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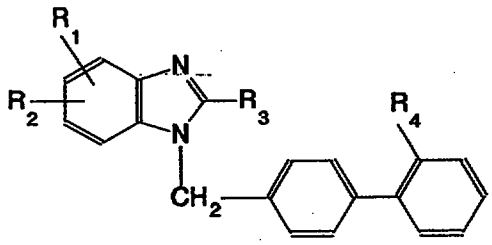
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Case 5/1099-FL

Benzimidazoles, pharmaceutical compositions containing these compounds and processes for preparing them

The present invention relates to new benzimidazoles of general formula



(I),

the tautomers and the salts thereof, particularly, for pharmaceutical use, the physiologically acceptable salts thereof with inorganic or organic acids or bases, which are useful angiotensin-antagonists, particularly angiotensin-II-antagonists, pharmaceutical compositions containing these compounds, the use thereof and processes for preparing them.

In general formula I above:

R_1 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group, a C_{3-7}-cycloalkyl group, a fluoromethyl, difluoromethyl or trifluoromethyl group,

R_2 denotes a phthalimino or homophthalimino group, whilst a carbonyl group in a phthalimino group may be replaced

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by a methylene group and a methylene group in a homophthalimino group may be substituted by one or two C_{1-3}-alkyl groups,

a 5-, 6- or 7-membered alkyleneimino group (optionally substituted by one or two C_{1-3}-alkyl groups) in which a methylene group is replaced by a carbonyl or sulphonyl group,

a maleic acid imido group optionally mono- or disubstituted by a C_{1-3}-alkyl group or by a phenyl group, whilst the substituents may be identical or different,

a benzimidazol-2-yl or 4,5,6,7-tetrahydro-benzimidazol-2-yl group optionally substituted in the 1-position by a C_{1-6}-alkyl group or by a C_{3-5}-cycloalkyl group (whilst the phenyl nucleus of one of the above-mentioned benzimidazole groups may additionally be substituted by a fluorine atom or a methyl or trifluoromethyl group), an imidazo[2,1-b]thiazol-6-yl, imidazo[1,2-a]pyridin-2-yl, 5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl, 3-chloro-5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyrimidin-2-yl, imidazo[4,5-b]pyridin-2-yl, imidazo[4,5-c]pyridin-2-yl, imidazo[1,2-c]pyrimidin-2-yl, imidazo[1,2-a]pyrazin-2-yl, imidazo[1,2-b]-pyridazin-2-yl, imidazo[4,5-c]pyridin-2-yl, purin-8-yl, imidazo[4,5-b]pyrazin-2-yl, imidazo[4,5-c]pyridazin-2-yl or imidazo[4,5-d]pyridazin-2-yl group, a pyrrolidine, piperidine or pyridine ring bound via a carbon atom, whilst a phenyl group may be condensed on to the pyridine ring via two adjacent carbon atoms and a methylene group adjacent to the N-atom in a pyrrolidine or piperidine ring may be replaced by a carbonyl group, or

an R_7-NR_6-CO-NR_5- group wherein

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R_5 denotes a hydrogen atom, a C_{1-5}-alkyl group, a cyclohexyl or benzyl group,

R_6 denotes a hydrogen atom, a C_{1-6}-alkyl group, an allyl, cyclohexyl, benzyl or phenyl group,

R_7 denotes a hydrogen atom or a C_{1-3}-alkyl group or

R_6 and R_7 together with the nitrogen atom between them denote a an unbranched cyclic C_{4-6}-alkyleneimino group or a morpholino group or

R_5 and R_6 together denote a C_{2-3}-alkylene group,

R_3 denotes a C_{1-5}-alkyl group, a C_{3-5}-cycloalkyl group or a C_{1-3}-alkoxy group and

R_4 denotes a tetrazolyl group substituted in the 1- or 2-position by an R_a-CO-O-CH_2- group, or an R_b-CO-O-(R_cCH)-O-CO-, R_aO-CO- or R_bO-CO-O-(R_cCH)-O-CO- group, wherein

R_a denotes a straight-chained or branched C_{1-6}-alkyl group, a C_{5-7}-cycloalkyl group, a benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, methoxymethyl or cinnamyl group,

R_b denotes a straight-chained or branched C_{1-6}-alkyl group, a C_{5-7}-cycloalkyl group, a phenyl, benzyl, 1-phenylethyl, 2-phenylethyl or 3-phenylpropyl group and

R_c denotes a hydrogen atom or a methyl group,

or if

(i) R_1 and R_2 are as hereinbefore defined and R_3 denotes

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an alkoxy group, R_4 may denote a carboxy, 1H-tetrazolyl or 2H-tetrazolyl group or, if

(ii) R_1 is as hereinbefore defined, R_2 has the meanings given hereinbefore with the exception of the 1-methyl-benzimidazol-2-yl group and R_3 denotes a cyclopropyl group, R_4 may represent a carboxy group or, if

(iii) R_1 and R_3 are as hereinbefore defined and R_2 denotes a butanesultam-1-yl group, R_4 may denote a carboxy group or, if

(iv) R_1 is as hereinbefore defined, R_2 denotes a 1-methyl-5-fluoro-benzimidazol-2-yl group and R_3 denotes an ethyl group, R_4 may represent a carboxy, 1H-tetrazolyl or 2H-tetrazolyl group.

As examples of the definitions of groups R_1 to R_4 mentioned hereinbefore,

R_1 may denote, for example, a hydrogen atom or in the 4-position a fluorine, chlorine or bromine atom, a methyl, ethyl, n-propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, difluoromethyl or trifluoromethyl group,

R_2 may denote a phthalimino, homophthalimino, 4,4-dimethyl-homophthalimino, 1-oxo-isoindolin-2-yl, 2-oxo-pyrrolidino, 2-oxo-piperidino, 2-oxo-hexamethyleneimino, propanesultam-1-yl, butanesultam-1-yl, pentanesultam-1-yl, maleic acid imido, 2-methyl-maleic acid imido, 2-phenyl-maleic acid imido, 2,3-dimethyl-maleic acid imido, 3-methyl-2-phenyl-maleic acid imido, 2,3-diphenyl-maleic acid imido, piperidin-2-yl, piperidin-2-on-1-yl, quinolin-2-yl, isoquinolin-1-yl, isoquinolin-3-yl, pyridin-2-yl, benzimidazol-2-yl,

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1-methyl-benzimidazol-2-yl, 1-ethyl-benzimidazol-2-yl, 1-n-propyl-benzimidazol-2-yl, 1-isopropyl-benzimidazol-2-yl, 1-n-butyl-benzimidazol-2-yl, 1-isobutyl-benzimidazol-2-yl, 1-n-pentyl-benzimidazol-2-yl, 1-n-hexyl-benzimidazol-2-yl, 1-cyclopropyl-benzimidazol-2-yl, 1-cyclobutyl-benzimidazol-2-yl, 1-cyclopentyl-benzimidazol-2-yl, 1-cyclohexyl-benzimidazol-2-yl, 5-fluoro-1-methyl-benzimidazol-2-yl, 6-fluoro-1-methyl-benzimidazol-2-yl, 5-trifluoromethyl-benzimidazol-2-yl, 5-trifluoromethyl-1-methyl-benzimidazol-2-yl, imidazo[1,2-a]pyridin-2-yl, 5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl, 3-chloro-5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl,imidazo[1,2-a]pyrimidin-2-yl, imidazo[4,5-b]pyridin-2-yl, imidazo[4,5-c]pyridin-2-yl, imidazo[2,1-b]thiazol-6-yl, imidazo[1,2-c]pyrimidin-2-yl, imidazo[1,2-a]pyrazin-2-yl, imidazo[1,2-b]pyridazin-2-yl, imidazo[4,5-c]pyridin-2-yl, purin-8-yl, imidazo[4,5-b]pyrazin-2-yl, imidazo[4,5-c]pyridazin-2-yl, imidazo[4,5-d]pyridazin-2-yl, aminocarbonylamino, methylaminocarbonylamino, dimethylaminocarbonylamino, N-methylaminocarbonyl-methylamino, N-(dimethylaminocarbonyl)-methylamino, N-dimethylaminocarbonyl-ethylamino, N-dimethylaminocarbonylisopropylamino, N-(dimethylaminocarbonyl)-n-pentylamino, N-methylaminocarbonylethylamino, N-methylaminocarbonyl-n-pentylamino, N-methylaminocarbonyl-n-hexylamino, N-methylaminocarbonyl-n-octylamino, N-methylaminocarbonyl-cyclohexylamino, ethylamino-carbonylamino, N-ethylaminocarbonyl-methylamino, N-ethylaminocarbonyl-ethylamino, N-ethylaminocarbonyl-n-hexylamino, N-ethylaminocarbonyl-n-heptylamino, N-ethylaminocarbonyl-cyclohexylamino, diethylaminocarbonylamino, N-(diethylaminocarbonyl)-methylamino, N-(diethylaminocarbonyl)-ethylamino, N-(diethylaminocarbonyl)-n-butylamino, N-(diethylaminocarbonyl)-n-hexylamino, N-

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(diethylaminocarbonyl)-n-octylamino, isopropylaminocarbonylamino, N-isopropylaminocarbonyl-methylamino, n-butylaminocarbonylamino, N-(n-butyl-aminocarbonyl)-methylamino, N-(n-butylaminocarbonyl)-ethylamino, N-(n-butylaminocarbonyl)-isopropylamino, N-(n-butylaminocarbonyl)-n-butylamino, N-(n-butylaminocarbonyl)-n-hexylamino, N-(n-butylaminocarbonyl)-cyclohexylamino, N-(di-(n-butyl)-aminocarbonyl)-amino, N-(di-(n-butyl)-aminocarbonyl)-methylamino, N-(di-(n-butyl)-aminocarbonyl)-ethylamino, N-(di-(n-butyl)-aminocarbonyl)-n-butylamino, N-(di-(n-butyl)-aminocarbonyl)-n-hexylamino, N-(n-pentylaminocarbonyl)-methylamino, N-(n-pentylaminocarbonyl)-ethylamino, N-(n-hexylaminocarbonyl)-ethylamino, n-hexylaminocarbonylamino, n-heptylaminocarbonylamino, n-octylaminocarbonylamino, N-(n-hexylaminocarbonyl)-n-butylamino, N-(n-hexylaminocarbonyl)-n-pentylamino, N-(n-hexylaminocarbonyl)-n-hexylamino, N-(n-hexylaminocarbonyl)-cyclohexylamino, di-(n-hexyl)-aminocarbonylamino, N-(di-(n-hexyl)-aminocarbonyl)-methylamino, N-((n-hexyl)-methylaminocarbonyl)-amino, cyclohexylaminocarbonylamino, N-cyclohexylaminocarbonyl-methylamino, N-cyclohexylaminocarbonyl-ethylamino, N-cyclohexylaminocarbonyl-n-butylamino, N-cyclohexylaminocarbonyl-isobutylamino, N-cyclohexylaminocarbonyl-n-pentylamino, N-cyclohexylaminocarbonyl-n-hexylamino, N-cyclohexylaminocarbonyl-cyclohexylamino, N-(ethyl-cyclohexylaminocarbonyl)-methylamino, N-(propyl-cyclohexylaminocarbonyl)-methylamino, N-(n-butyl-cyclohexylaminocarbonyl)-methylamino, allylaminocarbonylamino, benzylaminocarbonylamino, N-benzylaminocarbonyl-isobutylamino, phenylaminocarbonylamino, pyrrolidinocarbonylamino, pyrrolidinocarbonyl-methylamino, piperidinocarbonylamino,

