

Novel β -amino and β -azido carboxylic acid derivatives, their preparation and use as endothelin receptor antagonists

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

- Endothelin is a peptide which is composed of 21 amino acids and
10 which is synthesized and released by vascular endothelium. Endothelin 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 vessel tone. It is known that this
15 vasoconstriction is caused by binding of endothelin to its receptor (Nature, 332 (1988) 411-415; FEBS Letters, 231, (1988) 440-444, and Biochem. Biophys. Res. Commun., 154, (1988) 868-875).
- 20 Increased or abnormal release of endothelin causes persistent vasoconstriction in peripheral, renal and cerebral blood vessels, which may lead to diseases. As reported in the literature, endothelin is involved in a number of diseases. These include: hypertension, acute myocardial infarct, pulmonary hypertension, ,
25 Raynaud's syndrome, cerebral vasospasms, stroke, benign prostate hypertrophy, atherosclerosis, asthma and prostate cancer (J. Vascular Med. Biology 2, (1990) 207, J. Am. Med. Association 264, (1990) 2868, Nature 344, (1990) 114, N. Engl. J. Med. 322, (1989) 205, N. Engl. J. Med. 328, (1993) 1732, Nephron 66, (1994)
30 373, Stroke 25, (1994) 904, Nature 365, (1993) 759, J. Mol. Cell. Cardiol. 27, (1995) A234; Cancer Research 56, (1996) 663, Nature Medicine 1, (1995) 944).

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

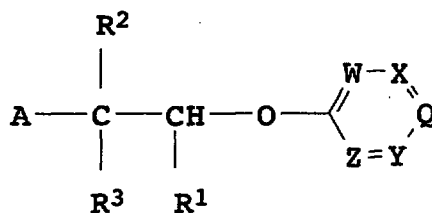
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- It is an object of the present invention to provide endothelin receptor antagonists which bind to the ET_A and/or ET_B receptor. The invention relates to β -amino and β -azido carboxylic acid
45 derivatives of the formula I

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where R¹ is tetrazole [sic] or a group



15 where R has the following meaning:

a) a radical OR^4 , where R^4 is:

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

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

30 C₃-C₈-alkenyl or C₃-C₈-alkynyl, it being possible for these groups in turn to carry one to five halogen atoms;

35 R⁴ can furthermore be phenyl which may carry one to five halogen atoms and/or one to three of the following radicals: nitro, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, hydroxyl, C₁-C₄-alkoxy, mercapto, C₁-C₄-alkylthio, amino, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂;

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

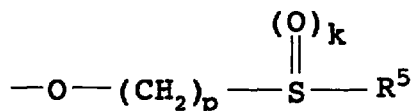
c) a group

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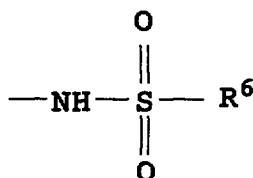
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where k can assume the values 0, 1 and 2, p the values 1, 2, 3 and 4, and R⁵ is

10 C₁-C₄-alkyl, C₃-C₈-cycloalkyl, C₃-C₈-alkenyl, C₃-C₈-alkynyl or phenyl, which may be substituted by one or more, eg. one to three, of the following radicals:

d) a radical

15



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where R⁶ is:

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

C₁-C₄-haloalkyl or phenyl, unsubstituted or substituted in particular as mentioned under C).

30

The other substituents have the following meanings:

A is NR⁷R⁸ or azido;

35 W and Z (which may be identical or different) are:

nitrogen or methine; with the proviso that Q = nitrogen if W and Z = methine;

40 X is nitrogen or CR⁹;

Y is nitrogen or CR¹⁰;

45 Q is nitrogen or CR¹¹; with the proviso that X = CR⁹ and Y = CR¹⁰ if Q = nitrogen



R² and R³ (which may be identical or different) are:

5 phenyl or naphthyl, each of which may substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, mercapto, C₁-C₄-alkyl, C₂-C₄-alkenyl, C₂-C₄-alkynyl, C₁-C₄-hydroxyalkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, phenoxy, C₁-C₄-haloalkoxy, C₁-C₄-alkylthio, amino, NH(C₁-C₄-alkyl), 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

15 phenyl or naphthyl which are linked 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;

20 C₅-C₆-cycloalkyl, it being possible for these radicals to be substituted in each case 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;

25 R⁷ is hydrogen, C₁-C₈-alkyl, C₃-C₈-alkenyl or C₃-C₈-alkynyl, C₁-C₅-alkylcarbonyl, it being possible for these radicals to be substituted in each case one or more times by: halogen, hydroxyl, mercapto, carboxyl, nitro, amino, cyano, C₁-C₄-alkoxy, C₃-C₆-alkenyloxy, C₃-C₆-alkynyloxy, C₁-C₄-alkylthio, C₁-C₄-haloalkoxy, C₁-C₄-alkoxycarbonyl, C₃-C₈-alkylcarbonylalkyl, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂, C₃-C₈-cycloalkyl, hetaryloxy or hetaryl, five- or six-membered, containing one to three nitrogen atoms and/or one sulfur or oxygen atom, phenoxy or phenyl, it being possible for all 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-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, amino, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂, phenyl, or C₁-C₄-alkylthio;

40 phenyl or naphthyl, which can in each case 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, carboxyl, 45 NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂, dioxomethylene [sic] or dioxoethylene [sic];

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C₃-C₈-cycloalkyl, it being possible for these radicals to be substituted in each case 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 or;

R⁷ is linked to R⁸ via 4 or 5 CH₂ groups to give a 5- or 6-membered ring;

10 R⁸ is hydrogen, C₁-C₄-alkyl;

or R⁸ is linked to R⁷ via 4 or 5 CH₂ groups to give a 5- or 6-membered ring;

15 R⁹ and R¹⁰ (which may be identical or different) are:

hydrogen, halogen, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₃-C₆-alkenyloxy, C₃-C₆-alkynyloxy, C₁-C₄-alkylthio, C₁-C₄-alkylcarbonyl, C₁-C₄-alkoxycarbonyl, hydroxyl, NH₂, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂

25 C₁-C₄-alkyl, C₂-C₄-alkenyl, C₂-C₄-alkynyl, it being possible for these radicals to be substituted by halogen, hydroxyl, mercapto, carboxyl, cyano;

or CR⁹ or CR¹⁰ is linked to CR¹¹ as indicated for R¹¹ to give a 5- or 6-membered ring,

30 R¹¹ is hydrogen, halogen, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₃-C₆-alkenyloxy, C₃-C₆-alkynyloxy, C₁-C₄-alkylthio, C₁-C₄-alkylcarbonyl, C₁-C₄-alkoxycarbonyl, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂, hydroxyl, carboxyl, cyano, amino, mercapto;

35 C₁-C₄-alkyl, C₂-C₄-alkenyl, C₂-C₄-alkynyl, it being possible for these radicals to be substituted one or more times by: halogen, hydroxyl, mercapto, carboxyl, cyano, amino, C₁-C₄-alkoxy;

40 or CR¹¹ forms together with CR⁹ or CR¹⁰ a 5- or 6-membered alkylene- or alkenylene ring which may be substituted by one or two C₁-C₄-alkyl groups, and in which in each case one or more methylene groups may be replaced by oxygen, sulfur, -NH or -N(C₁-C₄-alkyl);

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The definitions applying herein and hereafter are:

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

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

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

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

- 15 C₁-C₄-haloalkyl can be linear or branched, eg. fluoromethyl, difluoromethyl, trifluoromethyl, chlorodifluoromethyl, dichlorofluoromethyl, trichloromethyl, 1-fluoroethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2-chloro-2,2-difluoroethyl, 2,2-dichloro-2-fluoroethyl,
20 2,2,2-trichloroethyl or pentafluoroethyl;

- C₁-C₄-haloalkoxy can be linear or branched, eg. difluoromethoxy, trifluoromethoxy, chlorodifluoromethoxy, 1-fluoroethoxy,
25 2,2-difluoroethoxy, 1,1,2,2-tetrafluoroethoxy, 2,2,2-trifluoroethoxy, 2-chloro-1,1,2-trifluoroethoxy, 2-fluoroethoxy or pentafluoroethoxy;

- C₁-C₄-alkyl can be linear or branched, eg. methyl, ethyl,
30 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, eg. ethenyl, 1-propen-3-yl, 1-propen-2-yl, 1-propen-1-yl, 2-methyl-1-propenyl,
35 1-butenyl or 2-butenyl;

C₂-C₄-alkynyl can be linear or branched, eg. ethynyl, 1-propyn-1-yl, 1-propyn-3-yl, 1-butyne-4-yl or 2-butyne-4-yl;

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

- C₃-C₆-alkenyloxy can be linear or branched, eg. allyloxy,
45 2-buten-1-yloxy or 3-buten-2-yloxy;

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

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

10 C₁-C₅-alkylcarbonyl can be linear or branched, eg. acetyl, ethylcarbonyl or 2-propylcarbonyl;

15 C₁-C₄-alkoxycarbonyl can be linear or branched, eg. metoxycarbonyl [sic], ethoxycarbonyl, n-propoxycarbonyl, i-propoxycarbonyl or n-butoxycarbonyl;

C₃-C₈-alkylcarbonylalkyl can be linear or branched eg. 2-oxo-1-propyl, 3-oxo-1-butyl or 3-oxo-2-butyl

20 C₁-C₈-alkyl can be linear or branched eg. C₁-C₄-alkyl, pentyl, hexyl, heptyl or octyl;

25 C₃-C₈-alkenyl can be linear or branched, eg. 1-propen-3-yl, 1-propen-2-yl, 1-propen-1-yl, 2-methyl-1-propenyl, 1-buten-4-yl, 2-buten-3-yl, 1-penten-5-yl, 1-hexen-6-yl, 3-hexen-6-yl, 2-hepten-7-yl or 1-octen-8-yl;

30 C₃-C₈-alkynyl can be linear or branched eg. 1-propyn-1-yl, 1-propyn-3-yl, 1-butyn-4-yl, 2-butyn-4-yl, 2-pentyn-5-yl, 3-hexyn-6-yl, 3-heptyn-7-yl, 2-octyn-8-yl;

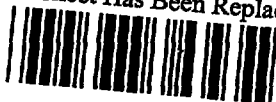
Halogen is, for example, fluorine, chlorine, bromine, iodine.

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

Preferred prodrugs are those whose release takes place under
40 conditions prevailing in certain compartments of the body, eg. in the stomach, intestine, blood circulation, liver.

The compounds I and the intermediates for preparing them, eg. II and III, may have one or more asymmetrically substituted carbon
45 atoms. Compounds of this type can exist as pure enantiomers or

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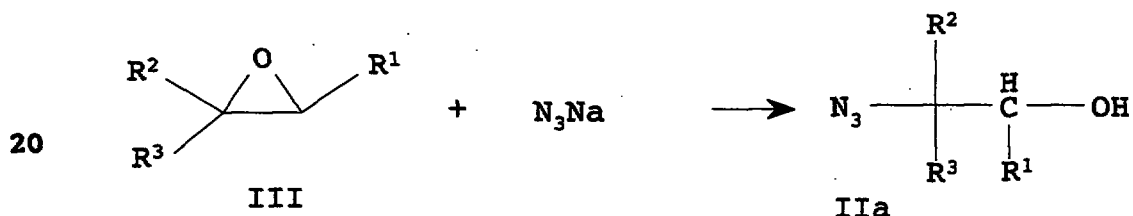
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pure diastereomers or as mixture thereof. It is preferred to use an enantiomerically pure compound as active ingredient.

5 The invention further relates to the use of the abovementioned carboxylic acid derivatives to produce drugs, in particular to produce inhibitors of ET_A and/or ET_B receptors. The novel compounds are suitable as antagonists as defined at the outset.

10 Preparation of compounds of the formula II where A is an azido group (IIa) starts from the epoxides III which can be synthesized, for example, as described in WO 96/11914. These epoxides III can then be reacted with an azide such as sodium azide. This is done by reacting the compounds of the formula III with the azide in the molar ratio of about 1:1 to 1:7 at from 20
15 to 150°C to give IIa.



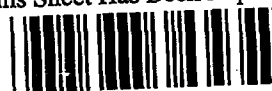
25 The reaction may also take place in the presence of a diluent. All solvents which are inert toward the reagents can be used for this purpose.

30 Examples of such solvents or 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, ethyl chloride and trichloroethylene, ethers such as diisopropyl ether, dibutyl ether, methyl tert-butyl ether, dioxane and tetrahydrofuran,
35 nitriles such as acetonitrile and propionitrile, amides such as dimethylformamide, dimethylacetamide and N-methylpyrrolidone, sulfoxides and sulfones such as dimethyl sulfoxide and sulfolane.

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

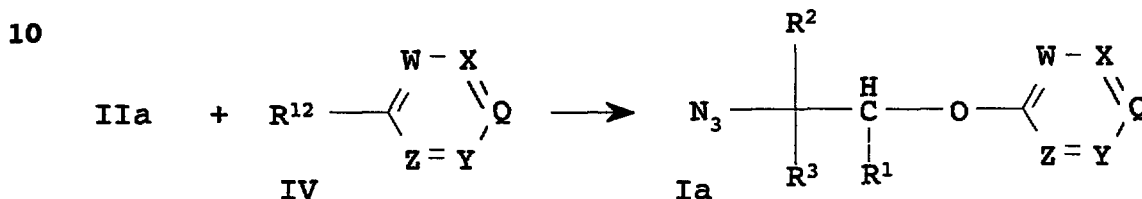
The presence of a catalyst may be advantageous. Suitable
45 catalysts are strong organic and inorganic acids, and Lewis acids. Examples thereof include sulfuric acid, hydrochloric acid,

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trifluoroacetic acid, p-toluenesulfonic acid, boron trifluoride etherate and triflates of the rare earths.

- 5 The preparation of the novel compounds of the formula I where A is an azido group (Ia) can be prepared [sic], for example, by reacting the carboxylic acid derivatives of the formula IIa where the substituents have the stated meanings with compounds of the formula IV.



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- R¹² in formula IV is halogen or R¹³-SO₂- where R¹³ can be C₁-C₄-alkyl, C₁-C₄-haloalkyl or phenyl, and the conditions [sic] specified at the outset apply to W,X,Y,Z and Q. The reaction preferably takes place in an inert solvent or diluent with the addition of a suitable base, ie. a base which effects deprotonation of the intermediate IIa, at a temperature in the range from room temperature to the boiling point of the solvent.

- 25 Compounds of the formula IV are known, and some of them can be bought or can be prepared in a generally known manner.

- 30 Compounds of type Ia with R¹ = COOH can be obtained directly by deprotonating the intermediate IIa where R¹ is COOH with two equivalents of a suitable base, and reacting with compounds of the formula IV. 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.

- 35 The base which can be used is 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.

