BAla-AHCP-Ile N-3-pyridylmethanamide
6-BOC-aminohexanoyl-Phe-Gly-AHCP-Ile N-m-aminomethyl-
benzylamide
6-BOC-aminohexanoyl-Phe-BAla-AHCP-Ile N-m-aminomethyl-
5 benzylamide
6-BOC-aminohexanoyl-Phe-Gly-AHCP-Ile N-p-dimethylamino-
methyl-benzylamide
6-BOC-aminohexanoyl-Phe-BAla-AHCP-Ile N-p-dimethylamino-
methyl-benzylamide
10 6-BOC-aminohexanoyl-Phe-Gly-AHCP-Ile N-5-tetrazolyl-
methanamide
6-BOC-aminohexanoyl-Phe-BAla-AHCP-Ile N-5-tetrazolyl-
methanamide
6-BOC-aminohexanoyl-Phe-Gly-AHCP-Ile N-3-dimethylamino-
15 propylamide
6-BOC-aminohexanoyl-Phe-BAla-AHCP-Ile N-3-dimethylamino-
propylamide
6-BOC-aminohexanoyl-Phe-Gly-AHCP-Ile N-2-sulfoethylamide
6-BOC-aminohexanoyl-Phe-BAla-AHCP-Ile N-2-sulfoethylamide
20
3-[6-BOC-aminohexanoyl-Phe]-propionyl-AHCP-Ile AMPA
3-[6-BOC-aminohexanoyl-Phe]-propionyl-AHCP-Ile ADPA
4-[6-BOC-aminohexanoyl-Phe]-3-thiabutyl-AHCP-Ile AMPA
4-[6-BOC-aminohexanoyl-Phe]-3-thiabutyl-AHCP-Ile ADPA
25
7-BOC-aminoheptanoyl-Phe-Gly-AHCP-Ile AMPA
7-BOC-aminoheptanoyl-Phe-Gly-AHCP-Ile ADPA
7-BOC-aminoheptanoyl-Phe-Gly-AHCP-Ile AMPA
7-BOC-aminoheptanoyl-Phe-Gly-AHCP-Ile ADPA
30
8-BOC-aminooctanoyl-Phe-Gly-AHCP-Ile AMPA, m.p. 162°
8-BOC-aminooctanoyl-Phe-Gly-AHCP-Ile ADPA
8-BOC-aminooctanoyl-Phe-BAla-AHCP-Ile AMPA, m.p. 203° (dec.)
8-BOC-aminooctanoyl-Phe-BAla-AHCP-Ile ADPA
35
Dimethylaminoacetyl-Phe-Gly-AHCP-Ile AMPA
3-Dimethylamino-propionyl-Phe-Gly-AHCP-Ile AMPA

4-Dimethylamino-butyl-Phe-Gly-AHCP-Ile AMPA,
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- m.p. 198-199°; dihydrochloride m.p. 131° (decomposition)
4-Dimethylamino-butyryl-Phe-Gly-AHCP-Ile ADPA,
dihydrochloride m.p. 131°
4-Dimethylamino-butyryl-Phe-Gly-AHCP-Ile p-sulfamoyl-
5 anilide, hydrochloride m.p. 136-140°
4-Dimethylamino-butyryl-Phe-Gly-AHCP-Leu AMPA
4-Dimethylamino-butyryl-Phe-Gly-AHCP-Leu ADPA
4-Dimethylamino-butyryl-Phe- β Ala-AHCP-Ile AMPA,
dihydrochloride m.p. 196° (decomposition)
10 4-Dimethylamino-butyryl-Phe- β Ala-AHCP-Ile ADPA
4-Dimethylamino-butyryl-Phe- β Ala-AHCP-Leu AMPA
4-Dimethylamino-butyryl-Phe- β Ala-AHCP-Leu ADPA

4-Dimethylaminobutyryl-Mal-Gly-AHCP-Ile AMPA
15 4-Dimethylaminobutyryl-Mal-Gly-AHCP-Ile ADPA
4-Dimethylaminobutyryl-Mal- β Ala-AHCP-Ile AMPA
4-Dimethylaminobutyryl-Mal- β Ala-AHCP-Ile ADPA

5-Dimethylamino-pentanoyl-Phe-Gly-AHCP-Ile AMPA
20 5-Dimethylamino-pentanoyl-Phe-Gly-AHCP-Ile ADPA
5-Dimethylamino-pentanoyl-Phe-Gly-AHCP-Leu AMPA
5-Dimethylamino-pentanoyl-Phe-Gly-AHCP-Leu ADPA
5-Dimethylamino-pentanoyl-Phe- β Ala-AHCP-Ile AMPA
5-Dimethylamino-pentanoyl-Phe- β Ala-AHCP-Ile ADPA
25 5-Dimethylamino-pentanoyl-Phe- β Ala-AHCP-Leu AMPA
5-Dimethylamino-pentanoyl-Phe- β Ala-AHCP-Leu ADPA

6-Dimethylamino-hexanoyl-Phe-Gly-AHCP-Ile AMPA
6-Dimethylamino-hexanoyl-Phe-Gly-AHCP-Ile ADPA
30 6-Dimethylamino-hexanoyl-Phe-Gly-AHCP-Leu AMPA
6-Dimethylamino-hexanoyl-Phe-Gly-AHCP-Leu ADPA
6-Dimethylamino-hexanoyl-Phe- β Ala-AHCP-Ile AMPA
6-Dimethylamino-hexanoyl-Phe- β Ala-AHCP-Ile ADPA
6-Dimethylamino-hexanoyl-Phe- β Ala-AHCP-Leu AMPA
35 6-Dimethylamino-hexanoyl-Phe- β Ala-AHCP-Leu ADPA

3-[6-Dimethylamino-hexanoyl-Phe]-propionyl-AHCP-Ile AMPA
3-[6-Dimethylamino-hexanoyl-Phe]-propionyl-AHCP-Ile ADPA
3-[6-Dimethylamino-hexanoyl-Phe]-3-thiabutyryl-AHCP-Ile
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AMPA

4-[6-Dimethylamino-hexanoyl-Phe]-3-thiabutyryl-AHCP-Ile

ADPA

- 5 6-Dimethylamino-hexanoyl-Mal-Gly-AHCP-Ile AMPA
6-Dimethylamino-hexanoyl-Mal-Gly-AHCP-Ile ADPA
6-Dimethylamino-hexanoyl-Mal-BAla-AHCP-Ile AMPA
6-Dimethylamino-hexanoyl-Mal-BAla-AHCP-Ile ADPA
7-Dimethylamino-heptanoyl-Phe-Gly-AHCP-Ile AMPA
10 8-Dimethylamino-octanoyl-Phe-Gly-AHCP-Ile AMPA

(4-Piperidyl)-acetyl-Phe-Gly-AHCP-Ile AMPA, dihydrochloride
m.p. 232°
(4-Piperidyl)-acetyl-Phe-Gly-AHCP-Ile ADPA
15 (4-Piperidyl)-acetyl-Phe-BAla-AHCP-Ile AMPA, dihydrochloride
m.p. 75°
(4-Piperidyl)-acetyl-Phe-BAla-AHCP-Ile ADPA

Piperidinoacetyl-Phe-Gly-AHCP-Ile AMPA
20 Piperidinoacetyl-Phe-Gly-AHCP-Ile ADPA
Piperidinoacetyl-Phe-BAla-AHCP-Ile AMPA
Piperidinoacetyl-Phe-BAla-AHCP-Ile ADPA

3-Piperidino-propionyl-Phe-Gly-AHCP-Ile AMPA
25 3-Piperidino-propionyl-Phe-Gly-AHCP-Ile ADPA
3-Piperidino-propionyl-Phe-BAla-AHCP-Ile AMPA, m.p. 188°
3-Piperidino-propionyl-Phe-BAla-AHCP-Ile ADPA

4-Pyrrolidino-butyryl-Phe-Gly-AHCP-Ile AMPA, dihydrochloride, oil
30 4-Pyrrolidino-butyryl-Phe-Gly-AHCP-Ile ADPA
4-Pyrrolidino-butyryl-Phe-BAla-AHCP-Ile AMPA
4-Pyrrolidino-butyryl-Phe-BAla-AHCP-Ile ADPA

4-Piperidino-butyryl-Phe-Gly-AHCP-Ile AMPA, dihydrochloride
35 m.p. 79°
4-Piperidino-butyryl-Phe-Gly-AHCP-Ile ADPA
4-Piperidino-butyryl-Phe-BAla-AHCP-Ile AMPA, m.p. 199°
4-Piperidino-butyryl-Phe-BAla-AHCP-Ile ADPA