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hexamethyleneiminocarbonylamino, morpholinocarbonylamino, 3,4,5,6-tetrahydro-2-pyrimidon-1-yl, 3-methyl-3,4,5,6-tetrahydro-2-pyrimidon-1-yl, 3-ethyl-3,4,5,6-tetrahydro-2-pyrimidon-1-yl, 3-n-propyl-3,4,5,6-tetrahydro-2-pyrimidon-1-yl, 3-isopropyl-3,4,5,6-tetrahydro-2-pyrimidon-1-yl, 3-n-butyl-3,4,5,6-tetrahydro-2-pyrimidon-1-yl, 3-isobutyl-3,4,5,6-tetrahydro-2-pyrimidon-1-yl, 3-n-pentyl-3,4,5,6-tetrahydro-2-pyrimidon-1-yl, 3-n-hexyl-3,4,5,6-tetrahydro-2-pyrimidon-1-yl, 3-cyclopentyl-3,4,5,6-tetrahydro-2-pyrimidon-1-yl, 3-cyclohexyl-3,4,5,6-tetrahydro-2-pyrimidon-1-yl, 3-cycloheptyl-3,4,5,6-tetrahydro-2-pyrimidon-1-yl, 3-benzyl-3,4,5,6-tetrahydro-2-pyrimidon-1-yl, 3,4,5,6-tetrahydro-2(1H)-pyrimidon-1-yl, 3-methyl-3,4,5,6-tetrahydro-2(1H)-pyrimidon-1-yl, 3-ethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidon-1-yl, 3-n-propyl-3,4,5,6-tetrahydro-2(1H)-pyrimidon-1-yl, 3-isopropyl-3,4,5,6-tetrahydro-2(1H)-pyrimidon-1-yl, 3-benzyl-3,4,5,6-tetrahydro-2(1H)-pyrimidon-1-yl, 3-(2-phenylethyl)-3,4,5,6-tetrahydro-2(1H)-pyrimidon-1-yl or 3-(3-phenylpropyl)-3,4,5,6-tetrahydro-2(1H)-pyrimidon-1-yl group,

R_3 may denote a methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert.butyl, n-pentyl, 1-methyl-butyl, 2-methyl-butyl, 3-methyl-butyl, cyclopropyl, cyclobutyl, cyclopentyl, methoxy, ethoxy, n-propoxy or isopropoxy group and

R_4 may denote a hydroxycarbonyl, methoxycarbonyl, ethoxycarbonyl, n-propyloxycarbonyl, isopropyloxycarbonyl, n-butyloxycarbonyl, isobutyloxycarbonyl, tert.butyloxycarbonyl, n-pentyloxycarbonyl, isoamyloxycarbonyl, n-hexyloxycarbonyl, cyclopentyloxycarbonyl, cyclohexyloxycarbonyl, benzyloxycarbonyl, 1-phenylethyloxycarbonyl, 2-phenylethyloxycarbonyl, 3-

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phenylpropyloxycarbonyl, methoxymethoxycarbonyl, cinnamyloxycarbonyl, acetoxymethoxycarbonyl, propionyloxymethoxycarbonyl, n-butyryloxymethoxycarbonyl, isobutyryloxymethoxycarbonyl, n-pentanoyloxymethoxycarbonyl, isopentanoyloxymethoxycarbonyl, pivaloyloxymethoxycarbonyl, n-hexanoyloxymethoxycarbonyl, cyclopentanoyloxymethoxycarbonyl, cyclohexanoyloxymethoxycarbonyl, phenylacetoxymethoxycarbonyl, 2-phenylpropionyloxymethoxycarbonyl, 3-phenylpropionyloxymethoxycarbonyl, 4-phenylbutyryloxymethoxycarbonyl, benzoyloxymethoxycarbonyl, 1-acetoxyethoxycarbonyl, 1-propionyloxyethoxycarbonyl, 1-n-butyryloxyethoxycarbonyl, 1-isobutyryloxyethoxycarbonyl, 1-n-pentanoyloxyethoxycarbonyl, 1-isopentanoyloxyethoxycarbonyl, 1-pivaloyloxyethoxycarbonyl, 1-n-hexanoyloxyethoxycarbonyl, 1-cyclopentanoyloxyethoxycarbonyl, 1-cyclohexanoyloxyethoxycarbonyl, 1-phenylacetoxyethoxycarbonyl, 1-(1-phenylpropionyloxy)-ethoxycarbonyl, 1-(2-phenylpropionyloxy)-ethoxycarbonyl, 1-(3-phenylbutyryloxy)-ethoxycarbonyl, 1-benzoyloxyethoxycarbonyl, methoxycarbonyloxymethoxycarbonyl, ethoxycarbonyloxymethoxycarbonyl, n-propyloxycarbonyloxymethoxycarbonyl, isopropyloxycarbonyloxymethoxycarbonyl, n-butyloxycarbonyloxymethoxycarbonyl, isobutyloxycarbonyloxymethoxycarbonyl, tert.butyloxycarbonyloxymethoxycarbonyl, n-pentyloxycarbonyloxymethoxycarbonyl, isoamyloxycarbonyloxymethoxycarbonyl, n-hexyloxycarbonyloxymethoxycarbonyl, cyclopentyloxycarbonyloxymethoxycarbonyl, cyclohexyloxycarbonyloxymethoxycarbonyl, benzyloxycarbonyloxymethoxycarbonyl, 1-phenylethoxycarbonyloxymethoxycarbonyl, 2-phenylethoxycarbonyloxymethoxycarbonyl, 3-phenylpropyloxycarbonyloxymethoxycarbonyl,

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cinnamyloxycarbonyloxymethoxycarbonyl, 1-(methoxycarbonyloxy)-ethoxycarbonyl, 1-(ethoxycarbonyloxy)-ethoxycarbonyl, 1-(n-propyloxycarbonyloxy)-ethoxycarbonyl, 1-(isopropyloxycarbonyloxy)-ethoxycarbonyl, 1-(n-butyloxycarbonyloxy)-ethoxycarbonyl, 1-(isobutyloxycarbonyloxy)-ethoxycarbonyl, 1-(tert.butyloxycarbonyloxy)-ethoxycarbonyl, 1-(n-pentyloxycarbonyloxy)-ethoxycarbonyl, 1-(isoamyloxycarbonyloxy)-ethoxycarbonyl, 1-(n-hexyloxycarbonyloxy)-ethoxycarbonyl, 1-(cyclopentyloxycarbonyloxy)-ethoxycarbonyl, 1-(cyclohexyloxycarbonyloxy)-ethoxycarbonyl, cyclopentylcarbonyloxymethoxycarbonyl, 1-(benzyloxycarbonyloxy)-ethoxycarbonyl, 1-(1-phenylethoxycarbonyloxy)-ethoxycarbonyl, 1-(2-phenylethoxycarbonyloxy)-ethoxycarbonyl, 1-(3-phenylpropyloxycarbonyloxy)-ethoxycarbonyl, 1-(cinnamyloxycarbonyloxy)-ethoxycarbonyl, cyano, 1H-tetrazolyl, 1-triphenylmethyl-tetrazolyl, 2-triphenylmethyl-tetrazolyl, 1-acetoxymethyl-tetrazolyl, 2-acetoxymethyl-tetrazolyl, 1-propionyloxymethyl-tetrazolyl, 2-propionyloxymethyl-tetrazolyl, 1-butyryloxymethyl-tetrazolyl, 2-butyryloxymethyl-1-isobutyl, 1-isobutyryloxymethyl-tetrazolyl, 2-isobutyryloxymethyl-tetrazolyl, 1-pivaloyloxymethyl-tetrazolyl, 2-pivaloyloxymethyl-tetrazolyl, 1-ethoxycarbonyloxymethyl-tetrazolyl, 2-ethoxycarbonyloxymethyl-tetrazolyl, 1-[1-(ethoxycarbonyloxy)-ethyl]-tetrazolyl, 2-[1-(ethoxycarbonyloxy)-ethyl]-tetrazolyl, 1-[1-(cyclohexyloxycarbonyloxy)-ethyl]-tetrazolyl or 2-[1-(cyclohexyloxycarbonyloxy)-ethyl]-tetrazolyl group.

Particularly preferred compounds of general formula I above are those wherein

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R_1 denotes a hydrogen atom or in the 4-position a chlorine atom, a C_{1-3}-alkyl group or a trifluoromethyl group,

R_2 denotes a phthalimino or homophthalimino group, whilst a carbonyl group in a phthalimino group may be replaced by a methylene group,

a 5-, 6- or 7-membered alkyleneimino group in which a methylene group is replaced by a carbonyl or sulphonyl group,

a maleic acid imido group optionally mono- or disubstituted by a methyl or phenyl group, whilst the substituents may be identical or different,

a benzimidazol-2-yl or 4,5,6,7-tetrahydro-benzimidazol-2-yl group optionally substituted in the 1-position by a C_{1-6}-alkyl group or by a cycloalkyl group (whilst the phenyl nucleus of one of the above-mentioned benzimidazole groups may additionally be substituted by a fluorine atom or a methyl or trifluoromethyl group), an imidazo[2,1-b]thiazol-6-yl, imidazo[1,2-a]pyridin-2-yl, 5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl, 3-chloro-5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyrimidin-2-yl, imidazo[4,5-b]pyridin-2-yl, imidazo[4,5-c]pyridin-2-yl, imidazo[1,2-c]pyrimidin-2-yl, imidazo[1,2-a]pyrazin-2-yl, imidazo[1,2-b]pyridazin-2-yl, imidazo[4,5-c]pyridin-2-yl, purin-8-yl, imidazo[4,5-b]pyrazin-2-yl, imidazo[4,5-c]pyridazin-2-yl or imidazo[4,5-d]pyridazin-2-yl group or

an R_7-NR_6-CO-NR_5- group wherein

R_5 denotes a hydrogen atom, a C_{1-5}-alkyl group, a cyclohexyl or benzyl group,

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R_6 denotes a hydrogen atom, a C_{1-6}-alkyl group, an allyl, cyclohexyl, benzyl or phenyl group,

R_7 denotes a hydrogen atom or a C_{1-3}-alkyl group or

R_6 and R_7 together with the nitrogen atom between them denote a straight-chained C_{4-6}-alkyleneimino group or a morpholino group or

R_5 and R_6 together denote a C_{2-3}-alkylene group,

R_3 denotes a C_{1-5}-alkyl group, a C_{3-5}-cycloalkyl group or a C_{2-3}-alkoxy group and

R_4 denotes a tetrazolyl group substituted in the 1- or 2-position by an R_a-CO-O-CH_2- group, or an R_b-CO-O-(R_cCH)-O-CO-, R_aO-CO- or R_bO-CO-O-(R_cCH)-O-CO- group, wherein

R_a denotes a straight-chained or branched C_{1-6}-alkyl group, a C_{5-7}-cycloalkyl group, a benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, methoxymethyl or cinnamyl group,

R_b denotes a straight-chained or branched C_{1-6}-alkyl group, a C_{5-7}-cycloalkyl group, a phenyl, benzyl, 1-phenylethyl, 2-phenylethyl or 3-phenylpropyl group and

R_c denotes a hydrogen atom or a methyl group,

or, if

(i) R_1 and R_2 are as hereinbefore defined and R_3 denotes an alkoxy group, R_4 may denote a carboxy, 1H-tetrazolyl or 2H-tetrazolyl group or, if

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(ii) R_1 is as hereinbefore defined, R_2 has the meanings given hereinbefore with the exception of the 1-methyl-benzimidazol-2-yl group and R_3 denotes a cyclopropyl group, R_4 may represent a carboxy group or, if

(iii) R_1 and R_3 are as hereinbefore defined and R_2 denotes a butanesultam-1-yl group, R_4 may denote a carboxy group or, if

(iv) R_1 is as hereinbefore defined, R_2 denotes a 1-methyl-5-fluoro-benzimidazol-2-yl group and R_3 denotes an ethyl group, R_4 may represent a carboxy, 1H-tetrazolyl or 2H-tetrazolyl group,

the tautomers and the salts thereof.

