

Novel carboxylic acid derivatives, their preparation and use

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

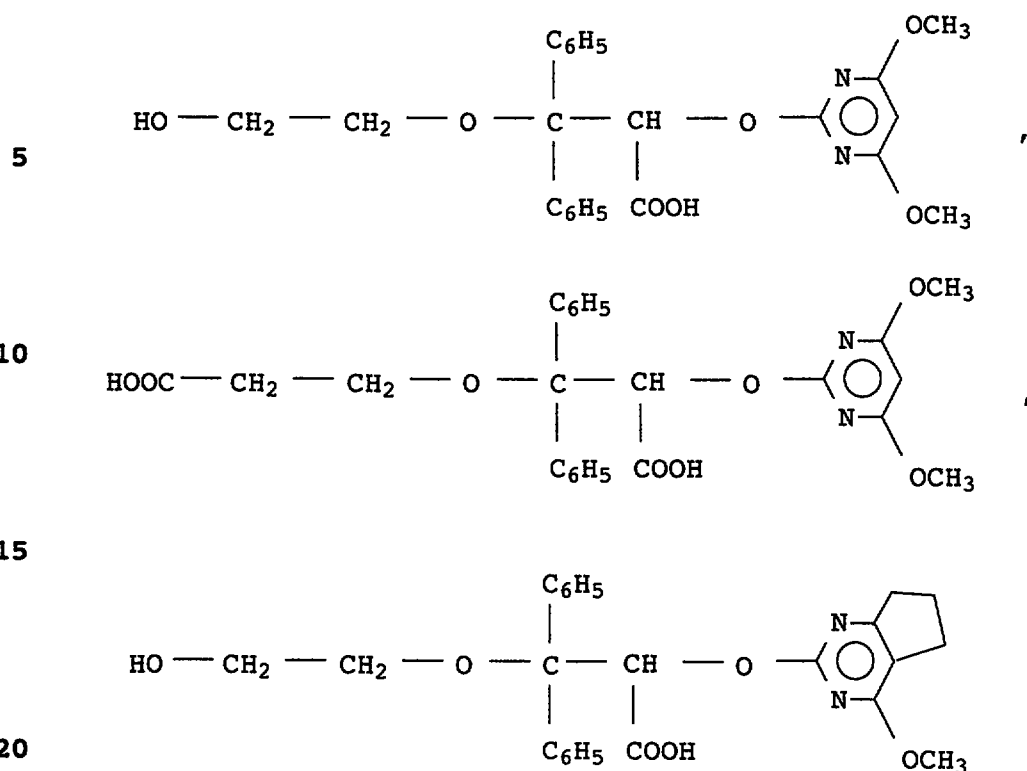
Endothelin is a peptide which is composed of 21 amino acids and is synthesized and released by the vascular endothelium. Endothelin exists in three isoforms, ET-1, ET-2 and ET-3. In the following text, "endothelin" or "ET" signifies one or all isoforms of endothelin. Endothelin is a potent vasoconstrictor and has a potent effect on vessel tone. It is known that this 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 vasoconstriction in the peripheral, renal and cerebral blood vessels, which may lead to illnesses. It has been reported in the literature that endothelin is involved in a number of illnesses; these include hypertension, myocardial infarct, heart failure, kidney failure, pulmonary hypertension, Raynaud's syndrome, cerebral vasospasms, atherosclerosis, stroke, benign prostate hypertrophy and asthma (Japan J. Hypertension 12, 79 (1989), J. Vascular Med. Biology 2, 207 (1990), J. Am. Med. Association 264, 2868 (1990), Nature 344, 11 (1990), N. Engl. J. Med. 322, 205 (1989), N. Engl. J. Med. 328, 1732 (1993), Nephron 66, 373 (1994), Strake 25, 904 (1994), Nature 365, 759 (1993), J. Mol. Cell. Cardiol. 27, A234 (1995), Cancer Research 56, 663 (1996)).

Accordingly, substances which specifically inhibit the binding of endothelin to the receptor ought also to antagonize the various abovementioned physiological effects of endothelin and therefore be valuable drugs.

The German Patent Application with the file number P 44 36 851.8 describes the following compounds as endothelin receptor antagonists:

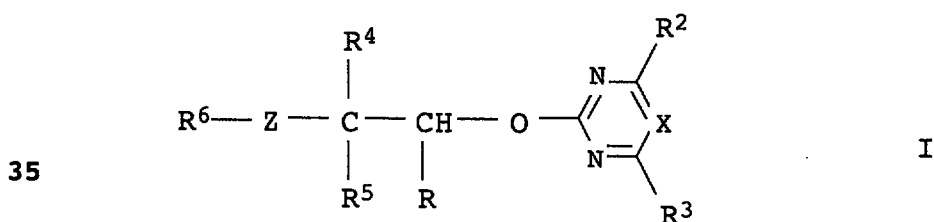
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We have now found that certain carboxylic acid derivatives are
 25 good inhibitors of endothelin receptors and that these compounds
 simultaneously have a relatively low plasma binding.

The invention relates to carboxylic acid derivatives of the
 formula I

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where R is a formyl group, tetrazole [sic], nitrile [sic], a
 group COOH or a radical which can be hydrolyzed to COOH, and the
 40 other substituents have the following meanings:

R² halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-ha-
 loalkoxy or C₁-C₄-alkylthio;

45 X nitrogen or CR¹⁴, where R¹⁴ is hydrogen or C₁₋₅-alkyl, or CR¹⁴
 forms together with CR³ a 5- or 6-membered alkenylene or
 alkenylene ring which can be substituted by one or

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two C₁₋₄-alkyl groups and in which in each case one methylene group can be replaced by oxygen, sulfur, -NH or -NC₁₋₄-alkyl;

5 R³ halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, -NH-O-C₁₋₄-alkyl, C₁-C₄-alkylthio or CR³ is linked to CR¹⁴ as indicated above to form a 5- or 6-membered ring;

10 R⁴ and R⁵ (which may be identical or different): phenyl or naphthyl, each of which can be substituted by one or more of the following radicals: halogen, nitro, cyano,

hydroxyl, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, phenoxy, C₁-C₄-alkylthio, amino, C₁-C₄-alkylamino or C₁-C₄-dialkylamino;

20 phenyl or naphthyl which are connected together in ortho positions by a direct linkage, a methylene, ethylene or ethenylene group, an oxygen or sulfur atom or an SO₂, NH or N-alkyl group, or C₃-C₇-cycloalkyl;

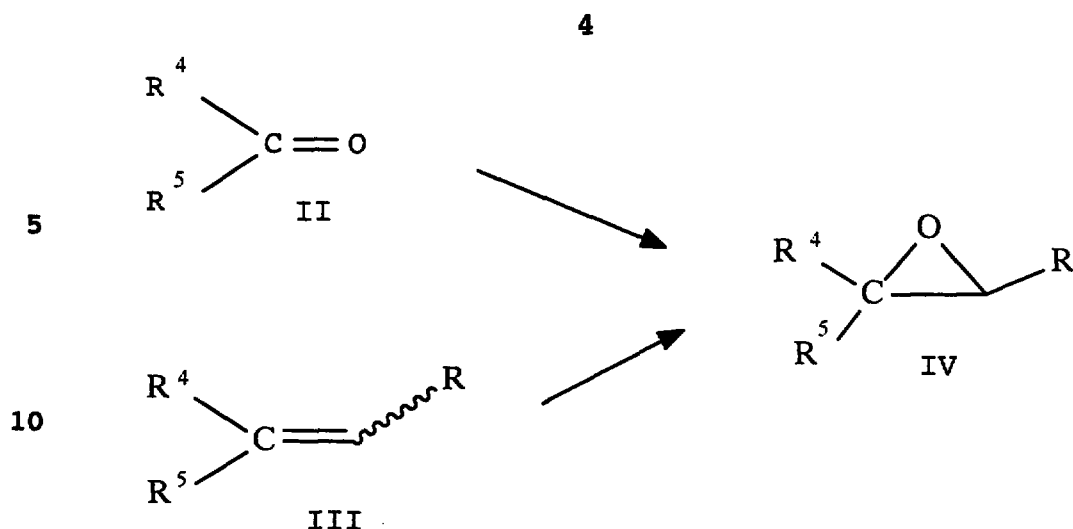
25 R⁶ C₁-C₁₀-alkyl, C₃-C₁₀-alkenyl or C₃-C₁₀-alkynyl, the radicals each being substituted one or more times by hydroxyl, mercapto, carboxyl, $\begin{matrix} R_z \\ R_y \end{matrix} \text{N} - \text{CO} -$, where R_y and R_z are, independently of one another, hydrogen or C₁-C₅-alkyl; sulfonyl, cyano, guanidino;

Z sulfur or oxygen.

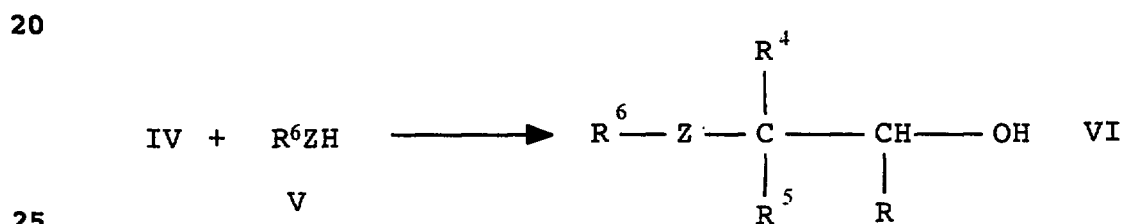
30 The compounds, and the intermediates for preparing them, eg. IV and VI, may have one or more asymmetrically substituted carbon atoms. Such compounds may exist as pure enantiomers and pure diastereomers or as a mixture thereof. The use of an enantiomerically pure compound as active substance is preferred.

The invention furthermore relates to the use of the abovementioned carboxylic acid derivatives for producing drugs, in particular for producing endothelin-receptor inhibitors.

40 The compounds according to the invention are prepared starting from the epoxides IV, which are obtained in a conventional way, eg. as described in J. March, Advanced Organic Chemistry, 2nd Ed., 1983, pages 862 and 750 from the ketones II or the olefins
45 III:



Carboxylic acid derivatives of the general formula VI can be prepared by reacting the epoxides of the general formula IV (eg. with $R = ROOR^{10}$ [sic]) with alcohols or thiols of the general formula V where R^6 and Z have the meanings stated in claim 1.



For this purpose, compounds of the general formula IV are heated with a compound of the formula V in the molar ratio of about 1:1 to 1:7, preferably 1 to 3 mol equivalents, at from 50 to 200°C, preferably 80 to 150°C.

Other functional groups in R^6 are initially protected in a conventional way for the reaction with compounds of the formula IV; for example, alcohols can be protected as acetates, diols as acetals and carboxyl groups as esters. The protective groups can be eliminated after the reaction of compounds of the formula VI with VII.

The reaction may also take place in the presence of a diluent. It is possible to use for this purpose all solvents which are inert toward the reagents used.

Examples of such solvents or diluents are water, aliphatic, alicyclic and aromatic hydrocarbons, which may in each case be chlorinated, such as hexane, cyclohexane, petroleum ether, naphtha, benzene, toluene, xylene, methylene chloride, chloroform, carbon tetrachloride, ethyl chloride and trichloroethylene, ethers such

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as diisopropyl ether, dibutyl ether, methyl tert-butyl ether, propylene oxide, dioxane and tetrahydrofuran, ketones such as acetone, methyl ethyl ketone, methyl isopropyl ketone and methyl isobutyl ketone, nitriles such as acetonitrile and propionitrile, 5 alcohols such as methanol, ethanol, isopropanol, butanol and ethylene glycol, esters such as ethyl acetate and amyl acetate, amides such as dimethylformamide and dimethylacetamide, sulfoxides and sulfones, such as dimethyl sulfoxide and sulfolane, bases such as pyridine, N-methylpyrrolidone, cyclic ureas such as 10 1,3-dimethyl-2-imidazolidinone and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone.

The reaction is preferably carried out at a temperature in the range from 0°C to the boiling point of the solvent or mixture of 15 solvents.

The presence of a catalyst may be advantageous. Suitable catalysts in this case are strong organic and inorganic acids, and Lewis acids. Examples thereof are, inter alia, sulfuric acid, 20 hydrochloric acid, trifluoroacetic acid, p-toluenesulfonic acid, boron trifluoride etherate and titanium(IV) alcoholates.

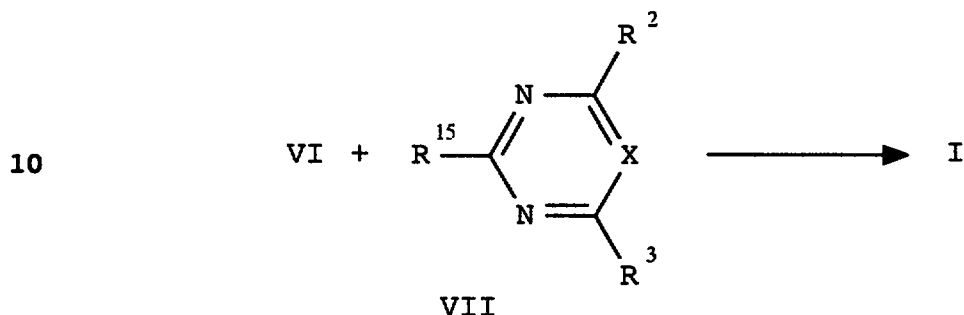
Compounds of the general formula VI can be obtained in enantiomerically pure form by starting from enantiomerically pure compounds of the formula IV and reacting them with compounds of the 25 formula V in the manner described.

It is furthermore possible to obtain enantiomerically pure compounds of the formula VI by carrying out a classical racemate 30 resolution with racemic or diastereomeric compounds of the formula VI using suitable enantiomerically pure bases such as brucine, strychnine, quinine, quinidine, chinchonidine [sic], chinchonine [sic], yohimbine, morphine, dehydroabietylamine, ephedrine (-), (+), deoxyephedrine (+), (-), threo-2-amino-1-(p- 35 nitrophenyl)-1,3-propanediol (+), (-), threo-2-(N,N-dimethylamino)-1-(p-nitrophenyl)-1,3-propanediol (+), (-), threo-2-amino-1-phenyl-1,3-propanediol (+), (-), α-methylbenzylamine (+), (-), α-(1-naphthyl)ethylamine (+), (-), α-(2-naphthyl)ethylamine (+), (-), aminomethylpinone, 40 N,N-dimethyl-1-phenylethylamine, N-methyl-1-phenylethylamine, 4-nitrophenylethylamine, pseudoephedrine, norephedrine, norpseudoephedrine, amino acid derivatives, peptide derivatives.

