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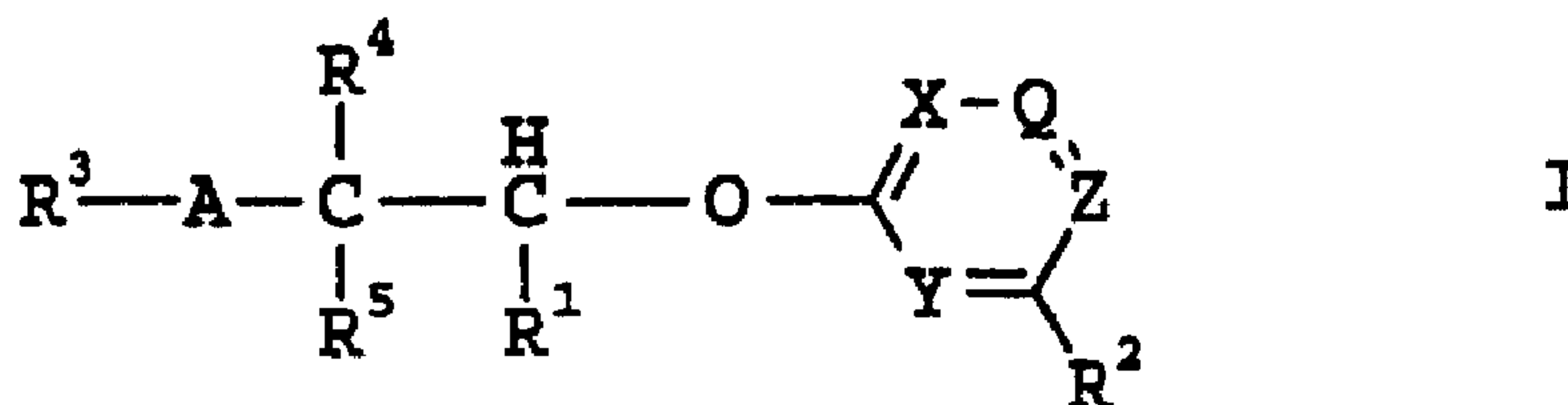
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(54) Titre : NOUVEAUX DERIVES D'ACIDE CARBOXYLIQUE COMPRENANT DES HETEROCYCLES D'AZOTE
SUBSTITUES PAR ARYLE, LEUR PREPARATION ET LEUR UTILISATION COMME ANTAGONISTES DU
RECEPTEUR D'ENTHOLINE

(54) Title: NOVEL CARBOXYLIC ACID DERIVATIVES COMPRISING ARYL-SUBSTITUTED NITROGEN
HETEROCYCLES, THEIR PRODUCTION AND THEIR USE AS ENDOTHELIN RECEPTOR ANTAGONISTS



(57) **Abrégé/Abstract:**

The invention relates to carboxylic acid derivatives of formula (I), whereby the substituents have the meanings as explained in the description. The invention also relates to the production and use of said novel carboxylic acid derivatives as endothelin receptor antagonists.



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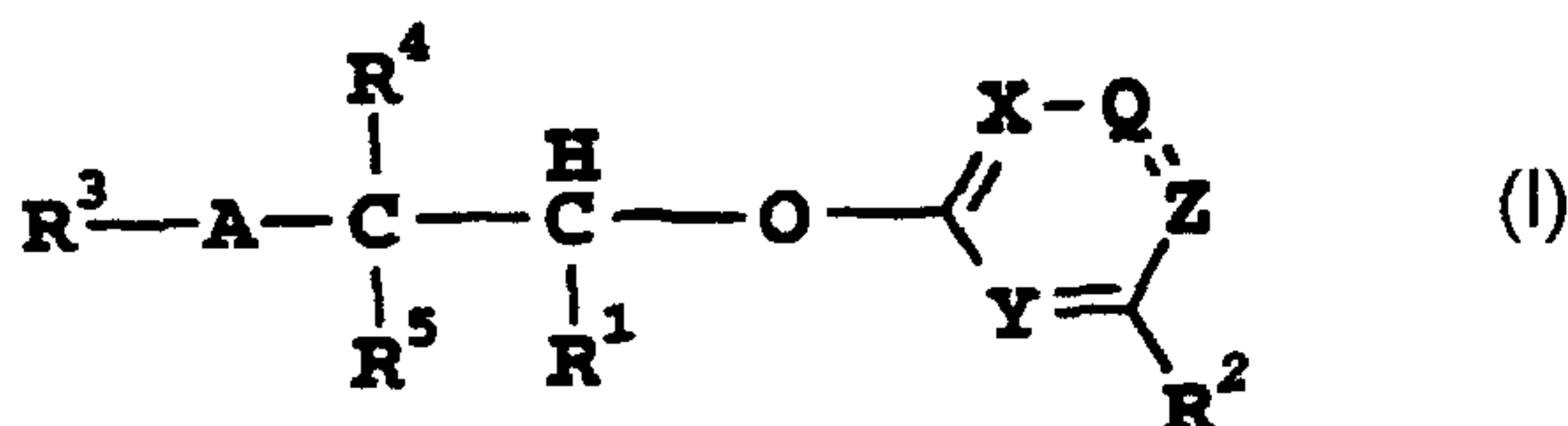
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der PCT-Gazette verwiesen.(54) Title: CARBOXYLIC ACID DERIVATIVES COMPRISING ARYL-SUBSTITUTED NITROGEN HETEROCYCLES,
THEIR PRODUCTION AND THEIR USE AS ENDOTHELIN RECEPTOR ANTAGONISTS(54) Bezeichnung: CARBONSÄUREDERIVATE MIT ARYLSUBSTITUIERTEN STICKSTOFFHETEROCYCLEN, IHRE
HERSTELLUNG UND VERWENDUNG ALS ENDOTHELIN-REZEPTOR-ANTAGONISTEN(57) Abstract: The invention relates to carboxylic acid
derivatives of formula (I), whereby the substituents
have the meanings as explained in the description. The
invention also relates to the production and use of said
novel carboxylic acid derivatives as endothelin receptor
antagonists.(57) Zusammenfassung: Die vorliegende Erfindung betrifft Carbonsäurederivate der Formel (I), wobei die Substituenten die in der
Beschreibung erläuterte Bedeutung haben, die Herstellung und Verwendung als Endothelinrezeptorantagonisten.

WO 00/73276 A3

NOVEL CARBOXYLIC ACID DERIVATIVES COMPRISING ARYL-
SUBSTITUTED NITROGEN HETEROCYCLES, THEIR PRODUCTION AND
THEIR USE AS ENDOTHELIN RECEPTOR ANTAGONISTS

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

10 Endothelin is a peptide composed of 21 amino acids, which is synthesized and released by vascular endothelium. Endothelin exists in three isoforms, ET-1, ET-2 and ET-3. In the following, "endothelin" or "ET" designates one or all isoforms of endothelin. Endothelin is a potent vasoconstrictor and has a strong effect on vessel tone. It is known that this vasoconstriction is caused by the 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).

20 Increased or abnormal release of endothelin causes persistent vasoconstriction in peripheral, renal and cerebral blood vessels, which may lead to diseases. As reported in the literature, endothelin is involved in a number of diseases. These include: hypertension, acute myocardial infarct, pulmonary hypertension, Raynaud's syndrome, cerebral vasospasms, stroke, benign prostate hypertrophy, atherosclerosis, asthma and prostate cancer (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), Nature Medicine 1, 944, (1995)).

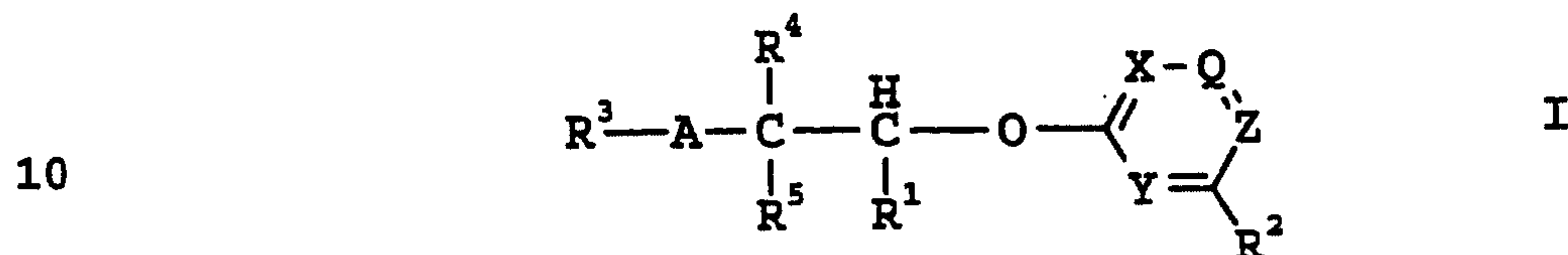
At least two endothelin receptor subtypes, ET_A and ET_B receptors, have to date been described in the literature (Nature 348, 730 (1990), Nature 348, 732 (1990)). Accordingly, substances which inhibit the binding of endothelin to one or both receptors should antagonize the physiological effects of endothelin and therefore represent valuable drugs.

30 The preparation and use of endothelin receptor antagonists has already been described in WO 95/26716, WO 96/11914, WO 97/38980, WO 97/38982, WO98/09953, WO98/27070, WO 98/58916, WO 99/11629, DE 19748238.4, DE 19806438.1, DE 19809144.3 and DE 19836044.4. These are compounds which each comprise a heteroaromatic system with at least one nitrogen but no phenyl substitution.

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It is an object of the present invention to provide further endothelin receptor antagonists with valuable pharmacological properties.

- 5 The invention relates to carboxylic acid derivatives of the formula I



in which R¹ is tetrazolyl or a group



in which R has the following meaning:

- 20 a) a radical OR⁶ in which R⁶ is:

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

25

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

30

A C₂-C₆-alkenyl or C₃-C₆-alkynyl group, it being possible for these groups in turn to carry one to five halogen atoms;

35

R⁶ can also be a phenyl radical which may carry one to five halogen atoms and/or one to three of the following radicals: nitro, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, hydroxyl, C₁-C₄-alkoxy, mercapto, C₁-C₄-alkylthio, amino, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂;

40

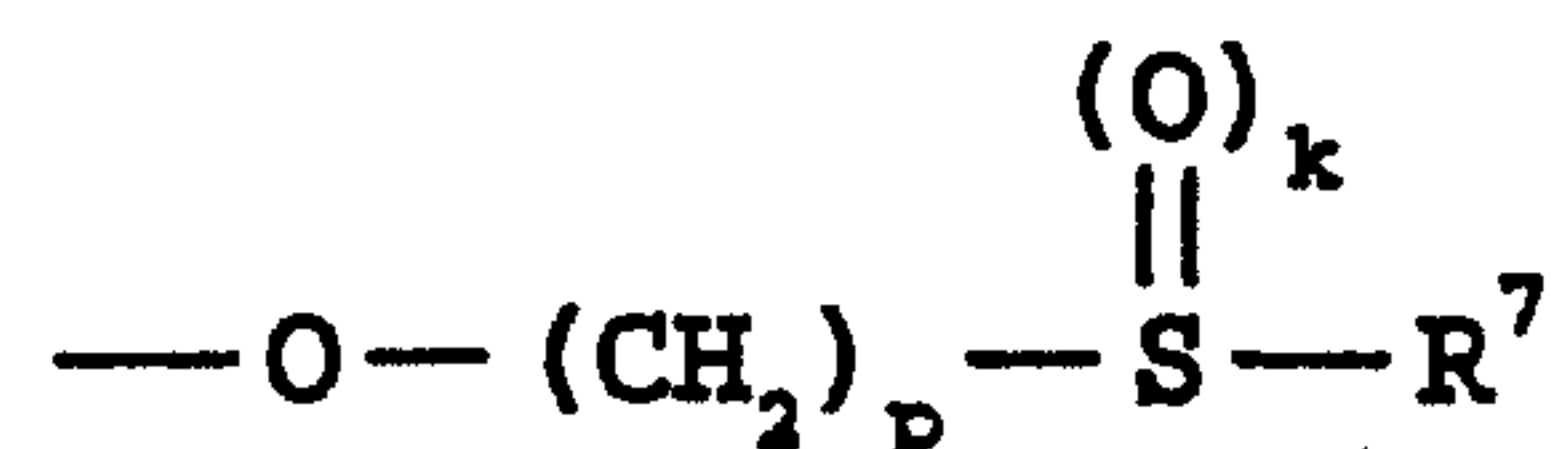
- b) a 5-membered heteroaromatic system which is linked via a nitrogen atom, such as pyrrolyl, pyrazolyl, imidazolyl and triazolyl, which may carry one to two halogen atoms
- 45