5-Pyrrolidino-pentanoyl-Phe-Gly-AHCP-Ile AMPA, dihydrochloride, oil

5-Pyrrolidino-pentanoyl-Phe-Gly-AHCP-Ile ADPA

5-Pyrrolidino-pentanoyl-Phe- β Ala-AHCP-Ile AMPA, m.p. 231°

5-Pyrrolidino-pentanoyl-Phe- β Ala-AHCP-Ile ADPA

5

5-Piperidino-pentanoyl-Phe-Gly-AHCP-Ile AMPA, dihydrochloride
m.p. 62°

5-Piperidino-pentanoyl-Phe-Gly-AHCP-Ile ADPA

5-Piperidino-pentanoyl-Phe- β Ala-AHCP-Ile AMPA, m.p. 202°

10 5-Piperidino-pentanoyl-Phe- β Ala-AHCP-Ile ADPA

6-CBZ-amino-hexanoyl-Phe-Gly-AHCP-Ile AMPA,

6-CBZ-amino-hexanoyl-Phe-Gly-AHCP-Ile ADPA, m.p. 167 - 168°
(decomposition)

15 6-CBZ-amino-hexanoyl-Phe- β Ala-AHCP-Ile AMPA

6-CBZ-amino-hexanoyl-Phe- β Ala-AHCP-Ile ADPA

2-CBZ-amino-2-methyl-propionyl-Phe-Gly-AHCP-Ile AMPA,
m.p. 128°

2-CBZ-amino-2-methyl-propionyl-Phe-Gly-AHCP-Ile ADPA

20 2-CBZ-amino-2-methyl-propionyl-Phe- β Ala-AHCP-Ile AMPA,
m.p. 191-192°

2-CBZ-amino-2-methyl-propionyl-Phe- β Ala-AHCP-Ile ADPA

2-CBZ-amino-2-methyl-propionyl-Mal-Gly-AHCP-Ile AMPA,
m.p. 185-186°

25 2-CBZ-amino-2-methyl-propionyl-Mal-Gly-AHCP-Ile ADPA

2-CBZ-amino-2-methyl-propionyl-Mal- β Ala-AHCP-Ile AMPA,
m.p. 191-192°

2-CBZ-amino-2-methyl-propionyl-Mal- β Ala-AHCP-Ile ADPA.

30 Example 5

4-BOC-amino-piperidinocarbonyl-Phe- β Ala-AHCP-Ile
AMPA is obtained in analogy to Example 4 from 4-BOC-amino-
piperidinocarbonyl-Phe-OH (m.p. 158-159°) and H- β Ala-
AHCP-Ile AMPA (obtainable from BOC- β Ala-AHCP-Ile AMPA (m.p.
35 163-164°)), m.p. 185° (decomposition).

The following are obtained analogously

3,6-Dioxaheptanoyl-Phe-Gly-AHCP-Ile AMPA, m.p. 130°

[obtainable via BOC-Gly-AHCP-Ile AMPA (m.p. 151°) and

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H-Gly-AHCP-Ile AMPA]

3,6-Dioxaheptanoyl-Phe-Gly-AHCP-Ile ADPA

3,6-Dioxaheptanoyl-Phe- β Ala-AHCP-Ile AMPA

3,6-Dioxaheptanoyl-Phe- β Ala-AHCP-Ile ADPA

5

3,6,9-Trioxadecanoyl-Phe-Gly-AHCP-Ile AMPA, m.p. 110°;
hydrochloride m.p. 85°

3,6,9-Trioxadecanoyl-Phe-Gly-AHCP-Ile ADPA

3,6,9-Trioxadecanoyl-Phe- β Ala-AHCP-Ile AMPA

10 3,6,9-Trioxadecanoyl-Phe- β Ala-AHCP-Ile ADPA

4-BOC-amino-piperidinocarbonyl-Phe-Gly-AHCP-Ile AMPA,
m.p. 152-153°

4-BOC-amino-piperidinocarbonyl-Phe-Gly-AHCP-Ile ADPA

15 4-BOC-amino-piperidinocarbonyl-Phe-Gly-AHCP-Leu AMPA

4-BOC-amino-piperidinocarbonyl-Phe-Gly-AHCP-Leu ADPA

4-BOC-amino-piperidinocarbonyl-Phe- β Ala-AHCP-Ile AMPA

4-BOC-amino-piperidinocarbonyl-Phe- β Ala-AHCP-Ile ADPA,
m.p. 173-174°

20 4-BOC-amino-piperidinocarbonyl-Phe- β Ala-AHCP-Ile N-2-
pyridylmethanamide

4-BOC-amino-piperidinocarbonyl-Phe- β Ala-AHCP-Ile N-3-
pyridylmethanamide, m.p. 145°

4-BOC-amino-piperidinocarbonyl-Phe- β Ala-AHCP-Leu AMPA, m.p. 181-182°

25 4-BOC-amino-piperidinocarbonyl-Phe- β Ala-AHCP-Leu ADPA

4-BOC-amino-piperidinocarbonyl-Phe-Gly-AHCH-Ile AMPA

4-BOC-amino-piperidinocarbonyl-Phe-Sta-Ile AMPA

4-BOC-amino-piperidinocarbonyl-Phe-AHPP-Ile AMPA

30 4-Dimethylamino-piperidinocarbonyl-Phe-Gly-AHCP-Ile AMPA, m.p. 124-125°

4-Dimethylamino-piperidinocarbonyl-Phe-Gly-AHCP-Ile ADPA

4-Dimethylamino-piperidinocarbonyl-Phe- β Ala-AHCP-Ile AMPA
dihydrochloride, m.p. 261° (dec.)

4-Dimethylamino-piperidinocarbonyl-Phe- β Ala-AHCP-Ile ADPA

35 4-Ethoxycarbonyl-piperidinocarbonyl-Phe-Gly-AHCP-Ile AMPA

4-Ethoxycarbonyl-piperidinocarbonyl-Phe-Gly-AHCP-Ile ADPA

4-Ethoxycarbonyl-piperidinocarbonyl-Phe- β Ala-AHCP-Ile AMPA, m.p. 132-133°

4-Ethoxycarbonyl-piperidinocarbonyl-Phe- β Ala-AHCP-Ile ADPA

N-(Ethoxycarbonylmethyl)-carbamoyl-Phe-Gly-AHCP-Ile AMPA
N-(Ethoxycarbonylmethyl)-carbamoyl-Phe-Gly-AHCP-Ile ADPA
N-(Ethoxycarbonylmethyl)-carbamoyl-Phe- β Ala-AHCP-Ile AMPA
N-(Ethoxycarbonylmethyl)-carbamoyl-Phe- β Ala-AHCP-Ile ADPA

5

N-(4-Methoxycarbonylbutyl)-carbamoyl-Phe-Gly-AHCP-Ile AMPA
N-(4-Methoxycarbonylbutyl)-carbamoyl-Phe-Gly-AHCP-Ile ADPA
N-(4-Methoxycarbonylbutyl)-carbamoyl-Phe- β Ala-AHCP-Ile AMPA
N-(4-Methoxycarbonylbutyl)-carbamoyl-Phe- β Ala-AHCP-Ile ADPA

10

N-(6-Methoxycarbonylhexyl)-carbamoyl-Phe-Gly-AHCP-Ile AMPA
N-(6-Methoxycarbonylhexyl)-carbamoyl-Phe-Gly-AHCP-Ile ADPA
N-(6-Methoxycarbonylhexyl)-carbamoyl-Phe- β Ala-AHCP-Ile AMPA
N-(6-Methoxycarbonylhexyl)-carbamoyl-Phe- β Ala-AHCP-Ile ADPA.

15

Example 6

6-Methoxycarbonyl-hexanoyl-Phe-Gly-AHCP-Ile ADPA,
m.p. 176-177°, is obtained in analogy to Example 4 by
condensation of 6-methoxycarbonyl-hexanoyl-Phe-Gly-OH with
H-AHCP-Ile ADPA.