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The compounds of the general formula I according to the invention can be prepared, for example, by reacting the carboxylic acid derivatives of the general formula VI in which the substituents have the stated meaning with compounds of the general formula VII

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where R^{15} is halogen or $\text{R}^{16}-\text{SO}_2-$, where R^{16} can be C_1 - C_4 -alkyl, C_1 - C_4 -haloalkyl or phenyl. The reaction preferably takes place in one of the abovementioned inert diluents with the addition of a suitable base, ie. a base which deprotonates the intermediate VI, at a temperature in the range from room temperature to the boiling point of the solvent.

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Compounds of the formula VII are known, and some of them can be bought, or they can be prepared in a conventional manner.

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It is possible to use as base 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, eg. sodium or potassium carbonate, an alkali metal or alkaline earth metal hydroxide such as sodium or potassium hydroxide, an organo-metallic compound such as butyllithium or an alkali metal amide such as lithium diisopropylamide or lithium amide.

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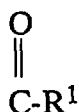
Compounds of the formula I can also be prepared by starting from the corresponding carboxylic acids, ie. compounds of the formula I where R^1 is hydroxyl, and initially converting these in a conventional way into an activated form, such as a halide, an anhydride or imidazolid, and then reacting the latter with an appropriate hydroxyl compound HOR^{10} . This reaction can be carried out in conventional solvents and often requires the addition of a base, in which case those mentioned above are 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 dehydrating agent such as a carbodiimide.

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Compounds of the formula I can also be prepared by starting from the salts of the appropriate carboxylic acids, ie. from compounds of the formula I where R is a group COR¹ and R¹ is OM, 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 R¹-A where A is a conventional nucleofugic leaving group, for example halogen such as chlorine, bromine, iodine or aryl- or alkylsulfonyl which is unsubstituted or substituted by halogen, alkyl or haloalkyl, such as toluenesulfonyl and methylsulfonyl, or another equivalent leaving group. Compounds of the formula R¹-A with a reactive substituent A are known or can easily be obtained with general expert knowledge. This reaction can be carried out in conventional solvents and is advantageously carried out with the addition of a base, in which case those mentioned above are suitable.

The radical R in formula I can be varied widely. R is, for example, a group

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where R¹ has the following meanings:

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a) hydrogen;

b) a succinylimidoxy [sic] group;

30 c) a 5-membered heteroaromatic system linked via a nitrogen atom, such as pyrrolyl, pyrazolyl, imidazolyl and triazolyl, which may carry one or two halogen atoms, in particular fluorine and chlorine, and/or one or two of the following radicals:

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C₁-C₄-alkyl such as methyl, ethyl, 1-propyl, 2-propyl, 2-methyl-2-propyl, 2-methyl-1-propyl, 1-butyl, 2-butyl;

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C₁-C₄-haloalkyl, in particular C₁-C₂-haloalkyl such as 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 and pentafluoroethyl;

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5 C₁-C₄-haloalkoxy, in particular C₁-C₂-haloalkoxy such as difluoromethoxy, trifluoromethoxy, chlorodifluoromethoxy, 1-fluoroethoxy, 2-fluoroethoxy, 2,2-difluoroethoxy, 1,1,2,2-tetrafluoroethoxy, 2,2,2-trifluoroethoxy, 2-chloro-1,1,2-trifluoroethoxy and pentafluoroethoxy, in particular trifluoromethoxy;

10 C₁-C₄-alkoxy such as methoxy, ethoxy, propoxy, 1-methylethoxy, butoxy, 1-methylpropoxy, 2-methylpropoxy, 1,1-dimethylethoxy, in particular methoxy, ethoxy and 1-methylethoxy;

15 C₁-C₄-alkylthio such as methylthio, ethylthio, propylthio, 1-methylethylthio, butylthio, 1-methylpropylthio, 2-methylpropylthio, 1,1-dimethylethylthio, in particular methylthio and ethylthio;

d) R¹ is furthermore a radical



25 where m is 0 or 1 and R⁷ and R⁸, which can be identical or different, have the following meanings:

hydrogen,

30 C₁-C₈-alkyl, in particular C₁-C₄-alkyl as mentioned above;

35 C₃-C₆-alkenyl such as 2-propenyl, 2-butenyl, 3-butenyl, 1-methyl-2-propenyl, 2-methyl-2-propenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-methyl-2-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 1-methyl-3-butenyl, 2-methyl-3-butenyl, 3-methyl-3-butenyl, 1,1-dimethyl-2-propenyl, 1,2-dimethyl-2-propenyl, 1-ethyl-2-propenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 1-methyl-2-pentenyl, 2-methyl-2-pentenyl, 40 3-methyl-2-pentenyl, 4-methyl-2-pentenyl, 3-methyl-3-pentenyl, 4-methyl-3-pentenyl, 1-methyl-4-pentenyl, 2-methyl-4-pentenyl, 3-methyl-4-pentenyl, 4-methyl-4-pentenyl, 1,1-dimethyl-2-butenyl, 1,1-dimethyl-3-butenyl, 45 1,2-dimethyl-2-butenyl, 1,2-dimethyl-3-butenyl, 1,3-dimethyl-2-butenyl, 1,3-dimethyl-3-butenyl, 2,2-dimethyl-3-butenyl, 2,3-dimethyl-2-butenyl,

2,3-dimethyl-3-butenyl, 1-ethyl-2-butenyl, 1-ethyl-3-butenyl, 2-ethyl-2-butenyl, 2-ethyl-3-butenyl, 1,1,2-trimethyl-2-propenyl, 1-ethyl-1-methyl-2-propenyl and 1-ethyl-2-methyl-2-propenyl, in particular 2-propenyl, 2-butenyl, 3-methyl-2-butenyl and 3-methyl-2-pentenyl;

C₃-C₆-alkynyl such as 2-propynyl, 2-butyne, 3-butyne, 1-methyl-2-propynyl, 2-pentyne, 3-pentyne, 4-pentyne, 1-methyl-3-butyne, 2-methyl-3-butyne, 1-methyl-2-butyne, 1,1-dimethyl-2-propynyl, 1-ethyl-2-propynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-methyl-2-pentyne, 1-methyl-2-pentyne, 1-methyl-3-pentyne, 1-methyl-4-pentyne, 2-methyl-3-pentyne, 2-methyl-4-pentyne, 3-methyl-4-pentyne, 4-methyl-2-pentyne, 1,1-dimethyl-2-butyne, 1,1-dimethyl-3-butyne, 1,2-dimethyl-3-butyne, 2,2-dimethyl-3-butyne, 1-ethyl-2-butyne, 1-ethyl-3-butyne, 2-ethyl-3-butyne and 1-ethyl-1-methyl-2-propynyl, preferably 2-propynyl, 2-butyne, 1-methyl-2-propynyl and 1-methyl-2-butyne, in particular 2-propynyl;

C₃-C₈-cycloalkyl, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and [sic] cycloheptyl, cyclooctyl, it being possible for these alkyl, cycloalkyl, alkenyl and alkynyl groups each to carry one to five halogen atoms, in particular fluorine or chlorine, and/or one or two of the following groups:

C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₄-alkylthio, C₁-C₄-haloalkoxy as mentioned above, C₃-C₆-alkenyloxy, C₃-C₆-alkenylthio, C₃-C₆-alkynyloxy, C₃-C₆-alkynylthio, where the alkenyl and alkynyl constituents present in these radicals preferably correspond to the abovementioned meanings;

C₁-C₄-alkylcarbonyl such as, in particular, methylcarbonyl, ethylcarbonyl, propylcarbonyl, 1-methylethylcarbonyl, butylcarbonyl, 1-methylpropylcarbonyl, 2-methylpropylcarbonyl and 1,1-dimethylethylcarbonyl;

C₁-C₄-alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, propyloxycarbonyl, 1-methylethoxycarbonyl, butyloxycarbonyl, 1-methylpropyloxycarbonyl, 2-methylpropyloxycarbonyl and 1,1-dimethylethoxycarbonyl;

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C₃-C₆-alkenylcarbonyl, C₃-C₆-alkynylcarbonyl, C₃-C₆-alkenyloxy-carbonyl and C₃-C₆-alkynyloxy-carbonyl, where the alkenyl and alkynyl radicals preferably have the definitions detailed above;

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phenyl, unsubstituted or substituted one or more times, eg. one to three times by halogen, nitro, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy or C₁-C₄-alkylthio, such as 2-fluorophenyl, 3-chlorophenyl, 4-bromophenyl, 2-methylphenyl, 3-nitrophenyl, 4-cyanophenyl, 2-trifluoromethylphenyl, 3-methoxyphenyl, 4-trifluoroethoxyphenyl, 2-methylthiophenyl, 2,4-dichlorophenyl, 2-methoxy-3-methylphenyl, 2,4-dimethoxyphenyl, 2-nitro-5-cyanophenyl and 2,6-difluorophenyl;

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di-C₁-C₄-alkylamino such as, in particular, dimethylamino, dipropylamino, N-propyl-N-methylamino, N-propyl-N-ethylamino, diisopropylamino, N-isopropyl-N-methylamino, N-isopropyl-N-ethylamino, N-isopropyl-N-propylamino;

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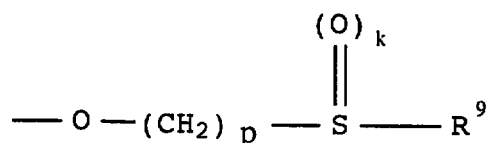
R⁷ and R⁸ furthermore phenyl which can be substituted by one or more, eg. one to three, of the following radicals: halogen, nitro, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy or C₁-C₄-alkylthio as mentioned above in particular;

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or R⁷ and R⁸ together form a C₄-C₇-alkylene chain which is closed to form a ring and is unsubstituted or substituted, eg. substituted by C₁-C₄-alkyl, and which may contain a hetero atom selected from the group of oxygen, sulfur or nitrogen, such as -(CH₂)₄-, -(CH₂)₅-, -(CH₂)₆-, -(CH₂)₇-, -(CH₂)₂-O-(CH₂)₂-, -CH₂-S-(CH₂)₃-, -(CH₂)₂-O-(CH₂)₃-, -NH-(CH₂)₃-, -CH₂-NH-(CH₂)₂-, -CH₂-CH=CH-CH₂-, -CH=CH-(CH₂)₃-;

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35 e) R¹ is furthermore a group



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in which k assumes the values 0, 1 and 2, p assumes the values 1, 2, 3 and 4, and R⁹ is

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C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl or unsubstituted or substituted phenyl, as mentioned above in particular;

f) R^1 is furthermore a radical OR^{10} where R^{10} is:

hydrogen, the cation of an alkali metal such as lithium, sodium, potassium or the cation of an alkaline earth metal such as calcium, magnesium and barium, or an environmentally compatible organic ammonium ion such as tertiary C_1 - C_4 -alkylammonium or the ammonium ion;

C_3 - C_8 -cycloalkyl as mentioned above, which may carry one to three C_1 - C_4 -alkyl groups;

C_1 - C_8 -alkyl such as, in particular, methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,2-dimethylpropyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethylbutyl, 2-ethylbutyl, 1-ethyl-2-methylpropyl, which may carry one to five halogen atoms, in particular fluorine and chlorine, and/or one of the following radicals:

C_1 - C_4 -alkoxy, C_1 - C_4 -alkylthio, cyano, C_1 - C_4 -alkylcarbonyl, C_3 - C_8 -cycloalkyl [sic], C_1 - C_4 -alkoxycarbonyl, phenyl, phenoxy or phenylcarbonyl, it being possible for the aromatic radicals in turn each to carry one to five halogen atoms and/or one to three of the following radicals: nitro, cyano, C_1 - C_4 -alkyl, C_1 - C_4 -haloalkyl, C_1 - C_4 -alkoxy, C_1 - C_4 -haloalkoxy and/or C_1 - C_4 -alkylthio as mentioned above in particular;

a C_1 - C_8 -alkyl group as mentioned above, which can carry one to five halogen atoms, in particular fluorine and/or chlorine, and carries one of the following radicals: a 5-membered heteroaromatic system containing one to three nitrogen atoms, or a 5-membered heteroaromatic system containing one nitrogen atom and one oxygen or sulfur atom, which system may carry one to four halogen atoms and/or one or two of the following radicals:

nitro, cyano, C_1 - C_4 -alkyl, C_1 - C_4 -haloalkyl, C_1 - C_4 -alkoxy, phenyl, C_1 - C_4 -haloalkoxy and/or C_1 - C_4 -alkylthio. Particular mention may be made of: 1-pyrazolyl, 3-methyl-1-pyrazolyl, 4-methyl-1-pyrazolyl, 3,5-dimethyl-1-pyrazolyl, 3-phenyl-1-pyrazolyl, 4-phenyl-1-pyrazolyl, 4-chloro-1-pyrazolyl, 4-bromo-1-pyrazolyl, 1-imidazolyl,

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1-benzimidazolyl, 1,2,4-triazol-1-yl, 3-methyl-1,2,4-triazol-1-yl, 5-methyl-1,2,4-triazol-1-yl, 1-benzotriazolyl, 3-isopropyl-5-isoxazolyl, 3-methyl-5-isoxazolyl, 2-oxazolyl, 2-thiazolyl, 2-imidazolyl, 3-ethyl-5-isoxazolyl,
 5 3-phenyl-5-isoxazolyl, 3-tert-butyl-5-isoxazolyl;

a C₂-C₆-alkyl group which carries in position 2 one of the following radicals: C₁-C₄-alkoxyimino, C₃-C₆-alkynyloxyimino, C₃-C₆-haloalkenyloxyimino or benzyloxyimino;
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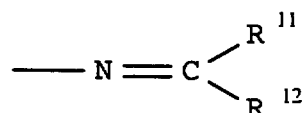
a C₃-C₆-alkenyl or C₃-C₆-alkynyl group, it being possible for these groups in turn to carry one to five halogen atoms;

