

Novel carboxylic acid derivatives which carry keto side chains, and their preparation and use as endothelin receptor antagonists

- 5 The present invention relates to novel carboxylic acid derivatives, their preparation and use.

Endothelin is a peptide constructed from 21 amino acids, which is synthesized and released by vascular endothelium. Endothelin
10 exists in three isoforms, ET-1, ET-2 and ET-3. Below, "endothelin" or "ET" designates one or all isoforms of endothelin. Endothelin is a potent vasoconstrictor and has a strong effect on vascular tone. It is known that this vasoconstriction is caused by the binding of endothelin to its
15 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 a lasting vascular contraction in peripheral, renal and cerebral blood
20 vessels, which can lead to diseases. As reported in the literature, endothelin is involved in a number of illnesses. These include: hypertension, acute myocardial infarct, pulmonary hypertension, Raynaud's syndrome, cerebral vasospasms, stroke, benign prostate hypertrophy, atherosclerosis and asthma (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 (1993), J. Mol. Cell. Cardiol. 27, A234 (1995); Cancer Research 56, 663 (1996)).
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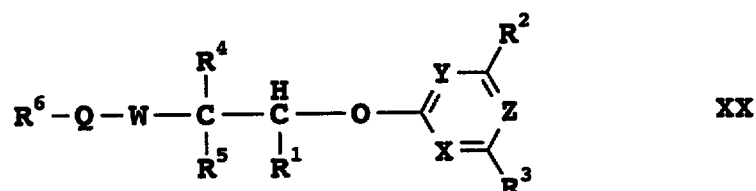
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At least two endothelin receptor subtypes, the ET_A and ET_B receptor, have been described in the literature at present (Nature 348, 730 (1990), Nature 348, 732 (1990)). Accordingly, substances which inhibit the binding of endothelin to both
35 receptors should antagonize physiological effects of endothelin and therefore be valuable pharmaceuticals.

Mixed endothelin receptor antagonists are those compounds which bind to the ET_A and ET_B receptor with approximately equal
40 affinity. Approximately equal affinity for the receptors exists when the quotient of the affinities is greater than 0.05 (preferably 0.1) and smaller than 20 (preferably 10).

The patent application DE 19636046.3 describes mixed ET_A/ET_B
45 receptor antagonists. The spacer Q (see formula XX), which corresponds in length to a C₂-C₄-alkyl chain, is important for these compounds.

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Mixed receptor antagonists are also obtained with the spacer
 $\text{Q} = \text{COCR}^7\text{R}^8$ (see formula I).

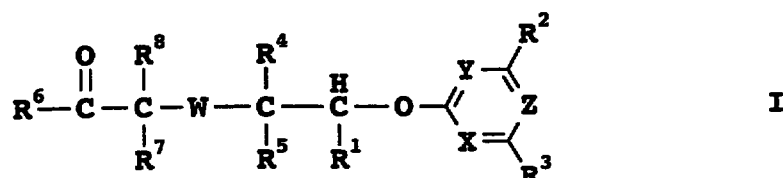
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The object of the invention is to identify compounds which bind
 with approximately equal affinity to the ET_A and the ET_B receptor
 and have more advantageous properties compared with the mixed
 endothelin receptor antagonists already known.

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The invention relates to carboxylic acid derivatives of the
 formula I

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25 in which the substituents have the following meanings:

R^1 is tetrazole [sic] or a group

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R is

a) a radical OR^9 , in which R^9 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 C_1 - C_4 -alkylammonium or the
 ammonium ion;

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C_3 - C_8 -cycloalkyl, C_1 - C_8 -alkyl, CH_2 -phenyl, which can be
 substituted by one or more of the following radicals:
 halogen, nitro, cyano, C_1 - C_4 -alkyl, C_1 - C_4 -haloalkyl, hydroxyl,
 C_1 - C_4 -alkoxy, mercapto, C_1 - C_4 -alkylthio, amino,
 $\text{NH}(\text{C}_1$ - C_4 -alkyl), $\text{N}(\text{C}_1$ - C_4 -alkyl) $_2$;

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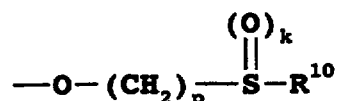
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a C₃-C₆-alkenyl or a C₃-C₆-alkynyl group, where these groups for their part can carry one to five halogen atoms;

5 a phenyl radical which can 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;

10 b) a 5-membered heteroaromatic which is linked via a nitrogen atom, such as pyrrolyl, pyrazolyl, imidazolyl and triazolyl, and which can carry one or two halogen atoms, or one or two C₁-C₄-alkyl [lacuna] or one or two C₁-C₄-alkoxy groups,

15 c) a group



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in which k [lacuna] assume the values 0, 1 and [sic] 2, p [lacuna] assume the values 1, 2, 3 and [sic] 4 and R¹⁰ is

25 C₁-C₄-alkyl, C₃-C₈-cycloalkyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl or phenyl, which can be substituted by one or more, e.g. one to three, of the following radicals:

30 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



in which R¹¹ is:

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

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phenyl, which can 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;

5
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, or CR² is linked to CR¹² as
10 indicated under Z to give a 5- or 6-membered ring;

X is nitrogen or methine;

Y is nitrogen or methine;

15
Z is nitrogen or CR¹², in which R¹² is hydrogen, halogen, C₁-C₄-haloalkyl or C₁-C₄-alkyl, or CR¹², together with CR² or CR³, forms a 5- or 6-membered alkylene or alkenylene ring, which can be substituted by one or two C₁-C₄-alkyl groups and
20 in which one or more methylene groups in each case can be replaced by oxygen, sulfur, -NH or N(C₁-C₄-alkyl), where at least one of the ring members X, Y or Z is nitrogen;

R³ is hydrogen, hydroxyl, NH₂, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂,
25 halogen, C₁-C₄-alkyl, C₂-C₄-alkenyl, C₂-C₄-alkynyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₁-C₄-hydroxyalkyl, C₁-C₄-alkylthio, or CR³ is linked to CR¹² as indicated under Z to give a 5- or 6-membered ring;

30 R⁴ and R⁵ (which can be identical or different) are:

phenyl or naphthyl, each of which can be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, mercapto, C₁-C₄-alkyl, C₂-C₄-alkenyl, C₂-C₄-alkynyl,
35 C₁-C₄-haloalkyl, C₁-C₄-alkoxy, phenoxy, carboxyl, C₁-C₄-haloalkoxy, C₁-C₄-alkylthio, amino, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂ or phenyl, which can be mono- or polysubstituted, e.g. mono- to trisubstituted, by halogen, nitro, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy,
40 C₁-C₄-haloalkoxy or C₁-C₄-alkylthio;

phenyl or naphthyl, which are connected to one another in the ortho-position via a direct bond, a methylene, ethylene or ethenylene group, an oxygen or sulfur atom or an SO₂, NH or
45 N-alkyl group;

C₃-C₈-cycloalkyl;

R⁶ is C₃-C₈-cycloalkyl, where these radicals in each case can be mono- or polysubstituted by: halogen, hydroxyl, mercapto, carboxyl, nitro, cyano, C₁-C₄-alkoxy, C₁-C₄-alkyl, C₂-C₄-alkenyl, C₂-C₄-alkynyl, C₃-C₆-alkenyloxy, C₃-C₆-alkynyloxy, C₁-C₄-alkylthio, C₁-C₄-haloalkoxy, C₁-C₄-alkylcarbonyl, C₁-C₄-alkoxycarbonyl, C₃-C₈-alkylcarbonylalkyl, carboxamide, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂, or phenyl which can be mono- or polysubstituted, e.g. mono- to trisubstituted, by halogen, nitro, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy or C₁-C₄-alkylthio;

phenyl or naphthyl, each of which can be substituted by one or more of the following radicals: halogen, R¹⁵, nitro, mercapto, carboxyl, cyano, hydroxyl, amino, C₁-C₄-alkyl, C₂-C₄-alkenyl, C₂-C₄-alkynyl, C₃-C₆-alkenyloxy, C₁-C₄-haloalkyl, C₃-C₆-alkynyloxy, C₁-C₄-alkylcarbonyl, C₁-C₄-alkoxycarbonyl, carboxamide, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, phenoxy, C₁-C₄-alkylthio, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂, dioxomethylene, dioxoethylene or phenyl, which can be mono- or polysubstituted, e.g. mono- to trisubstituted, by halogen, nitro, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy or C₁-C₄-alkylthio;

a five- or six-membered heteroaromatic, comprising one to three nitrogen atoms and/or a sulfur or oxygen atom, which can carry one to four halogen atoms and/or one or two of the following radicals: C₁-C₄-alkyl, C₂-C₄-alkenyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₁-C₄-alkylthio, phenyl or phenoxy, where the phenyl radicals for their part can 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;

R⁷ and R⁸ (which can be identical or different) are:
hydrogen, C₁-C₄-alkyl;

R¹⁵ is C₁-C₄-alkyl, C₁-C₄-alkylthio, C₁-C₄-alkoxy, each of which carries one of the following radicals: hydroxyl, carboxyl, amino, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂, carboxamide or CON(C₁-C₄-alkyl)₂;

W is sulfur or oxygen.