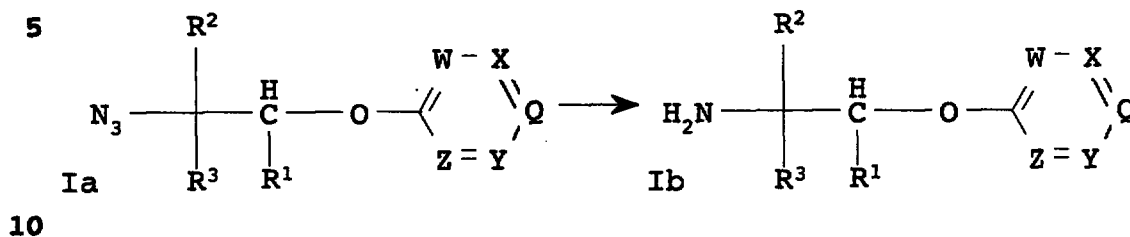
- 45 Novel compounds of the formula I where A is an amino group (Ib) are prepared starting from compounds Ia. This is done by reacting the compounds of the formula Ia with hydrogen in the presence of a catalyst such as palladium or platinum in a solvent at from 20

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to 100°C. The compounds Ia can also be converted into Ib in the presence of triphenylphosphine.



If R¹ is an ester, the amino group in Ib can be alkylated or converted into the amide by generally known methods. The ester group can then be cleaved with acid or base to the carboxylic acid.

15

Compounds of the formula II where A is substituted amine [sic] (IIc) can also be prepared directly from the epoxide III by opening with an amine. The substances IIc can then be reacted

20 with IV as described above to give the novel compounds I.

Compounds of the formula I can also be prepared by starting from the corresponding carboxylic acids, ie. compounds of the formula I where R¹ is COOH, and initially converting these in a

25 conventional way into an activated form, such as a halide, an anhydride or imidazolidine, and then reacting the latter with an appropriate hydroxyl compound HOR⁴ or sulfonamide H₂NSO₂R⁶. This reaction can be carried out in the usual solvents and often requires addition of a base, in which case those mentioned above

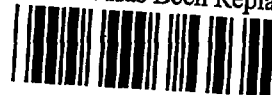
30 are suitable. These two steps can also be simplified, for example, by allowing the carboxylic acid to act on the hydroxyl compound or the sulfonamide in the presence of a dehydrating agent such as a carbodiimide.

35 Compounds of the formula I can also be prepared in addition by starting from salts of the corresponding carboxylic acids, ie. from compounds of the formula I where R¹ is COR and R is OM [sic] where M can be an alkali metal cation or the equivalent of an alkaline earth metal cation. These salts can be reacted with many

40 compounds of the formula R-D where D is a usual nucleofugic leaving group, for example halogen such as chlorine, bromine, iodine or aryl- or alkylsulfonyl which is unsubstituted or substituted by halogen, alkyl or haloalkyl, eg. toluenesulfonyl and methylsulfonyl, or another equivalent leaving group.

45 Compounds of the formula R-D with a reactive substituent D are known or can easily be obtained with general expert knowledge. This reaction can be carried out in conventional solvents,

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advantageously with the addition of a base, in which case those mentioned above are suitable. Compounds of the formula I where R^1 is tetrazole [sic] can be prepared by methods similar to those described in WO 96/11914 from the corresponding carboxylic acids 5 (formula I with $R^1 = \text{COOH}$).

It is necessary in some cases to use generally known protective group techniques to prepare the novel compounds I. If, for example, A is to be $\text{HOCH}_2\text{CONH-}$, the hydroxyl group can initially 10 be protected as benzyl ether, which is then cleaved at a suitable stage in the reaction sequence.

Compounds of the formula I and II can be obtained in 15 enantiomerically pure form by carrying out a classical racemate resolution with suitable enantiomerically pure bases, as described, for example, in WO 96/11914, on racemic or diastereomeric compounds of the formula I and II.

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

25 A is NR^7R^8 or azido;

W and Z, (which may be identical or different) are:

30 nitrogen or methine; with the proviso that Q = nitrogen if W and Z = methine;

X is nitrogen or CR^9 ;

Y is nitrogen or CR^{10} ;

35 Q is nitrogen or CR^{11} ; with the proviso that X = CR^9 and Y = CR^{10} if Q = nitrogen;

furthermore Q for which, in addition to the stated conditions, 40 the following applies: Y = CR^{10} or X = CR^9 if Q = CR^{11} .

R^2 and R^3 (which may be identical or different) are:

45 phenyl or naphthyl, each of which may substituted by one or more of the following radicals: halogen, cyano, hydroxyl, mercapto, $\text{C}_1\text{-C}_4\text{-alkyl}$, $\text{C}_1\text{-C}_4\text{-haloalkyl}$, $\text{C}_1\text{-C}_4\text{-alkoxy}$, phenoxy, $\text{C}_1\text{-C}_4\text{-haloalkoxy}$, $\text{C}_1\text{-C}_4\text{-alkylthio}$, amino, $\text{NH}(\text{C}_1\text{-C}_4\text{-alkyl})$,

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$N(C_1-C_4\text{-alkyl})_2$ or phenyl which may be substituted one or more times, eg. one to three times, by halogen, cyano, $C_1-C_4\text{-alkyl}$, $C_1-C_4\text{-haloalkyl}$, $C_1-C_4\text{-alkoxy}$, $C_1-C_4\text{-haloalkoxy}$ or $C_1-C_4\text{-alkylthio}$; or

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phenyl or naphthyl which are linked together in orthopositions via a direct linkage, a methylene, ethylene or ethenylene group, an oxygen or sulfur atom or an SO_2 -, NH - or $N\text{-alkyl}$ group;

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R^7 is hydrogen, $C_1-C_8\text{-alkyl}$, $C_3-C_8\text{-alkenyl}$ or $C_3-C_8\text{-alkynyl}$, $C_1-C_5\text{-alkylcarbonyl}$, it being possible for these radicals to be substituted in each case one or more times by: halogen, hydroxyl, mercapto, carboxyl, amino, cyano, $C_1-C_4\text{-alkoxy}$, $C_3-C_6\text{-alkenyloxy}$, $C_3-C_6\text{-alkynyloxy}$, $C_1-C_4\text{-alkylthio}$, $C_1-C_4\text{-haloalkoxy}$, $C_1-C_4\text{-alkoxycarbonyl}$, $NH(C_1-C_4\text{-alkyl})$, $N(C_1-C_4\text{-alkyl})_2$, $C_3-C_8\text{-cycloalkyl}$, hetaryloxy or hetaryl, five- or six-membered, containing one to three nitrogen atoms and/or one sulfur or oxygen atom, phenoxy or phenyl, it being possible for all said aryl radicals in turn to be substituted one or more times, eg. one to three times, by halogen, hydroxyl, mercapto, carboxyl, cyano, $C_1-C_4\text{-alkyl}$, $C_1-C_4\text{-haloalkyl}$, $C_1-C_4\text{-alkoxy}$, $C_1-C_4\text{-haloalkoxy}$, amino, $NH(C_1-C_4\text{-alkyl})$, $N(C_1-C_4\text{-alkyl})_2$, or $C_1-C_4\text{-alkylthio}$;

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phenyl or naphthyl, which can in each case be substituted by one or more of the following radicals: halogen, cyano, hydroxyl, amino, $C_1-C_4\text{-alkyl}$, $C_1-C_4\text{-haloalkyl}$, phenoxy, $C_1-C_4\text{-alkoxy}$, $C_1-C_4\text{-haloalkoxy}$, $C_1-C_4\text{-alkylthio}$, dioxomethylene [sic], $NH(C_1-C_4\text{-alkyl})$, $N(C_1-C_4\text{-alkyl})_2$ or dioxoethylene [sic];

30

$C_3-C_8\text{-cycloalkyl}$, it being possible for these radicals to be substituted in each case one or more times by: halogen, hydroxyl, mercapto, carboxyl, $C_1-C_4\text{-alkyl}$, $C_2-C_4\text{-alkenyl}$, $C_2-C_4\text{-alkynyl}$, $C_1-C_4\text{-alkoxy}$, $C_1-C_4\text{-alkylthio}$, $C_1-C_4\text{-haloalkoxy}$;

35

40

R^8 is hydrogen;

R^9 and R^{10} (which may be identical or different):

45

hydrogen, halogen, $C_1-C_4\text{-alkoxy}$, $C_1-C_4\text{-haloalkoxy}$, $C_1-C_4\text{-alkylthio}$, $NH(C_1-C_4\text{-alkyl})$, $N(C_1-C_4\text{-alkyl})_2$;



C₁-C₄-alkyl, C₂-C₄-alkenyl, it being possible for these radicals to be substituted by halogen, hydroxyl, mercapto, cyano;

- 5 or CR⁹ or CR¹⁰ is linked to CR¹¹ as indicated for R¹¹ to give a 5- or 6-membered ring;

- R¹¹ is hydrogen, halogen, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₁-C₄-alkylthio, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂, cyano;
10 C₁-C₄-alkyl, C₂-C₄-alkenyl, it being possible for these radicals to be substituted in each case one or more times by: halogen, cyano, C₁-C₄-alkoxy;

- 15 or CR¹¹ forms together with CR⁹ or CR¹⁰ a 5- or 6-membered alkylene or alkenylene ring which may be substituted by one or two C₁-C₄-alkyl groups, and in which in each case one or more methylene groups can be replaced by oxygen, sulfur, -NH or -N(C₁-C₄-alkyl);

20

Particularly 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:

25

A is NR⁷R⁸ or azido;

W and Z (which may be identical or different) are:

30

nitrogen or methine; with the proviso that Q = nitrogen if W and Z = methine;

X is nitrogen or CR⁹;

35

Y is nitrogen or CR¹⁰;

Q is nitrogen or CR¹¹; with the proviso that X = CR⁹ and Y = CR¹⁰ if Q = nitrogen, and Y = CR¹⁰ or X = CR⁹ if Q = CR¹¹;

40

R² and R³ (which may be identical or different) are:

- 45 phenyl which may be substituted by one or more of the following radicals: halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, phenoxy, C₁-C₄-alkylthio, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂ or phenyl which can be substituted one or more



times, eg. one to three times, by halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy or C₁-C₄-alkylthio; or

5 phenyl groups which are linked together in orthopositions by a direct linkage, a methylene, ethylene or ethenylene group, an oxygen or sulfur atom or an SO₂, NH or N-alkyl group;

10 R⁷ is hydrogen, C₁-C₈-alkyl, C₃-C₈-alkenyl or C₃-C₈-alkynyl, C₁-C₅-alkylcarbonyl, it being possible for these radicals to be substituted in each case one or more times by: halogen, hydroxyl, carboxyl, amino, C₁-C₄-alkoxy, C₁-C₄-alkylthio, C₁-C₄-alkoxycarbonyl, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂, C₃-C₈-cycloalkyl, hetaryloxy or hetaryl, five- or
15 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, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, amino, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂, or
20 C₁-C₄-alkylthio;

phenyl or naphthyl, each of which can be substituted by one or more of the following radicals: halogen, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, phenoxy, C₁-C₄-alkoxy, C₁-C₄-alkylthio, dioxomethylene [sic] or dioxoethylene [sic];
25

C₅-C₆-cycloalkyl, it being possible for these radicals in each case to be substituted one or more times by: C₁-C₄-alkyl, C₁-C₄-alkoxy;
30

R⁸ is hydrogen;

35 R⁹ and R¹⁰ (which may be identical or different) are:

hydrogen, C₁-C₄-alkoxy, C₁-C₄-alkylthio, N(C₁-C₄-alkyl)₂;

40 C₁-C₄-alkyl, it being possible for these radicals to be substituted by halogen;

or CR⁹ or CR¹⁰ is linked to CR¹¹ as indicated for R¹¹ to give a 5- or 6-membered ring;

45 R¹¹ is hydrogen, C₁-C₄-alkoxy, C₁-C₄-alkylthio, cyano;

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C₁-C₄-alkyl, it being possible for these radicals in each case to be substituted one or more times by halogen;

5 or CR¹¹ forms together with CR⁹ or CR¹⁰ a 5- or 6-membered alkylene or alkenylene ring which may be substituted by one or two C₁-C₄-alkyl groups and in which, in each case, one or more methylene groups can be replaced by oxygen, sulfur, -NH or -N(C₁-C₄-alkyl);

10 The compounds of the present invention offer a novel potential treatment of hypertension, pulmonary hypertension, myocardial infarct, chronic heart failure, 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 hyperplasia, ischemic and intoxication-induced kidney failure or hypertension, cyclosporin-induced kidney failure, metastasis and growth of mesenchymal tumors, cancer, 20 prostate cancer, contrast agent-induced kidney failure, pancreatitis, gastrointestinal ulcers.

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

30 The combinations can be administered together in one pharmaceutical form or temporally and spatially separate.

35 The factors to be taken into account in respect of dosage and mode of administration are the same as for the corresponding single substances.

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

The invention further relates to the use of the novel compounds for photoaffinity labeling of endothelin receptors. Particularly 45 suitable for this purpose are those compounds of the formula I where A is azido.

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

Receptor-binding studies

5

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

10 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 serum (PAA Laboratories GmbH, Linz, No. A15-022), 1 mM glutamine
15 (Gibco No. 25030-024), 100 U/ml penicillin and 100 µg/ml streptomycin (Gibco, Sigma No. P-0781). After 48 hours, the cells were washed with PBS and incubated with 0.05% trypsin-containing PBS at 37°C for 5 minutes. This was followed by neutralization with medium, and the cells were collected by centrifugation at
20 300 x g.

For membrane preparation, the cells were adjusted to a concentration of 10^8 cells/ml of buffer (50 mM Tris-HCl buffer, pH 7.4) and then disintegrated with ultrasound Branson Sonifier 250,
25 40-70 seconds/constant/output [sic] 20).

Binding assays

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

45

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Testing of ET antagonists in vivo:

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.

In control animals, intravenous administration of 1 µg/kg ET1 results in a marked rise in blood pressure which persists for a
10 lengthy period.

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

Oral testing of ET receptor antagonists:

Male normotensive rats (Sprague Dawley, Janvier) weighing
20 250-350 g are pretreated with the test substances orally. 80 minutes later, the animals are anesthetized with urethane, and the carotid artery (for measuring the blood pressure) and the jugular vein (administration of big endothelin/endothelin 1) are catheterized.
25

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

35 The novel compounds can be administered orally or parenterally (subcutaneously, intravenously, intramuscularly, intraperitoneally) in a conventional way. Administration can also take place with vapors or sprays through the nasopharyngeal
40 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 from about 0.5 to 50 mg/kg of body
45 weight on oral administration and from about 0.1 to 10 mg/kg of body weight on parenteral administration.





The novel compounds can be administered 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 aids such as tablet binders, bulking agents, preservatives, tablet disintegrants, flow regulators, plasticizers, wetting agents, dispersants, emulsifiers, solvents, release-slowing agents, antioxidants and/or propellant gases (cf. H. Sucker et al.: Pharmazeutische Technologie, Thieme-Verlag, Stuttgart, 1991). The administration forms obtained in this way normally contain from 0.1 to 90% by weight of active ingredient.

15 Synthesis Examples

Example 1:

20 Methyl 2-hydroxy-3-azido-3,3-diphenylpropionate

3.8 g (59.0 mmol) of sodium azide and 3.1 g (59.0 mmol) of ammonium chloride were introduced into 80 ml of methanol. 5 g (19.7 mmol) of methyl 3,3-diphenyl-2,3-epoxypropionate were added to this suspension, which was then stirred at room temperature for 48 hours. The mixture was concentrated, water was added, and the aqueous phase was extracted several times with ethyl acetate. The combined organic phases were then dried over magnesium sulfate, the solvent was distilled off, and the residue was purified by chromatography. 1.2 g (4 mmol, 21% yield) of pure product were isolated.