R¹⁰ is furthermore 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, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy and/or C₁-C₄-alkylthio as mentioned above in particular;
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a 5-membered heteroaromatic system which is linked via a nitrogen atom and contains one to three nitrogen atoms and which can carry one or two halogen atoms and/or one or two of the following radicals: C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, phenyl, C₁-C₄-haloalkoxy and/or C₁-C₄-alkylthio.
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Particular mention may be made of: 1-pyrazolyl, 3-methyl-1-pyrazolyl, 4-methyl-1-pyrazolyl, 3,5-dimethyl-1-pyrazolyl, 3-phenyl-1-pyrazolyl, 4-phenyl-1-pyrazolyl, 4-chloro-1-pyrazolyl, 4-bromo-1-pyrazolyl, 1-imidazolyl, 1-benzimidazolyl,
 25 1,2,4-triazol-1-yl, 3-methyl-1,2,4-triazol-1-yl, 5-methyl-1,2,4-triazol-1-yl, 1-benzotriazolyl, 3,4-dichloro-1-imidazolyl;
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R¹⁰ is furthermore a group
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where R¹¹ and R¹², which can be identical or different, are:
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C₁-C₈-alkyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl, C₃-C₈-cycloalkyl, it being possible for these radicals to carry a C₁-C₄-alkoxy, C₁-C₄-alkylthio and/or an unsubstituted or substituted phenyl radical;
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phenyl which may be substituted by one or more, for example one to three, of the following radicals: halogen, nitro, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy or C₁-C₄-alkylthio,

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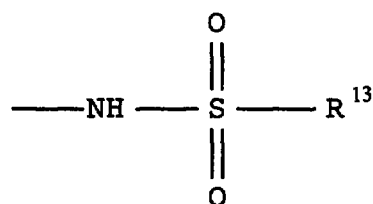
where these radicals correspond to those mentioned above in particular;

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or R¹¹ and R¹² together form a C₃-C₁₂-alkylene chain which may carry one to three C₁-C₄-alkyl groups and may contain a hetero atom from the group of oxygen, sulfur and nitrogen;

g) R¹ is furthermore a radical

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where R¹³ is:

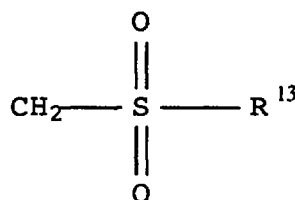
C₁-C₄-alkyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl, C₃-C₈-cycloalkyl, it being possible for these radicals to carry a C₁-C₄-alkoxy, C₁-C₄-alkylthio and/or phenyl radical;

25

phenyl, unsubstituted or substituted;

h) R¹ is a radical

30



35

where R¹³ has the abovementioned meaning.

R can furthermore be:

40

tetrazole [sic] or nitrile [sic].

With a view to the biological effect, preferred carboxylic acid derivatives of the general formula I, both as pure enantiomers and pure diastereomers or as a mixture thereof, are those in

45 which the substituents have the following meanings:

14

- R² the C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy and C₁-C₄-alkylthio groups and halogen atoms specified for R¹, in particular chlorine, methyl, methoxy, ethoxy, difluoromethoxy and trifluoromethoxy;
- 5 X nitrogen or CR¹⁴ where
- R¹⁴ hydrogen or alkyl, or CR¹⁴ forms together with CR³ a 4- or 5-membered alkylene or alkenylene ring in which, in each case, a methylene group can be replaced by oxygen or sulfur, such as -CH₂-CH₂-O-, -CH=CH-O-, -CH₂-CH₂-CH₂-O-, -CH=CH-CH₂O-, in particular hydrogen, -CH₂-CH₂-O-, -CH(CH₃)-CH(CH₃)-O-, -C(CH₃)=C(CH₃)-O-, -CH=C(CH₃)-O- or -C(CH₃)=C(CH₃)-S;
- 10 R³ the C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy and C₁-C₄-alkylthio groups and halogen atoms mentioned for R¹, in particular chlorine, methyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy or is linked to R¹⁴ as mentioned above to form a 5- or 6-membered ring;
- 20 R⁴ and R⁵ are phenyl or naphthyl, each of which can be substituted by one or more, eg. one to three, of the following radicals: halogen, nitro, cyano, hydroxyl, mercapto, amino, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₁-C₄-alkylthio, C₁-C₄-alkylamino, di-C₁-C₄-alkylamino, C₁-C₄-alkylcarbonyl, C₁-C₄-alkoxycarbonyl;
- 25 phenyl or naphthyl which are connected together in ortho positions by a direct linkage, a methylene, ethylene or ethenylene group, an oxygen or sulfur atom or an SO₂, NH or N-alkyl group, or C₃-C₇-cycloalkyl;
- 30 R⁶ C₁-C₄-alkyl, C₃-C₅-alkenyl, where the radicals are each substituted once or twice by hydroxyl, mercapto, carboxyl or cyano;
- 35 Z sulfur or oxygen.

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

- R² C₁-C₄-alkyl, C₁-C₄-alkoxy,
- 45 X nitrogen or CR¹⁴ where

15

- R¹⁴ is hydrogen or alkyl, or CR¹⁴ forms together with CR³ a 4- or 5-membered alkylene or alkenylene ring, such as -CH₂-CH₂-CH₂- or -CH=CH-CH₂-, in which, in each case, a methylene group can be replaced by oxygen or sulfur, such as -CH₂-CH₂-O-,
- 5 -CH=CH-O-, -CH₂-CH₂-CH₂-O-, -CH=CH-CH₂O-, in particular hydrogen,
- CH₂-CH₂-O-, -CH(CH₃)-CH(CH₃)-O-, -C(CH₃)=C(CH₃)-O-,
- CH=C(CH₃)-O- or -C(CH₃)=C(CH₃)-S;
- 10 R³ the C₁-C₄-alkyl-, C₁-C₄-alkoxy, C₁-C₄-alkylthio groups mentioned for R¹, or is linked to R¹⁴ as mentioned above to form a 5- or 6-membered ring;
- 15 R⁴ and R⁵ phenyl (identical or different), which can be substituted by one or more, eg. one to three, of the following radicals: halogen, nitro, hydroxyl, C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₄-alkylthio or
- 20 R⁴ and R⁵ are phenyl groups which are connected together in ortho positions by a direct linkage, a methylene, ethylene or ethenylene group, an oxygen or sulfur atom or an SO₂, NH or N-alkyl group; or
- 25 R⁴ and R⁵ are C₃-C₇-cycloalkyl;
- R⁶ C₁-C₃-alkyl, C₃-C₄-alkenyl, where the radicals are each substituted once or twice by hydroxyl or are substituted once by carboxyl;
- 30 Z sulfur or oxygen.

The compounds of the present invention provide a novel therapeutic potential for the treatment of hypertension, pulmonary hypertension, myocardial infarct, angina pectoris, acute kidney failure, renal insufficiency, cerebral vasospasms, cerebral ischemia, subarachnoid hemorrhages, migraine, asthma, atherosclerosis, endotoxic shock, endotoxin-induced organ failure, intravascular coagulation, restenosis after angioplasty, benign prostate hyperplasia, or hypertension or kidney failure caused by ischemia or intoxication, and cancers, especially prostate and skin cancer.

The invention further relates to the combination of compounds of the formula I with inhibitors of the renin-angiotensin system (RAS). RAS inhibitors are disclosed in, for example, EP 634 175.

16

The combinations according to the invention are suitable for treating disorders for which compounds of the formula I also show efficacy on their own, especially for treating hypertomy [sic] and chronic heart failure.

5

The good effect of the compounds can be shown in the following tests:

Receptor binding studies

10

Cloned human ET_A receptor-expressing CHO cells and guinea pig cerebellar membranes with > 60% ET_B compared with ET_A receptors were used for the binding studies.

15 Membrane preparation

The ET_A receptor-expressing CHO cells were grown in F_{12} medium containing 10% fetal calf serum, 1% glutamine, 100 U/ml penicillin and 0.2% streptomycin (Gibco BRL, Gaithersburg, MD, USA).

- 20 After 48 h, the cells were washed with PBS and incubated with 0.05% trypsin-containing PBS for 5 min. Neutralization was then carried out with F_{12} medium, and the cells were collected by centrifugation at 300 x g. To lyse the cells, the pellet was briefly washed with lysis buffer (5 mM tris-HCl, pH 7.4 with 10%
25 glycerol) and then incubated at a concentration of 10^7 cells/ml of lysis buffer at 4°C for 30 min. The membranes were centrifuged at 20,000 x g for 10 min, and the pellet was stored in liquid nitrogen.

- 30 Guinea pig cerebella were homogenized in a Potter-Elvehjem homogenizer and obtained by differential centrifugation at 1000 x g for 10 min and repeated centrifugation of the supernatant at 20,000 x g for 10 min.

35 Binding assays

- 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 $MnCl_2$, 40 µg/ml bacitracin and 0.2% BSA) at a concentration
40 of 50 µg of protein per assay mixture and incubated with 25 pM [^{125}I [sic]]- ET_1 (ET_A receptor assay) or 25 pM [^{125}I [sic]]-RZ₃ (ET_B receptor assay) in the presence and absence of test substance at 25°C. The nonspecific binding was determined using $10^{-7}M$ ET_1 . After 30 min, filtration through GF/B glass fiber filters (What-
45 man, England) in a Skatron cell collector (Skatron, Lier, Norway) was carried out to separate free and bound radioligand, and the filters were washed with ice-cold tris-HCl buffer, pH 7.4 with

0.2% BSA. The radioactivity collected on the filters was quantified using a Packard 2200 CA liquid scintillation counter.

Functional in vitro assay system to look for endothelin receptor 5 (subtype A) antagonists

This assay system is a functional, cell-based assay for endothelin receptors. When certain cells are stimulated with endothelin 1 (ET1) they show an increase in the intracellular calcium
10 concentration. This increase can be measured in intact cells loaded with calcium-sensitive dyes.

1-Fibroblasts which have been isolated from rats and in which an endogenous endothelin receptor of the A subtype had been detected
15 were loaded with the fluorescent dye Fura 2-am as follows: after trypsinization, the cells were resuspended in buffer A (120 mM NaCl, 5 mM KCl, 1.5 mM MgCl₂, 1 mM CaCl₂, 25 mM HEPES, 10 mM glucose, pH 7.4) to a density of 2×10^6 /ml and incubated with Fura 2-am (2 μ M), Pluronic [sic] F-127 (0.04%) and DMSO (0.2%) at
20 37°C in the dark for 30 min. The cells were then washed twice with buffer A and resuspended at 2×10^6 /ml.

The fluorescence signal from 2×10^5 cells per ml with Ex/Em 380/510 was recorded continuously at 30°C. The test substances
25 and, after an incubation time of 3 min, ET1 were [lacuna] to the cells, the maximum change in the fluorescence was determined. The response of the cells to ET1 without previous addition of a test substance was used as control and was set equal to 100%.

30 Testing of ET antagonists in vivo

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

35

In control animals, intravenous administration of 1 μ g/kg ET1 leads to a distinct rise in blood pressure which persists for a lengthy period.

40 The test animals received an i.v. injection of the test compounds (1 ml/kg) 5 min before the administration of ET1. To determine the ET-antagonistic properties, the rise in blood pressure in the test animals was compared with that in the control animals.

45 Endothelin-1-induced sudden death in mice

The principle of the test is the inhibition of the sudden heart death caused in mice by endothelin, which is probably induced by constriction of the coronary vessels, by pretreatment with endothelin receptor antagonists. Intravenous injection of 10 nmol/kg of endothelin in a volume of 5 ml/kg of body weight results in death of the animals within a few minutes.

The lethal endothelin-1 dose is checked in each case on a small group of animals. If the test substance is administered intravenously, the endothelin-1 injection which was lethal in the reference group usually takes place 5 min thereafter. With other modes of administration, the times before administration are extended, where appropriate up to several hours.

The survival rate is recorded, and effective doses which protect 50% of the animals (ED 50) from endothelin-induced heart death for 24 h or longer are determined.

Functional test on vessels for endothelin receptor antagonists

20

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.

25

Potential endothelin antagonists are administered to other preparations of the same vessel 15 min before starting the endothelin dose-effect plot. The effects of the endothelin are calculated as percent of the K⁺-induced contraction. Effective endothelin antagonists result in a shift to the right in the endothelin dose-effect plot.

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

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, as a rule, 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.

The novel compounds can be used in conventional solid or liquid pharmaceutical administration forms, eg. as uncoated or (film) coated tablets, capsules, powders, granules, suppositories, solu-

tions, ointments, creams or sprays. These are produced in a conventional way. The active substances can for this purpose be processed with conventional pharmaceutical aids such as tablet binders, bulking agents, preservatives, tablet disintegrants, flow
5 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 normally contain from 0.1 to 90% by weight of
10 the active substance.

Synthesis examples

Example 1

15

Methyl 3-(2-acetoxyethoxy)-2-hydroxy-3,3-diphenylpropionate

7.95 g (31.3 mmol) of methyl 3,3-diphenyl-2,3-epoxypropionate were dissolved in 20 ml of diethyl ether under N₂ and cooled to
20 0°C, and 5.87 ml (31.3 mmol) of 2-hydroxyethyl acetate (50% strength) and 3 drops of BF₃·Et₂O were added. After removal of the ice bath, the mixture was stirred at RT for 2 h.

The reaction solution was washed successively with NaCl solution
25 and NaHCO₃ solution, and the organic phase was dried over MgSO₄ and concentrated. 12.3 g of a pale yellow oil were obtained and were reacted without further purification and characterization.

Example 2

30

Methyl 3-(2-acetoxyethoxy)-2-(4-methoxy-6-methyl-2-pyrimidin- yloxy)-3,3-diphenylpropionate

4 g (11.1 mmol) of methyl 3-(2-acetoxyethoxy)-2-hydroxy-3,3-di-
35 phenylpropionate were dissolved in 20 ml of DMF under N₂, 770 mg (5.6 mmol) of K₂CO₃ and 2.24 g (11.1 mmol) of 2-methanesulfonyl-4-methoxy-6-methylpyrimidine were added, and the mixture was stirred at 80°C for 2 h. It was subsequently diluted with 20 ml of H₂O and extracted twice with 30 ml of diethyl ether, the organic
40 phase was dried over MgSO₄ and concentrated, and the residue was purified by chromatography on silica gel with ethyl acetate/cyclohexane mixtures. 4.8 g (90%) of a colorless oil were obtained.