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

c) a group

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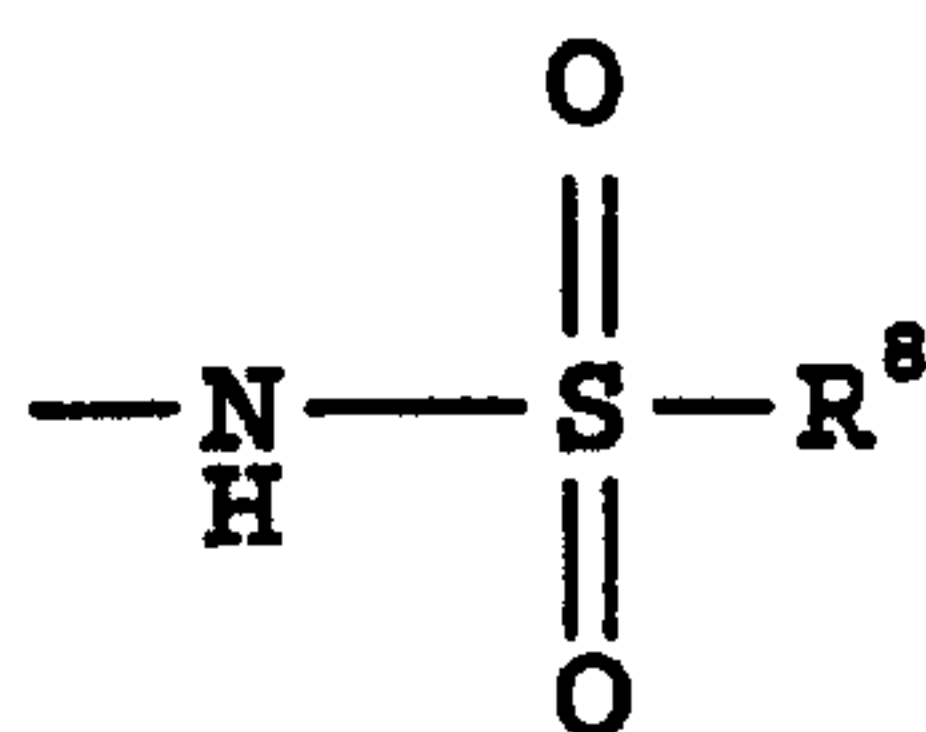
in which k assumes the values 0, 1 and 2, p assumes the values 1, 2, 3 and 4, and R⁷ is

15

C₁-C₄-alkyl, C₃-C₈-cycloalkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl or 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, hydroxyl, C₁-C₄-alkoxy, C₁-C₄-alkylthio, mercapto, amino, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂;

20

d) a radical



25

in which R⁸ is:

30

C₁-C₄-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₃-C₈-cycloalkyl, it being possible for these radicals to carry a C₁-C₄-alkoxy, C₁-C₄-alkylthio and/or a phenyl radical as mentioned under c);

35

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

The other substituents have the following meanings:

40 R² phenyl or phenoxy, benzyl, benzyloxy, it being possible for all the aryl radicals to carry one to five halogen atoms and/or one to three of the following radicals: hydroxyl, mercapto, carboxyl, nitro, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₃-C₆-alkenyloxy, 45 C₃-C₆-alkynyloxy, C₁-C₄-alkylthio, C₁-C₄-haloalkoxy, C₁-C₄-alkylcarbonyl, R⁹, C₁-C₄-alkoxycarbonyl, (C₁-C₄-alkyl)NHcarbonyl, (C₁-C₄-alkyl)₂Ncarbonyl,

4

C₃-C₈-alkylcarbonylalkyl, amino, NH(C₁-C₄-alkyl),
N(C₁-C₄-alkyl)₂, phenoxy or phenyl, it being possible for said
aryl radicals in turn to be substituted once to three times
by halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy,
5 C₁-C₄-haloalkoxy, methylenedioxy, ethylenedioxy,
C₁-C₄-alkylthio;

a five- or six-membered heteroaromatic system which contains
one to three nitrogen atoms and/or one sulfur or oxygen atom
10 and which may carry one to four halogen atoms and/or one to
two of the following radicals: C₁-C₄-alkyl, C₁-C₄-haloalkyl,
C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₁-C₄-alkylthio, phenyl,
phenoxy or phenylcarbonyl, it being possible for the phenyl
radicals in turn to carry one to five halogen atoms and/or
15 one to three of the following radicals: C₁-C₄-alkyl,
C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy and/or
C₁-C₄-alkylthio;

C₃-C₈-cycloalkyl which may carry one to three of the following
20 radicals: C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy,
C₁-C₄-haloalkoxy, C₁-C₄-alkylthio.

R³ hydrogen;

25 C₁-C₈-alkyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl or C₃-C₈-cycloalkyl,
it being possible for each of these radicals to be
substituted one or more times by: hydroxyl, mercapto,
carboxyl, halogen, nitro, cyano, C₁-C₄-alkoxy,
C₃-C₆-alkenyloxy, C₃-C₆-alkynyloxy, C₁-C₄-alkylthio,
30 C₁-C₄-haloalkoxy, C₁-C₄-alkylcarbonyl, C₁-C₄-alkoxycarbonyl,
(C₁-C₄-alkyl)NHcarbonyl, (C₁-C₄-alkyl)₂Ncarbonyl,
C₃-C₈-alkylcarbonylalkyl, amino, NH(C₁-C₄-alkyl),
N(C₁-C₄-alkyl)₂, phenoxy, phenyl or hetaryl, five- or
six-membered, containing one to three nitrogen atoms and/or
35 one sulfur or oxygen atom, it being possible for all said
aryl and hetaryl radicals to be substituted once to three
times by: halogen, nitro, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl,
C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, mercapto, carboxyl, hydroxyl,
amino, R⁹, C₁-C₄-alkoxycarbonyl, NH(C₁-C₄-alkyl),
40 N(C₁-C₄-alkyl)₂, methylenedioxy, ethylenedioxy,
C₁-C₄-alkylthio, phenyl or phenoxy;

phenyl or naphthyl, each of which may be substituted by one
or more of the following radicals: halogen, nitro, cyano,
45 hydroxyl, amino, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy,

5

C₁-C₄-haloalkoxy, phenoxy, C₁-C₄-alkylthio, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂ or methylenedioxy or ethylenedioxy;

5 a five- or six-membered heteroaromatic system which contains one to three nitrogen atoms and/or one sulfur or oxygen atom and which may carry one to four halogen atoms and/or one to two of the following radicals: C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₁-C₄-alkylthio, phenyl, phenoxy or phenylcarbonyl, it being possible for the phenyl
10 radicals in turn to 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.

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

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

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

or C₃-C₇-cycloalkyl.

30 X and Y (which may be identical or different): nitrogen or methine; with the proviso that if X = Y = methine then Z = nitrogen.

Z nitrogen or CR¹⁰.

35

Q nitrogen or CR¹¹; with the proviso that if X = Y = Z = nitrogen then Q = CR¹¹.

R⁹ C₁-C₄-alkyl, C₁-C₄-alkylthio, C₁-C₄-alkoxy, each of which
40 carry one of the following radicals: hydroxyl, carboxyl, amino, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂, carbamoyl or CON(C₁-C₄-alkyl)₂.

R¹⁰ hydrogen, halogen, hydroxyl, NH₂, NH(C₁-C₄-alkyl),
45 N(C₁-C₄-alkyl)₂, 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 CR¹⁰ forms together

6

with CR¹¹ a 5- or 6-membered alkylene or alkenylene ring which may be substituted by one or two C₁-C₄-alkyl groups and in which in each case one or more methylene groups can be replaced by oxygen, sulfur, -NH or -N(C₁-C₄-alkyl);

5

phenyl which may carry one to three of the following radicals: C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₁-C₄-alkylthio.

- 10 R¹¹ hydrogen, hydroxyl, NH₂, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂, halogen, C₁-C₄-alkyl, C₂-C₄-alkenyl, C₂-C₄-alkynyl, C₃-C₆-alkenyloxy, C₁-C₄-alkylcarbonyl, C₁-C₄-alkoxycarbonyl, C₁-C₄-hydroxyalkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, -NH-O-C₁-C₄-alkyl, C₁-C₄-alkylthio,
- 15 C₃-C₈-cycloalkyl or CR¹¹ forms together with CR¹⁰ and as indicated for R¹⁰ a 5- or 6-membered ring;

phenyl or phenoxy, each of which may carry one to five halogen atoms and/or one to three of the following radicals:

- 20 hydroxyl, mercapto, carboxyl, nitro, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₃-C₆-alkenyloxy, C₃-C₆-alkynyloxy, C₁-C₄-alkylthio, C₁-C₄-haloalkoxy, C₁-C₄-alkylcarbonyl, R⁹, C₁-C₄-alkoxycarbonyl, (C₁-C₄-alkyl)NHcarbonyl, (C₁-C₄-alkyl)₂Ncarbonyl,
- 25 C₃-C₈-alkylcarbonylalkyl, amino, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂, phenoxy or phenyl, it being possible for said aryl radicals in turn to be substituted once to three times by halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, methylenedioxy, ethylenedioxy,
- 30 C₁-C₄-alkylthio;

a five- or six-membered heteroaromatic system which contains one to three nitrogen atoms and/or one sulfur or oxygen atom and which may carry one to four halogen atoms and/or one to

35 two of the following radicals: C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₁-C₄-alkylthio, phenyl, phenoxy or phenylcarbonyl, it being possible for the phenyl radicals in turn to carry one to five halogen atoms and/or one to three of the following radicals: C₁-C₄-alkyl,

40 C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy and/or C₁-C₄-alkylthio.

A sulfur or oxygen.

- 45 The following definitions apply in this connection and hereinafter:

7

an alkali metal is, for example, lithium, sodium, potassium;

an alkaline earth metal is, for example, calcium, magnesium, barium;

5

organic ammonium ions are protonated amines such as, for example, ethanolamine, diethanolamine, ethylenediamine, diethylamine or piperazine;

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

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;

20

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;

30

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, 5 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, for example 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;

20

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

The invention further relates to compounds from which the compounds of the formula I can be liberated (called prodrugs),

25 for example amides of the acids embraced by formula I.

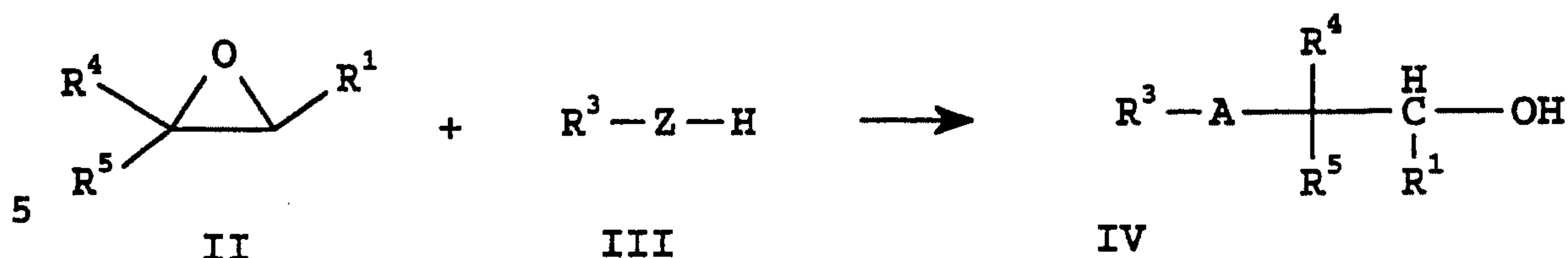
Preferred prodrugs are those with which the liberation takes place under conditions like those prevailing in particular compartments of the body, for example in the stomach, intestine, 30 bloodstream, liver.

The compounds, and the intermediates for preparing them, such as, for example, II and IV, may have one or more asymmetric substituted carbon atoms. Compounds of this type may be in the 35 form of pure enantiomers or pure diastereomers or a mixture thereof. The use of an enantiomerically pure compound as active ingredient is preferred.

The invention further relates to the use of the abovementioned 40 carboxylic acid derivatives for producing drugs, in particular for producing inhibitors for endothelin receptors.

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

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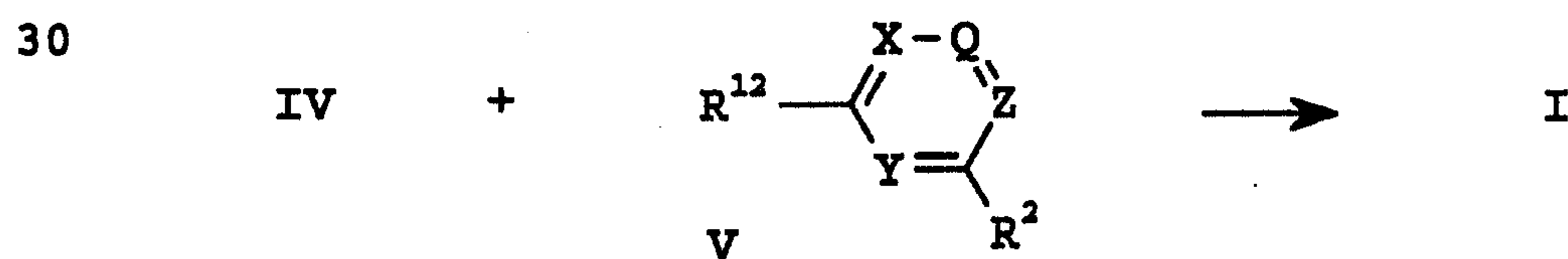


Compounds of the general formula III either are known or can be synthesized, for example, by reducing the corresponding
 10 carboxylic acids or esters thereof, or by other generally known methods.

