

Novel carboxylic acid derivatives, their preparation and use as mixed ET_A/ET_B receptor antagonists

5 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 vascular endothelium. Endothelin
 10 exists in three isoforms, ET-1, ET-2 and ET-3. "Endothelin" or "ET" hereinafter refers to one or all isoforms of endothelin. Endothelin is a potent vasoconstrictor and has a strong effect on vascular tone. It is known that this vasoconstriction is caused by the binding of endothelin to its receptor (Nature, 332 (1988)
 15 411-415; FEBS Letters, 231 (1988) 440-444 and Biochem. Biophys. Res. Commun., 154 (1988) 868-875).

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

30 The literature at present describes at least two subtypes of endothelin receptors, ET_A and ET_B receptors, (Nature 348 (1990) 730 and 732). According to this, substances which inhibit the binding of endothelin to the two receptors ought to antagonize
 35 the physiological effects of endothelin and therefore represent valuable drugs.

WO 96/11914 describes carboxylic acid derivatives which, however, bind with high affinity to the ET_A receptor and with a
 40 considerably lower affinity to the ET_B receptor (called ET_A-specific antagonists).

We refer here to antagonists as ET_A-specific when their affinity for the ET_A receptor is at least ten times higher than their
 45 affinity for the ET_B receptor.

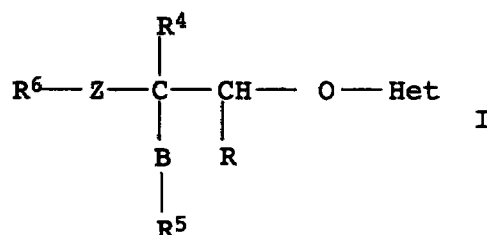
It is an object of the present invention to provide endothelin

receptor antagonists which bind with roughly the same affinity to the ET_A and the ET_B receptors (called mixed antagonists).

Roughly the same affinity for the receptors means that the ratio of the affinities is greater than 0.1 and less than 10.

The invention relates to carboxylic acid derivatives of the formula I carboxylic acid derivatives of the formula I [sic]

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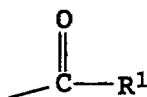


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where the substituents have the following meanings:

R is tetrazole [sic] or a group

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R^1 is a radical OR⁷

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in which R^7 is:

hydrogen, the cation of an alkali metal, the cation of an alkaline earth metal or a physiologically tolerated organic

30 ammonium ion;

C_3 - C_8 -cycloalkyl, C_1 - C_8 -alkyl,

CH_2 -phenyl, unsubstituted or substituted,

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C_3 - C_6 -alkenyl or a C_3 - C_6 -alkynyl group, unsubstituted or substituted, or

phenyl, unsubstituted or substituted,

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R^2 is hydrogen, hydroxyl, NH_2 , $NH(C_1-C_4-alkyl)$, $N(C_1-C_4-alkyl)_2$, halogen, $C_1-C_4-alkyl$, $C_2-C_4-alkenyl$, $C_2-C_4-alkynyl$, $C_1-C_4-haloalkyl$, $C_1-C_4-alkoxy$, $C_1-C_4-haloalkoxy$ or $C_1-C_4-alkylthio$, or CR^2 is linked to CR^{10} as indicated below to give a 5- or 6-membered ring, or, if Het is a five-membered ring, CR^2 can together with CR^3 be a 5- or 6-membered alkenyl or alkynyl [sic] ring which is

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unsubstituted or substituted;

X is nitrogen or methine;

5 Y is nitrogen or methine;

W is nitrogen or CR¹⁰, where R¹⁰ is hydrogen or C₁₋₄-alkyl, or CR¹⁰ forms together with CR² or CR³ a 5- or 6-membered alkylene or alkenylene ring which is unsubstituted or substituted and in which in each case one or more methylene groups can be replaced by oxygen, sulfur, -NH or -N(C₁₋₄-alkyl);

15 R³ is hydrogen, hydroxyl, NH₂, NH(C₁₋₄-alkyl), N(C₁₋₄-alkyl)₂, halogen, C₁₋₄-alkyl, C₂₋₄-alkenyl, C₂₋₄-alkynyl, C₁₋₄-haloalkyl, C₁₋₄-alkoxy, C₁₋₄-haloalkoxy, C₁₋₄-alkylthio; or CR³ is linked to CR¹⁰ as indicated above to give a 5- or 6-membered ring;

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

phenyl or naphthyl, unsubstituted or substituted, or

25 phenyl or naphthyl which are linked together in the 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

C₃₋₈-cycloalkyl, unsubstituted or substituted;

30

R⁶ is hydrogen, C₁₋₈-alkyl, C₃₋₈-alkenyl or C₃₋₈-alkynyl, it being possible for each of these radicals to be substituted one or more times by: halogen, hydroxyl, mercapto, carboxyl, nitro, amino, cyano, C₁₋₄-alkoxy, C₃₋₆-alkenyloxy,

35 C₃₋₆-alkynyloxy, C₁₋₄-alkylthio, C₁₋₄-haloalkoxy, C₁₋₄-alkylcarbonyl, C₁₋₄-alkoxycarbonyl, C₃₋₈-alkylcarbonylalkyl, NH(C₁₋₄-alkyl), N(C₁₋₄-alkyl)₂, C₃₋₈-cycloalkyl, hetaryloxy or hetaryl, five- or

40 six-membered, containing one to three nitrogen atoms and/or one sulfur or oxygen atom, phenoxy or phenyl, it being possible for said aryl radicals in turn to be substituted one or more times, eg. one to three times, by halogen, hydroxyl, mercapto, carboxyl, nitro, cyano, C₁₋₄-alkyl, C₁₋₄-haloalkyl, C₁₋₄-alkoxy, C₁₋₄-haloalkoxy, amino, 45 NH(C₁₋₄-alkyl), N(C₁₋₄-alkyl)₂ or C₁₋₄-alkylthio;

phenyl or naphthyl, each of which can be substituted by one

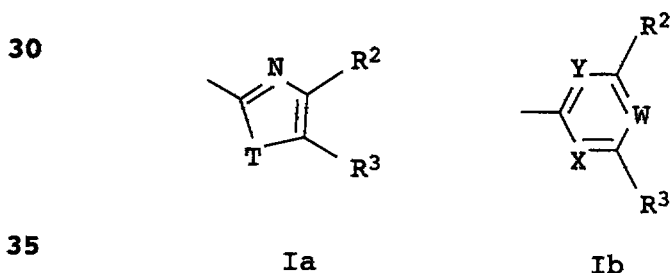
or more of the following radicals: halogen, nitro, cyano, hydroxyl, amino, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, phenoxy, C₁-C₄-alkylthio, C₁-C₄-alkylamino, C₁-C₄-dialkylamino, dioxomethylene [sic] or dioxoethylene [sic];

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

C₃-C₈-cycloalkyl, it being possible for these radicals to be substituted one or more times by: halogen, hydroxyl, mercapto, carboxyl, nitro, cyano, C₁-C₄-alkyl, C₂-C₄-alkenyl, C₂-C₄-alkynyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₁-C₄-alkylthio, C₁-C₄-haloalkoxy;

Z is sulfur or oxygen;
B is C₂-C₄-alkylene

Het is a heterocyclic radical of the formula Ia or Ib



with T = O, S, NR⁸

R⁸ is C₁-C₆-alkyl

and the physiologically tolerated salts and the enantiomerically pure forms.

In this connection and hereinafter, the following definitions apply:

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

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

C₃-C₈-cycloalkyl is, for example, cyclopropyl, cyclobutyl,
5 cyclopentyl, cyclohexyl, cycloheptyl oder cyclooctyl;

C₁-C₄-haloalkyl can be linear or branched, such as fluoromethyl,
difluoromethyl, trifluoromethyl, chlorodifluoromethyl,
dichlorofluoromethyl, trichloromethyl, 1-fluoroethyl,
10 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;

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

20 C₁-C₄-alkyl can be linear or branched, such as methyl, ethyl,
1-propyl, 2-propyl, 2-methyl-2-propyl, 2-methyl-1-propyl, 1-butyl
or 2-butyl;

C₂-C₄-alkenyl can be linear or branched, such as ethenyl,
25 1-propen-3-yl, 1-propen-2-yl, 1-propen-1-yl, 2-methyl-1-propenyl,
1-butenyl or 2-butenyl;

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

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

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

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

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

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

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

Preferred prodrugs are those where the release takes place under conditions like those prevailing in certain compartments of the body, eg. in the stomach, intestine, bloodstream, liver.

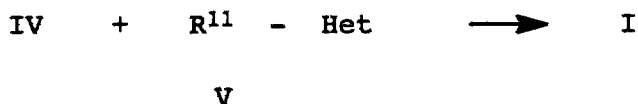
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The compounds according to the invention where the substituents have the meanings stated under formula I can be prepared, for example, by reacting the carboxylic acid derivatives of the formula IV, where the substituents have the stated meaning, with 5 compounds of the formula V.



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R^{11} in formula V is halogen or $\text{R}^{12}-\text{SO}_2-$, where R^{12} can be C_1-C_4 -alkyl, C_1-C_4 -haloalkyl or phenyl. In addition, at least one of the ring members X or Y or Z is nitrogen. The reaction preferably takes place in an inert solvent or diluent with the 15 addition of a suitable base, i.e. of a base which deprotonates the intermediate IV, at a temperature in the range from room temperature to the boiling point of the solvent.

Compounds of type I with $\text{R} = \text{COOH}$ can furthermore be obtained 20 directly when the intermediate IV where R is COOH is deprotonated with two equivalents of a suitable base and reacted with compounds of the 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.

