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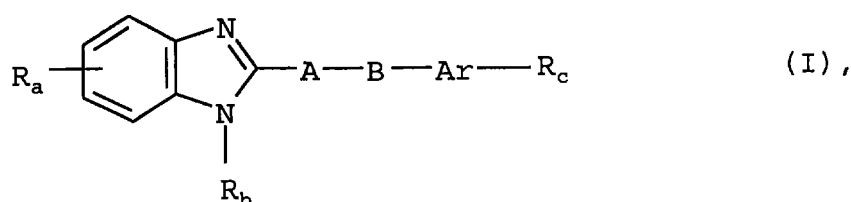


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Benzimidazoles, the preparation thereof and their use as
pharmaceutical compositions

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The present invention relates to benzimidazoles of general
formula



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their tautomers, their stereoisomers, the mixtures
thereof, their prodrugs, the derivatives thereof which
contain a group which is negatively charged under
physiological conditions instead of a carboxy group, and
15 the salts thereof, particularly the physiologically
acceptable salts thereof with inorganic or organic acids
or bases which have valuable properties.

The compounds of the above general formula I wherein R_c
20 denotes a cyano group are valuable intermediates for
preparing the other compounds of general formula I, and
the compounds of the above general formula I wherein R_c
denotes one of the following amidino groups, as well as
their tautomers, their stereoisomers, the mixtures
25 thereof, their prodrugs, the derivatives thereof which
contain a group which is negatively charged under
physiological conditions instead of a carboxy group, and
their salts, particularly the physiologically acceptable
salts thereof with inorganic or organic acids, and the
30 stereoisomers thereof have valuable pharmacological
properties, particularly an antithrombotic activity.



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The present application thus relates to the new compounds of the above general formula I as well as the preparation thereof, the pharmaceutical compositions containing the pharmacologically active compounds, the preparation and
5 use thereof.

In the above general formula

Ar denotes a phenylene or naphthylene group optionally
10 substituted by a fluorine, chlorine or bromine atom, by a trifluoromethyl, C₁₋₃-alkyl or C₁₋₃-alkoxy group,

a thienylene, thiazolylene, pyridinylen, pyrimidinylene, pyrazinylene or pyridazinylene group optionally
15 substituted in the carbon skeleton by a C₁₋₃-alkyl group,

A denotes a C₁₋₃-alkylene group,

B denotes an oxygen or sulphur atom, a methylene,
20 carbonyl, sulphinyl or sulphonyl group, an imino group optionally substituted by a C₁₋₃-alkyl group wherein the alkyl moiety may be mono- or disubstituted by a carboxy group,

25 R_a denotes an R₁-CO-C₃₋₅-cycloalkyl group wherein

R₁ denotes a C₁₋₃-alkoxy, amino, C₁₋₄-alkylamino or di-(C₁₋₄-alkyl)-amino group wherein each alkyl moiety may be substituted by a carboxy group,

30

a 4- to 7-membered cycloalkyleneimino or cycloalkenyleneimino group which may be substituted by a hydroxy group or by one or two C₁₋₃-alkyl groups, whilst an alkyl substituent may simultaneously be substituted
35 by a hydroxy, C₁₋₃-alkoxy, carboxy, carboxy-C₁₋₃-alkoxy, carboxy-C₁₋₃-alkylamino, N-(C₁₋₃-alkyl)-N-(carboxy-C₁₋₃-alkyl)-amino, carboxy-C₁₋₃-alkylaminocarbonyl,

N-(C₁₋₃-alkyl)-N-(carboxy-C₁₋₃-alkyl)-aminocarbonyl,
carboxy-C₁₋₃-alkylaminocarbonylamino, 1-(C₁₋₃-alkyl)-
3-(carboxy-C₁₋₃-alkyl)-aminocarbonylamino, 3-(C₁₋₃-alkyl)-
3-(carboxy-C₁₋₃-alkyl)-aminocarbonylamino or 1,3-di-
5 (C₁₋₃-alkyl)-3-(carboxy-C₁₋₃-alkyl)-aminocarbonylamino
group,

a 4- to 7-membered cycloalkenyleneimino group
substituted by a hydroxy group,

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a 5- to 7-membered cycloalkyleneimino group optionally
substituted by a C₁₋₃-alkyl group, to which a phenyl ring
is fused via two adjacent carbon atoms,

15 a morpholino, piperazino, N-(C₁₋₃-alkyl)-piperazino,
pyrrolino, 3,4-dehydro-piperidino or pyrrol-1-yl group,

an R₂-CX-C₃₋₅-cycloalkyl group wherein

20 R₂ denotes a phenyl, naphthyl or monocyclic 5- or
6-membered heteroaryl group optionally substituted by a
C₁₋₃-alkyl group, wherein the 6-membered heteroaryl group
contains one, two or three nitrogen atoms and the
5-membered heteroaryl group contains an imino group
25 optionally substituted by a C₁₋₃-alkyl group, an oxygen
or sulphur atom or an imino group optionally substituted
by a C₁₋₃-alkyl group and an oxygen or sulphur atom or
one or two nitrogen atoms and the abovementioned alkyl
substituent may be substituted by a carboxy, carboxy-
30 C₁₋₃-alkoxy, carboxy-C₁₋₃-alkylamino or N-(C₁₋₃-alkyl)-
carboxy-C₁₋₃-alkylamino group, and

X denotes an oxygen atom, a C₁₋₃-alkylimino,
C₁₋₃-alkoxyimino, C₁₋₃-alkylhydrazino, di-(C₁₋₃-alkyl)-
35 hydrazino, C₂₋₄-alkanoylhydrazino, N-(C₁₋₃-alkyl)-
C₂₋₄-alkanoylhydrazino or C₁₋₃-alkylidene group each of
which may be substituted in the alkyl or alkanoyl moiety

or in the alkyl and alkanoyl moieties by a carboxy group,

5 a C₁₋₃-alkyl or C₃₋₅-cycloalkyl group substituted by an imidazole or imidazolone group wherein

the imidazole ring may be substituted by a phenyl or carboxy group and by one or two C₁₋₃-alkyl groups or by one, two or three C₁₋₃-alkyl groups, wherein the
10 substituents may be identical or different and one of the abovementioned alkyl substituents may simultaneously be substituted by a carboxy group or may be substituted in the 2 or 3 position by an amino, C₂₋₄-alkanoylamino, C₁₋₃-alkylamino, N-(C₂₋₄-alkanoyl)-C₁₋₃-alkylamino or di-
15 (C₁₋₃-alkyl)-amino group, and

the imidazolone ring may be substituted by a C₁₋₃-alkyl group, whilst the alkyl substituent may be substituted by a carboxy group or in the 2 or 3 position by an
20 amino, C₂₋₄-alkanoylamino, C₁₋₃-alkylamino, N-(C₂₋₄-alkanoyl)-C₁₋₃-alkylamino or di-(C₁₋₃-alkyl)-amino group, and

25 additionally a phenyl or pyridine ring may be fused to the abovementioned imidazole or imidazolone rings via two adjacent carbon atoms,

an imidazolidine-2,4-dione-5-yl group which may be substituted by one or two C₁₋₃-alkyl groups, whilst at the
30 same time an alkyl substituent may be substituted by a carboxy group,

a C₁₋₄-alkyl group which is substituted

35 by a C₁₋₃-alkyl-Y₁-C₁₋₃-alkyl, HOOC-C₁₋₃-alkyl-Y₁-C₁₋₃-alkyl, tetrazolyl-C₁₋₃-alkyl-Y₂, R₃NR₄- or R₃NR₄-C₁₋₃-alkyl group and

by an isoxazolidinylcarbonyl group optionally substituted by a C₁₋₃-alkyl group, by a pyrrolino-carbonyl, 3,4-dehydro-piperidinocarbonyl, pyrrol-1-yl-carbonyl, carboxy, aminocarbonyl, C₁₋₃-alkylaminocarbonyl, di-(C₁₋₃-alkyl)-aminocarbonyl or 4- to 7-membered cycloalkyleneiminocarbonyl group, whilst in the abovementioned groups the cycloalkyleneimino moiety may be substituted by one or two C₁₋₃-alkyl groups and at the same time each alkyl moiety or alkyl substituent in the abovementioned C₁₋₃-alkylaminocarbonyl, di-(C₁₋₃-alkyl)-aminocarbonyl or cycloalkyleneiminocarbonyl groups may be substituted by a carboxy group, and the remaining hydrogen atoms of the C₁₋₄-alkyl group may be wholly or partially replaced by fluorine atoms wherein

R₃ denotes a hydrogen atom or a C₁₋₃-alkyl group optionally substituted by a carboxy group and

R₄ denotes a hydrogen atom, a C₁₋₃-alkyl-Y₁-C₁₋₃-alkyl-Y₂, carboxy-C₁₋₃-alkyl-Y₁-C₁₋₃-alkyl-Y₂, C₁₋₃-alkyl-Y₂ or carboxy-C₁₋₃-alkyl-Y₂ group or

R₃ and R₄ together with the nitrogen atom between them denote an 4- to 7-membered cycloalkyleneimino group optionally substituted by a carboxy, C₁₋₃-alkyl or carboxy-C₁₋₃-alkyl group wherein

Y₁ denotes a carbon-carbon bond, an oxygen atom, a sulphenyl, sulphinyl, sulphonyl, -NH-, -NH-CO- or -NH-CO-NH- group and

Y₂ denotes a carbon-nitrogen bond or a carbonyl, sulphonyl, imino or -NH-CO- group, wherein the carbonyl group of the -NH-CO- group is linked to the nitrogen atom of the R₃NR₄- group, and the imino groups occurring

in the definition of the groups Y_1 and Y_2 may each additionally be substituted by a C_{1-3} -alkyl or carboxy- C_{1-3} -alkyl group,

- 5 a C_{1-3} -alkyl or C_{3-5} -cycloalkyl group substituted by a R_5NR_6 -group wherein

R_5 denotes a hydrogen atom, a C_{1-3} -alkyl, C_{5-7} -cycloalkyl, phenylcarbonyl, phenylsulphonyl or pyridinyl group and

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R_6 denotes a C_{1-3} -alkyl, carboxy- C_{1-3} -alkyl or carboxy- C_{1-3} -alkylcarbonyl group,

- 15 a C_{1-3} -alkyl group which is substituted by a C_{2-4} -alkanoyl or C_{5-7} -cycloalkanoyl group and by a C_{1-3} -alkyl group substituted by a chlorine, bromine or iodine atom,

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

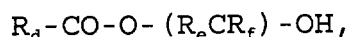
- 20 R_c denotes a cyano group or an amidino group optionally substituted by one or two C_{1-3} -alkyl groups.

The carboxy groups mentioned in the definitions of the abovementioned groups may also be replaced by a group
25 which can be converted *in vivo* into a carboxy group or by a group which is negatively charged under physiological conditions, or

the amino and imino groups mentioned in the definitions of
30 the abovementioned groups may also be substituted by a group which can be cleaved *in vivo*. Groups of this kind are described, for example, in WO 98/46576 and by N.M. Nielson et al. in International Journal of Pharmaceutics 39, 75-85 (1987).

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A group which can be converted *in vivo* into a carboxy group may be, for example, a hydroxymethyl group, a carboxy group esterified with an alcohol, wherein the alcoholic moiety is preferably a C₁₋₆-alkanol, a phenyl-C₁₋₃-alkanol, a C₃₋₉-cycloalkanol, whilst a C₅₋₈-cycloalkanol may additionally be substituted by one or two C₁₋₃-alkyl groups, a C₅₋₈-cycloalkanol wherein a methylene group in the 3- or 4-position is replaced by an oxygen atom or by an imino group optionally substituted by a C₁₋₃-alkyl, phenyl-C₁₋₃-alkyl, phenyl-C₁₋₃-alkoxycarbonyl or C₂₋₆-alkanoyl group and the cycloalkanol moiety may additionally be substituted by one or two C₁₋₃-alkyl groups, a C₄₋₇-cycloalkenol, a C₃₋₅-alkenol, a phenyl-C₃₋₅-alkenol, a C₃₋₅-alkynol or phenyl-C₃₋₅-alkynol, with the proviso that no bond to the oxygen atom starts from a carbon atom which carries a double or triple bond, a C₃₋₈-cycloalkyl-C₁₋₃-alkanol, a bicycloalkanol with a total of 8 to 10 carbon atoms, which may additionally be substituted in the bicycloalkyl moiety by one or two C₁₋₃-alkyl groups, a 1,3-dihydro-3-oxo-1-isobenzofuranol or an alcohol of formula



wherein

R_d denotes a C₁₋₈-alkyl, C₅₋₇-cycloalkyl, phenyl or phenyl-C₁₋₃-alkyl group,

R_e denotes a hydrogen atom, a C₁₋₃-alkyl, C₅₋₇-cycloalkyl or phenyl group and

R_f denotes a hydrogen atom or a C₁₋₃-alkyl group,

a group which is negatively charged under physiological conditions may be a tetrazol-5-yl, phenylcarbonylamino-carbonyl, trifluormethylcarbonylamino-carbonyl, C₁₋₆-alkylsulphonylamino, phenylsulphonylamino,

benzylsulphonylamino, trifluoromethylsulphonylamino, C₁₋₆-alkylsulphonylamino-carbonyl, phenylsulphonylamino-carbonyl, benzylsulphonylamino-carbonyl or perfluoro-C₁₋₆-alkylsulphonylamino-carbonyl group

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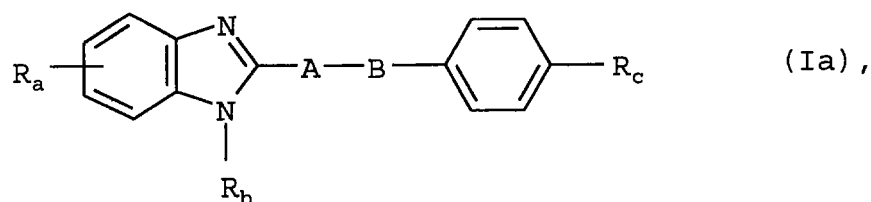
- and a group which can be cleaved *in vivo* from an imino or amino group may be, for example, a hydroxy group, an acyl group such as a benzoyl group optionally mono- or disubstituted by fluorine, chlorine, bromine or iodine
- 10 atoms, by C₁₋₃-alkyl or C₁₋₃-alkoxy groups, wherein the substituents may be identical or different, a pyridinoyl group or a C₁₋₁₆-alkanoyl group such as the formyl, acetyl, propionyl, butanoyl, pentanoyl or hexanoyl group, a 3,3,3-trichloropropionyl or allyloxycarbonyl group, a
- 15 C₁₋₁₆-alkoxycarbonyl or C₁₋₁₆-alkylcarbonyloxy group wherein hydrogen atoms may be wholly or partially replaced by fluorine or chlorine atoms, such as the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert. butoxycarbonyl, pentoxycarbonyl,
- 20 hexoxycarbonyl, octyloxycarbonyl, nonyloxycarbonyl, decyloxycarbonyl, undecyloxycarbonyl, dodecyloxycarbonyl, hexadecyloxycarbonyl, methylcarbonyloxy, ethylcarbonyloxy, 2,2,2-trichloroethylcarbonyloxy, propylcarbonyloxy, isopropylcarbonyloxy, butylcarbonyloxy,
- 25 tert.butylcarbonyloxy, pentylcarbonyloxy, hexylcarbonyloxy, octylcarbonyloxy, nonylcarbonyloxy, decylcarbonyloxy, undecylcarbonyloxy, dodecylcarbonyloxy or hexadecylcarbonyloxy group, a phenyl-C₁₋₆-alkoxycarbonyl group such as the benzyloxycarbonyl, phenylethoxycarbonyl
- 30 or phenylpropoxycarbonyl group, a 3-amino-propionyl group wherein the amino group may be mono- or disubstituted by C₁₋₆-alkyl or C₃₋₇-cycloalkyl groups and the substituents may be identical or different, a C₁₋₃-alkylsulphonyl-
- C₂₋₄-alkoxycarbonyl, C₁₋₃-alkoxy-C₂₋₄-alkoxy-
- 35 C₂₋₄-alkoxycarbonyl, R_d-CO-O-(R_dCR_f)-O-CO-, C₁₋₆-alkyl-CO-NH-

(R_gCR_h)-O-CO- or C_{1-6} -alkyl-CO-O-(R_gCR_h)-(R_gCR_h)-O-CO- group wherein R_d to R_f are as hereinbefore defined,

5 R_g and R_h , which may be identical or different, denote hydrogen atoms or C_{1-3} -alkyl groups.

Moreover, the saturated alkyl and alkoxy moieties which contain more than 2 carbon atoms mentioned in the above definitions also include the branched isomers thereof, such as, for example, the isopropyl, tert.butyl, isobutyl group etc.

