

PCT Trans/12
9805326-7-
1/055 copy/

IN THE MATTER OF a Singapore
Application corresponding to
PCT Application PCT/EP97/01688

I, Stephen DRANE BSc PhD BDÜ,
c/o Europa House, Marsham Way, Gerrards Cross, Buckinghamshire,
England, do solemnly and sincerely declare that I am conversant
with the English and German languages and am a competent
translator thereof, and that to the best of my knowledge and
belief the following is a true and correct translation of the
PCT Application filed under No. PCT/EP97/01688.

Date: 7 September 1998



S. DRANE

For and on behalf of RWS Translations Ltd.

PCT
WJ/LTA/HM/PAT/8015259
D & N

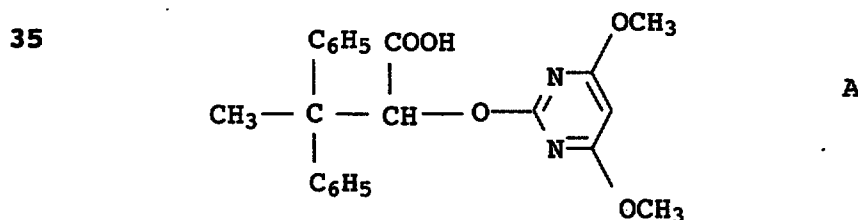
Novel α -hydroxy acid derivatives, their preparation and use

The present invention relates to novel α -hydroxy acid deriva-
5 tives, their preparation and use.

Endothelin is a peptide which is composed of 21 amino acids and is synthesized and released by the vascular endothelium. Endothelin exists in three isoforms, ET-1, ET-2 and ET-3. "Endothelin" or "ET" hereinafter signifies one or all isoforms of endothelin. Endothelin is a potent vasoconstrictor and has a great effect on vascular 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).

Increased or abnormal [sic] release of endothelin causes a persistent contraction in peripheral, renal and cerebral blood vessels, which may lead to disorders. As reported in the literature, endothelin is involved in a number of disorders; these include hypertension, myocardial infarct, heart failure, kidney failure, pulmonary hypertension, Raynaud's syndrome, cerebral vasospasms, atherosclerosis, stroke, benign prostate hypertrophy and asthma (Japan J. Hypertension [sic] 12, 79 (1989), 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 [sic] 66, 373 (1994), Stroke 25, 904 (1994), Nature 365, 759 (1993), J. Mol. Cell. Cardiol. 27, A234 (1995), Cancer Research 56, 663 (1996)).

A compound having the formula A



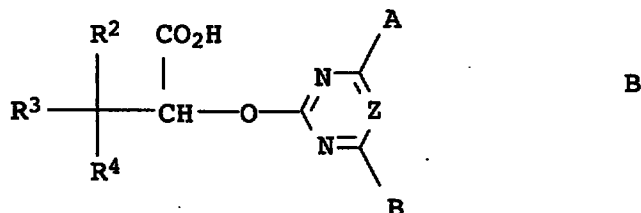
is mentioned in the European patent application with the file number P 44 36 851.8 (page 32, compound I-28). However, this compound cannot be prepared by the preparation process mentioned
45 in this patent application.

2

Compounds of the formula B where R³ can be, for example, phenyl, and R² and R⁴ can be hydrogen or C₁-C₄-alkyl, are described in the European patent with the number 0 347 811 B1 as substances with herbicidal activity.

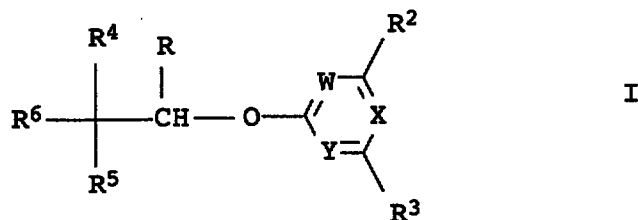
5

10



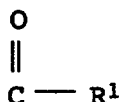
The invention relates to the α-hydroxy carboxylic acid derivatives of the formula I

20



25 where R is formyl, a tetrazole [sic], nitrile [sic], a group COOH or a radical which can be hydrolyzed to COOH. R is, for example, a group

30



where R¹ has the following meanings:

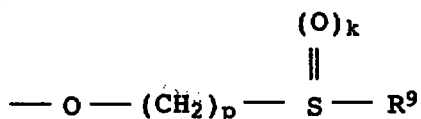
35 a) hydrogen

b) a succinylimidoxy [sic] group

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

45 d) R¹ furthermore a group

3



5

where k can assume the values 0, 1 and 2, p can assume the values 1, 2, 3 and 4, and R⁹ is

C₁-C₄-alkyl, C₃-C₇-cycloalkyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl or unsubstituted or substituted phenyl which can be substituted
 10 by one or more, eg. 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, C₁-C₄-alkylamino, C₁-C₄-dialkylamino;

15 e) R¹ furthermore a radical OR¹⁰, where R¹⁰ is:

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

C₃-C₈-cycloalkyl, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl,

25 C₁-C₈-alkyl, in particular C₁-C₄-alkyl such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl;

CH₂-phenyl which can be substituted by one or more of the following radicals: halogen, nitro, cyano, C₁-C₄-alkyl,
 30 C₁-C₄-haloalkyl, hydroxyl, C₁-C₄-alkoxy, mercapto, C₁-C₄-alkylthio, amino, C₁-C₄-alkylamino, C₁-C₄-dialkylamino,

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

35

R¹⁰ can furthermore be a phenyl radical which can carry one to five halogen atoms and/or one to three of the following radicals: nitro, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl,
 40 hydroxyl, C₁-C₄-alkoxy, mercapto, C₁-C₄-alkylthio, amino, C₁-C₄-alkylamino, C₁-C₄-dialkylamino;

a 5-membered heteroaromatic system which is linked via a nitrogen atom and contains one to three nitrogen atoms, and which may carry one or two halogen atoms and/or one or two of
 45 the following radicals: C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, phenyl, C₁-C₄-haloalkoxy and/or C₁-C₄-alkylthio. Particular mention may be made of: 1-pyrazolyl,

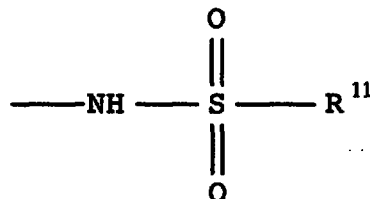
4

3-methyl-1-pyrazolyl, 4-methyl-1-pyrazolyl,
 3,5-dimethyl-1-pyrazolyl, 3-phenyl-1-pyrazolyl,
 4-phenyl-1-pyrazolyl, 4-chloro-1-pyrazolyl,
 4-bromo-1-pyrazolyl, 1-imidazolyl, 1-benzimidazolyl,
 1,2,4-triazol-1-yl, 3-methyl-1,2,4-triazol-1-yl,
 5-methyl-1,2,4-triazol-1-yl, 1-benzotriazolyl,
 3,4-dichloroimidazol-1-yl;

f) R^1 furthermore a radical

10

15



where R^{11} is:

20

C_1 - C_4 -alkyl, C_3 - C_6 -alkenyl, C_3 - C_6 -alkynyl, C_3 - C_8 -cycloalkyl, it
 being possible for these radicals to carry a C_1 - C_4 -alkoxy,
 C_1 - C_4 -alkylthio and/or a phenyl radical;

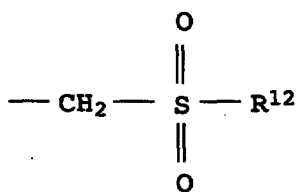
25

phenyl which is unsubstituted or substituted, in particular
 as mentioned above;

g) R^1 a radical

30

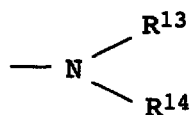
35



where R^{12} has the same meanings as R^{11} ;

h) R^1 can furthermore be

40



45

where R^{13} and R^{14} can be identical or different and have the
 following meanings:

hydrogen, C₁-C₇-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-alkanyl [sic], C₃-C₇-alkynyl, benzyl, phenyl, unsubstituted or substituted, as described above

- 5 or R¹³ and R¹⁴ together form a C₄-C₇-alkylene chain which is closed to a ring, is unsubstituted or substituted by C₁-C₄-alkyl, for example, and may contain a hetero atom, eg. oxygen, nitrogen or sulfur, such as -(CH₂)₄-, -(CH₂)₅-,
 10 -(CH₂)₆-, -(CH₂)₇-, -(CH₂)₂-O-(CH₂)₂-, -(CH₂)₂-S-(CH₂)₂-,
 -CH₂-NH-(CH₂)₂-, -(CH₂)₂-NH-(CH₂)₂-.

The other substituents have the following meanings:

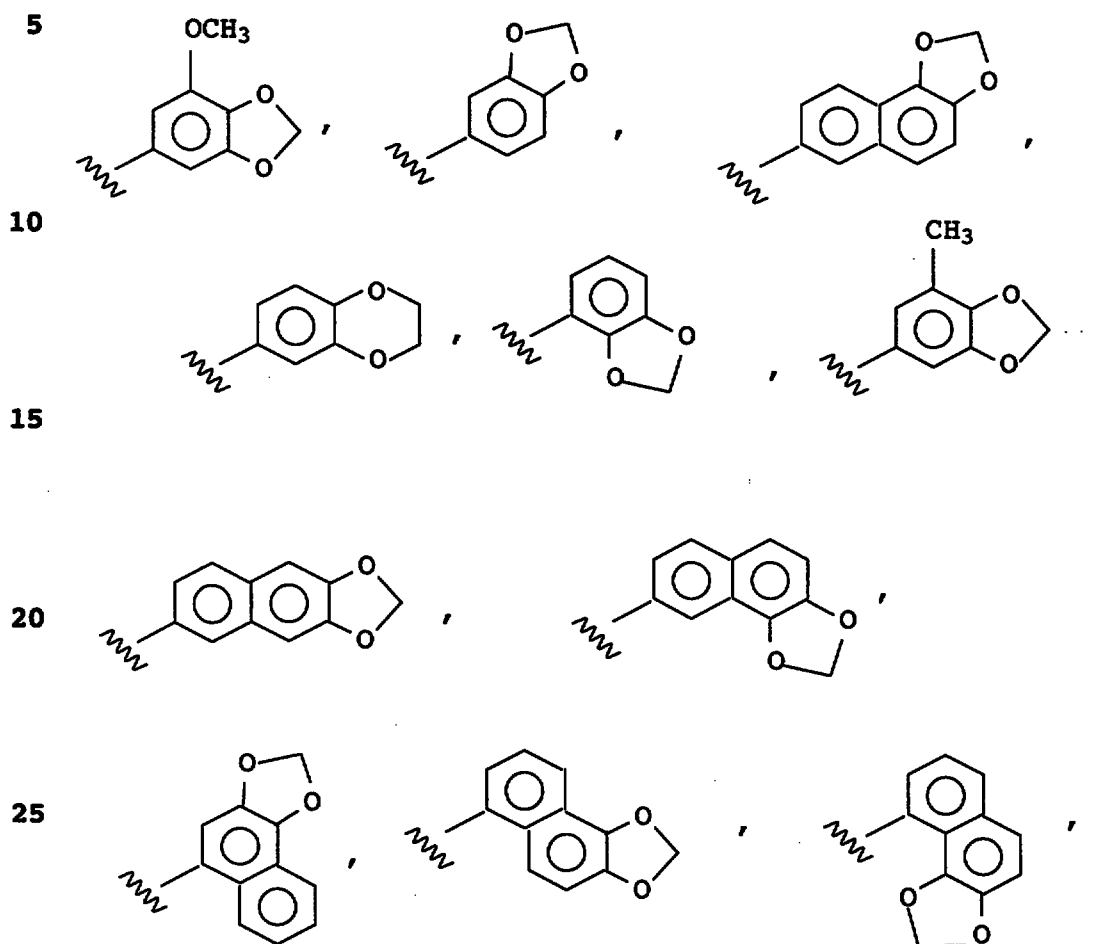
- W nitrogen or C-NO₂, furthermore W can be a CH group when one
 15 or more of the substituents R², R³, R¹⁵ and/or R¹⁶ are a nitro group, or when X and/or Y are nitrogen;
- R² is hydrogen, halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl,
 20 C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, hydroxyl, mercapto, C₁-C₄-alkylthio, nitro, amino, C₁-C₄-alkylamino or C₁-C₄-dialkylamino, cyano, phenyl, optionally substituted once to three times by halogen, hydroxyl, amino, mono- or dialkyl (C₁-C₃)-amino, C₁-C₃-alkyl, C₁-C₃-alkoxy, mercapto or C₁-C₃-alkylthio, carboxyl, C₁-C₃-alkylcarboxyl;
- 25 or
- a five- or six-membered heteroaromatic system containing one to three nitrogen atoms and/or one sulfur or oxygen atom,
 30 which carries one to three substituents as described above;
- R² can furthermore form, with the adjacent carbon atom and X, a 5- or 6-membered alkylene or alkylidene [sic] ring in each of which one or two carbon atoms can be replaced by a hetero atom such as nitrogen, sulfur or oxygen, and which can be
 35 substituted once to three times by the following radicals: halogen, nitro, cyano, hydroxyl, mercapto, C₁-C₃-alkyl, C₁-C₃-haloalkyl, C₁-C₃-alkoxy, C₁-C₃-alkylthio, amino, C₁-C₃-alkylamino, C₁-C₃-dialkylamino;
- 40 X is nitrogen or CR¹⁵ where R¹⁵ is hydrogen, nitro, C₁-C₅-alkyl or C₂-C₅-alkenyl, optionally substituted once or twice by hydroxyl, carboxyl or phenyl, which in turn can be substituted by C₁-C₃-alkyl, hydroxyl or carboxyl;
 45 C₁-C₆-alkoxy, C₁-C₆-alkylthio, phenyl, hydroxyl, mercapto, nitro, amino, C₁-C₄-alkylamino, C₁-C₄-dialkylamino, cyano or carboxyl;

- it is furthermore possible for CR¹⁵ to be linked to R² to give a 5- or 6-membered ring as described above, or CR¹⁵ can form with R³ and its adjacent carbon atom a 5- or 6-membered alkylene or alkylidene [sic] ring in each of which one or two carbon atoms can be replaced by nitrogen, oxygen or sulfur, and the 5- or 6-membered ring may optionally be substituted once to three times by the following radicals:
- halogen, nitro, cyano, hydroxyl, mercapto, C₁-C₃-alkyl, C₁-C₃-haloalkyl, C₁-C₃-alkoxy, C₁-C₃-alkylthio, amino, C₁-C₃-alkylamino, C₁-C₃-dialkylamino or carboxyl; nitrogen in the 5-membered ring may also be substituted by a formyl or acetyl group;
- R³ can have the same meanings as R², R² and R³ can be identical or different; it is furthermore possible for R³ to form with the adjacent carbon atom and with X a 5- or 6-membered ring as described above; it is furthermore possible for R³ to form together with the adjacent carbon atom and Y a 5- or 6-membered alkylene or alkylidene [sic] ring in each of which one or two carbon atoms can be replaced by nitrogen, oxygen or sulfur; the 5- or 6-membered ring may optionally be substituted once to three times by the following radicals:
- halogen, nitro, cyano, hydroxyl, mercapto, C₁-C₃-alkyl, C₁-C₃-haloalkyl, C₁-C₃-alkoxy, C₁-C₃-alkylthio, amino, C₁-C₃-alkylamino, C₁-C₃-dialkylamino or carboxyl; nitrogen in the 5-membered ring may also be substituted by a formyl or acetyl group;
- Y is nitrogen or CR¹⁶ where R¹⁶ is hydrogen, C₁-C₅-alkyl, C₁-C₅-alkoxy, C₁-C₅-alkylthio, nitro, phenyl, hydroxyl, halogen, cyano, amino, C₁-C₄-alkylamino, C₁-C₄-dialkylamino, mercapto or carboxyl, or CR¹⁶ forms together with R³ and its adjacent carbon atom a 5- or 6-membered ring as described above;
- R⁴ is phenyl, naphthyl, dihydro- or tetrahydronaphthyl, which can be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, phenoxy, phenyl, C₁-C₄-alkylthio, amino, C₁-C₄-alkylamino or C₁-C₄-dialkylamino, it being possible for two radicals on adjacent carbon atoms to form, together with the latter, a five- or six-membered ring which is linked by an alkylene or alkylidene [sic] group and in which one or more methylene or methylidene [sic] groups can be replaced by oxygen, such as -(CH₂)₃-, -(CH₂)₄-, -CH=CH-O-, -O-CH₂-O-, -O-(CH₂)₂-O-,

7

-CH=CH-CH₂- or -O-CH=CH-O-;

R⁴ can be, for example, the following radicals:



R⁴ can furthermore be a five- or six-membered heteroaromatic system which contains a nitrogen, sulfur or oxygen atom and which can carry one or two of the following radicals:

35 halogen, cyano, nitro, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, phenoxy, C₁-C₄-alkylthio, C₁-C₄-alkylamino or C₁-C₄-dialkylamino;

40 in addition, R⁴ and R⁵ can be phenyl groups which are connected 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;