Here and in the following text, the following definitions apply:

5 An alkali metal is, for example, lithium, sodium or potassium;

An alkaline earth metal is, for example, calcium, magnesium or barium;

10 C₃-C₈-cycloalkyl is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl;

C₁-C₄-haloalkyl can be linear or branched such as, for example, fluoromethyl, difluoromethyl, trifluoromethyl,

15 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 can 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,

25 2-fluoroethoxy or pentafluoroethoxy;

C₁-C₄-alkyl can 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 can 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;

35 C₂-C₄-alkynyl can be linear or branched such as, for example, ethynyl, 1-propyn-1-yl, 1-propyn-3-yl, 1-butyne-4-yl or 2-butyne-4-yl;

C₁-C₄-alkoxy can be linear or branched such as, for example,

40 methoxy, ethoxy, propoxy, 1-methylethoxy, butoxy, 1-methylpropoxy, 2-methylpropoxy or 1,1-dimethylethoxy;

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

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C₃-C₆-alkynyloxy can be linear or branched such as, for example, 2-propyn-1-yloxy, 2-butyn-1-yloxy or 3-butyn-2-yloxy;

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

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

10

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

15 C₃-C₈-alkylcarbonylalkyl can be linear or branched, e.g. 2-oxoprop-1-yl, 3-oxobut-1-yl or 3-oxobut-2-yl;

C₁-C₈-alkyl can 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 or iodine.

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

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Preferred prodrugs are those in which the release takes place under those conditions which prevail in certain body compartments, e.g. in the stomach, intestine, blood circulation or liver.

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The compounds I and also the intermediates for their preparation, such as, for example, II, III, IV, V and VI, can have one or more asymmetrically substituted carbon atoms. Such compounds can be present as pure enantiomers or pure diastereomers or as a mixture thereof. The use of an enantiomerically pure compound as an active compound is preferred.

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The invention further relates to the use of the abovementioned carboxylic acid derivatives for the production of drugs, in

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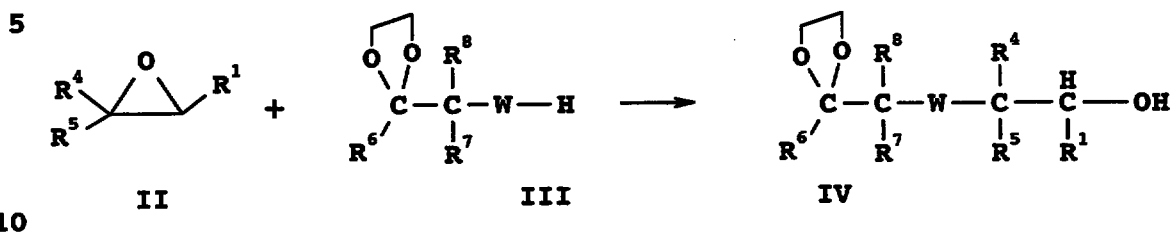
particular for the production of inhibitors for ET_A and ET_B receptors. The compounds according to the invention are suitable as mixed antagonists, as were defined at the outset.

The preparation of the compounds having the general formula IV in which W is sulfur or oxygen can be carried out as described in WO

45 96/11914.

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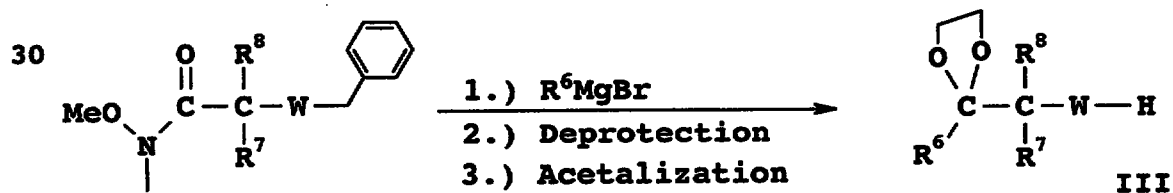
In this reaction, the later keto group is protected as a cyclic acetal; however, other protective groups are also conceivable, such as, for example, dimethyl acetal.



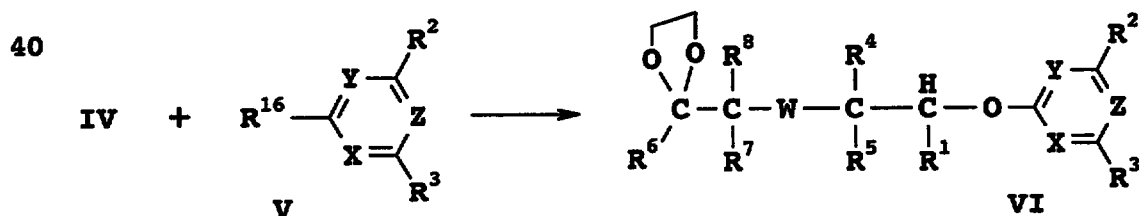
Compounds of the formula IV can be obtained in enantiomerically pure form by starting from enantiomerically pure compounds of the formula II and reacting them with compounds of the formula III as described in WO 96/11914.

Furthermore, enantiomeric compounds of the formula IV can be obtained by carrying out a classical resolution with suitable enantiomerically pure bases using racemic or diastereomeric compounds of the formula IV. Suitable bases of this type are, for example, 4-chlorophenylethylamine and bases such as are mentioned in WO 96/11914.

The preparation of compounds of the general formula II was described in WO 96/11914, while compounds of the general formula III are either known or can be synthesized by generally known methods such as, for example:



35 Carboxylic acid derivatives of the general formula IV can then be reacted with compounds of the general formula V, substances of the type VI being obtained.



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In formula V, R^{16} is halogen or $R^{17}-SO_2-$, where R^{17} can be C_1-C_4 -alkyl, C_1-C_4 -haloalkyl or phenyl. Furthermore, at least one of the ring members X or Y or Z is nitrogen. The reaction preferably takes place in an inert solvent or diluent with
5 addition of a suitable base, i.e. of a base which brings about a deprotonation of the intermediate IV, in a temperature range from room temperature up to the boiling point of the solvent.

Compounds of the type VI with $R^1 = COOH$ can be obtained directly
10 in this manner if the intermediate IV, in which R^1 is $COOH$, is deprotonated using two equivalents of a suitable base and reacted with compounds of the general formula V. Here too, the reaction takes place in an inert solvent and in a temperature range from room temperature up to the boiling point of the solvent.

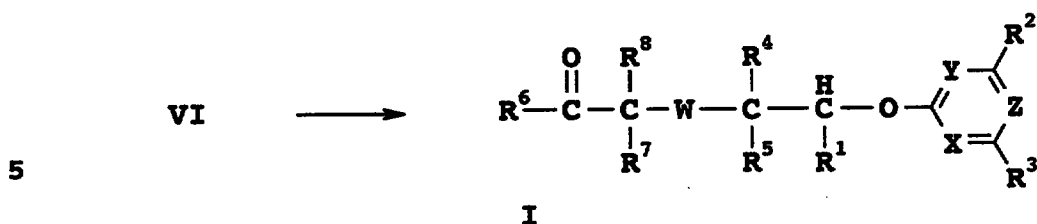
15 Examples of such solvents or diluents are aliphatic, alicyclic and aromatic hydrocarbons, each of which can be optionally chlorinated, such as, for example, hexane, cyclohexane, petroleum ether, naphtha, benzene, toluene, xylene, methylene chloride,
20 chloroform, carbon tetrachloride, ethyl chloride and trichloroethylene, ethers, such as, for example, diisopropyl ether, dibutyl ether, methyl tert-butyl ether, propylene oxide, dioxane and tetrahydrofuran, nitriles, such as, for example, acetonitrile and propionitrile, acid amides, such as, for
25 example, dimethylformamide, dimethylacetamide and N-methylpyrrolidone, and sulfoxides and sulfones, such as, for example, dimethyl sulfoxide and sulfolane.

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

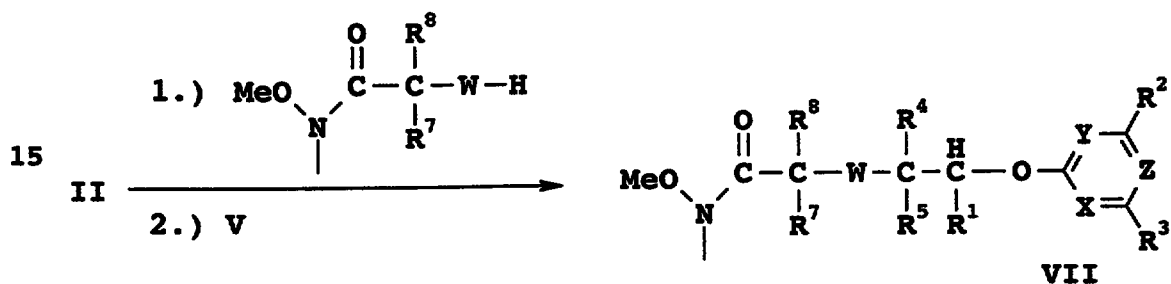
The base used can be an alkali metal or alkaline earth metal hydride such as sodium hydride, potassium hydride or calcium hydride, a carbonate such as an alkali metal carbonate, e.g.
35 sodium or potassium carbonate, an alkali metal or alkaline earth metal hydroxide such as sodium or potassium hydroxide, an organometallic compound such as butyllithium or an alkali metal amide such as lithium diisopropylamide or lithium amide.

