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(54) Titre : PEPTIDES ANTAGONISTES DE LA BRADYKININE
(54) Title: PEPTIDES HAVING BRADYKININ ANTAGONIST ACTION

(57) Abrégé/Abstract:
Peptides having bradykinin antagonist action Peptides of the formula I A-B-C-E-F-K-(D)-Phe-G-M-F'-I (I) in which a stands for hydrogen, alkyl, alkanoyl, alkoxy-carbonyl, alkysulfonyl, cycloalkyl, aryl, aryloyl, arysulfonyl, heteroaryl or an amino acid which may optionally be subsituted, B is a basic amino acid, C denotes a dipeptide or tripeptide, E stands for the radical of an aromatic amino acid, F independently of one another denotes an amino acid which is optionally substituted in the side chain or a direct bond, G is an amino acid, F' is as defined for F, -NH-$(CH_2)_{2-8}$ or may optionally denote a direct bond, I is -OH, -NH_2 or -NHC_2H_5 and K denotes a radical -NH-$(CH_2)_{1-4}$-CO- or stands for a direct bond, have bradykinin antagonist action. Their therapeutic utility includes all pathological states which are mediated, caused or supported by bradykinin and bradykinin-related peptides. The peptides of the formula I are prepared by known methods of peptide synthesis.

HOE 89/F 261

Abstract of the disclosure:

Peptides having bradykinin antagonist action

Peptides of the formula I

A-B-C-E-F-K-(D)-Phe-G-M-F'-I (I)

in which A stands for hydrogen, alkyl, alkanoyl, alkoxycarbonyl, alkylsulfonyl, cycloalkyl, aryl, aryloyl, arylsulfonyl, heteroaryl or an amino acid which may optionally be substituted, B is a basic amino acid, C denotes a dipeptide or tripeptide, E stands for the radical of an aromatic amino acid, F independently of one another denotes an amino acid which is optionally substituted in the side chain or a direct bond, G is an amino acid, F' is as defined for F, $-NH-(CH_2)_{2-8}$ or may optionally denote a direct bond, I is $-OH$, $-NH_2$ or $-NHC_2H_5$ and K denotes a radical $-NH-(CH_2)_{1-4}-CO-$ or stands for a direct bond, have bradykinin antagonist action. Their therapeutic utility includes all pathological states which are mediated, caused or supported by bradykinin and bradykinin-related peptides. The peptides of the formula I are prepared by known methods of peptide synthesis.

HOECHST AKTIENGESELLSCHAFT HOE 89/F 261 Dr.WI/gm

Description

Peptides having bradykinin antagonist action

The invention relates to novel peptides having bradykinin antagonist action and to a process for their preparation.

Bradykinin antagonist peptides are described in WO 86/07263 in which, inter alia, L-Pro in position 7 of the peptide hormone bradykinin or other bradykinin analogs is replaced by a D-amino acid, such as D-Phe, D-Thi, D-Pal, CDF, D-Nal, MDY, D-Phg, D-His, D-Trp, D-Tyr, D-hPhe, D-Val, D-Ala, D-His, D-Ile, D-Leu and DOMT.

The invention is based on the object of finding novel active peptides having bradykinin antagonist action.

This object is achieved by the peptides of the formula I

A-B-C-E-F-K-(D)-Phe-G-M-F'-I (I),

in which

A a_1) denotes hydrogen,

(C_1-C_8)-alkyl,

(C_1-C_8)-alkanoyl,

(C_1-C_8)-alkoxycarbonyl or

(C_1-C_8)-alkylsulfonyl,

in which in each case 1, 2 or 3 hydrogen atoms are optionally replaced by 1, 2 or 3 identical or different radicals from the series comprising

carboxyl,

amino,

(C_1-C_4)-alkyl,

(C_1-C_4)-alkylamino,

hydroxyl,

(C_1-C_4)-alkoxy,

halogen,

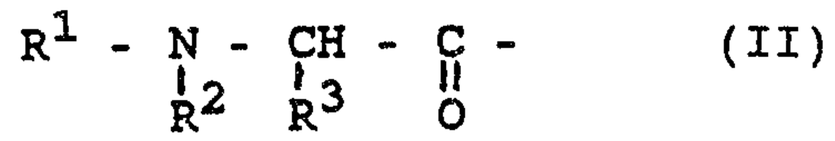
di-(C_1-C_4)-alkylamino,

carbamoyl,
sulfamoyl,
(C_1-C_4)-alkoxycarbonyl,
(C_6-C_{12})-aryl and
(C_6-C_{12})-aryl-(C_1-C_5)-alkyl, or in which in each case 1 hydrogen atom is optionally replaced by a radical from the series comprising
(C_3-C_8)-cycloalkyl,
(C_1-C_4)-alkylsulfonyl,
(C_1-C_4)-alkylsulfinyl,
(C_6-C_{12})-aryl-(C_1-C_4)-alkylsulfonyl,
(C_6-C_{12})-aryl-(C_1-C_4)-alkylsulfinyl,
(C_6-C_{12})-aryloxy,
(C_3-C_9)-heteroaryl and
(C_3-C_9)-heteroaryloxy
and
1 or 2 hydrogen atoms are replaced by 1 or 2 identical or different radicals from the series comprising
carboxyl,
amino,
(C_1-C_4)-alkylamino,
hydroxyl,
(C_1-C_4)-alkoxy,
halogen,
di-(C_1-C_4)-alkylamino,
carbamoyl,
sulfamoyl,
(C_1-C_4)-alkoxycarbonyl,
(C_6-C_{12})-aryl and
(C_6-C_{12})-aryl-(C_1-C_5)-alkyl,
a_2) denotes (C_3-C_8)-cycloalkyl,
carbamoyl, which may be optionally substituted on the nitrogen by (C_1-C_6)-alkyl or (C_6-C_{12})-aryl,
(C_6-C_{12})-aryl,
(C_7-C_{13})-aryloyl,
(C_6-C_{12})-arylsulfonyl,
(C_3-C_9)-heteroaryl, or (C_3-C_9)-heteroaryloyl,
where in the radicals defined under a_1) and a_2) in each case aryl, heteroaryl, aryloyl, arylsulfonyl and

heteroaryloyl is optionally substituted by 1, 2, 3 or 4 identical or different radicals from the series comprising

carboxyl,
amino,
nitro,
(C_1-C_4)-alkylamino,
hydroxyl,
(C_1-C_4)-alkyl,
(C_1-C_4)-alkoxy,
halogen,
cyano,
di-(C_1-C_4)-alkylamino,
carbamoyl,
sulfamoyl and
(C_1-C_4)-alkoxycarbonyl, or

a_3) denotes a radical of the formula II



(II)