Particularly preferred compounds of general formula I above are those wherein

R_1 denotes a hydrogen atom or in the 4-position a methyl group,

R_2 denotes an imidazo[1,2-a]pyridin-2-yl, 5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl, 3-chloro-5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl, 1-methyl-benzimidazol-2-yl, 1-methyl-5-fluoro-benzimidazol-2-yl or butanesultam-1-yl group,

R_3 denotes a C_{2-4}-alkyl group, a cyclopropyl group or a C_{2-3}-alkoxy group and

R_4 denotes a tetrazolyl group substituted in the 1- or 2-position by an R_a-CO-O-CH_2- group, or an R_b-CO-O-(R_cCH)-O-CO-, R_aO-CO- or R_bO-CO-O-(R_cCH)-O-CO- group, whilst

R_a denotes a straight-chained or branched C_{1-6}-alkyl

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group, a C_{5-7}-cycloalkyl group, a benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, methoxymethyl or cinnamyl group,

R_b denotes a straight-chained or branched C_{1-6}-alkyl group, a C_{5-7}-cycloalkyl group, a phenyl, benzyl, 1-phenylethyl, 2-phenylethyl or 3-phenylpropyl group and

R_c denotes a hydrogen atom or a methyl group,

and the compounds

4'-[(2-cyclopropyl-4-methyl-6-(4,5,6,7-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid,

4'-[(2-ethoxy-4-methyl-6-(4,5,6,7-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid,

4'-[(2-ethoxy-4-methyl-6-(4,5,6,7-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl,

4'-[(2-cyclopropyl-4-methyl-6-(imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid,

4'-[(2-ethoxy-4-methyl-6-(imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid,

4'-[(2-ethoxy-4-methyl-6-(imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl,

4'-[(2-ethoxy-4-methyl-6-(1-methyl-benzimidazol-2-yl)-

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benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl,

4'-[(2-ethyl-4-methyl-6-(1-methyl-5-fluoro-benzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl,

4'-[(2-ethyl-4-methyl-6-(1-methyl-5-fluoro-benzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid and

4'-[(2-n-propyl-4-methyl-6-(butanesultam-1-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid,

the tautomers and the salts thereof.

The following compounds are particularly preferred:

4'-[(2-ethyl-4-methyl-6-(1-methyl-5-fluoro-benzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid,

4'-[(2-n-propyl-4-methyl-6-(butanesultam-1-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid,

4'-[(2-cyclopropyl-4-methyl-6-(imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid,

4'-[(2-cyclopropyl-4-methyl-6-(5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid and

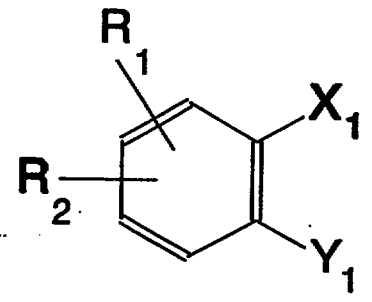
4'-[(2-ethoxy-4-methyl-6-(1-methyl-benzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl,

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the tautomers and the salts thereof.

According to the invention, the compounds are obtained by the following methods:

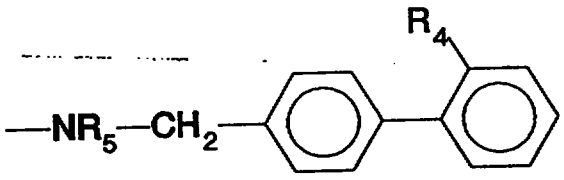
a) cyclising a compound of general formula



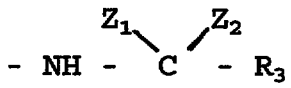
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(II)

optionally formed in the reaction mixture, wherein
R_1 and R_2 are as hereinbefore defined,
one of the groups X_1 or Y_1 represents a group of general formula



and the other group X_1 or Y_1 represents a group of general formula



wherein
R_3 and R_4 are as hereinbefore defined,
R_5 represents a hydrogen atom or an R_3CO- group, wherein
R_3 is as hereinbefore defined,
Z_1 and Z_2, which may be identical or different, represent amino, or hydroxy or mercapto groups optionally substituted by C_{1-6}-alkyl groups or
Z_1 and Z_2 together represent an oxygen or sulphur atom, an imino group optionally substituted by a C_{1-3}-alkyl

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group, or an alkylenedioxy or alkylenedithio group each having 2 or 3 carbon atoms.

The cyclisation is conveniently carried out in a solvent or mixture of solvents such as ethanol, isopropanol, glacial acetic acid, benzene, chlorobenzene, toluene, xylene, glycol, glycolmonomethylether, diethyleneglycol dimethylether, sulpholane, dimethylformamide, tetralin or in an excess of the acylating agent used to prepare the compound of general formula II, e.g. in the corresponding nitrile, anhydride, acid halide, ester or amide, e.g. at temperatures between 0 and 250°C, but preferably at the boiling temperature of the reaction mixture, optionally in the presence of a condensing agent such as phosphorusoxychloride, thionylchloride, sulphurylchloride, sulphuric acid, p-toluenesulphonic acid, methanesulphonic acid, hydrochloric acid, phosphoric acid, polyphosphoric acid, acetic anhydride or optionally in the presence of a base such as potassium ethoxide or potassium tert.-butoxide. However, the cyclisation may also be carried out without a solvent and/or condensing agent.

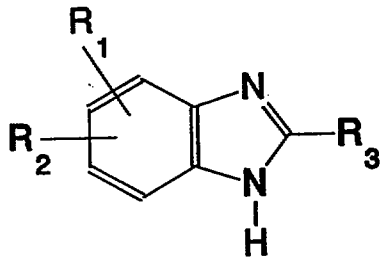
However, it is particularly advantageous to carry out the reaction by preparing a compound of general formula II in the reaction mixture by reducing a corresponding o-nitro-amino compound, optionally in the presence of a carboxylic acid of general formula R_3COOH, or by acylation of a corresponding o-diamino compound. When the reduction of the nitro group is broken off at the hydroxylamine stage, the N-oxide of a compound of general formula I is obtained in the subsequent cyclisation. The resulting N-oxide is then converted by reduction into a corresponding compound of general formula I.

The subsequent reduction of the N-oxide of formula I

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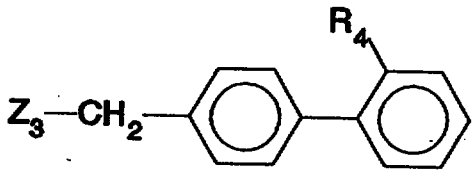
obtained is preferably carried out in a solvent such as water, water/ethanol, methanol, glacial acetic acid, ethyl acetate or dimethylformamide with hydrogen in the presence of a hydrogenation catalyst such as Raney nickel, platinum or palladium/charcoal, with metals such as iron, tin or zinc in the presence of an acid such as acetic acid, hydrochloric acid or sulphuric acid, with salts such as iron(II)sulphate, tin(II)chloride or sodium dithionite, or with hydrazine in the presence of Raney nickel, at temperatures between 0 and 50°C, but preferably at ambient temperature.

b) Reaction of a benzimidazole of general formula



(III)

wherein
R_1 to R_3 are defined as hereinbefore, with a biphenyl compound of general formula



(IV)

wherein
R_4 is defined as hereinbefore and
Z_3 represents a nucleophilic leaving group such as a halogen atom, e.g. a chlorine, bromine or iodine atom, or a substituted sulphonyloxy group, e.g. a

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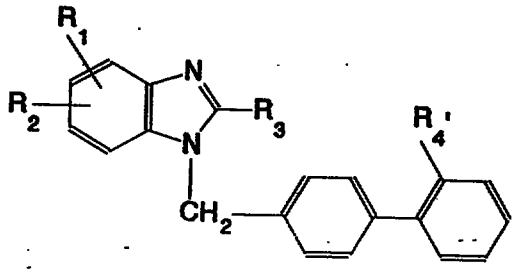
methanesulphonyloxy, phenylsulphonyloxy or p-toluenesulphonyloxy group.

The reaction is conveniently carried out in a solvent or mixture of solvents such as methylene chloride, diethylether, tetrahydrofuran, dioxane, dimethyl-sulphoxide, dimethylformamide or benzene, optionally in the presence of an acid binding agent such as sodium carbonate, potassium carbonate, sodium hydroxide, potassium tert.-butoxide, sodium hydride, triethylamine or pyridine, whilst the latter two may simultaneously also be used as solvent, preferably at temperatures between 0 and 100°C, e.g. at temperatures between ambient temperature and 50°C.

In the reaction, a mixture of the 1- and 3- isomers is preferably obtained which can if desired subsequently be resolved into the corresponding 1- and 3- isomers, by crystallisation or chromatography using a substrate such as silica gel or aluminium oxide.

c) In order to prepare a compound of general formula I wherein R_4 represents a carboxy group:

Converting a compound of general formula



(V)

wherein
R_1 to R_3 are defined as hereinbefore, and
R_4' represents a group which may be converted into a carboxy group by hydrolysis, thermolysis or

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hydrogenolysis.

For example, functional derivatives of the carboxy group such as the unsubstituted or substituted amides, esters, thiolesters, orthoesters, iminoethers, amidines or anhydrides, the nitrile group or the tetrazolyl group may be converted by hydrolysis into a carboxy group, esters with tertiary alcohols, e.g. the tert.butylester, may be converted by thermolysis into a carboxy group and esters with aralkanols, e.g. the benzylester, may be converted by hydrogenolysis into a carboxy group.