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Examples of such solvents and diluents are aliphatic, alicyclic and aromatic hydrocarbons, each of which may be chlorinated, such as hexane, cyclohexane, petroleum ether, naphtha, benzene, toluene, xylene, methylene chloride, chloroform, carbon 30 tetrachloride, ethyl chloride and trichloroethylene, ethers such as diisopropyl ether, dibutyl ether, methyl tert-butyl ether, propylene oxide, dioxane and tetrahydrofuran, nitriles such as acetonitrile and propionitrile, amides such as dimethylformamide, dimethylacetamide and N-methylpyrrolidone, sulfoxides and 35 sulfones such as dimethyl sulfoxide and sulfolane.

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

40 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, eg. sodium or potassium carbonate, an alkali metal or alkaline earth metal hydroxide such as sodium or potassium hydroxide, an 45 organometallic compound such as butyllithium or an alkali metal amide such as lithium diisopropylamide or lithium amide.

Compounds of the formula I can also be prepared by starting from the corresponding carboxylic acids, i.e. compounds of the formula I where R^1 is COOH, and converting them initially in a conventional way into an activated form, such as an acid halide, 5 anhydride or imidazolidine, and then reacting the latter with an appropriate hydroxyl compound HOR⁷. This reaction can be carried out in conventional solvents and often requires addition of a base, in which case those mentioned above are suitable. These two steps can, for example, also be simplified by allowing the 10 carboxylic acid to act on the hydroxyl compound in the presence of a dehydrating agent such as a carbodiimide.

It is additionally possible to prepare compounds of the formula I by starting from salts of the appropriate carboxylic acids, i.e. 15 from compounds of the formula I where R^1 is a group COR and R 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 R-A, where A is a conventional nucleofugic leaving group, for example halogen such as chlorine, 20 bromine, iodine or unsubstituted or halogen-, alkyl- or haloalkyl-substituted aryl or alkylsulfonyl such as toluenesulfonyl and methylsulfonyl, or another equivalent leaving group. Compounds of the formula R-A with a reactive substituent A are known or can easily be obtained with general expert 25 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.

With a view to the biological effect, preferred carboxylic acid 30 derivatives of the formula I, both as pure enantiomers and pure diastereomers and as mixture thereof, are those where the substituents have the following meanings:

R^1 COOR⁷ in which R⁷ is:
35 hydrogen, the cation of an alkali metal, the cation of an alkaline earth metal or a physiologically tolerated organic ammonium ion;

40 C₃-C₈-cycloalkyl, C₁-C₈-alkyl,

CH₂-phenyl, unsubstituted or substituted,

C₃-C₆-alkenyl or a C₃-C₆-alkynyl group, unsubstituted or 45 substituted, or

phenyl, unsubstituted or substituted. [sic]

- R² hydrogen, hydroxyl, halogen, N(C₁-C₄-alkyl)₂, C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₄-alkylthio, C₁-C₄-haloalkyl, C₁-C₄-haloalkoxy, or CR² is linked to CR¹⁰ as indicated below to form a 5- or 6-membered ring, or, if Het is a five-membered ring, CR² can together with CR³ be a 5- or 6-membered alkenyl or alkylenyl [sic] ring which is unsubstituted or substituted;
- X nitrogen or methine;
- Y nitrogen or methine;
- W nitrogen or CR¹⁰, where R¹⁰ is hydrogen or C₁-C₄-alkyl, or CR¹⁰ forms together with CR² or CR³ 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 a methylene group can be replaced by oxygen or sulfur, such as -CH₂-CH₂-O-, -CH₂-CH₂-CH₂-O-, -CH=CH-O-, -CH=CH-CH₂O-, -CH(CH₃)-CH(CH₃)-O-, -CH=C(CH₃)-O-, -C(CH₃)=C(CH₃)-O-, or -C(CH₃)=C(CH₃)-S;
- At least one of the ring members X, Y or W is nitrogen.
- R³ hydrogen, hydroxyl, halogen, N(C₁-C₄-alkyl)₂, C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₄-alkylthio, C₁-C₄-haloalkyl, C₁-C₄-haloalkoxy, or CR³ is linked to CR¹⁰ as indicated above to give a 5- or 6-membered ring, or, if Het is a five-membered ring, CR² can together with CR³ be a 5- or 6-membered alkenyl or alkylenyl [sic] ring which is unsubstituted or substituted;
- 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, mercapto, amino, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, phenoxy, C₁-C₄-alkylthio, NH(C₁-C₄-alkyl) or N(C₁-C₄-alkyl)₂ or phenyl which may be 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; or
- 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
- C₃-C₈-cycloalkyl;

- R⁶ C₃-C₈-cycloalkyl, it being possible for these radicals to be substituted one or more times by: halogen, hydroxyl, mercapto, carboxyl, nitro, cyano, C₁-C₄-alkoxy, C₁-C₄-alkyl, C₂-C₄-alkenyl, C₂-C₄-alkynyl, C₃-C₆-alkenyloxy, C₃-C₆-alkynyloxy, C₁-C₄-alkylthio, C₁-C₄-haloalkoxy, C₁-C₄-alkylcarbonyl, C₁-C₄-alkoxycarbonyl, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂ or phenyl which can be substituted one or more times, for example one to three times, by halogen, nitro, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy or C₁-C₄-alkylthio;

- phenyl or naphthyl, each of which can be substituted by one or more of the following radicals: halogen, nitro, mercapto, carboxyl, cyano, hydroxyl, amino, C₁-C₄-alkyl, C₂-C₄-alkenyl, C₂-C₄-alkynyl, C₃-C₆-alkenyloxy, C₁-C₄-haloalkyl, C₃-C₆-alkynyloxy, C₁-C₄-alkylcarbonyl, C₁-C₄-alkoxycarbonyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, phenoxy, C₁-C₄-alkylthio, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂, dioxomethylene [sic], dioxoethylene [sic] or phenyl which may be 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;

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

- Z sulfur or oxygen;

B C₂-C₄ alkylene

- 40 Het a heterocyclic group of the formula Ia or Ib with T = 0, S.

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

- 45 R' COOH;
X, Y N;

- W CR¹⁰;
 R², R³ hydrogen, hydroxyl, NH₂, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂,
 halogen, C₁-C₄-alkyl, C₂-C₄-alkenyl, C₂-C₄-alkynyl,
 C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy or
 5 C₁-C₄-alkylthio, or CR² is linked to CR¹⁰ as indicated below
 to give a 5- or 6-membered ring, or, if Het is a
 five-membered ring, CR² can together with CR³ be a 5- or
 6-membered alkylene or alkylene [sic] ring which is
 unsubstituted or substituted;
- 10 R⁴ phenyl which may be substituted by one or more of the
 following radicals: halogen, nitro, cyano, hydroxyl,
 mercapto, amino, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy,
 C₁-C₄-haloalkoxy, phenoxy, C₁-C₄-alkylthio, NH(C₁-C₄-alkyl) or
 15 N(C₁-C₄-alkyl)₂ or phenyl which may be 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; or
- 20 R⁵ phenyl or 3,4-dimethoxyphenyl
- R⁶ C₅-C₇-cycloalkyl, it being possible for these radicals in each
 case to be substituted one or more times by: C₁-C₄-alkoxy,
 C₁-C₄-alkyl, C₁-C₄-alkylthio, halogen, hydroxyl, carboxyl,
 25 cyano, trifluoromethyl, acetyl, or phenyl which may be
 substituted one or more times, eg. one to three times, by
 halogen, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy,
 C₁-C₄-haloalkoxy or C₁-C₄-alkylthio;
- 30 phenyl or naphthyl, each of which may be substituted by one
 or more of the following radicals: halogen, nitro, mercapto,
 carboxyl, cyano, hydroxyl, amino, C₁-C₄-alkyl,
 C₁-C₄-haloalkyl, acetyl, C₁-C₄-alkoxycarbonyl, C₁-C₄-alkoxy,
 C₁-C₄-haloalkoxy, phenoxy, C₁-C₄-alkylthio, NH(C₁-C₄-alkyl),
 35 N(C₁-C₄-alkyl)₂, dioxomethylene [sic], dioxoethylene [sic] or
 phenyl which may be 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;
- 40 a five- or six-membered heteroaromatic system comprising one
 to three nitrogen atoms and/or one sulfur or oxygen atom,
 which may carry one to four halogen atoms and/or one to two
 of the following radicals: C₁-C₄-alkyl, C₁-C₄-haloalkyl,
 45 C₁-C₄-alkoxy, trifluoromethoxy, C₁-C₄-alkylthio, phenyl or
 phenoxy, 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, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy and/or C₁-C₄-alkylthio;

Z sulfur or oxygen;

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B C₃-alkylene

Het Ia with R² and R³ methyl and T = O, S.

- 10 The compounds of the present invention provide a novel therapeutic potential for treating hypertension, pulmonary hypertension, myocardial infarct, angina pectoris, acute/chronic kidney failure, renal insufficiency, cerebral vasospasms, cerebral ischemia, subarachnoid hemorrhages, migraine, asthma, 15 atherosclerosis, endotoxic shock, endotoxin-induced organ failure, intravascular coagulation, restenosis after angioplasty, benign prostate hypoplasia, ischemic and intoxication-induced kidney failure and hypotension, metastasis and growth of mesenchymal tumors, contrast agent-induced kidney failure, 20 pancreatitis, gastrointestinal ulcers.

The invention further relates to combination products comprising endothelin receptor antagonists of the formula I and inhibitors of the renin-angiotensin system. Inhibitors of the renin- 25 angiotensin system are renin inhibitors, angiotensin II antagonists and, in particular, angiotensin converting enzyme (ACE) inhibitors.

- These combination products are particularly suitable for treating 30 and preventing hypertension and its sequelae, and for treating heart failure.

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

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Receptor binding studies

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

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Membrane preparation

- 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 45 serum (PAA Laboratories GmbH, Linz, No. A15-022), 1 mM glutamine (Gibco No. 25030-024), 100 U/ml penicillin and 100 µg/ml streptomycin (Gibco, [sic] Sigma No. P-0781). After 48 hours, the

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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 collection of the cells by centrifugation at 300 x g.

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For the 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 by ultrasound (Branson Sonifier 250, 40-70 seconds/constant/output [sic] 20).

