

Novel carboxylic acid derivatives having a 5-substituted pyrimidine ring, their preparation and use

- 5 The present invention relates to novel carboxylic acid derivatives having a 5-substituted pyrimidine ring, to their preparation and use.

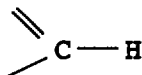
Endothelin is a peptide which is composed of 21 amino acids and
 10 is synthesized and released by the vascular endothelium. Endothelin exists in three isoforms, ET-1, ET-2 and ET-3. In the following text, "endothelin" or "ET" signifies one or all isoforms of endothelin. Endothelin is a potent vasoconstrictor and has a potent effect on vessel tone. It is known that this
 15 vasoconstriction is caused by binding of endothelin to its receptor (Nature, 332, 411-415, 1988; FEBS Letters, 231, 440-444, 1988 and Biochem. Biophys. Res. Commun., 154, 868-875, 1988).

Increased or abnormal release of endothelin causes persistent
 20 vasoconstriction in the peripheral, renal and cerebral blood vessels, which may lead to disorders. It has been reported in the literature that endothelin is involved in a number of disorders; these include hypertension, acute myocardial infarct, pulmonary hypertension, Raynaud's disease, cerebral vasospasms, stroke,
 25 benign prostatic hypertrophy, atherosclerosis, asthma and cancer of the prostate (J. Vascular Med. Biology 2, 207 (1990), J. Am. Med. Association 264, 2868 (1990), Nature 344, 114 (1990), N. Engl. J. Med. 322, 205 (1989), N. Engl. J. Med. 328, 1732 (1993), Nephron 66, 373 (1994), Stroke 25, 904 (1994), Nature 365, 759
 30 (1993), J. Mol. Cell. Cardiol. 27, A234 (1995); Cancer Research 56, 663 (1996), Nature Medicine 1, 944, (1995)).

At least two endothelin receptor subtypes, the ET_A and ET_B receptors, are currently described in the literature (Nature 348,
 35 730 (1990), Nature 348, 732 (1990)). Consequently, substances which inhibit binding of endothelin to one or both receptors should antagonize physiological effects of endothelin and should therefore be valuable drugs.

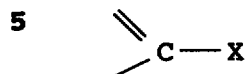
40 Carboxylic acid derivatives and their use as endothelin antagonists are described in WO 95/26716, WO 96/11914, WO 97/9294, WO 97/12878, WO 97/38980, WO 97/38981. These compounds carry a nitrogen atom or a group

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at the 5-position of the heterocycle.

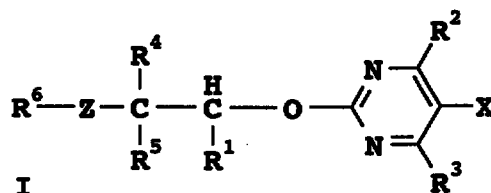
In contrast, the compounds according to the invention have in this position a group



where X is halogen, hydroxyl or C₁-C₄-haloalkyl. Compared to the known endothelin antagonists, the compounds according to the
10 invention are, for example, metabolized more favorably in the body.

The present invention relates to carboxylic acid derivatives of the formula I

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where R¹ is tetrazole or a group



in which R is:

a) a radical OR⁷, where R⁷ is:

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hydrogen, the cation of an alkali metal, the cation of an alkaline earth metal, a physiologically tolerable organic ammonium ion such as tertiary C₁-C₄-alkylammonium or the ammonium ion;

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C₃-C₈-cycloalkyl, C₁-C₈-alkyl, CH₂-phenyl which may be substituted by one or more of the following radicals: halogen, nitro, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, hydroxyl, C₁-C₄-alkoxy, mercapto, C₁-C₄-alkylthio, amino,

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NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂;

a C₃-C₆-alkenyl or a C₃-C₆-alkynyl group, it being possible for these groups for their part to carry one to five halogen
45 atoms;

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R⁷ may furthermore be a phenyl radical which may carry one to five halogen atoms and/or one to three of the following radicals: nitro, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, hydroxyl, C₁-C₄-alkoxy, mercapto, C₁-C₄-alkylthio, amino,

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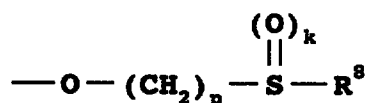
NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂;

b) a 5-membered heteroaromatic such as pyrrolyl, pyrazolyl, imidazolyl and triazolyl which is attached via a nitrogen atom and which may carry one to two halogen atoms, or one to two C₁-C₄-alkyl or one to two C₁-C₄-alkoxy groups.

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c) a group

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in which k may be 0, 1 or 2, p may be 1, 2, 3 or 4 and R⁸ is

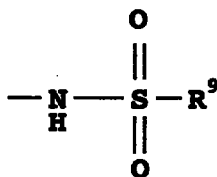
20 C₁-C₄-alkyl, C₃-C₈-cycloalkyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl or phenyl which may be substituted by one or more, for example by one to three, of the following radicals:

25 halogen, nitro, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, hydroxyl, C₁-C₄-alkoxy, C₁-C₄-alkylthio, mercapto, amino,

NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂.

d) a radical

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where R⁹ is:

40 C₁-C₄-alkyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl, C₃-C₈-cycloalkyl, where these radicals may carry a C₁-C₄-alkoxy, C₁-C₄-alkylthio and/or a phenyl radical as mentioned under c);

phenyl which may be substituted by one to three of the following radicals: halogen, nitro, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, hydroxyl, C₁-C₄-alkoxy, C₁-C₄-alkylthio, mercapto, amino, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂.

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The other substituents are as defined below:

- R^2 is hydrogen, hydroxyl, NH_2 , $NH(C_1-C_4-alkyl)$, $N(C_1-C_4-alkyl)_2$,
 halogen, $C_1-C_4-alkyl$, $C_2-C_4-alkenyl$, $C_2-C_4-alkynyl$,
 5 $C_1-C_4-hydroxyalkyl$, $C_1-C_4-haloalkyl$, $C_1-C_4-alkoxy$,
 $C_1-C_4-haloalkoxy$ or $C_1-C_4-alkylthio$, morpholine;
- X is halogen, $C_1-C_4-haloalkyl$, hydroxyl;
- 10 R^3 is hydrogen, hydroxyl, NH_2 , $NH(C_1-C_4-alkyl)$, $N(C_1-C_4-alkyl)_2$,
 halogen, $C_1-C_4-alkyl$, $C_2-C_4-alkenyl$, $C_2-C_4-alkynyl$,
 $C_1-C_4-hydroxyalkyl$, $C_1-C_4-haloalkyl$, $C_1-C_4-alkoxy$,
 $C_1-C_4-haloalkoxy$, $-NH-O-C_1-C_4-alkyl$, $C_1-C_4-alkylthio$;
- 15 R^4 and R^5 (which may be identical or different) are:
- phenyl or naphthyl which may be substituted by one or more of
 the following radicals: halogen, nitro, cyano, hydroxyl,
 $C_1-C_4-alkyl$, $C_1-C_4-haloalkyl$, $C_1-C_4-alkoxy$, $C_1-C_4-haloalkoxy$,
 20 phenoxy, mercapto, alkylcarbonyl, alkoxycarbonyl,
 $C_1-C_4-alkylthio$, amino, $NH(C_1-C_4-alkyl)$, $N(C_1-C_4-alkyl)_2$; or
- phenyl or naphthyl which are ortho-linked with each other via
 a direct bond, a methylene, ethylene, or ethenylene group, an
 25 oxygen or sulfur atom or an SO_2- , $NH-$ or $N-alkyl$ group; or
- a five- or six-membered heteroaromatic containing one to
 three nitrogen atoms and/or one sulfur or oxygen atom which
 may carry one to four halogen atoms and/or one to two of the
 following radicals: $C_1-C_4-alkyl$, $C_1-C_4-haloalkyl$,
 30 $C_1-C_4-alkoxy$, $C_1-C_4-haloalkoxy$, $C_1-C_4-alkylthio$, phenyl,
 phenoxy or phenylcarbonyl, where the phenyl radicals for
 their part may carry one to five halogen atoms and/or one to
 three of the following radicals: $C_1-C_4-alkyl$, $C_1-C_4-haloalkyl$,
 35 $C_1-C_4-alkoxy$, $C_1-C_4-haloalkoxy$ and/or $C_1-C_4-alkylthio$;
- or $C_3-C_7-cycloalkyl$;
- R^6 is hydrogen,
 40 $C_1-C_8-alkyl$, $C_3-C_6-alkenyl$, $C_3-C_6-alkynyl$ or $C_3-C_8-cycloalkyl$,
 where these radicals may in each case be mono- or
 polysubstituted by: hydroxyl, mercapto, carboxyl, halogen,
 nitro, cyano, $C_1-C_4-alkoxy$, $C_3-C_6-alkenyloxy$,
 45 $C_3-C_6-alkynyloxy$, $C_1-C_4-alkylthio$, $C_1-C_4-haloalkoxy$,
 $C_1-C_4-alkylcarbonyl$, $C_1-C_4-alkoxycarbonyl$, $C_3-C_8-alkylcarbonyl$,
 $C_3-C_8-alkylcarbonyl$, amino, $NH(C_1-C_4-alkyl)$, $N(C_1-C_4-alkyl)_2$, phenoxy or

