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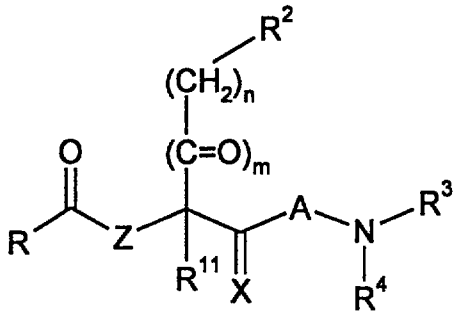
DR. KARL THOMAE GMBH
D-88397 BIBERACH

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Modified amino acids, medicaments containing these compounds and processes for their preparation

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The present invention relates to modified amino acids of general formula



(I),

their tautomers, their diastereomers, their enantiomers, their mixtures and salts thereof, particularly physiologically acceptable salts thereof with inorganic or organic acids or bases, pharmaceutical compositions containing these compounds, the use thereof and processes for preparing them.

In the above general formula I

R denotes an unbranched C_{1-7}-alkyl group which may be substituted in the ω-position

by a C_{4-10}-cycloalkyl group,

by one or two phenyl groups, by a 1-naphthyl, 2-naphthyl or biphenylyl group,

by a 1,3-dihydro-2H-2-oxobenzimidazol-1-yl, 2,4(1H,3H)-dioxoquinazolin-1-yl, 2,4(1H,3H)-dioxoquinazolin-3-yl, 2,4(1H,3H)-dioxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-3-yl, 2(1H)-oxoquinolin-3-yl, 2(1H)-oxoquinoxalin-3-yl, 1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl, 1,3-dihydro-2H-2-oxoimidazopyridinyl, 1,3-dihydro-2(2H)-oxoimidazo[4,5-c]quinolin-3-yl, 1,3-dihydro-2H-2-oxoimidazol-1-yl or 3,4-dihydro-2(1H)-oxopyrimidin-3-yl group, wherein the latter two groups may each be mono- or disubstituted in the 4- and/or 5-position or in the 5- and/or 6-position by lower straight chained or branched alkyl groups, by phenyl, biphenylyl, pyridinyl, diazinyl, furyl, thienyl, pyrrolyl, 1,3-oxazolyl, 1,3-thiazolyl, isoxazolyl, pyrazolyl-1-methylpyrazolyl, imidazolyl or 1-methylimidazolyl groups and the substituents may be identical or different,

by a 5-membered heteroaromatic ring linked via a carbon atom, which contains a nitrogen, oxygen or sulphur atom or, in addition to a nitrogen atom, contains an oxygen, sulphur or additional nitrogen atom, whilst a nitrogen atom of an imino group may be substituted by an alkyl group,

or by a 6-membered heteroaromatic ring linked via a carbon atom, which contains one, two or three nitrogen atoms,

whilst a 1,4-butadienylene group may be attached both to the above-mentioned 5-membered heteroaromatic monocyclic rings and to the 6-membered heteroaromatic monocyclic rings, in each case via two adjacent carbon atoms, and the bicyclic heteroaromatic rings thus formed may also be bound via a carbon atom of the 1,4-butadienylene group,

an unbranched C_{1-6}-alkylamino group optionally substituted at the nitrogen atom by a C_{1-6}-alkyl group or by a phenylmethyl group, which may be substituted in the ω-position

by a C_{4-10}-cycloalkyl group,

by one or two phenyl groups, by a 1-naphthyl, 2-naphthyl or biphenylyl group,

by a 1H-indol-3-yl, 1,3-dihydro-2H-2-oxobenzimidazol-1-yl, 2,4(1H,3H)-dioxoquinazolin-1-yl, 2,4(1H,3H)-dioxoquinazolin-3-yl, 2,4(1H,3H)-dioxothieno-[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-3-yl, 2(1H)-oxoquinolin-3-yl, 2(1H)-oxoquinoxalin-3-yl, 1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl, 1,3-dihydro-4-(3-thienyl)-2H-2-oxoimidazol-1-yl, 1,3-dihydro-4-phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-5-phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-2(2H)-oxoimidazo-[4,5-c]quinolin-3-yl, 3,4-dihydro-5-phenyl-2(1H)-oxopyrimidin-3-yl, 3,4-dihydro-6-phenyl-2(1H)-

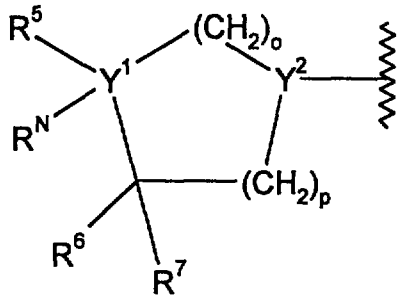
oxopyrimidin-3-yl- or 1,3-dihydro-2H-2-oxoimidazo-[4,5-b]pyridin-3-yl- group,

by a 5-membered heteroaromatic ring linked via a carbon atom, which contains a nitrogen, oxygen or sulphur atom or, in addition to a nitrogen atom, contains an oxygen, sulphur or an additional nitrogen atom, whilst a nitrogen atom of an imino group may be substituted by an alkyl group, or

by a 6-membered heteroaromatic ring linked via a carbon atom, containing 1, 2 or 3 nitrogen atoms, whilst a 1,4-butadienylene group may be attached both to the 5-membered and to the 6-membered heteroaromatic monocyclic rings, in each case via two adjacent carbon atoms, and the bicyclic heteroaromatic rings thus formed may also be bound via a carbon atom of the 1,4-butadienylene group,

whilst the phenyl, naphthyl and biphenylyl groups mentioned above for the substitution of the alkyl and alkylamino groups in the ω-position and optionally also partially hydrogenated mono- and bicyclic heteroaromatic rings in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms or by alkyl groups, C_{3-8}-cycloalkyl groups, nitro, alkoxy, phenyl, phenylalkoxy, trifluoromethyl, alkoxycarbonyl, alkoxycarbonylalkyl, carboxy, carboxyalkyl, dialkylaminoalkyl, hydroxy, amino, acetylamino, propionylamino, benzoyl, benzoylamino, benzoylmethylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, (1-pyrrolidinyl)carbonyl, (1-piperidinyl)carbonyl, (hexahydro-1H-azepin-1-yl)carbonyl, (4-methyl-1-piperazinyl)carbonyl, (4-morpholinyl)carbonyl, alkanoyl, cyano, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl groups,

wherein the substituents may be identical or different and the above-mentioned benzoyl, benzoylamino and benzoylmethylamino groups may in turn additionally be substituted in the phenyl moiety by a fluorine, chlorine or bromine atom or by an alkyl, trifluoromethyl, amino or acetylamino group,
or the group of formula



(II),

wherein

p denotes the number 1 or 2,

o denotes the number 2 or 3 or, if Y^1 and Y^2 are not simultaneously nitrogen atoms, o may also denote 1.

Y^1 denotes the nitrogen atom if R^5 is a free pair of electrons, or the carbon atom,

Y^2 is the nitrogen atom or the group >CH-,

R^5 is a free pair of electrons if Y^1 denotes the nitrogen atom or, if Y^1 denotes the carbon atom, R^5 denotes a hydrogen atom, a C_{1-3}-alkyl group, a hydroxy, cyano, aminocarbonyl, carboxy, alkoxycarbonyl, aminocarbonylamino, phenylmethyl or phenyl group,

R^6 denotes the hydrogen atom or, provided that Y^1 is not a nitrogen atom, R^6 together with R^5 may denote an additional bond,

R^7 denotes the hydrogen atom or, provided that Y^1 is not a nitrogen atom and R^5 and R^6 together constitute an additional bond, R^7 together with R^N may also denote a 1,4-butadienylene group,

R^N denotes a hydrogen atom or a C_{1-6}-alkyl group which may be mono- or disubstituted in the ω-position

by a C_{5-7}-cycloalkyl group, by a 1-naphthyl, 2-naphthyl, hydroxy, alkoxy, amino, alkylamino, dialkylamino, piperidinyl, morpholinyl, pyrrolidinyl, hexahydro-1H-1-azepinyl, aminocarbonyl, alkylaminocarbonyl, acetylamino, cyano, aminocarbonylamino or alkylaminocarbonylamino group or by phenyl, pyridinyl or diazinyl groups, whilst these substituents may be identical or different,

a C_{5-7}-cycloalkyl group, a phenyl, pyridinyl, cyano, amino, benzoylamino, aminocarbonyl, alkylaminocarbonyl, alkoxycarbonyl, phenylalkoxycarbonyl, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, N-(aminocarbonyl)-N-alkylamino, N-(alkyl-aminocarbonyl)-N-alkylamino, N-(alkylaminocarbonyl)-N-phenylamino, phenylaminocarbonylamino, [phenyl(alkylamino)]carbonylamino, N-(phenylaminocarbonyl)-N-alkylamino, N-(phenylaminocarbonyl)-N-phenylamino, benzoylaminocarbonylamino, phenylalkylamino-carbonylamino, pyridinylaminocarbonylamino, N-(aminocarbonyl)-N-phenylamino, N-(alkylaminocarbonyl)-N-phenylamino, N-(aminocarbonylaminocarbonyl)-N-

phenylamino, N-(pyridinyl)-N-(aminocarbonyl)amino, N-(pyridinyl)-N-(alkylaminocarbonyl)amino, phenylamino, pyridinylamino, 4-[3,4-dihydro-2(1H)-oxo-quinazolin-3-yl]-1-piperidinyl or diazinylamino group,

a saturated, mono- or di- unsaturated 5- to 7-membered aza, diaza, triaza, oxaza, thiaza, thiadiaza- or S,S-dioxido-thiadiaza- heterocycle.

wherein the above-mentioned heterocycles may be linked via a carbon or nitrogen atom and

may contain one or two carbonyl groups adjacent to a nitrogen atom,

may be substituted at one of the nitrogen atoms by an alkyl, alkanoyl, aroyl, hydroxycarbonylalkyl, alkoxycarbonylalkyl, phenylalkoxycarbonylalkyl, phenylmethyl or phenyl group,

may be substituted at one or two carbon atoms by a branched or unbranched alkyl group or by a phenyl, phenylmethyl, naphthyl, biphenylyl, pyridinyl, diazinyl, furyl, thienyl, pyrrolyl, 1,3-oxazolyl, 1,3-thiazolyl, isoxazolyl, pyrazolyl, 1-methyl-pyrazolyl, imidazolyl or 1-methylimidazolyl group, wherein the substituents may be the same or different,

and wherein a C_{3-6}-alkylene group may additionally be attached to the above-mentioned heterocycles via two adjacent carbon atoms or an olefinic double bond of one of the above-mentioned unsaturated heterocycles may be fused with a benzene, pyridine, diazine, 1,3-oxazole, thiophene, furan, thiazole, pyrrole, N-methyl-

pyrrole, quinoline, imidazole or N-methyl-imidazole ring,

or if Y^1 is not a nitrogen atom and R^5 and R^6 together denote an additional bond, R^N together with R^7 may also denote the 1,4-butadienylene group,

or, if Y^1 is a carbon atom, R^N together with R^5, including Y^1, also denotes a carbonyl group or a saturated or monounsaturated 5- or 6-membered 1,3-diaza-heterocycle which may optionally contain one or two carbonyl groups in the ring and, if it is unsaturated, may be benzofused at the double bond and may be substituted at one of the nitrogen atoms by a methyl, aminocarbonyl, hydroxycarbonylalkyl, alkoxycarbonylalkyl, phenylalkoxycarbonylalkyl, phenylmethyl or phenyl group,

whilst the phenyl, pyridinyl, diazinyl, furyl, thienyl, pyrrolyl, 1,3-oxazolyl, 1,3-thiazolyl, isoxazolyl, pyrazolyl, 1-methylpyrazolyl, imidazolyl- or 1-methylimidazolyl groups contained in the residues mentioned under R^5, R^7 and R^N, as well as benzo, thieno, pyrido- and diazino-fused heterocycles in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms, by alkyl groups, C_{3-8}-cycloalkyl groups, nitro, alkoxy, alkylthio, alkylsulphinyl, alkylsulphonyl, alkylsulphonylamino, phenyl, phenylalkoxy, trifluoromethyl, alkoxycarbonyl, alkoxycarbonylalkyl, carboxy, carboxyalkyl, dialkylaminoalkyl, hydroxy, amino, acetylamino, propionylamino, benzoyl, benzoylamino, benzoylmethylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, hydroxyalkylaminocarbonyl, (4-morpholinyl)carbonyl, (1-pyrrolidinyl)carbonyl, (1-piperidinyl)carbonyl, (hexahydro-1-azepinyl)carbonyl, (4-methyl-1-

piperazinyl)carbonyl, methylenedioxy, aminocarbonylamino, aminocarbonylaminoalkyl, alkylaminocarbonylamino, alkanoyl, cyano, trifluoromethoxy, trifluormethylthio, trifluoromethylsulphinyl- or trifluoromethylsulphonyl groups, wherein the substituents may be identical or different and the above-mentioned benzoyl, benzoylamino, benzoylaminocarbonylamino and benzoylmethylamino groups may in turn additionally be substituted in the phenyl moiety by a fluorine, chlorine or bromine atom or by an alkyl, trifluoromethyl, amino- or acetylamino group

and unless otherwise specified the alkyl groups contained in the above-mentioned radicals may contain 1 to 5 carbon atoms,

X denotes an oxygen atom or 2 hydrogen atoms,

Z denotes a methylene group or the group $-NR^1$, wherein

R^1 denotes a hydrogen atom or an alkyl or phenylalkyl group,

R^{11} denotes a hydrogen atom, a C_{1-3}-alkyl group, an alkoxycarbonyl group having a total of 2 to 4 carbon atoms or a phenylmethyl group,

n denotes the number 1 or 2 or, if m is 1, n may also be 0,

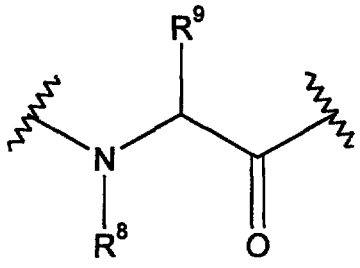
m denotes the number 0 or 1,

R^2 denotes a phenyl, 1-naphthyl, 2-naphthyl, 1,2,3,4-tetrahydro-1-naphthyl, 1H-indol-3-yl, 1-methyl-1H-indol-3-yl, 1-formyl-1H-indol-3-yl, 1-(1,1-dimethylethoxycarbonyl)-1H-indol-3-yl, 4-imidazolyl, 1-methyl-4-imidazolyl, 2-thienyl, 3-thienyl, thiazolyl, 1H-indazol-3-yl, 1-methyl-

1H-indazol-3-yl, benzo[b]fur-3-yl, benzo[b]thien-3-yl, pyridinyl, quinolinyl or isoquinolinyl group,

whilst the above-mentioned aromatic and heteroaromatic groups in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms or by branched or unbranched alkyl groups, C_{3-8}-cycloalkyl groups, phenylalkyl groups, alkenyl, alkoxy, phenyl, phenylalkoxy, trifluoromethyl, alkoxycarbonylalkyl, carboxyalkyl, alkoxycarbonyl, carboxy, dialkylaminoalkyl, dialkylaminoalkoxy, hydroxy, nitro, amino, acetylamino, propionylamino, benzoyl, benzoylamino, benzoylmethylamino, methylsulphonyloxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkanoyl, cyano, tetrazolyl, phenyl, pyridinyl, thiazolyl, furyl, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl- or trifluoromethylsulphonyl groups, and the substituents may be identical or different and the above-mentioned benzoyl, benzoylamino- and benzoylmethylamino groups may in turn additionally be substituted in the phenyl moiety by a fluorine, chlorine or bromine atom, or by an alkyl, trifluoromethyl, amino or acetylamino group,

A denotes a bond or the divalent group of formula



(III),

(which is linked to the NR^3R^4 group via the -CX group)

wherein

R^8 and R^9 together denote an n-propylene group or

R^8 denotes a hydrogen atom or an alkyl- or phenylalkyl group and

R^9 denotes a hydrogen atom or a branched or unbranched C_{1-5}-alkyl group which, if it is unbranched, may be substituted in the ω-position by a hydroxy, mercapto, amino, alkylamino, dialkylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidinyl, hexahydro-1-azepinyl, methylthio, hydroxycarbonyl, aminocarbonyl, aminoiminomethylamino, aminocarbonylamino, phenyl, 1H-indol-3-yl, 1-methyl-1H-indol-3-yl, 1-formyl-1H-indol-3-yl, 4-imidazolyl, 1-methyl-4-imidazolyl, 1-naphthyl, 2-naphthyl- or pyridinyl group, whilst the above-mentioned heterocycles, phenyl and naphthyl groups may in turn be mono-, di- or trisubstituted in the carbon skeleton by fluorine, chlorine or bromine atoms or by methyl, alkoxy, trifluoromethyl, hydroxy, amino, acetylamino, aminocarbonyl, cyano, trifluoromethoxy, methylsulphonyloxy, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl groups, wherein the substituents may be identical or different, and wherein the hydroxy, mercapto, amino, guanidino, indolyl and imidazolyl groups contained in the groups mentioned for R^9 may be substituted with the protecting groups commonly used in peptide chemistry, preferably with the acetyl, benzyloxycarbonyl or tert.butyloxycarbonyl group,

R^3 denotes a hydrogen atom,

a C_{1-7}-alkyl group which may be substituted in the ω-position by a cyclohexyl, phenyl, pyridinyl, diazinyl, hydroxy, amino, alkylamino, dialkylamino, carboxy,

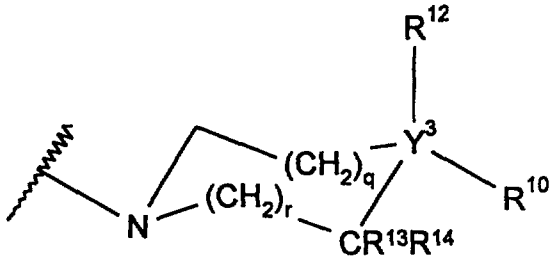
aminocarbonyl, aminocarbonylamino, acetylamino, 1-pyrrolidinyl, 1-piperidinyl, 4-(1-piperidinyl)-1-piperidinyl, 4-morpholinyl, hexahydro-1H-1-azepinyl, [bis-(2-hydroxyethyl)]amino, 4-alkyl-1-piperazinyl or 4-(ω-hydroxyalkyl)-1-piperazinyl group,

a phenyl or pyridinyl group,

wherein the above-mentioned heterocyclic groups and phenyl groups may additionally be mono-, di- or trisubstituted in the carbon skeleton by fluorine, chlorine or bromine atoms or by methyl, alkoxy, trifluoromethyl, hydroxy, amino, acetylamino, aminocarbonyl, cyano, methylsulphonyloxy, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl groups and the substituents may be identical or different,

R^4 denotes a hydrogen atom or a C_{1-3}-alkyl group optionally substituted by a phenyl or pyridinyl group or

R^3 and R^4 together with the enclosed nitrogen atom denote a group of general formula



(IV),

wherein

Y^3 denotes a carbon atom or, if R^{12} denotes a free pair of electrons, Y^3 may also be the nitrogen atom,

r denotes the number 0, 1 or 2,

q denotes the number 0, 1 or 2,

R^{10} denotes a hydrogen atom or an amino, alkylamino, dialkylamino, alkyl, cycloalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, aminoiminomethyl, aminocarbonylamino, alkylaminocarbonylamino, cycloalkylaminocarbonylamino, phenylaminocarbonylamino, aminocarbonylalkyl, aminocarbonylaminoalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, carboxyalkyl or carboxy group,

a phenyl, pyridinyl, diazinyl, 1-naphthyl, 2-naphthyl, pyridinylcarbonyl- or phenylcarbonyl- group which may be mono-, di- or trisubstituted in the carbon skeleton by fluorine, chlorine or bromine atoms, or by alkyl, alkoxy, methylsulphonyloxy, trifluoromethyl, hydroxy, amino, acetylamino, aminocarbonyl, aminocarbonylamino, aminocarbonylaminomethyl, cyano, carboxy, carbalkoxy, carboxyalkyl, carbalkoxyalkyl, alkanoyl, ω-(dialkylamino)alkanoyl, ω-(dialkylamino)alkyl, ω-(dialkylamino)hydroxyalkyl, ω-(carboxy)alkanoyl, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl groups, whilst the substituents may be identical or different,

a 1,3-dihydro-2-oxo-2H-imidazolyl, 2,4(1H,3H)-dioxopyrimidinyl or 3,4-dihydro-2(1H)-oxopyrimidinyl group bound via a nitrogen atom, which may be substituted by a phenyl group or fused at the double bond to a benzene, pyridine or diazine ring,

a 1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl group,

a 4- to 10-membered azacycloalkyl group, a 5- to 10-membered oxaza, thiaza- or diazacycloalkyl group or a 6- to 10-membered azabicycloalkyl group,

wherein the above-mentioned mono- and bicyclic heterocycles may be bound via a nitrogen or carbon atom and

may be substituted by a C_{1-7}-alkyl group, by an alkanoyl, dialkylamino, phenylcarbonyl, pyridinylcarbonyl, carboxyalkanoyl, carboxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, alkylsulphonyl, cycloalkyl- or cycloalkylalkyl group, by a cycloalkylcarbonyl, aza-cycloalkylcarbonyl, diazacycloalkylcarbonyl or oxazacycloalkylcarbonyl group optionally substituted in the ring,

whilst the alicyclic parts contained in these substituents may comprise 3 to 10 ring members and the heteroalicyclic parts may comprise 4 to 10 ring members and

the above-mentioned phenyl and pyridinyl groups may in turn be mono- , di- or trisubstituted by fluorine, chlorine or bromine atoms, by alkyl, alkoxy, methylsulphonyloxy, trifluoromethyl, hydroxy, amino, acetylamino, aminocarbonyl, aminocarbonylamino, aminocarbonylaminomethyl, cyano, carboxy, carbalkoxy, carboxyalkyl, carbalkoxyalkyl, alkanoyl, ω-(dialkylamino)alkanoyl, ω-(carboxy)alkanoyl, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl or

trifluoromethylsulphonyl groups, whilst the substituents may be identical or different, or

R^{10} together with R^{12} and Y^3 denotes a 4- to 7-membered cycloaliphatic ring in which a methylene group may be replaced by an -NH- or -N(alkyl)- group,

whilst a hydrogen atom bound to a nitrogen atom within the group R^{10} may be replaced by a protecting group,

R^{12} denotes a hydrogen atom,

a C_{1-4}-alkyl group, wherein an unbranched alkyl group may be substituted in the ω-position by a phenyl, pyridinyl, diazinyl, amino, alkylamino, dialkylamino, 1-pyrrolidinyl, 1-piperidinyl, 4-methyl-1-piperazinyl, 4-morpholinyl- or hexahydro-1H-1-azepinyl group,

an alkoxycarbonyl, cyano or aminocarbonyl group or a free pair of electrons, if Y^3 denotes a nitrogen atom, and

R^{13} and R^{14} in each case denote a hydrogen atom or,

if Y^3 is a carbon atom, R^{12} together with R^{14} also denotes another carbon-carbon bond, wherein R^{10} is as hereinbefore defined and R^{13} denotes a hydrogen atom or

if Y^3 is a carbon atom, R^{12} together with R^{14} also denotes another carbon-carbon bond and R^{10} together with R^{13} and the enclosed double bond denotes a partially hydrogenated or aromatic 5- to 7-membered mono- or bicyclic carbocycle or heterocycle,

whilst all the above-mentioned alkyl and alkoxy groups and the alkyl groups present within the other groups mentioned may contain 1 to 7 carbon atoms, unless otherwise specified,

all the above-mentioned cycloalkyl groups and the cycloalkyl groups present within the other groups named may contain 5 to 10 carbon atoms, unless otherwise specified, and

the term "aroyl group" used above denotes, for example, the benzoyl or naphthoyl group.

The protecting groups mentioned in the foregoing definitions and hereinafter are the protecting groups which are commonly known from peptide chemistry, particularly

a phenylalkoxycarbonyl group having 1 to 3 carbon atoms in the alkoxy moiety, optionally substituted in the phenyl nucleus by a halogen atom, by a nitro or phenyl group or by one or two methoxy groups,

for example the benzyloxycarbonyl, 2-nitro-benzyloxy-carbonyl, 4-nitro-benzyloxycarbonyl, 4-methoxy-benzyloxycarbonyl, 2-chloro-benzyloxycarbonyl, 3-chloro-benzyloxy-carbonyl, 4-chloro-benzyloxycarbonyl, 4-Biphenylyl-α, α-dimethyl-benzyloxycarbonyl or 3,5-dimethoxy-α,α-dimethyl-benzyloxycarbonyl group,

an alkoxycarbonyl group having a total of 1 to 5 carbon atoms in the alkyl moiety,

for example the methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl,

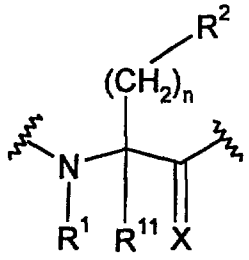
n-butoxycarbonyl, 1-methylpropoxycarbonyl, 2-methylpropoxycarbonyl or tert.butyloxycarbonyl group,

the allyloxycarbonyl, 2,2,2-trichloro-(1,1-dimethyl-ethoxy)carbonyl or 9-fluorenylmethoxycarbonyl group or

the formyl, acetyl or trifluoroacetyl group.

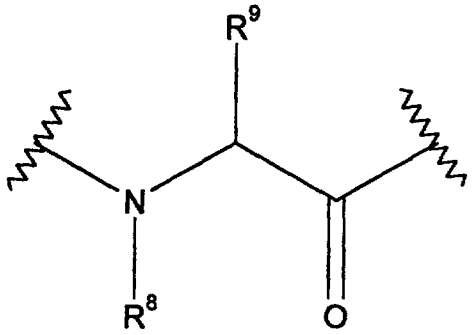
The present invention relates to racemates, where the compounds of general formula I have only one chiral element. However, the application also covers the individual diastereomeric pairs of antipodes or mixtures thereof which occur when there is more than one chiral element in the compounds of general formula (I).

Particularly preferred are compounds of general formula I wherein Z denotes NR^1 and m assumes the value 0 and which are in the D- or (R)-configuration with regard to the partial amino acid structure of the formula



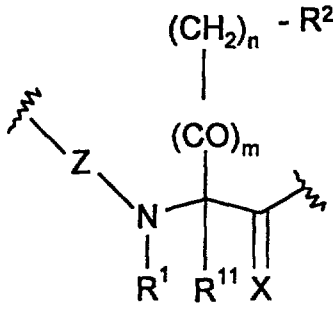
(V)

and which are in the L- or (S)-configuration with regard to the partial amino acid structure of formula



(III)

which may be present in the group A. As for the other compounds covered by general formula I, the preferred isomers are those which are spatially constructed analogously to the (R)-configured partial structure of formula V with regard to the partial structure of formula VI



(VI)

The compounds of general formula I have valuable pharmacological properties based on their selective CGRP-antagonistic properties. The invention further relates to medicaments containing these compounds, their use and the preparation thereof.

A subgroup of compounds of general formula I which deserves special mention comprises those wherein

A, R^2, R^3, R^4, R^{11}, X, Z and m and n are as hereinbefore defined and

R denotes an unbranched C_{1-6}-alkylamino group optionally substituted at the nitrogen atom by a C_{1-6}-alkyl group or

by a phenylmethyl group, which may be substituted in the ω-position

by a C_{4-10}-cycloalkyl group,

by one or two phenyl groups, by a 1-naphthyl, 2-naphthyl or biphenylyl group,

by a 1H-indol-3-yl, 1,3-dihydro-2H-2-oxobenzimidazol-1-yl, 2,4(1H,3H)-dioxoquinazolin-1-yl, 2,4(1H,3H)-dioxoquinazolin-3-yl, 2,4(1H,3H)-dioxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-3-yl, 2(1H)-oxoquinolin-3-yl, 2(1H)-oxoquinoxalin-3-yl, 1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl, 1,3-dihydro-4-(3-thienyl)-2H-2-oxoimidazol-1-yl, 1,3-dihydro-4-phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-5-phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-2(2H)-oxoimidazo[4,5-c]quinolin-3-yl, 3,4-dihydro-5-phenyl-2(1H)-oxopyrimidin-3-yl, 3,4-dihydro-6-phenyl-2(1H)-oxopyrimidin-3-yl- or 1,3-dihydro-2H-2-oxoimidazo-[4,5-b]pyridin-3-yl- group,

by a 5-membered heteroaromatic ring linked via a carbon atom, which contains a nitrogen, oxygen or sulphur atom or, in addition to a nitrogen atom, contains an oxygen, sulphur or an additional nitrogen atom, whilst a nitrogen atom of an imino group may be substituted by an alkyl group, or

by a 6-membered heteroaromatic ring linked via a carbon atom and containing 1, 2 or 3 nitrogen atoms,

whilst a 1,4-butadienylene group may be attached both to the 5-membered and to the 6-membered heteroaromatic monocyclic rings via two adjacent carbon atoms in each case and the bicyclic heteroaromatic rings thus formed may also be bound via a carbon atom of the 1,4-butadienylene group,

whilst the phenyl, naphthyl and biphenylyl groups mentioned above for the substitution of the alkylamino groups in the ω-position and optionally partially hydrogenated mono- and bicyclic heteroaromatic rings in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms, by alkyl groups, C_{3-8}-cycloalkyl groups, nitro, alkoxy, phenyl, phenylalkoxy, trifluoromethyl, alkoxycarbonyl, alkoxycarbonylalkyl, carboxy, carboxyalkyl, dialkylaminoalkyl, hydroxy, amino, acetylamino, propionylamino, benzoyl, benzoylamino, benzoylmethylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, (1-pyrrolidinyl)carbonyl, (1-piperidinyl)carbonyl, (hexahydro-1H-azepin-1-yl)carbonyl, (4-methyl-1-piperazinyl)carbonyl, (4-morpholinyl)carbonyl, alkanoyl, cyano, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl- or trifluoromethylsulphonyl groups, whilst the substituents may be identical or different and the above-mentioned benzoyl, benzoylamino- and benzoylmethylamino groups in turn may additionally be substituted in the phenyl moiety by a fluorine, chlorine or bromine atom or by an alkyl, trifluoromethyl, amino or acetylamino group,

whilst all the above-mentioned alkyl and alkoxy groups and the alkyl groups present within the other groups mentioned may contain 1 to 4 carbon atoms, unless otherwise stated,

their tautomers, their diastereomers, their enantiomers, mixtures thereof and the salts thereof.

Another subgroup of compounds of general formula I deserving special mention comprises those wherein

R^2, R^3, R^4, R^{11}, X, Z and m and n are defined as for the first subgroup hereinbefore,

R denotes an unbranched C_{1-7}-alkyl group which may be substituted in the ω-position

by a C_{4-10}-cycloalkyl group,

by one or two phenyl groups, by a 1-naphthyl, 2-naphthyl- or biphenylyl- group,

by a 1,3-dihydro-2H-2-oxobenzimidazol-1-yl, 2,4(1H,3H)-dioxoquinazolin-1-yl, 2,4(1H,3H)-dioxoquinazolin-3-yl, 2,4(1H,3H)-dioxothieno-[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-3-yl, 2(1H)-oxoquinolin-3-yl, 2(1H)-oxoquinoxalin-3-yl, 1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl, 1,3-dihydro-2H-2-oxoimidazopyridinyl, 1,3-dihydro-2(2H)-oxoimidazo[4,5-c]quinolin-3-yl, 1,3-dihydro-2H-2-oxoimidazol-1-yl- or 3,4-dihydro-2(1H)-oxopyrimidin-3-yl- group, whilst the latter two groups may each be mono- or disubstituted in the 4- and/or 5-position or in the 5- and/or 6-position by lower straight-chained or branched alkyl groups, by phenyl, biphenylyl, pyridinyl, diazinyl, furyl, thienyl, pyrrolyl, 1,3-oxazolyl, 1,3-thiazolyl, isoxazolyl, pyrazolyl- 1-methylpyrazolyl, imidazolyl

or 1-methylimidazolyl groups, and the substituents may be identical or different,

by a 5-membered heteroaromatic ring linked via a carbon atom, which contains a nitrogen, oxygen or sulphur atom or in addition to a nitrogen atom contains an oxygen, sulphur or an additional nitrogen atom, whilst a nitrogen atom of an imino group may be substituted by an alkyl group,

or by a 6-membered heteroaromatic ring linked via a carbon atom, which contains one, two or three nitrogen atoms,

whilst a 1,4-butadienylene group may be attached both to the above-mentioned 5-membered and to the 6-membered heteroaromatic monocyclic rings, in each case via two adjacent carbon atoms, and the bicyclic heteroaromatic rings thus formed may also be bound via a carbon atom of the 1,4-butadienylene group,

whilst the phenyl, naphthyl- and biphenylyl- groups mentioned hereinbefore for the substitution of the alkyl groups in the ω-position and optionally partially hydrogenated mono- and bicyclic heteroaromatic rings in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms, by alkyl groups, C_{3-8}-cycloalkyl groups, nitro, alkoxy, phenyl, phenylalkoxy, trifluoromethyl, alkoxycarbonyl, alkoxycarbonylalkyl, carboxy, carboxyalkyl, dialkylaminoalkyl, hydroxy, amino, acetylamino, propionylamino, benzoyl, benzoylamino, benzoylmethylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, (1-pyrrolidinyl)carbonyl, (1-piperidinyl)carbonyl, (hexahydro-1H-azepin-1-yl)carbonyl, (4-methyl-1-piperazinyl)carbonyl, (4-morpholinyl)carbonyl, alkanoyl,

cyano, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl groups, whilst the substituents may be identical or different and the above-mentioned benzoyl, benzoylamino and benzoylmethylamino groups may in turn additionally be substituted in the phenyl moiety by a fluorine, chlorine or bromine atom or by an alkyl, trifluoromethyl, amino or acetylamino group, and

A denotes a single bond,

whilst all the above-mentioned alkyl and alkoxy groups and the alkyl groups present within the other groups mentioned may contain 1 to 4 carbon atoms unless otherwise stated,

their tautomers, their diastereomers, their enantiomers and the salts thereof.

Preferred compounds of the above general formula I are those wherein

R denotes an unbranched C_{1-5}-alkyl group which may be substituted in the ω-position

by a C_{4-7}-cycloalkyl group,

by one or two phenyl groups, by a 1-naphthyl, 2-naphthyl or (4-biphenylyl) group,

by a 1,3-dihydro-2H-2-oxobenzimidazol-1-yl, 2,4(1H,3H)-dioxoquinazolin-1-yl, 2,4(1H,3H)-dioxoquinazolin-3-yl, 2,4(1H,3H)-dioxothieno-[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-1-yl, 3,4-dihydro-

2(1H)-oxoquinazolin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-3-yl, 2(1H)-oxoquinolin-3-yl, 2(1H)-oxoquinoxalin-3-yl, 1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl, 1,3-dihydro-2H-2-oxoimidazopyridinyl, 1,3-dihydro-2(2H)-oxoimidazo[4,5-c]quinolin-3-yl, 1,3-dihydro-2H-2-oxoimidazol-1-yl or 3,4-dihydro-2(1H)-oxopyrimidin-3-yl group, whilst the latter two groups may each be mono- or disubstituted in the 4- and/or 5-position or in the 5- and/or 6-positions by lower straight-chained or branched alkyl groups, by phenyl, biphenylyl, pyridinyl, diazinyl, furyl, thienyl, pyrrolyl, 1,3-oxazolyl, 1,3-thiazolyl, isoxazolyl, pyrazolyl- 1-methylpyrazolyl, imidazolyl or 1-methylimidazolyl groups, and the substituents may be identical or different,

by a 5-membered heteroaromatic ring linked via a carbon atom and containing a nitrogen, oxygen or sulphur atom or, in addition to a nitrogen atom, an oxygen, sulphur or additional nitrogen atom, whilst a nitrogen atom of an imino group may be substituted by an alkyl group,

or by a 6-membered heteroaromatic ring linked via a carbon atom and containing one or two nitrogen atoms,

whilst a 1,4-butadienylene group may be attached both to the 5-membered and to the 6-membered heteroaromatic monocyclic rings via two adjacent carbon atoms in each case and the bicyclic heteroaromatic rings thus formed may also be bound via a carbon atom of the 1,4-butadienylene group,

or an unbranched C_{1-4}-alkylamino group optionally substituted at the nitrogen atom by a C_{1-3}-alkyl group or

by a phenylmethyl group, which may be substituted in the ω-position

by a C_{4-7}-cycloalkyl group,

by one or two phenyl groups, by a 1-naphthyl, 2-naphthyl or (4-biphenylyl) group,

by a 1H-indol-3-yl, 1,3-dihydro-2H-2-oxobenzimidazol-1-yl, 2,4(1H,3H)-dioxoquinazolin-1-yl, 2,4(1H,3H)-dioxoquinazolin-3-yl, 2,4(1H,3H)-dioxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-3-yl, 2(1H)-oxoquinolin-3-yl, 2(1H)-oxoquinoxalin-3-yl, 1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl, 1,3-dihydro-4-(3-thienyl)-2H-2-oxoimidazol-1-yl, 1,3-dihydro-4-phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-5-phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-2(2H)-oxoimidazo[4,5-c]quinolin-3-yl, 3,4-dihydro-5-phenyl-2(1H)-oxopyrimidin-3-yl, 3,4-dihydro-6-phenyl-2(1H)-oxopyrimidin-3-yl or 1,3-dihydro-2H-2-oxo-imidazo[4,5-b]pyridin-3-yl group,

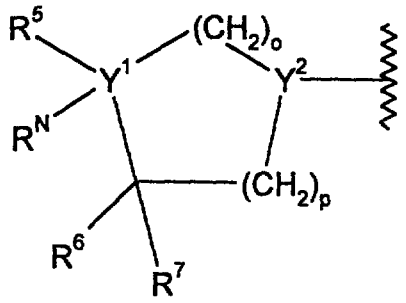
by a 5-membered heteroaromatic ring linked via a carbon atom and containing a nitrogen, oxygen or sulphur atom or, in addition to a nitrogen atom, an oxygen, sulphur or additional nitrogen atom, whilst a nitrogen atom of an imino group may be substituted by an alkyl group,

or by a 6-membered heteroaromatic ring linked via a carbon atom and containing 1 or 2 nitrogen atoms,

whilst a 1,4-butadienylene group may be attached to both the 5-membered and to the 6-membered heteroaromatic monocyclic rings via two adjacent carbon atoms in each case and the bicyclic heteroaromatic rings thus formed may also be bound via a carbon atom of the 1,4-butadienylene group,

whilst the phenyl, naphthyl and biphenylyl groups mentioned above for the substitution of the alkyl and alkylamino groups in the ω-position and optionally also partially hydrogenated mono- and bicyclic heteroaromatic rings in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms or by alkyl groups, C_{5-7}-cycloalkyl groups, nitro, alkoxy, phenyl, phenylalkoxy, trifluoromethyl, alkoxycarbonyl, alkoxycarbonylalkyl, carboxy, carboxyalkyl, dialkylaminoalkyl, hydroxy, amino, acetylamino, propionylamino, benzoyl, benzoylamino, benzoylmethylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, (1-pyrrolidinyl)carbonyl, (1-piperidinyl)carbonyl, (hexahydro-1H-azepin-1-yl)carbonyl, (4-methyl-1-piperazinyl)carbonyl, (4-morpholinyl)carbonyl, alkanoyl, cyano, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl groups, wherein the substituents may be identical or different and the above-mentioned benzoyl, benzoylamino and benzoylmethylamino groups may in turn additionally be substituted in the phenyl moiety by a fluorine, chlorine or bromine atom or by an alkyl, trifluoromethyl, amino or acetylamino group,

or the group of formula



(II),

wherein

p denotes the number 1 or 2,

o denotes the number 2 or, if Y^1 and Y^2 are not simultaneously nitrogen atoms, o may also denote 1.

Y^1 denotes the nitrogen atom if R^5 is a free pair of electrons, or the carbon atom,

Y^2 is the nitrogen atom or the group >CH-,

R^5 is a free pair of electrons if Y^1 denotes the nitrogen atom or, if Y^1 denotes the carbon atom, R^5 denotes a hydrogen atom, a C_{1-3}-alkyl group, a hydroxy, cyano, aminocarbonyl, carboxy, alkoxycarbonyl, aminocarbonylamino, phenylmethyl or phenyl group,

R^6 denotes the hydrogen atom or, provided that Y^1 is not a nitrogen atom, R^6 together with R^5 may denote an additional bond,

R^7 denotes the hydrogen atom or, provided that Y^1 is not a nitrogen atom and R^5 and R^6 together constitute an additional bond, R^7 together with R^N may also denote a 1,4-butadienylene group,

R^N denotes the hydrogen atom or a C_{1-3}-alkyl group, which may be monosubstituted in the ω-position

by a C_{5-7}-cycloalkyl group or by a 1-naphthyl, 2-naphthyl, hydroxy, alkoxy, amino, alkylamino, dialkylamino, piperidinyl, morpholinyl, pyrrolidinyl, hexahydro-1H-1-azepinyl, aminocarbonyl, alkylaminocarbonyl, acetylamino, cyano, aminocarbonylamino or alkyl-aminocarbonylamino group, or may be mono- or disubstituted by phenyl, pyridinyl or diazinyl groups, whilst these substituents may be identical or different,

a cyclohexyl, phenyl, pyridinyl, cyano, amino, benzoylamino, aminocarbonyl, alkylaminocarbonyl, alkoxycarbonyl, phenylalkoxycarbonyl, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, N-(aminocarbonyl)-N-alkylamino, N-(alkylaminocarbonyl)-N-alkylamino, N-(alkylaminocarbonyl)-N-phenylamino, phenylamino-carbonylamino, [N-phenyl(alkylamino)]carbonylamino, N-(phenylaminocarbonyl)-N-alkylamino, N-(phenylaminocarbonyl)-N-phenylamino, benzoylaminocarbonylamino, phenylalkylamino-carbonylamino, pyridinylaminocarbonylamino, N-(aminocarbonyl)-N-phenylamino, N-(alkylamino-carbonyl)-N-phenylamino, N-(aminocarbonyl-aminocarbonyl)-N-phenylamino, N-(pyridinyl)-N-(amino-carbonyl)amino, N-(pyridinyl)-N-(alkylaminocarbonyl)amino, phenylamino, pyridinylamino, diazinylamino or 4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl group,

a saturated, mono- or diunsaturated 5- to 7-membered aza, diaza, triaza, oxaza, thiaza, thiadiaza- or S,S-dioxidothiadiaza heterocycle,

whilst the above-mentioned heterocycles may be linked via a carbon or nitrogen atom and

may contain one or two carbonyl groups adjacent to a nitrogen atom,

may be substituted at one of the nitrogen atoms by an alkyl, alkanoyl, aroyl, hydroxycarbonylalkyl, alkoxycarbonylalkyl, phenylalkoxycarbonylalkyl, phenylmethyl or phenyl group,

may be substituted at one or two carbon atoms by a branched or unbranched alkyl group, by a phenyl, phenylmethyl, naphthyl, biphenylyl, pyridinyl, diazinyl, furyl, thienyl, pyrrolyl, 1,3-oxazolyl, 1,3-thiazolyl, isoxazolyl, pyrazolyl, 1-methylpyrazolyl, imidazolyl or 1-methylimidazolyl group, whilst the substituents may be identical or different,

and wherein a C_{3-4}-alkylene group may additionally be attached to the above-mentioned heterocycles via two adjacent carbon atoms or an olefinic double bond of one of the above-mentioned unsaturated heterocycles may be fused with a benzene, pyridine, diazine, 1,3-oxazole, thiophene, furan, thiazole, pyrrole, N-methyl-pyrrole, quinoline, imidazole or N-methyl-imidazole ring,

or, provided that Y^1 is not a nitrogen atom and R^5 and R^6 together denote an additional bond, R^N together

with R^7 may also denote the 1,4-butadienylene group or,

if Y^1 denotes a carbon atom, R^N together with R^5, with the inclusion of Y^1, may also denote a carbonyl group or a saturated or monounsaturated 5- or 6-membered 1,3-diaza-heterocycle which may contain one or two carbonyl groups in the ring adjacent to a nitrogen atom and, if it is unsaturated, may also be benzo-fused at the double bond and substituted at one of the nitrogen atoms by a methyl, aminocarbonyl, hydroxycarbonylalkyl, alkoxycarbonylalkyl, phenylalkoxycarbonylalkyl, phenylmethyl or phenyl group,

whilst the phenyl, pyridinyl, diazinyl, furyl, thienyl, pyrrolyl, 1,3-oxazolyl, 1,3-thiazolyl, isoxazolyl, pyrazolyl, 1-methylpyrazolyl, imidazolyl or 1-methylimidazolyl groups contained in the residues mentioned under R^5, R^7 and R^N, as well as benzo-, thieno-, pyrido- and diazino-fused heterocycles in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms, by alkyl groups, C_{4-7}-cycloalkyl groups, nitro, alkoxy, alkylthio, alkylsulphinyl, alkylsulphonyl, alkylsulphonylamino, phenyl, phenylalkoxy, trifluoromethyl, alkoxycarbonyl, alkoxycarbonylalkyl, carboxy, carboxyalkyl, dialkylaminoalkyl, hydroxy, amino, acetylamino, propionylamino, benzoyl, benzoylamino, benzoylmethylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, hydroxyalkylaminocarbonyl, (4-morpholinyl)carbonyl, (1-pyrrolidinyl)carbonyl, (1-piperidinyl)carbonyl, (hexahydro-1-azepinyl)carbonyl, (4-methyl-1-piperazinyl)carbonyl, methylenedioxy, aminocarbonylamino, aminocarbonylaminoalkyl, alkylaminocarbonylamino, alkanoyl, cyano,

trifluoromethoxy, trifluormethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl groups, wherein the substituents may be identical or different and the alkyl groups contained in the above-mentioned groups may contain 1 to 3 carbon atoms unless otherwise specified,

X denotes the oxygen atom or 2 hydrogen atoms,

Z denotes the methylene group or the group $-NR^1-$ wherein

R^1 denotes a hydrogen atom or a C_{1-3}-alkyl group,

R^{11} denotes a hydrogen atom, a C_{1-3}-alkyl group or an alkoxycarbonyl group having 2 to 4 carbon atoms altogether,

n denotes the number 1 or 2 or, if m is 1, n may also be 0,

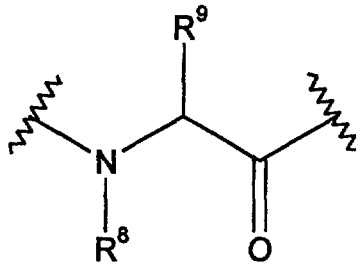
m denotes the number 0 or 1,

R^2 denotes a phenyl, 1-naphthyl, 2-naphthyl, 1,2,3,4-tetrahydro-1-naphthyl, 1H-indol-3-yl, 1-methyl-1H-indol-3-yl, 1-formyl-1H-indol-3-yl, 1-(1,1-dimethylethoxycarbonyl)-1H-indol-3-yl, 4-imidazolyl, 1-methyl-4-imidazolyl, 2-thienyl, 3-thienyl, thiazolyl, 1H-indazol-3-yl, 1-methyl-1H-indazol-3-yl, benzo[b]fur-3-yl, benzo[b]thien-3-yl, pyridinyl, quinolinyl or isoquinolinyl group,

whilst the above-mentioned aromatic and heteroaromatic groups in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms, or by branched or unbranched alkyl groups, C_{4-7}-cycloalkyl groups, phenylalkyl groups, alkenyl, alkoxy, phenyl, phenylalkoxy, trifluoromethyl, alkoxycarbonylalkyl, carboxyalkyl, alkoxycarbonyl, carboxy, dialkylaminoalkyl, dialkylaminoalkoxy, hydroxy,

nitro, amino, acetylamino, propionylamino, benzoyl, benzoylamino, benzoylmethylamino, methylsulphonyloxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkanoyl, cyano, tetrazolyl, phenyl, pyridinyl, thiazolyl, furyl, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl groups, and the substituents may be identical or different,

A denotes a bond or the divalent group of formula



(III),

(linked to the R^3R^4N- group of general formula (I) via the carbonyl group)

wherein

R^8 and R^9 together denote an n-propylene group or

R^8 denotes a hydrogen atom or a C_{1-3}-alkyl group and

R^9 denotes a hydrogen atom or a branched or unbranched C_{1-4}-alkyl group which, if it is unbranched, may be substituted in the ω-position

by a hydroxy, mercapto, amino, alkylamino, dialkylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidinyl, hexahydro-1-azepinyl, methylthio, hydroxycarbonyl, aminocarbonyl, aminoiminomethylamino, aminocarbonylamino, phenyl, 1H-indol-3-yl, 1-methyl-1H-indol-3-yl,

1-formyl-1H-indol-3-yl, 4-imidazolyl, 1-methyl-4-imidazolyl, 1-naphthyl, 2-naphthyl- or pyridinyl group, whilst the above-mentioned heterocycles and phenyl groups may in turn be mono-, di- or trisubstituted in the carbon skeleton by fluorine, chlorine or bromine atoms, or by methyl, alkoxy, trifluoromethyl, hydroxy, amino, acetylamino, aminocarbonyl, cyano, trifluoromethoxy, methylsulphonyloxy, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl groups, whilst the substituents may be identical or different and any hydroxy, mercapto, amino, guanidino, indolyl and imidazolyl groups contained in the groups mentioned for R^9 may be substituted by a protecting group,

R^3 denotes a hydrogen atom,

a C_{1-4}-alkyl group which may be substituted in the ω-position by a cyclohexyl, phenyl, pyridinyl, diazinyl, hydroxy, amino, alkylamino, dialkylamino, carboxy, aminocarbonyl, aminocarbonylamino, acetylamino, 1-pyrrolidinyl, 1-piperidinyl, 4-(1-piperidinyl)-1-piperidinyl, 4-morpholinyl, hexahydro-1H-azepin-1-yl, [bis-(2-hydroxyethyl)]amino, 4-methyl-1-piperazinyl- or 4-(ω-hydroxyalkyl)-1-piperazinyl group,

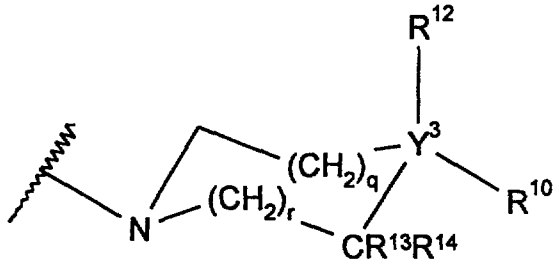
a phenyl or pyridinyl group,

wherein the above-mentioned heterocyclic radicals and phenyl groups may additionally be mono-, di- or trisubstituted in the carbon skeleton by fluorine, chlorine or bromine atoms or by methyl, alkoxy, trifluoromethyl, hydroxy, amino, acetylamino, aminocarbonyl, cyano, methylsulphonyloxy,

trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl groups and the substituents may be identical or different,

R^4 denotes a hydrogen atom or a methyl or ethyl group optionally substituted by a phenyl or pyridinyl group

or R^3 and R^4 together with the enclosed nitrogen atom denote a group of general formula



(IV),

wherein

Y^3 denotes a carbon atom or, if R^{12} denotes a free pair of electrons, Y^3 may also be the nitrogen atom,

r denotes the number 0, 1 or 2,

q denotes the number 0, 1 or 2,

R^{10} denotes a hydrogen atom or an amino, alkylamino, dialkylamino, alkyl, cycloalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, aminoiminomethyl, aminocarbonylamino, alkylaminocarbonylamino, cycloalkylaminocarbonylamino, phenylaminocarbonylamino, aminocarbonylalkyl, aminocarbonylaminoalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, carboxyalkyl or carboxy group,

a phenyl, pyridinyl, diazinyl, 1-naphthyl, 2-naphthyl, pyridinylcarbonyl or phenylcarbonyl group which may be mono-, di- or trisubstituted in the carbon skeleton by fluorine, chlorine or bromine atoms, or by alkyl, alkoxy, methylsulphonyloxy, trifluoromethyl, hydroxy, amino, acetylamino, aminocarbonyl, aminocarbonylamino, amino-carbonylaminomethyl, cyano, carboxy, carbalkoxy, carboxyalkyl, carbalkoxyalkyl, alkanoyl, ω-(dialkylamino)alkanoyl, ω-(dialkylamino)alkyl, ω-(dialkylamino)hydroxyalkyl, ω-(carboxy)alkanoyl, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl- oder trifluoromethyl-sulphonyl groups, whilst the substituents may be identical or different,

a 1,3-dihydro-2-oxo-2H-imidazolyl, 2,4(1H,3H)-dioxopyrimidinyl or 3,4-dihydro-2(1H)-oxopyrimidinyl group bound via a nitrogen atom, which may be substituted by a phenyl group or fused at the double bond to a benzene, pyridine or diazine ring,

a 1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl group,

a 4- to 10-membered azacycloalkyl group, a 5- to 10-membered oxaza, thiaza or diazacycloalkyl group or a 6- to 10-membered azabicycloalkyl group,

wherein the above-mentioned mono- and bicyclic heterocycles may be bound via a nitrogen or carbon atom and

may be substituted by a C_{1-7}-alkyl group, by an alkanoyl, dialkylamino, phenylcarbonyl, pyridinylcarbonyl, carboxyalkanoyl, carboxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl,

aminocarbonyl, alkylaminocarbonyl, alkylsulphonyl, cycloalkyl or cycloalkylalkyl group, by a cycloalkylcarbonyl, aza-cycloalkylcarbonyl, diazacycloalkylcarbonyl or oxazacycloalkylcarbonyl group optionally alkyl substituted in the ring,

whilst the alicyclic parts contained in these substituents may comprise 3 to 10 ring members and the heteroalicyclic parts may comprise 4 to 10 ring members and

the above-mentioned phenyl and pyridinyl groups may in turn be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms, by alkyl, alkoxy, methylsulphonyloxy, trifluoromethyl, hydroxy, amino, acetylamino, aminocarbonyl, aminocarbonylamino, aminocarbonylaminomethyl, cyano, carboxy, carbalkoxy, carboxyalkyl, carbalkoxyalkyl, alkanoyl, ω-(dialkylamino)alkanoyl, ω-(carboxy)alkanoyl, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl groups, whilst the substituents may be identical or different, or

R^{10} together with R^{12} and Y^3 denotes a 4- to 7-membered cycloaliphatic ring in which a methylene group may be replaced by an -NH- or -N(alkyl)- group,

whilst a hydrogen atom bound to a nitrogen atom within the group R^{10} may be replaced by a protecting group,

R^{12} denotes a hydrogen atom, a C_{1-2}-alkyl group which may be substituted in the ω-position by a phenyl, pyridinyl, diazinyl, amino, alkylamino, dialkylamino, 1-pyrrolidinyl, 1-piperidinyl, 4-methyl-1-piperazinyl, 4-morpholinyl or hexahydro-1H-azepin-1-yl- group,

an alkoxycarbonyl, cyano- or aminocarbonyl group or a free pair of electrons, if Y^3 denotes a nitrogen atom, and

R^{13} and R^{14} in each case denote a hydrogen atom or,

if Y^3 is a carbon atom, R^{12} together with R^{14} also denotes another carbon-carbon bond, wherein R^{10} is as hereinbefore defined and R^{13} denotes a hydrogen atom or

if Y^3 is a carbon atom, R^{12} together with R^{14} also denotes another carbon-carbon bond and R^{10} together with R^{13} and the enclosed double bond denotes a partially hydrogenated or aromatic 5- to 7-membered mono- or bicyclic carbocycle or heterocycle,

whilst all the above-mentioned alkyl and alkoxy groups and the alkyl groups present within the other groups mentioned may contain 1 to 4 carbon atoms, unless otherwise specified,

all the above-mentioned cycloalkyl groups and the cycloalkyl groups present within the other groups named may contain 5 to 7 carbon atoms, unless otherwise specified, and

the term "aroyl group" used above denotes, for example, the benzoyl or naphthoyl group,

their tautomers, their diastereomers, their enantiomers and their salts.

One subgroup of preferred compounds of general formula I deserving special mention comprises those wherein

A, R^2, R^3, R^4, R^{11}, X, Z and m and n are defined as given hereinbefore for the preferred compounds of general formula I,

R denotes an unbranched C_{1-4}-alkylamino group optionally substituted at the nitrogen atom by a C_{1-3}-alkyl group or by a phenylmethyl group, which may be substituted in the ω-position

by a C_{4-7}-cycloalkyl group,

by one or two phenyl groups, by a 1-naphthyl, 2-naphthyl or (4-biphenylyl) group,

by a 1H-indol-3-yl, 1,3-dihydro-2H-2-oxobenzimidazol-1-yl, 2,4(1H,3H)-dioxoquinazolin-1-yl, 2,4(1H,3H)-dioxoquinazolin-3-yl, 2,4(1H,3H)-dioxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-3-yl, 2(1H)-oxoquinolin-3-yl, 2(1H)-oxoquinoxalin-3-yl, 1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl, 1,3-dihydro-4-(3-thienyl)-2H-2-oxoimidazol-1-yl, 1,3-dihydro-4-phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-5-phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-2(2H)-oxoimidazo[4,5-c]quinolin-3-yl, 3,4-dihydro-5-phenyl-2(1H)-oxopyrimidin-3-yl, 3,4-dihydro-6-phenyl-2(1H)-

oxopyrimidin-3-yl or 1,3-dihydro-2H-2-oxo-imidazo[4,5-b]pyridin-3-yl group,

by a 5-membered heteroaromatic ring linked via a carbon atom, and containing a nitrogen, oxygen or sulphur atom or, in addition to a nitrogen atom, an oxygen, sulphur or additional nitrogen atom, whilst a nitrogen atom of an imino group may be substituted by an alkyl group,

or by a 6-membered heteroaromatic ring linked via a carbon atom and containing 1 or 2 nitrogen atoms, whilst a 1,4-butadienylene group may be attached both to the 5-membered and to the 6-membered heteroaromatic monocyclic rings via two adjacent carbon atoms in each case and the bicyclic heteroaromatic rings thus formed may also be bound via a carbon atom of the 1,4-butadienylene group,

whilst the phenyl, naphthyl and biphenylyl groups mentioned above for the substitution of the alkylamino groups in the ω-position and optionally partially hydrogenated mono- and bicyclic heteroaromatic rings in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms, by alkyl groups, C_{5-7}-cycloalkyl groups, nitro, alkoxy, phenyl, phenylalkoxy, trifluoromethyl, alkoxycarbonyl, alkoxycarbonylalkyl, carboxy, carboxyalkyl, dialkylaminoalkyl, hydroxy, amino, acetylamino, propionyl-amino, benzoyl, benzoylamino, benzoylmethylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, (1-pyrrolidinyl)carbonyl, (1-piperidinyl)carbonyl, (hexahydro-1H-azepin-1-yl)carbonyl, (4-methyl-1-piperazinyl)carbonyl, (4-morpholinyl)carbonyl, alkanoyl, cyano, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl groups, whilst the substituents may be identical or different and

the above-mentioned benzoyl, benzoylamino- and benzoylmethylamino groups in turn may additionally be substituted in the phenyl moiety by a fluorine, chlorine or bromine atom or by an alkyl, trifluoromethyl, amino or acetylamino group,

whilst all the above-mentioned alkyl and alkoxy groups and the alkyl groups present within the other groups mentioned may contain 1 to 4 carbon atoms, unless otherwise stated,

their tautomers, their diastereomers, their enantiomers, mixtures thereof and the salts thereof.

Another subgroup of compounds of general formula I deserving special mention comprises those wherein

R^2, R^3, R^4, R^{11}, X, Z and m and n are defined as for the first preferred subgroup hereinbefore,

R denotes an unbranched C_{1-5}-alkyl group which may be substituted in the ω-position

by a C_{4-7}-cycloalkyl group,

by one or two phenyl groups, by a 1-naphthyl, 2-naphthyl or (4-biphenylyl) group,

by a 1,3-dihydro-2H-2-oxobenzimidazol-1-yl, 2,4(1H,3H)-dioxoquinazolin-1-yl, 2,4(1H,3H)-dioxoquinazolin-3-yl, 2,4(1H,3H)-dioxothieno-[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-3-yl, 2(1H)-oxoquinolin-3-yl, 2(1H)-

oxoquinoxalin-3-yl, 1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl, 1,3-dihydro-2H-2-oxoimidazopyridinyl, 1,3-dihydro-2(2H)-oxoimidazo[4,5-c]quinolin-3-yl, 1,3-dihydro-2H-2-oxoimidazol-1-yl or 3,4-dihydro-2(1H)-oxopyrimidin-3-yl group, whilst the latter two groups may each be mono- or disubstituted in the 4- and/or 5-position or in the 5- and/or 6-position by lower straight-chained or branched alkyl groups, by phenyl, biphenylyl, pyridinyl, diazinyl, furyl, thienyl, pyrrolyl, 1,3-oxazolyl, 1,3-thiazolyl, isoxazolyl, pyrazolyl-1-methylpyrazolyl, imidazolyl or 1-methylimidazolyl groups, and the substituents may be identical or different,

by a 5-membered heteroaromatic ring linked via a carbon atom, which contains a nitrogen, oxygen or sulphur atom or in addition to a nitrogen atom contains an oxygen, sulphur or an additional nitrogen atom, whilst a nitrogen atom of an imino group may be substituted by an alkyl group,

or by a 6-membered heteroaromatic ring linked via a carbon atom, which contains one or two nitrogen atoms,

whilst a 1,4-butadienylene group may be attached both to the 5-membered and to the 6-membered heteroaromatic monocyclic rings, in each case via two adjacent carbon atoms, and the bicyclic heteroaromatic rings thus formed may also be bound via a carbon atom of the 1,4-butadienylene group,

whilst the phenyl, naphthyl and biphenylyl groups mentioned hereinbefore for the substitution of the alkyl groups in the ω-position and optionally partially

hydrogenated mono- and bicyclic heteroaromatic rings in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms, by alkyl groups, C_{5-7}-cycloalkyl groups, nitro, alkoxy, phenyl, phenylalkoxy, trifluoromethyl, alkoxycarbonyl, alkoxycarbonylalkyl, carboxy, carboxyalkyl, dialkylaminoalkyl, hydroxy, amino, acetylamino, propionylamino, benzoyl, benzoylamino, benzoylmethylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, (1-pyrrolidinyl)carbonyl, (1-piperidinyl)carbonyl, (hexahydro-1H-azepin-1-yl)carbonyl, (4-methyl-1-piperazinyl)carbonyl, (4-morpholinyl)carbonyl, alkanoyl, cyano, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl groups, whilst the substituents may be identical or different and the above-mentioned benzoyl, benzoylamino and benzoylmethylamino groups may in turn additionally be substituted in the phenyl moiety by a fluorine, chlorine or bromine atom or by an alkyl, trifluoromethyl, amino or acetylamino group, and

A denotes a single bond,

whilst all the above-mentioned alkyl and alkoxy groups and the alkyl groups present within the other groups mentioned may contain 1 to 4 carbon atoms unless otherwise stated,

their tautomers, their diastereomers, their enantiomers, mixtures thereof and the salts thereof.

Preferred compounds of the above general formula I are those wherein

R denotes an unbranched C_{1-3}-alkyl group which may be substituted in the ω-position

by a C_{5-7}-cycloalkyl group,

by one or two phenyl groups, by a 1-naphthyl, 2-naphthyl or (4-biphenylyl) group,

by a 1,3-dihydro-2H-2-oxobenzimidazol-1-yl, 1,3-dihydro-2H-2-oxoimidazol-1-yl or 3,4-dihydro-2(1H)-oxopyrimidin-3-yl group, whilst the latter two groups may be substituted in the carbon skeleton by a phenyl, pyridinyl or diazinyl group,

by a 5-membered heteroaromatic ring linked via a carbon atom and containing a nitrogen, oxygen or sulphur atom or two nitrogen atoms, wherein a nitrogen of an imino group may be substituted by an alkyl group,

or may be substituted by a pyridinyl group,

whilst a 1,4-butadienylene group may be attached both to the 5-membered heteroaromatic monocyclic rings and to the pyridinyl group, in each case via two adjacent carbon atoms, and the bicyclic heteroaromatic rings thus formed may also be bound via a carbon atom of the 1,4-butadienylene group,

or an unbranched C_{1-4}-alkylamino group optionally substituted at the nitrogen atom by a methyl or ethyl group, which may be substituted in the ω-position

by a C_{5-7}-cycloalkyl group,

by one or two phenyl groups, by a 1-naphthyl, 2-naphthyl or (4-biphenylyl) group,

by a 1H-indol-3-yl, 1,3-dihydro-2H-2-oxobenzimidazol-1-yl, 2(1H)-oxoquinolin-3-yl, 1,3-dihydro-4-phenyl-

2H-2-oxoimidazol-1-yl, 1,3-dihydro-5-phenyl-2H-2-oxoimidazol-1-yl, 3,4-dihydro-5-phenyl-2(1H)-oxopyrimidin-3-yl, 3,4-dihydro-6-phenyl-2(1H)-oxopyrimidin-3-yl or 1,3-dihydro-2H-2-oxoimidazo-[4,5-b]pyridin-3-yl group,

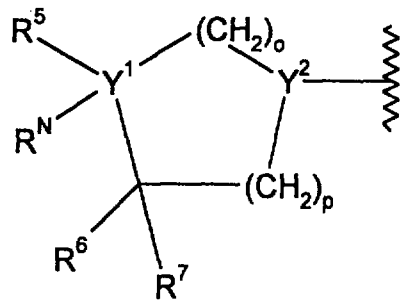
by a 5-membered heteroaromatic ring linked via a carbon atom and containing a nitrogen, oxygen or sulphur atom or two nitrogen atoms, whilst a nitrogen atom of an imino group may be substituted by an alkyl group,

or by a pyridinyl group,

whilst a 1,4-butadienylene group may be attached both to the 5-membered heteroaromatic monocyclic rings and to the pyridinyl group, in each case via two adjacent carbon atoms, and the bicyclic heteroaromatic rings thus formed may also be bound via a carbon atom of the 1,4-butadienylene group,

whilst the phenyl, naphthyl and biphenylyl groups mentioned hereinbefore for the substitution of the alkyl and alkylamino groups in the ω-position as well as optionally partially hydrogenated mono- and bicyclic heteroaromatic rings may additionally be mono- or disubstituted in the carbon skeleton by fluorine, chlorine or bromine atoms or by alkyl, nitro, alkoxy, trifluoromethyl, hydroxy, amino, acetylamino, propionylamino, alkanoyl, cyano or trifluoromethoxy groups, whilst the substituents may be the same or different,

or the group of formula



(II),

wherein

p denotes the number 1 or 2,

o denotes the number 2 or, if Y^1 and Y^2 are not simultaneously nitrogen atoms, it may also denote the number 1,

Y^1 denotes the nitrogen atom if R^5 denotes a free pair of electrons, or the carbon atom,

Y^2 denotes the nitrogen atom or the group >CH-,

R^5 denotes a free pair of electrons if Y^1 denotes the nitrogen atom or, if Y^1 denotes the carbon atom, R^5 denotes a hydrogen atom, a C_{1-3}-alkyl group, a hydroxy, cyano, aminocarbonyl, carboxy, alkoxycarbonyl or aminocarbonylamino group or a phenylmethyl or phenyl group optionally substituted at the aromatic moiety by a fluorine, chlorine or bromine atom or by a methyl, methoxy, ethoxy, trifluoromethyl, hydroxy, amino or acetylamino group,

R^6 denotes the hydrogen atom or, if Y^1 is not a nitrogen atom, R^6 together with R^5 may also denote an additional bond,

R^7 denotes the hydrogen atom or, provided that Y^1 is not a nitrogen atom and R^5 and R^6 together denote an

additional bond, R^7 together with R^N may also denote the 1,4-butadienylene group,

R^N denotes the hydrogen atom or a C_{1-3}-alkyl group, which may be monosubstituted in the ω-position

by a C_{5-7}-cycloalkyl group or by a 1-naphthyl, 2-naphthyl, hydroxy, alkoxy, amino, alkylamino, dialkylamino, piperidinyl, morpholinyl, pyrrolidinyl, hexahydro-1H-1-azepinyl, aminocarbonyl, methylaminocarbonyl, acetylamino, cyano, aminocarbonylamino or alkyl-aminocarbonylamino group, or may be mono- or disubstituted by phenyl, pyridinyl or diazinyl groups, whilst these substituents may be identical or different,

a cyclohexyl, phenyl, pyridinyl, cyano, amino, benzoylamino, aminocarbonyl, alkylaminocarbonyl, alkoxycarbonyl, phenylalkoxycarbonyl, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, N-(aminocarbonyl)-N-alkylamino, N-(alkylaminocarbonyl)-N-alkylamino, N-(alkylaminocarbonyl)-N-phenylamino, phenylamino-carbonylamino, [N-phenyl(alkylamino)]carbonylamino, N-(phenylaminocarbonyl)-N-alkylamino, N-(phenylaminocarbonyl)-N-phenylamino, benzoylaminocarbonylamino, phenylalkylamino-carbonylamino, pyridinylaminocarbonylamino, N-(aminocarbonyl)-N-phenylamino, N-(alkylamino-carbonyl)-N-phenylamino, N-(aminocarbonyl-aminocarbonyl)-N-phenylamino, N-(pyridinyl)-N-(amino-carbonyl)amino, N-(pyridinyl)-N-(alkylaminocarbonyl)amino, phenylamino, pyridinylamino, diazinylamino or 4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl group,

a saturated, mono- or diunsaturated 5- to 7-membered aza, diaza, triaza, oxaza, thiaza, thiadiaza or S,S-dioxido-thiadiaza heterocycle,

whilst the above-mentioned heterocycles may be linked via a carbon or nitrogen atom and

may contain one or two carbonyl groups adjacent to a nitrogen atom,

may be substituted at one of the nitrogen atoms by an alkyl, alkanoyl, hydroxycarbonylalkyl, alkoxycarbonylalkyl, phenylalkoxycarbonylalkyl, phenylmethyl or phenyl group,

may be substituted at one or two carbon atoms by a methyl, phenyl, phenylmethyl, naphthyl, biphenylyl, thienyl, pyridinyl or diazinyl group, wherein the substituents may be identical or different,

and wherein a C_{3-4}-alkylene group may additionally be attached to the above-mentioned heterocycles via two adjacent carbon atoms or an olefinic double bond of one of the above-mentioned heterocycles may be fused to a thiophene, benzene, pyridine, quinoline or diazine ring,

or, if Y^1 is not a nitrogen atom and R^5 and R^6 together denote an additional bond, R^N together with R^7 may also denote a 1,4-butadienylene group or,

if Y^1 denotes a carbon atom, R^N together with R^5 with the inclusion of Y^1 may also denote a carbonyl group or a saturated or monounsaturated 5- or 6-membered 1,3-diaza-heterocycle which may contain one or two

carbonyl groups in the ring adjacent to a nitrogen atom and, if it is unsaturated, may also be benzo-fused at the double bond and may be substituted at one of the nitrogen atoms by a methyl, aminocarbonyl, hydroxycarbonylalkyl, alkoxycarbonylalkyl, phenylalkoxycarbonylalkyl, phenylmethyl or phenyl group,

whilst the phenyl, pyridinyl or diazinyl groups contained in the groups mentioned under R^N and the thieno-, benzo-, pyrido- or diazino-condensed heterocycles in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms, by methyl groups, nitro, methoxy, ethoxy, methylsulphonylamino, trifluoromethyl, alkoxycarbonyl, alkoxycarbonylalkyl, carboxy, carboxyalkyl, hydroxy, amino, acetylamino, propionylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, hydroxyalkylaminocarbonyl, (4-morpholinyl)-carbonyl, (1-pyrrolidinyl)carbonyl, (1-piperidinyl)carbonyl, (hexahydro-1-azepinyl)carbonyl, (4-methyl-1-piperazinyl)carbonyl, methylenedioxy, aminocarbonylamino, aminocarbonylaminoalkyl, methylaminocarbonylamino, acetyl, cyano or trifluoromethoxy groups, whilst the substituents may be identical or different,

and the alkyl groups contained in the above-mentioned radicals may contain 1 to 3 carbon atoms, unless otherwise specified,

X denotes an oxygen atom or 2 hydrogen atoms,

Z denotes a methylene group or the group $-NR^1-$ wherein

R^1 is a hydrogen atom or a methyl group,

R^{11} denotes the hydrogen atom or a methyl or methoxycarbonyl group,

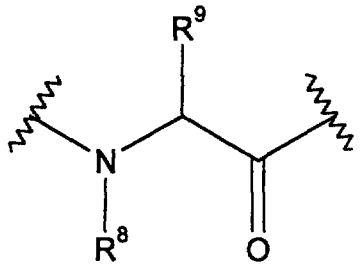
n denotes the number 1 or 2 or, if m is the number 1, n may also denote 0,

m denotes the number 0 or 1,

R^2 denotes a phenyl, 1-naphthyl, 2-naphthyl, 1,2,3,4-tetrahydro-1-naphthyl, 1H-indol-3-yl, 1-methyl-1H-indol-3-yl, 1-formyl-1H-indol-3-yl, 1-(1,1-dimethylethoxycarbonyl)-1H-indol-3-yl, 4-imidazolyl, 1-methyl-4-imidazolyl, 2-thienyl, 3-thienyl, thiazolyl, pyridinyl or quinolinyl group,

wherein the above-mentioned aromatic and heteroaromatic groups may additionally be mono-, di- or trisubstituted in the carbon skeleton by fluorine, chlorine or bromine atoms, by branched or unbranched C_{1-5}-alkyl groups, allyl, vinyl, methoxy, ethoxy, propoxy, 1-methylethoxy, dimethylaminoethoxy, trifluoromethyl, hydroxy, nitro, amino, acetylamino, propionylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, acetyl, cyano, methylsulphonyloxy or trifluoromethoxy groups, by tetrazolyl, phenyl pyridinyl, thiazolyl or furyl groups and the substituents may be identical or different, or

A denotes a bond or the divalent group of formula



(III),

(linked to the NR^3R^4- group of general formula (I) via the carbonyl group)

wherein

R^8 and R^9 together denote an n-propylene group or

R^8 denotes the hydrogen atom or the methyl group and

R^9 denotes a hydrogen atom or an unbranched C_{1-4}-alkyl group which may be substituted in the ω-position

by a hydroxy, amino, methylamino, dimethylamino, hydroxycarbonyl, aminocarbonyl, aminoimino-methylamino, aminocarbonylamino, phenyl or pyridinyl group, wherein the phenyl and pyridinyl group may in turn be substituted in the carbon skeleton by a fluorine, chlorine or bromine atom or by a methyl, methoxy, trifluoromethyl, hydroxy, amino, acetylamino, aminocarbonyl or cyano group and wherein any hydroxy, amino and guanidino groups contained in the groups given for R^9 may be substituted by a protecting group, e.g. the phenylmethoxycarbonyl or tert.butyloxy-carbonyl group,

R^3 denotes a hydrogen atom,

a C_{1-4}-alkyl group optionally substituted in the ω-position by a cyclohexyl, phenyl, pyridinyl, hydroxy, amino,

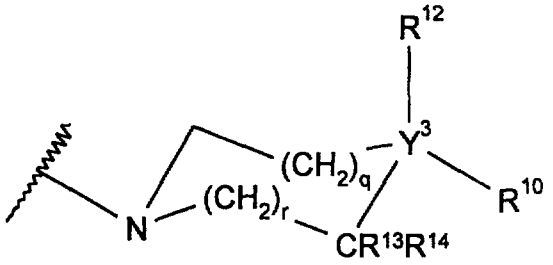
methylamino, dimethylamino, carboxy, aminocarbonyl, aminocarbonylamino, acetylamino, 1-pyrrolidinyl, 1-piperidinyl or 4-(1-piperidinyl)-1-piperidinyl group,

a phenyl or pyridinyl group,

whilst the above-mentioned phenyl and pyridinyl groups may additionally be substituted in the carbon skeleton by a fluorine, chlorine or bromine atom or by a methyl, methoxy, trifluoromethyl, hydroxy, amino, acetylamino, aminocarbonyl or cyano group,

R^4 denotes the hydrogen atom or a C_{1-2}-alkyl group optionally substituted by a phenyl or pyridinyl group

or R^3 and R^4 together with the enclosed nitrogen atom denote a group of general formula



(IV),

wherein

Y^3 denotes a carbon atom or, if R^{12} denotes a free pair of electrons, Y^3 may also be a nitrogen atom,

r denotes the number 0, 1 or 2,

q denotes the number 0, 1 or 2,

with the proviso that the sum of the numbers given for r and q is 0, 1, 2 or 3,

R^{10} denotes a hydrogen atom, an alkyl, cycloalkyl, dialkylamino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, phenylaminocarbonylamino, alkoxycarbonyl, alkoxycarbonylmethyl, carboxymethyl or carboxy group,

a phenyl, pyridinyl, diazinyl, pyridinylcarbonyl or phenylcarbonyl group which may be mono- or disubstituted in the carbon skeleton by fluorine, chlorine or bromine atoms, or by methyl, ethyl, propyl, methoxy, hydroxy, ω-(dialkylamino)-alkyl, ω-(dialkylamino)hydroxyalkyl or alkanoyl groups, whilst the substituents may be identical or different,

a 1,3-dihydro-2-oxo-2H-imidazolyl, 2,4(1H,3H)-dioxopyrimidinyl or 3,4-dihydro-2(1H)-oxopyrimidinyl group bound via a nitrogen atom, which may be substituted by a phenyl group or may be fused at the double bond to a benzene, pyridine or diazine ring,

a 5- to 7-membered azacycloalkyl group, a 4- to 7-membered oxaza- or diazacycloalkyl group or a 7- to 9-membered azabicycloalkyl group,

wherein the above-mentioned mono- and bicyclic heterocycles are bound via a nitrogen or a carbon atom and

may be substituted by a C_{1-7}-alkyl group, or by an alkanoyl, dialkylamino, phenylcarbonyl, carboxyalkanoyl, carboxyalkyl, alkoxycarbonylalkyl or alkoxycarbonyl group having 1 to 4 carbon atoms in the alkoxy moiety, alkylsulphonyl, cycloalkyl or cycloalkylalkyl group or by an azacycloalkylcarbonyl or diazacycloalkylcarbonyl group optionally alkyl-substituted in the ring,

whilst the alicyclic groups contained in these substituents may comprise 3 to 7 ring members and the heteroalicyclic groups may comprise 4 to 7 ring members and

the above-mentioned phenylcarbonyl group may be substituted by a fluorine, chlorine or bromine atom or by a methyl, methoxy, trifluoromethyl, hydroxy, amino or acetylamino group, or

R^{10} together with R^{12} and Y^3 denotes a 4- to 6-membered cycloaliphatic ring in which a methylene group may be replaced by an -NH- or -N(CH_3)- group,

whilst a hydrogen atom bound to a nitrogen atom within the group R^{10} may be replaced by a protecting group, e.g. the phenylmethoxycarbonyl or tert.butyloxycarbonyl group,

R^{12} denotes a hydrogen atom, a C_{1-2}-alkyl group which may be substituted in the ω-position by a phenyl, pyridinyl, amino, alkylamino, dialkylamino, 1-pyrrolidinyl, 1-piperidinyl or 4-methyl-1-piperazinyl group,

a methoxycarbonyl or ethoxycarbonyl, cyano or aminocarbonyl group or a free pair of electrons, if Y^3 denotes a nitrogen atom, and

R^{13} and R^{14} each denote a hydrogen atom or,

if Y^3 is a carbon atom, R^{12} together with R^{14} also denotes another carbon-carbon bond, wherein R^{10} is as hereinbefore defined and R^{13} denotes a hydrogen atom, or

if Y^3 is a carbon atom, R^{12} together with R^{14} also denotes another carbon-carbon bond and R^{10} together with R^{13} and the enclosed double bond denotes a partially hydrogenated or aromatic 5- or 6-membered mono- or bicyclic carbocycle or heterocycle, containing one or two nitrogen atoms,

whilst all the above-mentioned alkyl and alkoxy groups and the alkyl groups present within the other groups named may contain 1 to 3 carbon atoms, unless otherwise stated, and

all the above-mentioned cycloalkyl groups and the cycloalkyl groups present within the other groups named may contain 5 to 7 carbon atoms, unless otherwise specified,

their tautomers, their diastereomers, their enantiomers, mixtures thereof and the salts thereof.

One subgroup of particularly preferred compounds of general formula I deserving special mention comprises those wherein

A, R^2, R^3, R^4, R^{11}, X, Z and m and n are defined as for the particularly preferred compounds of general formula I hereinbefore and

R denotes an unbranched C_{1-4}-alkylamino group optionally substituted at the nitrogen atom by a methyl or ethyl group, which may be substituted in the ω-position

by a C_{5-7}-cycloalkyl group,

by one or two phenyl groups, by a 1-naphthyl, 2-naphthyl or (4-biphenylyl) group,

by a 1H-indol-3-yl, 1,3-dihydro-2H-2-oxobenzimidazol-1-yl, 2(1H)-oxoquinolin-3-yl, 1,3-dihydro-4-phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-5-phenyl-2H-2-oxoimidazol-1-yl, 3,4-dihydro-5-phenyl-2(1H)-oxopyrimidin-3-yl, 3,4-dihydro-6-phenyl-2(1H)-oxopyrimidin-3-yl or 1,3-dihydro-2H-2-oxoimidazo-[4,5-b]pyridin-3-yl group,

by a 5-membered heteroaromatic ring linked via a carbon atom and containing a nitrogen, oxygen or sulphur atom or two nitrogen atoms, whilst a nitrogen atom of an imino group may be substituted by an alkyl group,

or by a pyridinyl group,

whilst a 1,4-butadienylene group may be attached both to the 5-membered heteroaromatic monocyclic rings and also to the pyridinyl group, in each case via two adjacent carbon atoms, and the bicyclic heteroaromatic rings thus formed may also be bound via a carbon atom of the 1,4-butadienylene group,

whilst the phenyl, naphthyl and biphenylyl groups mentioned hereinbefore for the substitution of the alkylamino groups in the ω-position, as well as optionally any partially hydrogenated mono- and bicyclic heteroaromatic rings, may additionally be mono- or disubstituted in the carbon skeleton by fluorine, chlorine or bromine atoms or by alkyl, nitro, alkoxy, trifluoromethyl, hydroxy, amino, acetylamino, propionylamino, alkanoyl, cyano or trifluoromethoxy groups, whilst the substituents may be identical or different,

whilst all the above-mentioned alkyl and alkoxy groups and the alkoxy groups present within the other named radicals may contain 1 to 3 carbon atoms unless otherwise stated,

their tautomers, their diastereomers, their enantiomers, mixtures thereof and the salts thereof.

Another subgroup of particularly preferred compounds of general formula I which deserves special mention comprises those compounds wherein

R^2, R^3, R^4, R^{11}, X, Z and m and n are as hereinbefore defined for the first-mentioned particularly preferred subgroup,

R denotes an unbranched C_{1-3}-alkyl group which may be substituted in the ω-position

by a C_{5-7}-cycloalkyl group,

by one or two phenyl groups, by a 1-naphthyl, 2-naphthyl or (4-biphenylyl) group,

by a 1,3-dihydro-2H-2-oxobenzimidazol-1-yl, 1,3-dihydro-2H-2-oxoimidazol-1-yl or 3,4-dihydro-2(1H)-oxopyrimidin-3-yl group, whilst the latter two groups may be substituted in the carbon skeleton by a phenyl, pyridinyl or diazinyl group,

by a 5-membered heteroaromatic ring linked via a carbon atom and containing a nitrogen, oxygen or sulphur atom or two nitrogen atoms, wherein a nitrogen atom of an imino group may be substituted by an alkyl group,

or by a pyridinyl group,

whilst a 1,4-butadienylene group may be attached both to the 5-membered heteroaromatic monocyclic rings and also to the pyridinyl group via two adjacent carbon atoms in each case and the bicyclic heteroaromatic rings thus formed may also be bound via a carbon atom of the 1,4-butadienylene group,

whilst the phenyl, naphthyl and biphenylyl groups mentioned hereinbefore for the substitution of the alkyl groups in the ω-position as well as optionally any partially hydrogenated mono- and bicyclic heteroaromatic rings may additionally be mono- or disubstituted in the carbon skeleton by fluorine, chlorine or bromine atoms or by alkyl, nitro, alkoxy, trifluoromethyl, hydroxy, amino, acetylamino, propionylamino, alkanoyl, cyano or trifluoromethoxy groups wherein the substituents may be identical or different,

and A denotes a single bond,

whilst all the above-mentioned alkyl and alkoxy groups and the alkyl groups present within the other groups mentioned may contain 1 to 3 carbon atoms unless otherwise specified,

their tautomers, their diastereomers, their enantiomers and their salts.

More particularly preferred compounds of the above general formula I are those wherein

R denotes an unbranched C_{1-3}-alkyl group which may be substituted in the ω-position

by a C_{5-7}-cycloalkyl group,

by one or two phenyl groups, by a 1-naphthyl, 2-naphthyl or (4-biphenylyl) group, whilst the above-mentioned aromatic groups may additionally be substituted by a fluorine, chlorine or bromine atom or by a methyl, methoxy, amino or acetylamino group,

by a 2-pyrrolyl, 3-pyrrolyl, pyridinyl, 1H-indol-3-yl, quinolinyl or isoquinolinyl group,

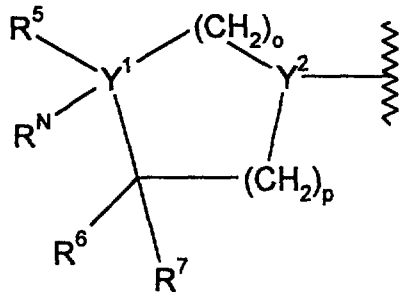
or an unbranched C_{1-4}-alkylamino group which is optionally additionally substituted at the nitrogen atom by a methyl or ethyl group and which may be substituted in the ω-position

by a C_{5-7}-cycloalkyl group,

by a phenyl group which may be mono- or disubstituted by fluorine, chlorine or bromine atoms, or by methyl, nitro, methoxy, trifluoromethyl, hydroxy, amino or acetylamino groups, whilst the substituents may be identical or different,

by a 2-pyrrolyl, 3-pyrrolyl, pyridinyl, 1H-indol-3-yl, quinolinyl or isoquinolinyl group,

or the group of formula



(II),

wherein

p denotes the number 1 or 2,

o denotes the number 2 or, if Y^1 and Y^2 are not simultaneously nitrogen atoms, it may also denote the number 1,

Y^1 denotes the nitrogen atom if R^5 denotes a free pair of electrons, or the carbon atom,

Y^2 denotes the nitrogen atom or the group >CH-,

R^5 denotes a free pair of electrons, if Y^1 denotes the nitrogen atom or, if Y^1 denotes the carbon atom, R^5 may denote the hydrogen atom, a C_{1-2}-alkyl group or the cyano or phenyl group,

R^6 denotes the hydrogen atom or, provided that Y^1 is not a nitrogen atom, R^6 together with R^5 may also denote an additional bond,

R^7 denotes the hydrogen atom or, provided that Y^1 is not a nitrogen atom and R^5 and R^6 together denote an additional bond, R^7 together with R^N may also denote the 1,4-butadienylene group,

R^N denotes the hydrogen atom or a C_{1-3}-alkyl group, which may be substituted in the ω-position

by one or two phenyl or pyridinyl groups, wherein the substituents may be identical or different,

or by a hydroxy or methoxy group,

a phenyl group which may be mono- or disubstituted by fluorine, chlorine or bromine atoms or by methyl groups, nitro, methoxy, ethoxy, trifluoromethyl, hydroxy or cyano groups, whilst the substituents may

be identical or different, or a phenyl group substituted by a methylenedioxy group,

a 2-pyridinyl or 4-pyridinyl group,

an amino, benzoylamino, aminocarbonyl, methylaminocarbonyl, methoxycarbonyl, ethoxycarbonyl, aminocarbonylamino, methylaminocarbonylamino, N-(aminocarbonyl)-N-methylamino, N-(methylaminocarbonyl)-N-methylamino, N-(aminocarbonyl)-N-(4-fluorophenyl)amino, N-(methylaminocarbonyl)-N-phenylamino, phenylaminocarbonylamino, [N-phenyl(methylamino)]-carbonylamino, N-(phenylaminocarbonyl)-N-methylamino, N-(phenylaminocarbonyl)-N-phenylamino, benzoylaminocarbonylamino, N-(aminocarbonyl)-N-phenylamino group or a phenylamino group optionally substituted in the phenyl ring by an aminocarbonylamino or methylsulphonylamino group,

a 1,3-dihydro-4-phenyl-2H-2-oxoimidazol-1-yl, a 1,3-dihydro-4-(3-thienyl)-2H-2-oxoimidazol-1-yl, 1,3-dihydro-5-phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-2(2H)-oxobenzimidazol-1-yl, 1,3,3a,4,5,6,7,7a-octahydro-2(2H)-oxo-benzimidazol-1-yl, 1H-indol-3-yl, 2,4(1H,3H)-dioxoquinazolin-3-yl, 1,3-dihydro-2(2H)-oxoimidazo[4,5-b]pyridin-3-yl, 1,3(2H)-dioxo-1H-isoindol-2-yl, 1H-benzimidazol-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-3-yl, 3,4-dihydro-2(1H)-oxoquinazolin-1-yl, 2(3H)-oxobenzoxazol-3-yl, 1,3-dihydro-2(2H)-oxo-imidazo[4,5-d]pyrimidin-3-yl, 2,3,4,5-tetrahydro-2(1H)-oxo-1,3-benzodiazepin-3-yl, 3,4-dihydro-2(1H)-oxopyrido[2,3-d]pyrimidin-3-yl, 2(1H)-oxoquinolin-3-yl, 3,4-dihydro-2(1H)-oxoquinolin-3-yl, 2(1H)-oxoquinoxalin-3-yl, 3,4,4a,5,6,7,8,8a-

octahydro-2(1H)-oxoquinazolin-3-yl, 1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl, 2,4(1H,3H)-dioxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl, 2,4-dihydro-5-phenyl-3(3H)-oxo-1,2,4-triazol-2-yl, 1,3-dihydro-5-methyl-4-phenyl-2(2H)-oxoimidazol-1-yl, 2,5-dioxo-4-phenylimidazolidin-1-yl, 2,5-dioxo-4-(phenylmethyl)-imidazolidin-1-yl, 3,4-dihydro-2,2-dioxido-2,1,3-benzothiadiazin-3-yl, 1,3-dihydro-4-(4-biphenylyl)-2(2H)-oxoimidazol-1-yl, 1,3-dihydro-4-(2-naphthyl)-2(2H)-oxoimidazol-1-yl, 1,3-dihydro-4,5-diphenyl-2(2H)-oxoimidazol-1-yl, 1,3-dihydro-2(2H)-oxoimidazo[4,5-c]quinolin-3-yl, 4-phenyl-2(1H)-oxopyrimidin-1-yl, 4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl, 3,4-dihydro-2(1H)-oxopyrido[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2[1H]-oxopyrido[4,3-d]pyrimidin-3-yl or 2,3-dihydro-4(1H)-oxoquinazolin-3-yl group,

wherein the above-mentioned mono- and bicyclic heterocycles may be substituted at one of the nitrogen atoms by a methoxycarbonylmethyl group and/or

the above-mentioned mono- and bicyclic heterocycles may be mono-, di- or trisubstituted in the carbon skeleton and/or at the phenyl groups contained in these groups by fluorine, chlorine or bromine atoms, or by methyl, trifluoromethyl, methoxy, hydroxy, amino, nitro, phenyl, phenylmethyl, carboxy, methoxycarbonyl, ethoxycarbonyl, aminocarbonyl, methylaminocarbonyl, hydroxyethylaminocarbonyl, (4-morpholinyl)carbonyl, (1-piperidinyl)carbonyl or (4-methyl-1-piperazinyl)carbonyl groups wherein the substituents may be identical or different and

multiple substitution with the last three substituents is ruled out,

or, provided that Y^1 is not a nitrogen atom and R^5 and R^6 together denote an additional bond, R^N together with R^7 also denotes the 1,4-butadienylene group,

or, provided that Y^1 denotes a carbon atom, R^N together with R^5 with the inclusion of Y^1 may also denote a carbonyl group or saturated or monounsaturated five- or six-membered 1,3-diaza-heterocycle,

which may contain a carbonyl group in the ring, adjacent to a nitrogen atom,

may be substituted by a phenyl group at one of the nitrogen atoms

and, if it is unsaturated, may also be benzo-condensed at the double bond,

X denotes an oxygen atom or 2 hydrogen atoms,

Z denotes a methylene group or the group $-NR^1$, wherein

R^1 denotes a hydrogen atom or a methyl group,

R^{11} denotes a hydrogen atom, a methoxycarbonyl, ethoxycarbonyl or methyl group,

n denotes the number 1 and m denotes the number 0 or

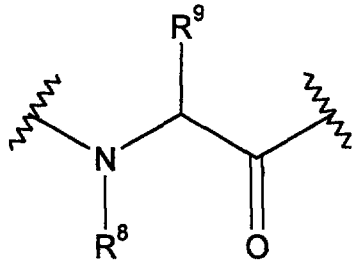
n denotes the number 0 and m denotes the number 1,

R^2 denotes a phenyl, 1-naphthyl, 2-naphthyl, 1,2,3,4-tetrahydro-1-naphthyl, 1H-indol-3-yl, 1-methyl-1H-indol-3-

yl, 1-(1,1-dimethylethoxycarbonyl)-1H-indol-3-yl, 2-thienyl, 3-thienyl, thiazolyl or alkylthiazolyl group having 1 to 3 carbon atoms in the alkyl moiety, a pyridinyl or quinolinyl group,

wherein the above-mentioned phenyl and naphthyl groups may be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms or by branched or unbranched C_{1-5}-alkyl groups, by C_{1-3}-alkoxy groups, by vinyl, allyl, trifluoromethyl, methylsulphonyloxy, 2-(dimethylamino)ethoxy, hydroxy, cyano, nitro or amino groups, by tetrazolyl, phenyl, pyridinyl, thiazolyl or furyl groups and the substituents may be identical or different, and multiple substitution with the last five substituents is ruled out,

A denotes a bond or the divalent group of formula



(III),

(linked to the group $-NR^3R^4$ of formula (I) via the carbonyl group)

wherein

R^8 and R^9 together denote an n-propylene group or

R^8 denotes the hydrogen atom or the methyl group and

R^9 denotes the hydrogen atom or an unbranched C_{1-4}-alkyl group,

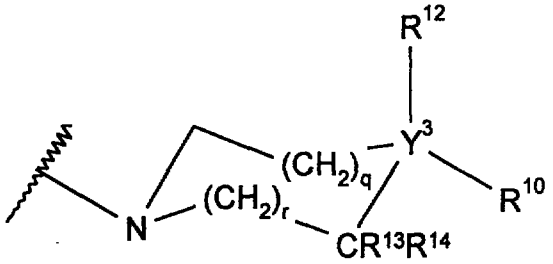
which may be substituted in the ω-position by an amino, methylamino, dimethylamino, aminoiminomethylamino or aminocarbonylamino group, whilst in the above-mentioned substituents a hydrogen atom bound to a nitrogen atom may be replaced by a protecting group, e.g. the phenylmethoxycarbonyl or tert.butyloxycarbonyl group,

R^3 denotes a hydrogen atom or

a C_{1-4}-alkyl group optionally substituted in the ω-position by an amino, methylamino, dimethylamino- or 4-(1-piperidinyl)-1-piperidinyl group,

R^4 denotes a hydrogen atom or a methyl or ethyl group

or R^3 and R^4 together with the enclosed nitrogen atom denote a group of general formula



(IV),

wherein

Y^3 denotes the carbon atom or, if R^{12} denotes a free pair of electrons, Y^3 may also denote a nitrogen atom,

r denotes the number 1,

q denotes the number 1,

R^{10} denotes the hydrogen atom, an alkyl, dialkylamino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, phenylaminocarbonylamino, alkoxycarbonyl, alkoxycarbonylmethyl, carboxymethyl or carboxy group or a cycloalkyl group having 4 to 7 carbon atoms in the ring,

a benzoyl, pyridinylcarbonyl, phenyl, pyridinyl or diazinyl group, each of which may be substituted in the carbon skeleton by a fluorine, chlorine or bromine atom, or by an acetyl, methyl, ethyl or methoxy group, or by a dimethylaminoalkyl group having 1 to 4 carbon atoms in the alkyl moiety optionally hydroxysubstituted in the alkyl moiety,

a 1,3-dihydro-2-oxo-2H-imidazolyl group bound via a nitrogen atom, which may be fused to a benzene or pyridine ring at the double bond,

a 1-pyrrolidinyl, 1-piperidinyl, 4-(dimethylamino)-1-piperidinyl, 4-piperidinyl or 4-morpholinyl group, wherein the nitrogen atom of the 4-piperidinyl group may be substituted by an alkanoyl- or alkyl group each having 1 to 7 carbon atoms or by a benzoyl, methylsulphonyl, 3-carboxypropionyl, cyclopropylmethyl, alkoxycarbonylmethyl or carboxymethyl group or by a protecting group, e.g. the phenylmethoxycarbonyl or tert.butyloxycarbonyl group, or it may represent a hexahydro-1H-1-azepinyl, 8-methyl-8-azabicyclo[3,2,1]oct-3-yl, 4-alkyl-1-piperazinyl, hexahydro-4-alkyl-1H-1,4-diazepin-1-yl, 1-alkyl-4-piperidinylcarbonyl or 4-alkyl-1-piperazinylcarbonyl group,

or

R^{10} together with R^{12} and Y^3 denotes a 5-membered cycloaliphatic ring in which a methylene group may be replaced by an -NH- or -N(CH3)- group,

R^{12} denotes a hydrogen atom, a C_{1-2}-alkyl group which may be substituted in the ω-position by a 1-pyrrolidinyl, 1-piperidinyl or 4-methyl-1-piperazinyl group,

a methoxycarbonyl or ethoxycarbonyl or a cyano group,

a free pair of electrons if Y^3 denotes a nitrogen atom, and

R^{13} and R^{14} each denote a hydrogen atom or,

provided that Y^3 is a carbon atom, R^{12} together with R^{14} may also denote an additional carbon-carbon bond, wherein R^{10} is as hereinbefore defined and R^{13} denotes a hydrogen atom or,

provided that Y^3 is a carbon atom, R^{12} together with R^{14} may also denote an additional carbon-carbon bond and R^{10} together with R^{13} and the enclosed double bond denotes an indole group fused on via the 5-membered ring,

whilst all the above-mentioned alkyl groups and the alkyl groups present within the other named groups may contain 1 to 3 carbon atoms, unless otherwise specified,

their tautomers, their diastereomers, their enantiomers and their salts.