45

20

¹H-NMR (CDCl₃) δ: 2.10 (s, 3H); 2.35 (s, 3H); 3.50 (s, 3H); 3.85 (s, 6H); 4.00 (m, 2H); 4.30 (m, 2H); 6.00 (s, 1H), 6.25 (s, 1H) 7.20 - 7.50 (m, 10H)

5 Example 3

3-(2-Hydroxyethoxy)-2-(4-methoxy-6-methyl-2-pyrimidinyl-
loxy)-3,3-diphenylpropionic acid

- 10 4.8 g (10 mmol) of methyl 3-(2-acetoxyethoxy)-2-(4-methoxy-6-methyl-2-pyrimidinyl-
thoxy)-3,3-diphenylpropionate [sic] were dissolved in 80 ml of dioxane and 40ml of 1N KOH solution and stirred at 90°C for 8 h. The solution was diluted with 50 ml of H₂O and extracted with diethyl ether. The aqueous phase was
15 neutralized with 10 ml of 1N HCl solution and extracted twice with diethyl ether, and the organic phase was dried and concentrated. The residue was purified by chromatography on silica gel with cyclohexane/ethyl acetate mixtures, and crystallization from diethyl ether/hexane resulted in 1.2 g (28%) of colorless crystals.
20

¹H-NMR (CDCl₃) δ: 2.25 (s, 3H); 3.55 (m, 2H); 3.65-3.85 (m, 3H); 3.90 (s, 6H), 6.10 (s, 1H); 6.25 (s, 1H); 6.40 (broad, 1H), 7.20 - 7.60 (m, 10H)

25

Example 4

Methyl 3-(2-hydroxy-2-methoxycarbonyl-1,1-diphenylethoxy)-2,2-dimethylpropionate

30

- 12.7 g (50 mmol) of methyl 3,3-diphenyl-2,3-epoxypropionate were dissolved in 50 ml of diethyl ether, 6.6 g (50 mmol) of methyl 3-hydroxy-2,2-dimethylpropionate and 1 ml of BF₃·Et₂O were added, and the mixture was stirred at room temperature for 18 h. The
35 solvent was evaporated off, and the oily residue was reacted without further purification and characterization.

Example 5

- 40 Methyl 3-[2-methoxycarbonyl-2-(4-methoxy-6-methyl-2-pyrimidinyl-
loxy)-1,1-diphenylethoxy]-2,2-dimethylpropionate

- 10 g (25.9 mmol) of methyl 3-(2-hydroxy-2-methoxycarbonyl-1,1-diphenylethoxy)-2,2-dimethylpropionate were dissolved in 40 ml of
45 DMF under N₂, 1.78 g (13 mmol) of K₂CO₃ and 5.2 g (25.9 mmol) of 2-methanesulfonyl-4-methoxy-6-methylpyrimidine were added, and the mixture was stirred at 80°C for 2 h. It was subsequently di-

21

luted with 40 ml of H₂O and extracted twice with 30 ml of diethyl ether, the organic phase was dried over MgSO₄ and concentrated, and the residue was purified by chromatography on silica gel with ethyl acetate/cyclohexane mixtures. Crystallization from diethyl ether/hexane resulted in 11.8 g (90%) of the product as colorless crystals.

Melting point: 143°C

10 Example 6

3-[2-Carboxy-2-(4-methoxy-6-methyl-2-pyrimidinyl-2-oxo)-1,1-diphenylethoxy]-2,2-dimethylpropionic acid

15 10.1 g (20 mmol) of methyl 3-[2-methoxycarbonyl-2-(4-methoxy-6-methyl-2-pyrimidinyl-2-oxo)-1,1-diphenylethoxy]-2,2-dimethylpropionate were dissolved in 50 ml of dioxane and 50 ml of 2N NaOH solution and stirred at 80°C for 4 h. The solution was diluted with 300 ml of H₂O and extracted with 100 ml of ethyl acetate. The aqueous phase was neutralized with 1N HCl and extracted with ethyl acetate, and the organic phase was dried over MgSO₄, filtered and concentrated. The oily residue was crystallized from diethyl ether/hexane to result in 4.1 g (42%) of colorless crystals.

25

¹H-NMR (CDCl₃) δ: 1.10 (s, 3H); 1.20 (s, 3H); 2.50 (s, 3H); 3.65 (d, 1H); 3.80 (s, 3H); 3.90 (d, 1H); 5.95 (s, 1H); 6.25 (s, 1H); 7.20 - 7.50 (m, 10H)

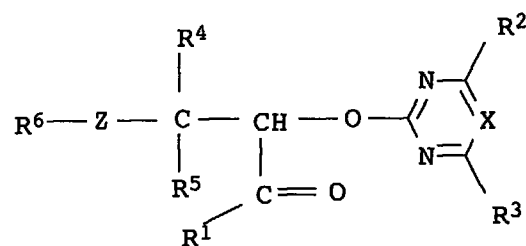
30 The compounds listed in Table 1 can be prepared in similar ways.

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40

45

Table 1



No.	R ¹	R ⁴ , R ⁵	R ⁶	R ²	R ³	X	Z
1.	OH	Phenyl	H ₂ NC(O)-CH ₂ -	OMe	CH ₂ -CH ₂ -CH ₂ -C		O
2.	OH	Phenyl	HO-CH ₂ -CH ₂ -	OMe	Me	CH	O
3.	OH	Phenyl	HO-CH ₂ -CH ₂ -	Me	Me	CH	O
4.	OH	Phenyl	HO-CH ₂ -CH ₂ -	Me	Et	CH	O
5.	OH	Phenyl	HO-CH ₂ -CH ₂ -	OMe	CH ₂ -CH ₂ -CH ₂ -C		O
6.	OH	Phenyl	HO-CH ₂ -CH ₂ -	OMe	O-CH ₂ -CH ₂ -C		O
7.	OH	Phenyl	HO-CH ₂ -CH ₂ -	Me	CH ₂ -CH ₂ -CH ₂ -C		O
8.	OH	Phenyl	HO-CH ₂ -CH ₂ -	OMe	OMe	N	O
9.	OH	Phenyl	HO-CH ₂ -CH ₂ -	NMe ₂	NMe ₂	N	O
10.	OH	Phenyl	HO-CH ₂ -CH ₂ -	Et	Et	CH	O
11.	OH	Phenyl	HO-CH ₂ -CH(OH)-CH ₂ -	OMe	OMe	CH	O

No.	R ¹	R ⁴ , R ⁵	R ⁶	R ²	R ³	X	Z
12.	OH	Phenyl	HO-CH ₂ -CH(OH)-CH ₂ -	OMe	Me	CH	O
13.	OH	Phenyl	HO-CH ₂ -CH(OH)-CH ₂ -	Me	Me	CH	O
14.	OH	Phenyl	HO-CH ₂ -CH(OH)-CH ₂ -	Me	Et	CH	O
15.	OH	Phenyl	HO-CH ₂ -CH(OH)-CH ₂ -	OMe	CH ₂ -CH ₂ -CH ₂ -C		O
16.	OH	Phenyl	HO-CH ₂ -CH(OH)-CH ₂ -	OMe	O-CH ₂ -CH ₂ -C		O
17.	OH	Phenyl	HO-CH ₂ -CH(OH)-CH ₂ -	Me	CH ₂ -CH ₂ -CH ₂ -C		O
18.	OH	Phenyl	HO-CH ₂ -CH(OH)-CH ₂ -	OMe	OMe	N	O
19.	OH	Phenyl	HO-CH ₂ -CH(OH)-CH ₂ -	NMe ₂	NMe ₂	N	O
20.	OH	Phenyl	HO-CH ₂ -CH(OH)-CH ₂ -	Et	Et	CH	O
21.	OH	o-F-phenyl	HO-CH ₂ -CH ₂ -	OMe	Me	CH	O
22.	OH	o-F-phenyl	HO-CH ₂ -CH ₂ -	Me	Me	CH	O
23.	OH	m-F-phenyl	HO-CH ₂ -CH ₂ -	Me	Et	CH	O
24.	OH	m-OMe-phenyl	HO-CH ₂ -CH ₂ -	OMe	CH ₂ -CH ₂ -CH ₂ -C		O
25.	OH	m-Me-phenyl	HO-CH ₂ -CH ₂ -	OMe	O-CH ₂ -CH ₂ -C		O
26.	OH	p-Cl-phenyl	HO-CH ₂ -CH ₂ -	Me	CH ₂ -CH ₂ -CH ₂ -C		O
27.	OH	p-F-phenyl	HO-CH ₂ -CH ₂ -	OMe	OMe	N	O
28.	OH	m-OMe-phenyl	HO-CH ₂ -CH ₂ -	NMe ₂	NMe ₂	N	O
29.	OH	m-OMe-phenyl	HO-CH ₂ -CH ₂ -	Et	Et	CH	O
30.	OH	o-F-phenyl	HO-CH ₂ -CH(OH)-CH ₂ -	OMe	OMe	CH	O
31.	OH	m-F-phenyl	HO-CH ₂ -CH(OH)-CH ₂ -	OMe	Me	CH	O
32.	OH	m-Me-phenyl	HO-CH ₂ -CH(OH)-CH ₂ -	Me	Me	CH	O

No.	R ¹	R ⁴ , R ⁵	R ⁶	R ²	R ³	X	Z
33.	OH	m-OMe-phenyl	HO-CH ₂ -CH(OH)-CH ₂ -	Me	Et	CH	O
34.	OH	p-Me-phenyl	HO-CH ₂ -CH(OH)-CH ₂ -	OMe	CH ₂ -CH ₂ -CH ₂ -C		O
35.	OH	p-Cl-phenyl	HO-CH ₂ -CH(OH)-CH ₂ -	OMe	O-CH ₂ -CH ₂ -C		O
36.	OH	p-F-phenyl	HO-CH ₂ -CH(OH)-CH ₂ -	Me	CH ₂ -CH ₂ -CH ₂ -C		O
37.	OH	m-Me-phenyl	HO-CH ₂ -CH(OH)-CH ₂ -	OMe	OMe	N	O
38.	OH	p-Cl-phenyl	HO-CH ₂ -CH(OH)-CH ₂ -	NMe ₂	NMe ₂	N	O
39.	OH	p-Cl-phenyl	HO-CH ₂ -CH(OH)-CH ₂ -	Et	Et	CH	O
40.	OH	Phenyl	(HO-CH ₂) ₂ CH-CH ₂ -	OMe	OMe	CH	O
41.	OH	Phenyl	(HO-CH ₂) ₂ CH-CH ₂ -	OMe	Me	CH	O
42.	OH	Phenyl	(HO-CH ₂) ₂ CH-CH ₂ -	Me	Me	CH	O
43.	OH	Phenyl	(HO-CH ₂) ₂ CH-CH ₂ -	Me	Et	CH	O
44.	OH	Phenyl	(HO-CH ₂) ₂ CH-CH ₂ -	OMe	CH ₂ -CH ₂ -CH ₂ -C		O
45.	OH	Phenyl	(HO-CH ₂) ₂ CH-CH ₂ -	OMe	O-CH ₂ -CH ₂ -C		O
46.	OH	Phenyl	(HO-CH ₂) ₂ CH-CH ₂ -	Me	CH ₂ -CH ₂ -CH ₂ -C		O
47.	OH	Phenyl	(HO-CH ₂) ₂ CH-CH ₂ -	OMe	OMe	N	O
48.	OH	Phenyl	(HO-CH ₂) ₂ CH-CH ₂ -	NMe ₂	NMe ₂	N	O
49.	OH	Phenyl	(HO-CH ₂) ₂ CH-CH ₂ -	Et	Et	CH	O
50.	OH	Phenyl	CH ₃ -CH ₂ -(HO-CH ₂) ₂ C-CH ₂ -	OMe	OMe	CH	O
51.	OH	Phenyl	CH ₃ -CH ₂ -(HO-CH ₂) ₂ C-CH ₂ -	OMe	Me	CH	O
52.	OH	Phenyl	CH ₃ -CH ₂ -(HO-CH ₂) ₂ C-CH ₂ -	Me	Me	CH	O
53.	OH	Phenyl	CH ₃ -CH ₂ -(HO-CH ₂) ₂ C-CH ₂ -	Me	Et	CH	O