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Binding assays

For the ET_A and ET_B receptor binding assays, the membranes were suspended in the incubation buffer (50 mM tris-HCl, pH 7.4 with 5 mM $MnCl_2$, 40 μ g/ml bacitracin and 0.2% BSA) in a concentration of 50 μ g of protein per assay mixture and incubated at 25°C with 25 pM [^{125}I] [^{125}I] [^{125}I]- ET_1 (ET_A receptor assay) or 25 pM [^{125}I] [^{125}I] [^{125}I]- ET_3 (ET_B receptor assay) in the presence and absence of a test substance. The nonspecific binding was determined with 10^{-7} M ET_1 . After 30 min, filtration through GF/B glass fiber filters (Whatman, England) in a Skatron cell collector (Skatron, Lier, Norway) separated free from 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.

Tests on the 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 [sic].

Intravenous administration of 1 μ g/kg ET_1 to control animals led to a distinct rise in blood pressure which persisted for a lengthy period.

The test animals received i.v. injections (1 ml/kg) of the test compounds 30 min before the ET_1 administration. To determine the ET -antagonistic properties, the changes in blood pressure of the test animals were compared with those for the control animals.

Oral testing of the mixed ET_A and ET_B antagonists:

Male normotensive rats (Sprague Dawley, Janvier) weighing 250-350 g are pretreated orally with the test substances. 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.

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

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

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 about 0.5-50 mg/kg of bodyweight on oral administration and about 0.1-10 mg/kg of bodyweight on parenteral administration.

The novel compounds can be used in conventional solid or liquid pharmaceutical forms, eg. 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 auxiliaries 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 forms obtained in this way normally contain from 0.1 to 90% by weight of active ingredient.

Synthesis examples

40

Example 1:

Methyl 2,3-epoxy-3,6-diphenylhexanoate

45 1.4 g (31 mmol) of 50% sodium hydride were added in portions over the course of 8 hours to a solution of 4 g (17.8 mmol) of 1,4-diphenyl-1-butanone and 2.7 ml (31 mmol) of methyl

15

chloroacetate in 60 ml of THF. After the ketone had completely reacted, the reaction mixture was added to ice-water and extracted ether. The organic phase was dried over magnesium sulfate and, after the solvent had been distilled off, it was possible to isolate 5.5 g of an oil which was reacted further.

Example 2:

Methyl 2-hydroxy-3-methoxy-3,6-diphenylhexanoate

10

2 g (6.75 mmol) of methyl 2,3-epoxy-3,6-diphenylhexanoate were introduced with 0.5 ml of methanol into 20 ml of dichloromethane, and 5 drops of boron trifluoride etherate were added. After 2 hours, the mixture was concentrated and the residue was purified by MPLC (cyclohexane/ethyl acetate gradient) to isolate 530 mg of one diastereomer, 720 mg of the second diastereomer and 800 mg of a mixed fraction.

Example 3:

20

2-Hydroxy-3-methoxy-3,6-diphenylhexanoic acid (one diastereomer, stereochemistry unknown)

The second diastereomer (720 mg, 2.2 mmol) was dissolved in 9 ml of dioxane, and 4.5 ml of 1N sodium hydroxide solution were added. The mixture was stirred for 16 hours and then, after addition of water, extracted with ether. The aqueous phase was acidified with citric acid and extracted with ether, the organic phase was dried with [sic] over magnesium sulfate, and the solvent was distilled off. 936 mg of an oil were isolated and were immediately reacted further.

Example 4:

2-(4-Methoxy-6-methyl-2-pyrimidinyl)-3-methoxy-3,6-diphenylhexanoic acid (one diastereomer)

195 mg (4.4 mmol) of 50% sodium hydride, 465 mg (1.5 mmol) of 2-hydroxy-3-methoxy-3,6-diphenylhexanoic acid and 291 mg (1.5 mmol) of 3,4-dimethyl-2-methylsulfonepyrimidine [sic] were mixed in 20 ml of DMF and stirred at room temperature for 2 hours. The reaction mixture was added to 100 ml of ice-water, acidified with citric acid and extracted with ether. The organic phase was dried with magnesium sulfate, and the solvent was distilled off. The residue was purified by MPLC (cyclohexane/ethyl acetate gradient) to isolate 103 mg of one diastereomer.

16

¹H-NMR (200 MHz, CDCl₃): 7.1-7.5 ppm (10 H, m), 6.2 (1 H, s), 5.6 (1 H, s), 3.8 (3 H, s), 3.3 (3 H, s), 2.5-2.8 (3 H, m), 2.3 (3 H, s), 2.0 (1 H, m), 1.5-1.8 (2 H, m).

5 ESI MS: M⁺ = 436

Example 5:

Methyl 2,3-epoxy-3-phenyl-6-(3,4-methoxyphenyl)hexanoate [sic]
10 (mixture of diastereomers):

12.6 g (44 mmol) of 1-phenyl-4-(3,4-dimethoxy)phenyl-1-butanone [sic] were dissolved together with 8.3 g of methyl chloroacetate in 50 ml of DMF and, at room temperature, 3.7 g of 50% sodium
15 hydride suspension were added in portions over the course of 1 hour. Reaction of the precursor was complete after a total of 1.5 hours, and the reaction solution was added to 300 ml of ice-water. The aqueous phase was acidified with citric acid and extracted several times with ether, and the organic phase was
20 separated off, washed and dried over magnesium sulfate. The solvent was distilled off to isolate 13 g of an oil which could be immediately reacted further.

Example 6:

25

Methyl 2-hydroxy-3-(2-(3,4-dimethoxyphenyl)ethoxy)-3-phenyl-6-(3,4-dimethoxyphenyl)hexanoate

A mixture of 3.6 g (10 mmol) of methyl 2,3-epoxy-3-phenyl-
30 6-(3,4-methoxyphenyl)hexanoate [sic], 1.8 g (10 mmol) of 2-(3,4-dimethoxy)ethanol [sic] and 100 mg of p-toluenesulfonic acid in 50 ml of dichloromethane was stirred for one hour while cooling in ice. The reaction solution was added to a saturated sodium bicarbonate solution, and the organic phase was separated
35 off and dried over magnesium sulfate. The solvent was distilled off, and 4.7 g of residue was purified by MPLC (gradient: cyclohexane/ethyl acetate) to isolate 750 mg of a mixture of diastereomers.

40 Example 7:

2-Hydroxy-3-(2-(3,4-dimethoxyphenyl)ethoxy)-3-phenyl-6-(3,4-dimethoxyphenyl)hexanoic acid

45 2.1 ml of 1N sodium hydroxide solution were added to 750 mg (1.4 mmol) of methyl 2-hydroxy-3-(2-(3,4-dimethoxyphenyl)ethoxy)-3-phenyl-6-(3,4-dimethoxyphenyl)hexanoate dissolved in 4.2 ml of

dioxane, and the mixture was stirred at room temperature for 16 hours. 100 ml of water were added to the mixture, which was then extracted with ether. It was subsequently neutralized with hydrochloric acid, the aqueous phase was extracted with ether, 5 the ether phase was dried with magnesium sulfate, and the solvent was distilled off. 620 mg of an oil were isolated and were immediately employed further.

Example 8:

10

2-(4,6-Dimethyl-2-pyrimidinyloxy)-3-(2-(3,4-dimethoxyphenyl)-ethoxy)-3-phenyl-6-(3,4-dimethoxyphenyl)hexanoic acid

164 mg (3.42 mmol) of sodium hydride, 600 mg (1.14 mmol) of 15 2-hydroxy-3-(2-(3,4-dimethoxyphenyl)ethoxy)-3-phenyl-6-(3,4-dimethoxyphenyl)hexanoic acid and 223 mg (1.2 mmol) of 3,4-dimethyl-2-methylsulfonepyrimidine [sic] were mixed in 10 ml of DMF and stirred at room temperature for 6 hours. The reaction mixture was added to 100 ml of ice-water, acidified with citric 20 acid and extracted with ether. The organic phase was dried with magnesium sulfate, and the solvent was distilled off. The residue was purified by flash chromatography (cyclohexane/ethyl acetate gradient) to isolate 115 mg of one crystalline diastereomer.

25 Diast. I:

Melting point: 93-96°C

ESI MS: M+ = 630

Example 9:

30

2-(4,6-Dimethyl-2-pyrimidinyloxy)-3-(3,4-dimethoxybenzyloxy)-3-phenyl-6-(3,4-dimethoxyphenyl)hexanoic acid

Diast. I:

35 Melting point: 130-133°C

ESI MS: M+ = 616

Example 10:

40 2-(4,6-Dimethyl-2-pyrimidinyloxy)-3-(4-methoxyphenoxy)-3-phenyl-6-(3,4-dimethoxyphenyl)hexanoic acid

Diast. I:

Melting point: 118-122°C

45 ESI MS: M+ = 572

Example 11:

2-(4,6-Dimethyl-2-pyrimidinyloxy)-3-methoxy-3-phenyl-6-(3,4-dimethoxyphenyl)hexanoic acid

5

Diast. I:

Melting point: 135-138°C

ESI MS: M⁺ = 480

10 Diast. II:

Melting point: 128-134°C

ESI MS: M⁺ = 480

Example 12:

15

2-(4,6-Dimethyl-2-pyrimidinyloxy)-3-methoxy-3,6-diphenylhexanoic acid

1H-NMR (200 MHz, CDCl₃): 7.1-7.5 ppm (10 H, m), 6.7 (1 H, s), 5.8 (1 H, s), 3.3 (3 H, s), 2.5-2.7 (3 H, m), 2.3 (6 H, s), 2.0-2.1 (1 H, m), 1.6-1.8 (2 H, m).