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- phenyl where the abovementioned aryl radicals may be mono- or polysubstituted, for example phenyl or phenoxy mono- to trisubstituted by halogen, nitro, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, mercapto, carboxyl, hydroxyl, amino, R¹², C₁-C₄-alkoxycarbonyl, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂, dioxomethylene, dioxoethylene or C₁-C₄-alkylthio;
- phenyl or naphthyl, each of which may be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, amino, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, phenoxy, C₁-C₄-alkylthio, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂ or dioxomethylene or dioxoethylene;
- a five- or six-membered heteroaromatic containing one to three nitrogen atoms and/or one sulfur or oxygen atom, which may carry one to four halogen atoms and/or one to two of the following radicals: C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₁-C₄-alkylthio, phenyl, phenoxy or phenylcarbonyl, where the phenyl radicals for their part may carry one to five halogen atoms and/or one to three of the following radicals: C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy and/or C₁-C₄-alkylthio;
- with the proviso that R⁶ can only be hydrogen if Z is not a single bond;
- R¹² is C₁-C₄-alkyl, C₁-C₄-alkylthio, C₁-C₄-alkoxy, which may carry one of the following radicals: hydroxyl, carboxyl, amino, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂, carboxamide or CON(C₁-C₄-alkyl)₂;
- Z is sulfur, oxygen or a single bond.
- For this and further below, the following definitions apply:
- an alkali metal is, for example, lithium, sodium, potassium;
- an alkaline earth metal is, for example, calcium, magnesium, barium;
- organic ammonium ions are protonated amines such as, for example, ethanolamine, diethanolamine, ethylenediamine, diethylamine or piperazine;

C₃-C₇-cycloalkyl is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl;

5 C₁-C₄-haloalkyl may be linear or branched, such as, for example, fluoromethyl, difluoromethyl, trifluoromethyl, chlorodifluoromethyl, dichlorofluoromethyl, trichloromethyl, 1-fluoroethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2-chloro-2,2-difluoroethyl, 2,2-dichloro-2-fluoroethyl, 2,2,2-trichloroethyl or pentafluoroethyl;

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C₁-C₄-haloalkoxy may be linear or branched, such as, for example, difluoromethoxy, trifluoromethoxy, chlorodifluoromethoxy, 1-fluoroethoxy, 2,2-difluoroethoxy, 1,1,2,2-tetrafluoroethoxy, 2,2,2-trifluoroethoxy, 2-chloro-1,1,2-trifluoroethoxy, 15 2-fluoroethoxy or pentafluoroethoxy;

C₁-C₄-alkyl may be linear or branched, such as, for example, methyl, ethyl, 1-propyl, 2-propyl, 2-methyl-2-propyl, 2-methyl-1-propyl, 1-butyl or 2-butyl;

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C₂-C₄-alkenyl may be linear or branched, such as, for example, ethenyl, 1-propen-3-yl, 1-propen-2-yl, 1-propen-1-yl, 2-methyl-1-propenyl, 1-butenyl or 2-butenyl;

25 C₂-C₄-alkynyl may be linear or branched, such as, for example, ethynyl, 1-propin-1-yl, 1-propin-3-yl, 1-butin-4-yl or 2-butin-4-yl;

30 C₁-C₄-alkoxy may be linear or branched, such as, for example, methoxy, ethoxy, propoxy, 1-methylethoxy, butoxy, 1-methylpropoxy, 2-methylpropoxy or 1,1-dimethylethoxy;

35 C₃-C₆-alkenyloxy may be linear or branched, such as, for example, allyloxy, 2-buten-1-yloxy or 3-buten-2-yloxy;

C₃-C₆-alkynyloxy may be linear or branched, such as, for example, 2-propin-1-yloxy, 2-butin-1-yloxy or 3-butin-2-yloxy;

40 C₁-C₄-alkylthio may be linear or branched, such as, for example, methylthio, ethylthio, propylthio, 1-methylethylthio, butylthio, 1-methylpropylthio, 2-methylpropylthio or 1,1-dimethylethylthio;

45 C₁-C₄-alkylcarbonyl may be linear or branched, such as, for example, acetyl, ethylcarbonyl or 2-propylcarbonyl;

C₁-C₄-alkoxycarbonyl may be linear or branched, such as, for example, methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, i-propoxycarbonyl or n-butoxycarbonyl;

- 5 C₃-C₈-alkylcarbonylalkyl may be linear or branched, such as, for example, 2-oxoprop-1-yl, 3-oxobut-1-yl or 3-oxobut-2-yl;

C₁-C₈-alkyl may be linear or branched, such as, for example, C₁-C₄-alkyl, pentyl, hexyl, heptyl or octyl;

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halogen is, for example, fluorine, chlorine, bromine, iodine.

The invention further relates to those compounds from which the compounds of the formula I can be released (prodrugs).

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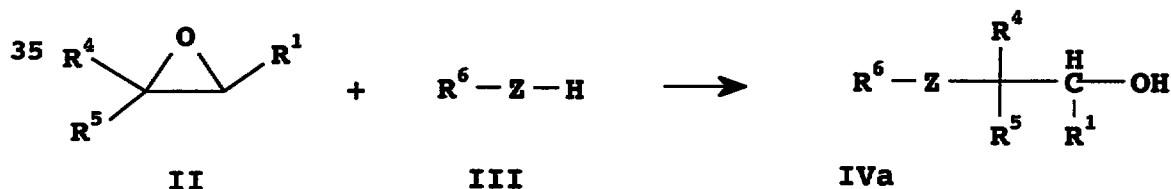
Preference is given to those prodrugs where the release occurs under the conditions which prevail in certain compartments of the body, for example in the stomach, the intestine, the bloodstream or the liver.

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The compounds and also the intermediates for their preparation, such as, for example, II and IV, may have one or more asymmetrically substituted carbon atoms. Such compounds may be present as pure enantiomers or pure diastereomers or as mixtures thereof. Preference is given to the use of an enantiomerically pure compound as active compound.

25 The invention furthermore relates to the use of the above-mentioned carboxylic acid derivatives for preparing drugs, in particular for preparing inhibitors for endothelin receptors.

The compounds of the formula IV in which Z is sulfur or oxygen (IVa) can be prepared as described in WO 96/11914.



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Compounds of the formula III are either known or can be synthesized, for example, by reduction of the corresponding carboxylic acids or esters thereof, or by other generally known methods.

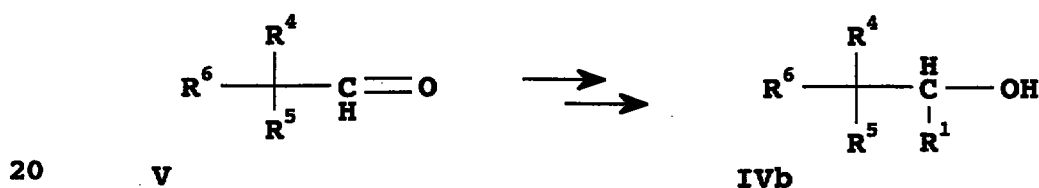
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Compounds of the formula IVa can be obtained in enantiomerically pure form by an acid-catalyzed transesterification, as described in DE 19636046.3.

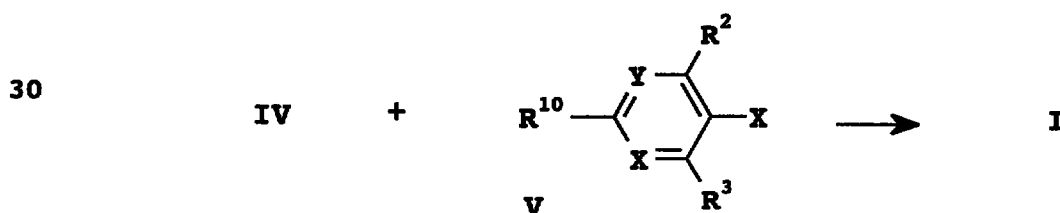
5 Furthermore, enantiomerically pure compounds of the formula IVa can be obtained by carrying out a classic racemate separation on racemic or diastereomeric compounds of the formula IVa using suitable enantiomerically pure bases. Suitable bases are, for example, 4-chlorophenylethylamine and the bases which are
10 mentioned in WO 96/11914.