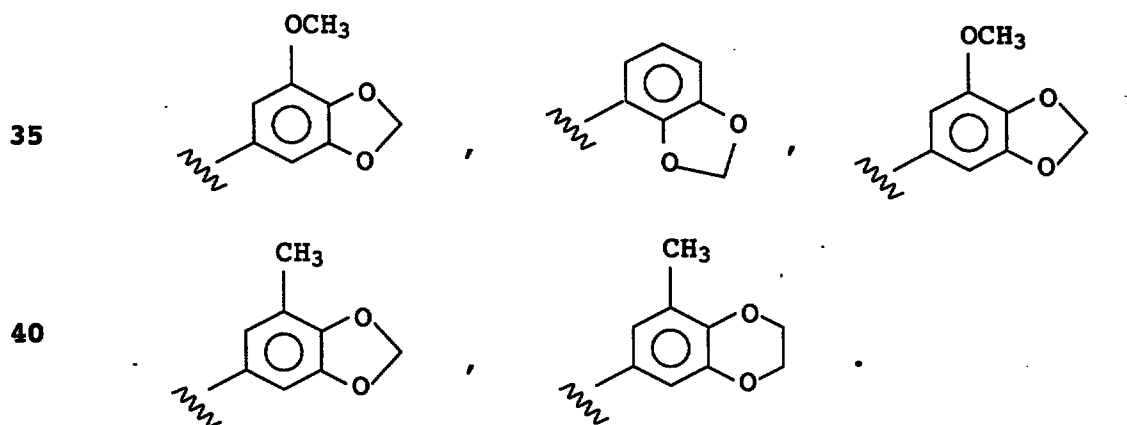
R⁵ can have the same meanings as R⁴, it being possible for R⁴ and R⁵ to be identical or different;

45

- R^6 is hydrogen, C_1 - C_8 -alkyl, C_2 - C_8 -alkenyl or C_3 - C_8 -alkynyl, it being possible for each of these radicals to be substituted one or more times by: halogen, nitro, cyano, C_1 - C_4 -alkoxy, hydroxyl, C_1 - C_4 -alkylthio, mercapto, C_1 - C_4 -haloalkoxy, carboxyl, C_1 - C_4 -alkylcarboxyl, C_1 - C_4 -alkylcarbonyl, amino, C_1 - C_4 -alkylamino, C_1 - C_4 -dialkylamino or phenyl, or naphthyl which can in turn be substituted one or more times by: halogen, nitro, cyano, hydroxyl, C_1 - C_4 -alkoxy, C_1 - C_4 -alkyl, C_1 - C_4 -haloalkyl, C_1 - C_4 -haloalkoxy, mercapto, C_1 - C_4 -alkylthio, amino, C_1 - C_4 -alkylamino, C_1 - C_4 -dialkylamino or phenoxy, R^6 is furthermore C_1 - C_4 -alkyl which is substituted by phenoxymethyl in which the phenyl group can be substituted once or twice by halogen, methyl or methoxy;
- R^6 is furthermore also a C_1 - C_8 -alkyl, C_3 - C_8 -alkenyl or C_3 - C_8 -alkynyl chain which is substituted by of the following radicals:

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

- or one of the following radicals:



45

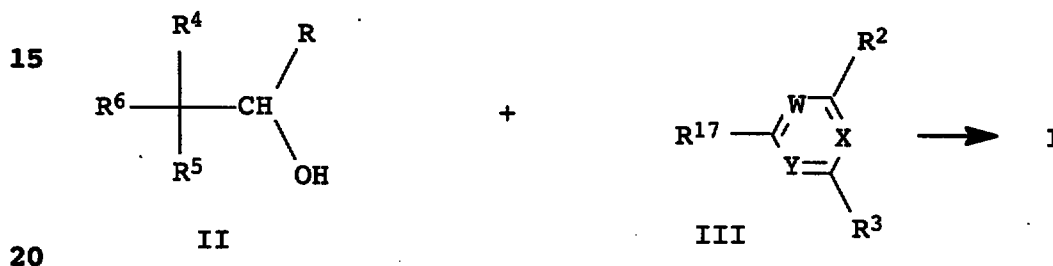
The compounds and the intermediates II for preparing them may

have one or more asymmetrically substituted carbon atoms. Such compounds may be in the form of pure enantiomers or pure diastereomers or of a mixture thereof. It is preferred to use an enantiomerically pure compound as active substance.

5

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

10 The compounds according to the invention are prepared by reacting a hydroxy acid derivative II in which the substituents have the stated meaning with compounds of the general formula III,



where R¹⁷ is halogen or R¹⁸ -SO₂-, where R¹⁸ can be C₁-C₄-alkyl, C₁-C₄-haloalkyl or phenyl.

25 The reaction preferably takes place in an inert diluent with the addition of a suitable base, ie. a base which deprotonates the intermediate II, at a temperature in the range from room temperature to the boiling point of the solvent.

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

35 such as diisopropyl ether, dibutyl ether, propylene oxide, dioxane and tetrahydrofuran, ketones such as acetone, methyl ethyl ketone, methyl isopropyl ketone and methyl isobutyl ketone, nitriles such as acetonitrile and propionitrile, alcohols such as methanol, ethanol, isopropanol, butanol and ethylene glycol,

40 esters such as ethyl acetate and amyl acetate, amides such as dimethylformamide and dimethylacetamide, sulfoxides and sulfones, such as dimethyl sulfoxide and sulfolane, and bases such as pyridine, N-methylpyrrolidone, cyclic ureas such as 1,3-dimethyl-2-imidazolidinone and 1,3-dimethyl-3,4,5,6-

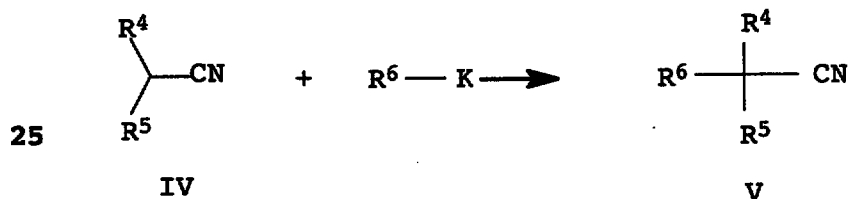
45 tetrahydro-2(1H)-pyrimidinone. The reaction is preferably carried

out at a temperature in the range from 0°C to the boiling point of the solvent or mixture of solvents.

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 organometallic compound such as butyllithium or an alkali metal amide such as lithium diisopropylamide or lithium amide, or tertiary amines, eg. triethylamine, pyridine, 4-N,N-dimethylaminopyridine, imidazole or diazobicycloundecane [sic].

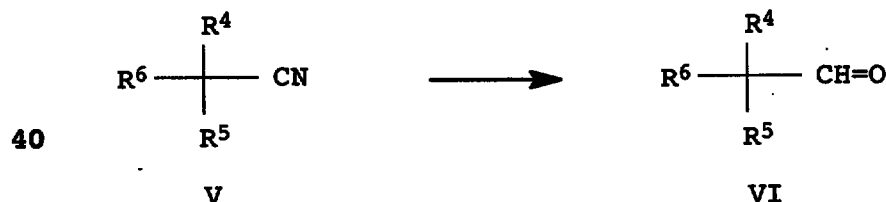
The invention also relates to compounds of the formula II which are unknown. They can be prepared in a known manner.

For example, compounds of the formula II can be prepared by converting a nitrile of the formula IV, by alkylation with the aid of a base and of a compound R⁶-K, into a nitrile V



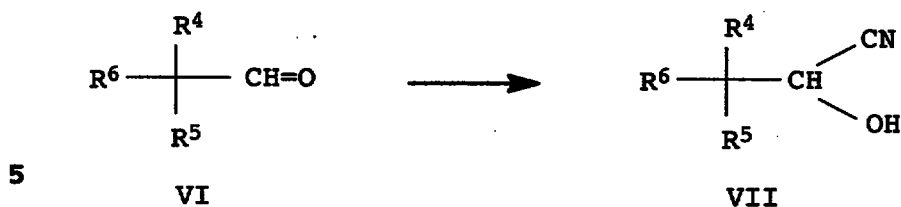
as described, for example, in Ca. J. of Chem. 47 (1969) 1587 et seq., where K is a leaving group such as halogen, tosylate, mesylate or triflate.

The nitriles V are then reduced to aldehydes VI as described in Synth. Comm. 19 (1989) 355 et seq. or J. Am. Chem. Soc. 107 (1985) 4577 et seq. Reducing agents which can be used are metal hydrides such as LiAlH₄ or (n-Bu)₂AlH.



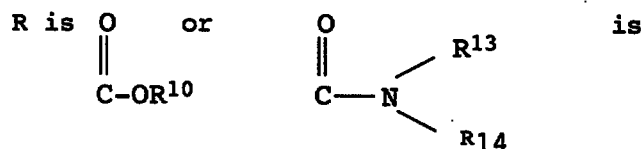
The aldehydes VI are converted by known methods (as described, for example, in Chem. Pharm. Bull. 37 (1989) 2570-2) into the corresponding cyanohydrins VII:

11

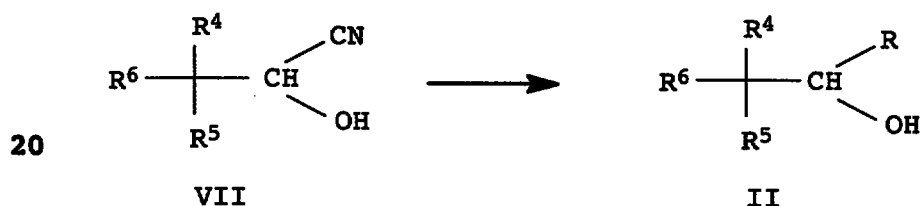


Cyanohydrins VII can be converted by hydrolysis, for example with aqueous HCl, or by the Pinner method with HCl gas in alcohol R¹⁰OH, into α-hydroxy carboxylic acid derivatives II where

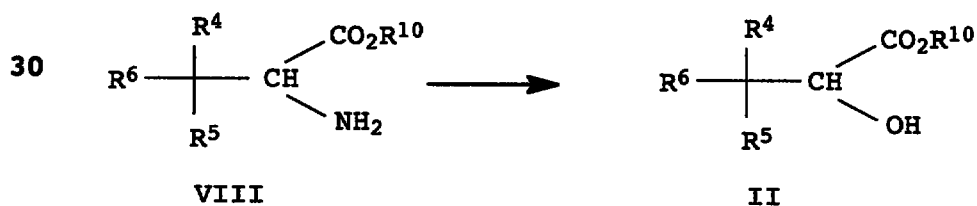
10



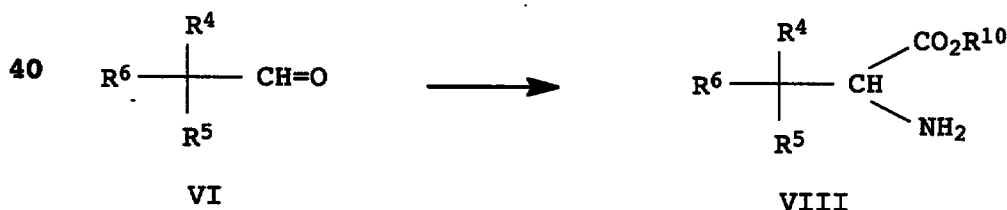
15



Compounds II can also be prepared by diazotizing an amino acid derivative VIII by known methods, eg. with sodium nitrite and aqueous sulfuric acid, and hydrolyzing to the hydroxy acid derivative II as described, for example, in Synthesis (1987), 479-80.

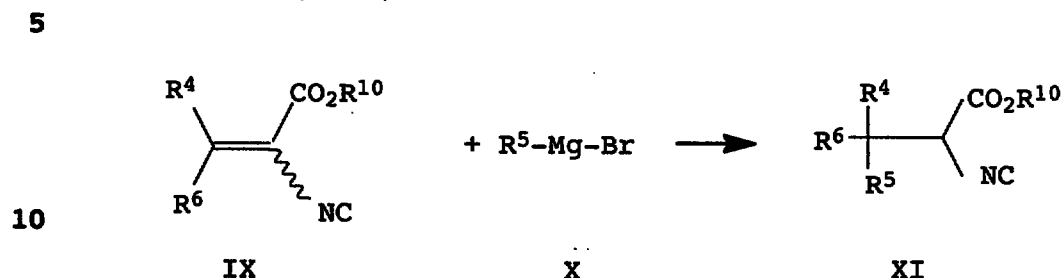


35 Amino acid derivatives VIII can be prepared, for example, in a Strecker reaction from the aldehydes VI, eg. as disclosed in Angew. Chem. Int. Ed. 26 (1987), 557 et seq.

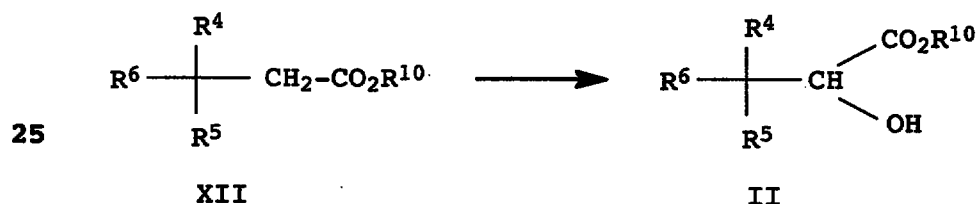


45

In addition, compounds VIII can be prepared by reacting a compound IX with a Grignard compound X, and hydrolyzing the product XI with acid to VIII, similar to the description in Liebigs Ann. (1977) 1174-1182:

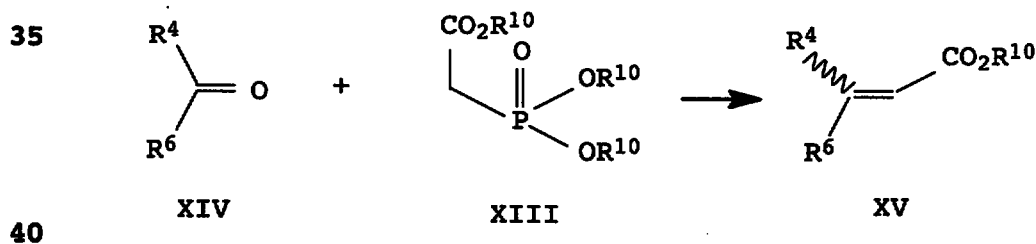


Compounds II can furthermore be synthesized by electrophilic oxidation of carboxylic acid derivatives XII, eg. with oxygen after deprotonation, as described in Tetrahedron Letters 21 20 (1975) 1731-4, or with Davis' reagent



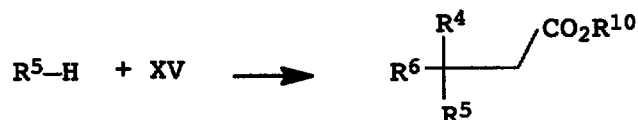
as described in J. Org. Chem. 47 (1982) 1775-77.

30 Compounds XII can be prepared by reacting a suitable phosphonate compound XIII with a carbonyl compound XIV in a Wittig-Horner reaction to give the unsaturated compound XV.



Compound XV can then be converted by a method from Chem. Ber. 64
(1931) 1493 et seq. with R⁵-H in the presence of a Friedel-Crafts
catalyst such as aluminum trichloride into the carboxylic acid
45 derivative XVI.

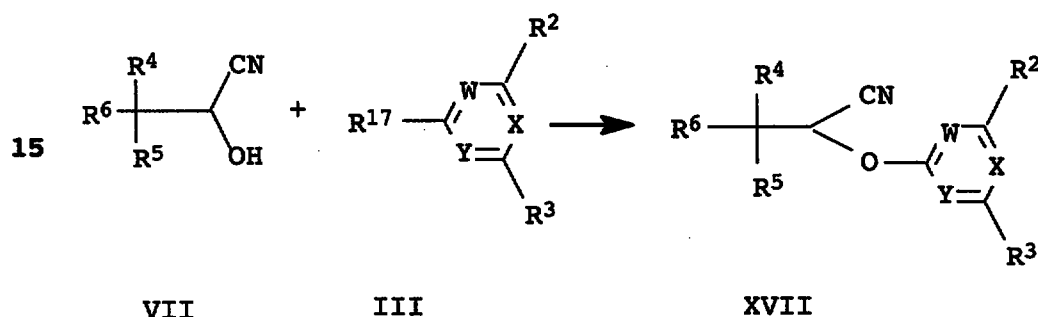
13



5

XVI

Compounds I can also be prepared by reacting cyanohydrins VII with
10 compounds III to give nitriles XVII.

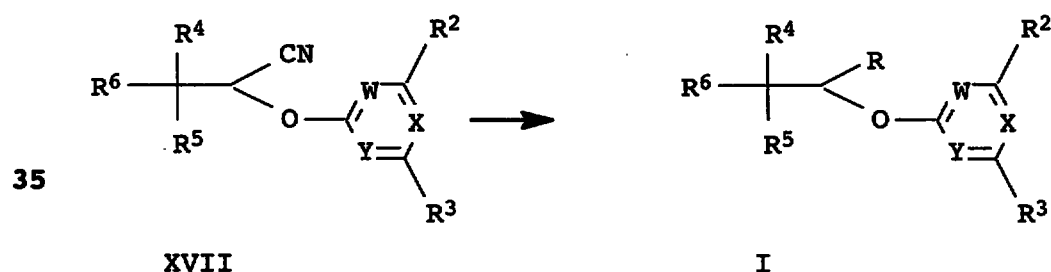


20

The reaction preferably takes place in an inert solvent with the
addition of a suitable base as described previously.

25 Compounds XVII can then be converted in a known manner, for
example by reaction with acids such as hydrochloric acid or
sulfuric acid, with or without addition of an alcohol into
compounds of type I.