20

The following are obtained analogously

3-Methoxycarbonyl-propionyl-Phe-Gly-AHCP-Ile AMPA
3-Methoxycarbonyl-propionyl-Phe-Gly-AHCP-Ile ADPA
3-Methoxycarbonyl-propionyl-Phe- β Ala-AHCP-Ile AMPA
3-Methoxycarbonyl-propionyl-Phe- β Ala-AHCP-Ile ADPA

25

4-Ethoxycarbonyl-butyryl-Phe-Gly-AHCP-Ile AMPA
4-Ethoxycarbonyl-butyryl-Phe-Gly-AHCP-Ile ADPA
4-Ethoxycarbonyl-butyryl-Phe- β Ala-AHCP-Ile AMPA
4-Ethoxycarbonyl-butyryl-Phe- β Ala-AHCP-Ile ADPA

30

5-Ethoxycarbonyl-pentanoyl-Phe-Gly-AHCP-Ile AMPA
5-Ethoxycarbonyl-pentanoyl-Phe-Gly-AHCP-Ile ADPA
5-Ethoxycarbonyl-pentanoyl-Phe- β Ala-AHCP-Ile AMPA
5-Ethoxycarbonyl-pentanoyl-Phe- β Ala-AHCP-Ile ADPA

35

6-Methoxycarbonyl-hexanoyl-Phe-Gly-AHCP-Ile AMPA,
m.p. 88-89°

- 6-Methoxycarbonyl-hexanoyl-Phe-Gly-AHCP-Leu AMPA
6-Methoxycarbonyl-hexanoyl-Phe-Gly-AHCP-Leu ADPA
6-Methoxycarbonyl-hexanoyl-Phe-BAla-AHCP-Ile AMPA
6-Methoxycarbonyl-hexanoyl-Phe-BAla-AHCP-Ile ADPA
5 6-Methoxycarbonyl-hexanoyl-Phe-BAla-AHCP-Leu AMPA
6-Methoxycarbonyl-hexanoyl-Phe-BAla-Leu ADPA
- 4-CBZ-amino-butyryl-Phe-Gly-AHCP-Ile AMPA
4-CBZ-amino-butyryl-Phe-Gly-AHCP-Ile ADPA
10 4-CBZ-amino-butyryl-Phe-BAla-AHCP-Ile AMPA, m.p. 210-211°
4-CBZ-amino-butyryl-Phe-BAla-AHCP-Ile ADPA
- 5-CBZ-amino-pentanoyl-Phe-Gly-AHCP-Ile AMPA
5-CBZ-amino-pentanoyl-Phe-Gly-AHCP-Ile ADPA
15 5-CBZ-amino-pentanoyl-Phe-BAla-AHCP-Ile AMPA
5-CBZ-amino-pentanoyl-Phe-BAla-AHCP-Ile ADPA
- 6-CBZ-amino-hexanoyl-Mal-Gly-AHCP-Ile AMPA, m.p. 179-180°
6-CBZ-amino-hexanoyl-Mal-Gly-AHCP-Ile ADPA, m.p. 186-187°
20 6-CBZ-amino-hexanoyl-Mal-BAla-AHCP-Ile AMPA, m.p. 208-209°
6-CBZ-amino-hexanoyl-Mal-BAla-AHCP-Ile ADPA, m.p. 244°
(decomposition)
- 6-N'-Cyanoguanidino-hexanoyl-Phe-Gly-AHCP-Ile AMPA
25 6-N'-Cyanoguanidino-hexanoyl-Phe-Gly-AHCP-Ile ADPA
6-N'-Cyanoguanidino-hexanoyl-Phe-BAla-AHCP-Ile AMPA
6-N'-Cyanoguanidino-hexanoyl-Phe-BAla-AHCP-Ile ADPA
- 3-Benzyloxysulfonyl-propionyl-Phe-Gly-AHCP-Ile AMPA
30 3-Benzyloxysulfonyl-propionyl-Phe-Gly-AHCP-Ile ADPA
3-Benzyloxysulfonyl-propionyl-Phe-BAla-AHCP-Ile AMPA
3-Benzyloxysulfonyl-propionyl-Phe-BAla-AHCP-Ile ADPA
- 2S-Isopropyl-4S-hydroxy-5S-(BOC-amino-piperidino-
35 carbonyl-Phe-Gly-amino)-7-methyl-octanoyl-Ile AMPA
2S-Isopropyl-4S-hydroxy-5S-(BOC-amino-piperidino-
carbonyl-Phe-Gly-amino)-7-methyl-octanoyl-Ile ADPA
2S-Isopropyl-4S-hydroxy-5S-(BOC-amino-piperidino-
carbonyl-Phe-BAla-amino)-7-methyl-octanoyl-Ile AMPA, m.p. 199-200°
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2S-Isopropyl-4S-hydroxy-5S-(BOC-amino-piperidino-carbonyl-Phe- β Ala-amino)-7-methyl-octanoyl-Ile ADPA.

Example 7

- 5 8-BOC-amino-octanoyl-Phe-Gly-AHCP-Ile p-sulfamoylanilide, m.p. 154-157°, is obtained in analogy to Example 4 by condensation of 8-BOC-amino-octanoyl-Phe-Gly-AHCP-OH with H-Ile p-sulfamoylanilide.

The following are obtained analogously

10

4-BOC-amino-butyryl-Phe-Gly-AHCP-Ile p-sulfamoylanilide
4-BOC-amino-butyryl-Phe-Gly-AHCP-Leu p-sulfamoylanilide
4-BOC-amino-butyryl-Phe- β Ala-AHCP-Ile p-sulfamoylanilide
4-BOC-amino-butyryl-Phe- β Ala-AHCP-Leu p-sulfamoylanilide

15

5-BOC-amino-pentanoyl-Phe-Gly-AHCP-Ile p-sulfamoylanilide
5-BOC-amino-pentanoyl-Phe-Gly-AHCP-Leu p-sulfamoylanilide
5-BOC-amino-pentanoyl-Phe- β Ala-AHCP-Ile p-sulfamoylanilide
5-BOC-amino-pentanoyl-Phe- β Ala-AHCP-Leu p-sulfamoylanilide

20

6-BOC-amino-hexanoyl-Phe-Gly-AHCP-Ile p-sulfamoylanilide, m.p. 158-161°
6-BOC-amino-hexanoyl-Phe-Gly-AHCP-Leu p-sulfamoylanilide
6-BOC-amino-hexanoyl-Phe- β Ala-AHCP-Ile p-sulfamoylanilide

25

6-BOC-amino-hexanoyl-Phe- β Ala-AHCP-Leu p-sulfamoylanilide

7-BOC-amino-heptanoyl-Phe-Gly-AHCP-Ile p-sulfamoylanilide
7-BOC-amino-heptanoyl-Phe-Gly-AHCP-Leu p-sulfamoylanilide
7-BOC-amino-heptanoyl-Phe- β Ala-AHCP-Ile p-sulfamoylanilide

30

7-BOC-amino-heptanoyl-Phe- β Ala-AHCP-Leu p-sulfamoylanilide

8-BOC-amino-octanoyl-Phe-Gly-AHCP-Leu p-sulfamoylanilide
8-BOC-amino-octanoyl-Phe- β Ala-AHCP-Ile p-sulfamoylanilide
8-BOC-amino-octanoyl-Phe- β Ala-AHCP-Leu p-sulfamoylanilide

4-Dimethylamino-butyryl-Phe-Gly-AHCP-Abu AMPA

35

4-Dimethylamino-butyryl-Phe-Gly-AHCP-Ala AMPA

4-Dimethylamino-butyryl-Phe-Gly-AHCP-Cal AMPA
4-Dimethylamino-butyryl-Phe-Gly-AHCP-Met AMPA
4-Dimethylamino-butyryl-Phe-Gly-AHCP-Nle AMPA
4-Dimethylamino-butyryl-Phe-Gly-AHCP-Nva AMPA
5 4-Dimethylamino-butyryl-Phe-Gly-AHCP-Phe AMPA
4-Dimethylamino-butyryl-Phe-Gly-AHCP-Trp AMPA
4-Dimethylamino-butyryl-Phe-Gly-AHCP-Tyr AMPA
4-Dimethylamino-butyryl-Phe-Gly-AHCP-Val AMPA.

10 Example 8

6-BOC-amino-hexanoyl-Phe-Gly-AHCP-Ile-Ala AMPA is obtained in analogy to Example 4 from 6-BOC-amino-hexanoyl-Phe-Gly-AHCP-Ile-OH and H-Ala AMPA.

15 Example 9

6-CBZ-amino-hexanoyl-Phe-BAla-AHCP-Ile AMPA, m.p. 200-201°, is obtained in analogy to Example 4 from 6-CBZ-amino-hexanoyl-Phe-BAla-AHCP-Ile-OH and 4-amino-5-aminomethyl-2-methylpyrimidine.

20 The following are obtained analogously:

4-Methyl-piperidino-carbonyl-Phe-BAla-AHCP-Ile AMPA
4-Hydroxy-piperidino-carbonyl-Phe-BAla-AHCP-Ile AMPA,
hydrochloride, m.p. 176° (dec.)