ESI MS: M⁺ = 420

25 Example 13:

2-(4,6-Dimethyl-2-pyrimidinyloxy)-3-hex-3E-enoxy-3,6-diphenylhexanoic [sic] acid

30 Diast. I:

Melting point: 110-114°C

ESI MS: M⁺ = 488

Diast. II:

35 ESI MS: M⁺ = 488

Example 14:

2-(4,6-Dimethyl-2-pyrimidinyloxy)-3-(2-(3,4-dimethoxyphenyl)-ethoxy)-3,6-diphenylhexanoic acid

40

Diast. I:

Melting point: 87-88°C

ESI MS: M⁺ = 570

45

Diast. II:

Melting point: 87-88°C

ESI MS: M+ = 570

Example 15:

5 2-(4-Methoxy-6-methyl-2-pyrimidinyloxy)-3-(2-(3,4-dimethoxy-phenyl)ethoxy)-3,6-diphenylhexanoic acid

Diast. I:

Melting point: 141-142°C

10 ESI MS: M+ = 586

Example 16:

2-(4,6-Dimethyl-2-pyrimidinyloxy)-3-(3,4-dimethoxybenzyloxy)-
15 3,6-diphenylhexanoic acid

Diast. I:

1H-NMR (200 MHz, CDCl₃): 7.1-7.5 ppm (10 H, m), 6.9 (3 H, m), 6.7 (1 H, s), 5.8 (1 H, s), 4.4 (1 H, d), 4.3 (1 H, d), 3.9 (3 H, s),
20 3.85 (3 H, s), 2.5-2.7 (3 H, m), 2.3 (6 H, s), 2.0-2.3 (1 H, m), 1.7-1.9 (2 H, m).

ESI MS: M+ = 556

25 Example 17:

2-(4-Methoxy-6-methyl-2-pyrimidinyloxy)-3-(3,4-dimethoxybenzyl-
oxy)-3,6-diphenylhexanoic acid

30 Diast. I:

1H-NMR (200 MHz, CDCl₃): 7.1-7.5 ppm (10 H, m), 6.9 (3 H, m), 6.25 (1 H, s), 5.75 (1 H, s), 4.45 (1 H, d), 4.35 (1 H, d), 3.9 (3 H, s), 3.85 (6 H, s), 2.4-2.7 (3 H, m), 2.3 (6 H, s), 2.0-2.2 (1 H, m), 1.7-1.9 (2 H, m).

35

ESI MS: M+ = 572

Example 18:

40 2-(4-Methoxy-6-methyl-2-pyrimidinyloxy)-3-(2-(2-thiophenyl-ethoxy)-3,6-diphenylhexanoic [sic] acid

3:1 mixture of diastereomers:

Decomposition: 85°C

45 ESI MS: M+ = 532

20

Example 19:

2-(4,6-Dimethyl-2-pyrimidinyloxy)-3-(2-(3,4,5-trimethoxyphenyl)-ethoxy)-3,6-diphenylhexanoic acid

5

Diast. I:

¹H-NMR (200 MHz, CDCl₃): 7.0-7.3 ppm (10 H, m), 6.65 (1 H, m), 6.4 (2 H, s), 5.75 (1 H, s), 3.9 (3 H, s), 3.85 (6 H, s), 3.5-3.7 (2 H, m), 2.8-2.9 (2 H, m), 2.3-2.5 (3 H, m), 2.3 (6 H, s), 2.0-2.3 (1 H, m), 1.5-1.7 (2 H, m).

ESI MS: M⁺ = 600

Example 20:

15

2-(4-Methoxy-6-methyl-2-pyrimidinyloxy)-3-(2-(3,4,5-trimethoxyphenyl)ethoxy)-3,6-diphenylhexanoic acid

Diast. I:

20 Melting point: 153-155°C

ESI MS: M⁺ = 616

Example 21:

25 2-(4,6-Dimethyl-2-pyrimidinyloxy)-3-(2-(4-hydroxy-3-methoxyphenyl)ethoxy)-3,6-diphenylhexanoic acid

Diast. I:

¹H-NMR (200 MHz, CDCl₃): 7.0-7.4 ppm (10 H, m), 6.9 (1 H, dm), 6.6-6.75 (3 H, m), 5.8 (1 H, s), 5.5 (OH), 3.9 (3 H, s), 3.85 (3 H, s), 3.5-3.7 (2 H, m), 2.8-2.9 (2 H, tr), 2.3-2.5 (3 H, m), 2.3 (6 H, s), 2.0-2.3 (1 H, m), 1.5-1.7 (2 H, m).

ESI MS: M⁺ = 556

35

Diast. II:

ESI MS: M⁺ = 556

Example 22:

40

2-(4-Methoxy-6-methyl-2-pyrimidinyloxy)-3-(2-(4-hydroxy-3-methoxyphenyl)ethoxy)-3,6-diphenylhexanoic acid

Diast. I:

45 Melting point: 154-157°C

ESI MS: M⁺ = 572

Example 23:

2-(4,6-Dimethyl-2-pyrimidinyloxy)-3-(4-carboxybenzyloxy)-
3,6-diphenylhexanoic acid

5

Diast. I:

¹H-NMR (200 MHz, CDCl₃): 8.0 (2 H, d), 7.1-7.5 ppm (12 H, m), 6.8 (1 H, m), 6.8 (1 H, s), 4.6 (1 H, d), 4.5 (1 H, d), 2.5-2.7 (3 H, m), 2.3 (6 H, s), 2.1-2.25 (1 H, m), 1.5-1.7 (2 H, m).

10

ESI MS: M⁺ = 540

Diast. II:

Melting point: 160-167°C

15 ESI MS: M⁺ = 540

Example 24:

2-(4-Methoxy-6-methyl-2-pyrimidinyloxy)-3-(4-carboxybenzyloxy)-
20 3,6-diphenylhexanoic acid

Diast. I:

¹H-NMR (200 MHz, CDCl₃): 8.0 (2 H, d), 7.1-7.5 ppm (12 H, m), 6.2 (1 H, m), 5.6 (1 H, s), 4.55 (1 H, d), 4.45 (1 H, d), 3.9 (3 H, s),
25 2.5-2.7 (3 H, m), 2.3 (3 H, s), 2.1-2.25 (1 H, m), 1.6-1.8 (2 H, m).

ESI MS: M⁺ = 556

30 Diast. II:

ESI MS: M⁺ = 556

Example 25:

35 2-(4,6-Dimethyl-2-pyrimidinyloxy)-3-(4-methoxyphenoxy)-
3,6-diphenylhexanoic acid

Diast. I:

¹H-NMR (200 MHz, CDCl₃): 7.1-7.5 ppm (10 H, m), 6.5-6.8 (5 H,
40 m), 5.9 (1 H, s), 3.75 (3 H, s), 2.2-2.7 (4 H, m), 2.3 (6 H, s),
1.5-1.7 (2 H, m).

ESI MS: M⁺ = 512

45 Diast. II:

ESI MS: M⁺ = 512

Example 26:

2-(4-Methoxy-6-methyl-2-pyrimidinyloxy)-3-(4-methoxyphenoxy)-
3,6-diphenylhexanoic acid

5

Diast. I:

¹H-NMR (200 MHz, CDCl₃): 7.1-7.5 ppm (10 H, m), 6.5-6.9 (4 H, m), 6.2 (1 H, s), 5.75 (1 H, s), 3.8 (3 H, s), 3.75 (3 H, s), 2.2-2.7 (4 H, m), 2.3 (3 H, s), 1.5-1.7 (2 H, m).

10

ESI MS: M⁺ = 528

Diast. II:

ESI MS: M⁺ = 528

15

Example 27:

2-(4,6-Dimethyl-2-pyrimidinyloxy)-3-(3-(3,4,5-trimethoxyphenyl)-
2E-propenoxy)-3,6-diphenylhexanoic [sic] acid

20

Diast. I:

¹H-NMR (200 MHz, CDCl₃): 7.1-7.4 ppm (10 H, m), 6.6 (1 H, s), 6.55 (2 H, s), 6.3 (1 H, s), 6.2 (1 H, dtr), 5.9 (1 H, d), 4.0 4.2 (1 H, m), 3.85 (3 H, s), 3.8 (3 H, s), 3.75 (3 H, s), 3.4 (1 25 H, m), 2.4-2.7 (3 H, m), 2.3 (6 H, s), 2.0-2.1 (1 H, m), 1.5-1.7 (2 H, m).

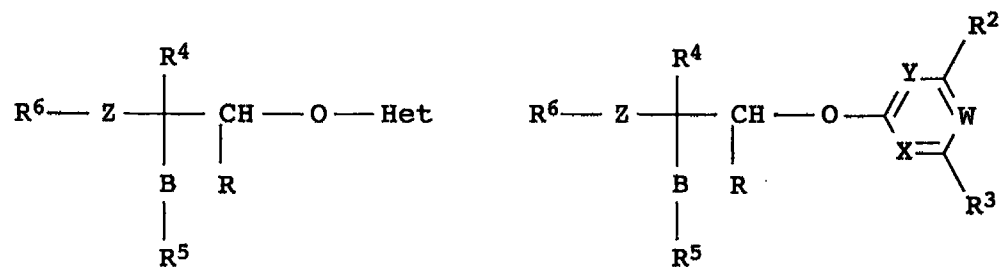
ESI MS: M⁺ = 612

30 The compounds listed in Table 1 can be prepared in a similar way or as described in the general part.

35

40

45



Nr.	R	R ⁴	R ⁵	R ⁶	Z	B	R ²	R ³	W	X	Y	Het
I-1	COOH	Phenyl	Phenyl	Me	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-2	COOH	Phenyl	Phenyl	Me	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-3	COOH	Phenyl	Phenyl	Me	S	CH ₂ CH ₂ CH ₂	CF ₃	Me	CH	N	N	-
I-4	COOH	Phenyl	Phenyl	Me	O	CH ₂ CH ₂ CH ₂	OMe	(CH ₂ CH ₂ CH ₂ C)		N	N	-
I-5	COOH	Phenyl	Phenyl	Me	O	CH ₂ CH ₂ CH ₂	OMe	(OCH ₂ CH ₂ C)		N	N	-
I-6	COOH	Phenyl	Phenyl	Me	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	1)
I-7	COOH	Phenyl	Phenyl	Me	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2) 2*
I-8	COOH	Phenyl	Phenyl	4-OMe-Phenyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	1) 1*
I-9	COOH	Phenyl	Phenyl	4-OMe-Phenyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-10	COOH	Phenyl	Phenyl	4-OMe-Phenyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-11	COOH	Phenyl	Phenyl	4-OMe-Phenyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2) 2*
I-12	COOH	Phenyl	Phenyl	4-OMe-Phenyl	O	CH ₂ CH ₂ CH ₂	OMe	(CH ₂ CH ₂ CH ₂ C)		N	N	-
I-13	COOH	Phenyl	Phenyl	4-OMe-Phenyl	O	CH ₂ CH ₂ CH ₂	OMe	(OCH ₂ CH ₂ C)		N	N	-