R^1 is defined as A under a_1) or a_2),

R^2 denotes hydrogen or methyl,

R^3 denotes hydrogen or
(C_1-C_6)-alkyl, preferably (C_1-C_4)-alkyl,
which is optionally monosubstituted by
amino,
substituted amino,
hydroxyl,
carboxyl,
carbamoyl,
guanidino,
substituted guanidino,
ureido,
mercapto,
methylmercapto,
phenyl,
4-chlorophenyl,
4-fluorophenyl,
4-nitrophenyl,
4-methoxyphenyl,

4-hydroxyphenyl,
phthalimido,
4-imidazolyl,
3-indolyl,
2-thienyl,
3-thienyl,
2-pyridyl,
3-pyridyl or
cyclohexyl,

where substituted amino stands for a compound -NH-A- and substituted guanidino stands for a compound -NH-C(NH)-NH-A, in which A is defined as under a_1) or a_2);

B stands for a basic amino acid in the L- or D-configuration, which may be substituted in the side chain;

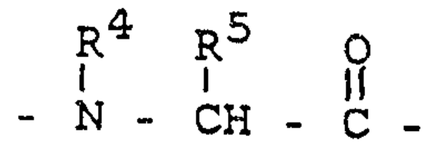
C stands for a compound of the formula IIIa or IIIb

G'-G'-Gly (IIIa)

G'-NH-$(CH_2)_n$-CO (IIIb),

in which

G' independently of one another denotes a radical of the formula IV



(IV)

in which

R^4 and R^5 together with the atoms carrying them form a heterocyclic mono-, bi- or tricyclic ring system having 2 to 15 carbon atoms, and

n is 2 to 8;

E stands for the radical of an aromatic amino acid;

F independently of one another denotes the radical of a neutral, acidic or basic, aliphatic or aromatic amino acid which may be substituted in the side chain, or stands for a direct bond;

(D)-Phe denotes D-phenylalanine which may be optionally substituted in the phenyl moiety;

G is as defined above for G' or denotes a direct bond;

F' is as defined for F, denotes a radical -NH-$(CH_2)_n$-, with n = 2 to 8, or, if G does not denote a direct

bond, can stand for a direct bond, and

I is -OH, $-NH_2$ or $-NHC_2H_5$,

K denotes the radical $-NH-(CH_2)_x-CO-$ with x = 1-4 or stands for a direct bond, and

M is as defined for F,

and their physiologically tolerable salts.

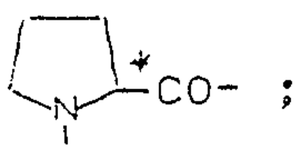
If not stated otherwise, the abbreviation of an amino acid radical without a stereodescriptor stands for the radical in the L-form (compare Schröder, Lübke, The Peptides, Volume I, New York 1965, pages XXII-XXIII; Houben-Weyl, Methoden der Organischen Chemie (Methods of Organic Chemistry), Volume XV/1 and 2, Stuttgart 1974), such as, for example,

Aad, Abu, γAbu, ABz, 2ABz, εAca, Ach, Acp, Adpd, Ahb, Aib, βAib, Ala, βAla, ΔAla, Alg, All, Ama, Amt, Ape, Apm, Apr, Arg, Asn, Asp, Asu, Aze, Azi, Bai, Bph, Can, Cit, Cys, Cyta, Daad, Dab, Dadd, Dap, Dapm, Dasu, Djen, Dpa, Dtc, Fel, Gln, Glu, Gly, Guv, hAla, hArg, hCys, hGln, hGlu, His, hIle, hLeu, hLys, hMet, hPhe, hPro, hSer, hThr, hTrp, hTyr, Hyl, Hyp, 3Hyp, Ile, Ise, Iva, Kyn, Lant, Lcn, Leu, Lsg, Lys, βLys, ΔLys, Met, Mim, Min, nArg, Nle, Nva, Oly, Orn, Pan, Pec, Pen, Phe, Phg, Pic, Pro, ΔPro, Pse, Pya, Pyr, Pza, Qin, Ros, Sar, Sec, Sem, Ser, Thi, βThi, Thr, Thy, Thx, Tia, Tle, Tly, Trp, Trta, Tyr, Val.

Suitable radicals of a heterocyclic ring system of the formula IV are in particular radicals of heterocycles of the group below:

pyrrolidine-2-carboxylic acid; piperidine-2-carboxylic acid;
1,2,3,4,-tetrahydroisoquinoline-3-carboxylic acid;
decahydroisoquinoline-3-carboxylic acid;
octahydroindole-2-carboxylic acid;
decahydroquinoline-2-carboxylic acid;
octahydrocyclopenta[b]pyrrole-2-carboxylic acid;