25 4-Methylamino-piperidino-carbonyl-Phe-BAla-AHCP-Ile AMPA
4-Acetamido-piperidino-carbonyl-Phe-BAla-AHCP-Ile AMPA, m.p. 183-187°
4-POA-amino-piperidino-carbonyl-Phe-BAla-AHCP-Ile AMPA
4-(2-Hydroxyethyl)-piperazino-carbonyl-Phe-BAla-AHCP-Ile
AMPA
30 4-Carbamoyl-piperidino-carbonyl-Phe-BAla-AHCP-Ile AMPA
4-(2-Trimethylammonia-ethyl)-piperazino-carbonyl-Phe-
BAla-AHCP-Ile AMPA chloride.

Example 10

35 A solution of 1.56 g of 5-dimethylaminopentyl isocyanate in 16 ml of THF is added dropwise at 20° to a stirred solution of 6.52 g of H-Phe-Gly-AHCP-Ile AMPA in 65 ml of THF. The mixture is stirred at 20° for 3 hours, and the usual working out results in N-(5-dimethylamino-
40 pentyl)-carbamoyl-Phe-Gly-AHCP-Ile AMPA.

The following are obtained analogously with the corresponding isocyanates:

- N-(2-Dimethylaminoethyl)-carbamoyl-Phe-Gly-AHCP-Ile AMPA
5 N-(2-Dimethylaminoethyl)-carbamoyl-Phe-BAla-AHCP-Ile AMPA
N-(3-Dimethylaminopropyl)-carbamoyl-Phe-Gly-AHCP-Ile AMPA
N-(3-Dimethylaminopropyl)-carbamoyl-Phe-BAla-AHCP-Ile AMPA
N-(5-Dimethylaminopentyl)-carbamoyl-Phe-BAla-AHCP-Ile AMPA,
m.p.184-185
10 N-(5-Dimethylaminopentyl)-carbamoyl-Mal-Gly-AHCP-Ile AMPA
N-(5-Dimethylaminopentyl)-carbamoyl-Mal-BAla-AHCP-Ile AMPA
3-[N-(5-Dimethylaminopentyl)-carbamoyl-Phe]-propionyl-
AHCP-Ile AMPA
4-[N-(5-Dimethylaminopentyl)-carbamoyl-Phe]-3-thiabutyryl-
15 AHCP-Ile AMPA.
Example 11

- A solution of 1 g of 4-BOC-amino-piperidinocarbonyl-
Phe-BAla-AHCP-Ile AMPA [obtainable by reaction of BOC-
AHCP-Ile AMPA (m.p. 218-220°) with HCl/dioxane to give
20 H-AHCP-Ile AMPA and reaction with 4-BOC-amino-piperidino-
carbonyl-Phe-BAla-OH] in 20 ml of 4 N HCl in dioxane is
stirred at 20° for 30 min and then evaporated. 4-Amino-
piperidinocarbonyl-Phe-BAla-AHCP-Ile AMPA dihydrochloride,
m.p. 229° (decomposition), is obtained. 2/3 citrate, m.p.172°
25 The following are obtained analogously from the
corresponding BOC derivatives:

- H-BAla-Phe-Gly-AHCP-Ile AMPA
H-BAla-Phe-Gly-AHCP-Ile ADPA
30 H-BAla-Phe-Gly-AHCP-Leu AMPA
H-BAla-Phe-Gly-AHCP-Leu ADPA

H-BAla-Phe-BAla-AHCP-Ile AMPA
H-BAla-Phe-BAla-AHCP-Ile ADPA
35 H-BAla-Phe-BAla-AHCP-Leu AMPA
H-BAla-Phe-BAla-AHCP-Leu ADPA

4-Aminobutyryl-Phe-Gly-AHCP-Ile AMPA, dihydrochloride,
m.p. 215° (decomposition)

4-Aminobutyryl-Phe-Gly-AHCP-Ile ADPA

4-Aminobutyryl-Phe-Gly-AHCP-Leu AMPA

4-Aminobutyryl-Phe-Gly-AHCP-Leu ADPA

5 4-Aminobutyryl-Phe-BAla-AHCP-Ile AMPA, dihydrochloride,
m.p. 199° (decomposition)

4-Aminobutyryl-Phe-BAla-AHCP-Ile ADPA

4-Aminobutyryl-Phe-BAla-AHCP-Leu AMPA

4-Aminobutyryl-Phe-BAla-AHCP-Leu ADPA

10

4-Aminobutyryl-Mal-Gly-AHCP-Ile AMPA

4-Aminobutyryl-Mal-Gly-AHCP-Ile ADPA

4-Aminobutyryl-Mal-BAla-AHCP-Ile AMPA

4-Aminobutyryl-Mal-BAla-AHCP-Ile ADPA

15

5-Aminopentanoyl-Phe-Gly-AHCP-Ile AMPA

5-Aminopentanoyl-Phe-Gly-AHCP-Ile ADPA

5-Aminopentanoyl-Phe-BAla-AHCP-Ile AMPA

5-Aminopentanoyl-Phe-BAla-AHCP-Ile ADPA

20

6-Aminohexanoyl-Phe-Gly-AHCP-Ile amide

6-Aminohexanoyl-Phe-BAla-AHCP-Ile amide

6-Aminohexanoyl-Phe-Gly-AHCP-Ile AMPA, dihydrochloride,
m.p. 180° (decomposition)

25 6-Aminohexanoyl-Phe-Gly-AHCP-Ile ADPA, m.p. 193-194°;
dihydrochloride, m.p. 106-107°

6-Aminohexanoyl-Phe-Gly-AHCP-Leu AMPA

6-Aminohexanoyl-Phe-Gly-AHCP-Leu ADPA

6-Aminohexanoyl-Phe-BAla-AHCP-Ile AMPA, m.p. 203° (de-

30 composition); dihydrochloride, m.p. 206° (decomposition)

6-Aminohexanoyl-Phe-BAla-AHCP-Ile ADPA

6-Aminohexanoyl-Phe-BAla-AHCP-Leu AMPA

6-Aminohexanoyl-Phe-BAla-AHCP-Leu ADPA

35 6-Aminohexanoyl-Mal-Gly-AHCP-Ile AMPA, dihydrochloride,
m.p. 201-202°

6-Aminohexanoyl-Mal-Gly-AHCP-Ile ADPA, dihydrochloride, m.p. 197-198°

6-Aminohexanoyl-Mal-BAla-AHCP-Ile AMPA, dihydrochloride, m.p. 192-193°

6-Aminohexanoyl-Mal-BAla-AHCP-Ile ADPA

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6-Aminohexanoyl-Phe-Gly-AHCP-Ile N-3-pyridylmethanamide,
dihydrochloride, m.p. 104° (dec.)

6-Aminohexanoyl-Phe-BAla-AHCP-Ile N-3-pyridylmethanamide

6-Aminohexanoyl-Phe-Gly-AHCP-Ile N-m-aminomethyl-benzyl-
amide

6-Aminohexanoyl-Phe-BAla-AHCP-Ile N-m-aminomethyl-benzyl-
amide

6-Aminohexanoyl-Phe-Gly-AHCP-Ile N-p-dimethylaminomethyl-
benzylamide

6-Aminohexanoyl-Phe-BAla-AHCP-Ile N-p-dimethylaminomethyl-
benzylamide

6-Aminohexanoyl-Phe-Gly-AHCP-Ile N-5-tetrazolylmethanamide

6-Aminohexanoyl-Phe-BAla-AHCP-Ile N-5-tetrazolylmethanamide

6-Aminohexanoyl-Phe-Gly-AHCP-Ile N-3-dimethylaminopropyl-
amide

6-Aminohexanoyl-Phe-BAla-Ile N-3-dimethylaminopropyl-
amide

6-Aminohexanoyl-Phe-Gly-AHCP-Ile N-2-sulfo-ethylamide

6-Aminohexanoyl-Phe-BAla-AHCP-Ile N-2-sulfo-ethylamide

3-[6-Aminohexanoyl-Phe]-propionyl-AHCP-Ile AMPA

3-[6-Aminohexanoyl-Phe]-propionyl-AHCP-Ile ADPA

4-[6-Aminohexanoyl-Phe]-3-thiabutyryl-AHCP-Ile AMPA

4-[6-Aminohexanoyl-Phe]-3-thiabutyryl-AHCP-Ile ADPA

7-Aminoheptanoyl-Phe-Gly-AHCP-Ile AMPA

7-Aminoheptanoyl-Phe-Gly-AHCP-Ile ADPA

7-Aminoheptanoyl-Phe-BAla-AHCP-Ile AMPA

7-Aminoheptanoyl-Phe-BAla-AHCP-Ile ADPA

8-Aminooctanoyl-Phe-Gly-AHCP-Ile-AMPA, dihydrochloride,
m.p. 165° (dec.)