A subgroup of most particularly preferred compounds of general formula I deserving special mention comprises those wherein

A, R^2, R^3, R^4, R^{11}, X, Z and m and n are as hereinbefore defined for the most particularly preferred compounds of general formula I and

R denotes an unbranched C_{1-4}-alkylamino group optionally substituted at the nitrogen atom by a methyl or ethyl group, which may be substituted in the ω-position

by a C_{5-7}-cycloalkyl group,

by a phenyl group, which may be mono- or disubstituted by fluorine, chlorine or bromine atoms or by methyl, nitro, methoxy, trifluoromethyl, hydroxy, amino or acetylamino groups, wherein the substituents may be identical or different, or

by a 2-pyrrolyl, 3-pyrrolyl, pyridinyl, 1H-indol-3-yl, quinolinyl or isoquinolinyl group,

their tautomers, their diastereomers, their enantiomers, mixtures thereof and salts thereof.

Another subgroup of most particularly preferred compounds of general formula I deserving special mention comprises those wherein

R^2, R^3, R^4, R^{11}, X, Z and m and n are as defined hereinbefore for the first-mentioned particularly preferred subgroup,

R denotes an unbranched C_{1-3}-alkyl group which may be substituted in the ω-position

by a C_{5-7}-cycloalkyl group,

by one or two phenyl groups, by a 1-naphthyl, 2-naphthyl or (4-biphenylyl) group, whilst the above-mentioned aromatic groups may be substituted by a fluorine, chlorine or bromine atom or by a methyl, methoxy, amino or acetylamino group,

or by a 2-pyrrolyl, 3-pyrrolyl, pyridinyl, 1H-indol-3-yl, quinolinyl- or isoquinolinyl group,

and A denotes a single bond,

their tautomers, their diastereomers, their enantiomers, mixtures thereof and the salts thereof.

The following are mentioned as examples of most particularly preferred compounds:

(1) 1-[N^2-[N-[[[2-(2-Methoxyphenyl)ethyl]amino]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(2) 1-[N^2-[N-[[[2-(3-Methoxyphenyl)ethyl]amino]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(3) 1-[N^2-[N-[[[2-(2,5-Dimethoxyphenyl)ethyl]amino]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(4) 1-[N^2-[N-[[[2-(3-Methoxyphenyl)ethyl]amino]carbonyl]-3,5-dibromo-D-tyrosyl]-L-arginyl]-4-(4-pyridinyl)-piperazine

(5) 1-[N^2-[N-[[[2-(2,3-dimethoxyphenyl)ethyl]amino]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

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(6) 1-[N^2-[N-[[[2-(3-Methoxyphenyl)ethyl]amino]carbonyl]-3,5-dibromo-D,L-tyrosyl]-D,L-lysyl]-4-(1-methyl-4-piperidinyl)-piperazine

(7) 1-[N^2-[N-[[[2-(3-Methoxyphenyl)ethyl]amino]carbonyl]-3,5-dibromo-D,L-tyrosyl]-D,L-lysyl]-4-(4-piperidinyl)-piperazine

(8) 1-[N^2-[N-[[[2-(3,4-dihydroxyphenyl)ethyl]amino]carbonyl]-3,5-dibromo-D,L-tyrosyl]-D,L-lysyl]-4-(4-pyridinyl)-piperazine

(9) 1-[N^2-[N-[4-(2-Methoxyphenyl)-1-piperazinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(10) 1-[N^2-[N-[4-(3-Methoxyphenyl)-1-piperazinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(11) 1-[N^2-[N-[[(2-Phenylethyl)amino]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(12) 1-[N^2-[N-[[[2-(4-Methoxyphenyl)ethyl]amino]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(13) 1-[N^2-[N-[[[2-(3-Methoxyphenyl)ethyl]amino]carbonyl]-3-(1-naphthyl)-D-alanyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(14) 1-[N^2-[N-[[[2-(3-Hydroxyphenyl)ethyl]amino]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(15) 1-[N^2-[N-[3-(3-Methoxyphenyl)-1-oxopropyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

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(16) 1-[N^2-[N-[[[2-(3-Methoxyphenyl)ethyl]methylamino]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(17) 1-[N^2-[N-(4-Phenyl-1-piperazinyl)carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(18) 1-[N^2-[N-[4-(2-Methylphenyl)-1-piperazinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(19) 1-[N^2-[N-[4-(1,3-Dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(20) 1-[N^2-[N-[[[2-(3-Methoxyphenyl)ethyl]amino]carbonyl]-3,5-dichloro-D,L-tyrosyl]-D,L-lysyl]-4-(4-pyridinyl)-piperazine

(21) 1-[N^2-[N-[4-(2-Methoxyphenyl)-1-piperazinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperidin

(22) 1-[N^2-[N-(4,4-Diphenyl-1-piperidinyl)carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(23) 1-[N^2-[N-(4-Phenyl-1-piperidinyl)carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(24) 1-[N^2-[N-[4-(4-Fluorophenyl)-1-oxobutyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(25) 1-[N^2-[N-[4,4-Diphenyl-1-oxobutyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(26) 1-[N^2-[N-[4-Cyclohexyl-1-oxobutyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

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(27) 1-[N^2-[N-[4-(4-Acetylaminophenyl)-1-oxobutyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(28) 1-[N^2-[N-[4-(2-Methoxyphenyl)-1-piperazinyl]carbonyl]-3,5-dichloro-D,L-tyrosyl]-D,L-lysyl]-4-(4-pyridinyl)-piperazine

(29) 1-[N^2-[N-[4-[3-(Trifluoromethyl)phenyl]-1-piperazinyl]carbonyl]-3,5-dibromo-D,L-tyrosyl]-D,L-lysyl]-4-(4-pyridinyl)-piperazine

(30) 1-[N^2-[N-[4-(2-Chlorophenyl)-1-piperazinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(31) 1-[N^2-[N-[4-(3,4-Methylenedioxyphenyl)-1-piperazinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(32) 1-[N^2-[N-(4-Methyl-1-piperazinyl)carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(33) 1-[N^2-[N-[4-(2-Hydroxyethyl)-1-piperazinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(34) 1-[N^2-[N-[4-(4-Pyridinyl)-1-piperazinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(35) 1-[N^2-[N-[4-(2-Pyridinyl)-1-piperazinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(36) 1-[N^2-[N-[4-(Diphenylmethyl)-1-piperazinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(37) 1-[N^2-[N-[4-(Phenylmethyl)-1-piperazinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

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(38) 1-[N^2-[N-[4-(4-Nitrophenyl)-1-piperazinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(39) 1-[N^2-[N-[4-(Ethoxycarbonyl)-1-piperazinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(40) 1-[N^2-[N-[[[3-(2-Methoxyphenyl)propyl]amino]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(41) 1-[N^2-[N-[[[2-(3-Bromophenyl)ethyl]amino]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(42) 1-[N^2-[N-[[[2-(3-Nitrophenyl)ethyl]amino]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(43) 1-[N^2-[N-[[[2-(3-Acetylaminophenyl)ethyl]amino]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(44) 1-[N^2-[N-[[[2-(3-Bromophenyl)ethyl]amino]carbonyl]-3,5-dibromo-D-tyrosyl]-N^6-(1,1-dimethylethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)-piperazine

(45) 1-[N^2-[N-[(1,2,4,5-Tetrahydro-3H-3-benzazepin-3-yl)carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(46) 1-[N^2-[N-[[[2-[3-(Trifluoromethyl)phenyl]ethyl]amino]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(47) 1-[N^2-[N-[[[2-(3-Fluorophenyl)ethyl]amino]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

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(48) 1-[N^2-[N-[4-(2-Methoxyphenyl)-1-piperazinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-fluorophenyl)-piperazine

(49) 1-[N^2-[4-Amino-3,5-dibromo-N-[[(2-phenylethyl)amino]carbonyl]-D-phenylalanyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(50) 1-[N^2-[N-[4-(2-Methoxyphenyl)-1-piperidinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(51) 1-[N^2-[N-[4-(3-Methoxyphenyl)-1,2,5,6-tetrahydro-1-piperidinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(52) 1-[N^2-[N-[4-(2-Methoxyphenyl)-1,2,5,6-tetrahydro-1-piperidinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(53) 1-[N^2-[N-[(4-Biphenylyl)acetyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(54) 1-[N^2-[N-[4-(4-Bromophenyl)-1-oxobutyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(55) 1-[N^2-[N-[4-(1H-Indol-3-yl)-1-oxobutyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(56) 1-[N^2-[N-(4,4-Diphenyl-1-piperidinyl)carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(57) 1-[N^2-[N-(4-Oxo-1-phenyl-1,3,8-triazaspiro[4,5]dec-8-yl)carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

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(58) 1-[N^2-[N-[4-(1,3-Dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-4-amino-3,5-dibromo-D-phenylalanyl]-L-lysyl]-4-(4-pyridinyl)-piperidine

(59) 1-[N^2-[N-[4-(1,3-Dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-4-amino-3,5-dibromo-D-phenylalanyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(60) 1-[N^2-[N-[4-(2-Chlorophenyl)-1-piperazinyl]carbonyl]-4-amino-3,5-dibromo-D-phenylalanyl]-L-lysyl]-4-(4-pyridinyl)-piperidine

(61) 1-[N^2-[N-[4-(2-Chlorophenyl)-1-piperazinyl]carbonyl]-4-amino-3,5-dibromo-D-phenylalanyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(62) 1-[N^2-[N-[4-(1,3-Dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-N^6-(1,1-dimethylethoxycarbonyl)-L-lysyl]-4-(2-pyridinyl)-piperazine

(63) 1-[N^2-[N-[[[2-(2-Cyclohexyl)ethyl]amino]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(64) 1-[N^2-[N-[4-(2-Chlorophenyl)-1-piperazinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperidine

(65) 1-[N^2-[N-[4-(1,3-Dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperidine

(66) 1-[N^2-[N-[4-(Aminocarbonyl)-1-piperidinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperidine

(67) 1-[N^2-[N-[[[2-(1H-Indol-3-yl)ethyl]amino]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

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(68) 1-[N^2-[N-[4-(1,3-Dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(2-methoxyphenyl)-piperazine

(69) 1-[N^2-[N-[4-(1,3-Dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(2-pyridinyl)-piperazine

(70) 1-[N^2-[N-(4-Oxo-1-phenyl-1,3,8-triazaspiro[4,5]dec-8-yl)carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(2-methoxyphenyl)-piperazine

(71) 1-[N^2-[N-(4,4-Diphenyl-1-piperidinyl)carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(2-pyridinyl)-piperazine

(72) 1-[N^2-[N-[4-(1,3-Dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-3,5-dibromo-D,L-phenylalanyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(73) 1-[N^2-[N-[4-(1,3-Dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-3,5-dibromo-D,L-phenylalanyl]-N^6-(1,1-dimethylethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)-piperazine

(74) 1-[N^2-[N-[4-(2,3-Dichlorophenyl)-1-piperazinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(75) 1-[N^2-[N-[4-(3,5-Dichlorophenyl)-1-piperazinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(76) 1-[N^2-[N-[4-(2-Cyanphenyl)-1-piperazinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

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(77) 1-[N^2-[N-(4-Oxo-1-phenyl-1,3,8-triazaspiro[4,5]dec-8-yl)carbonyl]-3,5-dibromo-D,L-phenylalanyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(78) 1-[N^2-[N-(4-Oxo-1-phenyl-1,3,8-triazaspiro[4,5]dec-8-yl)carbonyl]-3,5-dibromo-D,L-phenylalanyl]-N^6-(1,1-dimethylethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)-piperazine

(79) 1-[N^2-[N-[4-[4-Chloro-3-(trifluoromethyl)phenyl]-1-piperazinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(80) 1-[N^2-[N-[4-(1,3-Dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-N^6-(1,1-dimethylethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)-piperazine

(81) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperidine

(82) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperazine

(83) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperazine

(84) 1-[N-[[4-[3,4-Dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-3-(trifluoromethyl)-D,L-phenylalanyl]-4-[1-(1-methylethyl)-4-piperidinyl]-piperidine

(85) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-phenylpiperazine

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(86) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-6-methyl-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperazine

(87) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-5-methyl-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperazine

(88) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-5,6-dichloro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperazine

(89) 1-[4-Amino-3,5-dibromo-N-[[4-[1,3-dihydro-3-(methoxycarbonylmethyl)-2(2H)-oxobenzimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperazine

(90) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-piperidinyl)-piperidine

(91) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3,3a,4,5,6,7,7a-octahydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperazine

(92) 1-[4-Amino-3,5-dibromo-N-[[4-(benzoylamino)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperazine

(93) 1-[4-Amino-3,5-dibromo-N-[[4-(aminocarbonyl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperazine

(94) 1-[4-Amino-3,5-dibromo-N-[(4-Oxo-1-phenyl-1,3,8-triazaspiro[4,5]dec-8-yl)carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperazine

(95) 1-[3,5-Dibromo-N-[[4-(benzoylamino)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperazine

(96) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-6-methyl-2(2H)-oxo-benzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperazine

(97) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-5-methyl-2(2H)-oxo-benzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperazine

(98) 3,5-Dibromo-N^2-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosinamide

(99) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-methylpiperazine

(100) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperidinyl)piperazine

(101) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-phenylpiperazine

(102) 3,5-Dibromo-N^2-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-N,N-diethyl-D-tyrosinamide

(103) 3,5-Dibromo-N^2-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-N-[(4-(dimethylamino)butyl]-D-tyrosinamide

(104) 1-[3-Bromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine

(105) 1-[3-Bromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperazine

(106) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-[1-(1,1-dimethylethoxycarbonyl)-4-piperidinyl]piperazine

(107) 1-[4-Amino-3,5-dibromo-N-[(4-cyan-4-phenyl-1-piperidinyl)carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperazine

(108) 1-[3,5-Dibromo-N-[(4-oxo-1-phenyl-1,3,8-triazaspiro-[4,5]dec-8-yl)carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperazine

(109) 1-[3,5-Dibromo-N-[(4-cyan-4-phenyl-1-piperidinyl)carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperazine

(110) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(2-pyridinyl)-piperazine

(111) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(2-pyrimidinyl)-piperazine

(112) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(2-pyridinyl)-piperazine

(113) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4(pyrazinyl)-piperazine

(114) 1-[4-Amino-3,5-dibromo-N-[(4-oxo-1-phenyl-1,3,8-triazaspiro[4,5]dec-8-yl)carbonyl]-D-phenylalanyl]-4-(2-pyridinyl)-piperazine

(115) 1-[3,5-Dibromo-N-[(4-oxo-1-phenyl-1,3,8-triazaspiro-[4,5]dec-8-yl)carbonyl]-D-tyrosyl]-4-(2-pyridinyl)-piperazine

(116) 1-[4-Amino-3,5-dibromo-N-[[4-(2,4(1H,3H)-dioxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperazine

(117) 1-[3,5-Dibromo-N-[[4-(2,4(1H,3H)-dioxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperazine

(118) 1-[3,5-Dibromo-N-[[4-(aminocarbonyl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperazine

(119) 1-[4-Amino-3,5-dibromo-N-[(4-oxo-1-phenyl-1,3,8-triazaspiro[4,5]dec-8-yl)carbonyl]-D-phenylalanyl]-4-(pyrazinyl)-piperazine

(120) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(2-pyrimidinyl)-piperazine

(121) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxo-imidazo-[4,5-b]pyridin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperazine

(122) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxo-imidazo[4,5-b]pyridin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperazine

(123) cis-1-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-cyclohexyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperazine

(124) trans-1-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-cyclohexyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperazine

(125) 1-[N-[[4-(1,3-Dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-3,5-dimethyl-D,L-tyrosyl]-4-(4-pyridinyl)-piperazine

(126) 1-[N-[[4-(1,3-Dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-3,5-dimethyl-D,L-tyrosyl]-4-(4-pyridinyl)-piperidine

(127) 1-[N-[[4-(1,3-Dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-3,5-dimethyl-D,L-tyrosyl]-4-(1-piperidinyl)-piperidine

(128) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-fluorophenyl)-piperazine

(129) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(pyrazinyl)-piperazine

(130) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(2-methoxyphenyl)-piperazine

(131) 1-[4-Amino-3,5-dibromo-N-[(4-oxo-1-phenyl-1,3,8-triazaspiro[4,5]dec-8-yl)carbonyl]-D-phenylalanyl]-4-(2-methoxyphenyl)-piperazine

(132) 1-[4-Amino-3,5-dibromo-N-[(4-oxo-1-phenyl-1,3,8-triazaspiro[4,5]dec-8-yl)carbonyl]-D-phenylalanyl]-4-(4-fluorophenyl)-piperazine

(133) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(2-methoxyphenyl)-piperazine

(134) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(5-methoxy-4-pyrimidinyl)-piperazine

(135) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(5-methoxy-4-pyrimidinyl)-piperazine

(136) 1-[N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperazine

(137) 1-[4-Amino-N-[[4-(1H-benzimidazol-1-yl)-1-piperidinyl]carbonyl]-3,5-dibromo-D-phenylalanyl]-4-(4-pyridinyl)-piperidine

(138) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3(2H)-dioxo-1H-isoindol-2-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(139) 1-[N^2-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxoimidazo[4,5-b]pyridin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-N^6-(1,1-dimethylethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)-piperazine

(140) 1-[N^2-[3,5-Dibromo-N-[[4-(2,4(1H,3H)-dioxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-N^6-(1,1-dimethylethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)-piperazine

(141) 1-[N^2-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxoimidazo[4,5-b]pyridin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(142) 1-[N^2-[3,5-Dibromo-N-[[4-(2,4(1H,3H)-dioxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(143) 1-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine

(144) 1-[3,5-Dibromo-N-[(4'(3'H)-oxospiro[piperidine-4,2'(1'H)-quinazolin]-1-yl)carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine

(145) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxoimidazo-[4,5-b]pyridin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine

(146) 1-[N-[[4-(1,3-Dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D,L-3-(4-pyridinyl)alanyl]-4-(4-pyridinyl)-piperazine

(147) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxo-imidazo[4,5-b]pyridin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperazine

(148) 1-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine

(149) 1-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine

(150) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-5-(methoxycarbonyl)-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine

(151) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-5-(hydroxycarbonyl)-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine

(152) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxo-imidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine

(153) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-5-phenyl-2(2H)-oxo-imidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine

(154) 1-[N^2-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(155) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-fluorophenyl)-piperazine

(156) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(2-fluorophenyl)-piperazine

(157) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(2-fluorophenyl)-piperazine

(158) 1-[4-Amino-3,5-dibromo-N-[[4-(phenylaminocarbonylamino)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperazine

(159) 1-[4-Amino-3,5-dibromo-N-[[4-[N-(aminocarbonyl)-N-phenylamino]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(160) 1-[3,5-Dibromo-N-[[4-(aminocarbonylamino)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine

(161) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyrimidinyl)-piperazine

(162) 1-[3,5-Dibromo-N-[[4-[2(3H)-oxobenzoxazol-3-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine

(163) 1-[N-[[4-(Aminocarbonylamino)-1-piperidinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-4-(4-pyridinyl)-piperazine

(164) 1-[4-Amino-3,5-dibromo-N-[[4-(phenylaminocarbonylamino)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(165) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyrimidinyl)-piperazine

(166) 1-[3,5-Dibromo-N-[[4-(methylaminocarbonylamino)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine

(167) 1-[3,5-Dibromo-N-[[4-[N-(aminocarbonyl)-methylamino]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine

(168) 1-[N^2-[N-[[4-(Aminocarbonylamino)-1-piperidinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-N^6-(1,1-dimethylethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)-piperidine

(169) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(3-pyridinyl)-piperazine

(170) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(3-pyridinyl)-piperazine

(171) 1-[3,5-Dibromo-N-[[4-(phenylaminocarbonylamino)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperazine

(172) 1-[3,5-Dibromo-N-[[4-(phenylaminocarbonylamino)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine

(173) 1-[2,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D,L-phenylalanyl]-4-(4-pyridinyl)-piperidine

(174) 1-[2,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D,L-phenylalanyl]-4-(4-pyridinyl)-piperazine

(175) 1-[3,5-Dibromo-N-[[4-[N-(aminocarbonyl)-N-phenylamino]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperazine

(176) 1-[N^2-[3,5-Dibromo-N-[[4-(methylaminocarbonylamino)-1-piperidinyl]carbonyl]-D-tyrosyl]-N^6-(1,1-dimethylethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)-piperidine

(177) 1-[N^2-[3,5-Dibromo-N-[[4-[N-(aminocarbonyl)methylamino]-1-piperidinyl]carbonyl]-D-tyrosyl]-N^6-(1,1-dimethylethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)-piperidine

(178) 1-[3,5-Dibromo-N-[[4-[N-(methylaminocarbonyl)-methylamino]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine

(179) 1-[N^2-[N-[[4-(Aminocarbonylamino)-1-piperidinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperidine

(180) 1-[N^2-[3,5-Dibromo-N-[[4-[N-(methylaminocarbonyl)methylamino]-1-piperidinyl]carbonyl]-D-tyrosyl]-N^6-(1,1-dimethylethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)-piperidine

(181) 1-[N^2-[3,5-Dibromo-N-[[4-[N-(aminocarbonyl)methylamino]-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperidine

(182) 1-[N^2-[3,5-Dibromo-N-[[4-[N-(methylaminocarbonyl)amino]-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperidine

(183) 1-[N^2-[3,5-Dibromo-N-[[4-[N-(methylaminocarbonyl)methylamino]-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperidine

(184) 1-[N^2-[N-[[4-[N-(Aminocarbonyl)phenylamino]-1-piperidinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperidine

(185) 1-[N-[[4-[N-(Aminocarbonyl)phenylamino]-1-piperidinyl]carbonyl]-4-amino-3,5-dibromo-D-phenylalanyl]-4-(4-pyridinyl)-piperidine

(186) 1-[N-[[4-[N-(Aminocarbonyl)phenylamino]-1-piperidinyl]carbonyl]-4-amino-3,5-dibromo-D-phenylalanyl]-4-(4-pyridinyl)-piperazine

(187) 1-[N-[[4-[N-(Aminocarbonyl)phenylamino]-1-piperidinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-4-(4-pyridinyl)-piperidine

(188) 1-[N^2-[N-[[4-[2(3H)-Oxobenzoxazol-3-yl]-1-piperidinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-N^6-(1,1-dimethylethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)-piperazine

(189) 1-[4-Amino-3,5-dibromo-N-[[4-(1H-indol-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(190) 1-[N^2-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-N^6-(1,1-dimethylethoxycarbonyl)-L-lysyl]-4-(5-methoxy-4-pyrimidinyl)-piperazine

(191) 1-[N^2-[2,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-N^6-(1,1-dimethylethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)-piperazine

(192) 1-[N-[[4-[N-(Aminocarbonyl)phenylamino]-1-piperidinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-4-(4-pyridinyl)-piperazine

(193) 1-[3-Bromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-phenylpiperazine

(194) 1-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-cyclohexyl-4-piperidinyl)-piperazine

(195) 1-[N^2-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-N^6-(1,1-dimethylethoxycarbonyl)-L-lysyl]-4-(1-piperidinyl)-piperidine

(196) 1-[N^2-[N-[[4-(2-Cyanophenyl)-1-piperazinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-N^6-(1,1-dimethylethoxycarbonyl)-L-lysyl]-4-(1-piperidinyl)-piperidine

(197) 1-[N^2-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(1-piperidinyl)-piperidine

(198) 1-[N^2-[N-[[4-(2-Cyanophenyl)-1-piperazinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(1-piperidinyl)-piperidine

(199) 1-[3,5-Dichloro-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine

(200) 1-[3,5-Dichloro-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperazine

(201) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-6-hydroxy-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(202) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-morpholinyl)-piperidine

(203) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(ethoxycarbonyl)-piperidine

(204) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(dimethylamino)-piperidine

(205) 1-[3-Bromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine

(206) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-pyrrolidinyl)-piperidine

(207) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(methoxycarbonyl)-4-phenylpiperidine

(208) 1-[N^2-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-L-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(209) 1-[N^2-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-L-tyrosyl]-D-lysyl]-4-(4-pyridinyl)-piperazine

(210) 1-[N^2-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-D-lysyl]-4-(4-pyridinyl)-piperazine

(211) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(hydroxycarbonyl)-piperidine

(212) 1-[N^2-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-N^6,N^6-dimethyl-L-lysyl]-4-(4-pyridinyl)-piperazine

(213) 1-[N^2-[3-Bromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(1-piperidinyl)-piperidine

(214) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-piperidinyl)-piperazine

(215) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-piperidine

(216) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1,3-dihydro-2(2H)-oxoimidazo[4,5-b]pyridin-3-yl)-piperidine

(217) 1-[N^2-[3-Bromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-N^6-(1,1-dimethylethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)-piperazine

(218) 1-[N^2-[3-Bromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(219) (R)-1-[2-[N-[[4-(1,3-Dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-N-methylamino]-3-(3,5-dibromo-4-hydroxyphenyl)-propyl]-4-(1-piperidinyl)-piperidine

(220) (R)-1-[2-[N-[[4-(1,3-Dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]amino]-3-(3,5-dibromo-4-hydroxyphenyl)-propyl]-4-(1-piperidinyl)-piperidine

(221) 1-[N^2-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-N^6,N^6-dimethyl-L-lysyl]-4-(4-pyridinyl)-piperazine

(222) 3,5-Dibromo-N^2-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-N-[(2-[4-(1-piperidinyl)-1-piperidinyl]ethyl]-D-tyrosinamide

(223) 1-[3,5-Dibromo-N-[[4-[5-[(4-morpholinyl)carbonyl]-1,3-dihydro-2(2H)-oxobenzimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine

(224) 1-[3,5-Dibromo-N-[[4-[5-[(4-methyl-1-piperazinyl)carbonyl]-1,3-dihydro-2(2H)-oxobenzimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine

(225) 1-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperazine

(226) 1-[4-Amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(227) 1-[4-Amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(228) 1-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine

(229) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxoimidazo-[4,5-d]pyrimidin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine

(230) 1-[4-Amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine

(231) 1-[4-Amino-3,5-dibromo-N-[[4-(2,3,4,5-tetrahydro-2(1H)-oxo-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(232) 1-[N^2-[4-Amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-L-lysyl]-4-(1-piperidinyl)-piperidine

(233) 1-[N^2-[4-Amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(234) 1-[N^2-[4-Amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-L-lysyl]-4-(4-pyridinyl)-piperidine

(235) 1-[N^2-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(1-piperidinyl)-piperidine

(236) 1-[N^2-[3,5-Dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(237) 1-[N^2-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-L-lysyl]-4-(1-piperidinyl)-piperidine

(238) 1-[N^2-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(239) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine

(240) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperazine

(241) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(242) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperazine

(243) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine

(244) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperidinyl)-piperazine

(245) (R)-1-[2-[N-[[4-(3,4-dihydro-2(1H)-oxopyrido[2,3-d]pyrimidin-3-yl)-1-piperidinyl]carbonyl]amino]-3-(4-amino-3,5-dibromophenyl)-propyl]-4-(1-piperidinyl)-piperidine

(246) (R,S)-1-[2-[(3,5-Dibromo-4-hydroxyphenyl)methyl]-4-[4-(1,3-dihydro-2(2H)oxobenzimidazol-1-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-(1-piperidinyl)-piperidine

(247) 1-[N^2-[2,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-N^6-(1,1-dimethylethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)-piperidine

(248) 1-[N^2-[3,5-Dibromo-N-[[4-[2(3H)-oxobenzoxazol-3-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(249) 1-[N-[[4-[N-(Aminocarbonyl)phenylamino]-1-piperidinyl]carbonyl]-4-amino-3,5-dibromo-D-phenylalanyl]-4-[(1-piperidinyl)methyl]-piperidine

(250) 1-[N^2-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(5-methoxy-4-pyrimidinyl)-piperazine

(251) 1-[N^2-[2,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-L-lysyl]-4-(4-pyridinyl)-piperidine

(252) 1-[N^2-[2,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-L-phenylalanyl]-L-lysyl]-4-(4-pyridinyl)-piperidine

(253) 1-[N^2-[2,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(254) 1-[N^2-[3,5-Dibromo-N-[[4-[N-(Aminocarbonyl)phenylamino]-1-piperidinyl]carbonyl]-D-tyrosyl]-N^6-(1,1-dimethylethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)-piperazine

(255) 1-[N^2-[3,5-Dibromo-N-[[4-[N-(Aminocarbonyl)phenylamino]-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(256) 1-[N^2-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-L-lysyl]-4-(5-methoxy-4-pyrimidinyl)-piperazine

(257) 1-[N-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-glycyl]-4-(4-pyridinyl)-piperazine

(258) 1-[4-Amino-3,5-dibromo-N-[[4-(benzoylaminocarbonylamino)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperazine

(259) 1-[4-Amino-3,5-dibromo-N-[[4-(benzoylaminocarbonylamino)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(260) 1-[N-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-ß-alanyl]-4-(4-pyridinyl)-piperazine

(261) 1-[N-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-N-methylglycyl]-4-(4-pyridinyl)-piperazine

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(262) 1-[4-Amino-3,5-dibromo-N-[[4-[N-(phenylaminocarbonyl)phenylamino)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperazine

(263) 1-[N-[[4-(1,3-Dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-[3-(2-thienyl)-D-alanyl]-4-(1-piperidinyl)-piperidine

(264) 4-Amino-3,5-dibromo-N^2-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-N-methyl-N-[3-(4-methyl-1-piperazinyl)propyl]-D-phenylalaninamide

(265) 1-[N-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-glycyl]-4-(1-piperidinyl)-piperidine

(266) 1-[N-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxo-benzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-L-alanyl]-4-(4-pyridinyl)-piperazine

(267) 1-[N^2-[4-Amino-3,5-dibromo-N-[[4-[N-(methylaminocarbonyl)phenylamino]-1-piperidinyl]carbonyl]-D-phenylalanyl]-N^6-(1,1-dimethylethoxycarbonyl)-L-lysyl]-4-(1-piperidinyl)-piperidine

(268) 1-[N-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-L-alanyl]-4-(1-piperidinyl)-piperidine

(269) 1-[4-Amino-3,5-dibromo-N-[[4-[2(1H)-oxoquinolin-3-yl]-1-piperazinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(270) 1-[4-Amino-3,5-dibromo-N-[[4-[2(1H)-oxoquinolin-3-yl]-1-piperazinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperazine

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(271) 1-[N^2-[4-Amino-3,5-dibromo-N-[[4-[N-(methylaminocarbonyl)phenylamino]-1-piperidinyl]carbonyl]-D-phenylalanyl]-L-lysyl]-4-(1-piperidinyl)-piperidine

(272) 1-[N^2-[[4-(1,3-Dihydro-2(2H)oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-1-(1,1-dimethylethoxycarbonyl)-D-tryptyl]-4-(1-piperidinyl)-piperidine

(273) 1-[N-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-N-methylglycyl]-4-(1-piperidinyl)-piperidine

(274) 1-[4-Amino-3,5-dibromo-N-[[4-[2(1H)-oxoquinoxalin-3-yl]-1-piperazinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperazine

(275) 1-[4-Amino-3,5-dibromo-N-[[4-[2(1H)-oxoquinoxalin-3-yl]-1-piperazinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(276) 1-[4-Amino-3,5-dibromo-N-[[4-[N-(aminocarbonyl)-N-(4-fluorophenyl)amino]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperazine

(277) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-4-methyl-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(278) 1-[N^2-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-4-methyl-1-piperidinyl]carbonyl]-D-phenylalanyl]-N^6-(1,1-dimethylethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)-piperidine

(279) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[3-dimethylamino)propyl]-piperidine

(280) 1-[N^2-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-4-methyl-1-piperidinyl]carbonyl]-D-phenylalanyl]-L-lysyl]-4-(4-pyridinyl)-piperidine

(281) 1-[N-[[4-(1,3-Dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tryptyl]-4-(1-piperidinyl)-piperidine

(282) 1-[4-Amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(5-methoxy-4-pyrimidinyl)-piperazine

(283) 1-[N^2-[4-Amino-3,5-dibromo-N-[[4-[2(1H)-oxoquinolin-3-yl]-1-piperazinyl]carbonyl]-D-phenylalanyl]-L-lysyl]-4-(4-pyridinyl)-piperidine

(284) 1-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(5-methoxy-4-pyrimidinyl)-piperazine

(285) (R,S)-1-[2-[(3,5-Dibromo-4-hydroxyphenyl)methyl]-4-[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-(4-pyridinyl)-piperidine

(286) 3,5-Dibromo-N^2-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-N-[2-(4-methyl-1-piperazinyl)ethyl]-D-tyrosinamide

(287) 1-[N^2-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(288) 1-[3,5-Dibromo-N-[[4-(7,9-dihydro-6,8-dioxo-1H-purin-9-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine

(289) (R,S)-1-[2-[(3,5-Dibromo-4-hydroxyphenyl)methyl]-4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-(1-piperidinyl)-piperidine

(290) (R,S)-1-[2-[(3,5-Dibromo-4-hydroxyphenyl)methyl]-4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-(4-pyridinyl)-piperidine

(291) (R,S)-1-[2-(4-Amino-3,5-dibromobenzoyl)-4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-4-oxobutyl]-4-(4-pyridinyl)-piperidine

(292) (R)-1-[3-(3,5-Dibromo-4-hydroxyphenyl)-2-[N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]amino]propyl]-4-(1-piperidinyl)-piperidine

(293) 1-[N^6-Acetyl-N^2-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(294) 1-[N^2-[4-Amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-N^6,N^6-dimethyl-L-lysyl]-4-(4-pyridinyl)-piperazine

(295) 1-[N^2-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-N^6,N^6-dimethyl-L-lysyl]-4-(4-pyridinyl)-piperazine

(296) (R,S)-1-[2-(4-Amino-3,5-dibromobenzoyl)-4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-4-oxobutyl]-4-(1-piperidinyl)-piperidine

(297) (R)-1-[3-(4-Amino-3,5-dibromophenyl)-2-[N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-

piperidinyl]carbonyl]amino]propyl]-4-(1-piperidinyl)-piperidine

(298) (R)-1-[3-(4-Amino-3-bromophenyl)-2-[N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]amino]propyl]-4-(1-piperidinyl)-piperidine

(299) (R)-1-[3-(4-Amino-3,5-dibromophenyl)-2-[N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]amino]propyl]-4-(1-piperidinyl)-piperidine

(300) (R)-1-[3-(4-Amino-3-bromophenyl)-2-[N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]amino]propyl]-4-(1-piperidinyl)-piperidine

(301) (R)-1-[3-(3,5-Dibromo-4-hydroxyphenyl)-2-[N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]amino]propyl]-4-(1-piperidinyl)-piperidine

(302) (R,S)-1-[2-(4-Amino-3,5-dibromobenzoyl)-4-[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]-4-oxobutyl]-4-(1-piperidinyl)-piperidine

(303) 1-[4-Amino-N-[[4-[2-(aminocarbonylamino)phenylamino]-1-piperidinyl]carbonyl]-3,5-dibromo-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(304) 1-[4-Amino-3,5-dibromo-N-[[4-[3,4-dihydro-7-(methoxycarbonyl)-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(305) 1-[4-Amino-N-[[4-[2-(methylsulphonylamino)phenylamino]-1-piperidinyl]carbonyl]-3,5-dibromo-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(306) 1-[4-Amino-3,5-dibromo-N-[[4-[3,4-dihydro-7-(hydroxycarbonyl)-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(307) 1-[4-Amino-3,5-dibromo-N-[[4-[3,4-dihydro-7-(methoxycarbonyl)-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperidine

(308) 1-[4-Amino-3,5-dibromo-N-[[4-[3,4,4a,5,6,7,8,8a-octahydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(309) 1-[4-Amino-3,5-dibromo-N-[[4-[3,4-dihydro-7-(hydroxycarbonyl)-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperidine

(310) 1-[4-Amino-N-[[4-[7-(aminocarbonyl)-3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-3,5-dibromo-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(311) 1-[4-Amino-3,5-dibromo-N-[[4-[7-(2-hydroxyethylaminocarbonyl)-3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(312) 1-[4-Amino-N-[[4-[7-(aminocarbonyl)-3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-3,5-dibromo-D-phenylalanyl]-4-(4-pyridinyl)-piperidine

(313) 1-[4-Amino-3,5-dibromo-N-[[4-[7-(2-hydroxyethylaminocarbonyl)-3,4-dihydro-2(1H)-oxoquinazolin-

3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperidine

(314) 1-[4-Amino-3,5-dibromo-N-[[4-(1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(315) 1-[4-Amino-3,5-dibromo-N-[[4-(1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperazine

(316) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(5-methoxy-4-pyrimidinyl)-piperazine

(317) 1-[4-Amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxo-quinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-fluorophenyl)-piperazine

(318) 1-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-fluorophenyl)-piperazine

(319) 1-[4-Amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxo-quinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(2-fluorophenyl)-piperazine

(320) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(2-fluorophenyl)-piperazine

(321) 1-[3,5-Dibromo-N-[[4-(1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine

(322) trans-1-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-cyclohexyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine

(323) 1-[3,5-Dibromo-N-[[4-(3,4-dihydro-6,7-dimethoxy-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine

(324) 1-[N-[[4-(5-Chloro-3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-4-(4-pyridinyl)-piperidine

(325) 1-[3,5-Dibromo-N-[[3-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-pyrrolidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine

(326) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxo-imidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperazine

(327) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperidine

(328) 1-[3,5-Dibromo-N-[[4-(3,4-dihydro-8-methoxy-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine

(329) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-4-(4-methoxyphenyl)-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine

(330) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-(4-methoxyphenyl)-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperazine

(331) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-(4-methoxyphenyl)-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine

(332) 1-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine

(333) 1-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine

(334) 1-[N-[[4-(1,3-dihydro-4-[3-(trifluoromethyl)-phenyl]-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-3-(4-pyridinyl)-D,L-alanyl]-4-(4-pyridinyl)-piperazine

(335) 1-[4-Amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperidine

(336) 1-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine

(337) 1-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine

(338) (R)-1-[3-(4-Amino-3,5-dibromophenyl)-2-[N-[[4-(3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl)-1-piperidinyl]carbonyl]amino]propyl]-4-(1-piperidinyl)-piperidine

(339) (R)-1-[3-(4-Amino-3,5-dibromophenyl)-2-[N-[[4-(3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl)-1-

piperidinyl]carbonyl]amino]propyl]-4-(1-piperidinyl)-piperidine

(340) 1-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperidinyl)-piperidine

(341) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperidinyl)-piperidine

(342) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-(3-thienyl)-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine

(343) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-4-(3-thienyl)-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperidinyl)-piperidine

(344) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(hexahydro-1H-1-azepinyl)-piperidine

(345) 1-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(hexahydro-1H-1-azepinyl)-piperidine

(346) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine

(347) 1-[4-Amino-3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine

(348) 1-[4-Amino-3,5-dibromo-N-[[4-(2,4-dihydro-5-phenyl-3(3H)-oxo-1,2,4-triazol-2-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine

(349) 1-[4-Amino-3,5-dibromo-N-[[4-(2,4-dihydro-5-phenyl-3(3H)-oxo-1,2,4-triazol-2-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(350) 1-[4-Amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine

(351) 1-[4-Amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(352) 1-[3,5-Dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine

(353) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-4-(3-thienyl)-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine

(354) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D,L-tyrosyl]-4-(4-pyridinyl)-piperidine

(355) 1-[4-Amino-3,5-dibromo-N-[[4-(2,4-dihydro-5-phenyl-3(3H)-oxo-1,2,4-triazol-2-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperazine

(356) 1-[4-Amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(exo-8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-piperazine

(357) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-(3-thienyl)-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperazine

(358) 1-[3,5-Dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperidinyl)-piperazine

(359) 1-[4-Amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperazine

(360) 1-[4-Amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(361) 1-[4-Amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperazine

(362) 1-[4-Amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(363) 1-[4-Amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine

(364) 1-[3,5-Dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-

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piperidinyl]carbonyl]-D-tyrosyl]-4-(hexahydro-1H-1-azepinyl)-piperidine

(365) 1-[N2-[3,5-Dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(366) 1-[4-Amino-3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxo-quinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperidine

(367) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperidine

(368) 1-[4-Amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperidine

(369) 1-[4-Amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[4-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperazine

(370) 1-[4-Amino-3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperazine

(371) 1-[4-Amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperazine

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(372) 4-(1-Acetyl-4-piperidinyl)-1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-piperidine

(373) 1-[4-Amino-N-[[4-(6-bromo-3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-3,5-dibromo-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(374) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-5-methyl-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine

(375) 1-[4-Amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-(3-nitrophenyl)-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine

(376) 1-[4-Amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-(3-methoxyphenyl)-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine

(377) 1-[4-Amino-N-[[4-[4-(3-bromophenyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-3,5-dibromo-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine

(378) 1-[N^2-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-N^6-(1,1-dimethylethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)-piperazine

(379) 1-[3,5-Dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxo-imidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-fluorophenyl)-piperazine

(380) 1-[4-Amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-fluorophenyl)-piperazine

(381) 1-[3,5-Dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(3-pyridinyl)-piperazine

(382) 1-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(3-pyridinyl)-piperazine

(383) 1-[4-Amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(3-pyridinyl)-piperazine

(384) 1-[3,5-Dibromo-N-[[4-[1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperazine

(385) 1-[4-Amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(3-pyridinyl)-piperazine

(386) 1-[4-Amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(5-methoxy-4-pyrimidinyl)-piperazine

(387) 1-[4-Amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(2-pyridinyl)-piperazine

(388) 1-[4-Amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(2-pyridinyl)-piperazine

(389) 1-[4-Amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(phenylaminocarbonylamino)-piperidine

(390) 1-[4-Amino-3,5-dibromo-N-[[4-[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(5-methoxy-4-pyrimidinyl)-piperazine

(391) 1-[3,5-Dibromo-N-[[4-[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(5-methoxy-4-pyrimidinyl)-piperazine

(392) 1-[3,5-Dibromo-N-[[4-[4-phenyl-2(1H)-oxopyrimidin-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine

(393) 4-Cyano-1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-phenylpiperidine

(394) 1-[4-Amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyrimidinyl)-piperazine

(395) 1-[4-Amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyrimidinyl)-piperazine

(396) 1-[3,5-Dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyrimidinyl)-piperazine

(397) 1-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyrimidinyl)-piperazine

(398) 1-[4-Amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(399) 1-[4-Amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-(4-fluorophenyl)-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(5-methoxy-4-pyrimidinyl)-piperazine

(400) 1-[4-Amino-3,5-dibromo-N-[[4-[2(1H)-oxoquinolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(401) 2-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1,2,3,4-tetrahydro-5H-pyrido[4,3-b]indole

(402) 1-[4-Amino-3,5-dibromo-N-[[4-[2(1H)-oxoquinolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperazine

(403) 1-[4-Amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperazine

(404) 1-[4-Amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-ethylphenyl)-piperazine

(405) 1-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-fluorophenyl)-1,2,5,6-tetrahydropyridine

(406) 1-[3,5-Dibromo-N-[[4-[2(1H)-oxoquinolin-3-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperazine

(407) 1-[3,5-Dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinolin-3-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperazine

(408) 1-[4-Amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[4-(1-oxoethyl)phenyl]-piperazine

(409) 1-[4-Amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[4-(1-oxoethyl)phenyl]-piperazine

(410) 1-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-fluorobenzoyl)-piperidine

(411) 1-[4-Amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-cyano-4-phenylpiperidine

(412) 1-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-fluorophenyl)-piperidine

(413) 1-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-[(hexahydro-1-methyl-4-pyridinyl)carbonyl]-piperazine

(414) 1-[4-Amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[3-(dimethylamino)propyl]-piperazine

(415) 1-[4-Amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[3-(dimethylamino)propyl]-piperazine

(416) 1-[4-Amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-methyl-1-piperazinyl)-piperidine

(417) 1-[4-Amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-methyl-1-piperazinyl)-piperidine

(418) 1-[4-Amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(exo-8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-piperazine

(419) 1-[N-[4-[[1,3-Dihydro-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-3-(trifluoromethyl)-D,L-phenylalanyl]-4-(exo-8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-piperazine

(420) 1-[3,5-Dibromo-N-[[4-[7-(methoxycarbonyl)-3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine

(421) 1-[3,5-Dibromo-N-[[4-[7-(hydroxycarbonyl)-3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine

(422) 1-[3,5-Dibromo-N-[[4-[7-(methoxycarbonyl)-3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine

(423) 1-[3,5-Dibromo-N-[[4-[7-(hydroxycarbonyl)-3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine

(424) 1-[4-Amino-3,5-dibromo-N-[[4-[7-(methylaminocarbonyl)-3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperidine

(425) 1-[3,5-Dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-morpholinyl)-piperidine

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(426) 1-[4-Amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(dimethylamino)-piperidine

(427) 1-[3,5-Dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-pyrrolidinyl)-piperidine

(428) 1-[4-Amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-morpholinyl)-piperidine

(429) 1-[3,5-Dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(dimethylamino)-piperidine

(430) 1-[4-Amino-3,5-dibromo-N-[[4-[7-[(4-methyl-1-piperazinyl)carbonyl]-3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperidine

(431) 1-[4-Amino-3,5-dibromo-N-[[4-(2,5-dioxo-4-phenylimidazolidin-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(432) 1-[3,5-Dibromo-N-[[4-(2,5-dioxo-4-phenylimidazolidin-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine

(433) 1-[4-Amino-3,5-dibromo-N-[[4-[2,5-dioxo-4-(phenylmethyl)-imidazolidin-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperidine

(434) 1-[3,5-Dibromo-N-[[4-[2,5-dioxo-4-(phenylmethyl)imidazolidin-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine

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(435) 1-[4-Amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-pyrrolidinyl)-piperidine

(436) 1-[3,5-Dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperidinyl)-piperazine

(437) 1-[4-Amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperazine

(438) 1-[4-Amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-cyclohexylpiperazine

(439) 1-[3,5-Dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-cyclohexylpiperazine

(440) 1-[4-Amino-3,5-dibromo-N-[[4-(3,4-dihydro-2,2-dioxido-2,1,3-benzothiadiazin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(441) 1-[4-Amino-3,5-dibromo-N-[[4-(3,4-dihydro-2,2-dioxido-2,1,3-benzothiadiazin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine

(442) 1-[4-Amino-3,5-dibromo-N-[[4-(3,4-dihydro-2,2-dioxido-2,1,3-benzothiadiazin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperidine

(443) 1-[3,5-Dibromo-N-[[4-[1,3-dihydro-4-(4-fluorophenyl)-2(2H)-oxoimidazol-1-yl]-1-

piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperidinyl)-piperazine

(444) 1-[3,5-Dibromo-N-[[4-[1,3-dihydro-4-(4-fluorophenyl)-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine

(445) 1-[3,5-Dibromo-N-[[4-[1,3-dihydro-4-(4-fluorophenyl)-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperazine

(446) 1-[3,5-Dibromo-N-[[4-[1,3-dihydro-4-(4-fluorophenyl)-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperidinyl)-piperidine

(447) 1-[4-Amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-(4-fluorophenyl)-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperazine

(448) 1-[4-Amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-(4-fluorophenyl)-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine

(449) 1-[4-Amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-(4-fluorophenyl)-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(450) 1-[3,5-Dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-N-methyl-D-tyrosyl]-4-(4-pyridinyl)-piperidine

(451) (R,S)-1-[2-[(3,5-Dibromo-4-hydroxyphenyl)methyl]-4-[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]-1,4-dioxobutyl]-4-(4-pyridinyl)-piperazine

(452) (R,S)-1-[2-[(3,5-Dibromo-4-hydroxyphenyl)methyl]-4-[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]-1,4-dioxobutyl]-4-(4-pyridinyl)-piperazine

(453) (R,S)-1-[2-[(3,5-Dibromo-4-hydroxyphenyl)methyl]-4-[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperazine

(454) (R,S)-1-[2-[(3,5-Dibromo-4-hydroxyphenyl)methyl]-4-[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine

(455) (R,S)-1-[2-[(3,5-Dibromo-4-hydroxyphenyl)methyl]-4-[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]-1,4-dioxobutyl]-4-(1-piperidinyl)-piperidine

(456) 1-[3,4-Dichloro-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D,L-phenylalanyl]-4-(1-piperidinyl)-piperidine

(457) (R,S)-1-[2-[(3,5-Dibromo-4-hydroxyphenyl)methyl]-4-[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]-1,4-dioxobutyl]-4-(4-pyridinyl)-piperidine

(458) (R,S)-1-[2-[(3,5-Dibromo-4-hydroxyphenyl)methyl]-4-[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]-1,4-dioxobutyl]-4-(hexahydro-1H-1-azepinyl)-piperidine

(459) (R,S)-1-[2-[(3,5-Dibromo-4-hydroxyphenyl)methyl]-4-[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]-1,4-dioxobutyl]-4-(hexahydro-1H-1-azepinyl)-piperidine

(460) 1-[3,5-Dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-cycloheptylpiperazine

(461) 1-[3,5-Dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-cyclopentylpiperazine

(462) 1-[3,5-Dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-4-methoxy-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(463) 1-[3,5-Bis-(trifluoromethyl)-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D,L-phenylalanyl]-4-(4-pyridinyl)-piperazine

(464) 1-[3,5-Bis-(trifluoromethyl)-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D,L-phenylalanyl]-4-(1-piperidinyl)-piperidine

(465) 1-[3,5-Bis-(trifluoromethyl)-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D,L-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine

(466) 1-[4-Amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-(4-biphenylyl)-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(467) 1-[4-Amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-(2-naphthyl)-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(468) 1-[3,5-Dibromo-N-[[4-[1,3-dihydro-4-(2-naphthyl)-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine

(469) 1-[3-Bromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D,L-phenylalanyl]-4-(1-piperidinyl)-piperidine

(470) 1-[3,5-Dibromo-N-[[4-[1,3-dihydro-4-(4-biphenylyl)-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine

(471) 1-[N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-3-(4-biphenylyl)-D,L-alanyl]-4-(1-piperidinyl)-piperidine

(472) 1-[3,5-Dibromo-N-[[4-[1,3-dihydro-4-biphenylyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D,L-phenylalanyl]-4-(1-piperidinyl)-piperidine

(473) 1-[3,5-Dibromo-N-[[4-[1,3-dihydro-4-(2-methoxyphenyl)-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine

(474) 1-[4-Amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-(2-methoxyphenyl)-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(475) 1-[3,5-Bis-(trifluoromethyl)-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D,L-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine

(476) 1-[3,5-Bis-(trifluoromethyl)-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D,L-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperazine

(477) 1-[3,4-Dichloro-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D,L-phenylalanyl]-4-(4-pyridinyl)-piperazine

(478) 1-[3-Bromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D,L-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine

(479) 1-[3-Bromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D,L-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine

(480) 1-[3-Bromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D,L-phenylalanyl]-4-(4-pyridinyl)-piperidine

(481) 1-[4-Amino-3,5-dibromo-N-[[4-[4-(3,4-dichlorophenyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine

(482) 1-[4-Amino-3,5-dibromo-N-[[4-[4-(3,4-dichlorophenyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine

(483) 1-[4-Amino-N-[[4-[4-(3-chlorophenyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-3,5-dibromo-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine

(484) 1-[4-Amino-N-[[4-[4-(3-chlorophenyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-3,5-dibromo-D-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine

(485) 1-[4-Amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-benzoyl-4-piperidinyl)-piperidine

(486) 1-[4-Amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methylsulphonyl-4-piperidinyl)-piperidine

(487) 1-[4-Amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[1-(3-carboxy-1-oxopropyl)-4-piperidinyl]-piperidine

(488) 1-[4-Amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-hexyl-4-piperidinyl)-piperidine

(489) 1-[4-Amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-cyclopropylmethyl-4-piperidinyl)-piperidine

(490) 1-[3,5-Dibromo-N-[[4-(2,4-dihydro-5-phenyl-3(3H)-oxo-1,2,4-triazol-2-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperidinyl)-piperidine

(491) 1-[3,5-Dibromo-N-[[4-(2,4-dihydro-5-phenyl-3(3H)-oxo-1,2,4-triazol-2-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine

(492) 1-[3,5-Dibromo-N-[[4-(2,4-dihydro-5-phenyl-3(3H)-oxo-1,2,4-triazol-2-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperidinyl)-piperazine

(493) 1-[4-Amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[1-(ethoxycarbonylmethyl)-4-piperidinyl]-piperidine

(494) 1-[4-Amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[1-(carboxymethyl)-4-piperidinyl]-piperidine

(495) 1-[4-Amino-3,5-dibromo-N-[[4-[1,3-dihydro-4,5-diphenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine

(496) 1-[4-Amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[(4-pyridinyl)carbonyl]-piperazine

(497) 1-[3,5-Dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-methyl-1-piperazinyl)piperidine

(498) 1-[4-Amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(hexahydro-4-methyl-1H-1,4-diazepin-1-yl)piperidine

(499) 1-[4-Amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(hexahydro-4-methyl-1H-1,4-diazepin-1-yl)piperidine

(500) 1-[4-Amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[(1-methyl-4-piperidinyl)carbonyl]-piperazine

(501) 1-[3,5-Dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-methyl-1-piperazinyl)piperidine

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(502) 1-[3,5-Dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(hexahydro-4-methyl-1H-1,4-diazepin-1-yl)piperidine

(503) 1-[3,5-Dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(hexahydro-4-methyl-1H-1,4-diazepin-1-yl)piperidine

(504) 1-[4-Amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[(4-methyl-1-piperazinyl)carbonyl]-piperidine

(505) 1-[4-Amino-3,5-dibromo-N-[[4-[1,3-dihydro-2(2H)-oxoimidazo[4,5-c]quinolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)carbonyl]-piperidine

(506) 1-[N-[[4-[3,4-Dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-3-(trifluoromethyl)-D,L-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine

(507) 1-[3-Chloro-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D,L-phenylalanyl]-4-(1-piperidinyl)-piperidine

(508) (R,S)-1-[[4-[3,4-Dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]-2-[[3-(trifluoromethyl)phenyl]methyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine

(509) 1-[4-Amino-3,5-dibromo-N-[[4-[4-(3-bromophenyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(exo-8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-piperazine

(510) 1-[4-Amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-(3-methoxyphenyl)-2(2H)-oxoimidazol-1-yl]-1-

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piperidinyl]carbonyl]-D-phenylalanyl]-4-(exo-8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-piperazine

(511) 1-[N-[[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-3-methoxy-D,L-phenylalanyl]-4-(1-piperidinyl)-piperidine

(512) 1-[N-[[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-3-methoxy-D,L-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperazine

(513) 1-[N-[[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-3-methoxy-D,L-phenylalanyl]-4-(4-pyridinyl)-piperazine

(514) 1-[N-[[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-3-methoxy-D,L-phenylalanyl]-4-(exo-8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-piperazine

(515) 1-[N-[[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-3-methoxy-D,L-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperazine

(516) 1-[N^2-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-L-tyrosyl]-D-lysyl]-4-(4-pyridinyl)-piperazine

(517) 1-[N^2-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-D-lysyl]-4-(4-pyridinyl)-piperazine

(518) 1-[N^2-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-L-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

(519) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-(3-hydroxyphenyl)-2(2H)-oxoimidazol-1-yl)-1-

piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine

(520) 1-[4-Amino-N-[[4-[4-[3,5-bis-(trifluoromethyl)phenyl]-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-3,5-dibromo-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine

(521) 1-[4-Amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-piperidinyl)-piperidine

(522) 1-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-piperidinyl)-piperidine

(523) 1-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-4-(methylsulphonyloxy)-D-phenylalanyl]-4-[1-(methylsulphonyl)-4-piperidinyl]-piperidine

(524) 1-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-[1-(methylsulphonyl)-4-piperidinyl]-piperidine

(525) 1-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-[1-(cyclopropylmethyl)-4-piperidinyl]-piperidine

(526) 1-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-[1-(hydroxycarbonylmethyl)-4-piperidinyl]-piperidine

(527) 1-[N-[[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-3-(2-methyl-4-thiazolyl)-D,L-alanyl]-4-(1-piperidinyl)-piperidine

(528) 1-[N-[[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-3-(2-methyl-4-thiazolyl)-D,L-alanyl]-4-(4-pyridinyl)-piperazine

(529) (R,S)-1-[2-[(1-Naphthyl)methyl]-4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-(1-piperidinyl)-piperidine

(530) (R,S)-1-[2-[(1-Naphthyl)methyl]-4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine

(531) (R,S)-1-[2-[(3-Methoxyphenyl)methyl]-4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-(1-piperidinyl)-piperidine

(532) 1-[N-[[4-[3,4-Dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-3-ethenyl-D,L-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine

(533) 1-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxopyrido-[3,4-d]pyrimidin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine

(534) 1-[4-Amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxopyrido[3,4-d]pyrimidin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine

(535) 1-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxopyrido[3,4-d]pyrimidin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperazinyl)-piperidine

(536) 1-[4-Amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxopyrido[4,3-d]pyrimidin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(537) 1-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxopyrido[4,3-d]pyrimidin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine

(538) (R,S)-1-[2-[(1-Naphthyl)methyl]-4-[4-(3,4-dihydro-2(1H)-oxopyrido[3,4-d]pyrimidin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine

(539) (R,S)-1-[2-[(1-Naphthyl)methyl]-4-[4-(3,4-dihydro-2(1H)-oxopyrido[3,4-d]pyrimidin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperazinyl)-piperidine

(540) (R,S)-1-[2-[(1-Naphthyl)methyl]-4-[4-(3,4-dihydro-2(1H)-oxopyrido[3,4-d]pyrimidin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-(1-piperidinyl)-piperidine

(541) (R,S)-1-[2-[(3-Ethoxyphenyl)methyl]-4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperazinyl)-piperidine

(542) (R,S)-1-[2-[(3-Ethoxyphenyl)methyl]-4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-(1-piperidinyl)-piperidine

(543) (R,S)-1-[2-[(3-Ethoxyphenyl)methyl]-4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine

(544) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[[3-(1-methylethoxy)phenyl]methyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine

(545) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[[3-(1-methylethoxy)phenyl]methyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperazinyl)-piperidine

(546) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[[3-(1-methylethoxy)phenyl]methyl]-1,4-dioxobutyl]-4-(1-piperidinyl)-piperidine

(547) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dimethylphenyl)methyl]-1,4-dioxobutyl]-4-(1-piperidinyl)-piperidine

(548) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dimethylphenyl)methyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperazinyl)-piperidine

(549) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dimethylphenyl)methyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine

(550) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[[3-[2-(dimethylamino)ethoxy]phenyl]methyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperazinyl)-piperidine

(551) 1-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-[(1-methyl-4-piperazinyl)carbonyl]-piperidine

(552) 1-[4-Amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[4-(1-oxoethyl)-1-piperazinyl]-piperidine

(553) 1-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-[4-(1-oxoethyl)-1-piperazinyl]-piperidine

(554) 1-[4-Amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[4-(1-oxoethyl)-1-piperazinyl]-piperidine

(555) 1-[3,5-Dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-[4-(1-oxoethyl)-1-piperazinyl]-piperidine

(556) 1-[4-Amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[(1-methyl-4-piperazinyl)carbonyl]-piperazine

(557) 1-[4-Amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[(1-methyl-4-piperazinyl)carbonyl]-piperazine

(558) 1-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-[(4-pyridinyl)carbonyl]-piperazine

(559) 1-[4-Amino-3,5-dibromo-N-[(4-oxo-1-piperidinyl)carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine

(560) 1-[4-Amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[4-[4-(dimethylamino)butyl]phenyl]-piperazine

(561) 1-[4-Amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[4-[4-(dimethylamino)butyl]phenyl]-piperazine

(562) 1-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-[(1-methyl-4-piperazinyl)carbonyl]-piperazine

(563) 1-[3,5-Dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-[(1-methyl-4-piperazinyl)carbonyl]-piperazine

(564) 1-[4-Amino-N-[(4-amino-1-piperidinyl)carbonyl]-3,5-di-bromo-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine

(565) 1-[4-Amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[4-(dimethylamino)-1-piperidinyl]-piperidine

(566) 1-[4-Amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[4-(dimethylamino)-1-piperidinyl]-piperidine

(567) 1-[4-Amino-3,5-dibromo-N-[[4-[2(1H)-oxoquinolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-methyl-1-piperazinyl)-piperidine

(568) 1-[4-Amino-3,5-dibromo-N-[[4-[2(1H)-oxoquinolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[4-(dimethylamino)-1-piperidinyl]-piperidine

(569) 1-[3,5-Dibromo-N-[[4-[2(1H)-oxoquinolin-3-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-methyl-1-piperazinyl)-piperidine

(570) 1-[N^2-[[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-N'-methyl-D-tryptyl]-4-(1-methyl-4-piperidinyl)-piperidine

(571) 1-[N^2-[[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-N'-methyl-D-tryptyl]-4-(4-methyl-1-piperazinyl)-piperidine

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(572) 1-[N^2-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-N'-methyl-D-tryptyl]-4-(1-methyl-4-piperidinyl)-piperidine

(573) 1-[N^2-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-N'-methyl-D-tryptyl]-4-(4-methyl-1-piperazinyl)-piperidine

(574) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,4-dichlorophenyl)methyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine

(575) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,4-dichlorophenyl)methyl]-1,4-dioxobutyl]-4-(4-methyl-1-piperazinyl)-piperidine

(576) 1-[N^2-[[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-N'-(1,1-dimethylethoxycarbonyl)-D-tryptyl]-4-(4-methyl-1-piperazinyl)-piperidine

(577) 1-[N^2-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-N'-(1,1-dimethylethoxycarbonyl)-D-tryptyl]-4-(4-methyl-1-piperazinyl)-piperidine

(578) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dibromophenyl)methyl]-1,4-dioxobutyl]-4-(4-methyl-1-piperazinyl)-piperidine

(579) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dibromophenyl)methyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine

(580) 1-[N^2-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-N'-(1,1-dimethylethoxycarbonyl)-D-tryptyl]-4-(1-methyl-4-piperidinyl)-piperidine

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(581) 1-[N^2-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-N'-(1,1-dimethylethoxycarbonyl)-D-tryptyl]-4-(1-methyl-4-piperidinyl)-piperidine

(582) 1-[4-Amino-3,5-dibromo-N-[[4-(2,3-dihydro-4(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine

(583) 1-[N^2-[[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-N'-methyl-D-tryptyl]-4-[4-(dimethylamino)-1-piperidinyl]-piperidine

(584) 1-[N^2-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-N'-methyl-D-tryptyl]-4-[4-(dimethylamino)-1-piperidinyl]-piperidine

(585) 1-[4-Amino-N-[[4-[4-(4-amino-3,5-dibromophenyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-3,5-dibromo-D-phenylalanyl]-4-(1-piperidinyl)-piperidine

(586) 1-[4-Amino-N-[[4-[4-(4-amino-3,5-dibromophenyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-3,5-dibromo-D-phenylalanyl]-4-(4-methyl-1-piperazinyl)-piperidine

(587) 1-[N^2-[[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-N'-(1,1-dimethylethoxycarbonyl)-D-tryptyl]-4-[4-(dimethylamino)-1-piperidinyl]-piperidine

(588) 1-[N^2-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-N'-(1,1-dimethylethoxycarbonyl)-D-tryptyl]-4-[4-(dimethylamino)-1-piperidinyl]-piperidine

(589) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dibromo-4-methylphenyl)methyl]-1,4-dioxobutyl]-4-(4-methyl-1-piperazinyl)-piperidine

(590) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dibromo-4-methylphenyl)methyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine

(591) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[[3,4-difluoro-5-(trifluoromethyl)-phenyl]methyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine

(592) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[[3,4-difluoro-5-(trifluoromethyl)-phenyl]methyl]-1,4-dioxobutyl]-4-(4-methyl-1-piperazinyl)-piperidine

(593) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,4-dichlorophenyl)methyl]-1,4-dioxobutyl]-4-(ethoxycarbonyl)-piperidine

(594) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,4-dichlorophenyl)methyl]-1,4-dioxobutyl]-4-(ethoxycarbonylmethyl)-piperidine

(595) (R,S)-2-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,4-dichlorophenyl)methyl]-1,4-dioxobutyl]-6-methyl-2,6-diazaspiro[3,4]octane

(596) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,4-dichlorophenyl)methyl]-1,4-dioxobutyl]-4-(hydroxycarbonylmethyl)-piperidine

(597) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[[1-methyl-1H-indol-3-yl]methyl]-1,4-dioxobutyl]-4-(4-methyl-1-piperazinyl)-piperidine

(598) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[[1-methyl-1H-indol-3-yl]methyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine

(599) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-(ethoxycarbonyl)-2-[[1-methyl-1H-indol-3-yl]methyl]-1,4-dioxobutyl]-4-(4-methyl-1-piperazinyl)-piperidine

(600) (R,S)-1-[4-[4-(Aminocarbonylamino)-1-piperidinyl]-2-[[1-methyl-1H-indol-3-yl]methyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine

(601) (R,S)-1-[4-[4-(Aminocarbonylamino)-1-piperidinyl]-2-(ethoxycarbonyl)-2-[[1-methyl-1H-indol-3-yl]methyl]-1,4-dioxobutyl]-4-(4-methyl-1-piperazinyl)-piperidine

(602) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dibromo-4-methoxyphenyl)methyl]-1,4-dioxobutyl]-4-(4-methyl-1-piperazinyl)-piperidine

(603) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,4-dichlorophenyl)methyl]-1,4-dioxobutyl]-4-carboxypiperidine

(604) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dibromo-4-methoxyphenyl)methyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine

(605) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[[4-fluor-3-(trifluoromethyl)-phenyl]methyl]-1,4-dioxobutyl]-4-(4-methyl-1-piperazinyl)-piperidine

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(607) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[[4-fluor-3-(trifluoromethyl)-phenyl]methyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine

(607) 1-[N-[[4-[3,4-Dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-3-(trifluoromethyl)-D,L-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperazine

(608) 1-[N-[[4-[3,4-Dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-3-(trifluoromethyl)-D,L-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperazine

(609) 1-[N-[[4-[3,4-Dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-3-(trifluoromethyl)-D,L-phenylalanyl]-4-(1-piperidinyl)-piperidine

(610) 1-[N-[[4-[3,4-Dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-3-(trifluoromethyl)-D,L-phenylalanyl]-4-(4-pyridinyl)-piperazine

(611) 1-[N-[[4-[3,4-Dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-3-(trifluoromethyl)-D,L-phenylalanyl]-4-(4-pyridinyl)-piperidine

(612) (R,S)-1-[2-[(4-Amino-3,5-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-(1-piperidinyl)-piperidine

(613) 1-[3-Chloro-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D,L-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine

(614) 1-[3-Chloro-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D,L-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine

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(615) 1-[3-Chloro-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D,L-phenylalanyl]-4-(cyclopentyl)-piperazine

(616) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3-methylphenyl)methyl]-1,4-dioxobutyl]-4-(1-piperidinyl)-piperidine

(617) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[[3-(trifluoromethyl)-phenyl]methyl]-1,4-dioxobutyl]-4-(hexahydro-1H-1-azepinyl)-piperidine

(618) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[[3-(trifluoromethyl)-phenyl]methyl]-1,4-dioxobutyl]-4-(exo-8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-piperazine

(619) 1-[3-Bromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D,L-phenylalanyl]-4-(1-piperidinyl)-piperidine

(620) 1-[3-cyano-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D,L-phenylalanyl]-4-(1-piperidinyl)-piperidine

(621) 1-[N-[[4-[3,4-Dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-3-methyl-D,L-phenylalanyl]-4-(1-piperidinyl)-piperidine

(622) 1-[N-[[4-(1,3-Dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-3-methyl-D,L-phenylalanyl]-4-(1-piperidinyl)-piperidine

(623) 1-[3-Methyl-N-[[4-[3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl]-1-piperidinyl]carbonyl]-D,L-phenylalanyl]-4-(1-piperidinyl)-piperidine

(624) 1-[N-[[4-[1,3-Dihydro-4-(3-methoxyphenyl)-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-3-methyl-D,L-phenylalanyl]-4-(1-piperidinyl)-piperidine

(625) 1-[N-[[4-[1,3-Dihydro-4-[(3-(trifluoromethyl)-phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-3-methyl-D,L-phenylalanyl]-4-(1-piperidinyl)-piperidine

(626) 1-[3-Bromo-N-[[4-[1,3-dihydro-4-[(3-(trifluoromethyl)-phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D,L-phenylalanyl]-4-(1-piperidinyl)-piperidine

(627) 1-[3-Bromo-N-[[4-[3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl]-1-piperidinyl]carbonyl]-D,L-phenylalanyl]-4-(1-piperidinyl)-piperidine

(628) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[[3-(trifluoromethyl)-phenyl]methyl]-1,4-dioxobutyl]-4-(1-piperidinyl)-piperidine

(629) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[[3-(trifluoromethyl)-phenyl]methyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperazine

(630) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[[3-(trifluoromethyl)-phenyl]methyl]-1,4-dioxobutyl]-4-(4-pyridinyl)-piperazine

(631) (R,S)-4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-4-oxo-2-[[3-(trifluoromethyl)-phenyl]methyl]-N-[2-(4-methyl-1-piperazinyl)ethyl]-butanamide

(632) 1-[N-[[4-[3,4-Dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-3-(1H-tetrazol-5-yl)-D,L-phenylalanyl]-4-(1-piperidinyl)-piperidine

(633) 1-[3-Bromo-N-[[4-[1,3-dihydro-4-(3-methoxyphenyl)-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D,L-phenylalanyl]-4-(1-piperidinyl)-piperidine

(634) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(2-naphthyl)methyl]-1,4-dioxobutyl]-4-(1-piperidinyl)-piperidine

(635) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[[2-(trifluoromethyl)phenyl]methyl]-1,4-dioxobutyl]-4-(1-piperidinyl)-piperidine

(636) 1-[N-[[4-[3,4-Dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-3-nitro-D,L-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine

(637) (R,S)-1-[2-[(4-Amino-3,5-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine

(638) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[[2-(trifluoromethyl)phenyl]methyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine

(639) (R,S)-1-[2-[[3,5-Bis-(trifluoromethyl)phenyl]methyl]-4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine

(640) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,4-dimethoxyphenyl)methyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine

(641) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(2-naphthyl)methyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine

(642) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,4-dimethoxyphenyl)methyl]-1,4-dioxobutyl]-4-(1-piperidinyl)-piperidine

(643) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[[3-(trifluoromethyl)phenyl]methyl]-1,4-dioxobutyl]-4-(4-piperidinyl)-piperidine

(644) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl)-1-piperidinyl]-2-[[3-(trifluoromethyl)phenyl]methyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine

(645) (R,S)-1-[2-[(3-Bromophenyl)methyl]-4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine

(646) (R,S)-1-[2-[(3-Bromophenyl)methyl]-4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-(1-piperidinyl)-piperidine

(647) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[[3-(1-propen-3-yl)phenyl]methyl]-1,4-dioxobutyl]-4-(1-piperidinyl)-piperidine

(648) (R,S)-1-[2-[3-(Biphenylyl)methyl]-4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-(1-piperidinyl)-piperidine

(649) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[[3-(pyridinyl)phenyl]methyl]-1,4-dioxobutyl]-4-(1-piperidinyl)-piperidine

(650) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[[3-(2-thiazolyl)phenyl]methyl]-1,4-dioxobutyl]-4-(1-piperidinyl)-piperidine

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(651) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[[3-(2-furyl)phenyl]methyl]-1,4-dioxobutyl]-4-(1-piperidinyl)-piperidine.

(652) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3-propylphenyl)methyl]-1,4-dioxobutyl]-4-(1-piperidinyl)-piperidine

(653) (R,S)-1-[4-(2,4-Dihydro-5-phenyl-3(3H)-oxotriazol-2-yl)-1-piperidinyl]-2-[[3-(trifluoromethyl)phenyl]methyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine

(654) (R,S)-1-[4-[1,3-Dihydro-2(2H)-oxoimidazo[4,5-c]quinolin-3-yl]-1-piperidinyl]-2-[[3-(trifluoromethyl)phenyl]methyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine

(655) (R,S)-1-[2-[(4-Quinolinyl)methyl]-4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine

(656) (R,S)-1-[2-[(4-Quinolinyl)methyl]-4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-(1-piperidinyl)-piperidine

(657) 1-[2-[(1,2,3,4-Tetrahydro-1-naphthyl)methyl]-4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine (mixture of diastereomers)

(658) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,4-dibromophenyl)methyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine

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(659) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,4-dibromophenyl)methyl]-1,4-dioxobutyl]-4-(4-methyl-1-piperazinyl)-piperidine

(660) (R,S)-1-[2-[(4-Quinolinyl)methyl]-4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-(4-methyl-1-piperazinyl)-piperidine

(661) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(4-hydroxy-3,5-dimethylphenyl)methyl]-1,4-dioxobutyl]-4-(1-piperidinyl)-piperidine

(662) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(4-hydroxy-3,5-dimethylphenyl)methyl]-1,4-dioxobutyl]-4-(4-methyl-1-piperazinyl)-piperidine

(663) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(4-hydroxy-3,5-dimethylphenyl)methyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine

(664) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(4-methoxy-3,5-dimethylphenyl)methyl]-1,4-dioxobutyl]-4-(1-piperidinyl)-piperidine

(665) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(4-methoxy-3,5-dimethylphenyl)methyl]-1,4-dioxobutyl]-4-(4-methyl-1-piperazinyl)-piperidine

(666) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(4-methoxy-3,5-dimethylphenyl)methyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine

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(667) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(1-naphthyl)methyl]-1,4-dioxobutyl]-4-(4-methyl-1-piperazinyl)-piperidine

(668) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(1-naphthyl)methyl]-1,4-dioxobutyl]-4-(1-methylsulphonyl-4-piperidinyl)-piperidine

(669) (R,S)-1-[2-[3,5-Dibromo-4-methylphenyl)methyl]-4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-[4-[4-(dimethylamino)butyl]phenyl]-piperazine

(670) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[[4-(1,1-dimethylethyl)phenyl]methyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine

(671) (R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[[4-(1,1-dimethylethyl)phenyl]methyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine

(672) (R,S)-1-[2-[(3,4-Dichlorophenyl)methyl]-4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-[4-(dimethylaminomethyl)phenyl]-piperidine

and the salts thereof.

The compounds of general formula I are prepared by methods which are known in principle, particularly using processes derived from peptide chemistry (cf. for example Houben-Weyl, Methoden der Organischen Chemie, Vol. 15/2). The amino protecting groups used may be those described in Houben-Weyl, Methoden der Organischen Chemie, Vol. 15/1, of which urethane protecting groups such as the fluorenyl-methoxycarbonyl, phenylmethoxycarbonyl or tert.-

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butyloxycarbonyl group are preferred. Any functional groups present in the groups R^2 and/or A of the compounds of general formula I or in the precursors thereof are additionally protected by suitable protecting groups in order to prevent side reactions (cf. for example: G.B. Fields et al., Int. J. Peptide Protein Res. 35, 161 (1990); T.W. Greene, Protective Groups in Organic Synthesis). Examples of side-chain-protected amino acids of this kind include, in particular, Arg(NO_2), Arg(Mtr), Arg(di-Z), Arg(Pmc), Lys(Boc), Lys(Z), Orn(Boc), Orn(Z), Lys(Cl-Z) which are commercially obtainable, possibly in the form of derivatives. Particular care should be taken to ensure that so-called orthogonal combinations of protecting groups are used to protect the α-amino and the side chain amino group, e.g.:

Protection of the N (side chain)	N^{α}-protection
p-Toluenesulphonyl	Phenylmethoxycarbonyl tert.Butyloxycarbonyl
Phenylmethoxycarbonyl	(4-Methoxyphenyl)methoxycarbonyl tert. Butoxycarbonyl Adamantyloxycarbonyl Biphenylylisopropyloxycarbonyl Isonicotinoyloxycarbonyl o-Nitrophenylsulphenyl Formyl
tert. Butoxycarbonyl	Phenylmethoxycarbonyl p-Toluenesulphonyl o-Nitrophenylsulphenyl Biphenylylisopropyloxycarbonyl 9-Fluorenylmethoxycarbonyl
Acetyl, Trifluoroacetyl, Formyl, (2-Chlorophenyl)-methoxycarbonyl, (4-Chlorophenyl)methoxycarbonyl, 4-(Nitrophenyl)methoxycarbonyl, Phthaloyl	tert.Butyloxycarbonyl

Instead of protecting amino groups in the side chain, amino acids or derivatives thereof which carry precursor functions and in particular are substituted by nitro or cyano in the side chain, such as 5- cyanonorvalin may also be used.

The basic functions in the side chains of α-amino acids which are not commercially obtainable and which are characterised, for example, by (aminoiminomethyl) groups,

may be protected in the same way as is used for protecting the side chains of arginine and its derivatives (cf. also M. Bodanszky, "Peptide Chemistry", Springer-Verlag, 1988, p. 94-97); protecting groups which are particularly suitable for the (aminoiminomethyl)- group are the p-toluenesulphonyl, mesitylene sulphonyl- (Mts), methoxy-trimethylphenylsulphonyl- (Mtr), 2,2,5,7,8-pentamethyl-chroman-6-sulphonyl- (Pmc), pentachlorophenoxycarbonyl- and nitro-protecting groups.

For the actual coupling, the methods known from peptide chemistry are used (see Houben-Weyl, for example, Methoden der Organischen Chemie, Vol. 15/2). It is preferable to use carbodiimides such as dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC) or ethyl-(3-dimethyl-aminopropyl)-carbodiimide, O-(1H-benzotriazol-1-yl)-N,N-N',N'-tetramethyluronium hexafluorophosphate (HBTU) or tetrafluoroborate (TBTU) or 1H-benzotriazol-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP). By the addition of 1-hydroxybenzotriazole (HOBt) or 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine (HOObt) racemisation may additionally be suppressed, if desired, or the reaction rate may be increased. The couplings are normally carried out with equimolar amounts of the coupling components and the coupling reagent in solvents such as dichloromethane, tetrahydrofuran, acetonitrile, dimethylformamide (DMF), dimethylacetamide (DMA), N-methylpyrrolidone (NMP) or mixtures thereof and at temperatures between -30 and +30°C, preferably between -20 and +20°C. If necessary, N-ethyl-diisopropylamine (DIEA) is preferred as an additional auxiliary base (Hünig base).

The so-called "anhydride method" (cf. also M. Bodanszky, "Peptide Chemistry", Springer-Verlag 1988, p. 58-59; M. Bodanszky, "Principles of Peptide Synthesis", Springer-Verlag 1984, p. 21-27) was used as another coupling method for the synthesis of compounds of general

formula I. The "mixed anhydride method" is preferred, in the variant according to Vaughan (J.R. Vaughan Jr., J. Amer. Chem.Soc. 73, 3547 (1951)), in which the mixed anhydride is obtained from the optionally N^2-protected α-amino acid which is to be coupled, and the mono-isobutylcarbonate, using isobutylchlorocarbonate in the presence of base such as 4-methylmorpholine or 4-ethylmorpholine. The preparation of this mixed anhydride and the coupling with amines are carried out in a one-pot process using the above-mentioned solvents at temperatures between -20 and +20°C, preferably between 0 and +20°C.

Any protecting groups present in the side chains of α-amino acid partial structures are finally cleaved, after the formation of the N- and C-terminally substituted amino acid derivative, with suitable reagents which are also known from the literature in principle, specifically arylsulphonyl and hetarylsulphonyl protecting groups, preferably by acidolysis, i.e. by the action of strong acids, preferably trifluoroacetic acid, nitro- and arylmethoxycarbonyl protecting groups are preferably cleaved by hydrogenolysis, e.g. using hydrogen in the presence of palladium black and with glacial acetic acid as solvent. If the substrate contains functions which are sensitive to hydrogenolysis, e.g. halogen atoms such as chlorine, bromine or iodine, a phenylmethanol or hetarylmethanol function or some other benzyl heteroatom bond, particularly a benzyl-oxygen bond, the nitro group may also be cleaved non-hydrogenolytically, e.g. with zinc/2N trifluoroacetic acid (cf. also A. Turan, A. Patthy and S. Bajusz, Acta Chim. Acad. Sci. Hung, Tom. 85 (3), 327-332 [1975]; C.A. 83, 206526y [1975]), with tin(II)-chloride in 60% aqueous formic acid (see also: SUNSTAR KK, JA-A-3271-299), with zinc in the presence of acetic acid (cf. also: A. Malabarba, P. Ferrari, G. Cietto, R. Pallanza and M. Berti, J. Antibiot. 42 (12),

1800-1816 (1989)) or excess aqueous 20% titanium(III)-chloride in aqueous methanol and in the presence of aqueous ammonium acetate buffer at 24°C (see also: R.M. Freidinger, R. Hirschmann and D.F. Veber, J. Org. Chem. 43 (25), 4800-4803 [1978]).

Any precursor functions which may be present in the side chain of the α-amino acid may also subsequently be converted by hydrogenolysis into the desired amino functions; nitroalkyl groups yield aminoalkyl groups under conditions which will be familiar to the chemist, whilst the cyano group is converted into the aminomethyl group.

Alternatively, nitrile functions may also be reduced with complex hydrides which are selective in relation to other critical functions contained in the molecule, particularly amide groups (cf. also: J. Seyden-Penne, "Reductions by the Alumino- and Borohydrides in Organic Synthesis", VCH Publishers Inc., 1991, p. 132ff.), e.g. with sodium borohydride in methanol and in the presence of cobalt(II)-chloride, with sodium borohydride in tetrahydrofuran in the presence of trifluoroacetic acid or with tetrakis-(n-butyl)-ammonium borohydride in dichloromethane; the reduction of aliphatic nitro function to the primary amino function is also possible with sodium borohydride in the presence of tin(II)-chloride or copper(II)-acetylacetonate, without affecting the carboxamide groups present in type I compounds (see also: J. Seyden-Penne, ibid. p. 137ff.).

The following methods are particularly suitable for preparing the compounds of general Formula I according to the invention:

a) In order to prepare compounds of general formula I, wherein

R denotes an unbranched C_{1-7}-alkyl group which may be substituted in the ω-position

by a C_{4-10}-cycloalkyl group,

by one or two phenyl groups, by a 1-naphthyl, 2-naphthyl or biphenylyl group,

by a 1,3-dihydro-2H-2-oxobenzimidazol-1-yl, 2,4(1H,3H)-dioxoquinazolin-1-yl, 2,4(1H,3H)-dioxoquinazolin-3-yl, 2,4(1H,3H)-dioxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-3-yl, 2(1H)-oxoquinolin-3-yl, 2(1H)-oxoquinoxalin-3-yl, 1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl, 1,3-dihydro-2H-2-oxoimidazopyridinyl, 1,3-dihydro-2(2H)-oxoimidazo[4,5-c]quinolin-3-yl, 1,3-dihydro-2H-2-oxoimidazol-1-yl or 3,4-dihydro-2(1H)-oxopyrimidin-3-yl group, wherein the latter two groups may each be mono- or disubstituted in the 4- and/or 5-position or in the 5- and/or 6-position by lower straight chained or branched alkyl groups, by phenyl, biphenylyl, pyridinyl, diazinyl, furyl, thienyl, pyrrolyl, 1,3-oxazolyl, 1,3-thiazolyl, isoxazolyl, pyrazolyl-1-methylpyrazolyl, imidazolyl- or 1-methylimidazolyl-groups and the substituents may be identical or different,

by a 5-membered heteroaromatic ring linked via a carbon atom, which contains a nitrogen, oxygen or sulphur atom or, in addition to a nitrogen atom, contains an oxygen, sulphur or additional nitrogen

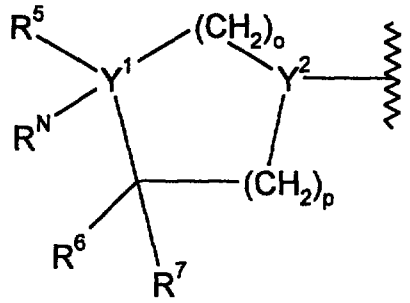
atom, whilst a nitrogen atom of an imino group may be substituted by an alkyl group,

or by a 6-membered heteroaromatic ring linked via a carbon atom, which contains one, two or three nitrogen atoms,

whilst a 1,4-butadienylene group may be attached both to the above-mentioned 5-membered heteroaromatic monocyclic rings and to the 6-membered heteroaromatic monocyclic rings, in each case via two adjacent carbon atoms, and the bicyclic heteroaromatic rings thus formed may also be bound via a carbon atom of the 1,4-butadienylene group, and

whilst the phenyl, naphthyl and biphenylyl groups mentioned above for the substitution of the alkyl groups in the ω-position and optionally also partially hydrogenated mono- and bicyclic heteroaromatic rings in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms or by alkyl groups, C_{3-8}-cycloalkyl groups, nitro, alkoxy, phenyl, phenylalkoxy, trifluoromethyl, alkoxycarbonyl, alkoxycarbonylalkyl, carboxy, carboxyalkyl, dialkylaminoalkyl, hydroxy, amino, acetylamino, propionylamino, benzoyl, benzoylamino, benzoylmethylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, (1-pyrrolidinyl)carbonyl, (1-piperidinyl)carbonyl, (hexahydro-1H-azepin-1-yl)carbonyl, (4-methyl-1-piperazinyl)carbonyl, (4-morpholinyl)carbonyl, alkanoyl, cyano, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl- or trifluoromethylsulphonyl groups, wherein the substituents may be identical or different and the above-mentioned benzoyl, benzoylamino and benzoylmethylamino groups may in turn additionally be substituted in the phenyl moiety by a fluorine, chlorine

or bromine atom or by an alkyl, trifluoromethyl, amino or acetylamino group,
or the group of formula



(II),

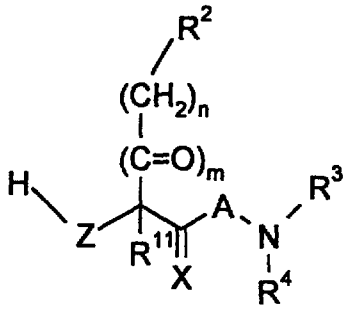
wherein
R^5, R^6, R^7, R^N, Y^1, o and p are as hereinbefore defined,
Y^2 denotes a CH- group and
Z denotes an NR^1- group, wherein R^1 is as hereinbefore defined:

coupling carboxylic acids of general formula VII,

$$RCO_2H \qquad \text{(VII)}$$

wherein
R is as hereinbefore defined,

with compounds of general formula VIII,



(VIII)

wherein

R^2, R^3, R^4, R^{11}, A, X, m and n are as hereinbefore defined, and

Z denotes an NR^1- group, wherein R^1 is as hereinbefore defined,

and, if necessary, subsequently cleaving any protecting groups or modifying precursor functions in accordance with the methods described hereinbefore.

The coupling is carried out using the methods known from peptide chemistry described above, particularly using DCC, DIC, HBTU, TBTU or BOP as reagents or using the mixed anhydride method.

b) In order to prepare compounds of general formula I wherein R is defined as in a), Z denotes the NR^1- group and R^1, R^2, R^3, R^4, R^{11}, A, X, m and n are as hereinbefore defined:

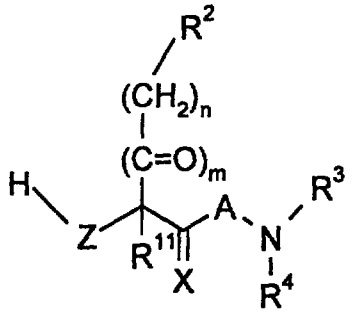
coupling compounds of general formula IX,

$$R - CO - Nu \qquad (IX)$$

wherein
R is defined as in a) and
Nu denotes a leaving group, for example a halogen atom such as the chlorine, bromine- or iodine atom, an alkylsulphonyloxy group having 1 to 10 carbon atoms in the alkyl moiety, a phenylsulphonyloxy or naphthylsulphonyloxy group optionally mono-, di- or trisubstituted by chlorine or bromine atoms or by methyl- or nitro groups, wherein the substituents may be identical or different, a 1H-imidazol-1-yl, a 1H-pyrazol-1-yl- optionally substituted by 1 or 2 methyl groups in the carbon skeleton, a 1H-1,2,4-triazol-1-yl, 1H-1,2,3-triazol-1-yl, 1H-1,2,3,4-tetrazol-1-yl, a vinyl, propargyl, p-nitrophenyl, 2,4-dinitrophenyl,

trichlorophenyl, pentachlorophenyl, pentafluorophenyl, pyranyl or pyridinyl, a dimethylaminyloxy, 2(1H)-oxopyridin-1-yloxy, 2,5-dioxopyrrolidin-1-yloxy, phthalimidyloxy, 1H-benzotriazol-1-yloxy or azide group,

with compounds of general formula VIII,



(VIII)

wherein

R^2, R^3, R^4, R^{11}, A, X, m and n are as hereinbefore defined and

Z denotes an NR^1- group, whilst R^1 is as hereinbefore defined,

and, if necessary, subsequently cleaving protecting groups or modifying precursor functions using the methods described above.

The reaction is carried out under Schotten-Baumann- or Einhorn- conditions, i.e. the components are reacted in the presence of at least one equivalent of an auxiliary base at temperatures between -50°C and +120°C, preferably between -10°C and +30°C, optionally in the presence of solvents. Auxiliary bases which may be used are preferably alkali-metal and alkaline earth metal hydroxides, e.g. sodium hydroxide, potassium hydroxide or barium hydroxide, alkali metal carbonates, e.g. sodium carbonate, potassium carbonate or cesium carbonate, alkali metal acetate, e.g. sodium- or potassium acetate, as well as tertiary amines, e.g. pyridine, 2,4,6-trimethylpyridine, quinoline, triethylamine, N-ethyl-diisopropylamine,

N-ethyl-dicyclohexylamine, 1,4-Diazabicyclo[2,2,2]octane or 1,8-diazabicyclo[5,4,0]undec-7-ene, whilst the solvents which may be used include, for example, dichloromethane, tetrahydrofuran, 1,4-dioxane, acetonitrile, dimethylformamide, dimethylacetamide, N-methyl-pyrrolidone or mixtures thereof; if alkali metal or alkaline earth metal hydroxides, alkali metal carbonates or -acetates are used as auxiliary bases, water may also be added to the reaction mixture as a cosolvent.

c) In order to prepare compounds of general formula I wherein

R denotes an unbranched C_{1-6}-alkylamino group optionally substituted at the nitrogen atom by a C_{1-6}-alkyl group or by a phenylmethyl group, which may be substituted in the ω-position

by a C_{4-10}-cycloalkyl group,

by one or two phenyl groups, by a 1-naphthyl, 2-naphthyl- or biphenylyl group,

by a 1H-indol-3-yl, 1,3-dihydro-2H-2-oxobenzimidazol-1-yl, 2,4(1H,3H)-dioxoquinazolin-1-yl, 2,4(1H,3H)-dioxoquinazolin-3-yl, 2,4(1H,3H)-dioxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-3-yl, 2(1H)-oxoquinolin-3-yl, 2(1H)-oxoquinoxalin-3-yl, 1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl, 1,3-dihydro-4-(3-thienyl)-2H-2-oxoimidazol-1-yl, 1,3-dihydro-4-phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-5-phenyl-

2H-2-oxoimidazol-1-yl, 1,3-dihydro-2(2H)-oxoimidazo[4,5-c]quinolin-3-yl, 3,4-dihydro-5-phenyl-2(1H)-oxopyrimidin-3-yl, 3,4-dihydro-6-phenyl-2(1H)-oxopyrimidin-3-yl- or 1,3-dihydro-2H-2-oxoimidazo-[4,5-b]pyridin-3-yl- group,

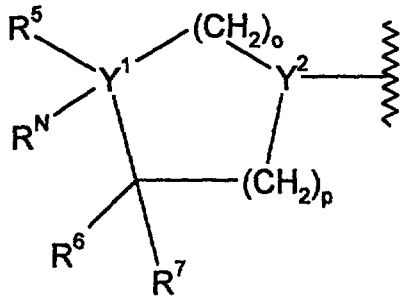
by a 5-membered heteroaromatic ring linked via a carbon atom, which contains a nitrogen, oxygen or sulphur atom or, in addition to a nitrogen atom, contains an oxygen, sulphur or an additional nitrogen atom, whilst a nitrogen atom of an imino group may be substituted by an alkyl group, or

by a 6-membered heteroaromatic ring linked via a carbon atom and containing 1, 2 or 3 nitrogen atoms, whilst a 1,4-butadienylene group may be attached both to the 5-membered and to the 6-membered heteroaromatic monocyclic rings via two adjacent carbon atoms in each case and the bicyclic heteroaromatic rings thus formed may also be bound via a carbon atom of the 1,4-butadienylene group,

whilst the phenyl, naphthyl and biphenylyl groups mentioned above for the substitution of the alkyl moiety of the alkylamino groups in the ω-position and optionally partially hydrogenated mono- and bicyclic heteroaromatic rings in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms, by alkyl groups, C_{3-8}-cycloalkyl groups, nitro, alkoxy, phenyl, phenylalkoxy, trifluoromethyl, alkoxycarbonyl, alkoxycarbonylalkyl, carboxy, carboxyalkyl, dialkylaminoalkyl, hydroxy, amino, acetylamino, propionylamino, benzoyl, benzoylamino, benzoylmethylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, (1-pyrrolidinyl)carbonyl, (1-piperidinyl)carbonyl, (hexahydro-1H-azepin-1-yl)carbonyl, (4-methyl-1-piperazinyl)carbonyl,

(4-morpholinyl)carbonyl, alkanoyl, cyano, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl- or trifluoromethylsulphonyl groups, whilst the substituents may be identical or different and the above-mentioned benzoyl, benzoylamino- and benzoylmethylamino groups in turn may additionally be substituted in the phenyl moiety by a fluorine, chlorine or bromine atom or by an alkyl, trifluoromethyl, amino- or acetylamino group,

or the group of formula



(II),

wherein

R^5, R^6, R^7, R^N, Y^1, o and p are as hereinbefore defined,

Y^2 denotes the N-atom and

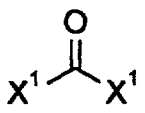
Z denotes the NR^1- group, wherein R^1 is as hereinbefore defined:

reacting amines of general formula X

$$R - H \qquad (X)$$

wherein

R is as hereinbefore defined, with carbonic acid derivatives of general XI

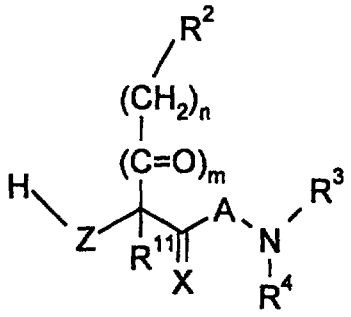


(XI)

wherein

X^1 is a nucleofugic group, preferably the 1H-imidazol-1-yl, 1H-1,2,4-triazol-1-yl, trichloromethoxy- or 2,5-dioxo-pyrrolidin-1-yloxy group,

and with compounds of general formula VIII,



(VIII)

wherein
R^2, R^3, R^4, R^{11}, A, X, m and n are as hereinbefore defined and
Z denotes an NR^1- group, wherein R^1 is as hereinbefore defined,

and, if necessary, subsequently cleaving any protecting groups or modifying any precursor functions using the method described hereinbefore.