40 The compounds according to the invention, in which the substituents have the meanings indicated under the general formula I, can finally be prepared by removing the keto protective group in the compounds of the formula VI. In the case of the ethylene glycol acetal, this can be carried out by acidic
45 hydrolysis.

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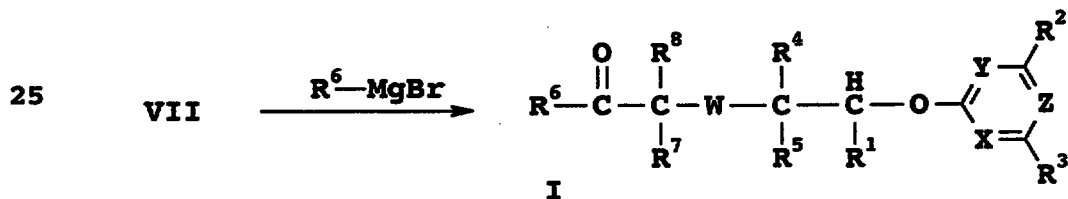


Compounds of the type I can furthermore be synthesized via
10 compounds having the formula VII



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The compounds having the general formula VII can then be reacted
with Grignard reagents to give the compounds of the formula I



30 Compounds of the formula I can also be prepared by starting from
the corresponding carboxylic acids, i.e. compounds of the formula
I in which R^1 is COOH , and first converting these in a customary
manner into an activated form such as an acid halide, an
anhydride or imidazolid and then reacting this with an
35 appropriate hydroxyl compound HOR^9 . This reaction can be carried
out in the customary solvents and often necessitates the addition
of a base, those mentioned above being suitable. 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
40 dehydrating agent such as a 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 where M can 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 $\text{R}^9\text{-A}$, A being a customary nucleofugic

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leaving group, for example halogen such as chlorine, bromine, iodine or aryl- or alkylsulfonyl optionally substituted by halogen, alkyl or haloalkyl, such as, for example, toluenesulfonyl and methylsulfonyl or another equivalent leaving
 5 group. Compounds of the formula R^9-A having a reactive substituent A are known or easy to obtain using the general expert knowledge. This reaction can be carried out in the customary solvents and is advantageously performed with addition of a base, those mentioned above being suitable.

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In some cases, the use of generally known protective group techniques is necessary for the preparation of the compounds I according to the invention. If, for example, R^6 is to be 4-hydroxyphenyl, the hydroxyl group can first be protected as a
 15 benzyl ether, which is then cleaved at a suitable stage in the reaction sequence.

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

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With respect to the biological action, carboxylic acid derivatives of the general formula I - both as pure enantiomers or pure diastereomers or as a mixture thereof - are preferred in which the substituents have the following meanings:

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R^2 is hydrogen, $N(C_1-C_4\text{-alkyl})_2$, $C_1-C_4\text{-alkyl}$, $C_1-C_4\text{-alkoxy}$, $C_1-C_4\text{-alkylthio}$, $C_1-C_4\text{-haloalkyl}$, $C_1-C_4\text{-haloalkoxy}$, hydroxymethyl or CR^2 is linked to CR^{12} as indicated under Z to give a 5- or 6-membered ring;

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X is nitrogen or methine;

Y is nitrogen or methine;

35 Z is nitrogen or CR^{12} , in which R^{12} is hydrogen, fluorine, trifluoromethyl or methyl or CR^{12} , together with CR^2 or CR^3 , forms a 5- or 6-membered alkylene or alkenylene ring which can be substituted by one or two methyl groups, and in which one methylene group in each case can be replaced by oxygen or
 40 sulfur, such as $-CH_2-CH_2-O-$, $-CH_2-CH_2-CH_2-O-$, $-CH=CH-O-$, $-CH=CH-CH_2O-$, $-CH(CH_3)-CH(CH_3)-O-$, $-CH=C(CH_3)-O-$, $-C(CH_3)=C(CH_3)-O-$ or $-C(CH_3)=C(CH_3)-S$;

at least one of the ring members X, Y or Z is nitrogen;

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R³ is hydrogen, N(C₁-C₄-alkyl)₂, C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₄-alkylthio, C₁-C₄-haloalkyl, C₁-C₄-haloalkoxy, hydroxymethyl or CR³ is linked to CR¹² linked as indicated under Z to give a 5- or 6-membered ring;

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R⁴ and R⁵ (which can be identical or different) are:

phenyl or naphthyl, each of which can be mono- to trisubstituted by halogen, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, phenoxy, C₁-C₄-alkylthio, NH(C₁-C₄-alkyl) or N(C₁-C₄-alkyl)₂ or phenyl, which can be mono- to trisubstituted by halogen, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy or C₁-C₄-alkylthio; or

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phenyl or naphthyl, each of which can be bonded to one another in the ortho-position via a direct bond, a methylene, ethylene or ethenylene group, an oxygen or sulfur atom or an SO₂-, NH- or N-alkyl-group;

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C₅-C₆-cycloalkyl;

R⁶ C₃-C₈-cycloalkyl, where these radicals [sic] in each case can be mono- to trisubstituted by: halogen, C₁-C₄-alkoxy, C₁-C₄-alkyl, C₁-C₄-alkylthio, C₁-C₄-haloalkoxy, C₁-C₄-alkoxycarbonyl or phenyl, which can be mono- to trisubstituted by halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy or C₁-C₄-alkylthio;

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phenyl or naphthyl, each of which can be mono- to trisubstituted by halogen, R¹⁵, cyano, hydroxyl, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkylcarbonyl, C₁-C₄-alkoxycarbonyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, phenoxy, C₁-C₄-alkylthio, NH(C₁-C₄-alkyl), N(C₂-C₄-alkyl)₂, dioxomethylene, dioxoethylene or phenyl, which can be mono- to trisubstituted by halogen, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy or C₁-C₄-alkylthio;

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

40

45

R⁷ and R⁸ (which can be identical or different) are:

hydrogen, C₁-C₄-alkyl;

5 R¹⁵ is methyl, ethyl, methoxy or ethoxy, each of which carries one of the following radicals: hydroxyl, carboxyl, amino, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂, carboxamide or CON(C₁-C₄-alkyl)₂;

10 W is sulfur or oxygen.

Particularly preferred compounds of the formula I - both as pure enantiomers or pure diastereomers or as a mixture thereof - are those in which the substituents have the following meanings:

15

R² is trifluoromethyl, C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₄-alkylthio, or CR² is linked to CR¹² as indicated under Z to give a 5- or 6-membered ring;

20 X is nitrogen or methine;

Y is nitrogen or methine;

25 Z is nitrogen or CR¹², in which R¹² is hydrogen, fluorine or methyl or CR¹², together with CR² or CR³, forms a 5- or 6-membered alkylene or alkenylene ring, in which one methylene group in each case can be replaced by oxygen or sulfur, such as -CH₂-CH₂-S-, -CH=CH-O-, -CH₂-CH₂-S- [sic];

30 at least one of the ring members X, Y or Z is nitrogen;

R³ is trifluoromethyl, C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₄-alkylthio or CR³ is linked to CR¹² as indicated under Z to give a 5- or 6-membered ring;

35

R⁴ and R⁵ (which can be identical or different) are:

40 phenyl or naphthyl, each of which can be mono- to trisubstituted by halogen, C₁-C₄-alkyl, C₁-C₄-alkoxy, phenoxy or phenyl, which can be mono- to trisubstituted by halogen, C₁-C₄-alkyl or C₁-C₄-alkoxy; or

45 phenyl or naphthyl, which can be bonded to one another in the ortho-position by a direct bond, a methylene, ethylene or ethenylene group or an SO₂ group;

cyclohexyl;

5 R⁶ is cyclohexyl which can be mono- to trisubstituted by C₁-C₄-alkoxy, C₁-C₄-alkyl, halogen or phenyl, which can be mono- to trisubstituted by halogen, C₁-C₄-alkyl, C₁-C₄-alkoxy;

10 phenyl or naphthyl, which in each case can be mono- to trisubstituted by halogen, R¹⁵, C₁-C₄-alkyl, C₁-C₄-haloalkyl, acetyl, C₁-C₄-alkoxycarbonyl, C₁-C₄-alkoxy, phenoxy, C₁-C₄-alkylthio, dioxomethylene, dioxoethylene or phenyl, which can be mono- to trisubstituted by halogen, C₁-C₄-alkyl, C₁-C₄-alkoxy, or C₁-C₄-alkylthio;

15 R⁷ and R⁸ (which can be identical or different) are: hydrogen, C₁-C₄-alkyl;

20 R¹⁵ is methoxy or ethoxy, each of which carries one of the following radicals: hydroxyl, carboxyl, carboxamide or CON(C₁-C₄-alkyl)₂;

W is sulfur or oxygen.