8-Aminooctanoyl-Phe-Gly-AHCP-Ile ADPA

8-Aminooctanoyl-Phe-BAla-AHCP-Ile AMPA, dihydrochloride, m.p. 165 (dec)

8-Aminooctanoyl-Phe-BAla-AHCP-Ile ADPA

4-Amino-piperidinocarbonyl-Phe-Gly-AHCP-Ile AMPA,
dihydrochloride, m.p. 160-161°

4-Amino-piperidinocarbonyl-Phe-Gly-AHCP-Ile ADPA

4-Amino-piperidinocarbonyl-Phe-Gly-AHCP-Leu AMPA

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4-Amino-piperidinocarbonyl-Phe-Gly-AHCP-Leu ADPA
4-Amino-piperidinocarbonyl-Phe- β Ala-AHCP-Ile AMPA
4-Amino-piperidinocarbonyl-Phe- β Ala-AHCP-Ile ADPA,
dihydrochloride, m.p. 159-160°
4-Amino-piperidinocarbonyl-Phe- β Ala-AHCP-Ile N-2-pyridyl-
methylamide
4-Amino-piperidinocarbonyl-Phe- β Ala-AHCP-Ile N-3-pyridyl-
methylamide, dihydrochloride, m.p. 176-177°
4-Amino-piperidinocarbonyl-Phe- β Ala-AHCP-Leu AMPA,
dihydrochloride, m.p. 280° (dec.)

4-Amino-piperidinocarbonyl-Phe- β Ala-AHCP-Leu ADPA
4-Amino-piperidinocarbonyl-Phe-Gly-AHCH-Ile AMPA
4-Amino-piperidinocarbonyl-Phe-Sta-Ile AMPA
4-Amino-piperidinocarbonyl-Phe-AHPP-Ile AMPA

2S-Isopropyl-4S-hydroxy-5S-(4-amino-piperidino-
carbonyl-Phe-Gly-amino)-7-methyl-octanoyl-Ile AMPA
2S-Isopropyl-4S-hydroxy-5S-(4-amino-piperidino-
carbonyl-Phe-Gly-amino)-7-methyl-octanoyl-Ile ADPA
2S-Isopropyl-4S-hydroxy-5S-(4-amino-piperidino-
carbonyl-Phe- β Ala-amino)-7-methyl-octanoyl-Ile AMPA,
dihydrochloride, m.p. 182-183°

2S-Isopropyl-4S-hydroxy-5S-(4-amino-piperidino-
carbonyl-Phe- β Ala-amino)-7-methyl-octanoyl-Ile ADPA

4-Amino-butyryl-Phe-Gly-AHCP-Ile p-sulfamoylanilide
4-Amino-butyryl-Phe-Gly-AHCP-Leu p-sulfamoylanilide
4-Amino-butyryl-Phe- β Ala-AHCP-Ile p-sulfamoylanilide
4-Amino-butyryl-Phe- β Ala-AHCP-Leu p-sulfamoylanilide

5-Amino-pentanoyl-Phe-Gly-AHCP-Ile p-sulfamoylanilide
5-Amino-pentanoyl-Phe-Gly-AHCP-Leu p-sulfamoylanilide
5-Amino-pentanoyl-Phe- β Ala-AHCP-Ile p-sulfamoylanilide
5-Amino-pentanoyl-Phe- β Ala-AHCP-Leu p-sulfamoylanilide

6-Amino-hexanoyl-Phe-Gly-AHCP-Ile p-sulfamoylanilide,
dihydrochloride, m.p. 98°

6-Amino-hexanoyl-Phe-Gly-AHCP-Leu p-sulfamoylanilide

6-Amino-hexanoyl-Phe- β Ala-AHCP-Ile p-sulfamoylanilide

6-Amino-hexanoyl-Phe- β Ala-AHCP-Leu p-sulfamoylanilide

7-Amino-heptanoyl-Phe-Gly-AHCP-Ile p-sulfamoylanilide
7-Amino-heptanoyl-Phe-Gly-AHCP-Leu p-sulfamoylanilide
7-Amino-heptanoyl-Phe- β Ala-AHCP-Ile p-sulfamoylanilide
7-Amino-heptanoyl-Phe- β Ala-AHCP-Leu p-sulfamoylanilide

5

8-Amino-octanoyl-Phe-Gly-AHCP-Ile p-sulfamoylanilide,
dihydrochloride, m.p. 102°

8-Amino-octanoyl-Phe-AHCP-Leu p-sulfamoylanilide

8-Amino-octanoyl-Phe- β Ala-AHCP-Ile p-sulfamoylanilide

10 8-Amino-octanoyl-Phe- β Ala-AHCP-Leu p-sulfamoylanilide.

Example 12

A mixture of 1 g of 6-methoxycarbonyl-hexanoyl-Phe-Gly-AHCP-Ile ADPA, 50 ml of dioxane and 20 ml of 2 N
15 NaOH (aqueous) is stirred at 20° for 3 hours. The usual
working up results in 6-carboxy-hexanoyl-Phe-Gly-AHCP-Ile
ADPA, m.p. 170-171°.

The following are obtained analogously by hydrolysis:

20 3-Carboxy-propionyl-Phe-Gly-AHCP-Ile AMPA
3-Carboxy-propionyl-Phe-Gly-AHCP-Ile ADPA
3-Carboxy-propionyl-Phe- β Ala-AHCP-Ile AMPA
3-Carboxy-propionyl-Phe- β Ala-AHCP-Ile ADPA

25 4-Carboxy-butyryl-Phe-Gly-AHCP-Ile AMPA
4-Carboxy-butyryl-Phe-Gly-AHCP-Ile ADPA
4-Carboxy-butyryl-Phe- β Ala-AHCP-Ile AMPA
4-Carboxy-butyryl-Phe- β Ala-AHCP-Ile ADPA

30 5-Carboxy-pentanoyl-Phe-Gly-AHCP-Ile AMPA
5-Carboxy-pentanoyl-Phe-Gly-AHCP-Ile ADPA
5-Carboxy-pentanoyl-Phe- β Ala-AHCP-Ile AMPA
5-Carboxy-pentanoyl-Phe- β Ala-AHCP-Ile ADPA

35 6-Carboxy-hexanoyl-Phe-Gly-AHCP-Ile AMPA, m.p. 185-186°
(decomposition); hydrochloride, m.p. 162° (decomposition)
6-Carboxy-hexanoyl-Phe-Gly-AHCP-Leu AMPA
6-Carboxy-hexanoyl-Phe-Gly-AHCP-Leu ADPA
6-Carboxy-hexanoyl-Phe- β Ala-AHCP-Ile AMPA

6-Carboxy-hexanoyl-Phe- β Ala-AHCP-Ile ADPA
6-Carboxy-hexanoyl-Phe- β Ala-AHCP-Leu AMPA
6-Carboxy-hexanoyl-Phe- β Ala-AHCP-Leu ADPA

5 4-Carboxy-piperidinocarbonyl-Phe-Gly-AHCP-Ile AMPA
4-Carboxy-piperidinocarbonyl-Phe-Gly-AHCP-Ile ADPA
4-Carboxy-piperidinocarbonyl-Phe- β Ala-AHCP-Ile AMPA,
hydrochloride, m.p. 212°(dec.)
4-Carboxy-piperidinocarbonyl-Phe- β Ala-AHCP-Ile ADPA

10

N-(Carboxymethyl)-carbamoyl-Phe-Gly-AHCP-Ile AMPA
N-(Carboxymethyl)-carbamoyl-Phe-Gly-AHCP-Ile ADPA
N-(Carboxymethyl)-carbamoyl-Phe- β Ala-AHCP-Ile AMPA
N-(Carboxymethyl)-carbamoyl-Phe- β Ala-AHCP-Ile ADPA

15

N-(4-Carboxybutyl)-carbamoyl-Phe-Gly-AHCP-Ile AMPA
N-(4-Carboxybutyl)-carbamoyl-Phe-Gly-AHCP-Ile ADPA
N-(4-Carboxybutyl)-carbamoyl-Phe- β Ala-AHCP-Ile AMPA
N-(4-Carboxybutyl)-carbamoyl-Phe- β Ala-AHCP-Ile ADPA

20

N-(6-Carboxyhexyl)-carbamoyl-Phe-Gly-AHCP-Ile AMPA
N-(6-Carboxyhexyl)-carbamoyl-Phe-Gly-AHCP-Ile ADPA
N-(6-Carboxyhexyl)-carbamoyl-Phe- β Ala-AHCP-Ile AMPA
N-(6-Carboxyhexyl)-carbamoyl-Phe- β Ala-AHCP-Ile ADPA.