The compounds of the formula IV in which Z is a single bond (IVb) can be prepared both racemically and in enantiomerically pure form, as described in WO 97/38981.

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The compounds according to the invention in which the substituents are as defined in the formula I can be prepared, for
25 example, by reacting the carboxylic acid derivatives of the formula IV in which the substituents are as defined with compounds of the formula V.



35 In the formula V, R¹⁰ is halogen or R¹¹-SO₂-, and R¹¹ can be C₁-C₄-alkyl, C₁-C₄-haloalkyl or phenyl. The reaction is preferably carried out in an inert solvent or diluent with addition of a suitable base, i.e. a base which effects a deprotonation of intermediate IV, in a temperature range of from room temperature
40 to the boiling point of the solvent.

Compounds of type I where R¹ = COOH can furthermore be obtained directly when the intermediate IV in which R¹ is COOH is deprotonated with two equivalents of a suitable base and reacted
45 with compounds of the formula V. The reaction is again carried

out in an inert solvent and in a temperature range of from room temperature to the boiling point of the solvent.

Examples of such solvents or diluents are aliphatic, alicyclic
5 and aromatic hydrocarbons, which may in each case be chlorinated,
such as, for example, hexane, cyclohexane, petroleum ether,
ligroin, benzene, toluene, xylene, methylene chloride,
chloroform, carbon tetrachloride, ethyl chloride and trichloro-
ethylene, ethers, such as, for example, diisopropyl ether,
10 diisobutyl ether, methyl tert-butyl ether, propylene oxide,
dioxane and tetrahydrofuran, nitriles, such as, for example,
acetonitrile and propionitrile, acid amides, such as, for
example, dimethylformamide, dimethylacetamide and
N-methylpyrrolidone, sulfoxides and sulfones, such as, for
15 example, dimethyl sulfoxide and sulfolane.

Compounds of the formula V are known, and some of them are
commercially available, or they can be prepared in a generally
known manner.

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An alkali metal or alkaline earth metal hydride, such as sodium
hydride, potassium hydride or calcium hydride, a carbonate, such
as an alkali metal carbonate, for example sodium carbonate or
potassium carbonate, an alkali metal or alkaline earth metal
25 hydroxide such as sodium hydroxide or potassium hydroxide, an
organometallic compound, such as butyllithium, or an alkali metal
amide, such as lithium diisopropylamide, may serve as base.

Compounds of the formula I can also be prepared by starting from
30 the corresponding carboxylic acids, i.e. compounds of the formula
I in which R^1 is COOH, and initially converting these in a
customary manner into an activated form, such as an acyl halide,
an anhydride or imidazolidine, and then reacting this with an
appropriate hydroxyl compound HOR^7 . This reaction can be carried
35 out in the customary solvents and often requires addition of a
base, such as, for example, triethylamine, pyridine, imidazole or
diazabicycloundecane. These two steps can also be simplified, for
example, by allowing the carboxylic acid to act on the hydroxyl
compound in the presence of a dehydrating agent, such as a
40 carbodiimide.

Moreover, compounds of the formula I can also be prepared by
starting from the salts of the corresponding carboxylic acids,
i.e. from compounds of the formula I in which R^1 is a group COOM
45 in which M may be an alkali metal cation or the equivalent of an
alkaline earth metal cation. These salts can be reacted with many
compounds of the formula R^7-A , A being a customary nucleofugic

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leaving group, for example halogen, such as chlorine, bromine, iodine or aryl- or alkylsulfonyl, such as, for example, toluene-sulfonyl and methylsulfonyl, which may be substituted by halogen, alkyl or haloalkyl, or another equivalent leaving group.

- 5 Compounds of the formula R^7-A having a reactive substituent A are known or can easily be obtained with general expert knowledge. This reaction can be carried out in the customary solvents and is advantageously carried out with the addition of a base, in which case those mentioned above are suitable.

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In some cases, generally known protective group techniques have to be employed for the preparation of the compounds I according to the invention. If, for example, $R^6 = 4$ -hydroxyphenyl, the hydroxyl group can initially be protected as benzyl ether which

- 15 is then cleaved at a suitable stage of the reaction sequence.

Compounds of the formula I in which R^1 is tetrazole can be prepared as described in WO 96/11914.

- 20 With a view to biological activity, preference is given to those carboxylic acid derivatives of the formula I - both as pure enantiomers or pure diastereomers or as mixtures thereof - in which the substituents are as defined below:

- 25 R^2 is hydrogen, hydroxyl, $N(C_1-C_4\text{-alkyl})_2$, C_1-C_4 -alkyl, C_1-C_4 -haloalkyl, C_1-C_4 -alkoxy, C_1-C_4 -haloalkoxy, C_1-C_4 -alkylthio, halogen;

X is halogen, trifluoromethyl;

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- R^3 is hydrogen, hydroxyl, $N(C_1-C_4\text{-alkyl})_2$, C_1-C_4 -alkyl, C_1-C_4 -haloalkyl, C_1-C_4 -alkoxy, C_1-C_4 -haloalkoxy, C_1-C_4 -alkylthio, halogen;

- 35 R^4 and R^5 are phenyl or naphthyl which may be substituted by one or more, for example by one to three, of the following radicals: halogen, cyano, hydroxyl, mercapto, amino, C_1-C_4 -alkyl, C_1-C_4 -haloalkyl, C_1-C_4 -alkoxy, C_1-C_4 -haloalkoxy, C_1-C_4 -alkylthio, $NH(C_1-C_4\text{-alkyl})_2$, $N(C_1-C_4\text{-alkyl})_2$,
40 C_1-C_4 -alkylcarbonyl, C_1-C_4 -alkoxycarbonyl;

phenyl or naphthyl which are ortho-linked to each other via a direct bond, a methylene, ethylene or ethenylene group, an oxygen or sulfur atom or an SO_2 , NH or $N(C_1-C_4\text{-alkyl})$ group

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- a five-membered heteroaromatic containing one or two nitrogen atoms and/or a sulfur or oxygen atom, which may carry one to two halogen atoms and/or one to two of the following radicals: C₁-C₄-alkyl, C₁-C₄-alkoxy, phenyl which for its part may carry one to three halogen atoms and/or one to three of the following radicals: C₁-C₄-alkyl, C₁-C₄-alkoxy or C₁-C₄-alkylthio;
- or C₃-C₇-cycloalkyl;
- R⁶ is C₁-C₈-alkyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl or C₃-C₈-cycloalkyl where these radicals may in each case be mono- or polysubstituted by: halogen, hydroxyl, cyano, C₁-C₄-alkoxy, C₃-C₆-alkenyloxy, C₃-C₆-alkynyloxy, C₁-C₄-alkylthio, C₁-C₄-haloalkoxy, C₁-C₄-alkylcarbonyl, hydroxycarbonyl, C₁-C₄-alkoxycarbonyl, NH(C₁-C₄-alkyl)₂, N(C₁-C₄-alkyl)₂, phenoxy or phenyl, where the abovementioned aryl radicals may be mono- or polysubstituted, for example mono- to trisubstituted, by halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, R¹², C₁-C₄-alkoxycarbonyl, dioxomethylene, dioxoethylene, C₁-C₄-alkylthio, phenyl or phenoxy;
- phenyl or naphthyl which may be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, amino, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, phenoxy, C₁-C₄-alkylthio, NH(C₁-C₄-alkyl)₂, N(C₁-C₄-alkyl)₂;
- a five- or six-membered heteroaromatic containing one to three nitrogen atoms and/or a sulfur or oxygen atom, which may carry one to four halogen atoms and/or one to two of the following radicals: C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₁-C₄-alkylthio, phenyl, phenoxy or phenylcarbonyl, where the phenyl radicals for their part may carry one to five halogen atoms and/or one to three of the following radicals: C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy and/or C₁-C₄-alkylthio;
- R¹² is C₁-C₄-alkyl, C₁-C₄-alkoxy, which carry one of the following radicals: hydroxyl, carboxamide or CON(C₁-C₄-alkyl)₂;
- Z is sulfur, oxygen or single bond.