Compounds of the formula IV can be obtained in enantiomerically pure form by acid-catalyzed transesterification as described in
 15 WO 98/09953.

It is also possible to obtain enantiomerically pure compounds of the formula IV by carrying out a conventional racemate resolution of racemic or diastereomeric compounds of the formula IV using
 20 suitable enantiomerically pure bases. Examples of suitable bases of this type are 4-chlorophenylethylamine and the bases mentioned in WO 96/11914.

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



35 R^{12} in formula V is halogen or $\text{R}^{13}-\text{SO}_2$ where R^{13} can be C_1 - C_4 -alkyl, C_1 - C_4 -haloalkyl or phenyl. The reaction preferably takes place in an inert solvent or diluent with the addition of a suitable base, i.e. a base which deprotonates the intermediate
 40 IV, at a temperature in the range from room temperature to the boiling point of the solvent.

If R^1 is an ester, the compounds with $\text{R}^1 = \text{COOH}$ can be prepared by acidic, basic or catalytic cleavage of the ester group.

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Compounds of type I with $R^1 = \text{COOH}$ can also be obtained directly by deprotonating the intermediate IV in which R^1 is COOH with two equivalents of a suitable base, and reacting with compounds of the general formula V. This reaction also takes place in an inert solvent and at a temperature in the range from room temperature to the boiling point of the solvent.

Examples of such solvents or diluents are aliphatic, alicyclic and aromatic hydrocarbons, each of which may optionally be chlorinated, such as, for example, hexane, cyclohexane, petroleum ether, naphtha, benzene, toluene, xylene, methylene chloride, 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, amides such as, for example, dimethylformamide, dimethylacetamide and N-methylpyrrolidone, sulfoxides and sulfones such as, for example, dimethyl sulfoxide and sulfolane.

20

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

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 alkali metal carbonate, for example 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.

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 initially converting these in a conventional way into an activated form such as an acid halide, anhydride or imidazolidine, and then reacting this with an appropriate hydroxyl compound HOR^7 . This reaction can be carried out in the conventional solvents and often requires addition of a base such as, for example, triethylamine, pyridine, imidazole or diazabicycloundecene. These two steps can also be simplified, for example, by allowing the carboxylic acid to act in the presence of a dehydrating agent such as a carbodiimide on the hydroxyl compound.

It is also possible to prepare compounds of the formula I by starting from salts of the corresponding carboxylic acids, i.e. from compounds of the formula I in which R^1 is a COOM group, where

11

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 R^1-D where D is a conventional nucleofugic leaving group, for example halogen such as chlorine, bromine, iodine or optionally halogen-, alkyl- or haloalkyl-substituted aryl- or alkylsulfonyl such as, for example, toluenesulfonyl and methylsulfonyl or another equivalent leaving group. Compounds of the formula R^1-D with a reactive substituent D are known or can easily be obtained with general expert knowledge. This reaction can be carried out in conventional solvents and is advantageously effected with addition of a base, in which case those mentioned above are suitable.

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

20 Compounds of the formula I in which R^1 is tetrazolyl can be prepared as described in WO 96/11914. Further possibilities are mentioned, for example, in: Synthesis, 767 (1993); J. Org. chem. 56, 2395 (1991).

25 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 mixtures thereof - are those in which the substituents have the following meanings:

30 R^2 phenyl or phenoxy, each of which may carry one to three of the following radicals: halogen, C_1-C_4 -alkyl, C_1-C_4 -haloalkyl, C_1-C_4 -alkoxy, C_1-C_4 -alkylthio, C_1-C_4 -haloalkoxy, C_1-C_4 -alkylcarbonyl, C_1-C_4 -alkoxycarbonyl, C_1-C_4 -alkyl, C_1-C_4 -haloalkyl, C_1-C_4 -alkoxy, C_1-C_4 -haloalkoxy, C_1-C_4 -alkylthio, phenyl which in turn may carry one to three of the following radicals: halogen, C_1-C_4 -alkyl, C_1-C_4 -haloalkyl, C_1-C_4 -alkoxy, C_1-C_4 -haloalkoxy, C_1-C_4 -alkylthio;

40 a five- or six-membered heteroaromatic system which contains one nitrogen atom and/or one sulfur or oxygen atom and which may carry one to two of the following radicals: halogen, C_1-C_4 -alkyl, C_1-C_4 -haloalkyl, C_1-C_4 -alkoxy, C_1-C_4 -haloalkoxy, C_1-C_4 -alkylthio, phenyl which in turn may carry one to three of the following radicals: halogen, C_1-C_4 -alkyl, C_1-C_4 -haloalkyl, C_1-C_4 -alkoxy, C_1-C_4 -haloalkoxy, C_1-C_4 -alkylthio;

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C₅-C₆-cycloalkyl.

R³ hydrogen;

- 5 C₁-C₈-alkyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl or C₃-C₈-cycloalkyl, it being possible for each of these radicals to be substituted one or more times by: hydroxyl, halogen, C₁-C₄-alkoxy, C₁-C₄-alkylthio, C₁-C₄-haloalkoxy, C₁-C₄-alkylcarbonyl, C₁-C₄-alkoxycarbonyl,
- 10 (C₁-C₄-alkyl)NHcarbonyl, (C₁-C₄-alkyl)₂Ncarbonyl, amino, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂, phenoxy or phenyl, hetaryl, five- or six-membered, containing one to three nitrogen atoms and/or one sulfur or oxygen atom, it being possible for said aryl and hetaryl radicals to be substituted once to three
- 15 times by: halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, R⁹, C₁-C₄-alkoxycarbonyl, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂, methylenedioxy, ethylenedioxy, C₁-C₄-alkylthio;
- 20 phenyl or naphthyl, each of which can be substituted by one or more of the following radicals: halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₁-C₄-alkylthio, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂, methylenedioxy or ethylenedioxy;
- 25 a five- or six-membered heteroaromatic system which contains one to three nitrogen atoms and/or one sulfur or oxygen atom and which may carry one to two of the following radicals: C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy,
- 30 C₁-C₄-alkylthio, phenyl which may in turn 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, C₁-C₄-alkylthio.
- 35 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, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy,
- 40 C₁-C₄-alkylthio; or
- phenyl or naphthyl which are linked together in ortho positions by a direct linkage, a methylene, ethylene or ethenylene group; or
- 45 cyclohexyl.

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- X and Y (which may be identical or different):
nitrogen or methine; with the proviso that if X = Y = methine
then Z = nitrogen.
- 5 Z nitrogen or CR¹⁰; with the proviso that if Z = nitrogen then
Q = CR¹¹.
- Q nitrogen or CR¹¹.
- 10 R⁹ C₁-C₄-alkyl, C₁-C₄-alkylthio, C₁-C₄-alkoxy, which carry one of
the following radicals: hydroxyl, carbamoyl or
CON(C₁-C₄-alkyl)₂.
- 15 R¹⁰ hydrogen, halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy,
C₁-C₄-haloalkoxy or C₁-C₄-alkylthio, or CR¹⁰ forms together
with CR¹¹ a 5- or 6-membered alkylene or alkenylene ring which
may be substituted by one or two methyl groups and in which
in each case one or more methylene groups can be replaced by
oxygen or sulfur.
- 20 R¹¹ hydrogen, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂, C₁-C₄-alkyl,
C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy,
C₁-C₄-alkylthio, C₅-C₆-cycloalkyl or CR¹¹ forms together with
CR¹⁰ as indicated under R¹⁰ a 5- or 6-membered ring;
- 25 phenyl or phenoxy, each of which may carry one to three of
the following radicals: halogen, C₁-C₄-alkoxy,
C₁-C₄-alkylthio, C₁-C₄-haloalkoxy, C₁-C₄-alkylcarbonyl,
C₁-C₄-alkoxycarbonyl, (C₁-C₄-alkyl)NHcarbonyl,
- 30 (C₁-C₄-alkyl)₂Ncarbonyl, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂;

a five- or six-membered heteroaromatic system which contains
one nitrogen atom and/or one sulfur or oxygen atom and which
may carry one to two of the following radicals: halogen,
- 35 C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy,
C₁-C₄-alkylthio, phenyl which may in turn carry one to three
of the following radicals: halogen, C₁-C₄-alkyl,
C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy,
C₁-C₄-alkylthio.
- 40 A sulfur or oxygen.

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

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- R² phenyl or phenoxy, each of which may carry one to three of the following radicals: halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-alkylthio, C₁-C₄-haloalkoxy;
- 5 a five- or six-membered heteroaromatic system which contains one nitrogen atom and/or one sulfur or oxygen atom and which may carry one to two of the following radicals: halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₁-C₄-alkylthio;
- 10 C₅-C₆-cycloalkyl.
- R³ hydrogen;
- 15 C₁-C₈-alkyl or C₃-C₆-cycloalkyl, it being possible for each of these radicals to be substituted once to three times by: hydroxyl, halogen, C₁-C₄-alkoxy, C₁-C₄-alkylthio, C₁-C₄-haloalkoxy, phenoxy, phenyl, hetaryl, five- or
- 20 six-membered, containing one nitrogen atom and/or one sulfur or oxygen atom, it being possible for said aryl and hetaryl radicals to be substituted once to three times by: halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, R⁹, methylenedioxy, ethylenedioxy, C₁-C₄-alkylthio;
- 25 phenyl or naphthyl, each of which may be substituted by one or more of the following radicals: halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₁-C₄-alkylthio, methylenedioxy or ethylenedioxy;
- 30 a five-membered heteroaromatic system which contains one sulfur or oxygen atom and which may carry one to two of the following radicals: C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₁-C₄-alkylthio.
- 35 R⁴ and R⁵ (which may be identical or different):
- phenyl or naphthyl, each of which may be substituted by one or more of the following radicals: halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy,
- 40 C₁-C₄-alkylthio; or
- phenyl or naphthyl which are connected in ortho positions by a direct linkage or a methylene group.

15

- X and Y (which may be identical or different):
nitrogen or methine; with the proviso that if X = Y = methine
then Z = nitrogen;
- 5 Z nitrogen or CR¹⁰.
- Q CR¹¹.
- 10 R⁹ C₁-C₄-alkyl, C₁-C₄-alkylthio, C₁-C₄-alkoxy, each of which may
carry a hydroxyl group.
- 15 R¹⁰ hydrogen, halogen, methyl, trifluoromethyl, methoxy, or CR¹⁰
forms together with CR¹¹ a 5- or 6-membered alkylene ring
which may be substituted by one or two methyl groups and in
which in each case one or more methylene groups may be
replaced by oxygen or sulfur.
- 20 R¹¹ hydrogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy,
C₁-C₄-haloalkoxy, C₁-C₄-alkylthio, C₅-C₆-cycloalkyl or CR¹¹
forms together with CR¹⁰ as indicated under R¹⁰ a 5- or
6-membered ring.
- A sulfur or oxygen.
- 25 The compounds of the present invention offer a novel potential
treatment of hypertension, pulmonary hypertension, myocardial
infarct, angina pectoris, arrhythmia, acute/chronic kidney
failure, chronic heart failure, renal insufficiency, cerebral
vasospasms, cerebral ischemia, subarachnoid hemorrhages,
30 migraine, asthma, atherosclerosis, endotoxic shock,
endotoxin-induced organ failure, intravascular coagulation,
restenosis after angioplasty and bypass operations, benign
prostate hyperplasia, erectile dysfunction, glaucoma, ischemic
and intoxication-induced kidney failure or hypertension,
35 metastasis and growth of mesenchymal tumors, contrast
agent-induced kidney failure, pancreatitis, gastrointestinal
ulcers.
- The invention further relates to combinations of endothelin
40 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
45 inhibitors are preferred.

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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). Examples
10 of such substances are antibodies directed against VEGF or specific binding proteins or else low molecular weight substances capable of specific inhibition of VEGF release or receptor binding.

15 The aforementioned combinations can be administered concurrently or sequentially. They can be employed either in a single pharmaceutical formulation or else in separate formulations. The administration form may also differ; for example, the endothelin receptor antagonists can be administered orally, and VEGF
20 inhibitors can be administered parenterally.

These combination products are particularly suitable for treating and preventing hypertension and its sequelae, and for treating heart failure.

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

Receptor-binding studies

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

Membrane preparation

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The ET_A or ET_B receptor-expressing CHO cells were grown 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 penicillin and 100 µg/ml
40 streptomycin (Sigma No. P-0781). After 48 hours, the cells were washed with PBS and incubated with 0.05% trypsin-containing PBS at 37°C for 5 minutes. This was followed by neutralization with medium, and the cells were collected by centrifugation at
300 x g.

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For membrane preparation, the cells were adjusted to a concentration of 10^8 cells/ml of buffer (50 mM Tris-HCl buffer, pH 7.4) and then disintegrated with ultrasound (Branson Sonifier 250, 40-70 seconds/constant output 20).

5

Binding assays

For the ET_A and ET_B receptor-binding assay, the membranes were suspended in incubation buffer (50 mM Tris-HCl, pH 7.4 with 5 mM $MnCl_2$, 40 mg/ml bacitracin and 0.2% BSA) in a concentration of 50 μ g of protein per assay mixture and incubated with 25 pM [^{125}I]- ET_1 (ET_A receptor assay) or 25 pM [^{125}I]- ET_3 (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 (Whatman, England) in a Skatron cell harvester (Skatron, Lier, Norway) separated 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 test on vessels for endothelin receptor antagonists

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.