Preferred compounds are those of general formula



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wherein

A denotes a C_{1-3} -alkylene group,

20 B denotes an oxygen or sulphur atom, a methylene, carbonyl, sulphinyl or sulphonyl group, an imino group optionally substituted by a C_{1-3} -alkyl group wherein the alkyl moiety may be mono- or disubstituted by a carboxy group,

25

R_a denotes an R_1 -CO- C_{3-5} -cycloalkyl group wherein

R_1 denotes a C_{1-3} -alkoxy, amino, C_{1-4} -alkylamino or di-
(C_{1-4} -alkyl)-amino group wherein each alkyl moiety may be
30 substituted by a carboxy group,

a 4- to 7-membered cycloalkyleneimino or cycloalkenyleneimino group which may be substituted by

one or two C₁₋₃-alkyl groups, whilst an alkyl substituent may simultaneously be substituted by a hydroxy, C₁₋₃-alkoxy, carboxy, carboxy-C₁₋₃-alkoxy, carboxy-C₁₋₃-alkylamino, N-(C₁₋₃-alkyl)-N-(carboxy-C₁₋₃-alkyl)-amino, carboxy-C₁₋₃-alkylaminocarbonyl, N-(C₁₋₃-alkyl)-N-(carboxy-C₁₋₃-alkyl)-aminocarbonyl, carboxy-C₁₋₃-alkylaminocarbonylamino, 1-(C₁₋₃-alkyl)-3-(carboxy-C₁₋₃-alkyl)-aminocarbonylamino, 3-(C₁₋₃-alkyl)-3-(carboxy-C₁₋₃-alkyl)-aminocarbonylamino or 1,3-di-(C₁₋₃-alkyl)-3-(carboxy-C₁₋₃-alkyl)-aminocarbonylamino group,

a 4- to 7-membered cycloalkenyleneimino group substituted by a hydroxy group,

a 5- to 7-membered cycloalkyleneimino group optionally substituted by a C₁₋₃-alkyl group, to which a phenyl ring is fused via two adjacent carbon atoms,

a morpholino, piperazino, N-(C₁₋₃-alkyl)-piperazino, pyrrolino, 3,4-dehydro-piperidino or pyrrol-1-yl group,

an R₂-CX-C₃₋₅-cycloalkyl group wherein

R₂ denotes a phenyl, naphthyl or monocyclic 5- or 6-membered heteroaryl group optionally substituted by a C₁₋₃-alkyl group, wherein the 6-membered heteroaryl group contains one, two or three nitrogen atoms and the 5-membered heteroaryl group contains an imino group optionally substituted by a C₁₋₃-alkyl group, an oxygen or sulphur atom or an imino group optionally substituted by a C₁₋₃-alkyl group and an oxygen or sulphur atom or one or two nitrogen atoms and the abovementioned alkyl substituent may be substituted by a carboxy, carboxy-C₁₋₃-alkoxy, carboxy-C₁₋₃-alkylamino or N-(C₁₋₃-alkyl)-carboxy-C₁₋₃-alkylamino group, and

X denotes an oxygen atom, a C₁₋₃-alkylimino, C₁₋₃-alkoxyimino, C₁₋₃-alkylhydrazino, di-(C₁₋₃-alkyl)-hydrazino, C₂₋₄-alkanoylhydrazino, N-(C₁₋₃-alkyl)-C₂₋₄-alkanoylhydrazino or C₁₋₃-alkylidene group each of which may be substituted in the alkyl or alkanoyl moiety or in the alkyl and alkanoyl moieties by a carboxy group,

a C₁₋₃-alkyl or C₃₋₅-cycloalkyl group substituted by an imidazole or imidazolone group wherein

the imidazole ring may be substituted by a phenyl or carboxy group and by one or two C₁₋₃-alkyl groups or by one, two or three C₁₋₃-alkyl groups, wherein the substituents may be identical or different and one of the abovementioned alkyl substituents may simultaneously be substituted by a carboxy group or may be substituted in the 2 or 3 position by an amino, C₂₋₄-alkanoylamino, C₁₋₃-alkylamino, N-(C₂₋₄-alkanoyl)-C₁₋₃-alkylamino or di-(C₁₋₃-alkyl)-amino group, and

the imidazolone ring may be substituted by a C₁₋₃-alkyl group, whilst the alkyl substituent may be substituted by a carboxy group or in the 2 or 3 position by an amino, C₂₋₄-alkanoylamino, C₁₋₃-alkylamino, N-(C₂₋₄-alkanoyl)-C₁₋₃-alkylamino or di-(C₁₋₃-alkyl)-amino group, and

additionally a phenyl or pyridine ring may be fused to the abovementioned imidazole or imidazolone rings via two adjacent carbon atoms,

an imidazolidine-2,4-dione-5-yl group which may be substituted by one or two C₁₋₃-alkyl groups, whilst at the same time an alkyl substituent may be substituted by a carboxy group,

a C₁₋₄-alkyl group which is substituted

by a C₁₋₃-alkyl-Y₁-C₁₋₃-alkyl, HOOC-C₁₋₃-alkyl-Y₁-C₁₋₃-alkyl,
tetrazolyl-C₁₋₃-alkyl-Y₂, R₃NR₄- or R₃NR₄-C₁₋₃-alkyl group
5 and

by an isoxazolidinylcarbonyl group optionally
substituted by a C₁₋₃-alkyl group, by a pyrro-
linocarbonyl, 3,4-dehydro-piperidinocarbonyl, pyrrol-
10 1-yl-carbonyl, carboxy, aminocarbonyl,
C₁₋₃-alkylaminocarbonyl, di-(C₁₋₃-alkyl)-aminocarbonyl or
4- to 7-membered cycloalkyleneiminocarbonyl group,
whilst in the abovementioned groups the
cycloalkyleneimino moiety may be substituted by one or
15 two C₁₋₃-alkyl groups and at the same time each alkyl
moiety or alkyl substituent in the abovementioned
C₁₋₃-alkylaminocarbonyl, di-(C₁₋₃-alkyl)-aminocarbonyl or
cycloalkyleneiminocarbonyl groups may be substituted by
a carboxy group, and the remaining hydrogen atoms of the
20 C₁₋₄-alkyl group may be wholly or partially replaced by
fluorine atoms wherein

R₃ denotes a hydrogen atom or a C₁₋₃-alkyl group
optionally substituted by a carboxy group and

25

R₄ denotes a hydrogen atom, a C₁₋₃-alkyl-
Y₁-C₁₋₃-alkyl-Y₂, carboxy-C₁₋₃-alkyl-Y₁-C₁₋₃-alkyl-Y₂,
C₁₋₃-alkyl-Y₂ or carboxy-C₁₋₃-alkyl-Y₂ group or

30

R₃ and R₄ together with the nitrogen atom between them
denote an 4- to 7-membered cycloalkyleneimino group
optionally substituted by a carboxy, C₁₋₃-alkyl or
carboxy-C₁₋₃-alkyl group wherein

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Y₁ denotes a carbon-carbon bond, an oxygen atom, a
sulphenyl, sulphinyl, sulphonyl, -NH-, -NH-CO- or
-NH-CO-NH- group and

Y₂ denotes a carbon-nitrogen bond or a carbonyl, sulphonyl, imino or -NH-CO- group, wherein the carbonyl group of the -NH-CO- group is linked to the nitrogen
5 atom of the R₃NR₄- group, and the imino groups occurring in the definition of the groups Y₁ and Y₂ may each additionally be substituted by a C₁₋₃-alkyl or carboxy-C₁₋₃-alkyl group,

10 a C₁₋₃-alkyl or C₃₋₅-cycloalkyl group substituted by a R₅NR₆-group wherein

R₅ denotes a hydrogen atom, a C₁₋₃-alkyl, C₅₋₇-cycloalkyl, phenylcarbonyl, phenylsulphonyl or pyridinyl group and
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R₆ denotes a C₁₋₃-alkyl, carboxy-C₁₋₃-alkyl or carboxy-C₁₋₃-alkylcarbonyl group,

a C₁₋₃-alkyl group which is substituted by a C₂₋₄-alkanoyl
20 or C₅₋₇-cycloalkanoyl group and by a C₁₋₃-alkyl group substituted by a chlorine, bromine or iodine atom,

R_b denotes a hydrogen atom or a C₁₋₃-alkyl group and

25 R_c denotes a cyano group or an amidino group which may be substituted by a hydroxy group, by one or two C₁₋₃-alkyl groups, or by one or two C₁₋₆-alkoxycarbonyl groups,

wherein the carboxy, amino and imino groups mentioned in
30 the definition of the abovementioned groups may also be substituted by a group which can be cleaved *in vivo*,

the tautomers, stereoisomers and salts thereof.

Particularly preferred compounds of the above general formula Ia are those wherein

A denotes a C₁₋₃-alkylene group,

5

B denotes an oxygen atom, a methylene, imino or N-(C₁₋₃-alkyl)-imino group wherein the alkyl moiety may be substituted by a carboxy group,

10 R_a denotes an C₃₋₅-cycloalkyl group substituted by the R₁-CO group in the 1 position wherein

R₁ denotes a C₁₋₃-alkoxy, amino, C₁₋₄-alkylamino or di-(C₁₋₄-alkyl)-amino group wherein each alkyl moiety may be substituted by a carboxy group,

15

a 4- to 7-membered cycloalkyleneimino group which may be substituted by a hydroxy group or by one or two C₁₋₃-alkyl groups, whilst an alkyl substituent may simultaneously be substituted by a hydroxy, C₁₋₃-alkoxy, carboxy, carboxy-C₁₋₃-alkoxy, carboxy-C₁₋₃-alkylamino, N-(C₁₋₃-alkyl)-N-(carboxy-C₁₋₃-alkyl)-amino, carboxy-C₁₋₃-alkylaminocarbonyl, N-(C₁₋₃-alkyl)-N-(carboxy-C₁₋₃-alkyl)-aminocarbonyl, carboxy-C₁₋₃-alkylaminocarbonylamino, 1-(C₁₋₃-alkyl)-3-(carboxy-C₁₋₃-alkyl)-aminocarbonylamino, 3-(C₁₋₃-alkyl)-3-(carboxy-C₁₋₃-alkyl)-aminocarbonylamino or 1,3-di-(C₁₋₃-alkyl)-3-(carboxy-C₁₋₃-alkyl)-aminocarbonylamino group,

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25

30 a 5- to 7-membered cycloalkyleneimino group optionally substituted by a C₁₋₃-alkyl group, to which a phenyl ring is fused via two adjacent carbon atoms,

a morpholino, piperazino, N-(C₁₋₃-alkyl)-piperazino, pyrrolino, 3,4-dehydro-piperidino or pyrrol-1-yl group,

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a C₃₋₅-cycloalkyl group substituted in the 1 position by the R₂-CX- group, wherein

5 R₂ denotes a phenyl, naphthyl or monocyclic 5- or 6-membered heteroaryl group optionally substituted by a C₁₋₃-alkyl group, wherein the 6-membered heteroaryl group contains one, two or three nitrogen atoms and the 5-membered heteroaryl group contains an imino group optionally substituted by a C₁₋₃-alkyl group, an oxygen
10 or sulphur atom or an imino group optionally substituted by a C₁₋₃-alkyl group and an oxygen or sulphur atom or one or two nitrogen atoms and the abovementioned alkyl substituent may be substituted by a carboxy, carboxy-C₁₋₃-alkoxy, carboxy-C₁₋₃-alkylamino or N-(C₁₋₃-alkyl)-
15 carboxy-C₁₋₃-alkylamino group, and

X denotes an oxygen atom, a C₁₋₃-alkylimino, C₁₋₃-alkoxyimino or C₁₋₃-alkylidene group, each of which
20 may be substituted in the alkyl or alkanoyl moiety by a carboxy group,

a C₁₋₃-alkyl group substituted in the 1 position by an imidazole or imidazolone group wherein

25 the imidazole ring may be substituted by a phenyl or carboxy group and by one or two C₁₋₃-alkyl groups or by one, two or three C₁₋₃-alkyl groups, wherein the substituents may be identical or different and one of the abovementioned alkyl substituents may simultaneously
30 be substituted by a carboxy group or may be substituted in the 2 or 3 position by an amino, C₂₋₄-alkanoylamino, C₁₋₃-alkylamino, N-(C₂₋₄-alkanoyl)-C₁₋₃-alkylamino or di-(C₁₋₃-alkyl)-amino group, and

35 the imidazolone ring may be substituted by a C₁₋₃-alkyl group, whilst the alkyl substituent may be substituted by a carboxy group or in the 2 or 3 position by an

amino, C₂₋₄-alkanoylamino, C₁₋₃-alkylamino,
N-(C₂₋₄-alkanoyl)-C₁₋₃-alkylamino or di-(C₁₋₃-alkyl)-amino
group, and

5 additionally a phenyl or pyridine ring may be fused to
the abovementioned imidazole or imidazolone rings via
two adjacent carbon atoms,

an imidazolidine-2,4-dione-5-yl group which may be
10 substituted by one or two C₁₋₃-alkyl groups, whilst at the
same time an alkyl substituent may be substituted by a
carboxy group,

a C₁₋₄-alkyl group which is substituted in the 1 position
15 by an R₃NR₄- or R₃NR₄-C₁₋₃-alkyl group and

by a pyrrolinocarbonyl, 2,3-dehydro-piperidinocarbonyl,
imidazol-1-yl-carbonyl, carboxy, aminocarbonyl,
20 C₁₋₃-alkylaminocarbonyl, di-(C₁₋₃-alkyl)-aminocarbonyl,
isoxazolidin-1-ylcarbonyl or 4- to 7-membered cyclo-
alkyleneiminocarbonyl group, whilst in the
abovementioned groups the cycloalkyleneimino moiety may
be substituted by one or two C₁₋₃-alkyl groups and at the
25 same time each alkyl moiety or alkyl substituent in the
abovementioned C₁₋₃-alkylaminocarbonyl, di-(C₁₋₃-alkyl)-
aminocarbonyl or cycloalkyleneiminocarbonyl groups may
be substituted by a carboxy group, and the remaining
hydrogen atoms of the C₁₋₄-alkyl group may be wholly or
30 partially replaced by fluorine atoms, wherein

R₃ denotes a hydrogen atom or a C₁₋₃-alkyl group
optionally substituted by a carboxy group and

35 R₄ denotes a hydrogen atom, a C₁₋₃-alkyl-Y₂ or carboxy-
C₁₋₃-alkyl-Y₂ group or

R_3 and R_4 together with the nitrogen atom between them denote a 4- to 7-membered cycloalkyleneimino group optionally substituted in the 1 position by a carboxy, C_{1-3} -alkyl or carboxy- C_{1-3} -alkyl group, wherein

5

Y_2 denotes a carbon-nitrogen bond or a carbonyl, imino or -NH-CO- group, wherein the carbonyl group of the -NH-CO- group is linked to the nitrogen atom of the R_3NR_4 - group, and the imino group occurring in the definition of the groups Y_2 may additionally be substituted by a C_{1-3} -alkyl or carboxy- C_{1-3} -alkyl group,

10

a C_{1-3} -alkyl or C_{3-5} -cycloalkyl group substituted in the 1 position by an R_5NR_6 - group, wherein

15

R_5 denotes a hydrogen atom, a C_{1-3} -alkyl, C_{5-7} -cycloalkyl, phenylcarbonyl, phenylsulphonyl or pyridinyl group and

20

R_6 denotes a C_{1-3} -alkyl, carboxy- C_{1-3} -alkyl or carboxy- C_{1-3} -alkylcarbonyl group,

a C_{1-3} -alkyl group which is substituted by a C_{2-4} -alkanoyl or C_{5-7} -cycloalkanoyl group and by a C_{1-3} -alkyl group substituted by a chlorine, bromine or iodine atom,

25

R_b denotes a C_{1-3} -alkyl group and

R_c denotes an amidino group which may optionally be substituted by a 2,2,2-trichloroethoxycarbonyl,

30

C_{1-8} -alkoxycarbonyl, acetoxymethyloxycarbonyl, benzyloxycarbonyl or benzoyl group, whilst the benzoyl moiety may be mono- or disubstituted by fluorine, chlorine, bromine or iodine atoms, by C_{1-3} -alkyl or C_{1-3} -alkoxy groups and the substituents may be identical or different,

35

the C₁₋₃-alkanol esters, the tautomers, stereoisomers and salts thereof.

