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(54) Titre : UTILISATION D'ANTAGONISTES DU RECEPTEUR B2 DE LA BRADYKININE POUR TRAITER  
L'OSTEOARTHROSE

(54) Title: USE OF BRADYKININ-B2 RECEPTOR ANTAGONISTS FOR TREATING OSTEOARTHRISIS

(57) **Abrégé/Abstract:**

Peptides that have a Bradykinin-antagonistic effect are suitable for the production of drugs for use in the prophylaxis and therapy of diseases whose progression is associated with an increased activity of matrix metalloproteinases. These diseases include degenerative articular diseases, for example osteoarthritis, spondylosis and chondroporosis after joint trauma or prolonged joint immobilization after meniscus or patella injuries or ruptures of a ligament.

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(54) Title: USE OF BRADYKININ-B2 RECEPTOR ANTAGONISTS FOR TREATING OSTEOARTHRISIS

(54) Bezeichnung: DIE VERWENDUNG VON ANTAGONISTEN DES BRADYKININ-B2 REZEPTORS ZUR BEHANDLUNG  
VON OSTEOARTHROSE(57) Abstract: Peptides that have a Bradykinin-antagonistic effect are suitable for the production of drugs for use in the prophylaxis  
and therapy of diseases whose progression is associated with an increased activity of matrix metalloproteinases. These diseases  
include degenerative articular diseases, for example osteoarthritis, spondylosis and chondroporosis after joint trauma or prolonged  
joint immobilization after meniscus or patella injuries or ruptures of a ligament.(57) Zusammenfassung: Peptide mit Bradykinin-antagonistischer Wirkung eignen sich zur Herstellung von Arzneimitteln  
zur Prophylaxe und Therapie von Erkrankungen, an deren Verlauf eine verstärkte Aktivität von Matrix-Metalloproteinasen  
beteiligt sind. Dazu gehören Erkrankungen wie degenerative Gelenkerkrankungen, beispielsweise Osteoarthritis, Spondylose  
sowie Knorpelschwund nach Gelenktrauma oder längerer Gelenksruhigstellung nach Meniskus- oder Patellaverletzungen oder  
Bänderrissen.

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## Use of bradykinin-B2 receptor antagonists for treating osteoarthritis

The invention relates to the use of peptides having bradykinin-antagonistic action for the production of pharmaceuticals for the treatment of degenerative joint diseases.

In degenerative joint diseases such as osteoarthritis, a slowly progressing destruction of the joint takes place, which is caused in particular by the proteolytic degradation of collagen by collagenases. Collagenases belong to the superfamily of the metalloproteinases (MP) or matrix metalloproteinases (MMPs). MMPs are capable of degrading fibrillar and nonfibrillar collagen and proteoglycans, which are all important constituents of the cartilaginous matrix. MMP 3 is involved in the biological degradation of the extracellular matrix and is found in increased levels in patients with osteoarthritis, which is why particular importance is ascribed to MMP 3 in the degradation of the joint matrix in osteoarthritis (Manicourt et al. (1994) *Arthritis and Rheumatism* 37:1774-83).

Bradykinin is a naturally occurring nonapeptide which has some pharmacological effects which lead to inflammation and pain. Peptides having bradykinin-antagonistic action have already been described in European patent EP 0 370 453 B1. It is further known that peptides having bradykinin-antagonistic action can be employed in the treatment of osteoarthritis or rheumatoid arthritis (AU 638 350). Osteoarthritis and rheumatoid arthritis are joint diseases having severe inflammatory phases in the course of the disease. Lerner et al. (*Arthritis and Rheumatism* (1987), 30, 530-540) report that, in the context of rheumatoid arthritis, bradykinin may actually enhance bone resorption, but does not stimulate the degradation of the cartilaginous matrix itself.