2-aza-bicyclo[2.2.2]octane-3-carboxylic acid;
2-azabicyclo[2.2.1]heptane-3-carboxylic acid;
2-azabicyclo[3.1.0]hexane-3-carboxylic acid;
2-azaspiro[4.4]nonane-3-carboxylic acid;
2-azaspiro[4.5]-decane-3-carboxylic acid;
spiro[(bicyclo[2.2..1]-heptane)-2,3pyrrolidine-5-carboxylic acid];
spiro[(bicyclo[2.2.2]octane)-2,3-pyrrolidine-5-carboxylic acid];
2-azatricyclo[4.3.0.$1^{6,9}$]decane-3-carboxylic acid;
decahydrocyclohepta[b]pyrrole-2-carboxylic acid;
decahydrocycloocta[b]pyrrole-2-carboxylic acid;
octahydrocyclotenta[c]pyrrole-2-carboxylic acid;
octahydroisoindole-1-carboxylic acid;
2,3,3a,4,6a-hexahydrocyclopenta[b]pyrrole-2-carboxylic acid;
2,3,3a,4,5,7a-hexahydroindole-2-carboxylic acid;
tetrahydrothiazole-4-carboxylic acid;
isoxalidine-3-carboxylic acid; pyrazolidine-3-carboxylic acid;
hydroxyproline-2-carboxylic acid; all of which may be optionally substituted: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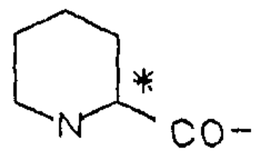
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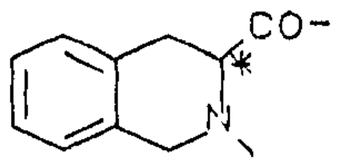
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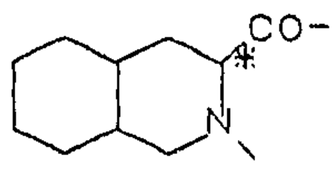
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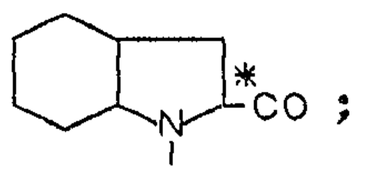
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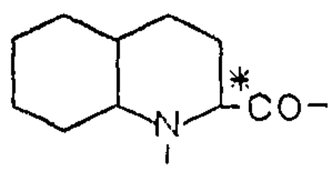
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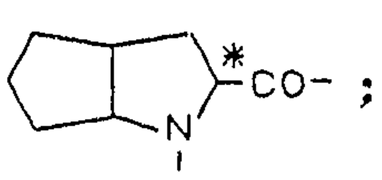
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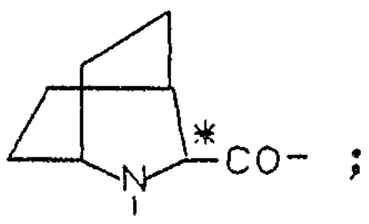
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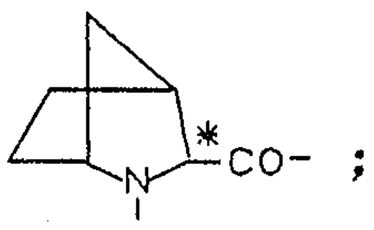
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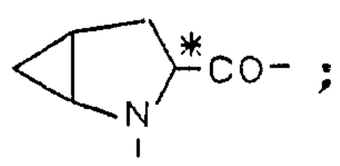
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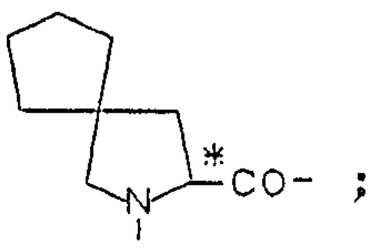
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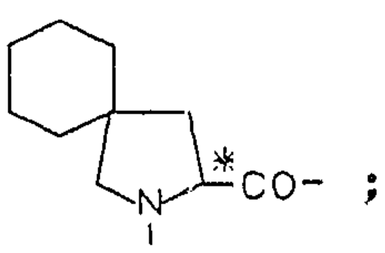
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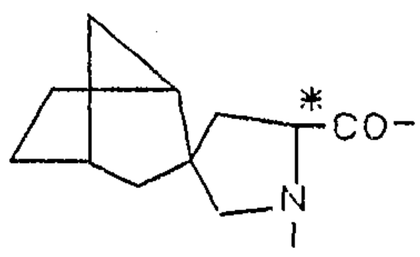
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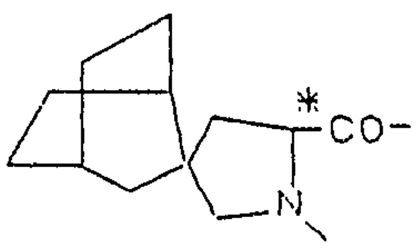
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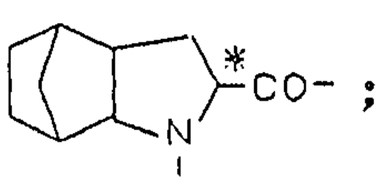
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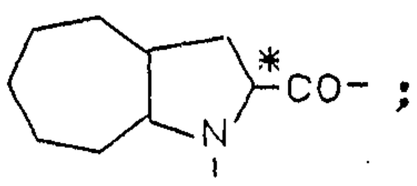
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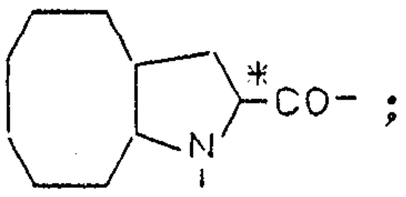
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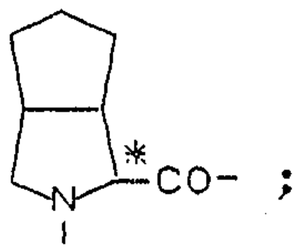
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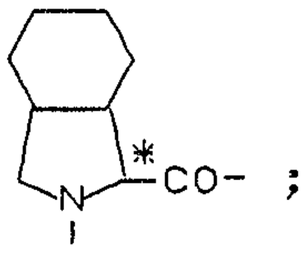
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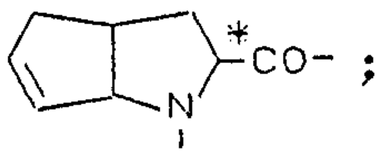
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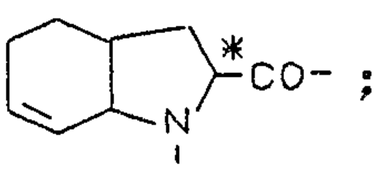
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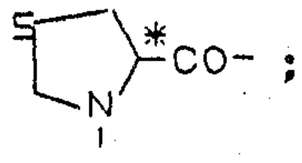
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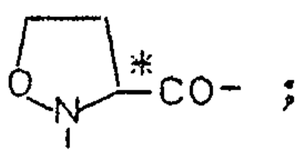
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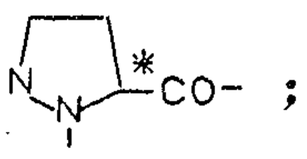
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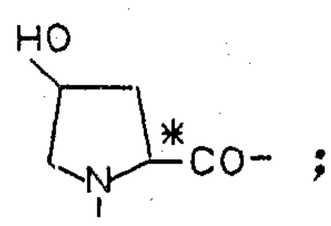
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The heterocycles based on the abovementioned radicals are known, for example, from