Most particularly preferred compounds of general formula I
5 are those wherein

A denotes a methylene group,

10 B denotes an oxygen atom or an imino group,

R_a denotes a cyclopropyl group substituted by the R₁-CO-
group in the 1 position, wherein

15 R₁ denotes a pyrrolidino or piperidino group optionally
substituted by a methyl or ethyl group wherein each
methyl or ethyl moiety may be substituted by a carboxy,
carboxy-C₁₋₃-alkoxy, carboxy-C₁₋₃-alkylamino or
N-(C₁₋₃-alkyl)-carboxy-C₁₋₃-alkylamino group,

20 a cyclopropyl group substituted in the 1 position by the
R₂-CX- group, wherein

25 R₂ denotes a phenyl, pyridyl, pyrazolyl group optionally
substituted by a C₁₋₃-alkyl group and

X denotes an oxygen atom, a C₁₋₃-alkoxyimino or
C₁₋₃-alkylidene group, each of which is substituted in
the alkyl or alkoxy moiety by a carboxy group,

30 a C₁₋₂-alkyl group substituted in the 1 position by an
imidazole group wherein the imidazole ring may be
substituted by a phenyl or carboxy group and by one or
two C₁₋₃-alkyl groups or by one, two or three C₁₋₃-alkyl
groups, wherein the substituents may be identical or
35 different and one of the abovementioned alkyl
substituents may simultaneously be substituted by a

carboxy group or may be substituted in the 2 or 3 position by an amino, C₂₋₄-alkanoylamino, C₁₋₃-alkylamino, N-(C₂₋₄-alkanoyl)-C₁₋₃-alkylamino or di-(C₁₋₃-alkyl)-amino group, whilst additionally a phenyl or pyridine ring may
5 be fused to the abovementioned imidazole rings via two adjacent carbon atoms,

a C₁₋₂-alkyl substituted in the 1 position by a benzimidazol-1-yl group, whilst the imidazolone ring may
10 be substituted by a methyl or ethyl group optionally substituted by a carboxy group,

a methyl or ethyl group which is substituted in the 1 position
15

by an R₃NR₄- or R₃NR₄-C₁₋₃-alkyl group and

by a di-(C₁₋₃-alkyl)-aminocarbonyl group, by an isoxazolidin-1-ylcarbonyl group, by a pyrrolidino-carbonyl or piperidinocarbonyl group substituted by a
20 C₁₋₃-alkyl group, whilst in the abovementioned groups each alkyl moiety or alkyl substituent in the abovementioned groups may be substituted by a carboxy group, wherein

25 R₃ denotes a hydrogen atom or a C₁₋₃-alkyl group optionally substituted by a carboxy group and

R₄ denotes a hydrogen atom, a C₁₋₃-alkyl-Y₂ or carboxy-C₁₋₃-alkyl-Y₂ group or
30

R₃ and R₄ together with the nitrogen atom between them denote a 4- to 7-membered cycloalkyleneimino group optionally substituted by a carboxy group, wherein
35

Y_2 denotes a carbon-nitrogen bond, a carbonyl group or an imino group optionally substituted by a C_{1-3} -alkyl group,

- 5 a C_{1-2} -alkyl group substituted in the 1 position by an R_5NR_6 - group, wherein

R_5 denotes a pyridinyl, phenylcarbonyl or phenylsulphonyl group and

10

R_6 denotes a C_{1-3} -alkyl or carboxy- C_{1-3} -alkyl group,

- an n-propyl group substituted in the 3 position by a chlorine atom, which is substituted in the 1 position by a
15 cyclopentylcarbonyl group,

a cyclopropyl group substituted in the 1 position by a cyclopentylamino group, which is substituted at the nitrogen atom by a carboxy- C_{1-3} -alkylcarbonyl group,

20

R_b denotes a methyl group and

- R_c denotes an amidino group which may optionally be substituted by a C_{1-8} -alkoxycarbonyl,
25 acetoxymethyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, benzyloxycarbonyl or benzoyl group,

particularly those compounds of general formula Ia wherein

- 30 A denotes a methylene group,

B denotes an imino group,

- R_a denotes a cyclopropyl group substituted by the R_1 -CO-
35 group in the 1 position, wherein

R_1 denotes a pyrrolidino or piperidino group optionally substituted by a methyl or ethyl group wherein each methyl or ethyl moiety may be substituted by a carboxy, carboxy- C_{1-3} -alkoxy, carboxy- C_{1-3} -alkylamino or
5 N-(C_{1-3} -alkyl)-carboxy- C_{1-3} -alkylamino group,

a cyclopropyl group substituted in the 1 position by the R_2 -CX group, wherein

10 R_2 denotes a phenyl, pyridyl, pyrazolyl group optionally substituted by a C_{1-3} -alkyl group and

X denotes an oxygen atom, a C_{1-3} -alkoxyimino or C_{1-3} -alkylidene group, each of which is substituted in
15 the alkyl or alkoxy moiety by a carboxy group,

a C_{1-2} -alkyl group substituted in the 1 position by an imidazole group wherein the imidazole ring may be substituted by one to three methyl groups or by two
20 methyl groups and an ethyl group, whilst additionally one of the abovementioned methyl or ethyl substituents may simultaneously be substituted by a carboxy group,

a methyl or ethyl group which is substituted in the 1
25 position

by an R_3NR_4 - or R_3NR_4 -CH₂- group and

by a di-(C_{1-3} -alkyl)-aminocarbonyl, by a pyrrolidinocarbonyl or piperidinocarbonyl group optionally
30 substituted by a C_{1-3} -alkyl group, whilst in the abovementioned groups each alkyl moiety or alkyl substituent may be substituted by a carboxy group, wherein

35

R_3 denotes a hydrogen atom or a C_{1-3} -alkyl group optionally substituted by a carboxy group and

R_4 denotes a C_{1-3} -alkyl- Y_2 or carboxy- C_{1-3} -alkyl- Y_2 group wherein

5 Y_2 denotes a carbon-nitrogen bond, a carbonyl group or an imino group optionally substituted by a C_{1-3} -alkyl group,

R_b denotes a methyl group and

10

R_c denotes an amidino group which may optionally be substituted by a C_{1-8} -alkoxycarbonyl, acetoxymethyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, benzyloxycarbonyl or benzoyl group,

15

whilst the abovementioned compounds in which the group R_a is in the 5 position are particularly preferred,

20 the C_{1-3} -alkanol esters, the tautomers, stereoisomers and salts thereof.

The following are mentioned as examples of particularly preferred compounds:

25 (a) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(pyrrolidin-1-yl-carbonyl)-cyclopropyl]-benzimidazole,

(b) (E/Z)-2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-
[(pyridin-2-yl)-(carboxymethyloxyimino)methylene]-
30 cyclopropyl]-benzimidazole,

(c) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(2-carboxyethylamino)-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole,

35

(d) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-[2-(2-carboxyethyl)-pyrrolidin-1-yl-carbonyl]cyclopropyl]-benzimidazole,

5 (e) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[2-(2-carboxyethyl)-4,5-dimethyl-imidazol-1-yl-methyl]-benzimidazole

(f) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(carboxy-
10 methylamino)-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole and

(g) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(N-methyl
15 carboxymethylcarbonylaminomethyl)-1-methyl-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole

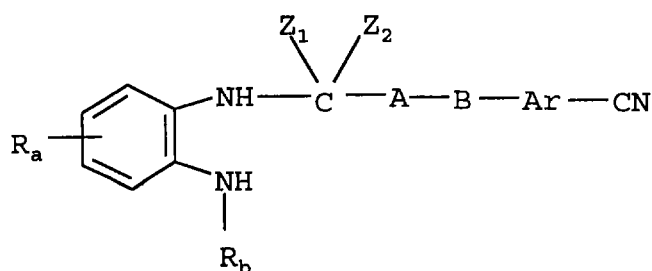
and the C₁₋₃-alkanol esters, the N-(C₁₋₈-alkoxycarbonyl), N-benzyloxycarbonyl and N-benzoyl-amidines, the tautomers, stereoisomers and salts thereof.

20

According to the invention, the compounds of general formula I are prepared by methods known *per se*, for example by the following methods:

25 a) In order to prepare a compound of general formula I wherein R_c denotes a cyano group:

cyclising a compound of general formula



(II),

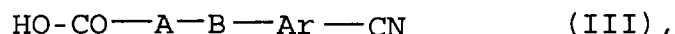
30

optionally formed in the reaction mixture,
wherein

R_a , R_b , Ar, A and B are as hereinbefore defined,
 Z_1 and Z_2 , which may be identical or different, denote
5 amino, hydroxy or mercapto groups optionally substituted
by alkyl groups with 1 to 6 carbon atoms or
 Z_1 and Z_2 together represent an oxygen or sulphur atom,
an imino group optionally substituted by an alkyl group
with 1 to 3 carbon atoms, an alkylenedioxy or
10 alkylenedithio group with 2 or 3 carbon atoms.

The cyclisation is expediently carried out in a solvent or
mixture of solvents such as ethanol, isopropanol, glacial
acetic acid, benzene, chlorobenzene, toluene, xylene,
15 glycol, glycol monomethyl ether, diethyleneglycol
dimethylether, sulpholane, dimethylformamide, tetraline or
in an excess of the acylating agent used to prepare the
compound of general formula II, e.g. in the corresponding
nitrile, anhydride, acid halide, ester or amide, for
20 example at temperatures between 0 and 250°C, but
preferably at the boiling temperature of the reaction
mixture, optionally in the presence of a condensing agent
such as phosphorus oxychloride, thionyl chloride,
sulphuryl chloride, sulphuric acid, p-toluenesulphonic
25 acid, methanesulphonic acid, hydrochloric acid, phosphoric
acid, polyphosphoric acid, acetic acid, acetic anhydride,
N,N-dicyclohexyl-carbodiimide or optionally in the
presence of a base such as potassium ethoxide or potassium
tert. butoxide. However, the cyclisation may also be
30 carried out without a solvent and/or condensing agent.

It is particularly advantageous to perform the reaction by
preparing a compound of general formula II in the reaction
mixture by reduction of a corresponding o-nitro compound
35 optionally in the presence of a carboxylic acid of general
formula

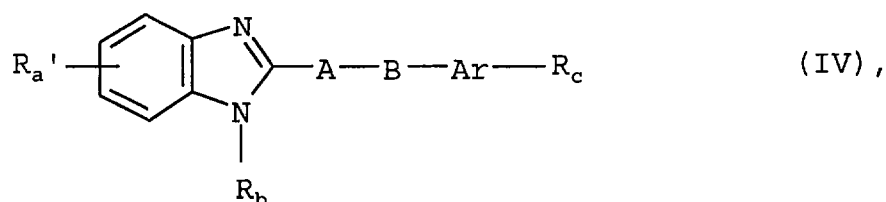


wherein

Ar, A and B are as hereinbefore defined, by acylation of a
corresponding amino compound optionally formed in the
5 reaction mixture.

b) In order to prepare a compound of general formula I
wherein R_a denotes an R_2 -CX'-C₃₋₅-cycloalkylene group,
wherein R_2 is as hereinbefore defined and X' denotes one
10 of the imino groups mentioned for X hereinbefore:

reacting a compound of general formula



15 wherein

R_b , Ar, A and B are as hereinbefore defined and
 R_a' denotes an R_2 -CO-C₃₋₅-cycloalkylene group, where

R_2 is as hereinbefore defined,

20

with an amine of general formula



25 wherein

X' denotes one of the imino groups mentioned for X
hereinbefore.

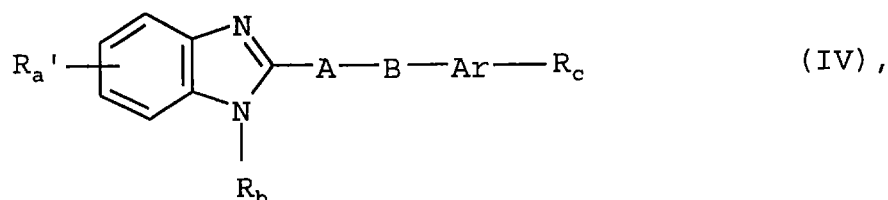
The reaction is preferably carried out in a solvent such
30 as methanol/toluene, ethanol, isopropanol or xylene and
expediently in the presence of a dehydrating agent such as
molecular sieve, sodium sulphate or calcium chloride
optionally in the presence of a base such as triethylamine

at temperatures between 50 and 100°C, preferably at the boiling temperature of the reaction mixture.

c) In order to prepare a compound of general formula I
 5 wherein R_a denotes an R_2 -CX"-C₃₋₅-cycloalkylene group,
 wherein R_2 is as hereinbefore defined and X" denotes one
 of the alkylidene groups mentioned for X hereinbefore:

reacting a compound of general formula

10



wherein

R_b , Ar, A and B are as hereinbefore defined and
 R_a' denotes an R_2 -CO-C₃₋₅-cycloalkylene group, where

15

R_2 is as hereinbefore defined,

with a phosphone of general formula

20



wherein

X" denotes one of the alkylidene groups mentioned for X
 hereinbefore and

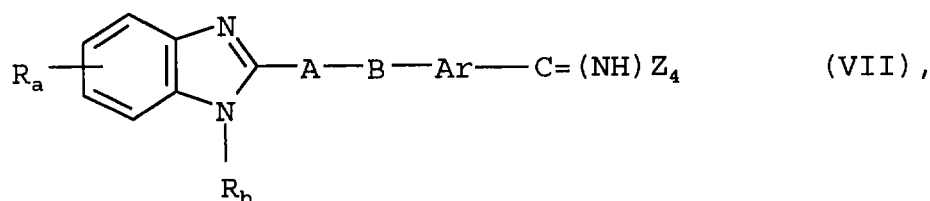
25 Z_3 denotes a triphenylphosphono or di-
 (C₁₋₃-alkoxy)phosphono group such as the triethoxyphosphono
 group.

The reaction is preferably carried out under protective
 30 gas in a solvent such as tetrahydrofuran,
 dimethylformamide, dioxane, diethylether or dimethyl
 sulphoxide in the presence of a base such as potassium
 tert. butoxide, sodium ethoxide or sodium hydride at

temperatures between -25 and 50°C, preferably at temperatures between -15° and ambient temperature.

- d) In order to prepare a compound of general formula I
 5 wherein R_c denotes an amidino group which may be substituted by one or two C₁₋₃-alkyl groups:

reacting a compound of general formula



10

optionally formed in the reaction mixture

wherein

- R_a, R_b, Ar, A and B are as hereinbefore defined and
 15 Z₄ denotes an alkoxy or aralkoxy group such as the methoxy, ethoxy, n-propoxy, isopropoxy or benzyloxy group or an alkylthio or aralkylthio group such as the methylthio, ethylthio, n-propylthio or benzylthio group, with an amine of general formula

20



wherein

- R₇ and R₈, which may be identical or different, each
 25 denote a hydrogen atom or a C₁₋₃-alkyl group, or with the salts thereof.

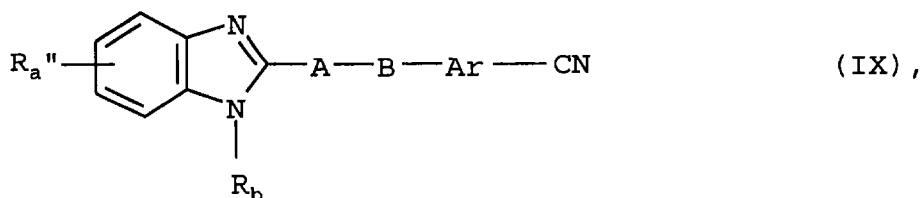
- The reaction is expediently carried out in a solvent such as methanol, ethanol, n-propanol, tetrahydrofuran or
 30 dioxane at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C, with an amine of general formula VIII or with a corresponding acid addition salt

such as for example ammonium carbonate or ammonium acetate.

A compound of general formula VII is obtained for example
5 by reacting a corresponding cyano compound with a
corresponding alcohol such as methanol, ethanol,
n-propanol, isopropanol or benzyl alcohol in the presence
of an acid such as hydrochloric acid or by reacting a
corresponding amide with a trialkyloxonium salt such as
10 triethyloxonium-tetrafluoroborate in a solvent such as
methylene chloride, tetrahydrofuran or dioxane at
temperatures between 0 and 50°C, but preferably at 20°C,
or a corresponding nitrile with hydrogen sulphide
expediently in a solvent such as pyridine or
15 dimethylformamide and in the presence of a base such as
triethylamine and subsequently alkylating the thioamide
formed with a corresponding alkyl or aralkyl halide.

e) In order to prepare a compound of general formula I
20 wherein R_a denotes an imidazolidin-2,4-dion-5-yl group
which may be substituted by one or two C_{1-3} -alkyl groups,
whilst at the same time an alkyl substituent may be
substituted by a carboxy or C_{1-3} -alkoxycarbonyl group:

25 cyclising a compound of general formula



optionally formed in the reaction mixture

30

wherein

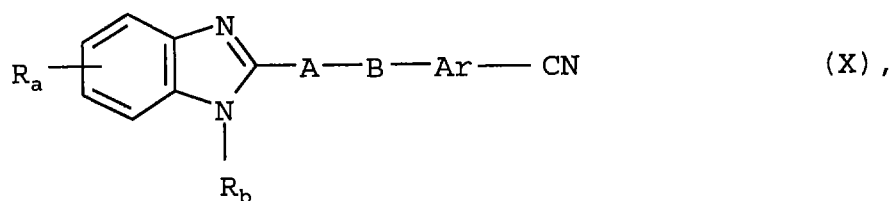
R_b , Ar, A and B are as hereinbefore defined and

R_a denotes an aminocarbonylamino group, substituted in the 3 position by a C_{1-3} -alkoxycarbonyl- C_{1-3} -alkyl group.

The reaction is preferably carried out in a solvent such as methanol, ethanol, n-propanol, isopropanol or benzyl alcohol in the presence of an acid such as hydrochloric acid at temperatures between 0 and 50°C, but preferably at 20°C.

f) In order to prepare a compound of general formula I wherein R_c denotes a hydroxyamidino group:

reacting a nitrile of general formula



15

wherein

R_a , R_b , Ar, A and B are as hereinbefore defined, with hydroxylamine or the salts thereof.

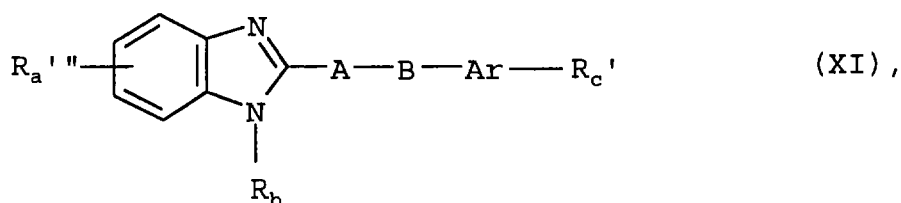
The reaction is expediently carried out in a solvent such as methanol, ethanol, n-propanol, water, methanol/water, tetrahydrofuran, tetrahydrofuran/water, dioxane or dioxane/water at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C.