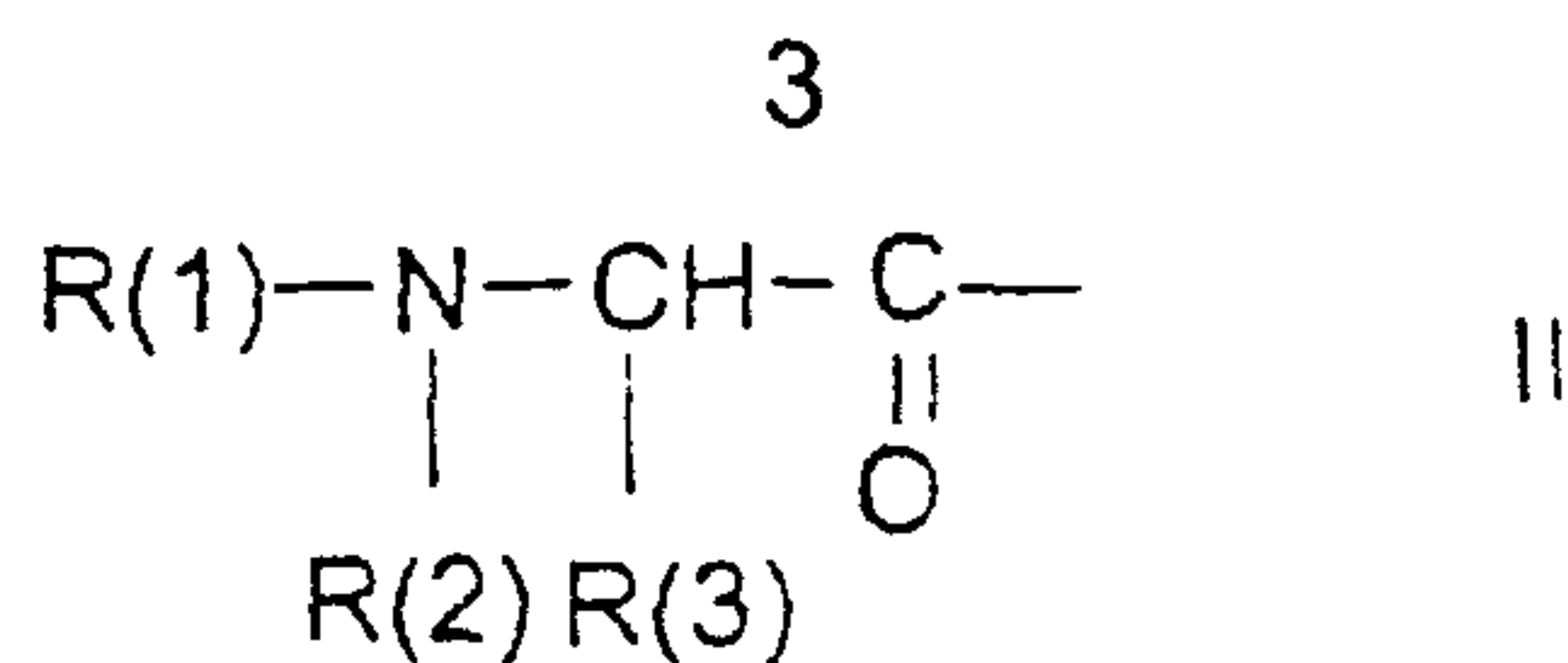
In the attempt to find active compounds for the treatment of degenerative joint diseases, it has now been found that the peptide employed according to the invention inhibits the release of MMPs such as MMP-3 (and MMP-1 and MMP-13). As a result, the matrix degradation can be inhibited significantly more effectively than only by the inhibition of MMPs themselves which have already been released or formed in the tissue.

The invention therefore relates to the use of the compound of the formula I



for the production of pharmaceuticals for the treatment of degenerative joint diseases, in which:

- A     a<sub>1</sub>)    is a hydrogen atom, (C<sub>1</sub>-C<sub>8</sub>)-alkyl, (C<sub>1</sub>-C<sub>8</sub>)-alkanoyl, (C<sub>1</sub>-C<sub>8</sub>)-alkoxycarbonyl or (C<sub>1</sub>-C<sub>8</sub>)-alkylsulfonyl, in which in each case 1, 2 or 3 hydrogen atoms are optionally replaced by 1, 2 or three identical or different radicals from the group consisting of carboxyl, amino, (C<sub>1</sub>-C<sub>4</sub>)-alkyl, (C<sub>1</sub>-C<sub>4</sub>)-alkylamino, hydroxyl, (C<sub>1</sub>-C<sub>3</sub>)-alkoxy, halogen, di-(C<sub>1</sub>-C<sub>4</sub>)-alkylamino, carbamoyl, sulfamoyl, (C<sub>1</sub>-C<sub>4</sub>)-alkoxycarbonyl, (C<sub>6</sub>-C<sub>12</sub>)-aryl and (C<sub>6</sub>-C<sub>12</sub>)-aryl-(C<sub>1</sub>-C<sub>5</sub>)-alkyl, or in which in each case 1 hydrogen atom is optionally replaced by a radical from the group consisting of (C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, (C<sub>1</sub>-C<sub>4</sub>)-alkylsulfonyl, (C<sub>1</sub>-C<sub>4</sub>)-alkylsulfinyl, (C<sub>6</sub>-C<sub>12</sub>)-aryl-(C<sub>1</sub>-C<sub>4</sub>)-alkylsulfonyl, (C<sub>6</sub>-C<sub>12</sub>)-aryl-(C<sub>1</sub>-C<sub>4</sub>)-alkylsulfinyl, (C<sub>6</sub>-C<sub>12</sub>)-aryloxy, (C<sub>3</sub>-C<sub>9</sub>)-heteroaryl and (C<sub>3</sub>-C<sub>9</sub>)-heteroaryloxy and 1 or 2 hydrogen atoms are replaced by 1 or 2 identical or different radicals from the group consisting of carboxyl, amino, (C<sub>1</sub>-C<sub>4</sub>)-alkylamino, hydroxyl, (C<sub>1</sub>-C<sub>4</sub>)-alkoxy, halogen, di-(C<sub>1</sub>-C<sub>4</sub>)-alkylamino, carbamoyl, sulfamoyl, (C<sub>1</sub>-C<sub>4</sub>)-alkyloxycarbonyl, (C<sub>6</sub>-C<sub>12</sub>)-aryl and (C<sub>6</sub>-C<sub>12</sub>)-aryl-(C<sub>1</sub>-C<sub>5</sub>)-alkyl,
- a<sub>2</sub>)    is (C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, carbamoyl, which can optionally be substituted on the nitrogen by (C<sub>1</sub>-C<sub>6</sub>)-alkyl or (C<sub>6</sub>-C<sub>12</sub>)-aryl, (C<sub>6</sub>-C<sub>12</sub>)-aryl, (C<sub>6</sub>-C<sub>12</sub>)-aryloyl, (C<sub>6</sub>-C<sub>12</sub>)-arylsulfonyl or (C<sub>3</sub>-C<sub>9</sub>)-heteroaryl or (C<sub>3</sub>-C<sub>9</sub>)-heteroaryloyl, where in the radicals defined under a<sub>1</sub>) and a<sub>2</sub>) heteroaryl, aryloyl, arylsulfonyl and heteroaryloyl in each case is optionally substituted by 1, 2, 3 or 4 different radicals from the group consisting of carboxyl, amino, nitro, hydroxyl, cyano, (C<sub>1</sub>-C<sub>4</sub>)-alkylamino, (C<sub>1</sub>-C<sub>4</sub>)-alkyl, (C<sub>1</sub>-C<sub>4</sub>)-alkoxy, halogen, di-(C<sub>1</sub>-C<sub>4</sub>)-alkylamino, carbamoyl, sulfamoyl and (C<sub>1</sub>-C<sub>4</sub>)-alkoxycarbonyl, or
- a<sub>3</sub>)    is a radical of the formula II,



where

R(1) is defined as A under a<sub>1</sub>) or a<sub>2</sub>),

R(2) is a hydrogen atom or methyl,

R(3) is a hydrogen atom or (C<sub>1</sub>-C<sub>6</sub>)-alkyl, where alkyl is unsubstituted or monosubstituted by amino, substituted amino, hydroxyl, 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 is a radical -NH-A- and substituted guanidino is a radical -NH-C(NH)-NH-A-, in which A is as defined under a<sub>1</sub>) or a<sub>2</sub>);