Nr.	R	R ⁴	R ⁵	R ⁶	Z	B	R ²	R ³	W	X	Y	Het
I-14	COOH	Phenyl	Phenyl	3,4-Di-OMe-Phenyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-15	COOH	Phenyl	Phenyl	3,4-Di-OMe-Phenyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-16	COOH	Phenyl	Phenyl	3,4-Di-OMe-Phenyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	1) 1*
I-17	COOH	Phenyl	Phenyl	3,4-Di-OMe-Phenyl	O	CH ₂ CH ₂ CH ₂	OMe	(CH ₂ CH ₂ CH ₂ C)		N	N	-
I-18	COOH	Phenyl	Phenyl	4-Cl-Phenyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-19	COOH	Phenyl	Phenyl	4-Cl-Phenyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-20	COOH	Phenyl	Phenyl	4-Cl-Phenyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	1)
I-21	COOH	Phenyl	Phenyl	4-Cl-Phenyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-22	COOH	Phenyl	Phenyl	4-Cl-Phenyl	O	CH ₂ CH ₂ CH ₂	OMe	(OCH ₂ CH ₂ C)		N	N	-
I-23	COOH	Phenyl	Phenyl	4-Me-Phenyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-24	COOH	Phenyl	Phenyl	4-Me-Phenyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-25	COOH	Phenyl	Phenyl	4-Me-Phenyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	1)
I-26	COOH	Phenyl	Phenyl	4-Me-Phenyl	O	CH ₂ CH ₂ CH ₂	OMe	(OCH ₂ CH ₂ C)		N	N	-
I-27	COOH	Phenyl	Phenyl	4-Me-Phenyl	O	CH ₂ CH ₂ CH ₂	OMe	(CH ₂ CH ₂ CH ₂ C)		N	N	-
I-28	COOH	Phenyl	Phenyl	4-Me-Phenyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-29	COOH	Phenyl	Phenyl	4-OMe-Benzyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-30	COOH	Phenyl	Phenyl	4-OMe-Benzyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-31	COOH	Phenyl	Phenyl	4-OMe-Benzyl	O	CH ₂ CH ₂ CH ₂	OMe	(CH ₂ CH ₂ CH ₂ C)		N	N	-
I-32	COOH	Phenyl	Phenyl	4-OMe-Benzyl	O	CH ₂ CH ₂ CH ₂	OMe	(OCH ₂ CH ₂ C)		N	N	-
I-33	COOEt	Phenyl	Phenyl	4-OMe-Benzyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	1)
I-34	COOH	Phenyl	Phenyl	4-OMe-Benzyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)

Nr.	R	R ⁴	R ⁵	R ⁶	Z	B	R ²	R ³	W	X	Y	Het
I-35	COOH	Phenyl	Phenyl	3,4-Di-OMe-Benzyl	O	CH ₂ CH ₂ CH ₂	Me	Me	Ch	N	N	-
I-36	COOH	Phenyl	Phenyl	3,4-Di-OMe-Benzyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-37	COOH	Phenyl	Phenyl	3,4-Di-OMe-Benzyl	O	CH ₂ CH ₂ CH ₂	OMe	(CH ₂ CH ₂ CH ₂ C)		N	N	-
I-38	COOH	Phenyl	Phenyl	3,4-Di-OMe-Benzyl	O	CH ₂ CH ₂ CH ₂	OMe	(OCH ₂ CH ₂ C)		N	N	-
I-39	COOH	Phenyl	Phenyl	3,4-Di-OMe-Benzyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	1)
I-40	COOH	Phenyl	Phenyl	3,4-Di-OMe-Benzyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-41	COOH	Phenyl	Phenyl	4-Me-Benzyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-42	COOH	Phenyl	Phenyl	4-Me-Benzyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-43	COOH	Phenyl	Phenyl	4-Me-Benzyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-44	COOH	Phenyl	Phenyl	4-COOH-Benzyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-45	COOH	Phenyl	Phenyl	4-COOH-Benzyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-46	COOH	Phenyl	Phenyl	4-COOH-Benzyl	O	CH ₂ CH ₂ CH ₂	OMe	(CH ₂ CH ₂ CH ₂ C)		N	N	-
I-47	COOH	Phenyl	Phenyl	4-COOH-Benzyl	O	CH ₂ CH ₂ CH ₂	OMe	(OCH ₂ CH ₂ C)		N	N	-
I-48	COOH	Phenyl	Phenyl	4-COOH-Benzyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	1)
I-49	COOH	Phenyl	Phenyl	4-COOH-Benzyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-50	COOH	Phenyl	Phenyl	4-Cl-Benzyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-51	COOH	Phenyl	Phenyl	4-Cl-Benzyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-52	COOH	Phenyl	Phenyl	4-Cl-Benzyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-53	COOH	Phenyl	Phenyl	4-SMe-Benzyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-54	COOH	Phenyl	Phenyl	4-SMe-Benzyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-55	COOH	Phenyl	Phenyl	4-SMe-Benzyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)

Nr.	R	R ⁴	R ⁵	R ⁶	Z	B	R ²	R ³	W	X	Y	Het
I-56	COOH	Phenyl	Phenyl	3-COOH-Benzyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-57	COOH	Phenyl	Phenyl	3-COOH-Benzyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-58	COOH	Phenyl	Phenyl	3-COOH-Benzyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-59	COOH	Phenyl	Phenyl	4-COOH-3-OMeBenzyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-60	COOH	Phenyl	Phenyl	4-COOH-3-OMeBenzyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-61	COOH	Phenyl	Phenyl	4-COOH-3-OMeBenzyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-62	COOH	Phenyl	Phenyl	4-COOH-3-OMeBenzyl	O	CH ₂ CH ₂ CH ₂	Ethyl	Me	CH	N	N	-
I-63	COOH	Phenyl	Phenyl	4-COOH-3-OMeBenzyl	O	CH ₂ CH ₂ CH ₂	CF ₃	Me	CH	N	N	-
I-64	COOH	Phenyl	Phenyl	4-COOH-3-OMeBenzyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	1)
I-65	COOH	Phenyl	Phenyl	4-COOH-3-MeBenzyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-66	COOH	Phenyl	Phenyl	4-COOH-3-MeBenzyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-67	COOH	Phenyl	Phenyl	4-COOH-3-MeBenzyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-68	COOH	Phenyl	Phenyl	4-COOH-3-MeBenzyl	O	CH ₂ CH ₂ CH ₂	OMe	(CH ₂ CH ₂ CH ₂ C)		N	N	-
I-69	COOH	Phenyl	Phenyl	4-Ethyl-Benzyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-70	COOH	Phenyl	Phenyl	4-Ethyl-Benzyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-71	COOH	Phenyl	Phenyl	4-Ethyl-Benzyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-72	COOH	Phenyl	Phenyl	2-Phenyl-Ethyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-73	COOH	Phenyl	Phenyl	2-Phenyl-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-74	COOH	Phenyl	Phenyl	2-Phenyl-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-75	COOH	Phenyl	Phenyl	2-(4-Me-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-76	COOH	Phenyl	Phenyl	2-(4-Me-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-

Nr.	R	R ⁴	R ⁵	R ⁶	Z	B	R ²	R ³	W	X	Y	Het
I-77	COOH	Phenyl	Phenyl	2-(4-Me-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	(OCH ₂ CH ₂ C)		N	N	-
I-78	COOH	Phenyl	Phenyl	2-(4-Me-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	(CH ₂ CH ₂ CH ₂ C)		N	N	-
I-79	COOH	Phenyl	Phenyl	2-(4-Me-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	1)
I-80	COOH	Phenyl	Phenyl	2-(4-Me-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-81	COOH	Phenyl	Phenyl	2-(4-OMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-82	COOH	Phenyl	Phenyl	2-(4-OMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-83	COOH	Phenyl	Phenyl	2-(4-OMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	(CH ₂ CH ₂ CH ₂ C)		N	N	-
I-84	COOH	Phenyl	Phenyl	2-(4-OMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	(OCH ₂ CH ₂ C)		N	N	-
I-85	COOH	Phenyl	Phenyl	2-(4-OMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	1)
I-86	COOH	Phenyl	Phenyl	2-(4-OMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-87	COOH	Phenyl	Phenyl	2-(4-OMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	CF ₃	Me	CH	N	N	-
I-88	COOH	Phenyl	Phenyl	2-(3,4-DiOMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-89	COOH	Phenyl	Phenyl	2-(3,4-DiOMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-90	COOH	Phenyl	Phenyl	2-(3,4-DiOMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	(CH ₂ CH ₂ CH ₂ C)		N	N	-
I-91	COOH	Phenyl	Phenyl	2-(3,4-DiOMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	(OCH ₂ CH ₂ C)		N	N	-
I-92	COOH	Phenyl	Phenyl	2-(3,4-DiOMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	1)
I-93	COOH	Phenyl	Phenyl	2-(3,4-DiOMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)