25 The compounds of the present invention offer a novel therapeutic potential for the treatment of hypertension, pulmonary high blood pressure, myocardial infarct, angina pectoris, arrhythmia, acute/chronic kidney failure, chronic cardiac insufficiency, renal insufficiency, cerebral vasospasms, cerebral ischemia, subarachnoid hemorrhages, migraine, asthma, atherosclerosis, 30 endotoxic shock, endotoxin-induced organ failure, intravascular coagulation, restenosis after angioplasty and bypass operations, benign prostate hyperplasia, ischemic kidney failure or hypertension and kidney failure or hypertension caused by intoxication, metastasis and growth of mesenchymal tumors, 35 contrast agent-induced kidney failure, pancreatitis and gastrointestinal ulcers.

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

15

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

The invention further relates to combinations of endothelin
5 receptor antagonists of the formula I and diuretics.

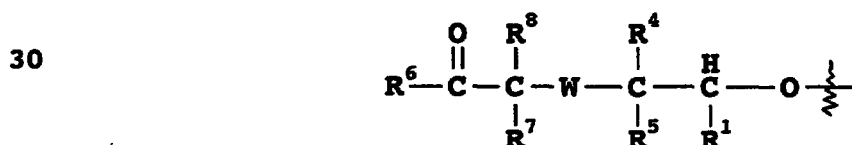
The invention further relates to combinations of endothelin receptor antagonists of the formula I and substances which block the action of VEGF (vascular endothelial growth factor). Such
10 substances are, for example, antibodies directed against VEGF or specific binding proteins or alternatively low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

15 The abovementioned combinations can be administered simultaneously or sequentially. They can be employed both in a single pharmaceutical formulation or alternatively in separate formulations. The administration form can also be different, for example the endothelin receptor antagonists can be administered
20 orally and VEGF inhibitors can be administered parenterally.

These combination preparations are especially suitable for the treatment and prevention of hypertension and its sequelae, and for the treatment of cardiac insufficiency.

25

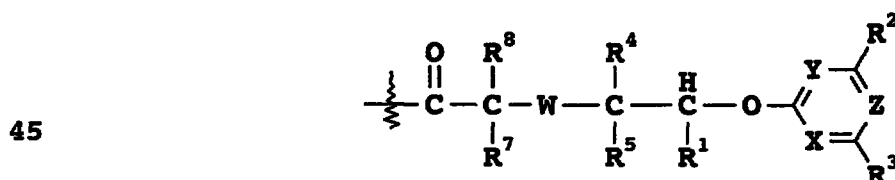
The invention further relates to a structural fragment of the formula



in which the radicals R^1 , R^4 , R^5 , R^6 , R^7 , R^8 and W have the
35 abovementioned meaning.

Such structural fragments are suitable as structural constituents of endothelin receptor antagonists, in particular of mixed endothelin receptor antagonists.

40 The invention further relates to endothelin receptor antagonists consisting of a structural fragment of the formula



in which the radicals R¹, R², R³, R⁴, R⁵, R⁷, R⁸, W, X, Y and Z have the abovementioned meanings, covalently linked to a group which has a molecular weight of at least 40, preferably at least 77.

5

The good action of the compounds can be shown in the following experiments:

Receptor binding studies

10

Cloned human ET_A or ET_B receptor-expressing CHO cells were employed for binding studies.

Membrane preparation

15

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

25

For the membrane preparation, the cells were adjusted to a concentration of 10⁸ cells/ml of buffer (50 mM tris·HCl [sic] buffer, pH 7.4) and then disintegrated by means of ultrasound (Branson Sonifier 250, 40-70 seconds/constant output 20).

30

Binding tests

For the ET_A and ET_B receptor binding tests, the membranes were suspended in incubation buffer (50 mM tris HCl, pH 7.4 with 5 mM MnCl₂, 40 µg/ml of bacitracin and 0.2% BSA) in a concentration of 50 µg of protein per test batch and incubated at 25°C with 25 pM of [125I]-ET₁ (ET_A receptor test) or 25 pM [125I]-ET₃ (ET_B receptor test) in the presence and absence of test substance. The nonspecific binding was determined with 10⁻⁷ M ET₁. After 30 min, the free and the bound radioligand was [sic] separated by filtration through GF/B glass fiber filters (Whatman, England) on a Skatron cell sampler (Skatron, Lier, Norway) 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.

Testing of the ET antagonists in vivo:

Male SD rats weighing 250-300 g were anesthetized with amobarbital, artificially respired, vagotomized and pithed. The 5 carotid artery and jugular vein were catheterized.

In control animals, the intravenous administration of 1 $\mu\text{g/kg}$ of ET1 leads to a distinct blood pressure increase, which lasts for a relatively long period.

10

The test compounds were injected i.v. (1 mg/kg) into the test animals 30 min before ET1 administration. For determination of the ET-antagonistic properties, the blood pressure changes in the test animals were compared with those in the control animals.

15

p.o. testing of the mixed ET_A and ET_B antagonists:

Male normotonic rats weighing 250-350 g (Sprague Dawley, Janvier) are orally pretreated with the test substances. 80 minutes later, 20 the animals are anesthetized with urethane and the carotid artery is catheterized (for blood pressure measurement) as well as the jugular vein (administration of big endothelin/endothelin 1).

After a stabilization phase, big endothelin (20 $\mu\text{g/kg}$, admin. vol. 25 0.5 ml/kg) or ET1 (0.3 $\mu\text{g/kg}$, admin. vol. 0.5 ml/kg) is administered intravenously. Blood pressure and heart rate are recorded continuously for 30 minutes. The clear and long-lasting blood pressure changes are calculated as the area under the curve (AUC). For determination of the antagonistic action of the test 30 substances, the AUC of the substance-treated animals is compared with the AUC of the control animals.

The compounds according to the invention can be administered orally or parenterally (subcutaneously, intravenously, 35 intramuscularly, intraperitoneally) in a customary manner. Administration can also be carried out through the nasopharynx using vapors or sprays.

The dose depends on the age, condition and weight of the patient 40 and on the type of administration. As a rule, the daily dose of active compound is between approximately 0.5 and 50 mg/kg of body weight in the case of oral administration and between approximately 0.1 and 10 mg/kg of body weight in the case of parenteral administration.

45

The novel compounds can be used as solids or liquids in the customary pharmaceutical administration forms, e.g. as tablets, film-coated tablets, capsules, powders, granules, sugar-coated tablets, suppositories, solutions, ointments, creams or sprays.

- 5 These are prepared in a customary manner. In this case, the active compounds can be processed using the customary pharmaceutical auxiliaries such as tablet binders, fillers, preservatives, tablet disintegrants, flow-regulating agents, plasticizers, wetting agents, dispersants, emulsifiers, solvents, 10 release-delaying agents, antioxidants and/or propellants (cf. H. Sucker et al.: Pharmazeutische Technologie [Pharmaceutical Technology], Thieme-Verlag, Stuttgart, 1991). The administration forms thus obtained normally contain the active compound in an amount from 0.1 to 90% by weight.

15

Synthesis examples

Example 1

- 20 Methyl 2-hydroxy-3,3-diphenyl-3-(2-phenyl-[1,3]-dioxolan-2-yl-methoxy)propionate

- p-Toluenesulfonic acid (0.50 g, 0.27 mmol) was added with ice-cooling to a solution of 2-phenyl-[1,3]-dioxolan-2-ylmethanol 25 (1.98 g, 11.0 mmol) and methyl 3,3-diphenyl-2,3-epoxypropionate (4.71 g, 13.2 mmol; purity according to HPLC: 71%) in anhydrous dichloromethane (100 ml) and the mixture was stirred at 0°C for 15 minutes. The resulting solution was washed with sodium hydrogen-carbonate solution, and the organic phase was separated off and 30 dried over magnesium sulfate. After filtering off the drying agent, the solvent was removed by distillation; the residual crude oil (4.70 g) was reacted further without further purification.

35 Example 2

2-Hydroxy-3,3-diphenyl-3-(2-phenyl-[1,3]-dioxolan-2-ylmethoxy)-propionic acid

- 40 Methyl 2-hydroxy-3-(2-phenyl)-[1,3]-dioxolan-2-yl-methoxy)-3,3-diphenyl propionate (4.60 g, crude) was dissolved in dioxane/water 2:1 (45 ml) and treated with sodium hydroxide (300 mg, 7.50 mmol). The mixture was warmed to 40°C and stirred for one hour. For work-up, it was diluted with water (150 ml) and 45 extracted twice with ethyl acetate. The aqueous phase was acidified with citric acid and extracted twice with ethyl acetate. The extracts obtained from the acidification were dried

over magnesium sulfate and the solvent was removed by distillation. 4.00 g of a crude oil were obtained, which was reacted further without further purification.