The theoretically two-step reactions are generally carried out as one-pot processes, preferably by reacting one of the two components X or VIII with equimolar amounts of the carbonic acid derivative of general formula XI in a suitable solvent at fairly low temperature, in the first step, and then adding at least equimolar amounts of the other component VIII or X and finishing the reaction at elevated temperature. The reactions with bis-(trichloromethyl)-carbonate are preferably carried out in the presence of at least 2 equivalents (based on bis-(trichloromethyl)-carbonat) of a tertiary base, e.g. triethylamine, N-ethyl-diisopropylamine, pyridine, 1,5-diazabicyclo[4,3,0]non-5-ene, 1,4-diazabicyclo[2,2,2]octane or 1,8-diazabicyclo[5,4,0]undec-7-ene. Examples of solvent, which should be anhydrous, include

tetrahydrofuran, dioxane, dimethylformamide, dimethylacetamide, N-methyl-2-pyrrolidone, 1,3-dimethyl-2-imidazolidinone or acetonitrile, if bis-(trichloromethyl)-carbonate is used as the carbonyl component, anhydrous chlorohydrocarbons such as dichloromethane, 1,2-dichloroethane or trichloroethylene are preferred. The reaction temperatures are between -30 and +25°C for the first step of the reaction, preferably between -5 and +10°C, and between +15°C and the boiling temperature of the solvent used, preferably between +20°C and +70°C for the second step of the reaction (cf. also: H. A. Staab and W. Rohr, "Synthesen mit heterocyclischen Amiden (Azoliden)", Neuere Methoden der Präparativen Organischen Chemie, Band V, p. 53 - 93, Verlag Chemie, Weinheim/Bergstr., 1967; P. Majer and R.S. Randad, J. Org. Chem. 59, 1937 - 1938 (1994); K. Takeda, Y. Akagi, A. Saiki, T. Sukahara und H. Ogura, Tetrahedron Letters 24 (42), 4569 - 4572 (1983)).

d) In order to prepare compounds of general formula I wherein the carbonyl group linked to the groups R and Z denotes a urea carbonyl group, in which the urea carbonyl is flanked by at least one NH- group, and wherein

R denotes an unbranched C_{1-6}-alkylamino group optionally additionally substituted at the nitrogen atom by a C_{1-6}-alkyl group or by a phenylmethyl group, which may be substituted in the ω-position

by a C_{4-10}-cycloalkyl group,

by one or two phenyl groups, by a 1-naphthyl, 2-naphthyl- or biphenylyl group,

by a 1H-indol-3-yl, 1,3-dihydro-2H-2-oxobenzimidazol-1-yl, 2,4(1H,3H)-dioxoquinazolin-1-yl, 2,4(1H,3H)-dioxoquinazolin-3-yl, 2,4(1H,3H)-dioxothieno[3,4-d]pyrimidin-3-yl,

3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-3-yl, 2(1H)-oxoquinolin-3-yl, 2(1H)-oxoquinoxalin-3-yl, 1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl, 1,3-dihydro-4-(3-thienyl)-2H-2-oxoimidazol-1-yl, 1,3-dihydro-4-phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-5-phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-2(2H)-oxoimidazo[4,5-c]quinolin-3-yl, 3,4-dihydro-5-phenyl-2(1H)-oxopyrimidin-3-yl, 3,4-dihydro-6-phenyl-2(1H)-oxopyrimidin-3-yl- or 1,3-dihydro-2H-2-oxoimidazo-[4,5-b]pyridin-3-yl- group,

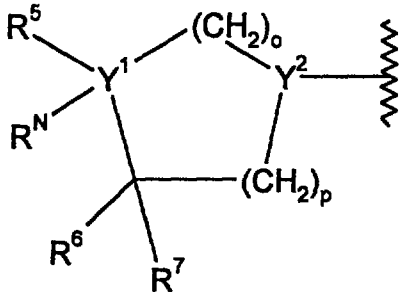
by a 5-membered heteroaromatic ring linked via a carbon atom, which contains a nitrogen, oxygen or sulphur atom or, in addition to a nitrogen atom, contains an oxygen, sulphur or an additional nitrogen atom, whilst a nitrogen atom of an imino group may be substituted by an alkyl group, or

by a 6-membered heteroaromatic ring linked via a carbon atom and containing 1, 2 or 3 nitrogen atoms, whilst a 1,4-butadienylene group may be attached both to the 5-membered and to the 6-membered heteroaromatic monocyclic rings via two adjacent carbon atoms in each case and the bicyclic heteroaromatic rings thus formed may also be bound via a carbon atom of the 1,4-butadienylene group,

whilst the phenyl, naphthyl and biphenylyl groups mentioned above for the substitution of the alkyl moiety of the alkylamino groups in the ω-position and optionally partially hydrogenated mono- and bicyclic heteroaromatic rings in the carbon skeleton may additionally be mono-,

di- or trisubstituted by fluorine, chlorine or bromine atoms, by alkyl groups, C_{3-8}-cycloalkyl groups, nitro, alkoxy, phenyl, phenylalkoxy, trifluoromethyl, alkoxycarbonyl, alkoxycarbonylalkyl, carboxy, carboxyalkyl, dialkylaminoalkyl, hydroxy, amino, acetylamino, propionylamino, benzoyl, benzoylamino, benzoylmethylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, (1-pyrrolidinyl)carbonyl, (1-piperidinyl)carbonyl, (hexahydro-1H-azepin-1-yl)carbonyl, (4-methyl-1-piperazinyl)carbonyl, (4-morpholinyl)carbonyl, alkanoyl, cyano, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl- or trifluoromethylsulphonyl groups, whilst the substituents may be identical or different and the above-mentioned benzoyl, benzoylamino- and benzoylmethylamino groups in turn may additionally be substituted in the phenyl moiety by a fluorine, chlorine or bromine atom or by an alkyl, trifluoromethyl, amino or acetylamino group,

or the group of formula



(II),

wherein

R^5, R^6, R^7, R^N, Y^1, o and p are as hereinbefore defined and Y^2 denotes the N-atom,

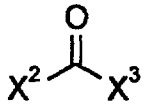
Z denotes the group NR^1 and

R^1 denotes a hydrogen atom or, provided that, R denotes an unbranched alkylamino group unsubstituted at the nitrogen atom and optionally substituted in the ω-position, R^1 may also denote an alkyl or phenylalkyl group:

Reacting amines of general formula X',

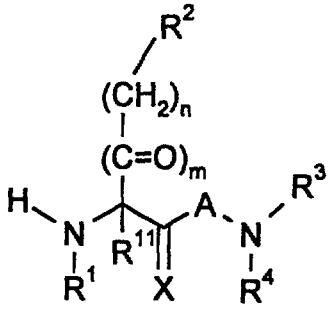
(X')

wherein R is as hereinbefore defined,
with carbonic acid derivatives of general formula XI',



(XI')

wherein
X^2 denotes a phenoxy group, if X^3 is the (1H)-1,2,3,4-tetrazol-1-yl group, the 4-nitrophenoxy group, if X^3 is the 4-nitrophenoxy group, and the chlorine atom if X^3 is the 2,4,5-trichlorophenoxy group, and with compounds of general formula VIII',



(VIII')

wherein
R^2, R^3, R^4, R^{11}, X, A, m and n are as hereinbefore defined and

R^1 denotes a hydrogen atom or, provided that R is an unbranched alkylamino group unsubstituted at the nitrogen

and optionally substituted in the ω-position, R^1 may also denote an alkyl or phenylalkyl group, and

if necessary, subsequently cleaving protecting groups or modifying precursor functions using the methods described hereinbefore.

The reactions are in two steps, in principle, with intermediate formation of urethanes, which can be isolated. However, the reactions may also be carried out as one-pot reactions. Preferably, in the first step, one of the two components X' or VIII' is reacted with equimolar amounts of the carbonic acid derivative of general formula XI' in a suitable solvent at low temperature, then at least equimolar amounts of the other component VIII' or X' are added and the reaction is completed at elevated temperature. The reactions are preferably carried out in anhydrous solvents, e.g. in tetrahydrofuran, dioxane, dimethylformamide, dimethylacetamide, N-methyl-2-pyrrolidone, 1,3-dimethyl-2-imidazolidinone, acetonitrile or anhydrous chlorohydrocarbons e.g. dichloromethane, 1,2-dichloroethane or trichloroethylene. The reaction temperatures are between -15 and +40°C, preferably between -10 and +25°C for the first step, between +20°C and the boiling temperature of the solvent used, preferably between +20°C and 100°C for the second reaction step (cf. also: R. W. Adamiak and J. Stawinski, Tetrahedron Letters 1977, 22, 1935 - 1936; A. W. Lipkowski, S. W. Tam and P. S. Portoghese, J. Med. Chem. 29, 1222 - 1225 (1986); J. Izdebski and D. Pawlak, Synthesis 1989, 423 - 425).

e) In order to prepare compounds of general formula I wherein Z denotes the group NH and

R denotes an unbranched C_{1-6}-alkylamino group optionally substituted at the nitrogen atom by a C_{1-6}-alkyl group or

by a phenylmethyl group, which may be substituted in the ω-position

by a C_{4-10}-cycloalkyl group,

by one or two phenyl groups, by a 1-naphthyl, 2-naphthyl or biphenylyl group,

by a 1H-indol-3-yl, 1,3-dihydro-2H-2-oxobenzimidazol-1-yl, 2,4(1H,3H)-dioxoquinazolin-1-yl, 2,4(1H,3H)-dioxoquinazolin-3-yl, 2,4(1H,3H)-dioxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-3-yl, 2(1H)-oxoquinolin-3-yl, 2(1H)-oxoquinoxalin-3-yl, 1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl, 1,3-dihydro-4-(3-thienyl)-2H-2-oxoimidazol-1-yl, 1,3-dihydro-4-phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-5-phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-2(2H)-oxoimidazo[4,5-c]quinolin-3-yl, 3,4-dihydro-5-phenyl-2(1H)-oxopyrimidin-3-yl, 3,4-dihydro-6-phenyl-2(1H)-oxopyrimidin-3-yl or 1,3-dihydro-2H-2-oxoimidazo-[4,5-b]pyridin-3-yl group,

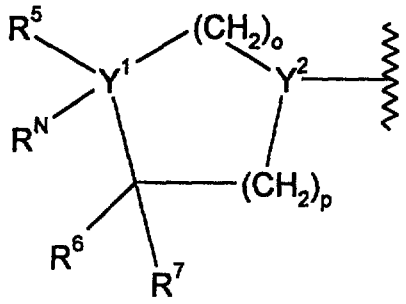
by a 5-membered heteroaromatic ring linked via a carbon atom, which contains a nitrogen, oxygen or sulphur atom or, in addition to a nitrogen atom, contains an oxygen, sulphur or an additional nitrogen atom, whilst a nitrogen atom of an imino group may be substituted by an alkyl group, or

by a 6-membered heteroaromatic ring linked via a carbon atom and containing 1, 2 or 3 nitrogen atoms,

whilst a 1,4-butadienylene group may be attached both to the 5-membered and to the 6-membered heteroaromatic monocyclic rings via two adjacent carbon atoms in each case and the bicyclic heteroaromatic rings thus formed may also be bound via a carbon atom of the 1,4-butadienylene group,

whilst the phenyl, naphthyl and biphenylyl groups mentioned above for the substitution of the alkyl groups in the ω-position and optionally partially hydrogenated mono- and bicyclic heteroaromatic rings in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms, by alkyl groups, C_{3-8}-cycloalkyl groups, nitro, alkoxy, phenyl, phenylalkoxy, trifluoromethyl, alkoxycarbonyl, alkoxycarbonylalkyl, carboxy, carboxyalkyl, dialkylaminoalkyl, hydroxy, amino, acetylamino, propionylamino, benzoyl, benzoylamino, benzoylmethylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, (1-pyrrolidinyl)carbonyl, (1-piperidinyl)carbonyl, (hexahydro-1H-azepin-1-yl)carbonyl, (4-methyl-1-piperazinyl)carbonyl, (4-morpholinyl)carbonyl, alkanoyl, cyano, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl groups, whilst the substituents may be identical or different and the above-mentioned benzoyl, benzoylamino- and benzoylmethylamino groups in turn may additionally be substituted in the phenyl moiety by a fluorine, chlorine or bromine atom or by an alkyl, trifluoromethyl, amino or acetylamino group,

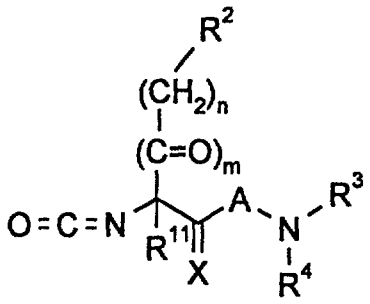
or the group of formula



(II),

wherein
R^5, R^6, R^7, R^N, Y^1, o and p are as hereinbefore defined and Y^2 denotes an N-atom:

Reacting isocyanates of general formula XII,



(XII)

wherein
R^2, R^3, R^4, R^{11}, A, X, m and n are as hereinbefore defined,

with amines of general formula X,

R - H (X)

wherein
R is as hereinbefore defined and, if necessary, subsequently cleaving protecting groups or modifying precursor functions using the processes described above.

The reaction is carried out at temperatures between 0°C and 150°C, preferably between 20°C and 100°C, optionally in the presence of anhydrous solvents, e.g. tetrahydrofuran, 1,4-dioxane, dimethylformamide,

dimethylacetamide, N-methyl-2-pyrrolidone or 1,3-dimethyl-2-imidazolidinone or mixtures thereof.

f) In order to prepare compounds of general formula I wherein

R denotes an unbranched C_{1-6}-alkylamino group unsubstituted at the nitrogen atom, which may be substituted in the ω-position

by a C_{4-10}-cycloalkyl group,

by one or two phenyl groups, by a 1-naphthyl, 2-naphthyl- or biphenylyl group,

by a 1H-indol-3-yl, 1,3-dihydro-2H-2-oxobenzimidazol-1-yl, 2,4(1H,3H)-dioxoquinazolin-1-yl, 2,4(1H,3H)-dioxoquinazolin-3-yl, 2,4(1H,3H)-dioxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-3-yl, 2(1H)-oxoquinolin-3-yl, 2(1H)-oxoquinoxalin-3-yl, 1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl, 1,3-dihydro-4-(3-thienyl)-2H-2-oxoimidazol-1-yl, 1,3-dihydro-4-phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-5-phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-2(2H)-oxoimidazo[4,5-c]quinolin-3-yl, 3,4-dihydro-5-phenyl-2(1H)-oxopyrimidin-3-yl, 3,4-dihydro-6-phenyl-2(1H)-oxopyrimidin-3-yl- or 1,3-dihydro-2H-2-oxoimidazo-[4,5-b]pyridin-3-yl- group,

by a 5-membered heteroaromatic ring linked via a carbon atom, which contains a nitrogen, oxygen or

sulphur atom or, in addition to a nitrogen atom, contains an oxygen, sulphur or an additional nitrogen atom, whilst a nitrogen atom of an imino group may be substituted by an alkyl group, or

by a 6-membered heteroaromatic ring linked via a carbon atom and containing 1, 2 or 3 nitrogen atoms, whilst a 1,4-butadienylene group may be attached both to the 5-membered and to the 6-membered heteroaromatic monocyclic rings via two adjacent carbon atoms in each case and the bicyclic heteroaromatic rings thus formed may also be bound via a carbon atom of the 1,4-butadienylene group,

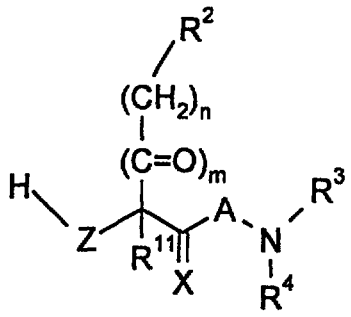
whilst the phenyl, naphthyl and biphenylyl groups mentioned above for the substitution of the alkylamino groups in the ω-position and optionally partially hydrogenated mono- and bicyclic heteroaromatic rings in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms, by alkyl groups, C_{3-8}-cycloalkyl groups, nitro, alkoxy, phenyl, phenylalkoxy, trifluoromethyl, alkoxycarbonyl, alkoxycarbonylalkyl, carboxy, carboxyalkyl, dialkylaminoalkyl, hydroxy, amino, acetylamino, propionylamino, benzoyl, benzoylamino, benzoylmethylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, (1-pyrrolidinyl)carbonyl, (1-piperidinyl)carbonyl, (hexahydro-1H-azepin-1-yl)carbonyl, (4-methyl-1-piperazinyl)carbonyl, (4-morpholinyl)carbonyl, alkanoyl, cyano, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl- or trifluoromethylsulphonyl groups, whilst the substituents may be identical or different and the above-mentioned benzoyl, benzoylamino- and benzoylmethylamino groups in turn may additionally be substituted in the phenyl moiety by a fluorine, chlorine or bromine atom or by an alkyl, trifluoromethyl, amino- or acetylamino group, and

Z denotes the NR^1- group wherein R^1 is as hereinbefore defined:

Reacting isocyanates of general formula XIII,

$$R{=}C{=}O \qquad (XIII)$$

wherein R is as hereinbefore defined, with compounds of general formula VIII,



(VIII)

wherein R^2, R^3, R^4, R^{11}, A, X, m and n are as hereinbefore defined and

Z denotes an NR^1- group, wherein R^1 is as hereinbefore defined,

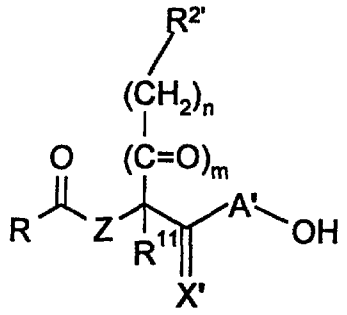
and, if necessary, subsequently cleaving any protecting groups or modifying the precursor functions using the methods described hereinbefore.

The reaction is carried out at temperatures between 0 and 150°C, preferably at temperatures between 20 and 100°C, and optionally in the presence of anhydrous solvents, e.g. tetrahydrofuran, 1,4-dioxane, dimethylformamide, dimethylacetamide, N-methyl-2-pyrrolidone or 1,3-dimethyl-2-imidazolidinone.

g) In order to prepare compounds of general formula I wherein R, Z, R^2, R^3, R^4, R^{11}, A, m and n have the meanings

given hereinbefore and X is as hereinbefore defined, provided that A does not denote a bond or X denotes an oxygen atom, if A denotes a single bond:

Coupling carboxylic acids of general formula XIV,



(XIV)

wherein
R, Z, R^{11}, m and n are as hereinbefore defined,
$R^{2'}$ has the meanings given for R^2 hereinbefore or denotes a group R^2 substituted by the above-mentioned protecting groups,
A' has the meanings given for A hereinbefore or, if A denotes the divalent group of an amino acid, it optionally bears in the side chain a precursor group for the group R^9, e.g. a cyanopropyl group,

to compounds of general formula XV,

$$H - NR^3R^4 \qquad (XV)$$

wherein
R^3 and R^4 are as hereinbefore defined,

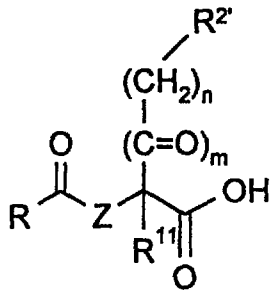
and if necessary subsequent cleaving of protective groups or modification of precursor functions using the methods described above.

The coupling is carried out using the methods known from peptide chemistry and described hereinbefore, particularly using DCC, DIC, HBTU, TBTU or BOP as reagents or using the mixed anhydride method.

If the starting compound XIV used is enantiomerically pure, partial racemisation of the C-terminal amino acid must be expected during the coupling step and possibly quantitative racemisation must be expected if triethylamine is used as the auxiliary base and dimethylformamide, dimethylacetamide or N-methyl-pyrrolidone is used as solvent.

h) In order to prepare compounds of general formula I wherein X denotes the oxygen atom:

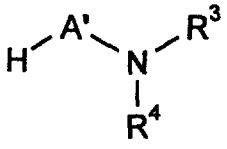
Coupling carboxylic acids of general formula XVI,



(XVI)

wherein
R, Z, R^{11}, m and n are as hereinbefore defined and
$R^{2'}$ has the meanings given for R^2 hereinbefore or denotes a group R^2 substituted by the above-mentioned protecting groups,

to compounds of general formula XVII,



(XVII)

wherein
A' has the meanings given for A hereinbefore or, if A denotes the divalent group of an amino acid, A' optionally

bears in the side chain a precursor group for the group R^9, e.g. a cyanopropyl group, and

R^3 and R^4 are as hereinbefore defined,

and if necessary subsequently cleaving protecting groups or modifying precursor functions using the methods described above.

The coupling is carried out using the methods known from peptide chemistry and described above, particularly using DCC, DIC, HBTU, TBTU or BOP as reagents or using the mixed anhydride method.

If the starting compound XVI used is enantiomerically pure, during the coupling step partial racemisation must be expected or, if triethylamine is used as the auxiliary base and dimethylformamide, dimethylacetamide or N-methylpyrrolidone is used as solvent, quantitative racemisation must be expected based on the chiral centre of XVI.

i) In order to prepare compounds of general formula I wherein

R' denotes an unbranched C_{1-6}-alkylamino group optionally substituted at the nitrogen atom by a C_{1-6}-alkyl group or by a phenylmethyl group, which may be substituted in the ω-position

by a C_{4-10}-cycloalkyl group,

by one or two phenyl groups, by a 1-naphthyl, 2-naphthyl or biphenylyl group,

by a 1H-indol-3-yl, 1,3-dihydro-2H-2-oxobenzimidazol-1-yl, 2,4(1H,3H)-dioxoquinazolin-1-yl, 2,4(1H,3H)-dioxoquinazolin-3-yl,

2,4(1H,3H)-dioxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-3-yl, 2(1H)-oxoquinolin-3-yl, 2(1H)-oxoquinoxalin-3-yl, 1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl, 1,3-dihydro-4-(3-thienyl)-2H-2-oxoimidazol-1-yl, 1,3-dihydro-4-phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-5-phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-2(2H)-oxoimidazo[4,5-c]quinolin-3-yl, 3,4-dihydro-5-phenyl-2(1H)-oxopyrimidin-3-yl, 3,4-dihydro-6-phenyl-2(1H)-oxopyrimidin-3-yl- or 1,3-dihydro-2H-2-oxoimidazo-[4,5-b]pyridin-3-yl- group,

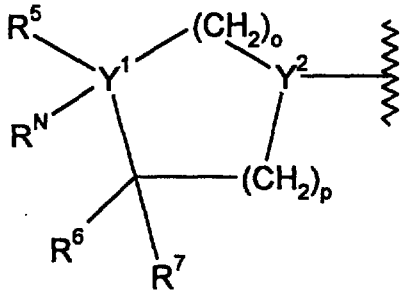
by a 5-membered heteroaromatic ring linked via a carbon atom, which contains a nitrogen, oxygen or sulphur atom or, in addition to a nitrogen atom, contains an oxygen, sulphur or an additional nitrogen atom, whilst a nitrogen atom of an imino group may be substituted by an alkyl group, or

by a 6-membered heteroaromatic ring linked via a carbon atom and containing 1, 2 or 3 nitrogen atoms, whilst a 1,4-butadienylene group may be attached both to the 5-membered and to the 6-membered heteroaromatic monocyclic rings via two adjacent carbon atoms in each case and the bicyclic heteroaromatic rings thus formed may also be bound via a carbon atom of the 1,4-butadienylene group,

whilst the phenyl, naphthyl and biphenylyl groups mentioned above for the substitution of the alkyl moiety of the alkylamino groups in the ω-position and optionally partially hydrogenated mono- and bicyclic heteroaromatic

rings in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms, by alkyl groups, C_{3-8}-cycloalkyl groups, nitro, alkoxy, phenyl, phenylalkoxy, trifluoromethyl, alkoxycarbonyl, alkoxycarbonylalkyl, carboxy, carboxyalkyl, dialkylaminoalkyl, hydroxy, amino, acetylamino, propionylamino, benzoyl, benzoylamino, benzoylmethylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, (1-pyrrolidinyl)carbonyl, (1-piperidinyl)carbonyl, (hexahydro-1H-azepin-1-yl)carbonyl, (4-methyl-1-piperazinyl)carbonyl, (4-morpholinyl)carbonyl, alkanoyl, cyano, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl groups, whilst the substituents may be identical or different and the above-mentioned benzoyl, benzoylamino and benzoylmethylamino groups in turn may additionally be substituted in the phenyl moiety by a fluorine, chlorine or bromine atom or by an alkyl, trifluoromethyl, amino or acetylamino group,

or the group of formula



(II),

wherein

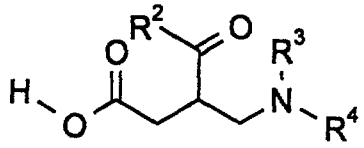
R^5, R^6, R^7, R^N, Y^1, o and p are as hereinbefore defined and Y^2 denotes an N-atom,

Z represents the methylene group,

X denotes two hydrogen atoms,

A denotes a single bond,
m denotes the value 1 and
n denotes the value 0:

Coupling carboxylic acids of general formula XVIII,



(XVIII)

wherein
R^2, R^3 and R^4 are as hereinbefore defined,

with amines of general formula X,

$$R - H \qquad (X)$$

wherein R is as hereinbefore defined.

The coupling is carried out using the methods known from peptide chemistry and described above, particularly using DCC, DIC, HBTU, TBTU or BOP as reagents or using the mixed anhydride method.

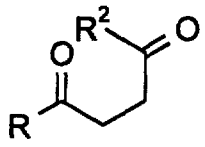
j) In order to prepare compounds of general formula I wherein
R^3 and R^4 have the meanings given hereinbefore with the exception of the hydrogen atoms, Z denotes a methylene group, X denotes two hydrogen atoms, A denotes a single bond, m is the number 1 and n is the number 0:

Reacting secondary amines of general formula XVa,

$$H\text{-}NR^{3'}R^{4'} \qquad (XVa)$$

wherein
$R^{3'}$ and $R^{4'}$ have the meanings given for R^3 and R^4 hereinbefore with the exception of hydrogen atoms,

with formaldehyde and CH-acid compounds of general formula XIX,

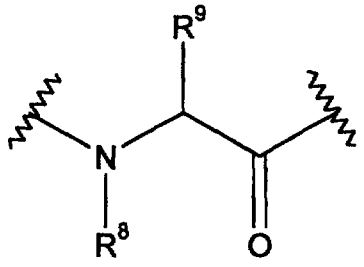


(XIX)

wherein
R is as hereinbefore defined and
R^2 is as hereinbefore defined, but with the proviso that any acid functions present such as hydroxy groups are appropriately protected by suitable protecting groups.

The reaction is preferably carried out in a slightly acidic medium, using alcohols, e.g. methanol or ethanol, or lower aliphatic carboxylic acids, such as glacial acetic acid, as solvents and at temperatures between room temperature and the boiling point of the solvent in question. In a preferred variant, an inorganic acid salt such as the hydrochloride of a secondary amine of general formula XVa is heated with paraformaldehyde and a ketone of general formula XIX in glacial acetic acid to temperatures between 50°C and 80°C.

k) In order to prepare compounds of general formula I wherein R, R^2, R^3, R^4, R^{11}, X, Z, m and n are as hereinbefore defined and A denotes the divalent group of formula III



(III),

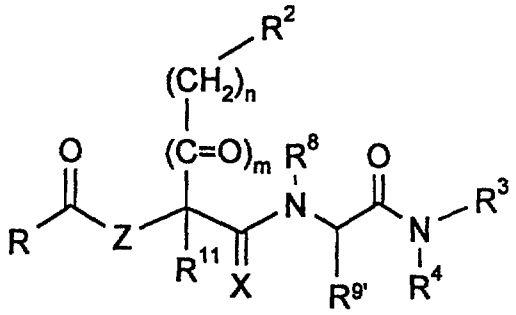
(linked to the NR^3R^4- group via the -CX- group)

wherein

R^8 denotes the hydrogen atom or an alkyl or phenylalkyl group and

R^9 denotes an unbranched C_{1-5}-alkyl group substituted in the ω-position by an aminoiminomethylamino group:

Reacting compounds of general formula XX,



(XX),

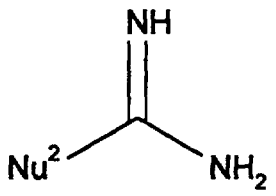
wherein

R, R^2, R^3, R^4, R^{11}, X, Z, m and n are as hereinbefore defined,

R^8 denotes a hydrogen atom or an alkyl or phenylalkyl group and

R^9 denotes an unbranched C_{1-5}-alkyl group substituted in the ω-position by a primary amino group,

with carbonic acid derivatives of general formula XXI,

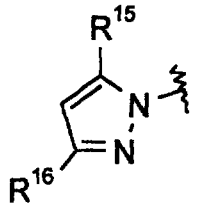


(XXI)

wherein

Nu^2 is a leaving group, e.g. an alkoxy, alkylthio, alkylsulphinyl or alkylsulphonyl group each having 1 to 10

carbon atoms in alkyl moiety, e.g. a methoxy, ethoxy, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, propylsulphinyl, isopropylsulphinyl, methylsulphonyl or ethylsulphonyl group, the chlorine atom, the SO_2H, SO_3H- or $OPOCl_2$- group, or the group of general formula XXII,



(XXII)

wherein

R^{15} and R^{16}, which may be identical or different, denote hydrogen atoms or C_{1-3}-alkyl groups.

Occasionally, for example when Nu^2 is an alkoxy group, instead of using the compounds of general formula XXI it is advantageous to use the inorganic acid salts thereof, e.g. the neutral sulphates or hydrochlorides thereof.

The reactions are carried out analogously to methods known from the literature (see G.B.L. Smith, J. Amer. Chem. Soc. 51, 476 [1929]; B. Rathke, Chem. Ber. 17, 297 [1884]; R. Phillips and H.T. Clarke, J. Amer. Chem. Soc. 45, 1755 [1923]; S.J. Angyal and W.K. Warburton, J. Amer. Chem. Soc. 73, 2492 [1951]; H. Lecher and F. Graf, Chem. Ber. 56, 1326 [1923]; J. Wityak, S.J. Gould, S.J. Hein and D.A. Keszler, J. Org. Chem. 52, 2179 [1987]; T. Teraji, Y. Nakai, G.J. Durant, WO-A-81/00109, Chem. Abstr. 94, 192336z [1981]; C.A. Maryanoff, R.C. Stanzione, J.N. Plampin and J.E. Mills, J. Org. Chem. 51, 1882-1884 [1986]; A.E. Miller and J.J. Bischoff, Synthesis 1986, 777; R.A.B. Bannard, A.A. Casselman, W.F. Cockburn and G.M. Brown, Can. J. Chem. 36, 1541 [1958]; Aktieselskabet Grea, Kopenhagen, DE 28 26 452-C2; K. Kim. Y-T. Lin and H.S. Mosher, Tetrah. Letters, 29, 3183-3186 [1988]; H.B.

Arzeno et al., Synth. Commun. 20, 3433-3437 [1990]; H. Bredereck and K. Bredereck, Chem. Ber. 94, 2278 [1961]; H. Eilingsfeld, G. Neubauer, M. Seefelder and H. Weidinger, Chem. Ber. 97, 1232 [1964]; P. Pruszynski, Can. J. Chem. 65, 626 [1987]; D.F. Gavin, W.J. Schnabel, E. Kober and M.A. Robinson, J. Org. Chem. 32, 2511 [1967]; N.K. Hart, S.R. Johns, J.A. Lamberton and R.I. Willing, Aust. J. Chem. 23, 1679 [1970]; CIBA Ltd., Belgisches Patent 655 403; Chem. Abstr. 64, 17481 [1966]; R.A.B. Bannard, A.A. Casselman, W.F. Cockburn and G.M. Brown, Can. J. Chem. 36, 1541 [1958]; J.P. Greenstein, J. Org. Chem. 2, 480 [1937]; F.L. Scott and J. Reilly, J. Amer. Chem. Soc. 74, 4562 [1952]; W.R. Roush and A.E. Walts, J. Amer. Chem. Soc. 106, 721 [1984], M.S. Bernatowicz, Y. Wu and G.R. Matsueda, J. Org. Chem. 57, 2497-2502 [1992]; H. Tsunematsu, T. Imamura and S. Makisumi, J. Biochem. 94, 123-128 [1983]) at temperatures between 0°C and +100°C, preferably between +40°C and +80°C, using inert solvents, e.g. dichloromethane, tetrahydrofuran, 1,4-dioxane, acetonitrile, dimethylformamide, dimethylacetamide, N-methyl-pyrrolidone or mixtures thereof and, depending on the nature of the Nu^2- group, frequently in the presence of auxiliary bases, especially alkali metal carbonates such as sodium- or potassium carbonate, or tertiary amines, preferably N-ethyl-diisopropylamine or triethylamine.

The amino acids of general formula I modified according to the invention contain at least one chiral centre. If the group A is also chiral, the compounds may occur in the form of two diastereomeric pairs of antipodes. The invention includes the individual isomers as well as the mixtures thereof.

The diastereomers are separated on the basis of their different physicochemical properties, e.g. by fractional crystallisation from suitable solvents, by high pressure

liquid or column chromatography using chiral or preferably achiral stationary phases.

Racemates covered by general formula I may be separated, for example, by HPLC on suitable chiral stationary phases (e.g. Chiral AGP, Chiralpak AD). Racemates which contain a basic or acidic function can also be separated by means of the diastereomeric optically active salts which are formed on reacting with an optically active acid, e.g. (+)- or (-)-tartaric acid, (+)- or (-)-diacetyl tartaric acid, (+)- or (-)-monomethyltartrate or (+)-camphor sulphonic acid or an optically active base such as (R)-(+)-1-phenylethylamine, (S)-(-)-1-phenylethylamine or (S)-brucine.

According to a conventional process for separating isomers, the racemate of a compound of general formula I is reacted with one of the above-mentioned optically active acids or bases in equimolar amounts in a solvent and the crystalline, diastereomeric, optically active salts obtained are separated on the basis of their different solubilities. This reaction may be carried out in solvents of any kind provided that they are sufficiently different in terms of the solubility of the salts. Preferably, methanol, ethanol or mixtures thereof are used, e.g. in a ratio by volume of 50:50. Then each of the optically active salts is dissolved in water, neutralised with a base such as sodium carbonate or potassium carbonate, sodium hydroxide solution or potassium hydroxide solution, and in this way the corresponding free compound is obtained in the (+)- or (-)-form.

The (R)-enantiomer alone or a mixture of two optically active diastereomeric compounds coming within the scope of general formula I may also be obtained by carrying out the

syntheses described above with a suitable reaction component in the (R)-configuration.

The starting materials of general formulae VII, IX, X, X', XI, XI', XIII, XV, XVa, XVII, XXI, XXII required to synthesis the compounds of general formula I as well as the amino acids used are commercially available or may be prepared by methods known from the literature.

Compounds of general formula VIII wherein Z denotes the group NR^1 and those of general formula VIII' wherein X denotes the oxygen atom may be obtained from commonly available starting materials using methods familiar to peptide chemists.

Isocyanates of general formula XII can easily be obtained from α-amino acid derivatives of general formula VIII' wherein R^1 denotes a hydrogen atom and the other groups are as hereinbefore defined, or from the hydrochlorides thereof by reacting with phosgene, diphosgene or triphosgene in the presence of pyridine (see also: J.S. Nowick, N.A. Powell, T.M. Nguyen and G. Noronha, J. Org. Chem. 57, 7364-7366 [1992]).

Carboxylic acids of general formulae XIV and XVI may be obtained from the corresponding carboxylic acid esters by saponification, preferably in the presence of lithium hydroxide.

The carboxylic acids of general formula XVIII are obtained by saponifying corresponding carboxylic acid esters which are in turn prepared from suitable secondary amines, 4-aryl-4-oxobutanoic acid esters and formaldehyde by Mannich reaction.

Compounds of general formula XIX may be obtained from suitable 4-oxobutanoic acids and amines of general formula X using conventional methods.

The intermediate compounds of general formula XX come under general formula I and are thus within the scope of the present application. These compounds may be obtained, for example, using processes a) to h) described herein.

The compounds of general formula I may be converted into their physiologically acceptable salts with inorganic or organic acids, particularly for pharmaceutical applications. Examples of suitable acids for this purpose include hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulphuric acid, methanesulphonic acid, p-toluenesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, mandelic acid, malic acid, citric acid, tartaric acid or maleic acid.

Moreover, if the new compounds of formula I thus obtained contain an acid function, for example a carboxy group, they may if desired be converted into the addition salts thereof with inorganic or organic bases, more particularly for pharmaceutical use, into the physiologically acceptable addition salts thereof. Bases which may be considered include, for example, sodium hydroxide, potassium hydroxide, ammonia, cyclohexylamine, dicyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

The new compounds of general formula I and the physiologically acceptable salts thereof have CGRP-antagonistic properties and exhibit good affinities in CGRP-receptor binding studies. The compounds exhibit CGRP-antagonistic properties in the pharmacological test systems described hereinafter.

The following experiments were carried out to demonstrate the affinity of compounds of general formula I for human CGRP-receptors and their antagonistic properties:

A. Binding studies with SK-N-MC-cells expressing human CGRP-receptor

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SK-N-MC-cells are cultivated in Dulbecco's modified Eagle Medium. The medium of confluent cultures is removed. The cells are washed twice with PBS-buffer (Gibco 041-04190 M), detached by the addition of PBS-buffer mixed with 0.02% EDTA and isolated by centrifuging. After resuspension in 20 ml of Balanced Salts Solution [BSS (in mM): NaCl 120, KCl 5.4, $NaHCO_3$ 16.2, $MgSO_4$ 0.8, $NaHPO_4$ 1.0, $CaCl_2$ 1.8, D-Glucose 5.5, HEPES 30, pH7.40] the cells are centrifuged twice at 100 x g and resuspended in BSS. After the cell number has been determined the cells are homogenised using an Ultra-Turrax and centrifuged for 10 minutes at 3000 x g. The supernatent is discarded and the pellet is recentrifuged and resuspended (1 ml/1000000 cells) in Tris-buffer (10 mM Tris, 50 mM NaCl, 5 mM $MgCl_2$, 1 mM EDTA, pH 7.40), enriched with 1% bovine serum albumin and 0.1% bacitracin. The homogenate is frozen at -80°C. The membrane preparations are stable for more than 6 weeks under these conditions.

After thawing, the homogenate is diluted 1:10 with assay buffer (50 mM Tris, 150 mM NaCl, 5 mM $MgCl_2$, 1 mM EDTA, pH 7.40) and homogenised for 30 seconds with an Ultra-Turrax. 230 µl of the homogenate are incubated at ambient temperature for 180 minutes with 50 pM of ^{125}I-Iodotyrosyl-Calcitonin-Gene-Related Peptide (Amersham) and increasing concentrations of the test substances in a total volume of 250 µl. Incubation is ended by rapid filtration using GF/B-glass fibre filters treated with polyethyleneimine (0.1%) by means of a cell harvester. The protein-bound radioactivity is measured using a gammacounter. The non-specific binding is defined as the radioactivity bound after the presence of 1 µM of human CGRP-alpha during incubation.

The concentration binding curves are analysed using a computer-aided non-linear curve adaptation.

The compounds of general formula I show IC_{50} values ≤ 10000 nM in the test described.

B. CGRP-Antagonism in SK-N-MC-cells

SK-N-MC-cells (1 million cells) are washed twice with 250 µl of incubation buffer (Hanks' HEPES, 1 mM 3-isobutyl-1-methylxanthine, 1% BSA, pH 7.4) and pre-incubated at 37°C for 15 minutes. After the addition of CGRP (10 µl) as agonist in increasing concentrations (10^{-11} to 10^{-6} M) or additionally of substance in 3 to 4 different concentrations, incubation is continued for a further 15 minutes.

Intracellular cAMP is then extracted by the addition of 20 µl of 1M HCl and centrifugation (2000 x g, 4°C for 15 minutes). The supernatants are frozen in liquid nitrogen and stored at -20°C.

The cAMP contents of the samples are determined by radioimmunoassay (Amersham) and the pA_2-values of antagonistically acting substances are determined graphically.

The compounds of general formula I display CGRP-antagonistic properties in a dosage range between 10^{-11} and 10^{-5} M in the *in vitro* test model described.

In view of their pharmacological properties the compounds of general formula I and the salts thereof with physiologically acceptable acids or bases are thus suitable for acute and prophylactic treatment of headache, particularly migraine and cluster headaches. Moreover,

the compounds of general formula I also have a beneficial effect on the following diseases: non-insulin-dependent diabetes mellitis (NIDDM), cardiovascular diseases, skin diseases, particularly thermal and radiation-induced skin damage including sunburn, inflammatory diseases, e.g. inflammatory joint diseases (arthritis), inflammatory lung diseases, allergic rhinitis, asthma, diseases which involve excessive vasodilation and resultant reductions in circulation, e.g. shock and sepsis, as well as morphine tolerance. In addition, the compounds of general formula I have the effect of alleviating pain in general.

The dosage needed to achieve such effects is appropriately 0.0001 to 3 mg/kg of body weight, preferably 0.01 to 1 mg/kg of body weight, by intravenous or subcutaneous route, and 0.01 to 10 mg/kg of body weight, preferably 0.1 to 10 mg/kg of body weight, when administered orally, nasally or by inhalation, in each case 1 to 3 times a day.

For this purpose, the compounds of general formula I prepared according to the invention may be formulated, optionally in combination with other active substances, such as antiemetics, prokinetics, neuroleptics, antidepressants, neurokinin-antagonists, anti-convulsants, histamine-H1-receptor antagonists, antimuscarinics, β-blockers, α-agonists and α-antagonists, ergot alkaloids, mild analgesics, non-steroidal antiphlogistics, corticosteroids, calcium-antagonists, 5-HT_{1D}-agonists or other antimigraine agents, together with one or more inert conventional carriers and/or diluents, e.g. corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethyleneglycol, propyleneglycol, cetylstearylalcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof, to produce conventional galenic preparations such as plain

or coated tablets, capsules, powders, suspensions, solutions, metering aerosol or suppositories.

Thus, additional active substances which may be considered for the above-mentioned combinations include, for example, meloxicam, ergotamine, dihydroergotamine, metoclopramide, domperidon, diphenhydramine, cyclizine, promethazine, chlorpromazine, dexamethasone, flunarizine, dextropropoxyphene, meperidine, propranolol, nadolol, atenolol, clonidine, indoramine, carbamazepine, phenytoin, valproate, amitryptilin, lidocaine, diltiazem or sumatriptan and other 5-HT_{1D}-agonists such as naratriptan, zolmitriptan, avitriptan, rizatriptan and eletriptan. The dosage for these active substances is appropriately 1/5 of the lowest dose normally recommended up to 1/1 of the normally recommended dosage, i.e. 20 to 100 mg of sumatriptan, for example.

The invention further relates to the use of the compounds of general formula I as valuable auxiliary agents for the production and purification (by affinity chromatography) of antibodies and, after suitable radiolabelling, e.g. by direct labelling with ^{125}I or ^{131}I or by tritiation of suitable precursors for example by replacing halogen atoms with tritium, in RIA- and ELISA assays and as diagnostic or analytical aids in neurotransmitter research.

The Examples which follow are intended to illustrate the invention:

Preliminary remarks:

There are satisfactory elementary analyses, IR, UV, ^{1}H-NMR and generally mass spectra as well, for all the compounds. Unless otherwise specified, R_f values were determined using TLC ready-made plates of silica gel 60 F_{254} (E. Merck, Darmstadt, Product No. 5729) without chamber saturation. If there are no details of configuration, it is undecided whether this is the pure enantiomer or whether partial or total racemisation has occurred. The following eluants or eluant mixtures were used for chromatography:

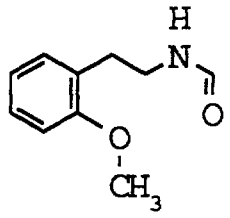
FM1 = dichloromethane/cyclohexane/methanol/ammonia 7/1.5/1.5/0.2 (v/v/v/v)
FM2 = dichloromethane/methanol/ammonia 7.5/2.5/0.5 (v/v/v)
FM3 = dichloromethane/methanol 8/2 (v/v)
FM4 = dichloromethane/ethyl acetate/methanol/cyclohexane/-conc. aqueous ammonia = 59/25/7,5/7,5/1 (v/v/v/v/v)
FM5 = ethyl acetate/dichloromethane = 7/3 (v/v)
FM6 = ethyl acetate/petroleum ether = 1/1 (v/v)
FM7 = dichloromethane/methanol/conc. aqueous ammonia = 80/20/1 (v/v/v)

The following abbreviations were used in the descriptions of the experiments:

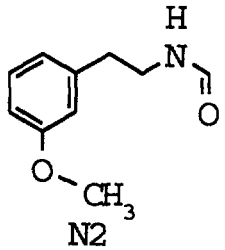
Mp.: melting point
(D): (decomposition)
DIEA: N,N-diisopropyl-ethylamine
Boc: (1,1-dimethylethoxy)carbonyl
TBTU: 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate
HOBt: 1-hydroxybenzotriazole-hydrate
CDT: 1,1'-carbonyldi(1,2,4-triazole)
THF: tetrahydrofuran
DMF: dimethylformamide
Fmoc: (9-fluorenylmethoxy)carbonyl
EE: ethyl acetate

PE: petroleum ether
LM: solvent
Lfd. No.: item number

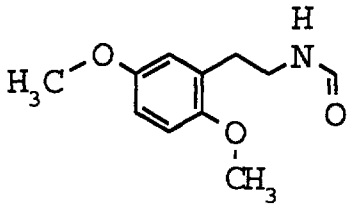
The meanings of the symbols made up of letters and numbers used in the Examples are given in the following summary:



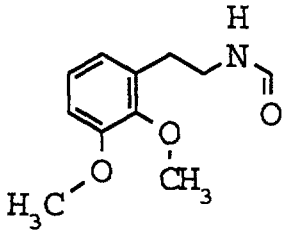
N1



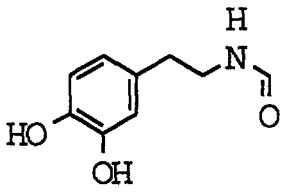
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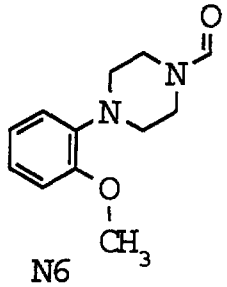
N3



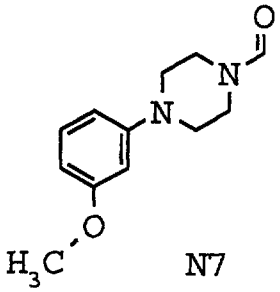
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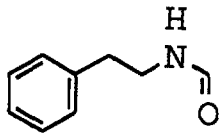
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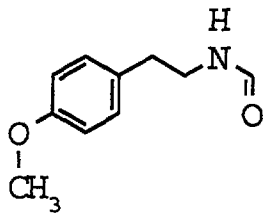
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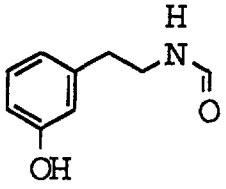
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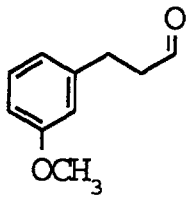
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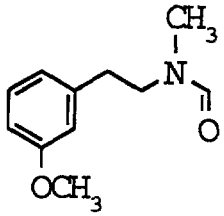
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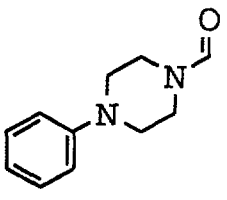
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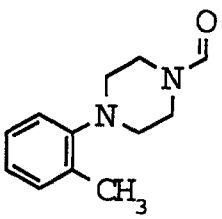
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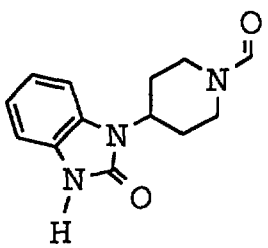
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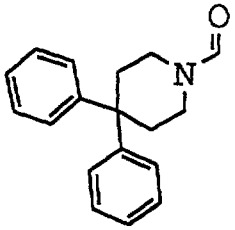
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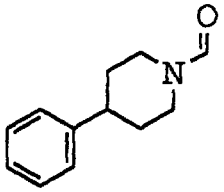
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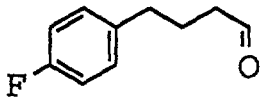
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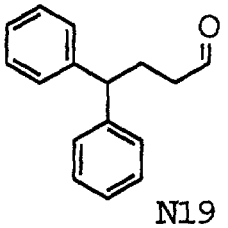
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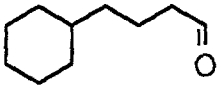
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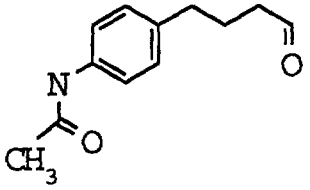
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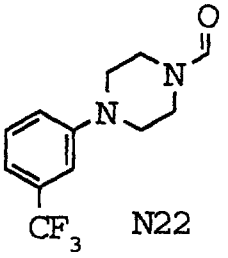
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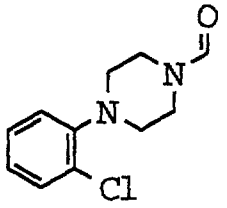
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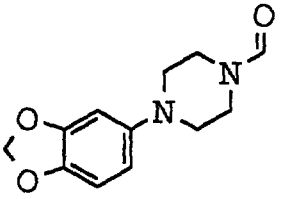
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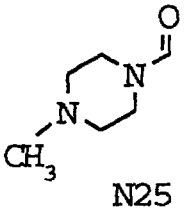
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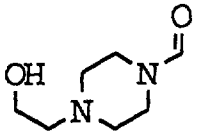
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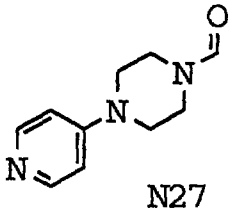
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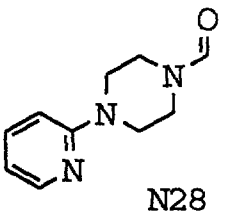
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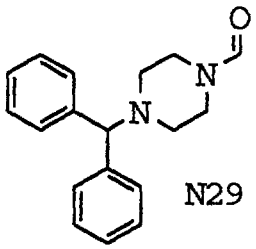
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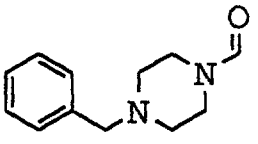
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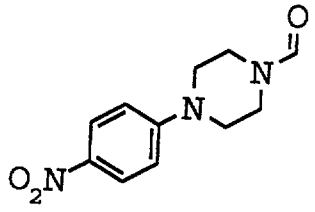
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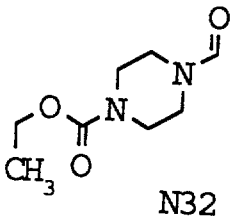
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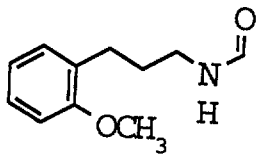
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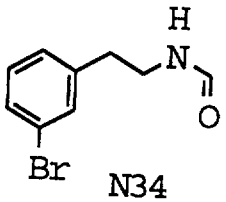
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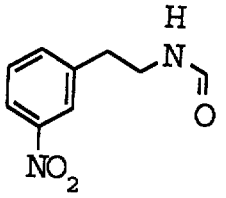
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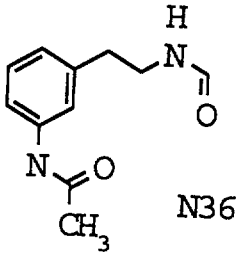
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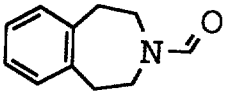
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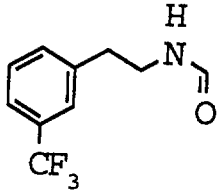
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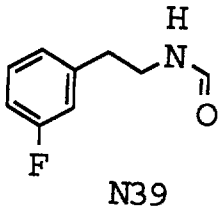
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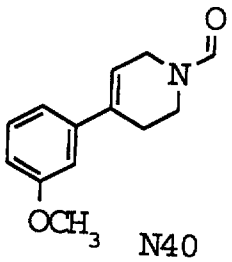
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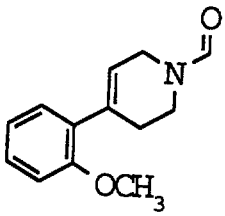
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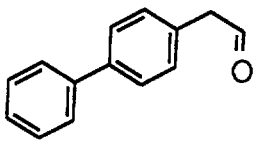
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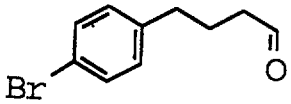
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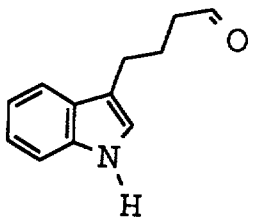
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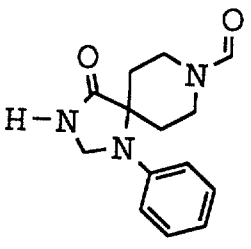
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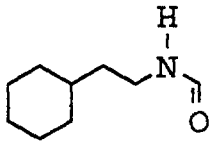
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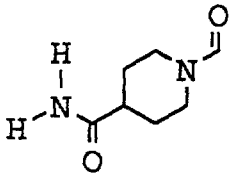
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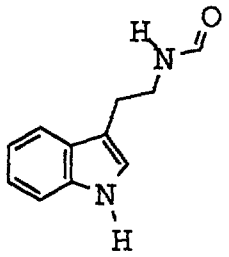
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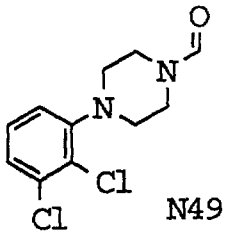
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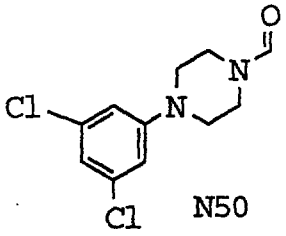
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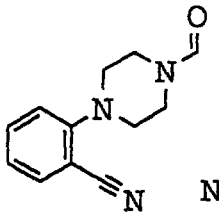
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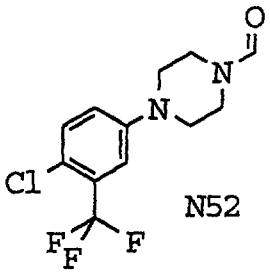
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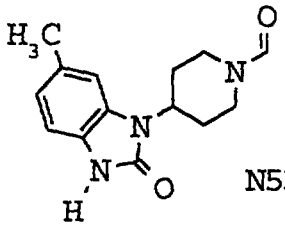
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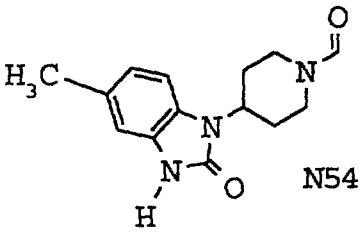
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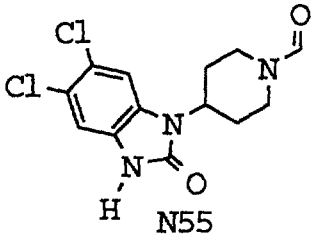
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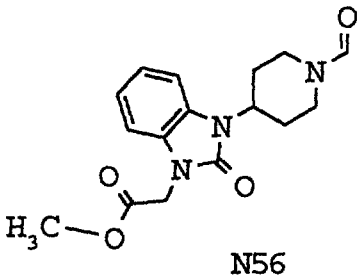
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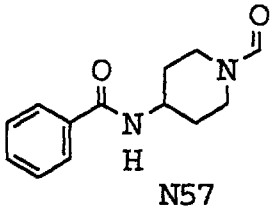
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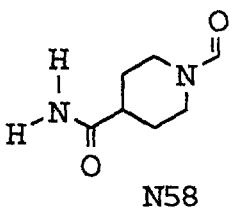
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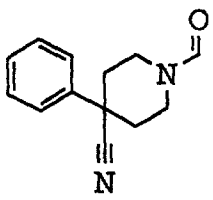
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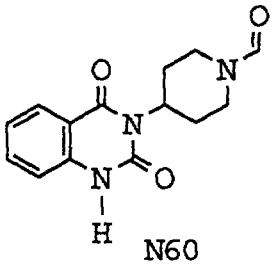
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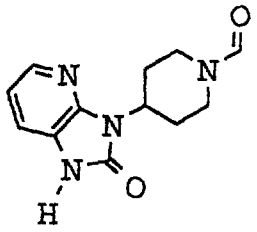
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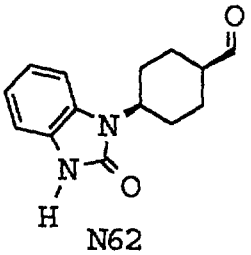


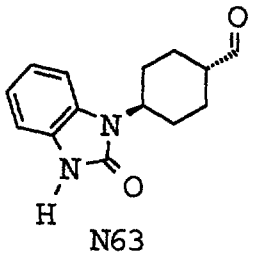
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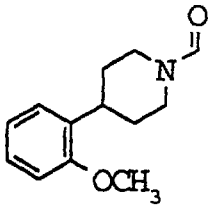


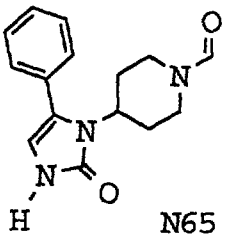
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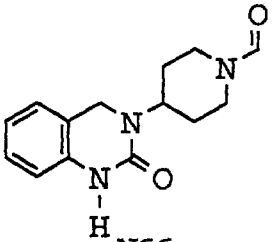

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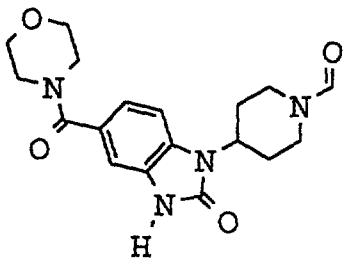

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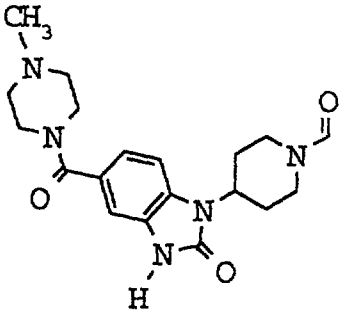

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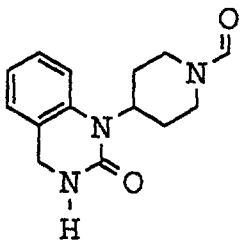

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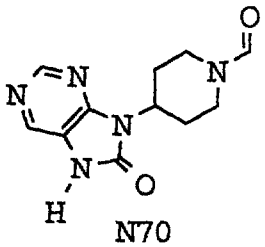

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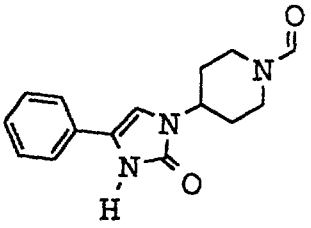

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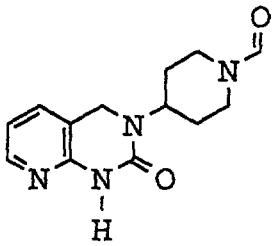

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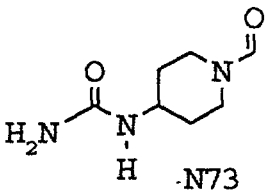

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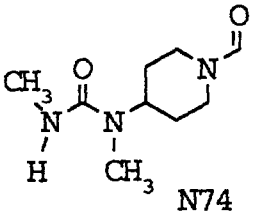

N69

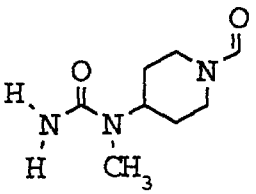

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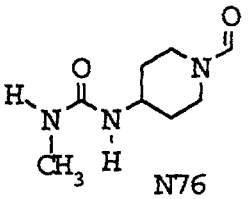

N71


N72

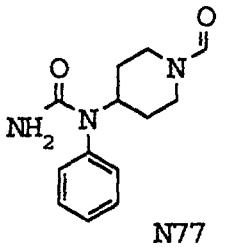

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N74

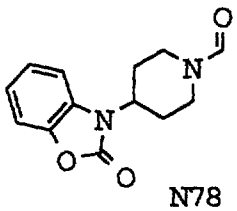

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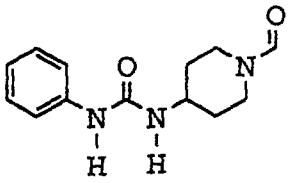
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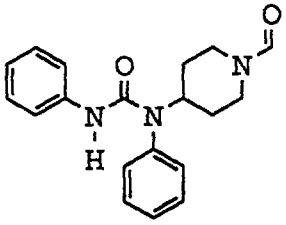
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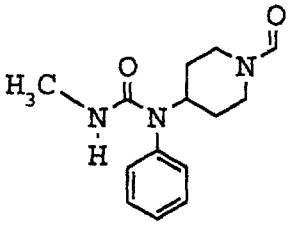
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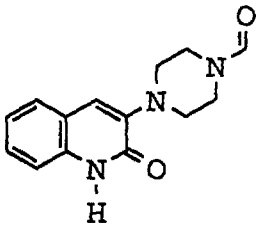
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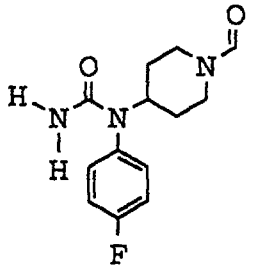
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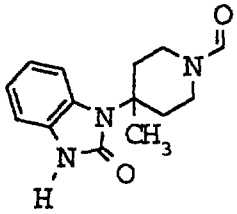
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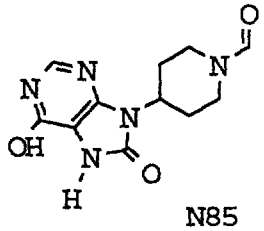
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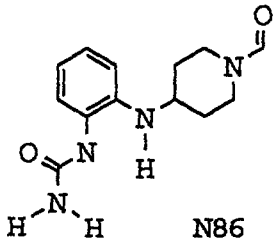
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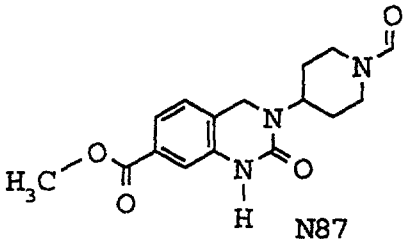
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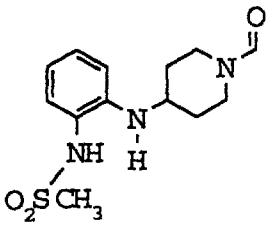
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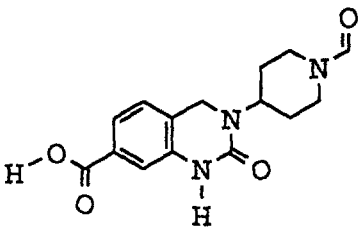
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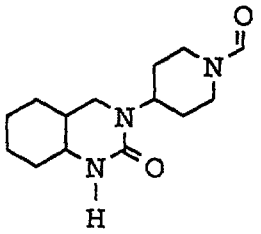
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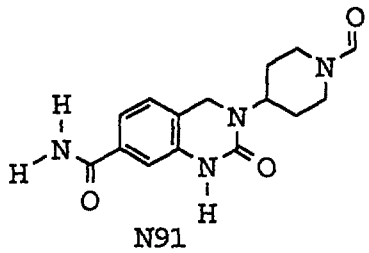
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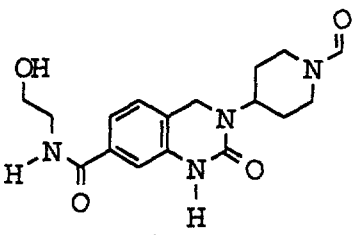
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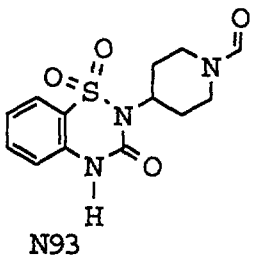
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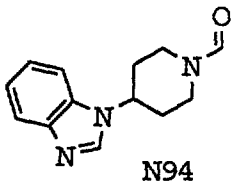
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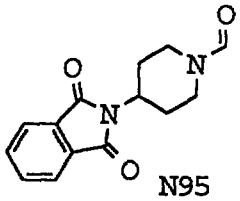
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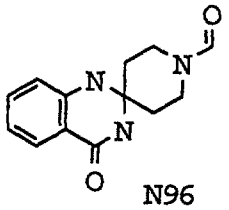
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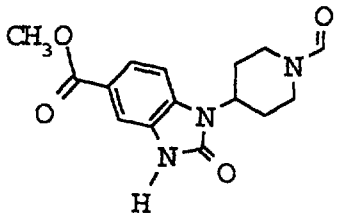
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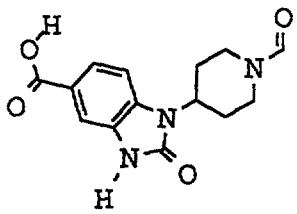
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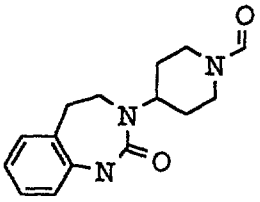
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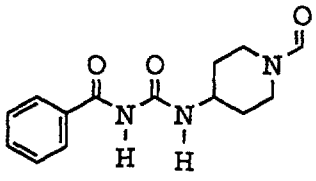
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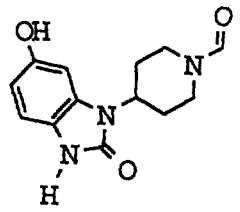
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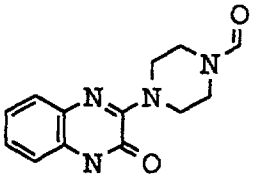
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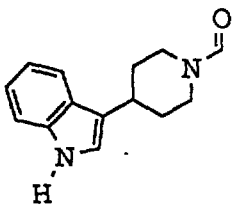
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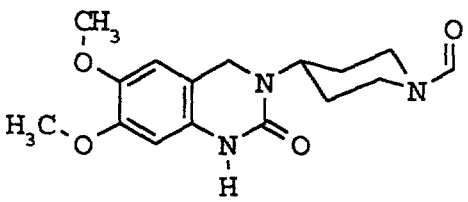
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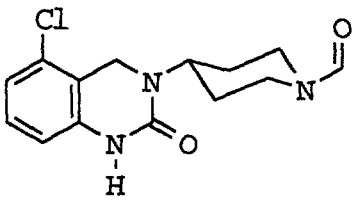
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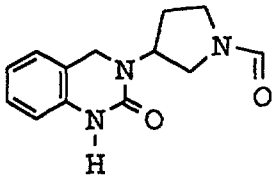
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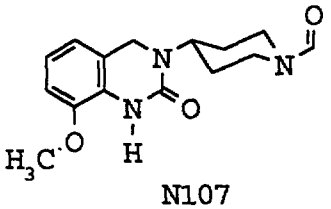
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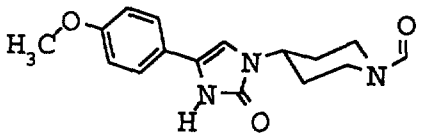
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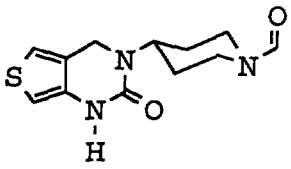
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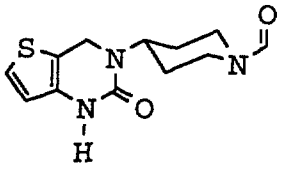
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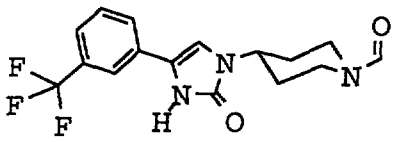
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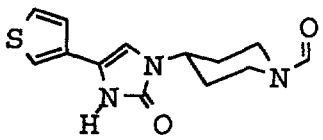
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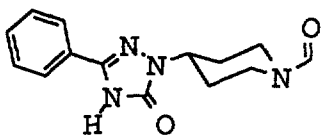
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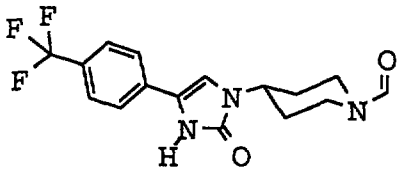
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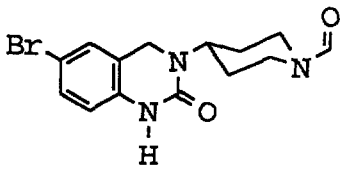
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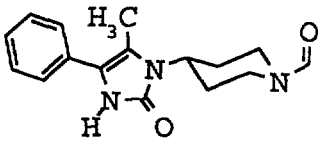
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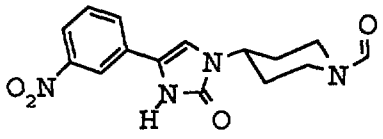
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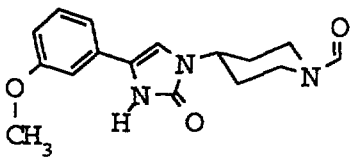
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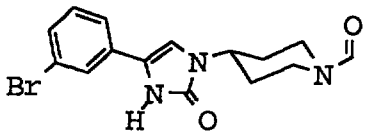
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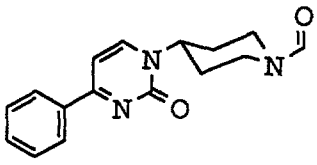
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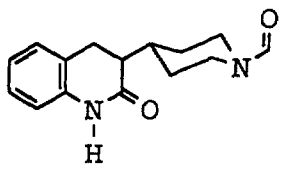
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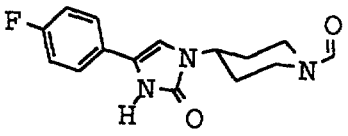
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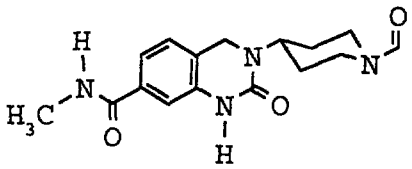
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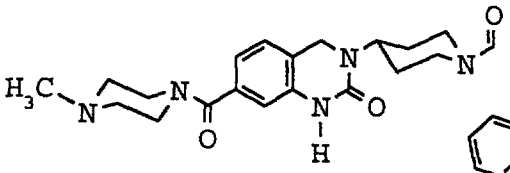
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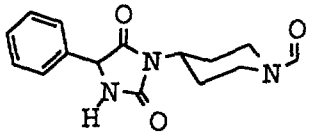
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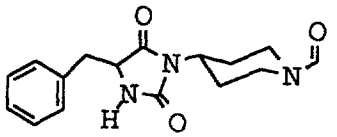
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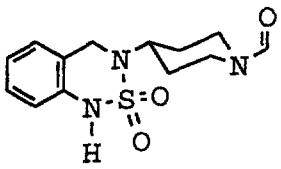
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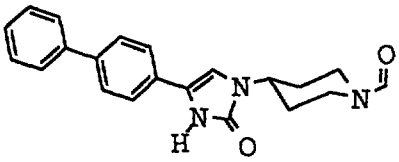
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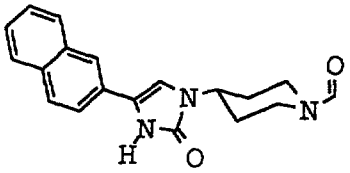
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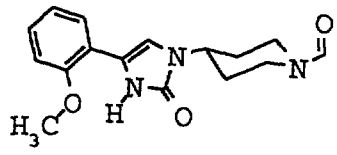
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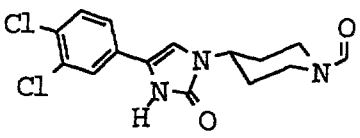
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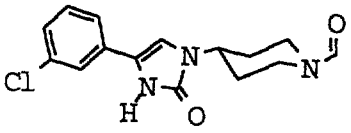
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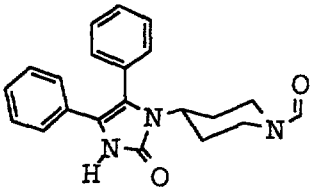
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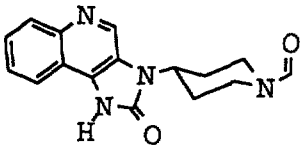
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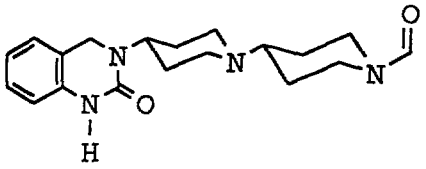
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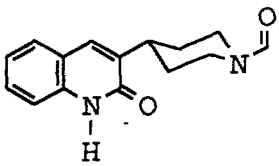
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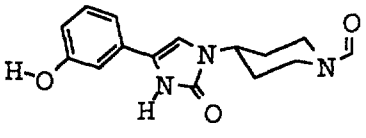
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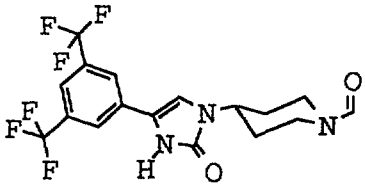
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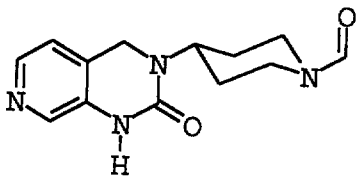
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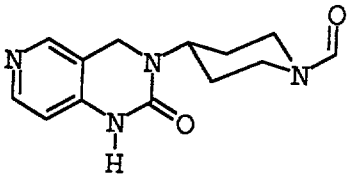
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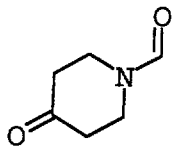
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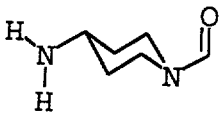
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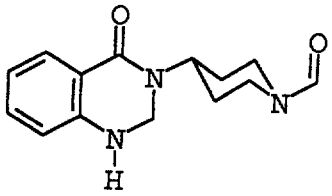
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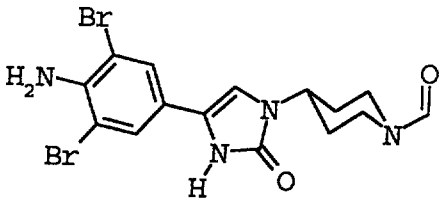
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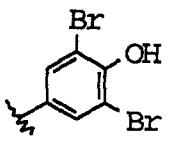
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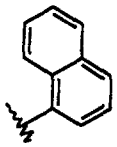


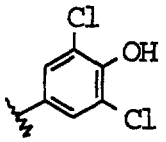
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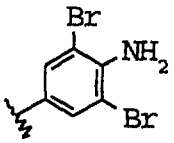


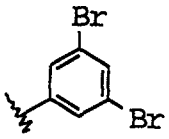
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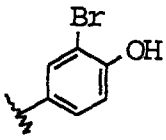

AS1

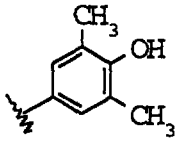

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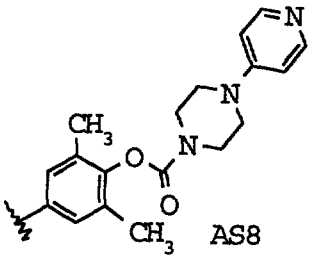

AS3

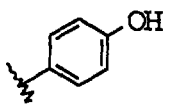

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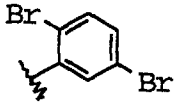

AS5

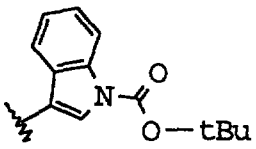

AS6

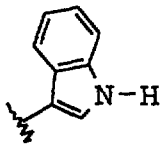

AS7

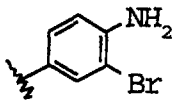

AS8

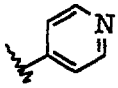

AS9

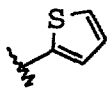

AS10

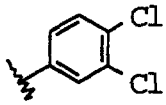

AS11

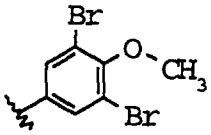

AS12

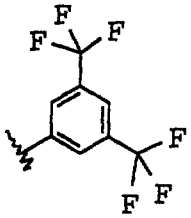

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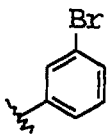

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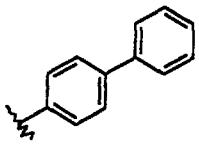

AS15

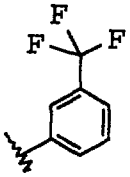

AS16

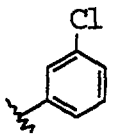

AS17

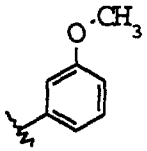

AS18

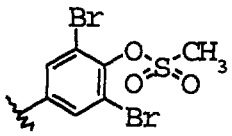

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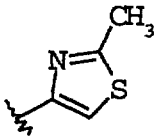

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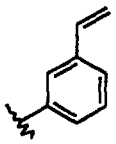

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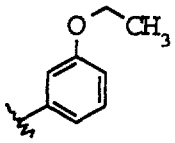

AS22

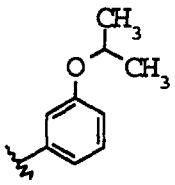

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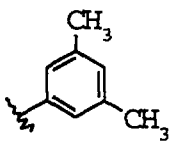

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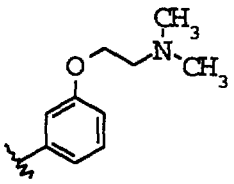

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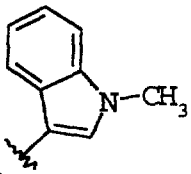

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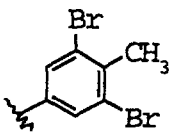

AS27

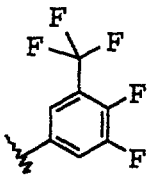

AS28

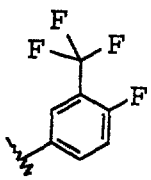

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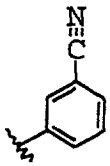

AS30

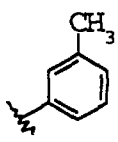

AS31

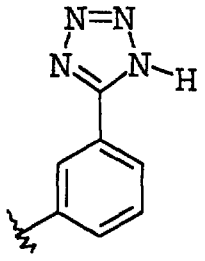

AS32


AS33

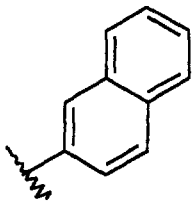

AS34


AS35

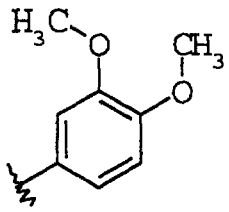

AS36



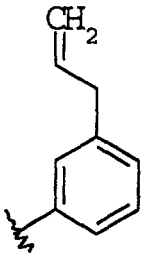
AS37



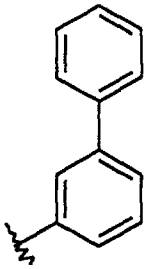
AS38



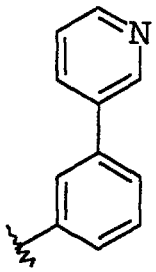
AS39



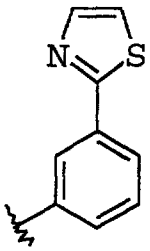
AS40



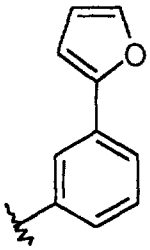
AS41



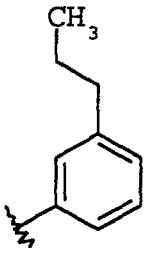
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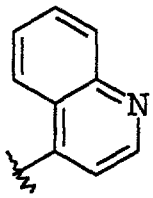
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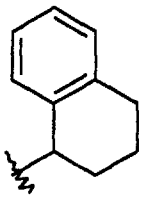
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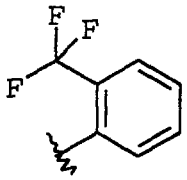
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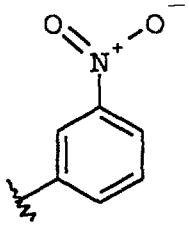
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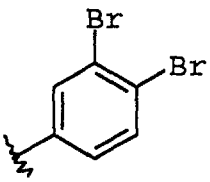
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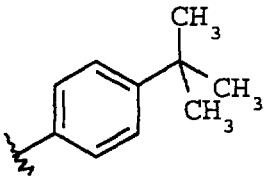
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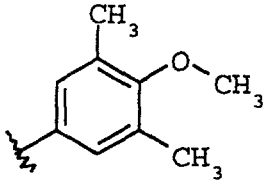
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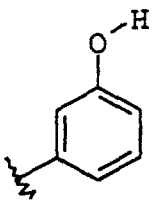
AS50



AS51



AS52

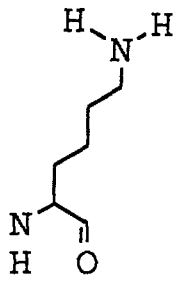


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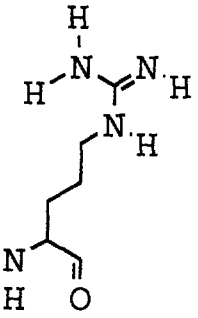
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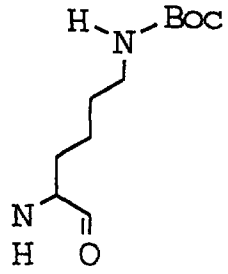
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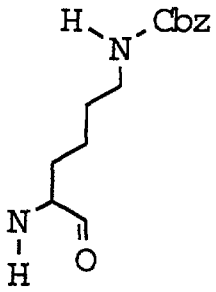
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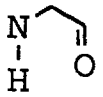
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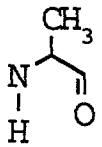
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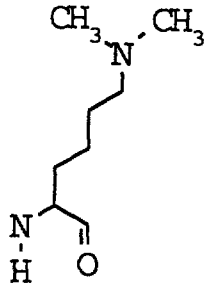
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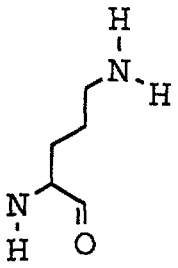
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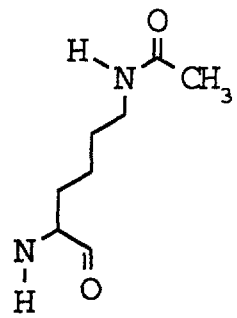
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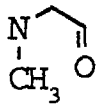
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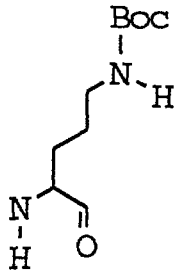
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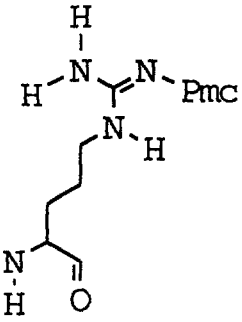
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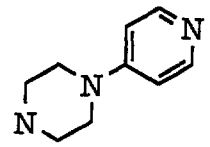
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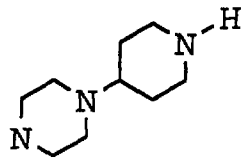
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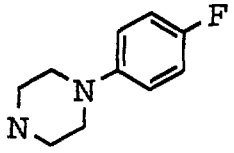
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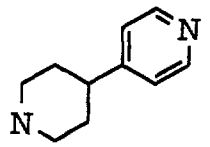
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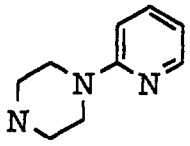
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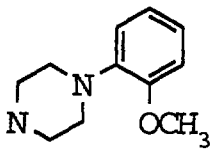
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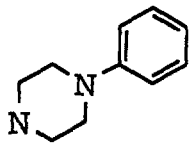
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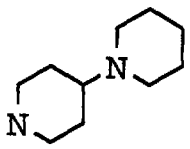
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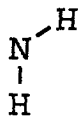
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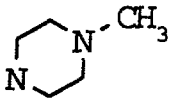
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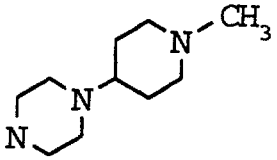
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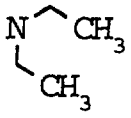
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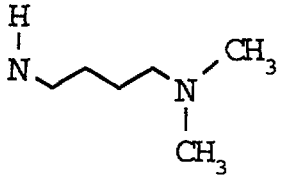
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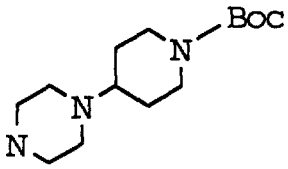
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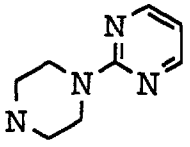
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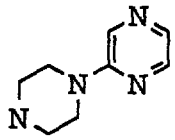
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C14



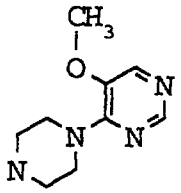
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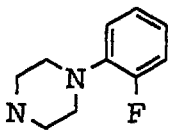
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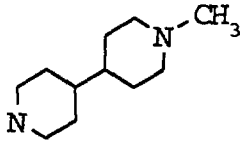
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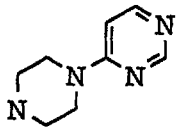
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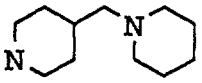
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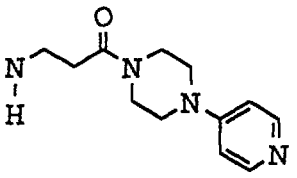
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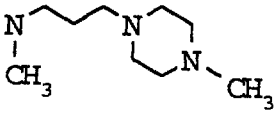
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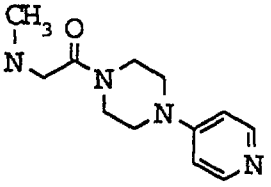
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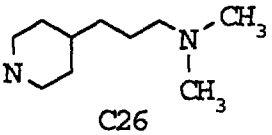
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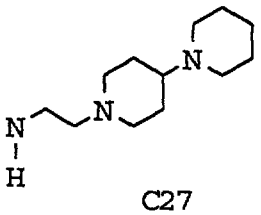
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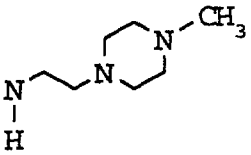
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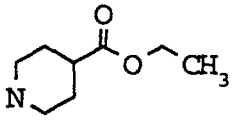
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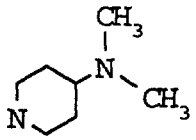
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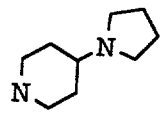
C28



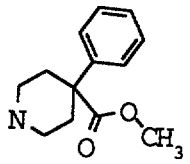
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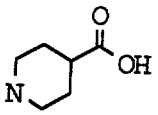
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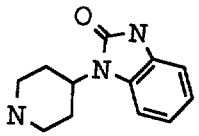
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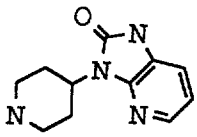
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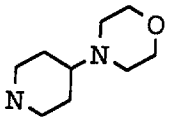
C33



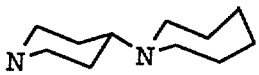
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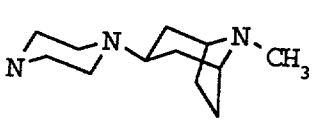
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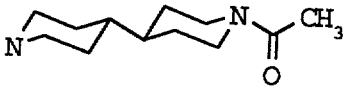
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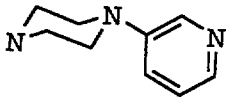
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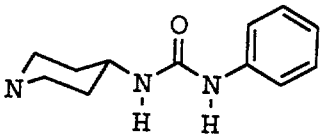
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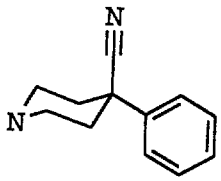
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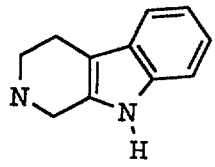
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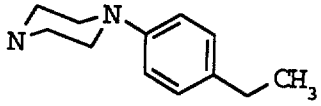
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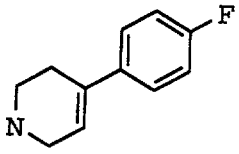
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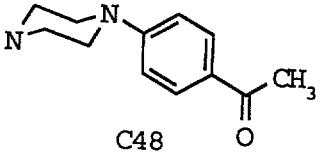
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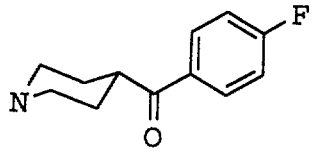
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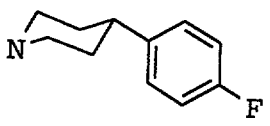
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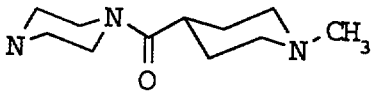
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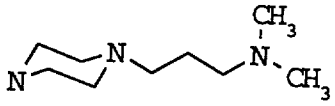
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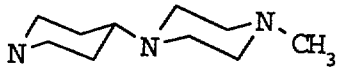
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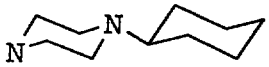
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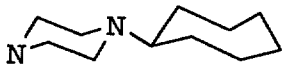
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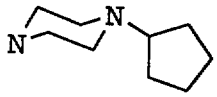
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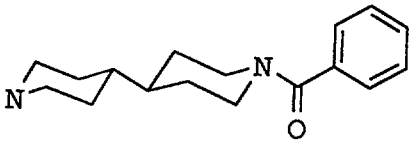
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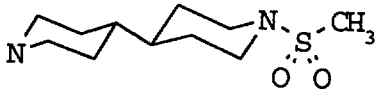
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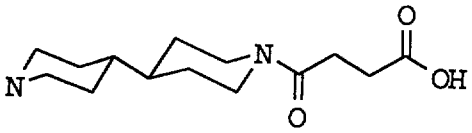
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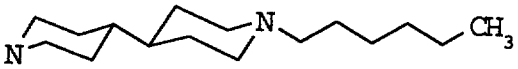
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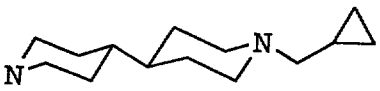
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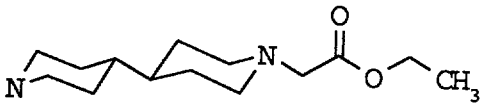
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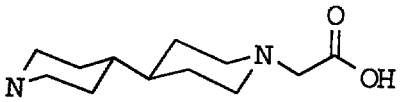
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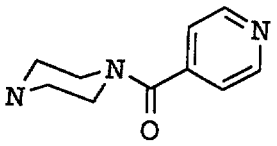
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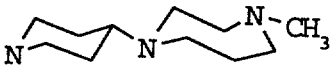
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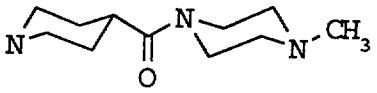
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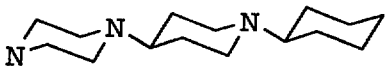
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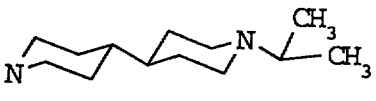
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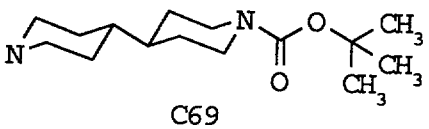
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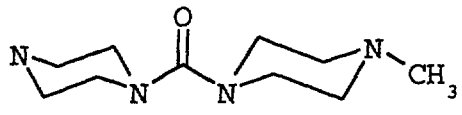
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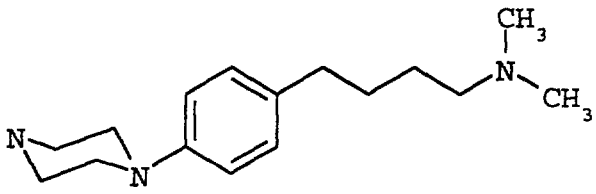
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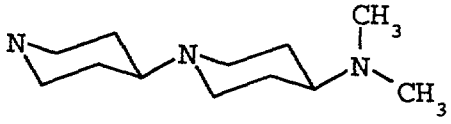
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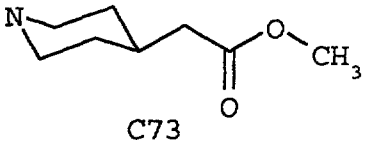
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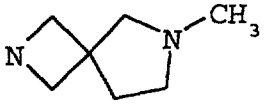
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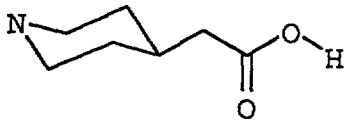
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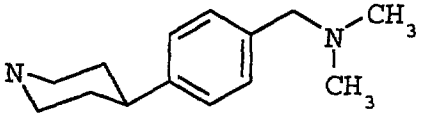
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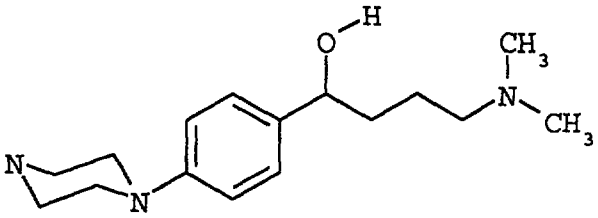
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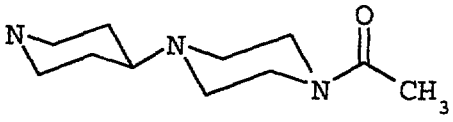
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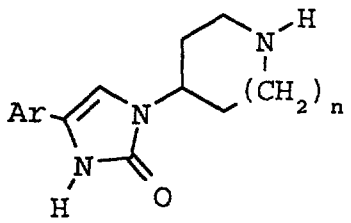
C78

S017001aus3.200

A. Preparation of intermediate compounds

Example A1

Preparation of compounds of the general structure:



1,3-dihydro-4-(3-methoxyphenyl)-1-(4-piperidinyl)-2H-imidazol-2-one

a) 4-[1,3-dihydro-4-(3-methoxyphenyl)-2(2H)-oxoimidazol-1-yl]-1-(1,1-dimethylethoxycarbonyl)-piperidine

To a mixture of 20.0 g (0.10 mol) of 4-amino-1-(1,1-dimethylethoxycarbonyl)piperidine, 8.2 g (0.1 mol) of anhydrous sodium acetate and 150 ml of dichloromethane was added dropwise, with stirring and whilst maintaining a reaction temperature of from 0°C to +10°C, a solution of 25.0 g (0.109 mol) of 3-methoxyphenacylbromide in 50 ml of dichloromethane was added dropwise. The mixture was stirred for 5 hours at room temperature, then 19.5 g (0.296 mol) of sodium cyanate, 18 ml of glacial acetic acid and 10 ml of water were added and stirring was continued for 12 hours at room temperature. The mixture was stirred into 1 l of ice water, the dichloromethane phase was separated off, washed twice with 200 ml of water, 5% aqueous sodium hydrogen carbonate solution, 20% aqueous citric acid solution and once more with water, dried over magnesium sulphate and evaporated down *in vacuo*. The residue was taken up in methanol.