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Particular preference is given to compounds of the formula I - both as pure enantiomers and pure diastereomers or as mixtures thereof - where the substituents are as defined below:

- 5 R² is C₁-C₄-alkyl, C₁-C₄-alkoxy, in particular methyl, ethyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy;
- X is fluorine, trifluoromethyl;
- 10 R³ is C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₄-alkylthio, in particular methyl, ethyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy;
- 15 R⁴ and R⁵ are phenyl (identical or different) which may be substituted by one or more, for example by one to three, of the following radicals: halogen, hydroxyl, C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₄-alkylthio or
- 20 R⁴ and R⁵ are phenyl groups which are ortho-linked to each other via a direct bond, a methylene, ethylene or ethenylene group, an oxygen or sulfur atom or an SO₂, NH or N(C₁-C₄-alkyl) group; or
- 25 thiazole, oxazole, thiophene or furan, where the above-mentioned heteroaromatics may be mono- to disubstituted by: halogen, C₁-C₄-alkyl, C₁-C₄-alkoxy;
- R⁴ and R⁵ are cyclohexyl;
- 30 R⁶ is C₁-C₈-alkyl, C₃-C₆-alkenyl or C₃-C₈-cycloalkyl, where these radicals may in each case be mono- or polysubstituted by: halogen, hydroxyl, cyano, C₁-C₄-alkoxy, C₃-C₆-alkenyloxy, C₁-C₄-alkylthio, phenoxy or phenyl, where the abovementioned aryl radicals may be mono- or polysubstituted, for example
- 35 mono- to trisubstituted, by C₁-C₄-alkyl, C₁-C₄-alkoxy, dioxomethylene, dioxoethylene, C₁-C₄-alkylthio;
- 40 phenyl or naphthyl which may be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, amino, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, phenoxy, C₁-C₄-alkylthio, C₁-C₄-alkylamino or C₁-C₄-dialkylamino;
- 45 a five- or six-membered heteroaromatic, containing a nitrogen atom and/or a sulfur or oxygen atom, which may carry one to four halogen atoms and/or one to two of the following radicals: C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy,

C₁-C₄-alkylthio, phenyl, phenoxy or phenylcarbonyl, where the phenyl radicals for their part may carry one to five halogen atoms and/or one to three of the following radicals:

5 C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy and/or C₁-C₄-alkylthio;

Y is sulfur, oxygen or a single bond.

The compounds of the present invention provide a novel
10 therapeutic potential for the treatment of hypertension, pulmonary hypertension, myocardial infarct, angina pectoris, arrhythmia, acute/chronic kidney failure, chronic cardiac insufficiency, renal insufficiency, cerebral vasospasms, cerebral ischemia, subarachnoid hemorrhages, migraine, asthma, arterio-
15 sclerosis, endotoxic shock, endotoxin-induced organ failure, intravascular coagulation, restenosis after angioplasty and bypass operations, benign prostatic hyperplasia, hypertension or kidney failure caused by ischemia or intoxication, metastasis and growth of mesenchymal tumors, contrast-agent-induced kidney
20 failure, pancreatitis, gastro-intestinal ulcers and erectile dysfunction.

The invention further relates to combinations of endothelin receptor antagonists of the formula I and inhibitors of the
25 renin-angiotensin system. Inhibitors of the renin-angiotensin system are renin inhibitors, angiotensin-II antagonists and angiotensin converting enzyme (ACE) inhibitors. Preference is given to combinations of endothelin receptor antagonists of the formula I and ACE inhibitors.

30

The invention furthermore relates to combinations of endothelin receptor antagonists of the formula I and beta blockers.

The invention furthermore relates to combinations of endothelin
35 receptor antagonists of the formula I and diuretics.

The invention furthermore relates to combinations of endothelin receptor antagonists of the formula I and substances which block the action of VEGF (vascular endothelial growth factor). Such
40 substances are, for example, antibodies directed against VEGF or specific binding proteins or else low-molecular-weight substances which are able to inhibit VEGF release or receptor binding specifically.

45 The abovementioned combinations can be administered simultaneously or one after the other at different times. They can be used both in a single pharmaceutical formulation and in separate

formulations. The application forms may also differ, for example the endothelin receptor antagonists may be administered orally and the VEGF inhibitors parenterally.

- 5 These combination preparations are suitable in particular for the treatment and prevention of hypertension and disorders resulting therefrom, and also for the treatment of cardiac insufficiency.

The high activity of the compounds can be demonstrated by the
10 following experiments:

Receptor binding studies

Cloned human ET_A or ET_B receptor-expressing CHO cells were used
15 for the binding studies.

Membrane preparation

The ET_A or ET_B receptor-expressing CHO cells were grown in a DMEM
20 NUT MIX F₁₂ medium (Gibco, No. 21331-020) containing 10% fetal calf serum (PAA Laboratories GmbH, Linz, No. A15-022), 1 mM glutamine (Gibco No. 25030-024), 100 U/ml penicillin and 100 µg/ml streptomycin (Gibco, Sigma No. P-0781). After 48 hours, the cells were washed with PBS and incubated with 0.05% trypsin-
25 containing PBS at 37°C for 5 minutes. The mixture was then neutralized with medium and the cells were collected by centrifugation at 300 x g.

For the membrane preparation, the cells were diluted to a
30 concentration of 10⁸ cells/ml of buffer (50 mM tris-HCl buffer, pH 7.4) and then disintegrated by ultrasound using a Branson Sonifier 250, for 40-70 seconds/constant output 20.

Binding assays

35

For the ET_A and ET_B receptor binding assay, the membranes were suspended in an incubation buffer (50 mM tris-HCl, pH 7.4 with 5 mM MnCl₂, 40 mg/ml of bacitracin and 0.2% BSA) at a concentration of 50 µg of protein per assay mixture and incubated at
40 25°C with 25 pM [¹²⁵I] ET₁ (ET_A receptor assay) or 25 pM [¹²⁵I] ET₃ (ET_B receptor assay) in the presence and absence of test substance. The nonspecific binding was determined using 10⁻⁷ M ET₁. After 30 min, filtration through GF/B glass fiber filters (Whatman, England) in a Skatron cell collector (Skatron, Lier,
45 Norway) was carried out to separate free and bound radioligand, and the filters were washed with ice-cold tris-HCl buffer, pH 7.4, containing 0.2% BSA. The radioactivity collected on the

filters was quantified using a Packard 2200 CA liquid scintillation counter.

Functional test on vessels for endothelin receptor antagonists

5

Segments of rabbit aorta are, after an initial tension of 2 g and a relaxation time of 1 h in Krebs-Henseleit solution at 37°C and pH 7.3-7.4, first induced to contract with K⁺. After washing out, an endothelin dose-effect plot up to the maximum is constructed.

10

Potential endothelin antagonists are administered to other preparations of the same vessel 15 minutes before starting the endothelin dose-effect plot. The effects of the endothelin are calculated as % of the K⁺-induced contraction. Effective

15 endothelin antagonists effect a shift to the right in the endothelin dose-effect plot.

Testing of ET antagonists in vivo:

20 Male SD rats weighing 250-300 g were anesthetized with amobarbital, artificially ventilated, vagotomized and pithed. The carotid artery and jugular vein were catheterized.

In control animals, intravenous administration of 1 µg/kg ET1
25 leads to a distinct rise in blood pressure which persists for a relatively long period.

The test animals received an i.v. injection of the test compounds (1 ml/kg) 30 min before the administration of ET1. To determine
30 the ET-antagonistic properties, the changes in blood pressure in the test animals were compared with those in the control animals.

Oral testing of the mixed ET_A and ET_B antagonists:

35 Male normotone rats weighing 250-350 g (Sprague Dawley, Janvier) are pretreated orally with the test substances. 80 minutes later, the animals are anesthetized with urethan and the A. carotis (for measuring blood pressure) and the V. jugularis (administration of big endothelin/endothelin 1) are catheterized.

40

After a stabilization phase, big endothelin (20 µg/kg, Appl. Vol. 0.5 ml/kg) or ET1 (0.3 µg/kg, appl. vol. 0.5 ml/kg) are administered intravenously. Blood pressure and heart frequency are continuously recorded over a period of 30 minutes. The distinct and
45 persistent changes in blood pressure are calculated as the area under the curve (AUC). To determine the antagonistic effect of the test substances, the AUC of the animals which have been

treated with the substance is compared with the AUC of the control animals.

The compounds according to the invention can be administered in a customary manner orally or parenterally (subcutaneously, intravenously, intramuscularly, intraperitoneally). Administration can also take place with vapors or sprays through the nasopharyngeal space.