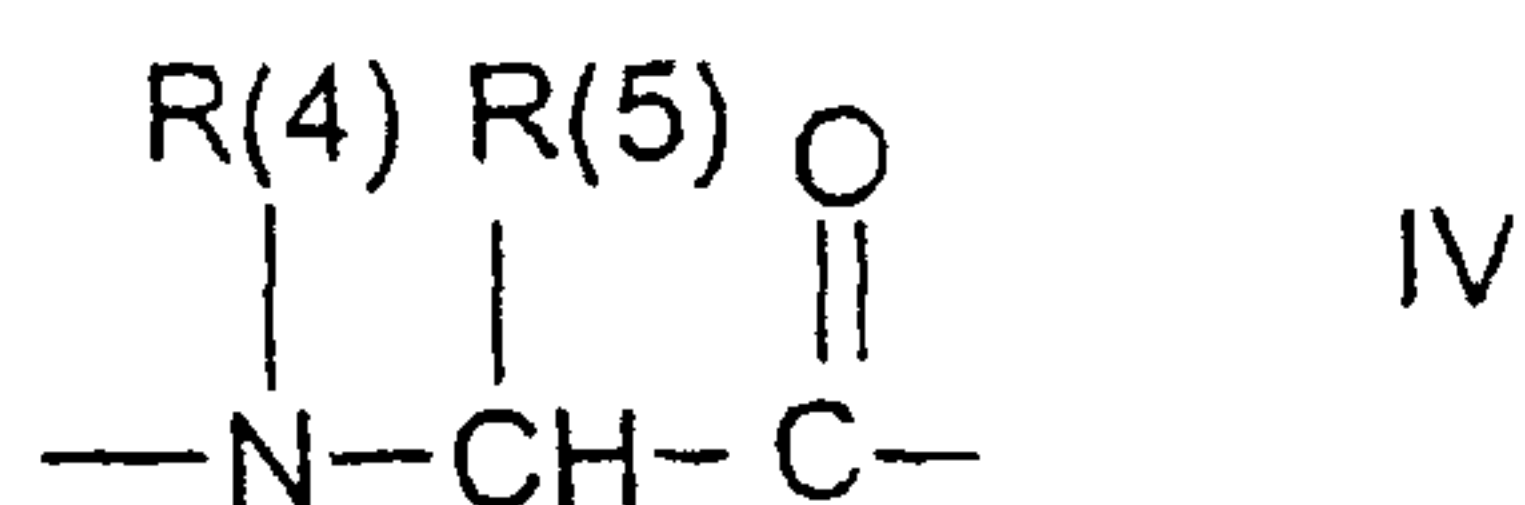
B is Arg, Lys, Orn, 2,4-diaminobutyroyl or an L-homoarginine radical,

where in each case the amino or the guanidino group of the side chain can be substituted by an A as described under a<sub>1</sub>) or a<sub>2</sub>);

X is a compound of the formula IIIa or IIIb



in which G' independently of one another is a radical of the formula IV



in which R(4) and R(5) together with the atoms carrying these is a heterocyclic mono-, bi- or tricyclic ring system having 2 to 15 carbon atoms, and n is 2 to 8;