25

Example 13

6-Amino-hexanoyl-Phe- β Ala-AHCP-Ile AMPA, m.p.
203° (decomposition), is obtained in analogy to Example
2 from 6-CBZ-amino-hexanoyl-Phe- β Ala-AHCP-Ile AMPA by
30 hydrogenolysis.

The following are obtained analogously by hydro-
genolysis of the corresponding CBZ derivatives:

35

2-Amino-2-methyl-propionyl-Phe-Gly-AHCP-Ile AMPA
2-Amino-2-methyl-propionyl-Phe-Gly-AHCP-Ile ADPA
2-Amino-2-methyl-propionyl-Phe- β Ala-AHCP-Ile AMPA,
dihydrochloride, m.p. 212°
2-Amino-2-methyl-propionyl-Phe- β Ala-AHCP-Ile ADPA
2-Amino-2-methyl-propionyl-Mal-Gly-AHCP-Ile AMPA
40 dihydrochloride, m.p. 118° (dec.)

2-Amino-2-methyl-propionyl-Mal-Gly-AHCP-Ile ADPA
2-Amino-2-methyl-propionyl-Mal- β Ala-AHCP-Ile AMPA

2-Amino-2-methyl-propionyl-Mal-BAla-AHCP-Ile ADPA.

Example 14

3-Sulpho-propionyl-Phe-Gly-AHCP-Ile AMPA is obtained in analogy to Example 2 from 3-benzyloxysulfonyl-propionyl-Phe-Gly-AHCP-Ile AMPA by hydrogenolysis.

The following are obtained analogously by hydrogenolysis of the corresponding benzyl esters:

- 10 3-Sulfo-propionyl-Phe-Gly-AHCP-Ile ADPA
- 3-Sulfo-propionyl-Phe-BAla-AHCP-Ile AMPA
- 3-Sulfo-propionyl-Phe-BAla-AHCP-Ile ADPA.

Example 15

- 15 a) 3-Oxo-4S-(4-dimethylaminobutyryl-Phe-Gly-amino)-5-cyclohexyl-pentanoyl-Ile AMPA is obtained in analogy to Example 4 from 4-dimethylaminobutyryl-Phe-Gly-OH and 3-oxo-4S-amino-5-cyclohexyl-pentanoyl-Ile AMPA.
- 20 b) A solution of 1 g of the abovementioned keto amide in 25 ml of CH₃OH is hydrogenated on 0.1 g of 10 % Pd-C at 20° and under 1 bar until H₂ uptake ceases. Filtration and evaporation result in a mixture of 3R- and 3S-hydroxy-4S-(4-dimethylaminobutyryl-Phe-Gly-amino)-5-cyclohexyl-pentanoyl-Ile AMPA.
- 25

Example 16

- 70 mg of hydroxylamine hydrochloride are added to
- 30 a solution of 763 mg of 3-oxo-4S-(4-dimethylaminobutyryl-Phe-Gly-amino)-5-cyclohexylpentanoyl-Ile AMPA and 1.43 g of Na₂CO₃·10 H₂O in 5 ml of methanol and 5 ml of water, and the mixture is stirred at 20° for 14 hours. The precipitated oxime is filtered off, dried, dissolved in
- 35 10 ml of methanol and hydrogenated on 0.5 g of Raney Ni at 20° and under 5 bar. The catalyst is filtered off, the filtrate is evaporated, the resulting mixture is separated on silica gel, and 3S-amino-4S-(4-dimethylaminobutyryl-Phe-Gly-amino)-5-cyclohexylpentanoyl-Ile AMPA

("4-dimethylaminobutyryl-Phe-Gly-DACP-Ile AMPA") is obtained; the 3R-amino epimer is also obtained.

Example 17

Analogously to Example 4, the following are obtained:

1-Methyl-4-piperidinyI-carbonyl-Phe- β Ala-AHCP-Ile-AMPA,
m.p. 187-189°

4-BOC-amino-piperidinocarbonyl-Phe- β Ala-Sta-Ile-AMPA,
m.p. 151-152°

6-BOC-amino-hexanoyl-N-Me-Mal-Gly-AHCP-Ile-AMPA,
m.p. 100° (dec.)

4-BOC-amino-piperidino-carbonyl-Phe- β Ala-AHCP-Gly-AMPA,
m.p. 181° (dec.)

3-(1-Methyl-2-piperidyl)-propionyl-Phe- β Ala-AHCP-Ile-AMPA,
m.p. 202°

3-(1-Methyl-2-piperidyl)-propionyl-Phe-Gly-AHCP-Ile-AMPA, oil

4-(1-Methyl-2-piperidyl)-butyryl-Phe-Gly-AHCP-Ile-AMPA,
diacetate, oil

4-(1-Methyl-2-piperidyl)-butyryl-Phe- β Ala-AHCP-Ile-AMPA,
diacetate, m.p. 206°

4-BOC-amino-piperidinocarbonyl-Phe- β Ala-AHCP-Ala-AMPA,
m.p. 181-182°

Pyrrolidinocarbonyl-Phe- β Ala-AHCP-Ile-AMPA, hydrochloride,
m.p. 136-137°

Morpholinocarbonyl-Phe- β Ala-AHCP-Ile-AMPA, hydrochloride,
m.p. 157-158°

4-BOC-amino-piperidinocarbonyl-Mal-Gly-AHCP-Ile-AMPA,
m.p. 193-194°

Piperidinocarbonyl-Phe- β Ala-AHCP-Ile-AMPA, hydrochloride,
m.p. 140-141°

4-BOC-amino-piperidinoacetyl-Phe-Gly-AHCP-Ile-AMPA, m.p. 135°

4-BOC-amino-piperidinocarbonyl-Phe- β Ala-AHCP-Nle-AMPA,
m.p. 145-146°

3-BOC-amino-3-methyl-butyl-Phe-Gly-AHCP-Ile-AMPA, m.p. 102°
(dec.)

- 4-BOC-amino-piperidinocarbonyl-Leu- β Ala-AHCP-Ile-AMPA,
m.p. 183° (dec.)
- 3-BOC-amino-3-methyl-butyryl-Phe-Gly-AHCP-Ile-(N-3-pyridyl-
methyl-amide), m.p. 90° (dec.)
- 5 4-Methylsulfonamido-piperidinocarbonyl-Phe- β Ala-AHCP-Ile-
AMPA, hydrochloride, m.p. 159-160°
- 4-(3-Hydroxypropyl)-piperazinocarbonyl-Phe- β Ala-AHCP-Ile-
AMPA, dihydrochloride, m.p. 182° (dec.)
- 4-BOC-piperazinocarbonyl-Phe- β Ala-AHCP-Ile-AMPA, m.p. 140-141°
- 10 Benzyl 4-BOC-amino-piperidinocarbonyl-Phe- β Ala-AHCP-Ile-amino-
acetate
- Benzyl 3-(4-BOC-amino-piperidinocarbonyl-Phe- β Ala-AHCP-Ile-
amino)-propionate
- Benzyl 4-(4-BOC-amino-piperidinocarbonyl-Phe- β Ala-AHCP-Ile-
amino)-butyrate
- 15 Benzyl 5-(4-BOC-amino-piperidinocarbonyl-Phe- β Ala-AHCP-Ile-
amino)-pentanoate, m.p. 102-103°
- Benzyl 6-(4-BOC-amino-piperidinocarbonyl-Phe- β Ala-AHCP-Ile-
amino)-hexanoate, m.p. 110-111°
- 20 4-Formamido-piperidinocarbonyl-Phe- β Ala-AHCP-Ile-AMPA
- 4-Trifluoroacetamido-piperidinocarbonyl-Phe- β Ala-AHCP-Ile-
AMPA
- 4-BOC-amino-piperidinocarbonyl-Phe- β Ala-AHCP-D-Ile-AMPA,
m.p. 164-165°
- 25 4-BOC-amino-piperidinocarbonyl-Mal- β Ala-AHCP-Ile-AMPA,
m.p. 183-184°
- 3-(4-BOC-amino-piperidinocarbonyl-Phe-amino)-3-methyl-
butyryl-AHCP-Ile-AMPA, m.p. 136-137°
- 4-BOC-amino-piperidinocarbonyl-D-Phe- β Ala-AHCP-Ile-AMPA,
m.p. 140-142°
- 30 4-BOC-amino-piperidinocarbonyl-Phe- β Ala-AHCP-OMe, m.p. 72-74°
- 4-BOC-amino-piperidinocarbonyl-Phe- β Ala-AHCP-Ile-OMe,
m.p. 114-115°

4-BOC-amino-piperidinoacetyl-Phe- β Ala-AHCP-Ile-AMPA,
m.p. 78-81°

4-Cyano-piperidinocarbonyl-Phe- β Ala-AHCP-Ile-AMPA

4-Dimethylaminomethyl-piperidinocarbonyl-Phe- β Ala-AHCP-
5 Ile-AMPA

4-BOC-aminomethyl-piperidinocarbonyl-Phe- β Ala-AHCP-Ile-AMPA

3-(2-Piperidyl)-propionyl-Phe- β Ala-AHCP-Ile-AMPA, tris-
(trifluoroacetate), oil

3-(2-Piperidyl)-propionyl-Phe-Gly-AHCP-Ile-AMPA, tri-
10 acetate, oil

4-(2-Piperidyl)-butyryl-Phe- β Ala-AHCP-Ile-AMPA, tri-
acetate, m.p. 110°

4-(2-Piperidyl)-butyryl-Phe-Gly-AHCP-Ile-AMPA, tri-
acetate, oil.