Melting point: 102-103°C

35 $^1\text{H-NMR}$ (200 MHz): 7.2 ppm (10 H, m), 5.1 (1 H, d), 3.5 (3 H, s), 3.4 (1 H, d).

Example 2:

40

Methyl 2-(4-methoxy-6-methyl-2-pyrimidinyl)-3-azido-3,3-diphenylpropionate

45 930 mg (6.7 mmol) of potassium carbonate, 1.4 g (6.7 mmol) of 4-methoxy-6-methyl-2-methylsulfonylpyrimidine and 2.0 g (6.7 mmol) of methyl 2-hydroxy-3-azido-3,3-diphenylpropionate were mixed in 20 ml of DMF. The mixture was stirred at 80°C for

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two hours. Cooling and addition of water were followed by extraction with ethyl acetate. The combined organic phases were dried over magnesium sulfate, and the solvent was distilled off. 2.9 g of a crude oil were isolated and were immediately reacted 5 further.

Example 3:

10 Methyl 2-(4-methoxy-6-methyl-2-pyrimidinyloxy)-3-amino-3,3-diphenylpropionate

2.8 g (6.7 mmol) of methyl 2-(4-methoxy-6-methyl-2-pyrimidinyloxy)-3-amino-3,3-diphenylpropionate were dissolved in 15 20 ml/40 ml of methanol/ethyl acetate, and a spatula tip of palladium on carbon was added. After the apparatus had been flushed with nitrogen and then with hydrogen, the solution was stirred under atmospheric pressure at room temperature for three hours. After conversion was complete, the palladium on carbon was 20 filtered off and the solvent was distilled off. 2.9 g of crystals were isolated and immediately reacted further.

Example 4:

25 2-(4-Methoxy-6-methyl-2-pyrimidinyloxy)-3-amino-3,3-diphenylpropionic acid (I-375)

840 mg (2.1 mmol) of methyl 2-(4-methoxy-6-methyl-2-pyrimidinyloxy)-3-amino-3,3-diphenylpropionate were added to a 30 mixture of 6.4 ml of dioxane and 3.2 ml of 1 N potassium hydroxide solution, and the mixture was stirred at 80°C for two hours. Cooling, addition of water and acidification were followed by extraction with ethyl acetate. The combined organic phases 35 were dried over magnesium sulfate, and the solvent was distilled off. The residue was stirred with ether, which allowed 190 mg (0.5 mmol, 25% yield) of crystals to be isolated.

¹H-NMR(360 MHz/DMSO/303K): 7.7 ppm (1 H, broad), 7.4 (4 H, m), 7.2 40 (6 H, m), 5.9 (1 H, broad), 5.1 (1 H, s), 3.2 (3 H, broad), 2.1 (3 H, s).

¹H-NMR (360 MHz/DMSO/323 K): 7.7 PPM [sic] (1 H, broad), 7.4 (4 H, m), 7.2 (6 H, m), 5.9 (1 H, s), 5.1 (1 H, s), 3.2 (3 H, s), 45 2.1 (3 H, s).

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Example 5:

2-(4,6-Dimethoxy-2-pyrimidinyloxy)-3-azido-3,3-diphenylpropionic acid (I-542)

5

1.1 g (2.5 mmol) of methyl 2-(4,6-dimethoxy-2-pyrimidinyloxy)-3-azido-3,3-diphenylpropionate were added to a mixture of 11 ml of dioxane and 5 ml of 1 N potassium hydroxide solution, and the mixture was stirred at 50°C for three hours. Cooling, addition of water and acidification were followed by extraction with ether. The combined organic phases were dried over magnesium sulfate, and the solvent was distilled off. 900 mg (2.1 mmol, 85% yield) of crystals were isolated.

15

Melting point: 164-165°C

ESI-MS: $M^+ = 421$

Example 6:

20

Methyl

2-(4,6-dimethoxy-2-pyrimidinyloxy)-3-acetylamino-3,3-diphenylpropionate

25

A catalytic amount of DMAP and 1 g (2.4 mmol) of methyl 2-(4,6-dimethoxy-2-pyrimidinyloxy)-3-amino-3,3-diphenylpropionate were dissolved in 10 ml of pyridine. While cooling in ice, 0.26 ml (3.7 mmol) of acetyl chloride was added dropwise, and the mixture was stirred at room temperature for 12 hours. Water was added, and the mixture was extracted with ether. The combined organic phases were dried over magnesium sulfate, and the solvent was distilled off. The residue was mixed with ether, and the compound starts to crystallize out after a short time (1 g, 2.2 mmol, 90% yield). The compound could be used further without further purification.

Example 7:

40

2-(4,6-Dimethoxy-2-pyrimidinyloxy)-3-acetylamino-3,3-diphenylpropionic acid (I-174)

1 g (2.2 mmol) methyl 2-(4,6-dimethoxy-2-pyrimidinyloxy)-3-acetylamino-3,3-diphenylpropionate was added to a mixture of 8.8 ml of dioxane and 4.4 ml of 1 N potassium hydroxide solution, and the mixture was stirred at 80°C for one hour. Cooling and



addition of water were followed by extraction once with ether. Acidification was then followed by extraction with methyl tert-butyl ether. The combined organic phases were dried over magnesium sulfate, and the solvent was distilled off. The residue
5 was stirred with ether to allow isolation of 640 mg (1.5 mmol, 67% yield) of crystals.

Melting point: 120-121°C

10 ESI-MS: $M^+ = 437$

Example 8:

Methyl 2-(4-methoxy-6,7-dihydro-5H-cyclopentapyrimidin-2-
15 yloxy)-3-azido-3,3-diphenylpropionate

743 mg (5.4 mmol) of potassium carbonate, 2.5 g (10.8 mmol) of 4-methoxy-6,7-dihydro-5H-cyclopenta-2-methylsulfonylpyrimidine and 3.0 g (10.8 mmol) of methyl 2-hydroxy-3-azido-3,3-
20 diphenylpropionate were mixed in 20 ml of DMF. The mixture was stirred at 60°C for three hours. Cooling and addition of water were followed by extraction with ethyl acetate. The combined organic phases were dried over magnesium sulfate, and the solvent was distilled off. 3.7 g (8.3 mmol, 77% yield) of crystals were
25 isolated and were immediately reacted further.

Example 9:

30 2-(4-Methoxy-6,7-dihydro-5H-cyclopentapyrimidin-2-yloxy)-3-azido-3,3-diphenylpropionic acid (I-518)

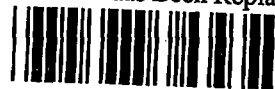
3.7 g (8.3 mmol) of methyl 2-(4-methoxy-6,7-dihydro-5H-cyclopentapyrimidin-2-yloxy)-3-azido-3,3-diphenylpropionate were
35 added to a mixture of 33 ml of dioxane and 17 ml of 1 N potassium hydroxide solution, and the mixture was stirred firstly at 50°C for two hour [sic] and then at room temperature for 12 hours. Water was added, and impurities were extracted with ether. Acidification was then followed by extraction with ether. The
40 combined organic phases were dried over magnesium sulfate, and the solvent was distilled off. The residue was crystallized from ether/n-hexane, allowing 2.6 g (5 mmol, 60% yield) of crystals to be isolated.

45 Melting point: 143-144°C

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ESI-MS: M^+ = 431

Example 10:

- 5 The following compounds were prepared in a similar way to the examples described above.

2-(4,6-Dimethoxy-2-pyrimidinyloxy)-3-amino-3,3-diphenylpropionic
10 acid (I-354)

Melting point: 159-160°C

ESI-MS: M^+ = 395

15 2-(4-Methoxy-6,7-dihydro-5H-cyclopentapyrimidin-2-yloxy)-3-amino-3,3-diphenylpropionic acid (I-334)

Melting point: 119-120°C

20 ESI-MS: M^+ = 405

2-(4,6-Dimethoxy-2-pyrimidinyloxy)-3-methoxyacetyl-amino-3,3-diphenylpropionic acid (I-535)

25 Melting point: 187-188°C

ESI-MS: M^+ = 467

2-(4,6-Dimethoxy-2-pyrimidinyloxy)-3-(2,2-dimethyl)-
30 propylcarbonylamino-3,3-diphenylpropionic [sic] acid (I-388)

Melting point: 198-199°C

35 $^1\text{H-NMR}$ (200 MHz): 7.5 ppm (2 H, m), 7.2 (8 H, m), 6.7 (1H, s), 6.5 (1 H, s), 5.7 (1 H, s), 3.8 (6 H, s), 2.1 (2 H, s), 1.0 (9 H, s).

2-(4,6-Dimethoxy-2-pyrimidinyloxy)-3-cyclopropylcarbonylamino-3,3-diphenylpropionic acid (I-227)

40 Melting point: 206-207°C

ESI-MS: M^+ = 463

2-(4,6-Dimethoxy-2-pyrimidinyloxy)-3-p-nitrobenzoylamino-3,3-diphenylpropionic acid (I-541)
45

Melting point: 219-220 [sic]

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ESI-MS: $M^+ = 544$

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

5

10

15

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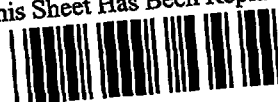
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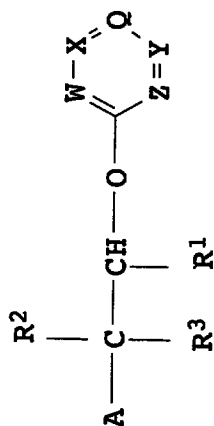


Table I

No.	R ¹	R ² , R ³	A	W	X	Q	Y	Z
I-1	COOH	Phenyl	CF ₃ CONH-	CH	C-Me	N	C-Me	N
I-2	COOH	Phenyl	CF ₃ CONH-	CH	C-OMe	N	C-Me	N
I-3	COOH	4-F-Phenyl	N ₃	CH	C-Me	N	C-OMe	N
I-4	COOH	4-F-Phenyl	N ₃	CH	C-Ethyl	N	C-Me	N
I-5	COOH	Phenyl	3,4-Di-OMe-Phenyl-CH ₂ -CONH-	N	N	C-Me	C-OMe	CH
I-6	COOH	Phenyl	3,4-Di-OMe-Phenyl-CH ₂ -CONH-	N	C-OMe	C-Me	N	CH
I-7	COOH	4-Cl-Phenyl	N ₃	N	C-Me	CH	C-Me	N
I-8	COOH	4-F-Phenyl	N ₃	N	C-Me	N	C-OMe	N
I-9	COOH	4-F-Phenyl	N ₃	N	C-Ethyl	N	C-Me	N
I-10	COOH	4-Me-Phenyl	N ₃	N	C-OMe	CH	C-Me	N
I-11	COOH	Phenyl	N ₃	N	C-CF ₃	CH	C-OMe	N
I-12	COOH	Phenyl	Ethyl-CONH-	N	C-Ethyl	CH	C-Me	N

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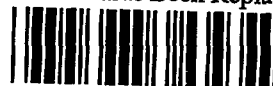
No.	R ¹	R ² , R ³	A	W	X	Q	Y	Z
I-13	COOH	Phenyl	Ethyl-CONH-	N		C-CH ₂ -CH ₂ -CH ₂ -C	C-OMe	N
I-14	COOH	Phenyl	N ₃	N	C-SMe	CH	C-Me	N
I-15	COOH	Phenyl	N ₃	N		C-CH ₂ -CH ₂ -CH ₂ -CH ₂ -C	C-OMe	N
I-16	COOH	Phenyl	3-OMe-4-OH-Phenyl-CH ₂ -CONH-	CH	C-Me	N	C-OMe	N
I-17	COOH	Phenyl	3-OMe-4-OH-Phenyl-CH ₂ -CONH-	CH	C-Ethyl	N	C-Me	N
I-18	COOH	Phenyl	N ₃	N		C-S-CH ₂ -CH ₂ -C	C-OMe	N
I-19	COOH	4-Cl-Phenyl	N ₃	N	C-Me	N	C-Me	N
I-20	COOH	Phenyl	N ₃	N	C-NH(CH ₃)	N	C-NH(CH ₃)	N
I-21	COOH	Phenyl	CF ₃ CONH-	N	C-OMe	C-Me	N	CH
I-22	COOH	Phenyl	CF ₃ CONH-	N	N	C-Me	C-OMe	N
I-23	COOH	Phenyl	N ₃	N	C-Ethyl	N	C-Ethyl	N
I-24	COOH	Phenyl	N ₃	N	N	CH	C-OMe	CH
I-25	COOH	Phenyl	3,4-Di-OMe-Phenyl-CH ₂ -CONH-	N	C-Me	N	C-OMe	N
I-26	COOH	Phenyl	3,4-Di-OMe-Phenyl-CH ₂ -CONH-	N	C-Ethyl	N	C-Me	N
I-27	COOH	Phenyl	N ₃	N	C-OMe	CH	N	CH
I-28	COOH	4-F-Phenyl	N ₃	N		C-O-CH ₂ -CH ₂ -C	C-OMe	N
I-29	COOH	4-F-Phenyl	N ₃	N	C-Me	N	C-Me	N
I-30	COOH	4-Me-Phenyl	N ₃	N	N	C-Me	C-OMe	N
I-31	COOH	Phenyl	N ₃	CH	C-Ethyl	N	C-Me	CH
I-32	COOH	Phenyl	Ethyl-CONH-	N	C-OMe	CH	C-Me	N
I-33	COOH	Phenyl	Ethyl-CONH-	N	C-OMe	CH	C-OMe	N
I-34	COOH	Phenyl	N ₃	CH	C-Me	N	C-Ethyl	N

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No.	R ¹	R ² , R ³	A	W	X	Q	Y	Z
I-35	COOH	4-Cl-Phenyl	N ₃	CH	C-OMe	N	C-Me	N
I-36	COOH	Phenyl	3-OMe-4-OH-Phenyl-CH ₂ -CONH-	CH	C-Me	N	C-Me	N
I-37	COOH	Phenyl	3-OMe-4-OH-Phenyl-CH ₂ -CONH-	CH	C-OMe	N	C-Me	N
I-38	COOMe	Phenyl	N ₃	CH	C-Me	N	C-OMe	N
I-39	COOH	Phenyl	N ₃	CH	C-OMe	N	C-OMe	N
I-40	COOH	4-F-Phenyl	H ₂ N-	N	C-Me	CH	C-Me	CH
I-41	COOH	Phenyl	CF ₃ CONH-	N	C-Ethyl	N	C-Me	N
I-42	COOH	Phenyl	CF ₃ CONH-	N	N	C-Me	C-OMe	CH
I-43	COOH	4-F-Phenyl	H ₂ N-	N	C-Me	CH	C-Me	N
I-44	COOH	4-Cl-Phenyl	H ₂ N-	N	C-OMe	CH	C-Me	N
I-45	COOH	Phenyl	3,4-Di-OMe-Phenyl-CH ₂ -CONH-	N	C-O-CH ₂ -CH ₂ -C	N	C-OMe	N
I-46	COOH	Phenyl	3,4-Di-OMe-Phenyl-CH ₂ -CONH-	N	C-Me	N	C-Me	N
I-47	COOH	Phenyl	H ₂ N-	N	C-CF ₃	CH	C-OMe	N
I-48	COOH	4-F-Phenyl	N ₃	N	C-Ethyl	CH	C-Me	N
I-49	COOH	4-F-Phenyl	N ₃	N	C-CH ₂ -CH ₂ -CH ₂ -C	N	C-OMe	N
I-50	COOH	Phenyl	H ₂ N-	N	C-Ethyl	CH	C-CF ₃	N
I-51	COOH	Phenyl	H ₂ N-	N	C-CH ₂ -CH ₂ -CH ₂ -C	N	C-Ethyl	N
I-52	COOH	Phenyl	CH ₃ CONH-	CH	C-Ethyl	N	C-Me	N
I-53	COOH	Phenyl	Ethyl-CONH-	N	C-Me	CH	C-Me	N
I-54	COOH	Phenyl	H ₂ N-	N	C-O-CH ₂ -CH ₂ -C	N	C-Ethyl	N
I-55	COOH	2-F-Phenyl	H ₂ N-	N	C-Me	N	C-Me	N
I-56	COOH	Phenyl	3-OMe-4-OH-Phenyl-CH ₂ -CONH-	N	N	C-Me	C-OMe	N