It was left to stand overnight, the precipitate which crystallised out was suction filtered, washed thoroughly with tert. butyl-methylether and after drying *in vacuo* 11.5 g (30.8% of theory) of colourless crystals were obtained.
MS: M^+ = 373

The following were obtained accordingly:

(1) 4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-(1,1-dimethylethoxycarbonyl)-piperidine
R_f: 0.51 (FM4)

(2) 4-[1,3-dihydro-4-(4-methoxyphenyl)-2(2H)-oxoimidazol-1-yl]-1-(1,1-dimethylethoxycarbonyl)-piperidine
yield: 23.8% of theory

(3) 4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-(1,1-dimethylethoxycarbonyl)-piperidine
IR(KBr): 1685.7 cm^{-1} (C=O)

(4) 4-[1,3-dihydro-5-methyl-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-(1,1-dimethylethoxycarbonyl)-piperidine
R_f: 0.23 (dichloromethane/methanol 9/1 v/v)
IR(KBr): 1687.6 cm^{-1} (C=O)
MS: M^+ = 357

(5) 4-[1,3-dihydro-4-(3-nitrophenyl)-2(2H)-oxoimidazol-1-yl]-1-(1,1-dimethylethoxycarbonyl)-piperidine
yield: 29.1% of theory
MS: M^+ = 388

(6) 4-[4-(3-bromophenyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-(1,1-dimethylethoxycarbonyl)-piperidine
yield: 13.1% of theory
IR(KBr): 1685 cm^{-1} (C=O)
MS: M^+ = 421/423 (Br)

(7) 4-[1,3-dihydro-4,5-diphenyl-2(2H)-oxoimidazol-1-yl]-1-(1,1-dimethylethoxycarbonyl)-piperidine
IR(KBr): 1680, 1699 cm^{-1} (C=O)
MS: M^+ = 419

(8) 4-[1,3-dihydro-4-(4-fluorophenyl)-2(2H)-oxoimidazol-1-yl]-1-(1,1-dimethylethoxycarbonyl)-piperidine
IR(KBr): 1682 cm^{-1} (C=O)
MS: M^+ = 388

(9) 4-[4-(4-biphenylyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-(1,1-dimethylethoxycarbonyl)-piperidine
yield: 21.6% of theory, colourless crystals
R_f: 0.6 (ethyl acetate)
IR(KBr): 1681.8 cm^{-1} (C=O)

(10) 4-[1,3-dihydro-4-(2-naphthyl)-2(2H)-oxoimidazol-1-yl]-1-(1,1-dimethylethoxycarbonyl)-piperidine
yield: 30% of theory, crystals
IR(KBr): 1679.9 cm^{-1} (C=O)

(11) 4-[1,3-dihydro-4-(2-methoxyphenyl)-2(2H)-oxoimidazol-1-yl]-1-(1,1-dimethylethoxycarbonyl)-piperidine
R_f: 0.86 (FM1)

(12) 4-[4-(3,4-dichlorophenyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-(1,1-dimethylethoxycarbonyl)-piperidine
yield: 62% of theory, colourless crystals
R_f: 0.34 (ethyl acetate)
IR(KBr): 1687 cm^{-1} (C=O)

(13) 4-[4-(3-chlorophenyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-(1,1-dimethylethoxycarbonyl)-piperidine
yield: 21% of theory
R_f: 0.6 (ethyl acetate/methanol 9/1 v/v)

(14) 4-[1,3-dihydro-4-(3-hydroxyphenyl)-2(2H)-oxoimidazol-1-yl]-1-(1,1-dimethylethoxycarbonyl)-piperidine
Yield: 60% of theory
IR(KBr): 1682 cm^{-1} (C=O)
MS: M^+ = 359

(15) 4-[4-[3,5-bis-(trifluoromethyl)phenyl]-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-(1,1-dimethylethoxycarbonyl)-piperidine
Yield: 3.2% of theory
IR(KBr): 1687.6 cm^{-1} (C=O)
R_f: 0.95 (dichloromethane/methanol 9/1 v/v)

(16) 4-[4-(4-amino-3,5-dibromophenyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-(1,1-dimethylethoxycarbonyl)-piperidine
Yield: 4.6% of theory
IR(KBr): 1684 cm^{-1} (C=O)
R_f: 0.48 (FM4; Macherey-Nagel POLYGRAM® SIL G/UV_{254} ready-made films for TLC)

b) 1,3-dihydro-4-(3-methoxyphenyl)-1-(4-piperidinyl)-2H-imidazol-2-one

The solution of 11.5 g (0.0308 mol) of 4-[1,3-dihydro-4-(3-methoxyphenyl)-2(2H)-oxoimidazol-1-yl]-1-(1,1-dimethylethoxycarbonyl)-piperidine in 150 ml of dichloromethane was mixed with 15 ml of trifluoroacetic acid and then stirred overnight at room temperature. The reaction mixture was evaporated down *in vacuo*, the residue was taken up in 10 ml of water and made distinctly ammoniacal. The resulting precipitate was suction filtered, washed thoroughly with water and dried overnight at 50°C *in vacuo*. 7.0 g (83.1% of theory) of colourless crystals were obtained, Rf value 0.2 (dichloromethane/methanol 9/1 v/v).

The following were obtained accordingly:

(1) 1,3-dihydro-4-phenyl-1-(4-piperidinyl)-2H-imidazol-2-one,
R_f: 0.22 (FM1; Macherey-Nagel POLYGRAM® SIL G/UV_{254} ready-made films for TLC)
IR(KBr): 1672 cm^{-1} (C=O)

(2) 1,3-dihydro-4-(4-methoxyphenyl)-1-(4-piperidinyl)-2H-imidazol-2-one
IR(KBr): 1670 cm^{-1} (C=O)
MS: M^+ = 273

(3) 1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-1-(4-piperidinyl)-2H-imidazol-2-one
IR(KBr): 1687.6 cm^{-1} (C=O)

(4) 1,3-dihydro-5-methyl-4-phenyl-1-(4-piperidinyl)-2H-imidazol-2-one
yield: 76.2% of theory
IR(KBr): 1679.9 cm^{-1} (C=O)
MS: M^+ = 257

(5) 1,3-dihydro-4-(3-nitrophenyl)-1-(4-piperidinyl)-2H-imidazol-2-one
yield: 94% of theory
IR(KBr): 1677.8 (C=O); 1137.8, 1197.6, 1349.9 (NO_2) cm^{-1}

(6) 4-(3-bromophenyl)-1,3-dihydro-1-(4-piperidinyl)-2H-imidazol-2-one
yield: quantitative
IR(KBr): 1676 cm^{-1} (C=O)

(7) 1,3-dihydro-4,5-diphenyl-1-(4-piperidinyl)-2H-imidazol-2-one
IR(KBr): 1670 cm^{-1} (C=O)
MS: M^+ = 319

(8) 1,3-dihydro-4-(4-fluorophenyl)-1-(4-piperidinyl)-2H-imidazol-2-one
yield: 30% of theory
R_f: 0.2 (eluant: ethyl acetate/methanol/conc. ammonia 9/1/0.3 v/v/v)
IR(KBr): 1682 cm^{-1} (C=O)

(9) 4-(4-biphenylyl)-1,3-dihydro-1-(4-piperidinyl)-2H-imidazol-2-one
yield: quantitative
IR(KBr) of the trifluoroacetate: 1679.9 cm^{-1} (C=O)

(10) 1,3-dihydro-4-(2-naphthyl)-1-(4-piperidinyl)-2H-imidazol-2-one
yield: 28.2% of theory
R_f: 0.03 (FM1)
IR(KBr) of the trifluoroacetate: 1678 cm^{-1} (C=O)

(11) 7-(2-methoxyphenyl)-1-(4-piperidinyl)-2H-imidazol-2-one
yield: 18.8% of theory
R_f: 0.22 (FM1)
IR(KBr) of the trifluoroacetate: 1681.6 cm^{-1} (C=O)

(12) 4-(3,4-dichlorophenyl)-1,3-dihydro-1-(4-piperidinyl)-2H-imidazol-2-one
yield: quantitative
IR(KBr) of the trifluoroacetate: 3197 (N-H); 1685 (C=O) cm^{-1}

(13) 4-(3-chlorophenyl)-1,3-dihydro-1-(4-piperidinyl)-2H-imidazol-2-one
Yield: 98% of theory
R_f: 0.25 (eluant: ethyl ethanoate/methanol/conc. ammonia 9/1/0.3 v/v/v)

(14) 1,3-dihydro-4-(3-hydroxyphenyl)-1-(4-piperidinyl)-2H-imidazol-2-one
Yield: 90% of theory
R_f: 0.075 (FM1)
IR(KBr): 1670 (C=O) cm^{-1}
MS: M^+ = 259

(15) 4-[3,5-bis-(trifluoromethyl)phenyl]-1,3-dihydro-1-(4-piperidinyl)-2H-imidazol-2-one
Yield: 71% of theory
R_f: 0.15 (FM1)
IR(KBr): 1701 (C=O) cm^{-1}
MS: M^+ = 379

(16) 4-(4-amino-3,5-dibromophenyl)-1,3-dihydro-1-(4-piperidinyl)-2H-imidazol-2-one
Yield: 44% of theory
R_f: 0.71 (FM1; Macherey-Nagel POLYGRAM® SIL G/UV_{254} ready-made films for TLC)
IR(KBr): 1676 (C=O) cm^{-1}

Example A2

2,4-dihydro-5-phenyl-2-(4-piperidinyl)-3H-1,2,4-triazol-3-one

a) 1-(9H-fluoren-9-ylmethoxycarbonyl)-4-piperidinone-(1,1-dimethylethoxycarbonyl)hydrazone

A mixture of 16.0 g (0.05 mol) of 1-(9H-fluoren-9-ylmethoxycarbonyl)-4-piperidinone, 7.25 g (0.055 mol) of tert. butyl hydrazinoformate and 250 ml of ethanol was refluxed for 1 hour. The solvent was distilled off *in vacuo*, the oily residue remaining was triturated with diethylether. The crystalline precipitate thus formed was suction filtered and washed with a little diethylether. After the product had been dried *in vacuo* 21.7 g (99.7% of

theory) of colourless crystals were obtained, m.p. 156 - 158°C (decomposition).

b) N-(1,1-dimethylethoxycarbonyl)-N'-[1-(9H-fluoren-9-ylmethoxycarbonyl)-4-piperidinyl]-hydrazine

A solution of 21.7 g (0.05 mol) of 1-(9H-fluoren-9-ylmethoxycarbonyl)-4-piperidinone-(1,1-dimethylethoxycarbonyl)-hydrazone in 200 ml of glacial acetic acid was hydrogenated in the presence of 2.0 g platinum (IV) oxide at room temperature and 3 bar of hydrogen pressure until the calculated volume of hydrogen had been taken up. The catalyst was filtered off, the filtrate was evaporated down *in vacuo* and the residue was dissolved in a little diethylether . The crystals precipitated after standing for 3 hours at room temperature were suction filtered, washed with a little diethylether and dried *in vacuo* at room temperature. 21.8 g (99.6% of theory) of colourless crystals of m.p. 135 - 137°C and R_f = 0.235 (eluant 3) were obtained.

ESI-MS: $(M+H)^+$ = 438

c) [1-(9H-fluoren-9-ylmethoxycarbonyl)-4-piperidinyl]-hydrazine-hydrochloride

21.8 g (0.0498 mol) of N-(1,1-dimethylethoxycarbonyl)-N'-[1-(9H-fluoren-9-ylmethoxycarbonyl)-4-piperidinyl]-hydrazine were dissolved in 100 ml of trifluoroacetic acid and stirred for 1 hour at room temperature. The excess trifluoroacetic acid was removed *in vacuo*, the residue was dissolved in 50 ml of water and made alkaline with 10% aqueous sodium carbonate solution. The solution was extracted thoroughly with dichloromethane, the combined extracts were dried over magnesium sulphate and evaporated down *in vacuo*. The residue thus obtained was taken up in ethyl acetate and converted into the hydrochloride by the addition of ethereal hydrogen chloride solution. After recrystallisation from anhydrous ethanol 6.2 g (33.3% of

theory) of colourless crystals of melting point 160-162°C were obtained.

$C_{20}H_{23}N_3O_2$ + HCl (373.88)

Calculated:	C 64.25	H 6.47	N 11.24	Cl 9.48
Found:	64.14	6.46	10.99	9.46

d) 2,4-dihydro-5-phenyl-2-[1-(9H-fluoren-9-ylmethoxycarbonyl)-4-piperidinyl]-3H-1,2,4-triazol-3-one

The solutions of 5.56 g (0.0165 mol) of [1-(9H-fluoren-9-ylmethoxycarbonyl)-4-piperidinyl]-hydrazine in 60 ml of tetrahydrofuran and 3.7 g (0.0177 mol) of N-(ethoxycarbonyl)-benzothionamide in 30 ml of tetrahydrofuran were combined and refluxed for 1 hour, whereupon hydrogen sulphide was released. The solvent was distilled off *in vacuo*, the oily residue remaining was boiled with a little acetonitrile. The mixture was allowed to cool, then additionally cooled from outside with ice water and the resulting precipitate was suction filtered. 4.0 g (52% of theory) of colourless crystals were obtained, melting point 142°C and R_f = 0.38 (eluant 4).
IR (KBr): 1685.7 cm^{-1} (C=O)

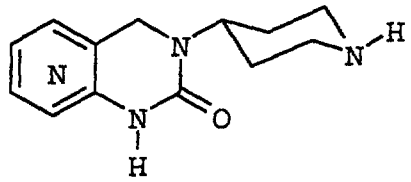
e) 2,4-dihydro-5-phenyl-2-(4-piperidinyl)-3H-1,2,4-triazol-3-one

A mixture of 9.0 g (0.0193 mol) of 2,4-dihydro-5-phenyl-2-[1-(9H-fluoren-9-ylmethoxycarbonyl)-4-piperidinyl]-3H-1,2,4-triazol-3-one, 50 ml of tetrahydrofuran and 70 ml of diethylamine was stirred at room temperature until the end of the reaction monitored by thin layer chromatography. The solvent was removed *in vacuo*, the residue remaining was mixed with 300 ml of water and subjected to ultrasound treatment for 30 minutes. The insoluble matter was separated off by suction filtering and the aqueous filtrate was evaporated down *in vacuo*. The residue thus obtained was boiled with a little methanol and after cooling it was suction filtered. After drying 0.58 g (12.3% of theory) of

colourless crystals of melting point 294°C (D) and R_f = 0.1 (eluant 1) were obtained.
IR (KBr): 1681.8 cm^{-1} (C=O)

Example A3

Preparation of compounds of general structure:



3,4-dihydro-3-(4-piperidinyl)-2(1H)-pyrido[2,3-d]-pyrimidinone

a) N-(2-Pyridinyl)-2,2-dimethylpropanamide
To a solution of 94.1 g (1.0 mol) of 2-aminopyridine and 173 ml (1.25 mol) of triethylamine in 400 ml of dichloromethane were added dropwise, whilst cooling with ice water, 132.5 g (1.099 mol) of pivaloyl chloride in 150 ml of dichloromethane. The mixture was stirred for 2 hours at room temperature and filtered to remove the triethylamine hydrochloride formed. The filtrate was washed with water and twice with 5% aqueous sodium hydrogen carbonate solution, then dried over sodium sulphate. After working up in the usual way 157.5 g (88.4% of theory) of colourless crystals of melting point 74-76°C were obtained.

The following was obtained in the same way:

N-(4-Pyridinyl)-2,2-dimethylpropanamide
Yield: 74% of theory
Mp. 137 - 140 °C (diisopropylether)
IR (KBr): 1687 cm^{-1} (C=O)

b) N-(3-formyl-2-pyridinyl)-2,2-dimethylpropanamide

Whilst maintaining a reaction temperature of -78°C, 781 ml (1.25 mol) of a 1.6-molar solution of n-butyllithium in n-hexane were added dropwise to a solution of 89.1 g (0.5 mol) of N-(2-pyridinyl)-2,2-dimethylpropanamide in 300 ml of anhydrous tetrahydrofuran. The mixture was allowed to heat slowly up to 0°C and stirred for 3 hours at this temperature. Then the mixture was again cooled to -78°C and whilst maintaining this temperature the solution of 109.6 g (1.5 mol) of dimethyformamide in 150 ml of anhydrous tetrahydrofuran was added dropwise thereto. The mixture was allowed to come up to 0°C and then stirred into 1 l of ice water. It was initially acidified with 12% aqueous hydrochloric acid, then made alkaline by the addition of solid potassium carbonate and extracted thoroughly with diethylether. The combined ether extracts were dried over sodium sulphate and evaporated down. The crystalline residue, after recrystallisation from diisopropylether, had an m.p. of 83°C. Yield: 94.0 g (91.2% of theory).

The following were obtained in the same way:

(1) N-(4-formyl-3-pyridinyl)-2,2-dimethylpropanamide

Yield: 52% of theory

Rf: 0.5 (dichloromethane/methanol/conc. ammonia 90/10/0.1 v/v/v)

IR (KBr) of the hydrochloride: 1695 cm^{-1} (C=O)

MS: M^+ = 206

(2) N-(3-formyl-4-pyridinyl)-2,2-dimethylpropanamide

The reddish oil obtained in a quantitative yield was further processed without more purification

c) N-[3-[[[1-(phenylmethyl)-4-piperidinyl]amino]methyl]-2-pyridinyl]-2,2-dimethylpropanamide

A solution of 8.2 g (0.0398 mol) of N-(3-formyl-2-pyridinyl)-2,2-dimethylpropanamide and 7.6 g (0.04 mol) of 4-amino-1-(phenylmethyl)piperidine in 80 ml of methanol was combined in batches with a total of 1.7 g (0.045 mol) of sodium borohydride and refluxed for a total of 24 hours. The solvent was removed *in vacuo*, the residue was distributed between water and ethyl acetate. The organic phase was dried over sodium sulphate and freed from solvent. The residue was triturated with diisopropylether and suction filtered. 6.0 g (39.6% of theory) of colourless crystals of melting point 138°C were obtained.

The following were obtained in the same way:

(1) N-[4-[[[1-(phenylmethyl)-4-piperidinyl]amino]methyl]-3-pyridinyl]-2,2-dimethylpropanamide
Yield: 94% of theory
Rf: 0.4 (dichloromethane/methanol/conc. ammonia 90/10/0.1 v/v/v)
The yellowish oil was used in the following stage without further purification

(2) N-[3-[[[1-(phenylmethyl)-4-piperidinyl]amino]methyl]-4-pyridinyl]-2,2-dimethylpropanamide
Yield: 11.6% of theory
IR(KBr): 1689 (C=O) cm^{-1}

d) 2-amino-3-[[[1-(phenylmethyl)-4-piperidinyl]-amino]methyl]-pyridine

A mixture of 6.0 g (0.0158 mol) of N-[3-[[[1-(phenylmethyl)-4-piperidinyl]amino]methyl]-2-pyridinyl]-2,2-dimethylpropanamide and 100 ml of conc. hydrochloric acid was refluxed for 3 hours. The mixture was evaporated down *in vacuo*, the residue remaining was dissolved in a little water and made alkaline by the addition of solid potassium carbonate. It was extracted thoroughly with ethyl acetate, the combined extracts were dried over sodium

sulphate and evaporated down *in vacuo*. The residue was thoroughly triturated with diisopropylether and yielded 4.2 g (89.7% of theory) of colourless crystals of melting point 114°C.

The following were obtained in the same way:

(1) 3-amino-4-[[[1-(phenylmethyl)-4-piperidinyl]amino]methyl]-pyridine
Yield: 96% of theory
R_f: 0.42 (dichloromethane/methanol/conc. ammonia 90/10/0.1 v/v/v)
The yellowish oil was used in the following stage without further purification

(2) 4-amino-3-[[[1-(phenylmethyl)-4-piperidinyl]amino]methyl]-pyridine
Yield: quantitative
The yellowish oil was used in the following stage without further purification

e) 3,4-dihydro-3-[1-(phenylmethyl)-4-piperidinyl]-2(1H)-pyrido[2,3-d]-pyrimidinone

A mixture of 4.2 g (0.0142 mol) of 2-amino-3-[[[1-(phenylmethyl)-4-piperidinyl]amino]methyl]-pyridine, 2.4 g (0.0148 mol) of N, N'-carbonyldiimidazole and 50 ml of dimethylformamide was heated to 100°C for 30 minutes. The still warm mixture was stirred into 300 ml of ice water, the precipitate formed was suction filtered and recrystallised from acetonitrile. After drying *in vacuo* 4.5 g (98.3% of theory) of colourless crystals of melting point 187°C were obtained.

The following were obtained in the same way:

(1) 3,4-dihydro-3-[1-(phenylmethyl)-4-piperidinyl]-2(1H)-pyrido[3,4-d]-pyrimidinone
Colourless crystals
Yield: 33% of theory
IR (KBr): 1676 cm^{-1} (C=O)
MS: M^+ = 322

(2) 3,4-dihydro-3-[1-(phenylmethyl)-4-piperidinyl]-2(1H)-pyrido[4,3-d]-pyrimidinone
Mp. 155 °C (D)
Yield: 99% of theory
IR (KBr): 1680 cm^{-1} (C=O)

f) 3,4-dihydro-3-(4-piperidinyl]-2(1H)-pyrido[2,3-d]-pyrimidinone

A solution of 4.7 g (0.0146 mol) of 3,4-dihydro-3-[1-(phenylmethyl)-4-piperidinyl]-2(1H)-pyrido[2,3-d]-pyrimidinone in 50 ml of methanol was hydrogenated at a temperature of 50°C and in the presence of 2.0 g of 20% palladium/charcoal until the uptake of hydrogen ceased. After removal of the catalyst and solvent 3.3 g (97.3% of theory) of a colourless oil of R_f = 0.35 (FM1) were obtained.
IR (KBr): 1660.6 cm^{-1} (C=O)
The following were obtained in the same way:

(1) 3,4-dihydro-3-(4-piperidinyl]-2(1H)-pyrido[3,4-d]-pyrimidinone
Colourless crystals
Yield: 95% of theory
IR (KBr): 1662 cm^{-1} (C=O)
MS: M^+ = 232

(2) 3,4-dihydro-3-(4-piperidinyl]-2(1H)-pyrido[4,3-d]-pyrimidinone
Yellowish resin
Yield: 97% of theory
IR (KBr): 1672 cm^{-1} (C=O)
R_f: 0.12 (FM1)

Example A4

Methyl 3,4-dihydro-3-(4-piperidinyl)-2(1H)-oxoquinazoline-7-carboxylate

a) (E)-1-(dimethylamino)-2-[4-(methoxycarbonyl)-2-nitrophenyl]-ethene

A mixture of 98.3 g (0.504 mol) of methyl 4-methyl-3-nitrobenzoate, 78.0 g (0.655 mol) of N,N-dimethylformamide dimethylacetal and 1 l of dimethylformamide was heated to 140°C for 3 hours. The solvent was distilled off *in vacuo*, the residue was triturated thoroughly with 1 l methanol. After drying *in vacuo* 119.5 g (94.7% of theory) of a red amorphous substance was obtained, which was further processed without any more purification.

b) 4-(Methoxycarbonyl)-2-nitrobenzaldehyde

To a mixture of 119.5 g (0.478 mol) of (E)-1-(dimethylamino)-2-[4-(methoxycarbonyl)-2-nitrophenyl]-ethene and 1.3 l of water/tetrahydrofuran mixture (1/1 v/v) were added, in batches, 308.0 g (1.44 mol) of sodium metaperiodate, whilst the reaction temperature was regulated at under +30°C by external cooling with ice water. The mixture was stirred for a further 2.5 hours at room temperature and then filtered. The precipitate was thoroughly washed with ethyl acetate. The organic phase was separated off, the aqueous phase was thoroughly extracted with ethyl acetate. The combined ethyl acetate phases were dried over sodium sulphate and evaporated down *in vacuo*. The oil which crystallised after one day was further processed without any more purification. Yield: 87 g (87% of theory).

c) Methyl 4-[[[1-(phenylmethyl)-4-piperidinyl]amino]methyl]-3-nitrobenzoate

To a solution of 41.0 g (0.215 mol) of 4-amino-1-(phenylmethyl)-piperidine and 45.0 g (0.215 mol) of 4-

(methoxycarbonyl)-2-nitrobenzaldehyde in 1 l methanol were added in batches, at room temperature, 8.3 g (0.22 mol) of sodium borohydride and the mixture was then stirred for 30 minutes at the same temperature. The mixture was stirred into 1 l of ice water and thoroughly extracted with tert. butyl-methylether. The combined extracts were dried over sodium sulphate and evaporated down *in vacuo*, the residue was dissolved in as little methanol as possible and converted into the hydrochloride by treatment with methanolic hydrogen chloride solution. The crystalline salt was suction filtered, washed with methanol and diethylether, then taken up in water and made alkaline with saturated aqueous potassium carbonate solution. The mixture obtained was extracted thoroughly with ethyl acetate, the combined ethyl acetate extracts were dried over sodium sulphate and evaporated down. 58.2 g (70.6% of theory) of a brownish-yellow oil were obtained, which was further processed without any more purification.

d) Methyl 3-amino-4-[[[1-(phenylmethyl)-4-piperidinyl]amino]methyl]-benzoate

A solution of 58.0 g (0.151 mol) of methyl 4-[[[1-(phenylmethyl)-4-piperidinyl]amino]methyl]-3-nitrobenzoate in 800 ml of methanol was hydrogenated in the presence of 10 g of 5% rhodium/charcoal for 7 hours at room temperature. The catalyst was filtered off, the filtrate was evaporated down *in vacuo*. 50.0 g (93.7% of theory) of colourless crystals were obtained, which were further processed without any more purification.

e) Methyl 3,4-dihydro-3-[1-(phenylmethyl)-4-piperidinyl]-2(1H)-oxoquinazolin-7-carboxylate

Prepared analogously to Example A3e) from methyl 3-amino-4-[[[1-(phenylmethyl)-4-piperidinyl]amino]methyl] -benzoate and N,N'-carbonyl-diimidazole in a yield of 66.3% of theory. Slightly yellowish crystals.
IR (KBr): 1714.6; 1664.5 cm^{-1} (C=O)

f) Methyl 3,4-dihydro-3-(4-piperidinyl)-2(1H)-oxoquinazolin-7-carboxylate

A solution of 35.5 g (0.0936 mol) of methyl 3,4-dihydro-3-[1-(phenylmethyl)-4-piperidinyl]-2(1H)-oxoquinazolin-7-carboxylate in 400 ml of methanol was hydrogenated in the presence of 5 g of 10% palladium/charcoal for 5 hours at 50°C. The catalyst was filtered off, the filtrate was evaporated down *in vacuo*. The residue was triturated with 150 ml of ethyl acetate and then suction filtered. After drying *in vacuo* 20.4 g (75.3% of theory) of colourless crystals were obtained, which were further processed without any more purification.

IR (KBr): 1718.5; 1672.2 cm^{-1} (C=O)

The following were prepared analogously:

(1) 3,4-dihydro-3-(4-piperidinyl)-2(1H)-quinazolinone
R_f: 0.3 (FM1)
IR (KBr): 1662.5 cm^{-1} (C=O)

(2) 3,4-dihydro-8-methoxy-3-(4-piperidinyl)-2(1H)-quinazolinone
R_f: 0.35 (FM1)

(3) 3,4-dihydro-6,7-dimethoxy-3-(4-piperidinyl)-2(1H)-quinazolinone
R_f: 0.40 (FM1)

Example A5

3,4-dihydro-3-(4-piperidinyl)-1H-thieno[3,4-d]pyrimidin-2-one-trifluoroacetate

a) Methyl 4-(ethoxycarbonylamino)-thiophene-3-carboxylate

A mixture of 50.0 g (0.258 mol) of methyl 4-aminothiophen-3-carboxylate-hydrochloride, 700 ml of toluene, 26 g (0.257 mol) of triethylamine and 27 ml (0.283 mol) of ethyl chlorocarbonate was refluxed for 5 hours. The insoluble matter was filtered off, the filtrate was evaporated down *in vacuo* and the residue was crystallised from petroleum ether. 59.0 g (99.8% of theory) of colourless crystals of melting point 52°C were obtained.

In the same way, crystalline methyl 3-(ethoxycarbonylamino)-thiophen-2-carboxylate was obtained from methyl 3-aminothiophene-2-carboxylate and ethyl chlorocarbonate in a yield of 98.7% of theory.
IR (KBr): 1739.7; 1622 cm^{-1} (C=O, C=C)

b) 4-(ethoxycarbonylamino)-thiophene-3-carboxaldehyde

Into an ice-cold suspension of 12.9 g (0.34 mol) of lithium aluminium hydride in 800 ml of tert. butyl-methylether was added dropwise, at a reaction temperature of about 0°C, a solution of 59.1 g (0.258 mol) of methyl 4-(ethoxycarbonylamino)-thiophene-3-carboxylate in 200 ml of tert. butyl-methylether, and the mixture was then stirred for a further 2 hours at 10°C. Then 13 ml of water, 13 ml of 2N aqueous sodium hydroxide solution and 39 ml of water were added dropwise one after another and the mixture was stirred for 1 hour at room temperature. It was filtered, and 500 g of activated manganese (IV) oxide were added in batches to the filtrate with stirring. After the completion of the reaction, which could be monitored by thin layer chromatography, the mixture was filtered again and the filtrate was then evaporated down *in vacuo*. The crystalline residue which solidified was further processed without any more purification. yield: 28.2 g (54.9% of theory).

In the same way 3-(ethoxycarbonylamino)-thiophene-2-carboxaldehyde was obtained from methyl 3-(ethoxycarbonylamino)-thiophene-2-carboxylate in a yield of 71.9% of theory.

c) 4-[[[1-(1,1-dimethylethoxycarbonyl)-4-piperidinyl]amino]methyl]-3-(ethoxycarbonylamino)-thiophene

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A mixture of 28.2 g (0.142 mol) of 4-(ethoxycarbonyl-amino)-thiophene-3-carboxaldehyde, 28.2 g (0.141 mol) of 4-amino-1-(1,1-dimethyl-ethoxycarbonyl)piperidine and 300 ml of toluene was refluxed using a water separator until water formation had ceased. The solvent was removed *in vacuo*, the residue was dissolved in 300 ml of methanol and at room temperature combined batchwise with 5.5 g (0.145 mol) of sodium borohydride. The mixture was stirred for a further hour at room temperature, then evaporated down *in vacuo* and the residue was distributed between water and tert. butyl-

methylether. The organic phase was dried over sodium sulphate and freed from solvent *in vacuo*. The oily residue was further processed without purification. Yield: 54.0 g (99.9% of theory).

In the same way 2-[[[1-(1,1-dimethylethoxycarbonyl)-4-piperidinyl]amino]methyl]-3-(ethoxycarbonylamino)-thiophene was obtained from 3-(ethoxycarbonylamino)-thiophene-2-carboxaldehyde, 4-amino-1-(1,1-dimethylethoxycarbonyl)piperidine and sodium borohydride in a yield of 100% of theory.
IR (KBr): 1728.1; 1693.4 cm^{-1} (C=O)

d) 3,4-dihydro-3-[1-(1,1-dimethylethoxycarbonyl)-4-piperidinyl]-1H-thieno[3,4-d]pyrimidin-2-one

A solution of 54.0 g (0.141 mol) of 4-[[[1-(1,1-dimethylethoxycarbonyl)-4-piperidinyl]amino]methyl]-3-(ethoxycarbonylamino)-thiophene in 300 ml of dimethylformamide was refluxed for 4 hours. After the end of the reaction, which could be monitored by thin layer chromatography, the still warm mixture was stirred into 1 l of ice water. The crystalline precipitate was suction filtered and dried at 30°C in a circulating air drier. Yield: 47.5 g (99.8% of theory).

In the same way 3,4-dihydro-3-[1-(1,1-dimethyl-ethoxycarbonyl)-4-piperidinyl]-1H-thieno[3,2-d]pyrimidin-2-one was obtained from 2-[[[1-(1,1-dimethylethoxycarbonyl)-4-piperidinyl]amino]methyl]-3-(ethoxycarbonyl-amino)-thiophene in a yield of 71% of theory. Colourless crystals of melting point 200°C (acetonitrile).
IR (KBr): 1683.8; 1654.8 cm^{-1} (C=O)

e) 3,4-dihydro-3-(4-piperidinyl)-1H-thieno[3,4-d]pyrimidin-2-one-trifluoroacetate

A mixture of 10.0 g (0.0296 mol) of 3,4-dihydro-3-[1-(1,1-dimethylethoxycarbonyl)-4-piperidinyl]-1H-

thieno[3,4-d]pyrimidin-2-one and 50 ml of trifluoroacetic acid was stirred at room temperature for 30 minutes. The residue remaining after removal of the excess trifluoroacetic acid was triturated with diethylether and suction filtered. 5.8 g (55.8% of theory) of colourless crystals were obtained, which were used without further purification.

IR (KBr): 1664.5 cm^{-1} (C=O)

In the same way, crystalline 3,4-dihydro-3-(4-piperidinyl)-1H-thieno[3,2-d]pyrimidin-2-one-trifluoracetate was obtained from 3,4-dihydro-3-[1-(1,1-dimethylethoxy-carbonyl)-4-piperidinyl]-1H-thieno-[3,2-d]pyrimidin-2-one and trifluoroacetic acid in a yield of 100% of theory.

IR (KBr): 1685.7; 1656.8 cm^{-1} (C=O)

Example A6

3,4-dihydro-3-(4-piperidinyl)-2(1H)quinolone-hydrochloride

A mixture of 1.1 g (4.949 mmol) of 3-(4-pyridinyl)-2(1H)-quinolone (D. R. Bragg and D. G. Wibberley, J. Chem. Soc. 1961, 5074 - 5077), 100 ml of ethanol, 5 ml (5 mmol) of 1N hydrochloric acid and 0.2 g platinum (IV) oxide was hydrogenated for 4 hours at room temperature. The catalyst was filtered off, the filtrate evaporated down *in vacuo* and the residue was triturated with isopropanol. The precipitated crystals were suction filtered, washed with isopropanol and diethylether and dried *in vacuo*. Yield: 0.64 g (56.2% of theory).

IR (KBr): 1666.4 cm^{-1} (C=O)

MS: M^+ = 230

m/e = 146, 84

Example A7

3-(4-Piperidinyl)-2(1H)-quinolone

A mixture of 8.6 g (0.0387 mol) of 3-(4-pyridinyl)-2(1H)-quinolone, 1.2 l of ethanol, 39 ml (0.039 mol) of 1N hydrochloric acid and 8.0 g of 10% palladium/charcoal was hydrogenated at a temperature of 40°C until about 0.08 mol of hydrogen had been taken up. The mixture was freed from catalyst, the filtrate was evaporated down *in vacuo*, the residue was taken up in 200 ml of water and made ammoniacal. Common salt was added up to saturation point and the mixture was continuously extracted with dichloromethane using a perforator. The dichloromethane phase was evaporated down, the residue remaining was separated from by-products by chromatography over silica gel using FM1 as eluant. The appropriate fractions were combined, freed from solvent, dissolved in a little isopropanol and converted with ethanolic hydrogen chloride solution into the hydrochloride. Colourless crystals.
Yield: 2.68 g (26.2% of theory).
MS: $M^+ = 228$
IR (KBr): 1651 cm^{-1} (C=O)

Example A8

5-chloro-3,4-dihydro-3-(4-piperidinyl)-2(1H)-quinazolinone

An ice-cold solution of 6.3 g (0.0177 mol) of 5-chloro-3,4-dihydro-3-[1-(phenylmethyl)-4-piperidinyl]-2(1H)-quinazolinone (prepared analogously to Example A4e)) in 50 ml of dichloromethane was mixed dropwise with 3.34 g (0.0234 mol) of α-chloroethyl chlorocarbonate whilst maintaining a reaction temperature of 0°C, after which the mixture was allowed to come back slowly to room temperature. The reaction mixture was evaporated down *in vacuo*, the residue was taken up in 50 ml of methanol and refluxed for 4 hours. After cooling, the colourless

precipitate formed was suction filtered. Yield: 2.0 g (42.5% of theory).
IR (KBr): 1666.4 cm^{-1} (C=O)

Example A9

6-bromo-3,4-dihydro-3-(4-piperidinyl)-2(1H)-quinazolinone-hydrobromide

To a solution of 6.16 g (0.075 mol) of sodium acetate and 11.565 g (0.05 mol) of 3,4-dihydro-3-(4-piperidinyl)-2(1H)-quinazolinone in a mixture of 150 ml of glacial acetic acid and 35 ml of water a solution of 8.8 g (0.055 mol) of anhydrous bromine in 20 ml of glacial acetic acid was added dropwise, with stirring and whilst maintaining a reaction temperature of 13 to 15°C. The mixture was filtered and the filtrate was evaporated down *in vacuo*. To remove any inorganic components the residue was taken up five times in 50 ml of dichloromethane, filtered and evaporated down, then triturated with a little acetonitrile, whereupon crystallisation occurred. The crystals were suction filtered, washed with acetonitrile/diethylether (1/1 v/v) and after drying *in vacuo* 5.5 g of colourless crystals of melting point 288°C (decomposition) were obtained. By working up the mother liquors a further 4.5 g of material of the same quality was obtained. Total yield: 10.0 g (51% of theory).

$C_{13}H_{17}Br_2N_3O$ (391.10)
Calculated: C 39.92 H 4.38 Br 40.86 N 10.74
Found: 39.72 4.36 41.56 10.24
IR (KBr): 1670.3 cm-1 (C=O)

Example A10

3-(4-piperidinyl)-2,4(1H,3H)-quinazolindione

a) 2-amino-N-[1-(phenylmethyl)-4-piperidinyl]-benzamide

To an ice-cold solution of 28 ml (134 mmol) of 4-amino-1-(phenylmethyl)piperidine in 200 ml of tetrahydrofuran were added, batchwise, 21.9 g (134 mmol) of isatoic acid anhydride. The resulting suspension was stirred for 2½ hours at room temperature and 2½ hours at reflux temperature, then freed from solvent. The residue was dissolved in 100 ml of hot ethanol, the resulting solution was filtered whilst hot after the addition of 5 g of activated charcoal. The crystal mass precipitated after cooling was suction filtered, washed with diisopropylether and dried *in vacuo* at 50°C. 28.3 g of colourless crystals were obtained. A further 5.1 g of a product of the same quality were isolated from the combined mother liquors. Total yield: 33.4 g (80.6% of theory).

IR (KBr): 1620 cm^{-1} (C=O)

MS: M^+ = 309

b) 3-[1-(phenylmethyl)-4-piperidinyl]-2,4(1H,3H)-quinazolindione

Prepared analogously to Example A3e) from 2-amino-N-[1-(phenylmethyl)-4-piperidinyl]-benzamide and N,N'-carbonyldiimidazole in a yield of 97.8% of theory. Colourless crystals of melting point 223°C.

IR (KBr): 1720; 1647 cm^{-1} (C=O)

MS: M^+ = 335

c) 3-(4-piperidinyl)-2,4(1H,3H)-quinazolindione

Prepared analogously to Example A3f) from 3-[1-(phenylmethyl)-4-piperidinyl]-2,4(1H,3H)-quinazolindione by hydrogenolysis in the presence of palladium/charcoal in a yield of 70% of theory.

R_f: 0.075 (FM1)

IR (KBr): 1703; 1657 cm^{-1} (C=O)

Example A11

3,4-dihydro-3-[1-(4-piperidinyl)-4-piperidinyl]-2(1H)-quinazolinone

a) 3,4-dihydro-3-[1-[1-(phenylmethyl)-4-piperidinyl]-4-piperidinyl]-2(1H)-quinazolinone

A mixture of 5.75 g (0.0249 mol) of 3,4-dihydro-3-(4-piperidinyl)-2(1H)-quinazolinone, 4.75 g (0.0251 mol) of 1-(phenylmethyl)-4-piperidinone and 100 ml of ethanol was treated for 30 minutes in an ultrasound bath, then mixed with 9.5 ml (0.031 mol) of titanium (IV) isopropoxide, whereby after 10 minutes a crystal mass was formed. Then heating was continued using the ultrasound bath for a further 2½ hours to a maximum of 35°C, the mixture was allowed to cool to room temperature and 1.05 g (0.0167 mol) of sodium cyanoborohydride were then added in batches, whilst maintaining the pH at 5 - 6 using dilute methanolic hydrogen chloride solution, and it was then kept for 24 hours at room temperature. After this time another 1.05 g (0.0167 mol) of sodium cyanoborohydride were added and the same procedure was used as above. After a total of 48 hours reaction time the mixture was decomposed by the addition of water and worked up in the usual way. The crude product obtained was purified by column chromatography over silica gel using FM4 as eluant. 7.05 g (70% of theory)of a colourless crystalline substance were obtained.

In the same way exo-4-(8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-1-(phenylmethyl)piperazine was obtained from tropinone and 1-(phenylmethyl)piperazine in a yield of 48.9% of theory. Colourless, amorphous substance, R_f = 0.36 (FM1).

b) 3,4-dihydro-3-[1-(4-piperidinyl)-4-piperidinyl]-2(1H)-quinazolinone

Prepared analogously to Example A3f) from 3,4-dihydro-3-[1-[1-(phenylmethyl)-4-piperidinyl]-4-piperidinyl]-2(1H)-quinazolinone by hydrogenolysis, but using Pearlman's catalyst, in a yield of 92% of theory. Colourless crystals, R_f = 0.48 (Macherey-Nagel, POLYGRAM® SIL G/UV_{254} ready-made films for TLC; eluant: dichloromethane/methanol/cyclohexane/conc. ammonia 68/20/10/5 v/v/v/v).

IR (KBr): 1660.6 cm^{-1} (C=O)

MS: M^+ = 314

Example A12

3-(4-piperidinyl)-3,4,4a,5,6,7,8,8a-octahydro-2(1H)-quinazolinone-acetate

A solution of 5.0 g (17.17 mmol) of 3,4-dihydro-3-(4-piperidinyl)-2(1H)-quinazolinone-acetate in 70 ml of methanol was hydrogenated at room temperature and in the presence of 1.0 g rhodium (III) oxide-platinum (IV) oxide hydrate catalyst (46.45% rhodium, 20.15% platinum) until the hydrogen uptake had ceased. The catalyst and solvent were removed, the residue was triturated with 10 ml of diisopropylether and a few drops of isopropanol and the resulting crystals were suction filtered. After drying *in vacuo* 4.4 g (86.2% of theory) of colourless crystals were obtained, R_f = 0.3 (eluant: dichloromethane/methanol/conc. ammonia 7.5/2.5/0.5 v/v/v).

IR (KBr): 1641 cm^{-1} (C=O)

MS: M^+ = 237

Example A13

1,1-dioxido-2-(4-piperidinyl)-3(4H)-1,2,4-benzothiadiazinone

a) 2-nitro-N-[1-(phenylmethyl)-4-piperidinyl]-benzenesulphonic acid amide

Whilst carrying out external cooling with ice water a solution of 44.3 g (0.2 mol) of 2-nitrobenzenesulphonyl chloride in 250 ml of chloroform was added dropwise to a solution of 38.0 g (0.2 mol) of 4-amino-1-(phenylmethyl)piperidine and 22.0 g (0.22 mol) of triethylamine in 250 ml of chloroform. After the cooling was stopped the mixture was stirred for a further 30 minutes at room temperature, the reaction mixture was then extracted twice with 1 l water. The aqueous extracts were extracted once more with 100 ml of dichloromethane, the combined organic phases were then dried over sodium sulphate and evaporated down *in vacuo*. The highly viscous light-brown substance obtained in a yield of 75.0 g (99.9% of theory) was further processed without any more purification.

IR (KBr): 3363.7 (NH); 1541.0 (NO_2); 1365.5 (NO_2 or SO_2); 1346.2 (NO_2 or SO_2); 1168.8 (SO_2) cm^{-1}

b) 2-amino-N-[1-(phenylmethyl)-4-piperidinyl]-benzenesulphonic acid amide

To a solution of 75.0 g (0.2 mol) of 2-nitro-N-[1-(phenylmethyl)-4-piperidinyl]-benzenesulphonic acid amide in 2.0 l ethanol was added dropwise, at room temperature, a solution of 174.0 g (0.828 mol) of sodium dithionite-dihydrate in 700 ml of water. After the heat of the exothermic reaction had died away the mixture was refluxed for 4.5 hours, then the ethanol was distilled off and the aqueous phase remaining was extracted thoroughly with dichloromethane.

The combined dichloromethane extracts were dried over sodium sulphate and evaporated down, the residue remaining was purified by column chromatography over silica gel using dichloromethane/methanol/conc. ammonia 80/20/0.25 (v/v/v) as eluant. 6.5 g (8.6% of theory) of a highly viscous oil were obtained.
IR(KBr): 1319.2, 1153.4 cm^{-1} (SO_2)

c) 1,1-dioxido-2-[1-(phenylmethyl)-4-piperidinyl]-3(4H)-1,2,4-benzothiadiazinone
Prepared analogously to Example A3e) from 2-amino-N-[1-(phenylmethyl)-4-piperidinyl]-benzenesulphonic acid amide and N, N'-carbonyldiimidazole in a yield of 78% of theory. Colourless crystals of melting point 169-171°C.
IR(KBr): 1693.4 (C=O); 1359.7, 1340.4, 1188.1 (SO_2) cm^{-1}

d) 1,1-dioxido-2-(4-piperidinyl)-3(4H)-1,2,4-benzothiadiazinone
Prepared analogously to Example A3f), but using Pearlman's catalyst instead of palladium/charcoal, in a yield of 90% of theory. Colourless, amorphous substance.
IR(KBr): 1705.0 (C=O) cm^{-1}

Example A14

3,4-dihydro-2,2-dioxido-3-(4-piperidinyl)-2,1,3-benzothiadiazine

a) 3,4-dihydro-2,2-dioxido-3-[1-(phenylmethyl)-4-piperidinyl]-2,1,3-benzothiadiazine
A solution of 11.0 g (0.0372 mol) of 2-amino-N-[1-(phenylmethyl)-4-piperidinyl]-benzenemethanamine in 200 ml of pyridine was added dropwise within 1.5 hours and at reflux temperature to a solution of 3.4 g (0.0354 mol) of sulphamide in 200 ml of pyridine and the mixture was then refluxed for 6 hours. The mixture was freed from solvent, the residue was purified by column chromatography using

ethyl acetate/methanol 9/1 (v/v) as eluant. 5.5 g (43.5% of theory) of a colourless amorphous substance were obtained.
IR(KBr): 1344.3, 1166.9 cm^{-1} (SO_2)

b) 3,4-dihydro-2,2-dioxido-3-(4-piperidinyl)-2,1,3-benzothiadiazine

Prepared analogously to Example A3f) from 3,4-dihydro-2,2-dioxido-3-[1-(phenylmethyl)-4-piperidinyl]-2,1,3-benzothiadiazine by catalytic hydrogenation in the presence of palladium/charcoal in a quantitative yield. Colourless, amorphous substance.
IR(KBr): 1263.3, 1105.1 cm^{-1} (SO_2)

Example A15

D,L-4-phenyl-1-(4-piperidinyl)-imidazolidine-2,5-dione

a) N^2-(1,1-dimethylethoxycarbonyl)-N-[1-(phenylmethyl)-4-piperidinyl]-D,L-phenylglycinamide

A mixture of 10.0 g (0.0398 mol) of N^2-(1,1-dimethylethoxycarbonyl)-D,L-phenylglycine, 7.57 g (0.0398 mol) of 4-amino-1-(phenylmethyl)piperidine, 10 ml of triethylamine, 12.8 g (0.0399 mol) of TBTU and 5.4 g (0.0353 mol) of N-hydroxybenzotriazole-hydrate in 200 ml of THF-DMF mixture (1/1 v/v) was stirred overnight at room temperature. The residue remaining after removal of the solvent was taken up in ethyl acetate, washed with saturated sodium hydrogen carbonate solution, dried over sodium sulphate and evaporated down *in vacuo*. 14.8 g (87.8% of theory) of a colourless, amorphous substance were obtained.
IR(KBr): 1701.1, 1676.0, 1652.9 cm^{-1} (C=O)

Analogously N^2-(1,1-dimethylethoxycarbonyl)-N-[1-(phenylmethyl)-4-piperidinyl]-D,L-phenylalaninamide was obtained from N^2-(1,1-dimethylethoxycarbonyl)-D,L-phenylalanine and 4-amino-1-(phenylmethyl)piperidine in a yield of 85% of theory. Colourless, amorphous substance, R_f

= 0.83 (eluant: dichloromethane/cyclohexane/methanol/conc. ammonia = 70/15/15/2 v/v/v/v).
IR(KBr): 1683.8, 1651.0 cm^{-1} (C=O)

b) N-[1-(phenylmethyl)-4-piperidinyl]-D,L-phenylglycinamide-bis-trifluoroacetate

Prepared analogously to Example A5e) from N^2-(1,1-dimethylethoxycarbonyl)-N-[1-(phenylmethyl)-4-piperidinyl]-D,L-phenylglycinamide and trifluoroacetic acid in a quantitative yield. Colourless, amorphous substance , Rf = 0.56 (FM1).

Analogously N-[1-(phenylmethyl)-4-piperidinyl]-D,L-phenylalaninamide-bis-trifluoracetate was obtained from N^2-(1,1-dimethylethoxycarbonyl)-N-[1-(phenylmethyl)-4-piperidinyl]-D,L-phenylalaninamide in a yield of 92% of theory.
IR(KBr): 1670.3 cm^{-1} (C=O)

c) D,L-4-phenyl-1-[1-(phenylmethyl)-4-piperidinyl]-imidazolidine-2,5-dione

Prepared analogously to Example A3e) from N-[1-(phenylmethyl)-4-piperidinyl]-D,L-phenylglycinamide and N,N'-carbonyldiimidazole in a yield of 57.3% of theory.
Colourless crystals, Rf = 0.68.
IR(KBr): 1774.4, 1712.7 cm^{-1} (C=O)

Analogously D,L-4-(phenylmethyl)-1-[1-(phenylmethyl)-4-piperidinyl]-imidazolidine-2,5-dione was obtained from N-[1-(phenylmethyl)-4-piperidinyl]-D,L-phenylalaninamide in a yield of 93% of theory. Colourless, fine crystals, Rf = 0.6 (eluant: dichloromethane/methanol/cyclohexane/conc. ammonia = 7/1.5/1.5/0.2 v/v/v/v).
IR(KBr): 1764.8, 1708.8 cm^{-1} (C=O)
MS: M^+ = 363

d) D,L-4-phenyl-1-(4-piperidinyl)-imidazolidine-2,5-dione

Prepared analogously to Example A3f) from D,L-4-phenyl-1-[1-(phenylmethyl)-4-piperidinyl]-imidazolidine-2,5-dione by hydrogenolysis in the presence of palladium/charcoal in a yield of 84.3% of theory. Colourless, amorphous substance, Rf = 0.5.
IR(KBr): 1766.7, 1706.9 cm^{-1} (C=O)

Analogously D,L-4-(phenylmethyl)-1-(4-piperidinyl)-imidazolidine-2,5-dione was obtained from D,L-4-(phenylmethyl)-1-[1-(phenylmethyl)-4-piperidinyl]-imidazolidine-2,5-dione. Colourless crystals, Rf = 0.24 (eluant: dichloromethane/methanol/cyclohexane/conc. ammonia = 7/1.5/1.5/0.2 v/v/v/v).
IR(KBr): 1766.7, 1705.0 cm^{-1} (C=O)

Example A16

1,3-dihydro-3-(4-piperidinyl)-2(2H)-imidazo[4,5-c]quinolone

a) 1-[2-(acetylamino)phenyl]-2-bromoethanone

45.0 g (0.282 mol) of dry bromine were added dropwise to a boiling solution of 50.0 g (0.282 mol) of 1-[2-(acetylamino)phenyl]ethanone in 400 ml of chloroform at room temperature. The solvent was distilled off, the residue was distributed between dichloromethane and saturated ice-cold sodium hydrogen carbonate solution. The organic phase was dried over sodium sulphate, evaporated down *in vacuo*, the residue was triturated with diethylether and suction filtered. After drying *in vacuo* 35.4 g (49% of theory) of colourless crystals were obtained, Rf = 0.48 (eluant: petroleum ether/ethyl acetate 2/1 v/v).
IR(KBr): 1685.69, 1664.47 cm^{-1} (C=O)
MS: M^+ = 255/257 (Br)

b) 4-[2-(acetylamino)phenyl]-1,3-dihydro-1-[1-(phenylmethyl)-4-piperidinyl]-2H-benzimidazol-2-one

To a solution of 26.3 g (0.138 mol) of 4-amino-1-(phenylmethyl)piperidine and 17.8 g (0.138 mol) of DIEA in 300 ml of dichloromethane was added dropwise a solution of 35.4 g (0.138 mol) of 1-[2-(acetylamino)phenyl]-2-bromoethanone in 150 ml of dichloromethane and the mixture was kept for a further 2 hours at room temperature. With external cooling with ice 13.5 g (0.20 mol) of sodium cyanate and 12 ml of glacial acetic acid were then added and the mixture was stirred overnight in a thawing ice bath. It was washed with water and saturated sodium hydrogen carbonate solution, dried over sodium sulphate and freed from solvent. The residue was triturated with 50 ml of ethyl acetate-methanol mixture (9/1 v/v), the resulting crystals were suction filtered, washed with ethyl acetate and dried *in vacuo*. 37.0 g (68.7% of theory) of colourless crystals were obtained, Rf = 0.41 (eluant: dichloromethane/methanol 9/1 v/v).
IR(KBr): 1678 cm^{-1} (C=O)
MS: M^+ = 390 (Br)

c) 4-(2-aminophenyl)-1,3-dihydro-1-[1-(phenylmethyl)-4-piperidinyl]-2H-imidazol-2-one

A mixture of 3.0 g (7.68 mmol) of 4-[2-(acetylamino)phenyl]-1,3-dihydro-1-[1-(phenylmethyl)-4-piperidinyl]-2H-imidazol-2-one, 50 ml of 5 N sodium hydroxide solution and 25 ml of ethanol was refluxed for 3 hours. After cooling the organic phase was separated off, dried over sodium sulphate and evaporated down *in vacuo*. A colourless amorphous substance was obtained in a quantitative yield, Rf = 0.53 (eluant: dichloromethane/methanol 9/1 v/v).

d) 1,3-dihydro-3-[1-(phenylmethyl)-4-piperidinyl]-2(2H)-imidazo[4,5-c]quinolone

A solution of 2.67 g (7.66 mmol) of 4-(2-aminophenyl)-1,3-dihydro-1-[1-(phenylmethyl)-4-piperidinyl]-2H-imidazol-2-one in 50 ml of chloroform was mixed with 3.0 g

of paraformaldehyde and refluxed for 3.5 hours. The residue remaining after evaporation of the solvent was taken up in 100 ml of methanol and acidified with methanolic hydrogen chloride solution. After stirring for one hour at room temperature the mixture was poured into 300 ml of saturated sodium hydrogen carbonate solution. The resulting mixture was extracted thoroughly with ethyl acetate, the combined extracts were dried over sodium sulphate and evaporated down *in vacuo*. The residue was purified by column chromatography over silica gel using FM4 as eluant. From the appropriate fractions 0.5 g (18.2% of theory) of a colourless, amorphous substance were isolated, Rf = 0.24 (FM4).

IR(KBr): 1689 cm^{-1} (C=O)

MS: M^+ = 358 (Br)

e) 1,3-dihydro-3-(4-piperidinyl)-2(2H)-imidazo[4,5-c]-quinolone

Prepared analogously to Example A3f) from 1,3-dihydro-3-[1-(phenylmethyl)-4-piperidinyl]-2(2H)-imidazo[4,5-c]quinolone by hydrogenolysis in the presence of palladium/charcoal in a yield of 98.5% of theory. Colourless crystals, Rf = 0.63 (FM1).

Example A17

Preparation of β-(methoxycarbonyl)-arenebutanoic acids

3,5-dibromo-4-hydroxy-β-(methoxycarbonyl)-benzenebutanoic acid

a) 4-(phenylmethoxy)-benzaldehyde

To a solution of 36.6 g (0.3 mol) of 4-hydroxybenzaldehyde in 100 ml of ethanol were added dropwise, one after another, a solution of 12.0 g (0.3 mol) of sodium hydroxide in 100 ml of water and a solution of 36.5 ml of (0.307 mol) of benzylbromide in 100 ml of ethanol and the mixture was

then kept for 1 hour at 50°C. The ethanol was extensively distilled off, finally *in vacuo*, the remaining aqueous emulsion was divided between water and ethyl acetate. The ethyl acetate phase was dried over sodium sulphate and evaporated down *in vacuo*. The residue remaining crystallised on trituration with petroleum ether and was recrystallised from diisopropylether. 48.0 g (75.4% of theory) of colourless crystals of melting point 118 - 122°C were obtained.

b) 3-(methoxycarbonyl)-4-[(4-phenylmethoxy)phenyl]-3-butenoic acid

To a freshly prepared solution of 2.3 g (0.1 mol) of sodium in 300 ml of anhydrous methanol were added 14.6 g (0.1 mol) of dimethyl succinate and after half an hour's stirring a solution of 21.2 g (0.1 mol) of 4-(phenylmethoxy)-benzaldehyde in 100 ml of anhydrous methanol were added dropwise. Then the mixture was refluxed for 6 hours, the methanol was distilled off under normal pressure and the remaining residue was kept for 30 minutes at a reaction temperature of 80°C. The viscous slurry obtained was stirred into 1 l of a glacial acetic acid-water mixture (1/1 v/v), the resulting mixture was extracted thoroughly with ethyl acetate. The combined ethyl acetate extracts were in turn extracted with saturated potassium carbonate solution. The potassium carbonate extracts were carefully acidified with acetic acid and then extracted thoroughly with ethyl acetate. These extracts were washed with water, dried over sodium sulphate and freed from solvent *in vacuo*. The residue was purified by column chromatography over silica gel using dichloromethane/petroleum ether/glacial acetic acid 25/74/1 (v/v/v). The colourless, partly crystallised mixture of diastereomers was obtained in a yield of 16.0 g (49% of theory). Rf = 0.68 (eluant: ethyl acetate/petroleum ether 1:2 v/v).

IR(KBr): 1699.2 cm^{-1} (C=O)

The following were obtained analogously:

(1) 3-(methoxycarbonyl)-4-[3-(trifluoromethyl)phenyl]-3-butenoic acid was obtained from 3-(trifluoromethyl)benzaldehyde and dimethyl succinate in a yield of 21% of theory.

IR(KBr): 1738, 1726 cm^{-1} (C=O)

ESI-MS: $(M-H)^-$ = 287

$(M+H)^+$ = 289

$(M+Na)^+$ = 311

(2) 3-(methoxycarbonyl)-4-(1-naphthyl)-3-butenoic acid was obtained from 1-naphthaldehyde and dimethyl succinate in a yield of 60% of theory.

Colourless oil

IR(KBr): 1712 cm^{-1} (C=O)

MS: M^+ = 270

(3) 3-(methoxycarbonyl)-4-[3,5-dimethyl-4-phenylmethoxyphenyl]-3-butenoic acid was obtained from 3,5-dimethyl-4-phenylmethoxybenzaldehyde and dimethyl succinate in a yield of 66% of theory.

Colourless oil which could be further processed without purification.

(4) 4-(4-amino-3,5-dibromophenyl)-3-(methoxycarbonyl)-3-butenoic acid was obtained from 4-amino-3,5-dibromobenzaldehyde and dimethyl succinate in a yield of 21% of theory.

(5) 3-(Methoxycarbonyl)-4-(3-phenylmethoxyphenyl)-3-butenoic acid was obtained from 3-phenylmethoxybenzaldehyde and dimethyl succinate in a yield of 37% of theory.

c) 4-hydroxy-β-(methoxycarbonyl)-benzenebutanoic acid

Prepared analogously to Example A3f) from 3-(methoxycarbonyl)-4-[(4-phenylmethoxy)phenyl]-3-butenoic acid by hydrogenolysis in the presence of palladium/charcoal in a yield of 96% of theory. Colourless

oil, Rf = 0.5 (eluant: ethyl acetate/petroleum ether/glacial acetic acid 66.3/33.3/0.4 v/v/v).

The following were obtained analogously:

(1) β-(methoxycarbonyl)-3-(trifluoromethyl)-benzenebutanoic acid was obtained from 3-(methoxycarbonyl)-4-[3-(trifluoromethyl)phenyl]-3-butenoic acid in a yield of 80% of theory. R_f = 0.59 (eluant: ethyl acetate/petroleum ether 1/1/ v/v).

ESI-MS: $(M-H)^-$ = 289

(2) β-(methoxycarbonyl)-1-naphthalinebutanoic acid was obtained from 3-(methoxycarbonyl)-4-(1-naphthyl)-3-butenoic acid, however using platinum(IV)-oxide as a catalyst, in a yield of 31% of theory.

IR (KBr): 1734, 1711 (C=O) cm^{-1}

MS: M^+ = 272

β-(methoxycarbonyl)-1,2,3,4-tetrahydro-1-naphthaline-butanoic acid was isolated as a by-product in a yield of 8.4% of theory

IR (KBr): 1736, 1712 (C=O) cm^{-1}

MS: M^+ = 276

(3) 3,5-dimethyl-4-hydroxy-β-(methoxycarbonyl)-benzene butanoic acid was obtained from 3-(methoxycarbonyl)-4-[3,5-dimethyl-4-phenylmethoxyphenyl]-3-butenoic acid in a yield of 48% of theory.

R_f = 0.11 (FM1)

IR (KBr): 1716 (C=O) cm^{-1}

MS: M^+ = 266

(4) 3-Hydroxy-β-(methoxycarbonyl)-benzene butanoic acid was obtained from 3-(Methoxycarbonyl)-4-(3-phenylmethoxyphenyl)-3-butenoic acid in a yield of 59% of theory.

R_f = 0.24 (petroleum ether/ethyl acetate/glacial acetic acid 6/4/0.2 v/v/v)

IR (KBr): 1714 (C=O) cm^{-1}

MS: M^+ = 238

(5) 4-Amino-β-(methoxycarbonyl)-benzene butanoic acid was obtained from 3-(methoxycarbonyl)-4-(4-amino-3,5-dibromophenyl)-3-butenoic acid and in the presence of triethylamine in a quantitative yield.
R_f = 0.53 (eluant: dichloromethane/methanol/glacial acetic acid 90/10/1.5 v/v/v))
IR (KBr): 1728 (C=O) cm^{-1}
MS: M^+ = 237

d) 3,5-dibromo-4-hydroxy-β-(methoxycarbonyl)-benzenebutanoic acid

To a solution of 12.0 g (0.05 mol) of 4-hydroxy-β-(methoxycarbonyl)-benzenebutanoic acid in 200 ml of glacial acetic acid were added 150 ml of water and 8.0 g sodium acetate and then a solution of 15.58 g (0.0975 mol) of bromine in 60 ml of glacial acetic acid was added dropwise. The mixture was stirred for a further hour at room temperature, then evaporated down to two thirds *in vacuo* and the residue was divided between water and ethyl acetate. The ethyl acetate extracts were washed with water, dried over sodium sulphate and evaporated down *in vacuo*. After stirring with diisopropylether a colourless crystal was obtained. Yield: 12.0 g (62.2% of theory). R_f = 0.4 (eluant: ethyl acetate/petroleum ether/glacial acetic acid 49.8/49.8/0.4 v/v/v).
IR(KBr): 1724 cm^{-1} (C=O)
MS: M^+ = 394/396/398 (Br_2)

Example A18

1-(3-pyridinyl)piperazine

a) 1-(phenylmethyl)-3-(3-pyridinyl)piperazine

To a solution of 5.0 g (0.0515 mol) of 3-fluoropyridine and 43.5 ml of 1-(phenylmethyl)piperazine in 300 ml of anhydrous diethylether was added dropwise, at boiling temperature, within 2.5 hours, 56 ml (0.112 mol) of a 2 molar solution of phenyllithium in a cyclohexane-diethylether mixture (7/3 v/v) and the resulting mixture was then kept at reflux temperature for a further 4 hours. The crude reaction product obtained as an oil after working up in the usual way was purified by column chromatography over silica gel (30 - 60 μm) using FM1/cyclohexane (7/3 v/v) as eluant. 12.0 g (92% of theory) of a colourless oil were obtained, Rf 0.52 (FM4; Macherey-Nagel, POLYGRAM® SIL G/UV_{254} Pre-coated plastic sheets for TLC).
MS: M^+ = 253

b) 1-(3-Pyridinyl)piperazine
Prepared analogously to Example A3f) from 1-(phenylmethyl)-3-(3-pyridinyl)piperazine by hydrogenolysis in the presence of palladium/charcoal in a yield of 55% of theory.
Colourless oil, Rf 0.35 (FM1).
IR(KBr): 1652.9 cm^{-1} (C=N)

Example A19

1-(1-cyclohexyl-4-piperidinyl)piperazine-tris-trifluoroacetate

a) 1-(1,1-dimethylethoxycarbonyl)-4-[1-(phenylmethyl)-4-piperidinyl]piperazine

A solution of 15.0 g (0.8054 mol) of 1-(1,1-dimethylethoxycarbonyl)piperazine and 14.26 ml (0.08053 mol) of 1-(phenylmethyl)-4-piperidinone in 250 ml of

methanol was adjusted to a pH of between 5 and 6 by dropwise addition of acetic acid and mixed in batches with a total of 4.13 g (0.0624 mol) of 95% sodium cyanoborohydride, whilst taking care to maintain a pH of 5 to 6 by further dropwise addition of acetic acid. After stirring for 18 hours at room temperature the mixture was evaporated down *in vacuo*, the residue was made alkaline with soda and divided between water and ethyl acetate. After working up the ethyl acetate phase in the usual way 21.76 g (75.2% of theory) of a highly viscous colourless oil were obtained, Rf 0.66 (FM1).

b) 1-(1,1-dimethylethoxycarbonyl)-4-(4-piperidinyl)piperazine

Prepared analogously to Example A3f) from 1-(1,1-dimethylethoxycarbonyl)-4-[1-(phenylmethyl)-4-piperidinyl]piperazine by hydrogenolysis, but using Pearlman's catalyst instead of palladium/charcoal, in a yield of 79.7% of theory.
Colourless crystals , Rf = 0.3 (FM1).

c) 1-(1,1-dimethylethoxycarbonyl)-4-(1-cyclohexyl-4-piperidinyl)piperazine

Prepared analogously to Example A19a) from 1-(1,1-dimethylethoxycarbonyl)-4-(4-piperidinyl)piperazine and cyclohexanone in a yield of 99% of theory. Colourless, highly viscous oil.
MS: M^+ = 251

d) 1-(1-cyclohexyl-4-piperidinyl)piperazine-tris-trifluoroacetate

Prepared analogously to Example A5e) from 1-(1,1-dimethylethoxycarbonyl)-4-(1-cyclohexyl-4-piperidinyl)piperazine and trifluoroacetic acid in a quantitative yield. Colourless crystals , Rf = 0.2 (FM1).

Example A20

1-(1-ethyl-4-piperidinyl)piperazine-trihydrochloride

a) 1-(1-ethyl-4-piperidinyl)-4-(phenylmethyl)piperazine
Prepared analogously to Example A19a) from 1-ethyl-4-piperidinone and 1-(phenylmethyl)piperazine in a yield of 71% of theory. Colourless, amorphous substance, Rf = 0.46 (FM4).

b) 1-(1-ethyl-4-piperidinyl)piperazine-trihydrochloride
A mixture of 36.3 g (0.126 mol) of 1-(1-ethyl-4-piperidinyl)-4-(phenylmethyl)piperazine, 300 ml of 1N hydrochloric acid and 200 ml of methanol was hydrogenated at room temperature and in the presence of 4.0 g of 10% palladium/charcoal until the uptake of hydrogen had ceased. After working up in the usual way 22.9 g (59.3% of theory) of a colourless, crystalline substance was obtained.
MS: M^+ = 197

In the same way exo-1-(8-methyl-8-azabicyclo[3,2,1]oct-3-yl)piperazine-trihydrochloride was obtained from exo-4-(8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-1-(phenylmethyl)piperazine (see Example A11a)) by hydrogenolysis in the presence of palladium/charcoal in a yield of 91% of theory.
MS: M^+ = 209

Example A21

1-ethyl-4-(4-piperidinyl)piperidine

a) 1-(phenylmethoxycarbonyl)-4-(4-piperidinyl)piperidine

To a mixture of 72.375 g (0.3 mol) of bipiperidine-dihydrochloride, 1500 ml of methanol, 75 ml of water and 100 mg of bromophenol blue were added dropwise, simultaneously, with stirring and at room temperature, a solution of 51.18 g

(0.3 mol) of benzyl chlorocarbonate in 75 ml of toluene and 6 N sodium hydroxide solution (about 80 ml) were added, so that the indicator colour changed continuously. After all had been added, which took about 4 hours, the mixture was diluted with 300 ml of water and the organic solvent was distilled off *in vacuo*. The aqueous phase remaining was acidified with hydrochloric acid, whilst being externally cooled, extracted thoroughly with diethylether and then made alkaline with 50% potassium hydroxide solution. The mixture was extracted thoroughly with dichloromethane, the combined dichloromethane extracts were dried over magnesium sulphate and evaporated down *in vacuo*. The colourless, highly viscous, slowly crystallising oil remaining was further processed without any more purification. Yield: 87.3 g (96.2% of theory).
IR(KBr): 1701.1 cm^{-1} (C=O)

b) 1-ethyl-4-[1-(phenylmethoxycarbonyl)-4-piperidinyl]piperidine

To a solution of 18.14 g (0.061 mol) of 1-(phenylmethoxycarbonyl)-4-(4-piperidinyl)piperidine in 450 ml of a methanol/water mixture (1/1 v/v) were added, with stirring, whilst maintaining a temperature of 15 to 20°C, 10.05 g (0.152 mol) of 95% sodium cyanoborohydride and 50 mg of bromocresol purple. Then a solution of 10.57 g (0.24 mol) of acetaldehyde in 50 ml of methanol and 1N hydrochloric acid were alternately added dropwise so that the colour of the mixture changed continuously from blue to yellow. After all had been added and the reaction had finished the mixture was adjusted to pH 2 with hydrochloric acid and extracted twice with 200 ml of diethylether. The aqueous phase was then made alkaline and extracted thoroughly with dichloromethane. The combined dichloromethane extracts were dried over magnesium sulphate and evaporated down *in vacuo*. The colourless crystallising residue remaining was purified by column chromatography over silica gel (30-60 µm) using FM1 as eluant. Yield of

colourless crystals of melting point 93-96°C: 7.9 g (39.2% of theory).
IR(KBr): 1699.2 cm^{-1} (C=O)

c) 1-ethyl-4-(4-piperidinyl)piperidine
A solution of 7.6 g (0.023 mol) of 1-ethyl-4-[1-(phenylmethoxycarbonyl)-4-piperidinyl]piperidine in a mixture of 70 ml of methanol, 30 ml of water and 10 ml of glacial acetic acid was hydrogenated in the presence of 10% palladium/charcoal at room temperature and 3 bar of hydrogen pressure until the uptake of hydrogen had ceased. After working up in the usual way the desired compound was obtained as a colourless oil in a quantitative yield.

Example A22

Hexahydro-1-methyl-4-(4-piperidinyl)-1H-1,4-diazepine

a) Hexahydro-1-methyl-4-[1-(phenylmethyl)-4-piperidinyl]-1H-1,4-diazepine
Prepared analogously to Example A11a) from hexahydro-1-methyl-1H-1,4-diazepine and 1-(phenylmethyl)-4-piperidinone in a yield of 35% of theory. Colourless viscous oil.
MS: M^+ = 287

The following were prepared in the same way:

(1) 1-methyl-4-[1-(phenylmethyl)-4-piperidinyl]-piperazine
from 1-methylpiperazine and 1-(phenylmethyl)-4-piperidinone
Yield: 39.9% of theory, colourless viscous oil

(2) 1-acetyl-4-[1-(phenylmethyl)-4-piperidinyl]piperazine
from 1-acetylpiperazine and 1-(phenylmethyl)-4-piperidinone
Yield: 24.2% of theory, colourless viscous oil
R_f: 0.46 (eluant: ethyl acetate/methanol/conc. ammonia 50/50/2 v/v/v)
IR(KBr): 1647 cm^{-1} (C=O)

MS: M^+ = 301

(3) 4-(dimethylamino)-1-[1-(phenylmethyl)-4-piperidinyl]-piperidine

from 4-(dimethylamino)piperidine and 1-(phenylmethyl)-4-piperidinone

Yield: 28.9% of theory; colourless viscous oil

R_f: 0.58 (eluant: ethyl acetate/methanol/conc. ammonia 50/50/2 v/v/v)

MS: M^+ = 301

(4) 1-(1,1-dimethylethoxycarbonyl)-4-[4-(phenylmethyl)-1-piperazinyl]piperidine

from 1-(1,1-dimethylethoxycarbonyl)-4-piperidinone and 1-(phenylmethyl)piperazine

Yield: 86.6% of theory. Colourless, amorphous substance

R_f: 0.58 (eluant: dichloromethane/methanol 9/1 v/v)

b) Hexahydro-1-methyl-4-(4-piperidinyl)-1H-1,4-diazepine

Prepared analogously to Example A3f) from hexahydro-1-methyl-4-[1-(phenylmethyl)-4-piperidinyl]-1H-1,4-diazepine by hydrogenolysis, but using Pearlman's catalyst instead of palladium/charcoal, in a quantitative yield. Colourless viscous oil.

MS: M^+ = 197

The following were obtained in the same way:

(1) 1-methyl-4-(4-piperidinyl)piperazine

from 1-methyl-4-[1-(phenylmethyl)-4-piperidinyl]piperazine in a quantitative yield. Colourless viscous oil.

MS: M^+ = 183

(2) 1-acetyl-4-(4-piperidinyl)piperazine

from 1-acetyl-4-[1-(phenylmethyl)-4-piperidinyl]piperazine in a yield of 81.9% of theory. Colourless crystals.

IR(KBr): 1631 cm^{-1} (C=O)

(3) 4-(dimethylamino)-1-(4-piperidinyl)piperidine
from 4-(dimethylamino)-1-[1-(phenylmethyl)-4-piperidinyl]-piperidine in a yield of 76.8% of theory. Colourless, amorphous substance.

(4) 1-(1,1-dimethylethoxycarbonyl)-4-(1-piperazinyl)piperidine-hydrochloride
from 1-(1,1-dimethylethoxycarbonyl)-4-[4-(phenylmethyl)-1-piperazinyl]piperidine-hydrochloride.
Yield: 96% of theory. Colourless crystals
R_f : 0.23 (eluant: dichloromethane/methanol 9/1 v/v)

Example A23

4-[(4-methyl-1-piperazinyl)carbonyl]-piperidine-bis-trifluoroacetate

a) 1-(1,1-dimethylethoxycarbonyl)-4-piperidinecarboxylic acid
To a mixture of 25.9 g (0.2 mol) of piperidine-4-carboxylic acid, 200 ml (0.2 mol) of 1N sodium hydroxide solution and 200 ml of tetrahydrofuran were added 48.0 g (0.22 mol) of di-tert. -butyl pyrocarbonate and the mixture was stirred overnight at room temperature. The tetrahydrofuran was distilled off, finally *in vacuo*, and the remaining aqueous solution was acidified with citric acid. The colourless crystals precipitated were suction filtered and dried at 40°C in a circulating air drier. Yield: 45.5 g (99.2% of theory).
IR(KBr): 1733.9, 1662.5 cm^{-1} (C=O)

b) 1-(1,1-dimethylethoxycarbonyl)-4-[(4-methyl-1-piperazinyl)carbonyl]-piperidine
Prepared analogously to Example A15a) from 1-(1,1-dimethylethoxycarbonyl)-4-piperidinecarboxylic acid and 1-methylpiperazine in the presence of TBTU in a yield of 76% of theory. Colourless, amorphous substance, Rf = 0.64

(eluant: dichloromethane/methanol/conc. ammonia 50/50/1 v/v/v).
IR(KBr): 1693, 1678 cm^{-1} (C=O)

The following were prepared in the same way:

(1) 1-methyl-4-[[4-(1,1-dimethylethoxycarbonyl)-1-piperazinyl]carbonyl]-piperidine
from 1-methyl-4-piperidinecarboxylic acid and 1-(1,1-dimethylethoxycarbonyl)piperazine in a yield of 97% of theory. Colourless crystals.
IR(KBr): 1683.8, 1629.8 cm^{-1} (C=O)

(2) 1-(1,1-dimethylethoxycarbonyl)-4-(isonicotinoyl)piperazine
from 1-(1,1-dimethylethoxycarbonyl)-piperazine and 4-pyridinecarboxylic acid in a yield of 76.8% of theory. Colourless crystals of melting point 139.2-140.2°C and R_f = 0.84 (eluant: dichloromethane/methanol/conc. ammonia 90/10/1 v/v/v).
IR(KBr): 1689.5, 1625.9 cm^{-1} (C=O)

c) 4-[(4-methyl-1-piperazinyl)carbonyl]-piperidine-bis-trifluoroacetate
prepared analogously to Example A5e) from 1-(1,1-dimethylethoxycarbonyl)-4-[(4-methyl-1-piperazinyl)carbonyl]-piperidine and trifluoroacetic acid in a yield of 89% of theory. Colourless, amorphous substance.

The following were prepared in the same way:

(1) 1-methyl-4-[(1-piperazinyl)carbonyl]-piperidine
from 1-methyl-4-[[4-(1,1-dimethylethoxycarbonyl)-1-piperazinyl]carbonyl]-piperidine and trifluoroacetic acid in a yield of 57% of theory. Colourless, amorphous substance.

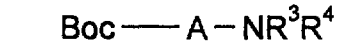
IR(KBr): 1679.9, 1645.2 cm^{-1} (C=O)
MS: M^+ = 211

(2) 4-(isonicotinoyl)piperazine-trifluoroacetate

from 1-(1,1-dimethylethoxycarbonyl)-4-(isonicotinoyl)piperazine and trifluoroacetic acid in a yield of 98.3% of theory. Colourless, amorphous substance.
IR(KBr): 1676.0 cm^{-1} (C=O)

Example A24

Preparation of compounds of the general structure:



1-[N^2-(1,1-dimethylethoxycarbonyl)-N^6-(phenylmethoxy-carbonyl)-L-lysyl]-4-(4-pyridinyl)piperazine

To a mixture of 18.8 g (0.0494 mol) of Boc-Lys(Z)-OH, 6.5 g (0.05 mol) of DIEA, 16 g (0.05 mol) of TBTU, 6.6 g (0.049 mol) of HOBt and 100 ml of dimethylformamide were added dropwise, with stirring, 8.1 g (0.0494 mol) of 1-(4-pyridinyl)piperazine, dissolved in 40 ml of DMF, and the mixture was stirred overnight at room temperature. The solvent was removed *in vacuo* and the residue was taken up in ethyl acetate. The ethyl acetate phase was then washed three times successively with 70 ml of saturated aqueous sodium hydrogen carbonate solution and once with 70 ml of saturated aqueous saline solution, dried over sodium sulphate and evaporated down *in vacuo*. 24.2 g (93.2% of theory) of a yellowish oil were obtained, which was used for the following reactions without further purification.
IR (KBr): 1650, 1713 cm^{-1} (C=O)
R_f (FM1): 0.59

The following were prepared analogously:

A	NR^3R^4	Remarks	% Yield	R_f	Eluant	IR [cm^{-1}]
A9	C1	THF as LM $KHSO_4$/NaCl soln	63.2	0.4	FM1	(KBr): C=O 1705.0/1649
A4	C1		93.2	0.59	FM1	(KBr): C=O 1647.7; 1712.7
A5	C1		66	0.55	FM1	(KBr): C=O 1655/1709
A5	C8		54	0.8	FM1	(KBr): C=O 1653/1713
A6	C8		91	0.8	FM1	(KBr): C=O 1645/1710.8
A10	C1		63	0.5	FM1	(KBr): C=O 1665/1695
A10	C8		30	0.41	FM4	(KBr): C=O 1662/1699

Example A25

Preparation of compounds of general formula:

$$Cbz\text{-}A\text{-}NR^3R^4$$

1-[N^2-(phenylmethoxycarbonyl)-N^6-(1,1-dimethyl-ethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)piperazine

To a mixture of 100 g (0.263 mol) of Z-Lys(Boc)-OH, 86.1 g (0.268 mol) of TBTU and 36.3 g (0.263 mol) of HOBt in 600 ml of dimethylformamide were added 43.0 g (0.263 mol) of 1-(4-pyridinyl)-piperazine and 47.2 ml (0.268 mol) of DIEA with stirring and the mixture was stirred overnight at room temperature. The reaction mixture was evaporated down *in vacuo* and the residue divided between ethyl acetate and aqueous saturated sodium hydrogen carbonate solution. The aqueous phase was extracted twice more with a mixture of ethyl acetate/methanol (10/1 , v/v) and the combined organic phases were washed once with saturated sodium hydrogen carbonate solution. The organic phase was, after drying over sodium

sulphate, evaporated down *in vacuo* and the residue was taken up in 750 ml of ethyl acetate and washed four times with 100 ml of water, six times with 100 ml of 1% potassium hydrogen sulphate solution, once with 100 ml of water, twice with 100 ml of 3% aqueous ammonia solution and twice with 100 ml of water. The organic phase was evaporated down after drying over sodium sulphate. 120 g (87% of theory) of the desired product were obtained as an oil, which was used without further purification for the subsequent reactions.

IR (KBr): 1709 cm^{-1} (C=O)

R_f (FM1): 0.59

EI - MS: M^+ = 525

The following were prepared analogously:

A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
A3	C4		100				
A3	C3	Triethylamine as base	100		0.8	FM1	(KBr): C=0 1643.3/1710.8
A11	C1		98.8		0.5	FM1	(KBr): C=O 1705.0/1643.3
A3	C1		81	EI: M+=525	0.59	FM1	(KBr): C=O 1708.8;
A3	C5	LC/SiO_2/FM4	95	YED:M=525	0.67	FM4	
A3	C6	THF,LC/SiO_2/FM4	92		0.82	FM4	(KBr): C=O 1710.8;1641.3
A3	C8	further reacted as crude product	100				

Example A26

Preparation of compounds of general formula:

$$H-A-NR^3R^4$$

1-[N^6-(phenylmethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)piperazine

To a mixture of 24.2 g (46 mmol) of 1-[N^2-(1,1-dimethylethoxycarbonyl)-N^6-(phenylmethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)piperazine and 150 ml of methylene chloride were added 50 ml of trifluoroacetic acid and the reaction mixture was stirred overnight at room temperature. The reaction mixture was neutralised by the addition of saturated aqueous sodium hydrogen carbonate solution, the organic phase was dried and evaporated down *in vacuo*. 12 g (62% of theory) of the desired compound were obtained as a colourless oil.

IR (KBr): 1648 cm^{-1} (C=O)

R_f (FM1): 0.5

The following were prepared analogously:

A	NR^3R^4	Remarks	% Yield	R_f	Eluant	IR [cm^{-1}]
A9	C1		100	0.4	FM2	(KBr): C=O 1676.0; 1645.2
A4	C1		61.5	0.48	FM1	(KBr): C=O 1647.7; 1712.7
A5	C1		55	0.42	FM1	(KBr): C=O 1651
A5	C8	further reacted as crude product	100	0.19	FM1	
A6	C1		82	0.3	FM1	(KBr): C=O 1647; 1676
A6	C8	further reacted as crude product	100	0.23	FM1	(KBr): C=O 1674
A10	C1		38	0.55	FM1	(KBr): C=O 1643
A10	C8	further reacted as crude product	100	0.15	FM1	

Example A27

Preparation of compounds of general formula:

$$H-A-NR^3R^4$$

1-[N^6-(1,1-dimethylethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)piperazine

A solution of 120 g (0.228 mol) of 1-[N^2-(phenylmethoxycarbonyl)-N^6-(1,1-dimethylethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)piperazine in 1000 ml of methanol and 240 ml of 1M aqueous potassium hydrogen sulphate solution was hydrogenated in the presence of 30 g palladium on charcoal (10%) at 20°C and 3 bar of hydrogen pressure until the uptake of hydrogen had ceased. The catalyst was filtered off, the filtrate evaporated down *in vacuo*, the residue was taken up in isopropanol/ methanol and adjusted to pH 7-8 by the addition of a concentrated aqueous ammonia solution. The solution was filtered and evaporated to dryness. 87 g (97% of theory) of an oil were obtained.

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IR (KBr): 1634, 1701 cm^{-1} (C=O)

R_f: 0.79 (ethyl acetate/methanol/conc. aqueous ammonia = 6/4/1 (v/v/v)

The following were prepared analogously:

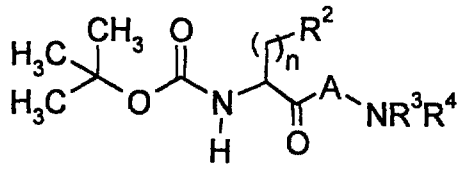
A	NR^3R^4	Remarks	% Yield	MS	R_f	Yield	IR [cm^{-1}]
A3	C4		93	ESI:M+H=391 (M+Na=413)	0.6	FM1	(KBr): C=0 1637.5; 1706.9
A3	C3		100		0.3	FM1	(KBr): C=0 1641.3; 1705
A11	C1		78.5		0.2	FM1	(KBr): C=O 1701.1; 1641.3
A7	C1	without $KHSO_4$	80.2		0.2	FM7	
A3	C1		97		0.79	ethyl acetate/methanol/ conc.aqueous ammonia 6/4/1 (v/v/v)	(KBr): C=O 1633.6; 1701.1
A3	C5	without $KHSO_4$	53		0.39	FM4	(KBr): C=O 1733.9; 1624.0
A3	C6	without $KHSO_4$	89		0.38	FM4	(KBr): C=O 1706.9; 1645.2
A3	C8	further reacted as crude product	100		0.3	FM1	

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Example A28

Preparation of compounds of general formula:



1-[N^2-[N-(1,1-dimethylethoxycarbonyl)-3,5-dibromo-D-tyrosyl]-N^6-(phenylmethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)-piperazine

To a mixture of 2.58 g (5.88 mmol) of N-[(1,1-dimethylethoxy)carbonyl]-3,5-dibromo-D-tyrosine, 1.03 g (8 mmol) of DIEA, 1.93 g (6 mmol) of TBTU, 0.79 g (5.8 mmol) of HOBt and 100 ml of dimethylformamide were added dropwise, 2.5 g (5.88 mmol) of 1-[N^6-[(phenylmethoxy)-carbonyl]-L-lysyl]-4-(4-pyridinyl)piperazine, dissolved in 50 ml of dimethylformamide, with stirring. The reaction mixture was stirred overnight at room temperature, then evaporated down *in vacuo* and the residue was taken up in ethyl acetate. The organic phase was washed twice with aqueous saturated sodium hydrogen carbonate solution and once with aqueous saturated saline solution, dried and evaporated down *in vacuo*. The purification was carried out by column chromatography (aluminium oxide, activity stage III (6% water content) (ICN Biomedicals), eluant: ethyl acetate/methanol/ammonia = 8/2/0.5 (v/v/v), followed by methanol/ammonia = 7/3 (v/v)). 4.0 g (80% of theory) of an amorphous substance were obtained.

IR (KBr): 1643, 1709 cm^{-1} (C=O)

R_f: 0.52 (FM1)

ESI-MS: $(M+H)^+$ = 845/847/849 (Br_2)

The following were prepared analogously (in each case n = 1):

R^2	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
AS7	A0	C4	LM: THF; reacted as crude product	100				
AS1	A0	C11	reacted as crude product	69				
AS4	A0	C20		59	ESI:$(M+H)^+$ = 600/2/4(Br_2)			(KBr): C=0 1639; 1707
AS1	A0	C4		71				
AS4	A0	C11		53		0.5	FM1	
AS7	A0	C1	reacted as crude product	100				(KBr): C=0 1644
AS4	A7	C1	NEt_3 as base, reacted as crude product	100		0.4	FM8	
AS1	A4	C1		80	ESI:$(M+H)^+$ = 845/7/9 (Br_2)	0.52	FM1	(KBr): C=O 1643.3; 1708.8
AS4	A0	C5	Boc-AS4 LC/SiO_2/FM5	83	EI:M^+ = 581/3/5(Br_2)	0.69	FM5	(KBr): C=O 1706.9; 1641.3
AS4	A0	C15	LC/SiO_2/FM4	86	EI:M^+ = 382/4/6(Br_2)	0.83	FM4	(KBr): C=O 1706.9; 1641.3
AS1	A0	C5	LC/SiO_2/FM5	81		0.5	FM5	(KBr): C=O 1705.0; 1637.5
AS4	A0	C16	LC/SiO_2/FM4 THF	85	EI:$(M+H)^+$ = 582/4/6(Br_2)	0.42	FM4	(KBr): C=O 1706.9; 1643.3
AS1	A0	C15	THF LC/SiO_2/FM4	76		0.53	FM4	(KBr): C=O 1701.1; 1637.5
AS4	A0	C3	LC/SiO_2/FM6	83	ESI:$(M+H)^+$ = 598/600/2(Br_2)	0.71	FM6	(KBr): C=O 1706.9; 1641.3
AS1	A0	C16	LC/SiO_2/FM4	85		0.35	FM1	(KBr): C=O 1705; 1641.3
AS1	A0	C6	LC/SiO_2/FM6	84		0.54	FM6	(KBr): C=O 1701.1; 1635.5
AS4	A0	C18	LC/SiO_2/FM4	95		0.66	FM4	(KBr): C=O 1705; 1641.3
AS1	A0	C37		90		0.43	FM1	(KBr): C=O 1645; 1714.5
AS4	A0	C37		95		0.51	FM4	(KBr): C=O 1643.3; 1705

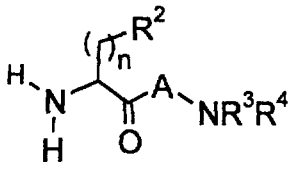
R^2	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
AS4	A0	C22		75				(KBr): C=O 1635.5; 1708.8
AS4	A0	C21		92	M^+ = 582/4/6(Br_2)	0.42	FM4	(KBr): C=O 1643; 1705
AS4	A5	C1		69	ESI:$(M+H)^+$ = 939/41/43(Br_2)			(KBr): C=O 1653; 1709
AS4	A0	C23		85				(KBr): C=O 1645; 1709
AS4	A10	C1		65	M^+ :652/4/6			(KBr): C=O 1649; 1707
AS4	A0	C24		79	M^+: 589/91/93			(KBr): C=O 1643; 1707
AS4	A5	C8		76				(KBr): C=O 1643; 1713
AS4	A6	C1		95				(KBr): C=O 1645; 1710.8
AS4	A6	C8		88	M^+: 657/9/61			(KBr): C=O 1628; 1713
AS4	A10	C8		46	ESI:$(M+H)^+$ = 858/60/62(Br_2)			(KBr): C=O 1647; 1707
AS4	A0	C26		46				(KBr): C=O 1637.5; 1707
AS1	A0	C1	further reacted as crude product	100				
AS1	A0	C8		55		0.3	Dichloro methane/ Methanol 9/1	(KBr): C=O 1632
AS1	A0	C18		84	ESI:$(M+H)^+$ = 613/5/7(Br_2)	0.4	FM4	(KBr): C=O 1641; 1707
AS1	A0	C3		81				(KBr): C=O 1638; 1701
AS1	A0	C21		70		0.28	FM4	(KBr): C=O 1643; 1707
AS4	A0	C6		47				(KBr): C=O 1639; 1707
AS4	A0	C19		90				(KBr): C=O 1639; 1707
AS9	A0	C1	further reacted as crude product	47				
AS1	A7	C1	NEt_3 as base; further reacted as crude product	83		0.28	FM1	
AS4	A0	C38		67		0.5	FM1	
AS4	A0	C37		84				

R^2	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
AS4	A0	C39		100 (raw)		0.68	FM1	
AS4	A0	C40		36				
AS1	A0	C42		90		0.43	FM1	(KBr): C=0 1645/1715
AS4	A0	C42		100		0.51	FM4	(KBr): C=0 1643/1705
AS1	A0	C43		78		0.9	EE/MeOH 95/5	(KBr): C=0 1636/ 1676/ 1659
AS1	A0	C44		47		0.9	EE/MeOH 95/5	(KBr): C=0 1638/1701
AS1	A0	C45		72	EI:M^+ = 591/3/5(Br_2)	0.9	EE/MeOH 9/1	(KBr): C=0 1638/1695
AS1	A0	C47		80	EI:M^+ = 596/98/600 (Br_2)	0.95	EE/MeOH 9/1	(KBr): C=0 1636/1705
AS1	A0	C49		89		0.9	EE/MeOH 9/1	(KBr): C=0 1636/1684
AS4	A0	C44		69		0.9	EE/MeOH 9/1	(KBr): C=0 1643/1707 ; CN 2235
AS1	A0	C50		93	EI:M^+ = 598/600/602 (Br2)	0.9	EE/MeOH 9/1	(KBr): C=0 1636/1705
AS1	A0	C51		100		0.1	EE/ MeOH/ NH_4OH 5/5/0.1	(KBr): C=0 1638/1707
AS4	A0	C52		63		0.56	FM1	(KBr): C=0 1641/1705
AS4	A0	C53		83	EI:M^+ = 601/3/5 (Br_2)			(KBr): C=0 1638/1705
AS4	A0	C64		41	ESI:$(M+H)^+$ = 610/12/14 (Br_2)			(KBr): C=0 1639/1701
AS1	A0	C53		66		0.45	CH_2Cl_2/ MeOH/ NH_4OH 70/30/1	(KBr): C=0 1639/1709
AS4	A0	C51		88		0.35	CH_2Cl_2/ MeOH/ NH_4OH 50/50/0.5	(KBr): C=0 1641/1691
AS4	A0	C66		77	EI:M^+ = 629/31/33 (Br_2)	0.75	CH_2Cl_2/ MeOH/ NH_4OH 9/1/0.1	(KBr): C=0 1641/1707
AS16	A0	C8		100		0.8	FM1	
AS16	A0	C1		56		0.5	EE/ MeOH/ NH_4OH 9/1/1	(KBr): C=0 1695
AS4	A0	C8		100				

R^2	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
AS1	A0	C53		70.0	EI: M^+ = 502/4/6 (Br_2)	0.10	CH_2Cl_2 / MeOH / NH4OH 70/30/1	(KBr): C=0 1676
AS4	A0	C70		47.0				(KBr): C=0 1645/1707
AS1	A0	C64		31.0		0.50	CH_2Cl_2 / MeOH / NH4OH 90/10/1	(KBr): C=0 1639/1707
AS1	A0	C70		20.0				
AS4	A0	C72		50.0		0.50	CH_2Cl_2 / MeOH / NH4OH 90/10/1	
AS19	A0	C8		98.0				
AS35	A0	C8		92.0		0.70	FM1	
AS36	A0	C8		65.0				

Example A29

Preparation of compounds of general formula:



1-(4-amino-3,5-dibromo-D-phenylalanyl)-4-(4-pyridinyl)piperazine

A mixture of 39 g (0.089 mol) of 4-amino-3,5-dibromo-N-[(1,1-dimethylethoxy)carbonyl]-D-phenylalanine, 35.7 g (0.111 mol) of TBTU, 12.3 g (0.089 mol) of HOBt, 14.5 g (0.089 mol) of 1-(4-pyridinyl)-piperazine and 19.6 ml of (0.111 mol) of DIEA in 1000 ml of tetrahydrofuran was stirred overnight at room temperature. The reaction mixture was extracted once with saturated aqueous saline solution and twice with saturated aqueous sodium hydrogen carbonate solution. The combined aqueous phases were extracted once with tetrahydrofuran and the combined tetrahydrofuran phases were washed once with saturated aqueous saline solution. After drying the organic phase with sodium sulphate it was evaporated down *in vacuo* and the residue was taken up in ethyl acetate. The ethyl acetate phase was filtered after drying again and evaporated down *in vacuo*. 52.5 g of the intermediate compound were obtained as a viscous oil, which was then mixed with 300 ml of methylene chloride and 80 ml of trifluoroacetic acid and stirred overnight at room temperature. The reaction mixture was evaporated down *in vacuo*, the residue formed was triturated with ether. 45.8 g (72% of theory) of the desired product were obtained as a white amorphous solid.