US-A-4,344,949, US-A-4,374,847, US-A-4,350,704, EP-A-50,800, EP-A-31,741, EP-A-51,020, EP-A-49,658, EP-A-49,605, EP-A-29,488, EP-A-46,953, EP-A-52,870, EP-A-271,865, DE-A-3,226,768, DE-A-3,151,690, DE-A-3,210,496, DE-A-3,211,397, DE-A-3,211,676, DE-A-3,227,055, DE-A-3,242,151, DE-A-3,246,503 and DE-A-3,246,757.

Some of these heterocycles are furthermore proposed in DE-A-3,818,850.3.

If not stated otherwise in the individual case, alkyl can be straight-chain or branched. The same applies to radicals derived therefrom such as alkoxy, aralkyl or alkanoyl.

(C_6-C_{12})-Aryl preferably denotes phenyl, naphthyl or biphenylyl. Radicals derived therefrom, such as aryloxy, aralkyl or aroyl, are to be formulated correspondingly.

Halo stands for fluorine, chlorine, bromine or iodine, preferably for chlorine.

Possible salts are, in particular, alkali metal or alkaline earth metal salts, salts with physiologically tolerable amines and salts with inorganic or organic acids such as, for example, HCl, HBr, H_2SO_4, H_3PO_4, maleic acid, fumaric acid, citric acid, tartaric acid and acetic acid.

Preferred peptides of the formula I are those in which

B denotes Arg, Lys, Orn, 2,4-diaminobutyroyl or an L-homoarginine radical, where in each case the amino or guanidino group of the side chain may be substituted by A as described under a_1) or a_2);

E stands for the radical of an aromatic amino acid in the L- or D-configuration, which contains 6 to 14 carbon atoms in the aryl moiety as ring members, such as phenylalanine which is optionally substituted by halogen in the 2-, 3- or 4-position, tyrosine, O-methyltyrosine, 2-thienylalanine, 2-pyridylalanine or naphthylalanine;

F' denotes the radical of a basic amino acid in the L- or D-configuration, such as Arg or Lys, where the guanidino group or amino group of the side chain may be replaced by A as described under a_1) or a_2), or denotes a radical $-NH-(CH_2)_n-$ with n = 2 to 8 and

K stands for the radical $-NH-(CH_2)_x-CO-$ with x = 2-4 or denotes a direct bond;

(D)-Phe denotes D-phenylalanine which may be optionally substituted in the phenyl moiety by halogen or (C_1-C_4)-alkoxy.

Particularly preferred peptides of the formula I are those in which

B denotes Arg, Orn or Lys, where the guanidino group or the amino group of the side chain is unsubstituted or may be substituted by (C_1-C_8)-alkanoyl, (C_7-C_{13})-aryloyl, (C_3-C_9)-heteroaryloyl, (C_1-C_8)-alkylsulfonyl or (C_6-C_{12})-arylsulfonyl, where the aryl, heteroaryl, aryloyl, arylsulfonyl and heteroaryloyl radicals may optionally be substituted, as described under a_2), with 1, 2, 3 or 4 identical or different radicals.

E denotes phenylalanine, 2-chlorophenylalanine, 3-chlorophenylalanine, 4-chlorophenylalanine, 2-fluorophenylalanine, 3-fluorophenylalanine, 4-fluorophenylalanine, tyrosine, O-methyltyrosine or β-(2-thienyl)alanine;

K stands for a direct bond and

M stands for a direct bond and

(D)-Phe denotes D-phenylalanine which may be optionally substituted by fluorine, chlorine, bromine or methoxy.

Very particularly preferred peptides of the formula I are those in which

A denotes hydrogen, (D)- or (L)-H-Arg, (D)- or (L)-H-Lys or (D)- or (L)-H-Orn,

B denotes Arg, Orn or Lys, where the guanidino group or the amino group of the side chain may be substituted by hydrogen, (C_1-C_8)-alkanoyl, (C_7-C_{13})-aryloyl, (C_3-C_9)-heteroaryloyl, (C_1-C_8)-alkylsulfonyl or (C_6-C_{12})-arylsulfonyl, where the aryl, heteroaryl, aryloyl, arylsulfonyl and heteroaryloyl radicals may optionally be substituted with 1, 2, 3 or 4 identical or different radicals from the series comprising methyl, methoxy and halogen.

C denotes Pro-Pro-Gly, Hyp-Pro-Gly or Pro-Hyp-Gly

E denotes Phe or Thia

F denotes Ser, Hser, Lys, Leu, Val, Nle, Ile or Thr

K stands for a direct bond

M stands for a direct bond

G stands for the radical of a heterocyclic ring system of the formula IV, where the radicals of the heterocycles pyrrolidine-2-carboxylic acid; piperidine-2-carboxylic acid; 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, cis- and trans-decahydroisoquinoline-3-carboxylic acid; cis-endo-,cis-exo-,trans-

octahydroindole-2-carboxylic acid, cis-endo-, cis-exo-, trans-octahydrocyclopentano[b]pyrrole-2-carboxylic acid or hydroxyproline-2-carboxylic acid are preferred,

F' denotes Arg

I stands for OH and

(D)-Phe denotes D-phenylalanine.