Nr.	R	R ⁴	R ⁵	R ⁶	Z	B	R ²	R ³	W	X	Y	Het
I-94	COOH	Phenyl	Phenyl	2-(4-COOH-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-95	COOH	Phenyl	Phenyl	2-(4-COOH-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-96	COOH	Phenyl	Phenyl	2-(4-COOH-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	(CH ₂ CH ₂ CH ₂ C)		N	N	-
I-97	COOH	Phenyl	Phenyl	2-(4-COOH-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	(OCH ₂ CH ₂ C)		N	N	-
I-98	COOH	Phenyl	Phenyl	2-(4-COOH-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	1)
I-99	COOH	Phenyl	Phenyl	2-(4-COOH-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-100	COOH	Phenyl	Phenyl	2-(4-SMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-101	COOH	Phenyl	Phenyl	2-(4-SMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-102	COOH	Phenyl	Phenyl	2-(4-SMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-103	COOH	Phenyl	Phenyl	2-(4-Cl-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-104	COOH	Phenyl	Phenyl	2-(4-Cl-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-105	COOH	Phenyl	Phenyl	2-(4-Cl-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-106	COOH	Phenyl	Phenyl	2-(3,4-DiCl-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-107	COOH	Phenyl	Phenyl	2-(3,4-DiCl-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-108	COOH	Phenyl	Phenyl	2-(3,4-DiCl-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	(OCH ₂ CH ₂ C)		N	N	-
I-109	COOH	Phenyl	Phenyl	2-(3,4-DiCl-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-110	COOH	Phenyl	Phenyl	2-(4-COOH-3-OMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-

Nr.	R	R ⁴	R ⁵	R ⁶	Z	B	R ²	R ³	W	X	Y	Het
I-111	COOH	Phenyl	Phenyl	2-(4-COOH-3-OMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-112	COOH	Phenyl	Phenyl	2-(4-COOH-3-OMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-113	COOH	Phenyl	Phenyl	3-Phenyl-Propyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-114	COOH	Phenyl	Phenyl	3-Phenyl-Propyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-115	COOH	Phenyl	Phenyl	3-Phenyl-Propyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-116	COOH	Phenyl	Phenyl	3-(3,4,5-triOMe-Phenyl)Prop-2E-enyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-117	COOH	Phenyl	Phenyl	3-(3,4,5-triOMe-Phenyl)Prop-2E-enyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-118	COOH	Phenyl	Phenyl	3-(3,4,5-triOMe-Phenyl)Prop-2E-enyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-119	COOH	Phenyl	Phenyl	2-(3,4-methylenedioxy-phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-120	COOH	Phenyl	Phenyl	2-(3,4-methylenedioxy-phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-121	COOH	Phenyl	Phenyl	2-(3,4-methylenedioxy-phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-122	COOH	Phenyl	Phenyl	2-(4-DiMethyl-amino-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-123	COOH	Phenyl	Phenyl	2-(4-DiMethyl-amino-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-124	COOH	Phenyl	Phenyl	2-(4-DiMethyl-amino-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)

Nr.	R	R ⁴	R ⁵	R ⁶	Z	B	R ²	R ³	W	X	Y	Het
I-125	COOH	Phenyl	Phenyl	2-(4-Hydroxy-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-126	COOH	Phenyl	Phenyl	2-(4-Hydroxy-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-127	COOH	Phenyl	Phenyl	2-(4-Hydroxy-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	-
I-128	COOH	Phenyl	Phenyl	2-(4-Hydroxy-3-OMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-129	COOH	Phenyl	Phenyl	2-(4-Hydroxy-3-OMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-130	COOH	Phenyl	Phenyl	2-(4-Hydroxy-3-OMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-131	COOH	Phenyl	Phenyl	2-(4-Ethoxy-3-Methoxy-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-132	COOH	Phenyl	Phenyl	2-(4-Ethoxy-3-Methoxy-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-133	COOH	Phenyl	Phenyl	2-(4-Ethoxy-3-Methoxy-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	1)
I-134	COOH	Phenyl	Phenyl	2-(3,5-DiOMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-135	COOH	Phenyl	Phenyl	2-(3,5-DiOMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-136	COOH	Phenyl	Phenyl	2-(3,5-DiOMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-137	COOH	Phenyl	3,4-DiOMe-Phenyl	Me	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-

Nr.	R	R ⁴	R ⁵	R ⁶	Z	B	R ²	R ³	W	X	Y	Het
I-138	COOH	Phenyl	3,4-DiOMe-Phenyl	Me	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-139	COOH	Phenyl	3,4-DiOMe-Phenyl	Me	O	CH ₂ CH ₂ CH ₂	CF ₃	Me	CH	N	N	-
I-140	COOH	Phenyl	3,4-DiOMe-Phenyl	Me	O	CH ₂ CH ₂ CH ₂	OMe	(CH ₂ CH ₂ CH ₂ C)		N	N	-
I-141	COOH	Phenyl	3,4-DiOMe-Phenyl	Me	O	CH ₂ CH ₂ CH ₂	OMe	(OCH ₂ CH ₂ C)		N	N	-
I-142	COOH	Phenyl	3,4-DiOMe-Phenyl	Me	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	1)
I-143	COOH	Phenyl	3,4-DiOMe-Phenyl	Me	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2) 2*
I-144	COOH	Phenyl	3,4-DiOMe-Phenyl	4-OMe-Phenyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	1) 1*
I-145	COOH	Phenyl	3,4-DiOMe-Phenyl	4-OMe-Phenyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-146	COOH	Phenyl	3,4-DiOMe-Phenyl	4-OMe-Phenyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-147	COOH	Phenyl	3,4-DiOMe-Phenyl	4-OMe-Phenyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2) 2*
I-148	COOH	Phenyl	3,4-DiOMe-Phenyl	4-OMe-Phenyl	O	CH ₂ CH ₂ CH ₂	OMe	(CH ₂ CH ₂ CH ₂ C)		N	N	-
I-149	COOH	Phenyl	3,4-DiOMe-Phenyl	4-OMe-Phenyl	O	CH ₂ CH ₂ CH ₂	OMe	(OCH ₂ CH ₂ C)		N	N	-
I-150	COOH	Phenyl	3,4-DiOMe-Phenyl	3,4-Di-OMe-Phenyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-

Nr.	R	R ⁴	R ⁵	R ⁶	Z	B	R ²	R ³	W	X	Y	Het
I-151	COOH	Phenyl	3,4-DiOMe-Phenyl	3,4-Di-OMe-Phenyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-152	COOH	Phenyl	3,4-DiOMe-Phenyl	3,4-Di-OMe-Phenyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	1) 1*
I-153	COOH	Phenyl	3,4-DiOMe-Phenyl	3,4-Di-OMe-Phenyl	O	CH ₂ CH ₂ CH ₂	OMe	(CH ₂ CH ₂ CH ₂ C)		N	N	-
I-154	COOH	Phenyl	3,4-DiOMe-Phenyl	4-Cl-Phenyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-155	COOH	Phenyl	3,4-DiOMe-Phenyl	4-Cl-Phenyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-156	COOH	Phenyl	3,4-DiOMe-Phenyl	4-Cl-Phenyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	1)
I-157	COOH	Phenyl	3,4-DiOMe-Phenyl	4-Cl-Phenyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-158	COOH	Phenyl	3,4-DiOMe-Phenyl	4-Cl-Phenyl	O	CH ₂ CH ₂ CH ₂	OMe	(OCH ₂ CH ₂ C)		N	N	-
I-159	COOH	Phenyl	3,4-DiOMe-Phenyl	4-Me-Phenyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-160	COOH	Phenyl	3,4-DiOMe-Phenyl	4-Me-Phenyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-161	COOH	Phenyl	3,4-DiOMe-Phenyl	4-Me-Phenyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	1)
I-162	COOH	Phenyl	3,4-DiOMe-Phenyl	4-Me-Phenyl	O	CH ₂ CH ₂ CH ₂	OMe	(OCH ₂ CH ₂ C)		N	N	-
I-163	COOH	Phenyl	3,4-DiOMe-Phenyl	4-Me-Phenyl	O	CH ₂ CH ₂ CH ₂	OMe	(CH ₂ CH ₂ CH ₂ C)		N	N	-

Nr.	R	R ⁴	R ⁵	R ⁶	Z	B	R ²	R ³	W	X	Y	Het
I-164	COOH	Phenyl	3,4-DiOMe-Phenyl	4-Me-Phenyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-165	COOH	Phenyl	3,4-DiOMe-Phenyl	4-OMe-Benzyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-166	COOH	Phenyl	3,4-DiOMe-Phenyl	4-OMe-Benzyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-167	COOH	Phenyl	3,4-DiOMe-Phenyl	4-OMe-Benzyl	O	CH ₂ CH ₂ CH ₂	OMe	(CH ₂ CH ₂ CH ₂ C)		N	N	-
I-168	COOH	Phenyl	3,4-DiOMe-Phenyl	4-OMe-Benzyl	O	CH ₂ CH ₂ CH ₂	OMe	(OCH ₂ CH ₂ C)		N	N	-
I-169	COOH	Phenyl	3,4-DiOMe-Phenyl	4-OMe-Benzyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	1)
I-170	COOH	Phenyl	3,4-DiOMe-Phenyl	4-OMe-Benzyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-171	COOH	Phenyl	3,4-DiOMe-Phenyl	3,4-Di-OMe-Benzyl	O	CH ₂ CH ₂ CH ₂	Me	Me	Ch	N	N	-
I-172	COOH	Phenyl	3,4-DiOMe-Phenyl	3,4-Di-OMe-Benzyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-173	COOH	Phenyl	3,4-DiOMe-Phenyl	3,4-Di-OMe-Benzyl	O	CH ₂ CH ₂ CH ₂	OMe	(CH ₂ CH ₂ CH ₂ C)		N	N	-
I-174	COOH	Phenyl	3,4-DiOMe-Phenyl	3,4-Di-OMe-Benzyl	O	CH ₂ CH ₂ CH ₂	OMe	(OCH ₂ CH ₂ C)		N	N	-
I-175	COOH	Phenyl	3,4-DiOMe-Phenyl	3,4-Di-OMe-Benzyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	1)
I-176	COOH	Phenyl	3,4-DiOMe-Phenyl	3,4-Di-OMe-Benzyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)