30



35

40 Compounds of the formula I can be obtained in enantiomerically
pure form by starting from enantiomeric compounds II, which can
be prepared by classical racemate resolution or by
enantioselective syntheses (such as, for example, Pure Appl.
Chem., 55 (1983) 1799 et seq.; Helv. Chim. Acta, 71 (1988) 224 et
45 seq.; J. Am. Chem. Soc., 110 (1988) 1547-1557; Chem. Eng. News
(1989) 25-27) in enantiomerically pure and, where appropriate,
diastereomerically pure form, and reacting these compounds II

with III as described above. Another possibility for obtaining enantiomerically pure compounds of the formula I is classical racemate resolution of racemic or diastereomeric compounds I with suitable enantiomerically pure bases such as brucine, strychnine, 5 quinine, quinidine, chinchonidine [sic], chinchonine [sic], yohimbine, morphine, dehydroabietylamine, ephedrine (-), (+), deoxyephedrine (+), (-), threo-2-amino-1-(p-nitrophenyl)-1,3-propanediol (+), (-), threo-2-(N,N-dimethylamino)-1-(p-nitrophenyl)-1,3-propanediol (+), (-) threo-2-amino-1-phenyl-1, 10 3-propanediol (+), (-), α -methylbenzylamine (+), (-), α -(1-naphthyl)ethylamine (+), (-), α -(2-naphthyl)ethylamine (+), (-), aminomethylpinone, N,N-dimethyl-1-phenylethylamine, N-methyl-1-phenylethylamine, 4-nitrophenylethylamine, pseudoephedrine, norephedrine, norpseudoephedrine, amino acid 15 derivatives and peptide derivatives.

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

- 20 R a carboxylic acid, a carboxylic acid salt or a group which can be hydrolyzed to a carboxylic acid, as described above.
- W nitrogen or C-NO₂;
- 25 X nitrogen or CR¹⁵ where R¹⁵ is hydrogen, nitro, C₁-C₅-alkyl or C₁-C₅-alkenyl, optionally substituted by hydroxyl, carboxyl or phenyl, which can in turn be substituted by C₁-C₃-alkyl, hydroxyl or carboxyl; C₁-C₄-alkoxy, C₁-C₄-alkylthio, hydroxyl, 30 nitro, amino, cyano or carboxyl, or CR¹⁵ forms with R² and the adjacent carbon atom a 5- or 6-membered alkylene or alkylidene [sic] ring in which one or two carbon atoms can be replaced by a hetero atom such as nitrogen, oxygen or sulfur, and which can be substituted once or twice by a C₁-C₃-alkyl or 35 C₁-C₃-alkoxy group; nitrogen in the 5-membered ring may additionally be substituted by a CHO or COCH₃ group;
- R² hydrogen, halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-alkylthio, nitro, amino, methylamino, dimethylamino or 40 cyano; R² can furthermore form with the adjacent carbon atom and X a 5- or 6-membered ring as described above;
- R³ hydrogen, halogen, C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkyl, C₁-C₄-alkylthio, nitro, amino, methylamino, dimethylamino or 45 cyano; R³ can furthermore form with the adjacent carbon atom and Y a 5- or 6-membered alkylene or alkylidene [sic] ring in which one or two carbon atoms can be replaced by nitrogen,

oxygen or sulfur and which can be substituted once or twice by a C₁-C₃-alkyl or C₁-C₃-alkoxy group; nitrogen in the 5-membered ring may also be substituted by a formyl or acetyl group;

5

Y nitrogen or CR¹⁶ where R¹⁶ is hydrogen, C₁-C₃-alkyl, C₁-C₃-alkoxy, C₁-C₃-alkylthio, nitro, halogen, cyano, amino, methylamino, dimethylamino or carboxyl, or if CR¹⁶ forms together with R³ and its adjacent carbon atom a 5- or 6-membered ring as described above;

10

R⁴ is phenyl or naphthyl which can be substituted by one or more of the following radicals:

15

halogen, hydroxyl, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-alkylthio or phenyl, and the aromatic system may furthermore be substituted, exclusively or in addition to the abovementioned radicals, by two radicals on adjacent carbon atoms which together represent a 1,3-dioxomethylene [sic] or 1,4-dioxoethylene [sic] group and form with the adjacent carbon atoms a 5- or 6-membered ring respectively;

20

in addition, R⁴ and R⁵ can be phenyl groups which are connected together in ortho positions by a direct linkage, a methylene, ethylene or ethenylene group, or an oxygen or sulfur atom;

25

R⁵ can have the same meanings as R⁴, it being possible for R⁴ and R⁵ to be identical or different;

30 R⁶ is hydrogen, C₁-C₆-alkyl, C₂-C₆-alkenyl or C₃-C₆-alkynyl, it being possible for each of these radicals to be substituted once to three times by:

35

halogen, cyano, C₁-C₃-alkoxy, hydroxyl, C₁-C₃-alkylthio, mercapto, C₁-C₃-haloalkoxy, carboxyl, C₁-C₃-alkylcarboxyl or phenyl, or naphthyl which can likewise be substituted once to three times by the following radicals:

40

halogen, cyano, hydroxyl, C₁-C₃-alkoxy, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₃-haloalkoxy, mercapto, C₁-C₃-alkylthio, phenyl or phenoxy, or, exclusively or in addition to the abovementioned radicals, two radicals on adjacent carbon atoms may together represent a 1,3-dioxomethylene [sic] or 1,4-dioxoethylene [sic] group, and R⁶ can furthermore be a phenylmethoxymethyl, -ethyl or -propyl group in which the phenyl group is substituted by methyl, methoxy or halogen.

45

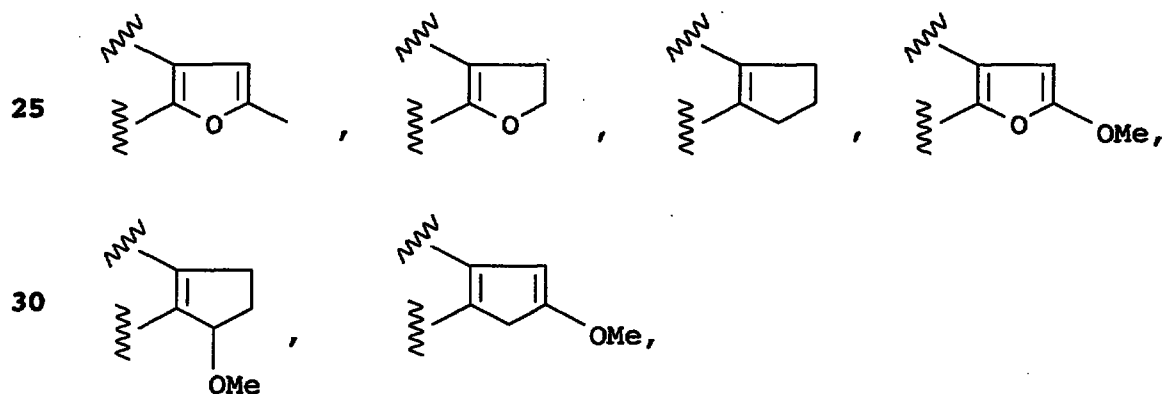
16

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

- 5 R a carboxylic acid, a carboxylic acid salt or a group which can be hydrolyzed to a carboxylic acid, as described above;
- W nitrogen;
- 10 X nitrogen or CR¹⁵ where R¹⁵ is hydrogen, C₁-C₅-alkyl or C₁-C₅-alkenyl, optionally substituted by hydroxyl, carboxyl or phenyl, which can in turn be substituted by C₁-C₃-alkyl, hydroxyl or carboxyl, C₁-C₃-alkoxy, C₁-C₃-alkylthio, hydroxyl, cyano or carboxyl, or CR¹⁵ forms with R³ and the adjacent
- 15 carbon atom a 5- or 6-membered alkylene or alkylidene [sic] ring in which one carbon atom can be replaced by oxygen and which can be substituted by a methoxy or methyl group;

for example, the 5- or 6-membered alkylene and alkylidene [sic] ring may have the following structures:

20



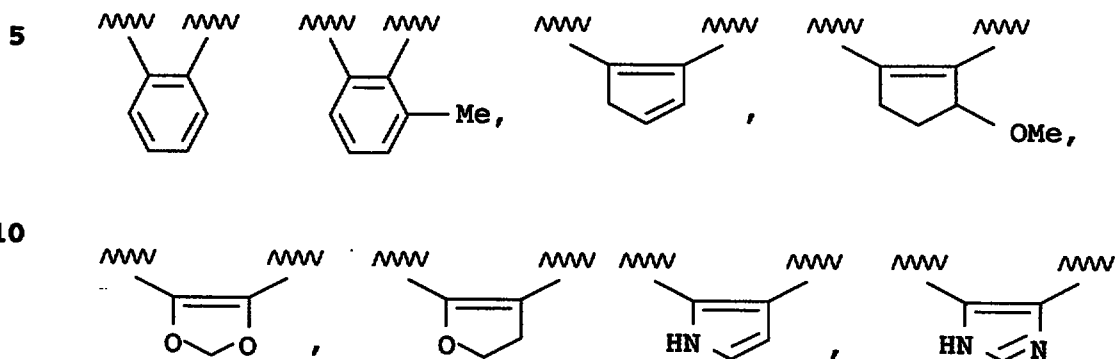
- 35 R² hydrogen, chlorine, methyl, ethyl, trifluoromethyl, nitro, methoxy, ethoxy, methylmercapto, amino, dimethylamino, methylamino; R² may furthermore form with the adjacent carbon atom and X a 5- or 6-membered ring as described above;
- 40 R³ hydrogen, chlorine, methyl, ethyl, trifluoromethyl, nitro, methoxy, ethoxy, methylmercapto, amino, methylamino or dimethylamino;

R³ may furthermore form with Y a 5- or 6-membered alkylene or alkylidene [sic] ring in which one or two carbon atoms may be replaced by nitrogen or oxygen, and which can be substituted

45

17

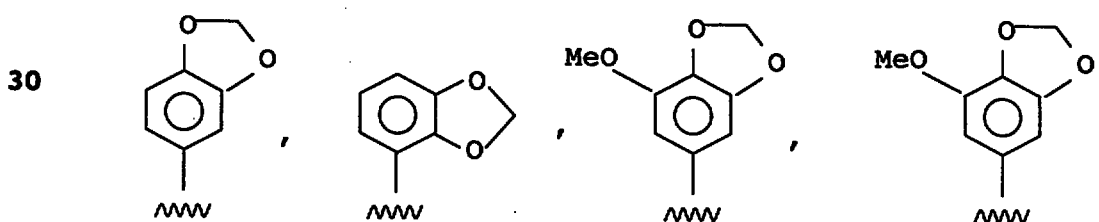
by a methyl or methoxy group; examples of such alkylene or alkylidene [sic] rings are:



15

Y nitrogen or CR¹⁶ where R¹⁶ is hydrogen, nitro, methyl, ethyl, chlorine or cyano, or CR¹⁶ forms with R³ and its adjacent carbon atom a 5- or 6-membered ring as described above;

20 R⁴ is phenyl which carries one or two of the following radicals: halogen, hydroxyl, methoxy, ethoxy, C₁-C₃-alkyl, trifluoromethyl, methylmercapto, ethylmercapto or phenyl; it is furthermore possible for two substituents to represent a dioxomethylene [sic] group, exclusively or in addition to
 25 other substituents; examples of such groups representing R⁴ are:



35

in addition, R⁴ and R⁵ can be phenyl group [sic] which are connected together in ortho positions by a direct linkage, a methylene or ethylene group;

40 R⁵ can have the same meanings as R⁴, and R⁴ and R⁵ can be identical or different;

R⁶ is hydrogen, C₁-C₆-alkyl or C₃-C₆-alkenyl, it being possible for each of these radicals to be substituted once or twice
 45 by:

chlorine, cyano, hydroxyl, carboxyl, methoxy, ethoxy, methylmercapto, methylcarboxyl, phenylmethoxy,

p-methylphenylmethoxy, p-methoxyphenylmethoxy, p-fluorophenylmethoxy, or phenyl which can be substituted once or twice by the following radicals:

- 5 chlorine, fluorine, cyano, hydroxyl, methoxy, ethoxy, trifluoromethyl, trifluoromethoxy, methylmercapto, phenyl or phenoxy, or, exclusively or in addition to the abovementioned radicals, two radicals on adjacent carbon atoms may represent a 1,3-dioxomethylene [sic] group.

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

20

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

Receptor binding studies

25

For binding studies, cloned human ET_A receptor-expressing CHO cells and guinea-pig cerebellar membranes with > 60% ET_B relative to ET_A receptors were employed.

30 Membrane preparation

- The ET_A receptor-expressing CHO cells were grown in F_{12} medium with 10% fetal calf serum, 1% glutamine, 100 U/ml penicillin and 0.2% streptomycin (Gibco BRL, Gaithersburg, MD, USA). After 48 h, the cells were washed with PBS and incubated with 0.05% trypsin-containing PBS for 5 min. After neutralization with F_{12} medium, the cells were collected by centrifugation at 300 x g. For cell lysis, the pellet was briefly washed with lysis buffer (5 mM Tris-HCl, pH 7.4 with 10% glycerol) and then incubated at a concentration of 10^7 cells/ml of lysis buffer at 4°C for 30 min. The membranes were centrifuged at 20,000 x g for 10 min, and the pellet was stored in liquid nitrogen.

45

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

5

Binding assays

For the ET_A and ET_B receptor binding assays, the membranes were suspended in incubation buffer (50 mM Tris-HCl, pH 7.4 with 5 mM
10 $MnCl_2$, 40 $\mu g/ml$ bacitracin and 0.2% BSA) at a concentration of 50 μg of protein per assay mixture and incubated at 25°C with 25 pM [^{125}I [sic]]- ET_1 (ET_A receptor assay) or 25 pM [^{125}I [sic]]- RZ_3 (ET_B receptor assay) in the presence and absence of test substance. The nonspecific binding was determined with
15 10^{-7} M ET_1 . Filtration through GF/B glass fiber filters (Whatman, England) in a Skatron cell collector (Skatron, Lier, Norway) after 30 min separated the free and the 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
20 quantified using a Packard 2200 CA liquid scintillation counter.

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

25 This assay system is a functional, cell-based assay for endothelin receptors. Certain cells show, when they are stimulated with endothelin 1 (ET_1), an increase in the intracellular calcium concentration. This increase can be measured in intact cells which have been loaded with
30 calcium-sensitive dyes.

1-Fibroblasts isolated from rats in which an endogenous endothelin receptor of the A subtype has been detected were loaded with the fluorescent dye Fura 2-am as follows: after
35 trypsinization, the cells were resuspended in buffer A (120 mM NaCl, 5 mM KCl, 1.5 mM $MgCl_2$, 1 mM $CaCl_2$, 25 mM HEPES, 10 mM glucose, pH 7.4) to a density of $2 \times 10^6/ml$ and incubated at 37°C in the dark with Fura 2-am (2 μM), Pluronic [sic] F-127 (0.04%) and DMSO (0.2%) for 30 min. The cells were then washed twice with
40 buffer A and resuspended at $2 \times 10^6/ml$.

The fluorescent signal with Ex/Em 380/510 from 2×10^5 cells per ml was continuously recorded at 30°C. The test substances and, after incubation for 3 min, ET_1 were [lacuna] to the cells, the
45 maximum change in fluorescence was determined. The response of the cells to ET_1 without previous addition of a test substance served as control and was set equal to 100%.

In vivo testing of ET antagonists

Male SD rats weighing 250 - 300 g were anesthetized with amobarbital, artificially ventilated, vagotomized and pithed. The 5 carotid artery and jugular vein were cathetized [sic].

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

10

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

15

"sudden death" induced by endothelin-1 in mice

The principle of the test comprises prevention of the sudden heart death caused in mice by endothelin, probably owing to

20 constriction of the coronary vessels, by pretreatment with endothelin receptor antagonists. Intravenous injection of 10 nmol/kg endothelin in a volume of 5 ml/kg of body weight is followed within a few minutes by the death of the animals.

25 The lethal endothelin-1 dose is checked on each occasion on a small group of animals. If the test substance is administered intravenously, usually the endothelin-1 injection which was lethal in the reference group takes place 5 min thereafter. With other modes of administration, the times between administrations 30 are longer, where appropriate up to several hours.

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

35

Functional test on vessels for endothelin receptor antagonists

Firstly a contraction is induced with K⁺ in segments of rabbit aorta after an initial tension of 2 g and a relaxation time of

40 1 h in Krebs-Henseleit solution at 37°C and a pH of 7.3 - 7.4. After washing out, an endothelin dose-effect plot is constructed up to the maximum.

Potential endothelin antagonists are administered to other

45 preparations of the same vessel 15 min before the start of the endothelin dose-effect plot. The effects of endothelin are calculated as a % of the K⁺ contraction. With effective endothelin

antagonists, the endothelin dose-effect plot is shifted to the right.

The compounds according to the invention can be administered
5 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.

10 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 substance 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.

15 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. For
20 this purpose, the active substances can 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.
25 H. Sucker et al.: Pharmazeutische Technologie, Thieme-Verlag, Stuttgart, 1991). The forms obtained in this way normally contain from 0.1 to 90% by weight of active substance.

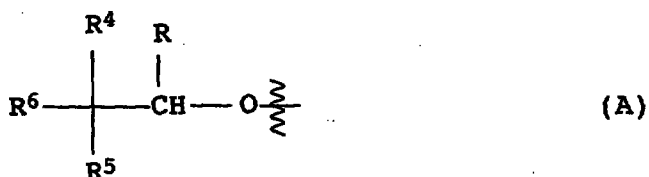
The invention further relates to the combination of compounds of
30 the formula I with inhibitors of the renin-angiotensin system (RAS). RAS inhibitors are disclosed in, for example, EP 634 175.