10 The dosage depends on the age, condition and weight of the patient and on the mode of administration. The daily dose of active substance is about 0.5-50 mg/kg of body weight on oral administration and about 0.1-10 mg/kg of body weight on parenteral administration.

15 The novel compounds can be used in the conventional solid or liquid pharmaceutical administration forms, for example as uncoated or film-coated tablets, capsules, powders, granules, suppositories, solutions, ointments, creams or sprays. These are produced in a conventional way. The active substances can for this purpose be processed with conventional pharmaceutical auxiliaries such as tablet binders, fillers, preservatives, tablet disintegrants, flow regulators, plasticizers, wetting agents, dispersants, emulsifiers, solvents, release-slowing agents, antioxidants and/or propellant gases (cf. H. Sucker et al.: Pharmazeutische Technologie, Thieme-Verlag, Stuttgart, 1991). The administration forms obtained in this way usually contain from 0.1 to 90% by weight of the active substance.

30 Synthesis examples

Example 1:

Methyl 2-(4,6-dimethoxy-5-fluoropyrimidin-2-yloxy)-
35 3-methoxy-3,3-diphenylpropionate

1.0 g (3.5 mmol) of methyl 2-hydroxy-3-methoxy-3,3-diphenylpropionate, dissolved in DMF, was added dropwise to a suspension of 0.18 g of NaH (4.2 mmol, 55% in white mineral oil) in 10 ml of DMF. The mixture was stirred at room temperature for 30 minutes and then admixed with 830 mg (4.8 mmol) of 4,6-dimethoxy-5-fluoro-2-methylsulfonylpyrimidine in 10 ml of DMF and stirred at room temperature for 2 hours. The reaction mixture was poured onto ice-water and extracted three times with diethyl ether. The ether phases were dried with magnesium sulfate and subsequently filtered, and the solvent was removed under reduced

pressure. The brown residue (1.7 g) was purified by MPLC, giving 1.3 g of the desired product which was directly reacted further.

Example 2:

5

2-(4,6-dimethoxy-5-fluoropyrimidin-2-yloxy)-3-methoxy-3,3-diphenylpropionic acid (A)

and

2-(4-methoxy-5-fluoro-6-hydroxypyrimidin-2-yloxy)-

10 3-methoxy-3,3-diphenylpropionic acid (B)

1.3 g (2.9 mmol) of methyl 2-(4,6-dimethoxy-5-fluoropyrimidin-2-yloxy)-3-methoxy-3,3-diphenylpropionate were dissolved in 10 ml of dioxane and admixed with 5.9 ml of 1 N KOH solution. The

15 mixture was stirred at reflux for four hours. Water was added to the reaction mixture, and the aqueous phase was extracted twice with ether. The aqueous phase was acidified with 1 N aqueous HCl and extracted with ether, the organic phase was dried over magnesium sulfate and the solvent was distilled off. The residue
20 was taken up in ether, and 100 mg of product B crystallized out. The mother liquor was admixed with n-hexane, giving 400 mg of product A as a solid.

A: ¹H NMR (CDCl₃, 500 MHz): 7.2-7.45 (m, 10H); 6.05 (s, 1H); 3.95
25 (s, 6H); 3.3 (s, 3H)

m.p.: 168-170°C

B: ¹H NMR (DMSO, 250 MHz): 7.1-7.4 (m, 10H); 6.05 (s, 1H); 3.9 (s,
30 3H); 3.3 (s, 3H)

m.p.: 115-117°C

Example 3:

35

Benzyl 2-(4-morpholino-5-fluoropyrimidin-2-yloxy)-3-methoxy-3,3-diphenylpropionate

3.3 g (9 mmol) of benzyl 2-hydroxy-3-methoxy-3,3-diphenyl-
40 propionate and 4-morpholino-5-fluoro-2-chloropyrimidine, dissolved in DMF, were added dropwise to a suspension of 9.96 g of K₂CO₃ (72 mmol) in 40 ml of DMF. The mixture was stirred initially at 90°C for 3 hours and subsequently at 130°C for 3
45 hours. The reaction mixture was poured onto ice-water and extracted three times with ethyl acetate. The ethyl acetate phases were dried using magnesium sulfate and subsequently filtered, and the solvent was removed under reduced pressure. The

18

brown residue (5.72 g) was purified by MPLC and directly reacted further.

Example 4:

5

2-(4-Morpholino-5-fluoropyrimidin-2-yloxy)-3-methoxy-3,3-diphenylpropionic acid

Using 300 mg of palladium on activated carbon (10%), a solution
10 of 0.9 g of benzyl 2-(4-morpholino-5-fluoropyrimidin-2-yloxy)-3-methoxy-3,3-diphenylpropionate in 30 ml of ethyl acetate was hydrogenated with hydrogen under atmospheric pressure at room temperature over a period of 3 hours. The reaction mixture was filtered and concentrated and the residue (900 mg) was purified
15 by MPLC.

¹H NMR (CDCl₃, 500 MHz): 8.95 (d, 1H); 7.2-7.5 (m, 10H); 6.05 (s, 1H); 3.8 (s, 8H); 3.3 (s, 3H)

20 m.p.: 174-175°C

The compounds listed in Table I can be prepared in a similar manner.

25

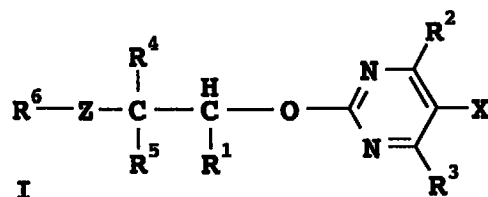
30

35

40

45

Table I



No.	R ¹	R ⁴ , R ⁵	R ⁶	R ²	R ³	X	Z
I-1	COOCH ₃	phenyl	methyl	OMe	OMe	F	O
I-2	COOH	phenyl	methyl	OMe	OMe	F	O
I-3	COOH	phenyl	CH ₃ -S-CH ₂ -CH ₂ -	OMe	OMe	F	O
I-4	COOH	phenyl	methyl	OMe	OMe	F	-
I-5	COOH	phenyl	ethyl	OMe	OMe	F	O
I-6	COOH	phenyl	isopropyl	OMe	OMe	F	O
I-7	COONa	phenyl	phenyl	OMe	Me	F	S
I-8	COOH	phenyl	3,4-di-OMe-phenyl-CH ₂ -CH ₂ -	OMe	OMe	F	O
I-9	COOH	phenyl	(CH ₃) ₂ -CH-SO ₂ -CH ₂ -CH ₂ -	OMe	OMe	F	O
I-10	COOH	phenyl	CH ₃ -S-CH ₂ -CH ₂ -	OMe	Me	F	O
I-11	COOH	phenyl	4-OMe-phenyl-CH ₂ -CH ₂ -	OMe	OMe	F	O
I-12	COOH	phenyl	methyl	Me	OMe	F	-
I-13	COOH	phenyl	(CH ₃) ₂ -CH-SO ₂ -CH ₂ -CH ₂ -	OMe	NH-OMe	F	O
I-14	COOH	phenyl	n-propyl	OMe	OMe	F	O
I-15	COOCH ₃	phenyl	n-propyl	OMe	OMe	CF ₃	O

No.	R ¹	R ⁴ , R ⁵	R ⁶	R ²	R ³	X	Z
I-16	COOH	phenyl	methyl	OMe	OMe	F	S
I-17	COOH	phenyl	n-propyl	OMe	OEt	F	O
I-18	COOH	phenyl	n-butyl	OMe	OMe	F	O
I-19	COOH	phenyl	isobutyl	OMe	OMe	F	O
I-20	COOH	phenyl	isobutyl	Me	Me	F	O
I-21	COOH	phenyl	3,4-di-OMe-phenyl-CH ₂ -CH ₂ -	Me	Me	F	O
I-22	COOH	phenyl	tert-butyl	OMe	Me	F	O
I-23	COOH	phenyl	cyclopropyl-CH ₂ -	Me	OMe	F	O
I-24	COOH	phenyl	methyl	OMe	CF ₃	F	-
I-25	COOH	phenyl	cyclopentyl	OMe	OMe	F	O
I-26	COOH	phenyl	cyclohexyl	Me	Me	F	O
I-27	COOH	phenyl	(CH ₃) ₃ C-CH ₂ -CH ₂ -	OEt	OEt	F	O
I-28	COOH	phenyl	3,4-dioxomethylene-benzyl	OMe	OMe	F	S
I-29	COOH	phenyl	(CH ₃) ₂ CH-CH ₂ -CH ₂ -CH ₂ -	OMe	OMe	F	O
I-30	COOH	phenyl	HO-CH ₂ -CH ₂ -	OEt	OMe	F	O
I-31	COOH	phenyl	HO ₂ C-(CH ₂) ₂ -	Et	Et	F	O
I-32	COOH	phenyl	cyclopropylmethylene	OMe	OMe	F	O
I-33	COOH	phenyl	H	Me	Me	F	O
I-34	COOH	phenyl	phenyl	OMe	OMe	F	O
I-35	COOH	phenyl	3,4-di-OMe-phenyl-CH ₂ -CH ₂ -	OMe	Me	F	O
I-36	COOH	phenyl	methyl	CH ₃	CH ₃	F	-
I-37	COOCH ₃	phenyl	phenyl	Me	Me	F	O
I-38	COOH	phenyl	4-isopropyl-phenyl	OMe	Me	F	O
I-39	COOH	phenyl	4-SMe-phenyl	OMe	OMe	F	O
I-40	COOH	phenyl	4-OMe-phenyl	Me	Me	F	O
I-41	COOH	phenyl	3-Et-phenyl	CF ₃	CF ₃	F	O