E is the radical of phenylalanine,

which is optionally substituted by halogen in the 2-, 3- or 4-ring position, or

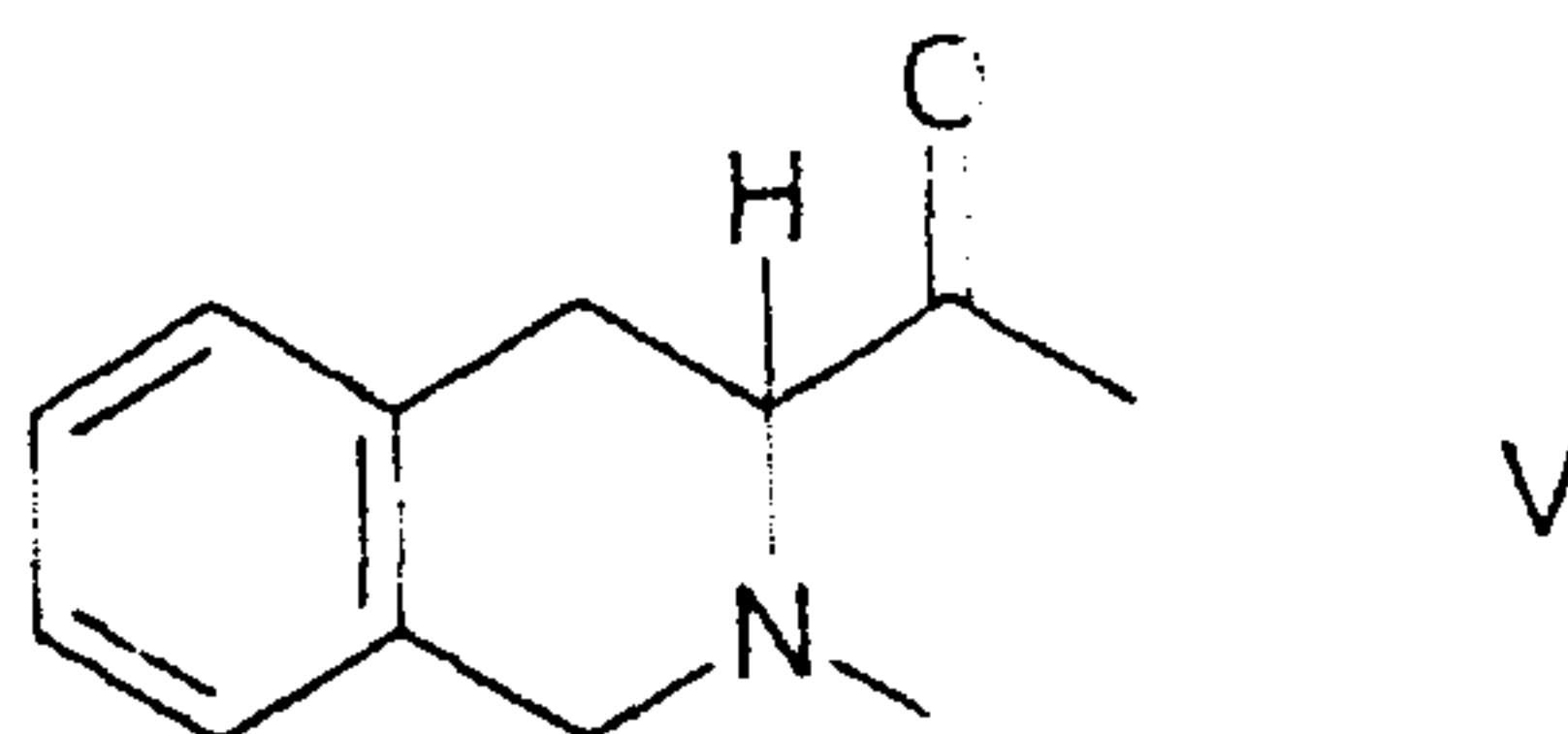
is tyrosine, O-methyltyrosine, 2-thienylalanine, 2-pyridyl-alanine or naphthylalanine;

F independently of one another is the radical of a neutral, acidic or basic aliphatic or aromatic amino acid,

which can be substituted in the side chain,

or is a covalent bond;

(D)-Tic is the radical of the formula V



G is G' or a covalent bond;

F' is the radical of a basic amino acid Arg or Lys in the L or D form or a covalent bond,

where the guanidino group or amino group of the side chain can be substituted by A as defined under a<sub>1</sub>) or a<sub>2</sub>),

or is a radical  $\text{-NH-(CH}_2\text{)}_n\text{-}$  where n is 2 – 8,

or a covalent bond;

I is -OH, -NH<sub>2</sub> or NHC<sub>2</sub>H<sub>5</sub>;

K is the radical  $\text{-NH-(CH}_2\text{)}_x\text{-CO}$  where x is 1 to 4 or a covalent bond;

M is defined as F,

and its physiologically tolerable salts.

A further subject of the invention is also the use according to the invention of the compound of the formula I, in which:

B is Arg, Orn or Lys,

where the guanidino group or the amino group of the side chain is unsubstituted or can be substituted by (C<sub>1</sub>-C<sub>8</sub>)-alkanoyl, (C<sub>7</sub>-C<sub>13</sub>)-aryloyl, (C<sub>3</sub>-C<sub>9</sub>)-heteroaryl-oxy, (C<sub>1</sub>-C<sub>8</sub>)-alkylsulfonyl or (C<sub>6</sub>-C<sub>12</sub>)-arylsulfonyl, where the aryl, heteroaryl, aryloyl, arylsulfonyl and hetero-aryloyl radicals can be substituted as described above under a<sub>2</sub>) by optionally 1, 2, 3 or 4 identical or different radicals;

- E is phenylalanine, 2-chlorophenylalanine, 3-chlorophenylalanine, 2-fluorophenylalanine, 3-fluorophenylalanine, 4-fluorophenylalanine, tyrosine, O-methyltyrosine or  $\beta$ -(2-thienyl)alanine;
- K is a covalent bond and
- M is a covalent bond.