THIS SHEET HAS BEEN
REPLACED



No.	R ¹	R ² , R ³	A	W	X	Q	Y	Z
I-57	COOH	Phenyl	3-OMe-4-OH-Phenyl-CH ₂ -CONH-	CH	C-Me	N	C-Me	CH
I-58	COOH	Phenyl	H ₂ N-	N	C-Me	N	C-SMe	N
I-59	COOH	Phenyl	H ₂ N-	N	C-Ethyl	N	C-CF ₃	N
I-60	COOH	Phenyl	H ₂ N-	N	N	CH	C-OMe	CH
I-61	COOH	Phenyl	CF ₃ CONH-	N	C-Me	N	C-Me	N
I-62	COOH	Phenyl	CF ₃ CONH-	N	C-Me	N	C-OMe	N
I-63	COOH	Phenyl	H ₂ N-	N	C-OMe	CH	N	CH
I-64	COOH	Phenyl	H ₂ N-	N	C-Me	C-Me	N	N
I-65	COOH	Phenyl	3,4-Di-OMe-Phenyl-CH ₂ -CONH-	N	C-Ethyl	CH	C-Me	N
I-66	COOH	Phenyl	3,4-Di-OMe-Phenyl-CH ₂ -CONH-	N	C-CH ₂ -CH ₂ -C	C-OMe	C-OMe	N
I-67	COOH	4-F-Phenyl	H ₂ N-	N	N	C-Me	C-OMe	N
I-68	COOH	4-F-Phenyl	N ₃	N	C-OMe	CH	C-Me	N
I-69	COOH	4-F-Phenyl	N ₃	N	C-OMe	CH	C-OMe	N
I-70	COOH	Phenyl	H ₂ N-	N	C-Me	CH	C-Me	CH
I-71	COOH	4-Cl-Phenyl	H ₂ N-	CH	C-Me	N	C-Me	N
I-72	COOH	Phenyl	CH ₃ CONH-	CH	C-Me	N	C-Me	CH
I-73	COOH	Phenyl	CH ₃ CONH-	CH	C-Me	N	C-Me	N
I-74	COOH	Phenyl	CH ₃ CONH-	CH	C-OMe	N	C-Me	N
I-75	COOH	Phenyl	CH ₃ CONH-	CH	C-Me	N	C-OMe	N
I-76	COOH	Phenyl	H ₂ N-	CH	C-OMe	N	C-OMe	N
I-77	COOH	Phenyl	H ₂ N-	CH	C-Me	N	C-Ethyl	N
I-78	COOH	Phenyl	3-OMe-4-OH-Phenyl-CH ₂ -CONH-	N	N	C-Me	C-OMe	CH

THIS SHEET HAS BEEN
REPLACED



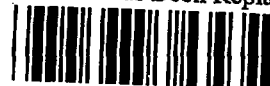
No.	R ¹	R ² , R ³	A	W	X	Q	Y	Z
I-79	COOH	Phenyl	3-OMe-4-OH-Phenyl-CH ₂ -CONH-	N	C-OMe	C-Me	N	CH
I-80	COOH	Phenyl	H ₂ N-	N	C-N(CH ₃) ₂	N	C-N(CH ₃) ₂	N
I-81	COOH	4-F-Phenyl	CH ₃ CONH-	N	C-Me	CH	C-Me	N
I-82	COOH	4-F-Phenyl	CH ₃ CONH-	N	C-OMe	CH	C-Me	N
I-83	COOH	Phenyl	CF ₃ CONH-	N	C-CH ₂ -CH ₂ -CH ₂ -C	C-OMe	C-OMe	N
I-84	COOH	Phenyl	CF ₃ CONH-	N	C-O-CH ₂ -CH ₂ -C	C-OMe	C-OMe	N
I-85	COOH	4-Cl-Phenyl	CH ₃ CONH-	N	C-OMe	CH	C-CF ₃	N
I-86	COOH	Phenyl	CH ₃ CONH-	N	C-Ethyl	CH	C-Me	N
I-87	COOH	Phenyl	3,4-Di-OMe-Phenyl-CH ₂ -CONH-	N	C-OMe	CH	C-Me	N
I-88	COOH	Phenyl	3,4-Di-OMe-Phenyl-CH ₂ -CONH-	N	C-OMe	CH	C-OMe	N
I-89	COOH	Phenyl	CH ₃ CONH-	N	C-CH ₂ -CH ₂ -CH ₂ -C	C-Me	C-Me	N
I-90	COOH	Phenyl	4-OMe-Phenyl-CONH-	CH	C-Ethyl	N	C-Me	N
I-91	COOH	4-F-Phenyl	N ₃	N	C-Me	CH	C-Me	N
I-92	COOH	Phenyl	CH ₃ CONH-	N	C-O-CH ₂ -CH ₂ -C	C-Me	C-Me	N
I-93	COOH	Phenyl	CH ₃ CONH-	N	C-CF ₃	N	C-Me	N
I-94	COOH	Phenyl	CH ₃ CONH-	N	C-OMe	C-Me	N	CH
I-95	COOH	Phenyl	CH ₃ CONH-	N	N	C-Me	C-OMe	N
I-96	COOH	4-F-Phenyl	CH ₃ CONH-	N	C-Me	N	C-OMe	N
I-97	COOH	4-F-Phenyl	CH ₃ CONH-	N	C-Ethyl	N	C-Me	N
I-98	COOH	Phenyl	3-OMe-4-OH-Phenyl-CH ₂ -CONH-	N	C-Me	N	C-OMe	N
I-99	COOH	Phenyl	3-OMe-4-OH-Phenyl-CH ₂ -CONH-	N	C-Ethyl	N	C-Me	N
I-100	COOH	Phenyl	CH ₃ CONH-	N	C-Me	C-Me	CH	CH

THIS SHEET HAS BEEN
REPLACED



No.	R ¹	R ² , R ³	A	W	X	Q	Y	Z
I-101	COOH	Phenyl	CH ₃ CONH-	N	CH	C-Me	N	CH
I-102	COOH	Phenyl	CH ₃ CONH-	N	N	C-Me	C-Me	N
I-103	COOH	Phenyl	CF ₃ CONH-	N	C-OMe	CH	C-OMe	N
I-104	COOH	Phenyl	CF ₃ CONH-	N	C-Ethyl	CH	C-Me	N
I-105	COOH	Phenyl	CH ₃ CONH-	N	C-Me	CH	C-Me	CH
I-106	COOH	Phenyl	CH ₃ CONH-	CH	C-Me	C-Me	CH	N
I-107	COOH	Phenyl	Cyclopropyl-CONH-	CH	C-Ethyl	N	C-Me	N
I-108	COOH	Phenyl	3,4-Di-OMe-Phenyl-CH ₂ -CONH-	N	C-Me	CH	C-Me	N
I-109	COOH	4-Cl-Phenyl	CH ₃ CONH-	CH	C-OMe	N	C-Me	N
I-110	COOH	Phenyl	4-OMe-Phenyl-CONH-	CH	C-Me	N	C-Me	N
I-111	COOH	Phenyl	4-OMe-Phenyl-CONH-	CH	C-OMe	N	C-Me	N
I-112	COOH	4-Me-Phenyl	CH ₃ CONH-	CH	C-Me	N	C-OMe	N
I-113	COOH	4-CF ₃ -Phenyl	CH ₃ CONH-	CH	C-Ethyl	N	C-Me	N
I-114	COOH	Phenyl	CH ₃ CONH-	N	C-Ethyl	N	C-Me	N
I-115	COOH	Phenyl	CH ₃ CONH-	N	N	C-Me	C-OMe	CH
I-116	COOH	Phenyl	HO-(CH ₂) ₂ -CONH-	N	C-Me	CH	C-Me	N
I-117	COOH	Phenyl	Benzyl-O-(CH ₂) ₂ -CONH-	N	C-OMe	CH	C-Me	N
I-118	COOH	Phenyl	3-OMe-4-OH-Phenyl-CH ₂ -CONH-	N	C-O-CH ₂ -CH ₂ -C		C-OMe	N
I-119	COOH	Phenyl	3-OMe-4-OH-Phenyl-CH ₂ -CONH-	N	C-Me	N	C-Me	N
I-120	COOH	4-F-Phenyl	Ethyl-CONH-	N	C-OMe	CH	C-OMe	N
I-121	COOH	4-F-Phenyl	Ethyl-CONH-	N	C-Ethyl	CH	C-Me	N
I-122	COOH	4-Cl-Phenyl	Ethyl-CONH-	N	C-CH ₂ -CH ₂ -CH ₂ -C		C-OMe	N
I-123	COOH	Phenyl	CF ₃ CONH-	N	C-Me	CH	C-Me	N

THIS SHEET HAS BEEN
REPLACED



No.	R ¹	R ² , R ³	A	W	X	Q	Y	Z
I-124	COOH	Phenyl	CF ₃ CONH-	N	C-OMe	CH	C-Me	N
I-125	COOMe	Phenyl	Ethyl-CONH-	N	C-O-CH ₂ -CH ₂ -C		C-OMe	N
I-126	COOH	Phenyl	HO-(CH ₂) ₂ -CONH-	N	C-Me	N	C-Me	N
I-127	COOH	Phenyl	Cyclopropyl-CONH-	CH	C-Me	N	C-Me	N
I-128	COOH	Phenyl	Cyclopropyl-CONH-	CH	C-OMe	N	C-Me	N
I-129	COOH	Phenyl	HO-(CH ₂) ₂ -CONH-	N	C-Me	N	C-OMe	N
I-130	COOH	Phenyl	4-OMe-Phenyl-CONH-	N	C-OMe	C-Me	N	CH
I-131	COOH	Phenyl	4-OMe-Phenyl-CONH-	N	N	C-Me	C-OMe	N
I-132	COOH	Phenyl	Benzyl-O-(CH ₂) ₂ -CONH-	N	C-Ethyl	N	C-Me	N
I-133	COOH	Phenyl	Benzyl-O-(CH ₂) ₂ -CONH-	N	N	C-Me	C-OMe	CH
I-134	COOH	Phenyl	CH ₃ CONH-	N	C-Me	N	C-Me	N
I-135	COOH	Phenyl	CH ₃ CONH-	N	C-Me	N	C-OMe	N
I-136	COOH	4-F-Phenyl	Ethyl-CONH-	N	C-OMe	C-Me	N	CH
I-137	COOH	Phenyl	HO-(CH ₂) ₂ -CONH-	N	N	C-Me	C-OMe	N
I-138	COOH	Phenyl	3-OMe-4-OH-Phenyl-CH ₂ -CONH-	N	C-Ethyl	CH	C-Me	N
I-139	COOH	Phenyl	3-OMe-4-OH-Phenyl-CH ₂ -CONH-	N	C-CH ₂ -CH ₂ -CH ₂ -C		C-OMe	N
I-140	COOH	Phenyl	Ethyl-CONH-	CH	C-Me	N	C-Me	CH
I-141	COOH	Phenyl	Ethyl-CONH-	CH	C-CF ₃	N	C-CF ₃	N
I-142	COOH	Phenyl	HO-(CH ₂) ₂ -CONH-	CH	C-OMe	CH	C-Me	N
I-143	COOH	Phenyl	(CH ₃) ₂ N-	CH	C-OMe	N	C-Me	N
I-144	COOH	Phenyl	(CH ₃) ₂ N-	CH	C-Ethyl	N	C-Me	N
I-145	COOH	Phenyl	Ethyl-CONH-	CH	C-CF ₃	N	C-OMe	N
I-146	COOH	Phenyl	HO-(CH ₂) ₂ -CONH-	CH	C-Ethyl	N	C-Me	N

THIS SHEET HAS BEEN
REPLACED



No.	R ¹	R ² , R ³	A	W	X	Q	Y	Z
I-147	COOH	Phenyl	Cyclopropyl-CONH-	N	C-OMe	C-Me	N	CH
I-148	COOH	Phenyl	Cyclopropyl-CONH-	N	N	C-Me	C-OMe	N
I-149	COOH	4-Cl-Phenyl	CH ₃ NH-	N	C-Me	CH	C-CF ₃	N
I-150	COOH	Phenyl	4-OMe-Phenyl-CONH-	N	C-Ethyl	N	C-Me	N
I-151	COOH	Phenyl	4-OMe-Phenyl-CONH-	N	N	C-Me	C-OMe	CH
I-152	COOH	Phenyl	CH ₃ NH-	N	C-SMe	CH	C-Me	N
I-153	COOH	Phenyl	CH ₃ NH-	N	C-OMe	CH	C-Ethyl	N
I-154	COOH	Phenyl	CH ₃ CONH-	N	C-CH ₂ -CH ₂ -CH ₂ -C		C-OMe	N
I-155	COOH	Phenyl	CH ₃ CONH-	N	C-O-CH ₂ -CH ₂ -C		C-OMe	N
I-156	COOH	Phenyl	CH ₃ NH-	N	C-Ethyl	CH	C-Me	N
I-157	COOH	Phenyl	CH ₃ NH-	N	C-CH ₂ -CH ₂ -CH ₂ -C		C-Me	N
I-158	COOH	Phenyl	3-OMe-4-OH-Phenyl-CH ₂ -CONH-	N	C-OMe	CH	C-Me	N
I-159	COOH	Phenyl	3-OMe-4-OH-Phenyl-CH ₂ -CONH-	N	C-OMe	CH	C-OMe	N
I-160	COOH	Phenyl	CH ₃ NH-	N	C-S-CH ₂ -CH ₂ -C		C-OMe	N
I-161	COOH	4-F-Phenyl	CH ₃ NH-	N	C-Me	N	C-Me	N
I-162	COOH	4-F-Phenyl	CH ₃ NH-	N	C-Me	N	C-OMe	N
I-163	COOH	Phenyl	(CH ₃) ₂ N-	N	N	C-Me	C-OMe	N
I-164	COOH	Phenyl	(CH ₃) ₂ N-	CH	C-Me	N	C-Me	N
I-165	COOH	Phenyl	CH ₃ NH-	N	C-Ethyl	N	C-Ethyl	N
I-166	COOH	Phenyl	CH ₃ NH-	N	N	CH	C-OMe	CH
I-167	COOH	Phenyl	Cyclopropyl-CONH-	N	C-Ethyl	N	C-Me	N
I-168	COOH	Phenyl	Cyclopropyl-CONH-	N	N	C-Me	C-OMe	CH
I-169	COOH	Phenyl	Ethyl-NH-	N	C-OMe	C-Me	N	CH