No.	R ¹	R ⁴ , R ⁵	R ⁶	R ²	R ³	X	Z
I-42	COOH	phenyl	2-Me-phenyl	OMe	OMe	F	O
I-43	COOH	phenyl	2-Cl-phenyl	OMe	OMe	F	O
I-44	COOH	2-Me-phenyl	methyl	OMe	OMe	F	S
I-45	COOH	phenyl	3-Br-phenyl	OMe	OMe	F	O
I-46	COOH	phenyl	4-F-phenyl	OMe	OMe	F	O
I-47	COOH	phenyl	4-F-phenyl	Me	Me	F	O
I-48	COOH	phenyl	methyl	Et	Me	F	-
I-49	COOH	phenyl	4-Me-phenyl	OMe	OMe	F	O
I-50	COOH	phenyl	3-NO ₂ -phenyl	Me	OMe	F	O
I-51	COOH	phenyl	2-HO-phenyl	OMe	OMe	F	O
I-52	COOH	phenyl	3,4-di-OMe-phenyl	OMe	OMe	F	O
I-53	COOH	phenyl	3,4-dioxomethylene-phenyl	Me	Me	F	O
I-54	COOH	phenyl	methyl	Et	Et	F	S
I-55	COOH	phenyl	3,4,5-tri-OMe-phenyl	OMe	OMe	F	O
I-56	COOH	phenyl	benzyl	OMe	OMe	F	O
I-57	COOH	phenyl	2-Cl-benzyl	OMe	Me	F	O
I-58	COOH	phenyl	3-Br-benzyl	OMe	CF ₃	F	O
I-59	COOH	phenyl	4-F-benzyl	OMe	OMe	Cl	O
I-60	COOH	phenyl	2-Me-benzyl	CF ₃	OMe	F	O
I-61	COOH	phenyl	methyl	Et	Et	F	-
I-62	COOH	phenyl	2-Me-benzyl	Me	OMe	F	O
I-63	COOH	phenyl	3,4-di-Me-phenyl-CH ₂ -CH ₂ -	OMe	H	F	O
I-64	COOH	phenyl	3-Et-benzyl	OMe	OMe	F	O
I-65	COOH	phenyl	4-isopropyl-benzyl	Me	Me	F	O
I-66	COOH	phenyl	4-OMe-3-propyl-benzyl	OMe	OMe	F	O
I-67	COOH	phenyl	2-Me-5-propyl-benzyl	Me	OMe	F	O

No.	R ¹	R ⁴ , R ⁵	R ⁶	R ²	R ³	X	Z
I-68	COOH	phenyl	2-Me-5-propyl-benzyl	Et	Et	F	O
I-69	COOH	phenyl	4-Me-2-propyl-benzyl	OMe	OMe	F	O
I-70	COOH	4-F-phenyl	methyl	OMe	OMe	F	O
I-71	COOCH ₃	4-F-phenyl	methyl	Et	Et	F	O
I-72	COOH	4-Cl-phenyl	methyl	OMe	OMe	F	O
I-73	COOH	phenyl	methyl	OMe	OMe	F	-
I-74	COOH	4-Me-phenyl	methyl	OMe	OMe	F	O
I-75	COOH	4-OMe-phenyl	ethyl	OMe	OMe	F	O
I-76	COOH	4-Me-phenyl	methyl	Me	Me	F	O
I-77	COOH	phenyl	3,4-di-OMe-phenyl-CH ₂ -CH ₂ -	Et	Et	F	O
I-78	COOH	3-CF ₃ -phenyl	n-propyl	OMe	OMe	F	O
I-79	COOH	phenyl	3,4-di-OMe-phenyl-CH ₂ -CH ₂ -	Et	Me	F	O
I-80	COOH	4-F-phenyl	ethyl	OMe	OMe	F	O
I-81	COOH	phenyl	3-OMe-phenyl-CH ₂ -CH ₂ -	Et	Me	F	O
I-82	COOCH ₃	phenyl	methyl	OMe	OMe	F	S
I-83	COOH	3-Cl-phenyl	ethyl	OMe	OMe	F	O
I-84	COOH	2-F-phenyl	methyl	OMe	OMe	F	O
I-85	COOH	2-F-phenyl	methyl	OMe	OMe	F	O
I-86	COOH	2-Me-phenyl	methyl	OMe	OMe	F	O
I-87	COOH	phenyl	3,4-di-Cl-phenyl-CH ₂ -CH ₂ -	Et	Me	F	O
I-88	COOH	phenyl	3,4-di-Cl-phenyl-CH ₂ -CH ₂ -	OMe	OMe	F	O
I-89	COOH	4-CF ₃ -phenyl	methyl	OMe	OMe	F	O
I-90	COOH	phenyl	ethyl	Me	Me	F	-
I-91	COOH	phenyl	methyl	OMe	OEt	F	O
I-92	COOCH ₃	phenyl	methyl	OMe	OEt	F	O
I-93	COOH	phenyl	ethyl	OMe	NH-OMe	F	O

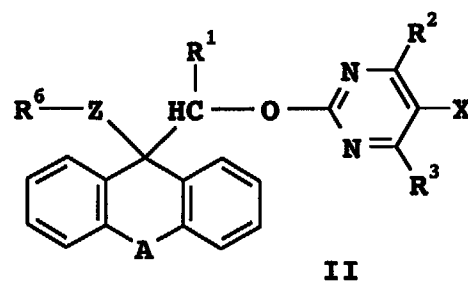
No.	R ¹	R ⁴ , R ⁵	R ⁶	R ²	R ³	X	Z
I-94	COOH	4-OCF ₃ -phenyl	n-propyl	OMe	OCF ₃	F	O
I-95	COOH	phenyl	propyl	OMe	OCF ₃	F	S
I-96	COOH	phenyl	propyl	Me	Me	F	-
I-97	COOH	phenyl	methyl	OMe	CF ₃	F	O
I-98	COOH	4-F-phenyl	benzyl	Me	Me	F	O
I-99	COOH	phenyl	3-Cl-phenyl-CH ₂ -CH ₂ -	Et	Me	F	O
I-100	COOH	phenyl	4-Cl-phenyl-CH ₂ -CH ₂ -	OMe	OMe	F	O
I-101	COOH	4-phenyl	3,4-di-Cl-phenyl-CH ₂ -CH ₂ -	Et	Me	F	O
I-102	COOH	4-phenyl	3,4-di-Cl-phenyl-CH ₂ -CH ₂ -	OMe	OMe	F	O
I-103	COOH	phenyl	3,5-di-Cl-phenyl-CH ₂ -CH ₂ -	Et	Me	F	O
I-104	COOH	phenyl	3,5-di-OMe-phenyl-CH ₂ -CH ₂ -	OMe	OMe	F	O
I-105	COOH	phenyl	phenyl	OMe	OMe	F	S
I-106	COOH	phenyl	3,4-di-Cl-phenyl-CH ₂ -CH ₂ -	Et	Me	F	S
I-107	COOH	phenyl	3,4-di-OMe-phenyl-CH ₂ -CH ₂ -	OMe	OMe	F	O
I-108	COOH	phenyl	3,4-di-Me-phenyl-CH ₂ -CH ₂ -	Et	Me	F	O
I-109	COOH	phenyl	3,4-di-Et-phenyl-CH ₂ -CH ₂ -	OMe	OMe	F	O
I-110	COOH	4-F-phenyl	H	OMe	Me	F	O
I-111	COOH	phenyl	3,4-di-Me-phenyl-CH ₂ -CH ₂ -	Et	Me	F	S
I-112	COOH	phenyl	4-isopropyl-phenyl-CH ₂ -CH ₂ -	OMe	OMe	F	O
I-113	COOH	4-F-phenyl	3,4-di-Me-phenyl-CH ₂ -CH ₂ -	Et	Me	F	O
I-114	COOH	phenyl	4-Et-phenyl-CH ₂ -CH ₂ -	OMe	OMe	F	O
I-115	COOH	phenyl	methyl	Me	Me	F	O
I-116	COOH	phenyl	methyl	Et	Et	F	O
I-117	COOH	phenyl	methyl	Me	Me	CF ₃	O
I-118	CONHSO ₂ phenyl	phenyl	ethyl	OMe	CF ₃	F	-
I-119	COOH	phenyl	methyl	OMe	Me	F	O