The invention further relates to the use according to the invention of the compound of the formula I, in which:

- A is a hydrogen atom, (D)- or (L)-H-Arg, (D)- or (L)-H-Lys or (D)- or (L)-H-Orn;
- B is Arg, Orn or Lys,  
 where the guanidino group or the amino group of the side chain can be substituted by a hydrogen atom, (C<sub>1</sub>-C<sub>8</sub>)-alkanoyl, (C<sub>6</sub>-C<sub>12</sub>)-aryloyl, (C<sub>3</sub>-C<sub>9</sub>)-heteroaryloyl, (C<sub>1</sub>-C<sub>8</sub>)-alkylsulfonyl or (C<sub>6</sub>-C<sub>12</sub>)-arylsulfonyl, where the aryl, heteroaryl, aryloyl, arylsulfonyl and heteroaryloyl radicals can optionally be substituted by 1, 2, 3 or 4 identical or different radicals from the group consisting of methyl, methoxy and halogen;
- C is Pro-Pro-Gly, Hyp-Pro-Gly or Pro-Hyp-Gly;
- E is Phe or Thia;
- F is Ser, Hser, Lys, Leu, Val, Nle, Ile or Thr;
- K is a covalent bond
- M is a covalent bond
- G is the radical of a heterocyclic ring system of the formula IV, selected from the radicals of the heterocycles pyrrolidine (A), piperidine (B), tetrahydroisoquinoline (C), cis- or trans-decahydroisoquinoline (D), cis-endo-octahydroindole (E), cis-exo-octahydroindole (E), trans-octahydroindole (E), cis-endo-, cis-exo-, trans-octahydrocyclopentano[b]pyrrole (F), or hydroxyproline (V);
- F' is Arg;
- I is OH.

The invention also relates to the use according to the invention of a compound of the formula I, which is selected from the group:

- H-(D)-Arg-Arg-Pro-Hyp-Gly-Thia-Ser-(D)-Tic-Oic-Arg-OH,  
 H-(D)-Arg-Arg-Pro-Pro-Gly-Thia-Ser-(D)-Tic-Oic-Arg-OH,

H-(D)-Arg-Arg-Pro-Hyp-Gly-Phe-Ser-(D)-Tic-Oic-Arg-OH,  
 H-(D)-Arg-Arg-Hyp-Pro-Gly-Phe-Ser-(D)-Tic-Oic-Arg-OH and  
 H-(D)-Arg-Arg-Pro-Pro-Gly-Phe-Ser-(D)-Tic-Oic-Arg-OH.

The invention also relates to the use according to the invention of  
 D-arginyl-L-arginyl-L-prolyl-L-prolylglycyl-3-(2-thienyl)-L-alanyl-L-seryl-(3R)-  
 1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-(2S,3aS,7aS)-octahydro-1H-  
 indole-2-carbonyl-L-arginine; which is also known under the name  
 HOE 140.

The term "(C<sub>1</sub>-C<sub>8</sub>)-alkyl" is understood as meaning hydrocarbon radicals  
 whose carbon chain is straight-chain or branched and contains 1 to 8  
 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl,  
 tertiary-butyl, pentyl, isopentyl, neopentyl, hexyl, 2,3-dimethylbutyl, heptyl,  
 neohexyl or octyl.

The term "halogen" is understood as meaning fluorine, chlorine, bromine or  
 iodine.

The term "(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl" is understood as meaning radicals which are  
 derived from 3- to 8-membered monocycles such as cyclopropyl,  
 cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl.