Nr.	R	R ⁴	R ⁵	R ⁶	Z	B	R ²	R ³	W	X	Y	Het
I-177	COOH	Phenyl	3,4-DiOMe-Phenyl	4-Me-Benzyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-178	COOH	Phenyl	3,4-DiOMe-Phenyl	4-Me-Benzyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-179	COOH	Phenyl	3,4-DiOMe-Phenyl	4-Me-Benzyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-180	COOH	Phenyl	3,4-DiOMe-Phenyl	4-COOH-Benzyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-181	COOH	Phenyl	3,4-DiOMe-Phenyl	4-COOH-Benzyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-182	COOH	Phenyl	3,4-DiOMe-Phenyl	4-COOH-Benzyl	O	CH ₂ CH ₂ CH ₂	OMe	(CH ₂ CH ₂ CH ₂ C)		N	N	-
I-183	COOH	Phenyl	3,4-DiOMe-Phenyl	4-COOH-Benzyl	O	CH ₂ CH ₂ CH ₂	OMe	(OCH ₂ CH ₂ C)		N	N	-
I-184	COOH	Phenyl	3,4-DiOMe-Phenyl	4-COOH-Benzyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	1)
I-185	COOH	Phenyl	3,4-DiOMe-Phenyl	4-COOH-Benzyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-186	COOH	Phenyl	3,4-DiOMe-Phenyl	4-Cl-Benzyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-187	COOH	Phenyl	3,4-DiOMe-Phenyl	4-Cl-Benzyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-188	COOH	Phenyl	3,4-DiOMe-Phenyl	4-Cl-Benzyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-189	COOH	Phenyl	3,4-DiOMe-Phenyl	4-SMe-Benzyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-

Nr.	R	R ⁴	R ⁵	R ⁶	Z	B	R ²	R ³	W	X	Y	Het
I-190	COOH	Phenyl	3,4-DiOMe-Phenyl	4-SMe-Benzyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-191	COOH	Phenyl	3,4-DiOMe-Phenyl	4-SMe-Benzyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-192	COOH	Phenyl	3,4-DiOMe-Phenyl	3-COOH-Benzyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-193	COOH	Phenyl	3,4-DiOMe-Phenyl	3-COOH-Benzyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-194	COOH	Phenyl	3,4-DiOMe-Phenyl	3-COOH-Benzyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-195	COOH	Phenyl	3,4-DiOMe-Phenyl	4-COOH-3-OMeBenzyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-196	COOH	Phenyl	3,4-DiOMe-Phenyl	4-COOH-3-OMeBenzyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-197	COOH	Phenyl	3,4-DiOMe-Phenyl	4-COOH-3-OMeBenzyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-198	COOH	Phenyl	3,4-DiOMe-Phenyl	4-COOH-3-OMeBenzyl	O	CH ₂ CH ₂ CH ₂	Ethyl	Me	CH	N	N	-
I-199	COOH	Phenyl	3,4-DiOMe-Phenyl	4-COOH-3-OMeBenzyl	O	CH ₂ CH ₂ CH ₂	CF ₃	Me	CH	N	N	-
I-200	COOH	Phenyl	3,4-DiOMe-Phenyl	4-COOH-3-OMeBenzyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	1)
I-201	COOH	Phenyl	3,4-DiOMe-Phenyl	4-COOH-3-MeBenzyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-202	COOH	Phenyl	3,4-DiOMe-Phenyl	4-COOH-3-MeBenzyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-

Nr.	R	R ⁴	R ⁵	R ⁶	Z	B	R ²	R ³	W	X	Y	Het
I-203	COOH	Phenyl	3,4-DiOMe-Phenyl	4-COOH-3-MeBenzyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-204	COOH	Phenyl	3,4-DiOMe-Phenyl	4-COOH-3-MeBenzyl	O	CH ₂ CH ₂ CH ₂	OMe	(CH ₂ CH ₂ CH ₂ C)		N	N	-
I-205	COOH	Phenyl	3,4-DiOMe-Phenyl	4-Ethyl-Benzyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-206	COOH	Phenyl	3,4-DiOMe-Phenyl	4-Ethyl-Benzyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-207	COOH	Phenyl	3,4-DiOMe-Phenyl	4-Ethyl-Benzyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-208	COOH	Phenyl	3,4-DiOMe-Phenyl	2-Phenyl-Ethyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-209	COOH	Phenyl	3,4-DiOMe-Phenyl	2-Phenyl-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-210	COOH	Phenyl	3,4-DiOMe-Phenyl	2-Phenyl-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-211	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-Me-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-212	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-Me-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-213	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-Me-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	(OCH ₂ CH ₂ C)		N	N	-
I-214	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-Me-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	(CH ₂ CH ₂ CH ₂ C)		N	N	-
I-215	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-Me-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	1)

Nr.	R	R ⁴	R ⁵	R ⁶	Z	B	R ²	R ³	W	X	Y	Het
I-216	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-Me-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-217	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-OMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-218	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-OMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-219	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-OMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	(CH ₂ CH ₂ CH ₂ C)		N	N	-
I-220	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-OMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	(OCH ₂ CH ₂ C)		N	N	-
I-221	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-OMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	1)
I-222	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-OMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-223	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-OMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	CF ₃	Me	CH	N	N	-
I-224	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(3,4-DiOMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-225	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(3,4-DiOMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-226	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(3,4-DiOMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	(CH ₂ CH ₂ CH ₂ C)		N	N	-
I-227	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(3,4-DiOMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	(OCH ₂ CH ₂ C)		N	N	-
I-228	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(3,4-DiOMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	1)

Nr.	R	R ⁴	R ⁵	R ⁶	Z	B	R ²	R ³	W	X	Y	Het
I-229	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(3,4-DiOMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-230	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-COOH-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-231	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-COOH-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-232	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-COOH-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	(CH ₂ CH ₂ CH ₂ C)		N	N	-
I-233	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-COOH-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	(OCH ₂ CH ₂ C)		N	N	-
I-234	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-COOH-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	1)
I-235	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-COOH-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-236	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-SMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-237	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-SMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-238	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-SMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-239	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-Cl-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-240	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-Cl-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-241	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-Cl-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)

Nr.	R	R ⁴	R ⁵	R ⁶	Z	B	R ²	R ³	W	X	Y	Het
I-242	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(3,4-DiCl-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-243	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(3,4-DiCl-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-244	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(3,4-DiCl-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	(OCH ₂ CH ₂ C)		N	N	-
I-245	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(3,4-DiCl-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-246	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-COOH-3-OMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-247	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-COOH-3-OMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-248	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-COOH-3-OMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-249	COOH	Phenyl	3,4-DiOMe-Phenyl	3-Phenyl-Propyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-250	COOH	Phenyl	3,4-DiOMe-Phenyl	3-Phenyl-Propyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-251	COOH	Phenyl	3,4-DiOMe-Phenyl	3-Phenyl-Propyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-252	COOH	Phenyl	3,4-DiOMe-Phenyl	3-(3,4,5-triOMe-Phenyl)Prop-2E-enyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-253	COOH	Phenyl	3,4-DiOMe-Phenyl	3-(3,4,5-triOMe-Phenyl)Prop-2E-enyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-254	COOH	Phenyl	3,4-DiOMe-Phenyl	3-(3,4,5-triOMe-Phenyl)Prop-2E-enyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)

Nr.	R	R ⁴	R ⁵	R ⁶	Z	B	R ²	R ³	W	X	Y	Het
I-255	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(3,4-methylenedioxy-phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-256	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(3,4-methylenedioxy-phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-257	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(3,4-methylenedioxy-phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-258	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-DiMethyl-amino-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-259	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-DiMethyl-amino-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-260	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-DiMethyl-amino-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-261	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-Hydroxy-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-262	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-Hydroxy-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-263	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-Hydroxy-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	-
I-264	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-Hydroxy-3-OMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-265	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-Hydroxy-3-OMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-266	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-Hydroxy-3-OMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)

Nr.	R	R ⁴	R ⁵	R ⁶	Z	B	R ²	R ³	W	X	Y	Het
I-267	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-Ethoxy-3-Methoxy-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-268	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-Ethoxy-3-Methoxy-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-269	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(4-Ethoxy-3-Methoxy-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	1)
I-270	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(3,5-DiOMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-271	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(3,5-DiOMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-272	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(3,5-DiOMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-273	COOH	Phenyl	Phenyl	Me	O	CH ₂ CH ₂	Me	Me	CH	N	N	-
I-274	COOH	Phenyl	Phenyl	Me	O	CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-275	COOH	Phenyl	Phenyl	Me	O	CH ₂ CH ₂	OMe	(CH ₂ CH ₂ CH ₂ C)		N	N	-
I-276	COOH	Phenyl	Phenyl	Me	O	CH ₂ CH ₂	OMe	(OCH ₂ CH ₂ C)		N	N	-
I-277	COOH	Phenyl	Phenyl	Me	O	CH ₂ CH ₂	Ethyl	Me	CH	N	N	-
I-278	COOH	Phenyl	Phenyl	Me	O	CH ₂ CH ₂	-	-	-	-	-	1)
I-279	COOH	Phenyl	Phenyl	Me	O	CH ₂ CH ₂	-	-	-	-	-	2)
I-280	COOH	4-OMe Phenyl	Phenyl	Me	O	CH ₂ CH ₂	Me	Me	CH	N	N	-
I-281	COOH	4-OMe Phenyl	Phenyl	Me	O	CH ₂ CH ₂	OMe	Me	CH	N	N	-