No.	R ¹	R ⁴ , R ⁵	R ⁶	R ²	R ³	X	Z
54.	OH	Phenyl	CH ₃ -CH ₂ -(HO-CH ₂) ₂ C-CH ₂ -	OMe	CH ₂ -CH ₂ -CH ₂ -C		O
55.	OH	Phenyl	CH ₃ -CH ₂ -(HO-CH ₂) ₂ C-CH ₂ -	OMe	O-CH ₂ -CH ₂ -C		O
56.	OH	Phenyl	CH ₃ -CH ₂ -(HO-CH ₂) ₂ C-CH ₂ -	Me	CH ₂ -CH ₂ -CH ₂ -C		O
57.	OH	Phenyl	CH ₃ -CH ₂ -(HO-CH ₂) ₂ C-CH ₂ -	OMe	OMe	N	O
58.	OH	Phenyl	CH ₃ -CH ₂ -(HO-CH ₂) ₂ C-CH ₂ -	NMe ₂	NMe ₂	N	O
59.	OH	Phenyl	CH ₃ -CH ₂ -(HO-CH ₂) ₂ C-CH ₂ -	Et	Et	CH	O
60.	OH	o-F-phenyl	(HO-CH ₂) ₂ CH-CH ₂ -	OMe	OMe	CH	O
61.	OH	m-F-phenyl	(HO-CH ₂) ₂ CH-CH ₂ -	OMe	Me	CH	O
62.	OH	p-F-phenyl	(HO-CH ₂) ₂ CH-CH ₂ -	Me	Me	CH	O
63.	OH	m-OMe-phenyl	(HO-CH ₂) ₂ CH-CH ₂ -	Me	Et	CH	O
64.	OH	m-Me-phenyl	(HO-CH ₂) ₂ CH-CH ₂ -	OMe	CH ₂ -CH ₂ -CH ₂ -C		O
65.	OH	p-Cl-phenyl	(HO-CH ₂) ₂ CH-CH ₂ -	OMe	O-CH ₂ -CH ₂ -C		O
66.	OH	p-Me-phenyl	(HO-CH ₂) ₂ CH-CH ₂ -	Me	CH ₂ -CH ₂ -CH ₂ -C		O
67.	OH	m-F-phenyl	(HO-CH ₂) ₂ CH-CH ₂ -	OMe	OMe	N	O
68.	OH	m-OMe-phenyl	(HO-CH ₂) ₂ CH-CH ₂ -	NMe ₂	NMe ₂	N	O
69.	OH	m-OMe-phenyl	(HO-CH ₂) ₂ CH-CH ₂ -	Et	Et	CH	O
70.	OH	p-Me-phenyl	CH ₃ -CH ₂ -(HO-CH ₂) ₂ C-CH ₂ -	OMe	OMe	CH	O
71.	OH	p-Cl-phenyl	CH ₃ -CH ₂ -(HO-CH ₂) ₂ C-CH ₂ -	OMe	Me	CH	O
72.	OH	m-OMe-phenyl	CH ₃ -CH ₂ -(HO-CH ₂) ₂ C-CH ₂ -	Me	Me	CH	O
73.	OH	m-Me-phenyl	CH ₃ -CH ₂ -(HO-CH ₂) ₂ C-CH ₂ -	Me	Et	CH	O
74.	OH	m-F-phenyl	CH ₃ -CH ₂ -(HO-CH ₂) ₂ C-CH ₂ -	OMe	CH ₂ -CH ₂ -CH ₂ -C		O

No.	R ¹	R ⁴ , R ⁵	R ⁶	R ²	R ³	X	Z
75.	OH	p-F-phenyl	CH ₃ -CH ₂ -(HO-CH ₂) ₂ C-CH ₂ -	OMe	O-CH ₂ -CH ₂ -C		O
76.	OH	o-F-phenyl	CH ₃ -CH ₂ -(HO-CH ₂) ₂ C-CH ₂ -	Me	CH ₂ -CH ₂ -CH ₂ -C		O
77.	OH	p-Cl-phenyl	CH ₃ -CH ₂ -(HO-CH ₂) ₂ C-CH ₂ -	OMe	OMe	N	O
78.	OH	m-F-phenyl	CH ₃ -CH ₂ -(HO-CH ₂) ₂ C-CH ₂ -	NMe ₂	NMe ₂	N	O
79.	OH	m-F-phenyl	CH ₃ -CH ₂ -(HO-CH ₂) ₂ C-CH ₂ -	Et	Et	CH	O
80.	OH	Phenyl	HO-(CH ₂) ₃ -	OMe	OMe	CH	O
81.	OH	Phenyl	HO-(CH ₂) ₃ -	OMe	Me	CH	O
82.	OH	Phenyl	HO-(CH ₂) ₃ -	Me	Me	CH	O
83.	OH	Phenyl	HO-(CH ₂) ₃ -	Me	Et	CH	O
84.	OH	Phenyl	HO-(CH ₂) ₃ -	OMe	CH ₂ -CH ₂ -CH ₂ -C		O
85.	OH	Phenyl	HO-(CH ₂) ₃ -	OMe	O-CH ₂ -CH ₂ -C		O
86.	OH	Phenyl	HO-(CH ₂) ₃ -	Me	CH ₂ -CH ₂ -CH ₂ -C		O
87.	OH	Phenyl	HO-(CH ₂) ₃ -	OMe	OMe	N	O
88.	OH	Phenyl	HO-(CH ₂) ₃ -	NMe ₂	NMe ₂	N	O
89.	OH	Phenyl	HO-(CH ₂) ₃ -	Et	Et	CH	O
90.	OH	Phenyl	HO-(CH ₂) ₄ -	OMe	OMe	CH	O
91.	OH	Phenyl	HO-(CH ₂) ₄ -	OMe	Me	CH	O
92.	OH	Phenyl	HO-(CH ₂) ₄ -	Me	Me	CH	O
93.	OH	Phenyl	HO-(CH ₂) ₄ -	Me	Et	CH	O
94.	OH	Phenyl	HO-(CH ₂) ₄ -	OMe	CH ₂ -CH ₂ -CH ₂ -C		O
95.	OH	Phenyl	HO-(CH ₂) ₄ -	OMe	O-CH ₂ -CH ₂ -C		O

No.	R ¹	R ⁴ , R ⁵	R ⁶	R ²	R ³	X	Z
96.	OH	Phenyl	HO-(CH ₂) ₄ -	Me	CH ₂ -CH ₂ -CH ₂ -C		O
97.	OH	Phenyl	HO-(CH ₂) ₄ -	OMe	OMe	N	O
98.	OH	Phenyl	HO-(CH ₂) ₄ -	NMe ₂	NMe ₂	N	O
99.	OH	Phenyl	HO-(CH ₂) ₄ -	Et	Et	CH	O
100.	OH	o-F-phenyl	HO-(CH ₂) ₃ -	OMe	Me	CH	O
101.	OH	o-F-phenyl	HO-(CH ₂) ₃ -	Me	Me	CH	O
102.	OH	m-F-phenyl	HO-(CH ₂) ₃ -	Me	Et	CH	O
103.	OH	m-OMe-phenyl	HO-(CH ₂) ₃ -	OMe	CH ₂ -CH ₂ -CH ₂ -C		O
104.	OH	m-Me-phenyl	HO-(CH ₂) ₃ -	OMe	O-CH ₂ -CH ₂ -C		O
105.	OH	p-Cl-phenyl	HO-(CH ₂) ₃ -	Me	CH ₂ -CH ₂ -CH ₂ -C		O
106.	OH	p-F-phenyl	HO-(CH ₂) ₃ -	OMe	OMe	N	O
107.	OH	m-OMe-phenyl	HO-(CH ₂) ₃ -	NMe ₂	NMe ₂	N	O
108.	OH	m-OMe-phenyl	HO-(CH ₂) ₃ -	Et	Et	CH	O
109.	OH	o-F-phenyl	HO-(CH ₂) ₄ -	OMe	OMe	CH	O
110.	OH	m-F-phenyl	HO-(CH ₂) ₄ -	OMe	Me	CH	O
111.	OH	m-Me-phenyl	HO-(CH ₂) ₄ -	Me	Me	CH	O
112.	OH	m-OMe-phenyl	HO-(CH ₂) ₄ -	Me	Et	CH	O
113.	OH	p-Me-phenyl	HO-(CH ₂) ₄ -	OMe	CH ₂ -CH ₂ -CH ₂ -C		O
114.	OH	p-Cl-phenyl	HO-(CH ₂) ₄ -	OMe	O-CH ₂ -CH ₂ -C		O
115.	OH	p-F-phenyl	HO-(CH ₂) ₄ -	Me	CH ₂ -CH ₂ -CH ₂ -C		O
116.	OH	m-Me-phenyl	HO-(CH ₂) ₄ -	OMe	OMe	N	O

No.	R ¹	R ⁴ , R ⁵	R ⁶	R ²	R ³	X	Z
117.	OH	p-Cl-phenyl	HO-(CH ₂) ₄ -	NMe ₂	NMe ₂	N	O
118.	OH	p-Cl-phenyl	HO-(CH ₂) ₄ -	Et	Et	CH	O
119.	OH	Phenyl	HO ₂ C-CH ₂ -	OMe	OMe	CH	O
120.	OH	Phenyl	HO ₂ C-CH ₂ -	OMe	OEt	CH	O
121.	OH	Phenyl	HO ₂ C-CH ₂ -	OMe	Me	CH	O
122.	OH	Phenyl	HO ₂ C-CH ₂ -	Me	Me	CH	O
123.	OH	Phenyl	HO ₂ C-CH ₂ -	Me	Et	CH	O
124.	OH	Phenyl	HO ₂ C-CH ₂ -	OMe	CH ₂ -CH ₂ -CH ₂ -C		O
125.	OH	Phenyl	HO ₂ C-CH ₂ -	OMe	O-CH ₂ -CH ₂ -C		O
126.	OH	Phenyl	HO ₂ C-CH ₂ -	Me	CH ₂ -CH ₂ -CH ₂ -C		O
127.	OH	Phenyl	HO ₂ C-CH ₂ -	OMe	OMe	N	O
128.	OH	Phenyl	HO ₂ C-CH ₂ -	NMe ₂	NMe ₂	N	O
129.	OH	Phenyl	HO ₂ C-CH ₂ -	Et	Et	CH	O
130.	OH	Phenyl	HO ₂ C-(CH ₂) ₂ -	OMe	OMe	CH	O
131.	OH	Phenyl	HO ₂ C-(CH ₂) ₂ -	OMe	Me	CH	O
132.	OH	Phenyl	HO ₂ C-(CH ₂) ₂ -	Me	Me	CH	O
133.	OH	Phenyl	HO ₂ C-(CH ₂) ₂ -	Me	Et	CH	O
134.	OH	Phenyl	HO ₂ C-(CH ₂) ₂ -	OMe	CH ₂ -CH ₂ -CH ₂ -C		O
135.	OH	Phenyl	HO ₂ C-(CH ₂) ₂ -	OMe	O-CH ₂ -CH ₂ -C		O
136.	OH	Phenyl	HO ₂ C-(CH ₂) ₂ -	Me	CH ₂ -CH ₂ -CH ₂ -C		O
137.	OH	Phenyl	HO ₂ C-(CH ₂) ₂ -	OMe	OMe	N	O

No.	R ¹	R ⁴ , R ⁵	R ⁶	R ²	R ³	X	Z
138.	OH	Phenyl	HO ₂ C-(CH ₂) ₂ -	NMe ₂	NMe ₂	N	O
139.	OH	Phenyl	HO ₂ C-(CH ₂) ₂ -	Et	Et	CH	O
140.	OH	o-F-phenyl	HO ₂ C-CH ₂ -	OMe	Me	CH	O
141.	OH	o-F-phenyl	HO ₂ C-CH ₂ -	Me	Me	CH	O
142.	OH	m-F-phenyl	HO ₂ C-CH ₂ -	Me	Et	CH	O
143.	OH	m-OMe-phenyl	HO ₂ C-CH ₂ -	OMe	CH ₂ -CH ₂ -CH ₂ -C		O
144.	OH	m-Me-phenyl	HO ₂ C-CH ₂ -	OMe	O-CH ₂ -CH ₂ -C		O
145.	OH	p-Cl-phenyl	HO ₂ C-CH ₂ -	Me	CH ₂ -CH ₂ -CH ₂ -C		O
146.	OH	p-F-phenyl	HO ₂ C-CH ₂ -	OMe	OMe	N	O
147.	OH	m-OMe-phenyl	HO ₂ C-CH ₂ -	NMe ₂	NMe ₂	N	O
148.	OH	o-F-phenyl	HO ₂ C-(CH ₂) ₂ -	OMe	OMe	CH	O
149.	OH	m-F-phenyl	HO ₂ C-(CH ₂) ₂ -	OMe	Me	CH	O
150.	OH	m-Me-phenyl	HO ₂ C-(CH ₂) ₂ -	Me	Me	CH	O
151.	OH	m-OMe-phenyl	HO ₂ C-(CH ₂) ₂ -	Me	Et	CH	O
152.	OH	p-Me-phenyl	HO ₂ C-(CH ₂) ₂ -	OMe	CH ₂ -CH ₂ -CH ₂ -C		O
153.	OH	p-Cl-phenyl	HO ₂ C-(CH ₂) ₂ -	OMe	O-CH ₂ -CH ₂ -C		O
154.	OH	p-F-phenyl	HO ₂ C-(CH ₂) ₂ -	Me	CH ₂ -CH ₂ -CH ₂ -C		O
155.	OH	m-OMe-phenyl	HO ₂ C-(CH ₂) ₂ -	OMe	OMe	N	O
156.	OH	p-Cl-phenyl	HO ₂ C-(CH ₂) ₂ -	NMe ₂	NMe ₂	N	O
157.	OH	p-Cl-phenyl	HO ₂ C-(CH ₂) ₂ -	Et	Et	CH	O
158.	OH	Phenyl	HO ₂ C-(CH ₂) ₃ -	OMe	OMe	CH	O

No.	R ¹	R ⁴ , R ⁵	R ⁶	R ²	R ³	X	Z
159.	OH	Phenyl	HO ₂ C-(CH ₂) ₃ -	OMe	Me	CH	o
160.	OH	Phenyl	HO ₂ C-(CH ₂) ₃ -	Me	Me	CH	o
161.	OH	Phenyl	HO ₂ C-(CH ₂) ₃ -	Me	Et	CH	o
162.	OH	Phenyl	HO ₂ C-(CH ₂) ₃ -	OMe	CH ₂ -CH ₂ -CH ₂ -C		o
163.	OH	Phenyl	HO ₂ C-(CH ₂) ₃ -	OMe	O-CH ₂ -CH ₂ -C		o
164.	OH	Phenyl	HO ₂ C-(CH ₂) ₃ -	Me	CH ₂ -CH ₂ -CH ₂ -C		o
165.	OH	Phenyl	HO ₂ C-(CH ₂) ₃ -	OMe	OMe	N	o
166.	OH	Phenyl	HO ₂ C-(CH ₂) ₃ -	NMe ₂	NMe ₂	N	o
167.	OH	Phenyl	HO ₂ C-(CH ₂) ₃ -	Et	Et	CH	o
168.	OH	Phenyl	HO ₂ C-CH(CH ₃)-CH ₂ -	OMe	OMe	CH	o
169.	OH	Phenyl	HO ₂ C-CH(CH ₃)-CH ₂ -	OMe	Me	CH	o
170.	OH	Phenyl	HO ₂ C-CH(CH ₃)-CH ₂ -	Me	Me	CH	o
171.	OH	Phenyl	HO ₂ C-CH(CH ₃)-CH ₂ -	Me	Et	CH	o
172.	OH	Phenyl	HO ₂ C-CH(CH ₃)-CH ₂ -	OMe	CH ₂ -CH ₂ -CH ₂ -C		o
173.	OH	Phenyl	HO ₂ C-CH(CH ₃)-CH ₂ -	OMe	O-CH ₂ -CH ₂ -C		o
174.	OH	Phenyl	HO ₂ C-CH(CH ₃)-CH ₂ -	Me	CH ₂ -CH ₂ -CH ₂ -C		o
175.	OH	Phenyl	HO ₂ C-CH(CH ₃)-CH ₂ -	OMe	OMe	N	o
176.	OH	Phenyl	HO ₂ C-CH(CH ₃)-CH ₂ -	NMe ₂	NMe ₂	N	o
177.	OH	Phenyl	HO ₂ C-CH(CH ₃)-CH ₂ -	Et	Et	CH	o
178.	OH	o-F-phenyl	HO ₂ C-(CH ₂) ₃ -	OMe	Me	CH	o
179.	OH	o-F-phenyl	HO ₂ C-(CH ₂) ₃ -	Me	Me	CH	o