The hydrolysis is appropriately carried out either in the presence of an acid such as hydrochloric acid, sulphuric acid, phosphoric acid, trichloroacetic acid or trifluoroacetic acid or in the presence of a base such as sodium hydroxide or potassium hydroxide, in a suitable solvent such as water, water/methanol, ethanol, water/ethanol, water/isopropanol, water/dioxane, methylene chloride or chloroform, at temperatures between -10°C and 120°C, e.g. at temperatures between ambient temperature and the boiling temperature of the reaction mixture. When hydrolysis is carried out in the presence of an organic acid such as trichloroacetic acid or trifluoroacetic acid, any alcoholic hydroxy groups present may simultaneously be converted into a corresponding acyloxy group such as the trifluoroacetoxy group.

If R_4' in a compound of general formula V represents a cyano or aminocarbonyl group, these groups may also be converted into a carboxy group with a nitrite, e.g. sodium nitrite, in the presence of an acid such as sulphuric acid, which may simultaneously also be used as solvent, at temperatures between 0 and 50°C.

If R_4' in a compound of general formula V represents for example a tert.-butyloxycarbonyl group, the tert.-butyl

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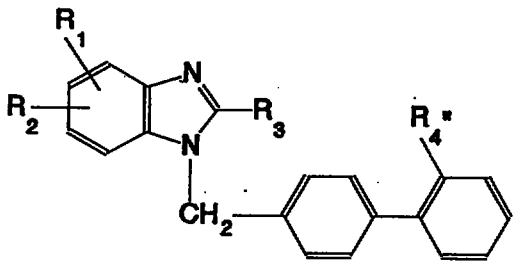
group may also be thermally cleaved, optionally in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran or dioxane and preferably in the presence of a catalytic amount of an acid such as p-toluenesulphonic acid, sulphuric acid, phosphoric acid or polyphosphoric acid, preferably at the boiling temperature of the solvent used, e.g. at temperatures between 40°C and 100°C.

If R_4' in a compound of general formula V represents, for example, a benzyloxycarbonyl groupthe benzyl group may also be hydrogenolytically cleaved in the presence of a hydrogenation catalyst such as palladium/charcoal, in a suitable solvent such as methanol, ethanol, ethanol/water, glacial acetic acid, ethyl acetate, dioxane or dimethylformamide, preferably at temperatures between 0 and 50°C, e.g. at ambient temperature, under a hydrogen pressure of 1 to 5 bar. During hydrogenolysis, other groups may be reduced at the same time, e.g. a nitro group may be reduced to an amino group, a benzyloxy group to a hydroxy group, a vinylidene group to the corresponding alkylidene group or a cinnamic acid group to the corresponding phenyl-propionic acid group, or they may be replaced by hydrogen atoms, e.g. a halogen atom may be replaced by a hydrogen atom.

d) In order to prepare a compound of general formula I wherein R_4 represents a 1H-tetrazolyl group:

Cleaving a protecting group from a compound of general formula

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(VI)

wherein
R_1, R_2 and R_3 are defined as hereinbefore and
R_4" represents a 1H-tetrazolyl group protected in the 1- or 3-position by a protecting group.

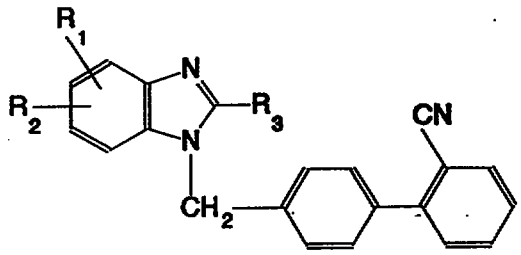
Suitable protecting groups include, for example, the triphenylmethyl, tributyl tin or triphenyl tin groups.

The cleaving of a protecting group used is preferably carried out in the presence of a hydrohalic acid, preferably in the presence of hydrochloric acid, in the presence of a base such as sodium hydroxide or alcoholic ammonia, in a suitable solvent such as methylene chloride, methanol, methanol/ammonia, ethanol or isopropanol, at temperatures between 0 and 100°C, but preferably at ambient temperature or, if the reaction is carried out in the presence of alcoholic ammonia, at elevated temperatures, e.g. at temperatures between 100 and 150°C, preferably at temperatures between 120 and 140°C.

e) In order to prepare a compound of general formula I wherein R_4 represents a 1H-tetrazolyl group:

Reaction of a compound of general formula

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(VII)

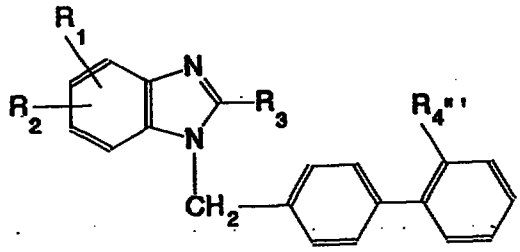
wherein
R_1 to R_3 are defined as hereinbefore, with hydrazoic acid or the salts thereof.

The reaction is preferably carried out in a solvent such as benzene, toluene or dimethylformamide, at temperatures between 80 and 150°C, preferably at 125°C. Advantageously, either the hydrazoic acid is liberated during the reaction from an alkali metal azide, e.g. from sodium azide, in the presence of a weak acid such as ammonium chloride, or the tetrazolide salt obtained in the reaction mixture by reacting with a salt of hydrazoic acid, preferably with aluminium azide or tributyl tin azide, which are also conveniently prepared in the reaction mixture by reacting aluminium chloride or tributyl tin chloride with an alkali metal azide such as sodium azide, is subsequently liberated by acidification with a dilute acid such as 2N hydrochloric acid or 2N sulphuric acid.

f) In order to prepare a compound of general formula I wherein R_4 denotes a tetrazolyl group substituted in the 1- or 2-position by an R_a-CO-O-CH_2- group, or it denotes an R_aO-CO-, R_b-CO-O-(R_cCH)-O-CO- or R_bO-CO-O-(R_cCH)-O-CO- group:

Reacting a compound of general formula

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(VIII)

wherein
R_1 to R_3 are as hereinbefore defined and
R_4"' denotes a carboxy, 1H-tetrazolyl or 2H-tetrazolyl group, with a compound of general formula

$$Z_4 - Y_2 \qquad \text{(IX)}$$

wherein
Y_2 denotes an R_a-CO-O-CH_2-, R_b-CO-O-(R_cCH)-, R_bO-CO-O-(R_cCH)- or R_a- group, wherein R_a to R_c are as hereinbefore defined and
Z_4 denotes a nucleophilic leaving group such as a halogen atom, e.g. a chlorine or bromine atom, or, if Y denotes an R_a- group, Z_4 may also represent a hydroxy group.

The reaction is conveniently carried out by esterification with a corresponding alcohol or with a corresponding reactive derivative such as the halide, conveniently in a solvent or mixture of solvents such as water, methylene chloride, chloroform, ether, tetrahydrofuran, dioxane or dimethylformamide or in an excess of the acylating agent as solvent, optionally in the presence of an acid activating or dehydrating agent such as thionylchloride, with the anhydrides, esters or halides thereof optionally in the presence of an inorganic or tertiary organic base such as sodium hydroxide, potassium carbonate, triethylamine or pyridine, whilst the latter two may simultaneously be used as solvent, at temperatures between -25 and 100°C,

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but preferably at temperatures between -10 and 80°C.

In the reactions described hereinbefore, any reactive groups present such as hydroxy or imino groups may be protected during the reaction by means of conventional protecting groups which are split off again after the reaction.

By way of example, protecting groups for a hydroxy group may include a trimethylsilyl, acetyl, benzoyl, methyl, ethyl, tert.butyl, benzyl or tetrahydropyranyl group and protecting groups for an imino group may include an acetyl, benzoyl, ethoxycarbonyl or benzyl group.

The optional subsequent cleaving of a protecting group used is preferably carried out by hydrolysis in an aqueous solvent, e.g. in water, isopropanol/water, tetrahydrofuran/water or dioxane/water, in the presence of an acid such as hydrochloric acid or sulphuric acid or in the presence of an alkali metal base such as sodium hydroxide or potassium hydroxide, at temperatures between 0 and 100°C, preferably at the boiling temperature of the reaction mixture. However, a benzyl group is preferably cleaved by hydrogenolysis, e.g. with hydrogen in the presence of a catalyst such as palladium/charcoal, in a solvent such as methanol, ethanol, ethyl acetate or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid, at temperatures between 0 and 50°C, but preferably at ambient temperature, and under a hydrogen pressure of from 1 to 7 bar, but preferably from 3 to 5 bar.

An isomer mixture of a compound of general formula I thus obtained may if desired be resolved by chromatography using a substrate such as silica gel or aluminium oxide.

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Moreover, the compounds of general formula I obtained may be converted into the acid addition salts thereof, more particularly for pharmaceutical use into the physiologically acceptable salts thereof with inorganic or organic acids. Suitable acids for this purpose include hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid.

Furthermore, the new compounds of general formula I thus obtained, if they contain a carboxy or 1H-tetrazolyl group, may if desired subsequently be converted into the salts thereof with inorganic or organic bases, more particularly for pharmaceutical use into the physiologically acceptable salts thereof. Suitable bases include for example sodium hydroxide, potassium hydroxide, cyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

The compounds of general formulae II to IX used as starting materials are known from the literature in some cases or may be obtained by methods known from the literature.

Thus, for example, a compound of general formula II is obtained by alkylation of a corresponding o-amino-acylamino compound with a compound of general formula IV. The o-amino-acylamino compound required for this is obtained by reduction of a corresponding o-nitro-acylamino compound which is in turn obtained by nitration of a corresponding acylamino-acetophenone, subsequent conversion of the resulting corresponding o-nitro-acylamino-acetophenone into the corresponding ω-bromo-acetophenone, subsequent cyclisation of the ω-bromo-acetophenone with a corresponding acid amide and subsequent reduction of the nitro group. Before the reduction of the nitro group, an oxazol-4-yl compound thus obtained may be converted into the corresponding

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imidazol-4-yl compound by means of a corresponding amine, preferably with ammonia, under pressure, or an imidazol-4-yl compound unsubstituted in the 1-position obtained in this way may be converted by alkylation into a corresponding imidazol-4-yl compound alkylated in the 1-position.

A starting compound of general formula III is obtained by reduction and cyclisation of an o-nitro-acylamino compound as described hereinbefore.

A starting compound of general formulae V, VI, VII and VIII is obtained by reacting a compound of general formula III with a corresponding compound of general formula IV.

The new compounds of general formula I and the physiologically acceptable salts thereof have valuable pharmacological properties. They are angiotensin-antagonists, particularly angiotensin-II-antagonists.

By way of example, the following compounds

A = 4'-[(2-ethyl-4-methyl-6-(1-methyl-5-fluoro-benzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid,

B = 4'-[(2-n-propyl-4-methyl-6-(butanesultam-1-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid,

C = 4'-[(2-cyclopropyl-4-methyl-6-(imidazo[1,2-a]-pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid,

D = 4'-[(2-cyclopropyl-4-methyl-6-(5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid and

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E = 4'-[(2-ethoxy-4-methyl-6-(1-methyl-benzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl,

were investigated for their biological activities as follows:

Description of method: angiotensin-II-receptor binding

The tissue (rat's lung) is homogenised in Tris buffer (50 mMol Tris, 150 mMol NaCl, 5 mMol EDTA, pH 7.40) and centrifuged twice for 20 minutes each time at 20,000 x g. The finished pellet is resuspended in incubation buffer (50 mMol Tris, 5 mMol $MgCl_2$, 0.2% BSA, pH 7.40) 1:75, based on the moist weight of the tissue. Each 0.1 ml of homogenate is incubated for 60 minutes at 37°C with 50 pM [^{125}I]-angiotensin-II (NEN, Dreieich, FRG) and increasing concentrations of the test substance in a total volume of 0.25 ml. The incubation is ended by rapid filtration through glass fibre filter mats. The filters are each washed with 4 ml of ice cold buffer (25 mMol Tris, 2.5 mMol $MgCl_2$, 0.1% BSA, pH 7.40). The bound radioactivity is measured in a gamma-counter. The corresponding IC_{50} value is determined from the dosage-activity curve.