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.

35

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 catheterized.

45

In control animals, intravenous administration of 1 μ g/kg ET_1 results in a marked rise in blood pressure which persists for a lengthy period.

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

5

Oral testing of mixed ET_A and ET_B antagonists:

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

15 After a stabilization period, big endothelin (20 µg/kg, admin. vol. 0.5 ml/kg) or ET1 (0.3 µg/kg, admin. vol. 0.5 ml/kg) is given intravenously. Blood pressure and heart rate are recorded continuously for 30 minutes. The marked and long-lasting changes in blood pressure are calculated as the area under the curve (AUC). To determine the antagonistic effect of the test substances, the AUC for the animals treated with substance is compared with the AUC for the control animals.

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

30 The dosage depends on the age, condition and weight of the patient and on the mode of administration. As a rule, the daily dose of active ingredient is from about 0.5 to 50 mg/kg of body weight on oral administration and from about 0.1 to 10 mg/kg of body weight on parenteral administration.

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The novel compounds can be administered in conventional solid or liquid pharmaceutical forms, e.g. as uncoated or (film-)coated tablets, capsules, powders, granules, suppositories, solutions, ointments, creams or sprays. These are produced in a conventional way. The active ingredients can for this purpose be processed with conventional pharmaceutical aids such as tablet binders, bulking agents, preservatives, tablet disintegrants, flow regulators, plasticizers, wetting agents, dispersants, emulsifiers, solvents, release-slowing agents, antioxidants and/or propellant gases (cf. H. Sucker et al.: Pharmazeutische Technologie, Thieme-Verlag, Stuttgart, 1991). The administration

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forms obtained in this way normally contain from 0.1 to 90% by weight of active ingredient.

Synthesis examples:

5

Example 1:

4-Methyl-2-methylsulfanyl-6-phenylpyrimidine

- 10 1 molar sodium hydroxide solution (4.10 ml; 4.10 mmol) and iodomethane (86 μ l; 194 mg; 1.37 mmol) were successively added to a solution of 4-methyl-6-phenylpyrimidine-2-thiol (300 mg; 1.37 mmol with 92% purity; synthesized by the method of D.J. Brown et al., Aust. J. Chem. 1984, 37, 155) in methanol (15 ml).
- 15 The mixture was stirred at room temperature for 16 hours; it was then diluted with water (50 ml) and acidified with hydrochloric acid. The mixture was extracted with ethyl acetate (3 $\times$), the combined organic phases were dried over magnesium sulfate, and the solvent was removed in vacuo. 290 mg (1.24 mmol, 91% yield,
- 20 HPLC purity 93%) of the required pyrimidine were obtained.

Example 2:

2-Methanesulfonyl-4-methyl-6-phenylpyrimidine

25

- Oxone[®] (Aldrich; 973 mg; 1.58 mmol) and 4 molar sodium hydroxide solution (0.85 ml; 3.33 mmol) were simultaneously added to a solution of 4-methyl-2-methylsulfanyl-6-phenylpyrimidine (278 mg, 1.19 mmol with 93% purity) in methanol (10 ml) and water (10 ml)
- 30 while cooling in ice in such a way that the pH was always pH 2-3. The mixture was then stirred at room temperature for 16 h, and the reaction was then stopped by dilution with water (75 ml). The mixture was extracted with ether (2 $\times$) and then with ethyl acetate (1 $\times$); the combined organic phases were dried over magnesium
- 35 sulfate, and the solvent was removed in vacuo. 290 mg (1.11 mmol, 93% yield, HPLC purity 95%) of the required sulfonylpyrimidine were obtained; it was used further without further purification.

Example 3:

40

3-Ethoxy-2-(4-methyl-6-phenylpyrimidin-2-yloxy)-3,3-diphenylpropionic acid (I-180)

- 50% sodium hydride (72 mg, 1.51 mmol) and then a solution of
- 45 3-ethoxy-2-hydroxy-3,3-diphenylpropionic acid (150 mg, 0.50 mmol; synthesis described in WO 96/11914) in dimethyl formamide were added to a solution of 2-methanesulfonyl-4-methyl-6-phenyl-

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pyrimidine (145 mg; 0.55 mmol with 95% purity) in anhydrous dimethylformamide (10 ml), and the mixture was stirred at room temperature. After 3 hours, the sulfonylpyrimidine was completely consumed but the hydroxy acid had not yet reacted completely, so
5 that a further 30 mg of the sulfonylpyrimidine were added. After stirring at room temperature for a further hour, the reaction was virtually complete and it was stopped by adding water. Acidification with hydrochloric acid was followed by extraction with ether (3x). The ethereal extracts were extracted with 1 molar
10 potassium hydroxide solution; the aqueous alkaline extracts were combined and again acidified and extracted three times with ether. The ethereal extracts resulting from this were dried over magnesium sulfate and evaporated. The remaining crude product was purified by flash chromatography on silica gel and isolated by
15 freeze drying. 47 mg of the target compound (0.09 mmol; 19% yield) were obtained.

$^1\text{H-NMR}$ (200 MHz, CDCl_3): 7.9-8.1 (m, 2 H); 7.1-7.7 (m, 14 H); 6.5 (s, 1 H); 3.3-3.7 (m, 2 H); 2.5 (s, 3 H); 1.2 (t, 3 H).

20

ESI-MS: $\text{M}^+ = 454$.

Example 4:

25 3-Methoxy-2-(4-methyl-6-phenylpyrimidin-2-yloxy)-3,3-diphenylpropionic acid (I-58)

$^1\text{H-NMR}$ (200 MHz, CDCl_3): 7.9-8.1 (m, 2 H); 7.2-7.7 (m, 14 H); 6.4 (s, 1 H); 3.3 (s, 3 H); 2.5 (s, 3 H).

30

ESI-MS: $\text{M}^+ = 440$.

Example 5:

35 2-Methylsulfanyl-6-phenylpyrimidin-4-ol

1 molar sodium hydroxide solution (15.0 ml; 15.0 mmol) and iodomethane (0.33 ml; 735 mg; 5.18 mmol) were successively added to a solution of 2-mercapto-6-phenylpyrimidin-4-ol (1.06 g; 5.18 mmol; synthesized by the method of H.I. Skulnick et al., J. Med. Chem. 1986, 29 (8), 1499) in methanol (10 ml). The mixture was stirred at room temperature for 30 minutes; it was then diluted with water (100 ml) and acidified with hydrochloric acid. The mixture was extracted with ethyl acetate (3x), the combined
45 organic phases were dried over magnesium sulfate, and the solvent

0050/50031

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was removed in vacuo. 750 mg (3.44 mmol, 66% yield) of the required product were obtained.

Example 6:

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4-Chloro-2-methylsulfanyl-6-phenylpyrimidine

A solution of 2-methylsulfanyl-6-phenylpyrimidin-4-ol (854 mg; 3.91 mmol) in phosphorus oxychloride (10.0 ml) was heated with stirring to 80°C and stirred at this temperature for 2 hours. After cooling, the phosphorus oxychloride was removed in vacuo; the residue was taken up in ethyl acetate and washed with water (3×). The organic phase was dried over magnesium sulfate, and the solvent was evaporated off in vacuo. Evaporation once again with toluene afforded the required chloropyrimidine in 95% purity (950 mg; 3.81 mmol; 97% yield).

Example 7:

20 4-Methoxy-2-methylsulfanyl-6-phenylpyrimidine

30% strength methanolic sodium methanolate solution (4.50 ml) was added to a mixture of 4-chloro-2-methylsulfanyl-6-phenylpyrimidine (950 mg, 3.81 mmol with 95% purity) in anhydrous methanol (15 ml) under a nitrogen atmosphere. The resulting mixture was heated to boiling and refluxed at this temperature for 90 minutes. It was then stirred at room temperature for 16 hours, and the solvent was evaporated off. The residue was mixed with water and extracted with ethyl acetate (3×). The organic phase was dried over magnesium sulfate and evaporated. The required compound was obtained in the form of yellow crystals (854 mg; 3.60 mmol; 94%).

Example 8:

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2-Methanesulfonyl-4-methoxy-6-phenylpyrimidine

Oxone® (Aldrich; 3.32 g; 5.40 mmol) and 4 molar sodium hydroxide solution (2.50 ml; 10.0 mmol) were simultaneously added to a solution of 4-methoxy-2-methylsulfanyl-6-phenylpyrimidine (854 mg, 3.60 mmol) in methanol (15 ml) and water (15 ml) while cooling in ice in such a way that the pH was always at pH 2-3. The mixture was then stirred at room temperature for 16 h, and the reaction was then stopped by dilution with water (75 ml). The mixture was extracted with ethyl acetate (2×); the combined organic phases were dried over magnesium sulfate, and the solvent was removed in vacuo. 928 mg (3.17 mmol, 88% yield, HPLC purity

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90%) of the required sulfonylpyrimidine were obtained; it was used further without further purification.

Example 9:

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3-Methoxy-2-(4-methoxy-6-phenylpyrimidin-2-yloxy)-3,3-diphenylpropionic acid (I-64)

50% sodium hydride (106 mg; 2.20 mmol) was added to a stirred solution of 3-methoxy-2-hydroxy-3,3-diphenylpropionic acid (200 mg; 0.73 mmol; synthesis described in WO 96/11914) in anhydrous dimethylformamide (10 ml) while cooling in ice under a nitrogen atmosphere. After 10 minutes, 2-methanesulfonyl-4-methoxy-6-phenylpyrimidine (320 mg; 1.09 mmol with 90% purity) dissolved in a little dimethylformamide was added. The cooling bath was removed, and the mixture was stirred at room temperature for 16 hours. The reaction was then stopped by cautious addition of water, followed by acidification with hydrochloric acid and extraction with ether (3x). The ethereal extracts were extracted with 1 molar potassium hydroxide solution; the aqueous alkaline extracts were combined and again acidified and extracted three times with ether. The ethereal extracts obtained thereby were dried over magnesium sulfate and, after addition of some hexane, evaporated at low temperature. 317 mg (0.67 mmol; 92% yield) of the target compound were obtained.

¹H-NMR (200 MHz, CDCl₃): 7.9-8.1 (m, 2 H); 7.2-7.6 (m, 13 H); 6.8 (s, 1 H); 6.3 (s, 1 H); 3.9 (s, 3 H); 3.3 (s, 3 H).

30

Melting point: 110-115°C.

Example 10:

35 3-Ethoxy-2-(4-methoxy-6-phenylpyrimidin-2-yloxy)-3,3-diphenylpropionic acid (I-95)

Example 11:

40 3-Methoxy-2-[4-methoxy-6-(4-trifluoromethylphenyl)pyrimidin-2-yloxy]-3,3-diphenylpropionic acid (I-6)

¹H-NMR (200 MHz, d₆-DMSO): 8.3 (d, 2 H); 7.8 (d, 2 H); 7.4 (m app t, 4 H); 7.1 (s, 1 H); 7.0-7.3 (m, 6 H); 6.3 (s, 1 H); 3.9 (s, 3 H); 3.4 (s, 3 H).

45

ESI-MS: $M^+ = 524$.

Example 12:

5 3-Ethoxy-2-[4-methoxy-6-(4-trifluoromethylphenyl)pyrimidin-2-yloxy]-3,3-diphenylpropionic acid (I-159)

$^1\text{H-NMR}$ (200 MHz, CDCl_3): 8.0 (d, 2 H); 7.7 (d, 2 H); 7.6 (m, 2 H); 7.2-7.5 (m, 8 H); 6.8 (s, 1 H); 6.4 (s, 1 H); 4.0 (s, 3 H); 3.5
10 (mc, 2 H); 1.3 (t, 3 H).

ESI-MS: $M^+ = 538$.

Example 13:

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2-[4-(4-Isopropylphenyl)-6-methoxypyrimidin-2-yloxy]-3-methoxy-3,3-diphenylpropionic acid (I-87)

$^1\text{H-NMR}$ (200 MHz, CDCl_3): 7.9 (d, 2 H); 7.6 (m app d, 2 H); 7.2-7.4
20 (m, 10 H); 6.8 (s, 1 H); 6.4 (s, 1 H); 3.9 (s, 3 H); 3.3 (s, 3 H); 2.9 (sept, 1 H); 1.3 (d, 6 H).

ESI-MS: $M^+ = 498$.

25 Example 14:

2,4-Dichloro-6-ethyl-[1,3,5]-triazine

A 2 molar solution of ethylmagnesium chloride in tetrahydrofuran
30 (100 ml; 200 mmol) was added dropwise over the course of 20 minutes to a solution of cyanuric chloride (23.1 g; 184 mmol) in anhydrous toluene (200 ml) while cooling in ice under a nitrogen atmosphere. The temperature gradually rose to 15°C during this; after completion of the addition, the mixture was stirred at room
35 temperature for 2 hours. To stop the reaction, water (40 ml) was very cautiously (NB) added to the mixture and, after addition of solid magnesium sulfate (40 g), it was filtered. The filtrate was evaporated and the residue was extracted with hexane. Evaporation of the hexane was followed by purification by flash
40 chromatography on silica gel; 8.80 g (49.4 mmol; 40% yield) of an oil were obtained.