No.	R ¹	R ⁴ , R ⁵	R ⁶	R ²	R ³	X	Z
180.	OH	m-F-phenyl	HO ₂ C-(CH ₂) ₃ -	Me	Et	CH	o
181.	OH	m-OMe-phenyl	HO ₂ C-(CH ₂) ₃ -	OMe	CH ₂ -CH ₂ -CH ₂ -C		o
182.	OH	m-OMe-phenyl	HO ₂ C-(CH ₂) ₃ -	OMe	O-CH ₂ -CH ₂ -C		o
183.	OH	p-Cl-phenyl	HO ₂ C-(CH ₂) ₃ -	Me	CH ₂ -CH ₂ -CH ₂ -C		o
184.	OH	p-F-phenyl	HO ₂ C-(CH ₂) ₃ -	OMe	OMe	N	o
185.	OH	m-OMe-phenyl	HO ₂ C-(CH ₂) ₃ -	NMe ₂	NMe ₂	N	o
186.	OH	m-OMe-phenyl	HO ₂ C-(CH ₂) ₃ -	Et	Et	CH	o
187.	OH	o-F-phenyl	HO ₂ C-CH(CH ₃)-CH ₂	OMe	OMe	CH	o
188.	OH	m-F-phenyl	HO ₂ C-CH(CH ₃)-CH ₂	OMe	Me	CH	o
189.	OH	m-Me-phenyl	HO ₂ C-CH(CH ₃)-CH ₂	Me	Me	CH	o
190.	OH	m-OMe-phenyl	HO ₂ C-CH(CH ₃)-CH ₂	Me	Et	CH	o
191.	OH	p-Me-phenyl	HO ₂ C-CH(CH ₃)-CH ₂	OMe	CH ₂ -CH ₂ -CH ₂ -C		o
192.	OH	p-Cl-phenyl	HO ₂ C-CH(CH ₃)-CH ₂	OMe	O-CH ₂ -CH ₂ -C		o
193.	OH	p-F-phenyl	HO ₂ C-CH(CH ₃)-CH ₂	Me	CH ₂ -CH ₂ -CH ₂ -C		o
194.	OH	m-Me-phenyl	HO ₂ C-CH(CH ₃)-CH ₂	OMe	OMe	N	o
195.	OH	p-Cl-phenyl	HO ₂ C-CH(CH ₃)-CH ₂	NMe ₂	NMe ₂	N	o
196.	OH	p-Cl-phenyl	HO ₂ C-CH(CH ₃)-CH ₂	Et	Et	CH	o
197.	OH	Phenyl	HO ₂ C-C(CH ₃) ₂ -CH ₂ -	OMe	OMe	CH	o
198.	OH	Phenyl	HO ₂ C-C(CH ₃) ₂ -CH ₂ -	OMe	Me	CH	o
199.	OH	Phenyl	HO ₂ C-C(CH ₃) ₂ -CH ₂ -	Me	Me	CH	o
200.	OH	Phenyl	HO ₂ C-C(CH ₃) ₂ -CH ₂ -	Me	Et	CH	o

No.	R ¹	R ⁴ , R ⁵	R ⁶	R ²	R ³	X	Z
201.	OH	Phenyl	HO ₂ C-C(CH ₃) ₂ -CH ₂ -	OMe	CH ₂ -CH ₂ -CH ₂ -C		O
202.	OH	Phenyl	HO ₂ C-C(CH ₃) ₂ -CH ₂ -	OMe	O-CH ₂ -CH ₂ -C		O
203.	OH	Phenyl	HO ₂ C-C(CH ₃) ₂ -CH ₂ -	Me	CH ₂ -CH ₂ -CH ₂ -C		O
204.	OH	Phenyl	HO ₂ C-C(CH ₃) ₂ -CH ₂ -	OMe	OMe	N	O
205.	OH	Phenyl	HO ₂ C-C(CH ₃) ₂ -CH ₂ -	NMe ₂	NMe ₂	N	O
206.	OH	Phenyl	HO ₂ C-C(CH ₃) ₂ -CH ₂ -	Et	Et	CH	O
207.	OH	Phenyl	H ₂ NC(O)-CH ₂ -	OMe	OMe	CH	O
208.	OH	Phenyl	H ₂ NC(O)-CH ₂ -	OMe	Me	CH	O
209.	OH	Phenyl	H ₂ NC(O)-CH ₂ -	Me	Me	CH	O
210.	OH	Phenyl	H ₂ NC(O)-CH ₂ -	Me	Et	CH	O
211.	OH	Phenyl	H ₂ NC(O)-CH ₂ -	OMe	CH ₂ -CH ₂ -CH ₂ -C		O
212.	OH	Phenyl	H ₂ NC(O)-CH ₂ -	OMe	O-CH ₂ -CH ₂ -C		O
213.	OH	Phenyl	H ₂ NC(O)-CH ₂ -	Me	CH ₂ -CH ₂ -CH ₂ -C		O
214.	OH	Phenyl	H ₂ NC(O)-CH ₂ -	OMe	OMe	N	O
215.	OH	Phenyl	H ₂ NC(O)-CH ₂ -	NMe ₂	NMe ₂	N	O
216.	OH	Phenyl	H ₂ NC(O)-CH ₂ -	Et	Et	CH	O
217.	OH	o-F-phenyl	HO ₂ C-C(CH ₃) ₂ -CH ₂ -	OMe	Me	CH	O
218.	OH	o-F-phenyl	HO ₂ C-C(CH ₃) ₂ -CH ₂ -	Me	Me	CH	O
219.	OH	m-F-phenyl	HO ₂ C-C(CH ₃) ₂ -CH ₂ -	Me	Et	CH	O
220.	OH	m-OMe-phenyl	HO ₂ C-C(CH ₃) ₂ -CH ₂ -	OMe	CH ₂ -CH ₂ -CH ₂ -C		O
221.	OH	m-Me-phenyl	HO ₂ C-C(CH ₃) ₂ -CH ₂ -	Me	O-CH ₂ -CH ₂ -C		O

No.	R ¹	R ⁴ , R ⁵	R ⁶	R ²	R ³	X	Z
222.	OH	p-Cl-phenyl	HO ₂ C-C(CH ₃) ₂ -CH ₂ -	Me	CH ₂ -CH ₂ -CH ₂ -C		O
223.	OH	p-F-phenyl	HO ₂ C-C(CH ₃) ₂ -CH ₂ -	OMe	OMe	N	O
224.	OH	m-OMe-phenyl	HO ₂ C-C(CH ₃) ₂ -CH ₂ -	NMe ₂	NMe ₂	N	O
225.	OH	m-OMe-phenyl	HO ₂ C-C(CH ₃) ₂ -CH ₂ -	Et	Et	CH	O
226.	OH	o-F-phenyl	H ₂ NC(O)-CH ₂ -	OMe	OMe	CH	O
227.	OH	m-F-phenyl	H ₂ NC(O)-CH ₂ -	OMe	Me	CH	O
228.	OH	m-Me-phenyl	H ₂ NC(O)-CH ₂ -	Me	Me	CH	O
229.	OH	m-OMe-phenyl	H ₂ NC(O)-CH ₂ -	Me	Et	CH	O
230.	OH	p-Me-phenyl	H ₂ NC(O)-CH ₂ -	Me	CH ₂ -CH ₂ -CH ₂ -C		O
231.	OH	p-Cl-phenyl	H ₂ NC(O)-CH ₂ -	OMe	O-CH ₂ -CH ₂ -C		O
232.	OH	p-F-phenyl	H ₂ NC(O)-CH ₂ -	Me	CH ₂ -CH ₂ -CH ₂ -C		O
233.	OH	m-Me-phenyl	H ₂ NC(O)-CH ₂ -	OMe	OMe	N	O
234.	OH	p-Cl-phenyl	H ₂ NC(O)-CH ₂ -	NMe ₂	NMe ₂	N	O
235.	OH	p-Cl-phenyl	H ₂ NC(O)-CH ₂ -	Et	Et	CH	O
236.	OH	Phenyl	H ₂ NC(O)-(CH ₂) ₂ -	OMe	OMe	CH	O
237.	OH	Phenyl	H ₂ NC(O)-(CH ₂) ₂ -	OMe	Me	CH	O
238.	OH	Phenyl	H ₂ NC(O)-(CH ₂) ₂ -	Me	Me	CH	O
239.	OH	Phenyl	H ₂ NC(O)-(CH ₂) ₂ -	Me	Et	CH	O
240.	OH	Phenyl	H ₂ NC(O)-(CH ₂) ₂ -	Me	CH ₂ -CH ₂ -CH ₂ -C		O
241.	OH	Phenyl	H ₂ NC(O)-(CH ₂) ₂ -	OMe	O-CH ₂ -CH ₂ -C		O
242.	OH	Phenyl	H ₂ NC(O)-(CH ₂) ₂ -	Me	CH ₂ -CH ₂ -CH ₂ -C		O

No.	R ¹	R ⁴ , R ⁵	R ⁶	R ²	R ³	X	Z
243.	OH	Phenyl	H ₂ NC(O)-(CH ₂) ₂ -	OMe	OMe	N	O
244.	OH	Phenyl	H ₂ NC(O)-(CH ₂) ₂ -	NMe ₂	NMe ₂	N	O
245.	OH	Phenyl	H ₂ NC(O)-(CH ₂) ₂ -	Et	Et	CH	O
246.	OH	Phenyl	H ₂ NC(NH)-CH ₂ -	OMe	OMe	CH	O
247.	OH	Phenyl	H ₂ NC(NH)-CH ₂ -	OMe	Me	CH	O
248.	OH	Phenyl	H ₂ NC(NH)-CH ₂ -	Me	Me	CH	O
249.	OH	Phenyl	H ₂ NC(NH)-CH ₂ -	Me	Et	CH	O
250.	OH	Phenyl	H ₂ NC(NH)-CH ₂ -	OMe	CH ₂ -CH ₂ -CH ₂ -C		O
251.	OH	Phenyl	H ₂ NC(NH)-CH ₂ -	OMe	O-CH ₂ -CH ₂ -C		O
252.	OH	Phenyl	H ₂ NC(NH)-CH ₂ -	Me	CH ₂ -CH ₂ -CH ₂ -C		O
253.	OH	Phenyl	H ₂ NC(NH)-CH ₂ -	OMe	OMe	N	O
254.	OH	Phenyl	H ₂ NC(NH)-CH ₂ -	NMe ₂	NMe ₂	N	O
255.	OH	Phenyl	H ₂ NC(NH)-CH ₂ -	Et	Et	CH	O
256.	OH	o-F-phenyl	H ₂ NC(O)-(CH ₂) ₂ -	OMe	Me	CH	O
257.	OH	o-F-phenyl	H ₂ NC(O)-(CH ₂) ₂ -	Me	Me	CH	O
258.	OH	m-F-phenyl	H ₂ NC(O)-(CH ₂) ₂ -	Me	Et	CH	O
259.	OH	m-OMe-phenyl	H ₂ NC(O)-(CH ₂) ₂ -	OMe	CH ₂ -CH ₂ -CH ₂ C		O
260.	OH	m-OMe-phenyl	H ₂ NC(O)-(CH ₂) ₂ -	OMe	O-CH ₂ -CH ₂ C		O
261.	OH	p-Cl-phenyl	H ₂ NC(O)-(CH ₂) ₂ -	Me	CH ₂ -CH ₂ -CH ₂ C		O
262.	OH	p-F-phenyl	H ₂ NC(O)-(CH ₂) ₂ -	OMe	OMe	N	O
263.	OH	m-OMe-phenyl	H ₂ NC(O)-(CH ₂) ₂ -	NMe ₂	NMe ₂	N	O

No.	R ¹	R ⁴ , R ⁵	R ⁶	R ²	R ³	X	Z
264.	OH	m-OMe-phenyl	H ₂ NC(O)-(CH ₂) ₂ -	Et	Et	CH	O
265.	OH	o-F-phenyl	H ₂ NC(NH)-CH ₂ -	OMe	OMe	CH	O
266.	OH	m-F-phenyl	H ₂ NC(NH)-CH ₂ -	OMe	Me	CH	O
267.	OH	m-Me-phenyl	H ₂ NC(NH)-CH ₂ -	Me	Me	CH	O
268.	OH	m-OMe-phenyl	H ₂ NC(NH)-CH ₂ -	Me	Et	CH	O
269.	OH	p-Me-phenyl	H ₂ NC(NH)-CH ₂ -	OMe	CH ₂ -CH ₂ -CH ₂ -C		O
270.	OH	p-Cl-phenyl	H ₂ NC(NH)-CH ₂ -	OMe	O-CH ₂ -CH ₂ -C		O
271.	OH	p-F-phenyl	H ₂ NC(NH)-CH ₂ -	Me	CH ₂ -CH ₂ -CH ₂ -C		O
272.	OH	m-Me-phenyl	H ₂ NC(NH)-CH ₂ -	OMe	OMe	N	O
273.	OH	p-Cl-phenyl	H ₂ NC(NH)-CH ₂ -	NMe ₂	NMe ₂	N	O
274.	OH	p-Cl-phenyl	H ₂ NC(NH)-CH ₂ -	Et	Et	CH	O
275.	OH	Phenyl	H ₂ NC(NH)-(CH ₂) ₂ -	OMe	OMe	CH	O
276.	OH	Phenyl	H ₂ NC(NH)-(CH ₂) ₂ -	OMe	Me	CH	O
277.	OH	Phenyl	H ₂ NC(NH)-(CH ₂) ₂ -	Me	Me	CH	O
278.	OH	Phenyl	H ₂ NC(NH)-(CH ₂) ₂ -	Me	Et	CH	O
279.	OH	Phenyl	H ₂ NC(NH)-(CH ₂) ₂ -	OMe	CH ₂ -CH ₂ -CH ₂ -C		O
280.	OH	Phenyl	H ₂ NC(NH)-(CH ₂) ₂ -	OMe	O-CH ₂ -CH ₂ -C		O
281.	OH	Phenyl	H ₂ NC(NH)-(CH ₂) ₂ -	Me	CH ₂ -CH ₂ -CH ₂ -C		O
282.	OH	Phenyl	H ₂ NC(NH)-(CH ₂) ₂ -	OMe	OMe	N	O
283.	OH	Phenyl	H ₂ NC(NH)-(CH ₂) ₂ -	NMe ₂	NMe ₂	N	O
284.	OH	Phenyl	H ₂ NC(NH)-(CH ₂) ₂ -	Et	Et	CH	O