Substances A to E show the following IC_{50} values in the test described:

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Substance	IC_{50} [nM]
A	7.4
B	0.9
C	1.7
D	1.3
E	3.3

In view of their pharmacological properties, the new compounds and the physiologically acceptable salts thereof are suitable for the treatment of hypertension and cardiac insufficiency and also for treating ischaemic peripheral circulatory disorders, myocardial ischaemia (angina), for the prevention of the progression of cardiac insufficiency after myocardial infarct and for treating diabetic nephropathy, glaucoma, gastrointestinal diseases and bladder diseases.

Furthermore, the new compounds and the physiologically acceptable salts thereof are suitable for treating pulmonary diseases, e.g. lung oedema and chronic bronchitis, for preventing arterial re-stenosis after angioplasty, for preventing thickening of the vascular walls after vascular operations, arteriosclerosis and diabetic angiopathy. Because of the effect of angiotensin on the release of acetylcholine and dopamine in the brain, the new angiotensin antagonists are also suitable for alleviating central nervous system disorders, e.g. depression, Alzheimer's disease, Parkinson's syndrome and bulimia, as well as disorders of cognitive functions.

The dosage required to achieve these effects in adults is appropriately, when administered intravenously, 0.5 to 100 mg, preferably 1 to 70 mg, and, when administered orally, 0.1 to 200 mg, preferably 1 to 100 mg, 1 to 3 times a day. For this purpose, the compounds of general formula I prepared according to the invention,

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optionally in conjunction with other active substances such as, for example, hypotensive agents, ACE inhibitors, diuretics and/or calcium antagonists, may be incorporated together with one or more inert conventional carriers and/or diluents, e.g. with corn starch, lactose, glucose, micro-crystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethyleneglycol, propylene-glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof, in conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions or suppositories.

Examples of additional active substances which may be used in the combinations mentioned above include bendroflumethiazide, chlorothiazide, hydrochlorothiazide, spironolactone, benzothiazide, cyclothiazide, ethacrinic acid, furosemide, metoprolol, prazosin, atenolol, propranolol, (di)hydralazine-hydrochloride, diltiazem, felodipine, nicardipine, nifedipine, nisoldipine, nitrendipine, captopril, enalapril, lisinopril, cilazapril, quinapril, fosinopril and ramipril. The dosage of these active substances is conveniently 1/5 of the lowest dose normally recommended up to 1/1 of the normally recommended dosage, that is for example 15 to 200 mg of hydrochlorothiazide, 125 to 2000 mg of chlorothiazide, 15 to 200 mg of ethacrinic acid, 5 to 80 mg of furosemide, 20 to 480 mg of propranolol, 5 to 60 mg of felodipine, 5 to 60 mg of nifedipine or 5 to 60 mg of nitrendipine.

The following Examples are intended to illustrate the invention:

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Example 1

4'-[(2-Ethyl-4-methyl-6-(1-methyl-5-fluoro-benzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid

a) 2-Ethyl-4-methyl-6-(1-methyl-5-fluoro-benzimidazol-2-yl)-benzimidazole

A mixture of 4.5 g (21 mMol) of 1-methylamino-2-amino-4-fluoro-benzene-dihydrochloride and 4.3 g (21 mMol) of 2-ethyl-4-methyl-benzimidazol-6-yl-carboxylic acid is stirred for four hours at 140°C in 100 g of polyphosphoric acid, then stirred into about 300 g of ice water and made alkaline with concentrated ammonia solution. The crude product precipitated is suction filtered, dried and then purified by column chromatography (300 g of silica gel; methylene chloride/ethanol = 95:5).
Yield: 3.1 g (48% of theory),
R_f value: 0.24 (silica gel; methylene chloride/ethanol = 19:1)

b) Tert.butyl 4'-[(2-ethyl-4-methyl-6-(1-methyl-5-fluoro-benzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylate

616 mg (5.5 mMol) of potassium tert.butoxide are added to a solution of 1.55 g (5 mMol) of 2-ethyl-4-methyl-6-(1-methyl-5-fluoro-benzimidazol-2-yl)-benzimidazole in 30 ml of dimethylsulphoxide and the resulting mixture is stirred for 15 minutes at ambient temperature. Then 1.9 g (5.5 mMol) of tert.butyl 4'-bromomethyl-biphenyl-2-carboxylate are added and stirring is continued for a further 20 hours at ambient temperature. The mixture is then stirred into about 80 ml of saturated sodium chloride solution, the crude product precipitated is suction filtered and purified by column chromatography (150 g silica gel; eluant: methylene chloride/ethanol =

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98:2).
Yield: 1.4 g (50% of theory),
R_f value: 0.47 (silica gel; methylene chloride/ethanol = 19:1)

c) 4'-[(2-Ethyl-4-methyl-6-(1-methyl-5-fluoro-benzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid

A solution of 1.4 g (2.4 mMol) of tert.butyl 4'-[(2-ethyl-4-methyl-6-(1-methyl-5-fluoro-benzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylate and 15 ml of trifluoroacetic acid in 30 ml of methylene chloride is stirred for 14 hours at ambient temperature, then concentrated by evaporation, the residue is mixed with about 30 ml of water and made alkaline with 2N sodium hydroxide solution. After extracting twice with 30 ml of diethyl ether, the aqueous phase is acidified with 20% citric acid. The crude product precipitated is suction filtered and purified by column chromatography (100 g silica gel; eluant: methylene chloride/ethanol = 96:4).
Yield: 850 mg (69% of theory),
Melting point: 246-248°C
$C_{32}H_{27}FN_4O_2$ (518.60)

Calculated:	C	74.11	H	5.25	N 10.80
Found:		73.95		5.34	10.80

Mass spectrum: m/e = 518

Example 2

4'-[(2-n-Propyl-4-methyl-6-(butanesultam-1-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid

Prepared analogously to Example 1 from tert.butyl 4'-[(2-n-propyl-4-methyl-6-(butanesultam-1-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylate and trifluoroacetic acid.
Yield: 87% of theory,

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Melting point: 269-271°C

$C_{29}H_{31}N_3O_4S$ (517.65)

Calculated: C 67.29 H 6.04 N 8.12

Found: 67.56 6.12 8.28

R_f value: 0.39 (silica gel; methylene chloride/ethanol = 9:1)

Mass spectrum: m/e = 517

Example 3

4'-[(2-Cyclopropyl-4-methyl-6-(imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid

---

Prepared analogously to Example 1 from tert.butyl 4'-[(2-cyclopropyl-4-methyl-6-(imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylate and trifluoroacetic acid.

Yield: 50% of theory,

Melting point: 245-248°C

$C_{32}H_{26}N_4O_2$ (498.59)

Calculated: C 77.09 H 5.26 N 11.24

Found: 76.88 5.37 11.30

R_f value: 0.63 (silica gel; methylene chloride/ethanol = 9:1)

Mass spectrum: m/e = 498

Example 4

4'-[(2-Cyclopropyl-4-methyl-6-(5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid

---

Prepared analogously to Example 1 from tert.butyl 4'-[(2-cyclopropyl-4-methyl-6-(5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylate and trifluoroacetic acid.

Yield: 53% of theory,

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Melting point: 310-312°C

$C_{32}H_{30}N_4O_2$ (502.62)

Calculated: C 76.47 H 6.02 N 11.15

Found: 76.23 5.97 10.85

R_f value: 0.17 (silica gel; methylene chloride/ethanol = 9:1)

Mass spectrum: m/e = 502

Example 5

4'-[(2-Ethyl-4-methyl-6-(1-methyl-5-fluoro-benzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

---

a) 4'-[(2-Ethyl-4-methyl-6-(1-methyl-5-fluoro-benzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-2-cyano-biphenyl

616 mg (5.5 mMol) of potassium tert.butoxide are added to a solution of 1.55 g (5 mMol) of 2-ethyl-4-methyl-6-(1-methyl-5-fluoro-benzimidazol-2-yl)-benzimidazole in 30 ml of dimethylsulphoxide and the mixture is stirred for 15 minutes at ambient temperature. Then 1.5 g (5.5 mMol) of 4'-bromomethyl-2-cyano-biphenyl are added and the resulting mixture is stirred for a further 20 hours at ambient temperature. Then the mixture is stirred into approximately 80 ml of saturated sodium chloride solution, the crude product precipitated is suction filtered and purified by column chromatography (150 g of silica gel; eluant: methylene chloride/ethanol = 97:3).

Yield: 1.9 g (76% of theory),

R_f value: 0.43 (silica gel; methylene chloride/ethanol = 19:1)

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b) 4'-[(2-Ethyl-4-methyl-6-(1-methyl-5-fluoro-benzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

A solution of 1.9 g (3.8 mMol) of 4'-[(2-ethyl-4-methyl-6-(1-methyl-5-fluoro-benzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-2-cyano-biphenyl, 4.1 g (76 mMol) of ammonium chloride and 4.9 g (76 mMol) of sodium azide in 30 ml of dimethylformamide is heated to 140°C for 15 hours, then a further 2.0 g of ammonium chloride and 2.4 g of sodium azide are added and the mixture is heated for another 4 hours to 140°C. Then the solution is stirred into about 80 ml of saturated sodium chloride solution, the crude product precipitated is suction filtered and purified by column chromatography (150 g of silica gel; eluant: methylene chloride/ethanol = 19:1).
Yield: 1.25 g (61% of theory),
Melting point: 267-269°C
$C_{32}H_{27}FN_8$ (542.60)

Calculated:	C	70.84	H	5.02	N 20.65
Found:		70.52		5.04	20.82

R_f value: 0.60 (silica gel; methylene chloride/ethanol = 9:1)
Mass spectrum: m/e = 542

Example 6

4'-[(2-Ethoxy-4-methyl-6-(1-methyl-benzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

a) 4'-[(2-Ethoxy-4-methyl-6-(1-methyl-benzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-2-(2-triphenylmethyl-tetrazol-5-yl)-biphenyl

To a solution of 570 mg (1.86 mMol) of 2-ethoxy-4-methyl-6-(1-methyl-benzimidazol-2-yl)-benzimidazole in 20 ml of dimethylsulphoxide are added 224 mg (2.0 mMol) of potassium tert.butoxide and the mixture is stirred for 15 minutes at ambient temperature. Then 1.11 g