Example 15:

45 2-Chloro-4-ethyl-6-phenyl-[1,3,5]-triazine

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A solution of 2,4-dichloro-6-ethyl-[1,3,5]-triazine (1.78 g; 10.0 mmol) in anhydrous dichloromethane (50 ml) was cooled to -10 to -20°C under a nitrogen atmosphere and a 2 molar solution of phenylmagnesium chloride in tetrahydrofuran (5.50 ml; 11.0 mmol) was added over the course of 5 minutes. The mixture was allowed to warm to room temperature and was then stirred at room temperature for 1 hour. The reaction was stopped by cautious addition of water (3 ml); this was followed by addition of 3 g of solid magnesium sulfate. After removal of insolubles by filtration, the solvent was evaporated off and the remaining oil was purified by chromatography. 1.35 g of an oil were obtained; despite chromatography, its HPLC purity was only 66% (4.07 mmol; 41% yield).

15 Example 16:

Benzyl 3-ethoxy-2-hydroxy-3,3-diphenylpropionate

Absolute ethanol (10.0 ml) and boron trifluoride etherate (3-4 drops) were successively added to a solution of benzyl 3,3-diphenyloxirane-2-carboxylate (10.0 g; 30.3 mmol with 92% purity) in anhydrous ether (100 ml) while cooling in ice under a nitrogen atmosphere. The cooling bath was removed, and the mixture was stirred at room temperature for 2 hours. Washing with saturated sodium bicarbonate solution and water was followed by drying over magnesium sulfate and evaporation. The residue was purified by crystallization from ether/n-hexane; 6.60 g (17.5 mmol; 58% yield) of the pure hydroxy ester were obtained.

¹H-NMR (270 MHz, CDCl₃): 7.2-7.5 (m, 15 H); 5.2 (d, 1 H); 5.0 (s, 2 H); 3.4 (m, 1 H); 3.2 (m, 1 H); 3.0 (d, 1 H); 1.1 (t, 3 H).

Example 17:

Benzyl 3-ethoxy-2-(4-ethyl-6-phenyl-[1,3,5]-triazin-2-yloxy)-3,3-diphenylpropionate (I-17)

A solution of benzyl 3-ethoxy-2-hydroxy-3,3-diphenylpropionate (376 mg; 1.00 mmol) and 2-chloro-4-ethyl-6-phenyl-[1,3,5]-triazine (497 mg; 1.50 mmol with 66% purity) in anhydrous dimethylformamide (30 ml) was mixed with potassium carbonate (276 mg; 2.00 mmol) and stirred at room temperature for 16 hours. The mixture was diluted with water (150 ml), acidified with citric acid and extracted with ether (2×). The combined ethereal extracts were dried over magnesium sulfate, and the solvent was removed in vacuo; the oily residue was purified by flash

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chromatography. 431 mg (0.77 mmol, 77% yield) of the pure target compound were obtained.

Example 18:

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3-Ethoxy-2-(4-ethyl-6-phenyl-[1,3,5]-triazin-2-yloxy)-3,3-diphenylpropionic acid (I-102)

A solution of benzyl 3-ethoxy-2-(4-ethyl-6-phenyl-[1,3,5]-triazin-2-yloxy)-3,3-diphenylpropionate (430 mg; 0.77 mmol) in ethyl acetate (60 ml) was mixed under protective gas with a palladium/carbon hydrogenation catalyst and then stirred under a hydrogen atmosphere at room temperature for 3 days. The mixture was then filtered to remove catalyst and was evaporated.

15 Crystallization of the oily residue from n-hexane afforded 187 mg (0.40 mmol; 52% yield) of the pure carboxylic acid.

$^1\text{H-NMR}$ (200 MHz, CDCl_3): 8.4 (d, 2 H); 7.2-7.7 (m, 13 H); 6.5 (s, 1 H); 3.5-3.7 (m, 1 H); 3.25-3.45 (m, 1 H); 2.9 (q, 2 H); 20 1.2-1.4 (m, 6 H).

ESI-MS: $\text{M}^+ = 469$.

The following were prepared analogously:

25

Example 19:

2-(4-Ethyl-6-phenyl-[1,3,5]-triazin-2-yloxy)-3-methoxy-3,3-diphenylpropionic acid (I-109)

30

$^1\text{H-NMR}$ (200 MHz, CDCl_3): 8.5 (d, 2 H); 7.2-7.7 (m, 13 H); 6.5 (s, 1 H); 3.3 (s, 3 H); 2.9 (q, 2 H); 1.3 (t, 3 H).

ESI-MS: $\text{M}^+ = 455$.

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Example 20:

2-[4-Ethyl-6-(4-methoxyphenyl)-[1,3,5]-triazin-2-yloxy]-3-methoxy-3,3-diphenylpropionic acid (I-23)

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$^1\text{H-NMR}$ (200 MHz, CDCl_3): 8.4 (d, 2 H); 7.5-7.6 (m, 2 H); 7.2-7.5 (m, 8 H); 7.0 (d, 2 H); 6.4 (s, 1 H); 3.9 (s, 3 H); 3.3 (s, 3 H); 2.9 (q, 2 H); 1.3 (t, 3 H).

45 ESI-MS: $\text{M}^+ = 485$.

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Example 21:

3-Ethoxy-2-[4-ethyl-6-(4-methoxyphenyl)-[1,3,5]-triazin-2-yloxy]-
3,3-diphenylpropionic acid (I-147)

5

¹H-NMR (200 MHz, CDCl₃): 8.4 (d, 2 H); 7.5-7.6 (m, 2 H); 7.2-7.5
(m, 8 H); 7.0 (d, 2 H); 6.5 (s, 1 H); 3.9 (s, 3 H); 3.3-3.7
(m, 2 H); 2.8 (q, 2 H); 1.35 (t, 3 H); 1.25 (t, 3 H).

10 ESI-MS: M⁺ = 499.

Example 22:

2-[4,6-Diphenyl)-[1,3,5]-triazin-2-yloxy]-3-methoxy-3,3-diphenyl-
15 propionic acid (I-29)

¹H-NMR (200 MHz, CDCl₃): 8.6 (d, 4 H); 7.2-7.7 (m, 16 H); 6.5
(s, 1 H); 3.3 (s, 3 H).

20 ESI-MS: M⁺ = 503.

Example 23:

2-[4,6-Diphenyl)-[1,3,5]-triazin-2-yloxy]-3-ethoxy-3,3-diphenyl-
25 propionic acid (I-41)

¹H-NMR (200 MHz, CDCl₃): 8.6 (d, 4 H); 7.2-7.7 (m, 16 H); 6.6
(s, 1 H); 3.3-3.7 (m, 2 H); 1.3 (t, 3 H).

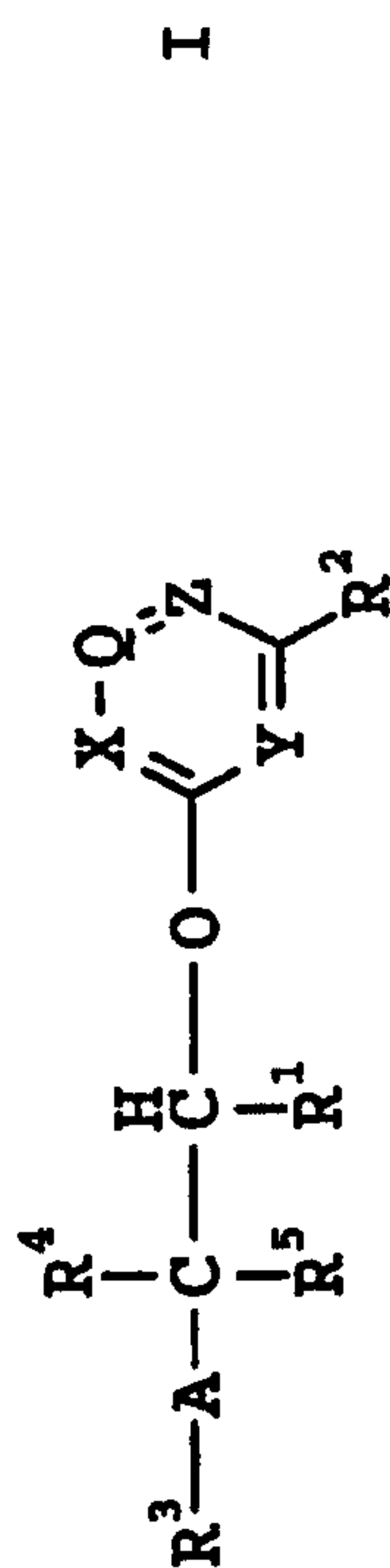
30 ESI-MS: M⁺ = 517.

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

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No.	R ¹	R ⁴ , R ⁵	R ³	R ²	X	Y	Z	Q	A
I-1	COOCH ₃	3-Cl-Phenyl-	H		N	N	CH	C-OMe	O
I-2	COOH	4-OMe-Phenyl-	Methyl		N	N	CH	C-Me	O
I-3	COOH	4-Me-Phenyl-	Ethyl		N	N	CH	C-OMe	O
I-4	COOH	4-CF ₃ O-Phenyl-	i-Propyl		N	N	CH	C-OMe	O
I-5	COOH	3-HO-Phenyl-	CH ₂ =CH-CH ₂ -		N	N	CH	COMe	O
I-6	COOH	Phenyl	Methyl		N	N	CH	C-OMe	O
I-7	COONa	3-SMe-Phenyl-	(CH ₃) ₂ C=CH-CH ₂ -		N	N	N	C-Me	O
I-8	COOH	4-H ₂ N-Phenyl-	CH ₃ -C=C-CH ₂ -		N	N	CH	CH	O
I-9	COOH	Phenyl	Cyclopropyl-		N	N	CH	C-CF ₃	O
I-10	COOH	Phenyl	Cyclopentyl-		N	N	CH	C-NHOMe	O
I-11	COONa	Phenyl	HO-CH ₂ -CH ₂ -		N	N	CH	C-SMe	O
I-12	COOH	Phenyl	CH ₃ -CH(SH)-CH ₂		N	N	CH	C-Et	O
I-13	COOH	Phenyl	HOOC-CH ₂ -CH ₂ -		N	N	CH	C-OEt	O
I-14	COOH	Phenyl	CF ₃ -CH ₂ -		N	N	CH	C-NHOMe	O
I-15	COOCH ₃	Phenyl	4-Me-Cyclohexyl-		N	N	CH	C-Et	O
I-16	COOH	Phenyl	CH ₃ -O-CH ₂ -CH ₂ -		N	N	CH	C-Me	S

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No.	R ¹	R ⁴ , R ⁵	R ³	R ²	X	Y	Z	Q	A
I-17	COOH	Phenyl	Ethyl	Phenyl-	N	N	N	C-Et	O
I-18	COOH	Phenyl	CH ₃ -CH ₂ -S-CH ₂ -CH ₂ -	4-H ₂ NOC-Phenyl-	N	N	CH	C-OMe	O
I-19	COOH	Phenyl	CF ₃ -O-CH ₂ -CH ₂ -	3-(Acetyl-CH ₂)-Phenyl-	N	N	CH	C-Me	O
I-20	COOH	4-Cl-Phenyl-	CH ₃ OOC-CH ₂ -CH ₂ -	2-Thienyl-	N	N	CH	C-OMe	O
I-21	COOH	3-Me-4-F-Phenyl-	H ₂ NCO-CH ₂ -CH ₂ -	3-Furyl-	N	N	CH	C-Me	O
I-22	COOH	4-Me-Phenyl-	(Butyl) ₂ NCO-CH ₂ -CH ₂ -	2-Pyrrolyl	N	N	N	C-NHMe	O
I-23	COOH	Phenyl	Methyl	4-OMe-Phenyl-	N	N	N	C-Et	O
I-24	COOH	4-Cl-Phenyl-	Cyclohexyl-CH ₂ -CH ₂ -CH ₂ -	3-Me-2-Furyl	N	N	N	C-N(Me) ₂	O
I-25	COOH	3-F-Phenyl-	Cyclopentyl-CH=CH-CH ₂ -	3-F ₃ C-2-Thienyl	N	N	CH	C-OMe	O
I-26	COOH	2-F-Phenyl-	Phenyl-CH=CH-CH ₂ -	3-Thienyl-	N	N	CH	C-Me	O
I-27	COOH	2-Me-Phenyl-	Phenyl-O-CH ₂ -CH ₂ -	4-OMe-2-Furyl	N	N	CH	C-OEt	O
I-28	COOH	Phenyl	2-Thienyl-CH ₂ -CH ₂ -	4-Thiazolyl-	N	N	CH	C-Allyl	O
I-29	COOH	Phenyl	Methyl	Phenyl-	N	N	N	C-Phenyl	O
I-30	COOH	Phenyl	3-Furyl-CH ₂ -CH ₂ -	5-Oxazolyl-	N	N	CH	C-OMe	S
I-31	COOH	Phenyl	2-Thiazolyl-CH ₂ -CH ₂ -	3-OMe-Phenyl	N	N	CH	C-OMe	O
I-32	COOH	Phenyl	4-F-Phenyl-CH ₂ -CH ₂ -	2-OMe-Phenyl	N	N	CH	C-OPropyl	O
I-33	COOH	Phenyl	3,4-Di-OMe-Phenyl-CH ₂ -CH ₂ -	2-Et-Phenyl-	N	N	CH	C-Et	O
I-34	COOH	Phenyl	3-NC-Phenyl-CH ₂ -CH ₂ -	3-Me-4-OMe-Phenyl-	N	N	CH	C-Me	O
I-35	COONa	Phenyl	Methyl	4-OMe-Phenyl-	N	CH	N	C-OMe	O
I-36	CONHSO ₂ CH ₃	Phenyl	Methyl	Phenyl-	N	CH	N	OMe	O
I-37	COOH	Phenyl	4-Me-Phenyl-CH ₂ -	3-Et-Phenyl	N	N	CH	C-OMe	O
I-38	COOH	Phenyl	4-OEt-Phenyl-CH ₂ -	4-OMe-Cyclohexyl-	N	N	CH	C-OMe	O