IR (KBr): 1643, 1674 cm^{-1} (C=O)

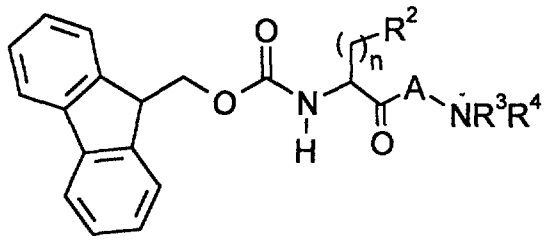
R_f : 0.36 (ethyl acetate/methanol = 6/4 (v/v))

The following were prepared analogously (in each case n = 1):

R^2	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
AS7	A0	C8	Crude product; Boc-cleaving with pure TFA	84				
AS4	A0	C8		63	ESI: $(M+H)^+$ = 486/88/90(Br_2)			(KBr): C=0 1632
AS4	A0	C4		63	ESI: $(M+H)^+$ = 481/3/5(Br_2)			(KBr): C=0 1620
AS1	A9	C1		55		0.25	FM2	(KBr): C=O 1674.1; 1643.3
AS4	A0	C8		81	ESI: $(M+H)^+$ = 486/8/90 (Br_2)	0.6	FM2	(KBr): C=O 1629.8
AS4	A0	C1		72		0.38	Ethyl acetate/ Methanol = 6/4 (v/v)	(KBr): C=O 1643.3; 1674.1
AS1	A0	C20		30				
AS4	A0	C65		41	EI: M^+ = 515/17/19(Br_2)			(KBr): C=0 1618
AS1	A0	C65		15	ESI: $(M+H)^+$ = 517/19/21 (Br_2)	0.08	FM1	(KBr): C=0 1635
AS4	A0	C78		77.0	ESI: $(M+H)^+$ = 529/31/33 (Br_2)	0.30	CH_2Cl_2 / MeOH / NH4OH =90/10/1	(KBr): C=0 1674
AS1	A0	C78		60.0	ESI: $(M+H)^+$ = 531/33/35 (Br_2)	0.10	CH_2Cl_2 / MeOH / NH4OH =80/20/1	(KBr): C=0 1670
AS4	A0	C71		43.0		0.20	CH_2Cl_2 / MeOH / NH4OH =90/10/1	(KBr): C=0 1678
AS31	A0	C20		39.0	EI: M^+ = 382	0.30	CH_2Cl_2 / MeOH / NH4OH =80/20/1	(KBr): C=0 1678
AS31	A0	C53		83.0	EI: M^+ = 383			(KBr): C=0 1678

Example A30

Preparation of compounds of general formula:



1-[N^2-[N-(9-fluorenylmethoxycarbonyl)-3,5-dibromo-D-tyrosyl]-N^6-(1,1-dimethylethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)-piperazine

A mixture of 63 g (0.1123 mol) of N-[(9-fluorenylmethoxy)carbonyl]-3,5-dibromo-D-tyrosine, 44 g (0.1123 mol) of 1-[N^6-(1,1-dimethylethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)-piperazine, 39.7 g (0.1235 mol) of TBTU, 15.5 g (0.1123 mol) of HOBt, 21.7 ml (0.1235 mol) of DIEA and 600 ml of dimethylformamide was stirred for 20 hours at room temperature. The reaction mixture was evaporated down *in vacuo* and the residue divided between ethyl acetate/methanol (10/1 v/v) and saturated aqueous sodium hydrogen carbonate solution. The organic phase was washed once with saturated aqueous sodium hydrogen carbonate solution and after drying evaporated down *in vacuo*. The residue was recrystallised twice from isopropanol (22.6g; 22% of theory), the mother liquors were combined, evaporated down and purified by column chromatography (MN-silica gel 60, Macherey-Nagel, 70-230 mesh ASTM; eluant: ethyl acetate/ methanol = 8/2 (v/v)). A further 28.0 g (26.7% of theory) of the desired end product were obtained. Total yield: 49% of theory.

IR (KBr): 1641, 1705 cm^{-1} (C=O)

R_f: 0.46 (ethyl acetate/methanol = 6/4 (v/v))

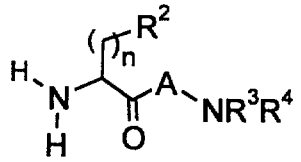
ESI-MS: $(M+H)^+$ = 933/935/937 (Br_2)

The following were prepared analogously:

R^2	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
AS1	A3	C1		48	ESI: $(M+H)^+$ = 933/5/7 (Br_2)	0.46	Ethyl acetate/ Methanol = 6/4 (v/v)	(KBr): C=O 1641.3; 1705.0
AS1	A3	C5	THF/SiO2/FM4	80	ESI: $(M+H)^+$ = 933/5/7(Br_2)	0.72	FM1	(KBr): C=O 1701.1; 1635.5
AS1	A3	C6	THF	60	ESI: M^- = 960/2/4 (Br_2)	0.47	FM4	(KBr): C=O 1712.7; 1631.7
AS5	A3	C1	THF LC/SiO2/FM4 Diastereomer	61	ESI: $(M+H)^+$ = 917/19/21 (Br_2)	0.36	FM4	(KBr): C=O 1708.8; 1645.2
AS10	A0	C1	THF	90		0.52	FM4	
AS1	A3	C18		73		0.46	FM1	(KBr): C=O 1635.5; 1712.7
AS10	A3	C1	THF	85				(KBr): C=O 1643.3; 1708.8
AS10	A3	C4	THF	82				(KBr): C=O 1639.4; 1710.8
AS10	A3	C1	THF	85				(KBr): C=O 1643; 1709
AS4	A3	C18		94	ESI: $(M+H)^+$ = 963/5/7 (Br_2)			(KBr): C=O 1633.6; 1711
AS15	A0	C8		90				(KBr): C=O 1635.5; 1617.5
AS12	A0	C8		44	ESI: $(M+H)^+$ = 577			(KBr): C=O 1630; 1714.6
AS10	A0	C4		88		0.49	FM4	(KBr): C=O 1635.5; 1716.5
AS1	A3	C1		70		0.7	FM7	

Example A31

Preparation of compounds of general formula:



1-[N^2-(3,5-dibromo-D-tyrosyl)-N^6-(1,1-dimethylethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)-piperazine

To a mixture of 63 g (0.1123 mol) of N-[(9-fluorenylmethoxy)carbonyl]-3,5-dibromo-D-tyrosine, 44 g (0.1123 mol) of 1-[N^6-(1,1-dimethylethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)piperazine, 39.7 g (0.1235 mol) of TBTU, 15.5 g (0.1123 mol) of HOBt and 1500 ml of

tetrahydrofuran were slowly added dropwise 21.7 ml (0.1235 mol) of DIEA and the reaction mixture was then stirred for 2 hours at room temperature. After the addition of 200 ml of diethylamine the mixture was again stirred overnight at room temperature. The reaction mixture was mixed with 1000 ml of saturated saline solution, stirred thoroughly and the aqueous phase was separated off. After extracting the aqueous phase three times with 500 ml of tetrahydrofuran and combining the organic phases the mixture was washed three times with 500 ml of saturated aqueous saline solution, three times with 200 ml of saturated aqueous sodium hydrogen carbonate solution and once with 500 ml of saturated aqueous saline solution. The organic phase was dried and then evaporated down *in vacuo*. The residue was purified by column chromatography (MN-silica gel 60, Macherey-Nagel, 70-230 mesh ASTM, eluant: ethyl acetate/methanol/conc. aqueous ammonia = 8/1/0.25 (v/v/v)). 40.0 g (50% of theory)of the desired end product were obtained.

IR (KBr): 1641, 1699 cm^{-1} (C=O)

R_f: 0.2 (ethyl acetate/methanol/conc. aqueous ammonia = 6/4/1 (v/v/v))

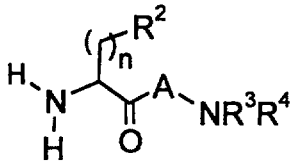
ESI-MS: $(M+H)^+$ = 711/713/715 (Br_2)

The following were prepared analogously (in each case n = 1):

R^2	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
AS4	A3	C8	crude	43				
AS4	A3	C1	crude	100		0.4	FM1	
AS4	A3	C4		79	ESI: $(M+H)^+$ = 709/11/13 (Br_2)	0.7	FM7	(KBr): C=0 1637.5; 1705
AS4	A0	C69		82	ESI: $(M+H)^+$ = 587/9/81 (Br_2)			(KBr): C=0 1618/ 1645/ 1690
AS4	A0	C46		38		0.55	CH_2Cl_2/ MeOH/ NH_4OH 90/10/1	(KBr): C=0 1614/1639
AS4	A0	C48		54	EI: M^+ = 522/4/6 (Br_2)	0.52	CH_2Cl_2/ MeOH/ NH_4OH 90/10/2	(KBr): C=0 1638
AS11	A0	C53		71.0	EI: M^+ = 469	0.20	CH_2Cl_2 / MeOH / NH4OH 90/10/1	(KBr): C=0 1637/1732
AS11	A0	C20		45.0	EI: M^+ =468	0.40	CH_2Cl_2 / MeOH / NH4OH 90/10/1	(KBr): C=0 1635/1732
AS31	A0	C72		100.0	EI: M^+ = 411	0.45	FM1	(KBr): C=0 1664
AS11	A0	C72		33.0	EI: M^+ = 497	0.30	FM1	(KBr): C=0 1630/1641

Example A32

Preparation of compounds of general formula:



1-[N^2-(3,5-dibromo-D-tyrosyl)-N^6-(phenylmethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)-piperazine

To a mixture of 4 g (4.7 mmol) of 1-[N^2-[N-(1,1-dimethylethoxycarbonyl)-3,5-dibromo-D-tyrosyl]-N^6-

(phenylmethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)-piperazine and 80 ml of methylene chloride were added 20 ml of trifluoroacetic acid and the reaction mixture was stirred overnight at room temperature. The reaction mixture was neutralised by the addition of saturated aqueous sodium hydrogen carbonate solution, the organic phase was dried over sodium sulphate and evaporated down *in vacuo*. 2.2 g (64% of theory) of an amorphous solid were obtained.

IR (KBr): 1643, 1680 cm^{-1} (C=O)

R_f: 0.5 (FM1)

ESI-MS: $(M+H)^+$ = 745/747/749 (Br_2)

The following were prepared analogously (in each case n = 1):

R^2	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]	Mp(°C)
AS7	A0	C4	crude product pure TFA	51		0.30	FM1		
AS1	A0	C11		95	ESI: $(M+H)^+$ = 503/5/7 (Br_2)			(KBr): C=0 1676	
AS4	A0	C20		100	ESI: $(M+H)^+$ = 500/2/4 (Br_2)				
AS1	A0	C4		100	ESI: $(M+H)^+$ = 481/3/5 (Br_2)			(KBr): C=0 1678	
AS4	A0	C11		74					

R^2	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]	Mp. (°C)
AS7	A0	C1	reacted as crude product	100					
AS4	A7	C1	reacted as crude product	100		0.40	EE/ MeOH 7/3 v/v		
AS1	A4	C1		64	ESI: $(M+H)^+$ =745/7/9 (Br_2)	0.50	FM1	(KBr): C=O 1643.3; 1679.9	
AS4	A0	C5		89		0.32	FM4	(KBr): C=O 1637.5	
AS4	A0	C15		93		0.33	FM4	(KBr): C=O 1618.2	
AS1	A0	C5		89		0.25	FM4	(KBr): C=O 1639.4	154-157
AS4	A0	C16	LC/ SiO_2/ FM4	90		0.30	FM4	(KBr): C=O 1635.5	
AS1	A0	C15		89		0.20	FM4	(KBr): C=O 1639.4	160-164
AS4	A0	C3	LC/ SiO_2/ FM4	98		0.37	FM4	(KBr): C=O 1683.8;	
AS4	A0	C6		89		0.28	FM4	(KBr): C=O 1637.5	
AS1	A0	C16		95		0.57	FM1	(KBr): C=O 1683.8	
AS1	A0	C6	LC/ SiO_2/ FM4	56	EI: M^+= 511/3/5 (Br_2)	0.24	FM4	(KBr): C=O 1637.5	
AS4	A0	C18		90	EI: M^+ = 512/4/6 (Br_2)	0.50	FM1	(KBr): C=O 1624.0	
AS4	A0	C37		93		0.24	FM4	(KBr): C=O 1635.5; 1684	
AS4	A0	C22		88	M^+ = 502/4/6 (Br_2)			(KBr): C=O 1618.2	
AS4	A0	C21		52	M^+ = 482/4/6 (Br_2)	0.55	FM1	(KBr): C=O 1681.8	
AS1	A0	C37		89		0.32	FM1	(KBr): C=O 1681.8	
AS4	A5	C1		roh				(KBr): C=O 1645; 1676	
AS4	A0	C23		88				(KBr): C=O 1643	
AS4	A10	C1		47	ESI: $(M+H)^+$ = 553/5/7 (Br_2)			(KBr): C=O 1653	
AS4	A5	C8		67	M^+ = 543/5/7			(KBr): C=O 1645	
AS4	A6	C1		59				(KBr): C=O 1643	
AS4	A0	C24		94	M^+= 489/91/93			(KBr): C=O 1618; 1637.5	
AS4	A6	C8		70				(KBr): C=O 1639.4	

R^2	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]	Mp. (°C)
AS4	A10	C8		82	M^+ = 557/9/61			(KBr): C=O 1651	
AS4	A0	C26		88				(KBr): C=O 1626	
AS1	A0	C1		96	ESI: $(M+H)^+$ = 483/5/7 (Br_2)	0.18	FM1	(KBr): C=O 1680	
AS1	A0	C8	crude	69					
AS1	A0	C18		82		0.27	FM1	(KBr): C=O 1684	
AS1	A0	C3		100		0.38	FM1	(KBr): C=O 1682	
AS1	A0	C21		89		0.26	FM1	(KBr): C=O 1595; 1615	
AS4	A0	C3		99		0.37	FM4	(KBr): C=O 1618; 1636; 1683	
AS4	A0	C19		98	ESI: $(M+H)^+$ = 498/500/502 (Br_2)	0.47	FM4	(KBr): C=O 1638; 1682	
AS9	A0	C1	crude product	96					
AS1	A7	C1		37		0.42	FM7		
AS4	A0	C38		80		0.25	FM1		
AS4	A0	C37		86					
AS4	A0	C39		73					
AS4	A0	C40		92	EI: M^+ = 515/7/9			(KBr): C=0 1674	
AS1	A0	C42		100 crude		0.32	FM1	(KBr): C=0 1682	
AS4	A0	C42		95		0.24	FM4	(KBr): C=0 1636/1684	
AS1	A0	C43		66		0.1	FM7	(KBr): C=0 1659	
AS1	A0	C44		59		0.15	CH_2Cl_2/ MeOH/ NH_4OH 90/10/1	(KBr): C=0 1676	
AS1	A0	C45		82	ESI: $(M+H)^+$ = 492/4/6 (Br_2)	0.10	EE/MeOH 9/1	(KBr): C=0 1678	
AS1	A0	C47		89		0.52	FM7	(KBr): C=0 1634/1666	
AS1	A0	C49		84		0.15	CH_2Cl_2/ MeOH/ NH_4OH	(KBr): C=0 1678	
AS4	A0	C44		93	EI: M^+= 504/6/8 (Br_2)	0.45	EE/ MeOH 9/1	(KBr): C=0 1653 ; CN 2239	
AS1	A0	C50		100	EI: M^+= 498/500/502 (Br_2)	0.10	EE/ MeOH 9/1	(KBr): C=0 1636	
AS1	A0	C51		100	EI: M^+ = 530/2/4 (Br_2)	0.05	EE/ MeOH/ NH4OH 5/5/0.1	(KBr): C=0 1678	

R^2	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]	Mp. (°C
AS4	A0	C52		97		0.15	FM1	(KBr): C=0 1620/1688	
AS4	A0	C53		58	ESI: $(M+H)^+$ = 502/4/6 (Br_2)	0.05	EE/ MeOH/ NH4OH 5/5/0.1	(KBr): C=0 1678	
AS4	A0	C64		100				(KBr): C=0 1647/1678	
AS1	A0	C53		70	EI: M^+ = 502/4/6 (Br_2)	0.15	CH_2Cl_2/ MeOH/ NH_4OH 70/30/1	(KBr): C=0 1676	
AS4	A0	C51		100		0.05	CH_2Cl_2/ MeOH/ NH_4OH	(KBr): C=0 1680	
AS4	A0	C66		100		0.27	CH_2Cl_2/ MeOH/ NH_4OH		
AS16	A0	C8		76		0.40	FM1		
AS16	A0	C1		28		0.20	EE/ MeOH/ NH_4OH 9/1/1		
AS4	A0	C70		96		0.20	EE/MEOH /NH4OH 80/20/0.5	(KBr): C=0 1676	
AS1	A0	C64		100	EI: M^+ = 510/1214			(KBr): C=0 1674	
AS1	A0	C70		100				(KBr): C=0 1674	
AS4	A0	C72		100	ESI: $(M+H)^+$ = 530/2/4 (Br_2)	0.10	CH_2Cl_2 / MeOH / NH4OH 80/20/1	(KBr): C=0 1678	
AS19	A0	C8		100					
AS35	A0	C8		72		0.60	FM1		
AS36	A0	C8		80		0.52	FM1	(KBr): C=0 1674	

Example A33

4-(4-pyridinyl)-1-[3-(4-pyridinyl)-D,L-alanyl]-piperazine-hydrochloride

16.4 g (0.04 mol) of 1-[N-[(1,1-dimethylethoxy)carbonyl]-3-(4-pyridinyl)-D,L-alanyl]-4-(4-pyridinyl)-piperazine, dissolved in 100 ml of methanol, were mixed with 20 ml of ethereal hydrochloric acid and the reaction mixture was heated to 40°C. The desired compound crystallised out of the reaction mixture.

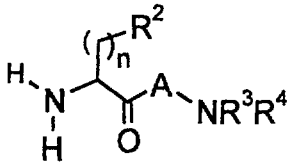
yield: 9.2 g (60% of theory)

R_f: 0.1 (FM1)

Mp.: 198 - 200°C

Example A34

Preparation of compounds of general formula:



1-[N^2-(3,5-dibromo-D-tyrosyl)-N^6-(1,1-dimethylethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)-piperazine

A mixture of 50 g (53.5 mmol) of 1-[N^2-[N-(9-fluorenyl-methoxycarbonyl)-3,5-dibromo-D-tyrosyl]-N^6-(1,1-dimethylethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)-piperazine and 300 ml of diethylamine was heated to 60°C with stirring. 100 ml of methanol were added and stirring was continued for a further 5 hours at 60°C. The reaction mixture was evaporated down *in vacuo* and the residue was purified by column chromatography (MN-silica gel 60, Macherey-Nagel, 70-230 mesh ASTM, eluant:

ethyl acetate/methanol = 6/4 (v/v)). 26 g (68% of theory) of a white foam were obtained.

IR (KBr): 1641, 1691 cm^{-1} (C=O)

R_f: 0.2 (ethyl acetate/methanol/conc. aqueous ammonia = 6/4/1 (v/v/v))

ESI- MS: $(M+H)^+$ = 710/712/714 (Br_2)

The following were prepared analogously:

R^2	A	NR^3R^4	n	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
AS1	A3	C4	1		85	ESI:M+H= 710/2/4(Br_2)	0.2	FM1	(KBr): C=0 1635.5; 1695.3
AS1	A3	C8	1		98				(KBr): C=0 1635; 1705
AS1	A3	C1	1		68	EI: M+=710/2/4 (Br_2)	0.2	Ethyl acetate/ methanol/ NH_4OH = 6/4/1 (v/v/v)	(KBr): C=O 1641.3; 1691.5
AS1	A3	C5	1	THF as solvent; purified by column chromatography silica gel / FM1	56	ESI:M+H= 711/3/5(Br_2)	0.3	FM1	(KBR):C=O 1695.3; 1635.5
AS1	A3	C6	1	THF as solvent; purified by column chromatograpy silica gel/ FM1	90	EI:M+= 739/41/43 (Br_2)	0.49	FM1	(KBr): C=O 1695.3; 1629.8
AS5	A3	C1	1	THF as solvent;purified by column chromatography silica gel/ FM4; diastereomer	93		0.25/ 0.37	FM4	(KBr): C=O 1705.0; 1643.3
AS10	A0	C1	1		71		0.5	FM1	(KBr): C=O 1641.3
AS1	A3	C18	1		94				(KBr): C=O 1647; 1722.5
AS10	A3	C1	1		49	M+= 694/6/8(Br_2)			(KBr): C=O 1643; 1703
AS10	A3	C4	1		46	ESI:M+H= 694/6/8(Br_2)			(KBr): C=O 1639.4; 1705
AS10	A3	C4	1		46	ESI:M+H= 694/6/8(Br_2)			(KBr): C=O 1639.4; 1705
AS10	A3	C1	1		49	M+= 694/68/70 (Br_2)			(KBr): C=O 1643; 1703
AS4	A3	C18	1		46	ESI:M+H= 741/3/5(Br_2)			(KBr): C=O 1641.3; 1705
AS15	A0	C8	1		100	M+:321			(KBr): C=O 1637.5
AS12	A0	C8	1		81				(KBr): C=O 1630
AS10	A0	C4	1	THF as solvent	68		0.38	FM4	(KBr): C=O 1635.5
AS1	A3	C1	0	crude product	100		0.3	FM7	

Example A35

1-[N^2-[N-[[[2-(2-methoxyphenyl)ethyl]amino]carbonyl]-3,5-dibromo-D-tyrosyl]-N^6-(phenylmethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)-piperazine

To a solution of 1.0 g (1.34 mmol) of 1-[N^2-(-3,5-dibromo-D-tyrosyl)-N^6-(phenylmethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)-piperazine in 80 ml of tetrahydrofuran were added 0.28 g (1.6 mmol) of 2-methoxyphenethyl isocyanate and the mixture was stirred for 3 days at room temperature. The reaction mixture was evaporated down *in vacuo* and the residue was purified by column chromatography (MN-silica gel 60, Macherey-Nagel, 70-230 mesh ASTM, eluant: methylene chloride/methanol/-cyclohexane/ammonia = 350/75/75/10 (v/v/v/v)). 0.5 g (40% of theory) of a colourless amorphous solid was obtained.

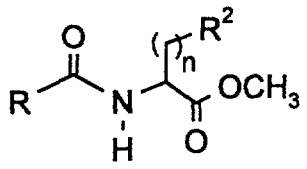
IR (KBr): 1639 cm^{-1} (C=O)

R_f: 0.49 (FM1)

ESI-MS: $(M+H)^+$ = 922/924/926 (Br_2)

Example A36

Preparation of compounds of general formula:



methyl 4-amino-3,5-dibromo-N^2-[[(2-phenylethyl)amino]-carbonyl]-D-phenylalanine

A mixture of 1.27 g (7.73 mmol) of CDT in 150 ml of tetrahydrofuran was mixed, whilst cooling with ice, with 0.72 ml (5.15 mmol) of triethylamine and 2.0 g (5.15 mmol) of methyl-4-amino-3,5-dibromo-D-phenylalanine-hydrochloride, stirred for a further 30 minutes whilst cooling with ice and stirred for 1 hour at room

temperature. Then 0.82 ml (6.44 mmol) of benzene ethanamine were added and the mixture was refluxed for 5 hours. The reaction mixture was evaporated down *in vacuo*, the residue was taken up in ethyl acetate and washed with saturated aqueous sodium hydrogen carbonate solution. After drying the organic phase the solvent was removed *in vacuo*, the residue was stirred with ether and the precipitate was filtered off. 1.69 g (66% of theory) of an amorphous solid were obtained.

IR (KBr): 1632, 1732 cm^{-1} (C=O)

R_f: 0.63 (ethyl acetate)

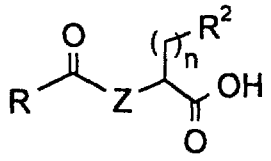
ESI-MS: $(M+H)^+$ = 498/500/502 (Br_2)

The following were prepared in the same way (in each case n = 1):

RCO	R^2	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
N6	AS1	further reacted as crude product	100		0.60	FM1	
N15	AS6	DMF/THF = 1/1 (v/v) as solvent	100	ESI: $(M+H)^+$ = 517/9 (Br)	0.65	FM1	(KBr): C=O 1745.5; 1676.0
N2	AS1		99		0.53	FM1	(KBr): C=O 1716.
N8	AS4		66	ESI: $(M+H)^+$ = 498/500/502 (Br_2)	0.63	ethyl acetate	(KBr): C=O 1631.7; 1732.0
N15	AS4		92		0.85	ethyl acetate/ methanol = 8/2 (v/v)	(KBr): C=O 1620.1; 1737.8
N23	AS4		95	EI: M^+ = 572/4/6/8 (Br_2,Cl)	0.86	ethyl acetate/ methanol = 8/2 (v/v)	(KBr): C=O 1732.0; 1641.3
N2	AS2		100	EI: M^+ = 406	0.86	FM1	(KBr): C=O 1629.8; 1722.3; 1741.6
N15	AS1	DIEA	47		0.75	FM1	
N15	AS3		38		0.60	t.-Butyl-methylether/ Petroleum ether = 9:1 v/v)	(KBr): C=O 1695.
N66	AS21		76		0.60	EE	(KBr): C=0 1662/ 1734
N66	AS1		100				
N66	AS4		63		0.56	FM1	
N122	AS1		95				
N122	AS4		88				
N66	AS17		22	ESI: $(M+H)^+$ = 623/5/7 (Br_2)	0.25	FM1	(KBr): C=0 1663/1740
N66	AS18		65		0.53	EE	
N66	AS19		79		0.50	FM1	(KBr): C=0 1663/1734
N66	AS5		90	ESI: $(M+H)^+$ = 607/09/11 (Br_2)	0.78	FM1	(KBr): C=0 1637 1663/ 1740
N66	AS22		68		0.74	FM1	
N66	AS23		100				(KBr): C=0 1738/1662
N66	AS25		100	ESI: $(M+H)^+$ = 472	0.52	FM1	
N66	AS49		100		0.80	FM1	

Example A37

Preparation of compounds of general formula:



4-amino-3,5-dibromo-N^2-[4-(2-chlorophenyl)-1-piperazinyl]carbonyl]-D-phenylalanine

To a solution of 2.8 g (4.9 mmol) of methyl 4-amino-3,5-dibromo-N^2-[4-(2-chlorophenyl)-1-piperazinyl]carbonyl]-D-phenylalanine in a mixture of 30 ml of methanol and 20 ml of water were added 0.25 g (10.0 mmol) of lithium hydroxide and the mixture was then stirred for 3 hours at room temperature. After the addition of 2.0 g (50 mmol) of sodium hydroxide the mixture was diluted with 50 ml of water. The reaction mixture was stirred for 15 minutes in an ultrasound bath, then stirred overnight at room temperature and evaporated down *in vacuo*. The residue was mixed with 100 ml of water and the aqueous phase was extracted twice with 50 ml of ether. By the addition of 2 M aqueous hydrochloric acid the aqueous phase was adjusted to a pH of 3 - 4 and extracted three times with ethyl acetate. The combined ethyl acetate phases were washed once with water, then dried and evaporated down *in vacuo*. 1.6 g (58% of theory) of a yellowish-brown oil were obtained.

IR (KBr): 1616, 1724 cm^{-1} (C=O)

R_f: 0.33 (ethyl acetate/methanol = 8/2 (v/v))

ESI-MS: $(M+H)^+$ = 557/559/561/563 (Br_2, Cl)

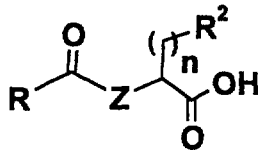
The following were prepared in the same way (in each case n = 1):

RCO	Z	R^2	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
N8	N-H	AS4		62	ESI: $(M-H)^-$ = 482/4/6 (Br_2)	0.61	Ethyl acetate/ Methanol = 6/4 (v/v)	(KBr): C=O 1612.4, 1724.3;-OH, -NH- 3386.8; 3483.2
N15	N-H	AS4		64	ESI: $(M-H)^-$ = 578/80/82 (Br_2); $(M+H)^+$ = 580/2/4 (Br_2); $(M+Na)^+$ = 602/4/6 (Br_2)	0.10	Ethyl acetate/ Methanol = 8/2 (v/v)	(KBr): C=O 1703.0
N23	N-H	AS4		58	ESI: $(M-H)^-$ = 557/59/61/63 (Br_2,Cl)	0.33	Ethyl acetate/ Methanol = 8/2 (v/v)	(KBr): C=O 1616.3; 1724.3
N15	N-H	AS1	no addition of sodium-hydroxide	59	ESI: $(M-H)^-$ = 579/81/83 (Br_2)	0.72	EE/ MeOH/ NH_4OH = 6/4/1 (v/v/v)	(KBr): C=O 1695.3
N66	N-H	AS21		95		0.48	EE/ AcOH 10/0.02 (v/v)	(KBr): C=0 1639
N66	CH2	AS1		85		0.38	CH_2Cl_2/ MeOH/ AcOH 9/1/0,15 (v/v/v)	
N71	CH2	AS1		66.6	ESI: $(M+H)^+$ = 606/08/10 (Br_2)	0.38	CH_2Cl_2/ MeOH/ AcOH 9/1/0,15 (v/v/v)	(KBr): C=0 1622/1680
N66	N-H	AS18		100	ESI: $(M-H)^-$ = 557	0.26	EE/ AcOH 9/0.01 (v/v)	
N66	N-H	AS19		98		0.22	CH_2Cl_2/ MeOH/ AcOH 9/1/0,15 (v/v/v)	(KBr): C=0 1665/1740
N66	N-H	AS5		73	ESI: $(M-H)^-$ = 577/79/81 (Br_2)	0.23	FM1	(KBr): C=0 1632/1705
N66	N-H	AS22		78		0.30	FM1	(KBr): C=0 1668/1739
N66	CH2	AS21		79		0.34	EE/ AcOH 9/0.01 (v/v)	(KBr): C=0 1643/1703
N66	CH2	AS1		90		0.30	EE/MeOH 9/1 (v/v)	
N15	CH2	AS1		78	ESI: $(M-H)^-$ = 578/80/82 (Br_2)	0.30	EE/ AcOH 9/0.01 (v/v)	(KBr): C=0 1728/1672

RCO	Z	R^2	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
N66	N-H	AS25		99				
N66	CH_2	AS2		100				(KBr): C=0 1645/1712
N66	CH_2	AS23		70				
N139	CH_2	AS2		50				(KBr): C=0 1630/1662/ 1707
N66	CH_2	AS27		93		0.20	FM1	
N66	CH_2	AS28	LiOH	100		0.30	FM1	
N66	CH_2	AS4		72		0.53	FM1	(KBr): C=0 1639/1701
N66	CH_2	AS36		74	ESI: $(M-H)^-$ = 434	0.36	FM1	(KBr): C=0 1645/1701
N66	CH_2	AS38		69				
N66	CH_2	AS48		47	EI: M^+ = 489	0.30	FM1	(KBr): C=0 1645
N66	N-H	AS49		47		0.10	FM1	
N66	CH_2	AS18		60		0.15	EE	
N66	CH_2	AS39		96				
N109	CH_2	AS21		81				
N113	CH_2	AS21		76		0.20	EE/AcOH 99/1	
N134	CH_2	AS21		89		0.15	EE/AcOH 99/1	
N66	CH_2	AS47		100	ESI: $(M+H)^+$ = 476			(KBr): C=0 1645/1716
N66	CH_2	AS7		60		0.20	FM1	(KBr): C=0 1649/1722
N66	CH_2	AS52		95	ESI: $(M+H)^+$ = 480	0.15	FM1	(KBr): C=0 1643/1722

Example A38

Preparation of compounds of general formula:



3,5-dibromo-N-[[[2-(3-methoxyphenyl)ethyl]-amino]carbonyl]-D-tyrosine

A mixture of 24 g (46.3 mmol) of methyl 3,5-dibromo-N-[[[2-(3-methoxyphenyl) ethyl]amino]carbonyl]-D-tyrosine and 5.0 g (50 mmol) of lithium hydroxide in 200 ml of water was stirred for 1 hour at 60 C. The solid product was suction filtered and the filtrate was washed with 200 ml of ethyl acetate. By the addition of 1 M aqueous hydrochloric acid the aqueous phase was adjusted to a pH of 3 - 4 and extracted 3 times with 150 ml of ethyl acetate. The combined ethyl acetate phases were washed once with water, dried over sodium sulphate and evaporated down *in vacuo*. The residue was triturated with ether. 9.1 g (38% of theory) of a colourless solid were obtained.

IR (KBr): 1719 cm^{-1} (C=O)

R_f: 0.57 (ethyl acetate/methanol/glacial acetic acid = 9.5/0.5/0.2 (v/v/v))

The following were prepared in the same way (in each case n = 1):

RCO	Z	R^2	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
N6	N-H	AS1		100		0.20	FM1	(KBr): C=0 1625.9; 1730
N15	N-H	AS6	H_2O/ MeOH = 1/1 (v/v) as solvent	85	ESI: $(M-H)^-$ = 501/3 (Br)	0.53	EE/ MeOH/ AcOH = 9/1/0.1 (v/v/v)	(KBr): C=O 1695.3
N2	N-H	AS1		75		0.57	EE/methanol /glacial acetic acid 9.5/0.5/0.2 (v/v/v)	(KBr): C=O 1718.5
N2	N-H	AS2		71		0.20	FM1	(KBr): C=O 1625.9; 1693.4; 1718.5; -NH- 3357.9
N15	N-H	AS3	H_2O/ MeOH = 1/1 (v/v) as solvent	57		0.30	EE/ MeOH = 1/1 (v/v)	(KBr): C=O 1693.4
N66		AS1		75		0.05	EE/MeOH 8/2	
N66		AS4		85				
N122		AS1		44				
N122		AS4		85				
N66	N-CH3	AS1		58	ESI: $(M-H)^-$ = 607/09/11 (Br_2)	0.20	EE	(KBr): C=0 1607/ 1655/ 1711
N66	N-H	AS17		55		0.03	FM1	
N15	CH2	AS1		78	ESI: $(M-H)^-$ = 578/80/82 (Br_2)	0.30	EE/ MeOH 9/1 (v/v)	(KBr): C=0 1672/ 1728
N66	N-H	AS23		79.0		0.22	FM1	(KBr): C=0 1738/1664

Example A39

methyl N^6-[(1,1-dimethylethoxy)carbonyl]-N^2-[N-[[[2-(3-methoxyphenyl)ethyl]amino]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysine

To a mixture of 10 g (19.4 mmol) of 3,5-dibromo-N-[[[2-(3-methoxyphenyl)ethyl] amino]carbonyl]-D-tyrosine, 2.6 g (20 mmol) of DIEA, 6.4 g (20 mmol) of TBTU, 2.64 g (19.5 mmol) of HOBt and 200 ml of dimethylformamide was added dropwise, with stirring, a solution of 5.04 g (19.4 mmol) of H-Lys(Boc)-OMe in 50 ml of

dimethylformamide and the mixture was stirred overnight at room temperature. The reaction mixture was evaporated down *in vacuo* and the residue was taken up in 250 ml of ethyl acetate. The ethyl acetate phase was then washed twice with 100 ml of saturated aqueous sodium hydrogen carbonate solution, once with 100 ml of 20% aqueous citric acid solution and finally once with 100 ml of saturated aqueous saline solution. The organic phase was dried with sodium sulphate, evaporated down *in vacuo* and the residue was purified by column chromatography (MN-silica gel 60, Macherey-Nagel, 70-230 mesh ASTM, eluant: ethyl acetate/ petroleum ether = 2/1 (v/v)). After removal of the solvent *in vacuo* the residue was triturated with ether, the amorphous solid obtained (9.5 g; 66% of theory) was suction filtered and dried.

IR (KBr): 1632; 1657, 1682, 1734 cm^{-1} (C=O)

R_f: 0.64 (ethyl acetate)

ESI-MS: $(M+H)^+$ = 757/759/761 (Br_2)

$(M+Na)^+$ = 779/781/783 (Br_2)

Example A40

N^6-[(1,1-dimethylethoxy)carbonyl]-N^2-[N-[[[2-(3-methoxyphenyl)ethyl]amino]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysine

A mixture of 7.75 g (10.4 mmol) of methyl N^6-[(1,1-dimethylethoxy)carbonyl]-N^2-[N-[[[2-(3-methoxyphenyl)ethyl]amino]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysine, 3.5 g (140 mmol) of lithium hydroxide and 150 ml of water was stirred overnight at room temperature. The aqueous phase was washed once with ethyl acetate, acidified by the addition of 1 M aqueous potassium hydrogen sulphate solution and then extracted with ethyl acetate. The organic phase was dried over sodium sulphate and evaporated down *in vacuo*. 6.9 g (91% of theory) of a yellowish oil were obtained.

IR (KBr): 1653 cm^{-1} (C=O)

R_f: 0.7 (ethyl acetate/methanol/glacial acetic acid = 9/0.5/0.5 (v/v/v))
ESI-MS: $(M-H)^-$ = 741/743/745 (Br_2)

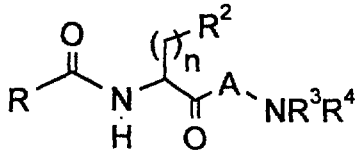
Example A41

1-[N^2-[N-(phenylmethoxycarbonyl)-3,5-dichloro-D-tyrosyl]-N^6-(1,1-dimethylethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)-piperazine

A mixture of 5 g (13.0 mmol) of 3,5-dichloro-N-[(phenylmethoxy)carbonyl]-D-tyrosine, 5.1 g (13.0 mmol) of 1-[N^6-[(1,1-dimethylethoxy)carbonyl]-L-lysyl]-4-(4-pyridinyl)-piperazine, 1.81 g (14 mmol) of DIEA, 4.17 g (13 mmol) of TBTU, 1.75 g (13.0 mmol) of HOBt and 200 ml of tetrahydrofuran was stirred at room temperature overnight. The reaction mixture was evaporated down *in vacuo*, the residue was taken up in ethyl acetate/methanol (95/5) and washed twice with saturated aqueous sodium hydrogen carbonate solution. The organic phase was dried, evaporated down *in vacuo* and the residue was purified by column chromatography (MN-silica gel 60, Macherey-Nagel, 70-230 mesh ASTM, eluant: ethyl acetate/methanol = 6/4 (v/v)). 6.0 g (61% of theory) of a yellowish oil were obtained.
R_f: 0.47 (FM1)
ESI-MS: $(M+H)^+$ = 757/759/761 (Cl_2)

Example A42

Preparation of compounds of general formula:



1-[N^2-[N-[[[2-(3-methoxyphenyl)ethyl]amino]carbonyl]-3,5-dibromo-D-tyrosyl]-N6-[(1,1-dimethylethoxy)-

carbonyl]-L-lysyl]-4-(1-methyl-4-piperidinyl)-piperazine

To a mixture of 1.1 g (1.5 mmol) of N^6-[(dimethylethoxy)carbonyl]-N^2-[N-[[[2-(3-methoxyphenyl)ethyl]amino]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysine, 0.79 g (6.1 mmol) of DIEA, 0.52 g (1.6 mmol) of TBTU, 0.2 g (1.5 mmol) of HOBt and 100 ml of dimethylformamide was added dropwise a solution of 0.44 g (1.5 mmol) of 1-(1-methyl-4-piperidinyl)-piperazine in 30 ml of dimethylformamide at room temperature, the mixture was then stirred overnight and evaporated down *in vacuo*. The residue was taken up in ethyl acetate/methanol (95/5), washed twice with 70 ml of aqueous saturated sodium hydrogen carbonate solution, dried over sodium sulphate and evaporated down *in vacuo*. 1.1 g (81% of theory) of a colourless foam were obtained.

R_f: 0.34 (ethyl acetate/methanol/conc. aqueous ammonia = 7/2/1 (v/v/v))

The following was prepared analogously (n = 1):

RCO	R^2	A	NR^3R^4	Remarks	% Yield	R_f	Eluant	IR [cm^{-1}]
N15	AS1	A11	C1	KHSO4-solution	70	0.40	FM3	(KBr): C=O1697.3; 1641.3

Example A43

1-[N^2-(3,5-dichloro-D-tyrosyl)-N^6-[(1,1-dimethylethoxy)carbonyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

A solution of 6 g (7.9 mmol) of 1-[N^2-[N-[(phenylmethoxy)carbonyl]-3,5-dichloro-D-tyrosyl]-N^6-[(1,1-dimethylethoxy)carbonyl]-L-lysyl]-4-(4-pyridinyl)-piperazine in a mixture of 200 ml of methanol and 20 ml of aqueous 1 M potassium hydrogen sulphate solution was

hydrogenated in the presence of 0.5 g palladium black as catalyst at room temperature under 3 bar of hydrogen pressure for 40 minutes. The catalyst was filtered off, the reaction mixture was evaporated to dryness *in vacuo* and the residue adjusted to a pH of about 10 by the addition of 2 ml of concentrated aqueous ammonia solution. The product was extracted several times with isopropanol, the combined isopropanol extracts were evaporated down *in vacuo* and the residue was purified by column chromatography (LiChroprep, Si60 particle size: 20-40 µm, Messrs. Merck (Darmstadt); eluant: methylene chloride / methanol / ammonia = 350/75/75/10 (v/v/v/v)). 2.5 g (51% of theory) of a colourless amorphous solid substance were obtained.

IR (KBr): 1641, 1705 cm^{-1} (C=O)

R_f: 0.27 (FM1)

Example A44

Preparation of compounds of general formula:

Fmoc-A-NR^3R^4

1-[N^2-[(9-fluorenylmethoxy)carbonyl]-N^G-(2,2,5,7,8-pentamethylchroman-6-sulphonyl)-L-arginyl]-4-(4-pyridinyl)-piperazine

To a mixture of 7.0 g (10.6 mmol) of Fmoc-Arg(Pmc)-OH, 1.42 g (11.0 mmol) of DIEA, 3.53 g (11.0 mmol) of TBTU, 1.35 g (11.0 mmol) of HOBt and 50 ml of DMF was added dropwise with stirring a solution of 1.74 g (10.6 mmol) of 1-(4-pyridinyl)-piperazine in 20 ml of DMF. The reaction mixture was stirred for a further 3.5 hours at room temperature and then evaporated down at 40°C in a high vacuum. The residue was dissolved in ethyl acetate, the organic phase was washed twice with saturated aqueous sodium hydrogen carbonate solution, dried over sodium sulphate and evaporated down *in vacuo*. The

residue was triturated with diethylether, suction filtered and dried. 7.85 g (96% of theory) of the desired end product were obtained, which was reacted without further purification.

R_f: 0.5 (FM1)

The following was prepared analogously:

A	NR^3R^4	% Yield	R_f	Eluant	IR [cm^{-1}]
A3	C18	60	0.55	FM4	(KBr): C=O 1643; 1711

Example A45

Preparation of compounds of general formula:

$$H—A—NR^3R^4$$

1-[N^G-(2,2,5,7,8-pentamethylchroman-6-sulphonyl)-L-arginyl]-4-(4-pyridinyl)-piperazine

A solution of 8.5 g (11.1 mmol) of 1-[N^2-[(9-fluorenylmethoxy)carbonyl]-N^G-(2,2,5,7,8-pentamethylchroman-6-sulphonyl)-L-arginyl]-4-(4-pyridinyl)-piperazine in 100 ml of THF was mixed with 16 ml of diethylamine and then stirred for 2.5 hours at room temperature. The reaction mixture was evaporated down *in vacuo* and the residue was purified by column chromatography (MN-silica gel 60, Macherey-Nagel, 70-230 mesh ASTM, eluant: FM1). 3.3 g (54% of theory) of an amorphous solid were obtained.

R_f: = 0.19 (FM1)

IR(KBr): 1637 cm^{-1} (C=O)

The following was prepared analogously:

A	NR^3R^4	% Yield	IR [cm^{-1}]
A3	C18	80	(KBr): C=O 1637.5; 1705

Example A46

1-[N^6,N^6-dimethyl-N^2-[(phenylmethoxy)carbonyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

9.6 g (18.3 mmol) of 1-[N^6-[(1,1-dimethylethoxy)-carbonyl]-N^2-[(phenylmethoxy)carbonyl]-L-lysyl]-4-(4-pyridinyl)-piperazine were stirred overnight in 200 ml of a 5% solution of trifluoroacetic acid in dichloromethane. The reaction mixture was then evaporated down *in vacuo*. 13.47 g (97% of theory) of the desired 1-[N^2-[(phenylmethoxy)carbonyl]-L-lysyl]-4-(4-pyridinyl)-piperazine were obtained as the trifluoroacetate salt. Then 7.0 g (9.1 mmol) of the crude product were dissolved in 200 ml of water and 4.1 ml of a 40% formaldehyde solution (45.6 mmol) were added whilst cooling with an ice bath. The reaction mixture was stirred for 10 minutes at room temperature, carefully mixed with 1.5 g (40 mmol) of sodium borohydride whilst cooling with an ice bath, then mixed with 4.1 ml of a 40% formaldehyde solution (45.6 mmol) whilst cooling externally with ice, after which the reaction mixture was stirred for a further 10 minutes at room temperature and again mixed with 1.5 g (40 mmol) of sodium borohydride whilst cooling with an ice bath. The pH of the reaction mixture was monitored continuously during the reaction and kept between pH 3 and pH 6 by dropwise addition of trifluoroacetic acid. The mixture was then stirred for 30 minutes at 5°C, adjusted to pH 10 by the addition of potassium carbonate and extracted four times with 50 ml of ethyl acetate. The combined

organic phases were dried, evaporated down *in vacuo* and the residue was purified by column chromatography (MN-silica gel 60, Macherey-Nagel, 70-230 mesh ASTM, eluant: ethyl acetate/methanol/conc. aqueous ammonia = 6.5/3/0.3 (v/v/v)). 2.3 g (56% of theory) of a colourless oil were obtained.

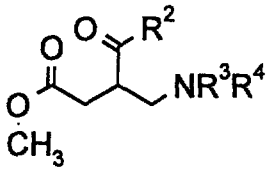
IR (KBr): 1711, 1649 cm^{-1} (C=O)

R_f: 0.2 (FM7)

ESI-MS: $(M+H)^+$ = 454

Example A47

Preparation of compounds of general formula:



methyl (R,S)-4-amino-3,5-dibromo-γ-oxo-β-[[4-(4-pyridinyl)-1-piperidinyl]methyl]-benzenebutanoate

A mixture of 10 g (27 mmol) of methyl 4-amino-3,5-dibromo-γ-oxo-benzenebutanoate, 5.4 g (27 mmol) of 4-(4-pyridinyl)-piperidine and 1.5 g (45 mmol) of paraformaldehyde was suspended in 20 ml of glacial acetic acid and heated with stirring in an oil bath (bath temperature: 100°C). After 3 hours a further 1.5 g (45 mmol) of paraformaldehyde were added and the mixture was stirred for a further 3 hours at 100°C and then for 1 hour at 125°C. The solvent was removed *in vacuo* and the residue was taken up in 800 ml of water. The aqueous phase was made alkaline by the addition of sodium carbonate and extracted twice with 500 ml of ethyl acetate. The combined ethyl acetate extracts were dried, evaporated down *in vacuo* and the residue was purified by column chromatography (MN-silica gel 60, Macherey Nagel, 70-230 mesh ASTM, eluant: ethyl acetate/methanol =

9:1)). 1.0 g (6.8% of theory) of the desired end product were obtained as an oil.

IR(KBr): 1716.5 cm^{-1}

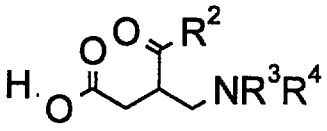
R_f: 0.7 (FM1)

The following was prepared analogously:

R2	NR^3R^4	% Yield	R_f	Eluant	IR [cm^{-1}]
AS4	C8	35	0.68	FM1	(KBr): C=O 1672.2; 1733.9

Example A48

Preparation of compounds of general formula:



(R,S)-4-amino-3,5-dibromo-γ-oxo-β-[[4-(4-pyridinyl)-1-piperidinyl]methyl]-benzenebutanoic acid

A mixture of 1.0 g (1.9 mmol) of methyl (R,S)-4-amino-3,5-dibromo-γ-oxo-β-[[4-(4-pyridinyl)-1-piperidinyl]methyl]-phenylbutanoate, 5 ml of 1 N sodium hydroxide solution and 50 ml of dioxane was stirred overnight at room temperature and for 1 hour at 60°C. The reaction mixture was then neutralised by the addition of 5 ml of 1N hydrochloric acid, evaporated down *in vacuo* and the residue was dried in a vacuum drying chamber. 0.97 g (100% of theory) of the desired product was obtained, which was further reacted without any purification.

R_f: 0.15 (FM1)

The following was prepared analogously:

R^2	NR^3R^4	% Yield	R_f	Eluant	IR [cm^{-1}]
AS4	C8	96	0.2	FM1	(KBr): C=O 1660

Example A49

3,5-dibromo-4-hydroxy-β-(methoxycarbonyl)-benzenebutanoic acid

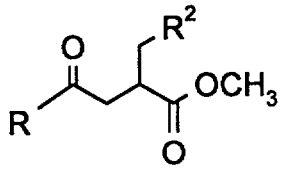
To a solution of 12 g (0.043 mol) of 4-hydroxy-β-(methoxycarbonyl)-benzenebutanoic acid in 200 ml of acetic acid were added 150 ml of water and 8 g of sodium acetate, a solution of 5 ml of bromine in 60 ml of acetic acid was added dropwise with stirring, then the reaction mixture was extensively evaporated down *in vacuo* and the residue was stirred into water. The aqueous phase was repeatedly extracted with ethyl acetate, and the combined organic phases were washed with water. The organic extracts were dried, evaporated down *in vacuo* and the solid residue was recrystallised from diisopropylether. 12 g (70% of theory) of the desired end product were obtained.

R_f: 0.4 (ethyl acetate/petroleum ether/glacial acetic acid = 5/5/0.4 (v/v/v)

ESI-MS: $(M+H)^+$ = 394/6/8 (Br_2)

Example A50

Preparation of compounds of general formula:



methyl (R,S)-2-[(3,5-dibromo-4-hydroxyphenyl)methyl]-4-[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]-4-oxo-butanoate

A solution of 2.0 g (5 mmol) of 3,5-dibromo-4-hydroxy-β-(methoxycarbonyl)-benzenebutanoic acid in 80 ml of THF was mixed with 1.6 g (5 mmol) of TBTU, 0.76 g (5 mmol) of HOBt, 1.25 g (5 mmol) of 4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)piperidine and 1.03 g (8 mmol) of DIEA with stirring. The reaction mixture was stirred for 6 hours at room temperature and then evaporated down *in vacuo*. The residue was mixed with saturated aqueous sodium hydrogen carbonate solution and extracted several times with ethyl acetate. The combined organic extracts were washed successively with saturated aqueous sodium hydrogen carbonate solution and water, dried over sodium sulphate and evaporated down *in vacuo*. 3.0 g (50% of theory) of the desired product was obtained, which was further reacted without purification.

IR (KBr): 1714.8 cm^{-1} (C=O)

R_f: 0.7 (ethyl acetate/petroleum ether = 7/3 (v/v))

The following were prepared analogously:

RCO	R^2	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
N66	AS1	98		0.66	FM1	
N66	AS2	100		0.77	FM1	(KBr): C=O 1664/1734
N139	AS2	100	EI: M^+ = 486	0.30	FM1	(KBr): C=O 1643 / 1672 / 1732
N66	AS4	28	EI: M^+ = 606/08/10 (Br_2)	0.33	FM4	(KBr): C=O 1666/1734
N66	AS36	63		0.56	FM4	
N66	AS38	92				
N66	AS48	100		0.68	FM1	
N66	AS18	22				
N66	AS39	100				
N109	AS21	39		0.35	EE	(KBr): C=O 1639/1734
N113	AS21	57		0.15	EE/PE 95/5	
N134	AS21	80		0.15	EE	
N66	AS7	100		0.75	FM1	
N66	AS53	40				

Example A51

(R)-1-[2-amino-3-(3,5-dibromo-4-hydroxyphenyl)propyl]-4-(1-piperidinyl)-piperidine

To a suspension of 3.8 g (100 mmol) of lithium aluminium hydride in 400 ml of THF were added in batches, with stirring and at room temperature, 14.4 g (20 mmol) of 1-(3,5-dibromo-D-tyrosyl)-4-(1-piperidinyl)-piperidine within 30 minutes. The reaction mixture was kept for 30 minutes at room temperature and refluxed for 2 hours and then neutralised by the careful addition of 1 ml of water and 5.1 ml of concentrated aqueous hydrochloric acid. After the addition of 100 ml of methanol the solid precipitate was suction filtered and the filtrate was evaporated down *in vacuo*. The residue was purified by column chromatography (MN-silica gel 60, Macherey-Nagel, 70-230 mesh ASTM, eluant: methylene chloride/methanol/conc. aqueous ammonia = 8/2/0.2 (v/v/v)). 5.4 g (57% of theory) of the desired product was obtained as an amorphous solid.

IR (KBr): 3420 cm^{-1} (NH_2)

R_f: 0.4 (FM2)

ESI-MS: M^+ = 473/475/477 (Br_2)

The following was prepared analogously:

(R)-1-[2-amino-3-(4-amino-3,5-dibromophenyl)propyl]-4-(1-piperidinyl)-piperidine from 1-(4-amino-3,5-dibromo-D-phenylalanyl)-4-(1-piperidinyl)-piperidine in a yield of 56.5% of theory, Rf 0.12 (eluant: dichloromethane/methanol/cyclohexane/conc. ammonia 7/1.5/1.5/0.2 (v/v/v/v)).

Example A52

(R)-1-[3-(4-amino-3,5-dibromophenyl)-2-[N-[(1,1-dimethylethoxy)carbonyl]amino]propyl]-4-(1-piperidinyl)-piperidine

To a solution of 10 g (0.017 mol) of 1-[4-amino-3,5-dibromo-N-[(1,1-dimethylethoxy)carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine in 350 ml of dioxane were added 3.1 g (0.082 mol) of sodium borohydride and the reaction mixture was cooled to 5°C. Then a solution of 4.92 g (0.082 mol) of acetic acid in 100 ml of dioxane was added dropwise with stirring. The reaction mixture was stirred for a further hour at room temperature and for 3 hours at 85°C. Then ice water was added, the organic solvent was removed *in vacuo* and the aqueous residue was repeatedly extracted with methylene chloride. The combined organic phases were dried, evaporated down *in vacuo* and the residue was purified by column chromatography (MN-silica gel 60, Macherey-Nagel, 70-230 mesh ASTM, eluant: methylene chloride/methanol/cyclohexane/conc. aqueous ammonia = 3600/150/150/20 (v/v/v/v). 4.1g (42% of theory) of a colourless foam were obtained.
IR (KBr): 1705 cm^{-1} (C=O)

Example A53

(R)-1-[2-amino-3-(4-amino-3,5-dibromophenyl)propyl]-4-(1-piperidinyl)-piperidine

To a mixture of 4 g (7 mmol) of (R)-1-[3-(4-amino-3,5-dibromophenyl)-2-[N-[(1,1-dimethylethoxy)carbonyl]-amino]propyl]-4-(1-piperidinyl)-piperidine and 100 ml of methylene chloride, 40 ml of trifluoroacetic acid were slowly added dropwise, with stirring, at 10°C. The reaction mixture was stirred for 2 hours at room temperature and then evaporated down *in vacuo*. The residue was mixed with ice water, made basic by the

addition of concentrated aqueous ammonia solution and extracted three times with 200 ml of diethylether. The combined ether extracts were dried and evaporated down *in vacuo*. 3.4 g (100% of theory) of an amorphous solid were obtained.

IR (KBr): 1683.8, 1616.3 (C=O)

R_f: 0.02 (FM 4)

Example A54

methyl (R,S)-4-[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]-4-oxo-2-[[3-(trifluoromethyl)phenyl]-methyl]-butanoate

Prepared analogously to Example A15a) from methyl (R,S)-3-carboxy-2-[[3-(trifluoromethyl)phenyl]methyl]-propanoate and 3,4-dihydro-3-(4-piperidinyl)-2(1H)-quinazolinone in a yield of 27.3% of theory. Colourless, amorphous substance, Rf = 0.25 (eluant: ethyl acetate).

MS: M^+ = 503

The following was obtained in the same way:

methyl (R,S)-4-[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]-4-oxo-2-[(3,5-dibromo-4-hydroxyphenyl)methyl]-butanoate from methyl (R,S)-3-carboxy-2-[(3,5-dibromo-4-hydroxyphenyl)methyl]-propanoate and 3,4-dihydro-3-(4-piperidinyl)-2(1H)-quinazolinone in a yield of 98% of theory, Rf = 0.66 (eluant: dichloromethane/cyclohexane/methanol/conc. ammonia 7/1.5/1.5/0.2 (v/v/v/v)).

Example A55

(R,S)-4-[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]-4-oxo-2-[(3,5-dibromo-4-hydroxyphenyl)methyl]-butanoic acid

A mixture of 3.0 g (4.92 mmol) of methyl (R,S)-4-[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]-4-oxo-2-[(3,5-dibromo-4-hydroxyphenyl)methyl]-butanoate, 30 ml (30 mmol) of 1N sodium hydroxide solution and 20 ml of methanol was stirred for 3 hours at room temperature, then diluted with 100 ml of water and 30 ml of 1N hydrochloric acid were added dropwise. The precipitate was suction filtered and dried at 50°C in a circulating air drier. Colourless, amorphous substance , Rf = 0.38 (eluant: dichloromethane/methanol/glacial acetic acid 9/1/0.15 (v/v/v)). Yield: 2.5 g (85.4% of theory).

The following was obtained in the same way:

(R,S)-4-[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]-4-oxo-2-[[3-(trifluoromethyl)phenyl]methyl]-butanoic acid from methyl(R,S)-4-[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]-4-oxo-2-[[3-(trifluoromethyl)phenyl]methyl]-butanoate in a yield of 79% of theory, Rf = 0.34 (eluant: ethyl acetate/glacial acetic acid 99.8/0.2 (v/v)).
IR(KBr): 1703, 1643 cm^{-1} (C=O)

Example A56

Methyl 3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-N-methyl-D-tyrosine

a) 1-(chlorocarbonyl)-4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]piperidine

To a mixture of 7.0 ml (about 14 mmol) of a 20% solution of phosgene in toluene and 2.02 g (20 mmol) of triethylamine in 300 ml of tetrahydrofuran was added in batches, while

maintaining a reaction temperature of about 0°C, a suspension of 1.5 g (5.60 mmol) of 4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]piperidine-hydrochloride in 100 ml of tetrahydrofuran. The mixture was stirred for another hour at a temperature between 0°C and +5°C, filtered to remove the resulting triethylamine-hydrochloride and the filtrate was freed from solvent. The residue was triturated with diisopropyl ether and suction filtered. After drying *in vacuo* 0.7 g (42.6% of theory) of colourless crystals were obtained, Rf = 0.17 (eluant: dichloromethane/acetone 9.5/0.5 (v/v)), which was further processed without any further purification.

b) Methyl 3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-N-methyl-D-tyrosine

To a solution of 4.9 g (13.3 mmol) of methyl 3,5-dibromo-N-methyl-D-tyrosine and 4.04 g (40 mmol) of triethylamine in 500 ml of tetrahydrofuran was added dropwise, at room temperature, within 3 hours, a solution of 3.92 g (13.34 mmol) of 1-(chlorocarbonyl)-4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]piperidine in 1 l tetrahydrofuran. The mixture was then heated for 12 hours to reflux temperature, left to cool and filtered to remove the precipitated triethylamine. The filtrate was evaporated down, the residue was divided between ethyl acetate and 20% aqueous citric acid. The organic phase was dried over sodium sulphate, again evaporated down *in vacuo*, the residue was purified by column chromatography over silica gel using ethyl acetate/petroleum ether 9/1 (v/v) as eluant. Working up the appropriate fractions yielded 3.2 g (38.5% of theory) of a colourless, amorphous substance, Rf = 0.45 (eluant: ethyl acetate).

IR(KBr): 1739.7, 1660.6 cm^{-1} (C=O)

ESI-MS: $(M+H)^+$ = 623/625/627 (Br_2)

$(M+Na)^+$ = 645/647/649 (Br_2)

$(M+K)^+$ = 661/663/665 (Br_2)

Example A57

Methyl 3,5-dibromo-4-methoxy-D-phenylalanine

To a mixture of 5.5 g (14.12 mmol) of 3,5-dibromo-4-methoxy-D-phenylalanine-hydrochloride and 55 ml of methanol were added 150 ml of a saturated methanolic hydrogen chloride solution and the mixture was stirred for 20 hours at room temperature. The residue remaining after evaporation of the solvent was stirred with 50 ml of water and adjusted to pH 8 with saturated sodium hydrogen carbonate solution. The precipitate was suction filtered, stirred with 10 ml of isopropanol and left to stand overnight. The insoluble matter was filtered off and the filtrate was evaporated down *in vacuo*. The residue was further reacted as a crude product. Yield: 1.0 g (28.7% of theory) of a colourless oil , Rf = 0.55 (eluant: dichloromethane/ethyl acetate/cyclohexane/methanol/conc. ammonia = 300/80/25/25/3 (v/v/v/v/v)).

Example A58

1-(4-amino-3,5-dibromo-D-phenylalanyl)-4-(4-pyrimidinyl)-piperazine

a) 1-(2-chloro-4-pyrimidinyl)-4-(phenylmethyl)piperazine

A mixture of 9.9 g (0.0664 mol) of 2,4-dichloropyrimidine, 200 ml of water and 11.7 ml (0.0673 mol) of 1-(phenylmethyl)piperazine was heated to 40°C for 2 hours in an ultrasound bath. After cooling the mixture was made alkaline with potassium carbonate and extracted thoroughly with ethyl acetate. The crude product obtained after working up in the usual way was purified by column chromatography over silica gel (30-60 µm) using FM2 and FM4 (2/1 v/v) as eluant. Working up the appropriate fractions yielded 7.4 g (38.6% of theory) of a colourless oil, Rf = 0.51 (FM4; Macherey-Nagel POLYGRAM® SIL G/UV_{254}, ready-made films for TLC).

MS: M^+ = 288/290 (Cl)

b) 1-(4-pyrimidinyl)piperazine

A solution of 7.4 g (0.0256 mol) of 1-(2-chloro-4-pyrimidinyl)-4-(phenylmethyl)piperazine in 100 ml of ethanol was hydrogenated in the presence of 2 g of 10% palladium/charcoal for 4 hours at 40°C under 5 bar of hydrogen pressure. The crude product obtained after conventional working up was purified by column chromatography over silica gel (30-60 µm) using FM1/cyclohexane 9/1 (v/v) as eluant. Colourless crystals, Rf = 0.3 (FM1/cyclohexane 9/1 (v/v)); Macherey-Nagel POLYGRAM® SIL G/UV_{254}, ready-made films for TLC). Yield: 1.7 g (40.7% of theory).

c) 1-[4-amino-3,5-dibromo-N-(1,1-dimethylethoxycarbonyl)-D-phenylalanyl)-4-(4-pyrimidinyl)piperazine

Prepared analogously to Example A15a) from 4-amino-3,5-dibromo-N-(1,1-dimethylethoxycarbonyl)-D-phenylalanine and 1-(4-pyrimidinyl)piperazine in the presence of TBTU in a yield of 92% of theory. Colourless, amorphous substance, Rf = 0.42 (FM4; Macherey-Nagel POLYGRAM® SIL G/UV_{254}, ready-made films for TLC).

IR(KBr): 1705.0, 1643.3 cm^{-1} (C=O)

MS: M^+ = 582/584/586 (Br_2)

d) 1-(4-amino-3,5-dibromo-D-phenylalanyl)-4-(4-pyrimidinyl)piperazine

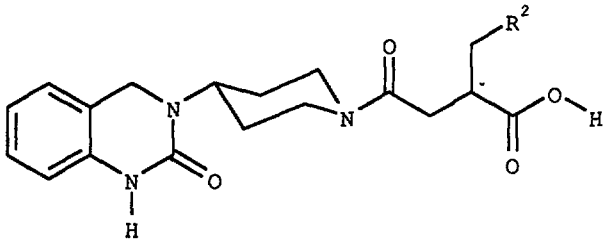
Prepared analogously to Example A1b) from 1-[4-amino-3,5-dibromo-N-(1,1-dimethylethoxycarbonyl)-D-phenylalanyl)-4-(4-pyrimidinyl)piperazine in a yield of 52% of theory. Colourless, amorphous substance, Rf = 0.55 (FM1; Macherey-Nagel POLYGRAM® SIL G/UV_{254}, ready-made films for TLC).

IR(KBr): 1681.8 cm^{-1} (C=O)

MS: M^+ = 482/484/486 (Br_2)

Example A59

Preparation of compounds of general formula:



(R,S)-4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[[4-(1,1-dimethylethyl)phenyl]methyl]-4-oxobutanoic acid

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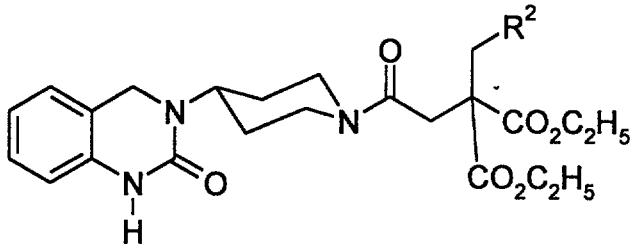
A mixture of 4.8 g (8.3 mMol) of ethyl 4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[[4-(1,1-dimethylethyl)phenyl]methyl]-2-(ethoxycarbonyl)-4-oxobutanoate, 200 ml of ethanol and 41.5 ml of 1N sodium hydroxide solution was refluxed for 3 hours.
The ethanol was removed *in vacuo*, then the residue was diluted with 50 ml of water and adjusted to pH 3 with 1N aqueous hydrochloric acid. The precipitated substance was suction filtered, thoroughly washed with water and then dried *in vacuo*. 3.8 g (96% of theory) of colourless crystals of Mp. 139 - 141 °C were obtained, R_f = 0.65 (eluant: EE/MeOH/glacial acetic acid 90/10/1 v/v/v).
IR(KBr): 1724, 1647 cm^{-1} (C=O)
MS: no M^+, m/e = 246, 231, 147

The following were prepared analogously:

R^2	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
AS29		100				
AS16		17	ESI: $(M+H)^+$ = 488/90/92 (Cl_2)	0.30	EE / MeOH / AcOH 80/10/1	
AS5		62		0.60	CH_2Cl_2 / MeOH / NH_4OH 90/10/1	
AS32		100	ESI: $(M+Na)^+$ = 614/6/8 (Br_2)	0.67	EE / MeOH / AcOH 90/10/1	(KBr): C=0 1645/1728
AS33		90	EI: M^+ = 525	0.20	EE / MeOH / AcOH 90/10/1	(KBr): C=0 1643/1701
AS31		100		0.20	CH_2Cl_2 / MeOH / NH_4OH 80/20/1	
AS17		100	ESI: $(M+H)^+$ = 608/10/12 (Br_2)	0.50	EE / MeOH / AcOH 90/10/1	(KBr): C=0 1643
AS34		76	ESI: $(M-H)^-$ = 506	0.65	EE / MeOH / AcOH 90/10/1	
AS19		70		0.46	EE / MeOH / AcOH 9/1/0.5	(KBr): C=0 1643/1701
AS46		78	ESI: $(M-H)^-$ = 471	0.20	FM1	(KBr): C=0 1647
AS50		97		0.05	EE	
AS2	LiOH instead of NaOH	86	ESI: $(M+H)^+$ = 472			(KBr): C=0 1643/1705
AS29		100	ESI: $(M-H)^-$ = 448			(KBr): C=0 1645/1705
AS31		87				

Example A60

Preparation of compounds of general formula:



Ethyl 4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[[4-(1,1-dimethylethyl)phenyl]methyl]-2-(ethoxycarbonyl)-4-oxobutanoate

A mixture of 2.31 g (10 mMol) of 4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-piperidine, 3.64 g (10 mMol) of β,β-bis-(ethoxycarbonyl)-4-(1,1-dimethylethyl)-benzenebutanoic acid, 5 ml of triethylamine, 3.5 g (11 mMol) of TBTU, 200 ml of tetrahydrofuran and 20 ml dimethylformamide was stirred for 5 hours at room temperature. The solvent was removed *in vacuo* and the residue taken up in dichloromethane, the resulting solution was dried over sodium sulphate and freed from the solvent. After purification by column chromatography on 400 g of silica gel (Amicon, 35 - 70 µm, ethyl acetate as eluant), 4.8 g (83% of theory) of a colourless, amorphous substance were obtained, R_f = 0.63 (eluant: EE).

IR(KBr): 1734, 1668, 1653 cm^{-1} (C=O)

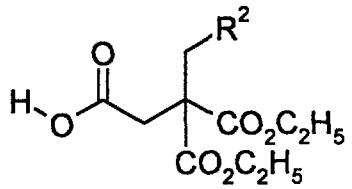
MS: M^+ = 577 (Br_2)

The following were prepared analogously:

R^2	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
AS29	75		0.8	FM1	
AS16	59		0.5	EE	
AS5	65	EI: M^+ = 677/79/81 (Br_2)	0.7	FM4	(KBr): C=0 1649 / 1668 / 1734
AS32	74		0.5	FM4	(KBr): C=0 1647 / 1668 / 1734
AS33	85		0.5	EE	(KBr): C=0 1649/1734
AS31	82	EI: M^+ = 574	0.5	CH_2Cl_2 / MeOH / NH_4OH 90/10/1	(KBr): C=0 1658/1741
AS17	93	EI: M^+ = 707/09/11 (Br_2)	0.5	EE	(KBr): C=0 1645 / 1666 / 1736 / 1759
AS34	75	EI: M^+ = 607	0.8	EE	(KBr): C=0 1649 / 1668 / 1736
AS19	67		0.8	FM1	(KBr): C=0 1647 / 1668 / 1734
AS46	80	EI: M^+ = 572	0.8	FM1	(KBr): C=0 1737
AS50	78	EI: M^+ = 677/9/81 (Br_2)	0.6	EE	(KBr): C=0 1645 / 1666 / 1730
AS2	51				

Example A61

Preparation of compounds of general formula:



β,β-bis-(ethoxycarbonyl)-1-methyl-1H-indol-3-butanoic acid

Produced analogously to Example A1b) from tert.-butyl β,β-bis-(ethoxycarbonyl)-1-methyl-1H-indol-3-butanoate through the action of trifluoroacetic acid in dichloromethane in a yield of 63.5% of theory. Colourless crystals of Mp. 127 - 130 °C (diisopropylether).

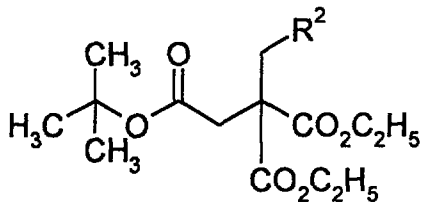
IR(KBr): 1738, 1712 cm^{-1} (C=O)

The following were prepared analogously:

R^2	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
AS29	100				
AS16	100		0.7	EE / MeOH / AcOH 97.5/2.2/0.25	
AS5	100		0.5	PE/EE 2/1	
AS32	100		0.58	PE/EE 2/1	(KBr): C=0 1759/1711
AS33	100				(KBr): C=0 1736
AS17	52				(KBr): C=0 1707 / 1726 / 1755
AS34	90		0.8	EE / MeOH / AcOH 97.5/2.5/0.25	(KBr): C=0 1705/1743
AS19	100		0.76	PE / EE / AcOH 6/3/1	(KBr): C=0 1738
AS46	92		0.35	FM1	(KBr): C=0 1732
AS50	71				(KBr): C=0 1712 / 1734 / 1759
AS2	31	EI: M^+ = 272	0.42	PE / EE / AcOH 6/4/0.2	(KBr): C=0 1711/1734

Example A62

Preparation of compounds of general formula:



Tert.-butyl β,β-bis-(ethoxycarbonyl)-3,5-dimethylbenzenebutanoate

To a solution of 13.8 g (50.2 mMol) of diethyl [(1,1-dimethylethoxycarbonyl)methyl]-malonoate in 400 ml of anhydrous tetrahydrofuran, 2.3 g (52.7 mMol) of sodium hydride was added whilst being externally cooled with iced water. After stirring for 30 minutes, and maintaining a reaction temperature of 0 to +5 °C, the solution of 10.0 g (50.2 mMol) of 3,5-dimethylbenzylbromide in 80 ml tetrahydrofuran was added dropwise and the mixture allowed to warm to room temperature within 14 hours. The reaction mixture was freed from the solvent *in vacuo*, 200 ml of 10% citric acid was added to the residue and the resulting mixture was thoroughly extracted with ethyl acetate. After the usual working up, the combined extracts yielded 19.7 g (100% of theory) of a colourless oil of R_f = 0.67 (eluant: dichloromethane), which was used in the following steps without further purification.

The following were prepared analogously:

R^2	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
AS29		100				
AS16		62		0.6	CH_2Cl_2	
AS5		91	ESI: $(M+H)^+$ = 521/3/5 (Br_2)	0.8	PE/EE 2/1	(KBr): C=O 1734
AS32		96		0.76	PE/EE 2/1	(KBr): C=O 1734
AS33		78		0.55	CH_2Cl_2	(KBr): C=O 1736
AS31	With use of 3-(dimethylaminomethyl)-1-methyl-1H-indol-methoiodide	74	EI: M^+ = 417	0.7	Toluene / t-BME 4/1	(KBr): C=O 1734
AS17		70	EI: M^+ = 550/52/54 (Br_2)	0.5	CH_2Cl_2	(KBr): C=O 1734
AS34		93	EI: M^+ = 450	0.5	CH_2Cl_2/PE 1/1	(KBr): C=O 1736
AS19		87		0.89	CH_2Cl_2	(KBr): C=O 1736
AS46		54	EI: M^+ = 415	0.7	FM4	
AS50		60	EI: M^+ = 520/22/24 (Br_2)	0.7	CH_2Cl_2	(KBr): C=O 1734

Example A63

(phenylmethyl)-β,β-bis-(ethoxycarbonyl)-4-(1,1-dimethylethyl)-benzenebutanoate

Prepared analogously to Example A62 from diethyl[(phenylmethoxycarbonyl)methyl]-malonoate and 4-(1,1-dimethylethyl)-benzylbromide in the presence of sodium hydride in a yield of 53% of theory.
Colourless oil of R_f = 0.21 (eluant: dichloromethane/petroleum ether 2/1 v/v).
IR(KBr): 1738 cm^{-1} (C=O)

Example A64

Methyl 4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[[3-(1-methylethoxy)phenyl]methyl]-4-oxobutanoate

To a solution of 2.0 g (4.43 mMol) of methyl 4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3-hydroxyphenyl)methyl]-4-oxobutanoate in 30 ml of anhydrous dimethylformamide, 0.2 g (4.4 mMol) of a 55% suspension of sodium hydride in paraffin oil was added. After stirring for 30 minutes at room temperature, 0.5 ml (4.8 mMol) of isopropyliodide was added dropwise, and kept for two hours each at room temperature and at 70 °C. The residue remaining after removal of the volatile constituents was divided between water and ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried over magnesium sulphate and was again evaporated down. The raw product was purified by column chromatography on silica gel (60 µm), first using dichloromethane, later methanol/conc. ammonia (9/1 v/v) as eluants. Yield was 0.9 g (42% of theory) of a colourless, amorphous substance of R_f = 0.32 (FM4).

IR(KBr): 1734, 1668 cm^{-1} (C=O)

MS: M^+ = 493

In the same way, methyl 4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3-ethoxyphenyl)-methyl]-4-oxobutanoate was obtained from methyl 4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3-hydroxyphenyl)methyl]-4-oxobutanoate and ethyliodide in a yield of 67% of theory. Colourless, amorphous substance of R_f = 0.29 (FM4).

IR(KBr): 1734, 1666 cm^{-1} (C=O)

MS: M^+ = 479

Example A65

β,β-bis-(ethoxycarbonyl)-4-(1,1-dimethylethyl)-benzenebutanoic acid

Prepared analogously to example A58b) from phenyl methyl β,β-bis-(ethoxycarbonyl)-4-(1,1-dimethylethyl)-benzenebutanoate by catalytic hydrogenation in the presence of palladium/charcoal in a yield of 95% of theory.
Colourless, highly-viscous oil of R_f = 0.16 (eluant: dichloromethane).
IR(KBr): 1739 cm^{-1} (C=O)

Example A66

1-methyl-4-[(1-piperazinyl)carbonyl]-piperazine-bis-(trifluoroacetate)

a) 4-[[4-(1,1-dimethylethoxycarbonyl)-1-piperazinyl]carbonyl]-1-methylpiperazine
To a solution of 1.1 g of triphosgene (3.7 mMol) in 20 ml of dichloromethane, a mixture of 1.2 g (10 mMol) of 1-methylpiperazine, 0.38 ml (22 mMol) of DIEA and 35 ml of dichloromethane was added dropwise at room temperature within 30 minutes, and then the solution of 1.9 g (10 mMol) of 1-(1,1-dimethylethoxycarbonyl)piperazine and 0.38 ml of DIEA in 20 ml dichloromethane were added. After stirring for an hour at room temperature, insoluble matter was filtered off and the filtrate evaporated down *in vacuo*. After purification of the raw product on silica gel (Amicon, 35 - 70 μm), using dichloromethane/methanol/conc. ammonia(80/20/1 v/v/v) for elution, 700 mg (22% of theory) of colourless crystals were obtained of Mp. 130 °C.
IR(KBr): 1691, 1641 cm^{-1} (C=O)

b) 1-methyl-4-[(1-piperazinyl)carbonyl]-piperazine-bis-(trifluoroacetate)

Prepared analogously to Example A1b), but omitting the treatment with aqueous ammonia, from 4-[[4-(1,1-dimethyl-ethoxycarbonyl)-1-piperazinyl]carbonyl]-1-methylpiperazine and trifluoroacetic acid in a yield of 99.6% of theory.
Colourless, amorphous substance of R_f = 0.17 (eluant: dichloromethane/methanol/conc. ammonia 50/50/0.5).
IR(KBr): 1678 cm^{-1} (C=O)
MS: M^+ = 212

Example A67

1-[4-[4-(dimethylamino)butyl]phenyl]-piperazine-dihydrochloride

a) N,N-dimethyl-4-fluoro-γ-oxobenzenebutanoic acid amide

To a solution of 30.5 g (0.155 Mol) of 4-fluoro-γ-oxobenzenebutanoic acid in 470 ml tetrahydrofuran, 35.0 g (0.216 Mol) of N,N'-carbonyldiimidazole was added with stirring and at room temperature and held at room temperature for a further 2.5 hours. Then, 13.7 g (0.304 Mol) of dimethylamine was added under strong external cooling by means of an ice-ethanol mixture. After the mixture had stood at room temperature for 12 hours, the solvent was removed *in vacuo*, the residue was divided between dichloromethane and 10% aqueous citric acid solution, the organic phase was dried over sodium sulphate and once again evaporated down *in vacuo*. After purification by column chromatography (eluant: ethyl acetate) on silica gel the crude product yielded 30.22 g (87% of theory) of colourless crystals of R_f = 0.31 (eluant: ethyl acetate/glacial acetic acid 99.99/0.01).
IR(KBr): 1680, 1647 cm^{-1} (C=O)

b) N,N-dimethyl-γ-oxo-4-[4-(phenylmethyl)-1-piperazinyl]-benzenebutanoic acid amide

The mixture of 33.48 g (0.15 Mol) of N,N-dimethyl-4-fluoro-γ-oxobenzenebutanoic acid amide, 29.6 g (0.168 Mol) of 1-(phenylmethyl)piperazine and 6 ml of DIEA was refluxed for 6 hours. Another 30 g (0.17 Mol) of (phenylmethyl)piperazine was added, and the mixture was refluxed for a further 7 hours. The mixture was taken up in a little dichloromethane, and purified by column chromatography on silica gel, using dichloromethane/methanol/conc. ammonia 99/1/0.5 for elution. The residue obtained from the appropriate fractions was stirred with diisopropylether, the formed crystals were then recrystallised from ethanol. 42.22 g (74% of theory) of colourless crystals were obtained, R_f = 0.69 (eluant: dichloromethane/methanol/conc. ammonia 95/5/0.5 v/v/v).
IR(KBr): 1662, 1643 cm^{-1} (C=O)

c) 4-[4-[4-(dimethylamino)-1-hydroxybutyl]phenyl]-1-(phenylmethyl)piperazine

Prepared analogously to example A51 from N,N-dimethyl-γ-oxo-4-[4-(phenylmethyl)-1-piperazinyl]-benzenebutanoic acid amide by reduction with lithium aluminium hydride in a yield of 61% of theory. Colourless, amorphous substance of R_f = 0.62 (eluant: ethyl acetate/methanol 1/1 v/v).
MS: M^+ = 367

d) 1-[4-[4-(dimethylamino)butyl]phenyl]-piperazine-dihydrochloride

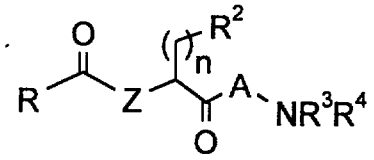
Prepared analogously to example A20b) from 4-[4-[4-(dimethylamino)-1-hydroxybutyl]phenyl]-1-(phenylmethyl)piperazine by catalytic hydrogenation in the presence of palladium/charcoal and hydrochloric acid in a quantitative yield. Colourless, amorphous substance of R_f = 0.37 (eluant: ethyl acetate/methanol 50/50/0.5 v/v/v).

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B. Preparation of the final compounds

Example 1

Preparation of compounds of general formula:



1-[N-[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-4-(4-pyridinyl)-piperazine (No. 83)

A mixture of 2 g (3.44 mmol) of 3.5-dibromo-N^2-[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]-carbonyl]-D-tyrosine, 0.59 g (3.6 mmol) of 1-(4-pyridinyl)-piperazine, 1.27 g (3.96 mmol) of TBTU, 0.47 g (3.44 mmol) of HOBt, 0.7 ml (3.96 mmol) of DIEA and 100 ml tetrahydrofuran was stirred overnight at ambient temperature. The reaction mixture was extracted once with saturated aqueous saline solution, twice with saturated aqueous sodium hydrogen carbonate solution and again with saturated aqueous saline solution. The organic phase was dried, evaporated down *in vacuo* and the crude product was then purified by column chromatography (MN-silica gel 60, Macherey-Nagel, 70-230 mesh ASTM, eluant: ethyl acetate/methanol = 9/1/ (v/v/)). 550 mg (22% of theory) of an amorphous solid were obtained.