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(2.0 mMol) of 4'-bromomethyl-2-(2-triphenylmethyl-tetrazol-5-yl)-biphenyl are added and the mixture is stirred for a further 3 hours at ambient temperature. Then the mixture is stirred into about 50 ml of saturated sodium chloride solution, the crude product precipitated is suction filtered and purified by column chromatography (100 g silica gel; eluant: ethyl acetate/petroleum ether = 4:1).
Yield: 860 mg (59% of theory),
R_f value: 0.56 (silica gel; ethyl acetate/petroleum ether = 4:1)

b) 4'-[(2-Ethoxy-4-methyl-6-(1-methyl-benzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

A mixture of 830 mg (1.06 mMol) of 4'-[(2-ethoxy-4-methyl-6-(1-methyl-benzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-2-(2-triphenylmethyl-tetrazol-5-yl)-biphenyl, 2.5 ml of 1N sodium hydroxide solution and 20 ml of ethanol is stirred for 2 hours at 80°C. The solution is then evaporated down, the residue is mixed with about 30 ml of water and made slightly acidic with glacial acetic acid. It is then extracted three times with about 20 ml of methylene chloride, the combined organic extracts are washed with 20 ml of water and concentrated by evaporation. The crude product thus obtained is purified by column chromatography (50 g silica gel; methylene chloride/ethanol = 97:3).
Yield: 430 mg (75% of theory),
Melting point: 194-197°C
$C_{32}H_{28}N_8O$ (540.60)

Calculated:	C	71.10	H	5.22	N 20.73
Found:		69.99		5.36	20.54

Mass spectrum: m/e = 540

Example 7

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4'-[(2-Ethoxy-4-methyl-6-(imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid-hydrate

---

Prepared analogously to Example 1 from tert.butyl 4'-[(2-ethoxy-4-methyl-6-(imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 72% of theory,
Melting point: 207-209°C
$C_{31}H_{26}N_4O_3 \times H_2O$ (520.60)

Calculated:	C	71.52	H	5.42	N 10.76
Found:		71.22		5.37	10.76

R_f value: 0.36 (silica gel; methylene chloride/ethanol = 19:1)

Example 8

Mixture of
4'-[(2-n-Propyl-4-methyl-6-(butanesultam-1-yl)-benzimidazol-1-yl)-methyl]-2-[1-(pivaloyloxymethyl)-tetrazol-5-yl]-biphenyl and
4'-[(2-n-Propyl-4-methyl-6-(butanesultam-1-yl)-benzimidazol-1-yl)-methyl]-2-[2-(pivaloyloxymethyl)-tetrazol-5-yl]-biphenyl

---

A solution of 400 mg (0.74 mMol) of 4'-[(2-n-propyl-4-methyl-6-(butanesultam-1-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl, 0.16 ml (1.1 mMol) of chloromethyl pivalate and 194 mg (1.1 mMol) of potassium carbonate-dihydrate in 10 ml of dimethylformamide is stirred for 14 hours at ambient temperature, then stirred into about 50 ml of saturated sodium chloride solution and extracted three times with about 20 ml of methylene chloride. The combined organic extracts are washed with water and evaporated down. The crude product thus obtained is purified by column chromatography (50 g silica gel; eluant: methylene

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chloride/ethanol = 98:2).
Yield: 400 mg (82% of theory),
Melting point: amorphous
$C_{35}H_{41}N_7O_4S$ (655.80)

Calculated:	C	64.10	H	6.30	N	14.95	S 4.88
Found:		63.99		6.22		14.80	5.03

R_f value: 0.46 (silica gel; methylene chloride/ethanol = 19:1)

Example 9

Mixture of
4'-[(2-n-Propyl-4-methyl-6-(5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-2-[1-(pivaloyloxymethyl)-tetrazol-5-yl]-biphenyl and
4'-[(2-n-Propyl-4-methyl-6-(5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-2-[2-(pivaloyloxymethyl)-tetrazol-5-yl]-biphenyl

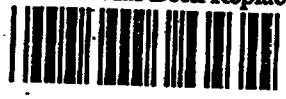
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Prepared analogously to Example 8 from 4'-[(2-n-propyl-4-methyl-6-(5,6,7,8-tetrahydro-imidazo[1,2-a]-pyridin-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl and chloromethylpivalate.
Yield: 75% of theory,
Melting point: 203-205°C
$C_{38}H_{42}N_8O_2$ (642.80)

Calculated:	C	71.00	H	6.59	N	17.43
Found:		70.85		6.63		17.43

R_f value: 0.43 (silica gel; methylene chloride/ethanol = 19:1)
Mass spectrum: m/e = 642

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Example 10

4'-[(2-n-Propyl-4-methyl-6-(5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-2-[1-(cyclohexyloxycarbonyloxy)-ethyloxycarbonyl]-biphenyl

---

A solution of 504 mg (1.0 mMol) of 4'-[(2-n-propyl-4-methyl-6-(5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid, 600 mg of 1-(cyclohexyloxycarbonyloxy)-ethyliodide and 350 mg of potassium carbonate in 25 ml of dimethylsulphoxide is stirred for 14 hours at ambient temperature, then stirred into about 70 ml of saturated sodium chloride solution and extracted three times with 30 ml of ethyl acetate. The combined organic extracts are washed with water and evaporated down. The crude product thus obtained is purified by column chromatography (100 g silica gel; eluant: methylene chloride/ethanol = 98:2).
Yield: 325 mg (48% of theory),
Melting point: 162-164°C
$C_{41}H_{46}N_4O_5$ (674.85)

Calculated:	C	72.97	H	6.87	N 8.30
Found:		72.63		6.77	8.17

R_f value: 0.52 (silica gel; methylene chloride/ethanol = 19:1)
Mass spectrum: m/e = 674

Example 11

4'-[(2-n-Propyl-4-methyl-6-(5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-2-(pivaloyloxymethyloxycarbonyl)-biphenyl

---

Prepared analogously to Example 8 from 4'-[(2-n-propyl-4-methyl-6-(5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic

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acid and chloromethylpivalate in dimethylformamide.
Yield: 76% of theory,
Melting point: 142-144°C
$C_{38}H_{42}N_4O_4$ (618.79)
Calculated: C 73.76 H 6.84 N 9.09
Found: 73.60 6.92 9.17
R_f value: 0.40 (silica gel; methylene chloride/ethanol = 19:1)
Mass spectrum: m/e = 618

Example 12

4'-[(2-n-Propyl-4-methyl-6-(butanesultam-1-yl)-benzimidazol-1-yl)-methyl]-2-(pivaloyloxymethyloxy-carbonyl)-biphenyl

---

Prepared analogously to Example 8 from 4'-[(2-n-propyl-4-methyl-6-(butanesultam-1-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid and chloromethylpivalate in dimethylformamide.
Yield: 70% of theory,
Melting point: Oil
$C_{35}H_{41}N_3O_6S$ (631.80)
Calculated: C 66.54 H 6.54 N 6.65 S 5.08
Found: 66.21 6.67 6.54 5.34
R_f value: 0.49 (silica gel; methylene chloride/ethanol = 19:1)
Mass spectrum: m/e = 631

Example 13

4'-[(2-n-Propyl-4-methyl-6-(5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-2-[1-(ethoxycarbonyloxymethyloxy)-carbonyl]-biphenyl

---

Prepared analogously to Example 8 from 4'-[(2-n-propyl-4-methyl-6-(5,6,7,8-tetrahydro-imidazo[1,2-a]-pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic

acid and 1-(ethoxycarbonyloxy)-methylchloride in dimethylformamide.

Yield: 38.5% of theory,

Melting point: 123-125°C

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$C_{37}H_{40}N_4O_5$ (620.76)

Calculated: C 71.59 H 6.50 N 9.03

Found: 71.57 6.58 9.03

R_f value: 0.33 (silica gel; methylene chloride/ethanol = 19:1)

Mass spectrum: m/e = 620

Example 14

4'-[(2-Ethoxy-4-methyl-6-(imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

Prepared analogously to Example 6 from 4'-[(2-ethoxy-4-methyl-6-(imidazo[1,2-a]-pyridin-2-yl)-benzimidazol-1-yl)-methyl]-2-(2-triphenylmethyl-tetrazol-5-yl)-biphenyl and sodium hydroxide solution in ethanol.

Example 15

4'-[(2-Ethoxy-4-methyl-6-(5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl

Prepared analogously to Example 6 from 4'-[(2-ethoxy-4-methyl-6-(5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-2-(2-triphenylmethyl-tetrazol-5-yl)-biphenyl and sodium hydroxide solution in ethanol.

Example 16

4'-[(2-Ethoxy-4-methyl-6-(5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid

---

Prepared analogously to Example 1 from tert.butyl 4'-[(2-ethoxy-4-methyl-6-(5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 63% of theory,
Melting point: 238-240°C
R_f value: 0.62 (silica gel; methylene chloride/ethanol = 9:1)

Example 17

4'-[(2-Ethyl-4-methyl-6-(butanesultam-1-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid

---

Prepared analogously to Example 1 from tert.butyl 4'-[(2-ethyl-4-methyl-6-(butanesultam-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylate and trifluoroacetic acid in methylene chloride.
Yield: 68% of theory,
Melting point: > 240°C
$C_{28}H_{29}N_3O_4S$ (503.60)

Calculated:	C	66.77	H	5.80	N 8.34
Found:		66.57		5.69	8.30

R_f value: 0.36 (silica gel; methylene chloride/ethanol = 9:1)

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Example 18

4'-[(2-Ethyl-4-methyl-6-(3-chloro-5,6,7,8-tetrahydro-imidazo-[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid

---

Prepared analogously to Example 1 from tert.butyl 4'-[(2-ethyl-4-methyl-6-(3-chloro-5,6,7,8-tetrahydro-imidazo-[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylate and trifluoro-acetic acid in methylene chloride.
Yield: 43% of theory,
Melting point: 295-297°C
$C_{32}H_{29}ClN_4O_2$ (525.06)

Calculated:	C	70.91	H	5.57	N	10.67	Cl 6.75
Found:		70.81		5.54		10.56	6.83

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In the Examples of Pharmaceutical Formulations which follow, any suitable compound of formula I, particularly those wherein R_4 represents a tetrazolyl group substituted in the 1- or 2-position by an R_a-CO-O-CH_2- group, or R_4 denotes a carboxy, 1H-tetrazolyl, R_aO-CO-, R_b-CO-O-(R_cCH)-O-CO- or R_bO-CO-O-(R_cCH)-O-CO- group, may be used as the active substance:

Example I

Ampoules containing 50 mg of active substance per 5 ml

Active substance	50 mg
KH_2PO_4	2 mg
Na_2HPO_4 x $2H_2O$	50 mg
NaCl	12 mg
Water for injections ad	5 ml

Preparation:

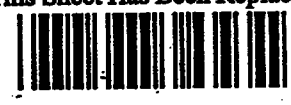
The buffer substances and isotonic substance are dissolved in some of the water. The active substance is added and, once it has been completely dissolved, water is added to make up the required volume.

Example II

Ampoules containing 100 mg of active substance per 5 ml

Active substance	100 mg
Methyl glucamine	35 mg
Glycofurol	1000 mg
Polyethyleneglycol-polypropylene-glycol block polymer	250 mg
Water for injections ad	5 ml

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Preparation:

Methyl glucamine is dissolved in some of the water and the active substance is dissolved with stirring and heating. After the addition of solvents, water is added to make up the desired volume.