THIS SHEET HAS BEEN
REPLACED



No.	R ¹	R ² , R ³	A	W	X	Q	Y	Z
I-170	COOH	Phenyl	4-OMe-Phenyl-CONH-	N	C-Me	N	C-Me	N
I-171	COOH	Phenyl	4-OMe-Phenyl-CONH-	N	C-Me	N	C-OMe	N
I-172	COOH	Phenyl	Ethyl-NH-	N	N	C-Me	C-OMe	N
I-173	COOH	Phenyl	CH ₃ NH-	CH	C-Me	N	C-Ethyl	N
I-174	COOH	Phenyl	CH ₃ CONH-	N	C-OMe	CH	C-OMe	N
I-175	COOH	Phenyl	CH ₃ CONH-	N	C-Ethyl	CH	C-Me	N
I-176	COOH	4-F-Phenyl	CH ₃ NH-	CH	C-Me	N	C-OMe	N
I-177	COOH	4-Cl-Phenyl	CH ₃ NH-	CH	C-Ethyl	N	C-Me	N
I-178	COOH	Phenyl	Benzyl-NH-	CH	C-Ethyl	N	C-Me	N
I-179	COOH	Phenyl	3-OMe-4-OH-Phenyl-CH ₂ -CONH-	N	C-Me	CH	C-Me	N
I-180	COOH	Phenyl	(CH ₂) ₅ N-	N	C-Me	CH	C-Me	N
I-181	COOH	Phenyl	(CH ₃) ₂ N-	N	C-SMe	CH	C-Me	N
I-182	COOH	Phenyl	(CH ₃) ₂ N-	N	C-Ethyl	CH	C-Ethyl	N
I-183	COOH	Phenyl	(CH ₃) ₂ N-	N	N	C-Me	C-OMe	CH
I-184	COOH	Phenyl	(CH ₃) ₂ N-	N	C-OMe	C-Me	N	CH
I-185	COOH	4-F-Phenyl	(CH ₃) ₂ N-	N	C-Ethyl	CH	C-Me	N
I-186	COOH	Phenyl	(CH ₃) ₂ N-	N	C-CH ₂ -CH ₂ -CH ₂ -C	C-CH ₂ -CH ₂ -CH ₂ -C	C-Ethyl	N
I-187	COOH	Phenyl	Cyclopropyl-CONH-	N	C-Me	N	C-Me	N
I-188	COOH	Phenyl	Cyclopropyl-CONH-	N	C-Me	N	C-OMe	N
I-189	COOH	Phenyl	(CH ₃) ₂ N-	N	C-O-CH ₂ -CH ₂ -C	C-O-CH ₂ -CH ₂ -C	C-Me	N
I-190	COOH	Phenyl	4-OMe-Phenyl-CONH-	N	C-CH ₂ -CH ₂ -CH ₂ -C	C-CH ₂ -CH ₂ -CH ₂ -C	C-OMe	N
I-191	COOH	Phenyl	4-OMe-Phenyl-CONH-	N	C-O-CH ₂ -CH ₂ -C	C-O-CH ₂ -CH ₂ -C	C-OMe	N
I-192	COOH	Phenyl	(CH ₃) ₂ N-	N	C-NH(CH ₃)	N	C-NH(CH ₃)	N

THIS SHEET HAS BEEN
REPLACED



No.	R ¹	R ² , R ³	A	W	X	Q	Y	Z
I-193	COOH	Phenyl	(CH ₃) ₂ N-	N	C-N(CH ₃) ₂	N	C-N(CH ₃) ₂	N
I-194	COOH	Phenyl	CH ₃ CONH-	N	C-Me	CH	C-Me	N
I-195	COOH	Phenyl	CH ₃ CONH-	N	C-OMe	CH	C-Me	N
I-196	COOH	Phenyl	(CH ₃) ₂ N-	N	C-Ethyl	N	C-Ethyl	N
I-197	COOH	Phenyl	(CH ₃) ₂ N-	N	N	CH	C-OMe	CH
I-198	COOH	Phenyl	Benzyl-NH-	CH	C-Me	N	C-Me	N
I-199	COOH	Phenyl	Benzyl-NH-	CH	C-Me	N	C-OMe	N
I-200	COOH	4-F-Phenyl	(CH ₃) ₂ N-	N	C-OMe	C-Me	N	CH
I-201	COOH	4-F-Phenyl	(CH ₃) ₂ N-	N	N	C-Me	C-OMe	N
I-202	COOH	Phenyl	(CH ₂) ₄ N-	CH	C-Me	N	C-Me	N
I-203	COOH	Phenyl	(CH ₃) ₂ N-	N	C-Me	N	C-OMe	N
I-204	COOH	Phenyl	(CH ₃) ₂ N-	N	C-Ethyl	N	C-Me	N
I-205	COOH	Phenyl	(CH ₃) ₂ N-	CH	C-OMe	N	C-CF ₃	N
I-206	COOH	Phenyl	(CH ₃) ₂ N-	CH	C-Ethyl	N	C-Ethyl	N
I-207	COOH	Phenyl	Cyclopropyl-CONH-	N	C-CH ₂ -CH ₂ -CH ₂ -C		C-OMe	N
I-208	COOH	Phenyl	Cyclopropyl-CONH-	N	C-O-CH ₂ -CH ₂ -C		C-OMe	N
I-209	COOH	Phenyl	CCl ₃ CONH-	N	C-Me	CH	C-Me	N
I-210	COOH	Phenyl	4-OMe-Phenyl-CONH-	N	C-OMe	CH	C-OMe	N
I-211	COOH	Phenyl	4-OMe-Phenyl-CONH-	N	C-Ethyl	CH	C-Me	N
I-212	COOH	Phenyl	CF ₃ CONH-	N	C-OH	C-F	C-Me	N
I-213	COOH	Phenyl	CF ₃ CONH-	N	C-OMe	C-Me	C-OMe	N
I-214	COOH	Phenyl	H ₂ N-	CH	C-Me	N	C-OMe	N
I-215	COOH	Phenyl	H ₂ N-	CH	C-Ethyl	N	C-Me	N
I-216	COOH	Phenyl	CF ₃ CONH-	N	C-Ethyl	C-Me	CH	N

THIS SHEET HAS BEEN
REPLACED



No.	R ¹	R ² , R ³	A	W	X	Q	Y	Z
I-217	COOH	Phenyl	CF ₃ CONH-	N		C-CH ₂ -CH ₂ -CH ₂ -CH ₂ -C	C-OMe	N
I-218	COOH	Phenyl	Benzyl-NH-	N	C-OMe	C-Me	N	CH
I-219	COOH	Phenyl	Benzyl-NH-	N	N	C-Me	C-OMe	N
I-220	COOH	Phenyl	CF ₃ CONH-	N		C-O-CH ₂ -CH ₂ -C	C-Ethyl	N
I-221	COOH	Phenyl	CF ₃ CONH-	N	C-Ethyl	N	C-Ethyl	N
I-222	COOH	Phenyl	CF ₃ CONH-	N	C-Me	C-Me	CH	CH
I-223	COOH	Phenyl	(CH ₃) ₂ N-	N		C-O-CH ₂ -CH ₂ -C	C-OMe	N
I-224	COOH	Phenyl	(CH ₃) ₂ N-	N	C-Me	N	C-Me	N
I-225	COOH	Phenyl	CF ₃ CONH-	N		C-CH=CH-CH=CH-C	C-Me	N
I-226	COOH	4-F-Phenyl	CF ₃ CONH-	N	N	C-Me	C-OMe	CH
I-227	COOH	Phenyl	Cyclopropyl-CONH-	N	C-OMe	CH	C-OMe	N
I-228	COOH	Phenyl	Cyclopropyl-CONH-	N	C-Ethyl	CH	C-Me	N
I-229	COOH	4-F-Phenyl	CF ₃ CONH-	N	C-OMe	C-Me	N	CH
I-230	COOH	Phenyl	4-OMe-Phenyl-CONH-	N	C-Me	CH	C-Me	N
I-231	COOH	Phenyl	4-OMe-Phenyl-CONH-	N	C-OMe	CH	C-Me	N
I-232	COOH	4-Cl-Phenyl	CF ₃ CONH-	N	N	C-Me	C-OMe	N
I-233	COOMe	Phenyl	CF ₃ CONH-	CH	C-Me	N	C-Me	N
I-234	COOH	Phenyl	H ₂ N-	CH	C-Me	N	C-Me	N
I-235	COOH	Phenyl	H ₂ N-	CH	C-OMe	N	C-Me	N
I-236	COOH	4-F-Phenyl	CF ₃ CONH-	CH	C-OMe	N	C-Me	N
I-237	COOH	4-F-Phenyl	CF ₃ CONH-	CH	C-Me	N	C-OMe	N
I-238	COOH	Phenyl	Benzyl-NH-	N	C-Ethyl	N	C-Me	N
I-239	COOH	Phenyl	Benzyl-NH-	N	N	C-Me	C-OMe	CH
I-240	COOH	Phenyl	CF ₃ CONH-	CH	C-Ethyl	N	C-Ethyl	N

THIS SHEET HAS BEEN
REPLACED



No.	R ¹	R ² , R ³	A	W	X	Q	Y	Z
I-241	COOH	Phenyl	Ethyl-OCH ₂ CONH-	N	C-Me	CH	C-Me	N
I-242	COOH	Phenyl	Phenyl-OCH ₂ CONH-	N	C-OMe	CH	C-Me	N
I-243	COOH	Phenyl	(CH ₃) ₂ N-	N	C-Ethyl	CH	C-Me	N
I-244	COOH	Phenyl	(CH ₃) ₂ N-	N		C-CH ₂ -CH ₂ -CH ₂ -C	C-OMe	N
I-245	COOH	Phenyl	4-OMe-Phenyl-OCH ₂ CONH-	N	C-OMe	CH	C-OMe	N
I-246	COOH	Phenyl	i-Propyl-OCH ₂ CONH-	N	C-Ethyl	CH	C-Me	N
I-247	COOH	Phenyl	Cyclopropyl-CONH-	N	C-Me	CH	C-Me	N
I-248	COOH	Phenyl	Cyclopropyl-CONH-	N	C-OMe	CH	C-Me	N
I-249	COOH	Phenyl	MeOCH ₂ CONH-	N		C-CH ₂ -CH ₂ -CH ₂ -C	C-Me	N
I-250	COOH	Phenyl	HOCH ₂ CONH-	CH	C-Me	N	C-OMe	N
I-251	COOH	Phenyl	HOCH ₂ CONH-	CH	C-Ethyl	N	C-Me	N
I-252	COOH	Phenyl	MeOCH ₂ CONH-	N		C-O-CH ₂ -CH ₂ -C	C-Ethyl	N
I-253	COOH	Phenyl	Ethyl-OCH ₂ CONH-	N	C-Me	N	C-Me	N
I-254	COOH	Phenyl	H ₂ N-	N	N	C-Me	C-OMe	N
I-255	COOH	Phenyl	H ₂ N-	CH	C-Me	N	C-Me	CH
I-256	COOH	Phenyl	3,4-Di-OMe-Phenyl-O-CH ₂ CONH-	N	C-Me	N	C-OMe	N
I-257	COOH	4-F-Phenyl	MeOCH ₂ CONH-	N	C-Ethyl	N	C-Me	N
I-258	COOH	Phenyl	Benzyl-NH-	N	C-Me	N	C-Me	N
I-259	COOH	Phenyl	Benzyl-NH-	N	C-Me	N	C-OMe	N
I-260	COOH	4-F-Phenyl	MeOCH ₂ CONH-	N	N	C-Me	C-OMe	CH
I-261	COOH	Phenyl	4-Cl-Phenyl-OCH ₂ CONH-	N	C-OMe	C-Me	N	CH
I-262	COOH	Phenyl	i-Propyl-OCH ₂ CONH-	N	N	C-Me	C-OMe	N
I-263	COOH	Phenyl	(CH ₃) ₂ N-	N	C-OMe	CH	C-Me	N

THIS SHEET HAS BEEN
REPLACED



No.	R ¹	R ² , R ³	A	W	X	Q	Y	Z
I-264	COOH	Phenyl	(CH ₃) ₂ N-	N	C-OMe	CH	C-OMe	N
I-265	COOH	Phenyl	n-Butyl-OCH ₂ CONH-	CH	C-Me	N	C-Me	CH
I-266	COOH	Phenyl	n-Propyl-OCH ₂ CONH-	CH	C-Me	N	C-Me	N
I-267	COOH	Phenyl	t-Bu-CH ₂ CONH-	CH	C-Me	N	C-OMe	N
I-268	COOH	Phenyl	t-Bu-CH ₂ CONH-	CH	C-Ethyl	N	C-Me	N
I-269	COOH	Phenyl	i-Propyl-OCH ₂ CONH-	CH	C-OMe	N	C-Me	N
I-270	COOH	Phenyl	HOCH ₂ CONH-	CH	C-Me	N	C-Me	N
I-271	COOH	Phenyl	HOCH ₂ CONH-	CH	C-OMe	N	C-Me	N
I-272	COOH	Phenyl	3,4-Di-OMe-Phenyl-O-CH ₂ CONH-	CH	C-Me	N	C-Ethyl	N
I-273	COOH	Phenyl	3,4-Di-OMe-Phenyl-O-CH ₂ CONH-	CH	C-Ethyl	N	C-Me	N
I-274	COOH	Phenyl	H ₂ N-	N	C-OMe	C-Me	N	CH
I-275	COOH	Phenyl	H ₂ N-	N	C-OMe	CH	N	N
I-276	COOH	Phenyl	n-Butyl-CONH-	N	C-Me	CH	C-Me	N
I-277	COOH	Phenyl	n-Butyl-CONH-	N	C-OMe	CH	C-Me	N
I-278	COOH	Phenyl	Benzyl-NH-	N	C-CH ₂ -CH ₂ -CH ₂ -C	C-OMe	C-OMe	N
I-279	COOH	Phenyl	Benzyl-NH-	N	C-O-CH ₂ -CH ₂ -C	C-OMe	C-OMe	N
I-280	COOH	Phenyl	n-Propyl-CONH-	N	C-OMe	CH	C-OMe	N
I-281	COOH	Phenyl	i-Propyl-CONH-	N	C-Ethyl	CH	C-Me	N
I-282	COOH	Phenyl	i-Propyl-CONH-	N	C-CH ₂ -CH ₂ -CH ₂ -C	C-OMe	C-OMe	N
I-283	COOH	Phenyl	CH ₃ NH-	CH	C-Ethyl	N	C-Me	N
I-284	COOH	Phenyl	(CH ₃) ₂ N-	N	C-Me	CH	C-Me	N
I-285	COOH	Phenyl	Cyclohexyl-CONH-	N	C-O-CH ₂ -CH ₂ -C	C-OMe	C-OMe	N
I-286	COOH	Phenyl	Cyclohexyl-CONH-	N	C-Me	N	C-Me	N