IR (KBr): 1601, 1636, 1696 cm^{-1} (C=O)

R_f: 0.67 (FM2)

ESI-MS: $(M+H)^+$ = 726/728/730 (Br_2)

The following were prepared analogously (in each case n = 1):

No.	RCO	Z	R^2	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
	N6	N-H	AS1	A3	C4		88	ESI: $(M+H)^+$ = 928/30/32 (Br_2)	0.8	FM1	(KBr): C=0 1629.8; 1708.8
193	N15	N-H	AS6	A0	C7	DMF as solvent	26	ESI: $(M+H)^+$ = 647/9 (Br)	0.9	EE/ MeOH/ AcOH 75/23/2 v/v/v	(KBr): C=O 1693.4; 1622.0
194	N66	N-H	AS1	A0	C67		49	ESI: $(M+H)^+$ = 828/30/32 (Br_2)	0.33	FM1	(KBr): C=O 1622/1664
202	N15	N-H	AS1	A0	C36	DMF as solvent; DIEA	9	ESI: $(M+H)^+$ = 733/5/7 (Br_2)	0.49	FM1	(KBr): C=O 1695.3; 1622.0 NH 3417.7
203	N15	N-H	AS1	A0	C29	DMF as solvent; DIEA	41	ESI: $(M-H)^-$ = 718/20/ 22 (Br_2)	0.58	EE/MeOH 9/1 v/v	(KBr): C=O 1695.3
204	N15	N-H	AS1	A0	C30	DMF as solvent; DIEA	27	ESI: $(M+H)^+$ = 691/3/5 (Br_2)	0.1	FM1	(KBr): C=O 1695.3; 1624.0
205	N15	N-H	AS6	A0	C8	DMF as solvent; DIEA	23	ESI: $(M+H)^+$ = 653/5 (Br)	0.46	FM1	(KBr): C=O 1695.3; 1622.0
206	N15	N-H	AS1	A0	C31	DMF as solvent; DIEA	33	ESI: $(M+H)^+$ = 717/19/21 (Br_2)	0.25	FM1	(KBr): C=O 1695.3; 1624.0
207	N15	N-H	AS1	A0	C32	DMF as solvent; DIEA	55	ESI: $(M-H)^-$ = 780/2/4 (Br_2)	0.46	FM1	(KBr): C=O 1690; 1650
212	N15	N-H	AS1	A7	C1	DMF as solvent; DIEA	37	ESI: $(M+H)^+$ = 882/4/6 (Br_2)	0.27	FM1	(KBr): C=O 1697.3; 1639.4 NH 3423.4
217	N15	N-H	AS6	A3	C1		51		0.9	FM1	(KBr): C=O 1693.4; 1641.3
222	N15	N-H	AS1	A0	C8	THF/DMF 1/1 as solvent NEt_3 as base	10	ESI: $(M+H)^+$ = 774/6/8 (Br_2)	0.35	FM1	(KBr): C=O 1695.3
286	N15	N-H	AS1	A0	C28	THF/DMF 1/1 as solvent NEt_3 as base	9	ESI: $(M+H)^+$ = 706/8/10 (Br_2)	0.4	FM1	(KBr): C=O 1699.2
81	N15	N-H	AS4	A0	C4		64	ESI: $(M+H)^+$ = 724/6/8 (Br_2); $(M+Na)^+$ = 746/48/50 (Br_2)	0.75	FM1	(KBr): C=O 1618.2; 1703.0

No.	RCO	Z	R^2	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
82	N15	N-H	AS4	A0	C1		53	ESI: $(M+H)^+$ = 725/7/9 (Br_2)	0.55	FM3	(KBr): C=O 1620.1; 1703.0
84	N66	N-H	AS21	A0	C68		31	ESI: $(M+H)^+$ = 683	0.52	FM1	(KBr): C=O 1608/ 1628/ 1666
85	N15	N-H	AS4	A0	C7		42	ESI: $(M+H)^+$ = 724/6/8 (Br_2); $(M+Na)^+$ = 746/48/50 (Br_2)	0.8	FM1	(KBr): C=O 1618.2; 1697.3; -NH-, $-NH_2$ 3379.1
90	N15	N-H	AS1	A0	C8		40	ESI: $(M+H)^+$ = 731/3/5 (Br_2)	0.78	FM2	(KBr): C=O 1624.0; 1697.3
	N2	N-H	AS2	A3	C1	DMF as solvent; DIEA	73	ESI: $(M+H)^+$ = 766	0.42	FM1	(KBr): C=O 1654.2; 1708.8
354	N15	N-H	AS1	A0	C4		21	ESI: $(M+H)^+$ =725/7/9 (Br_2); $(M+Na)^+$ = 747/49/51 (Br_2)	0.76	FM2	(KBr): C=O 1622.0; 1695.3; -OH, NH- 3417.7
98	N15	N-H	AS1	A0	C9		60	ESI: $(M+H)^+$ = 580/2/4 (Br_2) ; $(M-H)^-$ = 578/80/82 (Br_2); $(M+Na)^+$ = 602/4/6 (Br_2)	0.41	FM2	(KBr): C=O 1624.0; 1685.7; -OH, -NH- 3421.5
102	N15	N-H	AS1	A0	C12		43	ESI: $(M+H)^+$ = 636/38/40 (Br_2); $(M+Na)^+$ = 658/60/62 (Br_2)	0.76	FM2	(KBr): C=O 1622.0; 1695.3;
99	N15	N-H	AS1	A0	C10		54	ESI: $(M+H)^+$ = 663/5/7 (Br_2)	0.61	FM2	(KBr): C=O 1622.9; 1700.9; -OH, NH- 3421.5
100	N15	N-H	AS1	A0	C11		54	ESI: $(M+H)^+$ = 746/48/50 (Br_2)	0.5	FM2	(KBr): C=O 1624.0; 1695.3; -NH-, -OH 3423.4;
101	N15	N-H	AS1	A0	C7		62	ESI: $(M+H)^+$ = 725/7/9 (Br_2); $(M+Na)^+$ = 747/49/51 (Br_2)	0.82	FM2	(KBr): C=O 1622.0; 1695.3; -OH, NH- 3253.7

No.	RCO	Z	R^2	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
103	N15	N-H	AS1	A0	C13		37	ESI: $(M+H)^+$ = 679/81/83 (Br_2)	0.72	FM2	(KBr): C=O 1625.9; 1693.4; 1666.4; -OH, NH- 3409.9
106	N15	N-H	AS1	A0	C14		72	ESI: $(M+H)^+$ = 832/4/6 (Br_2); $(M+Na)^+$ = 854/6/8 (Br_2)	0.66	FM1	(KBr): C=O 1674.1; 1689.5
104	N15	N-H	AS6	A0	C4		36	ESI: $(M+H)^+$ = 647/9 (Br); $(M+Na)^+$ = 669/71 (Br); $(M-H)^-$ 645/7 (Br)	0.71	FM1	(KBr): C=O 1695.3
105	N15	N-H	AS6	A0	C1		25	ESI: $(M+H)^+$ = 648/50 (Br)	0.25	FM3	(KBr): C=O 1695.3
	N2	N-H	AS1	A12	C1	DMF as solvent; DIEA	72	ESI: $(M+H)^+$ = 1082/4/6 (Br_2)	0.4	FM1	KBr : C=O 1641
199	N15	N-H	AS3	A0	C8	THF/DMF = 9/1 (v/v) as solvent	86	ESI: $(M+H)^+$ = 643/5/7 (Br_2)	0.37	Ethyl acetate/ Methanol/ Petroleum ether =1/2/1(v/v/v)	KBr : C=O 1697; 1624
200	N15	N-H	AS3	A0	C1		40	ESI: $(M+H)^+$ = 638/40/42 (Br_2)	0.45	Ethyl acetate/ Methanol/ Petroleum ether =1/2/1(v/v/v)	KBr : C=O 1695; 1636
419	N66	N-H	AS21	A0	C38		28	ESI: $(M+H)^+$ = 682	0.1	FM1	(KBr): C=0 1628/ 1662
425	N66	N-H	AS1	A0	C36		42	ESI: $(M+H)^+$ = 747/49/51 (Br_2)	0.4	FM1	(KBr): C=0 1624/1657
426	N66	N-H	AS4	A0	C30		66	ESI: $(M+H)^+$ = 704/6/8 (Br_2)	0.45	FM1	(KBr): C=0 1618/1663
427	N66	N-H	AS1	A0	C31		38	ESI: $(M+H)^+$ = 731/3/5 (Br_2)	0.2	FM1	(KBr): C=0 1630/1653
428	N66	N-H	AS4	A0	C36		40	ESI:$(M+H)^+$ = 746/48/50 (Br_2)	0.6	FM1	(KBr): C=0 1618/1662
429	N66	N-H	AS1	A0	C30		47	ESI: $(M+H)^+$ = 705/7/9 (Br_2)	0.15	FM1	(KBr): C=0 1635/1653
435	N66	N-H	AS4	A0	C31		20	ESI: $(M+H)^+$ = 730/2/4 (Br_2)	0.55	FM1	(KBr): C=0 1608/1631

No.	RCO	Z	R^2	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
436	N66	N-H	AS1	A0	C11		15	ESI:$(M+H)^+$ = 760/2/4 (Br_2)	0.1	FM1	(KBr): C=0 1624/1653
437	N66	N-H	AS4	A0	C11		25	ESI: $(M+H)^+$ = 759/61/63 (Br_2)	0.5	FM1	(KBr): C=0 1622/1661
438	N66	N-H	AS4	A0	C54		13	ESI: $(M+H)^+$ = 744/6/8 (Br_2)	0.7	FM1	(KBr): C=0 1620/1660
439	N66	N-H	AS1	A0	C54		31	ESI: $(M+H)^+$ = 745/7/9 (Br_2)	0.5	FM1	(KBr): C=0 1626/1661
439	N66	N-H	AS1	A0	C54		31	ESI: $(M+H)^+$ = 745/7/9 (Br_2)	0.5	FM1	(KBr): C=0 1626/1661
443	N122	N-H	AS1	A0	C11		44	ESI: $(M+H)^+$ = 790/2/4 (Br_2)	0.1	FM1	(KBr): C=0 1624/1680
444	N122	N-H	AS1	A0	C8		62	ESI: $(M+H)^+$ = 775/7/9 (Br_2)	0.18	FM1	(KBr): C=0 1624/1678
445	N122	N-H	AS1	A0	C1		60	ESI: $(M+H)^+$ = 770/2/4 (Br_2)	0.2	FM1	(KBr): C=0 1630/1680
446	N122	N-H	AS1	A0	C20		59	ESI: $(M+H)^+$ = 789/91/93 (Br_2)	0.15	FM1	(KBr): C=0 1622/1680
447	N122	N-H	AS4	A0	C1		54	ESI: $(M+H)^+$ = 769/71/73 (Br_2)	0.6	FM1	(KBr): C=0 1622/1682
448	N122	N-H	AS4	A0	C20		68	ESI: $(M+H)^+$ = 788/90/92 (Br_2)	0.5	FM1	(KBr): C=0 1620/1682
449	N122	N-H	AS4	A0	C8		59	ESI: $(M+H)^+$ = 774/6/8 (Br_2)	0.58	FM1	(KBr): C=0 1620/1682
450	N66	N-CH_3	AS1	A0	C4		36	ESI: $(M+H)^+$ = 753/5/7 (Br_2)	0.39	FM1	(KBr): C=0 1653
451	N66	CH_2	AS1	A0	C1		20	ESI: $(M+H)^+$ = 739/41/43 (Br_2)	0.3	FM1	(KBr): C=0 1638
452	N71	CH_2	AS1	A0	C1		16	ESI: $(M+H)^+$ = 751/53/55 (Br_2)	0.4	FM1	(KBr): C=0 1638/1680
453	N66	CH_2	AS1	A0	C11		17	ESI: $(M+H)^+$ = 758/60/62 (Br_2)	0.13	FM1	(KBr): C=0 1636
454	N66	CH_2	AS1	A0	C20		33	ESI: $(M+H)^+$ = 757/59/61 (Br_2)	0.23	FM1	(KBr): C=0 1632
455	N71	CH_2	AS1	A0	C8		35	EI: M^+ = 755/7/9 (Br_2)	0.42	FM1	(KBr): C=0 1624/1684

No.	RCO	Z	R^2	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
457	N71	CH_2	AS1	A0	C4		49	ESI: $(M+H)^+$ = 750/2/4 (Br_2)	0.77	FM1	(KBr): C=0 1626/1682
458	N71	CH_2	AS1	A0	C37		25	ESI: $(M+H)^+$ = 769/71/73 (Br_2)	0.2	FM1	(KBr): C=0 1638/1682
459	N66	CH_2	AS1	A0	C37		50	EI: M^+ = 757/59/61 (Br_2)	0.2	FM1	(KBr): C=0 1636
460	N66	N-H	AS1	A0	C55		72	ESI: $(M+H)^+$ = 759/61/63 (Br_2)	0.27	EE/ MeOH/ NH_4OH = 8/1.5/0.1 v/v/v	(KBr): C=0 1626/1661
461	N66	N-H	AS1	A0	C56		77	ESI: $(M+H)^+$ = 731/3/5 (Br_2)	0.77	FM1	(KBr): C=0 1626/1661
462	N66	N-H	AS17	A0	C8		51	ESI: $(M+H)^+$ = 759/61/63 (Br_2)	0.44	FM1	(KBr): C=0 1628/1663
463	N66	N-H	AS18	A0	C1		59	ESI: $(M+H)^+$ = 704	0.7	FM1	(KBr): C=0 1661
464	N66	N-H	AS18	A0	C8		51	ESI: $(M+H)^+$ = 709	0.76	FM1	(KBr): C=0 1628/1663
465	N66	N-H	AS18	A0	C37		73	ESI: $(M+H)^+$ = 723	0.7	FM1	(KBr): C=0 1628/1663
469	N66	N-H	AS19	A0	C8		34	ESI: $(M+H)^+$ = 651/53 (Br)	0.34	FM1	(KBr): C=0 1626/1664
471	N66	N-H	AS20	A0	C8		41	ESI: $(M+H)^+$ = 649	0.68	FM1	(KBr): C=0 1624/1684
472	N66	N-H	AS5	A0	C8		26	ESI: $(M+H)^+$ = 729/31/33 (Br_2)	0.73	FM1	(KBr): C=0 1626/1664
475	N66	N-H	AS18	A0	C20		58	ESI: $(M+H)^+$ = 723	0.22	FM1	(KBr): C=0 1628/1664
476	N66	N-H	AS18	A0	C11		44	ESI: $(M+H)^+$ = 724	0.27	MeOH	(KBr): C=0 1630/1662
478	N66	N-H	AS19	A0	C37		62	ESI: $(M+H)^+$ = 665/7 (Br)	0.8	FM1	(KBr): C=0 1626/1662
479	N66	N-H	AS19	A0	C20		55	ESI: $(M+H)^+$ = 665/7 (Br)	0.64	FM1	(KBr): C=0 1664
480	N66	N-H	AS19	A0	C4		55	ESI: $(M+H)^+$ = 645/7 (Br)	0.77	FM1	(KBr): C=0 1628/1662
506	N66	N-H	AS21	A0	C20		46	ESI: $(M+H)^+$ = 655	0.75	FM1	(KBr): C=0 1626/1664
507	N66	N-H	AS22	A0	C8		65	ESI: $(M+H)^+$ = 607/9 (Cl)	0.78	FM1	(KBr): C=0 1624/1664
508	N66	CH_2	AS21	A0	C20		15	ESI: $(M+H)^+$ = 654	0.15	MeOH	(KBr): C=0 1639/1670
246	N15	CH_2	AS1	A0	C8		19	ESI: $(M+H)^+$ = 730/2/4 (Br_2)	0.35	EE/ MeOH/ NH_4OH 9/1/0.5 v/v/v	(KBr): C=0 1635/1707

No.	RCO	Z	R^2	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
285	N15	CH2	AS1	A0	C4		42	ESI: $(M+H)^+$ = 724/6/8 (Br_2)	0.45	EE/ MeOH/ NH_4OH 9/1/0.5 v/v/v	(KBr): C=0 1684/1711
289	N66	CH2	AS1	A0	C8		40	ESI: $(M+H)^+$ = 744/6/8 (Br_2)	0.38	EE/ MeOH/ NH_4OH 9/1/0.5 v/v/v	(KBr): C=0 1635/1668
290	N66	CH2	AS1	A0	C4		30	ESI: $(M+H)^+$ = 738/40/42 (Br_2)	0.45	EE/ MeOH/ NH_4OH 9/1/0.5 v/v/v	(KBr): C=0 1634/1664
511	N66	N-H	AS23	A0	C8	DMF	80	ESI: $(M+H)^+$ = 603	0,57	FM1	(KBr): C=0 1664/1626
512	N66	N-H	AS23	A0	C11	DMF	60	ESI: $(M+H)^+$ = 618	0,30	FM1	(KBr): C=0 1645
513	N66	N-H	AS23	A0	C1	DMF	54	ESI: $(M+H)^+$ = 598	0,50	FM1	(KBr): C=0 1662/1712
514	N66	N-H	AS23	A0	C38	DMF	65	ESI: $(M+H)^+$ = 644	0,20	FM1	(KBr): C=0 1664 / 1626 / 1712
515	N66	N-H	AS23	A0	C40	DMF	7	ESI: $(M+H)^+$ = 632	0,40	FM1	(KBr): C=0 1630/1662
527	N66	N-H	AS25	A0	C8		49	ESI: $(M+H)^+$ = 594	0,48	FM1	(KBr): C=0 1647
528	N66	N-H	AS25	A0	C1		29	ESI: $(M+H)^+$ = 589	0,48	FM1	(KBr): C=0 1646
529	N66	CH_2	AS2	A0	C8		27	ESI: $(M+H)^+$ = 622	0,50	FM1	(KBr): C=0 1635 / 1668 / 1716
530	N66	CH_2	AS2	A0	C20		5	EI: M^+ = 635	0,49	FM1	(KBr): C=0 1637 / 1668 / 1714
531	N66	CH_2	AS23	A0	C8		30	EI: M^+ = 601	0,50	FM1	
	N66	CH_2	AS23				95				
538	N139	CH_2	AS2	A0	C20		49	EI: M^+ = 636	0,30	FM1	(KBr): C=0 1635/1674
539	N139	CH_2	AS2	A0	C53		52	EI: M^+ = 637	0,30	FM1	(KBr): C=0 1637/1674
540	N139	CH_2	AS2	A0	C8		60		0,37	FM1	(KBr): C=0 1635/1674
541	N66	CH_2	AS27	A0	C53		32	EI: M^+ = 630	0,65	FM1	(KBr): C=0 1639/1670
542	N66	CH_2	AS27	A0	C8		32	EI: M^+ = 615	0,80	FM1	(KBr): C=0 1639/1670
543	N66	CH_2	AS27	A0	C20		21	EI: M^+ = 629	0,59	FM1	(KBr): C=0 1639/1672
544	N66	CH_2	AS28	A0	C20		35	EI: M^+ = 643	0,50	FM1	(KBr): C=0 1641/1670
545	N66	CH_2	AS28	A0	C53		54	EI: M^+ = 644	0,50	FM1	(KBr): C=0 1639/1670
546	N66	CH_2	AS28	A0	C8		53	EI: M^+ = 629	0,60	FM1	(KBr): C=0 1639/1672

No.	RCO	Z	R^2	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
547	N66	CH_2	AS29	A0	C8		14	EI: M^+ = 599	0,53	FM1	(KBr): C=0 1630
548	N66	CH_2	AS29	A0	C53		12	EI: M^+ = 614	0,48	FM1	
549	N66	CH_2	AS29	A0	C20		15	EI: M^+ = 613	0,48	FM1	(KBr): C=0 1637/1668
550	N66	CH_2	AS30	A0	C53		4		0,48	FM1	
574	N66	CH_2	AS16	A0	C20		55	EI: M^+ = 653/5/7 (Cl_2)	0,80	CH_2Cl_2 / MeOH / NH4OH 80/20/1	(KBr): C=0 1635/1670
575	N66	CH_2	AS16	A0	C53		54	EI: M^+ = 654/6/8 (Cl_2)	0,20	EE / MeOH / NH_4OH 70/30/3	(KBr): C=0 1635/1668
578	N66	CH_2	AS5	A0	C53		32	EI: M^+ = 742/4/6 (Br_2)	0,30	FM5	(KBr): C=0 1637/1670
579	N66	CH_2	AS5	A0	C20		37	EI: M^+ = 741/3/5 (Br_2)	0,50	FM5	(KBr): C=0 1635/1670
589	N66	CH_2	AS32	A0	C53		49	EI: M^+ = 756/58/60 (Br_2)	0,33	FM5	(KBr): C=0 1639/1670
590	N66	CH_2	AS32	A0	C20		36	EI: M^+ = 755/7/9 (Br_2)	0,47	FM5	(KBr): C=0 1658/1672
591	N66	CH_2	AS33	A0	C20		43	EI: M^+ = 689	0,40	EE / MeOH / NH_4OH 50/50/0.5	(KBr): C=0 1637/1670
592	N66	CH_2	AS33	A0	C53		52	EI: M^+ = 690	0,20	EE / MeOH / NH_4OH 70/30/5	(KBr): C=0 1633/1668
593	N66	CH_2	AS16	A0	C29		11	EI: M^+ = 628/30/32 (Cl_2)	0,65	EE/MeOH 9/1	(KBr): C=0 1606 / 1637 / 1668 / 1728
594	N66	CH_2	AS16	A0	C73		48	EI: M^+ = 628/30/32 (Cl_2)	0,50	EE/MeOH 9/1	(KBr): C=0 1637/ 1668 / 1736
595	N66	CH_2	AS16	A0	C74		10	EI: M^+ = 597/99/601 (Cl_2)	0,30	EE / MeOH / NH_4OH 50/50/0.5	
597	N66	CH_2	AS31	A0	C53		25	EI: M^+ = 639	0,30	CH_2Cl_2 / MeOH / NH_4OH 90/10/1	(KBr): C=0 1635/1668
598	N66	CH_2	AS31	A0	C20		31	EI: M^+ = 638	0,10	CH_2Cl_2 / MeOH / NH_4OH 90/10/0.3	(KBr): C=0 1635/1668

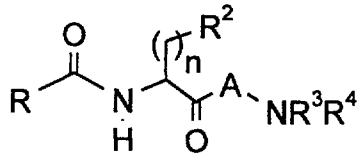
No.	RCO	Z	R^2	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
600	N73	CH_2	AS31	A0	C20		10	ESI: $(M+H)^+$ = 551	0.15	CH_2Cl_2 / MeOH / NH_4OH 90/10/1	(KBr): C=0 1628
602	N66	CH_2	AS17	A0	C53		56	EI: M^+ = 772/4/6 (Br_2)	0.25	EE / MeOH / NH_4OH 50/50/0.5	(KBr): C=0 1637/1668
603	N66	CH_2	AS16	A0	C33		93	EI: M^+ = 600/02/04 (Br_2)	0.75	EE / MeOH / AcOH 70/30/1	(KBr): C=0 1635/1716
604	N66	CH_2	AS17	A0	C20		47	EI: M^+ = 771/3/5 (Br_2)	0.20	EE / MeOH / NH_4OH 50/50/0.5	(KBr): C=0 1635/1668
605	N66	CH_2	AS34	A0	C53		70	EI: M^+ = 672	0.25	EE / MeOH / NH_4OH 60/40/0.5	(KBr): C=0 1633/1666
606	N66	CH_2	AS34	A0	C20		45	EI: M^+ = 671	0.15	EE / MeOH / NH_4OH 50/50/0.5	(KBr): C=0 1635/1668
607	N66	N-H	AS21	A0	C40		27	ESI: $(M+H)^+$ = 670	0.65	FM1	(KBr): C=0 1608 / 1628 / 1664
608	N66	N-H	AS21	A0	C11		34	ESI: $(M+H)^+$ = 656	0.50	FM1	(KBr): C=0 1606 / 1628 / 1664
609	N66	N-H	AS21	A0	C8		30	ESI: $(M+H)^+$ = 641	0.80	FM1	(KBr): C=0 1626/1664
610	N66	N-H	AS21	A0	C1		55	ESI: $(M+H)^+$ = 636	0.80	FM1	(KBr): C=0 1635/1662
611	N66	N-H	AS21	A0	C4		80	ESI: $(M+H)^+$ = 635	0.70	FM1	(KBr): C=0 1606 / 1628 / 1664
612	N66	CH_2	AS4	A0	C8		43	EI: M^+ = 742/4/6 (Br_2)	0.85	FM1	(KBr): C=0 1668 / 1631 / 1606
613	N66	N-H	AS22	A0	C20		62	ESI: $(M+H)^+$ = 621/23(Cl)	0.73	FM1	(KBr): C=0 1626/1664
614	N66	N-H	AS22	A0	C37		55	ESI: $(M+H)^+$ = 621/23 (Cl)	0.68	FM1	(KBr): C=0 1626/1664
615	N66	N-H	AS22	A0	C56		77	ESI: $(M+H)^+$ = 593	0.76	FM1	(KBr): C=0 1628/1664

No.	RCO	Z	R^2	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
616	N66	CH_2	AS36	A0	C8		32	ESI: $(M+H)^+$ = 585	0,76	FM1	(KBr): C=0 1637/1668
617	N66	CH_2	AS21	A0	C37		15	EI: M^+ = 653	0,15	MeOH	(KBr): C=0 1639/1670
618	N66	CH_2	AS21	A0	C38		24	EI: M^+ = 680	0,10	MeOH	(KBr): C=0 1639/1670
628	N66	CH_2	AS21	A0	C8		31	EI: M^+ = 639	0,25	MeOH	(KBr): C=0 1639/1670
629	N66	CH_2	AS21	A0	C11		43	EI: M^+ = 654	0,10	MeOH	(KBr): C=0 1641/1668
630	N66	CH_2	AS21	A0	C1		74	EI: M^+ = 634	0,10	MeOH	(KBr): C=0 1641/1668
631	N66	CH_2	AS21	A0	C28		63	EI: M^+ = 614	0,30	MeOH	(KBr): C=0 1666
634	N66	CH_2	AS38	A0	C8		35	ESI: $(M+H)^+$ = 622	0,25	MeOH	(KBr): C=0 1635/1668
635	N66	CH_2	AS48	A0	C8		40	EI: M^+ = 639	0,68	FM1	(KBr): C=0 1643/1670
636	N66	N-H	AS49	A0	C20		25	ESI: $(M+H)^+$ = 632	0,40	EE / MeOH / NH_4OH 9/1/0.5	(KBr): C=0 1664
637	N66	CH_2	AS4	A0	C20		11	ESI: $(M+H)^+$ = 757/59/61 (Br_2)	0,60	FM1	(KBr): C=0 1635/1668
638	N66	CH_2	AS48	A0	C20		11	ESI: $(M+H)^+$ = 654	0,66	FM1	(KBr): C=0 1641/1668
639	N66	CH_2	AS18	A0	C20		4	EI: M^+ = 721	0,10	MeOH	(KBr): C=0 1637/1670
640	N66	CH_2	AS39	A0	C20		38	EI: M^+ = 645	0,80	CH_2Cl_2 / MeOH / NH_4OH 8/2/0.3	(KBr): C=0 1635/1670
641	N66	CH_2	AS38	A0	C20		49	EI: M^+ = 635	0,80	CH_2Cl_2 / MeOH / NH_4OH 8/2/0.3	(KBr): C=0 1635/1668
642	N66	CH_2	AS39	A0	C8		45	EI: M^+ = 631	0,10	EE / MeOH / NH_4OH 9/1/0.3	(KBr): C=0 1635/1670
	N66	CH_2	AS21	A0	C69		70	EI: M^+ = 739			(KBr): C=0 1684
644	N109	CH_2	AS21	A0	C20		46	ESI: $(M+H)^+$ = 659	0,10	MeOH	(KBr): C=0 1643
645	N66	CH_2	AS19	A0	C20		21	EI: M^+ = 763/5 (Br)	0,53	FM1	(KBr): C=0 1669/1634
646	N66	CH_2	AS19	A0	C8		45	EI: M^+ = 649/651 (Br)	0,60	FM1	(KBr): C=0 1637/1668
653	N113	CH_2	AS21	A0	C20		55	EI: M^+ = 666	0,60	FM1	(KBr): C=0 1630/1701

No.	RCO	Z	R^2	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
654	N134	CH_2	AS21	A0	C20		22	EI: M^+ = 690	0,60	FM1	(KBr): C=0 1714
655	N66	CH_2	AS46	A0	C20		43	EI: M^+ = 636	0,50	FM1	(KBr): C=0 1630/1664
656	N66	CH_2	AS46	A0	C8		71	EI: M^+ = 622	0,60	FM1	(KBr): C=0 1635
657	N66	CH_2	AS47	A0	C20		63	EI: M^+ = 639	0,50	FM1	(KBr): C=0 1635 / 1668 / 1716
658	N66	CH_2	AS50	A0	C20		70	ESI: $(M+H)^+$ = 741/3/5 (Br_2)	0,20	EE / MeOH / NH_4OH 50/50/0.5	(KBr): C=0 1635/1668
659	N66	CH_2	AS50	A0	C53		60	ESI: $(M+H)^+$ = 743/5/7 (Br_2)	0,20	EE / MeOH / NH_4OH 50/50/0.5	(KBr): C=0 1635/1668
660	N66	CH_2	AS46	A0	C53		41	EI: M^+ = 637	0,65	FM1	(KBr): C=0 1630
661	N66	CH_2	AS7	A0	C8		75	EI: M^+ = 615	0,70	FM1	(KBr): C=0 1626/1660
662	N66	CH_2	AS7	A0	C53		41	EI: M^+ = 630	0,55	FM1	(KBr): C=0 1628/1662
663	N66	CH_2	AS7	A0	C20		78	EI: M^+ = 629	0,60	FM1	(KBr): C=0 1628/1662
664	N66	CH_2	AS52	A0	C8		66	EI: M^+ = 629	0,75	FM1	(KBr): C=0 1635
665	N66	CH_2	AS52	A0	C53		37	EI: M^+ = 644	0,70	FM1	(KBr): C=0 1633/1664
666	N66	CH_2	AS52	A0	C20		61	EI: M^+ = 643	0,80	FM1	(KBr): C=0 1635/1664
667	N66	CH_2	AS2	A0	C53		47	EI: M^+ = 636	0,60	FM1	(KBr): C=0 1630/1664
	N66	CH_2	AS2	A0	C69		78		0,75	FM1	
669	N66	CH_2	AS32	A0	C71		44	EI: M^+ = 834/6/8 (Br_2)	0,20	EE / MeOH / NH_4OH 50/50/0.5	(KBr): C=0 1641/1670
670	N66	CH_2	AS51	A0	C20	Preliminary stage special cases	47	EI: M^+ =641	0,15	EE / MeOH / NH_4OH 50/50/0.5	(KBr): C=0 1635/1664
671	N66	CH_2	AS51	A0	C53		45	EI: M^+ =642	0,15	EE / MeOH / NH_4OH 50/50/0.5	(KBr): C=0 1637/1670
672	N66	CH_2	AS16	A0	C76		55	EI: M^+ = 689/91/93 (Cl_2)	0,66	FM1	(KBr): C=0 1635

Example 2

Preparation of compounds of general formula:



1-[N^2-[4-amino-N-[[4-(2-chlorophenyl)-1-piperazinyl]-carbonyl]-3,5-dibromo-D-phenylalanyl]-L-lysyl]-4-(4-pyridinyl)piperazine-bis-(trifluoroacetate) (No. 61)

A mixture of 0.56 g (1.0 mmol) of 4-amino-N^2-[[4-(2-chlorophenyl)-1-piperazinyl]carbonyl]-3.5-dibromo-D-phenylalanine, 0.41 g (1.05 mmol) of 1-[N^6-(1.1-dimethylethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)piperazine, 0.35 g (1.10 mmol) of TBTU, 0.14 g (1.0 mmol) of HOBt, 0.2 ml (1.10 mmol) of DIEA and 100 ml of dimethylformamide was stirred overnight at ambient temperature. The reaction mixture was evaporated down *in vacuo* and divided between methylene chloride and saturated aqueous sodium hydrogen carbonate solution. The organic phase was then extracted once with saturated aqueous sodium hydrogen carbonate solution and with water, dried and evaporated down *in vacuo*. The crude product was purified by column chromatography (MN-silica gel 60, Macherey-Nagel, 70-230 mesh ASTM, eluant: ethyl acetate/methanol = 8/2 (v/v/)), taken up in 30 ml of methylene chloride and stirred with 3 ml of trifluoroacetic acid for 3 hours at ambient temperature. The reaction mixture was evaporated down *in vacuo*, the residue was triturated with ether and the obtained amorphous solid (0.43 g, 37% of theory) was suction filtered.

IR (KBr): 1643, 1678 cm^{-1} (C=O)

R_f: 0.6 (FM1)

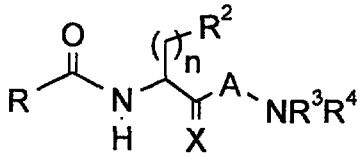
ESI-MS: $(M+H)^+$ = 832/834/836/838 (Br_2,Cl)

The following were prepared analogously (in each case n = 1):

No.	RCO	R^2	A	NR^3R^4	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
48	N6	AS1	A1	C3	79	ESI:M+H= 946/48/50 (Br_2)	0.3	FM1	(KBr): C=0 1652.9; 1674.1
213	N15	AS6	A1	C8	14.7	ESI: M+H=781/3 (Br)	0.45	FM2	(KBr): C=O 1691.5; 1629.8
49	N8	AS4	A1	C1	57.14	ESI: M+H= 757/59/61 (Br_2)	0.5	FM1	(KBr):C=O 1643.3; 1676.0
58	N15	AS4	A1	C4	21	ESI: M+H= 852/4/6 (Br_2)	0.57	FM1	(KBr): C=O 1635.5; 1695.3
59	N15	AS4	A1	C1	45.6	ESI: M+H= 853/5/7 (Br_2)	0.44	FM1	(KBr): C=O 1635.5; 1695.3
60	N23	AS4	A1	C4	19.2	ESI: M+H= 831/3/5/7 (Br_2,Cl)	0.65	FM1	(KBr): C=O 1633.6
61	N23	AS4	A1	C1	36.6	ESI:M+H= 832/4/6/8 (Br_2,Cl)	0.6	FM1	(KBr): C=O 1643.3; 1678.0

Example 3

Preparation of compounds of general formula:



1-[N^2-[3,5-dibromo-N-[[[(2-methoxyphenyl)methyl]amino]-carbonyl]-D,L-tyrosyl]-N^6-(phenylmethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)-piperazine

A tetrahydrofuran solution (50 ml) of 1.0 g (1.34 mmol) of 1-[N^2-(3,5-dibromo-D-tyrosyl)-N^6-(phenylmethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)-

piperazine was added dropwise over a period of 40 minutes to a suspension of 0.33 g (2.01 mmol) of CDT in 50 ml of tetrahydrofuran cooled to -10 °C and stirred. The reaction mixture was then stirred for 2 hours at ambient temperature and mixed with 0.22 ml (1.675 mmol) of 2-methoxybenzenemethanamine. Then the mixture was refluxed for 2 hours and stirred overnight at ambient temperature. The reaction mixture was evaporated down *in vacuo*, the residue was triturated with ether and the solid obtained (1.1 g; 90% of theory) was suction filtered and dried.

IR (KBr): 1641, 1717 cm^{-1} (C=O)

ESI-MS: $(M+H)^+$ = 908/910/912 (Br_2)

$(M+H+Na)^{++}$ = 466.7 (Br_2)

The following were prepared analogously:

No.	RCO	R^2	n	X	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]	Mp. (°C
195	N15	AS1	1	O	A3	C8		21	ESI: $(M+H)^+$ = 959/61/63 (Br_2)	0.8	FM7	(KBr): C=O 1699.2; 1635.5	
196	N51	AS1	1	O	A3	C8		26;1	ESI: $(M+H)^+$ = 929/31/33 (Br_2)	0.85	FM7	(KBr): C=O 1710; CN 2219.8	
201	N103	AS4	1	O	A0	C8	DIEA	34	ESI: $(M+H)^+$ = 746/8/50 (Br_2)	0.58	FM1	(KBr): C=O 1693.4; 1618.2	
215	N15	AS1	1	O	A0	C34	NEt_3 as base	92	ESI: $(M-H)^-$ = 778/80/ 82 (Br_2)	0.36	FM1	(KBr): C=O 1695.3	
216	N15	AS1	1	O	A0	C35	NEt_3 as base	69	ESI: $(M-H)^-$ = 779/81/ 82 (Br_2)	0.3	FM1	(KBr): C=O 1701.1	
221	N15	AS4	1	O	A7	C1	NEt_3 as base	39	ESI: $(M+H)^+$ = 881/3/5 (Br_2)	0.38	FM1	(KBr): C=O 1697.3; 1637.5	
288	N85	AS1	1	O	A0	C8	THF/DMF as solvent NEt_3	30	ESI: $(M+H)^+$ = 749/51/53 (Br_2)	0.3	MeOH	(KBr): C=O 1683.8; 1624.0; OH 3429.2	
293	N66	AS1	1	O	A9	C1	DIEA	11	ESI: $(M+H)^+$ = 910/2/4 (Br_2)	0.4	FM1	(KBr): C=O 1645.2	
295	N66	AS1	1	O	A7	C1	NEt_3 as base	70	ESI: $(M+H)^+$ = 896/8/ 900 (Br_2)	0.45	FM1	(KBr): C=O 1716.5; 1647.1	
303	N86	AS4	1	O	A0	C8	DIEA	20	ESI: $(M+H)^+$ = 747/9/ 51 (Br_2)	0.7	FM 2	(KBr): C=O 1618.2	
304	N87	AS4	1	O	A0	C8	THF as solvent; NEt_3 as base	30	ESI: $(M+H)^+$ = 802/4/6 (Br_2)	0.75	FM1	(KBr): C=O 1720.4; 1668.3; 1620.1; NH,NH2 3431.2; 3379.1	
305	N88	AS4	1	O	A0	C8	DIEA	45	ESI: $(M+H)^+$ = 782/4/6 (Br_2)	0.6	FM1	(KBr): C=O 1616; SO2 1323.1; 1151.4	
308	N90	AS4	1	O	A0	C8	DIEA	27	ESI: $(M+H)^+$ = 750/2/4 (Br_2)	0.5	FM1	(KBr): C=O 1637.5	
80	N15	AS1	1	O	A3	C1		62	ESI: $(M+H)^+$ = 954/6/8 (Br_2)	0.8	FM2	(KBr): C=O 1697.3; 1639.4	
	N8	AS1	1	O	A3	C1		66	ESI: $(M+H)^+$ = 858/60/62 (Br_2)	0.22	EtOAc/ methanol=6/4 (v/v)	(KBr): C=O 1641.3	
	N9	AS1	1	O	A3	C1		59	ESI: $(M+H)^+$ = 888/90/92 (Br_2)	0.22	EtOAc/ methanol=6/4 (v/v)	(KBr): C=O 1652.9	

No.	RCO	R^2	n	X	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]	Mp. (°C
	N2	AS1	1	O	A4	C1		40	ESI: $(M+H)^+$ = 922/4/6 (B_r); $(M+Na)^+$ = 944/6/8 (B_r)	0.45	FM1	(KBr): C=O 1641.3; 1710.8; OH,NH 3396.4	
	N4	AS1	1	O	A4	C1		73	ESI: $(M+H)^+$ = 952/4/6 (B_r)	0.13	FM1	(KBr): C=O 1641.3; 1714.6	
62	N15	AS1	1	O	A3	C5	purified by column chromato-graphy: silica gel/ FM4	65	ESI: $(M+H)^+$ = 1003/5/7 (B_r); (M+Na)+ = 1025/7/9(B_r)	0.27	FM1	(KBR):C=O 1685.7; 1635.5; OH, NH: 3419.6	
	N15	AS1	1	O	A3	C6	purified by column chromato-graphy: silica gel/ FM4	86	ESI: $(M+H)^+$ = 983/5/7 (B_r)	0.45	FM1	(KBr): C=O 1695.3; 1633.6	
73	N15	AS5	1	O	A3	C1	purified by column chromato-graphy: silica gel/ FM4; Diastereo-mers	64	ESI: $(M+H)^+$ = 938/40/42 (B_r)	0.75	FM1	(KBr): C=O1699.2; 1641.3	
78	N45	AS5	1	O	A3	C1	purified by column chromato-graphy: silica gel/ FM4; Diastereo-mers	44	ESI: $(M+H)^+$ = 952/4/6 (B_r)	0.73	FM1	(KBr): C=O 1712.7, 1637.5; -NH- 3300.0	
110	N15	AS4	1	O	A0	C5	purified by column chromato-graphy: silica gel/ FM4	82	ESI: $(M+H)^+$ = 725/7/9 (B_r)	0.79	FM1	(KBr): C=O 1620.1; 1514.0	
111	N15	AS4	1	O	A0	C15	purified by column chromato-graphy: silica gel/ FM4	58	ESI: M^+ = 726/28/30 (B_r)	0.77	FM1	(KBr): C=O 1697.3; 1620.1	
114	N45	AS4	1	O	A0	C5	purified by column chromato-graphy: silica gel/ FM4	75	ESI: $(M+H)^+$ = 739/41/43 (B_r)	0.78	FM1	(KBr): C=O 1710.8; 1620.1	
112	N15	AS1	1	O	A0	C5	purified by column chromato-graphy: silica gel/ FM4	45	ESI: $(M+H)^+$ = 726/28/30 (B_r)	0.33	FM1	(KBr): C=O 1695.3; 1624.0	

No.	RCO	R^2	n	X	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]	Mp. (°C)
115	N45	AS1	1	O	A0	C5	purified by column chromato-graphy: silica gel/ FM4	28	ESI: (M+H)$^+$ = 740/2/4 (Br)	0.35	FM1	(KBr): C=O 1710.8; 1622	
113	N15	AS4	1	O	A0	C16	purified by column chromato-graphy: silica gel/ FM4	56	ESI: (M+H)$^+$ = 726/8/30 (Br)	0.68	FM1	(KBr): C=O 1699.2; 1618.2	173-176
119	N45	AS4	1	O	A0	C16	purified by column chromato-graphy: silica gel/ FM4	81	ESI: (M+H)$^+$ = 762/4/6 (Br)	0.69	FM1	(KBr): C=O 1710.8; 1618.2	148-152
120	N15	AS1	1	O	A0	C15	purified by column chromato-graphy: silica gel/ FM4	27	ESI: (M+H)$^+$ = 749/51/53 (Br)	0.31	FM1	(KBr): C=O 1695.3	173-175
128	N15	AS4	1	O	A0	C3	purified by column chromato-graphy: silica gel/ FM4	61	ESI: (M+Na)$^+$ = 764/6/8 (Br)	0.72	FM1	(KBr): C=O 1699.2; 1618.2	174-177
130	N15	AS4	1	O	A0	C6	purified by column chromato-graphy: silica gel/ FM4	60	ESI: (M+H)$^+$ = 754/6/8 (Br)	0.7	FM1	(KBr): C=O 1703; 1620.1	150-154
129	N15	AS1	1	O	A0	C16	purified by column chromato-graphy: silica gel/ FM4	18	ESI: (M-H)$^-$ = 725/7/9 (Br)	0.27	FM1	(KBr): C=O 1693.4; 1627.8	173-176
131	N45	AS4	1	O	A0	C6	purified by column chromato-graphy: silica gel/ FM4	69	ESI: (M+H)$^+$ = 768/70/72 (Br)	0.73	FM1	(KBr): C=O 1712.7; 1620.1	159-162
132	N45	AS4	1	O	A0	C3	purified by column chromato-graphy: silica gel/ FM4	27	ESI: (M+Na)$^+$ = 778/80/2 (Br)	0.72	FM1	(KBr): C=O 1712.7; 1618.2	142-146
133	N15	AS1	1	O	A0	C6	purified by column chromato-graphy: silica gel/ FM4	24	ESI: (M+H)$^+$ = 755/7/9 (Br)	0.33	FM1	(KBr): C=O 1697.3; 1624.0	161-164
134	N15	AS4	1	O	A0	C18	purified by column chromato-graphy: silica gel/ FM4	69	ESI: (M+H)$^+$ = 756/8/60 (Br)	0.59	FM1	(KBr): C=O 1699.2; 1618.2	171-174

No.	RCO	R^2	n	X	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]	Mp. (°C
135	N15	AS1	1	O	A0	C18	purified by column chromato-graphy: silica gel/ FM4	17	ESI: (M+H)+ = 757/9/61 (Br_2)	0.25	FM1	(KBr): C=O 1691.5; 1625.9	74-77
	N29	AS1	1	O	A3	C1		61	ESI: (M+H)+ = 903/5/7 (Br_2)	0.62	FM7	(KBr): C=O 1641.3	
	N36	AS1	1	O	A3	C1		33	ESI: (M+H)+ = 915/7/9 (Br_2)	0.49	FM7	(KBr): C=O 1641.3	
44	N34	AS1	1	O	A3	C1		35	ESI: (M+H)+ = 936/38/40/42 (Br_3)	0.3	FM1	(KBr): C=O 1641.3	
378	N15	AS1	0	O	A3	C1		30	ESI: (M+H)+ = 940/2/4 (Br_2)	0.13	FM1	(KBr): C=O 1701.1; 1641.3	
	N48	AS1	1	O	A3	C1		52		0.58	FM7	(KBr): C=O 1641.3	
	N77	AS1	1	O	A3	C4		32	ESI: (M+H)+ = 955/7/9 (Br_2)			(KBr): C=O 1645; 1713	
294	N66	AS4	1	O	A7	C1	NEt_3 as base	31	ESI: (M+H)+ = 895/7/9 (Br_2)	0.3	FM1	(KBr): C=O 1653; 1772.5; 1716.5	
323	N104	AS1	1	O	A0	C4	DIEA	18	ESI: (M+H)+ = 799/801/803 (Br_2)	0.4	FM1	(KBr): C=0 1624	
324	N105	AS1	1	O	A0	C4	DIEA	24	ESI: (M+H)+ = 773/5/7/9 (Br_2/Cl)	0.38	FM1	(KBr): C=0 1624/1667	
325	N106	AS1	1	O	A0	C4	DIEA	22	ESI: (M+H)+ = 725/7/9(Br_2)	0.35	FM1	(KBr): C=0 1626/1662.5	
326	N71	AS1	1	O	A0	C1	DIEA	20	ESI: (M+H)+ = 752/4/6 (Br_2)	0.16	FM1	(KBr): C=0 1624/1680	
327	N71	AS4	1	O	A0	C4	DIEA	24	ESI: (M+H)+ = 750/2/4 (Br_2)	0.48	FM1	(KBr): C=0 1618/1682	
328	N107	AS1	1	O	A0	C4	DIEA	17	ESI: (M+H)+ = 769/71/73 (Br_2)	0.38	FM1	(KBr): C=0 1651	
329	N108	AS4	1	O	A0	C4	DIEA	16	ESI: (M+H)+ = 781/83/85(Br_2)	0.31	FM1	(KBr): C=0 1620/ 1674	
330	N108	AS4	1	O	A0	C1	DIEA/ DMF	15	ESI: (M+H)+ = 781/83/85(Br_2)	0.45	FM1	(KBr): C=0 1620/ 1678	
331	N108	AS4	1	O	A0	C20	DIEA/ DMF	15	ESI: (M+H)+ = 800/802/804 (Br_2)	0.4	FM1	(KBr): C=0 1616/1680	
332	N109	AS1	1	O	A0	C4	DIEA/ DMF	39	ESI: (M+H)+ = 745/7/9 (Br_2)	0.32	FM1	(KBr): C=0 1665	
333	N110	AS1	1	O	A0	C4	DIEA/ DMF	52	ESI: (M+H)+ = 745/7/9 (Br_2)	0.34	FM1	(KBr): C=0 1636	
334	N111	AS14	1	O	A0	C1	DIEA/ DMF	18	ESI: (M+H)+ = 649	0.5	FM1	(KBr): C=0 1626/1688	
335	N109	AS4	1	O	A0	C4	DIEA/ DMF	46	ESI: (M+H)+ = 744/6/8 (Br_2)	0.47	FM1	(KBr): C=0 1618	
336	N110	AS1	1	O	A0	C8	DIEA/ DMF	25	ESI: (M+H)+ = 751/3/5 (Br_2)	0.22	FM1	(KBr): C=0 1645	
337	N109	AS1	1	O	A0	C8	DIEA/ DMF	32	ESI: (M+H)+ = 751/3/5 (Br_2)	0.21	FM1	(KBr): C=0 1645	

No.	RCO	R^2	n	X	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]	Mp. (°C
338	N109	AS4	1	H2	A0	C8	DIEA/ DMF	38	ESI: $(M+H)^+$ = 736/8/40 (Br_2)	0.44	FM1	(KBr): C=0 1653	
339	N110	AS4	1	H2	A0	C8	DIEA/ DMF	39	ESI: $(M+H)^+$ = 736/8/40 (Br_2)	0.44	FM1	(KBr): C=0 1653	
340	N66	AS1	1	O	A0	C20	DIEA/ DMF	33	ESI: $(M+H)^+$ = 759/61/63 (Br_2)	0.12	FM1	(KBr): C=0 1618/1657	
341	N71	AS1	1	O	A0	C20	DIEA/ DMF	31	ESI: $(M+H)^+$ = 771/3/5 (Br_2)	0.1	FM1	(KBr): C=0 1620/1680	
342	N112	AS4	1	O	A0	C20	DIEA/ DMF	27	ESI: $(M+H)^+$ = 776/8/80 (Br_2)	0.47	FM1	(KBr): C=0 1618/1682	
343	N112	AS1	1	O	A0	C20	DIEA/ DMF	26	ESI: $(M+H)^+$ = 777/9/81 (Br_2)	0.11	FM1	(KBr): C=0 1624/1678	
344	N71	AS1	1	O	A0	C37	DIEA/ DMF	52	ESI: $(M+H)^+$ = 771/3/5(Br_2)	0.65	FM1	(KBr): C=0 1622/1680	
345	N66	AS1	1	O	A0	C37	DIEA/ DMF	50	ESI: $(M+H)^+$ = 759/61/63 (Br_2)	0.7	FM1	(KBr): C=0 1626/1659	
346	N71	AS4	1	O	A0	C37	DIEA/ DMF	37	ESI: $(M+H)^+$ = 770/72/74 (Br_2)	0.75	FM1	(KBr): C=0 1620/1682	
347	N6	AS4	1	O	A0	C37	DIEA/ DMF	45	ESI: $(M+H)^+$ = 758/60/62 (Br_2)	0.8	FM1	(KBr): C=0 1620/1663	
348	N113	AS4	1	O	A0	C20	DIEA/ DMF	24	ESI: $(M+H)^+$ = 771/3/5(BR2)	0.8	FM1	(KBr): C=0 1616/1701	
349	N113	AS4	1	O	A0	C8	DIEA/ DMF	40	ESI: $(M+H)^+$ = 757/59/61 (Br_2)	0.8	FM1	(KBr): C=0 1616/1699	
350	N111	AS4	1	O	A0	C20		33	ESI: $(M+H)^+$ = 838/40/42 (Br_2)	0.63	FM1	(KBr): C=0 1620/1688	
351	N111	AS4	1	O	A0	C8		39	ESI: $(M+H)^+$ = 824/6/8 (Br_2)	0.64	FM1	(KBr): C=0 1620/1688	
352	N111	AS1	1	O	A0	C8		36	ESI: $(M+H)^+$ = 825/7/9 (Br_2)	0.37	FM1	(KBr): C=0 1644/1688	
353	N112	AS1	1	O	A0	C8		24	ESI: (M+H)+ = 763/5/7 (Br_2)	0.28	FM1	(KBr): C=0 1624/1684	
355	N113	AS4	1	O	A0	C11	DIEA/ DMF	6	ESI: $(M+H)^+$ = 772/4/6 (Br_2)	0.5	FM1	(KBr): C=0 1620/1697	
356	N66	AS4	1	O	A0	C38	DIEA/ DMF	31	ESI: $(M+H)^+$ = 785/7/9 (Br_2)	0.23	FM1	(KBr): C=0 1624/1664	
357	N112	AS4	1	O	A0	C11	DIEA/ DMF	5	ESI: $(M+H)^+$ = 777/79/81 (Br_2)	0.37	FM1		
358	N111	AS1	1	O	A0	C11	DIEA/ DMF	13	ESI: $(M+H)^+$ = 840/42/44 (Br_2)	0.09	FM1	(KBr): C=0 1624/1686	
359	N111	AS4	1	O	A0	C11	DIEA/ DMF	24		0.39	FM1	(KBr): C=0 1622/1686	
360	N109	AS4	1	O	A0	C8	DIEA/ DMF	25	ESI: $(M+H)^+$ = 750/52/54 (Br_2)	0.7	FM1	(KBr): C=0 1618/1657	
361	N110	AS4	1	O	A0	C11	DIEA/ DMF	35	ESI: $(M+H)^+$ = 750/52/54 (Br_2)	0.5	FM1	(KBr): C=0 1622/1649	

No.	RCO	R^2	n	X	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]	Mp. (°C
362	N110	AS4	1	O	A0	C8	DIEA/ DMF	24	ESI: $(M+H)^+$ = 750/52/54 (B_r)	0.5	FM1	(KBr): C=0 1649	
363	N111	AS4	1	O	A0	C37	DIEA/ DMF	25		0.53	FM1	(KBr): C=0 1622/1688	
364	N111	AS1	1	O	A0	C37	DIEA/ DMF	24	ESI: $(M+H)^+$ = 839/41/43 (B_r)	0.3	FM1	(KBr): C=0 1624/1686	
366	N66	AS4	1	O	A0	C39		67	ESI: $(M+H)^+$ = 772/4/6 (B_r)	0.53	FM1	(KBr): C=0 1618/1665	
367	N71	AS4	1	O	A0	C39	DIEA/ DMF	12	ESI: $(M+H)^+$ = 784/6/8 (B_r)	0.52	FM1	(KBr): C=0 1618/1684	
368	N111	AS4	1	O	A0	C39	DIEA/ DMF	37	ESI: $(M+H)^+$ = 852/4/6 (B_r)	0.8	FM1	(KBr): C=0 1618/1686	
369	N114	AS4	1	O	A0	C8		15	ESI: $(M+H)^+$ = 824/6/8 (B_r)	0.58	FM1	(KBr): C=0 1618/1686	
370	N66	AS4	1	O	A0	C40	DIEA/ DMF	35	ESI: $(M+H)^+$ = 773/5/7 (B_r)	0.44	FM1	(KBr): C=0 1622/1660	
371	N111	AS4	1	O	A0	C40	DIEA/ DMF	58	ESI: $(M+H)^+$ = 853/5/7 (B_r)	0.44	FM1	(KBr): C=0 1622/1687	
373	N115	AS4	1	O	A0	C8	DIEA/ DMF	43	ESI: $(M+H)^+$ = 822/4/6/8 (B_r)	0.7	FM1	(KBr): C=0 1620/1670	
374	N116	AS4	1	O	A0	C20		27	ESI: $(M+H)^+$ = 784/6/8 (Br)	0.53	FM1	(KBr): C=0 1618/1680	
375	N117	AS4	1	O	A0	C20		23	ESI: $(M+H)^+$ = 815/7/9 (Br)	0.52	FM1	(KBr): C=0 1620/1687	
376	N118	AS4	1	O	A0	C20		30		0.56	FM1	(KBr): C=0 1620/1684	
377	N119	AS4	1	O	A0	C20		74	ESI: $(M+H)^+$ = 848/50/52/54 (Br_3)	0.61	FM1	(KBr): C=0 1616/1685	
418	N111	AS4	1	O	A0	C38	DIEA/ DMF	23	ESI: $(M+H)^+$ = 865/7/9 (Br)	0.27	FM1	(KBr): C=0 1622/1687	
490	N113	AS1	1	O	A0	C20	DIEA/ DMF	37	ESI: $(M+H)^+$ = 772/4/6 (B_r)	0.1	FM1	(KBr): C=0 1622/1699	
491	N113	AS1	1	O	A0	C8	DIEA/ DMF	94	ESI: $(M+H)^+$ = 758/60/62 (B_r)	0.37	FM1	(KBr): C=0 1624/1691	
492	N113	AS1	1	O	A0	C11	DIEA/ DMF	42	ESI: $(M+H)^+$ = 773/5/7 (B_r)	0.1	FM1	(KBr): C=0 1678	
495	N133	AS4	1	O	A0	C20		45	ESI: $(M+H)^+$ = 846/48/50 (B_r)	0.5	FM1	(KBr): C=0 1620/1682	
379	N71	AS1	1	O	A0	C3		39	ESI: $(M+H)^+$ = 769/71/73 (B_r)	0.41	FM4	(KBr): C=0 1680	
380	N71	AS4	1	O	A0	C3		40	ESI: $(M+H)^+$ = 768/70/72 (B_r)	0.47	FM4	(KBr): C=0 1618/1682	
381	N71	AS1	1	O	A0	C42		11	ESI: $(M+H)^+$ = 752/54/56 (B_r)	0.53	FM1	(KBr): C=0 1624/1682	
382	N66	AS1	1	O	A0	C42		18	ESI: $(M+H)^+$ = 740/42/44 (B_r)	0.16	FM4	(KBr): C=0 1630/1653	

No.	RCO	R^2	n	X	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]	Mp. (°C
383	N66	AS4	1	O	A0	C42		47	ESI: $(M+H)^+$ = 739/41/43 (Br_2)	0.25	FM4	(KBr): C=0 1626/1659	
384	N93	AS1	1	O	A0	C1		11	ESI: $(M+H)^+$ = 790/92/94 (Br_2)	0.2	FM7	(KBr): C=0 1636/1705	
385	N71	AS4	1	O	A0	C42		37	ESI: $(M+H)^+$ = 751/53/55 (Br_2)	0.3	FM4	(KBr): C=0 1620/1680	
386	N71	AS4	1	O	A0	C18		26	ESI: $(M+H)^+$ = 782/4/6 (Br_2)	0.27	FM4	(KBr): C=0 1620/1682	
387	N66	AS4	1	O	A0	C5		62	ESI: $(M+H)^+$ = 739/41/43 (Br_2)	0.38	FM4	(KBr): C=0 1626/1663	
388	N71	AS4	1	O	A0	C5		55	ESI: $(M+H)^+$ = 751/3/5 (Br_2)	0.39	FM4	(KBr): C=0 1618/1684	
389	N66	AS1	1	O	A0	C43		59	ESI: $(M+H)^+$ = 796/98/800 (Br_2)	0.32	CH_2Cl_2/ MeOH/ NH_4OH 9/1/0.1	(KBr): C=0 1653	
390	N135	AS4	1	O	A0	C18		5	ESI: $(M+H)^+$ = 853/5/7 (Br_2)	0.71	FM1	(KBr): C=0 1622/1653	
391	N135	AS1	1	O	A0	C18		6	ESI: $(M+H)^+$ = 854/6/8 (Br_2)	0.54	FM1	(KBr): C=0 1659	
392	N120	AS1	1	O	A0	C4		12	ESI: $(M+H)^+$ = 763/5/7 (Br_2)	0.41	CH_2Cl_2/ MeOH/ NH_4OH 9/1/0.1	(KBr): C=0 1618/1639	
393	N66	AS1	1	O	A0	C44		28	ESI: $(M+H)^+$ = 763/5/7 (Br_2)	0.5	CH_2Cl_2/ MeOH/ NH_4OH 9/1/0.1	(KBr): C=0 1659	
394	N66	AS4	1	O	A0	C21		37	ESI: $(M+H)^+$ = 740/42/44 (Br_2)	0.35	EE/ MeOH/ AcOH 75/25/0.5	(KBr): C=0 1659	
396	N71	AS1	1	O	A0	C21		49	ESI: (M+H)+ = 753/5/7 (Br_2)	0.3	EE/ MeOH/ AcOH 75/25/0.5	(KBr): C=0 1622/1678	
397	N66	AS1	1	O	A0	C21		62	ESI: $(M+H)^+$ = 741/3/5 (Br_2)	0.35	EE/ MeOH/ AcOH 75/25/0.5	(KBr): C=0 1649	
398	N121	AS4	1	O	A0	C8		80	ESI: $(M+H)^+$ = 743/5/7 (Br_2)	0.55	CH_2Cl_2/ MeOH/ NH_4OH 9/1/0.1	(KBr): C=0 1618/1668	
399	N122	AS4	1	O	A0	C18		40	ESI: (M+H)+ = 800/2/4 (Br_2)	0.62	FM1	(KBr): C=0 1622/1682	
400	N136	AS4	1	O	A0	C8		11	ESI: (M+H)+ = 741/3/5 (Br_2)	0.65	FM1	(KBr): C=0 1622/1653	
401	N66	AS1	1	O	A0	C45		19	ESI: $(M+H)^+$ = 749/51/53 (Br_2)	0.65	CH_2Cl_2/ MeOH/ NH_4OH 9/1/0.1	(KBr): C=0 1659	
402	N136	AS4	1	O	A0	C1		10	ESI: $(M+H)^+$ = 736/8/40 (Br_2)	0.42	CH_2Cl_2/ MeOH/ NH_4OH 9/1/0.1	(KBr): C=0 1649	

No.	RCO	R^2	n	X	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]	Mp. (°C
403	N121	AS4	1	O	A0	C1		25	ESI: $(M+H)^+$ = 738/40/42 (Br_2)	0.43	CH_2Cl_2/ MeOH/ NH_4OH 9/1/0.1	(KBr): C=0 1626/1676	
404	N66	AS4	1	O	A0	C46		58	ESI: $(M+H)^+$ = 766/8/70 (Br_2)	0.29	CH_2Cl_2/ MeOH/ NH_4OH 9/1/0.1	(KBr): C=0 1624/1663	
405	N66	AS1	1	O	A0	C47		40	ESI: $(M-H)^-$ = 752/4/6 (Br_2)	0.3	EE/ MeOH 9/1	(KBr): C=0 1659	
406	N136	AS1	1	O	A0	C1		16	ESI: $(M+H)^+$ = 737/39/41 (Br_2)	0.34	FM7	(KBr): C=0 1645	
407	N121	AS1	1	O	A0	C1		15	ESI: $(M+H)^+$ = 739/41/43 (Br_2)	0.36	FM7	(KBr): C=0 1638	
408	N71	AS4	1	O	A0	C48		47	ESI: $(M+H)^+$ = 792/4/6 (Br_2)	0.17	CH_2Cl_2/ MeOH/ NH_4OH 9/1/0.1	(KBr): C=0 1620/1680	
409	N66	AS4	1	O	A0	C48		31	ESI: $(M+H)^+$ = 780/2/4 (Br_2)	0.43	CH_2Cl_2/ MeOH/ NH_4OH 9/1/0.1	(KBr): C=0 1665/1736	
410	N66	AS1	1	O	A0	C49		51		0.24	EE/ MeOH 9/1	(KBr): C=0 1661	
411	N71	AS4	1	O	A0	C44		45	ESI: $(M+Na)^+$ = 796/98/800 (Br_2)	0.35	EE/ MeOH 9/1	(KBr): C=0 1728	
412	N66	AS1	1	O	A0	C50		58	ESI: $(M+H)^+$ = 756/58/60 (Br_2)	0.47	EE/ MeOH 9/1	(KBr): C=0 1642/1661	
413	N66	AS1	1	O	A0	C51		16	ESI: $(M+H)^+$ = 788/90/92 (Br_2)	0.47	EE/ MeOH/ NH_4OH 5/5/0.1	(KBr): C=0 1631	
414	N66	AS4	1	O	A0	C52		34	ESI: $(M+H)^+$ = 747/49/51 (Br_2)	0.54	FM1	(KBr): C=0 1622/1662	
415	N71	AS4	1	O	A0	C52		35	ESI: $(M+H)^+$ = 759/61/63 (Br_2)	0.52	FM1	(KBr): C=0 1620/1682	
416	N66	AS4	1	O	A0	C53		53	ESI: $(M+H)^+$ = 759/61/63 (Br_2)	0.45	CH_2Cl_2/ MeOH/ NH_4OH 9/1/0.1	(KBr): C=0 1620/1664	
417	N71	AS4	1	O	A0	C53		39	ESI: $(M+H)^+$ = 771/3/5 (Br_2)	0.43		(KBr): C=0 1620/1684	
496	N66	AS4	1	O	A0	C64		57		0.5	CH_2Cl_2/ MeOH/ NH_4OH 9/1/0.1	(KBr): C=0 1635	
497	N66	AS1	1	O	A0	C53		60	ESI: $(M+H)^+$ = 760/2/4 (Br_2)	0.31	CH_2Cl_2/ MeOH/ NH_4OH 50/50/0.5	(KBr): C=0 1676	
498	N66	AS4	1	O	A0	C65		60	ESI: $(M+H)^+$ = 760/2/4 (Br_2)	0.39	FM1	(KBr): C=0 1676	

No.	RCO	R^2	n	X	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]	Mp. (°C
499	N71	AS4	1	O	A0	C65		53	ESI: $(M+H)^+$ = 785/7/9 (Br_2)	0.39	FM1	(KBr): C=0 1618/1684	
500	N66	AS4	1	O	A0	C51		71	ESI: $(M+H)^+$ = 787/89/91 (Br_2)	0.15	CH_2Cl_2/ MeOH/ NH_4OH 9/1/0.1	(KBr): C=0 1628	
501	N71	AS1	1	O	A0	C53		71	ESI: $(M+H)^+$ = 772/4/6 (Br_2)	0.25	CH_2Cl_2/ MeOH/ NH_4OH 50/50/0.5	(KBr): C=0 1676	
502	N66	AS1	1	O	A0	C65		42	ESI: $(M+H)^+$ = 774/6/8 (Br_2)	0.15	FM1	(KBr): C=0 1626/1657	
503	N71	AS1	1	O	A0	C65		48	ESI: $M+H)^+$ = 786/88/90 (Br_2)	0.12	FM1	(KBr): C=0 1620/1682	
504	N66	AS4	1	O	A0	C66		67	ESI: $(M+H)^+$ = 787/89/91 (Br_2)	0.65	CH_2Cl_2/ MeOH/ NH_4OH 50/50/0.5	(KBr): C=0 1624	
297	N71	AS4	1	H2	A0	C8		9	ESI: $(M+H)^+$ = 742/4/6 (Br_2)	0.2	FM1	(KBr): C=0 1684	
298	N71	AS13	1	H2	A0	C8		6	ESI: $(M+H)^+$ = 664/6 (Br)	0.16	FM1	(KBr): C=0 1622/1682	
299	N66	AS4	1	H2	A0	C8		21	ESI: $(M+H)^+$ = 730/2/4 (Br_2)	0.25	FM1	(KBr): C=0 1666	
300	N66	AS13	1	H2	A0	C8		14	ESI: (M+H)+ = 652/4 (Br)	0.19	FM1	(KBr): C=0 1666	
301	N71	AS1	1	H2	A0	C8		26	ESI: $(M+H)^+$ = 743/5/7 (Br_2)	0.2	FM1	(KBr): C=0 1682	
420	N87	AS1	1	O	A0	C4		45	ESI: $(M+H)^+$ = 797/99/801 (Br_2)	0.5	FM1	(KBr): C=0 1624/ 1665/ 1719	
422	N87	AS1	1	O	A0	C8		35	ESI: (M+H)+ = 805/7/9 (Br_2)	0.54	FM1	(KBr): C=0 1628/ 1668/ 1720	
431	N125	AS4	1	O	A0	C8		89	ESI: $(M+H)^+$ = 772/4/6 (Br_2)	0.75	FM1	(KBr): C=0 1713/1773	
432	N125	AS1	1	O	A0	C4		59	ESI: $(M+H)^+$ = 767/69/71 (Br_2)	0.65	FM1	(KBr): C=0 1622/ 1711/ 1773	
433	N126	AS4	1	O	A0	C4		33	ESI: $(M+H)^+$ = 780/2/4 (Br_2)	0.65	FM1	(KBr): C=0 1709/1769	
434	N126	AS1	1	O	A0	C8		53	ESI: $(M+H)^+$ = 787/89/91(Br_2)	0.53	FM1	(KBr): C=0 1626/1707	
440	N127	AS4	1	O	A0	C8		67	ESI: $(M+H)^+$ = 780/2/4 (Br_2)	0.67	FM1	(KBr): C=0 1618	
441	N127	AS4	1	O	A0	C20		89	ESI: (M+H)+ = 794/6/8 (Br_2)	0.24	EE/ MeOH/ NH_4OH 8/1.5/0.3	(KBr): C=0 1618	
442	N127	AS4	1	O	A0	C4		83	ESI: $(M+H)^+$ = 774/6/8 (Br_2)	0.37	EE/ MeOH/ NH_4OH 8/1.5/0.3	(KBr): C=0 1616/1732	
456	N66	AS16	1	O	A0	C8		83	ESI: $(M+H)^+$ = 641/3/5 (Cl_2)	0.32	EE/ MeOH/ NH_4OH 8/1.5/0.1	(KBr): C=0 1624/1665	
466	N128	AS4	1	O	A0	C8		13	ESI: $(M+H)^+$ = 832/4/6 (Br_2)	0.63	FM1	(KBr): C=0 1684	

No.	RCO	R^2	n	X	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]	Mp. (°C
467	N129	AS4	1	O	A0	C8		16	ESI: $(M+H)^+$ = 806/08/10 (Br_2)	0,63	FM1	(KBr): C=0 1618/1682	
468	N129	AS1	1	O	A0	C8		28	ESI: $(M+H)^+$ = 807/09/11 (Br_2)	0,29	FM1	(KBr): C=0 1630/1680	
470	N128	AS1	1	O	A0	C8		81	ESI: $(M+H)^+$ = 835/7/9 (Br_3)	0,63	FM1	(KBr): C=0 1684	
473	N130	AS1	1	O	A0	C8		40	ESI: $(M+H)^+$ = 787/89/91 (Br_2)	0,51	FM1	(KBr): C=0 1624/1678	
474	N130	AS4	1	O	A0	C8		17	ESI: $(M+H)^+$ = 786/88/90 (Br_2)	0,71	FM1	(KBr): C=0 1618/1684	
477	N66	AS16	1	O	A0	C1		33	ESI: $(M+H)^+$ = 636/38/40(Cl_2)	0,53	EE/ MeOH/ NH_4OH 9/1/1 (v/v/v)	(KBr): C=0 1661	
481	N131	AS4	1	O	A0	C37		30	ESI: $(M+H)^+$ = 838/40/42/44 (Br_2; Cl_2)	0,15	CH_2Cl_2/ MeOH 7/3 (v/v)	(KBr): C=0 1618/1685	
482	N131	AS4	1	O	A0	C20		24	ESI: $(M+H)^+$ = 838/40/42/44 (Br_2; Cl_2)	0,15	CH_2Cl_2/ MeOH 7/3 (v/v)	(KBr): C=0 1618/1685	
483	N132	AS4	1	O	A0	C20		62	ESI: $(M+H)^+$ = 804/6/8/10 (Br_2; Cl)	0,55	FM1	(KBr): C=0 1684	
484	N132	AS4	1	O	A0	C37		85	ESI: $(M+H)^+$ = 804/6/8/10 (Br_2; Cl)	0,60	FM1	(KBr): C=0 1616/1686	
505	N134	AS4	1	O	A0	C8		81	ESI: $(M+H)^+$ = 781/3/5(Br2)	0,74	FM1	(KBr): C=0 1616/1714	
292	N66	AS1	1	H2	A0	C8		6	ESI: $(M+H)^+$ = 731/3/5(Br2)	0,25	FM1	(KBr): C=0 1607/1664	
245	N72	AS4	1	H2	A0	C8		19	ESI: $(M+H)^+$ = 731/3/5 (Br_3)	0,30	FM1	(KBr): C=0 1668	
220	N15	AS1	1	H2	A0	C8		6	ESI: $(M+H)^+$ = 717/19/21 (Br_2)	0,30	FM1	(KBr): C=0 1697,3	
307	N87	AS4	1	O	A0	C4		27	ESI: $(M+H)^+$ = 796/98/800 (Br_2)	0,50	FM1	(KBr): C=0 1618/ 1670/ 1718	
178	N74	AS1	1	O	A0	C4		33	ESI: $(M+H)^+$ = 679/81/83 (Br_2)	0,60	EE/ MeOH/ AcOH 50/50/1 (v/v/v)	(KBr): C=0 1624	
395	N71	AS4	1	O	A0	C21		22	ESI: $(M+H)^+$ = 752/4/6 (Br_3)	0,25	EE/ MeOH/ AcOH 50/25/0.5 (v/v/v)		
509	N119	AS4	1	O	A0	C38	DMF	45	ESI: $(M+H)^+$ = 875/7/9/81 (Br_3)	0.2	FM1	(KBr): C=0 1687/1618	
510	N118	AS4	1	O	A0	C38	DMF	34	ESI: $(M+H)^+$ = 827/29/31 (Br_2)	0.4	FM1	(KBr): C=0 1682/1620	
519	N137	AS4	1	O	A0	C20	THF/DMF	62	ESI: $(M+H)^+$ = 786/88/90 (Br_2)	0.1	FM1	(KBr): C=0 1618/1678	

No.	RCO	R^2	n	X	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]	Mp. (°C)
520	N138	AS4	1	O	A0	C20	THF/DMF	31	ESI: $(M+H)^+$ = 906/08/10 (Br_2)	0.45	FM1	(KBr): C=O 1693	
	N66	AS4	1	O	A0	C69	DMF	100					
533	N139	AS1	1	O	A0	C8		44	ESI: $(M+H)^+$ = 746/48/50 (Br_2)	0.1	FM5	(KBr): C=O 1628	
534	N139	AS4	1	O	A0	C20		60	ESI: $(M+H)^+$ = 759/61/63 (Br_2)	0.2	FM5	(KBr): C=O 1618/1672	
535	N139	AS1	1	O	A0	C53		34	ESI: $(M+H)^+$ = 761/63/65 (Br_2)	0.1	FM5	(KBr): C=O 1624/1670	
536	N140	AS4	1	O	A0	C8		40	ESI: $(M+H)^+$ = 745/7/9 (Br_2)	0.37	FM1	(KBr): C=O 1616/1676	
537	N140	AS1	1	O	A0	C8		33.4	ESI: $(M+H)^+$ = 746/48/50 (Br_2)	0.3	FM1	(KBr): C=O 1614/1672	
551	N66	AS1	1	O	A0	C66		41	ESI: $(M+H)^+$ = 788/90/92 (Br_2)	0.3	EE / MeOH / NH_4OH 50/50/0.5	(KBr): C=O 1628	
552	N66	AS4	1	O	A0	C78		83	ESI: $(M+H)^+$ = 787/89/91 (Br_2)	0.6	CH_2Cl_2 / MeOH / NH_4OH 80/20/1	(KBr): C=O 1620	
553	N66	AS1	1	O	A0	C78		30	ESI: $(M+H)^+$ = 788/90/92 (Br_2)	0.5	CH_2Cl_2 / MeOH / NH_4OH 80/20/1	(KBr): C=O 1626	
554	N71	AS4	1	O	A0	C78		67	ESI: $(M+H)^+$ = 799/801/803 (Br_2)	0.5	CH_2Cl_2 / MeOH / NH_4OH 80/20/1	(KBr): C=O 1622/1684	
555	N71	AS1	1	O	A0	C78		26	ESI: $(M+H)^+$ = 800/02/04 (Br_2)	0.5	CH_2Cl_2 / MeOH / NH_4OH 80/20/1	(KBr): C=O 1624/1684	
556	N66	AS4	1	O	A0	C70		71	ESI: $(M+H)^+$ = 788/90/92 (Br_2)	0.6	CH_2Cl_2 / MeOH / NH_4OH 50/50/0.5	(KBr): C=O 1653	
557	N71	AS4	1	O	A0	C70		27	ESI: $(M+H)^+$ = 800/02/04 (Br_2)	0.8	CH_2Cl_2 / MeOH / NH_4OH 50/50/0.5		
558	N66	AS1	1	O	A0	C64		61	ESI: $(M+H)^+$ = 790/92/94 (Br_2)	0.3	CH_2Cl_2 / MeOH / NH_4OH 90/10/1	(KBr): C=O 1635	
559	N141	AS4	1	O	A0	C20		80	ESI: $(M+H)^+$ = 626/28/30 (Br_2)	0.3	CH_2Cl_2 / MeOH / NH_4OH 90/10/1	(KBr): C=O 1618/1714	
560	N66	AS4	1	O	A0	C71		59	ESI: $(M+H)^+$ = 837/39/41 (Br_2)	0.3	CH_2Cl_2 / MeOH / NH_4OH 90/10/1	(KBr): C=O 1628/62	

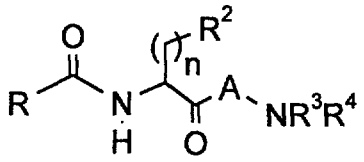
No.	RCO	R^2	n	X	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]	Mp. (°C
561	N71	AS4	1	O	A0	C71		56	ESI: $(M+H)^+$ = 849/51/53 (Br_2)	0.2	CH_2Cl_2 / MeOH / NH_4OH 90/10/1	(KBr): C=0 1618/1684	
562	N66	AS1	1	O	A0	C70		15	ESI: $(M+H)^+$ = 789/91/93 (Br_2)	0.6	CH_2Cl_2 / MeOH / NH_4OH 50/50/0.5	(KBr): C=0 1676	
563	N71	AS1	1	O	A0	C70		27	ESI: $(M+H)^+$ = 801/3/5 (Br_2)	0.6	CH_2Cl_2 / MeOH / NH_4OH 70/30/1	(KBr): C=0 1678	
565	N66	AS4	1	O	A0	C72		51	ESI: $(M+H)^+$ = 787/89/91 (Br_2)	0.2	CH_2Cl_2 / MeOH / NH_4OH 80/20/1	(KBr): C=0 1622/1658	
566	N71	AS4	1	O	A0	C72		65	ESI: $(M+H)^+$ = 799/801/803 (Br_2)	0.2	CH_2Cl_2 / MeOH / NH_4OH 80/20/1	(KBr): C=0 1620/1682	
567	N136	AS4	1	O	A0	C53		65	ESI: $(M+H)^+$ = 756/58/60 (Br_2)	0.5	CH_2Cl_2 / MeOH / NH_4OH 80/20/1	(KBr): C=0 1641	
568	N136	AS4	1	O	A0	C72		76	ESI: $(M+H)^+$ = 784/6/8 (Br_2)	0.2	CH_2Cl_2 / MeOH / NH_4OH 80/20/1	(KBr): C=0 1637	
569	N136	AS1	1	O	A0	C53		63	ESI: $(M+H)^+$ = 757/59/61 (Br_2)	0.4	CH_2Cl_2 / MeOH / NH_4OH 80/20/1	(KBr): C=0 1643	
570	N66	AS31	1	O	A0	C20		88	ESI: $(M+H)^+$ = 640	0.6	CH_2Cl_2 / MeOH / NH_4OH 80/20/1	(KBr): C=0 1622/1664	
571	N66	AS31	1	O	A0	C53		82	ESI: $(M+H)^+$ = 641	0.8	CH_2Cl_2 / MeOH / NH_4OH 80/20/1	(KBr): C=0 1664	
572	N71	AS31	1	O	A0	C20		100	ESI: $(M+H)^+$ = 652	0.4	CH_2Cl_2 / MeOH / NH_4OH 80/20/1	(KBr): C=0 1620/1684	
573	N71	AS31	1	O	A0	C53		48	ESI: $(M+H)^+$ = 653	0.4	CH_2Cl_2 / MeOH / NH_4OH 80/20/1	(KBr): C=0 1622/1684	
576	N66	AS11	1	O	A0	C53		35	ESI: $(M+H)^+$ = 727	0.65	CH_2Cl_2 / MeOH / NH_4OH 80/20/1	(KBr): C=0 1664/1732	
577	N71	AS11	1	O	A0	C53		73	ESI: $(M+H)^+$ = 739	0.18	EE / MeOH / NH_4OH 50/50/0.5	(KBr): C=0 1684/1734	

No.	RCO	R^2	n	X	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]	Mp. (°C
580	N66	AS11	1	O	A0	C20		65	ESI: $(M+H)^+$ = 706	0.5	CH_2Cl_2 / MeOH / NH_4OH 80/20/1	(KBr): C=O 1664/1732	
581	N71	AS11	1	O	A0	C20		38	ESI: $(M+H)^+$ = 738	0.2	CH_2Cl_2 / MeOH / NH_4OH 90/10/1	(KBr): C=O 1684/1734	
582	N143	AS4	1	O	A0	C20		61	ESI: $(M+H)^+$ = 758/60/62	0.5	CH_2Cl_2 / MeOH / NH_4OH 90/10/1	(KBr): C=O 1615	
583	N66	AS31	1	O	A0	C72		50	ESI: $(M+H)^+$ = 669	0.35	FM1	(KBr): C=O 1664	
584	N71	AS31	1	O	A0	C72		68	ESI: $(M+H)^+$ = 681	0.35	FM1	(KBr): C=O 1622/1684	
585	N144	AS4	1	O	A0	C8		50	ESI: $(M+H)^+$ = 927/29/31/33 (Br4)	0.43	FM5	(KBr): C=O 1616/1684	
586	N144	AS4	1	O	A0	C53		85	ESI: $(M+H)^+$ = 942/4/6/8 (Br_4)	0.67	FM1	(KBr): C=O 1680	
587	N66	AS11	1	O	A0	C72		37	ESI: $(M+H)^+$ = 755	0.35	FM1	(KBr): C=O 1622/1658/ 1732	
588	N71	AS11	1	O	A0	C72		81	ESI: $(M+H)^+$ = 767	0.5	FM1	(KBr): C=O 1684/1732	
619	N71	AS19	1	O	A0	C8		27.9		0.3	EE / MeOH / NH_4OH 9/1/0.3	(KBr): C=O 1622/1684	
620	N66	AS35	1	O	A0	C8		36	ESI: $(M-H)^-$ = 598	0.25	MeOH	(KBr): C=O 1628/1664	
621	N66	AS36	1	O	A0	C8		32	ESI: $(M-H)^-$ = 587	0.56	FM1	(KBr): C=O 1626/1666	
622	N71	AS36	1	O	A0	C8		32	ESI: $(M-H)^-$ = 599	0.44	FM1	(KBr): C=O 1622/1684	
623	N109	AS36	1	O	A0	C8		37	ESI: $(M-H)^-$ = 593	0.6	FM1	(KBr): C=O 1626/1649	
624	N118	AS36	1	O	A0	C8		55	ESI: $(M-H)^-$ = 629	0.6	FM1	(KBr): C=O 1622/1684	
625	N111	AS36	1	O	A0	C8		47	ESI: $(M-H)^-$ = 667	0.61	FM1	(KBr): C=O 1624/1687	
626	N111	AS19	1	O	A0	C8		20	ESI: $(M-H)^-$ = 731/3(Br)	0.28	EE / MeOH / NH_4OH 9/1/0.3	(KBr): C=O 1624/1687	
627	N109	AS19	1	O	A0	C8		16	ESI: $(M-H)^-$ = 657/9(Br)	0.28	EE / MeOH / NH_4OH 9/1/0.3	(KBr): C=O 1653	
633	N118	AS19	1	O	A0	C8		20	ESI: $(M+H)^+$ = 693/5 (Br)	0.18	EE / MeOH / NH_4OH 9/1/0.3	(KBr): C=O 1622/1684	
	N66	AS1	1	O	A0	C69		100		0.3	FM4	(KBr): C=O 1668	

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Example 4

Preparation of compounds of general formula:



1-[4-amino-3,5-dibromo-N-[4-(1,3,3a,4,5,6,7,7a-octahydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperazine (No. 91)

A mixture of 0.35 g (2.1 mmol) of CDT, 1.0 g (1.4 mmol) of 4-(1,3,3a,4,5,6,7,7a-octahydro-2(2H)-oxobenzimidazol-1-yl)-piperidine, 0.5 ml of (2.8 mmol) of DIEA and 100 ml of tetrahydrofuran was stirred for 1 hour whilst cooling with ice and then for 30 minutes at ambient temperature. With stirring 0.46 g (1.75 mmol) of 1-(4-amino-3,5-dibromo-D-phenylalanyl)-4-(4-pyridinyl)piperazine and 0.32 ml of (1.8 mmol) of DIEA were added and refluxed for 3 hours. The reaction mixture was diluted with 100 ml of ethyl acetate and the organic phase was washed twice with aqueous saturated sodium hydrogen carbonate solution. The combined aqueous phases were then extracted once with ethyl acetate/tetrahydrofuran = 1/1 (v/v) and the combined organic phases were washed once with saturated aqueous saline solution. After drying the organic phase and eliminating the solvent *in vacuo* the residue was purified by column chromatography (MN-silica gel 60, Macherey-Nagel, 70-230 mesh ASTM, eluant: ethyl acetate/methanol = 9/1 (v/v)). 120 mg (12% of theory) of a colourless foam were obtained.

IR (KBr): 1626. 1686 cm^{-1} (C=O)

R_f: 0.62 (FM3)

ESI-MS: $(M+H)^+$ = 731/733/735 (Br_2)

$(M+H+Na)^{++}$ = 377/378/379 (Br_2)

The following were prepared analogously (in each case n = 1):

No.	RCO	R^2	A	NR^3R^4	n	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]	Mp. (°C)
	N16	AS1	A3	C1	1	Triethylamine as base	31	ESI: $(M+H)^+$ = 974/6/8(B_5)	0.2	FM1	(KBr): C=0 1641.3; 1695.3	
86	N53	AS4	A0	C1	1	DMF as solvent	23	ESI: $(M+H)^+$ = 739/41/43 (B_5)	0.5	FM1	(KBr): C=0 1641.3; 1697.3	
87	N54	AS4	A0	C1	1	DMF as solvent	81	ESI: $(M+H)^+$ = 739/41/43 (B_5)	0.5	FM1	(KBr): C=0 1620.1; 1697.3	
92	N57	AS4	A0	C1	1	DMF as solvent	60	ESI: $(M+H)^+$ = 712/4/6 (B_5)	0.6	FM1	(KBr): C=0 1597; 1635.5	
93	N47	AS4	A0	C1	1		23	ESI: $(M+H)^+$ = 636/8/40 (B_5)	0.4	FM1	(KBr): C=0 1622; 1675	
94	N45	AS4	A0	C1	1		45	ESI: $(M+H)^+$ = 739/41/43 (B_5)	0.6	FM1	(KBr): C=0 1598.9; 1620.1	
95	N57	AS1	A0	C1	1	DMF as solvent	13	ESI: $(M+H)^+$ = 713/5/7(B_5)	0.2	FM 1	(KBr): C=0 1637.5	
96	N53	AS1	A0	C1	1		15	ESI: $(M+H)^+$ = 740/2/4 (B_5)	0.2	FM 1	(KBr): C=0 1633.6; 1687.6	
97	N54	AS1	A0	C1	1	DMF as solvent	31	ESI: $(M+H)^+$ = 740/2/4 (B_5)	0.2	FM 1	(KBr): C=0 1635.5; 1695.3	
107	N59	AS4	A0	C1	1		76	ESI: $(M+H)^+$ = 694/6/8 (B_5)	0.7	FM 1	(KBr): C=0 1597; 1635.5	
108	N45	AS1	A0	C1	1		37	ESI: $(M+H)^+$ = 740/2/4 (B_5)	0.3	FM 1	(KBr): C=0 1633.6; 1708.8	
109	N59	AS1	A0	C1	1		30	ESI: $(M+H)^+$ = 695/7/9 (B_5)	0.3	FM 1	(KBr): C=0 1647.4	
116	N60	AS4	A0	C1	1	DMF as solvent	80	ESI: $(M+H)^+$ = 753/5/7(B_5)	0.6	FM 1	(KBr): C=0 1623.7; 1676.1; 1712.7	
117	N60	AS1	A0	C1	1	DMF as solvent	50	ESI: $(M+H)^+$ = 754/6/8 (B_5)	0.4	FM 1	(KBr): C=0 1617; 1650; 1670; 1712.7	
118	N47	AS1	A0	C1	1		29	ESI: $(M+H)^+$ = 637/9/41 (B_5)	0.1	FM 1	(KBr): C=0 1639.4	
121	N61	AS1	A0	C1	1		12.4	ESI: $(M+H)^+$ = 727/9/31 (B_5)	0.2	FM 1	(KBr): C=0 1635.5; 1705	
122	N61	AS4	A0	C1	1		42	ESI: $(M+H)^+$ = 726/8/30 (B_5)	0.6	FM 1	(KBr): C=0 1620.1; 1706.9	
125	N15	AS7	A0	C1	1	NEt_3 as base	4.4	ESI: $(M+H)^+$ = 598	0.6	FM 1	(KBr): C=0 1708.8	
126	N15	AS7	A0	C4	1	NEt_3 as base	57	ESI: $(M+H)^+$ = 597	0.6	FM 1	(KBr): C=0 1622; 1708.8	188.0

No.	RCO	R^2	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]	m.p. (°C)
127	N15	AS7	A0	C8	NEt_3 as base	16	ESI:M+H= 603	0.6	FM 1	(KBr): C=0 1622; 1697.3	168-170
137	N94	AS4	A0	C4		42	ESI:M+H= 708/10/12 (Br_2)	0.8	FM1	(KBr): C=0 1618	
138	N95	AS4	A0	C8	NEt_3 as base	29	ESI:M+H= 743/5/7(Br_2)	0.8	FM1	(KBr): C=0 1713	
139	N61	AS1	A3	C1		41	ESI:M+H= 955/7/9(Br_2)	0.4	FM1	(KBr): C=0 1640; 1709	
140	N60	AS1	A3	C1		66	ESI:M+H= 982/4/6(Br_2)	0.5	FM1	(KBr): C=0 1645; 1712	
143	N66	AS1	A0	C4	DMF as solvent	69	ESI:M+H= 739/41/43 (Br_2)	0.4	FM1	(KBr): C=0 1624; 1659	
144	N96	AS1	A0	C4		54	ESI:M+H= 725/7/9(Br_2)	0.5	FM1	(KBr): C=0 1616	
145	N61	AS1	A0	C4		48	ESI:M+H= 724/6/8(Br_2)	0.6	FM1	(KBr): C=0 1624; 1709	
146	N15	AS14	A0	C1	DMF as solvent	53	ESI:M+H= 555	0.2	FM1	(KBr): C=0 1636; 1701	
147	N61	AS4	A0	C11		30	ESI:M+H= 746/48/50 (Br_2)	0.7	FM1	(KBr): C=0 1620; 1713	
148	N66	AS1	A0	C8	THF/DMF as solvent	58	ESI:M+H= 745/7/9 (Br_2)	0.7	FM1	(KBr): C=0 1628; 1663	
149	N69	AS1	A0	C4	THF/DMF as solvent	61	ESI:M+H= 739/41/43 (Br_2)	0.7	FM1	(KBr): C=0 1624; 1675	
150	N97	AS1	A0	C4	THF/DMSO as solvent	32	ESI:M+H= 783/85/87 (Br_2)	0.4	FM1	(KBr): C=0 1709	
152	N71	AS1	A0	C4		40	ESI:M+H= 751/53/55 (Br_2)	0.7	FM1	(KBr): C=0 1622; 1684	
153	N65	AS1	A0	C4		51	ESI:M+H = 751/53/55 (Br_2)	0.7	FM1	(KBr): C=0 1626; 1678	
	N66	AS1	A3	C1		37					
225	N66	AS1	A0	C1	THF/DMF as solvent	48	ESI:M+H= 740/42/44 (Br_2)	0.4	FM1	(KBr): C=0 1650; 1670	
226	N66	AS4	A0	C8	THF/DMF as solvent	88	ESI:M+H= 744/6/8 (Br_2)	0.6	FM1	(KBr): C=0 1618; 1661	
227	N69	AS4	A0	C8	THF/DMF as solvent	72	ESI:M+H = 744/6/8 (Br_2)	0.6	FM1	(KBr): C=0 1618; 1680	
228	N69	AS1	A0	C8	THF/DMF as solvent	69	ESI:M+H= 745/7/9 (Br_2)	0.5	FM1	(KBr): C=0 1628	
229	N70	AS1	A0	C4	THF/DMF as solvent	39	ESI:M+H= 727/29/31 (Br_2)	0.3	FM1	(KBr): C=0 1730	

No.	RCO	R^2	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]	m.p. (°C)
230	N66	AS4	A0	C20		49	ESI:M+H= 758/60/62 (Br_2)	0.6	FM1	(KBr): C=0 1614	
231	N99	AS4	A0	C8	THF/DMF as solvent	68	ESI:M+H= 758/60/62 (Br_2)	0.6	FM1	(KBr): C=0 1624	
239	N71	AS1	A0	C8	THF/DMF as solvent	59	ESI:M+H= 757/59/61 (Br_2)	0.5	FM1	(KBr): C=0 1626; 1680	
240	N71	AS4	A0	C11		35	ESI:M+H= 771/3/5 (Br_2)	0.7	FM1	(KBr): C=0 1615; 1684	
241	N71	AS4	A0	C8		88	ESI:M+H= 756/58/60 (Br_2)	0.7	FM1	(KBr): C=0 1620; 1682	
242	N71	AS4	A0	C1		40	ESI:M+H= 751/3/5(Br_2)	0.6	FM1	(KBr): C=0 1615; 1684	
243	N71	AS4	A0	C20		38	ESI:M+H= 770/2/4(Br_2)	0.7	FM1	(KBr): C=0 1618; 1684	
244	N71	AS1	A0	C11		36	ESI:M+H= 772/4/6(Br_2)	0.4	FM1	(KBr): C=0 1622; 1684	
	N5	AS1	A3	C1	NEt_3 as base	24	ESI: M+H=890/2/4 (Br_2)	0.06	FM1	(KBr): C=O 1641.3	
	N10	AS1	A3	C1	NEt_3 as base	55	ESI: M+H=874/6/8 (Br_2)	0.4	FM1	(KBr): C=O 1641.3	
	N12	AS1	A3	C1	NEt_3 as base	19.2	ESI: M+H=902/4/6 (Br_2)	0.4	FM1	(KBr): C=O 1639.4	
	N22	AS1	A3	C1	NEt_3 as base	35.5		0.5	FM1		
	N23	AS1	A3	C1	NEt_3 as base	31		0.5	FM1		
	N24	AS1	A3	C1	NEt_3 as base	26.6		0.5	FM1		
	N46	AS1	A3	C1	NEt_3 as base	36.2		0.5	FM1	(KBr): C=O 1641.3	
83	N15	AS1	A0	C1		36.7	ESI: M+H= 726/28/30 (Br_2)	0.6	FM2	(KBr): C=O 1641.3; 1695.3	
84	N15	AS1	A0	C4		36.3	ESI: M+H=725/7/9 (Br_2); M+Na= 747/49/51 (Br_2)	0.7	FM2	(KBr): C=O 1624.0; 1699.2	
88	N55	AS4	A0	C1		93.6	ESI: M+H= 793/5/7/9 (Br_2;Cl_2)	0.8	FM3	(KBr): C=O 1641.3; 1708.8	
89	N56	AS4	A0	C1		30	ESI: M+H= 797/799/801 (Br_2)	0.8	FM1	(KBr): C=O 1641.3; 1697.3; 1749.3	

No.	RCO	R^2	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]	m.p. (°C)
136	N15	AS9	A0	C1		14.6	ESI: M+H= 570	0.6	FM3	(KBr): C=O 1635.5; 1701.1	
91	N64	AS4	A0	C1		11.7	ESI: M+H= 731/3/5;	0.6	FM3	(KBr): C=O 1625.9; 1685.7	
	N16	AS1	A3	C5	purification by column chromato-graphy: silica gel/ FM4	74	ESI: M+H= 974/6/8(Br_2)	0.5	FM4	(KBr): C=O 1685.7; 1635.5	
155	N15	AS1	A0	C3		34	ESI:M+H= 743/5/7(Br_2)	0.5	FM1	(KBr): C=O 1626; 1695	165-9
156	N15	AS1	A0	C1		40	ESI:M+H= 743/5/7(Br_2)	0.5	FM1	(KBr): C=O 1624; 1695	155-9
157	N15	AS4	A0	C19		54	ESI:M+H= 742/4/6(Br_2)	0.8	FM1	(KBr): C=O 1616; 1697	151-4
158	N79	AS4	A0	C1		15	ESI:M+H= 727/29/31 (Br_2)	0.6	FM1	(KBr): C=O 1616; 1695; 1732	132-5
159	N77	AS4	A0	C8		34	ESI:M+H= 732/4/6(Br_2)	0.6	FM1	(KBr): C=O 1632	
160	N73	AS1	A0	C4		12	ESI:M-H= 649/51/53 (Br_2)	0.1	FM1	(KBr): C=O 1626	
170	N15	AS4	A0	C37		62	ESI:M-H= 725/7/9(Br_2)	0.5	FM1	(KBr): C=O 1620; 1701	165-70
171	N79	AS1	A0	C1		60	ESI:M+H= 728/30/32 (Br_2)	0.2	FM1	(KBr): C=O 1637.5	193-7
172	N79	AS1	A0	C8		27	ESI:M+H= 733/5/7 (Br_2)	0.3	FM1	(KBr): C=O 1622	163-9
185	N77	AS4	A0	C4		66	ESI:M+H= 726/28/30 (Br_2)	0.5	FM1	(KBr): C=O 1624	
186	N77	AS4	A0	C1		76	ESI:M+H= 727/29/31 (Br_2)	0.6	FM1	(KBr): C=O 1635.5	
187	N77	AS1	A0	C4		67	ESI:M+H= 727/29/31 (Br_2)	0.3	FM1	(KBr): C=O 1627.8	
188	N78	AS1	A3	C1		63	ESI:M+H= 955/7/9 (Br_2)	0.5	FM1	(KBr): C=O 1637.5; 1774.4; 1701	
189	N103	AS4	A0	C8		50	ESI:M+H= 713/5/7(Br_2)	0.7	FM1	(KBr): C=O 1616.3	
192	N77	AS1	A0	C1		47	ESI:M+H= 728/30/32 (Br_2)	0.2	FM1	(KBr): C=O 1643.3	
247	N15	AS10	A3	C4		60	ESI:M+H= 937/39/41 (Br_2)	0.6	FM1	(KBr): C=O 1639.4; 1701	

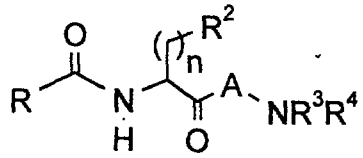
No.	RCO	R^2	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]	m.p. (°C)
249	N15	AS4	A0	C22		52	ESI:M+H= 744/6/8(Br_2)	0.6	FM1	(KBr): C=O 1695.3	
161	N15	AS4	A0	C21		32	ESI:M+H= 726/28/30 (Br_2)	0.6	FM1	(KBr): C=O 1622; 1701	163-7
162	N78	AS1	A0	C4		15	ESI:M+H= 726/28/30 (Br_2)	0.5	FM1	(KBr): C=O 1624; 1772.5	
163	N73	AS1	A0	C1		43	ESI:M+H= 752/4/6(Br_2)	0.07	FM1	(KBr): C=O 1637.5	
164	N79	AS4	A0	C8		48	ESI:M+H= 732/4/6(Br_2)	0.6	FM1	(KBr): C=O 1616.3	127-32
165	N15	AS1	A0	C21		27	ESI:M+H= 727/29/31 (Br_2)	0.3	FM1	(KBr): C=O 1697.3	184-9
166	N76	AS1	A0	C4		17	ESI:M+H= 665/7/9(Br_2)	0.2	FM1	(KBr): C=O 1616; 1734	
167	N75	AS1	A0	C4		20	ESI:M+H= 665/7/9(Br_2)	0.2	FM1	(KBr): C=O 1624	
168	N73	AS1	A3	C4		39	ESI:M+H= 879/81/83 (Br_2)	0.2	FM1	(KBr): C=O 1631.7	
169	N15	AS1	A0	C37		17	ESI:M+H= 726/28/30 (Br_2)	0.3	FM1	(KBr): C=O 1627.8; 1697.3	156-61
173	N15	AS10	A0	C4		66	ESI:M+H= 709/11/13 (Br_2)	0.68	FM1	(KBr): C=O 1627.8; 1656.8; 1695.3	283-4
174	N15	AS10	A0	C1		42	ESI:M+H= 710/2/4 (Br_2)	0.6	FM1	(KBr): C=O 1706.9	266-9
175	N77	AS1	A0	C8		36	ESI:M+H= 733/5/7(Br_2)	0.2	FM1	(KBr): C=O 1641.3	
176	N76	AS1	A3	C4		47	ESI:M+H= 893/5/7(Br_2)	0.2	FM1	(KBr): C=O 1635.5	
177	N75	AS1	A3	C4		53	ESI:M+H= 893/5/7(Br_2)	0.1	FM1	(KBr): C=O 1637.5	
180	N74	AS1	A3	C4		44	ESI:M+H= 907/9/11(Br_2)	0.3	FM1	(KBr): C=O 1631.7; 1689.5	
190	N15	AS1	A3	C18		44	ESI:M+H= 985/7/9(Br_2)	0.4	FM1	(KBr): C=O 1635.5; 1695.3	
191	N15	AS10	A3	C1		64	ESI:M+H= 938/40/42 (Br_2)	0.6	FM1	(KBr): C=O 1645.2; 1701	
	N15	AS10	A3	C4		91	ESI:M+H= 937/39/41 (Br_2)			(KBr): C=O 1643.3; 1701	
	N15	AS10	A3	C1		64	ESI:M+H= 938/40/42 (Br_2)			(KBr): C=O 1645; 1701	
254	N77	AS1	A3	C1		37	ESI:M+H= 956/8/60(Br_2)	0.3	FM1	(KBr): C=O 1641	

No.	RCO	R^2	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]	m.p. (°C)
	N15	AS4	A3	C18		90	ESI:M+H= 984/6/8(Br_2)			(KBr): C=O 1641.3; 1699	
257	N15	AS4	A5	C1		17	ESI:M+H= 782/4/6(Br_2)	0.53	FM1	(KBr): C=O 1643; 1697	
258	N100	AS4	A0	C1		69	ESI:M+H= 755/7/9(Br_2)	0.54	FM1	(KBr): C=O 1627.8; 1705	
259	N100	AS4	A0	C8		70	ESI:M+H= 760/2/4(Br_2)	0.54	FM1	(KBr): C=O 1695	
260	N15	AS4	A0	C23		39	ESI:M+H= 796/98/800 (Br_2)	0.36	FM1	(KBr): C=O 1635.5; 1699	
261	N15	AS4	A10	C1		26	ESI:M+H= 796/98/800 (Br_2)	0.38	FM1	(KBr): C=O 1631.4; 1701	
265	N15	AS4	A5	C8		20	ESI:M+H= 787/9/91(Br_2)	0.41	FM1	(KBr): C=O 1635.5; 1697	
266	N15	AS4	A6	C1		24	ESI:M+H= 796/98/800 (Br_2)	0.43	FM1	(KBr): C=O 1647; 1689.5	
262	N80	AS4	A0	C1		25	ESI:M+H= 803/5/7(Br_2)	0.54	FM1	(KBr): C=O 1637.5	
263	N15	AS15	A0	C8		64	ESI:M+H= 565	0.43	FM1	(KBr): C=O 1627.8; 1707	
264	N15	AS4	A0	C24		62	ESI:M+H= 733/5/7(Br_2)	0.4	FM1	(KBr): C=O 1622; 1701	
267	N81	AS4	A3	C8		46	ESI:M+H= 974/6/8(Br_2)	0.55	FM1	(KBr): C=O 1641; 1707	
268	N15	AS4	A6	C8		27	ESI:M+H= 801/3/5(Br_2)	0.5	FM1	(KBr): C=O 1633.6; 1697	
269	N82	AS4	A0	C8		86	ESI:M+H= 742/4/6(Br_2)	0.66	FM1	(KBr): C=O 1620; 1649	
270	N82	AS4	A0	C1		56	ESI:M+H=73 7/39/41(Br_2)	0.59	FM1	(KBr): C=O 1641	
272	N15	AS1	A0	C8		76	ESI:M+H= 698	0.6	FM1	(KBr): C=O 1627.8; 1714.6	
273	N15	AS4	A10	C8		68	ESI:M+H= 801/3/5(Br_2)	0.52	FM1	(KBr): C=O 1637.5; 1701	
274	N102	AS4	A0	C1		76	ESI:M+H= 738/40/42 (Br_2)	0.56	FM1	(KBr): C=O 1664.5	
275	N102	AS4	A0	C8		55	ESI:M+H= 743/5/7(Br_2)	0.59	FM1	(KBr): C=O 1618; 1664.5	
276	N83	AS4	A0	C1		30	ESI:M+H= 745/7/9(Br_2)	0.48	FM1	(KBr): C=O 1633.6	
277	N84	AS4	A0	C8		63	ESI:M+H= 744/6/8(Br_2)	0.54	FM1	(KBr): C=O 1616; 1691.5	

No.	RCO	R^2	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]	m.p. (°C)
278	N84	AS4	A3	C4		88	ESI:M+H= 966/8/70 (Br_2)	0.5	FM1	(KBr): C=O 1633.6; 1691.5	
279	N15	AS4	A0	C26		75	ESI:M+H= 732/4/6(Br_2)	0.4	FM1	(KBr): C=O 1618; 1709	
281	N15	AS12	A0	C8		21	ESI:M+H= 598	0.4	FM1	(KBr): C=O 1697	
282	N66	AS1	A0	C18		19	ESI:M+H= 770/2/4(Br_2)	0.5	FM1	(KBr): C=O 1624; 1660.6; 1734	
284	N66	AS1	A0	C18		29	ESI:M+H= 771/3/5(Br_2)	0.3	FM1	(KBr): C=O 1630; 1655	
314	N93	AS4	A0	C8		81	ESI:M+H= 794/6/8(Br_2)	0.5	FM1	(KBr): C=O 1618; 1701	
315	N93	AS4	A0	C1		77	ESI:M+H= 789/91/93 (Br_2)	0.5	FM1	(KBr): C=O 1627.6; 1705	
316	N65	AS1	A0	C18		15	ESI:M+H= 783/5/7(Br_2)	0.3	FM1	(KBr): C=O 1624; 1681.8	
317	N66	AS4	A0	C3		51	ESI:M+H= 778/80/82 (Br_2)	0.6	FM1	(KBr): C=O 1627.6; 1662.5	
318	N66	AS1	A0	C3		40	ESI:M+H= 557/9/61 (Br_2)	0.4	FM1	(KBr): C=O 1659	
319	N66	AS4	A0	C19		55	ESI:M+H= 778/80/82 (Br_2)	0.7	FM1	(KBr): C=O 1664.5	
320	N65	AS4	A0	C19		61	ESI:M+H= 768/70/72 (Br_2)	0.6	FM1	(KBr): C=O 1618; 1682	
321	N93	AS1	A0	C4		29	ESI:M+H= 789/91/93 (Br_2)	0.4	FM1	(KBr): C=O 1622; 1705	
	N15	AS1	A3	C5		47		0.3	FM1		
	N19	AS1	A3	C1		80	ESI:M+H= 933/5/7(Br_2)			(KBr): C=O 1641.3	

Example 5

Preparation of compounds of general formula:



1-[N^2-[N-(4-phenyl-1-piperazinyl)carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine (No. 17)

To a solution of 800 mg (0.86 mmol) of 1-[N^2-[N-(4-phenyl-1-piperazinyl)carbonyl]-3,5-dibromo-D-tyrosyl]-N^6-[(1,1-dimethylethoxy)carbonyl]-L-lysyl]-4-(4-pyridinyl)-piperazine in methanol were added 2 ml of methanol saturated with hydrogen chloride and the mixture was stirred overnight at ambient temperature. The reaction mixture was mixed with ethyl acetate until the hydrochloride was totally precipitated and the precipitate formed was filtered off. After washing the precipitate with water it was purified by column chromatography (MN-silica gel 60, Macherey-Nagel, 70-230 mesh ASTM, eluant: ethyl acetate/methanol/conc. aqueous ammonia = 5/5/0.5 (v/v/v)). 0.38 g (55% of theory) of an amorphous solid were obtained.