15 Example 18

Analogously to Example 11, the following are obtained from
the corresponding BOC derivatives:

4-Amino-piperidinocarbonyl-Phe- β Ala-Sta-Ile-AMPA, dihydro-
chloride, m.p. 196° (dec.)

20 4-Amino-Piperidinocarbonyl-Phe- β Ala-AHCP-Gly-AMPA, dihydro-
chloride, m.p. 266° (dec.)

4-Amino-piperidinocarbonyl-Phe- β Ala-AHCP-Ala-AMPA, dihydro-
chloride, m.p. 126-127°

4-Amino-piperidinocarbonyl-Mal-Gly-AHCP-Ile-AMPA, dihydro-
25 chloride, m.p. 192° (dec.)

4-Amino-piperidinoacetyl-Phe-Gly-AHCP-Ile-AMPA, trihydro-
chloride, m.p. 174°

3-Amino-3-methyl-butyl-Phe-Gly-AHCP-Ile-AMPA, dihydro-
chloride, m.p. 230°

30 4-Amino-piperidinocarbonyl-Leu- β Ala-AHCP-Ile-AMPA, dihydro-
chloride, m.p. 269° (dec.)

3-Amino-3-methyl-butyl-Phe-Gly-AHCP-Ile-(N-3-pyridyl-
methyl-amide), dihydrochloride, m.p. 100° (dec.)

4-Amino-piperidinocarbonyl-Phe- β -Ala-AHCP-D-Ile-AMPA,
dihydrochloride, m.p. 122° (dec.)
4-Amino-piperidinocarbonyl-Mal- β -Ala-AHCP-Ile-AMPA,
dihydrochloride, m.p. 116° (dec.)
3-(4-Amino-piperidinocarbonyl-Phe-amino)-3-methyl-butyryl-
AHCP-Ile-AMPA, dihydrochloride, m.p. 138°
4-Amino-piperidinocarbonyl-D-Phe- β -Ala-AHCP-Ile-AMPA,
dihydrochloride, m.p. 178° (dec.)
4-Amino-piperidinocarbonyl-Phe- β -Ala-AHCP-OH, hydrochloride,
m.p. 102-105°
4-Amino-piperidinocarbonyl-Phe- β -Ala-AHCP-Ile-OH, hydro-
chloride, m.p. 119-120°

Piperazinocarbonyl-Phe- β -Ala-AHCP-Ile-AMPA, dihydrochloride,
m.p. 183° (dec.)
4-Aminopiperidinoacetyl-Phe- β -Ala-AHCP-Ile-AMPA, trihydro-
chloride, m.p. 208-209°
4-Amino-piperidinocarbonyl-Phe- β -Ala-AHCP-Ile-amino-acetic
acid
3-(4-Amino-piperidinocarbonyl-Phe- β -Ala-AHCP-Ile-amino)-
propionic acid
4-(4-Amino-piperidinocarbonyl-Phe- β -Ala-AHCP-Ile-amino)-
butyric acid
5-(4-Amino-piperidinocarbonyl-Phe- β -Ala-AHCP-Ile-amino)-
pentanoic acid, hydrochloride, m.p. 146-148°
6-(4-Amino-piperidinocarbonyl-Phe- β -Ala-AHCP-Ile-amino)-
hexanoic acid, hydrochloride, m.p. 159-160°
4-Aminomethyl-piperidinocarbonyl-Phe- β -Ala-AHCP-Ile-AMPA.

Example 19

Analogously to Example 2, the following are obtained by
hydrogenolysis of the corresponding benzyl esters:

4-BOC-amino-piperidinocarbonyl-Phe- β -Ala-AHCP-Ile-amino-
acetic acid



3-(4-BOC-amino-piperidinocarbonyl-Phe- β Ala-AHCP-Ile-amino)-propionic acid

4-(4-BOC-amino-piperidinocarbonyl-Phe- β Ala-AHCP-Ile-amino)-butyric acid

5-(4-BOC-amino-piperidinocarbonyl-Phe- β Ala-AHCP-Ile-amino)-pentanoic acid, m.p. 157°

6-(4-BOC-amino-piperidinocarbonyl-Phe- β Ala-AHCP-Ile-amino)-hexanoic acid, m.p. 167-168°.

Example 20

Analogously to Example 12, the following are obtained by saponification of the corresponding methyl esters:

4-BOC-amino-piperidinocarbonyl-Phe- β Ala-AHCP-OH,
m.p. 112-113°

4-BOC-amino-piperidinocarbonyl-Phe- β Ala-AHCP-Ile-OH,
m.p. 93-95°.

Example 21

A mixture of 792 mg of 4-amino-piperidinocarbonyl-Phe- β Ala-AHCP-Ile-AMPA, 90 mg of 5-methylisothiourea, 5 ml of ethanol and 5 of water is stirred for 2 hours at 50°C. After working up as usual, 4-guanidinyl-piperidinocarbonyl-Phe- β Ala-AHCP-Ile-AMPA is obtained, m.p. 183°.

Example 22

A mixture of 792 mg of 4-amino-piperidinocarbonyl-Phe- β Ala-AHCP-Ile-AMPA, 115 mg (= 0.132 ml) of trimethylsilyl-isocyanate and 10 ml of THF is stirred for 16 hours at 20 °C. Thereafter, the mixture is stirred into water and worked up as usual, yielding 4-ureido-piperidinocarbonyl-Phe- β Ala-AHCP-Ile-AMPA, hydrochloride, m.p. 126-128° (dec.).

The following are obtained with the corresponding alkyl isocyanates:

- 4-(N'-Ethylureido)-piperidinocarbonyl-Phe- β Ala-AHCP-Ile-AMPA, hydrochloride, m.p. 170-171°,
- 5 4-(N'-Isopropylureido)-piperidinocarbonyl-Phe- β Ala-AHCP-Ile-AMPA, hydrochloride, m.p. 187° (dec.).

The examples which follow relate to pharmaceutical compositions.

Example A: Tablets

A mixture of 1 kg of 4-aminopiperidinocarbonyl-Phe-BAla-AHCP-Ile AMPA dihydrochloride, 4 kg of lactose, 1.2 kg of maize starch, 200 g of talc and 100 g of magnesium stearate is compressed in a customary manner to give tablets in such a way that each tablet contains 100 mg of active compound.

Example B: Coated tablets

Tablets are compressed in analogy to Example A and are then coated in a customary manner with a coating composed of sucrose, maize starch, talc, tragacanth and colourant.

Example C: Capsules

500 g of 6-aminohexanoyl-Phe-Gly-AHCP-Ile AMPA dihydrochloride are dispensed in a customary manner into hard gelatin capsules so that each capsule contains 500 mg of active compound.

Example D: Injection ampoules

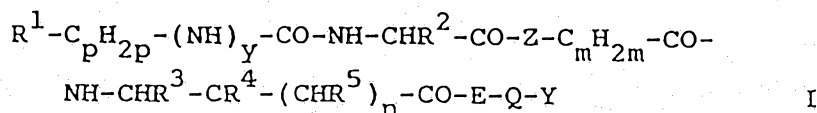
A solution of 100 g of the Na salt of 6-carboxy-hexanoyl-Phe-Gly-AHCP-Ile ADPA in 4 l of double-distilled water is adjusted to pH 6.5 with 2 N hydrochloric acid, filtered sterile and dispensed into injection ampoules. These are lyophilized under sterile conditions and sealed sterile. Each injection ampoule contains 50 mg of active compound.