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No.	R ¹	R ⁴ , R ⁵	R ³	R ²	X	Y	Z	Q	A
I-39	COOH	Phenyl	3-Cl-4-Me-Phenyl-CH ₂ -	Cyclopropyl-	N	N	CH	C-Me	O
I-40	COOCH ₃	Phenyl	2-CF ₃ -Phenyl-CH ₂ -CH ₂	Cyclopentyl-	N	N	CH	C-Me	O
I-41	COOH	Phenyl	Ethyl	Phenyl-	N	N	N	C-Phenyl	O
I-42	COOH	Phenyl	4-CF ₃ -O-Phenyl-CH ₂ -CH ₂ -CH ₂ -	3-Me-Cyclohexyl	N	N	CH	C-OMe	O
I-43	Tetrazolyl	Phenyl	Methyl	4-F-Phenyl-	N	N	CH	OMe	O
I-44	COOH	3-Me-Phenyl	Methyl	3-Cl-Phenyl-	N	N	N	OMe	O
I-45	COOH	Phenyl	3-HS-Phenyl-CH ₂ -CH ₂ -	4-i-Propyl-Phenyl	N	N	C-CH ₂ -CH ₂ -CH ₂ -C		O
I-46	COOH	Phenyl	4-HOOC-Phenyl-O-CH ₂ -CH ₂ -	3-OEt-4-OMe-Phenyl-	N	N	C-CH ₂ -CH ₂ -O-C		O
I-47	COOH	Phenyl	2-HO-Phenyl-CH ₂ -	4-F ₃ C-Phenyl-	N	N	C-CH ₂ -CH ₂ -S-C		O
I-48	COOH	Phenyl	3-H ₂ N-Phenyl-CH ₂ -CH ₂ -	2-SMe-Phenyl-	N	N	CH	C-CF ₃	O
I-49	COOH	Phenyl	4-(HOOC-CH ₂)-Phenyl-CH ₂ -	4-Me-Phenyl-	N	N	CH	C-OMe	O
I-50	COOH	4-F-Phenyl	Methyl	3-Br-Phenyl-	N	N	C-Me	C-Me	O
I-51	COOH	Phenyl	Methyl	4-OMe-Phenyl-	N	CH	N	C-Et	O
I-52	COOH	2-Me-Phenyl	3-CH ₃ OOO-Phenyl-CH ₂ -CH ₂	3-OMe-Phenyl-	N	N	N	C-Et	S
I-53	COOH	Phenyl	4-Me-2-Furyl-CH ₂ -	Benzyl	N	N	CH	C-Me	O
I-54	COOH	Phenyl	3,4-Methylenedioxyphenyl-CH ₂ -	4-OMe-Phenyl-O-	N	N	CH	CH	O
I-55	COOH	Phenyl	3,4-Ethylenedioxyphenyl-CH ₂ -CH ₂	3-Me-Phenyl-O-	N	N	CH	C-OMe	O
I-56	COOH	Phenyl	3-Me-4-SMe-Phenyl-CH ₂ -CH ₂ -	Benzyl-	N	N	CH	C-OMe	O
I-57	COOH	Phenyl	Methyl	4-Et-Phenyl-	N	N	CH	N	O
I-58	COOH	Phenyl	Methyl	Phenyl-	N	N	CH	C-Me	O
I-59	COOH	Phenyl	Phenyl-	Phenyl-	N	N	CH	C-Oet	O
I-60	COOH	Phenyl	2-Naphthyl-	Phenyl-O-	N	N	CH	C-SMe	O

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No.	R ¹	R ⁴ , R ⁵	R ³	R ²	X	Y	Z	Q	A
I-61	COOH	4-Cl-Phenyl-	4-Cl-Phenyl-	3-F-Phenyl-	N	N	N	C-N(Me) ₂	O
I-62	COOH	3-Me-4-F-Phenyl-	3-NC-Phenyl-	2,3-Di-Cl-Phenyl-	N	N	CH	C-Et	S
I-63	COOH	4-Me-Phenyl-	3-HO-Phenyl-	4-HO-Phenyl-	N	N	CH	C-Me	O
I-64	COOH	Phenyl	Methyl	Phenyl-	N	N	CH	C-OMe	O
I-65	COOH	4-Cl-Phenyl-	3,4,5-Tri-Me-Phenyl-	4-OMe-Phenyl-	N	N	CH	C-OMe	O
I-66	COOH	3-F-Phenyl-	4-H ₂ N-Phenyl-	4-OMe-Phenyl-O-	N	N	CH	C-Me	O
I-67	COOH	2-F-Phenyl-	3-F ₃ C-Phenyl-	3,4-Di-OMe-Phenyl-	N	N	CH	C-CF ₃	O
I-68	COOH	2-Me-Phenyl-	3,4-Di-OMe-Phenyl-	3-SMe-Phenyl-	N	N	CH	C-OMe	O
I-69	COOH	Phenyl	4-(F ₂ HC)-O-Phenyl-	4-CF ₃ -Phenyl-	N	N	CH	C-OMe	O
I-70	COOC ₂ H ₅	Phenyl	Methyl	3-Me-Phenyl-	N	N	CH	C-Me	O
I-71	COOH	Phenyl	Methyl	4-OMe-Phenyl-	N	N	CH	C-Me	O
I-72	COOH	Phenyl	3-SMe-4-OMe-Phenyl	3-CH ₃ -CO-Phenyl-	N	N	CH	C-OMe	O
I-73	COOH	Phenyl	3-MeNH-Phenyl-	3-(HOOC-CH ₂)-Phenyl	N	N	CH	C-Me	O
I-74	COOH	Phenyl	3,4-Methylenedioxyphenyl-	2-CH ₃ OOC-Phenyl-	N	N	N	C-N(Me) ₂	O
I-75	COOH	Phenyl	3,4-Ethylenedioxyphenyl-	3-H ₂ N-Phenyl-	N	N	CH	C-Me	O
I-76	COOH	Phenyl	4-Cl-2-Naphthyl	4-H ₂ NOC-Phenyl-	N	N	CH	C-Oet	O
I-77	COOH	Cyclohexyl	Methyl	2-OMe-Phenyl-	N	CH	CH	N	O
I-78	COOH	Phenyl	Methyl	3,4-Methylenedioxy-phenyl	N	CH	CH	N	S
I-79	COOH	Phenyl	H	3-(Acetyl-CH ₂)-Phenyl-	N	N	CH	C-Et	O
I-80	COOH	Phenyl	CH ₃ -CH(CH ₃)-CH ₂ -	2-Thienyl-	N	N	CH	C-OMe	O
I-81	COOH	Phenyl	i-Propyl	3-Furyl-	N	N	CH	C-Et	O
I-82	COOH	Phenyl	Butyl	2-Pyrrolyl	N	N	CH	C-OMe	O

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No.	R ¹	R ⁴ , R ⁵	R ³	R ²	X	Y	Z	Q	A
I-83	COOH	4-F-Phenyl	CH ₃ -CH=CH-CH ₂ -	3-Me-2-Furyl	N	N	CH	C-OMe	O
I-84	COOH	3-F-Phenyl	Methyl	3,4-Di-Me-Phenyl-	N	N	CH	N	O
I-85	COOH	3-OMe-Phenyl	Methyl	4-Me-Phenyl-	N	N	CH	N	O
I-86	COOCH ₃	4-F-Phenyl	(CH ₃) ₂ C=CH-CH ₂ -CH ₂ -	3-F ₃ C-2-Thienyl	N	N	CH	C-Et	O
I-87	COOH	Phenyl	Methyl	4-i-Propyl-Phenyl-	N	N	CH	C-OMe	O
I-88	COOH	4-Cl-Phenyl	CH ₃ -CH ₂ -C=C-CH ₂ -	3-Thienyl-	N	N	CH	C-OMe	O
I-89	COOH	4-Me-Phenyl	Cyclopropyl-	4-OMe-2-Furyl	N	N	CH	C-OMe	O
I-90	COOH	4-OMe-Phenyl	3-Me-Cyclopentyl-	4-Thiazolyl-	N	N	CH	C-OMe	O
I-91	COOH	4-Me-Phenyl	HO-CH-CH(OH)-CH ₂ -	5-Oxazolyl-	N	N	CH	C-Me	O
I-92	COOH	Phenyl	Methyl	3-Me-Phenyl-	N	CH	CH	C-CF ₃	O
I-93	COOH	3-F-Phenyl	Methyl	4-Et-Phenyl-	CH	CH	N	C-Me	O
I-94	COOH	Phenyl	HS-CH ₂ -CH ₂ -CH ₂ -	3-OMe-Phenyl	N	N	CH	C-Et	O
I-95	COOH	Phenyl	Ethyl	Phenyl-	N	N	CH	C-OMe	O
I-96	COOH	3-CF ₃ -Phenyl	CF ₃ -CF ₂ -	2-OMe-Phenyl	N	N	CH	C-OMe	O
I-97	COOH	Phenyl	HOOC-CH ₂ -CH ₂ -CH ₂ -	2-Et-Phenyl-	N	N	CH	C-Me	O
I-98	COOH	4-F-Phenyl	4-OMe-Cyclohexyl-	3-Me-4-OMe-Phenyl-	N	N	CH	C-Me	O
I-99	COOH	Phenyl	CH ₃ -CH ₂ -O-CH ₂ -CH ₂ -	3-Et-Phenyl	N	N	CH	C-Me	O
I-100	COOH	Phenyl	Methyl	4-OMe-Phenyl	CH	CH	N	C-OMe	O
I-101	CONHSO ₂ CH ₃	Phenyl	Methyl	3,4-Di-OMe-Phenyl-	CH	N	N	C-Et	O
I-102	COOH	Phenyl	Ethyl	Phenyl-	N	N	N	C-Et	O
I-103	COOCH ₃	Phenyl	CH ₃ -S-CH ₂ -CH ₂ -	4-OMe-Cyclohexyl-	N	N	CH	C-OMe	S
I-104	COOH	3-Cl-Phenyl	CF ₃ -O-CH ₂ -CH ₂ -	Cyclopropyl-	N	N	CH	C-OEt	O

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No.	R ¹	R ⁴ , R ⁵	R ³	R ²	X	Y	Z	Q	A
I-105	COOC ₂ H ₅	Phenyl	Ethyl	3-OEt-4-OMe-Phenyl-	N	N	CH	C-OMe	O
I-106	COOH	Phenyl	Ethyl	4-F ₃ C-Phenyl-	N	N	CH	C-OMe	O
I-107	COOH	2-F-Phenyl	CH ₃ OOC-CH ₂ -CH ₂ -CH ₂ -	Cyclopentyl-	N	N	CH	C-OEt	O
I-108	COOH	2-F-Phenyl	H ₂ NCO-CH ₂ -CH ₂ -CH ₂ -	3-Me-Cyclohexyl	N	N	CH	C-Propyl	O
I-109	COOH	Phenyl	Methyl	Phenyl-	N	N	N	C-Et	O
I-110	COOH	2-Me-Phenyl	(Butyl) ₂ NCO-CH ₂ -CH ₂ -CH ₂ -	4-i-Propyl-Phenyl	N	N	CH	C-Et	O
I-111	COOH	Phenyl	Methyl	4-SMe-Phenyl-	N	N	CH	C-OMe	O
I-112	COOCH ₃	2-F-Phenyl	Methyl	3-OMe-Phenyl	N	N	CH	CH	O
I-113	COOH	Phenyl	4-OMe-Cyclohexyl-CH ₂ -CH ₂ -	3-OEt-4-OMe-Phenyl-	N	N	CH	C-Et	O
I-114	COOH	Phenyl	Cyclopentyl-CH ₂ -CH ₂ -	4-F ₃ C-Phenyl-	N	N	CH	C-OMe	O
I-115	COOH	Phenyl	Ethyl	2-SMe-Phenyl-	N	N	CH	C-OMe	O
I-116	COOH	4-Cl-Phenyl	Ethyl	4-Me-Phenyl-	N	N	CH	CH	O
I-117	COOH	4-CF ₃ -Phenyl	3-Cl-Phenyl-CH=CH-CH ₂ -	2-SMe-Phenyl-	N	N	CH	C-OMe	O
I-118	COOH	Phenyl	4-OMe-Phenyl-O-CH ₂ -CH ₂ -	4-Me-Phenyl-	N	N	CH	C-OMe	O
I-119	COOH	Phenyl	3-Thienyl-CH ₂ -CH ₂ -	3-OMe-Phenyl-	N	N	CH	C-Me	S
I-120	COOC ₂ H ₅	3-Cl-Phenyl	Methyl	4-F ₃ C-Phenyl-	N	N	CH	C-Et	O
I-121	COOCH ₃	Phenyl	Methyl	3-OMe-Phenyl-	N	N	CH	C-OEt	O
I-122	COOCH ₃	Phenyl	4-Me-3-Furyl-CH ₂ -CH ₂ -	Benzyl	N	N	CH	C-OMe	O
I-123	COOH	Phenyl	4-Thiazolyl-CH ₂ -CH ₂ -	4-OMe-Phenyl-O-	N	N	CH	C-Me	O
I-124	COOH	4-OCF ₃ -Phenyl	4-Br-Phenyl-CH ₂ -CH ₂ -	3-Me-Phenyl-O-	N	N	CH	C-OCF ₃	O
I-125	COOH	Phenyl	3-OMe-4-OEt-Phenyl-CH ₂ -CH ₂ -	Benzyl-	N	N	CH	C-OCF ₃	S
I-126	COOH	Phenyl	3-NO ₂ -Phenyl-CH ₂ -CH ₂ -	Phenyl-	N	N	CH	C-CF ₃	O