Example III

Tablets containing 50 mg of active substance

Active substance	50.0 mg
Calcium phosphate	70.0 mg
Lactose	40.0 mg
Corn starch	35.0 mg
Polyvinylpyrrolidone	3.5 mg
Magnesium stearate	1.5 mg
	200.0 mg

Preparation:

The active substance, $CaHPO_4$, lactose and corn starch are uniformly moistened with an aqueous PVP solution. The mass is passed through a 2 mm screen, dried at 50°C in a circulating air dryer and screened again.

After the lubricant has been added, the granules are compressed in a tablet making machine.

Example IV

Coated tablets containing 50 mg of active substance

Active substance	50.0 mg
Lysine	25.0 mg
Lactose	60.0 mg

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Corn starch	34.0 mg
Gelatin	10.0 mg
Magnesium stearate	1.0 mg
	180.0 mg

Preparation:

The active substance is mixed with the excipients and moistened with an aqueous gelatin solution. After screening and drying, the granules are mixed with magnesium stearate and compressed to form tablet cores.

The cores thus produced are covered with a coating by known methods. A colouring may be added to the coating suspension or solution.

Example V

Coated tablets containing 100 mg of active substance

Active substance	100.0 mg
Lysine	50.0 mg
Lactose	86.0 mg
Corn starch	50.0 mg
Polyvinylpyrrolidone	2.8 mg
Microcrystalline cellulose	60.0 mg
Magnesium stearate	1.2 mg
	350.0 mg

Preparation:

The active substance is mixed with the excipients and moistened with an aqueous PVP solution. The moist mass is passed through a 1.5 mm screen and dried at 45°C. After drying, it is screened again and the magnesium stearate is added. This mixture is compressed into cores.

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The cores thus produced are covered with a coating by known methods. Colourings may be added to the coating suspension or solution.

Example VI

Capsules containing 250 mg of active substance

Active substance	250.0 mg
Corn starch	68.5 mg
Magnesium stearate	1.5 mg
	320.0 mg

Preparation:

The active substance and corn starch are mixed together and moistened with water. The moist mass is screened and dried. The dry granules are screened and mixed with magnesium stearate. The final mixture is packed into size 1 hard gelatin capsules.

Example VII

Oral suspension containing 50 mg of active substance per 5 ml

Active substance	50.0 mg
Hydroxyethylcellulose	50.0 mg
Sorbic acid	5.0 mg
70% sorbitol	600.0 mg
Glycerol	200.0 mg
Flavouring	15.0 mg
Water ad	5.0 ml

Preparation:

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Distilled water is heated to 70°C. Hydroxyethylcellulose is dissolved therein with stirring. By the addition of sorbitol solution and glycerol the mixture is cooled to ambient temperature. At ambient temperature, sorbic acid, flavouring and active substance are added. The suspension is evacuated with stirring to remove any air. One dose of 50 mg is contained in 5.0 ml.

Example VIII

Suppositories containing 100 mg of active substance

Active substance	100.0 mg
Solid fat	1600.0 mg
	1700.0 mg

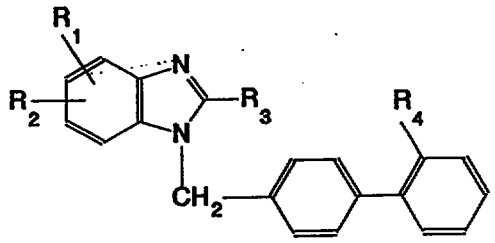
Preparation:

The hard fat is melted. At 40°C the ground active substance is homogeneously dispersed in the melt. It is cooled to 38°C and poured into slightly chilled suppository moulds.

* C L N S *

Claims

1. Benzimidazoles of general formula



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(I)

wherein

R_1 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group, a C_{3-7}-cycloalkyl group, a fluoromethyl, difluoromethyl or trifluoromethyl group,

R_2 denotes a phthalimino or homophthalimino group, whilst a carbonyl group in a phthalimino group may be replaced by a methylene group and a methylene group in a homophthalimino group may be substituted by one or two C_{1-3}-alkyl groups,

a 5-, 6- or 7-membered alkyleneimino group (optionally substituted by one or two C_{1-3}-alkyl groups) in which a methylene group is replaced by a carbonyl or sulphonyl group,

a maleic acid imido group optionally mono- or disubstituted by a C_{1-3}-alkyl group or by a phenyl group, whilst the substituents may be identical or different,

a benzimidazol-2-yl or 4,5,6,7-tetrahydro-benzimidazol-2-yl group optionally substituted in the 1-position by a C_{1-6}-alkyl group or by a C_{3-5}-cycloalkyl group (whilst the phenyl nucleus of one of the above-mentioned benzimidazole groups may additionally be substituted by a fluorine atom or a methyl or trifluoromethyl group),

* C L M S *

an imidazo[2,1-b]thiazol-6-yl, imidazo[1,2-a]pyridin-2-yl, 5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl, 3-chloro-5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyrimidin-2-yl, imidazo[4,5-b]pyridin-2-yl, imidazo[4,5-c]pyridin-2-yl, imidazo[1,2-c]pyrimidin-2-yl, imidazo[1,2-a]pyrazin-2-yl, imidazo[1,2-b]-pyridazin-2-yl, imidazo[4,5-c]pyridin-2-yl, purin-8-yl, imidazo[4,5-b]pyrazin-2-yl, imidazo[4,5-c]pyridazin-2-yl or imidazo[4,5-d]pyridazin-2-yl group, a pyrrolidine, piperidine or pyridine ring bound via a carbon atom, whilst a phenyl group may be condensed on to the pyridine ring via two adjacent carbon atoms and a methylene group adjacent to the N-atom in a pyrrolidine or piperidine ring may be replaced by a carbonyl group, or

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an R_7-NR_6-CO-NR_5- group wherein

R_5 denotes a hydrogen atom, a C_{1-5}-alkyl group, a cyclohexyl or benzyl group,

R_6 denotes a hydrogen atom, a C_{1-6}-alkyl group, an allyl, cyclohexyl, benzyl or phenyl group,

R_7 denotes a hydrogen atom or a C_{1-3}-alkyl group or

R_6 and R_7 together with the nitrogen atom between them denote a an unbranched cyclic group or a morpholino group or

R_5 and R_6 together denote a C_{2-3}-alkylene group,

R_3 denotes a C_{1-5}-alkyl group, a C_{3-5}-cycloalkyl group or a C_{1-3}-alkoxy group and

R_4 denotes a tetrazolyl group substituted in the 1- or 2-position by an R_a-CO-O-CH_2- group, or an R_b-CO-O-(R_cCH)-O-CO-, R_aO-CO- or R_bO-CO-O-(R_cCH)-O-CO-

group, wherein

R_a denotes a straight-chained or branched C_{1-6}-alkyl group, a C_{5-7}-cycloalkyl group, a benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, methoxymethyl or cinnamyl group,

R_b denotes a straight-chained or branched C_{1-6}-alkyl group, a C_{5-7}-cycloalkyl group, a phenyl, benzyl, 1-phenylethyl, 2-phenylethyl or 3-phenylpropyl group and

R_c denotes a hydrogen atom or a methyl group,

or if

(i) R_1 and R_2 are as hereinbefore defined and R_3 denotes an alkoxy group, R_4 may denote a carboxy, 1H-tetrazolyl or 2H-tetrazolyl group or, if

(ii) R_1 is as hereinbefore defined, R_2 has the meanings given hereinbefore with the exception of the 1-methyl-benzimidazol-2-yl group and R_3 denotes a cyclopropyl group, R_4 may represent a carboxy group or, if

(iii) R_1 and R_3 are as hereinbefore defined and R_2 denotes a butanesultam-1-yl group, R_4 may denote a carboxy group or, if

(iv) R_1 is as hereinbefore defined, R_2 denotes a 1-methyl-5-fluoro-benzimidazol-2-yl group and R_3 denotes an ethyl group, R_4 may represent a carboxy, 1H-tetrazolyl or 2H-tetrazolyl group,

the tautomers and the salts thereof.

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2. Benzimidazoles of general formula I according to claim 1, wherein

R_1 denotes a hydrogen atom or in the 4-position a chlorine atom, a C_{1-3}-alkyl group or a trifluoromethyl group,

R_2 denotes a phthalimino or homophthalimino group, whilst a carbonyl group in a phthalimino group may be replaced by a methylene group,

a 5-, 6- or 7-membered alkyleneimino group in which a methylene group is replaced by a carbonyl or sulphonyl group,

a maleic acid imido group optionally mono- or disubstituted by a methyl or phenyl group, whilst the substituents may be identical or different,

a benzimidazol-2-yl or 4,5,6,7-tetrahydro-benzimidazol-2-yl group optionally substituted in the 1-position by a C_{1-6}-alkyl group or by a cycloalkyl group (whilst the phenyl nucleus of one of the above-mentioned benzimidazole groups may additionally be substituted by a fluorine atom or a methyl or trifluoromethyl group), an imidazo[2,1-b]thiazol-6-yl, imidazo[1,2-a]pyridin-2-yl, 5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl, 3-chloro-5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyrimidin-2-yl, imidazo[4,5-b]pyridin-2-yl, imidazo[4,5-c]pyridin-2-yl, imidazo[1,2-c]pyrimidin-2-yl, imidazo[1,2-a]pyrazin-2-yl, imidazo[1,2-b]pyridazin-2-yl, imidazo[4,5-c]pyridin-2-yl, purin-8-yl, imidazo[4,5-b]pyrazin-2-yl, imidazo[4,5-c]pyridazin-2-yl or imidazo[4,5-d]pyridazin-2-yl group or

an R_7-NR_6-CO-NR_5- group wherein

R_5 denotes a hydrogen atom, a C_{1-5}-alkyl group, a cyclohexyl or benzyl group,

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R_6 denotes a hydrogen atom, a C_{1-6}-alkyl group, an allyl, cyclohexyl, benzyl or phenyl group,

R_7 denotes a hydrogen atom or a C_{1-3}-alkyl group or

R_6 and R_7 together with the nitrogen atom between them denote a straight-chained C_{4-6}-alkyleneimino group or a morpholino group or

R_5 and R_6 together denote a C_{2-3}-alkylene group,

R_3 denotes a C_{1-5}-alkyl group, a C_{3-5}-cycloalkyl group or a C_{2-3}-alkoxy group and

R_4 denotes a tetrazolyl group substituted in the 1- or 2-position by an R_a-CO-O-CH_2- group, or an R_b-CO-O-(R_cCH)-O-CO-, R_aO-CO- or R_bO-CO-O-(R_cCH)-O-CO- group, wherein

R_a denotes a straight-chained or branched C_{1-6}-alkyl group, a C_{5-7}-cycloalkyl group, a benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, methoxymethyl or cinnamyl group,

R_b denotes a straight-chained or branched C_{1-6}-alkyl group, a C_{5-7}-cycloalkyl group, a phenyl, benzyl, 1-phenylethyl, 2-phenylethyl or 3-phenylpropyl group and

R_c denotes a hydrogen atom or a methyl group,

or, if

(i) R_1 and R_2 are as hereinbefore defined and R_3 denotes an alkoxy group, R_4 may denote a carboxy, 1H-tetrazolyl or 2H-tetrazolyl group or, if

(ii) R_1 is as hereinbefore defined, R_2 has the meanings

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given hereinbefore with the exception of the 1-methyl-benzimidazol-2-yl group and R_3 denotes a cyclopropyl group, R_4 may represent a carboxy group or, if

(iii) R_1 and R_3 are as hereinbefore defined and R_2 denotes a butanesultam-1-yl group, R_4 may denote a carboxy group or, if

(iv) R_1 is as hereinbefore defined, R_2 denotes a 1-methyl-5-fluoro-benzimidazol-2-yl group and R_3 denotes an ethyl group, R_4 may represent a carboxy, 1H-tetrazolyl or 2H-tetrazolyl group,

the tautomers and the salts thereof.