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

The invention further relates to the use of a structural fragment of the formula (A)

40

45



where R-R⁶ have the meanings stated above for compounds of the
 10 formula I, as structural element in a pharmaceutically active
 compound with endothelin receptor-antagonizing action.

Synthesis examples

15 Example 1

2,2-Diphenylpropional [sic]

50.0 g (0.241 mol) of 2,2-diphenylpropionitrile were dissolved in
 20 200 ml of absolute diethyl ether, and 74.2 ml of a one-molar
 solution of LiAlH₄ in ether were added dropwise. The mixture was
 then refluxed for one hour and stirred at room temperature for
 16 hours.

25 Then 29 ml of water were added, the organic phase was separated
 off, and the aqueous phase was extracted with ether. The combined
 organic phases were dried with MgSO₄, and the solvent was stripped
 off under reduced pressure. 52.1 g of oily crude product were
 obtained and were immediately reacted further.

30

Example 2

2-Hydroxy-3,3-diphenylbutyronitrile

35 42.3 g (0.201 mol of 2,2-diphenylpropionitrile [sic] were
 dissolved in 230 ml of THF, and 41.4 g (0.217 mol) of
 p-toluenesulfonic acid were added. Then 14.09 g (0.217 mol) of
 KCN in 60 ml of water were added dropwise. The mixture was then
 heated at 40°C for 3 hours. The reaction mixture was concentrated
 40 to about 30% under reduced pressure, taken up in water and
 extracted three times with ethyl acetate. The combined organic
 phases were washed twice with sodium disulfite solution, dried
 with MgSO₄ and concentrated under reduced pressure. The crude
 product was chromatographed on silica gel with n-heptane/ethyl
 45 acetate (20:1). 41.2 g (86%) of
 2-hydroxy-3,3-diphenylbutyronitrile were obtained.

¹H-NMR[CDCl₃],

δ = 1.9 (s, 3H); 2,7 (d, 1H); 5.1 (d, 1H);
7.2 - 7.4 (m, 10H)

5

Example 3

Ethyl 2-hydroxy-3,3-diphenylbutyrate

10 1.0 g (4.2 mmol) of 2-hydroxy-3,3-diphenylbutyronitrile was dissolved in 10 ml of ethanol, and 10 ml of conc. HCl [sic] were added. The mixture was refluxed for 24 hours, and then the solvent was stripped off under reduced pressure, and the residue was taken up in water and extracted twice with ethyl acetate. The
15 combined organic phases were washed with 10% strength NaOH, dried with MgSO₄ and concentrated under reduced pressure. 0.8 g (67%) of product was obtained.

¹H-NMR[CDCl₃],

20

δ = 0.9 (t, 3H); 1.8 (s, 3H); 3.0 (d, 1H);
3.9 (q, 2H); 5.0 (d, 1H); 7.1 - 7.4 (m, 10H)

Example 4

25

2-Hydroxy-3,3-diphenylbutyramide

10.0 g (4.22 [sic] mmol) of 2-hydroxy-3,3-diphenylbutyronitrile were dissolved in 500 ml of methanol (abs.) and, at 5 - 10°C, HCl
30 was passed in for 3 hours. The mixture was then stirred at 5°C for 3 hours and at room temperature for 16 hours. Then 200 ml of 6 molar HCl were added and the mixture was evaporated to dryness under reduced pressure. The crude product was recrystallized from an ethyl acetate/heptane mixture. 2.5 g (23%) of
35 2-hydroxy-3,3-diphenylbutyramide were obtained as a white solid.

Example 5

Ethyl 2-hydroxy-3,3-diphenylbutyrate

40

2.15 g (8.4 mmol) of 2-hydroxy-3,3-diphenylbutyramide were dissolved in 15 ml of ethanol, 15 ml of conc. HCl were added and the mixture was refluxed for 40 hours. The solvent was stripped off under reduced pressure, and the residue was taken up in
45 water. The aqueous phase was extracted three times with ethyl acetate, and the combined organic phases were washed twice with 10% strength sodium hydroxide solution. Drying with MgSO₄ and

stripping off the solvent under reduced pressure resulted in 1.75 g (73%) of ethyl 2-hydroxy-3,3-diphenylbutyrate.

Example 6

5

2-Hydroxy-3,3-diphenylbutyric acid

1.75 g (6.2 mmol) of ethyl 2-hydroxy-3,3-diphenylbutyrate were dissolved in 10 ml of THF, and a solution of 0.23 g (9.3 mmol) of
10 LiOH in 6 ml of water was added. The mixture was stirred at room temperature for 16 hours and at 40°C for 4 hours. The mixture was subsequently concentrated under reduced pressure, taken up in water and washed with ethyl acetate. This was followed by acidification with HCl and extraction three times with ethyl
15 acetate. The combined ethyl acetate phases were dried with MgSO₄, and the solvent was stripped off under reduced pressure. The residue was chromatographed on silica gel with CH₂Cl₂/MeOH (2:1). 0.80 g (50%) of 2-hydroxy-3,3-diphenylbutyric acid was obtained.

20 ¹H-NMR[DMSO-d₆],

δ = 1.75 (s, 3H); 4.85 (s, 1H); 5.5 (s, broad, 1H);
7.1 - 7.4 (m, 10H), 12.2 (s, broad, 1H)

25 Example 7

2-(4,6-Dimethyl-2-pyrimidinyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-yl)-3,3-diphenylbutyric acid

0.29 g (9.5 mmol) of NaH were introduced into DMF and, under
30 nitrogen, 0.80 g (3.15 mmol) of 2-hydroxy-3,3-diphenylbutyric acid in 3 ml of DMF were added. After stirring at room temperature for 30 minutes, 0.45 g (3.15 mmol) of 4,6-dimethyl-1,2-chloro-pyrimidine in 4 ml of DMF were added, and the mixture was stirred at RT for 16 hours. After the solvent had been stripped off under
35 reduced pressure, the residue was taken up in water, acidified with HCl and extracted twice with ethyl acetate. The combined organic phases were dried with MgSO₄, and the solvent was stripped off under reduced pressure. The residue was chromatographed on silica gel with CH₂Cl₂/methanol (10:1).

40

0.37 g (32%) of 2-(4,6-dimethyl-2-pyridinyloxy)-3,3-diphenylbutyric [sic] acid of melting point 225-230°C was obtained.

¹H-NMR[DMSO-d₆],

45

25

δ = 1.95 (s, 3H); 2.3 (s, 6H); 5.95 (s, 1H));
6.8 (s, 1H); 7.0 - 7.45 (m, 10 H)

The compound was fractionated into its two enantiomers by
5 racemate resolution (see Table 2).

Example 8

Methyl 2-hydroxy-3,3-diphenylbutyrate

10

15.0 g (63.3 mmol) of 2-hydroxy-3,3-diphenylbutyronitrile were
dissolved in 250 ml of absolute methanol and, at 30 - 50°C, HCl
was passed in to saturation. The mixture was then refluxed for 72
hours and subsequently concentrated under reduced pressure, and
15 the residue was taken up in water. The aqueous phase was
extracted three times with ethyl acetate; the combined organic
phases were dried over MgSO_4 , the solvent was stripped off under
reduced pressure, and the residue was chromatographed on silica
gel with n-heptane/ethyl acetate (20:1).

20

1.2 g (7%) of methyl 2-hydroxy-3,3-diphenylbutyrate were
obtained.

$^1\text{H-NMR}$ [CDCl_3]

25

δ = 1.8 (s, 3H); 2.95 (d, 1H); 3.45 (s, 3H));
5.0 (d, 1H); 7.1 - 7.4 (m, 10 H)

Example 9

30

Methyl 2-(4,6-dimethoxy-2-pyrimidinyl)-3,3-diphenylbutyrate

1.2 g (4.4 mmol) of methyl 2-hydroxy-3,3-diphenylbutyrate were
dissolved in 10 ml of absolute DMF and, under nitrogen, 1.2 g
35 (8.8 mmol) of K_2CO_3 and 0.97 g (4.4 mmol) of
2-methanesulfonyl-4,6-dimethoxypyrimidine were added. The mixture
was stirred at room temperature for 16 hours. It was then
evaporated, and the residue was taken up in water and extracted
three times with ethyl acetate. The combined organic phases were
40 dried over MgSO_4 and concentrated. 1.8 g of crude product were
obtained and were reacted further without purification.

$^1\text{H-NMR}$ [CDCl_3]

45 δ = 2.0 (s, 3H); 3.25 (s, 3H); 3.9 (s, 6H));
5.75 (d, 1H); 5.8 (s, 1H); 7.1 - 7.3 (m, 10H)

Example 10

2-(4,6-Dimethoxy-2-pyrimidinyloxy)-3,3-diphenylbutyric acid

5 1.8 g (4.4 mmol) of methyl 2-(4,6-dimethoxy-2-pyrimidinyl-
0oxy)-3,3-diphenylbutyrate were dissolved in 25 ml of dioxane,
and 26.5 ml (26.5 mmol) of a 1M KOH solution were added, and the
mixture was stirred at 90°C for 6 hours. The mixture was then
concentrated, taken up in water and extracted three times with
10 ethyl acetate. The combined organic phases were dried over MgSO₄
and evaporated. The residue was recrystallized from ethanol.
1.12 g (65%) of 2-(4,6-dimethoxy-2-pyrimidinyloxy)-3,3-diphenyl-
butyric acid of melting point 229-234°C were obtained.

15 ¹H-NMR [DMSO-d₆]

δ = 1.9 (s, 3H); 3.85 (s, 6H); 5.85 (s, 1H);
5.95 (s, 1H); 7.1 - 7.4 (m, 10H); 12.5 (s, broad, 1H)

20 Example 11

2,2-Diphenylbutyronitrile

173 ml (0.259 mol) of a 1.5 M solution of LDA in THF were added
25 dropwise to a solution of 50.0 g (0.259 mol) of
diphenylacetonitrile in 500 ml of THF (abs.) at -78°C under argon,
and the mixture was then stirred at -30°C for one hour. Then, at
-78°C, 28.23 g (0.259 mol) of ethyl bromide were added. The
mixture was allowed to reach room temperature and was stirred for
30 16 hours. Subsequently, 80 ml of phosphate buffer (pH 7) were
added and the mixture was evaporated. The residue was taken up in
water and extracted three times with ethyl acetate. The combined
organic phases were dried over MgSO₄, and the solvent was stripped
off under reduced pressure. The crude product was chromatographed
35 on silica gel with n-heptane/acetic acid (20:1). 38.2 g (67%) of
2,2-diphenylbutyronitrile were obtained.

Example 12

40 2,2-Diphenylbutyraldehyde

21.1 g (95 mmol) of 2,2-diphenylbutyronitrile were dissolved in
100 ml of toluene and, at -78°C under nitrogen, 95 ml (95 mmol) of
a 1 M solution of diisobutylaluminum hydride were added dropwise.
45 The mixture was subsequently stirred at room temperature for 16
hours and then 60 ml of a mixture of saturated ammonium chloride
solution and 2 NH₂SO₄ [sic] in the ratio 2:1 was added, and the

27

mixture was stirred for 30 minutes. The phases were separated and the aqueous phase was extracted three times with ethyl acetate. The combined organic phases were dried over MgSO_4 and concentrated under reduced pressure. The crude product was chromatographed on 5 silica gel with dichloromethane. 19.0 g (89%) of 2,2-diphenylbutyraldehyde were obtained as a pale oil.

Example 13

10 2-Hydroxy-3,3-diphenylvaleronitrile

17.4 g (91.6 mmol) of p-toluenesulfonic acid $\cdot \text{H}_2\text{O}$, and then 5.9 g (91.6 mmol) of KCN in 25 ml of water, were added at 35°C to a solution of 19.09 g (84.8 mmol) of 2,2-diphenylbutyraldehyde in 15 97 ml of THF (abs.). The mixture was then stirred at 40°C for 4 hours and at room temperature for 16 hours. The mixture was evaporated to 1/3 of the volume, water was added, and the phases were separated. The aqueous phase was then extracted three times with ethyl acetate, and the combined organic phases were washed 20 with 10% strength sodium disulfite solution, dried over MgSO_4 and concentrated under reduced pressure. The crude product was chromatographed on silica gel with n-heptane/acetic acid (20:1). 19.5 g (92%) of 2-hydroxy-3,3-diphenylvaleronitrile were obtained as a pale oil.

25

 $^1\text{H-NMR}$ [CDCl_3]

δ = 0.7 (t, 3H); 2.2 - 2.5 (m, 3H); 5.25 (d, 1H); 7.1 - 7.4 (m, 10 H)

30

Example 14

2-(4,6-Dimethoxy-2-pyrimidinyl-2-yl)-3,3-diphenylvaleronitrile

35 7.0 g (27.9 mmol) of 2-hydroxy-3,3-diphenylvaleronitrile were dissolved in 100 ml of DMF (abs.) and, under nitrogen, 7.57 g (55.7 mmol) of potassium carbonate and 6.1 g (27.9 mmol) of 2-methanesulfonyl-4,6-dimethoxypyrimidine were added, and the mixture was stirred at room temperature for 72 hours. The mixture 40 was concentrated under reduced pressure, and the residue was taken up in water and extracted three times with ethyl acetate. The combined organic phases were dried over MgSO_4 , and the solvent was evaporated off. The crude product was chromatographed on silica gel with n-heptane/ethyl acetate (20:1). 8.8 g (81%) of 45 product were obtained.

¹H-NMR [CDCl₃]

δ = 0.8 (t, 3H); 2.45 (dq, 2H); 3.95 (s, 6H), 5.8 (s, 1H); 6.25 (s, 1H); 7.2-7.4 (m, 10 H)

5

Example 15

2-(4,6-Dimethoxy-2-pyrimidinyl-3,3-diphenylvaleric acid

10 0.5 g (1.3 mmol) of 2-(4,6-dimethoxy-2-pyrimidinyl-
oxy)-3,3-diphenylvaleronitrile was dissolved in 5 ml of ethanol
and, after addition of 5 ml of conc. HCl, the mixture was refluxed
for 3 hours. The mixture was then concentrated under reduced
pressure, and the residue was taken up in water and extracted
15 twice with ethyl acetate. The combined ethyl acetate phases were
dried over MgSO₄ and evaporated. The residue was chromatographed
by MPLC on reversed phase material with acetonitrile/water as
eluent [sic]. 0.17 g (32%) of
2-(4,6-dimethoxy-2-pyrimidinyl-3,3-diphenylvaleric [sic] acid
20 of melting point 78-87°C was obtained.

¹H-NMR [DMSO-d₆]

δ = 0.7 (t, 3H); 2.2-2.55 (m, 2H); 3.85 (s, 6H); 5.9 (s, 2H),
25 7.0-7.4 (m, 10H); 12.7 (s, broad, 1H)

The examples indicated in the following Table 1 can be prepared
by the methods described at the outset:

30 Example 16

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

35 The results are shown in Table 2.

40

45

Table 2

Receptor binding data (K_i values)

5	Compound	ET _A [nM/l] [sic]	ET _B [nM/l] [sic]
	I-3	4	325
	I-3 Enantiomer I	0.85	73
	I-3 Enantiomer I	450	>720
10	I-1	25	950
	I-2	3.5	290
	I-11	20	1400
	I-12	4	250
15	I-15	4	540
	I-20	5	445

20

25

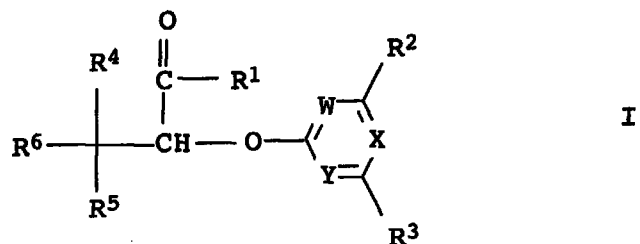
30

35

40

45

Table 1



No.	R ¹	R ⁴	R ⁵	R ⁶	R ²	X	R ³	Y	W
I-1	OH	Phenyl	Phenyl	Methyl	OCH ₃	CH	OCH ₃	N	N
I-2	OH	Phenyl	Phenyl	Methyl	CH ₃	CH	OCH ₃	N	N
I-3	OH	Phenyl	Phenyl	Methyl	CH ₃	CH	CH ₃	N	N
I-4	OH	Phenyl	Phenyl	Methyl	-O-CH ₂ -CH ₂ -C		OCH ₃	N	N
I-5	OH	Phenyl	Phenyl	Methyl	-CH ₂ -CH ₂ -CH ₂ -C		OCH ₃	N	N
I-6	OH	4-Ome-Phenyl	4-Ome-Phenyl	Methyl	OCH ₃	CH	OCH ₃	N	N
I-7	OH	Phenyl	Phenyl	Methyl	Ethyl	CH	Ethyl	N	N
I-8	OH	Phenyl	Phenyl	Methyl	Ethyl	CH	CH ₃	N	N
I-9	OH	Phenyl	Phenyl	Ethyl	Ethyl	CH	OCH ₃	N	N
I-10	OH	4-Me-Phenyl	4-Me-Phenyl	Ethyl	OCH ₃	CH	OCH ₃	N	N
I-11	OH	Phenyl	Phenyl	Ethyl	OCH ₃	CH	OCH ₃	N	N