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No.	R ¹	R ⁴ , R ⁵	R ³	R ²	X	Y	Z	Q	A
I-127	COOC ₂ H ₅	Phenyl	Methyl	4-OMe-Phenyl-	N	N	CH	C-Cl	O
I-128	COOH	4-F-Phenyl	Methyl	3-Me-Phenyl-	N	N	CH	C-OMe	O
I-129	COOH	4-F-Phenyl	3,4-Di-Me-Phenyl-CH ₂ -	Phenyl-O-	N	N	CH	C-Me	O
I-130	COOH	Phenyl	3-OEt-Phenyl-CH ₂ -	3-F-Phenyl-	N	N	CH	C-Me	O
I-131	COOH	Phenyl	Ethyl	3-OMe-Phenyl-	N	N	CH	C-Me	O
I-132	COOH	Phenyl	Methyl	Phenyl-	N	N	CH	C-Me	O
I-133	COOH	Phenyl	Methyl	Cyclopentyl-	N	N	CH	C-OMe	O
I-134	COOH	Phenyl	3,4-Di-Cl-Phenyl-CH ₂ -	2,3-Di-Cl-Phenyl-	N	N	CH	C-OMe	O
I-135	COOH	Phenyl	2-F-Phenyl-CH ₂ -CH ₂ -	4-HO-Phenyl-	N	N	CH	C-Me	O
I-136	COOH	Phenyl	4-Cl-Phenyl-CH ₂ -CH ₂ -CH ₂ -	4-OMe-Phenyl-	N	N	CH	C-OMe	O
I-137	CONHSO ₂ Phenyl	4-F-Phenyl	Methyl	4-OMe-Phenyl-	N	N	CH	C-OMe	O
I-138	COOC ₂ H ₅	Phenyl	Methyl	4-OMe-Phenyl-	N	N	CH	C-CF ₃	O
I-139	COOH	Phenyl	3-HS-Phenyl-O-CH ₂ -CH ₂ -	4-OMe-Phenyl-O-	N	N	CH	C-Et	O
I-140	COOH	Phenyl	4-HOOC-Phenyl-CH ₂ -CH ₂ -	3,4-Di-OMe-Phenyl-	N	N	CH	C-Et	O
I-141	COOH	Phenyl	2-HO-Phenyl-CH ₂ -CH ₂ -	3-SMe-Phenyl-	N	N	CH	C-Et	S
I-142	COOH	Phenyl	3-H ₂ N-Phenyl-CH ₂ -	4-CF ₃ -Phenyl-	N	N	CH	C-Et	S
I-143	COOH	Phenyl	4-(H ₂ NOC-CH ₂)-Phenyl-CH ₂ -	3-CH ₃ -CO-Phenyl-	N	N	CH	C-OMe	O
I-144	CONHSO ₂ Phenyl	4-F-Phenyl	Methyl	Phenyl-	N	N	CH	C-Me	O
I-145	COOCH ₃	Phenyl	Methyl	O-Phenyl-	N	N	CH	C-CF ₃	O
I-146	COOH	Phenyl	4-CH ₃ OOOC-Phenyl-CH ₂ -CH ₂ -	3-(HOOC-CH ₂)-Phenyl	N	N	CH	C-OMe	O
I-147	COOH	Phenyl	Ethyl	4-OMe-Phenyl-	N	N	N	C-Et	O
I-148	COOH	Phenyl	3-Me-2-Furyl-CH ₂ -	2-CH ₃ OOOC-Phenyl-	N	N	CH	C-OMe	O

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No.	R ¹	R ⁴ , R ⁵	R ³	R ²	X	Y	Z	Q	A
I-149	COOH	Phenyl	3,4-Methylenedioxyphenyl-CH ₂ -	3-H ₂ N-Phenyl-	N	N	CH	C-Me	O
I-150	COOH	4-F-Phenyl	3,4-Ethylenedioxyphenyl-CH ₂ -	4-H ₂ NOC-Phenyl-	N	N	CH	C-OMe	O
I-151	COOH	Phenyl	3-Me-4-SMe-Phenyl-CH ₂ -CH ₂ -	3-(Acetyl-CH ₂)-Phenyl-	N	N	CH	C-Me	S
I-152	COOH	Phenyl	Ethyl	Benzyl	N	N	CH	C-Me	S
I-153	COOH	Phenyl	Ethyl	4-OMe-Phenyl-O-	N	N	CH	C-OMe	O
I-154	COOH	Phenyl	4-OMe-Phenyl-	2-Thienyl-	N	N	CH	C-Me	O
I-155	COOH	4-F-Phenyl	2-Naphthyl-	3-Furyl-	N	N	CH	C-OMe	O
I-156	COOH	Phenyl	3,4-Di-Cl-Phenyl-	2-Pyrrolyl	N	N	CH	C-OMe	O
I-157	COOH	Phenyl	4-NC-Phenyl-	3-Me-2-Furyl	N	N	CH	C-Me	O
I-158	COOH	Phenyl	4-HO-Phenyl-	3-F ₃ C-2-Thienyl	N	N	CH	C-Et	O
I-159	COOH	Phenyl	Ethyl	4-F ₃ C-Phenyl-	N	N	CH	C-OMe	O
I-160	COOH	Phenyl	Ethyl	3-Me-Phenyl-O-	N	N	CH	C-OMe	O
I-161	COOH	Phenyl	Methyl	4-OMe-Phenyl	N	CH	N	C-OMe	S
I-162	COOH	Phenyl	3,5-Di-Me-Phenyl-	3-Thienyl-	N	N	N	N(Me) ₂	O
I-163	COOH	Phenyl	3-H ₂ N-Phenyl-	4-OMe-2-Furyl	N	N	CH	C-OMe	O
I-164	COOH	Cyclohexyl	4-F ₃ C-Phenyl-	4-Thiazolyl-	N	N	CH	C-OMe	O
I-165	COOH	Phenyl	3,4-Di-OMe-Phenyl-	5-Oxazolyl-	N	N	CH	C-Me	O
I-166	COOCH ₃	2-F-Phenyl	4-CF ₃ -O-Phenyl-	3-OMe-Phenyl	N	N	CH	C-OMe	O
I-167	COOH	Phenyl	Methyl	3,4-OMe-Phenyl-	N	CH	N	C-OMe	O
I-168	COOH	Phenyl	Methyl	4-Me-Phenyl-	N	CH	N	C-OMe	O
I-169	COOC ₂ H ₅	3-Cl-Phenyl	3-SMe-4-OEt-Phenyl-	2-OMe-Phenyl	N	N	CH	C-CF ₃	O
I-170	COOH	Phenyl	4-MeNH-Phenyl-	2-Et-Phenyl-	N	N	CH	C-CF ₂ -CF ₃	S

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No.	R ¹	R ⁴ , R ⁵	R ³	R ²	X	Y	Z	Q	A
I-171	COOCH ₃	Phenyl	3,4-Methylenedioxyphenyl	3-Me-4-OMe-Phenyl-	N	N	CH	C-OMe	O
I-172	COOC ₂ H ₅	Phenyl	3,4-Ethylenedioxyphenyl	3-Et-Phenyl	N	N	CH	C-Cl	O
I-173	COOH	3-CF ₃ -Phenyl	2-Me-3-Furyl-	4-OMe-Cyclohexyl-	N	N	CH	C-Me	S
I-174	COOH	Phenyl	Methyl	3-Furyl-	N	N	CH	CH	O
I-175	COOH	Phenyl	Methyl	4-i-Propyl-	N	N	CH	C-Me	O
I-176	COOH	Phenyl	2-Thienyl	Cyclopropyl-	N	N	CH	C-Me	S
I-177	COOH	Phenyl	Methyl	Cyclopentyl-	N	N	CH	C-OEt	O
I-178	COOH	4-Cl-Phenyl	Ethyl	3-Me-Cyclohexyl	N	N	CH	C-OMe	O
I-179	COOH	Phenyl	Ethyl	4-i-Propyl-Phenyl	N	N	CH	Vinyl	O
I-180	COOH	Phenyl	Ethyl	Phenyl-	N	N	CH	C-Me	O

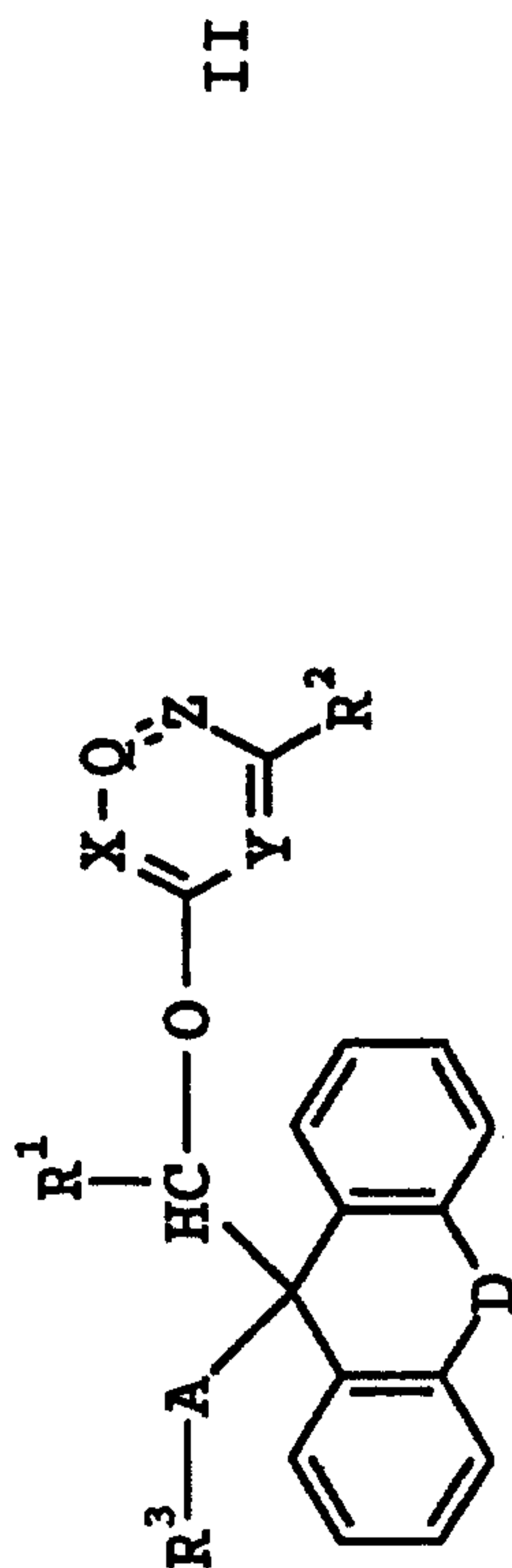


Table II

No.	R ¹	R ⁴ , R ⁵	D	R ³	R ²	X	Y	Z	Q	A
I-1	COOH	Phenyl	Bond	Methyl	Phenyl	N	N	CH	C-OMe	O
I-2	COOH	Phenyl	Bond	Methyl	Phenyl-	N	N	CH	C-Me	O
I-3	COOH	Phenyl	Bond	Ethyl	4-OMe-Phenyl-	N	N	CH	C-OMe	O
I-4	COOH	Phenyl	Bond	i-Propyl	3-F-Phenyl-	N	N	CH	C-OMe	O
I-5	COOH	Phenyl	Bond	CH ₂ =CH-CH ₂ -	4-i-Propyl-Phenyl-	N	N	CH	COMe	O
I-6	COOH	Phenyl	Bond	Methyl	4-F ₃ C-Phenyl-	N	N	CH	C-OMe	O
I-7	COONa	Phenyl	Bond	(CH ₃) ₂ C=CH-CH ₂ -	4-OMe-Phenyl-	N	N	N	C-Et	O
I-8	COOH	Phenyl	CH ₂	Methyl	4-OMe-Phenyl-	N	N	CH	CH	O
I-9	COOH	Phenyl	CH ₂	Methyl	4-OMe-Phenyl-	N	N	CH	C-CF ₃	O
I-10	COOH	Phenyl	CH ₂	Cyclopentyl-	3,4-Di-OMe-Phenyl-	N	N	CH	C-NHOMe	O
I-11	COOH	Phenyl	CH ₂	HO-CH ₂ -CH ₂ -	3-Me-Phenyl-	N	N	CH	C-SMe	O
I-12	COOH	Phenyl	CH ₂	CH ₃ -CH(SH)-CH ₂	4-CF ₃ -Phenyl-	N	N	CH	C-Et	O
I-13	COOH	Phenyl	CH ₂	Ethyl-	3-Me-Phenyl-	N	N	CH	C-Me	O
I-14	COOH	Phenyl	CH ₂	HOOC-CH ₂ -CH ₂ -	3-HO-Phenyl	N	N	CH	C-OMe	O

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Example 24:

The binding assay described above was used to measure receptor
5 binding data for the compounds listed below.