Example E. Suppositories

A mixture of 50 g of 4-dimethylaminobutyl-Phe-Gly-AHCP-Ile AMPA dihydrochloride with 10 g of soya lecithin and 140 g of cocoa butter is melted, poured into moulds and left to cool. Each suppository contains 250 mg of active compound.

The Claims defining the invention are as follows:

1. Amino acid derivatives of the formula I



in which

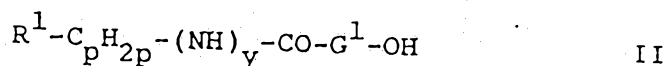
- R^1 is R^6R^7N- , $R^6-NH-C(=NH)-NH-$, $NC-NH-C(=NH)-NH-$, R^6OOC- , R^6O_3S- or $R^6-O-(CH_2CH_2O)_r-$,
 Z is $-O-$, $-CH_2-$, $-CH=CH-$, $-C\equiv C-$, $-NR^8-$, $-CH_2-O-$, $-CH_2-NR^8-$ or $-CH_2-S-$,
 E is 0 to 2 amino acid residues which are linked together in the manner of a peptide and are selected from the group comprising Abu, Ala, Cal, Gly, His, Ile, Leu, Met, Nle, Nva, Phe, Trp, Tyr and Val,
 Q is 0 or NR^{10} ,
 Y is $-C_tH_{2t}-R^{11}$, $-C_tH_{2t}-R^{12}$ or $-C_wH_{2w}-(CR^{13})_s-C_tH_{2t}-R^{11}$,
 R^2 , R^3 and R^{11} are each H, A, Ar, Ar-alkyl, Het, Het-alkyl, unsubstituted or singly or multiply, by A, AO and/or Hal, substituted cycloalkyl having 3-7 C atoms, cycloalkylalkyl having 4-11 C atoms, bicycloalkyl or tricycloalkyl each having 7-14 C atoms, bicycloalkylalkyl or tricycloalkylalkyl each having 8-18 C atoms,
 R^4 and R^{13} are each (H, OH), (H, NH₂) or = O,
 R^5 , R^8 and R^{10} are each H or A,
 R^6 and R^7 are each H, A or Ar-alkyl,
 R^7 is also $R^9-O-C_xH_{2x}-CO-$, $R^9-C_xH_{2x}-O-CO-$ or Ac,
 R^9 is A or Ar-alkyl,
 R^6R^7N is also a piperidinyl, morpholinyl, piperazinyl or pyrrolidinyl group which is unsubstituted or substituted by A, OH, NH₂, NHA, NA₂, NHAc, $NH-CO-C_xH_{2x}-O-R^9$, $NH-CO-O-C_xH_{2x}-R^9$, $NH-SO_2-A$,



hydroxyalkyl, COOH, COOA, CONH₂, CN, aminoalkyl, HAN-alkyl, A₂N-alkyl, A₃N[⊕]alkyl An[⊖], NH-CO-NH₂, NH-CO-NHA, NH-CO-NA₂, guanidinyl or guanidinyl-alkyl, is -SO₃H, -SO₂NH₂, -SO₂NHA, -SO₂NA₂, -NH₂, -NHA, -NA₂, -NH-C(=NH)-NH₂, -NH-C(=NH)-NHCN, -NH-CO-NH₂, -NH-CO-NHA, -NH-CO-NA₂, -NH-CS-NH₂, -NH-CS-NHA, -NH-CS-NA₂, -COOH, -COOA, -COO-alkyl-Ar, -CONH₂, -CONHA or -CONA₂,
 R¹² is 0 or 1,
 n and s are each 1 or 2,
 m, p, t,
 w and x are each 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10,
 r is 1, 2 or 3,
 Ar is phenyl which is unsubstituted or singly or multiply substituted by A, OA, Hal, CF₃, OH, NO₂, hydroxyalkyl, NH₂, NHA, NA₂, NHAc, SA, SO-A, SO₂-A, SO₂NH₂, SO₂NHA, COOH, COOA, CONH₂, CN, aminoalkyl, HAN-alkyl, A₂N-alkyl, A₃N[⊕]alkyl An[⊖] and/or guanidinyl-alkyl, or is unsubstituted naphthyl,
 Het is a saturated or unsaturated 5- or 6-membered heterocyclic radical which has 1-4 N, O and/or S atoms and can be fused with a benzene ring and/or can be singly or multiply substituted by A, OA, Hal, CF₃, OH, NO₂, carbonyl oxygen, NH₂, NHA, NA₂, NHAc, SA, SO-A, SO₂-A, SO₂NH₂, SO₂NHA, COOH, COOA, CONH₂, CN, NH-SO₂-A, Ar, Ar-alkyl, Ar-alkenyl, hydroxyalkyl and/or aminoalkyl, and/or whose N and/or S hetero atoms can also be oxidized,
 Hal is F, Cl, Br or I,
 Ac is H-CO-, A-CO-, CF₃-CO-, Ar-CO-, Ar-alkyl-CO- or A-NH-CO-,
 An[⊖] is an anion, which can also be absent if, in its stead, a carboxyl group contained in the compound of the formula I is in the form of a carboxylate anion,
 -alkyl- is an alkylene group having 1-8 C atoms, and
 A is alkyl having 1-8 C atoms,
 in which, furthermore, it is also possible for one or more -NH-CO- groups to be replaced by one or more -NA-CO- groups, as well as the salts thereof.

2. a) 6-(BOC-amino)-hexanoyl-Phe-Gly-AHCP-Ile AMPA;
- b) 6-Amino-hexanoyl-Phe-Gly-AHCP-Ile ADPA;
- c) 4-Dimethylamino-butyryl-Phe-Gly-AHCP-Ile AMPA;
- d) 4-Aminopiperidinocarbonyl-Phe-Gly-AHCP-Ile AMPA;
- e) 6-Methoxycarbonyl-hexanoyl-Phe-Gly-AHCP-Ile ADPA;
- f) 6-Carboxy-hexanoyl-Phe-Gly-AHCP-Ile ADPA;
- g) 4-Aminopiperidinocarbonyl-Phe-βAla-AHCP-Ile AMPA.

3. Process for the preparation of an amino acid derivative of the formula I, and of the salts thereof, characterized in that it is liberated from one of its functional derivatives by treatment with a solvolyzing or hydrogenolyzing agent, or in that a carboxylic acid of the formula II



in which G^1 is (a) absent,

- (b) $-NH-CHR^2-CO-$,
- (c) $-NH-CHR^2-CO-Z-C_mH_{2m}-CO-$,
- (d) $-NH-CHR^2-CO-Z-C_mH_{2m}-CO-W-$,
- (e) $-NH-CHR^2-CO-Z-C_mH_{2m}-CO-W-E^1-$,
- (f) $-NH-CHR^2-CO-Z-C_mH_{2m}-CO-W-E-$ and
W is $-NH-CHR^3-CR^4-(CHR^5)_n-CO-$

or one of the reactive derivatives thereof, is reacted with an amino compound of the formula III



- in which G^2 is (a) $-NH-CHR^2-CO-Z-C_mH_{2m}-CO-W-E-Q-Y$,
- (b) $-Z-C_mH_{2m}-CO-W-E-Q-Y$,
 - (c) $-W-E-Q-Y$,
 - (d) $-E-Q-Y$,
 - (e) $-E^2-Q-Y$,
 - (f) $-NR^{10}-Y$ and

$E^1 + E^2$ are together E,

and in that a functionally modified amino and/or hydroxyl group in a compound of the formula I is liberated where appropriate by treatment with solvolyzing or hydrogenolyzing agents, and/or for the preparation of a compound of the formula I, $R^4 = (H, OH)$ or (H, NH_2) , an amino keto
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acid derivative of the formula I, $R^4 = O$, is reduced or reductively aminated, and/or one radical R^1 is converted to another radical R^1 and/or a compound of the formula I is converted by treatment with an acid into one of the salts thereof.

4. Process for the preparation of pharmaceutical compositions, characterized in that a compound of the formula I and/or one of the physiologically acceptable salts thereof is converted together with at least one solid, liquid or semi-liquid vehicle or auxiliary and, where appropriate, in combination with one or more other active compound(s) into a suitable dosage form.

5. Pharmaceutical composition characterized by containing at least one compound of the formula I and/or one of the physiologically acceptable salts thereof.

6. Use of compounds of the formula I or of physiologically acceptable salts thereof for the preparation of a medicament.

7. Use of compounds of the formula I or of physiologically acceptable salts thereof for controlling renin-dependent hypertension or hyperaldosteronism.

8. Amino acid derivatives of the formula I substantially as herein described with reference to anyone of the examples.

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By Its Patent Attorneys

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