COMMONWEALTH OF AUSTRALIA

Patents Act 1952-1969

CONVENTION APPLICATION FOR A PATENT

(1) Here insert (in full) Name or Names of Applicant or Applicants, followed by Address (es),

xxI/We (1) HOECHST AKTIENGESELLSCHAFT

of 50 Bruningstrasse, D-6230 Frankfurt/Main 80,

Federal Republic of Germany

(2) Here insert Title of Invention.

hereby apply for the grant of a Patent for an invention entitled: (2)

RENIN-INHIBITING UREA DERIVATIVES OF DIPEPTIDES, A PROCESS FOR THE PREPARATION THEREOF, AGENTS CONTAINING THESE, AND THE USE THEREOF

(3) Here insert number(s) of basic application(s)

which is described in the accompanying complete specification. This application is a Convention application and is based on the application numbered (3)

P38 39 126.0

(4) Here insert Name of basic Country or Countries, and basic date or dates

for a patent or similar protection made in (4) Federal Republic of Germany on 19th November 1988

xMy/Our address for service is ~~Messrs Edwd. Waters & Sons, Patent Attorneys,~~ Watermark Patent & Trademark Attorneys

50 Queen Street, Melbourne, Victoria, Australia.

DATED this 16th day of November 1989

(5) Signature (s) of Applicant (s) or Seal of Company and Signatures of its Officers as prescribed by its Articles of Association.

(5) HOECHST AKTIENGESELLSCHAFT

by

Ian A. Scott

Registered Patent Attorney

S011467 17/11/89

To:

THE COMMISSIONER OF PATENTS.

Edwd. Waters & Sons, Melbourne.

Form 7 89/F220

COMMONWEALTH OF AUSTRALIA

Patents Act 1952

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION UNDER PART XVI. FOR A PATENT.

In support of the Convention application made under Part XVI. of the Patents Act 1952 by HOECHST AKTIENGESELLSCHAFT of 50, Brüningstrasse, D-6230 Frankfurt/Main 80, Federal Republic of Germany for a patent for an invention entitled:

Renin-inhibiting urea derivatives of dipeptides, a process for the preparation thereof, agents containing these, and the use thereof

We, Johann-Heinrich Reuter, Bodenheimer Straße 4, D-6500 Mainz, Franz Lapice, Sandweg 2, D-6233 Kelkheim (Taunus) Federal Republic of Germany do solemnly and sincerely declare as follows:

1. We are authorized by HOECHST AKTIENGESELLSCHAFT the applicant for the patent to make this declaration on its behalf.

2. The basic application as defined by Section 141 of the Act was made in the Federal Republic of Germany under No. P 38 39 126.0 on November 19, 1988 by HOECHST AKTIENGESELLSCHAFT

3. a) Wolfgang Rüger, Parkstraße 10, D-6233 Kelkheim (Taunus)
b) Hansjörg Urbach, Le Lavandoustraße 41, D-6242 Kronberg/Taunus
c) Dieter Ruppert, Schreyerstraße 30, D-6242 Kronberg/Taunus
d) Bernward Schölkens, Hölderlinstraße 62, D-6233 Kelkheim (Taunus)
a) - d) Federal Republic of Germany

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

The said HOECHST AKTIENGESELLSCHAFT is the assignee of the said Wolfgang Rüger, Hansjörg Urbach, Dieter Ruppert, Bernward Schölkens

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

DECLARED at Frankfurt/Main, Federal Republic of Germany this 6th day of October, 1989

To the Commissioner of Patents

HOECHST AKTIENGESELLSCHAFT

ppa. Reuter i.V. Lapice

Prokurist Authorized Signatory

PAT 510

(12) PATENT ABRIDGMENT (11) Document No. AU-B-44798/89
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 616071

(54) Title
RENIN-INHIBITING UREA DERIVATIVES OF DIPEPTIDES, A PROCESS FOR THE PREPARATION THEREOF, AGENTS CONTAINING THESE, AND THE USE THEREOF

International Patent Classification(s)
(51)[5] C07K 005/06 A61K 031/44 A61K 037/64 C07K 005/08

(21) Application No. : 44798/89 (22) Application Date : 17.11.89

(30) Priority Data

(31) Number (32) Date (33) Country
3839126 19.11.88 DE FEDERAL REPUBLIC OF GERMANY

(43) Publication Date : 09.08.90

(44) Publication Date of Accepted Application : 17.10.91

(71) Applicant(s)
HOECHST AKTIENGESELLSCHAFT

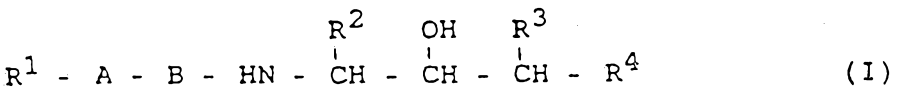
(72) Inventor(s)
WOLFGANG RUGER; HANSJORG URBACH; DIETER RUPPERT; BERNWARD SCHOLKENS

(74) Attorney or Agent
WATERMARK PATENT & TRADEMARK ATTORNEYS , Locked Bag 5, HAWTHORN VIC 3122

(56) Prior Art Documents
EP 231919
EP 283970
EP 372537

(57) Claim

1. A compound of the formula I



$$R^1 - A - B - HN - \underset{\displaystyle R^2}{CH} - \underset{\displaystyle OH}{CH} - \underset{\displaystyle R^3}{CH} - R^4 \qquad (I)$$

in which

R^1 denotes a radical of the formula II

$$R^a - NH - CO - \qquad (II)$$

in which

R^a denotes hydrogen, (C_1-C_{10})-alkyl which is optionally singly or doubly unsaturated and which is optionally substituted by up to 3 identical or different radicals from the series comprising hydroxyl, (C_1-C_7)-alkoxy, (C_1-C_7)-alkanoyloxy, carboxyl, (C_1-C_7)-alkoxycarbonyl, Cl, Br, amino, (C_1-C_7)-alkylamino, di-$(C_1-$

.../2

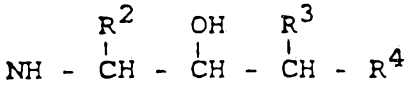
C_7)-alkylamino, (C_1-C_5)-alkoxycarbonylamino, (C_7-C_{15})-aralkoxycarbonylamino and 9-fluorenylmethyloxycarbonylamino, or (C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl, (C_6-C_{14})-aryl which is optionally substituted by one or two identical or different radicals from the series comprising F, Cl, Br, I, hydroxyl, (C_1-C_7)-alkoxy, (C_1-C_7)-alkyl, (C_1-C_7)-alkoxycarbonyl, amino, anilino which is optionally substituted by up to 2 halogen, and trifluoromethyl; (C_6-C_{14})-aryl-(C_1-C_6)-alkyl in which the aryl moiety is optionally substituted by one or two identical or different radicals from the series comprising F, Cl, Br, I, hydroxyl, (C_1-C_7)-alkoxy, (C_1-C_7)-alkyl, (C_1-C_7)-alkoxycarbonyl, amino, (C_1-C_7)-alkylamino, di-(C_1-C_7)-alkylamino, carboxyl, carboxymethoxy, amino-(C_1-C_7)-alkyl, (C_1-C_7)-alkylamino-(C_1-C_7)-alkyl, di-(C_1-C_7)-alkylamino-(C_1-C_7)-alkyl, (C_1-C_7)-alkoxycarbonylmethoxy, carbamoyl, sulfamoyl, (C_1-C_7)-alkoxysulfonyl, sulfo- and guanidinomethyl, or represents the radical of a 5- or 6-membered monocyclic or 9- or 10-membered bicyclic heteraromatic which has at least one carbon atom, 1-4 nitrogen atoms and/or 1 sulfur or oxygen atom also as ring members and is optionally substituted by one, two or three identical or different radicals from the series comprising F, Cl, Br, hydroxyl, (C_1-C_7)-alkoxy, (C_1-C_7)-alkyl, (C_1-C_7)-alkoxycarbonyl, amino or trifluoromethyl,

A denotes a radical, which is linked N-terminal with R^1 and C-terminal with B, of an amino acid from the series comprising phenylalanine, histidine, tyrosine, tryptophan, methionine, leucine, isoleucine, asparagine, aspartic acid, β-2-thienylalanine, β-3-thienylalanine, β-2-furylalanine, β-3-furylalanine, lysine, ornithine, valine, alanine, 2,4-diaminobutyric acid, arginine, 4-chlorophenylalanine, methionine sulfone, methionine sulfoxide, 2-pyridylalanine, 3-pyridylalanine, cyclohexyl-

.../3

alanine, cyclohexylglycine, im-methylhistidine, O-methyltyrosine, O-benzyltyrosine, O-tert.-butyltyrosine, phenylglycine, 1-naphthylalanine, 2-naphthylalanine, 4-nitrophenylalanine, norvaline, β-2-benzo[b]thienylalanine, β-3-benzo[b]thienylalanine, 2-fluorophenylalanine, 3-fluorophenylalanine, 4-fluorophenylalanine, norleucine, cysteine, S-methyl-cysteine, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, homophenylalanine, DOPA, O-dimethyl-DOPA, 2-amino-4-(2-thienyl)-butyric acid, benzodioxol-5-ylalanine, N-methylhistidine, 2-amino-4-(3-thienyl)butyric acid, 3-(2-thienyl)-serine, (Z)-dehydrophenylalanine, and (E)-dehydrophenylalanine,

B denotes a radical, which is linked N-terminal with A and C-terminal with

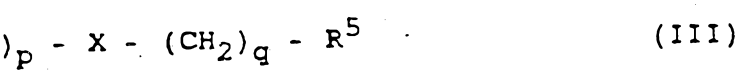


of an amino acid which is defined as under A,

R^2 denotes hydrogen, (C_1-C_{10})-alkyl, (C_4-C_7)-cycloalkyl, (C_4-C_7)-cycloalkyl-(C_1-C_4)-alkyl, (C_6-C_{14})-aryl or (C_6-C_{14})-aryl-(C_1-C_4)-alkyl, and

R^3 denotes hydrogen, (C_1-C_{10})-alkyl, (C_6-C_{14})-aryl or (C_6-C_{14})-aryl-(C_1-C_4)-alkyl,

R^4 denotes a radical of the formula III



(III)

in which, as desired, X can be absent or represents -O-, -S-, $-CF_2-$, -CO- or $-CHR^6-$,

p and q denote, independently of one another, 0, 1, 2, 3 or 4,

R^6 denotes hydrogen, (C_1-C_7)-alkyl, (C_1-C_5)-alkoxy (C_1-C_5)-alkylthio, (C_1-C_5)-alkylamino, -OH, $-N_3$,

.../4

-F, -Cl, -Br or -I, and

R^5 denotes hydrogen, -OH, $-NH_2$ or heteroaryl which can also be partially or completely hydrogenated, as well as the physiologically tolerated salts thereof.

616071

Form 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952-69

COMPLETE SPECIFICATION

(ORIGINAL)

Class Int. Class

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority :

Related Art :

Name of Applicant : HOECHST AKTIENGESELLSCHAFT

Address of Applicant : 50 Bruningstrasse, D-6230 Frankfurt/Main 80, Federal Republic of Germany

Actual Inventor: WOLFGANG RUGER, HANSJORG URBACH, DIETER RUPPERT and BERNWARD SCHOLKENS

Address for Service : Watermark Patent & Trademark Attorneys
50 QUEEN STREET, MELBOURNE, AUSTRALIA, 3000.