The invention furthermore relates to a process for the preparation of peptides of the formula I, which comprises

a) reacting a fragment having a C-terminal free carboxyl group or its activated derivative with an appropriate fragment having an N-terminal free amino group or

b) synthesizing the peptide stepwise, optionally splitting off one or more protective groups temporarily introduced for the protection of other functions in the compound obtained according to (a) or (b) and optionally converting the compounds of the formula I thus obtained into their physiologically tolerable salt.

The peptides of the present invention were prepared by generally known methods of peptide chemistry, see, for example, Houben-Weyl, Methoden der organischen Chemie (Methods of Organic Chemistry), Volume 15/2, preferably by means of solid phase synthesis such as described, for example, by B. Merrifield, J.Am.Chem.Soc. 85, 2149 (1963) or R. C. Sheppard, Int. J. Peptide Protein Res. 21, 118 (1983) or by equivalent known methods. Urethane protective groups such as, for example, the tert-butyloxycarbonyl(Boc) or fluorenylmethoxycarbonyl(Fmoc) protective group are used as α-amino protective group. If necessary for the prevention of side reactions or for the

synthesis of specific peptides, the functional groups in the side chain of amino acids are additionally protected by suitable protective groups (see, for example, T.W. Greene, "Protective Groups in Organic Synthesis"), where primarily,
Arg(Tos), Arg(Mts), Arg(Mtr), Arg(Pmc), Asp(OBzl), Asp(OBut), Cys(4-MeBzl), Cys(Acm), Cys(SBut), Glu(OBzl), Glu(OBut), His(Tos), His(Fmoc), His(Dnp), His(Trt), Lys(Cl-Z), Lys(Boc), Met(O), Ser(Bzl), Ser(But), Thr-(Bzl), Thr(But), Trp(Mts), Trp(CHO), Tyr(Br-Z), Tyr(Bzl) or Tyr(But) are employed.

Solid phase synthesis begins at the C-terminal end of the peptide with the coupling of a protected amino acid to an appropriate resin. Starting materials of this type may be obtained by linking a protected amino acid via an ester or amide bond to a polystyrene or polyacrylamide resin modified with a chloromethyl, hydroxymethyl, benzhydryl-amino(BHA) or methylbenzhydrylamino(MBHA) group. The resins used as support materials are commercially obtain-able. BHA and MBHA resins are usually used if the peptide synthesized is intended to have a free amide group at the C-terminus. If the peptide is intended to have a second-ary amide group at the C-terminal end, a chloromethyl or hydroxymethyl resin is used and the splitting off is carried out using the corresponding amines. If it is wished to obtain, for example, the ethylamide, the peptide can be split off from the resin using ethylamine, the splitting off of the side chain protective groups subsequently being carried out by means of other suitable reagents. If it is intended to retain the tert-butyl protective groups of the amino acid side chain in the peptide, the synthesis is carried out using the Fmoc protective group for temporary blocking of the α-amino group of the amino acid using the method described, for example, in R.C. Sheppard, J.Chem.Soc., Chem.Comm 1982, 587, the guanidino function of the arginine being protec-ted by protonation with pyridinium perchlorate and the protection of the other functionalized amino acids in the

side chain being carried out using benzyl protective groups which can be split off by means of catalytic transfer hydrogenation (A. Felix et al. J. Org. Chem. 13, 4194 (1978) or by means of sodium in liquid ammonia (W. Roberts, J.Am.Chem.Soc. 76, 6203 (1954)).

After splitting off the amino protective group of the amino acid coupled to the resin using a suitable reagent, such as, for example, trifluoroacetic acid in methylene chloride in the case of the Boc protective group or a 20% strength solution of piperidine in dimethylformamide in the case of the Fmoc protective group, the subsequently protected amino acids are successively coupled in the desired sequence. The intermediately resulting N-terminal protected peptide resins are deblocked by means of the reagents described above before linkage with the subsequent amino acid derivative.

All possible activating reagents used in peptide synthesis can be used as coupling reagents, see, for example, Houben-Weyl, Methoden der organischen Chemie (Methods of Organic Chemistry), Volume 15/2, in particular, however, carbodiimides such as, for example, N,N'-dicyclohexylcarbodiimide, N,N'-diisopropyl-carbodiimide or N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide. The coupling can in this case be carried out directly by addition of amino acid derivative and the activating reagent and, if desired, a racemization-suppressing additive such as, for example, 1-hydroxy-benzotriazole (HOBt) (W. König, R. Geiger, Chem. Ber. 103, 708 (1970)) or 3-hydroxy-4-oxo-3,4-dihydrobenzo-triazine (HOObt) (W. König, R. Geiger, Chem.Ber. 103, 2054 (1970)) to the resin or, however, the preactivation of the amino acid derivative as symmetrical anhydride or HOBt or HOObt ester can be carried out separately and the solution of the activated species in a suitable solvent can be added to the peptide resin capable of coupling.

The coupling or activation of the amino acid derivative with one of the abovementioned activating reagents can be carried out in dimethylformamide, N-methylpyrrolidone or methylene chloride or a mixture of the solvents mentioned. The activated amino acid derivative is customarily employed in a 1.5 to 4 fold excess. In cases in which an incomplete coupling takes place, the coupling reaction is repeated without previously carrying out the deblocking of the α-amino group of the peptide resin necessary for the coupling of the following amino acid.

The successful course of the coupling reaction can be monitored by means of the ninhydrin reaction, such as described, for example, by E. Kaiser et al. Anal. Biochem. 34 595 (1970). The synthesis can also be automated, for example using a peptide synthesizer model 430A from Applied Biosystems, it being possible either to use the synthesis program provided by the apparatus manufacturer or else, however, one set up by the user himself. The latter are in particular employed in the use of amino acid derivatives protected with the Fmoc group.