25

g) In order to prepare a compound of general formula I wherein R_a contains a carboxy group and R_c is as hereinbefore defined or R_a is as hereinbefore defined and R_c denotes an amidino group optionally substituted by a hydroxy group or by one or two C_{1-3} -alkyl groups:

30

converting a compound of general formula



wherein

R_b , Ar, A and B are as hereinbefore defined and R_a'' and R_c' have the meanings given for R_a and R_c with the
5 proviso that R_a contains a group which may be converted into a carboxy group by hydrolysis, treatment with an acid or base, thermolysis or hydrogenolysis and R_c is as hereinbefore defined or R_c denotes a group which may optionally be converted by hydrolysis, treatment with an
10 acid or base, thermolysis or hydrogenolysis into an amidino group substituted by a hydroxy group or by one or two C_{1-3} -alkyl groups and R_a is as hereinbefore defined,
is converted by hydrolysis, treatment with an acid or
15 base, thermolysis or hydrogenolysis into a compound of general formula I wherein R_a contains a carboxy group and R_c is as hereinbefore defined or R_a is as hereinbefore defined and R_c denotes an amidino group optionally substituted by a hydroxy group or by one or two C_{1-3} -alkyl
20 groups.

A group which may be converted into a carboxy group might be, for example, a carboxyl group protected by a protecting group, such as the functional derivatives
25 thereof, e.g. the unsubstituted or substituted amides, esters, thioesters, trimethylsilylesters, orthoesters or iminoesters thereof which are expediently converted by hydrolysis into a carboxyl group,
30 the esters thereof with tertiary alcohols, e.g. the tert.butyl ester, which are expediently converted into a carboxyl group by treatment with an acid or thermolysis, and

the esters thereof with aralkanols, e.g. the benzylester, which are expediently converted into a carboxyl group by hydrogenolysis.

5

The hydrolysis is expediently carried out either in the presence of an acid such as hydrochloric acid, sulphuric acid, phosphoric acid, acetic acid, trichloroacetic acid, trifluoroacetic acid or the mixtures thereof or in the
10 presence of a base such as lithium hydroxide, sodium hydroxide or potassium hydroxide in a suitable solvent such as water, water/methanol, water/ethanol, water/isopropanol, methanol, ethanol, water/tetrahydrofuran or water/dioxane at temperatures
15 between -10 and 120°C, e.g. at temperatures between ambient temperature and the boiling temperature of the reaction mixture.

If a compound of formula XI for example contains the
20 tert.butyl or tert.butyloxycarbonyl group, these may also be cleaved by treatment with an acid such as trifluoroacetic acid, formic acid, p-toluenesulphonic acid, sulphuric acid, hydrochloric acid, phosphoric acid or polyphosphoric acid optionally in an inert solvent such
25 as methylene chloride, chloroform, benzene, toluene, diethylether, tetrahydrofuran or dioxane preferably at temperatures between -10 and 120°C, e.g. at temperatures between 0 and 60°C, or thermally, optionally in an inert solvent such as methylene chloride, chloroform, benzene,
30 toluene, tetrahydrofuran or dioxane and preferably in the presence of a catalytic amount of an acid such as p-toluenesulphonic acid, sulphuric acid, phosphoric acid or polyphosphoric acid, preferably at the boiling temperature of the solvent used, e.g. at temperatures
35 between 40 and 120°C.

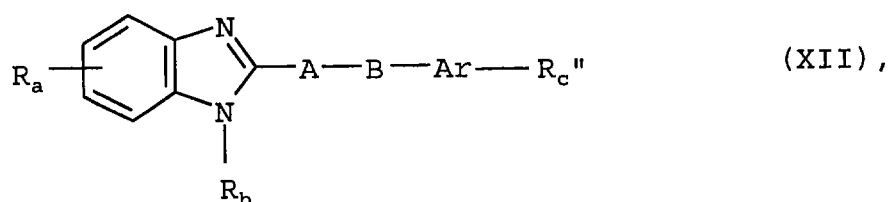
If a compound of formula XI contains, for example, a benzyloxy or benzyloxycarbonyl group, these may also be cleaved hydrogenolytically in the presence of a hydrogenation catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethanol/water, glacial acetic acid, ethyl acetate, dioxane or dimethylformamide, preferably at temperatures between 0 and 50°C, e.g. at ambient temperature, and at a hydrogen pressure of from 1 to 5 bar.

10

h) In order to prepare a compound of general formula I wherein R_c denotes an amidino group which is substituted by one or two C_{1-8} -alkoxycarbonyl groups or by a group which can be cleaved *in vivo*:

15

reacting a compound of general formula I



wherein

20 R_a , R_b , Ar, A and B are as hereinbefore defined and R_c'' denotes an amidino group, with a compound of general formula



25

wherein

R_9 denotes a C_{1-8} -alkoxycarbonyl group or the acyl group of one of the groups which can be cleaved *in vivo* mentioned hereinbefore and

30 Z_5 denotes a nucleofugic leaving group such as a halogenatom, e.g. a chlorine, bromine or iodine atom, or a p-nitrophenyl group.

The reaction is preferably carried out in a solvent such as methanol, ethanol, methylene chloride, tetrahydrofuran, toluene, dioxane, dimethyl sulphoxide or dimethylformamide
5 optionally in the presence of an inorganic or a tertiary organic base, preferably at temperatures between 20°C and the boiling temperature of the solvent used.

With a compound of general formula XIII wherein Z_5 denotes
10 a nucleofugic leaving group, the reaction is preferably carried out in a solvent such as methylene chloride, acetonitrile, tetrahydrofuran, toluene, acetone/water, dimethylformamide or dimethyl sulphoxide, optionally in the presence of a base such as sodium hydride, potassium
15 carbonate, potassium tert. butoxide or N-ethyl-diisopropylamine at temperatures between 0 and 60°C.

If according to the invention a compound of general formula I is obtained which contains a $(R_3NR_4)-C_{1-3}$ -alkyl
20 group wherein at least one of the groups R_3 or R_4 denotes a hydrogen atom, this may subsequently be converted with a corresponding isocyanate or carbamoyl halide into a corresponding urea compound of general formula I and/or

25 if a compound of general formula I is obtained which contains an NH_2-C_{1-3} -alkyl group, this may subsequently be converted with a corresponding acrylic acid ester into a corresponding 2-(C_{1-3} -alkoxycarbonyl)-ethyl compound of general formula I and/or

30 if a compound of general formula I is obtained which contains an $(R_3NR_4)-C_{1-3}$ -alkyl group wherein R_3 and R_4 each denote a hydrogen atom, this may subsequently be converted with a corresponding dihaloalkane into a corresponding
35 compound of general formula I wherein R_3 and R_4 together with the nitrogen atom between them [denote] a

corresponding 4- to 7-membered cycloalkyleneimino group and/or

5 if a compound of general formula I is obtained wherein R_c denotes an amidino group, this may subsequently be converted by reaction with a haloacetic acid derivative and subsequent hydrolysis and decarboxylation into a corresponding amidino compound substituted by one or two methyl groups and/or

10

if a compound of general formula I is obtained wherein R_c denotes a hydroxyamidino group, this may subsequently be converted into a corresponding amidino compound by catalytic hydrogenation and/or

15

if a compound of general formula I is obtained wherein R_a contains a carboxy group, this may subsequently be converted into a corresponding ester by esterification.

20 The subsequent preparation of a corresponding urea compound of general formula I is expediently carried out with a corresponding isocyanate or carbamoyl chloride, preferably in a solvent such as dimethylformamide and optionally in the presence of a tertiary organic base such
25 as triethylamine at temperatures between 0 and 50°C, preferably at ambient temperature,.

The subsequent preparation of a corresponding
2- (C_{1-3} -alkoxy-carbonyl)-ethyl-compound is carried out with
30 a corresponding acrylic acid ester, preferably in a solvent such as methanol, ethanol or isopropanol at temperatures between 50 and 100°C, preferably at the boiling temperature of the reaction mixture.

35 The subsequent preparation of a corresponding 4- to 7-membered cycloalkyleneimino compound of general formula I is expediently carried out with a corresponding

dihaloalkane, preferably in a solvent such as methanol, ethanol or isopropanol in the presence of a base such as sodium carbonate at temperatures between 50 and 100°C, preferably at the boiling temperature of the reaction mixture.

The subsequent alkylation is expediently carried out in a solvent such as methylene chloride, tetrahydrofuran, dioxane, dimethylsulphoxide, dimethylformamide or acetone optionally in the presence of a reaction accelerator such as sodium or potassium iodide and preferably in the presence of a base such as sodium carbonate or potassium carbonate or in the presence of a tertiary organic base such as N-ethyl-diisopropylamine or N-methyl-morpholine, which may simultaneously act as solvent, or optionally in the presence of silver carbonate or silver oxide at temperatures between -30 and 100°C, but preferably at temperatures between -10 and 80°C.

The subsequent hydrolysis is expediently carried out either in the presence of an acid such as hydrochloric acid, sulphuric acid, phosphoric acid, acetic acid, trichloroacetic acid, trifluoroacetic acid or mixtures thereof or in the presence of a base such as lithium hydroxide, sodium hydroxide or potassium hydroxide in a suitable solvent such as water, water/methanol, water/ethanol, water/isopropanol, methanol, ethanol, water/tetrahydrofuran or water/dioxane and subsequent decarboxylation in the presence of an acid as hereinbefore described at temperatures between -10 and 120°C, e.g. at temperatures between ambient temperature and the boiling temperature of the reaction mixture.

The subsequent esterification is carried out with a corresponding alcohol, conveniently in a solvent or mixture of solvents such as methylene chloride, benzene, toluene, chlorobenzene, tetrahydrofuran,

benzene/tetrahydrofuran or dioxan, but preferably in an excess of the alcohol used, optionally in the presence of an acid such as hydrochloric acid or in the presence of a dehydrating agent, e.g. in the presence of isobutyl

5 chloroformate, thionyl chloride, trimethylchlorosilane, sulphuric acid, hydrochloric acid, sulphuric acid, methanesulphonic acid, p-toluenesulphonic acid, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide,

10 N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, N,N'-carbonyldiimidazole or N,N'-thionyl-diimidazole, triphenylphosphine/carbon tetrachloride or triphenylphosphine/diethyl azodicarboxylate, optionally in the presence of a base such as potassium carbonate,

15 N-ethyl-diisopropylamine or N,N-dimethylamino-pyridine expediently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C, or with a corresponding halide in a solvent such as methylene chloride, tetrahydrofuran, dioxane, dimethylsulphoxide,

20 dimethylformamide or acetone, optionally in the presence of a reaction accelerator such as sodium or potassium iodide and preferably in the presence of a base such as sodium carbonate or potassium carbonate or in the presence of a tertiary organic base such as N-ethyl-

25 diisopropylamine or N-methyl-morpholine, which may simultaneously act as solvent, or optionally in the presence of silver carbonate or silver oxide at temperatures between -30 and 100°C, but preferably at temperatures between -10 and 80°C.

30

In the reactions described hereinbefore, any reactive groups present such as hydroxy, carboxy, amino, alkylamino or imino groups may be protected during the reaction by

35 conventional protecting groups which are cleaved again after the reaction.

For example, a protecting group for a hydroxy group may be a trimethylsilyl, acetyl, benzoyl, tert.butyl, trityl, benzyl or tetrahydropyranyl group,

- 5 protecting groups for a carboxy group may be a trimethylsilyl, methyl, ethyl, tert.butyl, benzyl or tetrahydropyranyl group and

10 protecting groups for an amino, alkylamino or imino group may be an acetyl, trifluoroacetyl, benzoyl, ethoxycarbonyl, tert.butoxycarbonyl, benzyloxycarbonyl, benzyl, methoxybenzyl or 2,4-dimethoxybenzyl group and additionally, for the amino group, a phthalyl group.

- 15 Any protecting group used is optionally subsequently cleaved for example by hydrolysis in an aqueous solvent, e.g. in water, isopropanol/water, tetrahydrofuran/water or dioxan/water, in the presence of an acid such as trifluoroacetic acid, hydrochloric acid or sulphuric acid
20 or in the presence of an alkali metal base such as lithium hydroxide, sodium hydroxide or potassium hydroxide or by ether splitting, e.g. in the presence of iodotrimethylsilane, at temperatures between 0 and 100°C, preferably at temperatures between 10 and 50°C.

25

- However, a benzyl, methoxybenzyl or benzyloxycarbonyl group is cleaved, for example, hydrogenolytically, e.g. with hydrogen in the presence of a catalyst such as palladium/charcoal in a solvent such as methanol, ethanol,
30 ethyl acetate, dimethylformamide, dimethylformamide/acetone or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid at temperatures between 0 and 50°C, but preferably at ambient temperature, and at a hydrogen
35 pressure of 1 to 7 bar, but preferably 3 to 5 bar.

A methoxybenzyl group may also be cleaved in the presence of an oxidant such as cerium(IV) ammonium nitrate in a solvent such as methylene chloride, acetonitrile or acetonitrile/water at temperatures between 0 and 50°C, but
5 preferably at ambient temperature.

A 2,4-dimethoxybenzyl group, however, is preferably cleaved in trifluoroacetic acid in the presence of anisol.

10 A tert.butyl or tert.butyloxycarbonyl group is preferably cleaved by treating with an acid such as trifluoroacetic acid or hydrochloric acid, optionally using a solvent such as methylene chloride, dioxan or ether.

15 A phthalyl group is preferably cleaved in the presence of hydrazine or a primary amine such as methylamine, ethylamine or n-butylamine in a solvent such as methanol, ethanol, isopropanol, toluene/water or dioxan at temperatures between 20 and 50°C.

20

An allyloxycarbonyl group is cleaved by treating with a catalytic amount of tetrakis-(triphenylphosphine)-palladium(0), preferably in a solvent such as
25 tetrahydrofuran and preferably in the presence of an excess of a base such as morpholine or 1,3-dimedone at temperatures between 0 and 100°C, preferably at ambient temperature and under an inert gas, or by treating with a catalytic amount of tris-(triphenylphosphine)-rhodium(I)
30 chloride in a solvent such as aqueous ethanol and optionally in the presence of a base such as 1,4-diazabicyclo[2.2.2]octane at temperatures between 20 and 70°C.

35 The compounds of general formulae II to XIII used as starting materials, some of which are known from the literature, may be obtained by methods known from the

literature and in addition their preparation is described in the Examples.

The chemistry of the compounds of general formula III is described, for example, by Jack Robinson in J. Chem. Soc. 1941, 744, that of the benzimidazoles is described by Katritzky and Rees in Comprehensive Heterocyclic Chemistry, Oxford, Pergamon Press, 1984, and by Schaumann in Hetarene III, Methoden der organischen Chemie (Houben-Weyl), 4th edition, Verlag Thieme, Stuttgart 1993.

Thus, for example, a compound of general formula II is obtained by acylating a corresponding o-diamino compound with a corresponding reactive derivative of a compound of general formula III,

a compound of general formulae IV, VII, IX, X, XI and XII is obtained by cyclisation of a corresponding substituted compound according to process a) and if necessary subsequent reduction of any nitro group present in the phenyl moiety, followed by acylation, amidation and/or halogenation.

Moreover, the compounds of general formula I obtained may be resolved into their enantiomers and/or diastereomers, as mentioned hereinbefore.

Thus, for example, the compounds of general formula I obtained which occur as racemates may be separated by methods known *per se* (cf. Allinger N. L. and Eliel E. L. in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) into their optical antipodes and compounds of general formula I with at least 2 asymmetric carbon atoms may be resolved into their diastereomers on the basis of their physical-chemical differences using methods known *per se*, e.g. by chromatography and/or

fractional crystallisation, and, if these compounds are obtained in racemic form, they may subsequently be resolved into the enantiomers as mentioned above.

5 The enantiomers are preferably separated by column separation on chiral phases or by recrystallisation from an optically active solvent or by reacting with an optically active substance which forms salts or derivatives such as e.g. esters or amides with the racemic
10 compound, particularly acids and the activated derivatives or alcohols thereof, and separating the diastereomeric mixture of salts or derivatives thus obtained, e.g. on the basis of their differences in solubility, whilst the free antipodes may be released from the pure diastereomeric
15 salts or derivatives by the action of suitable agents. Optically active acids in common use are e.g. the D- and L-forms of tartaric acid or dibenzoyltartaric acid, di-o-tolyltartaric acid, malic acid, mandelic acid, camphorsulphonic acid, glutamic acid, aspartic acid or
20 quinic acid. An optically active alcohol may be for example (+) or (-)-menthol and an optically active acyl group in amides, for example, may be a (+)-or (-)-menthyloxycarbonyl.

25 Furthermore, the compounds of formula I may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts with inorganic or organic acids. Acids which may be used for this purpose include for example hydrochloric acid,
30 hydrobromic acid, sulphuric acid, methanesulphonic acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid.

Moreover, if the new compounds of formula I contain a
35 carboxy group, they may subsequently, if desired, be converted into the salts thereof with inorganic or organic bases, particularly for pharmaceutical use into the

physiologically acceptable salts thereof. Suitable bases for this purpose include for example sodium hydroxide, potassium hydroxide, arginine, cyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

5

As already mentioned hereinbefore, the new compounds of general formula I and the salts thereof have valuable properties. Thus, the compounds of general formula I wherein R_c denotes a cyano group are valuable intermediate products for preparing the other compounds of general formula I, and the compounds of general formula I wherein R_c denotes one of the abovementioned amidino groups, and the tautomers, stereoisomers and the physiologically acceptable salts thereof have valuable pharmacological properties, particularly an antithrombotic activity, which is preferably based on an activity which influences thrombin or factor Xa, for example on a thrombin-inhibiting or factor Xa-inhibiting activity, on an activity which extends the aPTT time and on an inhibiting effect on related serine proteases such as, for example, trypsin, urokinase factor VIIa, factor IX, factor XI and factor XII.