Complete Specification for the invention entitled:

RENIN-INHIBITING UREA DERIVATIVES OF DIPEPTIDES, A PROCESS FOR THE PREPARATION THEREOF, AGENTS CONTAINING THESE, AND THE USE THEREOF

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

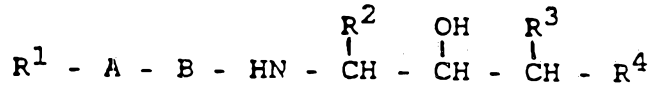
Description

Renin-inhibiting urea derivatives of dipeptides, a process for the preparation thereof, agents containing these, and the use thereof

EP-A 172,346, EP-A 172,347, EP-A 189,203, EP-A 229,667, EP-A 230,266, EP-A 255,082, EP-A 273,893 and EP-A 274,259 disclose dipeptide derivatives and the use thereof as renin-inhibitors.

New urea derivatives of dipeptides which highly effectively inhibit the enzyme renin in vitro and in vivo, as well as a new process for the preparation of these compounds, have now been found.

The invention relates to compounds of the formula I



$$R^1 - A - B - HN - \underset{\displaystyle R^2}{CH} - \underset{\displaystyle OH}{CH} - \underset{\displaystyle R^3}{CH} - R^4 \qquad (I)$$

in which

R^1 denotes a radical of the formula II

$$R^a - NH - CO - \qquad (II)$$

in which

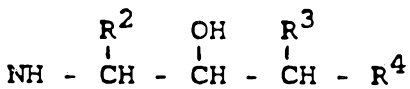
R^a denotes hydrogen, (C_1-C_{10})-alkyl which is optionally singly or doubly unsaturated and which is optionally substituted by up to 3 identical or different radicals from the series comprising hydroxyl, (C_1-C_7)-alkoxy, (C_1-C_7)-alkanoyloxy, carboxyl, (C_1-C_7)-alkoxycarbonyl, Cl, Br, amino, (C_1-C_7)-alkylamino, di-(C_1-C_7)-alkylamino, (C_1-C_5)-alkoxycarbonylamino, (C_7-C_{15})-aralkoxycarbonylamino and 9-fluorenylmethyl-

oxycarbonylamino, or (C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl, (C_6-C_{14})-aryl which is optionally substituted by one or two identical or different radicals from the series comprising F, Cl, Br, I, hydroxyl, (C_1-C_7)-alkoxy, (C_1-C_7)-alkyl, (C_1-C_7)-alkoxycarbonyl, amino, anilino which is optionally substituted by up to 2 halogen, and trifluoromethyl; (C_6-C_{14})-aryl-(C_1-C_6)-alkyl in which the aryl moiety is optionally substituted by one or two identical or different radicals from the series comprising F, Cl, Br, I, hydroxyl, (C_1-C_7)-alkoxy, (C_1-C_7)-alkyl, (C_1-C_7)-alkoxycarbonyl, amino, (C_1-C_7)-alkylamino, di-(C_1-C_7)-alkylamino, carboxyl, carboxymethoxy, amino-(C_1-C_7)-alkyl, (C_1-C_7)-alkylamino-(C_1-C_7)-alkyl, di-(C_1-C_7)-alkylamino-(C_1-C_7)-alkyl, (C_1-C_7)-alkoxycarbonylmethoxy, carbamoyl, sulfamoyl, (C_1-C_7)-alkoxysulfonyl, sulfo- and guanidinomethyl, or represents the radical of a 5- or 6-membered monocyclic or 9- or 10-membered bicyclic heteroaromatic which has at least one carbon atom, 1-4 nitrogen atoms and/or 1 sulfur or oxygen atom also as ring members and is optionally substituted by one, two or three identical or different radicals from the series comprising F, Cl, Br, hydroxyl, (C_1-C_7)-alkoxy, (C_1-C_7)-alkyl, (C_1-C_7)-alkoxycarbonyl, amino or trifluoromethyl,

A denotes a radical, which is linked N-terminal with R^1 and C-terminal with B, of an amino acid from the series comprising phenylalanine, histidine, tyrosine, tryptophan, methionine, leucine, isoleucine, asparagine, aspartic acid, β-2-thienylalanine, β-3-thienylalanine, β-2-furylalanine, β-3-furylalanine, lysine, ornithine, valine, alanine, 2,4-diaminobutyric acid, arginine, 4-chlorophenylalanine, methionine sulfone, methionine sulfoxide, 2-pyridylalanine, 3-pyridylalanine, cyclohexylalanine, cyclohexylglycine, im-methylhistidine, O-methyltyrosine, O-benzyltyrosine, O-tert.-butyltyrosine, phenylglycine, 1-naphthylalanine, 2-

naphthylalanine, 4-nitrophenylalanine, norvaline, β-2-benzo[b]thienylalanine, β-3-benzo[b]thienylalanine, 2-fluorophenylalanine, 3-fluorophenylalanine, 4-fluorophenylalanine, norleucine, cysteine, S-methyl-cysteine, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, homophenylalanine, DOPA, O-dimethyl-DOPA, 2-amino-4-(2-thienyl)-butyric acid, benzodioxol-5-ylalanine, N-methylhistidine, 2-amino-4-(3-thienyl)butyric acid, 3-(2-thienyl)-serine, (Z)-dehydrophenylalanine, and (E)-dehydrophenylalanine,

B denotes a radical, which is linked N-terminal with A and C-terminal with

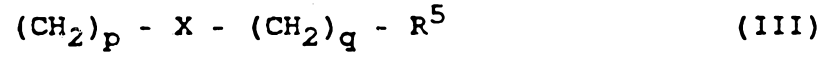


of an amino acid which is defined as under A,

R^2 denotes hydrogen, (C_1-C_{10})-alkyl, (C_4-C_7)-cycloalkyl, (C_4-C_7)-cycloalkyl-(C_1-C_4)-alkyl, (C_6-C_{14})-aryl or (C_6-C_{14})-aryl-(C_1-C_4)-alkyl, and

R^3 denotes hydrogen, (C_1-C_{10})-alkyl, (C_6-C_{14})-aryl or (C_6-C_{14})-aryl-(C_1-C_4)-alkyl,

R^4 denotes a radical of the formula III



(III)

in which, as desired, X can be absent or represents -O-, -S-, $-CF_2-$, -CO- or $-CHR^6-$,

p and q denote, independently of one another, 0, 1, 2, 3 or 4,

R^6 denotes hydrogen, (C_1-C_7)-alkyl, (C_1-C_5)alkoxy, (C_1-C_5)-alkylthio, (C_1-C_5)-alkylamino, -OH, $-N_3$, -F, -Cl, -Br or -I, and

R^5 denotes hydrogen, -OH, $-NH_2$ or heteroaryl which can also be partially or completely hydrogenated,

as well as the physiologically tolerated salts thereof.

The carbon atoms substituted by R^2, R^3 and R^6 can each have the R S or R,S configuration.

Alkyl can be straight-chain or branched. A corresponding statement applies to radicals derived therefrom such as, for example, alkoxy, alkylthio, alkylamino, dialkylamino, alkanoyl and aralkyl.

Cycloalkyl also means alkyl-substituted radicals such as, for example, 4-methylcyclohexyl or 2,3-dimethylcyclopentyl.

(C_6-C_{14})-aryl is, for example, phenyl, naphthyl, biphenylyl or fluorenyl; phenyl is preferred. A corresponding statement applies to radicals derived therefrom such as, for example, aryloxy, aroyl, aralkyl and aralkyloxy. Aralkyl means an unsubstituted or substituted (C_6-C_{14})-aryl radical which is linked to (C_1-C_6)-alkyl, such as, for example, benzyl, α- and β-naphthylmethyl, halobenzyl and alkoxybenzyl, but with aralkyl not being restricted to the said radicals.

A radical of a 5- or 6-membered monocyclic or 9- or 10-membered bicyclic heteroaromatic having at least one carbon atom, 1-4 nitrogen atoms and/or 1 sulfur or oxygen atom as ring members means radicals of heteroaromatics as defined, for example, in Katritzky, Lagowski, Chemistry of the Heterocycles, Berlin, Heidelberg 1968, pages 3 - 5. The heteroaromatic radical can be substituted by one, two or three, preferably one or two, identical or different radicals from the series comprising F, Cl, Br, hydoxyl, (C_1-C_7)-alkoxy, (C_1-C_7)-alkyl, (C_1-C_7)-alkoxycarbonyl, amino or trifluoromethyl. Examples of monocyclic heteroaromatics are thiophene, furan, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, 1,2,4-triazole, thiazole, tetrazole, isothiazole, oxazole and isoxazole. Examples of bicyclic heteroaromatics are benzothiophene, benzofuran, indole, isoindole, indazole, benzimidazole, quinoline, isoquinoline,

phthalazine, quinoxaline, quinazoline and cinnoline. A corresponding statement applies to the radicals derived from heteroaryl, such as, for example, completely or partially hydrogenated heteroaryl, heteroaryloxy, heteroaryl and heteroaryl-alkyl.

The amino acids A and B in formula I are linked together by an amide linkage and they are natural or unnatural α-amino acids of the L or D or D,L configuration, preferably of the L configuration.

Salts of compounds of the formula I mean, in particular, pharmaceutically utilizable or non-toxic salts.

Salts of these types are formed, for example, from compounds of the formula I which contain acidic groups, for example carboxyl, with alkali metals or alkaline earth metals such as Na, K, Mg and Ca, as well as with physiologically tolerated organic amines such as, for example, triethylamine and tri-(2-hydroxyethyl)-amine.

Compounds of the formula I which contain basic groups, for example an amino group or a guanidino group, form salts with inorganic acids such as, for example, hydrochloric acid, sulfuric acid or phosphoric acid and with organic carboxylic or sulfonic acids such as, for example, acetic acid, citric acid, benzoic acid, maleic acid, fumaric acid, tartaric acid and p-toluenesulfonic acid.