5 Example 3

2-(4-Methoxy-6-methylpyrimidin-2-yloxy)-3,3-diphenyl-3-(2-phenyl-[1,3]-dioxolan-2-ylmethoxy)propionic acid

- 10 50% strength sodium hydride (240 mg, 5.00 mmol) was added in 3 portions in the course of 3 minutes to a solution of 2-hydroxy-3-(2-phenyl-[1,3]-dioxolan-2-ylmethoxy)-3,3-diphenylpropionic acid (1.00 g, 1.62 mmol at 68% purity according to HPLC) in anhydrous DMF (15 ml). The mixture was stirred for 5 minutes and
- 15 2-methanesulfonyl-4,6-dimethylpyrimidine (421 mg, 2.00 mmol) were then added in portions. The mixture was stirred at room temperature for 16 hours. For work-up, the contents of the flask were poured onto ice water, then acidified with citric acid and extracted twice with ether. The organic extracts were dried over
- 20 magnesium sulfate and the solvent was removed by distillation. 1.75 g of an oil remained, which was further purified by flash chromatography and subsequent crystallization from ether/n-hexane. The title compound was obtained as a colorless solid (750 mg, 85% yield).

25

¹H-NMR (200 MHz, CDCl₃): 7.5 – 7.7 ppm (2 H, m), 7.2 – 7.4 (13 H, m), 6.3 (1 H, s), 6.2 (1 H, s), 4.2 – 4.4 (2 H, m), 4.1 (1 H, d), 3.9 (3 H, s), 3.8 – 4.0 (2 H, m), 3.6 (1 H, d), 2.4 (3 H, s).

30 Example 4

2-(4-Methoxy-6-methylpyrimidin-2-yloxy)-3-(2-oxo-2-phenylethoxy)-3,3-diphenylpropionic acid

- 35 p-Toluenesulfonic acid (50 mg) was added to a solution of 2-(4-methoxy-6-methylpyrimidin-2-yloxy)-3-(2-phenyl-[1,3]-dioxolan-2-ylmethoxy)-3,3-diphenylpropionic acid (600 mg, 1.11 mmol) in dioxane/water 1:1 (20 ml) and the resulting mixture was stirred at 80°C for 2 hours. After cooling, the mixture was
- 40 diluted with water and it was extracted twice with ether. The combined organic phases were dried over magnesium sulfate and the solvent was removed by distillation. The residue (550 mg) which remained was purified by crystallization from ether/n-hexane, subsequent flash chromatography and crystallization from
- 45 ether/n-hexane again. The title compound was obtained as a crystalline solid (163 mg, 30% yield).

20

$^1\text{H-NMR}$ (200 MHz, CDCl_3): 7.2 – 7.9 ppm (15 H, m), 6.2 (2 H, s br), 5.1 (2 H, m), 3.7 (3 H, s), 2.2 (3 H, s).

ESI-MS : $\text{M}^+ = 498$

5

The following compounds were prepared analogously:

Example 5

10 2-(4,6-Dimethylpyrimidin-2-yloxy)-3-(2-oxo-2-phenylethoxy)-3,3-diphenylpropionic acid

$^1\text{H-NMR}$ (200 MHz, CDCl_3): 7.8 ppm (2 H, d), 7.2 – 7.7 (13 H, m), 6.7 (1 H, s), 6.3 (1 H, s), 5.2 (1 H, d), 4.9 (1 H, d), 2.3 (6 H,

15 s).

ESI-MS: $\text{M}^+ = 482$

Example 6

20

3-[2-(4-Bromophenyl)-2-oxoethoxy]-2-(4,6-dimethylpyrimidin-2-yloxy)-3,3-diphenylpropionic acid*

$^1\text{H-NMR}$ (200 MHz, CDCl_3): 7.7 ppm (2 H, d), 7.6 (2 H, d), 7.2 – 7.5 (10 H, m), 6.7 (1 H, s), 6.2 (1 H, s), 5.1 (1 H, d), 4.9 (1 H, d), 2.3 (6 H, s).

25

ESI-MS: $\text{M}^+ = 560$

30 Example 7

3-[2-(4-Bromophenyl)-2-oxoethoxy]-2-(4-methoxy-6-methylpyrimidin-2-yloxy)-3,3-diphenylpropionic acid*

35 $^1\text{H-NMR}$ (200 MHz, CDCl_3): 7.7 ppm (2 H, d), 7.6 (2 H, d), 7.2 – 7.5 (10 H, m), 6.2 (1 H, s), 6.0 (1 H, s), 5.2 (1 H, d), 4.9 (1 H, d), 3.7 (3 H, s), 2.2 (3 H, s).

ESI-MS: $\text{M}^+ = 576$

40

* In the synthesis of 4-bromophenyl-substituted derivatives, boron trifluoride etherate was used instead of p-toluenesulfonic acid for the final acetal cleavage.

45

Example 8

Benzyl 2-hydroxy-3-[(methoxymethylcarbamoyl)methoxy]-
3,3-diphenylpropionate

5

Boron trifluoride etherate (0.10 ml) was slowly added to a solution, cooled to -78°C, of 2-hydroxy-*N*-methoxy-*N*-methylacetamide (1.19 g, 10.0 mmol) and benzyl 3,3-diphenyl-2,3-epoxypropionate (3.88 g, 11.0 mmol; purity according to HPLC: 94%) in
10 anhydrous dichloromethane (100 ml). The mixture was stirred for two hours and in this time gradually warmed to -20°C, and the reaction was stopped by cautious addition of aqueous sodium hydrogencarbonate solution. The organic phase was washed with sodium hydrogencarbonate solution and dried over magnesium
15 sulfate. After filtering off the drying agent, the solvent was removed by distillation; the residual crude oil (5.50 g) was reacted further without further purification.

Example 9

20

Benzyl 3-[(methoxymethylcarbamoyl)methoxy]-2-(4-methoxy-6-methylpyrimidin-2-yloxy)-3,3-diphenylpropionate

A solution of benzyl 2-hydroxy-3-[(methoxymethylcarbamoyl)-
25 methoxy]-3,3-diphenylpropionate (1.35 g, crude) was treated with ice-cooling with potassium carbonate (365 mg, 2.64 mmol) and, after 10 minutes, with 2-methanesulfonyl-4-methoxy-6-methylpyrimidine (320 mg, 1.45 mmol). Subsequently, it was stirred at 0°C for 30 minutes and then at room temperature for 16 hours. The
30 mixture was diluted with water, acidified with citric acid and extracted twice with ether. The combined organic phases was [sic] backwashed with water and dried over magnesium sulfate. After distilling off the solvent, a foam (1.60 g) remained, which was purified by flash chromatography and subsequent crystallization
35 from ether/*n*-hexane; 650 mg of the title compound were obtained.

Example 10

Benzyl 3-[2-(3,4-dimethoxyphenyl)-2-oxoethoxy]-2-(4-methoxy-
40 6-methylpyrimidin-2-yloxy)-3,3-diphenylpropionate

A 1-molar solution of 3,4-dimethoxyphenylmagnesium bromide in tetrahydrofuran (0.60 ml) was added at room temperature to a solution of benzyl 3-[(methoxymethylcarbamoyl)-methoxy]-
45 2-(4-methoxy-6-methylpyrimidin-2-yloxy)-3,3-diphenylpropionate (250 mg, 0.38 mmol, purity according to HPLC: 86%) in anhydrous tetrahydrofuran (25 ml). After stirring for 10 minutes, only

22

partial conversion was observed, therefore a 1-molar solution of 3,4-dimethoxyphenylmagnesium bromide in tetrahydrofuran (0.60 ml) was added dropwise again. The mixture was stirred for a further 10 minutes, then the solvent was evaporated. The residue was taken up in ethyl acetate/ether 1:2. After filtering off undissolved matter, the solvent was removed by distillation, and the oily residue (400 mg) was purified by flash chromatography. The title compound was obtained as a foam (125 mg, 49% yield with 95% purity according to HPLC).

10

$^1\text{H-NMR}$ (400 MHz, CDCl_3): 7.5 – 7.7 ppm (4 H, m), 7.4 (2 H, d), 7.2 – 7.3 (9 H, m), 6.9 (2 H, d), 6.8 (1 H, d), 6.3 (1 H, s), 6.2 (1 H, s), 5.4 (1 H, d), 5.0 (2 H, m), 4.7 (1 H, d), 3.9 (6 H, s), 3.7 (3 H, s), 2.3 (3 H, s).

15

The compounds in Table I can be prepared analogously or as described in the general section.

Example 11

20

Receptor binding data for the compounds listed below were measured as in the binding test described above.

The results are shown in Table 2.