20

For example, the compounds

25

A = 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(pyrrolidin-1-yl-carbonyl)cyclopropyl]-benzimidazole-hydrochloride,

30

B = (E/Z)-2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-[(pyridin-2-yl)-(carboxymethyloxyimino)methylene]-cyclopropyl]-benzimidazole-hydrochloride,

35

C = 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(2-carboxyethylamino)-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole-hydrochloride,

D = 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-[2-(2-carboxyethyl)-pyrrolidin-1-yl-carbonyl]cyclopropyl]-benzimidazole-hydrochloride,

5 E = 2-(4-amidinophenylaminomethyl)-1-methyl-5-[2-(2-carboxyethyl)-4,5-dimethyl-imidazol-1-yl-methyl]-benzimidazole-hydrochloride,

F = 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(carboxymethylamino)-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole-hydrochloride and

10

G = 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(N-methylcarboxymethylcarbonylaminomethyl)-1-methyl-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole-dihydrochloride

15

were investigated for their effect on extending the aPTT time as follows:

20 Materials:

- Plasma, from human citrated blood,
- PTT reagent, Boehringer Mannheim (524298),
- calcium solution (0.025 Mol/l), Behring Werke, Marburg (ORH 056/57),
- 25 - diethylbarbiturate acetate buffer, Behring Werke, Marburg (ORWH 60/61),
- Biomatic B10 coagulometer, Desaga, Wiesloch.

Method:

30

The aPTT time was determined using a Biomatic B10-coagulometer made by Messrs. Desaga.

The test substance was added to the test vessels prescribed by the manufacturer with 0.1 ml of human

35 citrate plasma and 0.1 ml of PTT reagent. The mixture was incubated for three minutes at 37°C. The clotting reaction

was started by the addition of 0.1 ml of calcium solution. Because of the design of the apparatus, the time taken for the mixture to clot was measured as the calcium solution was added. Mixtures to which 0.1 ml of DBA buffer had been
5 added were used as controls.

According to the definition the effective concentration of substance at which the aPTT time was double that of the control was determined by means of a dosage/activity
10 curve.

The following Table contains the values found:

substance	APTT time (ED ₂₀₀ in μ M)
A	0.12
B	0.42
C	0.31
D	0.29
E	0.29
F	0.20
G	0.17

15

The compounds prepared according to the invention are well tolerated, since no toxic side effects could be detected at therapeutic doses.

20

In view of their pharmacological properties the new compounds and the physiologically acceptable salts thereof are suitable for the prevention and treatment of venous and arterial thrombotic diseases, such as for example the
25 treatment of deep leg vein thrombosis, for preventing reocclusions after bypass operations or angioplasty (PT(C)A), and occlusion in peripheral arterial diseases

such as pulmonary embolism, disseminated intravascular coagulation, for preventing coronary thrombosis, stroke and the occlusion of shunts. In addition, the compounds according to the invention are suitable for antithrombotic support in thrombolytic treatment, such as for example with rt-PA or streptokinase, for preventing long-term restenosis after PT(C)A, for preventing metastasis and the growth of clot-dependent tumours and fibrin-dependent inflammatory processes, e.g. in the treatment of pulmonary fibrosis.

The dosage required to achieve such an effect is appropriately 0.1 to 30 mg/kg, preferably 0.3 to 10 mg/kg by intravenous route, and 0.1 to 50 mg/kg, preferably 0.3 to 30 mg/kg by oral route, in each case administered 1 to 4 times a day. For this purpose, the compounds of formula I prepared according to the invention may be formulated, optionally together with other active substances, with one or more inert conventional carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethyleneglycol, propyleneglycol, cetylstearyl alcohol, 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 or suppositories.

The Examples which follow are intended to illustrate the invention:

Example 1

2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(pyrrolidin-1-yl-carbonyl)cyclopropyl]-benzimidazole-hydrochloride

5

a. 1-(4-chloro-3-nitro-phenyl)-1-cyclopropanecarboxylic acid

To 350 ml of fuming nitric acid are added, in batches, at -25°C, 50.0 g (0.21 mol) of 1-(4-chlorophenyl)-1-cyclopropanecarboxylic acid. The solution is stirred for 15 minutes at -25°C and subsequently poured onto ice water. The product precipitated is suction filtered, washed with water and dried.

Yield: 58.5 g (95 % of theory),
15 R_f value: 0.45 (silica gel; methylene chloride/methanol = 9.5:0.5)

b. 1-(4-methylamino-3-nitro-phenyl)-1-cyclopropanecarboxylic acid

20 20.0 g (0.083 mol) of 1-(4-chloro-3-nitro-phenyl)-1-cyclopropanecarboxylic acid and 100 ml of methylamine solution (40% in H₂O) are heated to 80°C in a pressure vessel for five hours. The contents are evaporated to dryness, dissolved in water and acidified with glacial acetic acid. The product precipitated is suction filtered, washed with water and dried.

Yield: 16.9 g (93 % of theory),
R_f value: 0.58 (silica gel; methylene chloride/methanol = 9:1)

30

c. 4-[1-(pyrrolidin-1-yl-carbonyl)cyclopropyl]-2-nitro-N-methyl-aniline

2.4 g (0.01 mol) of 1-(4-methylamino-3-nitro-phenyl)-1-cyclopropanecarboxylic acid are dissolved in 50 ml dimethylformamide and after the addition of 3.2 g (0.01 mol) of O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate, 0.7 g (0.01 mol) of pyrrolidine and 1.1

g (0.01 mol) of N-methyl-morpholine stirred for 20 hours at ambient temperature. The solvent is distilled off and the residue is chromatographed on silica gel, eluting with methylene chloride. The desired fractions are concentrated
5 by evaporation, triturated with ether, suction filtered and dried.

Yield: 1.8 g (61 % of theory),

R_f value: 0.51 (silica gel; methylene chloride/methanol = 9:1)

10

d. 4-[1-(pyrrolidin-1-yl-carbonyl)cyclopropyl]-2-amino-N-methyl-aniline

1.8 g (6.2 mmol) of 4-[1-(pyrrolidin-1-yl-carbonyl)cyclopropyl]-2-nitro-N-methyl-aniline are
15 dissolved in 40 ml methanol and 40 ml methylene chloride and after the addition of 0.4 g of palladium on activated charcoal (10%) hydrogenated for 4 hours at ambient temperature. Then the catalyst is filtered off and the
20 residue is concentrated by evaporation.

Yield: 1.6 g (100 % of theory),

R_f value: 0.26 (silica gel; methylene chloride/methanol = 9:1)

25 e. 4-[1-(pyrrolidin-1-yl-carbonyl)cyclopropyl]-2-(4-cyanophenyl)aminomethylcarbonylamino-N-methyl-aniline

Prepared analogously to Example 1c from 4-[1-(pyrrolidin-1-yl-carbonyl)cyclopropyl]-2-amino-N-methyl-aniline, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium
30 tetrafluoroborate, 4-cyano-phenylglycine and triethylamine in dimethylformamide.

Yield: 66 % of theory,

R_f value: 0.51 (silica gel; methylene chloride/methanol = 9:1)

35

f. 2-(4-cyanophenylaminomethyl)-1-methyl-5-[1-(pyrrolidin-1-yl-carbonyl)cyclopropyl]-benzimidazole

1.7 g (0.004 mol) of 4-[1-(pyrrolidin-1-yl-carbonyl)cyclopropyl]-2-(4-cyanophenyl)-aminomethylcarbonylamino-N-methyl-aniline are refluxed in 7 ml of glacial acetic acid for 2 hours. The solvent is distilled off, the residue dissolved in water and extracted with methylene chloride. The organic phase is dried, concentrated by evaporation and subsequently chromatographed on silica gel, eluting with methylene chloride + 2 to 3% methanol.

Yield: 1.0 g (62 % of theory),
R_f value: 0.49 (silica gel; methylene chloride/methanol = 9:1)

g. 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(pyrrolidin-1-yl-carbonyl)cyclopropyl]-benzimidazole-hydrochloride

1.0 g (2.5 mmol) of 2-(4-cyanophenylaminomethyl)-1-methyl-5-[1-(pyrrolidin-1-yl-carbonyl)cyclopropyl]-benzimidazole are dissolved in 50 ml saturated ethanolic hydrochloric acid and stirred for 5 hours at ambient temperature. The solvent is distilled off, the residue dissolved in 50 ml absolute ethanol and mixed with 2.3 g (25 mmol) of ammonium carbonate. After 60 hours at ambient temperature the mixture is evaporated to dryness. The residue is chromatographed on silica gel, eluting with methylene chloride/methanol (7:1).

Yield: 700 mg (62 % of theory),
R_f value: 0.61 (silica gel; methylene chloride/methanol = 4:1)

C₂₄H₂₈N₆O x HCl (416.54/453.0)
mass spectrum: (M+H)⁺ = 417

The following compounds are obtained analogously to Example 1:

(1) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(3-methyl-piperidin-1-yl-carbonyl)cyclopropyl]-benzimidazole-hydrochloride

Yield: 45 % of theory,

5 R_f value: 0.25 (silica gel; methylene chloride/methanol = 4:1)

$C_{26}H_{32}N_6O \times HCl$ (444.59/481.05)

mass spectrum: $(M+H)^+ = 445$

10 (2) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(piperidin-1-yl-carbonyl)cyclopropyl]-benzimidazole-hydrochloride

Yield: 57 % of theory,

R_f value: 0.23 (silica gel; methylene chloride/methanol =
15 4:1)

$C_{25}H_{30}N_6O \times HCl$ (430.56/467.93)

mass spectrum: $(M+H)^+ = 431$

(3) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(4-methyl-piperazin-1-yl-carbonyl)cyclopropyl]-benzimidazole-hydrochloride

Yield: 32 % of theory,

R_f value: 0.26 (silica gel; methylene chloride/methanol/-
ammonia = 2:1:0.25)

25 $C_{25}H_{31}N_7O \times HCl$ (445.58/482.04)

mass spectrum: $(M+H)^+ = 446$

(4) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(2,3-dihydroindolin-1-yl-carbonyl)cyclopropyl]-benzimidazole-hydrochloride

30 Yield: 60 % of theory,

R_f value: 0.34 (silica gel; methylene chloride/methanol =
4:1)

$C_{28}H_{28}N_6O \times HCl$ (464.58/501.04)

35 mass spectrum: $(M+H)^+ = 465$

(5) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-((2-ethoxycarbonylethyl)-piperidin-1-yl-carbonyl)cyclopropyl]-benzimidazole-hydrochloride

Yield: 85 % of theory,

5 R_f value: 0.57 (silica gel; methylene chloride/methanol = 4:1)

$C_{30}H_{38}N_6O_3 \times HCl$ (530.67/567.13)

mass spectrum: $(M+H)^+ = 531$

10 (6) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-((2-ethoxycarbonylethyl)-pyrrolidin-1-yl-carbonyl)cyclopropyl]-benzimidazole-hydrochloride

Yield: 60 % of theory,

$C_{29}H_{36}N_6O_3 \times HCl$ (516.64/553.10)

15 mass spectrum: $(M+H)^+ = 517$

$(M+2H)^{++} = 259$

(7) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-[(N-(2-ethoxycarbonylethyl)-N-methyl-aminomethyl)-pyrrolidin-1-yl-carbonyl]cyclopropyl]-benzimidazole-hydrochloride

20 Yield: 65 % of theory,

$C_{31}H_{41}N_7O_3 \times HCl$ (559.72/ 596.18)

mass spectrum: $(M+H)^+ = 560$

$(M+2H)^{++} = 280.6$

25

(8) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-[(2-ethoxycarbonylmethyloxymethyl)-pyrrolidin-1-yl-carbonyl]cyclopropyl]-benzimidazole-hydrochloride

Yield: 61 % of theory,

30 R_f value: 0.20 (silica gel; methylene chloride/ethanol = 8:2 + 1 % glacial acetic acid)

$C_{29}H_{36}N_6O_4 \times HCl$ (532.66/569.11)

mass spectrum: $(M+H)^+ = 533$

$(M+2H)^{++} = 267$

35

Example 2

2- (4-amidinophenylaminomethyl) -1-methyl-5- (1-
cyclopentylcarbonyl-3-chloro-n-propyl) -benzimidazole-
5 hydrochloride

a. 4- [1- (cyclopentylcarbonyl) cyclopropyl] -chlorobenzene

2.4 g (0.1 mol) of magnesium chips are suspended in 10 ml
ether. After the addition of a spatula-tip of iodine,
10 14.9 g (0.1 mol) of bromocyclopentane are slowly added
dropwise to 40 ml of ether, the reaction being started off
initially by gentle heating. After the addition has ended
the mixture is refluxed for 30 minutes. Then a solution of
14.0 g (0.08 mol) of 1- (4-chlorophenyl) -1-
15 cyclopropanecarbonitrile in 75 ml ether is added and
refluxed for a further 3 hours. The reaction solution is
poured onto ice water, adjusted to pH 3 with hydrochloric
acid and extracted with ether. The organic extracts are
dried and concentrated by evaporation. The residue is
20 chromatographed on silica gel and eluted with petroleum
ether/ethyl acetate (19:1 and 15:1).
Yield: 3.0 g (12 % of theory),
R_f value: 0.58 (silica gel; petroleum ether/ethyl acetate
= 4:1)

25

b. 4- [1- (cyclopentylcarbonyl) cyclopropyl] -2-nitro-
chlorobenzene

Prepared analogously to Example 1a from 4- [1-
(cyclopentylcarbonyl) cyclopropyl] -chlorobenzene and fuming
30 nitric acid.
Yield: 87 % of theory,
R_f value: 0.60 (silica gel; petroleum ether/ethyl acetate
= 9:1)

c. 4-[1-(cyclopentylcarbonyl)cyclopropyl]-2-nitro-N-methyl-aniline

Prepared analogously to Example 1b from 4-[1-(cyclopentylcarbonyl)cyclopropyl]-2-nitro-chlorobenzene
5 and aqueous methylamine solution.
Yield: 18 % of theory,
R_f value: 0.54 (silica gel; methylene chloride/ethanol = 19:1)

10 d. 4-[1-(cyclopentylcarbonyl)cyclopropyl]-2-amino-N-methyl-aniline

2.3 g (7.9 mmol) of 4-[1-(cyclopentylcarbonyl)-cyclopropyl]-2-nitro-N-methyl-aniline are dissolved in 125 ml ethyl acetate and 25 ml ethanol and after the addition
15 of 1.0 g Raney nickel hydrogenated for 1.5 hours at ambient temperature. Then the catalyst is filtered off and the residue is concentrated by evaporation.
Yield: 2.0 g (98 % of theory),
R_f value: 0.15 (silica gel; methylene chloride/ethanol =
20 19:1)

e. 4-[1-(cyclopentylcarbonyl)cyclopropyl]-2-(4-cyanophenyl-aminomethylcarbonylamino)-N-methyl-aniline

Prepared analogously to Example 1c from 4-[1-(cyclopentylcarbonyl)cyclopropyl]-2-amino-N-methyl-aniline, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluroniumtetrafluoroborate, 4-cyano-phenylglycine and triethylamine in dimethylformamide.
Yield: 96 % of theory,
30 R_f value: 0.54 (silica gel; methylene chloride/ethanol = 19:1)

f. 2-(4-cyanophenylaminomethyl)-1-methyl-5-[1-(cyclopentylcarbonyl)-cyclopropyl]-benzimidazole

35 Prepared analogously to Example 1f from 4-[1-(cyclopentylcarbonyl)cyclopropyl]-2-(4-cyanophenyl-

aminomethylcarbonylamino)-N-methyl-aniline in glacial acetic acid.

Yield: 53 % of theory,

R_f value: 0.46 (silica gel; methylene chloride/ethanol =
5 19:1)

g. 2-(4-amidinophenylaminomethyl)-1-methyl-5-(1-cyclopentyl-carbonyl-3-chloro-n-propyl)-benzimidazole
hydrochloride

10 Prepared analogously to Example 1g from 2-(4-cyanophenylaminomethyl)-1-methyl-5-(1-cyclopentylcarbonyl-3-chloro-n-propyl)-benzimidazole and hydrochloric acid/ammonium carbonate in ethanol.

Yield: 61 % of theory,

15 C₂₅H₃₀ClN₅O x HCl (452.00/488.56)

mass spectrum: (M+H)⁺ = 452/4 (Cl)

Example 3

20 (E/Z)-2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-[(pyridin-3-yl)-(ethoxycarbonylmethyloxyimino)-methylene]cyclopropyl]-benzimidazole-hydrochloride

a. 1-[(pyridin-3-yl)-carbonyl]cyclopropyl-benzene

25 A solution of 21.4 g (0.135 mol) of 3-bromopyridine in 125 ml of ether is added dropwise at -40 to -50°C to 100 ml of butyllithium (1.6 M in hexane) and then stirred for 20 minutes at -40°C. The mixture is then cooled to -60°C and a solution of 20.1 g (0.14 mol) of 1-phenyl-cyclopropane-
30 carbonitrile in 125 ml ether is added dropwise. After it has all been added, the reaction mixture is heated to ambient temperature and stirred for 5 hours. The suspension is mixed with 20% hydrochloric acid and heated to 100°C for 30 minutes. After cooling, the mixture is
35 adjusted to pH 8 with 20% sodium hydroxide solution and extracted with ethyl acetate. The combined organic extracts are dried and concentrated by evaporation. The

residue is chromatographed on aluminium oxide, eluting with petroleum ether/ethyl acetate (9:1).