Preferred compounds of the formula I are those in which

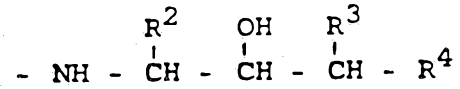
R^1 denotes a radical of the formula II in which

R^a denotes hydrogen, (C_1-C_{10})-alkyl, (C_1-C_4)-alkoxy-(C_1-C_{10})-alkyl, carboxy-(C_1-C_{10})-alkyl, (C_1-C_4)-alkoxycarbonyl-(C_1-C_{10})-alkyl, amino-(C_1-C_{10})-alkyl, diamino-(C_1-C_{10})-alkyl, (C_1-C_4)-alkylamino-(C_1-C_{10})-alkyl, di(C_1-C_4)alkylamino-(C_1-C_{10})-alkyl, N,N'-di-(C_1-C_4)-alkyldiamino-(C_1-C_{10})-alkyl, N,N,N',N'-tetra(C_1-C_4)-alkyldiamino-(C_1-C_{10})-alkyl, (C_1-C_4)-alkoxycarbonyl-

amino-(C_1-C_{10})-alkyl, (C_7-C_{15})-aralkoxycarbonylamino-(C_1-C_{10})-alkyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentyl-(C_1-C_6)-alkyl, cyclohexyl-(C_1-C_6)-alkyl, phenyl which is optionally substituted by one or two identical or different radicals from the series comprising F, Cl, Br, I, hydroxyl, (C_1-C_4)-alkoxy, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxycarbonyl, amino or trifluoromethyl, or (C_6-C_{10})-aryl-(C_1-C_6)-alkyl in which the aryl moiety can be substituted as phenyl above, or represents the radical of a 5- or 6-membered monocyclic or 9- or 10-membered bicyclic heteroaromatic which has at least one carbon atom, 1-4 nitrogen atoms and/or 1 sulfur or oxygen atom also as ring members and which is optionally substituted by one, two or three identical or different radicals from the series comprising F, Cl, Br, hydroxyl, (C_1-C_7)-alkoxy, (C_1-C_7)-alkyl, (C_1-C_7)-alkoxycarbonyl, amino or trifluoromethyl,

A denotes a radical, which is linked N-terminal with R^1 and C-terminal with B, of an amino acid from the series comprising phenylalanine, histidine, tyrosine, tryptophan, β-2-thienylalanine, β-3-thienylalanine, β-2-furylalanine, β-3-furylalanine, 4-chlorophenylalanine, 2-pyridylalanine, 3-pyridylalanine, cyclohexylalanine, cyclohexylglycine, im-methylhistidine, O-methyltyrosine, O-benzyltyrosine, O-tert.-butyltyrosine, phenylglycine, 1-naphthylalanine, 2-naphthylalanine, 4-nitrophenylalanine, 2-fluorophenylalanine, 3-fluorophenylalanine, 4-fluorophenylalanine, homophenylalanine, DOPA, O-dimethyl-DOPA, 2-amino-4-(2-thienyl)-butyric acid, benzodioxol-5-yl-alanine, N-methylhistidine, 2-amino-4-(3-thienyl)-butyric acid, 3-(2-thienyl)-serine, (Z)-dehydrophenylalanine or (E)-dehydrophenylalanine,

B denotes a radical, which is linked N-terminal with A and C-terminal with



of an amino acid from the series comprising phenylalanine, histidine, tyrosine, tryptophan, methionine, leucine, isoleucine, asparagine, aspartic acid, β-2-thienylalanine, β-3-thienylalanine, β-2-furylalanine, β-3-furylalanine, lysine, ornithine, valine, alanine, 2,4-diaminobutyric acid, arginine, 4-chlorophenylalanine, methionine sulfone, methionine sulfoxide, 2-pyridylalanine, 3-pyridylalanine, cyclohexylalanine, cyclohexylglycine, im-methylhistidine, O-methyltyrosine, O-benzyltyrosine, O-tert.-butyltyrosine, phenylglycine, 1-naphthylalanine, 2-naphthylalanine, 4-nitrophenylalanine, norvaline, β-2-benzo[b]thienylalanine, β-3-benzo[b]thienylalanine, 2-fluorophenylalanine, 3-fluorophenylalanine, 4-fluorophenylalanine, norleucine, cysteine, S-methyl-cysteine, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, homophenylalanine, DOPA, O-dimethyl-DOPA, 2-amino-4-(2-thienyl)-butyric acid, benzodioxol-5-yl-alanine, N-methylhistidine, 2-amino-4-(3-thienyl)-butyric acid, 3-(2-thienyl)-serine, (Z)-dehydrophenylalanine and (E)-dehydrophenylalanine,

R^2 denotes hydrogen, (C_1-C_{10})-alkyl, (C_4-C_7)-cycloalkyl, (C_4-C_7)-cycloalkyl-(C_1-C_4)-alkyl, (C_6-C_{14})-aryl or (C_6-C_{14})-aryl-(C_1-C_4)-alkyl,

R^3 denotes hydrogen, (C_1-C_{10})-alkyl, (C_6-C_{14})-aryl or (C_6-C_{14})-aryl-(C_1-C_4)-alkyl,

R^4 denotes a radical of the formula III in which, as desired,

X can be absent or represents -O-, -S-, $-CF_2-$, -CO- or $-CHR^6-$,

p and q denote, independently of one another, 0, 1, 2, 3 or 4,

R^6 denotes hydrogen, (C_1-C_7)-alkyl, (C_1-C_5)-alkoxy, (C_1-C_5)-alkylthio, (C_1-C_5)-alkylamino, -OH, $-N_3$, -F, -Cl, -Br or -I, and

R^5 denotes hydrogen, -OH, $-NH_2$ or heteroaryl which can also be partially or completely hydrogenated,

as well as the physiologically tolerated salts thereof.

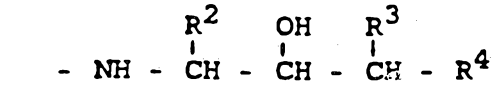
Especially preferred compounds of the formula I are those in which

R^1 denotes a radical of the formula II in which

R^a denotes hydrogen, (C_1-C_6)-alkyl, carboxy-(C_1-C_6)-alkyl, amino-(C_1-C_6)-alkyl, diamino-(C_1-C_6)-alkyl, (C_1-C_4)-alkylamino-(C_1-C_6)-alkyl, di-(C_1-C_4)-alkylamino-(C_1-C_6)-alkyl, N,N'-di-(C_1-C_4)-alkyldiamino-(C_1-C_6)-alkyl, N,N,N',N'-tetra-(C_1-C_4)-alkyldiamino-(C_1-C_6)-alkyl, (C_1-C_4)-alkoxycarbonylamino-(C_1-C_6)-alkyl or phenyl which is optionally substituted by one or two identical or different radicals from the series comprising F, Cl, hydroxyl or amino,

A denotes a radical, which is linked N-terminal with R^1 and C-terminal with B, of an amino acid from the series comprising phenylalanine, tyrosine, β-2-thienylalanine, β-3-thienylalanine, 4-chlorophenylalanine, O-methyltyrosine, O-benzyltyrosine, 1-naphthylalanine, 2-fluorophenylalanine, 3-fluorophenylalanine or 4-fluorophenylalanine,

B denotes a radical, which is linked N-terminal with A and C-terminal with



of an amino acid from the series comprising phenylalanine, histidine, leucine, asparagine, β-2-thienylalanine, β-3-thienylalanine, lysine, norvaline, 2-fluorophenylalanine, 3-fluorophenylalanine, 4-fluorophenylalanine, norleucine, S-methylcysteine or N-methylhistidine,

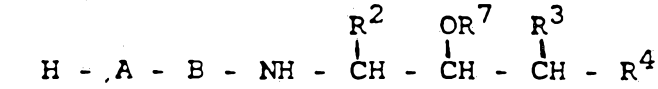
R^2 denotes isobutyl, cyclohexylmethyl or benzyl,

R^3 is hydrogen, and

R^4 represents a radical of the formula III in which

X is absent,
p is 0,
q denotes 0, 1, 2, 3 or 4, and
R^5 denotes 2-pyridyl, 4-pyridyl, 2-imidazolyl or 1-(C_1-C_4-alkyl)-2-imidazolyl,
as well as the physiologically tolerated salts thereof.

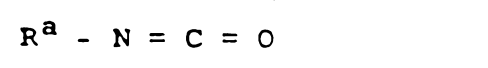
The invention furthermore relates to a process for the preparation of compounds of the formula I, which comprises reacting a compound of the general formula IV



$$H - A - B - NH - \underset{R^2}{CH} - \underset{OR^7}{CH} - \underset{R^3}{CH} - R^4 \qquad (IV)$$

in which A, B, R^2, R^3 and R^4 have the same meaning as in the general formula I, and in which R^7 denotes hydrogen or a protective group which can easily be eliminated, such as, for example, methoxymethyl, methylthiomethyl, benzyloxymethyl, tetrahydropyranyl, tert. butyl, allyl, benzyl or substituted benzyl, benzhydryl, trityl, trimethylsilyl, tert. butyldimethylsilyl, acetyl, pivaloyl, benzoyl, methyloxycarbonyl, ethyloxycarbonyl or benzyloxycarbonyl,

a) with an isocyanate of the general formula V

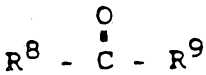


$$R^a - N = C = O \qquad (V),$$

in which R^a has the same meaning as in the general formula II, in a suitable organic solvent such as, for example, benzene, toluene, chlorobenzene, an aliphatic hydrocarbon, an aliphatic chlorinated hydrocarbon, diethyl ether, tetrahydrofuran, dioxane, acetone, acetonitrile, dimethylformamide, dimethyl sulfoxide or else dispensing with a solvent, in each case as desired with or without the

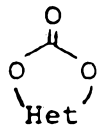
addition of a Lewis acid or of a Lewis base as catalyst, such as, for example, of a tertiary amine, preferably triethylamine, 1,4-diazabicyclo[2.2.2]-octane, cyclohexyldimethylamine, benzyldimethylamine, 4-methylmorpholine, tetramethylguanidine or 4-dimethylaminopyridine, at a temperature between -80°C and the boiling point of the solvent, preferably between -30°C and +80°C, and, where appropriate, eliminating the protective group R^7 again, or

b) in succession, firstly with a carbonic acid derivative of the general formula VI

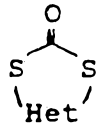


(VI),

in which R^8 and R^9 denote, independently of one another, halogen, (C_1-C_7)-alkoxy, (C_6-C_{12})-aryloxy, (C_1-C_7)-alkylthio, (C_6-C_{12})-arylthio or a radical Het or Het-O-, it being possible for Het to be a mono- or bicyclic heterocycle, or in which R^8 and R^9 belong, together with the C=O group, to a mono- or bicyclic heterocycle of the type



or



,

preferably with phosgene, 1,1'-carbonyldiimidazole, 1,1'-carbonyldi-(1,2,4)-triazole, di-(N-succinimidyl) carbonate, di-(1-benzotriazolyl) carbonate, N,N'-carbonylbis-(2-methylimidazole) or 4,6-diphenylthieno[3,4-d]-1,3-dioxol-2-one 5,5-dioxide (Steglich reagent), and subsequently with an amine of the general formula VII

$$R^a - NH_2 \qquad (VII),$$

in which R^a has the same meaning as in the general formula II, in an inert organic solvent, preferably toluene, methylene chloride, chloroform, tetrahydrofuran, dimethylformamide or acetonitrile, with or without the presence of an auxiliary base such as, for example, potassium carbonate, sodium carbonate, triethylamine, pyridine, 1,5-diazabicyclo[5.4.0]-undec-5-ene or 1,5-diazabicyclo[4.3.0]-non-5-ene, preferably pyridine, at a temperature between -80°C and the boiling point of the particular solvent, preferably between -80°C and +50°C, and, where appropriate, eliminating again by known methods the protective group R^7 as well as, where appropriate, protective groups temporarily introduced into the fragments A and B.