25

Table 2

Receptor binding data (K_i values)

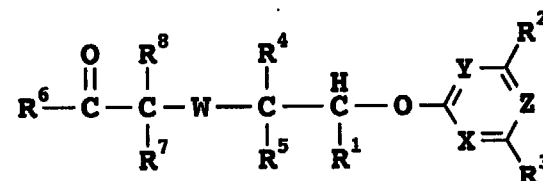
30

Compound	ET_A [nM]	ET_B [nM]
Example 4	10	114
Example 5	31	119
Example 6	18	168
Example 7	13	106
I-10	1.7	20
I-114	1.3	21

40

45

Table I



I

No.	R ¹	R ⁴ , R ⁵	R ⁶	R ⁷	R ⁸	R ²	R ³	Z	X	Y	W
I-1	COOH	Phenyl	4-OMe-phenyl	Me	Me	Me	Me	CH	N	N	O
I-2	COOH	Phenyl	3,4-Di-OMe-phenyl	H	H	OMe	OMe	CH	N	N	S
I-3	COOH	Phenyl	2-Naphthyl	H	H	CH ₂ OH	Me	CH	N	N	S
I-4	COOH	Phenyl	3-OMe-phenyl	Me	H	OMe	OMe	CH	N	N	S
I-5	COOH	Phenyl	3-OMe-phenyl	H	H	OMe	Me	CH	N	N	O
I-6	COOH	Phenyl	3-OMe-phenyl	Butyl	H	CH ₂ OH	Me	CH	N	N	O
I-7	COOH	Naphthyl, naphthyl	4-CF ₃ -phenyl	Me	Me	Me	Me	CH	N	N	O
I-8	COOH	Phenyl	3-Me-phenyl	H	H	OMe	CH ₂ -CH ₂ -CH ₂ -C		N	N	O
I-9	COOH	Phenyl	3-OMe-phenyl	H	H	OMe	O-CH ₂ -CH ₂ -C		N	N	O
I-10	COOH	Phenyl	3,4-Di-OMe-phenyl	H	H	OMe	Me	CH	N	N	O
I-11	COOH	Phenyl	4-OMe-phenyl	H	H	Ethyl	Ethyl	CH	N	N	O
I-12	COOH	4-F-Phenyl	3,5-Di-OMe-phenyl	H	H	CF ₃	Me	CH	N	N	S
I-13	COOH	Phenyl	2-Cl-phenyl	H	H	OMe	CF ₃	CH	N	N	O
I-14	COOH	Phenyl	3-Cl-phenyl	H	H	Me	Me	CH	N	N	O
I-15	COOH	4-Cl-phenyl	2-Cl-phenyl	H	H	OMe	CH ₂ -CH ₂ -CH ₂ -C		N	N	O

No.	R ¹	R ⁴ , R ⁵	R ⁶	R ⁷	R ⁸	R ²	R ³	Z	X	Y	W
I-16	COOH	Phenyl	4-Cl-phenyl	H	H	OMe	OMe	CH	N	N	S
I-17	COOH	Phenyl	2,3-Di-Cl-phenyl	H	H	OMe	Me	CH	N	N	O
I-18	COOH	Phenyl	3,4-Di-Cl-Phenyl	H	H	CH ₂ OH	Me	CH	N	N	O
I-19	COOH	4-Cl-phenyl, 4-F-phenyl	4-Cl-phenyl	H	H	OMe	Me	CH	N	N	O
I-20	COOH	4-F-phenyl	3,4-Di-Cl-phenyl	Me	Me	OMe	CH ₂ -CH ₂ -CH ₂ -C		N	N	O
I-21	COOH	Phenyl	3,4-Di-OMe-phenyl	H	H	H	OMe	Me	N	N	O
I-22	COOH	Phenyl	3,4-Me-Cl-phenyl	H	H	OMe	O-CH ₂ -CH ₂ -C		N	N	O
I-23	COOH	Phenyl	3,4-Me-Cl-phenyl	H	H	Ethyl	Ethyl	CH	N	N	S
I-24	COOH	Phenyl, 4-Cl-phenyl	3,4,5-Tri-OMe-phenyl	H	H	Me	Me	CH	N	N	S
I-25	COOH	4-F-phenyl	3,4-Me-Cl-phenyl	H	H	CF ₃	Me	CH	N	N	O
I-26	COOMe	4-Me-phenyl	3-Cl-Phenyl	H	H	OMe	O-CH ₂ -CH ₂ -C		N	N	O
I-27	COOH	4-F-phenyl	4-i-Propyl-phenyl	H	H	OMe	CF ₃	CH	N	N	O
I-28	COOH	Phenyl	3-Acetyl-phenyl	H	H	Me	Me	CH	N	N	O
I-29	COOH	Phenyl	4-OCF ₃ -phenyl	H	H	OMe	OMe	CH	N	N	O
I-30	COOH	Phenyl	3-Ethyl-phenyl	H	H	OMe	Me	CH	N	N	O
I-31	COOH	Naphthyl, naphthyl	Phenyl	H	H	OMe	OMe	CH	N	N	S
I-32	COOMe	Phenyl	3-OMe-4Me-phenyl	H	H	CH ₂ OH	Me	CH	N	N	O
I-33	COOH	Phenyl	4-Phenyl-phenyl	H	H	OMe	CH ₂ -CH ₂ -CH ₂ -C		N	N	O
I-34	COOH	Phenyl	Phenyl	Me	Me	OMe	O-CH ₂ -CH ₂ -C		N	N	O
I-35	COOH	3-OMe-phenyl	4-Cl-phenyl	H	H	Ethyl	Ethyl	CH	N	N	O
I-36	COOH	Phenyl	3,4-Di-F-phenyl	H	H	Ethyl	Ethyl	CH	N	N	S
I-37	COOH	Phenyl	Cyclohexyl	H	H	CF ₃	Me	CH	N	N	O
I-38	COOH	4-F-phenyl	Cyclopentyl	H	H	OMe	CF ₃	CH	N	N	O
I-39	COOH	Naphthyl, phenyl	3,4-Di-ethyl-phenyl	H	H	Ethyl	Ethyl	CH	N	N	O
I-40	COOH	Phenyl	4-Me-cyclohexyl	H	H	Me	Me	CH	N	N	O
I-41	COOH	Phenyl	4-CF ₃ -cyclohexyl	H	H	OMe	OMe	CH	N	N	S

No.	R ¹	R ⁴ , R ⁵	R ⁶	R ⁷	R ⁸	R ²	R ³	Z	X	Y	W
I-42	COOH	4- CF ₃ -phenyl	2,3-Di-Cl-phenyl	H	H	CF ₃	Me	CH	N	N	O
I-43	COOH	Phenyl	2-Pyridyl	H	H	OMe	Me	CH	N	N	O
I-44	COOH	4-F-phenyl	4-Pyridyl	H	H	CH ₂ OH	Me	CH	N	N	O
I-45	COOH	Phenyl	3-Thiophenyl	H	H	OMe	CH ₂ -CH ₂ -CH ₂ -C		N	N	O
I-46	COOH	Phenyl	2-SMe-phenyl	H	H	OMe	O-CH ₂ -CH ₂ -C		N	N	S
I-47	COOH	Phenyl	3,4-Methylenedioxyphenyl	H	H	Ethyl	Ethyl	CH	N	N	O
I-48	COOH	Phenyl	3-MeOOC-phenyl	H	H	CF ₃	Me	CH	N	N	O
I-49	COOH	Phenyl	4-(2-HO-ethyl)phenyl	Ethyl	H	OMe	CF ₃	CH	N	N	O
I-50	COOH	2-F-phenyl, 4-Me-phenyl	2,6-Di-OMe-phenyl	H	H	OMe	O-CH ₂ -CH ₂ -C		N	N	O
I-51	COOH	3,4-Di-F-phenyl	3,4-Di-Cl-phenyl	H	H	OMe	CF ₃	CH	N	N	O
I-52	COOH	Phenyl	3-Me ₂ NCOCH ₂ -phenyl	H	H	Me	Me	CH	N	N	O
I-53	COOH	Phenyl	4-(HOOC-CH ₂ -CH ₂)-phenyl	H	H	OMe	OMe	CH	N	N	O
I-54	COOMe	Phenyl	3,4-Di-OMe-phenyl	H	H	OMe	CH ₂ -CH ₂ -CH ₂ -C		N	N	O
I-55	COOH	Phenyl	1-Naphthyl	Me	H	OMe	Me	CH	N	N	O
I-56	COOH	Cyclohexyl	4-Phenyl-phenyl	H	H	Me	Me	CH	N	N	O
I-57	COOH	Cyclohexyl	Phenyl	H	H	OMe	OMe	CH	N	N	O
I-58	COOMe	2-F-phenyl, phenyl	4-Cl-phenyl	H	H	OMe	CH ₂ -CH ₂ -CH ₂ -C		N	N	O
I-59	COOH	3-Me-phenyl	3,4-Di-F-phenyl	Me	H	OMe	Me	CH	N	N	O
I-60	COOH	4-F-phenyl	Cyclohexyl	H	H	CH ₂ OH	Me	CH	N	N	O
I-61	COOH	4-F-phenyl, phenyl	4-Cl-phenyl	H	H	OMe	Me	CH	N	N	O
I-62	COOH	4-Me-phenyl, naphthyl	2-OMe-phenyl	H	H	Ethyl	Me	CH	N	N	O
I-63	COOH	3-Cl-phenyl	1-Naphthyl	H	H	OMe	CH ₂ -CH ₂ -CH ₂ -C		N	N	O
I-64	COOH	Phenyl	3,4-Di-OMe-phenyl	H	H	Ethyl	Ethyl	CH	N	N	O
I-65	COOH	4-Cl-phenyl	2-Naphthyl	H	H	OMe	O-CH ₂ -CH ₂ -C		N	N	S
I-66	COOH	Phenyl	4-OMe-naphth-2-yl	H	H	Ethyl	Ethyl	CH	N	N	O
I-67	COOH	Phenyl	3,4-Di-OMe-phenyl	H	H	OMe	O-CH ₂ -CH ₂ -C		N	N	O