After synthesis of the peptides in the previously described manner, the peptide can be split off from the resin using reagents, such as, for example, liquid hydrogen fluoride (preferably in the peptides prepared according to the Boc method) or trifluoroacetic acid (preferably in the peptides synthesized according to the Fmoc method). These reagents not only cleave the peptide from the resin but also the other side chain protective groups of the amino acid derivative. In this manner, the peptide is obtained in the form of the free acid in addition using BHA and MBHA resins. With the BHA or MBHA resins, the peptide is obtained as acid amide when splitting off is carried out using hydrogen fluoride or trifluoromethanesulfonic acid. Additional processes for the preparation of peptide amides are described in Europ. Patent Applications Nos. 271 865 and 322 348. The splitting off of the peptide amides from the resin here

is carried out by treatment with medium strength acids (for example trifluoroacetic acid) usually used in peptide synthesis, cation entrainer substances such as phenol, cresol, thiocresol, anisole, thioanisole, ethanedithiol, dimethyl sulfide, ethyl methyl sulfide or similar cation entrainers customary in solid phase synthesis being added individually or as a mixture of two or more of these auxiliaries. In this case, the trifluoroacetic acid can also be used diluted by suitable solvents, such as, for example, methylene chloride.

If the tert-butyl or benzyl side chain protective groups of the peptides are to be retained, the splitting off of the peptide synthesized on a particularly modified support resin is carried out using 1% trifluoroacetic acid in methylene chloride, such as described, for example, in R.C. Sheppard J.Chem. Soc., Chem. Comm. 1982, 587. If individual tert-butyl or benzyl side chain protective groups are to be retained, a suitable combination of synthesis and splitting off methods is used.

For the synthesis of peptides having a C-terminal amide grouping or an ω-amino or ω-guanidinoalkyl grouping, the modified support resin described by Sheppard is likewise used. After the synthesis, the peptide fully protected in the side chain is split off from the resin and subsequently reacted with the appropriate amine or ω-aminoalkylamine or ω-guanidinoalkylamine in classical solution synthesis, it being possible for optionally present additional functional groups to be temporarily protected in a known manner.

An additional process for the preparation of peptides having an ω-aminoalkyl grouping is described in EP-A 264 802.

The peptides of the present invention were preferably synthesized by two general protective group tactics using

the solid phase technique:

The synthesis was carried out using an automatic peptide synthesizer model 430 A from Applied Biosystems, with Boc or Fmoc protective groups for temporary blockage of the α-amino group.

When using the Boc protective group, the synthesis cycles pre-programmed by the manufacturer of the apparatus were used for the synthesis.

The synthesis of the peptides having a free carboxyl group on the C-terminal end was carried out on a 4-(hydroxymethyl)phenylacetamidomethylpolystyrene resin functionalized with the corresponding Boc amino acid (R.B. Merrifield, J. Org. Chem. 43, 2845 (1978)) from Applied Biosystems. An MBHA resin from the same firm was used for the preparation of the peptide amides. N,N'-Dicyclohexylcarbodiimide or N,N'-diisopropylcarbodiimide were used as activating reagents. Activation was carried out as the symmetrical anhydride, as the HOBt ester or HOOBt ester in CH_2Cl_2, CH_2Cl_2 - DMF mixtures or NMP. 2-4 equivalents of activated amino acid derivative were employed for the coupling. In cases in which the coupling took place incompletely, the reaction was repeated.

During the use of the Fmoc protective group for the temporary protection of the α-amino group, our own synthesis programs were used for synthesis using the automatic peptide synthesizer model 430A from Applied Biosystems. The synthesis was carried out on a p-benzyloxybenzyl alcohol resin (S. Wang, J.Am.Chem.Soc. 95, 1328 (1973)) from Bachem which was esterified by a known method (E. Atherton et al. J.C.S. Chem. Comm. 1981, 336) using the appropriate amino acid. The activation of the amino acid derivatives as HOBt or HOOBt esters was carried out directly in the amino acid cartridges provided by the apparatus manufacturer by addition of a

solution of diisopropylcarbodiimide in DMF to the previously weighed-in mixture of amino acid derivative and HOBt or HOObt. Fmoc-amino acid-OObt esters prepared in substance can likewise be employed as described in EP-A-247 573. The splitting off of the Fmoc protective group was carried out using a 20% strength solution of piperidine in DMF in the reaction vessel. The excess of reactive amino acid derivative used was 1.5 to 2.5 equivalents. If the coupling was not complete, it was repeated as in the Boc method.

The peptides according to the invention have, individually or in combination, a bradykinin antagonist action which can be tested in various models (see Handbook of Exp. Pharmacol. Vol. 25, Springer Verlag, 1970, p. 53-55), for example on the isolated rat uterus, on the guinea pig ileum or on the isolated pulmonary artery of the guinea pig.

For testing the peptides according to the invention on the isolated arteria pulmonalis, guinea pigs (Dunkin Hartley) having a weight of 400 - 450 g are sacrificed by a blow to the back of the neck.

The thorax is opened and the arteria pulmonalis is carefully dissected out. The surrounding tissue is carefully removed and the arteria pulmonalis is cut spirally at an angle of 45°.

The vessel strip of 2.5 cm length and 3-4 mm width is fixed in a 10 ml capacity organ bath which is filled with Ringer solution.

Composition of the solution in mmol/l

NaCl	154
KCl	5.6
$CaCl_2$	1.9
$NaHCO_3$	2.4
Glucose	5.0

95% O_2 and 5% CO_2 is bubbled through the solution, which is warmed to 37°C. The pH is 7.4 and the preload on the vessel strip is 1.0 g.

The isotonic contraction changes are detected using a lever arrangement and an HF modem (position sensor) from Hugo Sachs and recorded on a compensating recorder (BEC, Goerz Metrawatt SE 460).