The term "-(C<sub>6</sub>-C<sub>12</sub>)-aryl" is understood as meaning aromatic hydrocarbon  
 radicals having 6 to 14 carbon atoms in the ring. -(C<sub>6</sub>-C<sub>12</sub>)-aryl radicals are,  
 for example, phenyl, naphthyl, for example 1-naphthyl, 2-naphthyl,  
 biphenyl, for example 2-biphenyl, 3-biphenyl and 4-biphenyl, anthryl  
 or fluorenyl. Biphenyl radicals, naphthyl radicals and in particular phenyl  
 radicals are preferred aryl radicals.

The term "(C<sub>3</sub>-C<sub>9</sub>)-heteroaryl" is to be understood as meaning radicals such  
 as acridinyl, azetidyl, benzimidazolyl, benzofuranyl, benzothiofuranyl,  
 benzothiophenyl, benzoxazolyl, benzothiazolyl, benzotriazolyl, benzo-  
 tetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalinyl, carbazolyl,  
 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydro-  
 quinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuran[2,3-b]-tetrahydrofuran,  
 furanyl, furazanyl, imidazolidinyl, imidazolyl, imidazolyl, 1H-indazolyl,  
 indolinyl, indolizyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl,  
 isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl),  
 isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl,  
 oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl,  
 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, phenanthridinyl, phenanthrolinyl,  
 phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl,

piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyroazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridothiophenyl, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinoliziny, quinoxalinyl, quinuclidinyl, tetra-hydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thia-diazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thia-diazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl.

Pyridyl; such as 2-pyridyl, 3-pyridyl or 4-pyridyl; pyrrolyl; such as 2-pyrrolyl and 3-pyrrolyl; furyl; such as 2-furyl and 3-furyl; thiophenyl, thienyl; such as 2-thienyl and 3-thienyl; imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, tetrazolyl, pyridazinyl, pyrazinyl, pyrimidinyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, 1,3-benzodioxolyl, indazolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, chromanyl, isochromanyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, purinyl and pteridinyl are preferred.

The peptides employed according to the invention are prepared as described in EP 0 370 453 B1.

On account of the pharmacological properties, the compounds according to the invention are suitable for the selective prophylaxis and therapy of degenerative joint diseases such as osteoarthritis, spondylosis or chondroporosis after joint trauma or relatively long immobilization of a joint after meniscus or patella injuries or torn ligaments. The term "osteoarthritis" is understood as meaning a disease which chiefly develops in connection with a disparity between the strain on and the load capacity of the individual joint components and joint tissues, which is associated with increasing destruction of the cartilage and which is in the main not inflammatory. Damage to the joint cartilage, such as fraying, demedullation and hyalinization, followed by reactive changes in the subchondral bone, and also capsule changes, is prominent in the pathology. The term "spondylosis" is understood as meaning an arthrosis of the vertebral bodies, with this arthrosis being characterized by a noninflammatory loss of cartilage from the vertebral bodies and intervertebral disks.

The pharmaceuticals according to the invention can be administered by inhalative or transdermal administration or by subcutaneous, intraarticular, intraperitoneal or intravenous injection. Intraarticular administration or topical application is preferred.

Suitable solid or pharmaceutical preparation forms are, for example, suspensions, emulsions, or injectable solutions, and preparations having protracted release of active compound, in whose preparation customary excipients are used.

Preferably, the pharmaceutical preparations are prepared and administered in dose units, each unit containing as active constituent a certain dose of the compound of the formula I according to the invention. In the case of injection solutions in ampoule form, this dose can be up to approximately 300 mg, but preferably approximately 10 to 100 mg, in the case of injection solutions for intraarticular treatment up to approximately 300 micrograms, preferably 100 micrograms.

For the treatment of an adult patient, depending on the activity of the compound according to formula I, daily doses of approximately 0.01 mg/kg to 10 mg/kg of active compound are indicated in the case of systemic administration, in the case of the administration of injection solutions daily doses of 0.001 mg/kg to 0.005 mg/kg of active compound are indicated and in the case of topical or inhalative administration, daily doses of 0.01 mg/kg to 5 mg/kg of active compound are indicated. Under certain circumstances, however, higher or lower daily doses may also be appropriate. The daily dose can be administered either by single administration in the form of an individual dose unit or else a number of smaller dose units or by multiple administration of subdivided doses at specific intervals.