No.	R ¹	R ⁴ , R ⁵	R ⁶	R ²	R ³	X	Z
285.	OH	Phenyl	NC-CH ₂ -	OMe	OMe	CH	O
286.	OH	Phenyl	NC-CH ₂ -	OMe	Me	CH	O
287.	OH	Phenyl	NC-CH ₂ -	Me	Me	CH	O
288.	OH	Phenyl	NC-CH ₂ -	Me	Et	CH	O
289.	OH	Phenyl	NC-CH ₂ -	OMe	CH ₂ -CH ₂ -CH ₂ -C		O
290.	OH	Phenyl	NC-CH ₂ -	OMe	O-CH ₂ -CH ₂ -C		O
291.	OH	Phenyl	NC-CH ₂ -	Me	CH ₂ -CH ₂ -CH ₂ -C		O
292.	OH	Phenyl	NC-CH ₂ -	OMe	OMe	N	O
293.	OH	Phenyl	NC-CH ₂ -	NMe ₂	NMe ₂	N	O
294.	OH	Phenyl	NC-CH ₂ -	Et	Et	CH	O

Table 1 - continued

No.	R ¹	R ⁴ , R ⁵	R ⁶	R ²	R ³	X	Z
295.	OH	o-F-phenyl	H ₂ NC(NH)-(CH ₂) ₂ -	OMe	Me	CH	O
296.	OH	o-F-phenyl	H ₂ NC(NH)-(CH ₂) ₂ -	Me	Me	CH	O
297.	OH	m-F-phenyl	H ₂ NC(NH)-(CH ₂) ₂ -	Me	Et	CH	O
298.	OH	m-OMe-phenyl	H ₂ NC(NH)-(CH ₂) ₂ -	OMe	CH ₂ -CH ₂ -CH ₂ C		O
299.	OH	m-OMe-phenyl	H ₂ NC(NH)-(CH ₂) ₂ -	OMe	O-CH ₂ -CH ₂ C		O
300.	OH	p-Cl-phenyl	H ₂ NC(NH)-(CH ₂) ₂ -	Me	CH ₂ -CH ₂ -CH ₂ C		O
301.	OH	p-F-phenyl	H ₂ NC(NH)-(CH ₂) ₂ -	OMe	OMe	N	O
302.	OH	m-OMe-phenyl	H ₂ NC(NH)-(CH ₂) ₂ -	NMe ₂	NMe ₂	N	O
303.	OH	m-OMe-phenyl	H ₂ NC(NH)-(CH ₂) ₂ -	Et	Et	CH	O
304.	OH	o-F-phenyl	NC-CH ₂ -	OMe	OMe	CH	O
305.	OH	m-F-phenyl	NC-CH ₂ -	OMe	Me	CH	O
306.	OH	m-Me-phenyl	NC-CH ₂ -	Me	Me	CH	O
307.	OH	m-OMe-phenyl	NC-CH ₂ -	Me	Et	CH	O
308.	OH	p-Me-phenyl	NC-CH ₂ -	OMe	CH ₂ -CH ₂ -CH ₂ -C		O
309.	OH	p-Cl-phenyl	NC-CH ₂ -	OMe	O-CH ₂ -CH ₂ -C		O
310.	OH	p-F-phenyl	NC-CH ₂ -	Me	CH ₂ -CH ₂ -CH ₂ -C		O
311.	OH	m-Me-phenyl	NC-CH ₂ -	OMe	OMe	N	O
312.	OH	p-Cl-phenyl	NC-CH ₂ -	NMe ₂	NMe ₂	N	O
313.	OH	p-Cl-phenyl	NC-CH ₂ -	Et	Et	CH	O
314.	OH	Phenyl	NC(CH ₂) ₂ -	OMe	Me	CH	O

No.	R ¹	R ⁴ , R ⁵	R ⁶	R ²	R ³	X	Z
315.	OH	Phenyl	NC(CH ₂) ₂ -	Me	Me	CH	O
316.	OH	Phenyl	NC(CH ₂) ₂ -	Me	Et	CH	O
317.	OH	Phenyl	NC(CH ₂) ₂ -	OMe	CH ₂ -CH ₂ -CH ₂ C		O
318.	OH	Phenyl	NC(CH ₂) ₂ -	OMe	O-CH ₂ -CH ₂ C		O
319.	OH	Phenyl	NC(CH ₂) ₂ -	Me	CH ₂ -CH ₂ -CH ₂ C		O
320.	OH	Phenyl	NC(CH ₂) ₂ -	OMe	OMe	N	O
321.	OH	Phenyl	NC(CH ₂) ₂ -	NMe ₂	NMe ₂	N	O
322.	OH	Phenyl	NC(CH ₂) ₂ -	Et	Et	CH	O
323.	OH	Phenyl	NC(CH ₂) ₃ -	OMe	OMe	CH	O
324.	OH	Phenyl	NC(CH ₂) ₃ -	OMe	Me	CH	O
325.	OH	Phenyl	NC(CH ₂) ₃ -	Me	Me	CH	O
326.	OH	Phenyl	NC(CH ₂) ₃ -	Me	Et	CH	O
327.	OH	Phenyl	NC(CH ₂) ₃ -	OMe	CH ₂ -CH ₂ -CH ₂ -C		O
328.	OH	Phenyl	NC(CH ₂) ₃ -	OMe	O-CH ₂ -CH ₂ -C		O
329.	OH	Phenyl	NC(CH ₂) ₃ -	Me	CH ₂ -CH ₂ -CH ₂ -C		O
330.	OH	Phenyl	NC(CH ₂) ₃ -	OMe	OMe	N	O
331.	OH	Phenyl	NC(CH ₂) ₃ -	NMe ₂	NMe ₂	N	O
332.	OH	Phenyl	NC(CH ₂) ₃ -	Et	Et	CH	O
333.	OH	o-F-phenyl	NC-(CH ₂) ₂ -	OMe	Me	CH	O
334.	OH	o-F-phenyl	NC-(CH ₂) ₂ -	Me	Me	CH	O
335.	OH	m-F-phenyl	NC-(CH ₂) ₂ -	Me	Et	CH	O

No.	R ¹	R ⁴ , R ⁵	R ⁶	R ²	R ³	X	Z
336.	OH	m-OMe-phenyl	NC-(CH ₂) ₂ -	OMe	CH ₂ -CH ₂ -CH ₂ C		O
337.	OH	m-OMe-phenyl	NC-(CH ₂) ₂ -	OMe	O-CH ₂ -CH ₂ C		O
338.	OH	p-Cl-phenyl	NC-(CH ₂) ₂ -	Me	CH ₂ -CH ₂ -CH ₂ C		O
339.	OH	p-F-phenyl	NC-(CH ₂) ₂ -	OMe	OMe	N	O
340.	OH	m-OMe-phenyl	NC-(CH ₂) ₂ -	NMe ₂	NMe ₂	N	O
341.	OH	m-OMe-phenyl	NC-(CH ₂) ₂ -	Et	Et	CH	O
342.	OH	o-F-phenyl	NC-(CH ₂) ₃ -	OMe	OMe	CH	O
343.	OH	m-F-phenyl	NC-(CH ₂) ₃ -	OMe	Me	CH	O
344.	OH	m-Me-phenyl	NC-(CH ₂) ₃ -	Me	Me	CH	O
345.	OH	m-OMe-phenyl	NC-(CH ₂) ₃ -	Me	Et	CH	O
346.	OH	p-Me-phenyl	NC-(CH ₂) ₃ -	OMe	CH ₂ -CH ₂ -CH ₂ -C		O
347.	OH	p-Cl-phenyl	NC-(CH ₂) ₃ -	OMe	O-CH ₂ -CH ₂ -C		O
348.	OH	p-F-phenyl	NC-(CH ₂) ₃ -	Me	CH ₂ -CH ₂ -CH ₂ -C		O
349.	OH	m-Me-phenyl	NC-(CH ₂) ₃ -	OMe	OMe	N	O
350.	OH	p-Cl-phenyl	NC-(CH ₂) ₃ -	NMe ₂	NMe ₂	N	O
351.	OH	p-Cl-phenyl	NC-(CH ₂) ₃ -	Et	Et	CH	O
352.	OH	Phenyl	CH ₃ -SO ₂ -CH ₂ -	OMe	Me	CH	O
353.	OH	Phenyl	CH ₃ -SO ₂ -CH ₂ -	Me	Me	CH	O
354.	OH	Phenyl	CH ₃ -SO ₂ -CH ₂ -	Me	Et	CH	O
355.	OH	Phenyl	CH ₃ -SO ₂ -CH ₂ -	OMe	CH ₂ -CH ₂ -CH ₂ C		O
356.	OH	Phenyl	CH ₃ -SO ₂ -CH ₂ -	OMe	O-CH ₂ -CH ₂ C		O

No.	R ¹	R ⁴ , R ⁵	R ⁶	R ²	R ³	X	Z
357.	OH	Phenyl	CH ₃ -SO ₂ -CH ₂ -	Me	CH ₂ -CH ₂ -CH ₂ C		O
358.	OH	Phenyl	CH ₃ -SO ₂ -CH ₂ -	OMe	OMe	N	O
359.	OH	Phenyl	CH ₃ -SO ₂ -CH ₂ -	NMe ₂	NMe ₂	N	O
360.	OH	Phenyl	CH ₃ -SO ₂ -CH ₂ -	Et	Et	CH	O
361.	OH	Phenyl	H ₃ C-SO ₂ -CH ₂ -CH ₂ -	OMe	OMe	CH	O
362.	OH	Phenyl	H ₃ C-SO ₂ -CH ₂ -CH ₂ -	OMe	Me	CH	O
363.	OH	Phenyl	H ₃ C-SO ₂ -CH ₂ -CH ₂ -	Me	Me	CH	O
364.	OH	Phenyl	H ₃ C-SO ₂ -CH ₂ -CH ₂ -	Me	Et	CH	O
365.	OH	Phenyl	H ₃ C-SO ₂ -CH ₂ -CH ₂ -	OMe	CH ₂ -CH ₂ -CH ₂ -C		O
366.	OH	Phenyl	H ₃ C-SO ₂ -CH ₂ -CH ₂ -	OMe	O-CH ₂ -CH ₂ -C		O
367.	OH	Phenyl	H ₃ C-SO ₂ -CH ₂ -CH ₂ -	Me	CH ₂ -CH ₂ -CH ₂ -C		O
368.	OH	Phenyl	H ₃ C-SO ₂ -CH ₂ -CH ₂ -	OMe	OMe	N	O
369.	OH	Phenyl	H ₃ C-SO ₂ -CH ₂ -CH ₂ -	NMe ₂	NMe ₂	N	O
370.	OH	Phenyl	H ₃ C-SO ₂ -CH ₂ -CH ₂ -	Et	Et	CH	O
371.	OH	o-F-phenyl	H ₃ C-SO ₂ -CH ₂ -	OMe	Me	CH	O
372.	OH	o-F-phenyl	H ₃ C-SO ₂ -CH ₂ -	Me	Me	CH	O
373.	OH	m-F-phenyl	H ₃ C-SO ₂ -CH ₂ -	Me	Et	CH	O
374.	OH	m-OMe-phenyl	H ₃ C-SO ₂ -CH ₂ -	OMe	CH ₂ -CH ₂ -CH ₂ C		O
375.	OH	m-OMe-phenyl	H ₃ C-SO ₂ -CH ₂ -	OMe	O-CH ₂ -CH ₂ C		O
376.	OH	p-Cl-phenyl	H ₃ C-SO ₂ -CH ₂ -	Me	CH ₂ -CH ₂ -CH ₂ C		O
377.	OH	p-F-phenyl	H ₃ C-SO ₂ -CH ₂ -	OMe	OMe	N	O