After equilibration for 1 hour, the experiment is begun. After the vessel strips have achieved their maximum sensitivity to 2×10^{-7} mol/l of bradykinin - bradykinin leads to a contraction of the vessel strips - the peptides are allowed to act for 10 minutes in each case in the doses 5×10^{-8} - 1×10^{-5} mol/l and, after adding bradykinin again, the decrease in the effect of bradykinin as opposed to the control is compared.

For the detection of a partial agonistic effect, the peptides are used in the doses 1×10^{-5} - 1×10^{-3} mol/l.

The IC_{50} values of the peptides according to the invention calculated from the dose-effect curves are shown in Table 1.

Table 1:

Compound	IC_{50} [M]
H-(D)-Arg-Arg-Pro-Hyp-Gly-Phe-Ser-(D)-Phe-Oic-Arg-OH	1.4×10^{-8}

The therapeutic utility of the peptides according to the invention includes all pathological states which are mediated, caused or supported by bradykinin and bradykinin-related peptides. This includes, inter alia, traumas, such as wounds, burns, rashes, erythemas, edemas, angina, arthritis, asthma, allergies, rhinitis, shock, inflammations, low blood pressure, pain, itching and changed sperm motility.

The invention therefore also relates to the use of peptides of the formula I as medicaments, and to pharmaceutical preparations which contain these compounds.

Pharmaceutical preparations contain an effective amount of the active substance of the formula I - individually or in combination - together with an inorganic or organic pharmaceutically utilizable excipient.

Administration can be carried out enterally, parenterally - such as, for example, subcutaneously, i.m. or i.v. -, sublingually, epicutaneously, nasally, rectally, intravaginally, intrabuccally or by inhalation. The dosage of the active substance depends on the mammal species, the body weight, age and on the manner of administration.

The pharmaceutical preparations of the present invention are prepared in solution, mixing, granulating or tablet coating processes known per se.

For oral administration or application to the mucosa, the active compounds are mixed with the customary additives for this, such as excipients, stabilizers or inert diluents, and brought into suitable forms for administration, such as tablets, coated tablets, hard gelatin capsules, aqueous, alcoholic or oily suspensions or aqueous, alcoholic or oily solutions, by customary methods. Inert excipients which may be used are, for example, gum arabic, magnesia, magnesium carbonate, potassium phosphate, lactose, glucose, magnesium stearyl fumarate or starch, in particular maize starch. In this case, the preparation may be present both as dry and moist granules. Suitable oily excipients or solvents are, for example, vegetable or animal oils, such as sunflower oil and cod liver oil.

A preparation for topical application may be present as an aqueous or oily solution, lotion, emulsion or gel, ointment or fatty ointment or, if possible, in spray

form, it being possible to improve the adhesion, if desired, by addition of a polymer.

For the intranasal form of administration, the compounds are mixed with the customary auxiliaries for this, such as stabilizers or inert diluents, and brought into suitable forms for administration, such as aqueous, alcoholic or oily suspensions or aqueous, alcoholic or oily solutions, by customary methods. Chelating agents, ethylenediamine-N,N,N',N'-tetraacetic acid, citric acid, tartaric acid or their salts may be added to aqueous intranasal preparations. Administration of the nasal solutions can be carried out by means of metered atomizers or as nasal drops, having a viscosity-increasing component, or nasal gels or nasal creams.

For administration by inhalation, atomizers or pressurized gas packs using inert carrier gases can be used.

For intravenous, subcutaneous, epicutaneous or intradermal administration, the active compounds or their physiologically tolerable salts, if desired with the pharmaceutically customary auxiliaries, for example for isotonisizing or adjusting pH, and solubilizers, emulsifiers or other auxiliaries, are brought into solution, suspension or emulsion.

Because of the short half-lives of some of the medicaments described in body fluids, the use of injectable sustained release preparations is efficient. Medicament forms which may be used are, for example, oily crystal suspensions, microcapsules, rods or implants, it being possible to synthesize the latter from tissue-compatible polymers, in particular biodegradable polymers, such as, for example, those based on polylactic acid/ polyglycolic acid copolymers or human albumin.

A suitable dose range for forms for topical application

and administration by inhalation are solutions containing 0.01-5 mg/ml, and with forms for systemic administration 0.01-10 mg/kg is suitable.

List of abbreviations:

The abbreviations used for amino acids correspond to the three-letter code customary in peptide chemistry as described in Europ. J. Biochem. 138, 9 (1984). Additionally used abbreviations are listed below.

Acm	Acetamidomethyl
ε-Ahx	ε-Aminohexanoyl
Aoc	cis, endo-2-Azabicyclo[3.3.0]octane-3-S-carbonyl
Boc	tert-Butyloxycarbonyl
But	tert-Butyl
Bzl	Benzyl
CDF	Chloro-(D)-phenylalanyl
Cha	Cyclohexylalanyl
Chg	Cyclohexylglycyl
Cl-Z	4-Chlorobenzyloxycarbonyl
DMF	Dimethylformamide
DOMT	O-Methyl-(D)-threonyl
Dnp	2,4-Dinitrophenyl
Fmoc	9-Fluorenylmethoxycarbonyl
MDY	O-Methyl-(D)-tyrosyl
Me	Methyl
4-Mebzl	4-Methylbenzyl
Mtr	4-Methoxy-2,3,6-trimethylphenylsulfonyl
Mts	Mesitylene-2-sulfonyl
Nal	Napthylalanyl
NMP	N-Methylpyrrolidine
Npg	Neopentylglycyl
Oic	cis-endo-octahydroindol-2-ylcarbonyl
Opr	Isoxazolidin-3-ylcarbonyl
Pal	Pyridylalanyl
Pmc	2,2,5,7,8-Pentamethylchroman-6-sulfonyl
Tbg	tert-Butylglycyl
TFA	Trifluoroacetic acid

Tcs	4-Methylphenylsulfonyl
Thia	2-Thienylalanyl
Tic	1,2,3,4-Tetrahydroisoquinolin-3-ylcarbonyl
Trt	Trityl

The following examples are intended to illustrate the preferred methods for solid phase synthesis of the peptides according to the invention, without limiting the invention thereto.