Yield: 14.0 g (46 % of theory),

R_f value: 0.27 (aluminium oxide; petroleum ether/ethyl

5 acetate = 9:1)

b. 4-[1-[(pyridin-3-yl)-carbonyl]cyclopropyl]-nitrobenzene

Prepared analogously to Example 1a from 1-[(pyridin-3-yl)-carbonyl]cyclopropyl-benzene and fuming nitric acid.

10 Yield: 53.7 % of theory,

R_f value: 0.29 (aluminium oxide; petroleum ether/ethyl acetate = 4:1)

c. 4-[1-[(pyridin-3-yl)-carbonyl]cyclopropyl]-aniline

15 Prepared analogously to Example 2d from 4-[1-[(pyridin-3-yl)-carbonyl]cyclopropyl]-nitrobenzene and Raney nickel in ethyl acetate/ethanol.

Yield: 94 % of theory,

R_f value: 0.51 (silica gel; methylene chloride/ethanol =

20 19:1)

d. 4-[1-[(pyridin-3-yl)-carbonyl]cyclopropyl]-trifluoroacetylaniline

25 8.0 g (33.5 mmol) of 4-[1-[(pyridin-3-yl)-carbonyl]cyclopropyl]-aniline are dissolved in 100 ml chlorobenzene and after the addition of 15 ml trifluoroacetic anhydride the mixture is stirred for two hours at 110°C. The solvent is distilled off, the residue
30 stirred with petroleum ether/ether (9:1), suction filtered and dried.

Yield: 10.0 g (88 % of theory),

R_f value: 0.54 (silica gel; methylene chloride/ethanol =
19:1)

35

e. 4-[1-[(pyridin-3-yl)-carbonyl]cyclopropyl]-2-nitro-trifluoroacetylaniline

1.7 g (5 mmol) of 4-[1-[(pyridin-3-yl)-
5 carbonyl]cyclopropyl]-trifluoroacetylaniline are added
batchwise to 13 ml of conc. sulphuric acid and 16 ml of
65% nitric acid at -5°C. Then the mixture is stirred for a
further 30 minutes without cooling, poured onto ice water
and extracted with ethyl acetate. The organic extracts are
10 dried and concentrated by evaporation. The residue is
chromatographed on silica gel and eluted with methylene
chloride/ethanol (50:1 and 25:1). The desired fractions
are concentrated by evaporation, triturated with
ether/petroleum ether, suction filtered and dried.
15 Yield: 1.2 g (75 % of theory),
R_f value: 0.70 (silica gel; methylene chloride/ethanol =
19:1)

f. 4-[1-[(pyridin-3-yl)-carbonyl]cyclopropyl]-2-nitro-N-
20 trifluoroacetyl-N-methyl-aniline

1.15 g (3.0 mmol) of 4-[1-[(pyridin-3-yl)-
carbonyl]cyclopropyl]-2-nitro-trifluoroacetylaniline
are dissolved in 50 ml acetone and after the addition of
25 2.0 g potassium carbonate and 0.8 ml methyl iodide
refluxed for two hours. The insoluble matter is filtered
off and the solution is evaporated down. The residue is
chromatographed on silica gel, eluting with petroleum
ether/ethyl acetate (1:1 and 1:4).
30 Yield: 0.88 g (75 % of theory),
R_f value: 0.38 (silica gel; petroleum ether/ethyl acetate
= 1:1)

g. 4-[1-[(pyridin-3-yl)-carbonyl]cyclopropyl]-2-nitro-N-methyl-aniline

7.4 g (18.8 mmol) of 4-[1-[(pyridin-3-yl)-
5 carbonyl]cyclopropyl]-2-nitro-N-trifluoroacetyl-N-methyl-aniline are stirred in 200 ml of 20% potassium hydroxide solution for one hour at 30°C. Then the mixture is diluted with isopropanol, the organic phase is separated off, 10.0 g of aluminium oxide are added and the resulting mixture
10 is evaporated to dryness. The residue is chromatographed on aluminium oxide, eluting with petroleum ether/ethyl acetate (4:1 and 1:1).

Yield: 2.6 g (47 % of theory),
R_f value: 0.50 (silica gel; petroleum ether/ethyl acetate
15 = 1:1)

h. 4-[1-[(pyridin-3-yl)-carbonyl]cyclopropyl]-2-amino-N-methyl-aniline

20 Prepared analogously to Example 2d from 4-[1-[(pyridin-3-yl)-carbonyl]cyclopropyl]-2-nitro-N-methyl-aniline and Raney nickel in ethyl acetate/ethanol.

Yield: 98 % of theory,
R_f value: 0.51 (silica gel; methylene chloride/ethanol =
25 19:1)

i. 4-[1-[(pyridin-3-yl)-carbonyl]cyclopropyl]-2-(4-cyano-phenyl)-aminomethylcarbonylamino-N-methyl-aniline

30 Prepared analogously to Example 1c from 4-[1-[(pyridin-3-yl)-carbonyl]cyclopropyl]-2-amino-N-methyl-aniline, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate, 4-cyano-phenylglycine and triethylamine in dimethylformamide.

35 Yield: 97 % of theory,
R_f value: 0.48 (silica gel; methylene chloride/ethanol = 19:1)

k. 2-(4-cyanophenylaminomethyl)-1-methyl-5-[1-[(pyridin-3-yl)-carbonyl]cyclopropyl]-benzimidazole

- 5 Prepared analogously to Example 1f from 4-(pyridin-3-yl-carbonyl)cyclopropyl-2-(4-cyanophenyl)-aminomethylcarbonylamino-N-methyl-aniline in glacial acetic acid.
Yield: 76 % of theory,
10 R_f value: 0.52 (silica gel; methylene chloride/ethanol = 19:1)

1. (E/Z)-2-(4-cyanophenylaminomethyl)-1-methyl-5-[1-[(pyridin-3-yl)-(carboxymethyloxyimino)methylene]-cyclopropyl]benzimidazole

- 1.6 g (4.0 mmol) of 2-(4-cyanophenylaminomethyl)-1-methyl-5-[1-[(pyridin-3-yl)-carbonyl]cyclopropyl]-benzimidazole, 3.0 g (12 mmol) of carboxy-methoxylamine-hemihydrate, 0.84
20 ml of triethylamine, 12 g of molecular sieve 3A and 12 g of molecular sieve 4A are refluxed for 12 hours in 80 ml methanol and 40 ml toluene. Then the molecular sieve is filtered off and the filtrate is concentrated by
evaporation. The residue is stirred with water, suction
25 filtered and dried. The crude product is chromatographed on silica gel, eluting with methylene chloride/ethanol/glacial acetic acid (25:1:0 and 8:2:0.2).
Yield: 0.9 g (48 % of theory),
 R_f value: 0.34 (silica gel; methylene chloride/ethanol/-
30 glacial acetic acid = 8:2:0.2)

m. (E/Z)-2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-[(pyridin-3-yl)-(ethoxycarbonylmethyloxyimino)-methylene]cyclopropyl]-benzimidazole-hydrochloride

35

Prepared analogously to Example 1g from (E/Z)-2-(4-cyanophenylaminomethyl)-1-methyl-5-[1-[(pyridin-3-yl)-

(ethoxycarbonylmethyloxyimino)methylene]cyclopropyl]-benzimidazole and hydrochloric acid/ammonium carbonate in ethanol.

Yield: 60 % of theory,

- 5 R_f value: 0.28 (silica gel; methylene chloride/ethanol/-glacial acetic acid = 8:2:0.2)
 $C_{29}H_{31}N_7O_3 \times HCl$ (525.62/562.09)
mass spectrum: $(M+H)^+ = 526$

- 10 The following compounds are obtained analogously to Example 3:

- (1) (E/Z)-2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-
[(pyridine-2-yl)-(ethoxycarbonylmethyloxyimino)-
15 methylene]cyclopropyl]-benzimidazole-hydrochloride
Yield: 52 % of theory,

R_f value: 0.21 (silica gel; methylene
chloride/ethanol/glacial acetic acid = 8:2:0.2)
 $C_{29}H_{31}N_7O_3 \times HCl$ (525.62/562.09)

- 20 mass spectrum: $(M+H)^+ = 526$

- (2) (E/Z)-2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-
[phenyl-(ethoxycarbonylmethyloxyimino)-methylene]-
cyclopropyl]-benzimidazole-hydrochloride

- 25 Yield: 18 % of theory,

$C_{30}H_{32}N_6O_3 \times HCl$ (524.63/561.09)

mass spectrum: $(M+H)^+ = 525$

$(M-H+HCl)^- = 559/61$ (Cl)

- 30 (3) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(1-methyl-pyrazol-5-yl-carbonyl)cyclopropyl]-benzimidazole-hydrochloride

Yield: 10 % of theory,

$C_{24}H_{25}N_7O \times HCl$ (427.51/ 463.97)

- 35 mass spectrum: $(M+H)^+ = 428$

$(M+H+HCl)^- = 464/6$ (Cl)

(4) (E/Z)-2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-
[(1-methyl-pyrazol-5-yl)-(ethoxycarbonylmethyloxyimino)-
methylene]cyclopropyl]-benzimidazole-hydrochloride

Yield: 80 % of theory,

5 R_f value: 0.20 (silica gel; methylene chloride/ethanol =
8:2 + 1 % glacial acetic acid)

$C_{28}H_{32}N_8O_3 \times HCl$ (528.63/565.08)

mass spectrum: $(M+H)^+ = 529$

10 (5) (E/Z)-2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-
[phenyl-(3-ethoxycarbonyl-n-propyloxyimino)methylene]-
cyclopropyl]-benzimidazole-dihydrochloride

Yield: 47 % of theory,

R_f value: 0.06 (silica gel; methylene chloride/methanol =
15 9:1)

$C_{32}H_{36}N_6O_3 \times 2 HCl$ (552.69/625.60)

mass spectrum: $(M+H)^+ = 553$

Example 4

20

(E/Z)-2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-
[(pyridine-2-yl)-(carboxymethyloxyimino)methylene]-
cyclopropyl]-benzimidazole-hydrochloride

25 150 mg (E/Z)-2-(4-amidinophenylaminomethyl)-1-methyl-
5-[1-[(pyridin-2-yl)-(ethoxycarbonylmethyloxyimino)-
methylene]cyclopropyl]-benzimidazole-hydrochloride and 2.5
ml of 2N sodium hydroxide solution are stirred in 10 ml
ethanol for 5 hours at ambient temperature. The alcohol is
30 distilled off and the residue is adjusted to pH 5 with
hydrochloric acid. The crystalline product is suction
filtered, washed with water and dried.

Yield: 46 % of theory,

R_f value: 0.10 (silica gel; methylene chloride/ethanol/-
35 glacial acetic acid = 8:2:0.1)

$C_{27}H_{27}N_7O_3 \times HCl$ (497.58/534.05)

mass spectrum: $(M+H)^+ = 498$
 $(M+Na)^+ = 520$

The following compounds are obtained analogously to

5 Example 4:

(1) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-[2-(2-carboxyethyl)-piperidin-1-yl-carbonyl]cyclopropyl]-benzimidazole-hydrochloride

10 Yield: 94 % of theory,

R_f value: 0.57 (Reversed phase RP 18; methanol/5% sodium chloride solution = 3:2)

$C_{28}H_{34}N_6O_3 \times HCl$ (502.62/539.08)

mass spectrum: $(M+H)^+ = 503$

15 $(M+Na)^+ = 525$

(2) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(2-carboxyethylamino)-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole-hydrochloride

20 Yield: 98 % of theory,

R_f value: 0.73 (Reversed phase RP 8; methanol/5% sodium chloride solution = 1:2)

$C_{26}H_{33}N_7O_3 \times HCl$ (491.60/564.54)

mass spectrum: $(M+H)^+ = 492$

25 $(M+2H)^{++} = 247$

(3) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(3-carboxypropionylamino)-1-(ethoxycarbonyl)-ethyl]-benzimidazole-hydrochloride

30 Yield: 98 % of theory,

R_f value: 0.70 (RP 8; methanol/5% sodium chloride solution = 1 :2)

$C_{25}H_{30}N_6O_5 \times HCl$ (494.55/531.05)

mass spectrum: $(M+H)^+ = 495$

35 $(2M+H)^+ = 989$

(4) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(carboxymethylamino)-1-(pyrrolidin-1-yl-carbonyl)-methyl]-benzimidazole-hydrochloride

Yield: 87 % of theory,

5 $C_{24}H_{29}N_7O_3 \times HCl$ (463.54/500.04)

mass spectrum: $(M+H)^+ = 464$

$(M+2H)^+ = 232.6$

(5) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-[2-(2-carboxyethyl)-pyrrolidin-1-yl-carbonyl]cyclopropyl]-benzimidazole-hydrochloride

Yield: 94 % of theory,

$C_{27}H_{32}N_6O_3 \times HCl$ (488.59/525.05)

mass spectrum: $(M+H)^+ = 489$

15 $(M+Na)^+ = 511$

(6) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(carboxymethylcarbonylamino)-1-(pyrrolidin-1-yl-carbonyl)-methyl]-benzimidazole-hydrochloride

20 Yield: 49 % of theory,

$C_{25}H_{29}N_7O_4 \times HCl$ (491.55/528.01)

mass spectrum: $(M+H)^+ = 492$

$(M+H+Na)^{++} = 257.7$

(7) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(carboxymethylcarbonylamino)-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole-hydrochloride

Yield: 92 % of theory,

$C_{26}H_{31}N_7O_4 \times HCl$ (505.58/542.04)

30 mass spectrum: $(M+H)^+ = 506$

$(M+H+Na)^{++} = 264.7$

(8) 2-(4-amidinophenylaminomethyl)-1-methyl-5-(5-methyl-3-carboxymethyl-imidazolin-2,4-dion-5-yl)-benzimidazole-hydrochloride

35

Yield: 88 % of theory,

$C_{22}H_{23}N_7O_4 \times HCl$ (449.47/485.94)

mass spectrum: $(M+H)^+$ = 450
 $(M+2Na)^{++}$ = 247.7

5 (9) (E/Z)-2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-
[(pyridin-3-yl)-(carboxymethyloxyimino)methylene]-
cyclopropyl]-benzimidazole-hydrochloride

Yield: 54 % of theory,

$C_{27}H_{27}N_7O_3 \times HCl$ (497.56/534.09)

10 mass spectrum: $(M+H)^+$ = 498
 $(M+Na)^+$ = 520

(10) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-[2-(N-(2-carboxyethyl)-N-methyl-aminomethyl)-pyrrolidin-1-yl-carbonyl]cyclopropyl]-benzimidazole-hydrochloride

15 Yield: 100 % of theory,

$C_{29}H_{37}N_7O_3 \times HCl$ (531.66/568.12)

mass spectrum: $(M+H)^+$ = 532
 $(M-H)^-$ = 530

20 (11) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[N-(2-carboxyethyl)-N-(2-pyridyl)-aminomethyl]-benzimidazole-hydrochloride

Yield: 91 % of theory,

$C_{25}H_{27}N_7O_2 \times HCl$ (457.54/493.96)

25 mass spectrum: $(M+H)^+$ = 458

(12) 2-(4-amidinophenylaminomethyl)-1-methyl-5-(N-benzenesulphonyl-N-carboxymethyl-aminomethyl)-benzimidazole-hydrochloride

30 Yield: 84 % of theory,

$C_{25}H_{26}N_6O_4S \times HCl$ (506.59/543.06)

mass spectrum: $(M+H)^+$ = 507

(13) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[2-(2-carboxy-ethyl)-benzimidazole-1-yl-methyl]-benzimidazole-hydrochloride

Yield: 76% of theory,

$C_{27}H_{27}N_7O_2 \times HCl$ (481.56/518.05)

mass spectrum: $(M+H)^+ = 482$
 $(M+2H)^{2+} = 242$
 $(M+Na)^+ = 504$
5 $(M+H+Na)^{2+} = 253$
 $(M-H+2Na)^+ = 526$
 $(M+2Na)^{2+} = 264$

(14) 2-(4-amidinophenylaminomethyl)-1-methyl-5-(2-methyl-
10 4-carboxy-imidazol-1-yl-methyl)-benzimidazole-
hydrochloride

Yield: 61% of theory,

$C_{22}H_{23}N_7O_2 \times HCl$ (417.47/453.92)

mass spectrum: $(M+H)^+ = 418$

15

(15) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[3-(3-
carboxy-n-propyl)-benzimidazol-2-on-1-yl-methyl]-
benzimidazole-hydrochloride

Yield: 86% of theory,

20 $C_{28}H_{29}N_7O_3 \times HCl$ (511.59/548.04)

mass spectrum: $(M+H)^+ = 512$
 $(M+Na)^+ = 534$
 $(M+H+Na)^{2+} = 267.7$
 $(M+2Na)^{2+} = 278.8$

25

(16) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[3-(2-
carboxy-ethyl)-imidazo[4,5-b]pyridin-2-on-1-yl-methyl]-
benzimidazole-hydrochloride

Yield: 83% of theory,

30 $C_{26}H_{26}N_8O_3 \times HCl$ (498.55/535)

mass spectrum: $(M+H)^+ = 499$
 $(M+Na)^+ = 521$
 $(M-H)^- = 497$
 $(2M-H)^- = 995$

35

(17) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[2-(2-carboxyethyl)-4,5-dimethyl-imidazol-1-yl-methyl]-benzimidazole-hydrochloride