No.	R ¹	R ⁴	R ⁵	R ⁶	R ²	X	R ³	Y	W
I-12	OH	Phenyl	Phenyl	Ethyl	CH ₃	CH	OCH ₃	N	N
I-13	OCH ₃	Phenyl	Phenyl	Ethyl	CH ₃	CH	OCH ₃	N	N
I-14	OBenzyl	Phenyl	Phenyl	Ethyl	CH ₃	CH	OCH ₃	N	N
I-15	OH	Phenyl	Phenyl	Ethyl	CH ₃	CH	CH ₃	N	N
I-16	OH	Phenyl	Phenyl	Ethyl	-O-CH ₂ -CH ₂ -C		OCH ₃	N	N
I-17	OH	Phenyl	Phenyl	Ethyl	-CH ₂ -CH ₂ -CH ₂ -CH ₂		OCH ₃	N	N
I-18	OH	4-F-Phenyl	4-F-Phenyl	Ethyl	CH ₃	CH	OCH ₃	N	N
I-19	OH	4-F-Phenyl	4-F-Phenyl	Ethyl	CH ₃	CH	CH ₃	N	N
I-20	OH	Phenyl	Phenyl	HO-CH ₂	CH ₃	CH	OCH ₃	N	N
I-21	OH	Phenyl	Phenyl	HO-CH ₂	CH ₃	CH	OCH ₃	N	N
I-22	OH	Phenyl	Phenyl	HO-CH ₂	CH ₃	CH	Ethyl	N	N
I-23	OH	Phenyl	Phenyl	HO-CH ₂	-O-CH ₂ -CH ₂ -C		OCH ₃	N	N
I-24	OH	Phenyl	Phenyl	HO-CH ₂	-O-CH=CH-C		OCH ₃	N	N
I-25	OH	Phenyl	Phenyl	HO-CH ₂ -CH ₂	CH ₃	CH	CH ₃	N	N
I-26	OH	Phenyl	Phenyl	HO-CH ₂ -CH ₂	OCH ₃	CH	CH ₃	N	N
I-27	OBenzyl	Phenyl	Phenyl	HO-CH ₂ -CH ₂	OCH ₃	CH	CH ₃	N	N
I-28	OH	Phenyl	Phenyl	Benzyl-O-CH ₂	CH ₃	CH	CH ₃	N	N
I-29	OH	Phenyl	Phenyl	4-Me-Benzyl O-CH ₂	CH ₃	CH	CH ₃	N	N
I-30	OH	Phenyl	Phenyl	4-Me-Benzyl O-CH ₂	CH ₃	CH	CH ₃	N	N

No.	R ¹	R ⁴	R ⁵	R ⁶	R ²	X	R ³	Y	W
I-31	OH	Phenyl	Phenyl	HO-CH ₂ -(HO-CH)-CH ₂	CH ₃	CH	OCH ₃	N	N
I-32	OH	Phenyl	Phenyl	HO-CH ₂ -(HO-CH)-CH ₂	CH ₃	CH	CH ₃	N	N
I-33	OH	Phenyl	Phenyl	HO-CH ₂ -(HO-CH)-CH ₂	-O-CH ₂ -CH ₂ C		OCH ₃	N	N
I-34	OH	Phenyl	Phenyl	Cl-CH ₂ -CH ₂	CH ₃	CH	Ethyl	N	N
I-35	OH	Phenyl	Phenyl	Cl-CH ₂ -CH ₂	OCH ₃	CH	OCH ₃	N	N
I-36	OH	Phenyl	Phenyl	Propyl	CH ₃	CH	CH ₃	N	N
I-37	OH	Phenyl	Phenyl	Propyl	OCH ₃	CH	OCH ₃	N	N
I-38	OH	Phenyl	Phenyl	Propyl	CH ₃	CH	CH ₃	N	N
I-39	OH	Phenyl	Phenyl	Propyl	-CH ₂ -CH ₂ -CH ₂ -C		OCH ₃	N	N
I-40	OH	Phenyl	Phenyl	Propyl	-O-CH ₂ -CH ₂ -C		OCH ₃	N	N
I-41	OH	Phenyl	Phenyl	iso-Propyl	CH ₃	CH	OCH ₃	N	N
I-42	OH	4-Cl-Phenyl	4-Cl-Phenyl	Ethyl	CH ₃	CH	CH ₃	N	N
I-43	OH	4-Cl-Phenyl	4-Cl-Phenyl	Ethyl	CH ₃	CH	CH ₃	N	N
I-44	OBenzyl	Phenyl	Phenyl	Ethyl	CH ₃	CH	CH ₃	N	N
I-45	OH	Phenyl	Phenyl	4-Me-Phenyl-CH ₂ -CH ₂	CH ₃	CH	CH ₃	N	N
I-46	OH	Phenyl	Phenyl	4-OMe-Phenyl-CH ₂ -CH ₂	CH ₃	CH	CH ₃	N	N
I-47	OH	Phenyl	Phenyl	4-Cl-Phenyl-CH ₂ -CH ₂	CH ₃	CH	CH ₃	N	N

No.	R ¹	R ⁴	R ⁵	R ⁶	R ²	X	R ³	Y	W
I-48	OH	Phenyl	Phenyl	4-Me-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₃	CH	CH ₃	N	N
I-49	OH	Phenyl	Phenyl	4-OMe-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₃	CH	CH ₃	N	N
I-50	OH	Phenyl	Phenyl	4-Cl-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₃	CH	CH ₃	N	N
I-51	OH	Phenyl	Phenyl	4-OMe-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₃	CH	OCH ₃	N	N
I-52	OH	Phenyl	Phenyl	4-Me-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₃	CH	OCH ₃	N	N
I-53	OH	Phenyl	Phenyl	4-Cl-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₃	CH	OCH ₃	N	N
I-54	OH	Phenyl	Phenyl	4-OMe-Phenyl- CH ₂ -CH ₂ -CH ₂	-O-CH ₂ -CH ₂ -C		CH ₃	N	N
I-55	OH	Phenyl	Phenyl	4-Me-Phenyl- CH ₂ -CH ₂ -CH ₂	-O-CH ₂ -CH ₂ -C		CH ₃	N	N
I-56	OH	Phenyl	Phenyl	4-Cl-Phenyl- CH ₂ -CH ₂ -CH ₂	-O-CH ₂ -CH ₂ -C		OCH ₃	N	N
I-57	OH	4-F-Phenyl	4-F-Phenyl	4-OMe-Phenyl- CH ₂ -CH ₂ -CH ₂	-O-CH ₂ -CH ₂ -C		OCH ₃	N	N
I-58	OH	4-F-Phenyl	4-F-Phenyl	4-OMe-Phenyl- CH ₂ -CH ₂ -CH ₂	-O-CH ₂ -CH ₂ -C		OCH ₃	N	N
I-59	OH	4-F-Phenyl	4-F-Phenyl	4-Cl-Phenyl- CH ₂ -CH ₂ -CH ₂	-O-CH ₂ -CH ₂ -C		OCH ₃	N	N
I-60	OH	4-F-Phenyl	4-F-Phenyl	4-OMe-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₃	CH	CH ₃	N	N

No.	R ¹	R ⁴	R ⁵	R ⁶	R ²	X	R ³	Y	W
I-61	OH	4-F-Phenyl	4-F-Phenyl	4-Me-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₃	CH	CH ₃	N	N
I-62	OH	4-F-Phenyl	4-F-Phenyl	4-Cl-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₃	CH	CH ₃	N	N
I-63	OH	4-Me-Phenyl	4-Me-Phenyl	4-OMe-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₃	CH	CH ₃	N	N
I-64	OH	4-Me-Phenyl	4-Me-Phenyl	4-Me-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₃	CH	CH ₃	N	N
I-65	OH	4-Me-Phenyl	4-Me-Phenyl	4-Cl-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₃	CH	CH ₃	N	N
I-66	OH	Phenyl	Phenyl	HOOC-CH ₂	CH ₃	CH	CH ₃	N	N
I-67	OH	Phenyl	Phenyl	HOOC-CH ₂	CH ₃	CH	CH ₃	N	N
I-68	OH	Phenyl	Phenyl	HOOC-CH ₂	-O-CH ₂ -CH ₂ -C		OCH ₃	N	N
I-69	OH	Phenyl	Phenyl	HOOC-CH ₂	-CH ₂ -CH ₂ -CH ₂ -C		OCH ₃	N	N
I-70	OH	Phenyl	Phenyl	HOOC-CH ₂	Ethyl	CH	CH ₃	N	N
I-71	OH	Phenyl	Phenyl	HOOC-CH ₂	Ethyl	CH	Ethyl	N	N
I-72	OH	Phenyl	Phenyl	HOOC-CH ₂ -CH ₂	OCH ₃	CH	CH ₃	N	N
I-73	OH	Phenyl	Phenyl	HOOC-CH ₂ -CH ₂	CH ₃	CH	CH ₃	N	N
I-74	OH	Phenyl	Phenyl	HOOC-CH ₂ -CH ₂	Ethyl	CH	CH ₃	N	N
I-75	OH	Phenyl	Phenyl	HOOC-CH ₂ -CH ₂	-O-CH ₂ -CH ₂ -C		OCH ₃	N	N
I-76	OH	4-OMe-Phenyl	4-OMe-Phenyl	Methyl	OCH ₃	CH	OCH ₃	N	N
I-77	OH	--	--	--	CH ₃	CH	OCH ₃	N	N
I-78	OH	--	--	--	CH ₃	CH	CH ₃	N	N

No.	R ¹	R ⁴	R ⁵	R ⁶	R ²	X	R ³	Y	W
I-79	OH	—"	—"	—"	CH ₃	CH	Ethyl	N	N
I-80	OH	—"	—"	—"	-O-CH ₂ -CH ₂ -C		OCH ₃	N	N
I-81	OH	—"	—"	Ethyl	OCH ₃	CH	OCH ₃	N	N
I-82	OH	—"	—"	Ethyl	CH ₃	CH	OCH ₃	N	N
I-83	OH	—"	—"	Ethyl	CH ₃	CH	CH ₃	N	N
I-84	OH	—"	—"	4-Me-Benzyl- O-CH ₂	CH ₃	CH	OCH ₃	N	N
I-85	OH	—"	—"	—"	CH ₃	CH	CH ₃	N	N
I-86	OH	—"	—"	—"	CH ₃	CH	Ethyl	N	N
I-87	OH	—"	—"	4-OMe-Benzyl- O-CH ₂	OCH ₃	CH	CH ₃	N	N
I-88	OH	—"	—"	—"	CH ₃	CH	CH ₃	N	N
I-89	OH	—"	—"	—"	-O-CH ₂ -CH ₂ -C		OCH ₃	N	N
I-90	OH	—"	—"	4-OMe-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₃	CH	CH ₃	N	N
I-91	OH	—"	—"	—"	CH ₃	CH	CH ₃	N	N
I-92	OH	—"	—"	—"	-O-CH ₂ -CH ₂ -C		OCH ₃	N	N
I-93	OH	Phenyl	Phenyl	4-OMe-Phenyl- CH ₂ -CH ₂ -CH ₂ -CH ₂	CH ₃	CH	OCH ₃	N	N

No.	R ¹	R ⁴	R ⁵	R ⁶	R ²	X	R ³	Y	W
I-94	OH	Phenyl	Phenyl	4-OMe-Phenyl- CH ₂ -CH ₂ -CH ₂ -CH ₂	CH ₃	CH	CH ₃	N	N
I-95	OH	Phenyl	Phenyl	4-OMe-Phenyl- CH ₂ -CH ₂ -CH ₂ -CH ₂	-O-CH ₂ -CH ₂ -C		OCH ₃	N	N
I-96	OH	Phenyl	Phenyl	4-OMe-Phenyl- CH ₂ -CH ₂ -CH ₂ -CH ₂	CH ₃	CH	Ethyl	N	N
I-97	OH	Phenyl	Phenyl	4-Me-Phenyl- CH ₂ -CH ₂ -CH ₂ -CH ₂	CH ₃	CH	OCH ₃	N	N
I-98	OH	Phenyl	Phenyl	4-Me-Phenyl- CH ₂ -CH ₂ -CH ₂ -CH ₂	CH ₃	CH	CH ₃	N	N
I-99	OH	Phenyl	Phenyl	4-Me-Phenyl- CH ₂ -CH ₂ -CH ₂ -CH ₂	-O-CH ₂ -CH ₂ -C		OCH ₃	N	N
I-100	OH	Phenyl	Phenyl	4-Me-Phenyl- CH ₂ -CH ₂ -CH ₂ -CH ₂	Ethyl	CH	CH ₃	N	N
I-101	OH	Phenyl	Phenyl	Methyl	CH ₃	CH	SCH ₃	N	N
I-102	OH	Phenyl	Phenyl	Methyl	N(CH ₃) ₂	CH	N(CH ₃) ₂	N	N
I-103	OH	Phenyl	Phenyl	Methyl	OCH ₃	CH	SCH ₃	N	N
I-104	OH	Phenyl	Phenyl	Ethyl	CH ₃	CH	SCH ₃	N	N
I-105	OH	Phenyl	Phenyl	Ethyl	N(CH ₃) ₂	CH	N(CH ₃) ₂	N	N
I-106	OH	Phenyl	Phenyl	iso-Propyl	CH ₃	CH	SCH ₃	N	N
I-107	OH	Phenyl	Phenyl	4-OMe-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₃	CH	SCH ₃	N	N
I-108	OH	Phenyl	Phenyl	4-Me-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₃	CH	SCH ₃	N	N

No.	R ¹	R ⁴	R ⁵	R ⁶	R ²	X	R ³	Y	W
I-109	OH	Phenyl	Phenyl	4-SMe-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₃	CH	CH ₃	N	N
I-110	OH	Phenyl	Phenyl	4-SMe-Phenyl- CH ₂ -CH ₂ -CH ₂	OCH ₃	CH	CH ₃	N	N
I-111	OH	Phenyl	Phenyl	4-SMe-Phenyl- CH ₂ -CH ₂ -CH ₂	O-CH ₂ -CH ₂ -C-		OCH ₃	N	N
I-112	OH	Phenyl	Phenyl	4-SMe-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₂ -CH ₂ -CH ₂ -C-		OCH ₃	N	N
I-113	OH	4-F-Phenyl	4-F-Phenyl	4-SMe-Phenyl- CH ₂ -CH ₂ -CH ₂ -	CH ₃	CH	CH ₃	N	N
I-114	OH	4-F-Phenyl	4-F-Phenyl	4-SMe-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₃	CH	OCH ₃	N	N
I-115	OH	4-Me-Phenyl	4-Me-Phenyl	4-SMe-Phenyl- CH ₂ -CH ₂ -CH ₂	OCH ₃	CH	CH ₃	N	N
I-116	OH	4-Me-Phenyl	4-Me-Phenyl	4-SMe-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₃	CH	CH ₃	N	N
I-117	OH	4-Me-Phenyl	4-Me-Phenyl	4-SMe-Phenyl- CH ₂ -CH ₂ -CH ₂	O-CH ₂ -CH ₂ -C-		OCH ₃	N	N
I-118	OH	Phenyl	Phenyl	4-Ethyl-Phe- nyl-CH ₂ - CH ₂ -CH ₂	CH ₃	CH	CH ₃	N	N
I-119	OH	Phenyl	Phenyl	HO-CH ₂ -	CH ₃	CH	SCH ₃	N	N
I-120	OH	Phenyl	Phenyl	HO-CH ₂ -CH ₂	CH ₃	CH	SCH ₃	N	N
I-121	OH	Phenyl	Phenyl	HOOC-CH ₂ - CH ₂	CH ₃	CH	SCH ₃	N	N
I-122	OH	Phenyl	Phenyl	Methyl	OCH ₃	N	OCH ₃	N	N

No.	R ¹	R ⁴	R ⁵	R ⁶	R ²	X	R ³	Y	W
I-123	OH	Phenyl	Phenyl	Methyl	CH ₃	N	OCH ₃	N	N
I-124	OH	Phenyl	Phenyl	Methyl	CH ₃	N	CH ₃	N	N
I-125	OH	Phenyl	Phenyl	Methyl	Ethyl	N	Ethyl	N	N
I-126	OH	Phenyl	Phenyl	Methyl	Ethyl	N	CH ₃	N	N
I-127	OH	Phenyl	Phenyl	Ethyl	Ethyl	N	OCH ₃	N	N
I-128	OH	Phenyl	Phenyl	Ethyl	OCH ₃	N	OCH ₃	N	N
I-129	OH	Phenyl	Phenyl	Ethyl	CH ₃	N	OCH ₃	N	N
I-130	OH	Phenyl	Phenyl	Ethyl	CH ₃	N	CH ₃	N	N
I-131	OH	Phenyl	Phenyl	HO-CH ₂	CH ₃	N	OCH ₃	N	N
I-132	OH	Phenyl	Phenyl	HO-CH ₂	CH ₃	N	CH ₃	N	N
I-133	OH	Phenyl	Phenyl	HO-CH ₂	CH ₃	N	Ethyl	N	N
I-134	OH	Phenyl	Phenyl	HO-CH ₂ -CH ₂	CH ₃	N	CH ₃	N	N
I-135	OH	Phenyl	Phenyl	Benzyl-O-CH ₂	CH ₃	N	CH ₃	N	N
I-136	OH	Phenyl	Phenyl	4-Me-Benzyl-O-CH ₂	CH ₃	N	CH ₃	N	N
I-137	OH	Phenyl	Phenyl	4-OMe-Benzyl-O-CH ₂	CH ₃	N	CH ₃	N	N
I-138	OH	Phenyl	Phenyl	HO-CH ₂ -(HO-CH)-CH ₂	CH ₃	N	OCH ₃	N	N
I-139	OH	Phenyl	Phenyl	Propyl	CH ₃	N	OCH ₃	N	N
I-140	OH	Phenyl	Phenyl	Propyl	CH ₃	N	CH ₃	N	N
I-141	OH	Phenyl	Phenyl	Propyl	OCH ₃	N	OCH ₃	N	N