No.	R ¹	R ⁴ , R ⁵	R ⁶	R ²	R ³	X	Z
I-120	COOH	cyclohexyl	methyl	OMe	OMe	F	O
I-121	COOH	phenyl	methyl	OMe	OH	F	O
I-122	COOCH ₃	2-F-phenyl	methyl	OMe	OMe	F	O
I-123	COOC ₂ H ₅	3-Cl-phenyl	methyl	OMe	OMe	F	O
I-124	COOH	phenyl	phenyl	OMe	Me	F	S
I-125	COOCH ₃	phenyl	isopropyl	OMe	Me	F	O
I-126	COOC ₂ H ₅	phenyl	s-butyl	OMe	Cl	F	O
I-127	CONHSO ₂ phenyl	3-CF ₃ -phenyl	methyl	OMe	Cl	F	O
I-128	CONHSO ₂ phenyl	phenyl	ethyl	OMe	OMe	F	—
I-129	COOH	phenyl	2,3-di-Cl-phenyl-CH ₂ -CH ₂ -	Et	Me	F	O
I-130	COOH	phenyl	2,3-di-OMe-phenyl-CH ₂ -CH ₂ -	OMe	OMe	F	O
I-131	COOH	4-Cl-phenyl	3,4-di-Me-phenyl-CH ₂ -CH ₂ -	OMe	Me	F	O
I-132	COOH	phenyl	3,4-di-Et-phenyl-CH ₂ -CH ₂ -	OMe	Me	F	O
I-133	COOH	phenyl	2,6-di-Cl-phenyl-CH ₂ -CH ₂ -	Et	Me	F	S
I-134	COOH	phenyl	2,6-di-OMe-phenyl-CH ₂ -CH ₂ -	OMe	OMe	F	O
I-135	COOH	phenyl	2,6-di-Me-phenyl-CH ₂ -CH ₂ -	Et	Me	F	O
I-136	COOH	phenyl	2,5-di-Cl-phenyl-CH ₂ -CH ₂ -	OMe	OMe	F	O
I-137	COOC ₂ H ₅	phenyl	trifluoroethyl	Me	Me	F	O
I-138	COOH	phenyl	n-propyl	Et	Me	F	—
I-139	COOH	phenyl	HO-CH ₂ -(HO-CH)-CH ₂ -	Me	Me	F	O
I-140	COOH	phenyl	HO-CH ₂ -(HO-CH)-CH ₂ -	OMe	OMe	F	O
I-141	COOH	4-Cl-phenyl	HO-CH ₂ -(HO-CH)-CH ₂ -	OMe	Me	F	O
I-142	COOH	phenyl	HO-CH ₂ -CH ₂ -CH ₂ -	OMe	Me	F	O
I-143	COOH	phenyl	HO-CH ₂ -CH ₂ -CH ₂ -	Et	Me	F	S
I-144	COOH	phenyl	HO-CH ₂ -CH ₂ -CH ₂ -	OMe	OMe	F	O
I-145	COOH	phenyl	HO-CH ₂ -CH ₂ -CH ₂ -	Et	Me	F	O

I-146	COOH	phenyl	3-Cl-phenyl	OMe	Me	F	S
I-147	COOH	phenyl	HO-CH ₂ -CH ₂ -	OMe	OMe	F	O
I-148	COOH	phenyl	phenyl	Me	Me	F	O
I-149	COOH	phenyl	phenyl	Me	OMe	F	O
I-150	COOH	phenyl	phenyl	CF ₃	CF ₃	F	O
I-151	COOH	phenyl	phenyl	Et	OMe	F	O
I-152	COOH	phenyl	phenyl	Et	Et	F	O
I-153	COOH	phenyl	2-thiazolyl	OMe	OMe	F	O
I-154	COOCH ₃	2-F-phenyl	phenyl	OMe	OMe	F	O
I-155	COOC ₂ H ₅	3-Cl-phenyl	phenyl	OMe	OMe	F	O
I-156	COOCH ₃	phenyl	4-Br-phenyl	OMe	Me	F	O
I-157	COOC ₂ H ₅	phenyl	4-thiazolyl	OMe	Cl	F	O
I-158	COOH	phenyl	ethyl	OMe	OMe	F	-
I-159	COOH	4-F-phenyl	methyl	ethyl	OMe	F	O
I-160	CONHSO ₂ phenyl	4-F-phenyl	phenyl	OMe	OMe	F	O
I-161	COOC ₂ H ₅	phenyl	4-imidazolyl	OMe	CF ₃	F	O
I-162	CONHSO ₂ phenyl	4-CF ₃ -phenyl	phenyl	OMe	Cl	F	O
I-163	COOCH ₃	phenyl	4-F-phenyl	Me	OCF ₃	F	O
I-164	COOC ₂ H ₅	phenyl	2-dimethylaminophenyl	Me	Me	F	O
I-165	COOH	phenyl	propyl	Me	OMe	F	-
I-166	COOH	phenyl	n-pentyl	Me	Me	F	O
I-167	COOH	cyclohexyl	methyl	OMe	OMe	F	O
I-168	COOH	phenyl	methyl	morpholinyl	H	F	O
I-169	COOH	phenyl	phenyl	CF ₃	CF ₃	F	S
I-170	COOH	3-F-phenyl	methyl	OMe	OMe	F	O
I-171	COOH	3-OMe-phenyl	methyl	Me	OMe	F	O
I-172	COOH	phenyl	methyl	Et	CF ₃	F	O

I-173	COOH	3-F-phenyl	methyl	OMe	Me	F	O
I-174	COOH	phenyl	propyl	OMe	CF ₃	F	-
I-175	CONHSO ₂ phenyl	phenyl	methyl	Me	Me	F	O
I-176	CONHSO ₂ CH ₃	phenyl	methyl	Me	Me	F	O
I-177	COONa	phenyl	methyl	Et	Me	F	O
I-178	CONHSO ₂ CH ₃	phenyl	methyl	Et	Me	F	O
I-179	tetrazolyl	phenyl	methyl	OMe	OMe	F	O
I-180	COOH	phenyl	propyl	Et	Et	F	-
I-181	COOH	phenyl	propyl	OMe	OMe	F	-
I-182	COOH	3-Me-phenyl	methyl	OMe	OMe	F	O
I-183	COOH	4-F-phenyl	methyl	OMe	Me	F	O

Table II



No.	R ¹	A	R ⁶	R ²	R ³	X	Z
II-1	COOH	bond	methyl	OMe	OMe	F	O
II-2	COOH	CH ₂	methyl	OMe	OMe	F	O
II-3	COOH	CH ₂ -CH ₂	methyl	OMe	OMe	F	O
II-4	COOH	CH=CH	methyl	OMe	OMe	F	O
II-5	COOH	O	methyl	OMe	OMe	F	O
II-6	COOH	S	methyl	OMe	OMe	F	O
II-7	COOH	NH(CH ₃)	methyl	OMe	OMe	F	O
II-8	COOH	bond	isopropyl	OMe	OMe	F	O
II-9	COOH	bond	p-isopropylphenyl	OMe	OMe	F	O
II-10	COOH	bond	benzyl	OMe	OMe	F	O
II-11	COOH	CH=CH	ethyl	OMe	OMe	F	O
II-12	COOH	CH=CH	(CH ₃) ₂ -CH ₂ -CH ₂ -	OMe	OMe	F	O
II-13	COOH	CH=CH	cyclopropyl-CH ₂ -	OMe	OMe	F	O

Example 5

Using the binding assay described above, receptor binding data were measured for the compounds listed below.

The results are compiled in Table 3.

Table 3

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Receptor binding data (K_i values).