The results are shown in Table 2.

Table 2

10

Receptor binding data (K_i values)

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Compound	ET _A [nM]
I-180	83
I-102	130
I-109	133
I-23	5
I-147	14

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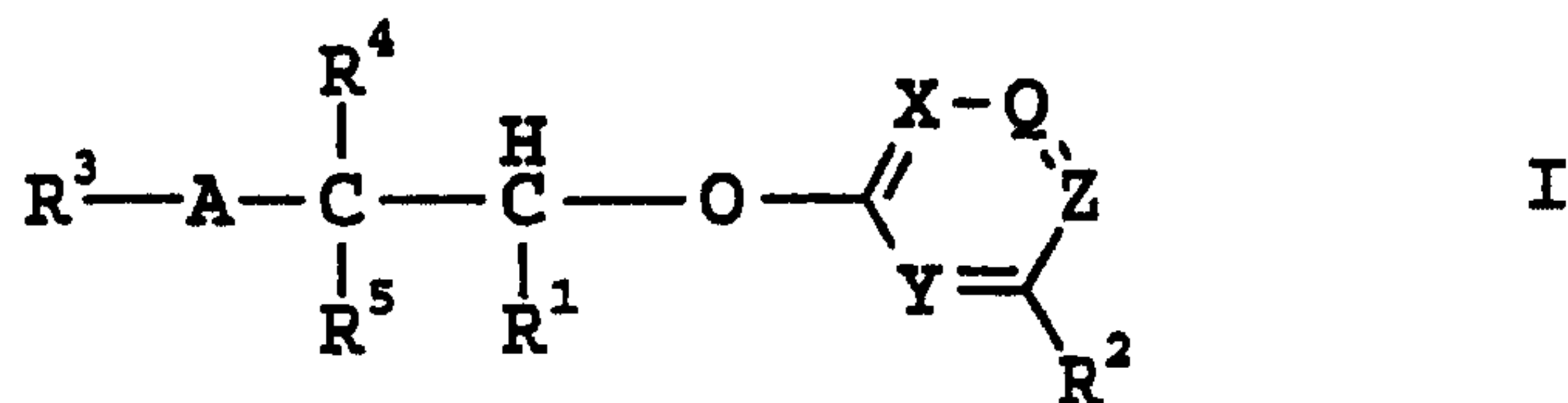
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38.

We claim:

1. A carboxylic acid derivative of the formula I

in which R¹ is tetrazolyl or a group

in which R has the following meaning:

a) a radical OR⁶ in which R⁶ is:

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

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

A C₂-C₆-alkenyl or C₃-C₆-alkynyl group, it being possible for these groups in turn to carry one to five halogen atoms;

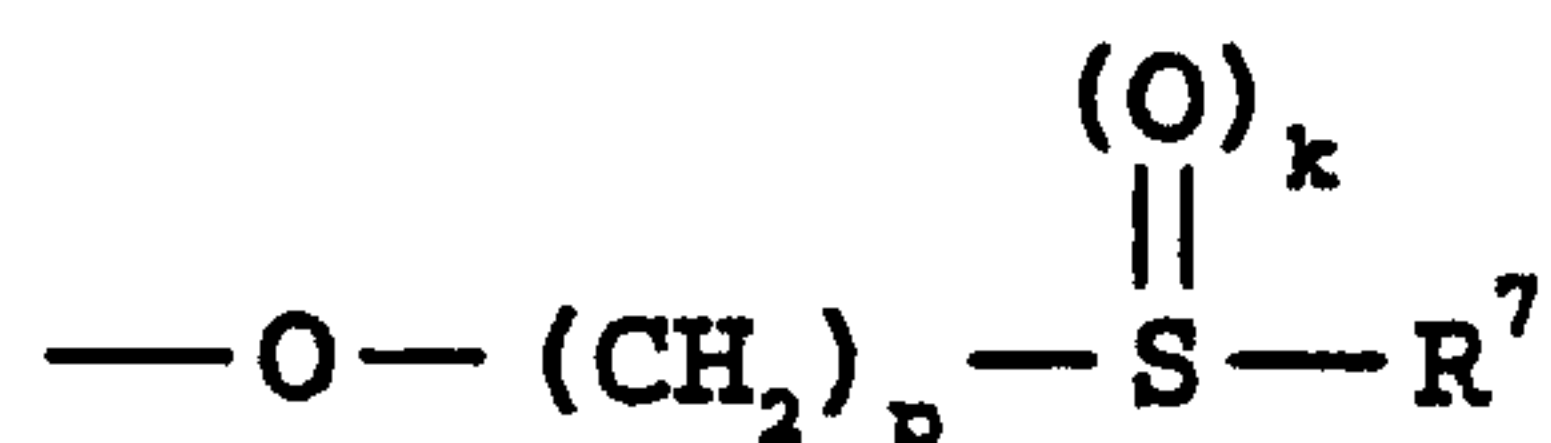
R⁶ can also be a phenyl radical which may carry one to five halogen atoms and/or one to three of the following radicals: nitro, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, hydroxyl, C₁-C₄-alkoxy, mercapto, C₁-C₄-alkylthio, amino, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂;

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

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c) a group



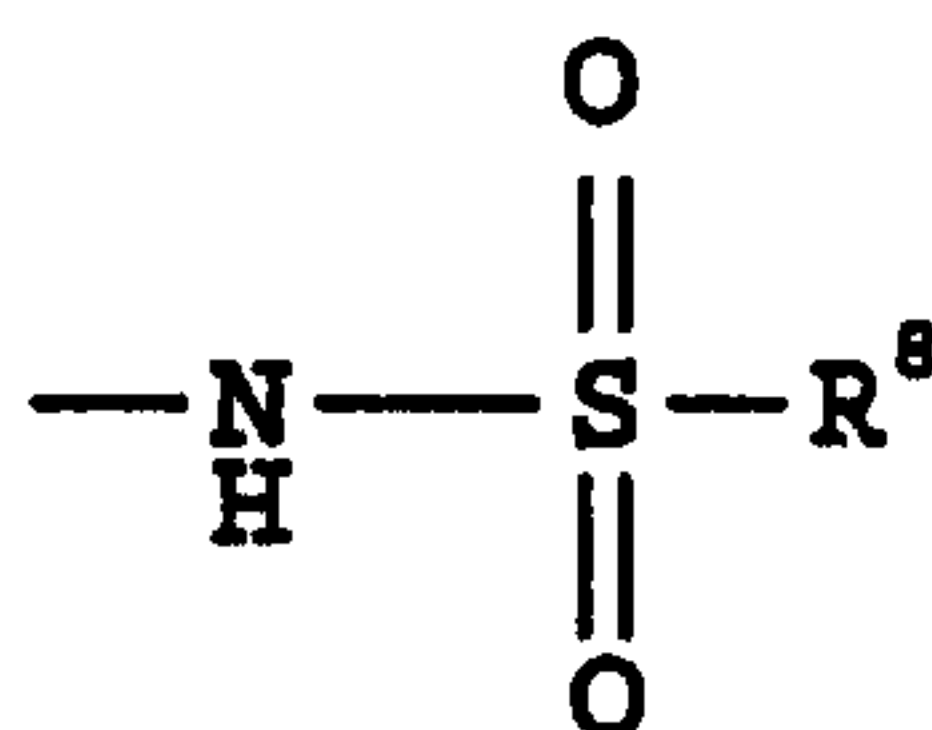
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in which k assumes the values 0, 1 and 2, p assumes the values 1, 2, 3 and 4, and R⁷ is

10 C₁-C₄-alkyl, C₃-C₈-cycloalkyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl or 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,
 hydroxyl, C₁-C₄-alkoxy, C₁-C₄-alkylthio, mercapto, amino,
 15 NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂;

d) a radical

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in which R⁸ is:

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C₁-C₄-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₃-C₈-cycloalkyl, it being possible for these radicals to carry a C₁-C₄-alkoxy, C₁-C₄-alkylthio and/or a phenyl radical as mentioned under c);

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

R² is benzyl, benzyloxy, phenyl or phenoxy, in each case optionally substituted; or

40

a five- or six-membered heteroaromatic system containing one to three nitrogen atoms and/or one sulfur or oxygen atom, in each case optionally substituted; or C₃-C₈-cycloalkyl, optionally substituted;

45

R³ is hydrogen;

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- C₁-C₈-alkyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl or C₃-C₈-cycloalkyl, it being possible for each of these radicals to be substituted one or more times by:
- 5 hydroxyl, mercapto, carboxyl, halogen, nitro, cyano, C₁-C₄-alkoxy, C₃-C₆-alkenyloxy, C₃-C₆-alkynyloxy, C₁-C₄-alkylthio, C₁-C₄-haloalkoxy, C₁-C₄-alkylcarbonyl, C₁-C₄-alkoxycarbonyl, (C₁-C₄-alkyl)NHcarbonyl, (C₁-C₄-alkyl)₂-Ncarbonyl, C₃-C₈-alkylcarbonylalkyl, amino, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂, phenoxy or phenyl,
- 10 hetaryl, five- or six-membered, containing one to three nitrogen atoms and/or one sulfur or oxygen atom, it being possible for all said aryl and hetaryl radicals optionally to be substituted; or
- 15 phenyl or naphthyl, optionally substituted; or
- a five- or six-membered heteroaromatic system containing one to three nitrogen atoms and/or one sulfur or oxygen atom, in each case optionally substituted;
- 20 R⁴ and R⁵ (which may be identical or different) are:
- phenyl or naphthyl, optionally substituted; or
- 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
- 30 C₃-C₇-cycloalkyl;
- X and Y (which can be identical or different) are: nitrogen or methine; with the proviso that if X = Y = methine then Z = nitrogen;
- 35 Z is nitrogen or CR¹⁰;
- Q is nitrogen or CR¹¹; with the proviso that if X = Y = Z = nitrogen then Q = CR¹¹;
- 40 R¹⁰ is hydrogen, halogen, hydroxyl, NH₂, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂, 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 CR¹⁰ forms
- 45 together with CR¹¹ a 5- or 6-membered alkylene or alkenylene ring which may be substituted by one or two C₁-C₄-alkyl groups and in which in each case one or more

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methylene groups can be replaced by oxygen, sulfur, -NH or -N(C₁-C₄-alkyl); or

phenyl, optionally substituted;

5

R¹¹ is hydrogen, hydroxyl, NH₂, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂, halogen, C₁-C₄-alkyl, C₂-C₄-alkenyl, C₂-C₄-alkynyl, C₃-C₆-alkenyloxy, C₁-C₄-alkylcarbonyl, C₁-C₄-alkoxycarbonyl, C₁-C₄-hydroxyalkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, -NH-O-C₁-C₄-alkyl, C₁-C₄-alkylthio, C₃-C₈-cycloalkyl or CR¹¹ forms, as indicated under R¹⁰, together with CR¹⁰ a 5- or 6-membered ring;

10

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phenyl or phenoxy, in each case optionally substituted; or

20

a five- or six-membered heteroaromatic system containing one to three nitrogen atoms and/or one sulfur or oxygen atom, in each case optionally substituted;

A is sulfur or oxygen;

25

and the physiologically tolerated salts, and the enantiomerically pure and diastereomerically pure forms.

2. The use of a carboxylic acid derivative I as claimed in claim 1 for treating diseases.

30

3. The use of a compound I as claimed in claim 1 as endothelin receptor antagonist.

35

4. The use of a carboxylic acid derivative I as claimed in claim 1 for producing drugs for treating diseases in which elevated endothelin levels occur.

40

5. The use of a carboxylic acid derivative I as claimed in claim 1 for producing drugs for treating diseases in which endothelin contributes to the development and/or progression.

45

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

42

7. A combination of a carboxylic acid derivative of the formula I as claimed in claim 1 and one or more active ingredients selected from inhibitors of the renin-angiotensin system such as renin inhibitors, angiotensin II antagonists, angiotensin converting enzyme (ACE) inhibitors, mixed ACE/neutral endopeptidase (NEP) inhibitors, β blockers, diuretics, calcium channel blockers and VEGF-blocking substances.
8. A pharmaceutical preparation for oral, parenteral or intraperitoneal use, comprising at least one carboxylic acid derivative I as claimed in claim 1, per single dose, in addition to conventional pharmaceutical excipients.