No.	R ¹	R ⁴ , R ⁵	R ⁶	R ²	R ³	X	Z
378.	OH	m-OMe-phenyl	H ₃ C-SO ₂ -CH ₂ -	NMe ₂	NMe ₂	N	O
379.	OH	m-OMe-phenyl	H ₃ C-SO ₂ -CH ₂ -	Et	Et	CH	O
380.	OH	o-F-phenyl	H ₃ C-SO ₂ -CH ₂ -CH ₂ -	OMe	OMe	CH	O
381.	OH	m-F-phenyl	H ₃ C-SO ₂ -CH ₂ -CH ₂ -	OMe	Me	CH	O
382.	OH	m-Me-phenyl	H ₃ C-SO ₂ -CH ₂ -CH ₂ -	Me	Me	CH	O
383.	OH	m-OMe-phenyl	H ₃ C-SO ₂ -CH ₂ -CH ₂ -	Me	Et	CH	O
384.	OH	p-Me-phenyl	H ₃ C-SO ₂ -CH ₂ -CH ₂ -	OMe	CH ₂ -CH ₂ -CH ₂ -C		O
385.	OH	p-Cl-phenyl	H ₃ C-SO ₂ -CH ₂ -CH ₂ -	OMe	O-CH ₂ -CH ₂ -C		O
386.	OH	p-F-phenyl	H ₃ C-SO ₂ -CH ₂ -CH ₂ -	Me	CH ₂ -CH ₂ -CH ₂ -C		O
387.	OH	m-Me-phenyl	H ₃ C-SO ₂ -CH ₂ -CH ₂ -	OMe	OMe	N	O
388.	OH	p-Cl-phenyl	H ₃ C-SO ₂ -CH ₂ -CH ₂ -	NMe ₂	NMe ₂	N	O
389.	OH	p-Cl-phenyl	H ₃ C-SO ₂ -CH ₂ -CH ₂ -	Et	Et	CH	O
390.	OH	Phenyl	HS-CH ₂ -CH ₂ -	OMe	Me	CH	O
391.	OH	Phenyl	HS-CH ₂ -CH ₂ -	Me	Me	CH	O
392.	OH	Phenyl	HS-CH ₂ -CH ₂ -	Me	Et	CH	O
393.	OH	Phenyl	HS-CH ₂ -CH ₂ -	OMe	CH ₂ -CH ₂ -CH ₂ C		O
394.	OH	Phenyl	HS-CH ₂ -CH ₂ -	OMe	O-CH ₂ -CH ₂ C		O
395.	OH	Phenyl	HS-CH ₂ -CH ₂ -	Me	CH ₂ -CH ₂ -CH ₂ C		O
396.	OH	Phenyl	HS-CH ₂ -CH ₂ -	OMe	OMe	N	O
397.	OH	Phenyl	HS-CH ₂ -CH ₂ -	NMe ₂	NMe ₂	N	O
398.	OH	Phenyl	HS-CH ₂ -CH ₂ -	Et	Et	CH	O

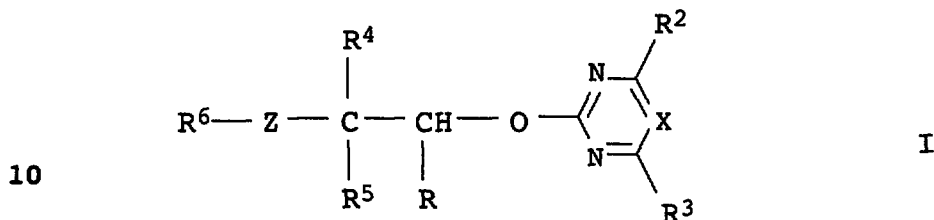
No.	R ¹	R ⁴ , R ⁵	R ⁶	R ²	R ³	X	Z
399.	OH	o-F-phenyl	H ₃ C-SO ₂ -CH ₂ -	OMe	Me	CH	O
400.	OH	o-F-phenyl	HS-CH ₂ -CH ₂ -	Me	Me	CH	O
401.	OH	m-F-phenyl	HS-CH ₂ -CH ₂ -	Me	Et	CH	O
402.	OH	m-OMe-phenyl	HS-CH ₂ -CH ₂ -	OMe	CH ₂ -CH ₂ -CH ₂ C		O
403.	OH	m-OMe-phenyl	HS-CH ₂ -CH ₂ -	OMe	O-CH ₂ -CH ₂ C		O
404.	OH	p-Cl-phenyl	HS-CH ₂ -CH ₂ -	Me	CH ₂ -CH ₂ -CH ₂ C		O
405.	OH	p-F-phenyl	HS-CH ₂ -CH ₂ -	OMe	OMe	N	O
406.	OH	m-OMe-phenyl	HS-CH ₂ -CH ₂ -	NMe ₂	NMe ₂	N	O
407.	OH	m-OMe-phenyl	HS-CH ₂ -CH ₂ -	Et	Et	CH	O



We claim:

1. A carboxylic acid derivative of the formula I

5



15 where R is tetrazole [sic], nitrile [sic] or a group
 $\text{C} - \begin{array}{c} \diagup \quad \diagdown \\ \text{O} \\ \text{R}^1 \end{array}$ and the other substituents have the following
meanings: [sic]

where R¹ has the following meanings:

- 20 a) hydrogen;
- b) a succinylimidoxy [sic] group;
- 25 c) a 5-membered heteroaromatic system linked via a nitrogen atom, such as pyrrolyl, pyrazolyl, imidazolyl and triazolyl, which may carry one or two halogen atoms, in particular fluorine and chlorine, and/or one or two of the following radicals:
- 30 C₁-C₄-alkyl such as methyl, ethyl, 1-propyl, 2-propyl, 2-methyl-2-propyl, 2-methyl-1-propyl, 1-butyl, 2-butyl;
- 35 C₁-C₄-haloalkyl, in particular C₁-C₂-haloalkyl such as 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 and pentafluoroethyl;
- 40 C₁-C₄-haloalkoxy, in particular C₁-C₂-haloalkoxy such as difluoromethoxy, trifluoromethoxy, chlorodifluoromethoxy, 1-fluoroethoxy, 2-fluoroethoxy, 2,2-difluoroethoxy, 1,1,2,2-tetrafluoroethoxy, 2,2,2-trifluoroethoxy, 2-chloro-1,1,2-trifluoroethoxy and pentafluoroethoxy, in
- 45 particular trifluoromethoxy;



C₁-C₄-alkoxy such as methoxy, ethoxy, propoxy, 1-methylethoxy, butoxy, 1-methylpropoxy, 2-methylpropoxy, 1,1-dimethylethoxy, in particular methoxy, ethoxy and 1-methylethoxy;

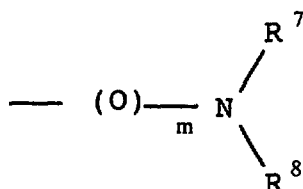
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C₁-C₄-alkylthio such as methylthio, ethylthio, propylthio, 1-methylethylthio, butylthio, 1-methylpropylthio, 2-methylpropylthio, 1,1-dimethylethylthio, in particular methylthio and ethylthio;

10

d) R¹ is furthermore a radical

15



where m is 0 or 1 and R⁷ and R⁸, which can be identical or different, have the following meanings:

20

hydrogen,

C₁-C₈-alkyl,

25

C₃-C₆-alkenyl,

C₃-C₆-alkynyl,

30

C₃-C₈-cycloalkyl, it being possible for these alkyl, cycloalkyl, alkenyl and alkynyl groups each to carry one to five halogen atoms, in particular fluorine or chlorine, and/or one or two of the following groups:

35

C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₄-alkylthio, C₁-C₄-haloalkoxy as mentioned above, C₃-C₆-alkenyloxy, C₃-C₆-alkenylthio, C₃-C₆-alkynyloxy, C₃-C₆-alkynylthio,

C₁-C₄-alkylcarbonyl,

40

C₁-C₄-alkoxycarbonyl,

C₃-C₆-alkenylcarbonyl, C₃-C₆-alkynylcarbonyl,

C₃-C₆-alkenyloxycarbonyl and C₃-C₆-alkynyloxycarbonyl,

45



45

phenyl, unsubstituted or substituted one or more times,
eg. from one to three times, by halogen, nitro, cyano,
C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-halo-
alkoxy or C₁-C₄-alkylthio,

5

di-C₁-C₄-alkylamino,

10

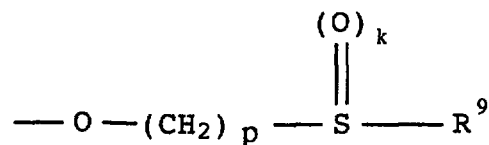
R⁷ and R⁸ are furthermore phenyl which can be substituted
by one or more of the following radicals: halogen, nitro,
cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy,
C₁-C₄-haloalkoxy or C₁-C₄-alkylthio,

15

or R⁷ and R⁸ together form a C₄-C₇-alkylene chain which is
closed to form a ring and may contain a hetero atom
selected from the group of oxygen, sulfur or nitrogen,

e) R¹ is furthermore a group

20



in which k assumes the values 0, 1 and 2, p assumes the
values 1, 2, 3 and 4, and R⁹ is

25

C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl
or unsubstituted or substituted phenyl,

30

f) R¹ is furthermore a radical OR¹⁰ where R¹⁰ is:

hydrogen, the cation of an alkali metal such as lithium,
sodium, potassium or the cation of an alkaline earth
metal such as calcium, magnesium and barium or an organic
ammonium ion;

35

C₃-C₈-cycloalkyl, which can carry one to three C₁-C₄-alkyl
groups;

40

C₁-C₈-alkyl which can carry one to five halogen atoms
and/or one of the following radicals:

45

C₁-C₄-alkoxy, C₁-C₄-alkylthio, cyano, C₁-C₄-alkylcarbonyl,
C₃-C₈-cycloalkyl [sic], C₁-C₄-alkoxycarbonyl, phenyl,
phenoxy or phenylcarbonyl, it being possible for the
aromatic radicals in turn each to carry one to five
halogen atoms and/or one to three of the following



radicals: nitro, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy and/or C₁-C₄-alkylthio;

5 a C₁-C₈-alkyl group which can carry one to five halogen atoms and carries one of the following radicals: a 5-membered heteroaromatic system containing one to three nitrogen atoms, or a 5-membered heteroaromatic system containing one nitrogen atom and one oxygen or sulfur atom, which system can carry one to four halogen atoms
10 and/or one or two of the following radicals:

nitro, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, phenyl, C₁-C₄-haloalkoxy and/or C₁-C₄-alkylthio;

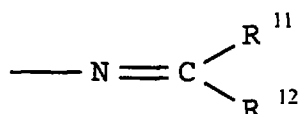
15 a C₂-C₆-alkyl group which carries in position 2 one of the following radicals: C₁-C₄-alkoxyimino, C₃-C₆-alkynyl-oxyimino, C₃-C₆-haloalkenyloxyimino or benzyloxyimino;

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

25 R¹⁰ is furthermore 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, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy and/or C₁-C₄-alkylthio;

30 a 5-membered heteroaromatic system which is linked via a nitrogen atom and contains one to three nitrogen atoms and which can carry one or two halogen atoms and/or one or two of the following radicals; [lacuna]

35 R¹⁰ is furthermore a group



40 where R¹¹ and R¹², which can be identical or different, are:

45 C₁-C₈-alkyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl, C₃-C₈-cycloalkyl, it being possible for these radicals to carry a C₁-C₄-alkoxy, C₁-C₄-alkylthio and/or an unsubstituted or substituted phenyl radical;



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phenyl which may be substituted by one or more of the following radicals: halogen, nitro, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy or C₁-C₄-alkylthio,

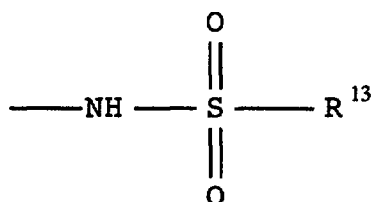
5

or R¹¹ and R¹² together form a C₃-C₁₂-alkylene chain which may carry one to three C₁-C₄-alkyl groups and may contain a hetero atom from the group of oxygen, sulfur and nitrogen;

10

g) R¹ is furthermore a radical

15



where R¹³ is:

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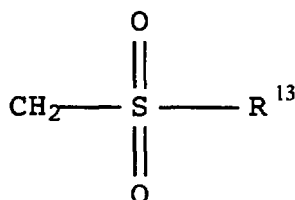
C₁-C₄-alkyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl, C₃-C₈-cycloalkyl, it being possible for these radicals to carry a C₁-C₄-alkoxy, C₁-C₄-alkylthio and/or phenyl radical;

phenyl, unsubstituted or substituted;

25

h) R¹ is a radical

30



35

where R¹³ has the abovementioned meaning.

R² halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy or C₁-C₄-alkylthio;

40

X nitrogen or CR¹⁴, where R¹⁴ is hydrogen or C₁₋₅-alkyl, or CR¹⁴ forms together with CR³ a 5- or 6-membered alkylene or alkenylene ring which can be substituted by one or two C₁₋₄-alkyl groups and in which in each case one methylene group can be replaced by oxygen, sulfur, -NH or -NC₁₋₄-alkyl;

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R³ halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, -NH-O-C₁₋₄-alkyl, C₁-C₄-alkylthio or CR³ is linked to CR¹⁴ as indicated above to form a 5- or 6-membered ring;

5

R⁴ and R⁵ (which may be identical or different):

phenyl or naphthyl, each of which can be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, phenoxy, C₁-C₄-alkylthio, amino, C₁-C₄-alkylamino or C₁-C₄-dialkylamino; or

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phenyl or naphthyl which are connected together in ortho positions by a direct linkage, a methylene, ethylene or ethenylene group, an oxygen or sulfur atom or an SO₂, NH or N-alkyl group, or C₃-C₇-cycloalkyl;

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R⁶ C₁-C₁₀-alkyl, C₃-C₁₀-alkenyl or C₃-C₁₀-alkynyl, the radicals each being substituted one or more times by hydroxyl, mercapto, carboxyl, $\begin{matrix} R_z \\ R_y \end{matrix} > N - CO -$, where R_y and R_z are, independently of one another, hydrogen or C₁-C₅-alkyl; sulfonyl, cyano, guanidino;

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Z sulfur or oxygen.

2. A carboxylic acid derivative as claimed in claim 1, wherein R is COOH.

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3. A carboxylic acid derivative as claimed in any of the preceding claims, wherein at least one of the radicals R⁴ and R⁵ is phenyl.

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4. A carboxylic acid derivative as claimed in claim 3, wherein R⁴ and R⁵ are both phenyl.

5. A carboxylic acid derivative as claimed in any of the preceding claims, wherein R⁶ is C₁-C₈-alkyl, unsubstituted or substituted by OH or C₁-C₄-alkoxy, and Z is O.

40

6. A carboxylic acid derivative as claimed in any of the preceding claims, wherein X is CH.

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7. A carboxylic acid derivative as claimed in any of the preceding claims, wherein at least one of the radicals R^2 , R^3 is C_1 - C_4 -alkyl.

- 5 8. The use of compounds as claimed in any of claims 1 to 7 for producing medicines for treating hypertension, pulmonary hypertension, acute and chronic kidney failure, chronic heart failure, cerebral ischemia, restenosis after angioplasty, prostate cancer.

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9. The use of a combination of a compound as claimed in any of claims 1 to 7 with an inhibitor of the renin-angiotensin system (RAS).

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