The compounds of the general formula IV are obtained from compounds of the general formula VIII

$$R^{10} - A - B - NH - \underset{|}{\overset{R^2}{CH}} - \underset{|}{\overset{OH}{CH}} - \underset{|}{\overset{R^3}{CH}} - R^4 \qquad (VIII)$$

in which R^2, R^3, R^4, A and B have the same meaning as in formula I, and in which R^{10} denotes an amino-protective group which can easily be eliminated, preferably tert. butyloxycarbonyl or benzyloxycarbonyl, by elimination of this protective group under the customary conditions, for example by acid or alkaline hydrolysis or hydrogenolysis, where appropriate with previous or subsequent protection of the hydroxyl functionality with one of the customary reagents suitable for introducing the radical R^7, such as, for example, methoxymethyl chloride, methylthiomethyl chloride, benzyloxymethyl chloride, dihydropyran, isobutene, allyl bromide,

benzyl bromide, diphenyldiazomethane, trityl chloride, trimethylsilyl chloride, tert.-butyldimethylsilyl chloride, acetic anhydride, pivaloyl chloride, benzoyl chloride, methyl chloroformate, ethyl chloroformate or benzyl chloroformate.

The compounds of the formula V, VI and VII are known from the literature, and most of them can be bought. The compounds of the formula VIII are disclosed in EP-A 255,082.

EP-A 255,082 additionally discloses a process for the preparation of the compounds of the formula I, which comprises coupling a fragment with a terminal carboxyl group, or the reactive derivative thereof, with a corresponding fragment with a free amino group, where appropriate eliminating (a) protective group(s) temporarily introduced to protect other functional groups, and converting the compound obtained in this way into the physiologically tolerated salt thereof where appropriate.

However, the process according to the invention differs advantageously in several ways from the conventional process:

A) In contrast to the process according to the invention, in the conventional processes two additional reaction steps are necessary in the introduction of the radical R^1, owing to the introduction and elimination of the protective group at the C-terminal end of the amino acid A-OH or of the dipeptide A-B-OH. In the process according to the invention the radical R^1 is introduced at the last stage at the unprotected N-terminus of the dipeptide by reaction with isocyanates or amines which, moreover, are available in large number and range of variation.

B) Radicals R^1 which contain an additional amino functionality can in the process according to the invention be introduced directly in the form of the amine R^a-NH_2 (formula VII) in unprotected form (see

Example 13) while, by contrast, in the conventional process this additional amino group must be initially protected and subsequently unblocked again.

C) The occurrence of side reactions is avoided in the process according to the invention by the absence of coupling auxiliaries at the last stage of the reaction sequence and the lack of activation of the C-terminal carboxyl functionality.

The compounds of the formula I according to the invention show enzyme-inhibiting properties; in particular they inhibit the action of the natural enzyme renin. Renin is a proteolytic enzyme from the class of aspartyl proteases which is secreted as a consequence of various stimuli (volume depletion, sodium deficiency, β-receptor stimulation) from the juxtaglomerular cells of the kidney into the blood circulation. There it eliminates the decapeptide angiotensin I from the angiotensinogen which is secreted by the liver. This decapeptide is converted by angiotensin converting enzyme (ACE) into angiotensin II. Angiotensin II plays an essential part in the regulation of blood pressure, because it raises the blood pressure directly by vasoconstriction. In addition, it stimulates the secretion of aldosterone from the adrenal and, in this way, via inhibition of sodium excretion, increases the extracellular fluid volume, which in turn contributes to raising the blood pressure. Inhibitors of the enzymatic activity of renin bring about a reduced formation of angiotensin I, the consequence of which is a reduced formation of angiotensin II. The lowering of the concentration of this active peptide hormone is the direct cause of the action of renin inhibitors to lower blood pressure.

The activity of renin inhibitors can be examined by in vitro tests. These entail measurement of the reduction in the formation of angiotensin I in various systems (human plasma, purified human renin).

1. Principle of the test

For example human plasma which contains both renin and angiotensinogen is incubated at 37°C with the compound to be tested. During this, angiotensin I is liberated from angiotensinogen under the action of renin and can subsequently be measured with a commercially available radioimmunoassay. This angiotensin liberation is inhibited by renin inhibitors.

2. Obtaining the plasma

The blood is obtained from volunteer subjects (about 0.5 l per person; Bluko sampler supplied by ASID Bonz und Sohn, Unterschleissheim) and collected in partially evacuated bottles while cooling in ice. Coagulation is prevented by addition of EDTA (final concentration 10 mM). After centrifugation (HS 4 (Sorvall) rotor, 3500 rpm, 0-4°C, 15 min; repeat if necessary) the plasma is cautiously removed by a pipette and frozen in suitable portions at -30°C. Only plasmas with sufficiently high renin activity are used for the test. Plasmas with low renin activity are activated by a cold treatment (-4°C, 3 days) (prorenin ⟶ renin).

3. Test procedure

Angiotensin I is determined using the Renin-Maia(R) kit (Serono Diagnostics S.A., Coinsins, Switzerland). The plasma is incubated in accordance with the instructions given therein:

Incubation mixture:	1000 µl of plasma (thawed at 0-4°C)
	100 µl of phosphate buffer (pH 7.4)
	(Addition of 10^{-4} M ramiprilate)
	10 µl of PMSF solution

10 µl of 0.1 % Genapol PFIC
12 µl of DMSO or test product

The test products are generally made into a 10^{-2} M solution in 100 % dimethyl sulfoxide (DMSO) and diluted appropriately with DMSO; the incubation mixture contains a maximum of 1 % DMSO.

The mixtures are mixed in ice and, for the incubation, placed in a water bath (37°C) for 1 hour. A total of 6 samples (100 µl each) are taken from an additional mixture without inhibitor and without further incubation for determination of the initial angiotensin I content of the plasma used.

The concentrations of the test products are chosen such that the range of 10-90 % enzyme inhibition is approximately covered (at least five concentrations). At the end of the incubation time, three 100 µl samples from each mixture are frozen in precooled Eppendorf tubes on dry ice and stored at about -25°C for the angiotensin I determination (mean from three separate samples).

Angiotensin I radioimmunoassay (RIA)

The instructions for use of the RIA kit (Renin-Maia(R) kit, Serono Diagnostics S.A., Coinsins, Switzerland) are followed exactly.

The calibration plot covers the range from 0.2 to 25.0 ng of angiotensin I per ml. The baseline angiotensin I content of the plasma is subtracted from all the measurements. The plasma renin activity (PRA) is reported as ng of ang I/ml x hour. PRA values in the presence of the test substances are related to a mixture without inhibitor (= 100 %) and reported as % activity remaining. The IC_{50} value is read off from the plot of % activity remaining against the concentration (M) of the test product (logarithmic scale).

The compounds of the general formula I described in the present invention show the following IC_{50} -values:

Example	IC_{50} (μM)
1	2,0
2	0,62
3	0,9
4	0,38
5	1,0
6	0,4
7	0,26
8	>10
9	6,5
10	> 1
11	0,9
12	5,5
13	0,34
14	8
29	0,65

Renin inhibitors bring about a lowering of blood pressure in salt-depleted animals. Because human renin differs from the renin of other species, primates (marmosets, Rhesus monkeys) are employed in the in vivo test of renin inhibitors. Primate renin and human renin have substantially homologous sequences. Endogenous renin release is stimulated by i.v. injection of furosemide. The test compounds are subsequently administered by continuous infusion, and their action on the blood pressure and heart rate is measured. The compounds of the present invention are active in this test in a dose range of about 0.1-5 mg/kg i.v. and on intraduodenal administration by gastroscope in the dose range of about 1-50 mg/kg. The compounds of the general formula I described in the present invention can be used as antihypertensives and for the treatment of cardiac insufficiency.

The invention therefore also relates to the use of compounds of the formula I as medicines and pharmaceutical products which contain these compounds. Use in primates, especially in humans, is preferred.

Pharmaceutical products contain an effective amount of the active substance of the formula I together with an inorganic or organic excipient which can be used in pharmacy. Intranasal, intravenous, subcutaneous or oral use is possible. The dosage of the active substance depends on the warm-blooded species, the body weight, age and the mode of administration.

The pharmaceutical products of the present invention are prepared in dissolving, mixing, granulating or coating processes known per se.

For a form for oral use, the active compounds are mixed with the additives customary for this purpose, such as excipients, stabilizers or inert diluents, and converted by customary methods into suitable dosage forms such as tablets, coated tablets, hard gelatin capsules, aqueous, alcoholic or oily suspensions or aqueous, alcoholic or oily solutions. Examples of inert vehicles which can be used are gum arabic, magnesia, magnesium carbonate, potassium phosphate, lactose, glucose, magnesium stearyl fumarate or starch, especially corn starch. This preparation can be carried out both as dry and wet granules. Examples of suitable oily excipients or solvents are vegetable or animal oils, such as sunflower oil and fish liver oil.

For subcutaneous or intravenous administration, the active compounds, or the physiologically tolerated salts thereof, are converted into solutions, suspensions or emulsions, if desired with the substances customary for this purpose, such as solubilizers, emulsifiers or other auxiliaries. Examples of suitable solvents are: water, physiological sodium chloride solutions or alcohols, for example ethanol, propanediol or glycerol, as well as sugar solutions such as glucose or mannitol solutions, or as a mixture of the various solvents mentioned.

List of abbreviations used:

Boc	tert.-butoxycarbonyl
DCI	desorption chemical ionization
DNP	2,4-dinitrophenyl
EI	electron impact
FAB	fast atom bombardment
M	molecular peak
MeOH	methanol
MS	mass spectrum
R.T.	room temperature
m.p.	melting point
Thi	β-2-thienylalanine

THF tetrahydrofuran

The other abbreviations used for amino acids correspond to the three-letter code customary in peptide chemistry, as is described, for example, in Eur. J. Biochem. 138, 9-37 (1984). Unless expressly indicated otherwise, the amino acids are always in the L configuration.

The examples which follow serve to illustrate the present invention without restricting it thereto.

Example 1:

1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(ethylamino-carbonyl-Phe-His)-amino)-3S-hexanol

1a) H-His(DNP)-OH

4 ml of HCl-saturated dimethoxyethane are added dropwise at 0-5°C to a solution of 0.42 g (1 mmol) of Boc-His(DNP)-OH in 5 ml of dimethoxyethane, and the mixture is stirred at 0-5°C for 1 hour and at room temperature for 3 hours. The reaction solution is concentrated in vacuo and evaporated twice more with toluene.
Yield: 0.5 g of the title compound as hydrochloride.
Rf (methylene chloride/MeOH/AcOH/water 70:30:1:1) = 0.16.

1b) Boc-Phe-His(DNP)-OH

0.362 g (1 mmol) of Boc-Phe hydroxysuccinimide ester dissolved in 5 ml of ethanol and 5 ml of THF is added at room temperature to 0.5 g (1 mmol) of H-His(DNP)-OH hydrochloride in 12.5 ml of 0.25 N sodium bicarbonate solution. The reaction mixture is stirred at room temperature for three days. Then 0.83 g of citric acid is added, when the title compound separates out as an oil. The product is extracted with methylene chloride, the

organic phase is dried over sodium sulfate and concentrated, a little ethyl acetate is added to the residue, and the title compound is precipitated by addition of diisopropyl ether and filtered off with suction.

Yield: 0.47 g (83 %)

Rf (methylene chloride/MeOH 7:3) = 0.43

MS (FAB) = 569 (M+1).