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Compound	ET _A [nM]	ET _B [nM]
I-2	7.4	1200
I-121	61	> 10000
I-168	4000	> 7000

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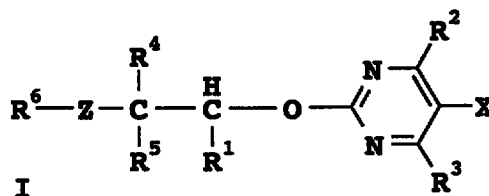
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We claim:

1. A carboxylic acid derivative of the formula I



where:

R¹ is tetrazole or a group



R is



- a) a radical OR⁷, where R⁷ is:

hydrogen, the cation of an alkali metal, the cation of an alkaline earth metal, a physiologically tolerable organic ammonium ion or ammonium ion;

C₃-C₈-cycloalkyl, C₁-C₈-alkyl, CH₂-phenyl which may be substituted by one or more of the following radicals: halogen, nitro, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, hydroxyl, C₁-C₄-alkoxy, mercapto, C₁-C₄-alkylthio, amino, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂;

a C₃-C₆-alkenyl or a C₃-C₆-alkynyl group, it being possible for these groups for their part to carry one to five halogen atoms;

R⁷ may furthermore be a phenyl radical which may carry one to five halogen atoms and/or one to three of the following radicals: nitro, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, hydroxyl, C₁-C₄-alkoxy, mercapto, C₁-C₄-alkylthio, amino,

NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂;

- b) a 5-membered heteroaromatic such as pyrrolyl, pyrazolyl, imidazolyl and triazolyl which is attached via a nitrogen atom and which may carry one to two halogen atoms, or one

to two C₁-C₄-alkyl or one to two C₁-C₄-alkoxy groups.

c) a group



in which k may be 0, 1 or 2, p may be 1, 2, 3 or 4 and R⁸ is

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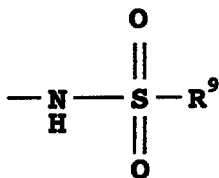
C₁-C₄-alkyl, C₃-C₈-cycloalkyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl or phenyl which may be substituted by one or more, for example by one to three, of the following radicals:

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halogen, nitro, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, hydroxyl, C₁-C₄-alkoxy, C₁-C₄-alkylthio, mercapto, amino, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂.

d) a radical

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where R⁹ is:

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C₁-C₄-alkyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl, C₃-C₈-cycloalkyl, where these radicals may carry a C₁-C₄-alkoxy, C₁-C₄-alkylthio and/or a phenyl radical as mentioned under c);

35

phenyl which may be substituted by one to three of the following radicals: halogen, nitro, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, hydroxyl, C₁-C₄-alkoxy, C₁-C₄-alkylthio, mercapto, amino, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂

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R² is hydrogen, hydroxyl, NH₂, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂, halogen, C₁-C₄-alkyl, C₂-C₄-alkenyl, C₂-C₄-alkynyl, C₁-C₄-hydroxyalkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy or C₁-C₄-alkylthio, morpholine;

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X is halogen, C₁-C₄-haloalkyl, hydroxyl;

5 R^3 is hydrogen, hydroxyl, NH_2 , $NH(C_1-C_4-alkyl)$,
 $N(C_1-C_4-alkyl)_2$, halogen, $C_1-C_4-alkyl$, $C_2-C_4-alkenyl$,
 $C_2-C_4-alkynyl$, $C_1-C_4-hydroxyalkyl$, $C_1-C_4-haloalkyl$,
 $C_1-C_4-alkoxy$, $C_1-C_4-haloalkoxy$, $-NH-O-C_1-C_4-alkyl$,
 $C_1-C_4-alkylthio$;

10 R^4 and R^5 (which may be identical or different) are:
phenyl or naphthyl which may be substituted by one or
more of the following radicals: halogen, nitro, cyano,
hydroxyl, $C_1-C_4-alkyl$, $C_1-C_4-haloalkyl$, $C_1-C_4-alkoxy$,
 $C_1-C_4-haloalkoxy$, phenoxy, mercapto, alkylcarbonyl,
alkoxycarbonyl, $C_1-C_4-alkylthio$, amino, $NH(C_1-C_4-alkyl)$,
 $N(C_1-C_4-alkyl)_2$; or

15 phenyl or naphthyl which are ortho-linked with each other
via a direct bond, a methylene, ethylene, or ethenylene
group, an oxygen or sulfur atom or an SO_2- , $NH-$ or
 $N-alkyl$ group; or

20 a five- or six-membered heteroaromatic containing one to
three nitrogen atoms and/or one sulfur or oxygen atom
which may carry one to four halogen atoms and/or one to
two of the following radicals: $C_1-C_4-alkyl$, $C_1-C_4-halo-$
25 $alkyl$, $C_1-C_4-alkoxy$, $C_1-C_4-haloalkoxy$, $C_1-C_4-alkylthio$,
phenyl, phenoxy or phenylcarbonyl, where the phenyl
radicals for their part may carry one to five halogen
atoms and/or one to three of the following radicals:
 $C_1-C_4-alkyl$, $C_1-C_4-haloalkyl$, $C_1-C_4-alkoxy$, $C_1-C_4-halo-$
30 $alkoxy$ and/or $C_1-C_4-alkylthio$;

or $C_3-C_7-cycloalkyl$;



35 R^6 is hydrogen,
 $C_1-C_8-alkyl$, $C_3-C_6-alkenyl$, $C_3-C_6-alkynyl$ or $C_3-C_8-cyclo-$
 $alkyl$, where these radicals may in each case be mono- or
polysubstituted by: hydroxyl, mercapto, carboxyl,
halogen, nitro, cyano, $C_1-C_4-alkoxy$, $C_3-C_6-alkenyloxy$,
40 $C_3-C_6-alkynyloxy$, $C_1-C_4-alkylthio$, $C_1-C_4-haloalkoxy$,
 $C_1-C_4-alkylcarbonyl$, $C_1-C_4-alkoxycarbonyl$, $C_3-C_8-alkylcar-$
 $bonylalkyl$, amino, $NH(C_1-C_4-alkyl)$, $N(C_1-C_4-alkyl)_2$,
phenyl which may be mono- or polysubstituted, for example
phenyl or phenoxy which may be mono- to trisubstituted by
45 halogen, nitro, cyano, $C_1-C_4-alkyl$, $C_1-C_4-haloalkyl$,
 $C_1-C_4-alkoxy$, $C_1-C_4-haloalkoxy$ or $C_1-C_4-alkylthio$;

phenyl or naphthyl, each of which may be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, amino, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, phenoxy, C₁-C₄-alkylthio, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂ or dioxomethylene or dioxoethylene;

a five- or six-membered heteroaromatic containing one to three nitrogen atoms and/or one sulfur or oxygen atom, which may carry one to four halogen atoms and/or one to two of the following radicals: C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₁-C₄-alkylthio, phenyl, phenoxy or phenylcarbonyl, where the phenyl radicals for their part may carry one to five halogen atoms and/or one to three of the following radicals: C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy and/or C₁-C₄-alkylthio;

with the proviso that R⁶ can only be hydrogen if Z is not a single bond;

Z is sulfur, oxygen or a single bond,



and the physiologically tolerable salts, and the enantiomerically pure and also the diastereomerically pure forms.

2. The use of the carboxylic acid derivatives I as claimed in claim 1 for treating disorders.

3. The use of the compounds I as claimed in claim 1 as endothelin receptor antagonists.

4. The use of the carboxylic acid derivatives I as claimed in claim 1 for preparing drugs for the treatment of disorders which are associated with increased endothelin levels.

5. The use of the carboxylic acid derivatives I as claimed in claim 1 for preparing drugs for the treatment of disorders in which endothelin contributes to the development and/or progression.

6. The use of the carboxylic acid derivatives I as claimed in claim 1 for the treatment of chronic cardiac insufficiency, restenosis, high blood pressure, pulmonary hypertension, acute/chronic kidney failure, cerebral ischemia, asthma, benign prostatic hyperplasia and cancer of the prostate.

7. A combination of carboxylic acid derivatives of the formula I as claimed in claim 1 and one or more active compounds, selected from inhibitors of the renin-angiotensin system such as renin inhibitors, angiotensin-II antagonists, angiotensin converting enzyme (ACE) inhibitors, mixed ACE/neutral endopeptidase (NEP) inhibitors, β -blockers, diuretics, calcium antagonists and VEGF-blocking substances.
8. A drug preparation for oral, parenteral and intra- parenteral administration which comprises per individual dose, in addition to the customary drug auxiliaries, at least one carboxylic acid derivative I as claimed in claim 1.

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