IR (KBr): 1639 cm^{-1} (C=O)

R_f: 0.55 (FM2)

ESI-MS: $(M+H)^+$ = 799/801/803 (Br_2)

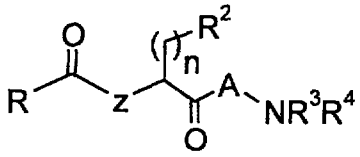
$(M+2H)^{++}$ = 400/401/402 (Br_2)

The following were prepared analogously (in each case n=1):

No.	RCO	R^2	A	NR^3R^4	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
11	N8	AS1	A1	C1	70	ESI: M+H=758/60/62 (Br_2)	0.43	FM2	(KBr): C=O 1656.8
12	N9	AS1	A1	C1	60	ESI M+H=788/90/92 (Br_2)	0.46	FM2	(KBr): C=O 1643.3
8	N5	AS1	A1	C1	53.7	ESI: M+H=790/2/4 (Br_2)	0.2	Methanol/ glacial acetic acid/water = 9/1/1 (v/v/v)	(KBr): C=O 1641.3
15	N11	AS1	A1	C1	56	ESI: M+H=773/5/7 (Br_2)	0.4	FM2	
5	N2	AS1	A1	C11	66.4	ESI: M+H=808/10/12 (Br_2)	0.39	FM2	(KBr): C=O 1656.8
7	N2	AS1	A1	C2	46.2	ESI: M+H=794/6/8 (Br_2)	0.13	FM2	(KBr): C=O 1637.5
13	N2	AS2	A1	C1	84.7	ESI: M+H=666	0.46	FM2	(KBr): C=O 1641.3

Example 6

Preparation of compounds of general formula:



1-[4-amino-3,5-dibromo-N^2-[N-[4-(2-chlorophenyl)-1-piperazinyl]carbonyl]-D-phenylalanyl]-L-lysyl]-4-(4-pyridinyl)-piperazine-bis-(trifluoroacetate) (No. 61)

To a mixture of 0.42 g (0.45 mmol) of 1-[4-amino-3,5-dibromo-N^2-[N-[4-(2-chlorophenyl)-1-piperazinyl]carbonyl]-D-phenylalanyl]-N6-[(1.1-dimethylethoxy)carbonyl]-L-lysyl]-4-(4-pyridinyl)-piperazine in 30 ml of methylene chloride were added 3 ml of trifluoroacetic acid. The reaction mixture was stirred for 3 hours at ambient

temperature and then evaporated down *in vacuo*. The remaining residue was triturated with ether and the resulting beige amorphous solid (0.43g; 37% of theory) was suction filtered.

IR (KBr): 1643, 1678 cm^{-1} (C=O)

R_f: 0.6 (FM1)

ESI-MS: $(M+H)^+$ = 832/834/836/838 (Br_2,Cl)

The following were prepared analogously:

No.	RCO	Z	R^2	A	NR^3R^4	n	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
21	N6	N-H	AS1	A1	C4	1		65	ESI: $(M+H)^+$ = 828/30/32 (Br_2)	0.3	FM1	(KBr): C=0 1635.5
22	N16	N-H	AS1	A1	C1	1		98	ESI: $(M+H)^+$ = 874/6/8 (Br_2)	0.2	FM1	(KBr): C=0 1643.3; 1676
141	N61	N-H	AS1	A1	C1	1		46	ESI: $(M+H)^+$ = 855/7/9 (Br_2)	0.1	FM1	(KBr): C=0 1634; 1705
142	N60	N-H	AS1	A1	C1	1		50	ESI: $(M+H)^+$ = 882/4/6 (Br_2)	0.1	FM1	(KBr): C=0 1643; 1711
154	N66	N-H	AS1	A1	C1	1		60	ESI: $(M+H)^+$ = 868/70/72 (Br_2)	0.1	FM1	(KBr): C=0 1645; 1653
197	N15	N-H	AS1	A1	C8	1		21	ESI: $(M+H)^+$ = 859/61/63 (Br_2)	0.18	FM7	(KBr): C=O 1678; 1201.6 CF3 1180.4; 1134.1
198	N51	N-H	AS1	A1	C8	1		27	ESI: $(M+H)^+$ = 829/31/33 (Br_2)	0.22	FM7	(KBr): C=O 1676; CN 2221.9; CF3 1203.5; 1180.4; 1132
218	N15	N-H	AS6	A1	C1	1		25.7	ESI: $(M+H)^+$ = 776/8 (Br)	0.45	FM1	(KBr): C=O 1695.3; 1635.5
287	N15	N-H	AS1	A8	C1	1		36.5	ESI: $(M+H)^+$ = 840/2/4 (Br_2)	0.5	FM2	(KBr): C=O 1695.3; 1637.5
19	N15	N-H	AS1	A1	C1	1		44	ESI: $(M+H)^+$ = 854/6/8 (Br_2)	0.43	FM2	(KBr): C=O 1695.3; 1637.5

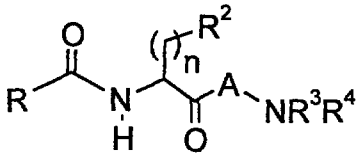
No.	RCO	Z	R^2	A	NR^3R^4	n	Remarks	% Ausbeute	MS	R_f	Eluant	IR [cm^{-1}]
14	N10	N-H	AS1	A1	C1	1		25.5	ESI: $(M+H)^+$ = 774/6/8 (Br_2)	0.33	FM2	(KBr): C=O 1683.8
16	N12	N-H	AS1	A1	C1	1		64.4	ESI: $(M+H)^+$ = 802/4/6 (Br_2)	0.55	FM2	(KBr): C=O 1639.4
29	N22	N-H	AS1	A1	C1	1		91.2	ESI: $(M+H)^+$ = 867/69/71 (Br_2)	0.5	FM2	(KBr): -NH- 3427.3; C=O 1643.3; 1678.0
30	N23	N-H	AS1	A1	C1	1		83.3	ESI: $(M+H)^+$ = 833/5/7/9 (Br_2,Cl)	0.5	FM2	(KBr): C=O 1643.3; 1676.0
31	N24	N-H	AS1	A1	C1	1		100	ESI: $(M+H)^+$ = 843/5/7 (Br_2)	0.51	FM2	(KBr): C=O 1645.2; 1676.0
63	N46	N-H	AS1	A1	C1	1		100	ESI: $(M+H)^+$ = 764/6/8 (Br_2)	0.58	FM2	(KBr): C=O 1643.3; 1676.0
68	N15	N-H	AS1	A1	C6	1		80	ESI: $(M+H)^+$ = 833/5/7 (Br_2)	0.18	FM1	(KBr): C=O 1683.8
69	N15	N-H	AS1	A1	C5	1		74	ESI: $(M+H)^+$ = 854/6/8(Br_2)	0.18	FM1	(KBr): C=O 1683.8;1639.4
70	N45	N-H	AS1	A1	C6	1		89	ESI: $(M+H)^+$ = 897/9/901 (Br_2)	0.2	FM1	(KBr): C=O 1695.3;1676.0
71	N16	N-H	AS1	A1	C5	1		82	ESI: $(M+H)^+$ = 874/6/8 (Br_2)	0.22	FM1	(KBr): C=O 1678.0; 1639.4
72	N15	N-H	AS5	A1	C1	1		97	ESI: $(M+H)^+$ = 838/40/42 (Br_2)	0.16/0.2	FM1	(KBr): C=O 1685.7; 1643.3
77	N45	N-H	AS5	A1	C1	1		66	ESI: $(M+H)^+$ = 852/4/6 (Br_2)	0.33/0.4	FM1	(KBr): C=O 1683.8;1645.2 NH3 3427.3
24	N18	N-H	AS1	A1	C1	1		94	ESI: $(M+H)^+$ = 775/7/9 (Br_2)	0.11	FM1	(KBr): C=O 1676.0; 1643.3
25	N19	N-H	AS1	A1	C1	1		92	ESI: $(M+H)^+$ = 833/5/7 (Br_2)	0.13	FM1	(KBr): C=O 1676.0; 1643.3
26	N20	N-H	AS1	A1	C1	1		98	EI: M^+ = 762/4/6 (Br_2)	0.11	FM1	(KBr): C=O 1676.0; 1643.3
27	N21	N-H	AS1	A1	C1	1		98	ESI: $(M+H)^+$ = 814/6/8 (Br_2)	0.04	FM1	(KBr): C=O 1676.0; 1645.2
41	N34	N-H	AS1	A1	C1	1		97	ESI: $(M+H)^+$ = 835/38/40/42 (Br_3)	0.08	FM1	(KBr): C=O 1676.0; 1643.3
42	N35	N-H	AS1	A1	C1	1		83	ESI: $(M+H)^+$ = 803/5/7(Br_2)	0.09	FM1	(KBr): C=O 1676.0; 1643.3
43	N36	N-H	AS1	A1	C1	1		87	ESI: $(M+H)^+$ = 815/7/9 (Br_2)	0.04	FM1	(KBr): C=O 1676.0; 1645.2
53	N42	N-H	AS1	A1	C1	1		89	ESI: $(M+H)^+$ = 805/7/9 (Br_2)	0.11	FM1	(KBr): C=O 1676.0; 1634.3

No.	RCO	Z	R^2	A	NR^3R^4	n	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
54	N43	N-H	AS1	A1	C1	1		84	ESI: $(M+H)^+$ = 835/7/9/41 (Br_3)	0.11	FM1	(KBr): C=O 1678.0; 1643.3
55	N44	N-H	AS1	A1	C1	1		95	ESI: $(M+H)^+$ = 796/8/800 (Br_2)	0.07	FM1	(KBr): C=O 1676.0; 1643.3
67	N48	N-H	AS1	A1	C1	1		90	ESI: $(M+H)^+$ = 797/99/801 (Br_2)	0.06	FM1	(KBr): C=O 1682.9; 1643.3
184	N77	N-H	AS1	A1	C4	1		88	ESI: $(M+H)^+$ = 855/7/9 (Br_2)	0.11	FM1	(KBr): C=O 1637.5; 1676
248	N78	N-H	AS1	A1	C1	1		97	ESI: $(M+H)^+$ = 855/7/9 (Br_2)	0.14	FM1	(KBr): C=O 1643.3; 1676 1772.5
181	N75	N-H	AS1	A1	C4	1		95	ESI: $(M+H)^+$ = 793/5/7 (Br_2)	0.04	FM1	(KBr): C=O 1637.5; 1676
182	N76	N-H	AS1	A1	C4	1		93	ESI: $(M+H)^+$ = 793/5/7 (Br_2)	0.04	FM1	(KBr): C=O 1637.5; 1678
183	N74	N-H	AS1	A1	C4	1		91	ESI: $(M+H)^+$ = 807/9/11 (Br_2)	0.08	FM1	(KBr): C=O 1635.5; 1678
250	N15	N-H	AS1	A1	C18	1		98	ESI: $(M+H)^+$ = 885/7/9 (Br_2)	0.14	FM1	(KBr): C=O 1633.6; 1680
251	N15	N-H	AS10	A1	C4	1		84	ESI: $(M+H)^+$ = 837/39/41 (Br_2)	0.27	FM1	(KBr): C=O 1635.5; 1693.4
252	N15	N-H	AS10	A1	C4	1		87	ESI: $(M+H)^+$ = 837/39/41 (Br_2)	0.31	FM1	(KBr): C=O 1637.5; 1685.7
253	N15	N-H	AS10	A1	C1	1		82	ESI: $(M+H)^+$ = 838/40/42 (Br_2)	0.18	FM1	(KBr): C=O 1690
255	N77	N-H	AS1	A1	C1	1		94	ESI: $(M+H)^+$ = 856/8/60 (Br_2)	0.08	FM1	(KBr): C=O 1645; 1676
256	N15	N-H	AS4	A1	C18	1		74	ESI: $(M+H)^+$ = 884/6/8 (Br_2)	0.28	FM1	(KBr): C=O 1633.6; 1683.8
271	N81	N-H	AS4	A1	C8	1		76	ESI: $(M+H)^+$ = 874/6/8 (Br_2)	0.2	FM1	(KBr): C=O 1674
280	N84	N-H	AS4	A1	C4	1		66	ESI: $(M+H)^+$ = 866/8/70 (Br_2)	0.26	FM1	(KBr): C=O 1635.5; 1685.7
	N15	N-H	AS1	A1	C1	0		98	ESI: $(M+H)^+$ = 840/2/4 (Br_2)	0.2	ButOH/ AcOH/ H2O = 4/1/1 (v/v/v)	(KBr): C=O 1643; 1680
179	N73	N-H	AS1	A1	C4	1		86	ESI: $(M+H)^+$ = 779/81/83 (Br_2)	0.03	FM1	(KBr): C=O 1642.8; 1676
	N66	N-H	AS4	A0		1		75	ESI: $(M+H)^+$ = 744/6/8 (Br_2)	0.3	FM1	(KBr): C=0 1620/1666
516	N66	N-H	AS1	A1	C1	1	Isomers of No. (154)	82		0.1	FM1	
517	N66	N-H	AS1	A1	C1	1	Isomers of No. (154)	80		0.1	FM1	
518	N66	N-H	AS1	A1	C1	1	Isomers of No. (154)	89		0.1	FM1	

No.	RCO	Z	R^2	A	NR^3R^4	n	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
521	N66	N-H	AS4	A0	C17	1	THF/DMF	75	ESI: $(M+H)^+$ = 744/6/8 (Br_2)	0.15	FM1	(KBr): C=0 1666/1620
522	N66	N-H	AS1	A0	C17	1	THF/DMF	100	ESI: $(M+H)^+$ = 745/7/9 (Br_2)	0.15	FM1	(KBr): C=0 1624/1655
643	N66	CH_2	AS21	A0	C17	1		53	ESI: $(M+H)^+$ = 640	0.35	FM1	(KBr): C=0 1635/1668
	N66	CH_2	AS2	A0	C17	1		100	EI: M^+ = 621	0.35	FM1	(KBr): C=0 1670

Example 7

Preparation of compounds of general formula:



1-[N^2-[N-[[[(2-methoxyphenyl)methyl]amino]carbonyl]-3,5-dibromo-D,L-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

A mixture of 910 mg (1.0 mmol) of 1-[N^2-[N-[[[2-(2-methoxyphenyl)methyl] amino]carbonyl]-3,5-dibromo-D,L-tyrosyl]-N^6-[(phenylmethoxy)carbonyl]-L-lysyl]-4-(4-pyridinyl)-piperazine, 50 ml of glacial acetic acid, 25 ml of a 33% solution of hydrogen bromide in glacial acetic acid and 2 ml of anisole was stirred overnight at ambient temperature. The reaction mixture was stirred into diethylether and the sticky precipitate formed was suction filtered. The crude product was purified by column chromatography (MN-silica gel 60, Macherey-Nagel, 70-230 mesh ASTM, eluant: ethyl acetate/methanol/ conc. aqueous ammonia = 8/2/0.2 (v/v/v)). 0.37 g (48% of theory) of an amorphous solid were obtained.

IR (KBr): 1630 cm^{-1} (C=O)

ESI-MS: $(M+H)^+$ = 774/776/778 (Br_2)

$(M+2H)^{++}$ = 387.7/388.7/389.7 (Br_2)

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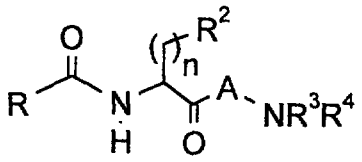
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The following were prepared analogously (in each case n = 1):

No.	RCO	R^2	A	NR^3R^4	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
1	N1	AS1	A1	C1	46.9	ESI: M+H=788/90/92 (Br_2)	0.36	FM1	(KBr): C=O 1627.8
2	N2	AS1	A1	C1	100	ESI: M+H=788/90/92 (Br_2)	0.48	FM2	(KBr): C=O 1641.3; NH, NH^+ 3419.6
5	N4	AS1	A1	C1	2.8	ESI: M+H=818/20/22 (Br_2)	0.52	FM2	

Example 8

Preparation of compounds of general formula:



1-[N^2-[N-[4-(4-fluorophenyl)-1-oxobutyl]-3,5-dibromo-D-tyrosyl]-N^6-[(1.1-dimethylethoxy)carbonyl]-L-lysyl]-4-(4-pyridinyl)-piperazine

To a solution of 0.18 g (0.001 mol) 4-(4-fluorophenyl)-butanoic acid in a mixture of 4 ml of dimethylformamide and 10 ml of tetrahydrofuran was added with stirring a mixture of 0.71 g (0.001 mol) 1-[N2-(3,5-dibromo-D-tyrosyl)-N^6-[(phenylmethoxy)carbonyl]-L-lysyl]-4-(4-pyridinyl)-piperazine, 0.32 g (0.001 mol) TBTU and 0.13g (0.001 mol) DIEA and the mixture was stirred in a nitrogen atmosphere for 2 days. The reaction mixture was then evaporated down *in vacuo* and the remaining residue was taken up in dichloromethane. The organic phase was with 20% aqueous citric acid solution and then extracted with

10% aqueous sodium hydrogen carbonate solution, dried over sodium sulphate, filtered and evaporated down *in vacuo*. After stirring the residue with ether 0.68 g (77% of theory) of the desired product remain as an amorphous residue.

IR (KBr): 1641, 1676 cm^{-1} (C=O)

R_f: 0.65 (FM2)

ESI-MS: $(M+H)^+$ = 875/877/879 (Br_2)

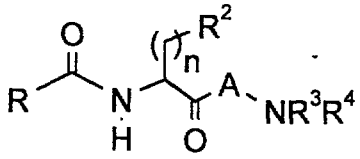
$(M+H+Na)^{++}$ = 449/450/451 (Br_2)

The following were prepared analogously (in each case n = 1):

No.	RCO	R^2	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
123	N62	AS1	A0	C1	DMF/THF as solvent	20	ESI: $(M+H)^+$ = 725/7/9 (Br_2)	0.3	FM 1	(KBr): C=0 1641.3; 1691.5
124	N63	AS1	A0	C1	DMF/THF as solvent	53	ESI: $(M+H)^+$ = 725/7/9 (Br_2)	0.2	FM 1	(KBr): C=0 1641.3; 1691.5
322	N63	AS1	A0	C8	DMF/THF as solvent	19	EI: M^+ = 729/31/33 (Br_2)	0.3	FM 1	(KBr): C=0 1629.8; 1695.3
	N11	AS1	A3	C1		46	ESI: $(M+H)^+$ = 873/5/7 (Br_2)			(KBr): C=O 1625.9; 1645.2
	N18	AS1	A3	C1	THF/DMF as solvent	77	ESI: $(M+H)^+$ = 875/7/9 (Br_2)	0.78	FM7	(KBr): C=O 1641.3
	N20	AS1	A3	C1	THF/DMF as solvent	88	ESI: $(M+H)^+$ = 863/5/7 (Br_2)	0.67	FM7	(KBr): C=O 1643.3
	N21	AS1	A3	C1	THF/DMF as solvent	78	ESI: $(M+H)^+$ = 917/6/8 (Br_2)	0.47	FM7	(KBr): C=O 1643.3
	N46	AS1	A3	C1	THF/DMF as solvent	80	ESI: $(M+H)^+$ = 905/7/9 (Br_2)	0.65	FM7	(KBr): C=O 1643.3
	N43	AS1	A3	C1	THF/DMF as solvent	75		0.75	FM7	(KBr): C=O 1645.2
	N44	AS1	A3	C1	THF/DMF as solvent	79	ESI: $(M+H)^+$ = 896/98/900 (Br_2)	0.65	FM7	(KBr): C=O 1629.8

Example 9

Preparation of compounds of general formula:



1-[N^2-[N-[[[(3-methoxyphenyl)ethyl]amino]carbonyl]-3,5-dichloro-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine-bis-(trifluoroacetate (No. 20)

To a suspension of 0.33 g (2 mmol) of CDT and 1 ml of triethylamine in about 30 ml of tetrahydrofuran, cooled to -10 °C, was added dropwise, with stirring, a solution of 1.0 g (1.6 mmol) of 1-[N^2(-3.5-dichloro-D-tyrosyl]-N^6-[(1.1-dimethylethoxy)carbonyl]-L-lysyl]-4-(4-pyridinyl)-piperazine in 50 ml of tetrahydrofuran within 60 minutes. The reaction mixture was stirred for 1 hour at 0 °C, then stirred for 2 hours at ambient temperature, mixed with a tetrahydrofuran solution of 0.24 g (1.6 mmol) of (3-methoxyphenyl)-ethanamine, refluxed for 3 hours and stirred overnight at ambient temperature. After elimination of the solvent *in vacuo* the residue was purified by column chromatography (MN-silica gel 60, Macherey-Nagel, 70-230 mesh ASTM, eluant: FM1). The resulting intermediate compound was stirred in a mixture of 5 ml of trifluoroacetic acid and 80 ml of dichloromethane overnight, the solvent was eliminated *in vacuo* and the residue triturated with ether. 709 mg (43% of theory) of the desired compound as an amorphous solid.

IR (KBr): 1643, 1676 cm^{-1} (C=O)

R_f: 0.41(FM2)

ESI-MS: $(M+H)^+$ = 700/702/704 (Br_2)

$(M+2H)^{++}$ = 350.7/351.7/352.7 (Br_2)

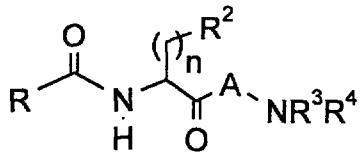
The following were prepared analogously (in each case n = 1):

No.	RCO	R^2	A	NR^3R^4	Remarks	% Yield	MS	R_f	Yield	IR [cm^{-1}]
23	N17	AS1	A1	C1	NEt_3 as base	55	ESI:M+H= 798/800/802 (Br_2)	0.2	FM1	(KBr): C=0 1643.3; 167
47	N39	AS1	A1	C1	NEt_3 as base	69.4	ESI:M+H= 676/78/80(Br_2)	0.1	FM1	(KBr): C=0 1645.2; 167
50	N64	AS1	A1	C1	NEt_3 as base	76	ESI:M+H= 828/830/832 (Br_2)	0.2	FM1	(KBr): C=0 1643.3; 167
51	N40	AS1	A1	C1	NEt_3 as base; Dehydration	79.7	ESI:M+H= 826/828/30 (Br_2)	0.2	FM1	(KBr): C=0 1643.3; 167
52	N41	AS1	A1	C1	NEt_3 as base; Dehydration	21.8	ESI:M+H= 826/828/30 (Br_2)	0.2	FM1	(KBr): C=0 1645.2; 1679.9
56	N16	AS1	A1	C4	NEt_3 as base	5	ESI:M+H= 873/75/77(Br_2)	0.3	FM1	(KBr): C=0 1637.5; 167
57	N45	AS1	A1	C4	NEt_3 as base	32	ESI:M+H= 867/9/71(Br_2)	0.2	FM1	(KBr): C=0 1635.5; 167
66	N47	AS1	A1	C4	NEt_3 as base	28.4	ESI:M+H= 764/6/8(Br_2)	0.1	FM1	(KBr): C=0 1635.5; 167
46	N38	AS1	A1	C1	NEt_3 as base	86	ESI:M+H= 826/28/30(Br_2)	0.35	FM1	(KBr): C=0 1645.2; 168
232	N66	AS4	A1	C8		69	ESI:M+H= 872/4/6 (Br_2)	0.33	FM1	(KBr): C=0 1645
233	N66	AS4	A1	C1	THF/DMF as solvent	16	ESI:M+H= 867/69/71(Br_2)	0.32	FM1	(KBr): C=0 1653
234	N66	AS4	A1	C4		68	ESI:M+H= 867/69/71 (Br_2)	0.42	FM1	(KBr): C=0 1645
235	N66	AS1	A1	C8		26	ESI:M+H= 873/5/7 (Br_2)	0.27	FM1	(KBr): C=0 1645
236	N71	AS1	A1	C1		30	ESI:M+H= 880/2/4 (Br_2)	0.22	FM1	(KBr): C=0 1636; 1678
237	N71	AS4	A1	C8		28	ESI:M+H = 884/6/8 (Br2)	0.25	FM1	
238	N71	AS4	A1	C1		20	ESI:M+H= 879/81/83 (Br_2)	0.3	FM1	(KBr): C=0 1641; 1682

No.	RCO	R^2	A	NR^3R^4	Remarks	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
18	N14	AS1	A1	C1	Cleaving of Boc protecting group with methanolic HCl solution	26.3	ESI: M+H=813/5/7 (Br_2)	0.55	FM2	(KBr): C=O 1641.3; 1716.5
17	N17	AS1	A1	C1	Cleaving of Boc protecting group with methanolic HCl solution	55.2	ESI: M^+ = 799/801/803 (Br_2)	0.55	FM2	(KBr): C=O 1639.4
9	N6	AS1	A1	C1	Cleaving of Boc protecting group with methanolic HCl solution	41.3	ESI: M+H= 829/31/33 (Br_2)	0.44	FM2	(KBr): C=O 1639.4
10	N7	AS1	A1	C1	Cleaving of Boc protecting group with methanolic HCl solution	57.6	ESI: M+H= 829/31/33 (Br_2)	0.32	FM2	(KBr): C=O 1639.4
20	N2	AS3	A1	C1		43	ESI: M+H= 700/2/4 (Br_2)	0.41	FM2	(KBr): C=O 1643.3; 1676.0
283	N102	AS4	A3	C4	NEt_3 as base	65	ESI:M+H= 864/6/8 (Br_2)	0.24	FM1	(KBr): C=O 1637.5; 1676

Example 10

Preparation of compounds of general formula:



1-[N^2-[N-[4-(2,3-dichlorophenyl)-1-piperazinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine-tris-(trifluoroacetate) (No. 74)

To a solution of 0.35 g (2.1 mmol) of CDT in 50 ml of tetrahydrofuran were added with cooling (0 °C) and stirring 1.0 g (1.4 mmol) of 1-[N^2-(3,5-dibromo-D-tyrosyl)-N^6-[(1,1-dimethylethoxy)carbonyl]-L-lysyl]-4-(4-pyridinyl)-piperazine and the mixture was stirred for 30

minutes at 0°C and for a further 30 minutes at ambient temperature. After the addition of 0.47 g (1.75 mmol) of 1-(2,3-dichlorophenyl)piperazine-hydrochloride and 0.25 ml of triethylamine the reaction mixture was refluxed for 5 hours and after cooling mixed with 70 ml of saturated aqueous sodium hydrogen carbonate solution. The organic phase was separated off, the aqueous phase was extracted twice with 50 ml of tetrahydrofuran. The combined organic phases were washed with saturated aqueous saline solution, dried over magnesium sulphate, filtered and evaporated down *in vacuo*. The residue was triturated with ether, suction filtered and then stirred for 2 hours with a mixture of 50 ml of dichloromethane and 5 ml of trifluoroacetic acid. After evaporation of the reaction mixture *in vacuo* and trituration of the residue with ether, 0.8 g (47% of theory) of an amorphous solid are left.

IR (KBr): 1643.3, 1676 cm^{-1} (C=O)

R_f: 0.78 (FM7)

ESI-MS: $(M+H)^+$ = 867/869/871/873/875 (Br_2, Cl_2)

$(M+2H)^{++}$ = 434/435/436/437 (Br_2, Cl_2)

The following were prepared in the same way (in each case n = 1):

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No.	RCO	R^2	A	NR^3R^4	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
36	N29	AS1	A1	C1	17.3	ESI : M+H = 889/91/93 (Br_2)	0.35	MeOH/ NH_4OH = 9/1 (v/v)	(KBr): C=O 1643.3; 1674.1
208	N15	AS1	A1	C1	53.5	ESI: M+H=854/6/8 (Br_2)	0.43	FM2	(KBr): C=O 1691.5; 1635.5
209	N15	AS1	A1	C1	47.7	ESI: M+H=854/6/8 (Br_2)	0.55	FM2	(KBr): C=O 1695.3; 1637.5
210	N15	AS1	A1	C1	28	ESI: M+H=854/6/8 (Br_2)	0.48	FM2	(KBr): C=O 1689.5; 1639.4
75	N50	AS1	A1	C1	16.5	ESI: M+H= 867/69/71/73/75 (Br_2,Cl_2)	0.63	FM2	(KBr): C=O 1643.3; 1676.0;
74	N49	AS1	A1	C1	47	ESI: M+H= 867/69/71/73/75 (Br_2,Cl_2)	0.65	FM2	(KBr): C=O 1643.3; 1676.0
76	N51	AS1	A1	C1	13.4	ESI: M+H=824/6/8 (Br_2)	0.58	FM2	(KBr): C=O 1643.3; 1676.0; CN 2219.9
79	N52	AS1	A1	C1	11.4	ESI: M+H=901/3/5/7 (Br_2, Cl)	0.59	FM2	(KBr): C=O 1645.2; 1676.3
45	N37	AS1	A1	C1	43	ESI: M+H=784/6/8 (Br_2)	0.6	FM2	(KBr): C=O 1643.3; 1678.0
39	N32	AS1	A1	C1	48.3	ESI: M+H=795/7/9 (Br_2)	0.57	FM2	(KBr): C=O 1643.3; 1678.0
38	N31	AS1	A1	C1	54.1	ESI: M+H=844/6/8 (Br_2)	0.6	FM2	(KBr): C=O 1643.3; 1678.0; NO2 1543.0
37	N30	AS1	A1	C1	61.6	ESI: M+H=813/5/7 (Br_2)	0.6	FM2	(KBr): C=O 1643.3; 1676.0
36	N29	AS1	A1	C1	17.3	ESI: M+H=889/91/93 (Br_2)	0.65	FM2	(KBr): C=O 1643.3; 1674.1
35	N28	AS1	A1	C1	74.8	ESI: M+H=800/2/4 (Br_2)	0.55	FM2	(KBr): C=O 1639.4;
34	N27	AS1	A1	C1	36.8	ESI: M+H=8OO/2/4 (Br_2)	0.43	FM2	(KBr): C=O 1641.3; 1714.6; NH+ 3409.9
32	N25	AS1	A1	C1	50	ESI: M+H=737/39/41 (Br_2)	0.44	FM2	(KBr): C=O 1645.2; 1678.3

No	RCO	R^2	A	NR^3R^4	% Yield	MS	R_f	Eluant	IR [cm^{-1}]
33	N26	AS1	A1	C1	42	ESI: $(M+H)^+$ = 767/69/71 (Br_2)	0.33	FM2	(KBr): C=O 1676.0
40	N33	AS1	A1	C1	14.5	ESI: $(M+H)^+$ = 802/4/6 (Br_2)	0.58	FM2	(KBr): C=O 1643.3; 1676.0
28	N6	AS3	A1	C1	67.2	ESI: $(M+H)^+$ = 741/3/5 (Cl_2)	0.43	FM2	(KBr): C=O 1641.3; 1716.5
64	N23	AS1	A1	C4	39	ESI: $(M+H)^+$ = 832/4/6/8 (Br_2,Cl)	0.68	FM2	(KBr): C=O 1627.8; 1678.0
65	N15	AS1	A1	C4	41	ESI: $(M+H)^+$ = 853/5/7 (Br_2)	0.61	FM2	(KBr): C=O 1631.7; 1695.3
365	N111	AS1	A1	C1	37	ESI: $(M+H)^+$ = 839/41/43 (Br_2)	0.09	FM1	(KBr): C=0 1626/1676

Example 11

1-[N2-[N-[[[2-(2,5-dimethoxyphenyl)ethyl]amino]carbonyl]-3,5 dibromo-D,L-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine (No. 3)

A mixture of 0.8 g (0.84 mmol) of 1-[N^2-[N-[[[2-(2,5-dimethoxyphenyl)ethyl]amino]carbonyl]-3,5-dibromo-D-tyrosyl]-N^6-[(phenylmethoxy)carbonyl]-L-lysyl]-4-(4-pyridinyl)-piperazine, 50 ml of glacial acetic acid, 25 ml of a 33% solution of hydrogen bromide in glacial acetic acid and 2 ml of anisole was stirred for 12 hours at ambient temperature. The reaction mixture was stirred into diethylether and the resulting precipitate was suction filtered. The solid residue was purified by column chromatography (MN-silica gel 60, Macherey-Nagel, 70-230 mesh ASTM, eluant: ethyl acetate/methanol/conc. aqueous ammonia = 8/2/0.2 (v/v/v)). 0.3 g (44% of theory) of the desired product was obtained as an amorphous solid.

IR (KBr): 1643.3 cm^{-1} (C=O)

R_f: 0.17 (ethyl acetate/methanol/conc. aqueous ammonia = 6/4/1)
ESI-MS: $(M+H)^+$ = 818/820/822 (Br_2)
$(M+2H)^{++}$ = 409.5/410.5/411.5 (Br_2)

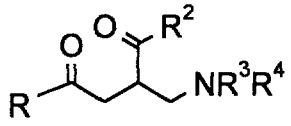
Example 12

1-[N^2-[3,5-dibromo-N-[[[2-(3-methoxyphenyl)ethyl]amino]carbonyl]-D-tyrosyl]-L-arginyl]-4-(4-pyridinyl)-piperazine-bis-(trifluoroacetate) (No. 4)

A stirred mixture of 20 ml of trifluoroacetic acid, 1.3 ml of anisole and 0.9 ml of ethanedithiol was mixed with 2.1 g (1.9 mmol) of solid 1-[N^2-[3,5-dibromo-N-[[[2-(3-methoxyphenyl)ethyl]amino]carbonyl]-N^G-(2,2,5,7,8-pentamethylchroman-6-sulphonyl)-D-tyrosyl]-L-arginyl]-4-(4-pyridinyl)-piperazine whilst cooling with ice and stirred for a further 45 minutes whilst cooling with ice, then for 3 hours at ambient temperature. The resulting precipitate was suction filtered and discarded, the filtrate was evaporated down *in vacuo*, the residue remaining was mixed with toluene and again evaporated down *in vacuo*. The resulting solid residue was triturated with a mixture of diethylether and acetone and the white solid formed was suction filtered and dried. 1.7 g (65% of theory) of the desired title compound were obtained.
IR (KBr): 1674, 1645 cm^{-1} (C=O)
R_f: 0.15 (FM: BuOH/AcOH/H_2O 4/1/1 (v/v/v))
ESI-MS: $(M+H)^+$ = 816/818/820 (Br_2)
$(M+2H)^{++}$ = 408.6/409.6/410.6 (Br_2)

Example 13

Preparation of compounds of general formula:



(R,S)-1-[2-(4-amino-3,5-dibromobenzoyl)-4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-4-oxobutyl]-4-(4-pyridinyl)-piperidine (No. 291)

A mixture of 0.97 g (1.8 mmol) of (R,S)-4-amino-3,5-dibromo-γ-oxo-β-[[4-(4-pyridinyl)-1-piperidinyl]methyl]-benzenebutanoic acid, 0.48g (1.8 mmol) of 4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-piperidine, 2 ml of triethylamine, 0.58 g (1.8 mmol) of TBTU, 0.24 g (1.8 mmol) of HOBt, 25 ml of THF and 25 ml of DMF was stirred for 4 hours at ambient temperature. The reaction mixture was evaporated down *in vacuo*, the residue was taken up in a mixture of ethyl acetate and methanol (95/5 (v/v)) and washed with saturated aqueous sodium hydrogen carbonate solution. The organic phase was dried and evaporated down *in vacuo*. The residue was purified by column chromatography (MN-silica gel 60, Macherey-Nagel, 70-230 mesh ASTM, eluant: ethyl acetate/methanol = 9/1 (v/v); then MN-silica gel 60, Macherey-Nagel, 70-230 mesh ASTM, eluant: methylene chloride/ethanol = 9/1 (v/v)). 0.2 g (15% of theory) of the desired product were obtained as a white amorphous solid.

IR (KBr): 1668.3 cm^{-1} (C=O)

R_f: 0.5 (FM2)

ESI-MS: $(M+H)^+$ = 737/739/741 (Br_2)

$(M+Na)^+$ = 759/761/763 (Br_2)

The following were prepared analogously:

No	RCO	R^2	NR3R4	% Yield	MS	R_f	Eluant	IR [cm-1]
291	N66	AS4	C4	15	ESI: $(M+H)^+$ = 737/39/41 (Br_2)	0.36	CH_2Cl_2/ EtOH	(KBr): C=0 1668
296	N66	AS4	C8	14	ESI: $(M+H)^+$ = 743/5/7 (Br_2)	0.66	FM1	(KBr): C=0 1668
302	N71	AS4	C8	19	ESI: $(M+H)^+$ = 755/7/9 (Br_2)	0.54	FM1	(KBr): C=0 1682

Example 14

1-[4-amino-N-[[4-[7-(aminocarbonyl)-3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-3,5-dibromo-D-phenylalanyl]-4-(4-pyridinyl)-piperidine (No. 312)

a) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-7-(methoxycarbonyl)-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperidine (No. 307)

Prepared analogously to Example 3 from methyl 3,4-dihydro-3-(4-piperidinyl)-2(1H)-oxoquinazoline-7-carboxylate, 1-[4-amino-3,5-dibromo-D-phenylalanyl]-4-(4-pyridinyl)-piperidine and CDT in a yield of 27.2% of theory.
Colourless, amorphous substance, Rf 0.5 (eluant: dichloromethane/ cyclohexane/ methanol/ conc. ammonia = 7/1.5/1.5/0.2 (v/v/v/v)).
IR(KBr): 1718.5, 1670.3, 1618.2 cm^{-1} (C=O)
ESI-MS: $(M+H)^+$ = 796/798/800 (Br_2)
$(M+Na)^+$ = 818/820/822 (Br_2)

The following were obtained accordingly:

From methyl-3,4-dihydro-3-(4-piperidinyl)-2(1H)-oxoquinazoline-7-carboxylate, 1-[4-amino-3,5-dibromo-D-phenylalanyl]-4-(1-piperidinyl)-piperidine and CDT in a yield of 30.3% of theory: 1-[4-amino-3,5-dibromo-N-[[4-

[3,4-dihydro-7-(methoxycarbonyl)-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine (No. 304), Rf = 0.75 (FM1).

IR(KBr): 1720.4, 1668.3, 1620.1 cm^{-1} (C=O)

ESI-MS: $(M+H)^+$ = 802/804/806 (Br_2)

$(M+Na)^+$ = 824/826/828 (Br_2)

From methyl-3,4-dihydro-3-(4-piperidinyl)-2(1H)-oxoquinazoline-7-carboxylate, 1-(3,5-dibromo-D-tyrosyl)-4-(1-piperidinyl)-piperidine and CDT in a yield of 35% of theory: 1-[3,5-dibromo-N-[[4-[7-(methoxycarbonyl)-3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine (No. 422), Rf 0.54 (eluant: dichloromethane/ cyclohexane/ methanol/ conc. ammonia = 7/1.5/1.5/0.2 (v/v/v/v)).

IR(KBr): 1720.4, 1668.3, 1627.8 cm^{-1} (C=O)

ESI-MS: $(M+H)^+$ = 803/805/807 (Br_2)

$(M+Na)^+$ = 825/827/829 (Br_2)

From methyl-3,4-dihydro-3-(4-piperidinyl)-2(1H)-oxoquinazoline-7-carboxylate, 1-(3,5-dibromo-D-tyrosyl)-4-(4-pyridinyl)-piperidine and CDT in a yield of 45% of theory: 1-[3,5-dibromo-N-[[4-[7-(methoxycarbonyl)-3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine (No. 420), R_f 0.56 (FM1).

IR(KBr): 1718.5, 1664.5, 1624.0 cm^{-1} (C=O)

ESI-MS: $(M+H)^+$ = 797/799/801 (Br_2)

$(M+Na)^+$ = 819/821/823 (Br_2)

b) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-7-(hydroxycarbonyl)-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperidine (No. 309)

Prepared analogously to Example A37) from 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-7-(methoxycarbonyl)-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-

D-phenylalanyl]-4-(4-pyridinyl)-piperidine by saponification with lithium hydroxide in a yield of 95% of theory. Colourless, amorphous substance, Rf 0.25 (eluant: dichloromethane/ methanol/ conc. ammonia = 7.5/2.5/0.5 (v/v/v)).

IR(KBr): 1666.4, 1614.3 cm^{-1} (C=O)

ESI-MS: $(M-H)^-$ = 780/782/784 (Br_2)

The following were obtained accordingly:

From 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-7-(methoxycarbonyl)-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine in a yield of 60.2% of theory: 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-7-(hydroxycarbonyl)-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine (No. 306), Rf 0.15 (FM1).

IR(KBr): 1635.5 cm^{-1}, broad (C=O)

ESI-MS: $(M+H)^+$ = 788/790/792 (Br_2)

$(M+Na)^+$ = 810/812/814 (Br_2)

From 1-[3,5-dibromo-N-[[4-[7-(methoxycarbonyl)-3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine in a yield of 62% of theory: 1-[3,5-dibromo-N-[[4-[7-(hydroxycarbonyl)-3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine (No. 423), Rf 0.03 (eluant: dichloromethane/ cyclohexane/ methanol/ conc. ammonia = 7/1.5/1.5/0.2 (v/v/v/v)).

IR(KBr): 1635.5 cm^{-1}, broad (C=O)

ESI-MS: $(M+H)^+$ = 789/791/793 (Br_2)

From 1-[3,5-dibromo-N-[[4-(1,3-dihydro-5-(methoxycarbonyl)-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine in a yield of 80% of theory: 1-[3,5-dibromo-N-

[[4-(1,3-dihydro-5-(hydroxycarbonyl)-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine (No. 151). Colourless, amorphous substance.

IR(KBr): 1701.1, 1625.9 cm^{-1} (C=O)

ESI-MS: $(M+H)^+$ = 767/769/771 (Br_2)

$(M+2H)^{++}$ = 383/384/385 (Br_2)

From 1-[3,5-dibromo-N-[[4-[7-(methoxycarbonyl)-3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine in a yield of 82% of theory: 1-[3,5-dibromo-N-[[4-[7-(hydroxycarbonyl)-3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine (No. 421), R_f 0.03 (FM1). Colourless, amorphous substance.

IR(KBr): 1625 wide cm^{-1} (C=O)

ESI-MS: $(M+H)^+$ = 783/785/787 (Br_2)

$(M+Na)^+$ = 805/807/809 (Br_2)

c) 1-[4-amino-N-[[4-[7-(aminocarbonyl)-3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-3,5-dibromo-D-phenylalanyl]-4-(4-pyridinyl)-piperidine (No. 312)

Prepared analogously to Example 1 from 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-7-(hydroxycarbonyl)-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperidine and ammonium carbonate in the presence of TBTU in a yield of 40.6% of theory. Colourless, amorphous substance, Rf 0.8 (eluant: dichloromethane/ methanol/ conc. ammonia = 7.5/2.5/0.5 (v/v/v)).

IR(KBr): 1670.3, 1616.3 cm^{-1} (C=O)

ESI-MS: $(M+H)^+$ = 781/783/785 (Br_2)

$(M+Na)^+$ = 803/805/807 (Br_2)

The following were obtained accordingly:

From 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-7-(hydroxycarbonyl)-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperidine and ethanolamine in a yield of 34.6% of theory: 1-[4-amino-3,5-dibromo-N-[[4-[7-(2-hydroxyethylaminocarbonyl)-3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperidine, (No. 313) Rf = 0.7 (eluant: dichloromethane/methanol/conc. ammonia = 7.5/2.5/0.5 v/v/v).

IR(KBr): 1662.5, 1618.2 cm^{-1} (C=O)

ESI-MS: $(M+H)^+$ = 825/827/829 (Br_2)

$(M+Na)^+$ = 847/849/851 (Br_2)

$(M+2H)^{++}$ = 413/414/415 (Br_2)

$(M+H+Na)^{++}$ = 424/425/426 (Br_2)

From 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-7-(hydroxycarbonyl)-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperidine and 1-methylpiperazine in a yield of 44.9% of theory: 1-[4-amino-3,5-dibromo-N-[[4-[7-[(4-methyl-1-piperazinyl)carbonyl]-3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperidine, (No. 430) Rf = 0.28 (eluant: ethyl acetate/methanol/conc. ammonia = 8/1.5/0.3 v/v/v).

IR(KBr): 1618.2 cm^{-1} (C=O)

ESI-MS: $(M+H)^+$ = 864/866/868 (Br_2)

$(M+Na)^+$ = 886/888/890 (Br_2)

$(M+2H)^{++}$ = 432/433/434.7 (Br_2)

From 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-7-(hydroxycarbonyl)-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperidine and methylammonium chloride in a yield of 37% of theory: 1-[4-amino-3,5-dibromo-N-[[4-[7-(methylaminocarbonyl)-3,4-dihydro-2(1H)-oxoquinazolin-3-

yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperidine, (No. 424) Rf = 0.49 (FM1).
IR(KBr): 1662.5, 1622 cm^{-1} (C=O)
ESI-MS: $(M+H)^+$ = 795/797/799 (Br_2)
$(M+Na)^+$ = 817/819/821 (Br_2)

From 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-7-(hydroxycarbonyl)-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine and ammonium carbonate in a yield of 12% of theory: 1-[4-amino-N-[[4-[7-(aminocarbonyl)-3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-3,5-dibromo-D-phenylalanyl]-4-(1-piperidinyl)-piperidine (No. 310), Rf = 0.7 (eluant: dichloromethane/methanol/conc. ammonia = 7.5/2.5/0.5 (v/v/v)).
IR(KBr): 1670.3, 1618.2 cm^{-1} (C=O)
ESI-MS: $(M+H)^+$ = 787/789/791 (Br_2)

From 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-7-(hydroxycarbonyl)-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine and ethanolamine in a yield of 11.4% of theory: 1-[4-amino-3,5-dibromo-N-[[4-[7-(2-hydroxyethylaminocarbonyl)-3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine (No. 311), Rf = 0.65 (eluant: dichloromethane/methanol/conc. ammonia = 7.5/2.5/0.5 (v/v/v)).
IR(KBr): 1660.6, 1620.1 cm^{-1} (C=O)
ESI-MS: $(M+H)^+$ = 831/833/835 (Br_2)
$(M+2H)^{++}$ = 416/417/418 (Br_2)
$(M+H+Na)^{++}$ = 427/428/429 (Br_2)

Example 15

4-(1-acetyl-4-piperidinyl)-1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-carbonyl]-D-phenylalanyl]-piperidine (No. 372)

a) 1-[4-amino-3,5-dibromo-D-phenylalanyl]-4-[1-(1,1-dimethylethoxycarbonyl)-4-piperidinyl]-piperidine

A mixture of 5.60 g (0.01 mol) of 4-amino-3,5-dibromo-N^2-(9-fluorenylmethoxycarbonyl)-D-phenylalanine, 1.35 g (0.01 mol) HOBt, 3.21 g (0.01 mol) TBTU, 1.29 g (0.01 mol) DIEA, 2.68 g (0.01 mol) 4-[1-(1,1-dimethyleth-oxycarbonyl)-4-piperidinyl]-piperidine and 150 ml of tetrahydrofuran was stirred for 2 hours at room temperature. After the reaction was complete 20 ml of diethylamine were added and the mixture was stirred for a further 18 hours at room temperature. The reaction mixture was evaporated down *in vacuo*, the residue was taken up in 200 ml of dichloromethane and washed successively with 100 ml of saturated sodium chloride solution and saturated sodium hydrogen carbonate solution and dried over magnesium sulphate. The reddish oil remaining after elimination of the solvent was purified by column chromatography on silica gel (30 - 60 µm) using firstly dichloromethane, then FM4 as eluant. The title compound was obtained in the form of a colourless amorphous substance and in a yield of 4.31 g (73.3% of theory).

IR(KBr): 1687.6 cm^{-1} (C=O)

MS: M^+ = 586/588/590 (Br_2)

b) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[1-(1,1-dimethylethoxycarbonyl)-4-piperidinyl]-piperidine

Prepared analogously to Example 4 from 1-[4-amino-3,5-dibromo-D-phenylalanyl]-4-[1-(1,1-dimethylethoxycarbonyl)-4-piperidinyl]-piperidine, CDT and 3,4-dihydro-3-(4-

piperidinyl)-2(1H)-quinazolinone in a quantitative yield. Colourless, amorphous substance.

IR(KBr): 1676 cm^{-1} (C=O)

MS: $(M+H)^+$ = 844/846/848 (Br_2)

$(M+Na)^+$ = 866/868/870 (Br_2)

c) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-piperidinyl)-piperidine (No. 521)

Prepared analogously to Example A1b), but using sodium hydroxide solution instead of ammonia, from 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[1-(1,1-dimethylethoxycarbonyl)-4-piperidinyl]-piperidine by treating with trifluoroacetic acid in a yield of 75% of theory. Colourless, amorphous substance.

IR(KBr): 1666.4, 1620.1 cm^{-1} (C=O)

MS: $(M+H)^+$ = 744/746/748 (Br_2)

$(M+2H)^{++}$ = 372/373/374.5 (Br_2)

d) 4-(1-acetyl-4-piperidinyl)-1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-piperidine (No. 372)

A solution of 0.372 g (0.499 mmol) of 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-piperidinyl)-piperidine and 0.07 g (5.5 mmol) of DIEA in 50 ml of dichloromethane was mixed with 0.043 g (5.48 mmol) of acetylene chloride dropwise whilst cooling externally with ice-water and then stirred for 1 hour at room temperature. The solvent was eliminated *in vacuo*, the residue was stirred with water and filtered. The filter residue was dried *in vacuo* and purified by column chromatography on silica gel (30-60 µm) using FM4 as eluant. The suitable eluates were evaporated down, the residue was triturated

with diethylether and suction filtered. 230 mg (58.5% of theory) of colourless crystals were obtained.

IR(KBr): 1622 cm^{-1} (C=O)

MS: $(M+H)^+$ = 786/788/790 (Br_2)

$(M+Na)^+$ = 808/810/812 (Br_2)

The following were obtained accordingly:

1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-benzoyl-4-piperidinyl)-piperidine (No. (485).

Colourless crystals

R_f 0.74 (FM1)

IR(KBr): 1626, 1668 cm^{-1} (C=O)

ESI-MS: $(M+H)^+$ = 848/850/852 (Br_2)

Example 16

1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methylsulphonyl-4-piperidinyl)-piperidine (No. 486)

A solution of 0.372 g (0.499 mmol) of 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-piperidinyl)-piperidine and 0.07 g (5.5 mmol) of DIEA in 50 ml of dichloromethane was mixed dropwise with 0.063 g (5.5 mmol) of methanesulphonylchloride whilst cooling externally with ice-water and then stirred for 1 hour at room temperature. The solvent was eliminated *in vacuo*, the residue was stirred with water and filtered. The filter residue was dried *in vacuo* and purified by column chromatography over silica gel (30-60 μm) using initially dichloromethane, then FM4 as eluant. The suitable eluates were evaporated

down, the residue was triturated with diethylether and suction filtered. 220 mg (53.5% of theory) of colourless crystals were obtained.

IR(KBr): 1668, 1618 cm^{-1} (C=O)

MS: $(M+H)^+$ = 822/824/826 (Br_2)

$(M+Na)^+$ = 844/846/848 (Br_2)

$(M+K)^+$ = 860/862/864 (Br_2)

The following were obtained accordingly:

(1) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-4-(methylsulphonyloxy)-D-phenylalanyl]-4-[1-(methylsulphonyl)-4-piperidinyl]-piperidine (No. (523)) in a yield of 12% of theory.

R_f 0.54 (FM1)

IR(KBr): 1628, 1665 cm^{-1} (C=O)

ESI-MS: $(M+H)^+$ = 901/903/905 (Br_2)

(2) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-[1-(methylsulphonyl)-4-piperidinyl]-piperidine (No. (524) in a yield of 12% of theory.

R_f 0.50 (FM1)

ESI-MS: $(M+H)^+$ = 823/825/827 (Br_2)

(3) (R,S)-1-[4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(1-naphthyl)methyl]-1,4-dioxobutyl]-4-(1-methylsulphonyl-4-piperidinyl)-piperidine (No. (668) in a yield of 56% of theory.

R_f 0.70 (FM1)

IR(KBr): 1630, 1666 cm^{-1} (C=O)

MS: M^+ = 699

Example 17

1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[1-(3-carboxy-1-oxopropyl)-4-piperidinyl]-piperidine (No. 487)

A mixture of 0.372 g (0.499 mmol) of 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-piperidinyl)-piperidine, 0.11 g (1.1 mmol) of succinic anhydride and 150 ml of tetrahydrofuran was refluxed for 1 hour. The reaction mixture was freed from solvent *in vacuo*, the residue was purified by column chromatography on silica gel (30-60 µm) using FM1 as eluant. The suitable eluates were evaporated down, the residue was triturated with diethylether and suction filtered. 175 mg (41.5% of theory) of colourless crystals were obtained.

IR(KBr): 1668, 1608 cm^{-1} (C=O)

MS: $(M-H)^-$ = 842/844/846 (Br_2)

$(M+Na)^+$ = 868/870/872 (Br_2)

Example 18

1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-hexyl-4-piperidinyl)-piperidine (No. 488)

A mixture of 0.372 g (0.499 mmol) of 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-piperidinyl)-piperidine, 0.05 g (0.499 mmol) of hexanal, 0.03 g (0.5 mmol) of glacial acetic acid and 150 ml of tetrahydrofuran was stirred for 1 hour at room temperature. After the addition of 0.116 g (0.52 mmol) of 95% sodium triacetoxyborohydride the mixture was kept for a further 2.5 hours at room temperature. The solvent was eliminated

in vacuo, the residue was divided between 20% aqueous sodium carbonate solution and dichloromethane, the organic phase was dried over magnesium sulphate and evaporated down. The residue was purified by column chromatography on silica gel (30 - 60 µm) using FM4 as eluant. The suitable eluates were evaporated down, the residue was triturated with diethylether and suction filtered. 100 mg (24.2% of theory) of colourless crystals were obtained.

IR(KBr): 1666, 1620 cm^{-1} (C=O)

MS: $(M+H)^+$ = 828/830/832 (Br_2)

$(M+Na)^+$ = 850/852/854 (Br_2)

The following were obtained accordingly:

(1) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-cyclopropylmethyl-4-piperidinyl)-piperidine (No. (489) in a yield of 23% of theory.

R_f 0.65 (FM1)

IR(KBr): 1622, 1666 cm^{-1} (C=O)

ESI-MS: $(M+H)^+$ = 798/800/802 (Br_2)

(2) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[1-(ethoxycarbonylmethyl)-4-piperidinyl]-piperidine (No. (493) in a yield of 43% of theory.

R_f 0.72 (FM1)

IR(KBr): 1620, 1666 cm^{-1} (C=O)

ESI-MS: $(M+H)^+$ = 730/732/734 (Br_2)

(3) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-[1-(cyclopropylmethyl)-4-piperidinyl]-piperidine (No. (525) in a yield of 46.5% of theory.

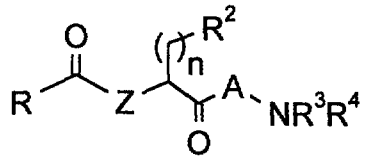
R_f 0.50 (FM1)

IR(KBr): 1622, 1662 cm^{-1} (C=O)

ESI-MS: $(M+H)^+$ = 799/801/803 (Br_2)

Example 19

Preparation of compounds of general formula:



1-[N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-3-ethenyl-D,L-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine (No. 532)

The mixture of 200 mg (3 mmol) 1-[3-bromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D,L-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine, 108 mg (0.33 mMol) vinyl-tributyl tin (ALDRICH No. 27143-8), 50 mg tetrakis-(triphenylphosphine)-palladium (Merck No. 818193), a trace of 2,6-di-tert.-butyl-4-methylphenol and 10 ml anhydrous toluene was refluxed for 5 hours. The cooled reaction mixture was filtered over an activated charcoal filter, the filtrate was evaporated in a vacuum. The residue was purified for elution by column chromatography over silica gel, initially using pure dichloromethane, then methanol/ conc. ammonia (9/1 v/v). The suitable eluates were triturated and suction filtered with tert.-butyl-methylether. Yield was 60 mg (32.6% of theory) of colourless crystals of R_f 0.25 (FM1).

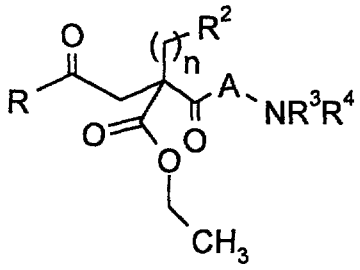
MS: M^+ = 612

The following were prepared analogously: (in each case, n=1):

No.	RCO	Z	R^2	A	NR^3R^4	% Yield	MS	Eluant	R_f	IR [cm^{-1}]
647	N66	CH_2	AS40	A0	C8	75	El: M^+ = 611	FM1	0.6	(KBr): C=0 1639/1668
648	N66	CH_2	AS41	A0	C8	56	El: M^+ = 647	FM1	0.7	(KBr): C=0 1639/1668
649	N66	CH_2	AS42	A0	C8	8	El: M^+ = 648	FM1	0.6	(KBr): C=0 1635/1668
650	N66	CH_2	AS43	A0	C8	11	El: M^+ = 654	FM1	0.6	(KBr): C=0 1635/1666
651	N66	CH_2	AS44	A0	C8	84	El: M^+ = 637	FM1	0.6	(KBr): C=0 1633/1664
652	N66	CH_2	AS45	A0	C8	83	El: M^+ = 613	FM1	0.6	(KBr): C=0 1637/1667

Example 20

Preparation of compounds of general formula:



(R,S)-1-[4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-(ethoxycarbonyl)-2-[[1-methyl-1H-indol-3-yl]methyl]-1,4-dioxobutyl]-4-(4-methyl-1-piperazinyl)-piperidine (No. 599)

Produced analogously to Example 1 from (R,S)-4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-(ethoxycarbonyl)-2-[[1-methyl-1H-indol-3-yl]methyl]-4-oxobutanoic acid, 4-(4-methyl-1-piperazinyl)piperidine and TBTU in a yield of 10% of theory. Colourless, amorphous substance of R_f = 0.2 (dichloromethane/methanol/conc. ammonia 90/10/1 v/v/v).

IR(KBr): 1722, 1662, 1637 cm^{-1} (C=O)

MS: M^+ = 711

Accordingly, (R,S)-1-[4-[4-(aminocarbonylamino)-1-piperidinyl]-2-(ethoxycarbonyl)-2-[[1-methyl-1H-indol-3-yl]methyl]-1,4-dioxobutyl]-4-(4-methyl-1-piperazinyl)-piperidine (No. 601) was obtained from (R,S)-4-[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]-2-(ethoxycarbonyl)-2-[[1-methyl-1H-indol-3-yl]methyl]-4-oxobutanoic acid, 4-(4-methyl-1-piperazinyl)piperidine and TBTU in a yield of 20% of theory. Colourless, amorphous substance of R_f = 0.25 (dichloromethane/methanol/conc. ammonia 90/10/1 v/v/v).

ESI-MS: $(M+H)^+$ = 624
$(M+Na)^+$ = 646
$(M+H+Na)^{++}$ = 323.8

Example 21

1-[3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(hydroxycarbonyl)-piperidine (No. 211)

Produced analogously to Example A38 from 1-[3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(ethoxycarbonyl)-piperidine and aqueous lithium hydroxide solution in a yield of 79% of theory. Colourless, amorphous substance of R_f 0.54 (ethyl ethanoate/methanol/glacial acetic acid 9/1/0.3 v/v/v).

IR(KBr): 1691.5, 1622.0 cm^{-1} (C=O)

ESI-MS: $(M-H)^-$ = 690/2/4 (Br_2)

Example 22

1-[3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-piperidinyl)-piperazine (No. 214)

Produced analogously to Example A24 from 3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosine, 1-(1,1-dimethylethoxycarbonyl)-4-(1-piperazinyl)piperidine and TBTU, and additional conversion of the obtained intermediate product with trifluoroacetic acid (in accordance with Example A1b) in a yield of 4.2% of theory. Colourless, amorphous substance of R_f 0.25 (FM1).
IR(KBr): 1624.0 cm^{-1} (C=O)
ESI-MS: $(M+H)^+$ = 732/4/6 (Br_2)

Example 23

(R)-1-[2-[N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-N-methylamino]-3-(3,5-dibromo-4-hydroxyphenyl)-propyl]-4-(1-piperidinyl)-piperidine (No. 219)

a) 1-(chlorocarbonyl)-4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-piperidine

To a solution of 3.0 g (13.8 mmol) 4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)piperidine and 2.7 ml (15 mMol) DIEA in 100 ml toluene, a solution of 1.8 ml (14.9 mMol) diphosgene in 15 ml toluene was added dropwise under external cooling with iced water, and the mixture was additionally kept at room temperature for 17 hours. The precipitate was suction filtered, washed with petroleum ether and dissolved in 50 ml dichloromethane. The obtained

solution was agitated twice each with 50 ml 7% aqueous sodium hydrogen carbonate solution, dried over sodium sulphate and evaporated in a vacuum. Yield was 3.0 g (78% of theory) of a colourless substance of R_f 0.25 (dichloromethane/acetone 9/1 v/v), which was further processed without more purification.

b) (R)-1-[3-(3,5-dibromo-4-hydroxyphenyl)-2-(N-methylamino)-propyl]-4-(1-piperidinyl)-piperidine

To a suspension of 2.3 g (60 mmol) lithium aluminium hydride in 100 ml anhydrous tetrahydrofuran, a solution of 11.0 g (18.66 mmol) 1-[3,5-dibromo-N-(1,1-dimethylethoxycarbonyl)-D-tyrosyl]-4-(1-piperidinyl)piperidine in 100 ml anhydrous tetrahydrofuran was added dropwise at room temperature whilst being stirred. It was stirred for a further 15 minutes at room temperature and then refluxed for 3 hours. 3 ml 20% aqueous ammonium chloride solution was added to the cooled mixture, then it was dried with magnesium sulphate. The filter cake was filtered and washed with 300 ml of an ethyl ethanoate-methanol mixture (1/1 v/v), and the combined filtrates were evaporated in a vacuum. The residue was purified by column chromatography over silica gel using ethyl ethanoate / methanol (8/2 v/v) for elution.

1. 2.9 g (31% of theory) of a colourless substance of R_f 0.13 (eluant: methanol) was isolated from the suitable fractions, which was identified as 1-(3,5-dibromo-N-methyl-D-tyrosyl)-4-(1-piperidinyl)piperidine:
IR(KBr): 1668.3 cm^{-1} (C=O)
MS: M^+ = 501/3/5 (Br_2)

and

2. 1.8 g (20% of theory) of a colourless substance of R_f 0.05 (eluant: methanol), which was identified as the sought compound:

ESI-MS: $(M+H)^+$ = 488/490/492 (Br_2)

$(M+2H)^{++}$ = 244/245/246.5 (Br_2)

c) (R)-1-[2-[N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-N-methylamino]-3-(3,5-dibromo-4-hydroxyphenyl)-propyl]-4-(1-piperidinyl)-piperidine (No. 219)

A solution of 0.57 g (2.02 mmol) 1-(chlorocarbonyl)-4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-piperidine in 30 ml dimethylformamide was added dropwise to the mixture of 0.9 g (1.84 mmol) (R)-1-[3-(3,5-dibromo-4-hydroxyphenyl)-2-(N-methylamino)-propyl]-4-(1-piperidinyl)-piperidine and 0.65 ml (3.7 mmol) DIEA in a mixture of 50 ml tetrahydrofuran and 20 ml dimethylformamide. It was stirred overnight at room temperature and the deposit was evaporated in a vacuum. The residue was treated with 300 ml of a tetrahydrofuran ethyl ethanoate mixture (1/1 v/v) and the resulting solution was agitated twice each with 100 ml of a saturated aqueous solution of sodium hydrogen carbonate, dried over sodium sulphate and evaporated in a vacuum. The residue was purified over silica gel by column chromatography using dichloromethane/methanol (8.5/1.5 v/v) for elution. 390 mg (29% of theory) of a colourless substance of R_f 0.46 (dichloromethane cyclohexane/methanol/conc. ammonia 75/15/15/2 v/v/v/v) were isolated from the suitable fractions:

IR(KBr): 1695.3, 1624.0 cm^{-1} (C=O)

ESI-MS: $(M+H)^+$ = 731/3/5 (Br_2)

Example 24

1-[3,5-dibromo-N-[[4-[5-[(4-morpholinyl)carbonyl]-1,3-dihydro-2(2H)-oxobenzimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine (No. 223)

100 mg (0.6 mMol) N,N'-carbonyldiimidazole was added to a solution of 400 mg (0.5 mMol) 1-[3,5-dibromo-N-[[4-(1,3-dihydro-5-(hydroxycarbonyl)-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine in 10 ml anhydrous tetrahydrofuran at room temperature, heated to 50 °C for 30 minutes and then 90 mg (1 mMol) morpholine was added. After heating to 50-60 °C for two hours, the solution was removed in a vacuum and the residue was purified over silica gel(30 - 60 µm) by column chromatography, initially using dichloromethane, then dichloromethane/methanol 9/1 (v/v), and finally dichloromethane/methanol/conc. ammonia 9/1/0.2 (v/v/v) as eluants. 250 mg (60% of theory) of an amorphous, colourless substance was yielded from the suitable extracts.

IR(KBr): 1712.7, 1625.9 cm^{-1} (C=O)

ESI-MS: $(M+H)^+$ = 838/840/842 (Br_2)

$(M+2H)^{++}$ = 419/420/421.5 (Br_2)

The following were obtained accordingly:

1-[3,5-dibromo-N-[[4-[5-[(4-methyl-1-piperazinyl)-carbonyl]-1,3-dihydro-2(2H)-oxobenzimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine (No. 224) from 1-[3,5-dibromo-N-[[4-(1,3-dihydro-5-(hydroxycarbonyl)-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine, 1-methylpiperazine and

N,N'-carbonyldiimidazole in a yield of 52% of theory. Colourless, amorphous substance.

IR(KBr): 1710.8, 1625.9 cm^{-1} (C=O)

ESI-MS: $(M+H)^+$ = 851/853/855 (Br_2)

$(M+2H)^{++}$ = 426/427/428 (Br_2)

Example 25

1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[1-(carboxymethyl)-4-piperidinyl]-piperidine (No. 494)

Produced analogously to Example A37, but using tetrahydrofuran instead of methanol, from 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[1-(ethoxycarbonylmethyl)-4-piperidinyl]-piperidine by the action of aqueous lithium hydroxide solution in a yield of 51% of theory. Colourless, amorphous substance.

ESI-MS: $(M-H)^-$ = 800/802/804 (Br_2)

$(M+H)^+$ = 802/804/806 (Br_2)

$(M+Na)^+$ = 824/826/828 (Br_2)

Example 26

1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-[1-(hydroxycarbonylmethyl)-4-piperidinyl]-piperidine (No. 526)

Produced analogously to Example 18 from 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-piperidinyl)-piperidine, ethyl glyoxylate and sodium triacetoxyborhydride and additional saponification with soda lye of the 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-

[1-(ethoxycarbonylmethyl)-4-piperidinyl]-piperidine, obtained as an intermediate product but not characterised, according to Example A55. A colourless, amorphous substance is obtained in a yield of 35% of theory.

IR(KBr): 1625.9 wide cm^{-1} (C=O)

ESI-MS: $(M+H)^+$ = 803/805/807 (Br_2)

$(M+Na)^+$ = 825/827/829 (Br_2)

Example 27

1-[4-amino-N-[(4-amino-1-piperidinyl)carbonyl]-3,5-dibromo-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine (No. 564)

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653 mg (10.4 mMol) 95% sodium cyanoborohydride (Aldrich 15.615-9) was stirred into the mixture of 930 mg (1.48 mMol) 1-[4-amino-3,5-dibromo-N-[(4-oxo-1-piperidinyl)carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine, 1143 mg (14.8 mMol) ammonium acetate (Merck No. 1115) and 30 ml anhydrous methanol at room temperature, and was stirred overnight. The deposit was adjusted to pH ≤ 2 with conc. hydrochloric acid and was evaporated in a vacuum. The residue is taken up in water and made alkaline with 40% soda lye. Exhaustive extraction with dichloromethane followed, then the combined extracts were dried over sodium sulphate and evaporated in a vacuum. The residue was purified over 100 g silica gel (Amicon, 35 - 70 µm) by column chromatography using dichloromethane/methanol/conc. ammonia(60/40/5 v/v/v) for elution. From the suitable fractions, 250 mg (27% of theory) of the sought substance was isolated as a colourless, amorphous product of R_f 0.15 (dichloromethane/methanol/conc. ammonia 50/50/0.5 v/v/v).

IR(KBr): 1618 wide cm^{-1} (C=O)

ESI-MS: $(M+H)^+$ = 627/629/631 (Br_2)

$(M+Na)^+$ = 649/651/653 (Br_2)
$(M+2H)^{++}$ = 314/315/316 (Br_2)

Example 28

(R,S)-1-[4-[4-(3,4-Dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,4-dichlorphenyl)methyl]-1,4-dioxobutyl]-4-(hydroxycarbonylmethyl)-piperidine
(No. 596)

Produced analogously to Example A55 from (R,S)-1-[4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,4-dichlorophenyl)methyl]-1,4-dioxobutyl]-4-(ethoxycarbonylmethyl)-piperidine by saponification with soda lye in a yield of 86% of theory. Colourless, amorphous substance of R_f 0.76 (ethyl ethanoate/methanol/glacial acetic acid 70/30/1 v/v/v).
IR(KBr): 1716, 1635 cm^{-1} (C=O)
ESI-MS: $(M-H)^-$ = 613/615/617 (Cl_2)
$(M+H)^+$ = 615/617/619 (Cl_2)
$(M+Na)^+$ = 637/639/641 (Cl_2)

Example 29

1-[N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-3-(1H-tetrazol-5-yl)-D,L-phenylalanyl]-4-(1-piperidinyl)-piperidine
(No. 632)

8.5 g (35 mMol) tributyl tin(IV)-azide (Synthesis 1976, 330) was added to a solution of 1.6 g (2.68 mMol) 1-[3-cyano-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D,L-phenylalanyl]-4-(1-piperidinyl)-piperidine in 400 ml toluene and the mixture was refluxed for 4 days. The residue remaining after dispellation of the solvent was stirred with ethyl ethanoate, the obtained precipitate was suction filtered and purified over silica

gel by column chromatography using FM1 as an eluent. After the usual further processing, yield is 400 mg (24% of theory) of colourless crystals of R_f 0.2 (FM1).

IR(KBr): 1653 cm^{-1} (C=O)

ESI-MS: $(M+H)^+$ = 641

$(M+Na)^+$ = 663

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The following Examples describe the preparation of pharmaceutically useful forms which contain as active substance any desired compound of general formula I:

Example I

Capsules for powder inhalation containing 1 mg of active substance

Composition:
1 capsule for powder inhalation contains:

Active substance	1.0 mg
Lactose	20.0 mg
Hard gelatine capsules	50.0 mg
	71.0 mg

Method of preparation:
The active substance is ground to the particle size required for inhalants. The ground active substance is homogeneously mixed with the lactose. The mixture is packed into hard gelatine capsules.

Example II

Inhalable solution for Respimat® containing 1 mg of active substance

Composition:
1 stroke contains:

Active substance	1.0	mg
Benzalkonium chloride	0.002	mg
Disodium edetate	0.0075	mg
Purified water ad	15.0	µl

Method of preparation:
The active substance and benzalkonium chloride are dissolved in water and transferred into Respimat® cartridges.

Example III

Inhalable solution for nebulisers containing 1 mg of active substance

Composition:
1 vial contains:

Active substance	0.1	g
Sodium chloride	0.18	g
Benzalkonium chloride	0.002	g
Purified water ad	20.0	ml

Method of preparation:
Active substance, sodium chloride and benzalkonium chloride are dissolved in water.

Example IV

Propellant gas metering aerosol containing 1 mg of active substance

Composition:
1 stroke contains:

Active substance	1.0	mg
Lecithin	0.1	%
Propellant gas ad	50.0	µl

Method of preparation:
The micronised active substance is homogeneously suspended in a mixture of lecithin and propellant gas. The suspension is transferred into a pressurised container with metering valve.

Example V

Nasal spray containing 1 mg of active substance

Composition:		
Active substance	1.0	mg
Sodium chloride	0.9	mg
Benzalkonium chloride	0.025	mg
Disodium edetate	0.05	mg
Purified water ad	0.1	ml

Method of preparation:

The active substance and adjuvants are dissolved in water and transferred into a suitable container.

Example VI

Injectable solution containing 5 mg of active substance per 5 ml

Composition:		
Active substance	5	mg
Glucose	250	mg
Human-serum-albumin	10	mg
Glycofurol	250	mg
Water for injections ad	5	ml

Preparation:

Glycofurol and glucose are dissolved in water for injections (WfI); human-serum-albumin is added; active substance is dissolved with heating; solution is made up to required volume with WfI; transferred into ampoules under nitrogen gas.

Example VII

Injectable solution containing 100 mg of active substance per 20 ml

Composition:

Active substance	100	mg
Monopotassium dihydrogen phosphate = KH_2PO_4	12	mg
Disodium hydrogen phosphate = $Na_2HPO_4 \cdot 2H_2O$	2	mg
Sodium chloride	180	mg.
Human-serum-albumin	50	mg
Polysorbate 80	20	mg
Water for injections ad	20	ml

Preparation:

Polysorbate 80, sodium chloride, monopotassium dihydrogen phosphate and disodium hydrogen phosphate are dissolved in water for injections (WfI); human-serum-albumin is added; active substance is dissolved with heating; solution is made up to required volume with WfI; transferred into ampoules.

Example VIII

Lyophilisate containing 10 mg of active substance

Composition:

Active substance	10	mg
Mannitol	300	mg
Human-serum-albumin	20	mg

Preparation:

Mannitol is dissolved in water for injections (WfI); human-serum-albumin is added; active substance is dissolved with heating; solution is made up to required volume with WfI; transferred into vials and freeze-dried.

Solvent for lyophilisate:

Polysorbate 80 = Tween 80	20	mg
Mannitol	200	mg
Water for injections ad	10	ml

Preparation:

Polysorbate 80 and mannitol are dissolved in water for injections (WfI) and transferred into ampoules.

Example IX

Tablets containing 20 mg of active substance

Composition:

Active substance	20	mg
Lactose	120	mg
Corn starch	40	mg
Magnesium stearate	2	mg
Povidon K 25	18	mg

Preparation:

Active substance, lactose and corn starch are homogeneously mixed; granulated with an aqueous solution of Povidon; mixed with magnesium stearate; pressed in a tablet press; weight of tablet 200 mg.

Example X

Capsules containing 20 mg of active substance

Composition:

Active substance	20	mg
Corn starch	80	mg
Highly dispersed silicic acid	5	mg
Magnesium stearate	2.5	mg

Preparation:
Active substance, corn starch and silicic acid are homogeneously mixed; mixed with magnesium stearate; then the mixture is packed into size 3 hard gelatine capsules using a capsule filling machine.

Example XI

Suppositories containing 50 mg of active substance

Composition:

Active substance	50	mg
Hard fat (adeps solidus) q.s. ad	1700	mg

Preparation:
Hard fat is melted at about 38°C; ground active substance is homogeneously dispersed in the molten hard fat; then after cooling to about 35°C the melt is poured into chilled moulds.

Example XII

Aqueous solution for nasal application containing 10 mg active substance

Composition:

Active substance	10.0	mg
Hydrochloric acid in quantity required for formation of a neutral salt		
Methylparahydroxybenzoate (PHB)	0.01	mg
Propylparahydroxybenzoate (PHB)	0.005	mg
Purified water ad	1.0	ml

Preparation:
The active substance is dissolved in purified water; Hydrochloric acid is added until the solution is clear; PHB methyl and propyl esters are added; the solution is

made up to required volume with purified water; the solution is sterile-filtered and is transferred into an appropriate container.

Example XIII

Aqueous solution for nasal application containing 5 mg active substance

Composition:

Active substance	5	mg
1,2-propandiol	300	mg
Hydroxyethylcellulose	5	mg
Sorbic acid	1	mg
Purified water ad	1	ml

Preparation:

The active substance is dissolved in 1,2-propandiol; a hydroxyethyl-cellulose solution is prepared in purified water containing sorbic acid and is added to the active substance solution; the solution is sterile-filtered and is transferred into an appropriate container.

Example XIV

Aqueous solution for intravenous application containing 5 mg active substance

Composition:

Active substance	5	mg
1,2-propandiol	300	mg
Mannitol	50	mg
Water for injections (WfI) ad	1	ml

Preparation:

The active substance is dissolved in 1,2-propandiol; the solution is approximately made up to the required volume

with WfI; the mannitol is added and the solution is made up to required volume with WfI; the solution is sterile-filtered, transferred into individual containers and autoclaved.

Example XV

Liposomal formulation for intravenous injection containing 7.5 mg active substance

Composition:

Active substance	7.5	mg
Egg-lecithin, e.g. lipoid E 80	100.0	mg
Cholesterol	50.0	mg
Glycerine	50.0	mg
Water for injections ad	1.0	ml

Preparation:

The active substance is dissolved in a mixture of lecithin and cholesterol; the solution is added to a mixture of glycerine and WfI and is homogenised by means of high-pressure homogenisation or microfluidiser technology; the liposomal formulation obtained in this manner is transferred into an appropriate container under aseptic conditions.

Example XVI

Suspension for nasal application containing 20 mg active substance

Composition:

Active substance	20.0	mg
Carboxymethylcellulose (CMC)	20.0	mg

Sodium monohydrogen phosphate/sodium-dihydrogen phosphate buffer pH 6.8		q.s.
Sodium chloride	8.0	mg
Methylparahydroxybenzoate	0.01	mg
Propylparahydroxybenzoate	0.003	mg
Purified water ad	1.0	ml

Preparation:

The active substance is suspended in an aqueous CMC solution; the other components are added to the suspension one after another and the suspension is made up to required volume with purified water.

Example XVII

Aqueous solution for subcutaneous application containing 10 mg active substance

Composition:

Active substance	10.0	mg
Sodium monohydrogen phosphate/ sodium dihydrogen phosphate buffer q.s. ad pH	7.0	
Sodium chloride	4.0	mg
Water for injections ad	0.5	ml

Preparation:

The active substance is dissolved in the phosphate buffer solution, after addition of the sodium chloride the solution is made up to required volume with water. The solution is sterile-filtered and is autoclaved after being transferred into an appropriate container.

Example XVIII

Aqueous solution for subcutaneous application containing 5 mg active substance

Composition:

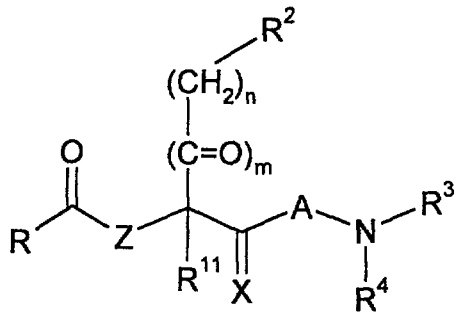
Active substance	5.0	mg
Polysorbate 80	0.5	mg
Water for injections ad	0.5	ml

Preparation:

The active substance is suspended in the polysorbate 80 solution and is reduced to a particle size of approx. 1 µm by means of a suitable dispersion technique (e.g. wet milling, high-pressure homogenisation, micro-fluidisation, etc.). The suspension is transferred into an appropriate container under aseptic conditions.

Patent Claims

1. Modified amino acids of general formula



(I),

wherein

R denotes an unbranched C_{1-7}-alkyl group which may be substituted in the ω-position

by a C_{4-10}-cycloalkyl group,

by one or two phenyl groups, by a 1-naphthyl, 2-naphthyl or biphenylyl group,

by a 1,3-dihydro-2H-2-oxobenzimidazol-1-yl, 2,4(1H,3H)-dioxoquinazolin-1-yl, 2,4(1H,3H)-dioxoquinazolin-3-yl, 2,4(1H,3H)-dioxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-3-yl, 2(1H)-oxoquinolin-3-yl, 2(1H)-oxoquinoxalin-3-yl, 1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl, 1,3-dihydro-2H-2-oxoimidazopyridinyl, 1,3-dihydro-2(2H)-oxoimidazo[4,5-c]quinolin-3-yl, 1,3-dihydro-2H-2-oxoimidazol-1-yl or 3,4-dihydro-2(1H)-oxopyrimidin-3-yl group, wherein the latter two groups may each be

* C L M S *

mono- or disubstituted in the 4- and/or 5-position or in the 5- and/or 6-position by lower straight chained or branched alkyl groups, by phenyl, biphenylyl, pyridinyl, diazinyl, furyl, thienyl, pyrrolyl, 1,3-oxazolyl, 1,3-thiazolyl, isoxazolyl, pyrazolyl-1-methylpyrazolyl, imidazolyl or 1-methylimidazolyl groups and the substituents may be identical or different,

by a 5-membered heteroaromatic ring linked via a carbon atom, which contains a nitrogen, oxygen or sulphur atom or, in addition to a nitrogen atom, contains an oxygen, sulphur or additional nitrogen atom, whilst a nitrogen atom of an imino group may be substituted by an alkyl group,

or by a 6-membered heteroaromatic ring linked via a carbon atom, which contains one, two or three nitrogen atoms,

whilst a 1,4-butadienylene group may be attached both to the above-mentioned 5-membered heteroaromatic monocyclic rings and to the 6-membered heteroaromatic monocyclic rings, in each case via two adjacent carbon atoms, and the bicyclic heteroaromatic rings thus formed may also be bound via a carbon atom of the 1,4-butadienylene group,

an unbranched C_{1-6}-alkylamino group optionally substituted at the nitrogen atom by a C_{1-6}-alkyl group or by a phenylmethyl group, which may be substituted in the ω-position

by a C_{4-10}-cycloalkyl group,

* C L M S *

by one or two phenyl groups, by a 1-naphthyl, 2-naphthyl or biphenylyl group,

by a 1H-indol-3-yl, 1,3-dihydro-2H-2-oxobenzimidazol-1-yl, 2,4(1H,3H)-dioxoquinazolin-1-yl, 2,4(1H,3H)-dioxoquinazolin-3-yl, 2,4(1H,3H)-dioxothieno-[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-3-yl, 2(1H)-oxoquinolin-3-yl, 2(1H)-oxoquinoxalin-3-yl, 1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl, 1,3-dihydro-4-(3-thienyl)-2H-2-oxoimidazol-1-yl, 1,3-dihydro-4-phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-5-phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-2(2H)-oxoimidazo-[4,5-c]quinolin-3-yl, 3,4-dihydro-5-phenyl-2(1H)-oxopyrimidin-3-yl, 3,4-dihydro-6-phenyl-2(1H)-oxopyrimidin-3-yl or 1,3-dihydro-2H-2-oxoimidazo-[4,5-b]pyridin-3-yl group,

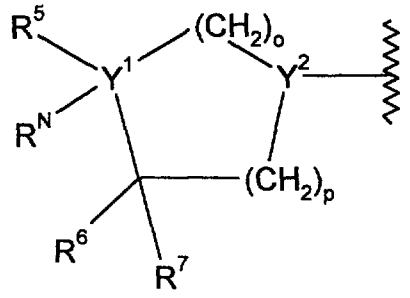
by a 5-membered heteroaromatic ring linked via a carbon atom, which contains a nitrogen, oxygen or sulphur atom or, in addition to a nitrogen atom, contains an oxygen, sulphur or an additional nitrogen atom, whilst a nitrogen atom of an imino group may be substituted by an alkyl group, or

by a 6-membered heteroaromatic ring linked via a carbon atom, containing 1, 2 or 3 nitrogen atoms, whilst a 1,4-butadienylene group may be attached both to the 5-membered and to the 6-membered heteroaromatic monocyclic rings, in each case via two adjacent carbon atoms, and the bicyclic

heteroaromatic rings thus formed may also be bound via a carbon atom of the 1,4-butadienylene group,

whilst the phenyl, naphthyl and biphenylyl groups mentioned above for the substitution of the alkyl and alkylamino groups in the ω-position and optionally also partially hydrogenated mono- and bicyclic heteroaromatic rings in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms or by alkyl groups, C_{3-8}-cycloalkyl groups, nitro, alkoxy, phenyl, phenylalkoxy, trifluoromethyl, alkoxycarbonyl, alkoxycarbonylalkyl, carboxy, carboxyalkyl, dialkylaminoalkyl, hydroxy, amino, acetylamino, propionylamino, benzoyl, benzoylamino, benzoylmethylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, (1-pyrrolidinyl)carbonyl, (1-piperidinyl)carbonyl, (hexahydro-1H-azepin-1-yl)carbonyl, (4-methyl-1-piperazinyl)carbonyl, (4-morpholinyl)carbonyl, alkanoyl, cyano, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl groups, wherein the substituents may be identical or different and the above-mentioned benzoyl, benzoylamino and benzoylmethylamino groups may in turn additionally be substituted in the phenyl moiety by a fluorine, chlorine or bromine atom or by an alkyl, trifluoromethyl, amino or acetylamino group,

or the group of formula



(II),

wherein

p denotes the number 1 or 2,

o denotes the number 2 or 3 or, if Y^1 and Y^2 are not simultaneously nitrogen atoms, o may also denote 1.

Y^1 denotes the nitrogen atom if R^5 is a free pair of electrons, or the carbon atom,

Y^2 is the nitrogen atom or the group >CH,

R^5 is a free pair of electrons if Y^1 denotes the nitrogen atom or, if Y^1 denotes the carbon atom, R^5 denotes a hydrogen atom, a C_{1-3}-alkyl group, a hydroxy, cyano, aminocarbonyl, carboxy, alkoxycarbonyl, aminocarbonylamino, phenylmethyl or phenyl group,

R^6 denotes the hydrogen atom or, provided that Y^1 is not a nitrogen atom, R^6 together with R^5 may denote an additional bond,

R^7 denotes the hydrogen atom or, provided that Y^1 is not a nitrogen atom and R^5 and R^6 together constitute an additional bond, R^7 together with R^N may also denote a 1,4-butadienylene group,

R^N denotes a hydrogen atom or a C_{1-6}-alkyl group which may be mono- or disubstituted in the ω-position

by a C_{5-7}-cycloalkyl group, by a 1-naphthyl, 2-naphthyl, hydroxy, alkoxy, amino, alkylamino, dialkylamino, piperidinyl, morpholinyl, pyrrolidinyl, hexahydro-1H-1-azepinyl, aminocarbonyl, alkylaminocarbonyl, acetylamino, cyano, aminocarbonylamino or

alkylaminocarbonylamino group or by phenyl, pyridinyl or diazinyl groups, whilst these substituents may be identical or different,

a C_{5-7}-cycloalkyl group, a phenyl, pyridinyl, cyano, amino, benzoylamino, aminocarbonyl, alkylaminocarbonyl, alkoxycarbonyl, phenylalkoxycarbonyl, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, N-(aminocarbonyl)-N-alkylamino, N-(alkyl-aminocarbonyl)-N-alkylamino, N-(alkylaminocarbonyl)-N-phenylamino, phenylaminocarbonylamino, [phenyl(alkylamino)]carbonylamino, N-(phenylaminocarbonyl)-N-alkylamino, N-(phenylaminocarbonyl)-N-phenylamino, benzoylaminocarbonylamino, phenylalkylamino-carbonylamino, pyridinylaminocarbonylamino, N-(aminocarbonyl)-N-phenylamino, N-(alkylaminocarbonyl)-N-phenylamino, N-(aminocarbonylaminocarbonyl)-N-phenylamino, N-(pyridinyl)-N-(aminocarbonyl)amino, N-(pyridinyl)-N-(alkylaminocarbonyl)amino, phenylamino, pyridinylamino, 4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl or diazinylamino group,

a saturated, mono- or di- unsaturated 5- to 7-membered aza, diaza, triaza, oxaza, thiaza, thiadiaza- or S,S-dioxido-thiadiaza- heterocycle.

wherein the above-mentioned heterocycles may be linked via a carbon or nitrogen atom and

may contain one or two carbonyl groups adjacent to a nitrogen atom,

may be substituted at one of the nitrogen atoms by an alkyl, alkanoyl, aroyl, hydroxycarbonylalkyl,

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alkoxycarbonylalkyl, phenylalkoxycarbonylalkyl, phenylmethyl or phenyl group,

may be substituted at one or two carbon atoms by a branched or unbranched alkyl group or by a phenyl, phenylmethyl, naphthyl, biphenylyl, pyridinyl, diazinyl, furyl, thienyl, pyrrolyl, 1,3-oxazolyl, 1,3-thiazolyl, isoxazolyl, pyrazolyl, 1-methyl-pyrazolyl, imidazolyl or 1-methylimidazolyl group, wherein the substituents may be the same or different,

and wherein a C_{3-6}-alkylene group may additionally be attached to the above-mentioned heterocycles via two adjacent carbon atoms or an olefinic double bond of one of the above-mentioned unsaturated heterocycles may be fused with a benzene, pyridine, diazine, 1,3-oxazole, thiophene, furan, thiazole, pyrrole, N-methyl-pyrrole, quinoline, imidazole or N-methyl-imidazole ring,

or if Y^1 is not a nitrogen atom and R^5 and R^6 together denote an additional bond, R^N together with R^7 may also denote the 1,4-butadienylene group,

or, if Y^1 is a carbon atom, R^N together with R^5, including Y^1, also denotes a carbonyl group or a saturated or monounsaturated 5- or 6-membered 1,3-diaza-heterocycle which may optionally contain one or two carbonyl groups in the ring and, if it is unsaturated, may be benzofused at the double bond and may be substituted at one of the nitrogen atoms by a methyl, aminocarbonyl, hydroxycarbonylalkyl, alkoxycarbonylalkyl, phenylalkoxycarbonylalkyl, phenylmethyl or phenyl group,

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whilst the phenyl, pyridinyl, diazinyl, furyl, thienyl, pyrrolyl, 1,3-oxazolyl, 1,3-thiazolyl, isoxazolyl, pyrazolyl, 1-methylpyrazolyl, imidazolyl- or 1-methylimidazolyl groups contained in the residues mentioned under R^5, R^7 and R^N, as well as benzo, thieno, pyrido- and diazino-fused heterocycles in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms, by alkyl groups, C_{3-8}-cycloalkyl groups, nitro, alkoxy, alkylthio, alkylsulphinyl, alkylsulphonyl, alkylsulphonylamino, phenyl, phenylalkoxy, trifluoromethyl, alkoxycarbonyl, alkoxycarbonylalkyl, carboxy, carboxyalkyl, dialkylaminoalkyl, hydroxy, amino, acetylamino, propionylamino, benzoyl, benzoylamino, benzoylmethylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, hydroxyalkylaminocarbonyl, (4-morpholinyl)carbonyl, (1-pyrrolidinyl)carbonyl, (1-piperidinyl)carbonyl, (hexahydro-1-azepinyl)carbonyl, (4-methyl-1-piperazinyl)carbonyl, methylenedioxy, aminocarbonylamino, aminocarbonylaminoalkyl, alkylaminocarbonylamino, alkanoyl, cyano, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl- or trifluoromethylsulphonyl groups, wherein the substituents may be identical or different and the above-mentioned benzoyl, benzoylamino, benzoylaminocarbonylamino and benzoylmethylamino groups may in turn additionally be substituted in the phenyl moiety by a fluorine, chlorine or bromine atom or by an alkyl, trifluoromethyl, amino- or acetylamino group

and unless otherwise specified the alkyl groups contained in the above-mentioned radicals may contain 1 to 5 carbon atoms,

X denotes an oxygen atom or 2 hydrogen atoms,

* C L M S *

Z denotes a methylene group or the group $-NR^1$, wherein

R^1 denotes a hydrogen atom or an alkyl or phenylalkyl group,

R^{11} denotes a hydrogen atom, a C_{1-3}-alkyl group, an alkoxycarbonyl group having a total of 2 to 4 carbon atoms or a phenylmethyl group,

n denotes the number 1 or 2 or, if m is 1, n may also be 0,

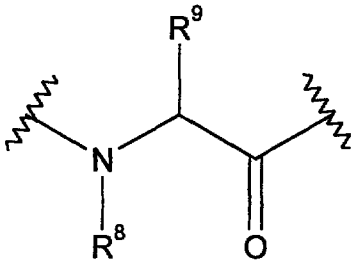
m denotes the number 0 or 1,

R^2 denotes a phenyl, 1-naphthyl, 2-naphthyl, 1,2,3,4-tetrahydro-1-naphthyl, 1H-indol-3-yl, 1-methyl-1H-indol-3-yl, 1-formyl-1H-indol-3-yl, 1-(1,1-dimethylethoxycarbonyl)-1H-indol-3-yl, 4-imidazolyl, 1-methyl-4-imidazolyl, 2-thienyl, 3-thienyl, thiazolyl, 1H-indazol-3-yl, 1-methyl-1H-indazol-3-yl, benzo[b]fur-3-yl, benzo[b]thien-3-yl, pyridinyl, quinolinyl or isoquinolinyl group,

whilst the above-mentioned aromatic and heteroaromatic groups in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms or by branched or unbranched alkyl groups, C_{3-8}-cycloalkyl groups, phenylalkyl groups, alkenyl, alkoxy, phenyl, phenylalkoxy, trifluoromethyl, alkoxycarbonylalkyl, carboxyalkyl, alkoxycarbonyl, carboxy, dialkylaminoalkyl, hydroxy, nitro, amino, acetylamino, propionylamino, benzoyl, benzoylamino, benzoylmethylamino, methylsulphonyloxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkanoyl, cyano, tetrazolyl, phenyl, pyridinyl, thiazolyl, furyl, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl- or trifluoromethylsulphonyl groups, and the substituents

may be identical or different and the above-mentioned benzoyl, benzoylamino and benzoylmethylamino groups may in turn additionally be substituted in the phenyl moiety by a fluorine, chlorine or bromine atom, or by an alkyl, trifluoromethyl, amino or acetylamino group,

A denotes a bond or the divalent group of formula



(III),

(which is linked to the NR^3R^4 group via the -CX group)

wherein

R^8 and R^9 together denote an n-propylene group or

R^8 denotes a hydrogen atom or an alkyl or phenylalkyl group and

R^9 denotes a hydrogen atom or a branched or unbranched C_{1-5}-alkyl group which, if it is unbranched, may be substituted in the ω-position by a hydroxy, mercapto, amino, alkylamino, dialkylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidinyl, hexahydro-1-azepinyl, methylthio, hydroxycarbonyl, aminocarbonyl, aminoiminomethylamino, aminocarbonylamino, phenyl, 1H-indol-3-yl, 1-methyl-1H-indol-3-yl, 1-formyl-1H-indol-3-yl, 4-imidazolyl, 1-methyl-4-imidazolyl, 1-naphthyl, 2-naphthyl- or pyridinyl group, whilst the above-mentioned heterocycles, phenyl and naphthyl groups may in turn be mono-, di- or trisubstituted in the carbon

skeleton by fluorine, chlorine or bromine atoms or by methyl, alkoxy, trifluoromethyl, hydroxy, amino, acetylamino, aminocarbonyl, cyano, trifluoromethoxy, methylsulphonyloxy, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl groups, wherein the substituents may be identical or different, and wherein the hydroxy, mercapto, amino,. guanidino, indolyl and imidazolyl groups contained in the groups mentioned for R^9 may be substituted with the protecting groups commonly used in peptide chemistry, preferably with the acetyl, benzyloxycarbonyl or tert. butyloxycarbonyl group,

R^3 denotes a hydrogen atom,

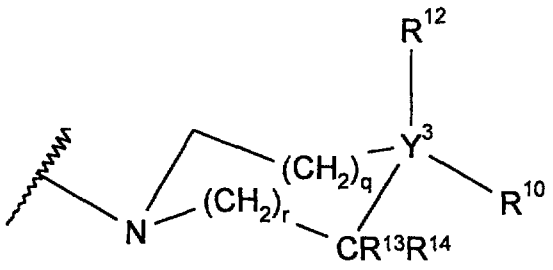
a C_{1-7}-alkyl group which may be substituted in the ω-position by a cyclohexyl, phenyl, pyridinyl, diazinyl, hydroxy, amino, alkylamino, dialkylamino, carboxy, aminocarbonyl, aminocarbonylamino, acetylamino, 1-pyrrolidinyl, 1-piperidinyl, 4-(1-piperidinyl)-1-piperidinyl, 4-morpholinyl, hexahydro-1H-1-azepinyl, [bis-(2-hydroxyethyl)]amino, 4-alkyl-1-piperazinyl or 4-(ω-hydroxyalkyl)-1-piperazinyl group,

a phenyl or pyridinyl group,

wherein the above-mentioned heterocyclic groups and phenyl groups may additionally be mono-, di- or trisubstituted in the carbon skeleton by fluorine, chlorine or bromine atoms or by methyl, alkoxy, trifluoromethyl, hydroxy, amino, acetylamino, aminocarbonyl, cyano, methylsulphonyloxy, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl groups and the substituents may be identical or different,

R^4 denotes a hydrogen atom or a C_{1-3}-alkyl group optionally substituted by a phenyl or pyridinyl group or

R^3 and R^4 together with the enclosed nitrogen atom denote a group of general formula



(IV),

wherein

Y^3 denotes a carbon atom or, if R^{12} denotes a free pair of electrons, Y^3 may also be the nitrogen atom,

r denotes the number 0, 1 or 2,

q denotes the number 0, 1 or 2,

R^{10} denotes a hydrogen atom or an amino, alkylamino, dialkylamino, alkyl, cycloalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, aminoiminomethyl, aminocarbonylamino, alkylaminocarbonylamino, cycloalkylaminocarbonylamino, phenylaminocarbonylamino, aminocarbonylalkyl, aminocarbonylaminoalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, carboxyalkyl or carboxy group,

a phenyl, pyridinyl, diazinyl, 1-naphthyl, 2-naphthyl, pyridinylcarbonyl or phenylcarbonyl group which may be mono-, di- or trisubstituted in the carbon skeleton by fluorine, chlorine or bromine atoms, or by alkyl, alkoxy, methylsulphonyloxy, trifluoromethyl, hydroxy, amino, acetylamino,

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aminocarbonyl, aminocarbonylamino, aminocarbonylaminomethyl, cyano, carboxy, carbalkoxy, carboxyalkyl, carbalkoxyalkyl, alkanoyl, ω-(dialkylamino)alkanoyl, ω-(dialkylamino)alkyl, ω-(dialkylamino)hydroxyalkyl, ω-(carboxy)alkanoyl, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl groups, whilst the substituents may be identical or different,

a 1,3-dihydro-2-oxo-2H-imidazolyl, 2,4(1H,3H)-dioxopyrimidinyl or 3,4-dihydro-2(1H)-oxopyrimidinyl group bound via a nitrogen atom, which may be substituted by a phenyl group or fused at the double bond to a benzene, pyridine or diazine ring,

a 1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl group,

a 4- to 10-membered azacycloalkyl group, a 5- to 10-membered oxaza, thiaza- or diazacycloalkyl group or a 6- to 10-membered azabicycloalkyl group,

wherein the above-mentioned mono- and bicyclic heterocycles may be bound via a nitrogen or carbon atom and

may be substituted by a C_{1-7}-alkyl group, by an alkanoyl, dialkylamino, phenylcarbonyl, pyridinylcarbonyl, carboxyalkanoyl, carboxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, alkylsulphonyl, cycloalkyl- or cycloalkylalkyl group, by a cycloalkylcarbonyl, azacycloalkylcarbonyl, diazacycloalkylcarbonyl or oxazacycloalkylcarbonyl group optionally substituted in the ring,

whilst the alicyclic parts contained in these substituents may comprise 3 to 10 ring members and the heteroalicyclic parts may comprise 4 to 10 ring members and

the above-mentioned phenyl and pyridinyl groups may in turn be mono- , di- or trisubstituted by fluorine, chlorine or bromine atoms, by alkyl, alkoxy, methylsulphonyloxy, trifluoromethyl, hydroxy, amino, acetylamino, aminocarbonyl, aminocarbonylamino, aminocarbonylaminomethyl, cyano, carboxy, carbalkoxy, carboxyalkyl, carbalkoxyalkyl, alkanoyl, ω-(dialkylamino)alkanoyl, ω-(carboxy)alkanoyl, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl groups, whilst the substituents may be identical or different, or

R^{10} together with R^{12} and Y^3 denotes a 4- to 7-membered cycloaliphatic ring in which a methylene group may be replaced by an -NH- or -N(alkyl)- group,

whilst a hydrogen atom bound to a nitrogen atom within the group R^{10} may be replaced by a protecting group,

R^{12} denotes a hydrogen atom,

a C_{1-4}-alkyl group, wherein an unbranched alkyl group may be substituted in the ω-position by a phenyl, pyridinyl, diazinyl, amino, alkylamino, dialkylamino, 1-pyrrolidinyl, 1-piperidinyl, 4-methyl-1-

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piperazinyl, 4-morpholinyl- or hexahydro-1H-1-azepinyl group,

an alkoxycarbonyl, cyano or aminocarbonyl group or a free pair of electrons, if Y^3 denotes a nitrogen atom, and

R^{13} and R^{14} in each case denote a hydrogen atom or,

if Y^3 is a carbon atom, R^{12} together with R^{14} also denotes another carbon-carbon bond, wherein R^{10} is as hereinbefore defined and R^{13} denotes a hydrogen atom or

if Y^3 is a carbon atom, R^{12} together with R^{14} also denotes another carbon-carbon bond and R^{10} together with R^{13} and the enclosed double bond denotes a partially hydrogenated or aromatic 5- to 7-membered mono- or bicyclic carbocycle or heterocycle,

whilst all the above-mentioned alkyl and alkoxy groups and the alkyl groups present within the other groups mentioned may contain 1 to 7 carbon atoms, unless otherwise specified,

all the above-mentioned cycloalkyl groups and the cycloalkyl groups present within the other groups named may contain 5 to 10 carbon atoms, unless otherwise specified,

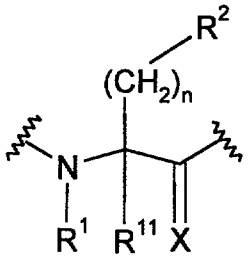
their tautomers, diastereomers, enantiomers, mixtures thereof and the salts thereof.