The amino acid derivatives below were used:

Fmoc-Arg(Mtr)-OH, Boc-(D)-Arg-OH, Fmoc-Arg(Pmc)-OH, Fmoc-Hyp-OH, Fmoc-Pro-OObt, Fmoc-Gly-OObt, Fmoc-Phe-OObt, Fmoc-Ser(tBu)-OObt, Fmoc-(D)-Phe-OH, Fmoc-Gln-OH, Fmoc-Aoc-OH, Fmoc-Thia-OH, Fmoc-Opr-OH, Fmoc-(D)-Asn-OH, Fmoc-β-Ala-OH, Fmoc-Oic-OH.

H-(D)-Arg-Arg-Pro-Hyp-Gly-Phe-Ser-(D)-Phe-Oic-Arg-OH

Example 1:

H-(D)-Arg-Arg-Pro-Hyp-Gly-Phe-Ser-(D)-Phe-Oic-Arg-OH was synthesized stepwise using a peptide synthesizer model 430 A from Applied Biosystems by the Fmoc method on a p-benzyloxybenzyl alcohol resin from Novabiochem (loading about 0.5 mmol/g of resin) esterified with Fmoc-Arg(Mtr)-OH. 1 g of the resin was employed and the synthesis was carried out with the aid of a synthesis program modified for the Fmoc method.

In each case 1 mmol of the amino acid derivative having a free carboxyl group together with 0.95 mmol of HOObt was weighed into the cartridges of the synthesizer. The preactivation of these amino acids was carried out directly in the cartridges by dissolving in 4 ml of DMF and adding 2 ml of a 0.55 mol solution of diisopropyl-carbodiimide in DMF.

The HOObt esters of the other amino acids were dissolved in 6 ml of NMP and then similarly coupled to the resin previously deblocked using 20% piperidine in DMF, like the amino acids preactivated in situ. After completion of

the synthesis, the peptide was split off from the resin using thioanisole and ethanedithiol as cation entrainers, with simultaneous removal of the side chain protective groups using trifluoroacetic acid. The residue obtained after stripping off the trifluoroacetic acid was repeatedly digested with ethyl acetate and centrifuged. The residue which remained was chromatographed on ®Sephadex LH 20 using 10% strength acetic acid. The fractions containing the pure peptide were combined and freeze-dried.

MS(FAB) : 1292.4 (M+H)

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A peptide of the formula I

A-B-C-E-F-K-(D)-Phe-G-M-F'-I (I)

in which

A denotes hydrogen, (D)- or (L)-H-Arg, (D)- or (L)-H-Lys or (D)- or (L)-H-Orn;

B denotes Arg, Orn, or Lys, where the guanidino group or the amino group of the side chain may be substituted by hydrogen, (C_1-C_8)-alkanoyl, (C_7-C_{13})-aryloyl, (C_3-C_9)-heteroaryloyl, (C_1-C_8)-alkylsulfonyl or (C_6-C_{12})-arylsulfonyl, where the aryl, heteroaryl, aryloyl, arylsulfonyl and heteroaryloyl radicals may optionally be substituted with 1, 2, 3 or 4 identical or different radicals selected from the group consisting of methyl, methoxy and halogen,

C denotes Pro Pro-Gly, Hyp-Pro-Gly or Pro-Hyp-Gly,

E denotes Phe or Thia.

F denotes Ser, Hser, Lys, Leu, Val, Nle, Ile or Thr,

K stands for a direct bond,

M stands for a direct bond,

G stands for a radical of a heterocyclic ring system of the formula IV

$$-N(R^4)-CH(R^5)-CO- \quad (IV)$$

in which R^4 and R^5 together with the atoms carrying them form a heterocyclic mono- or bicyclic ring system, where the ring system of the formula IV is chosen from the group comprising pyrrolidine-2-carboxylic acid, piperidine-2-carboxylic acid, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, cis- and trans-decahydroisoquinoline-3-carboxylic acid, cis-endo-, cis-exo-, trans-

octahydroindole-2-carboxylic acid, cis-endo-, cis-exo-, trans-octahydrocyclopentano[b]pyrrole-2-carboxylic acid and hydroxyproline-2-carboxylic acid,

F' denotes Arg,

I stands for OH,

(D)-Phe denotes D-phenylalanine

and its physiologically tolerable salt.

2. A peptide of the formula I as claimed in claim 1, in which

A denotes H-(D)-Arg,

B denotes Arg,

C denotes Pro-Pro-Gly- or Pro-Hyp-Gly,

F denotes Ser, and

G denotes cis, endo-octahydroindole-(2)-carbonyl,

3. A peptide of the formula I as claimed in claims 1 or 2, in which

A denotes H-(D)-Arg,

B denotes Arg,

C denotes Pro-Hyp-Gly,

E denotes Phe,

F denotes Ser, and

G denotes cis, endo-octahydroindole-(2)-carbonyl,

4. A method for the preparation of a peptide of the formula I as claimed in any one of claims 1 to 3, which comprises

(a) reacting a fragment having a C-terminal free carboxyl group or its activated derivative with an appropriate fragment having an N-terminal free amino group or

(b) synthesizing the peptide stepwise, optionally splitting off one or more protective groups temporarily introduced for the protection of other functions in the compound obtained according to (a) or (b) and optionally converting the compounds of the formula I thus obtained into their physiologically tolerable salt.

5. Use of a peptide of the formula I as claimed in any one of claims 1 to 3 for the preparation of a medicament for the treatment of pathological states which are mediated, caused or supported by bradykinin and bradykinin-related peptides.

6. The use according to claim 5 for the treatment of pathological states which are mediated, caused or supported by bradykinin and bradykinin-related peptides selected from the group consisting of wounds, burns, rashes, erythemas, edemas, angina, arthritis, asthma, allergies, rhinitis, shock, inflammation, low blood pressure, pain, itching and changed sperm motility.

7. A pharmaceutical composition comprising a peptide of the formula I as claimed in any one of claims 1 to 3 and a pharmaceutical utilizable excipient.