3. Benzimidazoles of general formula I according to claim 1 wherein

R_1 denotes a hydrogen atom or in the 4-position a methyl group,

R_2 denotes an imidazo[1,2-a]pyridin-2-yl, 5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl, 3-chloro-5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl, 1-methyl-benzimidazol-2-yl, 1-methyl-5-fluoro-benzimidazol-2-yl or butanesultam-1-yl group,

R_3 denotes a C_{2-4}-alkyl group, a cyclopropyl group or a C_{2-3}-alkoxy group and

R_4 denotes a tetrazolyl group substituted in the 1- or 2-position by an R_a-CO-O-CH_2- group, or an R_b-CO-O-(R_cCH)-O-CO-, R_aO-CO- or R_bO-CO-O-(R_cCH)-O-CO- group, whilst

R_a denotes a straight-chained or branched C_{1-6}-alkyl group, a C_{5-7}-cycloalkyl group, a benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl,

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methoxymethyl or cinnamyl group,

R_b denotes a straight-chained or branched C_{1-6}-alkyl group, a C_{5-7}-cycloalkyl group, a phenyl, benzyl, 1-phenylethyl, 2-phenylethyl or 3-phenylpropyl group and

R_c denotes a hydrogen atom or a methyl group,

and the compounds

4'-[(2-cyclopropyl-4-methyl-6-(4,5,6,7-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid,

4'-[(2-ethoxy-4-methyl-6-(4,5,6,7-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid,

4'-[(2-ethoxy-4-methyl-6-(4,5,6,7-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl,

4'-[(2-cyclopropyl-4-methyl-6-(imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid,

4'-[(2-ethoxy-4-methyl-6-(imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid,

4'-[(2-ethoxy-4-methyl-6-(imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl,

4'-[(2-ethoxy-4-methyl-6-(1-methyl-benzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl,

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4'-[(2-ethyl-4-methyl-6-(1-methyl-5-fluoro-benzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl,

4'-[(2-ethyl-4-methyl-6-(1-methyl-5-fluoro-benzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid and

4'-[(2-n-propyl-4-methyl-6-(butanesultam-1-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid,

the tautomers and the salts thereof.

4. The following compounds of general formula I according to claim 1:

(a) 4'-[(2-ethyl-4-methyl-6-(1-methyl-5-fluoro-benzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid,

(b) 4'-[(2-n-propyl-4-methyl-6-(butanesultam-1-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid,

(c) 4'-[(2-cyclopropyl-4-methyl-6-(imidazo[1,2-a]-pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid,

(d) 4'-[(2-cyclopropyl-4-methyl-6-(5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid and

(e) 4'-[(2-ethoxy-4-methyl-6-(1-methyl-benzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-2-(1H-tetrazol-5-yl)-biphenyl,
the tautomers and the salts thereof.

5. Physiologically acceptable salts of the compounds according to at least one of claims 1 to 4 with

inorganic or organic acids or bases.

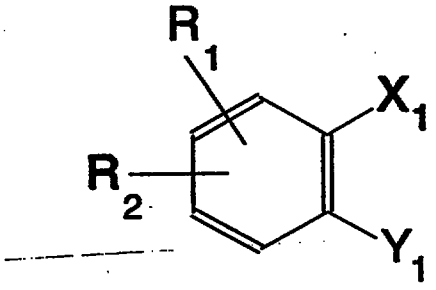
6. Pharmaceutical compositions containing a compound according to at least one of claims 1 to 4 or a physiologically acceptable salt according to claim 5, optionally together with one or more inert carriers and/or diluents.

7. Use of a compound according to at least one of claims 1 to 5 for preparing a pharmaceutical composition with an angiotensin-antagonistic activity.

8. Process for preparing a pharmaceutical composition according to claim 6, characterised in that a compound according to at least one of claims 1 to 5 is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

9. Process for preparing the benzimidazoles according to claims 1 to 5, characterised in that

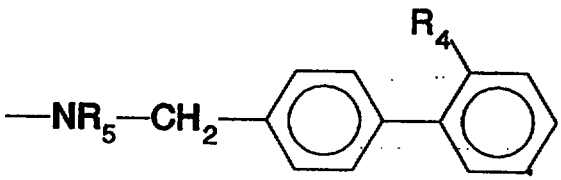
a) a compound of general formula



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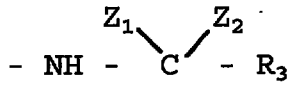
(II)

optionally formed in the reaction mixture, wherein
R_1 and R_2 are defined as in claims 1 to 4,
one of the groups X_1 or Y_1 represents a group of general formula



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and the other group X_1 or Y_1 represents a group of the general formula



wherein

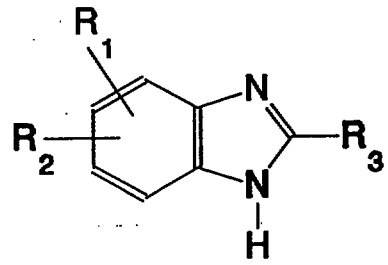
R_3 and R_4 are defined as in claims 1 to 4,
R_5 represents a hydrogen atom or an R_3CO- group, wherein R_3 is defined as hereinbefore,
Z_1 and Z_2, which may be identical or different, represent amino, hydroxy or mercapto groups optionally substituted by C_{1-6}-alkyl groups or
Z_1 and Z_2 together represent an oxygen or sulphur atom, an imino group optionally substituted by a C_{1-3}-alkyl group, or an alkylenedioxy or alkylenedithio group each having 2 or 3 carbon atoms,

is cyclised, and an N-oxide optionally obtained in this way is reduced, or

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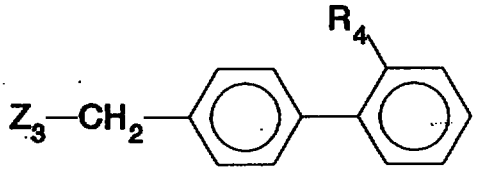
b) a benzimidazole of general formula



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(III)

wherein
R_1 to R_3 are defined as in claims 1 to 4, is reacted with a biphenyl compound of general formula

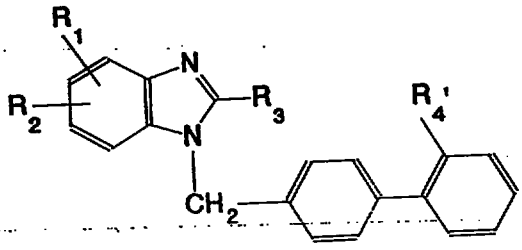


(IV)

wherein
R_4 is defined as in claims 1 to 4 and
Z_3 represents a nucleophilic leaving group, or

c) in order to prepare a compound of general formula I wherein R_4 represents a carboxy group, a compound of general formula

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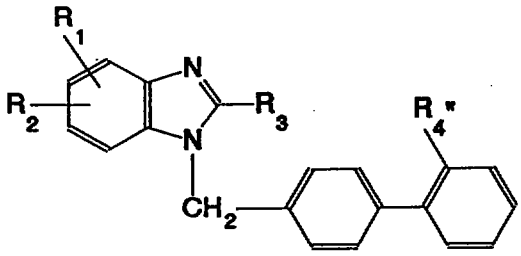


(V)

wherein
R_1 to R_3 are defined as in claims 1 to 4 and

R_4' represents a group which may be converted into a carboxy group by hydrolysis, thermolysis or hydrogenolysis, is converted into a corresponding carboxy compound, or

d) in order to prepare a compound of general formula I wherein R_4 represents a 1H-tetrazolyl group, a protecting group is cleaved from a compound of general formula

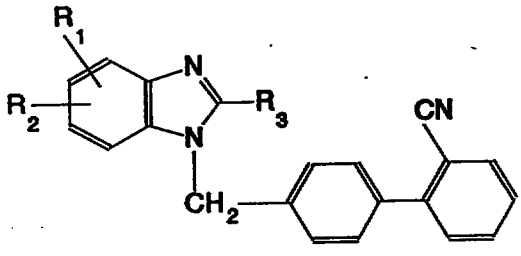


(VI)

wherein
R_1, R_2 and R_3 are defined as in claims 1 to 4 and
R_4" represents a 1H-tetrazolyl group protected in the 1- or 3-position by a protecting group, or

e) in order to prepare a compound of general formula I wherein R_4 represents a 1H-tetrazolyl group, a compound of general formula

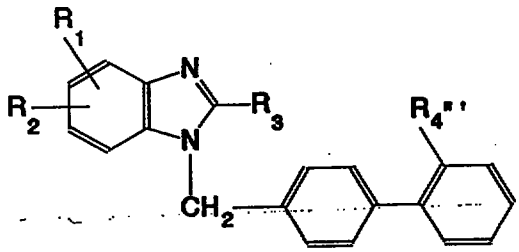
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(VII)

wherein
R_1 to R_3 are defined as in claims 1 to 4, is reacted with hydrazoic acid or the salts thereof, or

f) in order to prepare a compound of general formula I wherein R_4 denotes a tetrazolyl group substituted in the 1- or 2-position by an R_a-CO-O-CH_2- group or R_4 denotes an R_aO-CO-, R_b-CO-O-(R_cCH)-O-CO- or R_bO-CO-O-(R_cCH)-O-CO- group, a compound of general formula



(VIII)

wherein
R_1 to R_3 are defined as in claims 1 to 4 and
R_4"' denotes a carboxy, 1H-tetrazolyl or 2H-tetrazolyl group, is reacted with a compound of general formula

Z_4 - Y_2 (IX)

wherein

Y_2 denotes an R_a-CO-O-CH_2-, R_b-CO-O-(R_cCH)-, R_bO-CO-O-(R_cCH)- or R_a- group, wherein R_a to R_c are defined as in claims 1 to 4 and
Z_4 denotes a nucleophilic leaving group or, if Y denotes an R_a- group, Z_4 may denote a hydroxy group, and

if necessary a protecting group used during reactions a) to f) in order to protect any reactive groups is cleaved and/or

subsequently, if desired, a 1-, 3-isomer mixture of a compound of general formula I thus obtained is resolved by isomer separation into the 1- and 3-isomers thereof or

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a compound of general formula I thus obtained is converted into a salt thereof, more particularly, for pharmaceutical use, into a physiologically acceptable salt thereof with an inorganic or organic acid or base.

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