1c) 2S-Amino-1-cyclohexyl-6-(2-pyridyl)-3S-hexanol

5 ml of HCl-saturated dimethoxyethane are added dropwise to 214 mg (0.513 mmol) of 3-Boc-4S-cyclohexylmethyl-2,2-dimethyl-5-(3-(2-pyridyl)-propyl)-oxazolidine in 10 ml of dimethoxyethane in an ice bath, and the mixture is stirred at 0°C for one hour and at room temperature for 5 hours. The reaction solution is concentrated in vacuo and evaporated twice more with toluene.

Yield: 179 mg of the title compound as dihydochloride.

1d) 1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(Boc-Phe-His(DNP))-amino)-3S-hexanol

1.5 g (3.18 mmol) of 2S-amino-1-cyclohexyl-6-(2-pyridyl)-3S-hexanol dihydrochloride (Example 1c) and 1.8 g (3.18 mmol) of Boc-Phe-His(DNP)-OH (Example 1b) are dissolved in 15 ml of absolute dimethylformamide. To this is added 0.59 g (6.36 mmol) of 1-hydroxybenzotriazole hydrate, and the mixture is cooled to about 4°C in an ice bath. Successively added at this temperature are 2.44 ml (19.1 mmol) of N-ethylmorpholine and 0.65 g (3.18 mmol) of dicyclohexylcarbodiimide, and the mixture is stirred in the ice bath for 1 hour and at room temperature for 7 hours. After it has stood overnight, a further 0.9 g (1.59 mmol) of Boc-Phe-His(DNP)-OH, 0.28 g (3.18 mmol) of 1-hydroxybenzotriazole hydrate and 0.32 g (1.58 mmol) of dicyclohexylcarbodiimide are added, and the mixture is stirred at room temperature for a further 10 hours. The precipitate is filtered off with suction, the filtrate is concentrated in vacuo, the residue is dissolved in ethyl

acetate, and the solution is washed with saturated sodium bicarbonate solution, water and saturated sodium chloride solution, dried over sodium sulfate and concentrated, and the crude product (3.8 g) is purified by medium-pressure column chromatography on silica gel (methylene chloride/MeOH 98:2, 95:5, 9:1). 1.8 g (68 %) of the title compound are obtained.
Rf (methylene chloride/MeOH 9:1) = 0.46
MS (FAB) = 827 (M+1).

1e) 1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(H-Phe-His(DNP))-amino)-3S-hexanol

2 ml of ice-cold trifluoroacetic acid are poured onto 72 mg of 1-cyclohexyl-6-(2-pyridyl)-2S-(N-(Boc-Phe-His(DNP))-amino)-3S-hexanol at 0-5°C, and the mixture is stirred at this temperature for two hours. The reaction solution is concentrated in vacuo and evaporated twice with toluene.
Yield: 83 mg of the title compound as bis(trifluoroacetate).

1f) 1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(ethylamino-carbonyl-Phe-His(DNP))-amino)-3S-hexanol

83 mg (0.087 mmol) of 1-cyclohexyl-6-(2-pyridyl)-2S-(N-(H-Phe-His(DNP))-amino)-3S-hexanol bis(trifluoroacetate) (Example 1e) are dissolved in 2 ml of absolute dimethylformamide. To this are added successively, at room temperature, 0.0365 ml (0.26 mmol) of triethylamine and 0.01 ml (0.124 mmol) of ethyl isocyanate and the mixture is left to stand at room temperature overnight. Then 0.01 ml (0.124 mmol) of ethyl isocyanate is added once again and, one day later, a further 0.05 ml (0.62 mmol) of ethyl isocyanate, and the mixture is stirred at room temperature for a further 9 hours, poured onto ice-water and extracted with ethyl acetate. The combined organic phases are washed with saturated sodium

bicarbonate solution, water and saturated sodium chloride solution, dried and concentrated, and the crude product (84 mg) is purified by medium-pressure column chromatography on silica gel (methylene chloride/MeOH 98:2, 95:5, 9:1).
Yield: 48.6 mg (70 %) of the title compound
Rf (methylene chloride/MeOH 9:1) = 0.29
MS (FAB)= 798 (M+1)

1g) 1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(ethylamino-carbonyl-Phe-His)-amino)-3S-hexanol

0.1 ml (1 mmol) of thiophenol is added to 48.6 mg (0.061 mmol) of 1-cyclohexyl-6-(2-pyridyl)-2S-(N-(ethylaminocarbonyl-Phe-His(DNP))-amino)-3S-hexanol in 5 ml of acetonitrile, and the mixture is stirred at room temperature for 5 hours. The reaction solution is concentrated in vacuo, and the crude product is purified by medium-pressure column chromatography on silica gel (methylene chloride/ MeOH 98:2, 95:5, 9:1).
Yield: 12.3 mg of the title compound
MS (FAB) = 632 (M+1)

Example 2

1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(isopropylaminocarbonyl-Phe-Nva)-amino)-3S-hexanol

2a) Boc-Phe-Nva-OMe

15.0 g (0.056 mol) of Boc-Phe-OH and 9.4 g (0.056 mol) of Nva-OMe hydrochloride are dissolved in 250 ml of absolute methylene chloride. To this are added dropwise, while cooling in ice, first 38.6 ml (0.28 mol) of absolute triethylamine and then 36.4 ml of propanephosphonic anhydride (50 % in methylene chloride). The reaction solution is stirred at room temperature for 3 hours and left to stand overnight. To hydrolyze, it is poured onto

left to stand overnight. To hydrolyze, it is poured onto ice-water and stirred vigorously for 2 hours, and the organic phase is separated off and washed with 10 % strength citric acid solution, saturated sodium bicarbonate solution and water, dried over sodium sulfate and concentrated.
Yield: 20.8 g (98 %) of the title compound
Rf (methylene chloride/MeOH 9:1) = 0.64
MS (EI) = 378 (M)

2b) Boc-Phe-Nva-OH

20.1 g (0.053 mol) of Boc-Phe-Nva-OMe (Example 2a) are suspended in 30 ml of water and 30 ml of dioxane. 2.5 g (0.106 mol) of lithium hydroxide are introduced at room temperature, and the mixture is stirred at room temperature for 3 hours. The reaction solution is acidified with 10 % strength sodium bisulfate solution, and the product is filtered off with suction and stirred with diisopropyl ether.
Yield: 19.1 g (98 %),
Rf (methylene chloride/MeOH 9:1) = 0.18
MS (FAB) = 365 (M+1)

2c) 1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(Boc-Phe-Nva)-amino)-3S-hexanol

0.8 g of the title compound is obtained from 1.7 g (3.36 mmol) of 2S-amino-1-cyclohexyl-6-(2-pyridyl)-3S-hexanol dihydrochloride (Example 1c) and 1.22 g (3.36 mmol) of Boc-Phe-Nva-OH (Example 2b) in analogy to the process indicated in Example 1d).
Rf (methylene chloride/MeOH 9:1) = 0.53
MS (FAB) = 623 (M+1)

2d) 1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(H-Phe-Nva)-amino)-3S-hexanol

92 mg of the title compound are obtained as the dihydrochloride from 97 mg of 1-cyclohexyl-6-(2-pyridyl)-2S-(N-(Boc-Phe-Nva)-amino)-3S-hexanol (Example 2c) in analogy to the process indicated in Example 1a).

2e) 1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(isopropylamino-carbonyl-Phe-Nva)-amino)-3S-hexanol

92 mg (0.155 mmol) of 1-cyclohexyl-6-(2-pyridyl)-2S-(N-(H-Phe-Nva)-amino)-3S-hexanol dihydrochloride (Example 2d) are dissolved in 5 ml of absolute dimethylformamide. Successively added at room temperature are 0.104 ml (0.73 mmol) of triethylamine and 0.019 ml (0.19 mmol) of isopropyl isocyanate. The mixture is left to stand at room temperature over the weekend and concentrated in vacuo, the residue is taken up in ethyl acetate, the solution is washed with saturated sodium bicarbonate solution, water and saturated sodium chloride solution, dried over sodium sulfate and concentrated, and the crude product (98 mg) is purified by medium-pressure column chromatography on silica gel (methylene chloride/MeOH 95:5).
Yield: 13.3 mg of the title compound
Rf (methylene chloride/MeOH 9:1) = 0.39
MS (FAB) = 608 (M+1)

Example 3

1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(2,2-dimethylpropyl-aminocarbonyl-Phe-Nva)-amino)-3S-hexanol

A solution of 84 mg (0.16 mmol) of 1-cyclohexyl-6-(2-pyridyl)-2S-(N-(H-Phe-Nva)-amino)-3S-hexanol (Example 2d, liberated from the hydrochloride by treatment with sodium bicarbonate) in 10 ml of absolute methylene chloride is added dropwise at -75 to -70°C to 126 mg (0.32 mmol) of di(benzotriazolyl) carbonate in 10 ml of absolute methyl-

ene chloride and 0.026 ml (0.32 mmol) of pyridine, and the solution is stirred at this temperature for 1 hour. It is then allowed to reach room temperature, stirred for 3 hours and again cooled to -75°C. 0.0955 ml (0.8 mmol) of 2,2-dimethyl-1-propylamine is now added, and the mixture is stirred at -75°C for 2 hours and left to stand at room temperature overnight. The reaction solution is concentrated in vacuo, the residue is taken up in ethyl acetate, the solution is washed with saturated sodium bicarbonate solution, water and saturated sodium chloride solution, dried over sodium sulfate and concentrated, and the crude product (144 mg) is purified by medium-pressure column chromatography on silica gel (methylene chloride/MeOH 100:0, 98:2, 95:5).

Yield: 39 mg (39 %) of the title compound

Rf (methylene chloride/MeOH 9:1) = 0.32

MS (FAB) = 636 (M+1)

The compounds described in the following examples 4 to 14 were obtained using suitable starting materials and employing the processes described in Examples 1 to 3:

Example 4

1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(ethylaminocarbonyl-Phe-Nva)-amino)-3S-hexanol

Rf (methylene chloride/MeOH 9:1) = 0.42

MS (FAB) = 594 (M+1)

Example 5

1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(tert.butylamino-carbonyl-Phe-His)-amino)-3S-hexanol

Rf (methylene chloride/MeOH 9:1) =0.25

MS (FAB) = 660 (M+1)

Example 6

1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(tert.butylamino-carbonyl-Phe-Nva)-amino)-3S-hexanol

Rf (methylene chloride/MeOH 9:1) = 0.52
MS (FAB) = 622 (M+1)

Example 7

1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(tert.butylamino-carbonyl-Thi-Nva)-amino)-3S-hexanol

Rf (methylene chloride/MeOH 9:1) = 0.39
MS (FAB) = 628 (M+1)

Example 8

1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(tert.butylamino-carbonyl-Tyr(OMe)-Nva)-amino)-3S-hexanol

Rf (methylene chloride/MeOH 9:1) = 0.38
MS (FAB) = 652 (M+1)

Example 9

1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(tert.butylamino-carbonyl-Phe-Nva)-amino)-3R-hexanol

Rf (toluene/EtOH 9:1) = 0.33
MS (FAB) = 622 (M+1)

Example 10

1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(tert.butylamino-carbonyl-Phe-His)-amino)-3R-hexanol

Rf (methylene chloride/MeOH 9:1) = 0.32
MS (FAB) = 660 (M+1)

Example 11

1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(ethylaminocarbonyl-Phe-His)-amino)-3R-hexanol

MS (FAB) = 632 (M+1)

Example 12

1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(isopropylaminocarbonyl-Phe-Nva)-amino)-3R-hexanol

Rf (methylene chloride/MeOH 9:1) = 0.46
MS (FAB) = 608 (M+1)

Example 13

1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(2-amino-2-methylpropyl-aminocarbonyl-Phe-Nva)-amino)-3S-hexanol

Rf (methylene chloride/MeOH 7:3) = 0.09
MS (FAB) = 637 (M+1)

Example 14

(1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(tert.butylaminocarbonyl-Phe-Asn)-amino)-3S-hexanol

Rf (methylene chloride/MeOH 9:1) = 0.24
MS (FAB) = 637 (M+1)

The following compounds 15-28 were prepared in analogy to the "conventional" process described in EP-A 255,082.