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☑ Claim(s) : paged 414 to paged 417
☐ Drawing(s) : paged ..... to paged .....
☑ Abstract : paged 418 to paged .....

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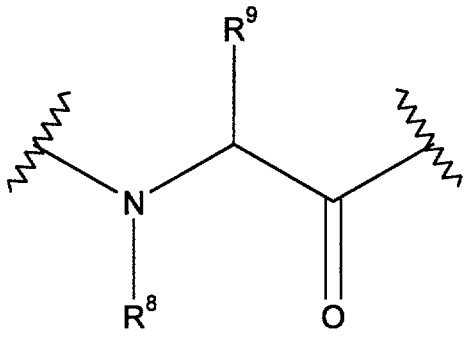
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2. Modified amino acids of general formula I according to claim 1, wherein the partial amino acid structure of the formula



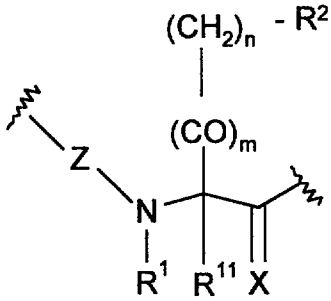
(V)

is in the D- or (R)-configuration and is in the L- or (S)-configuration with regard to the partial amino acid structure of formula



(III)

which may be present in the group A, or wherein the partial structure of formula VI



(VI)

is spatially constructed analogously to the (R)-configured partial structure of formula V.

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3. Modified amino acids of general formula I according to at least one of claims 1 or 2, wherein

R denotes an unbranched C_{1-5}-alkyl group which may be substituted in the ω-position

by a C_{4-7}-cycloalkyl group,

by one or two phenyl groups, by a 1-naphthyl, 2-naphthyl or (4-biphenylyl) group,

by a 1,3-dihydro-2H-2-oxobenzimidazol-1-yl, 2,4(1H,3H)-dioxoquinazolin-1-yl, 2,4(1H,3H)-dioxoquinazolin-3-yl, 2,4(1H,3H)-dioxothieno-[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-3-yl, 2(1H)-oxoquinolin-3-yl, 2(1H)-oxoquinoxalin-3-yl, 1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl, 1,3-dihydro-2H-2-oxoimidazopyridinyl, 1,3-dihydro-2(2H)-oxoimidazo[4,5-c]quinolin-3-yl, 1,3-dihydro-2H-2-oxoimidazol-1-yl or 3,4-dihydro-2(1H)-oxopyrimidin-3-yl group, whilst the latter two groups may each be mono- or disubstituted in the 4- and/or 5-position or in the 5- and/or 6-positions by lower straight-chained or branched alkyl groups, by phenyl, biphenylyl, pyridinyl, diazinyl, furyl, thienyl, pyrrolyl, 1,3-oxazolyl, 1,3-thiazolyl, isoxazolyl, pyrazolyl- 1-methylpyrazolyl, imidazolyl or 1-methylimidazolyl groups, and the substituents may be identical or different,

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by a 5-membered heteroaromatic ring linked via a carbon atom and containing a nitrogen, oxygen or sulphur atom or, in addition to a nitrogen atom, an oxygen, sulphur or additional nitrogen atom, whilst a nitrogen atom of an imino group may be substituted by an alkyl group,

or by a 6-membered heteroaromatic ring linked via a carbon atom and containing one or two nitrogen atoms,

whilst a 1,4-butadienylene group may be attached both to the 5-membered and to the 6-membered heteroaromatic monocyclic rings via two adjacent carbon atoms in each case and the bicyclic heteroaromatic rings thus formed may also be bound via a carbon atom of the 1,4-butadienylene group,

or an unbranched C_{1-4}-alkylamino group optionally substituted at the nitrogen atom by a C_{1-3}-alkyl group or by a phenylmethyl group, which may be substituted in the ω-position

by a C_{4-7}-cycloalkyl group,

by one or two phenyl groups, by a 1-naphthyl, 2-naphthyl or (4-biphenylyl) group,

by a 1H-indol-3-yl, 1,3-dihydro-2H-2-oxobenzimidazol-1-yl, 2,4(1H,3H)-dioxoquinazolin-1-yl, 2,4(1H,3H)-dioxoquinazolin-3-yl,
2,4(1H,3H)-dioxothieno[3,4-d]pyrimidin-3-yl,
3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl,
3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-1-yl,
3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl,
3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-1-yl,
3,4-dihydro-2(1H)-oxoquinazolin-1-yl, 3,4-dihydro-

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2(1H)-oxoquinazolin-3-yl, 2(1H)-oxoquinolin-3-yl, 2(1H)-oxoquinoxalin-3-yl, 1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl, 1,3-dihydro-4-(3-thienyl)-2H-2-oxoimidazol-1-yl, 1,3-dihydro-4-phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-5-phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-2(2H)-oxoimidazo[4,5-c]quinolin-3-yl, 3,4-dihydro-5-phenyl-2(1H)-oxopyrimidin-3-yl, 3,4-dihydro-6-phenyl-2(1H)-oxopyrimidin-3-yl or 1,3-dihydro-2H-2-oxo-imidazo[4,5-b]pyridin-3-yl group,

by a 5-membered heteroaromatic ring linked via a carbon atom and containing a nitrogen, oxygen or sulphur atom or, in addition to a nitrogen atom, an oxygen, sulphur or additional nitrogen atom, whilst a nitrogen atom of an imino group may be substituted by an alkyl group,

or by a 6-membered heteroaromatic ring linked via a carbon atom and containing 1 or 2 nitrogen atoms, whilst a 1,4-butadienylene group may be attached to both the 5-membered and to the 6-membered heteroaromatic monocyclic rings via two adjacent carbon atoms in each case and the bicyclic heteroaromatic rings thus formed may also be bound via a carbon atom of the 1,4-butadienylene group,

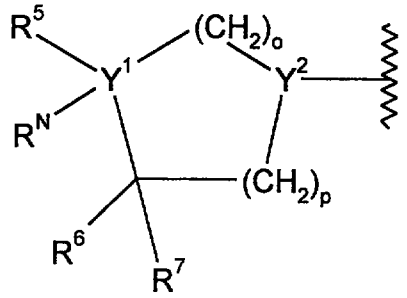
whilst the phenyl, naphthyl and biphenylyl groups mentioned above for the substitution of the alkyl and alkylamino groups in the ω-position and optionally also partially hydrogenated mono- and bicyclic heteroaromatic rings in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms or by alkyl groups, C_{5-7}-cycloalkyl groups, nitro, alkoxy, phenyl, phenylalkoxy, trifluoromethyl, alkoxycarbonyl, alkoxycarbonylalkyl, carboxy, carboxyalkyl, dialkylaminoalkyl, hydroxy, amino,

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acetylamino, propionylamino, benzoyl, benzoylamino, benzoylmethylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, (1-pyrrolidinyl)carbonyl, (1-piperidinyl)carbonyl, (hexahydro-1H-azepin-1-yl)carbonyl, (4-methyl-1-piperazinyl)carbonyl, (4-morpholinyl)carbonyl, alkanoyl, cyano, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl groups, wherein the substituents may be identical or different and the above-mentioned benzoyl, benzoylamino and benzoylmethylamino groups may in turn additionally be substituted in the phenyl moiety by a fluorine, chlorine or bromine atom or by an alkyl, trifluoromethyl, amino or acetylamino group,

or the group of formula



(II),

wherein

p denotes the number 1 or 2,

o denotes the number 2 or, if Y^1 and Y^2 are not simultaneously nitrogen atoms, o may also denote 1.

Y^1 denotes the nitrogen atom if R^5 is a free pair of electrons, or the carbon atom,

Y^2 is the nitrogen atom or the group >CH,

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R^5 is a free pair of electrons if Y^1 denotes the nitrogen atom or, if Y^1 denotes the carbon atom, R^5 denotes a hydrogen atom, a C_{1-3}-alkyl group, a hydroxy, cyano, aminocarbonyl, carboxy, alkoxycarbonyl, aminocarbonylamino, phenylmethyl or phenyl group,

R^6 denotes the hydrogen atom or, provided that Y^1 is not a nitrogen atom, R^6 together with R^5 may denote an additional bond,

R^7 denotes the hydrogen atom or, provided that Y^1 is not a nitrogen atom and R^5 and R^6 together constitute an additional bond, R^7 together with R^N may also denote a 1,4-butadienylene group,

R^N denotes the hydrogen atom or a C_{1-3}-alkyl group, which may be monosubstituted in the ω-position

by a C_{5-7}-cycloalkyl group or by a 1-naphthyl, 2-naphthyl, hydroxy, alkoxy, amino, alkylamino, dialkylamino, piperidinyl, morpholinyl, pyrrolidinyl, hexahydro-1H-1-azepinyl, aminocarbonyl, alkylaminocarbonyl, acetylamino, cyano, aminocarbonylamino or alkyl-aminocarbonylamino group, or may be mono- or disubstituted by phenyl, pyridinyl or diazinyl groups, whilst these substituents may be identical or different,

a cyclohexyl, phenyl, pyridinyl, cyano, amino, benzoylamino, aminocarbonyl, alkylaminocarbonyl, alkoxycarbonyl, phenylalkoxycarbonyl, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, N-(aminocarbonyl)-N-alkylamino, N-(alkylaminocarbonyl)-N-alkylamino, N-(alkylaminocarbonyl)-N-phenylamino, phenylamino-

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carbonylamino, [N-phenyl(alkylamino)]carbonylamino, N-(phenylaminocarbonyl)-N-alkylamino, N-(phenylaminocarbonyl)-N-phenylamino, benzoylaminocarbonylamino, phenylalkylamino-carbonylamino, pyridinylaminocarbonylamino, N-(aminocarbonyl)-N-phenylamino, N-(alkylamino-carbonyl)-N-phenylamino, N-(aminocarbonyl-aminocarbonyl)-N-phenylamino, N-(pyridinyl)-N-(amino-carbonyl)amino, N-(pyridinyl)-N-(alkylaminocarbonyl)amino, phenylamino, pyridinylamino, diazinylamino or 4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl group,

a saturated, mono- or diunsaturated 5- to 7-membered aza, diaza, triaza, oxaza, thiaza, thiadiaza- or S,S-dioxidothiadiaza heterocycle,

whilst the above-mentioned heterocycles may be linked via a carbon or nitrogen atom and

may contain one or two carbonyl groups adjacent to a nitrogen atom,

may be substituted at one of the nitrogen atoms by an alkyl, alkanoyl, aroyl, hydroxycarbonylalkyl, alkoxycarbonylalkyl, phenylalkoxycarbonylalkyl, phenylmethyl or phenyl group,

may be substituted at one or two carbon atoms by a branched or unbranched alkyl group, by a phenyl, phenylmethyl, naphthyl, biphenylyl, pyridinyl, diazinyl, furyl, thienyl, pyrrolyl, 1,3-oxazolyl, 1,3-thiazolyl, isoxazolyl, pyrazolyl, 1-methylpyrazolyl, imidazolyl or 1-methylimidazolyl group, whilst the substituents may be identical or different,

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and wherein a C_{3-4}-alkylene group may additionally be attached to the above-mentioned heterocycles via two adjacent carbon atoms or an olefinic double bond of one of the above-mentioned unsaturated heterocycles may be fused with a benzene, pyridine, diazine, 1,3-oxazole, thiophene, furan, thiazole, pyrrole, N-methyl-pyrrole, quinoline, imidazole or N-methyl-imidazole ring,

or, provided that Y^1 is not a nitrogen atom and R^5 and R^6 together denote an additional bond, R^N together with R^7 may also denote the 1,4-butadienylene group or,

if Y^1 denotes a carbon atom, R^N together with R^5, with the inclusion of Y^1, may also denote a carbonyl group or a saturated or monounsaturated 5- or 6-membered 1,3-diaza-heterocycle which may contain one or two carbonyl groups in the ring adjacent to a nitrogen atom and, if it is unsaturated, may also be benzo-fused at the double bond and substituted at one of the nitrogen atoms by a methyl, aminocarbonyl, hydroxycarbonylalkyl, alkoxycarbonylalkyl, phenylalkoxycarbonylalkyl, phenylmethyl or phenyl group,

whilst the phenyl, pyridinyl, diazinyl, furyl, thienyl, pyrrolyl, 1,3-oxazolyl, 1,3-thiazolyl, isoxazolyl, pyrazolyl, 1-methylpyrazolyl, imidazolyl or 1-methylimidazolyl groups contained in the residues mentioned under R^5, R^7 and R^N, as well as benzo, thieno, pyrido- and diazino-fused heterocycles in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms, by alkyl groups, C_{4-7}-cycloalkyl groups, nitro, alkoxy,



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alkylthio, alkylsulphinyl, alkylsulphonyl, alkylsulphonylamino, phenyl, phenylalkoxy, trifluoromethyl, alkoxycarbonyl, alkoxycarbonylalkyl, carboxy, carboxyalkyl, dialkylaminoalkyl, hydroxy, amino, acetylamino, propionylamino, benzoyl, benzoylamino, benzoylmethylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, hydroxyalkylaminocarbonyl, (4-morpholinyl)carbonyl, (1-pyrrolidinyl)carbonyl, (1-piperidinyl)carbonyl, (hexahydro-1-azepinyl)carbonyl, (4-methyl-1-piperazinyl)carbonyl, methylenedioxy, aminocarbonylamino, aminocarbonylaminoalkyl, alkylaminocarbonylamino, alkanoyl, cyano, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl groups, wherein the substituents may be identical or different and the alkyl groups contained in the above-mentioned groups may contain 1 to 3 carbon atoms unless otherwise specified,

X denotes the oxygen atom or 2 hydrogen atoms,

Z denotes the methylene group or the group $-NR^1-$ wherein

R^1 denotes a hydrogen atom or a C_{1-3}-alkyl group,

R^{11} denotes a hydrogen atom, a C_{1-3}-alkyl group or an alkoxycarbonyl group having 2 to 4 carbon atoms altogether,

n denotes the number 1 or 2 or, if m is 1, n may also be 0,

m denotes the number 0 or 1,

R^2 denotes a phenyl, 1-naphthyl, 2-naphthyl, 1,2,3,4-tetrahydro-1-naphthyl, 1H-indol-3-yl, 1-methyl-1H-indol-3-yl, 1-formyl-1H-indol-3-yl, 1-(1,1-dimethylethoxycarbonyl)-1H-indol-3-yl, 4-imidazolyl, 1-methyl-4-imidazolyl, 2-

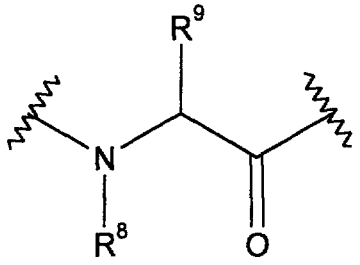
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thienyl, 3-thienyl, thiazolyl, 1H-indazol-3-yl, 1-methyl-1H-indazol-3-yl, benzo[b]fur-3-yl, benzo[b]thien-3-yl, pyridinyl, quinolinyl or isoquinolinyl group,

whilst the above-mentioned aromatic and heteroaromatic groups in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms, or by branched or unbranched alkyl groups, C_{4-7}-cycloalkyl groups, phenylalkyl groups, alkenyl, alkoxy, phenyl, phenylalkoxy, trifluoromethyl, alkoxycarbonylalkyl, carboxyalkyl, alkoxycarbonyl, carboxy, dialkylaminoalkyl, dialkylaminoalkoxy, hydroxy, nitro, amino, acetylamino, propionylamino, benzoyl, benzoylamino, benzoylmethylamino, methylsulphonyloxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkanoyl, cyano, tetrazolyl, phenyl, pyridinyl, thiazolyl, furyl, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl groups, and the substituents may be identical or different,

A denotes a bond or the divalent group of formula



(III),

(linked to the R^3R^4N- group of general formula (I) via the carbonyl group)

wherein

R^8 and R^9 together denote an n-propylene group or

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R^8 denotes a hydrogen atom or a C_{1-3}-alkyl group and

R^9 denotes a hydrogen atom or a branched or unbranched C_{1-4}-alkyl group which, if it is unbranched, may be substituted in the ω-position

by a hydroxy, mercapto, amino, alkylamino, dialkylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidinyl, hexahydro-1-azepinyl, methylthio, hydroxycarbonyl, aminocarbonyl, aminoiminomethylamino, aminocarbonylamino, phenyl, 1H-indol-3-yl, 1-methyl-1H-indol-3-yl, 1-formyl-1H-indol-3-yl, 4-imidazolyl, 1-methyl-4-imidazolyl, 1-naphthyl, 2-naphthyl- or pyridinyl group, whilst the above-mentioned heterocycles and phenyl groups may in turn be mono-, di- or trisubstituted in the carbon skeleton by fluorine, chlorine or bromine atoms, or by methyl, alkoxy, trifluoromethyl, hydroxy, amino, acetylamino, aminocarbonyl, cyano, trifluoromethoxy, methylsulphonyloxy, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl groups, whilst the substituents may be identical or different and any hydroxy, mercapto, amino, guanidino, indolyl and imidazolyl groups contained in the groups mentioned for R^9 may be substituted by a protecting group,

R^3 denotes a hydrogen atom,

a C_{1-4}-alkyl group which may be substituted in the ω-position by a cyclohexyl, phenyl, pyridinyl, diazinyl, hydroxy, amino, alkylamino, dialkylamino, carboxy, aminocarbonyl, aminocarbonylamino, acetylamino, 1-pyrrolidinyl, 1-piperidinyl,

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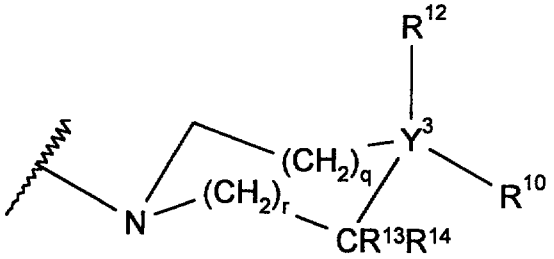
4-(1-piperidinyl)-1-piperidinyl, 4-morpholinyl, hexahydro-1H-azepin-1-yl, [bis-(2-hydroxyethyl)]amino, 4-methyl-1-piperazinyl- or 4-(ω-hydroxyalkyl)-1-piperazinyl group,

a phenyl or pyridinyl group,

wherein the above-mentioned heterocyclic radicals and phenyl groups may additionally be mono-, di- or trisubstituted in the carbon skeleton by fluorine, chlorine or bromine atoms or by methyl, alkoxy, trifluoromethyl, hydroxy, amino, acetylamino, aminocarbonyl, cyano, methylsulphonyloxy, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl groups and the substituents may be identical or different,

R^4 denotes a hydrogen atom or a methyl or ethyl group optionally substituted by a phenyl or pyridinyl group

or R^3 and R^4 together with the enclosed nitrogen atom denote a group of general formula



(IV),

wherein

Y^3 denotes a carbon atom or, if R^{12} denotes a free pair of electrons, Y^3 may also be the nitrogen atom,

r denotes the number 0, 1 or 2,

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q denotes the number 0, 1 or 2,

R^{10} denotes a hydrogen atom or an amino, alkylamino, dialkylamino, alkyl, cycloalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, aminoiminomethyl, aminocarbonylamino, alkylaminocarbonylamino, cycloalkylaminocarbonylamino, phenylaminocarbonylamino, aminocarbonylalkyl, aminocarbonylaminoalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, carboxyalkyl or carboxy group,

a phenyl, pyridinyl, diazinyl, 1-naphthyl, 2-naphthyl, pyridinylcarbonyl or phenylcarbonyl group which may be mono-, di- or trisubstituted in the carbon skeleton by fluorine, chlorine or bromine atoms, or by alkyl, alkoxy, methylsulphonyloxy, trifluoromethyl, hydroxy, amino, acetylamino, aminocarbonyl, aminocarbonylamino, aminocarbonylaminomethyl, cyano, carboxy, carbalkoxy, carboxyalkyl, carbalkoxyalkyl, alkanoyl, ω-(dialkylamino)alkanoyl, ω-(dialkylamino)alkyl, ω-(dialkylamino)hydroxyalkyl, ω-(carboxy)alkanoyl, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl groups, whilst the substituents may be identical or different,

a 1,3-dihydro-2-oxo-2H-imidazolyl, 2,4(1H,3H)-dioxopyrimidinyl or 3,4-dihydro-2(1H)-oxopyrimidinyl group bound via a nitrogen atom, which may be substituted by a phenyl group or fused at the double bond to a benzene, pyridine or diazine ring,

a 1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl group,

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a 4- to 10-membered azacycloalkyl group, a 5- to 10-membered oxaza, thiaza or diazacycloalkyl group or a 6- to 10-membered azabicycloalkyl group,

wherein the above-mentioned mono- and bicyclic heterocycles may be bound via a nitrogen or carbon atom and

may be substituted by a C_{1-7}-alkyl group, by an alkanoyl, dialkylamino, phenylcarbonyl, pyridinylcarbonyl, carboxyalkanoyl, carboxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, alkylsulphonyl, cycloalkyl or cycloalkylalkyl group, by a cycloalkylcarbonyl, aza-cycloalkylcarbonyl, diazacycloalkylcarbonyl or oxazacycloalkylcarbonyl group optionally alkyl substituted in the ring,

whilst the alicyclic parts contained in these substituents may comprise 3 to 10 ring members and the heteroalicyclic parts may comprise 4 to 10 ring members and

the above-mentioned phenyl and pyridinyl groups may in turn be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms, by alkyl, alkoxy, methylsulphonyloxy, trifluoromethyl, hydroxy, amino, acetylamino, aminocarbonyl, aminocarbonylamino, aminocarbonylaminomethyl, cyano, carboxy, carbalkoxy, carboxyalkyl, carbalkoxyalkyl, alkanoyl, ω-(dialkylamino)alkanoyl, ω-(carboxy)alkanoyl, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl groups, whilst the

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substituents may be identical or different, or

R^{10} together with R^{12} and Y^3 denotes a 4- to 7-membered cycloaliphatic ring in which a methylene group may be replaced by an -NH- or -N(alkyl)- group,

whilst a hydrogen atom bound to a nitrogen atom within the group R^{10} may be replaced by a protecting group,

R^{12} denotes a hydrogen atom, a C_{1-2}-alkyl group which may be substituted in the ω-position by a phenyl, pyridinyl, diazinyl, amino, alkylamino, dialkylamino, 1-pyrrolidinyl, 1-piperidinyl, 4-methyl-1-piperazinyl, 4-morpholinyl or hexahydro-1H-azepin-1-yl- group,

an alkoxycarbonyl, cyano- or aminocarbonyl group or a free pair of electrons, if Y^3 denotes a nitrogen atom, and

R^{13} and R^{14} in each case denote a hydrogen atom or,

if Y^3 is a carbon atom, R^{12} together with R^{14} also denotes another carbon-carbon bond, wherein R^{10} is as hereinbefore defined and R^{13} denotes a hydrogen atom or

if Y^3 is a carbon atom, R^{12} together with R^{14} also denotes another carbon-carbon bond and R^{10} together with R^{13} and the enclosed double bond denotes a partially hydrogenated or aromatic 5- to 7-membered mono- or bicyclic carbocycle or heterocycle,

whilst all the above-mentioned alkyl and alkoxy groups and the alkyl groups present within the other groups mentioned

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may contain 1 to 4 carbon atoms, unless otherwise specified,

all the above-mentioned cycloalkyl groups and the cycloalkyl groups present within the other groups named may contain 5 to 7 carbon atoms, unless otherwise specified,

their tautomers, their diastereomers, their enantiomers and their salts.

4. Modified amino acids of general formula I according to at least one of claims 1 or 2, wherein

R denotes an unbranched C_{1-3}-alkyl group which may be substituted in the ω-position

by a C_{5-7}-cycloalkyl group,

by one or two phenyl groups, by a 1-naphthyl, 2-naphthyl or (4-biphenylyl) group,

by a 1,3-dihydro-2H-2-oxobenzimidazol-1-yl, 1,3-dihydro-2H-2-oxoimidazol-1-yl or 3,4-dihydro-2(1H)-oxopyrimidin-3-yl group, whilst the latter two groups may be substituted in the carbon skeleton by a phenyl, pyridinyl or diazinyl group,

by a 5-membered heteroaromatic ring linked via a carbon atom and containing a nitrogen, oxygen or sulphur atom or two nitrogen atoms, wherein a nitrogen of an imino group may be substituted by an alkyl group,

or may be substituted by a pyridinyl group,

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whilst a 1,4-butadienylene group may be attached both to the 5-membered heteroaromatic monocyclic rings and to the pyridinyl group, in each case via two adjacent carbon atoms, and the bicyclic heteroaromatic rings thus formed may also be bound via a carbon atom of the 1,4-butadienylene group,

or an unbranched C_{1-4}-alkylamino group optionally substituted at the nitrogen atom by a methyl or ethyl group, and which may be substituted in the ω-position

by a C_{5-7}-cycloalkyl group,

by one or two phenyl groups, by a 1-naphthyl, 2-naphthyl or (4-biphenylyl) group,

by a 1H-indol-3-yl, 1,3-dihydro-2H-2-oxobenzimidazol-1-yl, 2(1H)-oxoquinolin-3-yl, 1,3-dihydro-4-phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-5-phenyl-2H-2-oxoimidazol-1-yl, 3,4-dihydro-5-phenyl-2(1H)-oxopyrimidin-3-yl, 3,4-dihydro-6-phenyl-2(1H)-oxopyrimidin-3-yl or 1,3-dihydro-2H-2-oxoimidazo-[4,5-b]pyridin-3-yl group,

by a 5-membered heteroaromatic ring linked via a carbon atom and containing a nitrogen, oxygen or sulphur atom or two nitrogen atoms, whilst a nitrogen atom of an imino group may be substituted by an alkyl group,

or by a pyridinyl group,

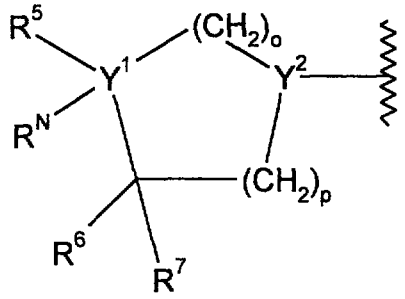
whilst a 1,4-butadienylene group may be attached both to the 5-membered heteroaromatic monocyclic rings and to the pyridinyl group, in each case via two adjacent carbon atoms, and the bicyclic

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heteroaromatic rings thus formed may also be bound via a carbon atom of the 1,4-butadienylene group,

whilst the phenyl, naphthyl and biphenylyl groups mentioned hereinbefore for the substitution of the alkyl and alkylamino groups in the ω-position as well as optionally partially hydrogenated mono- and bicyclic heteroaromatic rings may additionally be mono- or disubstituted in the carbon skeleton by fluorine, chlorine or bromine atoms or by alkyl, nitro, alkoxy, trifluoromethyl, hydroxy, amino, acetylamino, propionylamino, alkanoyl, cyano or trifluoromethoxy groups, whilst the substituents may be the same or different,

or the group of formula



(II),

wherein

p denotes the number 1 or 2,

o denotes the number 2 or, if Y^1 and Y^2 are not simultaneously nitrogen atoms, it may also denote the number 1,

Y^1 denotes the nitrogen atom if R^5 denotes a free pair of electrons, or the carbon atom,

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Y^2 denotes the nitrogen atom or the group >CH,

R^5 denotes a free pair of electrons if Y^1 denotes the nitrogen atom or, if Y^1 denotes the carbon atom, R^5 denotes a hydrogen atom, a C_{1-3}-alkyl group, a hydroxy, cyano, aminocarbonyl, carboxy, alkoxycarbonyl or aminocarbonylamino group or a phenylmethyl or phenyl group optionally substituted at the aromatic moiety by a fluorine, chlorine or bromine atom or by a methyl, methoxy, ethoxy, trifluoromethyl, hydroxy, amino or acetylamino group,

R^6 denotes the hydrogen atom or, if Y^1 is not a nitrogen atom, R^6 together with R^5 may also denote an additional bond,

R^7 denotes the hydrogen atom or, provided that Y^1 is not a nitrogen atom and R^5 and R^6 together denote an additional bond, R^7 together with R^N may also denote the 1,4-butadienylene group,

R^N denotes the hydrogen atom or a C_{1-3}-alkyl group, which may be monosubstituted in the ω-position

by a C_{5-7}-cycloalkyl group or by a 1-naphthyl, 2-naphthyl, hydroxy, alkoxy, amino, alkylamino, dialkylamino, piperidinyl, morpholinyl, pyrrolidinyl, hexahydro-1H-1-azepinyl, aminocarbonyl, methylaminocarbonyl, acetylamino, cyano, aminocarbonylamino or alkyl-aminocarbonylamino group, or may be mono- or disubstituted by phenyl, pyridinyl or diazinyl groups, whilst these substituents may be identical or different,

a cyclohexyl, phenyl, pyridinyl, cyano, amino, benzoylamino, aminocarbonyl, alkylaminocarbonyl,

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alkoxycarbonyl, phenylalkoxycarbonyl, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, N-(aminocarbonyl)-N-alkylamino, N-(alkylaminocarbonyl)-N-alkylamino, N-(alkylaminocarbonyl)-N-phenylamino, phenylaminocarbonylamino, [N-phenyl(alkylamino)]carbonylamino, N-(phenylaminocarbonyl)-N-alkylamino, N-(phenylaminocarbonyl)-N-phenylamino, benzoylaminocarbonylamino, phenylalkylaminocarbonylamino, pyridinylaminocarbonylamino, N-(aminocarbonyl)-N-phenylamino, N-(alkylaminocarbonyl)-N-phenylamino, N-(aminocarbonylaminocarbonyl)-N-phenylamino, N-(pyridinyl)-N-(aminocarbonyl)amino, N-(pyridinyl)-N-(alkylaminocarbonyl)amino, phenylamino, pyridinylamino, diazinylamino or 4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl group,

a saturated, mono- or diunsaturated 5- to 7-membered aza, diaza, triaza, oxaza, thiaza, thiadiaza or S,S-dioxido-thiadiaza heterocycle,

whilst the above-mentioned heterocycles may be linked via a carbon or nitrogen atom and

may contain one or two carbonyl groups adjacent to a nitrogen atom,

may be substituted at one of the nitrogen atoms by an alkyl, alkanoyl, hydroxycarbonylalkyl, alkoxycarbonylalkyl, phenylalkoxycarbonylalkyl, phenylmethyl or phenyl group,

may be substituted at one or two carbon atoms by a methyl, phenyl, phenylmethyl, naphthyl, biphenylyl, thienyl, pyridinyl or diazinyl group,

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wherein the substituents may be identical or different,

and wherein a C_{3-4}-alkylene group may additionally be attached to the above-mentioned heterocycles via two adjacent carbon atoms or an olefinic double bond of one of the above-mentioned heterocycles may be fused to a thiophene, benzene, pyridine, quinoline or diazine ring,

or, if Y^1 is not a nitrogen atom and R^5 and R^6 together denote an additional bond, R^N together with R^7 may also denote a 1,4-butadienylene group or,

if Y^1 denotes a carbon atom, R^N together with R^5 with the inclusion of Y^1 may also denote a carbonyl group or a saturated or monounsaturated 5- or 6-membered 1,3-diaza-heterocycle which may contain one or two carbonyl groups in the ring adjacent to a nitrogen atom and, if it is unsaturated, may also be benzo-fused at the double bond and may be substituted at one of the nitrogen atoms by a methyl, aminocarbonyl, hydroxycarbonylalkyl, alkoxycarbonylalkyl, phenylalkoxycarbonylalkyl, phenylmethyl or phenyl group,

whilst the phenyl, pyridinyl or diazinyl groups contained in the groups mentioned under R^N and the thieno, benzo, pyrido- or diazino-fused heterocycles in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms, by methyl groups, nitro, methoxy, ethoxy, methylsulphonylamino, trifluoromethyl, alkoxycarbonyl, alkoxycarbonylalkyl, carboxy, carboxyalkyl, hydroxy, amino, acetylamino, propionylamino, aminocarbonyl,

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methylaminocarbonyl, dimethylaminocarbonyl, hydroxyalkylaminocarbonyl, (4-morpholinyl)-carbonyl, (1-pyrrolidinyl)carbonyl, (1-piperidinyl)carbonyl, (hexahydro-1-azepinyl)carbonyl, (4-methyl-1-piperazinyl)carbonyl, methylenedioxy, aminocarbonylamino, aminocarbonylaminoalkyl, methylaminocarbonylamino, acetyl, cyano or trifluoromethoxy groups, whilst the substituents may be identical or different,

and the alkyl groups contained in the above-mentioned residues may contain 1 to 3 carbon atoms, unless otherwise specified,

X denotes an oxygen atom or 2 hydrogen atoms,

Z denotes a methylene group or the group $-NR^1-$ wherein

R^1 is a hydrogen atom or a methyl group,

R^{11} denotes the hydrogen atom or a methyl or methoxycarbonyl group,

n denotes the number 1 or 2 or, if m is the number 1, n may also denote 0,

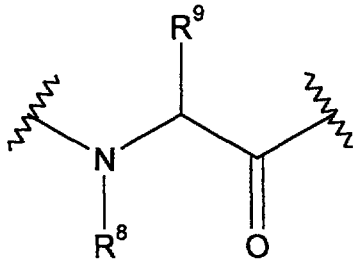
m denotes the number 0 or 1,

R^2 denotes a phenyl, 1-naphthyl, 2-naphthyl, 1,2,3,4-tetrahydro-1-naphthyl, 1H-indol-3-yl, 1-methyl-1H-indol-3-yl, 1-formyl-1H-indol-3-yl, 1-(1,1-dimethylethoxycarbonyl)-1H-indol-3-yl, 4-imidazolyl, 1-methyl-4-imidazolyl, 2-thienyl, 3-thienyl, thiazolyl, pyridinyl or quinolinyl group,

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wherein the above-mentioned aromatic and heteroaromatic groups may additionally be mono-, di- or trisubstituted in the carbon skeleton by fluorine, chlorine or bromine atoms, by branched or unbranched C_{1-5} alkyl groups, allyl, vinyl, methoxy, ethoxy, propoxy, 1-methylethoxy, dimethylaminoethoxy, trifluoromethyl, hydroxy, nitro, amino, acetylamino, propionylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, acetyl, cyano, methylsulphonyloxy or trifluoromethoxy groups, by tetrazolyl, phenyl pyridinyl, thiazolyl or furyl groups and the substituents may be identical or different, or

A denotes a bond or the divalent group of formula



(III),

(linked to the NR^3R^4- group of general formula (I) via the carbonyl group)

wherein

R^8 and R^9 together denote an n-propylene group or

R^8 denotes the hydrogen atom or the methyl group and

R^9 denotes a hydrogen atom or an unbranched C_{1-4}-alkyl group which may be substituted in the ω-position

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by a hydroxy, amino, methylamino, dimethylamino, hydroxycarbonyl, aminocarbonyl, aminoimino-methylamino, aminocarbonylamino, phenyl or pyridinyl group, wherein the phenyl and pyridinyl group may in turn be substituted in the carbon skeleton by a fluorine, chlorine or bromine atom or by a methyl, methoxy, trifluoromethyl, hydroxy, amino, acetylamino, aminocarbonyl or cyano group and wherein any hydroxy, amino and guanidino groups contained in the groups given for R^9 may be substituted by a protecting group, e.g. the phenylmethoxycarbonyl or tert. butyloxy-carbonyl group,

R^3 denotes a hydrogen atom,

a C_{1-4}-alkyl group optionally substituted in the ω-position by a cyclohexyl, phenyl, pyridinyl, hydroxy, amino, methylamino, dimethylamino, carboxy, aminocarbonyl, aminocarbonylamino, acetylamino, 1-pyrrolidinyl, 1-piperidinyl or 4-(1-piperidinyl)-1-piperidinyl group,

a phenyl or pyridinyl group,

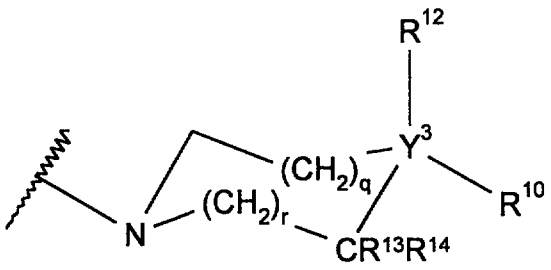
whilst the above-mentioned phenyl and pyridinyl groups may additionally be substituted in the carbon skeleton by a fluorine, chlorine or bromine atom or by a methyl, methoxy, trifluoromethyl, hydroxy, amino, acetylamino, aminocarbonyl or cyano group,

R^4 denotes the hydrogen atom or a C_{1-2}-alkyl group optionally substituted by a phenyl or pyridinyl group

or R^3 and R^4 together with the enclosed nitrogen atom denote a group of general formula

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(IV),

wherein

Y^3 denotes a carbon atom or, if R^{12} denotes a free pair of electrons, Y^3 may also be a nitrogen atom,

r denotes the number 0, 1 or 2,

q denotes the number 0, 1 or 2,

with the proviso that the sum of the numbers given for r and q is 0, 1, 2 or 3,

R^{10} denotes a hydrogen atom, an alkyl, cycloalkyl, dialkylamino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, phenylaminocarbonylamino, alkoxycarbonyl, alkoxycarbonylmethyl, carboxymethyl or carboxy group,

a phenyl, pyridinyl, diazinyl, pyridinylcarbonyl or phenylcarbonyl group which may be mono- or disubstituted in the carbon skeleton by fluorine, chlorine or bromine atoms, or by methyl, ethyl, propyl, methoxy, hydroxy, ω-(dialkylamino)-alkyl, ω-(dialkylamino)hydroxyalkyl or alkanoyl groups, whilst the substituents may be identical or different,

a 1,3-dihydro-2-oxo-2H-imidazolyl, 2,4(1H,3H)-dioxopyrimidinyl or 3,4-dihydro-2(1H)-oxopyrimidinyl group bound via a nitrogen atom, which may be substituted by a phenyl group or may be fused at the double bond to a benzene, pyridine or diazine ring,

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a 5- to 7-membered azacycloalkyl group, a 4- to 7-membered oxaza- or diazacycloalkyl group or a 7- to 9-membered azabicycloalkyl group,

wherein the above-mentioned mono- and bicyclic heterocycles are bound via a nitrogen or a carbon atom and

may be substituted by a C_{1-7}-alkyl group, or by an alkanoyl, dialkylamino, phenylcarbonyl, carboxyalkanoyl, carboxyalkyl, alkoxycarbonyl-alkyl or alkoxycarbonyl group having 1 to 4 carbon atoms in the alkoxy moiety, alkylsulphonyl, cycloalkyl or cycloalkylalkyl group or by an azacycloalkylcarbonyl or diazacycloalkylcarbonyl group optionally alkyl-substituted in the ring,

whilst the alicyclic groups contained in these substituents may comprise 3 to 7 ring members and the heteroalicyclic groups may comprise 4 to 7 ring members and

the above-mentioned phenylcarbonyl group may be substituted by a fluorine, chlorine or bromine atom or by a methyl, methoxy, trifluoromethyl, hydroxy, amino or acetylamino group, or

R^{10} together with R^{12} and Y^3 denotes a 4- to 6-membered cycloaliphatic ring in which a methylene group may be replaced by an -NH- or $-N(CH_3)-$ group,

whilst a hydrogen atom bound to a nitrogen atom within the group R^{10} may be replaced by a

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protecting group, e.g. the phenylmethoxycarbonyl or tert. butyloxycarbonyl group,

R^{12} denotes a hydrogen atom, a C_{1-2}-alkyl group which may be substituted in the ω-position by a phenyl, pyridinyl, amino, alkylamino, dialkylamino, 1-pyrrolidinyl, 1-piperidinyl or 4-methyl-1-piperazinyl group,

a methoxycarbonyl or ethoxycarbonyl, cyano or aminocarbonyl group or a free pair of electrons, if Y^3 denotes a nitrogen atom, and

R^{13} and R^{14} each denote a hydrogen atom or,

if Y^3 is a carbon atom, R^{12} together with R^{14} also denotes another carbon-carbon bond, wherein R^{10} is as hereinbefore defined and R^{13} denotes a hydrogen atom, or

if Y^3 is a carbon atom, R^{12} together with R^{14} also denotes another carbon-carbon bond and R^{10} together with R^{13} and the enclosed double bond denotes a partially hydrogenated or aromatic 5- or 6-membered mono- or bicyclic carbocycle or heterocycle, containing one or two nitrogen atoms,

whilst all the above-mentioned alkyl and alkoxy groups and the alkyl groups present within the other groups named may contain 1 to 3 carbon atoms, unless otherwise stated, and

all the above-mentioned cycloalkyl groups and the cycloalkyl groups present within the other groups named may contain 5 to 7 carbon atoms, unless otherwise specified,

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their tautomers, their diastereomers, their enantiomers, mixtures thereof and the salts thereof.

5. Modified amino acids of general formula I according to at least one of claims 1 or 2, wherein

R denotes an unbranched C_{1-3}-alkyl group which may be substituted in the ω-position

by a C_{5-7}-cycloalkyl group,

by one or two phenyl groups, by a 1-naphthyl, 2-naphthyl or (4-biphenylyl) group, whilst the above-mentioned aromatic groups may additionally be substituted by a fluorine, chlorine or bromine atom or by a methyl, methoxy, amino or acetylamino group,

by a 2-pyrrolyl, 3-pyrrolyl, pyridinyl, 1H-indol-3-yl, quinolinyl or isoquinolinyl group,

or an unbranched C_{1-4}-alkylamino group which is optionally additionally substituted at the nitrogen atom by a methyl or ethyl group and which may be substituted in the ω-position

by a C_{5-7}-cycloalkyl group,

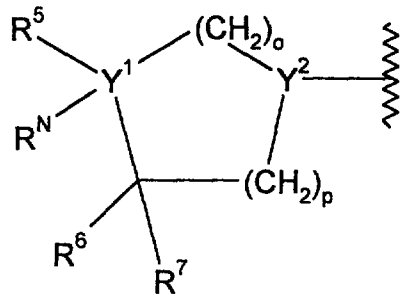
by a phenyl group which may be mono- or disubstituted by fluorine, chlorine or bromine atoms, or by methyl, nitro, methoxy, trifluoromethyl, hydroxy, amino or acetylamino groups, whilst the substituents may be identical or different,

by a 2-pyrrolyl, 3-pyrrolyl, pyridinyl, 1H-indol-3-yl, quinolinyl or isoquinolinyl group,

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or the group of formula



(II),

wherein

p denotes the number 1 or 2,

o denotes the number 2 or, if Y^1 and Y^2 are not simultaneously nitrogen atoms, it may also denote the number 1,

Y^1 denotes the nitrogen atom if R^5 denotes a free pair of electrons, or the carbon atom,

Y^2 denotes the nitrogen atom or the group >CH,

R^5 denotes a free pair of electrons, if Y^1 denotes the nitrogen atom or, if Y^1 denotes the carbon atom, R^5 may denote the hydrogen atom, a C_{1-2}-alkyl group or the cyano or phenyl group,

R^6 denotes the hydrogen atom or, provided that Y^1 is not a nitrogen atom, R^6 together with R^5 may also denote an additional bond,

R^7 denotes the hydrogen atom or, provided that Y^1 is not a nitrogen atom and R^5 and R^6 together denote an additional bond, R^7 together with R^N may also denote the 1,4-butadienylene group,

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R^N denotes the hydrogen atom or a C_{1-3}-alkyl group, which may be substituted in the ω-position

by one or two phenyl or pyridinyl groups, wherein the substituents may be identical or different, .

or by a hydroxy or methoxy group,

a phenyl group which may be mono- or disubstituted by fluorine, chlorine or bromine atoms or by methyl groups, nitro, methoxy, ethoxy, trifluoromethyl, hydroxy or cyano groups, whilst the substituents may be identical or different, or a phenyl group substituted by a methylenedioxy group,

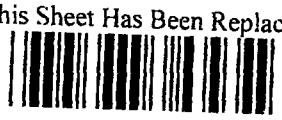
a 2-pyridinyl or 4-pyridinyl group,

an amino, benzoylamino, aminocarbonyl, methylaminocarbonyl, methoxycarbonyl, ethoxycarbonyl, aminocarbonylamino, methylaminocarbonylamino, N-(aminocarbonyl)-N-methylamino, N-(methylaminocarbonyl)-N-methylamino, N-(aminocarbonyl)-N-(4-fluorophenyl)amino, N-(methylaminocarbonyl)-N-phenylamino, phenylaminocarbonylamino, [N-phenyl(methylamino)]-carbonylamino, N-(phenylaminocarbonyl)-N-methylamino, N-(phenylaminocarbonyl)-N-phenylamino, benzoylaminocarbonylamino, N-(aminocarbonyl)-N-phenylamino group or a phenylamino group optionally substituted in the phenyl ring by an aminocarbonyl-amino or methylsulphonylamino group,

a 1,3-dihydro-4-phenyl-2H-2-oxoimidazol-1-yl, a 1,3-dihydro-4-(3-thienyl)-2H-2-oxoimidazol-1-yl, 1,3-dihydro-5-phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-2(2H)-oxobenzimidazol-1-yl, 1,3,3a,4,5,6,7,7a-octahydro-2(2H)-oxo-

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benzimidazol-1-yl, 1H-indol-3-yl, 2,4(1H,3H)-dioxoquinazolin-3-yl, 1,3-dihydro-2(2H)-oxoimidazo[4,5-b]pyridin-3-yl, 1,3(2H)-dioxo-1H-isoindol-2-yl, 1H-benzimidazol-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-3-yl, 3,4-dihydro-2(1H)-oxoquinazolin-1-yl, 2(3H)-oxobenzoxazol-3-yl, 1,3-dihydro-2(2H)-oxoimidazo[4,5-d]pyrimidin-3-yl, 2,3,4,5-tetrahydro-2(1H)-oxo-1,3-benzodiazepin-3-yl, 3,4-dihydro-2(1H)-oxopyrido[2,3-d]pyrimidin-3-yl, 2(1H)-oxoquinolin-3-yl, 3,4-dihydro-2(1H)-oxoquinolin-3-yl, 2(1H)-oxoquinoxalin-3-yl, 3,4,4a,5,6,7,8,8a-octahydro-2(1H)-oxoquinazolin-3-yl, 1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl, 2,4(1H,3H)-dioxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl, 2,4-dihydro-5-phenyl-3(3H)-oxo-1,2,4-triazol-2-yl, 1,3-dihydro-5-methyl-4-phenyl-2(2H)-oxoimidazol-1-yl, 2,5-dioxo-4-phenylimidazolidin-1-yl, 2,5-dioxo-4-(phenylmethyl)-imidazolidin-1-yl, 3,4-dihydro-2,2-dioxido-2,1,3-benzothiadiazin-3-yl, 1,3-dihydro-4-(4-biphenylyl)-2(2H)-oxoimidazol-1-yl, 1,3-dihydro-4-(2-naphthyl)-2(2H)-oxoimidazol-1-yl, 1,3-dihydro-4,5-diphenyl-2(2H)-oxoimidazol-1-yl, 1,3-dihydro-2(2H)-oxoimidazo[4,5-c]quinolin-3-yl, 4-phenyl-2(1H)-oxopyrimidin-1-yl, 4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl, 3,4-dihydro-2(1H)-oxopyrido[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2[1H]-oxopyrido[4,3-d]pyrimidin-3-yl or 2,3-dihydro-4(1H)-oxoquinazolin-3-yl group,

wherein the above-mentioned mono- and bicyclic heterocycles may be substituted at one of the nitrogen atoms by a methoxycarbonylmethyl group and/or



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the above-mentioned mono- and bicyclic heterocycles may be mono-, di- or trisubstituted in the carbon skeleton and/or at the phenyl groups contained in these groups by fluorine, chlorine or bromine atoms, or by methyl, trifluoromethyl, methoxy, hydroxy, amino, nitro, phenyl, phenylmethyl, carboxy, methoxycarbonyl, ethoxycarbonyl, aminocarbonyl, methylaminocarbonyl, hydroxyethylaminocarbonyl, (4-morpholinyl)carbonyl, (1-piperidinyl)carbonyl or (4-methyl-1-piperazinyl)carbonyl groups wherein the substituents may be identical or different and multiple substitution with the last three substituents is ruled out,

or, provided that Y^1 is not a nitrogen atom and R^5 and R^6 together denote an additional bond, R^N together with R^7 also denotes the 1,4-butadienylene group,

or, provided that Y^1 denotes a carbon atom, R^N together with R^5 with the inclusion of Y^1 may also denote a carbonyl group or a saturated or monounsaturated five- or six-membered 1,3-diaza-heterocycle,

which may contain a carbonyl group in the ring, adjacent to a nitrogen atom,

may be substituted by a phenyl group at one of the nitrogen atoms

and, if it is unsaturated, may also be benzo-condensed at the double bond,

X denotes an oxygen atom or 2 hydrogen atoms,

Z denotes a methylene group or the group $-NR^1$, wherein

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R^1 denotes a hydrogen atom or a methyl group,

R^{11} denotes a hydrogen atom, a methoxycarbonyl, ethoxycarbonyl or methyl group,

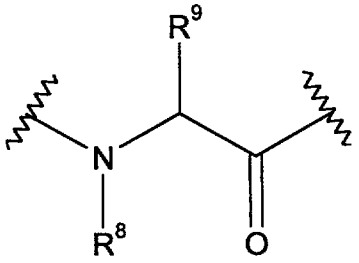
n denotes the number 1 and m denotes the number 0 or

n denotes the number 0 and m denotes the number 1,

R^2 denotes a phenyl, 1-naphthyl, 2-naphthyl, 1,2,3,4-tetrahydro-1-naphthyl, 1H-indol-3-yl, 1-methyl-1H-indol-3-yl, 1-(1,1-dimethylethoxycarbonyl)-1H-indol-3-yl, 2-thienyl, 3-thienyl, thiazolyl or alkylthiazolyl group having 1 to 3 carbon atoms in the alkyl moiety, a pyridinyl or quinolinyl group,

wherein the above-mentioned phenyl and naphthyl groups may be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms or by branched or unbranched C_{1-5}-alkyl groups, by C_{1-3}-alkoxy groups, by vinyl, allyl, trifluoromethyl, methylsulphonyloxy, 2-(dimethylamino)ethoxy, hydroxy, cyano, nitro or amino groups, by tetrazolyl, phenyl, pyridinyl, thiazolyl or furyl groups and the substituents may be identical or different, and multiple substitution with the last five substituents is ruled out,

A denotes a bond or the divalent group of formula



(III),

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(linked to the group $-NR^3R^4$ of formula (I) via the carbonyl group)

wherein

R^8 and R^9 together denote an n-propylene group or

R^8 denotes the hydrogen atom or the methyl group and

R^9 denotes the hydrogen atom or an unbranched C_{1-4}-alkyl group,

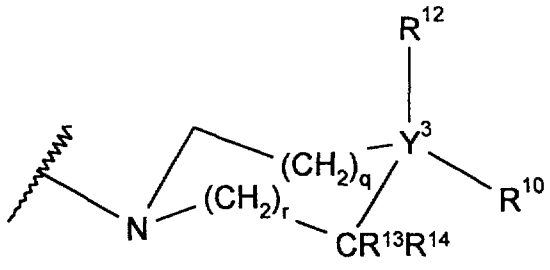
which may be substituted in the ω-position by an amino, methylamino, dimethylamino, aminoiminomethylamino or aminocarbonylamino group, whilst in the above-mentioned substituents a hydrogen atom bound to a nitrogen atom may be replaced by a protecting group, e.g. the phenylmethoxycarbonyl or tert. butyloxycarbonyl group,

R^3 denotes a hydrogen atom or

a C_{1-4}-alkyl group optionally substituted in the ω-position by an amino, methylamino, dimethylamino- or 4-(1-piperidinyl)-1-piperidinyl group,

R^4 denotes a hydrogen atom or a methyl or ethyl group

or R^3 and R^4 together with the enclosed nitrogen atom denote a group of general formula



(IV),

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wherein

Y^3 denotes the carbon atom or, if R^{12} denotes a free pair of electrons, Y^3 may also denote a nitrogen atom,

r denotes the number 1,

q denotes the number 1,

R^{10} denotes the hydrogen atom, an alkyl, dialkylamino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, phenylaminocarbonylamino, alkoxycarbonyl, alkoxycarbonylmethyl, carboxymethyl or carboxy group or a cycloalkyl group having 4 to 7 carbon atoms in the ring,

a benzoyl, pyridinylcarbonyl, phenyl, pyridinyl or diazinyl group, each of which may be substituted in the carbon skeleton by a fluorine, chlorine or bromine atom, or by an acetyl, methyl, ethyl or methoxy group, or by a dimethylaminoalkyl group having 1 to 4 carbon atoms in the alkyl moiety optionally hydroxysubstituted in the alkyl moiety,

a 1,3-dihydro-2-oxo-2H-imidazolyl group bound via a nitrogen atom, which may be fused to a benzene or pyridine ring at the double bond,

a 1-pyrrolidinyl, 1-piperidinyl, 4-(dimethylamino)-1-piperidinyl, 4-piperidinyl or 4-morpholinyl group, wherein the nitrogen atom of the 4-piperidinyl group may be substituted by an alkanoyl- or alkyl group each having 1 to 7 carbon atoms or by a benzoyl, methylsulphonyl, 3-carboxypropionyl, cyclopropylmethyl, alkoxycarbonylmethyl or

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carboxymethyl group or by a protecting group, e.g. the phenylmethoxycarbonyl or tert. butyloxycarbonyl group, or it may represent a hexahydro-1H-1-azepinyl, 8-methyl-8-azabicyclo[3,2,1]oct-3-yl, 4-alkyl-1-piperazinyl, hexahydro-4-alkyl-1H-1,4-diazepin-1-yl, 1-alkyl-4-piperidinylcarbonyl or 4-alkyl-1-piperazinylcarbonyl group,

or

R^{10} together with R^{12} and Y^3 denotes a 5-membered cycloaliphatic ring in which a methylene group may be replaced by an -NH- or -N(CH3)- group,

R^{12} denotes a hydrogen atom, a C_{1-2}-alkyl group which may be substituted in the ω-position by a 1-pyrrolidinyl, 1-piperidinyl or 4-methyl-1-piperazinyl group,

a methoxycarbonyl or ethoxycarbonyl or a cyano group,

a free pair of electrons if Y^3 denotes a nitrogen atom, and

R^{13} and R^{14} each denote a hydrogen atom or,

provided that Y^3 is a carbon atom, R^{12} together with R^{14} may also denote an additional carbon-carbon bond, wherein R^{10} is as hereinbefore defined and R^{13} denotes a hydrogen atom or,

provided that Y^3 is a carbon atom, R^{12} together with R^{14} may also denote an additional carbon-carbon bond and R^{10} together with R^{13} and the enclosed double bond denotes an indole group fused on via the 5-membered ring,

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whilst all the above-mentioned alkyl groups and the alkyl groups present within the other named groups may contain 1 to 3 carbon atoms, unless otherwise specified,

their tautomers, their diastereomers, their enantiomers and their salts.

6. Modified amino acids of general formula I according to claims 1 to 5, characterised in that these are described in Examples 1 to 29.

7. Physiologically acceptable salts of the compounds according to at least one of claims 1 to 6 with inorganic or organic acids or bases.

8. Pharmaceutical compositions containing a compound according to at least one of claims 1 to 6 or a physiologically acceptable salt according to claim 7 optionally together with one or more inert carriers and/or diluents.

9. Use of a compound according to at least one of claims 1 to 7 for the preparation of a pharmaceutical composition which is suitable for the acute and prophylactic treatment of headaches, for treating non-insulin dependent diabetes melitis, cardiovascular disorders, skin diseases, inflammatory diseases, allergic rhinitis, asthma, diseases accompanied by excessive vasodilatation and consequently reduced blood circulation, e.g. shock and sepsis, and morphine tolerance.

10. Process for preparing a pharmaceutical composition according to claim 8, characterised in that a compound according to at least one of claims 1 to 7 is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

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11. Process for preparing the compounds of general formula I according to claims 1 to 7, characterised in that

a) In order to prepare compounds of general formula I, wherein

R denotes an unbranched C_{1-7}-alkyl group which may be substituted in the ω-position

by a C_{4-10}-cycloalkyl group,

by one or two phenyl groups, by a 1-naphthyl, 2-naphthyl or biphenylyl group,

by a 1,3-dihydro-2H-2-oxobenzimidazol-1-yl, 2,4(1H,3H)-dioxoquinazolin-1-yl, 2,4(1H,3H)-dioxoquinazolin-3-yl, 2,4(1H,3H)-dioxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-3-yl, 2(1H)-oxoquinolin-3-yl, 2(1H)-oxoquinoxalin-3-yl, 1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl, 1,3-dihydro-2H-2-oxoimidazopyridinyl, 1,3-dihydro-2(2H)-oxoimidazo[4,5-c]quinolin-3-yl, 1,3-dihydro-2H-2-oxoimidazol-1-yl- or 3,4-dihydro-2(1H)-oxopyrimidin-3-yl group, wherein the latter two groups may each be mono- or disubstituted in the 4- and/or 5-position or in the 5- and/or 6-position by lower straight chained or branched alkyl groups, by phenyl, biphenylyl, pyridinyl, diazinyl, furyl, thienyl, pyrrolyl, 1,3-oxazolyl, 1,3-thiazolyl, isoxazolyl, pyrazolyl-

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1-methylpyrazolyl, imidazolyl- or 1-methylimidazolyl-groups and the substituents may be identical or different,

by a 5-membered heteroaromatic ring linked via a carbon atom, which contains a nitrogen, oxygen or sulphur atom or, in addition to a nitrogen atom, contains an oxygen, sulphur or additional nitrogen atom, whilst a nitrogen atom of an imino group may be substituted by an alkyl group, and

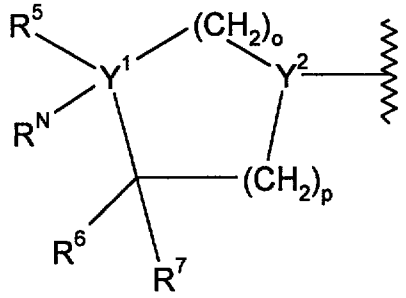
or by a 6-membered heteroaromatic ring linked via a carbon atom, which contains one, two or three nitrogen atoms,

whilst a 1,4-butadienylene group may be attached both to the above-mentioned 5-membered heteroaromatic monocyclic rings and to the 6-membered heteroaromatic monocyclic rings, in each case via two adjacent carbon atoms, and the bicyclic heteroaromatic rings thus formed may also be bound via a carbon atom of the 1,4-butadienylene group, and

whilst the phenyl, naphthyl and biphenylyl groups mentioned above for the substitution of the alkyl groups in the ω-position and optionally also partially hydrogenated mono- and bicyclic heteroaromatic rings in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms or by alkyl groups, C_{3-8}-cycloalkyl groups, nitro, alkoxy, phenyl, phenylalkoxy, trifluoromethyl, alkoxycarbonyl, alkoxycarbonylalkyl, carboxy, carboxyalkyl, dialkylaminoalkyl, hydroxy, amino, acetylamino, propionylamino, benzoyl, benzoylamino, benzoylmethylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, (1-pyrrolidinyl)carbonyl, (1-piperidinyl)carbonyl,

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(hexahydro-1H-azepin-1-yl)carbonyl, (4-methyl-1-piperazinyl)carbonyl, (4-morpholinyl)carbonyl, alkanoyl, cyano, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl- or trifluoromethylsulphonyl groups, wherein the substituents may be identical or different and the above-mentioned benzoyl, benzoylamino and benzoylmethylamino groups may in turn additionally be substituted in the phenyl moiety by a fluorine, chlorine or bromine atom or by an alkyl, trifluoromethyl, amino or acetylamino group,
or the group of formula



(II),

wherein
R^5, R^6, R^7, R^N, Y^1, o and p are as defined in claims 1 to 6,
Y^2 denotes a CH- group and
Z denotes an NR^1- group, wherein R^1 is as defined in claims 1 to 6:

a carboxylic acid of general formula VII,

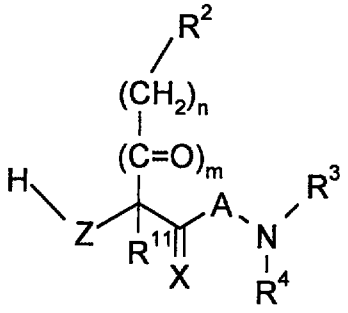
$$RCO_2H \qquad (VII)$$

wherein
R is as defined in claims 1 to 6,

is coupled with a compound of general formula VIII,

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(VIII)

wherein
R^2, R^3, R^4, R^{11}, A, X, m and n are defined as in claims 1 to 6, and

Z denotes an NR^1- group, wherein R^1 is defined as in claims 1 to 6,

and, if necessary, any protecting groups are subsequently cleaved from a compound thus obtained, or precursor functions are modified, or

b) In order to prepare compounds of general formula I wherein R is defined as in a), Z denotes the NR^1- group and R^1, R^2, R^3, R^4, R^{11}, A, X, m and n are defined as in claims 1 to 6:

a compound of general formula IX,

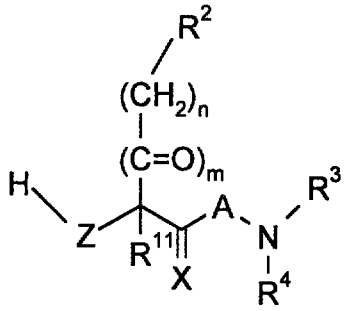
$$R - CO - Nu \qquad (IX)$$

wherein
R is defined as in a) and
Nu denotes a leaving group,

is coupled with a compound of general formula VIII,

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(VIII)

wherein

R^2, R^3, R^4, R^{11}, A, X, m and n are defined as in claims 1 to 6 and

Z denotes an NR^1- group, whilst R^1 is defined as in claims 1 to 6,

and, if necessary, protecting groups are subsequently cleaved from a compound thus obtained or precursor functions are modified or

c) in order to prepare compounds of general formula I wherein

R denotes an unbranched C_{1-6}-alkylamino group optionally substituted at the nitrogen atom by a C_{1-6}-alkyl group or by a phenylmethyl group, which may be substituted in the ω-position

by a C_{4-10}-cycloalkyl group,

by one or two phenyl groups, by a 1-naphthyl, 2-naphthyl- or biphenylyl group,

by a 1H-indol-3-yl, 1,3-dihydro-2H-2-oxobenzimidazol-1-yl, 2,4(1H,3H)-dioxoquinazolin-1-yl, 2,4(1H,3H)-dioxoquinazolin-3-yl,
2,4(1H,3H)-dioxothieno[3,4-d]pyrimidin-3-yl,
3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl,
3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-1-yl,

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3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-3-yl, 2(1H)-oxoquinolin-3-yl, 2(1H)-oxoquinoxalin-3-yl, 1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl, 1,3-dihydro-4-(3-thienyl)-2H-2-oxoimidazol-1-yl, 1,3-dihydro-4-phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-5-phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-2(2H)-oxoimidazo[4,5-c]quinolin-3-yl, 3,4-dihydro-5-phenyl-2(1H)-oxopyrimidin-3-yl, 3,4-dihydro-6-phenyl-2(1H)-oxopyrimidin-3-yl- or 1,3-dihydro-2H-2-oxoimidazo-[4,5-b]pyridin-3-yl- group,

by a 5-membered heteroaromatic ring linked via a carbon atom, which contains a nitrogen, oxygen or sulphur atom or, in addition to a nitrogen atom, contains an oxygen, sulphur or an additional nitrogen atom, whilst a nitrogen atom of an imino group may be substituted by an alkyl group, or

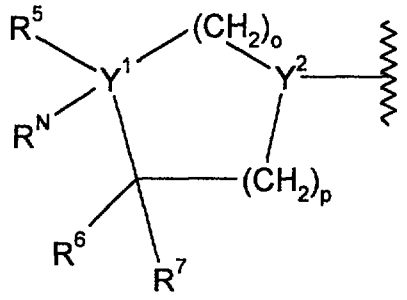
by a 6-membered heteroaromatic ring linked via a carbon atom and containing 1, 2 or 3 nitrogen atoms, whilst a 1,4-butadienylene group may be attached both to the 5-membered and to the 6-membered heteroaromatic monocyclic rings via two adjacent carbon atoms in each case and the bicyclic heteroaromatic rings thus formed may also be bound via a carbon atom of the 1,4-butadienylene group,

whilst the phenyl, naphthyl and biphenylyl groups mentioned above for the substitution of the alkyl moiety of the alkylamino groups in the ω-position and optionally partially hydrogenated mono- and bicyclic heteroaromatic rings in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms, by alkyl groups, C_{3-8}-cycloalkyl groups, nitro,

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alkoxy, phenyl, phenylalkoxy, trifluoromethyl, alkoxycarbonyl, alkoxycarbonylalkyl, carboxy, carboxyalkyl, dialkylaminoalkyl, hydroxy, amino, acetylamino, propionylamino, benzoyl, benzoylamino, benzoylmethylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, (1-pyrrolidinyl)carbonyl, (1-piperidinyl)carbonyl, (hexahydro-1H-azepin-1-yl)carbonyl, (4-methyl-1-piperazinyl)carbonyl, (4-morpholinyl)carbonyl, alkanoyl, cyano, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphynyl- or trifluoromethylsulphonyl groups, whilst the substituents may be identical or different and the above-mentioned benzoyl, benzoylamino- and benzoylmethylamino groups in turn may additionally be substituted in the phenyl moiety by a fluorine, chlorine or bromine atom or by an alkyl, trifluoromethyl, amino- or acetylamino group,

or the group of formula



(II),

wherein
R^5, R^6, R^7, R^N, Y^1, o and p are defined as in claims 1 to 6,
Y^2 denotes the N-atom and
Z denotes the NR^1- group, wherein R^1 is defined as in claims 1 to 6:

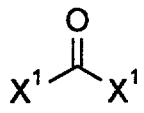
an amine of general formula X

R - H (X)

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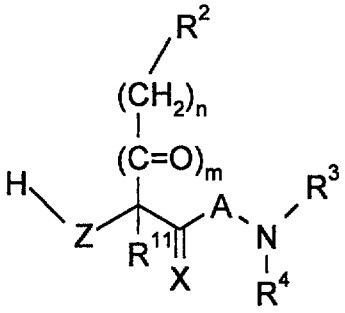
wherein
R is as hereinbefore defined, is reacted with a carbonic acid derivative of general XI



(XI)

wherein
X^1 is a nucleofugic group,

and with a compound of general formula VIII,



(VIII)

wherein
R^2, R^3, R^4, R^{11}, A, X, m and n are defined as in claims 1 to 6, and
Z denotes an NR^1- group, wherein R^1 is defined as in claims 1 to 6,

and, if necessary, protecting groups are subsequently cleaved from a compound thus obtained or precursor functions are modified, or

d) In order to prepare compounds of general formula I wherein the carbonyl group linked to the groups R and Z denotes a urea carbonyl group, in which the urea carbonyl is flanked by at least one NH- group, and wherein

R denotes an unbranched C_{1-6}-alkylamino group optionally additionally substituted at the nitrogen atom by a

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C_{1-6}-alkyl group or by a phenylmethyl group, which may be substituted in the ω-position

by a C_{4-10}-cycloalkyl group,

by one or two phenyl groups, by a 1-naphthyl, 2-naphthyl- or biphenylyl group,

by a 1H-indol-3-yl, 1,3-dihydro-2H-2-oxobenzimidazol-1-yl, 2,4(1H,3H)-dioxoquinazolin-1-yl, 2,4(1H,3H)-dioxoquinazolin-3-yl, 2,4(1H,3H)-dioxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-3-yl, 2(1H)-oxoquinolin-3-yl, 2(1H)-oxoquinoxalin-3-yl, 1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl, 1,3-dihydro-4-(3-thienyl)-2H-2-oxoimidazol-1-yl, 1,3-dihydro-4-phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-5-phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-2(2H)-oxoimidazo[4,5-c]quinolin-3-yl, 3,4-dihydro-5-phenyl-2(1H)-oxopyrimidin-3-yl, 3,4-dihydro-6-phenyl-2(1H)-oxopyrimidin-3-yl- or 1,3-dihydro-2H-2-oxoimidazo-[4,5-b]pyridin-3-yl- group,

by a 5-membered heteroaromatic ring linked via a carbon atom, which contains a nitrogen, oxygen or sulphur atom or, in addition to a nitrogen atom, contains an oxygen, sulphur or an additional nitrogen atom, whilst a nitrogen atom of an imino group may be substituted by an alkyl group, or

by a 6-membered heteroaromatic ring linked via a carbon atom and containing 1, 2 or 3 nitrogen atoms,

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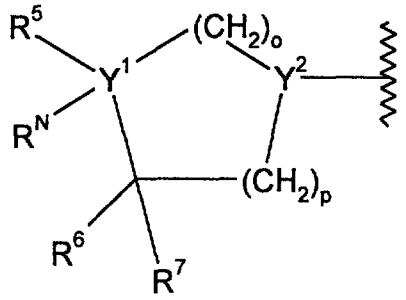
whilst a 1,4-butadienylene group may be attached both to the 5-membered and to the 6-membered heteroaromatic monocyclic rings via two adjacent carbon atoms in each case and the bicyclic heteroaromatic rings thus formed may also be bound via a carbon atom of the 1,4-butadienylene group,

whilst the phenyl, naphthyl and biphenylyl groups mentioned above for the substitution of the alkyl moiety of the alkylamino groups in the ω-position and optionally partially hydrogenated mono- and bicyclic heteroaromatic rings in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms, by alkyl groups, C_{3-8}-cycloalkyl groups, nitro, alkoxy, phenyl, phenylalkoxy, trifluoromethyl, alkoxycarbonyl, alkoxycarbonylalkyl, carboxy, carboxyalkyl, dialkylaminoalkyl, hydroxy, amino, acetylamino, propionylamino, benzoyl, benzoylamino, benzoylmethylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, (1-pyrrolidinyl)carbonyl, (1-piperidinyl)carbonyl, (hexahydro-1H-azepin-1-yl)carbonyl, (4-methyl-1-piperazinyl)carbonyl, (4-morpholinyl)carbonyl, alkanoyl, cyano, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphynyl- or trifluoromethylsulphonyl groups, whilst the substituents may be identical or different and the above-mentioned benzoyl, benzoylamino- and benzoylmethylamino groups in turn may additionally be substituted in the phenyl moiety by a fluorine, chlorine or bromine atom or by an alkyl, trifluoromethyl, amino- or acetylamino group,

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or the group of formula



(II),

wherein

R^5, R^6, R^7, R^N, Y^1, o and p are as defined in claims 1 to 6 and Y^2 denotes the N-atom,

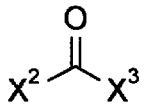
Z denotes the group NR^1 and

R^1 denotes a hydrogen atom or, provided that R denotes an unbranched alkylamino group unsubstituted at the nitrogen atom and optionally substituted in the ω-position, R^1 may also denote an alkyl or phenylalkyl group:

an amine of general formula X',

R - H (X')

wherein R is as hereinbefore defined,
is reacted with carbonic acid derivatives of general formula XI',



(XI')

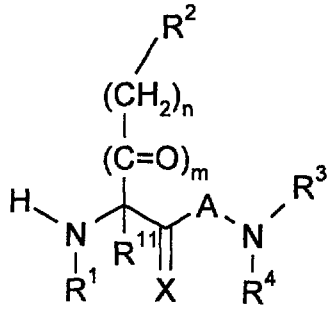
wherein

X^2 denotes a phenoxy group, if X^3 is the (1H)-1,2,3,4-tetrazol-1-yl- group, the 4-nitrophenoxy group, if X^3 is the 4-nitrophenoxy group, and the chlorine atom if X^3 is

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the 2,4,5-trichlorophenoxy group, and with a compound of general formula VIII',



(VIII')

wherein
R^2, R^3, R^4, R^{11}, X, A, m and n are defined as in claims 1 to 6, and

R^1 denotes a hydrogen atom or, provided that R is an unbranched alkylamino group unsubstituted at the nitrogen and optionally substituted in the ω-position, R^1 may also denote an alkyl or phenylalkyl group,

and, if necessary protecting groups are subsequently cleaved from a compound thus obtained or precursor functions are modified or

e) in order to prepare compounds of general formula I wherein Z denotes the group NH and

R denotes an unbranched C_{1-6}-alkylamino group optionally substituted at the nitrogen atom by a C_{1-6}-alkyl group or by a phenylmethyl group, which may be substituted in the ω-position

by a C_{4-10}-cycloalkyl group,

by one or two phenyl groups, by a 1-naphthyl, 2-naphthyl- or biphenylyl group,

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by a 1H-indol-3-yl, 1,3-dihydro-2H-2-oxobenzimidazol-1-yl, 2,4(1H,3H)-dioxoquinazolin-1-yl, 2,4(1H,3H)-dioxoquinazolin-3-yl, 2,4(1H,3H)-dioxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-3-yl, 2(1H)-oxoquinolin-3-yl, 2(1H)-oxoquinoxalin-3-yl, 1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl, 1,3-dihydro-4-(3-thienyl)-2H-2-oxoimidazol-1-yl, 1,3-dihydro-4-phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-5-phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-2(2H)-oxoimidazo[4,5-c]quinolin-3-yl, 3,4-dihydro-5-phenyl-2(1H)-oxopyrimidin-3-yl, 3,4-dihydro-6-phenyl-2(1H)-oxopyrimidin-3-yl or 1,3-dihydro-2H-2-oxoimidazo-[4,5-b]pyridin-3-yl group,

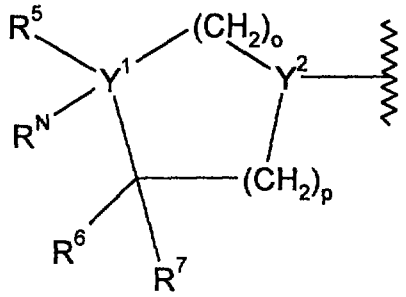
by a 5-membered heteroaromatic ring linked via a carbon atom, which contains a nitrogen, oxygen or sulphur atom or, in addition to a nitrogen atom, contains an oxygen, sulphur or an additional nitrogen atom, whilst a nitrogen atom of an imino group may be substituted by an alkyl group, or

by a 6-membered heteroaromatic ring linked via a carbon atom and containing 1, 2 or 3 nitrogen atoms, whilst a 1,4-butadienylene group may be attached both to the 5-membered and to the 6-membered heteroaromatic monocyclic rings via two adjacent carbon atoms in each case and the bicyclic heteroaromatic rings thus formed may also be bound via a carbon atom of the 1,4-butadienylene group,

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whilst the phenyl, naphthyl and biphenylyl groups mentioned above for the substitution of the alkyl groups in the ω-position and optionally partially hydrogenated mono- and bicyclic heteroaromatic rings in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms, by alkyl groups, C_{3-8}-cycloalkyl groups, nitro, alkoxy, phenyl, phenylalkoxy, trifluoromethyl, alkoxycarbonyl, alkoxycarbonylalkyl, carboxy, carboxyalkyl, dialkylaminoalkyl, hydroxy, amino, acetylamino, propionylamino, benzoyl, benzoylamino, benzoylmethylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, (1-pyrrolidinyl)carbonyl, (1-piperidinyl)carbonyl, (hexahydro-1H-azepin-1-yl)carbonyl, (4-methyl-1-piperazinyl)carbonyl, (4-morpholinyl)carbonyl, alkanoyl, cyano, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphynyl- or trifluoromethylsulphonyl groups, whilst the substituents may be identical or different and the above-mentioned benzoyl, benzoylamino- and benzoylmethylamino groups in turn may additionally be substituted in the phenyl moiety by a fluorine, chlorine or bromine atom or by an alkyl, trifluoromethyl, amino or acetylamino group,

or the group of formula



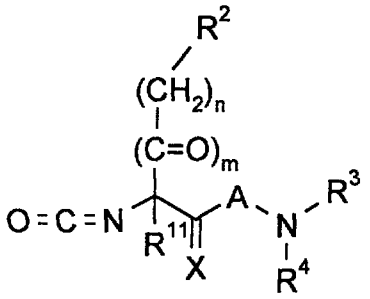
(II),

wherein

R^5, R^6, R^7, R^N, Y^1, o and p are defined as in claims 1 to 6 and Y^2 denotes an N-atom,

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an isocyanate of general formula XII,



(XII)

wherein
R^2, R^3, R^4, R^{11}, A, X, m and n are defined as in claims 1 to 6,

is reacted with an amine of general formula X,

$$R - H \qquad (X)$$

wherein
R is as hereinbefore defined,

and, if necessary, protecting groups are subsequently cleaved from a compound thus obtained or precursor functions are modified, or

f) in order to prepare compounds of general formula I wherein

R denotes an unbranched C_{1-6}-alkylamino group unsubstituted at the nitrogen atom, which may be substituted in the ω-position

by a C_{4-10}-cycloalkyl group,

by one or two phenyl groups, by a 1-naphthyl, 2-naphthyl- or biphenylyl group,

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by a 1H-indol-3-yl, 1,3-dihydro-2H-2-oxobenzimidazol-1-yl, 2,4(1H,3H)-dioxoquinazolin-1-yl, 2,4(1H,3H)-dioxoquinazolin-3-yl, 2,4(1H,3H)-dioxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-3-yl, 2(1H)-oxoquinolin-3-yl, 2(1H)-oxoquinoxalin-3-yl, 1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl, 1,3-dihydro-4-(3-thienyl)-2H-2-oxoimidazol-1-yl, 1,3-dihydro-4-phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-5-phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-2(2H)-oxoimidazo[4,5-c]quinolin-3-yl, 3,4-dihydro-5-phenyl-2(1H)-oxopyrimidin-3-yl, 3,4-dihydro-6-phenyl-2(1H)-oxopyrimidin-3-yl or 1,3-dihydro-2H-2-oxoimidazo-[4,5-b]pyridin-3-yl group,

by a 5-membered heteroaromatic ring linked via a carbon atom, which contains a nitrogen, oxygen or sulphur atom or, in addition to a nitrogen atom, contains an oxygen, sulphur or an additional nitrogen atom, whilst a nitrogen atom of an imino group may be substituted by an alkyl group, or

by a 6-membered heteroaromatic ring linked via a carbon atom and containing 1, 2 or 3 nitrogen atoms, whilst a 1,4-butadienylene group may be attached both to the 5-membered and to the 6-membered heteroaromatic monocyclic rings via two adjacent carbon atoms in each case and the bicyclic heteroaromatic rings thus formed may also be bound via a carbon atom of the 1,4-butadienylene group,

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whilst the phenyl, naphthyl and biphenylyl groups mentioned above for the substitution of the alkylamino groups in the ω-position and optionally partially hydrogenated mono- and bicyclic heteroaromatic rings in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms, by alkyl groups, C_{3-8}-cycloalkyl groups, nitro, alkoxy, phenyl, phenylalkoxy, trifluoromethyl, alkoxycarbonyl, alkoxycarbonylalkyl, carboxy, carboxyalkyl, dialkylaminoalkyl, hydroxy, amino, acetylamino, propionylamino, benzoyl, benzoylamino, benzoylmethylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, (1-pyrrolidinyl)carbonyl, (1-piperidinyl)carbonyl, (hexahydro-1H-azepin-1-yl)carbonyl, (4-methyl-1-piperazinyl)carbonyl, (4-morpholinyl)carbonyl, alkanoyl, cyano, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphynyl- or trifluoromethylsulphonyl groups, whilst the substituents may be identical or different and the above-mentioned benzoyl, benzoylamino- and benzoylmethylamino groups in turn may additionally be substituted in the phenyl moiety by a fluorine, chlorine or bromine atom or by an alkyl, trifluoromethyl, amino or acetylamino group, and

Z denotes an NR^1- group wherein R^1 is defined as in claims 1 to 6,

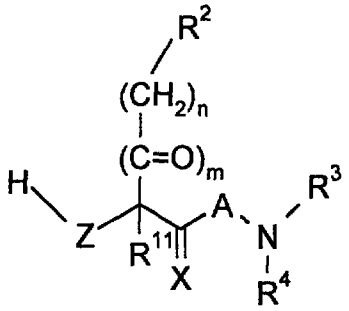
an isocyanate of general formula XIII,

$$R=C=O \qquad \text{(XIII)}$$

wherein R is as hereinbefore defined, is reacted with a compound of general formula VIII,

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(VIII)

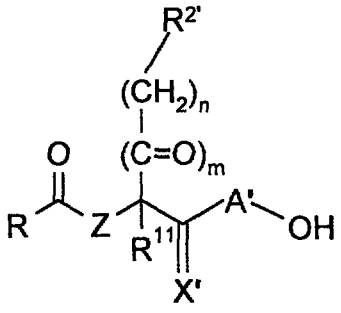
wherein R^2, R^3, R^4, R^{11}, A, X, m and n are defined as in claims 1 to 6, and

Z denotes an NR^1- group, wherein R^1 is defined as in claims 1 to 6,

and, if necessary, protecting groups are subsequently cleaved from a compound thus obtained or precursor functions are modified, or

g) in order to prepare compounds of general formula I, wherein X is defined as in claims 1 to 6, provided that A does not denote a bond, or X denotes an oxygen atom if A denotes a single bond:

a carboxylic acid of general formula XIV,



(XIV)

wherein
R, Z, R^{11}, m and n are defined as in claims 1 to 6,
$R^{2'}$ has the meanings given for R^2 in claims 1 to 6 or denotes a group R^2 substituted by a protecting group,
A' has the meanings given for A in claims 1 to 6 or, if A denotes the divalent group of an amino acid, A' optionally

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bears a precursor group for the group R^9 in the side chain,

is coupled with a compound of general formula XV,

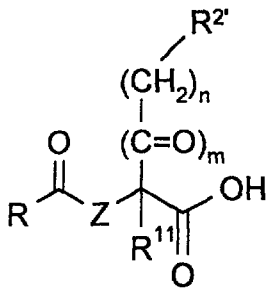
$$H - NR^3R^4 \qquad (XV)$$

wherein
R^3 and R^4 have the meanings given in claims 1 to 6,

and, if necessary, protecting groups are subsequently cleaved from a compound thus obtained or precursor functions are modified or

h) in order to prepare compounds of general formula I wherein X denotes an oxygen atom,

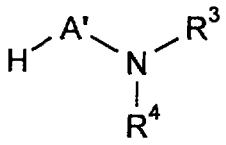
a carboxylic acid of general formula XVI,



(XVI)

wherein
R, Z, R^{11}, m and n are defined as in claims 1 to 6 and $R^{2'}$ has the meanings given for R^2 in claims 1 to 6 or denotes a group R^2 substituted by a protecting group,

is coupled with a compound of general formula XVII,



(XVII)

wherein

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A' has the meanings given for A in claims 1 to 6 or, if A denotes the divalent group of an amino acid, A' optionally bears a precursor group for the group R^9 in the side chain, and

R^3 and R^4 have the meanings given in claims 1 to 6,

and, if necessary, protecting groups are subsequently cleaved from a compound thus obtained or precursor functions are modified or

i) in order to prepare compounds of general formula I wherein

R denotes an unbranched C_{1-6}-alkylamino group optionally substituted at the nitrogen atom by a C_{1-6}-alkyl group or by a phenylmethyl group, which may be substituted in the ω-position

by a C_{4-10}-cycloalkyl group,

by one or two phenyl groups, by a 1-naphthyl, 2-naphthyl or biphenylyl group,

by a 1H-indol-3-yl, 1,3-dihydro-2H-2-oxobenzimidazol-1-yl, 2,4(1H,3H)-dioxoquinazolin-1-yl, 2,4(1H,3H)-dioxoquinazolin-3-yl, 2,4(1H,3H)-dioxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl, 3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-1-yl, 3,4-dihydro-2(1H)-oxoquinazolin-3-yl, 2(1H)-oxoquinolin-3-yl, 2(1H)-oxoquinoxalin-3-yl, 1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl, 1,3-dihydro-4-(3-thienyl)-2H-2-oxoimidazol-1-yl, 1,3-dihydro-4-

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phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-5-phenyl-2H-2-oxoimidazol-1-yl, 1,3-dihydro-2(2H)-oxoimidazo[4,5-c]quinolin-3-yl, 3,4-dihydro-5-phenyl-2(1H)-oxopyrimidin-3-yl, 3,4-dihydro-6-phenyl-2(1H)-oxopyrimidin-3-yl- or 1,3-dihydro-2H-2-oxoimidazo-[4,5-b]pyridin-3-yl- group,

by a 5-membered heteroaromatic ring linked via a carbon atom, which contains a nitrogen, oxygen or sulphur atom or, in addition to a nitrogen atom, contains an oxygen, sulphur or an additional nitrogen atom, whilst a nitrogen atom of an imino group may be substituted by an alkyl group, or

by a 6-membered heteroaromatic ring linked via a carbon atom and containing 1, 2 or 3 nitrogen atoms, whilst a 1,4-butadienylene group may be attached both to the 5-membered and to the 6-membered heteroaromatic monocyclic rings via two adjacent carbon atoms in each case and the bicyclic heteroaromatic rings thus formed may also be bound via a carbon atom of the 1,4-butadienylene group,

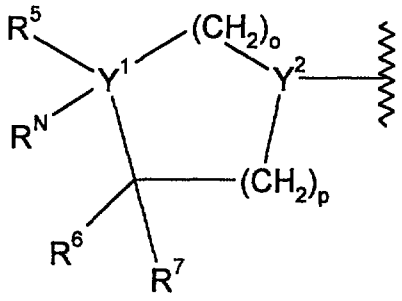
whilst the phenyl, naphthyl and biphenylyl groups mentioned above for the substitution of the alkyl moiety of the alkylamino groups in the ω-position and optionally partially hydrogenated mono- and bicyclic heteroaromatic rings in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms, by alkyl groups, C_{3-8}-cycloalkyl groups, nitro, alkoxy, phenyl, phenylalkoxy, trifluoromethyl, alkoxycarbonyl, alkoxycarbonylalkyl, carboxy, carboxyalkyl, dialkylaminoalkyl, hydroxy, amino, acetylamino, propionylamino, benzoyl, benzoylamino, benzoylmethylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, (1-pyrrolidinyl)carbonyl, (1-piperidinyl)carbonyl, (hexahydro-1H-azepin-1-

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yl)carbonyl, (4-methyl-1-piperazinyl)carbonyl, (4-morpholinyl)carbonyl, alkanoyl, cyano, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphynyl- or trifluoromethylsulphonyl groups, whilst the substituents may be identical or different and the above-mentioned benzoyl, benzoylamino- and benzoylmethylamino groups in turn may additionally be substituted in the phenyl moiety by a fluorine, chlorine or bromine atom or by an alkyl, trifluoromethyl, amino- or acetylamino group,

or the group of formula



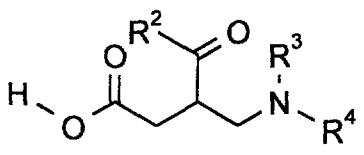
(II),

wherein

R^5, R^6, R^7, R^N, Y^1, o and p are defined as in claims 1 to 6 and Y^2 denotes the N-atom,

Z represents a methylene group,
X denotes two hydrogen atoms,
A denotes a single bond,
m denotes the value 1 and
n denotes the value 0,

a carboxylic acid of general formula XVIII,



(XVIII)

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wherein
R^2, R^3 and R^4 are defined as in claims 1 to 6,

is coupled with an amine of general formula X,

$$R - H \qquad (X)$$

wherein R is as hereinbefore defined, or

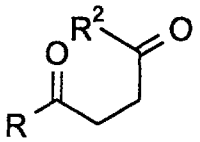
j) in order to prepare compounds of general formula I wherein
R^3 and R^4 have the meanings given in claims 1 to 6 with the exception of hydrogen atoms, Z denotes a methylene group, X denotes two hydrogen atoms, A denotes a single bond, m denotes the number 1 and n denotes the number 0,

a secondary amine of general formula XVa,

$$H\text{-}NR^{3'}R^{4'} \qquad (XVa)$$

wherein
$R^{3'}$ and $R^{4'}$ have the meanings given for R^3 and R^4 in claims 1 to 6, with the exception of hydrogen atoms,

is reacted with formaldehyde and a CH-acid compound of general formula XIX,



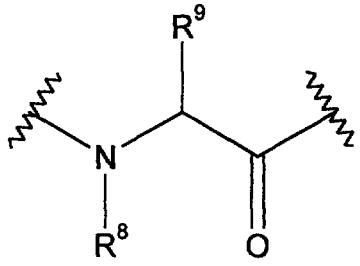
(XIX)

wherein
R is defined as in claims 1 to 6 and
R^2 is defined as in claims 1 to 6, but with the proviso that any acid functions present are appropriately protected by suitable protecting groups, or

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k) in order to prepare compounds of general formula I wherein A denotes the divalent group of formula III



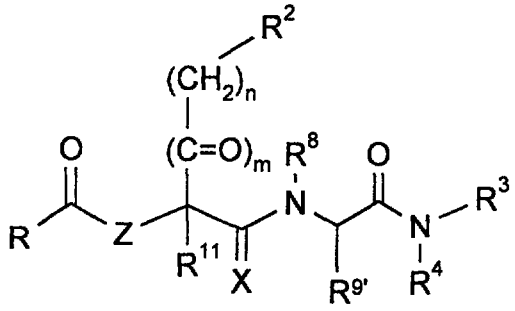
(III),

(linked to the NR^3R^4- group via the -CX- group)
wherein

R^8 denotes a hydrogen atom or an alkyl or phenylalkyl group and

R^9 denotes an unbranched C_{1-5}-alkyl group substituted in the ω-position by an aminoiminomethylamino group,

a compound of general formula XX,



(XX),

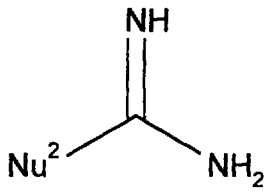
wherein

R, R^2, R^3, R^4, R^{11}, X, Z, m and n are defined as in claims 1 to 6,
R^8 denotes a hydrogen atom or an alkyl or phenylalkyl group and
R^9 denotes an unbranched C_{1-5}-alkyl group substituted in the ω-position by a primary amino group,

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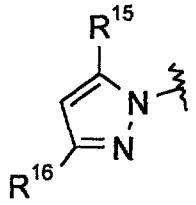
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is reacted with a carbonic acid derivative of general formula XXI,



(XXI)

wherein
Nu^2 is a leaving group or the group of general formula XXII,



(XXII)

wherein
R^{15} and R^{16}, which may be identical or different, denote hydrogen atoms or C_{1-3}-alkyl groups, and

if desired a protecting group used during the reactions described hereinbefore is cleaved again and/or

if desired a compound of general formula I thus obtained is resolved into its stereoisomers and/or

a compound of general formula I thus obtained is converted into the salts thereof, more particularly for pharmaceutical use into the physiologically acceptable salts thereof.

12. Use of the compounds of general formula I according to claims 1 to 7 for the production and purification of antibodies.

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13. Use of the labelled compounds of general formula I according to claims 1 to 7 in RIA and ELISA assays and as diagnostic or analytical aids in neurotransmitter research.

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