Yield: 68% of theory,

5 R_f value: 0.70 (Reversed phase RP 8; methanol/5% sodium chloride solution = 6:4)

$C_{25}H_{29}N_7O_2 \times HCl$ (459.56/496.01)

mass spectrum: $(M+H)^+ = 460$

$(M+Na)^+ = 482$

10 $(M+H+Na)^{2+} = 241$

(18) (E/Z)-2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-[phenyl-(carboxymethyloxyimino)methylene]cyclopropyl]-benzimidazole-dihydrochloride

15 Yield: 70% of theory,

$C_{28}H_{28}N_6O_3 \times 2HCl$ (496.57/569.5)

mass spectrum: $(M+H)^+ = 497$

$(M-H)^- = 495$

20 (19) (E/Z)-2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-[(pyridin-3-yl)-(carboxymethylidene)-methylene]cyclopropyl]-benzimidazole-hydrochloride

Yield: 37% of theory

R_f value: 0.45 (Reversed phase RP 8; methanol/5% sodium

25 chloride solution = 6:4)

$C_{27}H_{26}N_6O_2 \times HCl$ (466.55/503.0)

mass spectrum: $(M+H)^+ = 467$

(20) (E/Z)-2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-[(1-methyl-pyrazol-5-yl)-(carboxymethyloxyimino)-methylene]cyclopropyl]-benzimidazole-hydrochloride

30 Yield: 30% of theory,

R_f value: 0.25 (Reversed phase RP 8; (5% saline solution/methanol = 1:1)

35 $C_{26}H_{28}N_8O_3 \times HCl$ (500.58/537.03)

mass spectrum: $(M+H)^+ = 501$
 $(M-H)^- = 499$
 $(M+Cl)^+ = 535/537$ (Cl)

- 5 (21) (E/Z)-2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-
[phenyl-(3-carboxy-n-propyloxyimino)methylene]-
cyclopropyl]-benzimidazole-dihydrochloride
Yield: 37 % of theory,
R_f value: 0.35 (Reversed phase RP 8; 5% saline
10 solution/methanol = 3:2)
C₃₀H₃₂N₆O₃ x 2 HCl (524.64/597.55)
mass spectrum: $(M+H)^+ = 525$

Example 5

15

2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(pyrrolidin-
1-yl-carbonyl)-aminomethyl]-benzimidazole-hydrochloride

a. 5-(4-chlorophenyl)-imidazolidin-2,4-dione

- 20 15.0 g (0.11 mol) of 4-chlorobenzaldehyde, 51.3 g (0.53
mol) of ammonium carbonate and 7.6 g (0.12 mol) of
potassium cyanate are stirred in 150 ml water and 150 ml
methanol for 18 hours at 55° C. The solvent is distilled
off, the residue dissolved in water and extracted with
25 ethyl acetate. The combined organic extracts are dried and
concentrated by evaporation.
Yield: 8.6 g (38 % of theory),
melting point: 215° C

30 b. 5-(4-chloro-3-nitro-phenyl)-imidazolidin-2,4-dione

- Prepared analogously to Example 1a from 5-(4-
chlorophenyl)-imidazolidin-2,4-dione and fuming nitric
acid.
Yield: 52 % of theory,
35 R_f value: 0.63 (silica gel; methylene chloride/methanol =
9:1)

c. 4-chloro-3-nitro-phenylalanine-hydrochloride

560 mg (2.2 mmol) of 5-(4-chloro-3-nitro-phenyl)-imidazolidin-2,4-dione are refluxed for 24 hours in 20 ml of semiconc. hydrochloric acid. The solvent is distilled off, the residue dissolved in water, filtered to remove the insoluble matter and concentrated by evaporation. The residue is dissolved three times in ethanol, evaporated to dryness, triturated with ether, suction filtered and dried.

Yield: 380 mg (65 % of theory),
melting point: 186°C

d. 4-chloro-3-nitro-N-tert.butyloxycarbonyl-phenylalanine

5.7 g (17.8 mmol) of 4-chloro-3-nitro-phenylalanine-hydrochloride are dissolved in 50 ml dioxane and 25 ml water and, after the addition of 5.5 ml (39.1 mmol) of triethylamine and 4.8 g (21.3 mmol) of di-tert.butyl-dicarbonate, stirred for 18 hours at ambient temperature. Then the mixture is diluted with 0.5 M potassium hydrogen sulphate solution and extracted with ethyl acetate. The combined organic extracts are dried and concentrated by evaporation.

Yield: 6.3 g (100 % of theory),
R_f value: 0.20 (silica gel; methylene chloride/methanol = 9:1)

e. 2-(4-chloro-3-nitro-phenyl)-2-tert.butyloxycarbonylamino-1-(pyrrolidin-1-yl)-ethanone

Prepared analogously to Example 1c from 4-chloro-3-nitro-N-tert.butyloxycarbonyl-phenylalanine, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate, pyrrolidine and N-ethyl-diisopropylamine in tetrahydrofuran.

Yield: 68 % of theory,
melting point: 203°C

f. 2-(4-methylamino-3-nitro-phenyl)-2-
tert.butyloxycarbonylamino-1-(pyrrolidin-1-yl)-ethanone

- 5 Prepared analogously to Example 1b from 2-(4-chloro-3-nitro-phenyl)-2-tert.butyloxycarbonylamino-1-(pyrrolidin-1-yl)-ethanone and methylamine solution.
Yield: 76 % of theory,
R_f value: 0.33 (silica gel; cyclohexane/ethyl acetate =
10 1:1)

g. 2-(4-methylamino-3-amino-phenyl)-2-
tert.butyloxycarbonylamino-1-pyrrolidin-1-yl-ethanone

- 15 Prepared analogously to Example 1d from 2-(4-methylamino-3-nitro-phenyl)-2-tert.butyloxycarbonylamino-1-(pyrrolidin-1-yl)-ethanone and palladium on activated charcoal in methylene chloride/ethanol.
Yield: 100 % of theory,
20 R_f value: 0.12 (silica gel; cyclohexane/ethyl acetate = 1:1)

h. 2-[4-methylamino-3-(4-cyanophenylaminomethylcarbonylamino)-phenyl]-2-
25 tert.butyloxycarbonylamino-1-(pyrrolidin-1-yl)-ethanone

- Prepared analogously to Example 1c from 2-(4-methylamino-3-aminophenyl)-2-tert.butyloxycarbonylamino-1-(pyrrolidin-1-yl)-ethanone, O-(benzotriazol-1-yl)-N,N,N',N'-
30 tetramethyluronium tetrafluoroborate, 4-cyanophenylglycine and triethylamine in tetrahydrofuran.
Yield: 100 % of theory,
R_f value: 0.50 (silica gel; methylene chloride/methanol = 9:1)
35

i. 2-(4-cyanophenylaminomethyl)-1-methyl-5-[1-(pyrrolidin-1-yl-carbonyl)-aminomethyl]-benzimidazole

Prepared analogously to Example 1f from 2-[4-methylamino-
3-(4-cyanophenylaminomethylcarbonylamino)-phenyl]-2-
tert.butyloxycarbonylamino-1-(pyrrolidin-1-yl)-ethanone in
glacial acetic acid.

Yield: 30 % of theory,

R_f value: 0.19 (silica gel; methylene chloride/methanol =
9.5:0.5)

k. 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(pyrrolidin-1-yl-carbonyl)-aminomethyl]-benzimidazole-hydrochloride

Prepared analogously to Example 1g from 2-(4-
cyanophenylaminomethyl)-1-methyl-5-[1-(pyrrolidin-1-yl-
carbonyl)-aminomethyl]-benzimidazole and hydrochloric
acid/ammonium carbonate in ethanol.

Yield: 27 % of theory,

$C_{22}H_{27}N_7O \times HCl$ (405.50/441.96)

mass spectrum: $(M+H)^+ = 406$

The following compounds are obtained analogously to
Example 5:

25

(1) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(
pyrrolidin-1-yl-carbonyl)-N-acetyl-aminomethyl]-
benzimidazole-hydrochloride

Yield: 29 % of theory,

$C_{24}H_{29}N_7O_2 \times HCl$ (447.54/484.54)

mass spectrum: $(M+H)^+ = 448$

(2) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(
pyrrolidin-1-yl-carbonyl)-N-(2-ethoxycarbonyl-ethyl)-N-
methyl-aminomethyl]-benzimidazole-hydrochloride

Yield: 74 % of theory,

$C_{28}H_{37}N_7O_3 \times HCl$ (519.65/556.11)

mass spectrum: $(M+H)^+ = 520$

(3) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(pyrrolidin-1-yl-carbonyl)-N-(ethoxycarbonylmethyl)-aminomethyl]-benzimidazole-hydrochloride

Yield: 76 % of theory,

$C_{26}H_{33}N_7O_3 \times HCl$ (491.59/528.05)

mass spectrum: $(M+H)^+ = 492$

$(M+2H)^{++} = 246.7$

10

(4) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(pyrrolidin-1-yl-carbonyl)-N,N-di-(ethoxycarbonylmethyl)-aminomethyl]-benzimidazole-hydrochloride

Yield: 51 % of theory,

15 $C_{30}H_{39}N_7O_5 \times HCl$ (577.68/614.14)

mass spectrum: $(M+H)^+ = 578$

$(M+Na)^+ = 600$

(5) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(pyrrolidin-1-yl-carbonyl)-N-(ethoxycarbonylmethylcarbonyl)-aminomethyl]-benzimidazole-hydrochloride

Yield: 29 % of theory,

$C_{27}H_{33}N_7O_4 \times HCl$ (519.60/556.06)

25 mass spectrum: $(M+H)^+ = 520$

$(M+2H)^{++} = 260.7$

(6) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(pyrrolidin-1-yl-carbonyl)-N-(2-ethoxycarbonylethyl)-aminomethyl]-benzimidazole-hydrochloride

Yield: 84 % of theory,

30 $C_{27}H_{35}N_7O_3 \times HCl$ (505.62/542.62)

mass spectrum: $(M+H)^+ = 506$

$(M+2H)^{++} = 253.7$

35

Example 6

2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-[N-(2-ethoxy-carbonyl-ethyl)-amino]-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-
5 benzimidazole-hydrochloride

a. 5-(4-chloro-3-nitro-phenyl)-5-methyl-imidazolidin-2,4-dione

To 50 ml of fuming nitric acid are added batchwise at
10 -25° C to -35° C 10.0 g (4.45 mmol) of 5-(4-chloro-phenyl)-5-methyl-imidazolidin-2,4-dione. After 45 minutes at -25 to -20° C the reaction mixture is poured onto ice water. The crystalline product is suction filtered, washed with water and dried.

15 Yield: 10.5 g (100 % of theory),
melting point: 173-178° C

R_f value: 0.30 (silica gel; cyclohexane/ethyl acetate = 1:1)

20 b. 2-amino-2-(4-chloro-3-nitro-phenyl)-propionic acid

10.5 g (0.044 mol) of 5-(4-chloro-3-nitro-phenyl)-5-methyl-imidazolidine-2,4-dione are refluxed in 200 ml dioxane and 700 ml of 6N hydrochloric acid for 5 days. The solution is concentrated by evaporation, the residue is
25 taken up in water and extracted with ethyl acetate. The aqueous phase is concentrated by evaporation, mixed with toluene and evaporated to dryness. The residue is triturated with ether, suction filtered and dried.

Yield: 6.8 g (63 % of theory),

30 R_f value: 0.24 (Reversed phase RP8, 5% saline solution/methanol = 1:1)

c. 2-tert.butylloxycarbonylamino-2-(4-chloro-3-nitro-phenyl)-propionic acid

35

Prepared analogously to Example 5d from 2-amino-2-(4-chloro-3-nitro-phenyl)-propionic acid, di-tert.butyl

pyrocarbonate and triethylamine in dioxane.

Yield: 9.6 g (100 % of theory),

R_f value: 0.31 (Reversed phase RP8, 5% saline solution/methanol = 1:2)

5

d. 2-(4-chloro-3-nitro-phenyl)-2-
tert.butyloxycarbonylamino-1-(pyrrolidin-1-yl)-propanone

Prepared analogously to Example 1c from 2-

10 tert.butyloxycarbonylamino-2-(4-chloro-3-nitro-phenyl)-
propionic acid, O-(benzotriazol-1-yl)-N,N,N',N'-
tetramethyluronium tetrafluoroborate, pyrrolidine and N-
methymorpholine in dimethylformamide.

Yield: 94 % of theory,

15 R_f value: 0.11 (silica gel; cyclohexane/ethyl acetate =
1:1)

e. 2-(4-methylamino-3-nitro-phenyl)-2-
tert.butyloxycarbonylamino-1-(pyrrolidin-1-yl)-propanone

20

Prepared analogously to Example 1b from 2-(4-chloro-3-
nitro-phenyl)-2-tert.butyloxycarbonylamino-1-(pyrrolidin-
1-yl)-propanone and methylamine solution in
dimethylformamide at 160°C.

25 R_f value: 0.79 (silica gel; ethyl acetate/ethanol = 9:1)

f. 2-(4-methylamino-3-amino-phenyl)-2-
tert.butyloxycarbonylamino-1-pyrrolidin-1-yl-propanone

30 Prepared analogously to Example 1d from 2-(4-methylamino-
3-nitro-phenyl)-2-tert.butyloxycarbonylamino-1-
(pyrrolidin-1-yl)-propanone and palladium on activated
charcoal/hydrogen in methanol.

Yield: 100 % of theory,

35 R_f value: 0.63 (silica gel; ethyl acetate/ethanol = 9:1)

g. 2-[4-methylamino-3-(4-cyanophenylaminomethyl-carbonylamino)-phenyl]-2-tert.butyloxycarbonylamino-1-(pyrrolidin-1-yl)-propanone

- 5 Prepared analogously to Example 1c from 2-(4-methylamino-3-amino-phenyl)-2-tert.butyloxycarbonylamino-1-(pyrrolidin-1-yl)-propanone, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate, 4-cyanophenylglycine and N-methylmorpholine in dimethylformamide.
- 10 Yield: 37 % of theory,
R_f value: 0.47 (silica gel; ethyl acetate)

h. 2-(4-cyanophenylaminomethyl)-1-methyl-5-[1-(N-tert.butyloxycarbonylamino)-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole

- Prepared analogously to Example 1f from 2-[4-methylamino-3-(4-cyanophenylaminomethylcarbonylamino)-phenyl]-2-tert.butyloxycarbonylamino-1-(pyrrolidin-1-yl)-propanone
- 20 and glacial acetic acid.
Yield: 60 % of theory,
R_f value: 0.37 (silica gel; ethyl acetate)

i. 2-(4-cyanophenylaminomethyl)-1-methyl-5-[1-amino-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole

- 1.3 g (2.3 mmol) of 2-(4-cyanophenylaminomethyl)-1-methyl-5-[1-(N-tert.butyloxycarbonylamino)-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole are dissolved in 20 ml
- 30 dioxane and, after the addition of 40 ml of semiconc. hydrochloric acid, stirred for two hours at ambient temperature. The solution is mixed with ice, made alkaline with ammonia and extracted with ethyl acetate. The combined organic extracts are dried and concentrated by
- 35 evaporation.

Yield: 0.9 g (98 % of theory),
R_f value: 0.14 (silica gel; ethyl acetate/ethanol = 9:1)

k. 2-(4-cyanophenylaminomethyl)-1-methyl-5-[1-[N-(2-ethoxycarbonylethyl)-amino]-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole

5

0.4 g (1.04 mmol) of 2-(4-cyanophenylaminomethyl)-1-methyl-5-[1-amino-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole are dissolved in 10 ml ethanol and after the addition of 0.3 ml (2.7 mmol) of ethyl acrylate stirred
10 for 24 hours at 95°C. The solvent is distilled off and the residue is chromatographed on silica gel, eluting with methylene chloride/ethanol (20:1 and 4:1).

Yield: 0.16 g (31 % of theory),

R_f value: 0.26 (silica gel; ethyl acetate/ethanol = 9:1)

15

l. 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-[N-(2-ethoxycarbonylethyl)-amino]-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole-hydrochloride

20 Prepared analogously to Example 1g from 2-(4-cyanophenylaminomethyl)-1-methyl-5-[1-[N-(2-ethoxycarbonylethyl)-amino]-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole and hydrochloric acid/ammonium carbonate in ethanol.