THIS SHEET HAS BEEN
REPLACED



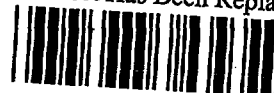
No.	R ¹	R ² , R ³	A	W	X	Q	Y	Z
I-287	COOH	Phenyl	t-Bu-CH ₂ CONH-	N	N	C-Me	C-OMe	N
I-288	COOH	Phenyl	t-Bu-CH ₂ CONH-	CH	C-Me	N	C-Me	N
I-289	COOH	Phenyl	n-Hexyl-CONH-	N	C-Me	N	C-OMe	N
I-290	COOH	Phenyl	HOCH ₂ CONH-	N	N	C-Me	C-OMe	N
I-291	COOH	Phenyl	HOCH ₂ CONH-	CH	C-Me	N	C-Me	CH
I-292	COOH	Phenyl	3-Hexen-1-yl-CONH-	N	C-Ethyl	N	C-Me	N
I-293	COOH	Phenyl	CH ₃ -CH=CH-CONH-	N	N	C-Me	C-OMe	CH
I-294	COOH	Phenyl	H ₂ N-	N	C-Ethyl	N	C-Me	N
I-295	COOH	Phenyl	H ₂ N-	N	N	C-Me	C-OMe	CH
I-296	COOH	Phenyl	CH ₃ -CH=CH-CONH-	N	C-OMe	C-Me	N	CH
I-297	COOH	Phenyl	n-Propyl-CONH-	N	N	C-Me	C-OMe	N
I-298	COOH	Phenyl	Benzyl-NH-	N	C-OMe	CH	C-OMe	N
I-299	COOH	Phenyl	Benzyl-NH-	N	C-Ethyl	CH	C-Me	N
I-300	COOH	Phenyl	n-Propyl-CONH-	CH	C-Me	N	C-Me	N
I-301	COOH	Phenyl	3-Hexen-1-yl-CONH-	CH	C-Me	N	C-OMe	N
I-302	COOH	4-F-Phenyl	t-Bu-CH ₂ CONH-	CH	C-Ethyl	N	C-Me	N
I-303	COOH	Phenyl	CH ₃ NH-	CH	C-Me	N	C-Me	N
I-304	COOH	Phenyl	CH ₃ NH-	CH	C-Me	N	C-OMe	N
I-305	COOH	Phenyl	Cyclobutyl-CONH-	N	C-Me	CH	C-Me	N
I-306	COOH	Phenyl	Cyclobutyl-CONH-	N	C-OMe	CH	C-Me	N
I-307	COOH	Phenyl	t-Bu-CH ₂ CONH-	N	N	C-Me	C-OMe	CH
I-308	COOH	Phenyl	t-Bu-CH ₂ CONH-	N	C-OMe	C-Me	N	CH
I-309	COOH	Phenyl	Cyclopentyl-CONH-	N	C-OMe	CH	C-OMe	N
I-310	COOH	Phenyl	HOCH ₂ CONH-	N	N	C-Me	C-OMe	CH

THIS SHEET HAS BEEN
REPLACED



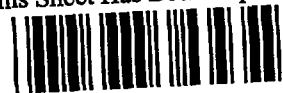
No.	R ¹	R ² , R ³	A	W	X	Q	Y	Z
I-311	COOH	Phenyl	HOCH ₂ CONH-	N	C-OMe	C-Me	N	CH
I-312	COOH	Phenyl	Cyclopentyl-CONH-	N	C-Ethyl	CH	C-Me	N
I-313	COOH	Phenyl	Cyclohexyl-CONH-	N	C-CH ₂ -CH ₂ -CH ₂ -C		C-OMe	N
I-314	COOH	Phenyl	H ₂ N-	N	C-Me	N	C-Me	N
I-315	COOH	Phenyl	H ₂ N-	N	C-Me	N	C-OMe	N
I-316	COOH	Phenyl	Cyclopropyl-CONH-	N	C-O-CH ₂ -CH ₂ -C		C-Ethyl	N
I-317	COOH	Phenyl	Cyclopropyl-CONH-	N	C-Ethyl	N	C-Ethyl	N
I-318	COOH	Phenyl	Benzyl-NH-	N	C-Me	CH	C-Me	N
I-319	COOH	Phenyl	Benzyl-NH-	N	C-OMe	CH	C-Me	N
I-320	COOH	4-F-Phenyl	Cyclopropyl-CONH-	N	C-Me	N	C-OMe	N
I-321	COOH	4-F-Phenyl	Cyclopropyl-CONH-	N	C-Ethyl	N	C-Me	N
I-322	COOH	Phenyl	Cyclobutyl-CONH-	N	N	C-Me	C-OMe	CH
I-323	COOH	Phenyl	CH ₃ NH-	N	C-OMe	C-Me	N	CH
I-324	COOH	Phenyl	CH ₃ NH-	N	N	C-Me	C-OMe	N
I-325	COOH	Phenyl	Cyclobutyl-CONH-	N	C-OMe	C-Me	N	CH
I-326	COOH	Phenyl	Cyclopentyl-CONH-	N	N	C-Me	C-OMe	N
I-327	COOH	Phenyl	t-Bu-CH ₂ CONH-	N	C-Me	N	C-OMe	N
I-328	COOH	Phenyl	t-Bu-CH ₂ CONH-	N	C-Ethyl	N	C-Me	N
I-329	COOH	Phenyl	Cyclopentyl-CONH-	CH	C-Me	N	C-Me	N
I-330	COOH	Phenyl	HOCH ₂ CONH-	N	C-Me	N	C-OMe	N
I-331	COOH	Phenyl	HOCH ₂ CONH-	N	C-Ethyl	N	C-Me	N
I-332	COOH	Phenyl	Cyclohexyl-CONH-	CH	C-OMe	N	C-Me	N
I-333	COOH	Phenyl	Cyclohexyl-CONH-	CH	C-Ethyl	N	C-Me	N
I-334	COOH	Phenyl	H ₂ N-	N	C-CH ₂ -CH ₂ -CH ₂ -C		C-OMe	N

THIS SHEET HAS BEEN
REPLACED



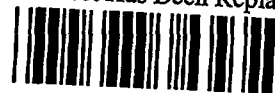
No.	R ¹	R ² , R ³	A	W	X	Q	Y	Z
I-335	COOH	Phenyl	H ₂ N-	N		C-O-CH ₂ -CH ₂ -C	C-OMe	N
I-336	COOH	Phenyl	3,4-Di-Cl-Phenyl-CH ₂ -CONH-	N	C-Me	CH	C-Me	N
I-337	COOH	Phenyl	3,4-Di-Cl-Phenyl-CH ₂ -CONH-	N	C-OMe	CH	C-Me	N
I-338	COOH	Phenyl	3,4-Di-OMe-Phenyl-(CH ₂) ₂ -NH-	CH	C-Me	N	C-OMe	N
I-339	COOH	Phenyl	3,4-Di-OMe-Phenyl-(CH ₂) ₂ -NH-	CH	C-Ethyl	N	C-Me	N
I-340	COOH	4-F-Phenyl	3,4-Di-OMe-Phenyl-CH ₂ -CONH-	N	C-OMe	CH	C-OMe	N
I-341	COOH	Phenyl	3,4-Di-Me-Phenyl-CH ₂ -CONH-	N	C-Ethyl	CH	C-Me	N
I-342	COOH	Phenyl	3,4-Di-Me-Phenyl-CH ₂ -CONH-	N		C-CH ₂ -CH ₂ -CH ₂ -C	C-OMe	N
I-343	COOH	Phenyl	CH ₃ NH-	N	C-Ethyl	N	C-Me	N
I-344	COOH	Phenyl	CH ₃ NH-	N	N	C-Me	C-OMe	CH
I-345	COOH	Phenyl	3,4-Di-Cl-Phenyl-CH ₂ -CONH-	N		C-O-CH ₂ -CH ₂ -C	C-OMe	N
I-346	COOH	Phenyl	3,4-Di-Me-Phenyl-CH ₂ -CONH-	N	C-Me	N	C-Me	N
I-347	COOH	Phenyl	t-Bu-CH ₂ CONH-	N		C-O-CH ₂ -CH ₂ -C	C-OMe	N
I-348	COOH	Phenyl	t-Bu-CH ₂ CONH-	N	C-Me	N	C-Me	N
I-349	COOH	Phenyl	3,5-Di-OMe-Phenyl-CH ₂ -CONH-	N	C-Me	N	C-OMe	N
I-350	COOH	Phenyl	HOCH ₂ CONH-	N		C-O-CH ₂ -CH ₂ -C	C-OMe	N
I-351	COOH	Phenyl	HOCH ₂ CONH-	N	C-Me	N	C-Me	N
I-352	COOH	Phenyl	3,5-Di-OMe-Phenyl-CH ₂ -CONH-	N	C-Ethyl	N	C-Me	N
I-353	COOH	Phenyl	2,3-Di-OMe-Phenyl-CH ₂ -CONH-	N	N	C-Me	C-OMe	CH
I-354	COOH	Phenyl	H ₂ N-	N	C-OMe	CH	C-OMe	N
I-355	COOH	Phenyl	H ₂ N-	N	C-Ethyl	CH	C-Me	N
I-356	COOH	Phenyl	3,5-Di-Me-Phenyl-CH ₂ -CONH-	N	C-OMe	C-Me	N	CH
I-357	COOH	Phenyl	3,5-Di-OMe-Phenyl-CH ₂ -CONH-	N	N	C-Me	C-OMe	N
I-358	COOH	Phenyl	3,4-Di-OMe-Phenyl-(CH ₂) ₂ -NH-	CH	C-Me	N	C-Me	N

THIS SHEET HAS BEEN
REPLACED



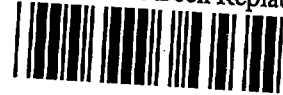
No.	R ¹	R ² , R ³	A	W	X	Q	Y	Z
I-359	COOH	Phenyl	3,4-Di-OMe-Phenyl-(CH ₂) ₂ -NH-	CH	C-OMe	N	C-Me	N
I-360	COOH	Phenyl	2,5-Di-OMe-Phenyl-CH ₂ -CONH-	CH	C-Me	N	C-Me	CH
I-361	COOH	Phenyl	3,5-Di-OMe-Phenyl-CH ₂ -CONH-	CH	C-Me	N	C-Me	N
I-362	COOH	Phenyl	2,4-Di-OMe-Phenyl-CH ₂ -CONH-	CH	C-OMe	N	C-Me	N
I-363	COOH	Phenyl	CH ₃ NH-	N	C-Me	N	C-Me	N
I-364	COOH	Phenyl	CH ₃ NH-	N	C-Me	N	C-OMe	N
I-365	COOH	Phenyl	3,4,5-Tri-OMe-Phenyl-CH ₂ -CONH-	CH	C-Me	N	C-OMe	N
I-366	COOH	Phenyl	3,4,5-Tri-OMe-Phenyl-CH ₂ -CONH-	CH	C-Ethyl	N	C-Me	N
I-367	COOH	Phenyl	t-Bu-CH ₂ CONH-	N	C-Ethyl	CH	C-Me	N
I-368	COOH	Phenyl	t-Bu-CH ₂ CONH-	N		C-CH ₂ -CH ₂ -CH ₂ -C	C-OMe	N
I-369	COOH	Phenyl	3,4-Di-Cl-Phenyl-(CH ₂) ₂ -NH-	N	C-Me	CH	C-Me	N
I-370	COOH	Phenyl	HOCH ₂ CONH-	N	C-Ethyl	CH	C-Me	N
I-371	COOH	Phenyl	HOCH ₂ CONH-	N		C-CH ₂ -CH ₂ -CH ₂ -C	C-OMe	N
I-372	COOH	Phenyl	3,4-Di-Cl-Phenyl-(CH ₂) ₂ -NH-	N	C-OMe	CH	C-Me	N
I-373	COOH	Phenyl	3,4-Di-Me-Phenyl-(CH ₂) ₂ -NH-	N	C-OMe	CH	C-OMe	N
I-374	COOH	Phenyl	H ₂ N-	N	C-Me	CH	C-Me	N
I-375	COOH	Phenyl	H ₂ N-	N	C-OMe	CH	C-Me	N
I-376	COOH	Phenyl	3,4-Di-Me-Phenyl-(CH ₂) ₂ -NH-	N	C-Ethyl	CH	C-Me	N
I-377	COOH	Phenyl	2,4-Di-OMe-Phenyl-(CH ₂) ₂ -NH-	N		C-CH ₂ -CH ₂ -CH ₂ -C	C-OMe	N
I-378	COOH	Phenyl	3,4-Di-OMe-Phenyl-(CH ₂) ₂ -NH-	N	C-OMe	C-Me	N	CH
I-379	COOH	Phenyl	3,4-Di-OMe-Phenyl-(CH ₂) ₂ -NH-	N	N	C-Me	C-OMe	N
I-380	COOH	Phenyl	3,4,5-Tri-OMe-Phenyl-(CH ₂) ₂ -NH-	N		C-O-CH ₂ -CH ₂ -C	C-OMe	N

THIS SHEET HAS BEEN
REPLACED



No.	R ¹	R ² , R ³	A	W	X	Q	Y	Z
I-381	COOH	Phenyl	3,4,5-Tri-OMe-Phenyl-(CH ₂) ₂ -NH-	N	C-Me	N	C-Me	N
I-382	COOH	Phenyl	3,4-Di-Me-Phenyl-(CH ₂) ₂ -NH-	N	C-Me	N	C-OMe	N
I-383	COOH	Phenyl	CH ₃ NH-	N		C-CH ₂ -CH ₂ -CH ₂ -C	C-OMe	N
I-384	COOH	Phenyl	CH ₃ NH-	N		C-O-CH ₂ -CH ₂ -C	C-OMe	N
I-385	COOH	Phenyl	3,5-Di-OMe-Phenyl-(CH ₂) ₂ -NH-	N	C-Ethyl	N	C-Me	N
I-386	COOH	Phenyl	3,5-Di-OMe-Phenyl-(CH ₂) ₂ -NH-	N	N	C-Me	C-OMe	CH
I-387	COOH	Phenyl	t-Bu-CH ₂ CONH-	N	C-OMe	CH	C-Me	N
I-388	COOH	Phenyl	t-Bu-CH ₂ CONH-	N	C-OMe	CH	C-OMe	N
I-389	COOH	Phenyl	2,4-Di-OMe-Phenyl-(CH ₂) ₂ -NH-	N	C-OMe	C-Me	N	CH
I-390	COOH	Phenyl	HOCH ₂ CONH-	N	C-OMe	CH	C-Me	N
I-391	COOH	Phenyl	HOCH ₂ CONH-	N	C-OMe	CH	C-OMe	N
I-392	COOH	Phenyl	3,4-Di-Me-Phenyl-(CH ₂) ₂ -NH-	N	N	C-Me	C-OMe	N
I-393	COOH	Phenyl	3,4-Di-Me-Phenyl-(CH ₂) ₂ -NH-	CH	C-Me	N	C-Me	N
I-394	COOH	Phenyl	N ₃	CH	C-Ethyl	N	C-Me	N
I-395	COOH	Phenyl	H ₂ N-	N	C-Me	CH	C-Me	CH
I-396	COOH	4-F-Phenyl	3,4-Di-OMe-Phenyl-(CH ₂) ₂ -NH-	CH	C-OMe	N	C-Me	N
I-397	COOH	4-F-Phenyl	3,4-Di-OMe-Phenyl-(CH ₂) ₂ -NH-	CH	C-Me	N	C-OMe	N
I-398	COOH	Phenyl	3,4-Di-OMe-Phenyl-(CH ₂) ₂ -NH-	N	C-Ethyl	N	C-Me	N
I-399	COOH	Phenyl	3,4-Di-OMe-Phenyl-(CH ₂) ₂ -NH-	N	N	C-Me	C-OMe	CH
I-400	COOH	Phenyl	3,4-Di-Me-Phenyl-(CH ₂) ₂ -NH-	CH	C-Ethyl	N	C-Me	N
I-401	COOH	Phenyl	4-OMe-Benzyl-NH-	N	C-Me	CH	C-Me	N
I-402	COOH	Phenyl	3,4-Di-OMe-Benzyl-NH-	N	C-OMe	CH	C-Me	N
I-403	COOH	Phenyl	CH ₃ NH-	N	C-OMe	CH	C-OMe	N