No.	R ¹	R ⁴	R ⁵	R ⁶	R ²	X	R ³	Y	W
I-142	OH	Phenyl	Phenyl	iso-Propyl	CH ₃	N	CH ₃	N	N
I-143	OH	4-OMe-Phenyl	4-OMe-Phenyl	Methyl	OCH ₃	N	OCH ₃	N	N
I-144	OH	4-OMe-Phenyl	4-OMe-Phenyl	Ethyl	CH ₃	N	OCH ₃	N	N
I-145	OH	4-OMe-Phenyl	4-OMe-Phenyl	Ethyl	CH ₃	N	CH ₃	N	N
I-146	OH	4-OMe-Phenyl	4-OMe-Phenyl	Methyl	CH ₃	N	CH ₃	N	N
I-147	OH	4-OMe-Phenyl	4-OMe-Phenyl	4-OMe-Phenyl- CH ₂ - CH ₂ -CH ₂	CH ₃	N	CH ₃	N	N
I-148	OH	4-OMe-Phenyl	4-OMe-Phenyl	4-OMe-Phenyl- CH ₂ - CH ₂ -CH ₂	CH ₃	N	OCH ₃	N	N
I-149	OH	4-Me-Phenyl	4-Me-Phenyl	Ethyl	CH ₃	N	OCH ₃	N	N
I-150	OH	4-Me-Phenyl	4-Me-Phenyl	Methyl	CH ₃	N	CH ₃	N	N
I-151	OH	4-Me-Phenyl	4-Me-Phenyl	4-OMe-Phenyl- CH ₂ - CH ₂ -CH ₂	CH ₃	N	CH ₃	N	N
I-152	OH	4-Me-Phenyl	4-Me-Phenyl	4-Me-Phenyl- CH ₂ - CH ₂ -CH ₂	CH ₃	N	CH ₃	N	N
I-153	OH	Phenyl	Phenyl	4-OMe-Phenyl- CH ₂ - CH ₂ -CH ₂	CH ₃	N	CH ₃	N	N
I-154	OH	Phenyl	Phenyl	4-Me-Phenyl- CH ₂ - CH ₂ -CH ₂	CH ₃	N	CH ₃	N	N

No.	R ¹	R ⁴	R ⁵	R ⁶	R ²	X	R ³	Y	W
I-155	OH	Phenyl	Phenyl	4-SMe-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₃	N	CH ₃	N	N
I-156	OH	Phenyl	Phenyl	4-SMe-Phenyl- CH ₂ -CH ₂ -CH ₂	OCH ₃	N	CH ₃	N	N
I-157	OH	Phenyl	Phenyl	HOOC-CH ₂	CH ₃	N	CH ₃	N	N
I-158	OH	Phenyl	Phenyl	Methyl	CH ₃	N	SCH ₃	N	N
I-159	OH	Phenyl	Phenyl	Methyl	N(CH ₃) ₂	N	N(CH ₃) ₂	N	N
I-160	OH	Phenyl	Phenyl	Ethyl	CH ₃	N	SCH ₃	N	N
I-161	OH	Phenyl	Phenyl	Methyl	OCH ₃	N	OCH ₃	CH	N
I-162	OH	Phenyl	Phenyl	Methyl	OCH ₃	N	CH ₃	CH	N
I-163	OH	Phenyl	Phenyl	Methyl	CH ₃	N	OCH ₃	CH	N
I-164	OH	Phenyl	Phenyl	Methyl	CH ₃	N	CH ₃	CH	N
I-165	OH	Phenyl	Phenyl	Methyl	CH ₃	N	Ethyl	CH	N
I-166	OH	Phenyl	Phenyl	Methyl	Ethyl	N	Ethyl	CH	N
I-167	OH	Phenyl	Phenyl	Methyl	Ethyl	N	CH ₃	CH	N
I-168	OH	Phenyl	Phenyl	Methyl	OCH ₃	N	SCH ₃	CH	N
I-169	OH	Phenyl	Phenyl	Methyl	OCH ₃	N	CF ₃	CH	N
I-170	OH	Phenyl	Phenyl	Ethyl	OCH ₃	N	OCH ₃	CH	N
I-171	OH	Phenyl	Phenyl	Ethyl	CH ₃	N	CH ₃	CH	N
I-172	OH	Phenyl	Phenyl	Ethyl	OCH ₃	N	CH ₃	CH	N
I-173	OH	Phenyl	Phenyl	Ethyl	CH ₃	N	OCH ₃	CH	N
I-174	OH	Phenyl	Phenyl	Ethyl	CH ₃	N	Ethyl	CH	N

No.	R ¹	R ⁴	R ⁵	R ⁶	R ²	X	R ³	Y	W
I-175	OH	Phenyl	Phenyl	Ethyl	Ethyl	N	Ethyl	CH	N
I-176	OH	Phenyl	Phenyl	Ethyl	Ethyl	N	CH ₃	CH	N
I-177	OH	Phenyl	Phenyl	Ethyl	OCH ₃	N	SCH ₃	CH	N
I-178	OH	Phenyl	Phenyl	Ethyl	OCH ₃	N	CF ₃	CH	N
I-179	OH	Phenyl	Phenyl	Propyl	CH ₃	N	CH ₃	CH	N
I-180	OH	Phenyl	Phenyl	Propyl	OCH ₃	N	CH ₃	CH	N
I-181	OH	Phenyl	Phenyl	Propyl	CH ₃	N	OCH ₃	CH	N
I-182	OH	Phenyl	Phenyl	HO-CH ₂	CH ₃	N	CH ₃	CH	N
I-183	OH	Phenyl	Phenyl	HO-CH ₂	OCH ₃	N	CH ₃	CH	N
I-184	OH	Phenyl	Phenyl	HO-CH ₂	CH ₃	N	OCH ₃	CH	N
I-185	OH	Phenyl	Phenyl	HO-CH ₂ (OH-CH)-CH ₂	CH ₃	N	CH ₃	CH	N
I-186	OH	Phenyl	Phenyl	HO-CH ₂ (OH-CH)-CH ₂	CH ₃	N	OCH ₃	CH	N
I-187	OH	Phenyl	Phenyl	HO-CH ₂ (OH-CH)-CH ₂	OCH ₃	N	CH ₃	CH	N
I-188	OH	Phenyl	Phenyl	4-Ome-Phenyl-CH ₂ -CH ₂ -CH ₂	CH ₃	N	CH ₃	CH	N
I-189	OH	Phenyl	Phenyl	4-Ome-Phenyl-CH ₂ -CH ₂ -CH ₂	OCH ₃	N	CH ₃	CH	N
I-190	OH	Phenyl	Phenyl	4-Ome-Phenyl-CH ₂ -CH ₂ -CH ₂	CH ₃	N	OCH ₃	CH	N
I-191	OH	Phenyl	Phenyl	4-Ome-Phenyl-CH ₂ -CH ₂ -CH ₂	Ethyl	N	CH ₃	CH	N

No.	R ¹	R ⁴	R ⁵	R ⁶	R ²	X	R ³	Y	W
I-192	OH	Phenyl	Phenyl	4-SMe-Phenyl- CH ₂ -CH ₂ -CH ₂	OCH ₃	N	CH ₃	CH	N
I-193	OH	Phenyl	Phenyl	4-SMe-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₃	N	OCH ₃	CH	N
I-194	OH	Phenyl	Phenyl	4-SMe-Phenyl- CH ₂ -CH ₂ -CH ₂	OCH ₃	N	CH ₃	CH	N
I-195	OH	Phenyl	Phenyl	4-SMe-Phenyl- CH ₂ -CH ₂ -CH ₂	Ethyl	N	Ethyl	CH	N
I-196	OH	Phenyl	Phenyl	4-SMe-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₃	N	Ethyl	CH	N
I-197	OH	Phenyl	Phenyl	HOOC-CH ₂	CH ₃	N	CH ₃	CH	N
I-198	OH	Phenyl	Phenyl	HOOC-CH ₂	CH ₃	N	Ethyl	CH	N
I-199	OH	Phenyl	Phenyl	HOOC-CH ₂	CH ₃	N	OCH ₃	CH	N
I-200	OH	Phenyl	Phenyl	HOOC-CH ₂	OCH ₃	N	CH ₃	CH	N
I-201	OH	4-F-Phenyl	4-F-Phenyl	Methyl	CH ₃	N	CH ₃	CH	N
I-202	OH	4-OMe-Phenyl	4-OMe-Phenyl	Methyl	CH ₃	N	CH ₃	CH	N
I-203	OH	4-Me-Phenyl	4-MePhenyl	Methyl	CH ₃	N	CH ₃	CH	N
I-204	OH	4-Me-Phenyl	4-MePhenyl	Ethyl	CH ₃	N	CH ₃	CH	N
I-205	OH	4-Me-Phenyl	4-Me-Phenyl	Ethyl	CH ₃	N	OCH ₃	CH	N
I-206	OH	4-Me-Phenyl	4-Me-Phenyl	Ethyl	OCH ₃	N	CH ₃	CH	N
I-207	OH	4-Me-Phenyl	4-Me-Phenyl	Ethyl	Ethyl	N	CF ₃	CH	N
I-208	OH	4-Me-Phenyl	4-Me-Phenyl	HOOC-CH ₂ -CH ₂	CH ₃	N	CH ₃	CH	N
I-209	OH	4-Me-Phenyl	4-Me-Phenyl	HOOC-CH ₂ -CH ₂	OCH ₃	N	CH ₃	CH	N

No.	R ¹	R ⁴	R ⁵	R ⁶	R ²	X	R ³	Y	W
I-210	OH	4-Me-Phenyl	4-Me-Phenyl	HOOC-CH ₂ -CH ₂	Ethyl	N	CH ₃	CH	N
I-211	OH	Phenyl	Phenyl	HOOC-CH ₂ -CH ₂	CH ₃	N	CH ₃	CH	N
I-212	OH	Phenyl	Phenyl	HOOC-CH ₂ -CH ₂	OCH ₃	N	CH ₃	CH	N
I-213	OH	Phenyl	Phenyl	HOOC-CH ₂ -CH ₂	Ethyl	N	CH ₃	CH	N
I-214	OH	Phenyl	Phenyl	HOOC-CH ₂ -CH ₂	Ethyl	N	CF ₃	CH	N
I-215	OH	Phenyl	Phenyl	HOOC-CH ₂ -CH ₂	CH ₃	N	OCH ₃	CH	N
I-216	OH	Phenyl	Phenyl	HOOC-CH ₂ -CH ₂	CH ₃	N	Ethyl	CH	N
I-217	OH	Phenyl	Phenyl	HOOC-CH ₂ -CH ₂	CF ₃	N	Ethyl	CH	N
I-218	OH	Phenyl	Phenyl	HO-CH ₂ -(HO-CH)-CH ₂	CF ₃	N	Ethyl	CH	N
I-219	OH	Phenyl	Phenyl	HO-CH ₂ -(HO-CH)-CH ₂	CH ₃	N	Ethyl	CH	N
I-220	OH	Phenyl	Phenyl	HO-CH ₂ -(HO-CH)-CH ₂	Ethyl	N	CH ₃	CH	N
I-221	OH	Phenyl	Phenyl	(HO-CH ₂) ₂ CH-CH ₂	CH ₃	N	CH ₃	CH	N
I-222	OH	Phenyl	Phenyl	(HO-CH ₂) ₂ CH-CH ₂	OCH ₃	N	CH ₃	CH	N
I-223	OH	Phenyl	Phenyl	(HO-CH ₂) ₂ CH-CH ₂	CH ₃	N	OCH ₃	CH	N
I-224	OH	Phenyl	Phenyl	(HO-CH ₂) ₂ CH-CH ₂	CH ₃	N	Ethyl	CH	N
I-225	OH	Phenyl	Phenyl	Methyl	CH=CH-CH=CH-C		CH ₃	CH	N
I-226	OH	Phenyl	Phenyl	Methyl	CH=CH-CH=CH-C		H	CH	N
I-227	OH	Phenyl	Phenyl	Methyl	CH ₃	CH	CH ₃	CH	N
I-228	OH	Phenyl	Phenyl	Methyl	CH ₃	CH	OCH ₃	CH	N

No.	R ¹	R ⁴	R ⁵	R ⁶	R ²	X	R ³	Y	W
I-229	OH	Phenyl	Phenyl	Methyl	CH ₃	CH	Ethyl	CH	N
I-230	OH	Phenyl	Phenyl	Methyl	Ethyl	CH	CH ₃	CH	N
I-231	OH	Phenyl	Phenyl	Ethyl	CH=CH-CH=CH-C		CH ₃	CH	N
I-232	OH	Phenyl	Phenyl	Ethyl	CH=CH-CH=CH-C		H	CH	N
I-233	OH	Phenyl	Phenyl	Propyl	CH=CH-CH=CH-C		CH ₃	CH	N
I-234	OH	Phenyl	Phenyl	Ethyl	CH ₂ -CH ₂ -CH ₂ -C		CH ₃	CH	N
I-235	OH	Phenyl	Phenyl	Methyl	CH ₂ -CH ₂ -CH ₂ -C		CH ₃	CH	N
I-236	OH	Phenyl	Phenyl	Propyl	CH ₂ -CH ₂ -CH ₂ -C		CH ₃	CH	N
I-237	OH	Phenyl	Phenyl	Ethyl	CH ₃	CH	Ethyl	CH	N
I-238	OH	Phenyl	Phenyl	Ethyl	CH ₃	CH	CH ₃	CH	N
I-239	OH	Phenyl	Phenyl	Ethyl	Ethyl	CH	CH ₃	CH	N
I-240	OH	Phenyl	Phenyl	Ethyl	CH ₃	CH	OCH ₃	CH	N
I-241	OH	Phenyl	Phenyl	Methyl	OCH ₃	XH	CH ₃	CH	N
I-242	OH	Phenyl	Phenyl	Methyl	O-CH ₂ -CH ₂ -C		H	CH	N
I-243	OH	Phenyl	Phenyl	Methyl	O-CH ₂ -CH ₂ -C		CH ₃	CH	N
I-244	OH	Phenyl	Phenyl	Ethyl	OCH ₃	CH	CH ₃	CH	N
I-245	OH	Phenyl	Phenyl	Ethyl	O-CH ₂ -CH ₂ -C		H	CH	N
I-246	OH	Phenyl	Phenyl	Ethyl	O-CH ₂ -CH ₂ -C		CH ₃	CH	N
I-247	OH	Phenyl	Phenyl	Ethyl	O-CH ₂ -O-C		H	CH	N
I-248	OH	Phenyl	Phenyl	Ethyl	O-CH ₂ -O-C		CH ₃	CH	N
I-249	OH	Phenyl	Phenyl	Ethyl	CH ₃	CH	CH=CH-CH=CH-C		N

No.	R ¹	R ⁴	R ⁵	R ⁶	R ²	X	R ³	Y	W
I-250	OH	Phenyl	Phenyl	Ethyl	OCH ₃	CH	CH=CH-CH=CH-C		N
I-251	OH	Phenyl	Phenyl	Methyl	CH ₃	CH	CH=CH-CH=CH-C		N
I-252	OH	Phenyl	Phenyl	Methyl	OCH ₃	CH	CH=CH-CH=CH-C		N
I-253	OH	Phenyl	Phenyl	Methyl	CH ₃	CH	O-CH ₂ -O-C		N
I-254	OH	Phenyl	Phenyl	Methyl	OCH ₃	CH	O-CH ₂ -O-C		N
I-255	OH	Phenyl	Phenyl	Ethyl	CH ₃	CH	O-CH ₂ -O-C		N
I-256	OH	Phenyl	Phenyl	Ethyl	OCH ₃	CH	O-CH ₂ -O-C		N
I-257	OH	Phenyl	Phenyl	Ethyl	CH ₃	CH	CH ₂ -CH ₂ -O-C		N
I-258	OH	Phenyl	Phenyl	Ethyl	OCH ₃	CH	CH ₂ -CH ₂ -O-C		N
I-259	OH	Phenyl	Phenyl	Methyl	CH ₃	CH	CH ₂ -CH ₂ -O-C		N
I-260	OH	Phenyl	Phenyl	Methyl	OCH ₃	CH	CH ₂ -CH ₂ -O-C		N
I-261	OH	Phenyl	Phenyl	Methyl	CH ₃	CH	N=CH-NH-C		N
I-262	OH	Phenyl	Phenyl	Methyl	OCH ₃	CH	N=CH-NH-C		N
I-263	OH	Phenyl	Phenyl	Ethyl	CH ₃	CH	N=CH-NH-C		N
I-264	OH	Phenyl	Phenyl	Ethyl	OCH ₃	CH	N=CH-NH-C		N
I-265	OH	Phenyl	Phenyl	Ethyl	CH ₃	CH	CH=CH-NH-C		N
I-266	OH	Phenyl	Phenyl	Ethyl	OCH ₃	CH	CH=CH-NH-C		N
I-267	OH	Phenyl	Phenyl	HO-CH ₂	CH ₃	CH	CH=CH-NH-C		N
I-268	OH	Phenyl	Phenyl	HO-CH ₂	OCH ₃	CH	CH=CH-NH-C		N
I-269	OH	Phenyl	Phenyl	HO-CH ₂ -CH ₂	CH ₃	CH	CH=CH-NH-C		N
I-270	OH	Phenyl	Phenyl	HO-CH ₂ -CH ₂	OCH ₃	CH	CH=CH-NH-C		N