No.	R ¹	R ⁴ , R ⁵	R ⁶	R ⁷	R ⁸	R ²	R ³	Z	X	Y	W
I-68	COOH	Phenyl	2-Cl-phenyl	H	H	OMe	CF ₃	C-CH ₃	N	N	O
I-69	Tetrazole [sic]	Phenyl	3-Cl-phenyl	H	H	Me	Me	CH	N	N	O
I-70	COOH	Phenyl	4-Cl-phenyl	H	H	H	H	CH	N	N	S
I-71	COOH	Phenyl	2,3-Di-Cl-phenyl	H	H	OH	Me	C-F	N	N	O
I-72	COOH	Phenyl	3,4-Di-Cl-phenyl	H	H	H	OMe	C-CH ₃	N	N	O
I-73	COOH	3-F-4-OMe-phenyl	3,4-Di-Cl-phenyl	H	H	Me	Me	CH	N	N	O
I-74	COOH	4-F-phenyl	3,4-Di-Cl-phenyl	Me	H	Me	CH ₂ -CH ₂ -CH ₂ -C		N	N	O
I-75	COOH	4-Cl-phenyl, 4-F-phenyl	Phenyl	H	H	OMe	OMe	CH	N	N	S
I-76	COOH	Phenyl	3,4-Me-Cl-phenyl	H	H	OMe	S-CH ₂ -CH ₂ -C		N	N	O
I-77	COOH	4-Ethyl-phenyl	3,4-Me-Cl-phenyl	H	H	OMe	OMe	CH	N	N	S
I-78	COOH	Phenyl	3,4-Me-Cl-phenyl	H	H	Ethyl	Ethyl	N	N	N	S
I-79	COOH	4-F-phenyl	3,4-Me-Cl-phenyl	H	H	OMe	OMe	N	CH	N	O
I-80	COOH	4-F-phenyl	4-i-Propyl-phenyl	H	H	Me	Me	N	CH	N	O
I-81	COOH	Phenyl	3,4-Di-OMe-phenyl	H	H	CF ₃	Me	CH	N	N	S
I-82	COOH	Phenyl	3-Acetyl-phenyl	H	H	H	OMe	CH	N	N	O
I-83	COOH	2-Me-phenyl	3,4-Me-Cl-phenyl	H	H	OMe	Me	CH	N	N	O
I-84	COOH	Phenyl	4-OCF ₃ -phenyl	H	H	OMe	OMe	N	CH	N	O
I-85	COOH	Phenyl	3-Ethyl-phenyl	H	H	Ethyl	Me	CH	N	N	O
I-86	COOMe	Phenyl	3-OMe-4Me-phenyl	H	H	OH	Me	C-F	N	N	O
I-87	COOH	Phenyl	4-Phenyl-phenyl	H	H	H	CH ₂ -CH ₂ -CH ₂ -C		N	N	O
I-88	COOH	Phenyl	Phenyl	H	H	H	O-CH ₂ -CH ₂ -C		N	N	O
I-89	COOH	Phenyl	3,4-Di-F-phenyl	H	H	Ethyl	Me	CH	N	N	S
I-90	COOH	Phenyl	Cyclohexyl	H	H	Me	Me	C-CH ₃	N	N	O
I-91	COOH	2-Me-phenyl	3,4-Me-Cl-phenyl	H	H	CH ₂ OH	Me	CH	N	N	O
I-92	COOH	4-F-phenyl, 4-Cl-phenyl	4-OMe-phenyl	H	H	OMe	Me	CH	N	N	O

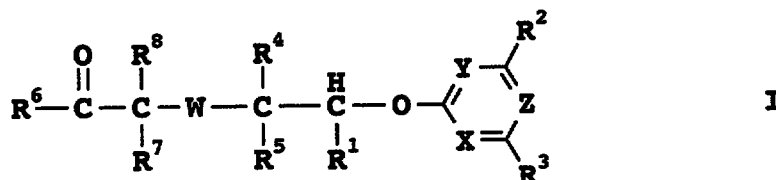
No.	R ¹	R ⁴ , R ⁵	R ⁶	R ⁷	R ⁸	R ²	R ³	Z	X	Y	W
I-93	COOH	4-F-phenyl	Cyclopentyl	H	H	OMe	Me	N	N	N	O
I-94	COOH	Phenyl	4-Me-cyclohexyl	H	H	OMe	Me	N	CH	N	O
I-95	Tetrazole [sic]	Phenyl	4-CF ₃ -cyclohexyl	H	H	OMe	OMe	CH	N	N	S
I-96	COOH	Phenyl	2-Pyridyl	H	H	Me	Me	CH	N	N	O
I-97	COOH	4-F-phenyl	4-Pyridyl	H	H	H	Me	CH	N	N	O
I-98	COOH	Phenyl	3-Thiophenyl	H	H	Me	CH ₂ -CH ₂ -CH ₂ -C		N	N	O
I-99	COOH	Phenyl	2-SMe-phenyl	H	H	H	O-CH ₂ -CH ₂ -C		N	N	S
I-100	COOH	Phenyl	3,4-Methylenedioxy-phenyl	H	H	SMe	Ethyl	CH	N	N	O
I-101	COOH	Phenyl	4-i-Propyl-phenyl	H	H	OMe	CH ₂ -CH ₂ -CH ₂ -C		N	N	O
I-102	COOH	4-SMe-phenyl	3-Acetyl-phenyl	Me	Me	OMe	O-CH ₂ -CH ₂ -C		N	N	O
I-103	COOH	Phenyl	3-MeOOC-phenyl	H	H	SMe	Me	CH	N	N	O
I-104	COOH	Phenyl	3,4-Di-OMe-phenyl	H	H	OMe	CF ₃	CH	N	N	O
I-105	COOH	Phenyl	4-(2-HO-ethyl)-phenyl	Ethyl	H	OMe	Me	N	CH	N	O
I-106	COOH	Phenyl	3-Me ₂ NCOCH ₂ -phenyl	H	H	Me	Me	C-CH ₃	N	N	O
I-107	COOH	Phenyl	4-(HOOC-CH ₂ -CH ₂)-phenyl	H	H	OMe	Me	C-CH ₃	N	N	O
I-108	COOH	3-OMe-phenyl	4-OCF ₃ -phenyl	H	H	Ethyl	Ethyl	CH	N	N	O
I-109	COOH	Phenyl	1-Naphthyl	H	H	H	Me	C-CH ₃	N	N	O
I-110	COOH	Phenyl	2-Naphthyl	H	H	H	OMe	CH	N	N	S
I-111	COOH	Phenyl, 4-Cl-phenyl	3,4-Di-OMe-phenyl	Me	Me	Me	Me	CH	N	N	O
I-112	COOH	4-Cl-phenyl	3-Ethyl-phenyl	Me	Me	CF ₃	Me	CH	N	N	O
I-113	COOH	4-Cl-phenyl	2-Cl-phenyl	H	H	Me	CH ₂ -CH ₂ -CH ₂ -C		N	N	O
I-114	COOH	Phenyl	3,4-Di-OMe-phenyl	H	H	Me	Me	CH	N	N	O
I-115	Tetrazol	Phenyl	3-Cl-phenyl	H	H	OMe	O-CH ₂ -CH ₂ -C		N	N	O
I-116	COOH	3-OMe-phenyl	4-Cl-phenyl	H	H	Me	Ethyl	C-CH ₃	N	N	O
I-117	COOH	4-CF ₃ -phenyl	2,3-Di-Cl-phenyl	H	H	Me	Me	CH	N	N	O