Example 15

1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(ethylaminocarbonyl-Phe-Nva)-amino)-3S-hexanol

15a) N-(Ethylaminocarbonyl)-Phe-OH

3.37 g (10 mmol) of Phe p-toluenesulfonate are dissolved in 10 ml of absolute tetrahydrofuran and, at room temperature, 2.4 ml (12 mmol) of freshly distilled hexamethyldisilazane are added, and the mixture is stirred for two hours. 0.97 ml (12 mmol) of ethyl isocyanate is added to the suspension, which is left to stand at room temperature overnight. The precipitate is filtered off with suction, the filtrate is cooled in an ice bath, filtered again and concentrated, and the residue is stirred with water. The precipitate is filtered off with suction and dried over phosphorus pentoxide.
Yield: 1.7 g (72 %)
Rf (methylene chloride/MeOH/water/glacial acetic acid 70:30:1:1) = 0.68
MS (DCI) = 237 (M+1)

15b) N-(Ethylcarbonylamino)-Phe-Nva-OMe

3.51 ml (25.4 mmol) of absolute triethylamine and 3.30 ml of propanephosphonic anhydride (50 % in methylene chloride) are successively added, while cooling in ice, to 1.2 g (5.08 mmol) of N-(ethylaminocarbonyl)-Phe-OH from Example 15a) and 0.85 g (5.08 mmol) of L-Nva-OMe hydrochloride in 30 ml of absolute methylene chloride, and the mixture is stirred at room temperature for 6 hours and left to stand overnight. To hydrolyze the reaction mixture it is poured onto ice-water, and the organic phase is separated off and washed three times each with 100 ml each time of 10 % strength citric acid solution, saturated sodium bicarbonate solution and water, dried over sodium sulfate and concentrated. The residue is stirred in a little cold diisopropyl ether, filtered off with suction and dried in vacuo.
Yield: 1.5 g (84 %)
Rf (methylene chloride/MeOH 9:1) = 0.49

15c) N-(Ethylaminocarbonyl)-Phe-Nva-OH

0.2 g of lithium hydroxide is added at room temperature to 1.5 g (4.29 mmol) of N-(ethylaminocarbonyl)-Phe-Nva-OMe from Example 15b) in 8 ml of water and 8 ml of dioxane, and the mixture is stirred for two hours. The reaction solution is acidified with 10 % strength sodium bisulfate solution, and the precipitate is filtered off with suction, stirred with diisopropyl ether and dried.

Yield: 1.3 g

Rf (toluene/ethanol 8:2) = 0.02

MS (DCI) = 336 (M+1)

15d) 2S-Amino-1-cyclohexyl-6-(2-pyridyl)-3S-hexanol dihydrochloride

5 ml of HCl-saturated dimethoxyethane are added dropwise to 214 mg (0.513 mmol) of 3-Boc-4S-cyclohexylmethyl-2,2-dimethyl-5-(3-(2-pyridyl)-propyl)-oxazolidine in 10 ml of dimethoxyethane in an ice bath, and the mixture is stirred at 0°C for one hour and at room temperature for 5 hours. The reaction solution is concentrated in vacuo and evaporated twice more with toluene.

Yield: 179 mg

15e) 1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(ethylamino-carbonyl-Phe-Nva)-amino)-3S-hexanol

160.5 mg (0.513 mmol) of 2S-amino-1-cyclohexyl-6-(2-pyridyl)-3S-hexanol dihydrochloride from Example 15d) and 172 mg (0.513 mmol) of N-(ethylamino-carbonyl)-Phe-Nva-OH from Example 15c) are dissolved in 2 ml of absolute dimethylformamide. 273 mg (1.03 mmol) of 1-hydroxybenzotriazole are added at room temperature, and the mixture is cooled to 0°C. At this temperature are added first 0.65 ml (5.13 mmol) of N-ethylmorpholine and then 106 mg (0.513 mmol) of

dicyclohexylcarbodiimide, and the mixture is stirred at room temperature for 5 hours. A further 100 mg (0.298 mmol) of N-(ethylaminocarbonyl)-Phe-Nva-OH are then added, and the mixture is left to stand overnight. The dicyclohexylurea is filtered off with suction, the filtrate is poured into water, and the mixture is extracted several times with ethyl acetate. The combined organic phases are washed with saturated sodium bicarbonate solution, water and sodium chloride solution, dried over sodium sulfate and concentrated, and the crude product (335 mg) is purified by medium-pressure column chromatography on silica gel (mobile phase methylene chloride/methanol 100:0, 98:2, 95:5, 9:1). 98 mg (32 %) of the title compound are obtained.

Rf (methylene chloride/MeOH 9:1) = 0.41

MS (FAB) = 594 (M+1)

Example 16

1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(tert.butylaminocarbonyl-Phe-His)-amino)-3S-hexanol

16a) N-(tert.butylaminocarbonyl)-Phe-OH

The title compound is obtained in analogy to Example 15a) from 3.37 g of L-phenylalanine p-toluenesulfonate and tert.butyl isocyanate.

Yield: 1.6 g (60 %)

Rf (methylene chloride/MeOH/water/glacial acetic acid 70:30:1:1) = 0.76

MS (DCI) = 265 (M+1)

16b) 2S-(N-(Boc-His(DNP))-amino)-1-cyclohexyl-6-(2-pyridyl)-3S-hexanol

0.55 ml of pivaloyl chloride is added dropwise at -5°C to 1.9 g of Boc-His(DNP)-OH, 0.36 ml of pyridine and 0.62 ml of N-ethylpiperidine in 50 ml of

methylene chloride. After 10 minutes at -5°C the mixture is stirred at +10°C for 10 minutes. After renewed cooling to -5°C 1.3 g of 2S-amino-1-cyclohexyl-6-(2-pyridyl)-3S-hexanol (liberated from the dihydrochloride from Example 15d) with sodium carbonate) in 20 ml of methylene chloride are added. After one hour at -5°C the mixture is left to stand at room temperature for 16 hours. 50 ml of saturated sodium carbonate solution are added, and the mixture is extracted three times with ethyl acetate. The combined organic extracts are dried over sodium sulfate and concentrated and purified by chromatography on silica gel (EE/MeOH 10:1).

Rf (EE/MeOH 10:1) = 0.25

MS (FAB) =680 (M+1)

16c) 2S-(N-His(DNP)-amino)-1-cyclohexyl-6-(2-pyridyl)-3S-hexanol dihydrochloride

26 ml of HCl-saturated dimethoxyethane are added dropwise at 0-5°C to 170 mg of 2S-(N-(Boc-His(DNP))-amino)-1-cyclohexyl-6-(2-pyridyl)-3S-hexanol from Example 16b) in 10 ml of dimethoxyethane, and the mixture is stirred in the ice bath for one hour and at room temperature for 4 hours. The reaction solution is concentrated and toluene is added and the mixture is concentrated twice more.

Yield: 167 mg of the title compound

16d) 1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(tert.butylaminocarbonyl-Phe-His(DNP))-amino)-3S-hexanol

The title compound is obtained starting from 167 mg (0.256 mmol) of 2S-(N-His(DNP)-amino)-1-cyclohexyl-6-(2-pyridyl)-3S-hexanol dihydrochloride (Example 16c) and 68 mg (0.256 mmol) of N-tert.butylaminocarbonyl-Phe-OH (Example 16a) in analogy to the process described in Example 15e).

Yield: 83.7 mg (40 %) of the title compound

Rf (methylene chloride/MeOH 9:1) = 0.44
MS (FAB) = 826 (M+1)

16e) 1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(tert.butylaminocarbonyl-Phe-His)-amino)-3S-hexanol

83 mg (0.1 mmol) of 1-cyclohexyl-6-(2-pyridyl)-2S-(N-(tert.butylaminocarbonyl-Phe-His(DNP))-amino)-3S-hexanol (Example 16d) are dissolved in 5 ml of acetonitrile and stirred with 0.1 ml (1 mmol) of thiophenol at room temperature for 6 hours. The reaction solution is concentrated in vacuo, and the residue is purified by medium-pressure column chromatography on silica gel (methylene chloride/MeOH 100:0, 98:2, 95:5, 9:1).
Yield: 51 mg (77 %) of the title compound
Rf (methylene chloride/MeOH 9:1) = 0.26
MS (FAB) = 660 (M+1)

Example 17

1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(tert.butylaminocarbonyl-Phe-Nva)-amino)-3S-hexanol

17a) N-tert.butylaminocarbonyl-Phe-Nva-OMe

The title compound is obtained from 264 mg (1 mmol) of N-tert.butylaminocarbonyl-Phe-OH (Example 16a) and 167 mg (1 mmol) of Nva-OMe hydrochloride by the process described in Example 15b).
Yield: 0.35 g (93 %)
Rf (methylene chloride/MeOH 9:1) = 0.69
MS (DCI) = 378 (M+1)

17b) N-tert.butylaminocarbonyl-Phe-Nva-OH

The title compound is obtained from 100 mg (0.265 mmol) of N-tert.butylaminocarbonyl-Phe-Nva-OMe (Example 17a) by the process described in Example

15c).
Yield: 90 mg (93 %)
MS (DCI) = 364 (M+1)

17c) 1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(tert.butylaminocarbonyl-Phe-Nva)-amino)-3S-hexanol

The title compound is obtained from 166 mg (0.529 mmol) of 2S-amino-1-cyclohexyl-6-(2-pyridyl)-3S-hexanol dihydrochloride (Example 15d) and 192 mg (0.529 mmol) of N-tert.butylaminocarbonyl-Phe-Nva-OH by the process described in Example 15e).
Yield: 121 mg (37 %)
Rf (methylene chloride/MeOH 9:1) = 0.52
MS (FAB) = 622 (M+1)

Example 18

(1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(tert.butylaminocarbonyl-Thi-Nva)-amino)-3S-hexanol

18a) N-tert.butylaminocarbonyl-Thi-OH

The title compound is obtained from 1.5 g (4.82 mmol) of L-thienylalanine p-toluenesulfonate and 0.68 ml (5.78 mmol) of tert.butyl isocyanate by the process described in Example 15a).
Yield: 0.7 g
Rf (methylene chloride/MeOH/AcOH/water 70:30:1:1) = 0.9
MS (FAB) = 271 (M+1)