No.	R ¹	R ⁴	R ⁵	R ⁶	R ²	X	R ³	Y	W
I-271	OH	Phenyl	Phenyl	Methyl	CH ₃	CH	CH=CH-NH-C	N	
I-272	OH	Phenyl	Phenyl	Methyl	OCH ₃	CH	CH=CH-NH-C	N	
I-273	OH	Phenyl	Phenyl	Methyl	CH ₃	N	CH=CH-NH-C	N	
I-274	OH	Phenyl	Phenyl	Methyl	OCH ₃	N	CH=CH-NH-C	N	
I-275	OH	Phenyl	Phenyl	Ethyl	CH ₃	N	CH=CH-NH-C	N	
I-276	OH	Phenyl	Phenyl	Ethyl	OCH ₃	N	CH=CH-NH-C	N	
I-277	OH	Phenyl	Phenyl	HO-CH ₂	CH ₃	N	CH=CH-NH-C	N	
I-278	OH	Phenyl	Phenyl	HO-CH ₂	OCH ₃	N	CH=CH-NH-C	N	
I-279	OH	Phenyl	Phenyl	Methyl	CH ₃	N	N=CH-NH-C	N	
I-280	OH	Phenyl	Phenyl	Ethyl	CH ₃	N	N=CH-NH-C	N	
I-281	OH	Phenyl	Phenyl	Propyl	CH ₃	N	N=CH-NH-C	N	
I-282	OH	Phenyl	Phenyl	HO-CH ₂ -CH ₂	CH ₃	N	N=CH-NH-C	N	
I-283	OH	Phenyl	Phenyl	Phenyl-CH ₂ -CH ₂	CH ₃	N	N=CH-NH-C	N	
I-284	OH	Phenyl	Phenyl	Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₃	N	N=CH-NH-C	N	
I-285	OH	Phenyl	Phenyl	4-Me-Phenyl- CH ₂ -CH ₂	CH ₃	N	N=CH-NH-C	N	
I-286	OH	Phenyl	Phenyl	Methyl	CH ₃	N	O-CH ₂ -CH ₂ -C	N	
I-287	OH	Phenyl	Phenyl	Ethyl	CH ₃	N	O-CH ₂ -CH ₂ -C	N	
I-288	OH	Phenyl	Phenyl	HO-CH ₂	CH ₃	N	O-CH ₂ -CH ₂ -C	N	
I-289	OH	Phenyl	Phenyl	HO-CH ₂ -CH ₂	CH ₃	N	O-CH ₂ -CH ₂ -C	N	
I-290	OH	Phenyl	Phenyl	Phenyl-CH ₂ -CH ₂	CH ₃	N	O-CH ₂ -CH ₂ -C	N	

No.	R ¹	R ⁴	R ⁵	R ⁶	R ²	X	R ³	Y	W
I-291	OH	Phenyl	Phenyl	Phenyl-CH ₂ -CH ₂	CH ₃	N	CH ₂ -CH ₂ -O-C		N
I-292	OH	Phenyl	Phenyl	Methyl	CH ₃	N	CH ₂ -CH ₂ -O-C		N
I-293	OH	Phenyl	Phenyl	Ethyl	CH ₃	N	CH ₂ -CH ₂ -O-C		N
I-294	OH	Phenyl	Phenyl	Ethyl	CH ₃	N	CH ₂ -CH ₂ -CH ₂ -C		N
I-295	OH	Phenyl	Phenyl	Ethyl	OCH ₃	N	CH ₂ -CH ₂ -CH ₂ -C		N
I-296	OH	Phenyl	Phenyl	Methyl	CH ₃	N	CH ₂ -CH ₂ -CH ₂ -C		N
I-297	OH	Phenyl	Phenyl	Methyl	OCH ₃	N	CH ₂ -CH ₂ -CH ₂ -C		N
I-298	OH	Phenyl	Phenyl	HO-CH ₂	CH ₃	N	CH ₂ -CH ₂ -CH ₂ -C		N
I-299	OH	Phenyl	Phenyl	HO-CH ₂ -CH ₂	CH ₃	N	CH ₂ -CH ₂ -CH ₂ -C		N
I-300	OH	Phenyl	Phenyl	Phenyl-CH ₂ -CH ₂	CH ₃	N	CH ₂ -CH ₂ -CH ₂ -C		N
I-301	OH	Phenyl	Phenyl	4-MeO-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₃	N	CH ₂ -CH ₂ -CH ₂ -C		N
I-302	OH	2-Naphthyl	Phenyl	Methyl	OCH ₃	N	OCH ₃	CH	N
I-303	OH	2-Naphthyl	Phenyl	Methyl	CH ₃	N	CH ₃	CH	N
I-304	OH	2-Naphthyl	Phenyl	Methyl	OCH ₃	N	CH ₃	CH	N
I-305	OH	2-Naphthyl	Phenyl	Methyl	CH ₃	N	OCH ₃	CH	N
I-306	OH	2-Naphthyl	Phenyl	Methyl	Ethyl	N	CH ₃	CH	N
I-307	OH	2-Naphthyl	Phenyl	Ethyl	OCH ₃	N	OCH ₃	CH	N
I-308	OH	2-Naphthyl	Phenyl	Ethyl	CH ₃	N	CH ₃	CH	N
I-309	OH	2-Naphthyl	Phenyl	Ethyl	OCH ₃	N	CH ₃	CH	N
I-310	OH	2-Naphthyl	Phenyl	Ethyl	CH ₃	N	OCH ₃	CH	N
I-311	OH	2-Naphthyl	Phenyl	Ethyl	Ethyl	N	CH ₃	CH	N

No.	R ¹	R ⁴	R ⁵	R ⁶	R ²	X	R ³	Y	W
I-312	OH	2-Naphthyl	Phenyl	Propyl	CH ₃	N	CH ₃	CH	N
I-313	OH	2-Naphthyl	Phenyl	Propyl	OCH ₃	N	CH ₃	CH	N
I-314	OH	2-Naphtyl [sic]	Phenyl	HO-CH ₂	CH ₃	N	CH ₃	CH	N
I-315	OH	2-Naphtyl [sic]	Phenyl	HO-CH ₂	OCH ₃	N	CH ₃	CH	N
I-316	OH	2-Naphtyl [sic]	Phenyl	HO-CH ₂	OCH ₃	N	OCH ₃	CH	N
I-317	OH	2-Naphtyl [sic]	Phenyl	HO-CH ₂ -CH ₂	OCH ₃	N	OCH ₃	CH	N
I-318	OH	2-Naphtyl [sic]	Phenyl	HO-CH ₂ -CH ₂	CH ₃	N	CH ₃	CH	N
I-319	OH	2-Naphtyl [sic]	Phenyl	HO-CH ₂ -CH ₂	OCH ₃	N	CH ₃	CH	N
I-320	OH	2-Naphtyl [sic]	Phenyl	p-Me-Phenyl- CH ₂ -CH ₂	CH ₃	N	CH ₃	CH	N
I-321	OH	2-Naphtyl [sic]	Phenyl	p-Me-Phenyl- CH ₂ -CH ₂	OCH ₃	N	CH ₃	CH	N
I-322	OH	2-Naphtyl [sic]	Phenyl	p-MeO-Phenyl- CH ₂ -CH ₂	CH ₃	N	OCH ₃	CH	N
I-323	OH	2-Naphtyl [sic]	Phenyl	p-MeO-Phenyl- CH ₂ -CH ₂	CH ₃	N	CH ₃	CH	N
I-324	OH	2-Naphtyl [sic]	Phenyl	p-Me-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₃	N	CH ₃	CH	N
I-325	OH	2-Naphtyl [sic]	Phenyl	p-Me-Phenyl- CH ₂ -CH ₂ -CH ₂	OCH ₃	N	CH ₃	CH	N
I-326	OH	2-Naphtyl [sic]	Phenyl	p-MeO-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₃	N	CH ₃	CH	N
I-327	OH	2-Naphtyl [sic]	Phenyl	p-MeO-Phenyl- CH ₂ -CH ₂ -CH ₂	OCH ₃	N	CH ₃	CH	N

No.	R ¹	R ⁴	R ⁵	R ⁶	R ²	X	R ³	Y	W
I-328	OH	2-Naphtyl [sic]	Phenyl	p-MeO-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₃	N	OCH ₃	CH	N
I-329	OH	2-Naphtyl [sic]	Phenyl	p-MeO-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₃	CH	CH ₃	N	N
I-330	OH	2-Naphtyl [sic]	Phenyl	p-MeO-Phenyl- CH ₂ -CH ₂ -CH ₂	OCH ₃	CH	CH ₃	N	N
I-331	OH	2-Naphtyl [sic]	Phenyl	p-MeO-Phenyl- CH ₂ -CH ₂ -CH ₂	OCH ₃	CH	OCH ₃	N	N
I-332	OH	2-Naphtyl [sic]	Phenyl	p-MeO-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₂ -CH ₂ -CH ₂ -C		CH ₃	N	N
I-333	OH	2-Naphtyl [sic]	Phenyl	p-MeO-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₂ -CH ₂ -CH ₂ -C		H	N	N
I-334	OH	2-Naphtyl [sic]	Phenyl	p-MeO-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₂ -CH ₂ -CH ₂ -C		OCH ₃	N	N
I-335	OH	2-Naphtyl [sic]	Phenyl	p-Me-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₂ -CH ₂ -CH ₂ -C		CH ₃	N	N
I-336	OH	2-Naphtyl [sic]	Phenyl	p-Me-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₂ -CH ₂ -CH ₂ -C		H	N	N
I-337	OH	2-Naphtyl [sic]	Phenyl	p-Me-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₂ -CH ₂ -CH ₂ -C		OCH ₃	N	N
I-338	OH	2-Naphtyl [sic]	Phenyl	HO-CH ₂ -CH ₂	CH ₂ -CH ₂ -CH ₂ -C		CH ₃	N	N
I-339	OH	2-Naphtyl [sic]	Phenyl	HO-CH ₂ -CH ₂	CH ₂ -CH ₂ -CH ₂ -C		H	N	N
I-340	OH	2-Naphtyl [sic]	Phenyl	HO ₂ C-CH ₂	CH ₂ -CH ₂ -CH ₂ -C		CH ₃	N	N
I-341	OH	2-Naphtyl [sic]	Phenyl	HO ₂ C-CH ₂	CH ₂ -CH ₂ -CH ₂ -C		H	N	N
I-342	OH	2-Naphtyl [sic]	Phenyl	Methyl	CH ₂ -CH ₂ -CH ₂ -C		CH ₃	N	N

No.	R ¹	R ⁴	R ⁵	R ⁶	R ²	X	R ³	Y	W
I-343	OH	2-Naphtyl [sic]	Phenyl	Methyl	CH ₂ -CH ₂ -CH ₂ -C		H	N	N
I-344	OH	2-Naphtyl [sic]	Phenyl	Ethyl	CH ₂ -CH ₂ -CH ₂ -C		CH ₃	N	N
I-345	OH	2-Naphtyl [sic]	Phenyl	Ethyl	CH ₂ -CH ₂ -CH ₂ -C		H	N	N
I-346	OH	2-Naphtyl [sic]	Phenyl	Ethyl	CH ₃	CH	CH ₃	N	N
I-347	OH	2-Naphtyl [sic]	Phenyl	Ethyl	OCH ₃	CH	CH ₃	N	N
I-348	OH	2-Naphtyl [sic]	Phenyl	Ethyl	Ethyl	CH	CH ₃	N	N
I-349	OH	2-Naphtyl [sic]	Phenyl	Ethyl	OCH ₃	CH	OCH ₃	N	N
I-350	OH	2-Naphtyl [sic]	Phenyl	Methyl	CH ₃	CH	CH ₃	N	N
I-351	OH	2-Naphtyl [sic]	Phenyl	Methyl	OCH ₃	CH	CH ₃	N	N
I-352	OH	2-Naphtyl [sic]	Phenyl	Methyl	OCH ₃	CH	OCH ₃	N	N
I-353	OH	2-Naphtyl [sic]	Phenyl	HO-CH ₂	CH ₃	CH	CH ₃	N	N
I-354	OH	2-Naphtyl [sic]	Phenyl	HO-CH ₂	OCH ₃	CH	CH ₃	N	N
I-355	OH	2-Naphtyl [sic]	Phenyl	HO-CH ₂	OCH ₃	CH	OCH ₃	N	N
I-356	OH	2-Naphtyl [sic]	Phenyl	HO-CH ₂	Ethyl	CH	CH ₃	N	N
I-357	OH	2-Naphtyl [sic]	Phenyl	HO-CH ₂ -CH ₂	CH ₃	CH	CH ₃	N	N
I-358	OH	2-Naphtyl [sic]	Phenyl	HO-CH ₂ -CH ₂	OCH ₃	CH	CH ₃	N	N
I-359	OH	2-Naphtyl [sic]	Phenyl	HO-CH ₂ -CH ₂	OCH ₃	CH	OCH ₃	N	N
I-360	OH	2-Naphtyl [sic]	Phenyl	HO ₂ C-CH ₂	CH ₃	CH	CH ₃	N	N
I-361	OH	2-Naphtyl [sic]	Phenyl	HO ₂ C-CH ₂	OCH ₃	CH	CH ₃	N	N
I-362	OH	2-Naphtyl [sic]	Phenyl	HO ₂ C-CH ₂	OCH ₃	CH	CH ₃	N	N
I-363	OH	2-Naphtyl [sic]	Phenyl	p-Me-Phenyl- CH ₂ -CH ₂	CH ₃	CH	CH ₃	N	N

No.	R ¹	R ⁴	R ⁵	R ⁶	R ²	X	R ³	Y	W
I-364	OH	2-Naphtyl [sic]	Phenyl	p-Me-Phenyl- CH ₂ -CH ₂	OCH ₃	CH	CH ₃	N	N
I-365	OH	2-Naphtyl [sic]	Phenyl	p-Me-Phenyl- CH ₂ -CH ₂	OCH ₃	CH	OCH ₃	N	N
I-366	OH	2-Naphtyl [sic]	Phenyl	p-Me-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₃	CH	CH ₃	N	N
I-367	OH	2-Naphtyl [sic]	Phenyl	p-Me-Phenyl- CH ₂ -CH ₂ -CH ₂	OCH ₃	CH	CH ₃	N	N
I-368	OH	2-Naphtyl [sic]	Phenyl	p-Me-Phenyl- CH ₂ -CH ₂ -CH ₂	OCH ₃	CH	OCH ₃	N	N
I-369	OH	2-Naphtyl [sic]	Phenyl	p-MeO-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₃	CH	CH ₃	N	N
I-370	OH	2-Naphtyl [sic]	Phenyl	p-MeO-Phenyl- CH ₂ -CH ₂ -CH ₂	OCH ₃	CH	CH ₃	N	N
I-371	OH	2-Naphtyl [sic]	Phenyl	p-MeO-Phenyl- CH=CH ₂ -CH ₂	CH ₃	CH	CH ₃	N	N
I-372	OH	2-Naphtyl [sic]	Phenyl	p-MeO-Phenyl- CH=CH ₂ -CH ₂	OCH ₃	CH	CH ₃	N	N
I-373	OH	1-Naphtyl [sic]	Phenyl	p-MeO-Phenyl- CH=CH ₂ -CH ₂	CH ₃	CH	CH ₃	N	N
I-374	OH	1-Naphtyl [sic]	Phenyl	p-MeO-Phenyl- CH=CH ₂ -CH ₂	OCH ₃	CH	CH ₃	N	N
I-375	OH	1-Naphtyl [sic]	Phenyl	p-MeO-Phenyl- CH=CH ₂ -CH ₂	OCH ₃	CH	OCH ₃	N	N
I-376	OH	1-Naphtyl [sic]	Phenyl	p-MeO-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₃	CH	CH ₃	N	N