No.	R ¹	R ⁴ , R ⁵	R ⁶	R ⁷	R ⁸	R ²	R ³	Z	X	Y	W
I-118	COOH	3,4-Di-F-phenyl	3,4-Di-Cl-phenyl	H	H	H	H	CH	N	N	O
I-119	COOH	3-F-4-OMe-phenyl	3,4-Di-Cl-phenyl	H	H	Me	Me	N	CH	N	O
I-120	COOH	4-Ethyl-phenyl	3,4-Me-Cl-phenyl	H	H	OMe	OMe	N	CH	N	S
I-121	COOH	2-Me-phenyl	3,4-Me-Cl-phenyl	H	H	OMe	H	C-CH ₃	N	N	O
I-122	COOH	2-Me-phenyl	3,4-Me-Cl-phenyl	H	H	H	H	CH	N	N	O
I-123	COOH	3,4-Di-Cl-phenyl	3-OMe-4Me-phenyl	H	H	OMe	CF ₃	CH	N	N	O
I-124	COOH	Phenyl	4-i-Propyl-phenyl	H	H	H	CH ₂ -CH ₂ -CH ₂ -C		N	N	O
I-125	COOH	4-F-phenyl, phenyl	4-OMe-phenyl	H	H	Me	Me	CH	N	N	O
I-126	COOH	4-SMe-phenyl	3-Acetyl-phenyl	Me	Me	OMe	S-CH ₂ -CH ₂ -C		N	N	O
I-127	COOH	3-OMe-phenyl	4-OCF ₃ -phenyl	H	H	Ethyl	Me	CH	N	N	O
I-128	COOH	4-Cl-phenyl	3-Ethyl-phenyl	Me	H	Me	Me	CH	N	N	O
I-129	COOH	3,4-Di-Cl-phenyl	3-OMe-4Me-phenyl	H	H	Me	Me	CH	N	N	O
I-130	COOH	Cyclohexyl	4-Phenyl-phenyl	H	H	Ethyl	Me	CH	N	N	O
I-131	COOH	Cyclohexyl	Phenyl	H	H	N(CH ₃) ₂	N(CH ₃) ₂	N	N	N	O
I-132	COOH	3-Me-phenyl	3,4-Di-F-phenyl	Me	H	OMe	H	CH	N	N	O



We claim:

1. A carboxylic acid derivative of the formula I



where the substituents have the following meanings:

R¹ is tetrazole [sic] or a group



[lacuna]

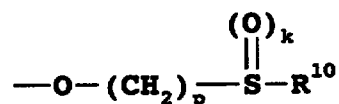
a) a radical OR⁹, in which R⁹ is:

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

C₃-C₈-cycloalkyl, C₁-C₈-alkyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl, CH₂-phenyl or phenyl, each of which is optionally substituted;

b) a 5-membered heteroaromatic which is linked via a nitrogen atom;

c) a group

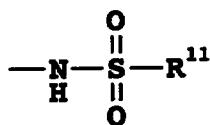


in which k can assume the values 0, 1 and [sic] 2, p can assume the values 1, 2, 3 and [sic] 4 and R¹⁰ is

C₁-C₄-alkyl, C₃-C₈-cycloalkyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl or optionally substituted phenyl;



d) a radical



5

in which R¹¹ is:

10 C₁-C₄-alkyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl, C₃-C₈-cycloalkyl,
where these radicals can carry a C₁-C₄-alkoxy,
C₁-C₄-alkylthio and/or a phenyl radical;

phenyl, which is optionally substituted;

15 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-haloalkyl, C₁-C₄-alkoxy,
C₁-C₄-haloalkoxy or C₁-C₄-alkylthio, or CR² is linked to
CR¹² as indicated below to give a 5- or 6-membered ring;

20 X is nitrogen or methine;

Y is nitrogen or methine;

25 Z is nitrogen or CR¹², in which R¹² is hydrogen or C₁-C₄-alkyl
or CR¹², together with CR² or CR³, forms a 5- or 6-membered
alkylene or alkenylene ring which can be optionally
substituted, and in which one or more methylene groups in
each case can be replaced by oxygen, sulfur, -NH or
-N(C₁-C₄-alkyl);

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R³ 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-haloalkyl, C₁-C₄-alkoxy,
C₁-C₄-haloalkoxy, C₁-C₄-alkylthio; or CR³ is linked to CR¹²
35 as indicated above to give a 5- or 6-membered ring;

R⁴ and R⁵ (which can be identical or different) are:

40 phenyl or naphthyl, each of which is optionally
substituted,

phenyl or naphthyl, which are bonded to one another in
the ortho-position by a direct bond, a methylene,
ethylene or ethenylene group, an oxygen or sulfur atom or
45 an SO₂, NH or N-alkyl group,
C₃-C₈-cycloalkyl, which is optionally substituted;



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R⁶ is optionally substituted C₃-C₈-cycloalkyl;

phenyl or naphthyl, which is optionally substituted;

5 a five- or six-membered heteroaromatic, comprising one to three nitrogen atoms and/or a sulfur or oxygen atom, and which can be optionally substituted;

R⁷ and R⁸ (which can be identical or different) are:

10

hydrogen or C₁-C₄-alkyl;

W is sulfur or oxygen.

15 2. A pharmaceutical preparation comprising at least one carboxylic acid derivative I as claimed in claim 1.

3. The use of the carboxylic acid derivatives as claimed in claim 1 for the treatment of diseases.

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

5. The use of the carboxylic acid derivatives I as claimed in claim 1 for the production of drugs for the treatment of diseases in which raised endothelin levels occur.

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6. The use as claimed in claim 5 for the treatment of chronic cardiac insufficiency, restenosis, high blood pressure, pulmonary high blood pressure, acute/chronic kidney failure, cerebral ischemia, benign prostate hyperplasia and prostate cancer.

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7. A pharmaceutical combination preparation comprising a carboxylic acid derivative as claimed in claim 1 and an inhibitor of the renin-angiotensine system or a mixed ACE/neutral endopeptidase (NEP) inhibitor or a β -blocker.

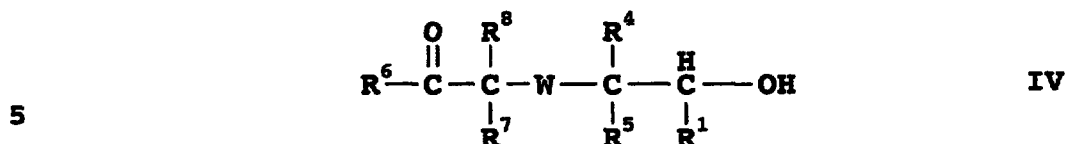
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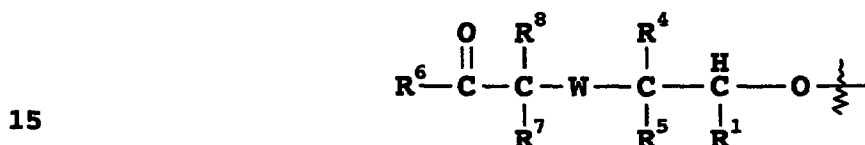


8. The use of compounds of the formula IV



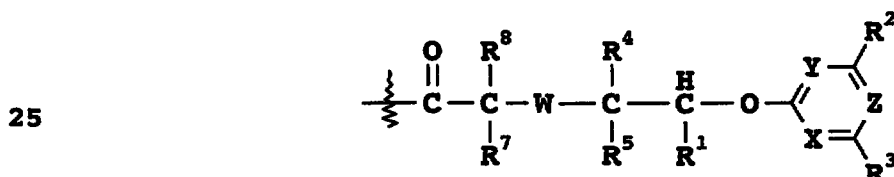
in which the radicals R^1 , R^4 , R^5 , R^6 , R^7 , R^8 and W have the meanings indicated in claim 1, as intermediate [sic] for the synthesis of endothelin receptor antagonists.

9. The use of a structural fragment of the formula



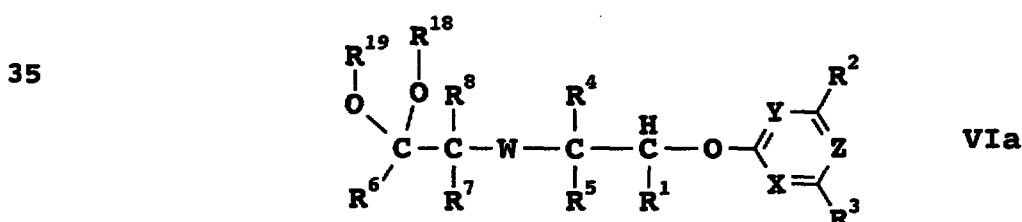
in which the radicals R^1 , R^4 , R^5 , R^6 , R^7 , R^8 and W have the meanings indicated in claim 1, as a structural constituent of an endothelin receptor antagonist.

10. The use of a structural fragment of the formula



in which the radicals R^1 , R^2 , R^3 , R^4 , R^5 , R^7 , R^8 , W , X , Y and Z have the meanings indicated in claim 1, as a structural constituent in an endothelin receptor antagonist.

11. A compound of the formula VIa



in which the radicals R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , W , X , Y and Z have the meanings indicated in claim 1 and R^{18} and R^{19} have the following meanings:

R^{18} and R^{19} (which can be identical or different) are:

C_1 - C_4 -alkyl or R^{18} , together with R^{19} , forms an ethylene or propylene bridge which can optionally be substituted by one to four methyl groups.

5 Abstract

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