The invention is illustrated below with the aid of examples.

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

|      |                                |
|------|--------------------------------|
| Oic  | octahydro-1H-indole-2-carbonyl |
| Thia | 2-thienylalanyl                |

Tic 1,2,3,4-tetrahydroisoquinolin-3-ylcarbonyl

HOE 140 was prepared as described in EP 0 370 453 B1.

#### Pharmacological examples

For the analysis of the disease-modifying action of HOE140 in a cell culture model relevant to cartilage, the MMP3 expression was analyzed in the chondrosarcoma cell line SW1353 (ATCC: HTB 94). For the experiments, SW1353 cells were cultured under standard conditions (37°C, 5% CO<sub>2</sub>) in DMEM-Glutamax with 10% of fetal calf serum (FCS) in plastic culture bottles. After detrypsinization of the cells, 50,000 cells were inoculated per well of a 96-well flat-bottom plate in medium without FCS and preincubated with the compound HOE140 in an incubator. After one hour, the cells were stimulated by addition of human IL1- $\beta$  (0.1 ng/ml, Roche) in a total volume of 300  $\mu$ l. After incubation for 24 hours under standard conditions, the cell culture supernatant was taken off, centrifuged for 5 minutes and frozen at -20°C until further analysis. The MMP3 expression in the cell culture supernatants was then analyzed by means of a commercial MMP3 ELISA test system (Amersham) according to the instructions of the manufacturer. In parallel to this, a WST cytotoxicity test was carried out with the remaining cells. For this, the commercial test system of Roche was used and the measurement was carried out according to the instructions of the manufacturer's protocol.

Table 1 below shows the results.

Bradykinin increases the MMP3 release by more than 30%. This increased release of MMP3 was inhibited by HOE140 in a dose-dependent manner.

Table 1 MMP- 3 release from SW cells

| Stimulation parameter                   | MMP-3 release     |    | Relative values<br>based on<br>starting value |
|-----------------------------------------|-------------------|----|-----------------------------------------------|
|                                         | MW<br>(OD 450 nm) | SD |                                               |
| unstimulated                            | 93                | 20 |                                               |
| IL1 $\alpha$ (0.05 ng/ml)               | 328               | 17 | 100                                           |
| IL1 $\alpha$ + bradykinin (0.1 $\mu$ M) | 433               | 32 | 132.0                                         |

|                                                                  |     |    |       |
|------------------------------------------------------------------|-----|----|-------|
| IL1 $\alpha$ + bradykinin (0.1 $\mu$ M)<br>+ 0.05 $\mu$ M HOE140 | 458 | 50 | 139.6 |
| IL1 $\alpha$ + bradykinin (0.1 $\mu$ M)<br>+ 0.1 $\mu$ M HOE140  | 371 | 8  | 113.1 |
| IL1 $\alpha$ + bradykinin (0.1 $\mu$ M)<br>+ 0.5 $\mu$ M HOE140  | 309 | 18 | 94.2  |
| IL1 $\alpha$ + bradykinin (0.1 $\mu$ M)<br>+ 1 $\mu$ M HOE140    | 306 | 27 | 93.3  |

## SEQUENCE LISTING

<110> Sanofi-Aventis Deutschland GmbH  
 <120> Use of Bradykinin-B2 Receptor Antagonists for Treating Osteoarthrosis  
 <130> 9982-895  
 <140> CA 2,514,152  
 <141> 2004-01-23  
 <150> DE 103 04 994.0  
 <151> 2003-02-07  
 <160> 1  
 <170> PatentIn version 3.3  
 <210> 1  
 <211> 10  
 <212> PRT  
 <213> Artificial Sequence  
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 <223> Description of Artificial Sequence: Peptide with D-Amino Acid  
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 <222> (8)..(9)  
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 <400> 1  
 Xaa Arg Pro Pro Gly Xaa Ser Xaa Xaa Arg  
 1 5 10

We claim

1. A use of compound D-arginyl-L-arginyl-L-prolyl-L-prolylglycyl-3-(2-thienyl)-L-alanyl-L-seryl-(3R)-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-(2S,3aS,7aS)-octahydro-1H-indole-2-carbonyl-L-arginine for the prophylaxis and therapy of osteoarthritis and spondylosis.