No.	R ¹	R ⁴	R ⁵	R ⁶	R ²	X	R ³	Y	W
I-377	OH	1-Naphtyl [sic]	Phenyl	p-MeO-Phenyl- CH ₂ -CH ₂ -CH ₂	OCH ₃	CH	CH ₃	N	N
I-378	OH	1-Naphtyl [sic]	Phenyl	p-MeO-Phenyl- CH ₂ -CH ₂ -CH ₂	OCH ₃	CH	OCH ₃	N	N
I-379	OH	1-Naphtyl [sic]	Phenyl	Phenylmethyl- O-CH ₂	CH ₃	CH	CH ₃	N	N
I-380	OH	1-Naphtyl [sic]	Phenyl	Phenylmethyl- O-CH ₂	OCH ₃	CH	CH ₃	N	N
I-381	OH	1-Naphtyl [sic]	Phenyl	HO-CH ₂	CH ₃	CH	CH ₃	N	N
I-382	OH	1-Naphtyl [sic]	Phenyl	HO-CH ₂	OCH ₃	CH	CH ₃	N	N
I-383	OH	1-Naphtyl [sic]	Phenyl	HO-CH ₂ -CH ₂	CH ₃	CH	CH ₃	N	N
I-384	OH	1-Naphtyl [sic]	Phenyl	HO-CH ₂ -CH ₂	OCH ₃	CH	CH ₃	N	N
I-385	OH	1-Naphtyl [sic]	Phenyl	Propyl	CH ₃	CH	CH ₃	N	N
I-386	OH	1-Naphtyl [sic]	Phenyl	Propyl	OCH ₃	CH	CH ₃	N	N
I-387	OH	1-Naphtyl [sic]	Phenyl	Ethyl	OCH ₃	CH	OCH ₃	N	N
I-388	OH	1-Naphtyl [sic]	Phenyl	Ethyl	OCH ₃	CH	CH ₃	N	N
I-389	OH	1-Naphtyl [sic]	Phenyl	Ethyl	CH ₃	CH	CH ₃	N	N
I-390	OH	1-Naphtyl [sic]	Phenyl	Methyl	CH ₃	CH	CH ₃	N	N
I-391	OH	1-Naphtyl [sic]	Phenyl	Methyl	OCH ₃	CH	CH ₃	N	N
I-392	OH	1-Naphtyl [sic]	Phenyl	Methyl	OCH ₃	CH	OCH ₃	N	N
I-393	OH	3,4-Dioxomethyl- enylphenyl [sic]	Phenyl	Methyl	CH ₃	CH	CH ₃	N	N

No.	R ¹	R ⁴	R ⁵	R ⁶	R ²	X	R ³	Y	W
I-394	OH	3,4-Dioxomethyl- enylphenyl [sic]	Phenyl	Methyl	OCH ₃	CH	CH ₃	N	N
I-395	OH	3,4-Dioxomethyl- enylphenyl [sic]	Phenyl	Methyl	OCH ₃	CH	OCH ₃	N	N
I-396	OH	3,4-Dioxomethyl- enylphenyl [sic]	Phenyl	Ethyl	CH ₃	CH	CH ₃	N	N
I-397	OH	3,4-Dioxomethyl- enylphenyl [sic]	Phenyl	Ethyl	OCH ₃	CH	CH ₃	N	N
I-398	OH	3,4-Dioxomethyl- enylphenyl [sic]	Phenyl	Ethyl	OCH ₃	CH	OCH ₃	N	N
I-399	OH	3,4-Dioxomethyl- enylphenyl [sic]	Phenyl	HO-CH ₂	CH ₃	CH	CH ₃	N	N
I-400	OH	3,4-Dioxomethyl- enylphenyl [sic]	Phenyl	HO-CH ₂	OCH ₃	CH	CH ₃	N	N
I-401	OH	3,4-Dioxomethyl- enylphenyl [sic]	Phenyl	HO-CH ₂ -CH ₂	CH ₃	CH	CH ₃	N	N
I-402	OH	3,4-Dioxomethyl- enylphenyl [sic]	Phenyl	HO-CH ₂ -CH ₂	OCH ₃	CH	CH ₃	N	N
I-403	OH	3,4-Dioxomethyl- enylphenyl [sic]	Phenyl	p-Me-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₃	CH	CH ₃	N	N
I-404	OH	3,4-Dioxomethyl- enylphenyl [sic]	Phenyl	p-Me-Phenyl- CH ₂ -CH ₂ -CH ₂	OCH ₃	CH	CH ₃	N	N
I-405	OH	3,4-Dioxomethyl- enylphenyl [sic]	Phenyl	p-MeO-Phenyl- CH ₂ -CH ₂ -CH ₂	CH ₃	CH	CH ₃	N	N

No.	R ¹	R ⁴	R ⁵	R ⁶	R ²	X	R ³	Y	W
I-406	OH	3,4-Dioxomethyl- enylphenyl [sic]	Phenyl	p-MeO-Phenyl- CH ₂ -CH ₂ -CH ₂	OCH ₃	CH	CH ₃	N	N
I-407	OH	3,4-Dioxomethyl- enylphenyl [sic]	Phenyl	p-MeO-Phenyl- CH ₂ -CH ₂ -CH ₂	OCH ₃	CH	OCH ₃	N	N

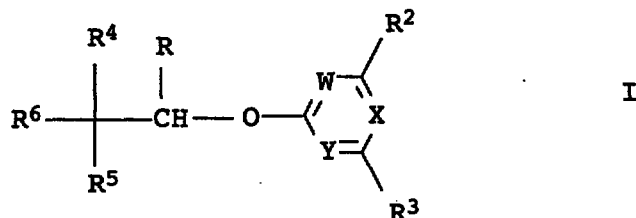


We claim:

1. An α -hydroxy carboxylic acid derivative of the formula I

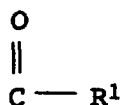
5

10



where R is a group

15



20

where R¹ has the following meanings:

a) hydrogen

b) a succinylimidoxy [sic] group

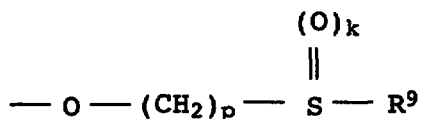
25

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

30

d) a group

35



40

where k can assume the values 0, 1 and 2, p can assume the values 1, 2, 3 and 4, and R⁹ is C₁-C₄-alkyl, C₃-C₇-cycloalkyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl or unsubstituted or substituted phenyl which can be substituted by one or more of the following radicals:

45



2

halogen, nitro, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, hydroxyl, C₁-C₄-alkoxy, C₁-C₄-alkylthio, mercapto, amino, C₁-C₄-alkylamino, C₁-C₄-dialkylamino;

5 e) R¹ furthermore a radical OR¹⁰, where R¹⁰ is:

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

C₃-C₈-cycloalkyl,

15 C₁-C₈-alkyl,

CH₂-phenyl which can be substituted by one or more of the following radicals: halogen, nitro, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, hydroxyl, C₁-C₄-alkoxy, mercapto,
20 C₁-C₄-alkylthio, amino, C₁-C₄-alkylamino, C₁-C₄-dialkylamino,

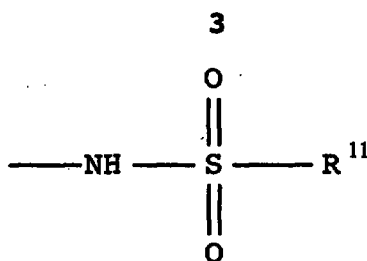
a C₃-C₆-alkenyl or C₃-C₆-alkynyl group, it being possible for this group in turn to carry one to five halogen
25 atoms;

R¹⁰ can furthermore be a phenyl radical which can carry one to five halogen atoms and/or one to three of the following radicals: nitro, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, hydroxyl, C₁-C₄-alkoxy, mercapto,
30 C₁-C₄-alkylthio, amino, C₁-C₄-alkylamino, C₁-C₄-dialkylamino;

a 5-membered heteroaromatic system which is linked via a nitrogen atom and contains one to three nitrogen atoms, and which may carry one or two halogen atoms and/or one or two of the following radicals: C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, phenyl, C₁-C₄-haloalkoxy and/or C₁-C₄-alkylthio,
35
40

f) R¹ furthermore a radical

45



5

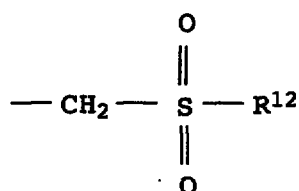
where R^{11} is:

10 C_1 - C_4 -alkyl, C_3 - C_6 -alkenyl, C_3 - C_6 -alkynyl, C_3 - C_8 -cycloalkyl, it being possible for these radicals to carry a C_1 - C_4 -alkoxy, C_1 - C_4 -alkylthio and/or a phenyl radical;

15 phenyl which is unsubstituted or substituted;

g) R^1 a radical

20

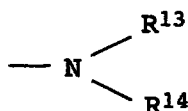


25

where R^{12} has the same meanings as R^{11} ;

h) R^1 can furthermore be

30



35

where R^{13} and R^{14} can be identical or different and have the following meanings:

40

hydrogen, C_1 - C_7 -alkyl, C_3 - C_7 -cycloalkyl, C_3 - C_7 -alkenyl, C_3 - C_7 -alkynyl, benzyl, phenyl, unsubstituted or substituted,

45

or R^{13} and R^{14} together form a C_4 - C_7 -alkylene chain which is closed to a ring, is unsubstituted or substituted by C_1 - C_4 -alkyl and may contain a hetero atom;

or R is a tetrazole [sic] or a nitrile [sic];



W is nitrogen, C-NO₂, a CH group when one or more of the substituents R², R³, R¹⁵ and/or R¹⁶ are a nitro group, or when X and/or Y are nitrogen;

5 R² is hydrogen, halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, hydroxyl, mercapto, C₁-C₄-alkylthio, nitro, amino, C₁-C₄-alkylamino or C₁-C₄-dialkylamino, cyano, phenyl, optionally substituted
10 once to three times by halogen, hydroxyl, amino, mono- or dialkyl (C₁-C₃)-amino, C₁-C₃-alkyl, C₁-C₃-alkoxy, mercapto or C₁-C₃-alkylthio, carboxyl, C₁-C₃-alkylcarboxyl; a five- or six-membered heteroaromatic system containing one to three nitrogen atoms and/or one sulfur or oxygen atom.

15 R² can furthermore form, with the adjacent carbon atom and X, a 5- or 6-membered alkylene or alkylidene [sic] ring in each of which one or two carbon atoms can be replaced by a hetero atom such as nitrogen, sulfur or
20 oxygen, and which can be substituted once to three times by the following radicals: halogen, nitro, cyano, hydroxyl, mercapto, C₁-C₃-alkyl, C₁-C₃-haloalkyl, C₁-C₃-alkoxy, C₁-C₃-alkylthio, amino, C₁-C₃-alkylamino, C₁-C₃-dialkylamino;

25 X is nitrogen or CR¹⁵ where R¹⁵ is hydrogen or C₁-C₅-alkyl, optionally substituted once or twice by hydroxyl or carboxyl; C₁-C₆-alkoxy, C₁-C₆-alkylthio, phenyl, benzyl, hydroxyl, mercapto, nitro, amino, C₁-C₄-alkylamino,
30 C₁-C₄-dialkylamino, cyano or carboxyl;

it is furthermore possible for CR¹⁵ to be linked to R² to give a 5- or 6-membered ring as described above, or CR¹⁵ can form with R³ and its adjacent carbon atom a 5- or
35 6-membered alkylene or alkylidene [sic] ring in each of which one or two carbon atoms can be replaced by nitrogen, oxygen or sulfur, and the 5- or 6-membered ring may optionally be substituted once to three times by the following radicals:

40 halogen, nitro, cyano, hydroxyl, mercapto, C₁-C₃-alkyl, C₁-C₃-haloalkyl, C₁-C₃-alkoxy, C₁-C₃-alkylthio, amino, C₁-C₃-alkylamino, C₁-C₃-dialkylamino or carboxyl; nitrogen in the 5-membered ring may also be substituted
45 by a formyl or acetyl group;

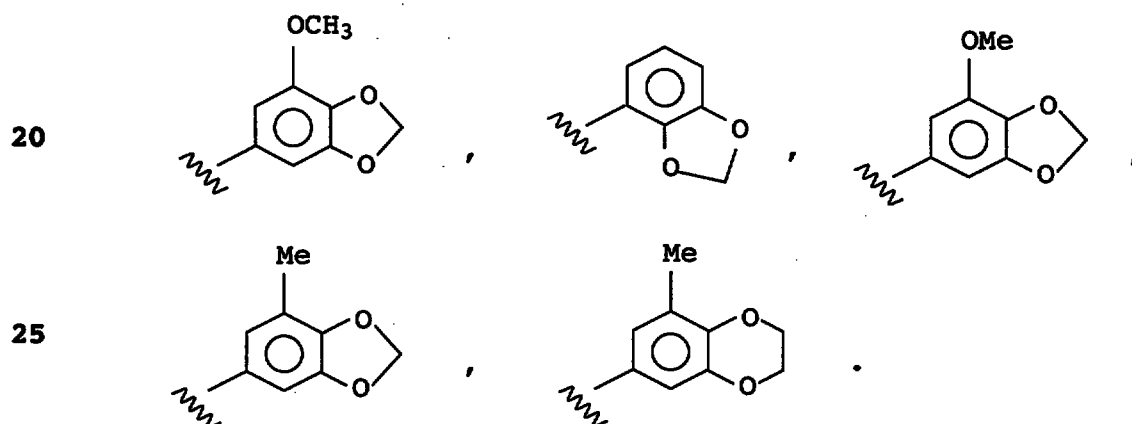


5

- R³** can have the same meanings as **R²**, **R²** and **R³** can be identical or different; it is furthermore possible for **R³** to form with the adjacent carbon atom and with **X** a 5- or 6-membered ring as described above; it is furthermore possible for **R³** to form together with the adjacent carbon atom and **Y** a 5- or 6-membered alkylene or alkylidene [sic] ring in each of which one or two carbon atoms can be replaced by nitrogen, oxygen or sulfur; the 5- or 6-membered ring may optionally be substituted once to three times by the following radicals:
halogen, nitro, cyano, hydroxyl, mercapto, C₁-C₃-alkyl, C₁-C₃-haloalkyl, C₁-C₃-alkoxy, C₁-C₃-alkylthio, amino, C₁-C₃-alkylamino, C₁-C₃-dialkylamino or carboxyl; nitrogen in the 5-membered ring may also be substituted by a formyl or acetyl group;
- Y** is nitrogen or CR¹⁶ where R¹⁶ is hydrogen, C₁-C₅-alkyl, C₁-C₅-alkoxy, C₁-C₅-alkylthio, nitro, phenyl, hydroxyl, halogen, cyano, amino, C₁-C₄-alkylamino, C₁-C₄-dialkylamino, mercapto or carboxyl, or CR¹⁶ form [sic] together with **R³** and its adjacent carbon atom a 5- or 6-membered ring as described above;
- R⁴** is phenyl, naphthyl, dihydro- or tetrahydronaphthyl, which can be substituted by one or more of the following radicals:
halogen, nitro, cyano, hydroxyl, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, phenoxy, phenyl, C₁-C₄-alkylthio, amino, C₁-C₄-alkylamino or C₁-C₄-dialkylamino, it being possible for two radicals on adjacent carbon atoms to form, together with the latter, a five- or six-membered ring which is linked by an alkylene or alkylidene [sic] group and in which one or more methylene or methyldene [sic] groups can be replaced by oxygen;
- R⁵** can have the same meanings as **R⁴**, it being possible for **R⁴** and **R⁵** to be identical or different;
- R⁶** is hydrogen, C₁-C₈-alkyl, C₃-C₈-alkenyl or C₃-C₈-alkynyl, it being possible for each of these radicals to be substituted one or more times by:
halogen, nitro, cyano, C₁-C₄-alkoxy, hydroxyl, C₁-C₄-alkylthio, mercapto, C₁-C₄-haloalkoxy, carboxyl, C₁-C₄-alkylcarboxy, C₁-C₄-alkylcarbonyl, amino, C₁-C₄-alkylamino, C₁-C₄-dialkylamino; a five- or six-membered heteroaromatic system which contains one to



- three nitrogen atoms and/or one sulfur or oxygen atom and which can carry one to four halogen atoms and/or one or 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; phenyl, naphthyl, which can in turn be substituted one or more times by: halogen, nitro, cyano, hydroxyl, C₁-C₄-alkoxy, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-haloalkoxy, mercapto, C₁-C₄-alkylthio, amino, C₁-C₄-alkylamino, C₁-C₄-dialkylamino or phenoxy; or one of the following radicals:



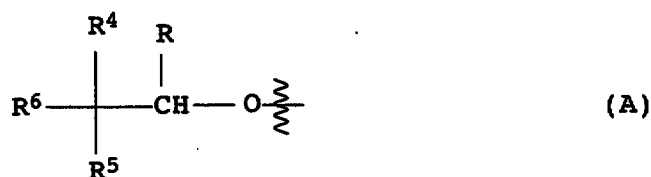
- 30 2. An α -hydroxy carboxylic acid derivative as claimed in claim 1, wherein R is COOH.
3. An α -hydroxy carboxylic acid derivative as claimed in any of the preceding claims, wherein at least one of the radicals R⁴ and R⁵ is phenyl.
- 35 4. An α -hydroxy carboxylic acid derivative as claimed in claim 3, wherein R⁴ and R⁵ are both phenyl.
- 40 5. An α -hydroxy carboxylic acid derivative as claimed in any of the preceding claims, wherein R⁶ is C₁-C₈-alkyl, unsubstituted or substituted by OH or C₁-C₄-alkoxy.
- 45 6. An α -hydroxy carboxylic acid derivative as claimed in any of the preceding claims, wherein X is CH.



7

7. An α -hydroxy carboxylic acid derivative as claimed in any of the preceding claims, wherein at least one of the radicals W, Y is nitrogen (N).
- 5 8. An α -hydroxy carboxylic acid derivative as claimed in any of the preceding claims, wherein at least one of the radicals R^2 , R^3 is C_1 - C_4 -alkyl.
9. The use of compounds as claimed in any of claims 1 to 8 for
10 producing medicines for treating hypertension, pulmonary hypertension, acute and chronic kidney failure, chronic heart failure, cerebral ischemia, restenosis after angioplasty, prostate cancer.
- 15 10. The use of a combination of a compound as claimed in any of claims 1 to 8 with an inhibitor of the renin-angiotensin system (RAS).
11. The use of a structural fragment of the formula (A)

20



25

where R - R^6 have the meanings stated in claim 1, as
30 structural element in a pharmaceutically active compound with endothelin receptor-antagonizing action.

35

40

45