18b) N-tert.butylaminocarbonyl-Thi-Nva-OMe

The title compound is obtained from 0.7 g (2.6 mmol) of N-tert.butylaminocarbonyl-Thi-OH (Example 18a) and 0.44 g (2.6 mmol) of Nva-OMe hydrochloride by the process described in Example 15b).
Yield: 0.8 g (80 %)

MS (FAB) = 384 (M+1)

18c) N-tert.Butylaminocarbonyl-Thi-Nva-OH

The title compound is obtained from 0.8 g (2.1 mmol) of N-tert.butylaminocarbonyl-Thi-Nva-OMe (Example 18b) by the process described in Example 15c).
Yield: 0.53 g (69 %)
Rf (methylene chloride/MeOH 9:1) = 0.08
MS (FAB) = 369 (M+1)

18d) 1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(tert.butylaminocarbonyl-Thi-Nva)-amino)-3S-hexanol

The title compound is obtained from 92 mg (0.25 mmol) of N-tert.butylaminocarbonyl-Thi-Nva-OH (Example 18c) and 87 mg (0.25 mmol) of 2S-amino-1-cyclohexyl-6-(2-pyridyl)-3S-hexanol dihydrochloride (Example 15d) in analogy to the process described in Example 15e).
Yield: 59.6 mg (38 %)
Rf (methylene chloride/MeOH 9:1) = 0.39
MS (FAB) = 628 (M+1)

Example 19

(1-Cyclohexyl-6-(2-pyridyl)-2S-(N-)tert.butylaminocarbonyl-Tyr(OMe)-Nva)-amino)-3S-hexanol

19a) N-tert.Butylaminocarbonyl-Tyr(OMe)-OH

The title compound is prepared from 3.0 g (8.16 mmol) of L-(O-methyltyrosine) p-toluenesulfonate and 1.15 ml (9.79 mmol) of tert.butyl isocyanate in analogy to the process described in Example 15a).
Yield: 1.7 g (70 %)
MS (FAB) = 295 (M+1)

19b) N-tert.Butylaminocarbonyl-Tyr(OMe)-Nva-OMe

The title compound is prepared from 0.7 g (2.38 mmol) of N-tert.butylaminocarbonyl-Tyr(OMe)-OH and 0.4 g (2.38 mmol) of Nva-OMe hydrochloride in analogy to the process described in Example 15b).
Yield: 0.8 g (82 %)
Rf (methylene chloride/MeOH 9:1) = 0.66
MS (FAB) = 408 (M+1)

19c) N-tert.Butylaminocarbonyl-Tyr(OMe)-Nva-OH

The title compound is obtained from 0.8 g (1.96 mmol) of N-tert.butylaminocarbonyl-Tyr(OMe)-Nva-OMe (Example 19b) in analogy to the process described in Example 15c).
Yield: 0.7 g (91 %)
Rf (methylene chloride/MeOH 9:1) = 0.13
MS (FAB) = 394 (M+1)

19d) 1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(tert.butylaminocarbonyl-Tyr(OMe)-Nva)-amino)-3S-hexanol

The title compound is obtained from 110 mg (0.28 mmol) of N-tert.butylaminocarbonyl-Tyr(OMe)-Nva-OH (Example 19c) and 98 mg (0,28 mmol) of 2S-amino-1-cyclohexyl-6-(2-pyridyl)-3S-hexanol (Example 15d) in analogy to the process described in Example 15e).
Yield: 35.2 mg (19 %)
Rf (methylene chloride/MeOH 9:1) = 0.38
MS (FAB) = 652 (M+1)

The compounds described in the following Examples 20 to 29 were obtained using suitable starting materials and employing the processes described in Examples 15 to 19:

Example 20

1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(tert.butylaminocarbonyl-Phe-Nva)-amino)-3R-hexanol

Rf (toluene/ethanol 9:1) = 0.32
MS (FAB) = 622 (M+1)

Example 21

1-Cyclohexyl-6-(3-pyridyl)-2S-(N-(tert.butylaminocarbonyl-Phe-His)-amino)-3R-hexanol

Rf (methylene chloride/MeOH 9:1) = 0.32
MS (FAB) = 660 (M+1)

Example 22

1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(ethylaminocarbonyl-Phe-His)-amino)-3R-hexanol

MS (FAB) = 632 (M+1)

Example 23

1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(isopropylaminocarbonyl-Phe-Nva)-amino)-3R-hexanol

Rf (methylene chloride/methanol 9:1) = 0.46
MS (FAB) = 608 (M+1)

Example 24

1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(2-amino-2-methylpropyl-aminocarbonyl-Phe-Nva)-amino)-3S-hexanol

Rf (methylene chloride/MeOH 7:3) = 0.09
MS (FAB) = 637 (M+1)

Example 25

1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(tert.butylaminocarbonyl-Phe-Asn)-amino)-3S-hexanol

Rf (methylene chloride/MeOH 9:1) = 0.24
MS (FAB) = 637 (M+1)

Example 26

1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(ethylaminocarbonyl-Phe-His)-amino)-3S-hexanol

MS (FAB) = 632 (M+1)

Example 27

1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(isopropylaminocarbonyl-Phe-Nva)-amino)-3S-hexanol

Rf (methylene chloride/MeOH 9:1) = 0.39
MS (FAB) = 608 (M+1)

Example 28

1-Cyclohexyl-6-(2-pyridyl)-2S-(N-(2,2-dimethylpropyl-aminocarbonyl-Phe-Nva)-amino)-3S-hexanol

Rf (methylene chloride/MeOH 9:1) = 0.51
MS (FAB) = 636 (M+1)

Example 29

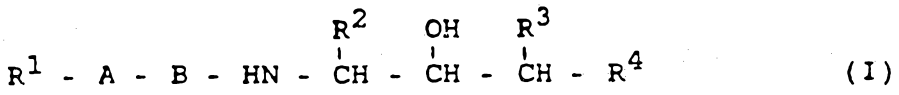
1-Cyclohexyl-6-(2-pyridyl)-2S-[N-[(1-carboxy-1-methyl-ethylaminocarbonyl)-Phe-Nva]-amino]-3S-hexanol

Rf (methylene chloride/MeOH 9:1) = 0,10
MS (FAB) = 652 (M+1)

~~Patent claims~~

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of the formula I



(I)

in which

R^1 denotes a radical of the formula II

(II)

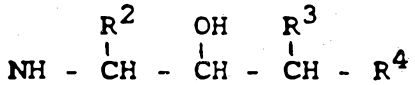
in which

R^a denotes hydrogen, (C_1-C_{10})-alkyl which is optionally singly or doubly unsaturated and which is optionally substituted by up to 3 identical or different radicals from the series comprising hydroxyl, (C_1-C_7)-alkoxy, (C_1-C_7)-alkanoyloxy, carboxyl, (C_1-C_7)-alkoxycarbonyl, Cl, Br, amino, (C_1-C_7)-alkylamino, di-(C_1-C_7)-alkylamino, (C_1-C_5)-alkoxycarbonylamino, (C_7-C_{15})-aralkoxycarbonylamino and 9-fluorenylmethyloxycarbonylamino, or (C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl, (C_6-C_{14})-aryl which is optionally substituted by one or two identical or different radicals from the series comprising F, Cl, Br, I, hydroxyl, (C_1-C_7)-alkoxy, (C_1-C_7)-alkyl, (C_1-C_7)-alkoxycarbonyl, amino, anilino which is optionally substituted by up to 2 halogen, and trifluoromethyl; (C_6-C_{14})-aryl-(C_1-C_6)-alkyl in which the aryl moiety is optionally substituted by one or two identical or different radicals from the series comprising F, Cl, Br, I, hydroxyl, (C_1-C_7)-alkoxy, (C_1-C_7)-alkyl, (C_1-C_7)-alkoxycarbonyl, amino, (C_1-C_7)-alkylamino, di-(C_1-C_7)-alkylamino, carboxyl, carboxymethoxy, amino-(C_1-C_7)-alkyl, (C_1-C_7)-alkylamino-(C_1-C_7)-alkyl,

di-(C_1-C_7)-alkylamino-(C_1-C_7)-alkyl, (C_1-C_7)-alkoxycarbonylmethoxy, carbamoyl, sulfamoyl, (C_1-C_7)-alkoxysulfonyl, sulfo- and guanidinomethyl, or represents the radical of a 5- or 6-membered monocyclic or 9- or 10-membered bicyclic heteraromatic which has at least one carbon atom, 1-4 nitrogen atoms and/or 1 sulfur or oxygen atom also as ring members and is optionally substituted by one, two or three identical or different radicals from the series comprising F, Cl, Br, hydroxyl, (C_1-C_7)-alkoxy, (C_1-C_7)-alkyl, (C_1-C_7)-alkoxycarbonyl, amino or trifluoromethyl,

A denotes a radical, which is linked N-terminal with R^1 and C-terminal with B, of an amino acid from the series comprising phenylalanine, histidine, tyrosine, tryptophan, methionine, leucine, isoleucine, asparagine, aspartic acid, β-2-thienylalanine, β-3-thienylalanine, β-2-furylalanine, β-3-furylalanine, lysine, ornithine, valine, alanine, 2,4-diaminobutyric acid, arginine, 4-chlorophenylalanine, methionine sulfone, methionine sulfoxide, 2-pyridylalanine, 3-pyridylalanine, cyclohexylalanine, cyclohexylglycine, im-methylhistidine, O-methyltyrosine, O-benzyltyrosine, O-tert.-butyltyrosine, phenylglycine, 1-naphthylalanine, 2-naphthylalanine, 4-nitrophenylalanine, norvaline, β-2-benzo[b]thienylalanine, β-3-benzo[b]thienylalanine, 2-fluorophenylalanine, 3-fluorophenylalanine, 4-fluorophenylalanine, norleucine, cysteine, S-methyl-cysteine, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, homophenylalanine, DOPA, O-dimethyl-DOPA, 2-amino-4-(2-thienyl)-butyric acid, benzodioxol-5-ylalanine, N-methylhistidine, 2-amino-4-(3-thienyl)butyric acid, 3-(2-thienyl)-serine, (Z)-dehydrophenylalanine, and (E)-dehydrophenylalanine,

B denotes a radical, which is linked N-terminal with A and C-terminal with



of an amino acid which is defined as under A,

R^2 denotes hydrogen, (C_1-C_{10})-alkyl, (C_4-C_7)-cycloalkyl, (C_4-C_7)-cycloalkyl-(C_1-C_4)-alkyl, (C_6-C_{14})-aryl or (C_6-C_{14})-aryl-(C_1-C_4)-alkyl, and

R^3 denotes hydrogen, (C_1-C_{10})-alkyl, (C_6-C_{14})-aryl or (C_6-C_{14})-aryl-(C_1-C_4)-alkyl,

R^4 denotes a radical of the formula III

(III)

in which, as desired, X can be absent or represents -O-, -S-, $-CF_2-$, -CO- or $-CHR^6-$,

p and q denote, independently of one another, 0, 1, 2, 3 or 4,

R^6 denotes hydrogen, (C_1-C_7)-alkyl, (C_1-C_5)-alkoxy (C_1-C_5)-alkylthio, (C_1-C_5)-alkylamino, -OH, $-N_3$, -F, -Cl, -Br or -I, and

R^5 denotes hydrogen, -OH, $-NH_2$ or heteroaryl which can also be partially or completely hydrogenated, as well as the physiologically tolerated salts thereof.