THIS SHEET HAS BEEN
REPLACED



No.	R ¹	R ² , R ³	A	W	X	Q	Y	Z
I-404	COOH	Phenyl	CH ₃ NH-	N	C-Ethyl	CH	C-Me	N
I-405	COOH	Phenyl	4-Cl-Benzyl-NH-	N	C-OMe	CH	C-OMe	N
I-406	COOH	Phenyl	4-OH-Benzyl-NH-	N	C-Ethyl	CH	C-Me	N
I-407	COOH	Phenyl	MeOCH ₂ CONH-	CH	C-OMe	N	C-Me	N
I-408	COOH	Phenyl	MeOCH ₂ CONH-	CH	C-Me	N	C-OMe	N
I-409	COOH	Phenyl	MeOCH ₂ CONH-	CH	C-Ethyl	N	C-Me	N
I-410	COOH	Phenyl	t-Bu-CH ₂ CONH-	N	C-Me	CH	C-Me	N
I-411	COOH	Phenyl	3,4-Di-OMe-Benzyl-NH-	N	C-CH ₂ -CH ₂ -CH ₂ -C		C-OMe	N
I-412	COOH	Phenyl	Phenyl-NH-	CH	C-Ethyl	N	C-Me	N
I-413	COOH	Phenyl	HOCH ₂ CONH-	N	C-Me	CH	C-Me	N
I-414	COOH	Phenyl	4-OMe-Benzyl-NH-	N	C-O-CH ₂ -CH ₂ -C		C-OMe	N
I-415	COOH	Phenyl	3-OMe-4-OH-Benzyl-NH-	N	C-Me	N	C-Me	N
I-416	COOH	Phenyl	N ₃	CH	C-OMe	N	C-Me	N
I-417	COOH	Phenyl	N ₃	CH	C-Me	N	C-OMe	N
I-418	COOH	Phenyl	4-Me-Benzyl-NH-	N	C-Me	N	C-OMe	N
I-419	COOH	Phenyl	3,4-Di-Me-Benzyl-NH-	N	C-Ethyl	N	C-Me	N
I-420	COOH	Phenyl	3,4-Di-OMe-Phenyl-(CH ₂) ₂ -NH-	N	C-Me	N	C-Me	N
I-421	COOH	Phenyl	3,4-Di-OMe-Phenyl-(CH ₂) ₂ -NH-	N	C-Me	N	C-OMe	N
I-422	COOH	Phenyl	4-Me-Benzyl-NH-	N	N	C-Me	C-OMe	CH
I-423	COOH	Phenyl	3-Cl-Benzyl-NH-	N	C-OMe	C-Me	N	CH
I-424	COOH	Phenyl	2-Cl-Benzyl-NH-	N	N	C-Me	C-OMe	N
I-425	COOH	Phenyl	CH ₃ NH-	N	C-Me	CH	C-Me	N
I-426	COOH	Phenyl	CH ₃ NH-	N	C-OMe	CH	C-Me	N
I-427	COOH	Phenyl	3,5-Di-OMe-Benzyl-NH-	CH	C-Me	N	C-Me	N

THIS SHEET HAS BEEN
REPLACED



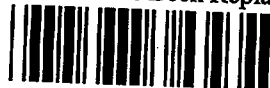
No.	R ¹	R ² , R ³	A	W	X	Q	Y	Z
I-428	COOH	4-F-Phenyl	Benzyl-NH-	CH	C-Me	N	C-OMe	N
I-429	COOH	Phenyl	MeOCH ₂ CONH-	CH	C-Me	N	C-Me	CH
I-430	COOH	Phenyl	MeOCH ₂ CONH-	CH	C-Me	N	C-Me	N
I-431	COOH	4-F-Phenyl	Benzyl-NH-	CH	C-Ethyl	N	C-Me	N
I-432	COOH	Phenyl	Phenyl-NH-	CH	C-Me	N	C-Me	N
I-433	COOH	Phenyl	Phenyl-NH-	CH	C-OMe	N	C-Me	N
I-434	COOH	Phenyl	3-Cl-4-OH-Phenyl-CH ₂ -CONH-	N	C-Me	CH	C-Me	N
I-435	COOH	Phenyl	3-Cl-4-OH-Phenyl-CH ₂ -CONH-	N	C-OMe	CH	C-Me	N
I-436	COOH	Phenyl	N ₃	CH	C-Me	N	C-Me	CH
I-437	COOH	Phenyl	N ₃	CH	C-Me	N	C-Me	N
I-438	COOH	Phenyl	3-Me-4-OH-Phenyl-CH ₂ -CONH-	N	C-OMe	CH	C-OMe	N
I-439	COOH	Phenyl	3-Me-4-OH-Phenyl-CH ₂ -CONH-	N	C-Ethyl	CH	C-Me	N
I-440	COOH	Phenyl	3,4-Di-OMe-Phenyl-(CH ₂) ₂ -NH-	N	C-CH ₂ -CH ₂ -CH ₂ -C		C-OMe	N
I-441	COOH	Phenyl	3,4-Di-OMe-Phenyl-(CH ₂) ₂ -NH-	N	C-O-CH ₂ -CH ₂ -C		C-OMe	N
I-442	COOH	Phenyl	3-OMe-4-OH-Phenyl-CH ₂ -CONH-	N	C-CH ₂ -CH ₂ -CH ₂ -C		C-Ethyl	N
I-443	COOH	Phenyl	3-OMe-4-OH-Phenyl-CH ₂ -CONH-	N	C-O-CH ₂ -CH ₂ -C		C-Me	N
I-444	COOH	Phenyl	2-OMe-4-OH-Phenyl-CH ₂ -CONH-	N	C-Me	N	C-Me	N
I-445	COOH	Phenyl	Ethyl-CONH-	CH	C-Me	N	C-OMe	N
I-446	COOH	Phenyl	Ethyl-CONH-	CH	C-Ethyl	N	C-Me	N
I-447	COOH	Phenyl	3-Cl-4-OH-Phenyl-CH ₂ -CONH-	N	C-Me	N	C-OMe	N
I-448	COOH	Phenyl	3,4-Di-OMe-Phenyl-CH ₂ -CONH-	N	C-Ethyl	N	C-Me	N
I-449	COOH	Phenyl	MeOCH ₂ CONH-	N	C-OMe	C-Me	N	CH

THIS SHEET HAS BEEN
REPLACED



No.	R ¹	R ² , R ³	A	W	X	Q	Y	Z
I-450	COOH	Phenyl	MeOCH ₂ CONH-	N	N	C-Me	C-OMe	N
I-451	COOH	Phenyl	3,4-Di-OH-Phenyl-CH ₂ -CONH-	N	N	C-Me	C-OMe	CH
I-452	COOH	Phenyl	Phenyl-NH-	N	C-OMe	C-Me	N	CH
I-453	COOH	Phenyl	Phenyl-NH-	N	N	C-Me	C-OMe	N
I-454	COOH	Phenyl	3-OH-4-OMe-Phenyl-CH ₂ -CONH-	N	C-OMe	C-Me	N	CH
I-455	COOH	Phenyl	3-OH-4-OMe-Phenyl-CH ₂ -CONH-	N	N	C-Me	C-OMe	N
I-456	COOH	Phenyl	N ₃	N	C-OMe	C-Me	N	CH
I-457	COOH	Phenyl	N ₃	N	N	C-Me	C-OMe	N
I-458	COOH	Phenyl	2-Cl-4-OH-Phenyl-CH ₂ -CONH-	CH	C-Me	N	C-Me	CH
I-459	COOH	Phenyl	3-Cl-4-OH-Phenyl-CH ₂ -CONH-	CH	C-Me	N	C-Me	N
I-460	COOH	Phenyl	3,4-Di-OMe-Phenyl-(CH ₂) ₂ -NH-	N	C-OMe	CH	C-OMe	N
I-461	COOH	Phenyl	3,4-Di-OMe-Phenyl-(CH ₂) ₂ -NH-	N	C-Ethyl	CH	C-Me	N
I-462	COOH	Phenyl	3-OMe-4-SMe-Phenyl-CH ₂ -CONH-	CH	C-OMe	N	C-Me	N
I-463	COOH	Phenyl	3-OMe-4-SMe-Phenyl-CH ₂ -CONH-	CH	C-Me	N	C-OMe	N
I-464	COOH	Phenyl	3,4-Di-OH-Phenyl-CH ₂ -CONH-	CH	C-Ethyl	N	C-Me	N
I-465	COOH	Phenyl	Ethyl-CONH-	CH	C-Me	N	C-Me	N
I-466	COOH	Phenyl	Ethyl-CONH-	CH	C-OMe	N	C-Me	N
I-467	COOH	Phenyl	Phenyl-NH-	N	C-CF ₃	CH	C-Me	N
I-468	COOH	4-F-Phenyl	Phenyl-NH-	N	C-OMe	CH	C-Me	N
I-469	COOH	Phenyl	MeOCH ₂ CONH-	N	C-Ethyl	N	C-Me	N
I-470	COOH	Phenyl	MeOCH ₂ CONH-	N	N	C-Me	C-OMe	CH

THIS SHEET HAS BEEN
REPLACED



No.	R ¹	R ² , R ³	A	W	X	Q	Y	Z
I-471	COOH	4-Cl-Phenyl	Phenyl-NH-	N	C-OMe	CH	C-OMe	N
I-472	COOH	Phenyl	Phenyl-NH-	N	C-Ethyl	N	C-Me	N
I-473	COOH	Phenyl	Phenyl-NH-	N	N	C-Me	C-OMe	CH
I-474	COOH	4-Me-Phenyl	Phenyl-NH-	N	C-Ethyl	CH	C-Me	N
I-475	COOH	Phenyl	Phenyl-NH-	N	C-CH ₂ -CH ₂ -CH ₂ -C		C-Me	N
I-476	COOH	Phenyl	N ₃	N	C-Ethyl	N	C-Me	N
I-477	COOH	Phenyl	N ₃	N	N	C-Me	C-OMe	CH
I-478	COOH	Phenyl	Phenyl-NH-	N		C-O-CH ₂ -CH ₂ -C	C-Me	N
I-479	COOH	Phenyl	Phenyl-NH-	N	C-N(CH ₃) ₂	N	C-N(CH ₃) ₂	N
I-480	COOH	Phenyl	3,4-Di-OMe-Phenyl-(CH ₂) ₂ -NH-	N	C-Me	CH	C-Me	N
I-481	COOH	Phenyl	3,4-Di-OMe-Phenyl-(CH ₂) ₂ -NH-	N	C-OMe	CH	C-Me	N
I-482	COOH	Phenyl	Phenyl-NH-	N	C-Ethyl	N	C-Ethyl	N
I-483	COOH	Phenyl	Phenyl-NH-	CH	C-Ethyl	CH	C-Me	N
I-484	COOH	Phenyl	Phenyl-NH-	N	N	C-OMe	CH	CH
I-485	COOH	Phenyl	Ethyl-CONH-	N	N	C-Me	C-OMe	N
I-486	COOH	Phenyl	Ethyl-CONH-	CH	C-Me	N	C-Me	CH
I-487	COOH	4-F-Phenyl	Phenyl-NH-	N	C-OMe	C-Me	N	CH
I-488	COOH	4-F-Phenyl	Phenyl-NH-	N	N	C-Me	C-OMe	N
I-489	COOH	Phenyl	MeOCH ₂ CONH-	N	C-Me	N	C-Me	N
I-490	COOH	Phenyl	MeOCH ₂ CONH-	N	C-Me	N	C-OMe	N
I-491	COOMe	Phenyl	Phenyl-NH-	CH	C-Me	N	C-Me	N
I-492	COOH	Phenyl	Phenyl-NH-	N	C-Me	N	C-Me	N
I-493	COOH	Phenyl	Phenyl-NH-	N	C-Me	N	C-OMe	N
I-494	COOH	Phenyl	Phenyl-NH-	CH	C-OMe	N	C-Ethyl	N
I-495	COOH	Phenyl	4-Cl-Phenyl-NH-	CH	C-Ethyl	N	C-Me	N

THIS SHEET HAS BEEN
REPLACED



No.	R ¹	R ² , R ³	A	W	X	Q	Y	Z
I-496	COOH	Phenyl	N ₃	N	C-Me	N	C-Me	N
I-497	COOH	Phenyl	N ₃	N	C-Me	N	C-OMe	N
I-498	COOH	Phenyl	Benzyl-OCH ₂ CONH-	N	C-Me	CH	C-Me	N
I-499	COOH	Phenyl	Benzyl-OCH ₂ CONH-	N	C-OMe	CH	C-Me	N
I-500	COOH	Phenyl	3,4-Di-OMe-Phenyl-CH ₂ -CONH-	CH	C-Me	N	C-OMe	N
I-501	COOH	Phenyl	3,4-Di-OMe-Phenyl-CH ₂ -CONH-	CH	C-Ethyl	N	C-Me	N
I-502	COOH	4-F-Phenyl	HOCH ₂ CONH-	N	C-OMe	CH	C-OMe	N
I-503	COOH	4-F-Phenyl	N ₃	CH	C-Me	N	C-Me	N
I-504	COOH	4-F-Phenyl	N ₃	CH	C-OMe	N	C-Me	N
I-505	COOH	4-F-Phenyl	HOCH ₂ CONH-	N	C-Ethyl	CH	C-Me	N
I-506	COOH	Phenyl	HOCH ₂ CONH-	N		C-CH ₂ -CH ₂ -CH ₂ -C	C-Me	N
I-507	COOH	Phenyl	Ethyl-CONH-	N	N	C-Me	C-OMe	CH
I-508	COOH	Phenyl	Ethyl-CONH-	N	C-OMe	C-Me	N	CH
I-509	COOH	Phenyl	HOCH ₂ CONH-	N		C-S-CH ₂ -CH ₂ -C	C-OMe	N
I-510	COOH	Phenyl	Benzyl-OCH ₂ CONH-	N	C-Me	N	C-Me	N
I-511	COOH	Phenyl	MeOCH ₂ CONH-	N		C-CH ₂ -CH ₂ -CH ₂ -C	C-OMe	N
I-512	COOH	Phenyl	MeOCH ₂ CONH-	N		C-O-CH ₂ -CH ₂ -C	C-OMe	N
I-513	COOH	4-Me-Phenyl	HOCH ₂ CONH-	N	C-Me	N	C-OMe	N
I-514	COOH	Phenyl	Phenyl-NH-	N		C-CH ₂ -CH ₂ -CH ₂ -C	C-OMe	N
I-515	COOH	Phenyl	Phenyl-NH-	N		C-O-CH ₂ -CH ₂ -C	C-OMe	N
I-516	COOH	Phenyl	HOCH ₂ CONH-	N	C-Ethyl	N	C-Ethyl	N
I-517	COOH	Phenyl	4-OMe-Benzyl-OCH ₂ CONH-	N	N	C-Me	C-OMe	CH
I-518	COOH	Phenyl	N ₃	N		C-CH ₂ -CH ₂ -CH ₂ -C	C-OMe	N
I-519	COOH	Phenyl	N ₃	N		C-O-CH ₂ -CH ₂ -C	C-OMe	N