Nr.	R	R ⁴	R ⁵	R ⁶	Z	B	R ²	R ³	W	X	Y	Het
I-282	COOH	4-OMe Phenyl	Phenyl	Me	O	CH ₂ CH ₂	-	-	-	-	-	2)
I-283	COOH	4-OMe Phenyl	Phenyl	Me	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-284	COOH	4-OMe Phenyl	Phenyl	Me	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-285	COOH	4-OMe Phenyl	Phenyl	Me	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	1)
I-286	COOH	4-OMe Phenyl	Phenyl	2(3,4-DiOMe- Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-287	COOH	4-OMe Phenyl	Phenyl	2(3,4-DiOMe- Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-288	COOH	4-OMe Phenyl	Phenyl	2(3,4-DiOMe- Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-289	COOH	Phenyl	Phenyl	2-(¹ Thiophenyl)-Ethyl [sic]	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-290	COOH	Phenyl	Phenyl	2-(¹ Thiophenyl)-Ethyl [sic]	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-291	COOH	Phenyl	Phenyl	2-(¹ Thiophenyl)-Ethyl [sic]	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-292	COOH	Phenyl	Phenyl	2-(3,4,5-Tri OMe- Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-293	COOH	Phenyl	Phenyl	2-(3,4,5-Tri OMe- Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-294	COOH	Phenyl	Phenyl	2-(3,4,5-Tri OMe- Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)

Nr.	R	R ⁴	R ⁵	R ⁶	Z	B	R ²	R ³	W	X	Y	Het
I-295	COOH	Phenyl	Phenyl	Hex-3E-enyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-
I-296	COOH	Phenyl	Phenyl	Hex-3E-enyl	O	CH ₂ CH ₂ CH ₂	OMe	Me	CH	N	N	-
I-297	COOH	Phenyl	Phenyl	Hex-3E-enyl	O	CH ₂ CH ₂ CH ₂	OMe	(CH ₂ CH ₂ CH ₂ C)		N	N	-
I-298	COOH	Phenyl	Phenyl	Hex-3E-enyl	O	CH ₂ CH ₂ CH ₂	OMe	(OCH ₂ CH ₂ C)		N	N	-
I-299	COOH	Phenyl	Phenyl	Hex-3E-enyl	O	CH ₂ CH ₂ CH ₂	OMe	OMe	CH	N	N	-
I-300	COOH	Phenyl	Phenyl	Hex-3E-enyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	1)
I-301	COOH	Phenyl	Phenyl	Hex-3E-enyl	O	CH ₂ CH ₂ CH ₂	-	-	-	-	-	2)
I-302	COOH	Phenyl	3,4-DiOMe-Phenyl	2-(3,4-Di OMe-Phenyl)-Ethyl	O	CH ₂ CH ₂ CH ₂	Me	Me	CH	N	N	-

1* = 2-(4,5-dimethyloxazolyl)

2* = 2-(4,5-dimethylthiazolyl)

Example 12

Receptor binding data were measured by the binding assay
5 described above for the compounds listed below.

The results are shown in Table 2.

Table 2

10

Receptor binding data (K_i values)

	Compound	ET _A K_i [nM]	ET _B K_i [nM]
15	I-2 one diast.	43	345
	I-224 one diast.	33	6.8
	I-171 one diast.	15.7	26.4
	I-145 one diast.	1100	13.6
	I-137 one diast.	60	11
20	I-1 one diast.	190	495
	I-88 one diast.	50	10
	I-89 one diast.	25	17
	I-35 one diast.	400	250
	I-36 one diast.	300	250
25	I-128 one diast.	46	9
	I-129 one diast.	23	10
	I-44 one diast.	205	365
	I-45 one diast.	40	255
	I-89 one diast.	35	93
30	I-10 one diast.	65	190
	I-116 one diast.	9	43
	I-290 one diast.	22	700
	I-292 one diast.	1.8	170
	I-293 one diast.	13	15
35	I-295 one diast.	215	1400

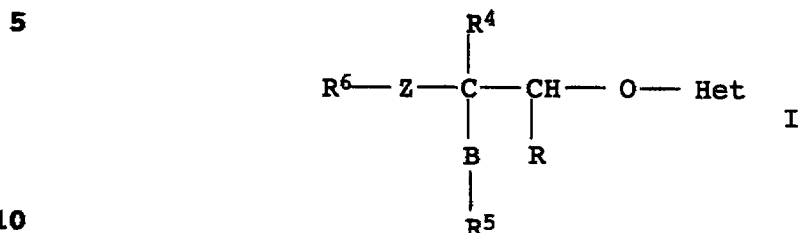
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We claim:

1. A carboxylic acid derivative of the formula I



where the substituents have the following meanings:

R is tetrazole [sic] or a group



R¹ is a radical OR⁷

20

in which R⁷ is:

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

C₃-C₈-cycloalkyl, C₁-C₈-alkyl,

CH₂-phenyl, unsubstituted or substituted,

30

C₃-C₆-alkenyl or a C₃-C₆-alkynyl group, unsubstituted or
substituted, or

phenyl, unsubstituted or substituted,

35

R² is hydrogen, hydroxyl, NH₂, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂,
halogen, C₁-C₄-alkyl, C₂-C₄-alkenyl, C₂-C₄-alkynyl,
C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy or
C₁-C₄-alkylthio, or CR² is linked to CR¹⁰ as indicated below
40 to give a 5- or 6-membered ring, or, if Het is a
five-membered ring, CR² can together with CR³ be a 5- or
6-membered alkenyl or alkylenyl [sic] ring which is
unsubstituted or substituted;

45 X is nitrogen or methine;

Y is nitrogen or methine;



- W is nitrogen or CR¹⁰, where R¹⁰ is hydrogen, halogen or C₁₋₄-alkyl, or CR¹⁰ forms together with CR² or CR³ a 5- or 6-membered alkylene or alkenylene ring which is unsubstituted or substituted and in which in each case one or more methylene groups can be replaced by oxygen, sulfur, -NH or -N(C₁₋₄-alkyl);
- 5
- R³ is hydrogen, hydroxyl, NH₂, NH(C₁₋₄-alkyl), N(C₁₋₄-alkyl)₂, 10 halogen, C₁₋₄-alkyl, C₂₋₄-alkenyl, C₂₋₄-alkynyl, C₁₋₄-haloalkyl, C₁₋₄-alkoxy, C₁₋₄-haloalkoxy, C₁₋₄-alkylthio; or CR³ is linked to CR¹⁰ as indicated above to give a 5- or 6-membered ring;
- 15 R⁴ and R⁵ (which may be identical or different) are:
- phenyl or naphthyl, unsubstituted or substituted, or
- phenyl or naphthyl which are linked together in the ortho 20 positions by a direct linkage, a methylene, ethylene, or ethenylene group, an oxygen or sulfur atom or an SO₂, NH or N-alkyl group
- C₃₋₈-cycloalkyl, unsubstituted or substituted;
- 25
- R⁶ is hydrogen, C₁₋₈-alkyl, C₃₋₈-alkenyl or C₃₋₈-alkynyl, it being possible for each of these radicals to be substituted one or more times by: halogen, hydroxyl, mercapto, carboxyl, nitro, amino, cyano, C₁₋₄-alkoxy, C₃₋₆-alkenyloxy, 30 C₃₋₆-alkynyloxy, C₁₋₄-alkylthio, C₁₋₄-haloalkoxy, C₁₋₄-alkylcarbonyl, C₁₋₄-alkoxycarbonyl, C₃₋₈-alkylcarbonylalkyl, NH(C₁₋₄-alkyl), N(C₁₋₄-alkyl)₂, C₃₋₈-cycloalkyl, hetaryloxy or hetaryl, five- or six-membered, containing one to three nitrogen atoms and/or 35 one sulfur or oxygen atom, phenoxy or phenyl, it being possible for said aryl radicals in turn to be substituted one or more times, eg. one to three times, by halogen, hydroxyl, mercapto, carboxyl, nitro, cyano, C₁₋₄-alkyl, C₁₋₄-haloalkyl, C₁₋₄-alkoxy, C₁₋₄-haloalkoxy, amino, 40 NH(C₁₋₄-alkyl), N(C₁₋₄-alkyl)₂ or C₁₋₄-alkylthio;
- phenyl or naphthyl, each of which can be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, amino, C₁₋₄-alkyl, C₁₋₄-haloalkyl, C₁₋₄-alkoxy, 45 C₁₋₄-haloalkoxy, phenoxy, C₁₋₄-alkylthio, C₁₋₄-alkylamino, C₁₋₄-dialkylamino, dioxomethylene [sic] or dioxoethylene [sic];



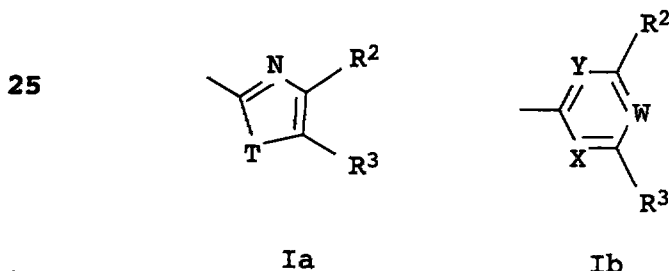
a five- or six-membered heteroaromatic system comprising one to three nitrogen atoms and/or one sulfur or oxygen atom, which may carry one to four halogen atoms and/or one to two of the following radicals: C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₁-C₄-alkylthio, phenyl, phenoxy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

C₃-C₈-cycloalkyl, it being possible for these radicals to be substituted one or more times by: halogen, hydroxyl, mercapto, carboxyl, nitro, cyano, C₁-C₄-alkyl, C₂-C₄-alkenyl, C₂-C₄-alkynyl, C₁-C₄-alkoxy, C₁-C₄-alkylthio, C₁-C₄-haloalkoxy;

Z is sulfur or oxygen;

B is C₂-C₄-alkylene

Het is a heterocyclic radical of the formula Ia or Ib



30 with T = O, S, NR⁸

R⁸ is C₁-C₆ alkyl

35 and the physiologically tolerated salts and the enantiomerically pure forms.

2. The use of a carboxylic acid derivative as claimed in claim 1 for producing drugs.

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