2. A compound of the formula I as claimed in claim 1, wherein

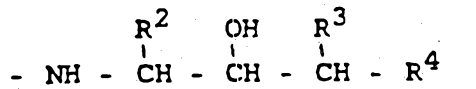
R^1 denotes a radical of the formula II in which

R^a denotes hydrogen, (C_1-C_{10})-alkyl, (C_1-C_4)-alkoxy-(C_1-C_{10})-alkyl, carboxy-(C_1-C_{10})-alkyl, (C_1-C_4)-alkoxycarbonyl-(C_1-C_{10})-alkyl, amino-(C_1-C_{10})-alkyl, diamino-(C_1-C_{10})-alkyl, (C_1-C_4)-alkylamino-(C_1-C_{10})-alkyl, di(C_1-C_4)alkylamino-(C_1-C_{10})-alkyl, N,N'-di-(C_1-C_4)-alkyldiamino-(C_1-C_{10})-alkyl, N,N,N',N'-tetra(C_1-C_4)-alkyldiamino-(C_1-C_{10})-alkyl, (C_1-C_4)-alkoxycarbonyl-amino-(C_1-C_{10})-alkyl, (C_7-C_{15})-aralkoxycarbonylamino-(C_1-C_{10})-alkyl, cyclopentyl, cyclohexyl, cycloheptyl,

cyclopentyl-(C_1-C_6)-alkyl, cyclohexyl-(C_1-C_6)-alkyl, phenyl which is optionally substituted by one or two identical or different radicals from the series comprising F, Cl, Br, I, hydroxyl, (C_1-C_4)-alkoxy, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxycarbonyl, amino or trifluoromethyl, or (C_6-C_{10})-aryl-(C_1-C_6)-alkyl in which the aryl moiety can be substituted as phenyl above, or represents the radical of a 5- or 6-membered monocyclic or 9- or 10-membered bicyclic heteroaromatic which has at least one carbon atom, 1-4 nitrogen atoms and/or 1 sulfur or oxygen atom also as ring members and which is optionally substituted by one, two or three identical or different radicals from the series comprising F, Cl, Br, hydroxyl, (C_1-C_7)-alkoxy, (C_1-C_7)-alkyl, (C_1-C_7)-alkoxycarbonyl, amino or trifluoromethyl,

A denotes a radical, which is linked N-terminal with R^1 and C-terminal with B, of an amino acid from the series comprising phenylalanine, histidine, tyrosine, tryptophan, β-2-thienylalanine, β-3-thienylalanine, β-2-furylalanine, β-3-furylalanine, 4-chlorophenylalanine, 2-pyridylalanine, 3-pyridylalanine, cyclohexylalanine, cyclohexylglycine, im-methylhistidine, O-methyltyrosine, O-benzyltyrosine, O-tert.-butyltyrosine, phenylglycine, 1-naphthylalanine, 2-naphthylalanine, 4-nitrophenylalanine, 2-fluorophenylalanine, 3-fluorophenylalanine, 4-fluorophenylalanine, homophenylalanine, DOPA, O-dimethyl-DOPA, 2-amino-4-(2-thienyl)-butyric acid, benzodioxol-5-yl-alanine, N-methylhistidine, 2-amino-4-(3-thienyl)-butyric acid, 3-(2-thienyl)-serine, (Z)-dehydrophenylalanine or (E)-dehydrophenylalanine,

B denotes a radical, which is linked N-terminal with A and C-terminal with



of an amino acid from the series comprising phenylalanine, histidine, tyrosine, tryptophan, methionine, leucine, isoleucine, asparagine, aspartic acid, β-2-thienylalanine, β-3-thienylalanine, β-2-furylalanine, β-3-furylalanine, lysine, ornithine, valine, alanine, 2,4-diaminobutyric acid, arginine, 4-chlorophenylalanine, methionine sulfone, methionine sulfoxide, 2-pyridylalanine, 3-pyridylalanine, cyclohexylalanine, cyclohexylglycine, im-methylhistidine, O-methyltyrosine, O-benzyltyrosine, O-tert.-butyltyrosine, phenylglycine, 1-naphthylalanine, 2-naphthylalanine, 4-nitrophenylalanine, norvaline, β-2-benzo[b]thienylalanine, β-3-benzo[b]thienylalanine, 2-fluorophenylalanine, 3-fluorophenylalanine, 4-fluorophenylalanine, norleucine, cysteine, S-methyl-cysteine, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, homophenylalanine, DOPA, O-dimethyl-DOPA, 2-amino-4-(2-thienyl)-butyric acid, benzodioxol-5-yl-alanine, N-methylhistidine, 2-amino-4-(3-thienyl)-butyric acid, 3-(2-thienyl)-serine, (Z)-dehydrophenylalanine and (E)-dehydrophenylalanine,

R^2 denotes hydrogen, (C_1-C_{10})-alkyl, (C_4-C_7)-cycloalkyl, (C_4-C_7)-cycloalkyl-(C_1-C_4)-alkyl, (C_6-C_{14})-aryl or (C_6-C_{14})-aryl-(C_1-C_4)-alkyl,

R^3 denotes hydrogen, (C_1-C_{10})-alkyl, (C_6-C_{14})-aryl or (C_6-C_{14})-aryl-(C_1-C_4)-alkyl,

R^4 denotes a radical of the formula III in which, as desired,

X can be absent or represents -O-, -S-, $-CF_2-$, -CO- or $-CHR^6-$,

p and q denote, independently of one another, 0, 1, 2, 3 or 4,

R^6 denotes hydrogen, (C_1-C_7)-alkyl, (C_1-C_5)-alkoxy, (C_1-C_5)-alkylthio, (C_1-C_5)-alkylamino, -OH, $-N_3$, -F, -Cl, -Br or -I, and

R^5 denotes hydrogen, -OH, $-NH_2$ or heteroaryl which can also be partially or completely hydrogenated,

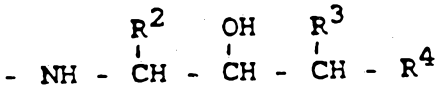
as well as the physiologically tolerated salts thereof.

3. A compound of the formula I as claimed in one or more of claims 1-2, wherein

R^1 denotes a radical of the formula II in which
R^a denotes hydrogen, (C_1-C_6)-alkyl, carboxy-(C_1-C_6)-alkyl, amino-(C_1-C_6)-alkyl, diamino-(C_1-C_6)-alkyl, (C_1-C_4)-alkylamino-(C_1-C_6)-alkyl, di-(C_1-C_4)-alkylamino-(C_1-C_6)-alkyl, N,N'-di-(C_1-C_4)-alkyldiamino-(C_1-C_6)-alkyl, N,N,N',N'-tetra-(C_1-C_4)-alkyldiamino-(C_1-C_6)-alkyl, (C_1-C_4)-alkoxycarbonylamino-(C_1-C_6)-alkyl or phenyl which is optionally substituted by one or two identical or different radicals from the series comprising F, Cl, hydroxyl or amino,

A denotes a radical, which is linked N-terminal with R^1 and C-terminal with B, of an amino acid from the series comprising phenylalanine, tyrosine, β-2-thienylalanine, β-3-thienylalanine, 4-chlorophenylalanine, O-methyltyrosine, O-benzyltyrosine, 1-naphthylalanine, 2-fluorophenylalanine, 3-fluorophenylalanine or 4-fluorophenylalanine,

B denotes a radical, which is linked N-terminal with A and C-terminal with



of an amino acid from the series comprising phenylalanine, histidine, leucine, asparagine, β-2-thienylalanine, β-3-thienylalanine, lysine, norvaline, 2-fluorophenylalanine, 3-fluorophenylalanine, 4-fluorophenylalanine, norleucine, S-methylcysteine or N-methylhistidine,

R^2 denotes isobutyl, cyclohexylmethyl or benzyl,

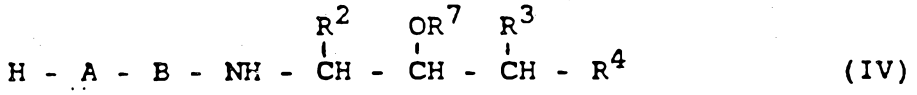
R^3 is hydrogen, and

R^4 represents a radical of the formula III in which
X is absent,
p is 0,
q denotes 0, 1, 2, 3 or 4, and

R^5 denotes 2-pyridyl, 4-pyridyl, 2-imidazolyl or 1-(C_1-C_4-alkyl)-2-imidazolyl,

as well as the physiologically tolerated salts thereof.

4. A process for the preparation of a compound of the formula I as claimed in one or more of claims 1-3, which comprises reacting a compound of the general formula IV



$$H - A - B - NH - \underset{\displaystyle R^2}{CH} - \underset{\displaystyle OR^7}{CH} - \underset{\displaystyle R^3}{CH} - R^4 \qquad (IV)$$

in which A, B, R^2, R^3 and R^4 have the same meaning as in claim 1, and in which R^7 denotes hydrogen or a protective group which can easily be eliminated,

a) with an isocyanate of the general formula V

$$R^a - N = C = O \qquad (V),$$

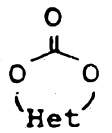
in which R^a has the same meaning as in claim 1, in a suitable organic solvent, or else dispensing with a solvent, in each case as desired with or without the addition of a Lewis acid or of a Lewis base as catalyst, at a temperature between -80°C and the boiling point of the solvent, and, where appropriate, eliminating the protective group R^7 again, or

b) in succession, firstly with a carbonic acid derivative of the general formula VI

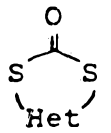
$$R^8 - \overset{\displaystyle O}{\overset{\|}{C}} - R^9 \qquad (VI),$$

in which R^8 and R^9 denote, independently of one another, halogen, (C_1-C_7)-alkoxy, (C_6-C_{12})-aryloxy,

(C_1-C_7)-alkylthio, (C_6-C_{12})-arylthio or a radical Het or Het-O-, it being possible for Het to be a mono- or bicyclic heterocycle, or in which R^8 and R^9 belong, together with the C=O group, to a mono- or bicyclic heterocycle of the type



or



,

preferably with phosgene, 1,1'-carbonyldiimidazole, 1,1'-carbonyldi-(1,2,4)-triazole, di-(N-succinimidyl) carbonate, di-(1-benzotriazolyl) carbonate, N,N'-carbonylbis-(2-methylimidazole) or 4,6-diphenylthieno[3,4-d]-1,3-dioxol-2-one 5,5-dioxide (Steglich reagent), and subsequently with an amine of the general formula VII

$$R^a - NH_2 \qquad \text{(VII)},$$

in which R^a has the same meaning as in claim 1, in an inert organic solvent, with or without the presence of an auxiliary base, at a temperature between -80°C and the boiling point of the particular solvent, and, where appropriate, eliminating again by known methods the protective group R^7 as well as, where appropriate, protective groups temporarily introduced into the fragments A and B.

5. The use of a compound of the formula I as claimed in one or more of claims 1-3 as a medicine.

6. The use of a compound of the formula I as claimed in one or more of claims 1-3 for the treatment of high blood pressure.

7. A pharmaceutical agent containing a compound of the

formula I as claimed in one or more of claims 1-3.

DATED this 16th day of November 1989.

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