THIS SHEET HAS BEEN
REPLACED



No.	R ¹	R ² , R ³	A	W	X	Q	Y	Z
I-520	COOH	Phenyl	4-OMe-Benzyl-OCH ₂ CONH-	N	C-OMe	C-Me	N	CH
I-521	COOH	4-F-Phenyl	HOCH ₂ CONH-	N	N	C-Me	C-OMe	N
I-522	COOH	Phenyl	3,4-Di-OMe-Phenyl-CH ₂ -CONH-	CH	C-Me	N	C-Me	N
I-523	COOH	Phenyl	3,4-Di-OMe-Phenyl-CH ₂ -CONH-	CH	C-OMe	N	C-Me	N
I-524	COOH	4-Cl-Phenyl	HOCH ₂ CONH-	CH	C-Me	N	C-Me	CH
I-525	COOH	4-F-Phenyl	N ₃	N	N	C-Me	C-OMe	N
I-526	COOH	4-F-Phenyl	N ₃	CH	C-Me	N	C-Me	CH
I-527	COOH	Phenyl	Phenyl-OCH ₂ CONH-	CH	C-Me	N	C-Me	N
I-528	COOH	Phenyl	4-OMe-Phenyl-OCH ₂ CONH-	CH	C-OMe	N	C-Me	N
I-529	COOH	Phenyl	Ethyl-CONH-	N	C-Me	N	C-OMe	N
I-530	COOH	Phenyl	Ethyl-CONH-	N	C-Ethyl	N	C-Me	N
I-531	COOH	Phenyl	Benzyl-OCH ₂ CONH-	CH	C-Me	N	C-OMe	N
I-532	COOH	4-F-Phenyl	HOCH ₂ CONH-	CH	C-Ethyl	N	C-Me	N
I-533	COOH	Phenyl	MeOCH ₂ CONH-	N	C-Me	CH	C-Me	N
I-534	COOH	Phenyl	MeOCH ₂ CONH-	N	C-OMe	CH	C-Me	N
I-535	COOH	Phenyl	MeOCH ₂ CONH-	N	C-OMe	CH	C-OMe	N
I-536	COOH	Phenyl	MeOCH ₂ CONH-	N	C-Ethyl	CH	C-Me	N
I-537	COOH	Phenyl	4-OH-Phenyl-CONH-	N	C-Me	CH	C-Me	N
I-538	COOH	Phenyl	Phenyl-NH-	N	C-OMe	CH	C-OMe	N
I-539	COOH	Phenyl	Phenyl-NH-	N	C-Ethyl	CH	C-Me	N
I-540	COOH	Phenyl	4-SMe-Phenyl-CONH-	N	C-OMe	CH	C-Me	N
I-541	COOH	Phenyl	4-NO ₂ -Phenyl-CONH-	N	C-OMe	CH	C-OMe	N
I-542	COOH	Phenyl	N ₃	N	C-OMe	CH	C-OMe	N
I-543	COOH	Phenyl	N ₃	N	C-Ethyl	CH	C-Me	N

THIS SHEET HAS BEEN
REPLACED



No.	R ¹	R ² , R ³	A	W	X	Q	Y	Z
I-544	COOH	Phenyl	4-Cl-Phenyl-CONH-	N	C-Ethyl	CH	C-Me	N
I-545	COOH	Phenyl	4-Ethyl-Phenyl-CONH-	N		C-CH ₂ -CH ₂ -CH ₂ -C	C-OMe	N
I-546	COOH	Phenyl	3,4-Di-OMe-Phenyl-CH ₂ -CONH-	N	N	C-Me	C-OMe	N
I-547	COOH	Phenyl	3,4-Di-OMe-Phenyl-CH ₂ -CONH-	CH	C-Me	N	C-Me	CH
I-548	COOH	4-F-Phenyl	4-OMe-Phenyl-CONH-	N		C-O-CH ₂ -CH ₂ -C	C-OMe	N
I-549	COOH	4-F-Phenyl	N ₃	N	N	C-Me	C-OMe	CH
I-550	COOH	4-F-Phenyl	N ₃	N	C-OMe	C-Me	N	CH
I-551	COOH	Phenyl	4-Cl-Phenyl-CONH-	N	C-Me	N	C-Me	N
I-552	COOH	Phenyl	3,4-Di-OMe-Phenyl-CONH-	N	C-Me	N	C-OMe	N
I-553	COOH	Phenyl	Ethyl-CONH-	N		C-O-CH ₂ -CH ₂ -C	C-OMe	N
I-554	COOH	Phenyl	Ethyl-CONH-	N	C-Me	N	C-Me	N
I-555	COOH	Phenyl	3,4-Di-OMe-Phenyl-CONH-	N	C-Ethyl	N	C-Me	N
I-556	COOH	Phenyl	4-Cl-Phenyl-CONH-	N	N	C-Me	C-OMe	CH
I-557	COOH	Phenyl	CF ₃ CONH-	CH	C-Me	N	C-OMe	N
I-558	COOH	Phenyl	CF ₃ CONH-	CH	C-Ethyl	N	C-Me	N
I-559	COOH	Phenyl	3,4-Di-Cl-Phenyl-CONH-	N	C-OMe	C-Me	N	CH
I-560	COOH	Phenyl	Phenyl-NH-	N	C-Me	CH	C-Me	N
I-561	COOH	Phenyl	Phenyl-NH-	N	C-OMe	CH	C-Me	N
I-562	COOH	Phenyl	3-OMe-4-OH-Phenyl-CONH-	N	N	C-Me	C-OMe	N
I-563	COOH	Phenyl	3-Cl-Phenyl-CONH-	CH	C-Me	N	C-Me	N
I-564	COOH	Phenyl	N ₃	N	C-Me	CH	C-Me	N
I-565	COOH	Phenyl	N ₃	N	C-OMe	CH	C-Me	N
I-566	COOH	Phenyl	2-Cl-Phenyl-CONH-	CH	C-OMe	N	C-Me	N
I-567	COOH	Phenyl	4-NO ₂ -Phenyl-CONH-	CH	C-Ethyl	N	C-Me	N

THIS SHEET HAS BEEN
REPLACED



Example 11

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

The results are shown in Table 2.

10 Table 2

Receptor binding data (K_i values)

15	Compound	ET _A [nM/l]	ET _B [nM/l]
	I-174	83	>7000
	I-227	225	2800
	I-334	600	6400
20	I-354	50	>6400
	I-375	300	7300
	I-388	1000	7000
	I-518	14	460
	I-535	35	7000
25	I-541	1000	>7000
	I-542	60	2200

30

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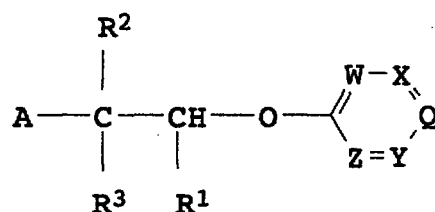
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Novel β -amino and β -azidocarboxylic acid derivatives, their preparation and use as endothelin receptor antagonists

5 Abstract

Carboxylic acid derivatives of the formula I

10



15

where the substituents have the meanings explained in the description are used as endothelin receptor antagonists.

20

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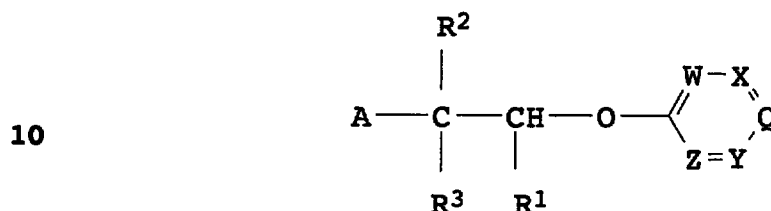
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5 1. A β -amino or β -azido carboxylic acid derivative of the formula I


$$\begin{array}{c} \text{O} \\ \parallel \\ \text{C}-\text{R} \end{array}$$

a) a radical OR^4 , where R^4 is:

30 C₃-C₈-cycloalkyl, C₁-C₈-alkyl, unsubstituted or substituted,

35 C₃-C₈-alkenyl or a C₃-C₈-alkynyl, unsubstituted or substituted, or

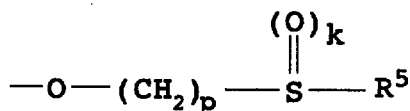
40 b) a 5-membered heteroaromatic system linked via a nitrogen atom,

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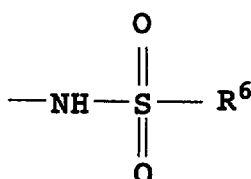
where k can assume the values 0, 1 and 2, p the values 1, 2, 3 and 4, and R⁵ is

10

C₁-C₄-alkyl, C₃-C₈-cycloalkyl, C₃-C₈-alkenyl, C₃-C₈-alkynyl or unsubstituted or substituted phenyl,

d) a radical

15



20

where R⁶ is:

25

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

C₁-C₄-haloalkyl or phenyl, unsubstituted or substituted.

30

A is NR⁷R⁸ or azido;

W and Z (which may be identical or different) are:

35

nitrogen or methine; with the proviso that Q = nitrogen if W and Z = methine;

X is nitrogen or CR⁹;

40

Y is nitrogen or CR¹⁰;

Q is nitrogen or CR¹¹; with the proviso that X = CR⁹ and Y = CR¹⁰ if Q = nitrogen;

45

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3

R² and R³ (which may be identical or different) are:

phenyl or naphthyl, unsubstituted or substituted, or

5

phenyl or naphthyl which are linked 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,

10

C₅-C₆-cycloalkyl, unsubstituted or substituted;

R⁷ is hydrogen, C₁-C₈-alkyl, C₃-C₈-alkenyl, C₃-C₈-alkynyl, C₁-C₅-alkylcarbonyl, it being possible for these radicals to be unsubstituted or substituted;

15

phenyl or naphthyl, unsubstituted or substituted; unsubstituted or substituted C₃-C₈-cycloalkyl;

20

or R⁷ is linked to R⁸ via 4 or 5 CH₂ groups to give a 5- or 6-membered ring;

R⁸ is hydrogen, C₁-C₄-alkyl;

25

or R⁸ is linked to R⁷ via 4 or 5 CH₂ groups to give a 5- or 6-membered ring;

R⁹ and R¹⁰ (which may be identical or different) are:

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hydrogen, halogen, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₃-C₆-alkenyloxy, C₃-C₆-alkynyloxy, C₁-C₄-alkylthio, C₁-C₄-alkylcarbonyl, C₁-C₄-alkoxycarbonyl, hydroxyl, NH₂, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂

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C₁-C₄-alkyl, C₂-C₄-alkenyl, C₂-C₄-alkynyl, it being possible for these radicals to be unsubstituted or substituted;

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or CR⁹ or CR¹⁰ is linked to CR¹¹ as indicated below to give a 5- or 6-membered ring,

R¹¹ is hydrogen, halogen, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₃-C₆-alkenyloxy, C₃-C₆-alkynyloxy, C₁-C₄-alkylthio, C₁-C₄-alkylcarbonyl, C₁-C₄-alkoxycarbonyl, NH(C₁-C₄-alkyl),

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$N(C_1-C_4\text{-alkyl})_2$, hydroxyl, carboxyl, cyano, amino, mercapto;

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$C_1-C_4\text{-alkyl}$, $C_2-C_4\text{-alkenyl}$, $C_2-C_4\text{-alkynyl}$, it being possible for these radicals to be unsubstituted or substituted;

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or CR^{11} forms together with CR^9 or CR^{10} a 5- or 6-membered alkylene or alkenylene ring which may unsubstituted or substituted, and in which in each case one or more methylene groups may be replaced by oxygen, sulfur, $-NH$ or $-N(C_1-C_4\text{-alkyl})$;

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and the physiologically tolerated salts, and the possible enantiomerically pure and diastereoisomerically pure forms.

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2. The use of a β -amino or β -azido carboxylic acid derivative as claimed in claim 1 for treating diseases.

3. The use of compounds I as claimed in claim 2 as endothelin receptor antagonists.

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

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5. The use of a β -amino or β -azido carboxylic acid derivative I as claimed in claim 1 for treating chronic heart failure, restenosis, high blood pressure, pulmonary hypertension, acute/chronic kidney failure, cerebral ischemia, benign prostate hyperplasia and prostate cancer.

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6. The use of a β -amino and β -azido carboxylic acid derivative I as claimed in claim 1 in combination with: inhibitors of the renin-angiotensin system such as renin inhibitors, angiotensin II antagonists and, in particular, angiotensin converting enzyme (ACE) inhibitors; mixed ACE/neutral endopeptidase (NEP) inhibitors; β blockers.

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7. A drug formulation for oral, parenteral or intraperitoneal [sic] administration comprising per single dose, besides conventional pharmaceutical auxiliaries, at least one carboxylic acid derivative I as claimed in claim 1.

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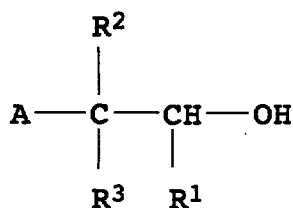
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8. A compound of the formula II

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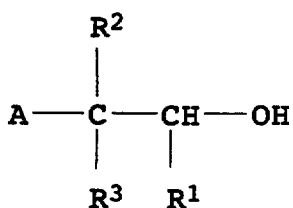


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where the radicals R^1 , R^2 , R^3 and A have the meanings stated in claim 1.

9. The use of compounds of the formula II,

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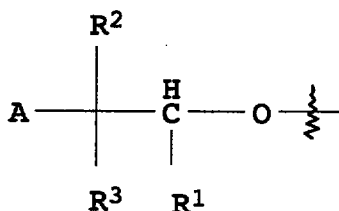
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where the radicals R^1 , R^2 , R^3 and A have the meanings stated in claim 1, as starting material for synthesizing endothelin receptor antagonists.

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10. A structural fragment of the formula

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where the radicals R^1 , R^2 , R^3 and A have the meanings stated in claim 1, as structural element in an endothelin receptor antagonist.

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