25 Yield: 96 % of theory,

C₂₈H₃₇N₇O₃ x HCl (519.65/556.11)

mass spectrum: (M+H)⁺ = 520

(M+Na)⁺ = 542

30 The following compounds are obtained analogously to Example 6:

(1) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(3-ethoxycarbonylpropionylamino)-1-ethoxycarbonyl-ethyl]-benzimidazole-hydrochloride

35

Yield: 69 % of theory,

C₂₇H₃₄N₆O₅ x HCl (522.62/555.08)

mass spectrum: $(M+H)^+$ = 523
 $(M+H+Na)^{++}$ = 273

(2) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(ethoxycarbonylmethylcarbonylamino)-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole-hydrochloride

Yield: 95 % of theory,

$C_{28}H_{35}N_7O_4 \times HCl$ (533.64/570.10)

mass spectrum: $(M+H)^+$ = 534
10 $(M+Na)^+$ = 556

(3) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(3-ethoxycarbonylpropionylamino)-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole-hydrochloride

15 Yield: 20 % of theory,

$C_{29}H_{37}N_7O_4 \times HCl$ (547.66/584.12)

mass spectrum: $(M+H)^+$ = 548
 $(M+H+Na)^{++}$ = 285.7

20 (4) 2-[4-amidinophenyl-N-(2-ethoxycarbonylethyl)-aminomethyl]-1-methyl-5-[1-dimethylamino-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole-hydrochloride

Yield: 91 % of theory,

$C_{30}H_{41}N_7O_3 \times HCl$ (547.71/584.17)

25 mass spectrum: $(M+H)^+$ = 548
 $(M-H)^-$ = 546

(5) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(2-ethoxycarbonylethylamino)-1-(dimethylaminocarbonyl)-ethyl]-benzimidazole-hydrochloride

30 Yield: 40 % of theory,

R_f value: 0.60 (Reversed phase RP 8; 5% saline solution/methanol = 1/1)

$C_{26}H_{35}N_7O_3 \times HCl$ (493.63/530.08)

35 mass spectrum: $(M+H)^+$ = 494
 $(M-H+2HCl)^-$ = 564/566/568 (Cl_2)

(6) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(ethoxycarbonylmethylamino)-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole-hydrochloride

Yield: 77 % of theory,

5 R_f value: 0.40 (silica gel; methylene chloride/methanol = 4:1 + 1 % glacial acetic acid)

$C_{27}H_{35}N_7O_3 \times HCl$ (505.63/542.08)

mass spectrum: $(M+H)^+ = 506$

10 (7) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(2-ethoxycarbonylethyl-amino)-1-(N-ethyl-N-methylaminocarbonyl)-ethyl]-benzimidazole-hydrochloride

Yield: 85 % of theory,

R_f value: 0.44 (silica gel; methylene chloride/ethanol =

15 9:1)

$C_{27}H_{37}N_7O_3 \times HCl$ (507.64/544.14)

mass spectrum: $(M+H)^+ = 508$

$(M+Cl)^- = 542/4$ (Cl)

20 (8) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(methoxycarbonylmethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole-hydrochloride

Yield: 99 % of theory,

R_f value: 0.21 (silica gel; methylene chloride/methanol =

25 4:1 + 1 % glacial acetic acid)

$C_{26}H_{33}N_7O_3 \times HCl$ (491.60/528.05)

mass spectrum: $(M+H)^+ = 492$

$(M-H+HCl)^- = 526/8$ (Cl)

$(M-H+2HCl)^- = 562/4/8$ (Cl₂)

30

(9) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(N,N-bis(ethoxycarbonylmethyl)amino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole-hydrochloride

Yield: 65 % of theory,

35 R_f value: 0.35 (silica gel; methylene chloride/methanol = 4:1 + 1 % glacial acetic acid)

$C_{31}H_{41}N_7O_5 \times HCl$ (591.72/628.17)

mass spectrum: $(M+H)^+$ = 592
 $(M-H+HCl)^-$ = 626/8 (Cl)
 $(M-H+2HCl)^-$ = 662/4/6 (Cl₂)

- 5 (10) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(ethoxycarbonylmethylamino)-1-(isoxazolidin-1-yl-carbonyl)-ethyl]-benzimidazole-hydrochloride
Yield: 9% of theory,
R_f value: 0.50 (Reversed phase RP 8; methanol/5% saline
10 solution = 3:2)
C₂₆H₃₃N₇O₄ x HCl (507.60/544.05)
mass spectrum: $(M+H)^+$ = 508
- (11) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(2-ethoxycarbonyl-ethylamino)-1-(isoxazolidin-1-yl-carbonyl)-ethyl]-benzimidazole-hydrochloride
15
- (12) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(ethoxycarbonylmethylamino)-1-(N-methyl-N-ethylaminocarbonyl)-ethyl]-benzimidazole-dihydrochloride
20
Yield: 58% of theory,
R_f value: 0.70 (Reversed phase RP 8; methanol/5% saline solution = 3:2)
C₂₆H₃₅N₇O₃ x 2 HCl (493.62/566.52)
25 mass spectrum: $(M+H)^+$ = 494
 $(M+HCl-H)^-$ = 528/30 (Cl)
- (13) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-((N,N-di-(ethoxycarbonylmethyl)-amino)-1-(N-methyl-N-ethylaminocarbonyl)-ethyl)-benzimidazole-dihydrochloride
30
Yield: 30% of theory,
R_f value: 0.40 (Reversed phase RP 8; methanol/5% saline solution = 3:2)
C₃₀H₄₁N₇O₅ x 2 HCl (579.71/652.62)
35 mass spectrum: $(M+H)^+$ = 580
 $(M-H)^-$ = 578

(14) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(ethoxycarbonylmethylamino)-1-(piperidinocarbonyl)-ethyl]-benzimidazole-dihydrochloride

5 Yield: 82% of theory,

R_f value: 0.60 (Reversed phase RP 8; methanol/5% saline solution = 3:2)

$C_{28}H_{37}N_7O_3 \times 2 HCl$ (519.65/592.75)

mass spectrum: $(M+H)^+ = 520$

10 $(M-H+HCl)^- = 534/6$ (Cl)

$(M-H+2HCl)^- = 590/2/4$ (Cl₂)

(15) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(ethoxycarbonylmethylamino)-1-(diethylaminocarbonyl)-ethyl]-benzimidazole-dihydrochloride

15

Yield: 88% of theory,

R_f value: 0.60 (Reversed phase RP 8; methanol/5% saline solution = 3:2)

$C_{27}H_{37}N_7O_3 \times 2 HCl$ (507.64/580.56)

20 Mass spectrum: $(M+H)^+ = 508$

$(M-H+2HCl)^- = 578/580/582$ (Cl₂)

(16) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(ethoxycarbonylmethyl-methylamino)-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole-dihydrochloride

25

Yield: 46 % of theory,

R_f value: 0.43 (silica gel; methylene chloride/methanol = 4:1 + 1% glacial acetic acid)

$C_{28}H_{37}N_7O_3 \times 2 HCl$ (519.65/592.56)

30 mass spectrum: $(M+H)^+ = 520$

$(M+Cl)^- = 554/6$ (Cl)

(17) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(tetrazol-5-yl-methylamino)-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole-dihydrochloride

35

(18) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(3-ethoxycarbonyl-propylamino)-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole-dihydrochloride

Yield: 95 % of theory,

- 5 R_f value: 0.50 (Reversed phase RP 8; methanol/5% saline solution = 1:1)

$C_{29}H_{39}N_7O_3 \times 2 HCl$ (533.68/606.58)

mass spectrum: $(M+H)^+$ = 534

10

Example 7

- 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-[N-cyclopentyl-N-(3-ethoxycarbonylpropionyl)-
15 amino]cyclopropyl]-benzimidazole-hydrochloride

a. 4-((1-tert.butyloxycarbonylamino)cyclopropyl)-2-nitro-N-methyl-aniline

- 20 15.0 g (63.5 mmol) of 4-((1-carboxy)cyclopropyl)-2-nitro-N-methyl-aniline and 17.6 ml (127 mmol) of triethylamine are dissolved in 250 ml of dichloromethane and 8.3 g (76 mmol) of ethyl chloroformate are added at 0°C. After one hour at ambient temperature 0.75 g tetrabutylammonium
25 bromide are added. Then a solution of 6.3 g (96 mmol) of sodium azide in 20 ml water is added dropwise. After one hour at 0°C the solution is diluted with water and extracted with ethyl acetate. The organic extracts are dried and concentrated by evaporation. The residue is
30 dissolved in 200 ml tert.butanol and refluxed for two hours. The solvent is concentrated by evaporation, the residue chromatographed on silica gel and eluted with methylene chloride.

Yield: 15.5 g (77 % of theory),

- 35 R_f value: 0.83 (silica gel; methylene chloride/methanol = 9.5:0.5)

b. 4-((1-amino)cyclopropyl)-2-nitro-N-methyl-aniline-hydrochloride

15.5 g (0.05 mol) of 4-[(1-tert.butyloxycarbonylamino)-
5 cyclopropyl]-2-nitro-N-methyl-aniline are dissolved in 50 ml ethanol and 50 ml ethanolic hydrochloric acid and stirred for 7 hours at ambient temperature. The solvent is distilled off, the residue triturated with ether, suction filtered and dried.

10 Yield: 98 % of theory,

R_f value: 0.44 (silica gel; methylene chloride/methanol = 9.5:0.5)

c. 4-[N-(1-cyclopentylamino)cyclopropyl]-2-nitro-N-methyl-aniline

12.0 g (0.05 mol) of 4-[(1-amino)cyclopropyl]-2-nitro-N-methyl-aniline-hydrochloride are dissolved in 500 ml of tetrahydrofuran and after the addition of 4.1 g (0.05 mol)
20 of cyclopentanone and 3.2 ml of glacial acetic acid, 13.6 g (0.064 mol) of sodium triacetoxymethylborohydride are added batchwise under a nitrogen atmosphere. After 16 hours at ambient temperature, the mixture is diluted with sodium hydrogen carbonate solution and extracted with ethyl
25 acetate. The organic extracts are dried and concentrated by evaporation. The residue is chromatographed on silica gel and eluted with ethyl acetate/cyclohexane (1:1).

Yield: 10.8 g (80 % of theory)

30 R_f value: 0.56 (silica gel; methylene chloride/methanol = 9.5:0.5)

d. 4-[1-(N-(3-ethoxycarbonylpropionyl)-N-cyclopentyl-amino)cyclopropyl]-2-nitro-N-methyl-aniline

35 1.0 g (3.6 mmol) of 4-[(1-cyclopentylamino)cyclopropyl]-2-nitro-N-methyl-aniline are dissolved in 30 ml tetrahydrofuran and after the addition of 0.45 g (4.4

mmol) of triethylamine, 0.65 g (4.4 mmol) of ethyl succinate chloride are added and the resulting mixture is stirred for four hours at ambient temperature. Then it is diluted with ethyl acetate and sodium hydrogen carbonate solution, the organic extracts are dried and concentrated by evaporation. The residue is chromatographed on silica gel, eluting with ethyl acetate/cyclohexane (1:1). Yield: 1.3 g (90 % of theory),
R_f value: 0.46 (silica gel; ethyl acetate/cyclohexane = 1:1)

e. 4-[1-(N-(3-ethoxycarbonylpropionyl)-N-cyclopentyl-amino)cyclopropyl]-2-amino-N-methyl-aniline

15 Prepared analogously to Example 1d 4-[1-(N-(3-ethoxycarbonylpropionyl)-N-cyclopentyl-amino)cyclopropyl]-2-nitro-N-methyl-aniline and palladium on activated charcoal/hydrogen in methylene chloride/ethanol. Yield: 100 % of theory,
20 R_f value: 0.18 (silica gel; ethyl acetate/cyclohexane = 1:1)

f. 4-[1-(N-(3-ethoxycarbonylpropionyl)-N-cyclopentyl-amino)cyclopropyl]-2-(4-cyanophenyl)-aminomethylcarbonylamino-N-methyl-aniline

Prepared analogously to Example 1c 4-[1-(N-(3-ethoxycarbonylpropionyl)-N-cyclopentyl-amino)cyclopropyl]-2-amino-N-methyl-aniline, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate, 4-cyanophenylglycine and triethylamine in dimethylformamide. Yield: 96 % of theory,
30 R_f value: 0.54 (silica gel; methylene chloride/methanol = 9.5:0.5)

35

g. 2-(4-cyanophenylaminomethyl)-1-methyl-5-[1-[N-cyclopentyl-N-(3-ethoxycarbonylpropionyl)-amino]-cyclopropyl]-benzimidazole

- 5 Prepared analogously to Example 1f from 4-[1-(N-(3-ethoxycarbonylpropionyl)-N-cyclopentyl-amino)cyclopropyl]-2-(4-cyanophenyl)-aminomethylcarbonylamino-N-methyl-aniline in glacial acetic acid.

Yield: 52 % of theory,

- 10 R_f value: 0.81 (silica gel; methylene chloride/methanol = 9:1)

- h. 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-[N-cyclopentyl-N-(3-ethoxycarbonylpropionyl)-aminocyclopropyl]-benzimidazole-hydrochloride

- Prepared analogously to Example 1g from 2-(4-cyanophenylaminomethyl)-1-methyl-5-[1-[N-cyclopentyl-N-(3-ethoxycarbonylpropionyl)-amino]cyclopropyl]-benzimidazole and hydrochloric acid/ammonium carbonate in ethanol.

- 20 Yield: 36 % of theory,
 $C_{30}H_{38}N_6O_3 \times HCl$ (530.68/567.14)
mass spectrum: $(M+H)^+ = 531$

- 25 Example 8

- 2-(4-amidinophenylaminomethyl)-1-methyl-5-(5-methyl-3-ethoxycarbonylmethyl-imidazolin-2,4-dion-5-yl)benzimidazole-hydrochloride

30

- a. 2-(4-cyanophenylaminomethyl)-1-methyl-5-[1-(ethoxycarbonylmethylaminocarbonylamino)-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole

- 35 1.0 g (2.5 mmol) of 2-(4-cyanophenylaminomethyl)-1-methyl-5-[1-amino-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole are dissolved in 10 ml dimethylformamide and

after the addition of 0.9 ml (7.9 mmol) of ethyl isocyanatoacetate stirred for 45 minutes at ambient temperature. The solution is poured onto ice water, the crystalline product is suction filtered and dried. The residue is chromatographed on silica gel, eluting with methylene chloride/ethanol/ammonia (20:1:0.01 and 10:1:0.01).

R_f value: 0.77 (silica gel; methylene chloride/ethanol/ammonia = 9:1:0.01)

10

b. 2-(4-amidinophenylaminomethyl)-1-methyl-5-(5-methyl-3-ethoxycarbonylmethyl-imidazolin-2,4-dion-5-yl)-benzimidazole-hydrochloride

15 Prepared analogously to Example 1g from 2-(4-cyanophenylaminomethyl)-1-methyl-5-[1-(ethoxycarbonylmethylaminocarbonylamino)-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole and hydrochloric acid/ammonium carbonate in ethanol.

20 Yield: 68 % of theory,
 $C_{24}H_{27}N_7O_4 \times HCl$ (477.52/513.99)
mass spectrum: $(M+H)^+ = 478$

Example 9

25

2-(4-amidinophenylaminomethyl)-1-methyl-5-[N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-aminomethyl]-benzimidazole-hydrochloride

30 a. 4-(2-tert.butyloxycarbonylethyl)-2-(pyridylaminomethyl)-2-nitro-chlorobenzene

13.4 g (0.053 mol) of 4-chloro-3-nitro-benzylbromide and 11.8 g (0.053 mol) of 2-tert.butyloxycarbonylethylamino-pyridine are stirred in 80 ml of N-ethyl-diisopropylamine for 3 hours at 90° C. The solution is concentrated by

evaporation, the residue chromatographed on silica gel, eluting with petroleum ether/ethyl acetate (8:2 and 7:3). Yield: 8.2 g (40 % of theory),
R_f value: 0.64 (silica gel; petroleum ether/ethyl acetate
5 = 8:2)

b. 4-(2-tert.butyloxycarbonylethyl)-2-
(pyridylaminomethyl)-2-nitro-N-methyl-aniline

10 Prepared analogously to Example 1b from 4-(2-tert.butyloxycarbonylethyl)-2-(pyridylaminomethyl)-2-nitro-chlorobenzene and methylamine solution. Yield: 20 % of theory,
R_f value: 0.65 (silica gel; methylene chloride/ethanol =
15 9:1)

c. 4-(2-tert.butyloxycarbonylethyl)-2-
(pyridylaminomethyl)-2-amino-N-methyl-aniline

20 1.6 g (4 mmol) of 4-(2-tert.butyloxycarbonylethyl)-2-(pyridylaminomethyl)-2-nitro-N-methyl-aniline are dissolved in 200 ml methanol and, after the addition of 2 g of Raney nickel, combined with 1 ml of hydrazine hydrate. The solution is stirred for 30 minutes at ambient
25 temperature and concentrated by evaporation. The residue is chromatographed on silica gel and eluted with methylene chloride/ethanol (95:5). Yield: 1.2 g (82 % of theory),
R_f value: 0.33 (silica gel; methylene chloride/ethanol =
30 9:1)

d. 2-(4-cyanophenylaminomethyl)-1-methyl-5-[N-(2-pyridyl)-
N-(2-ethoxycarbonylethyl)-aminomethyl]-benzimidazole

35 Prepared analogously to Example 1c from 4-(2-tert.butyloxycarbonylethyl)-2-(pyridylaminomethyl)-2-amino-N-methyl-aniline, O-(benzotriazol-1-yl)-N,N,N',N'-

tetramethyluronium tetrafluoroborate, 4-cyano-phenylglycine in tetrahydrofuran and glacial acetic acid.

Yield: 72 % of theory,

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

e. 2-(4-amidinophenylaminomethyl)-1-methyl-5-[N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-aminomethyl]-benzimidazole-hydrochloride

10

Prepared analogously to Example 1g from 4-[(5-(2-tert.butyloxycarbonylethyl)-2-pyridylaminomethyl-1-methyl-benzimidazole-2-yl)-methylamino]-benzonitrile and hydrochloric acid/ammonium carbonate in ethanol.

15 Yield: 59 % of theory,

C₂₇H₃₁N₇O₂ x HCl (485.59/522.1)

mass spectrum: (M+H)⁺ = 486

The following compounds are obtained analogously to

20 Example 9:

(1) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[N-(ethoxycarbonylmethyl)-benzenesulphonylaminomethyl]-benzimidazole-hydrochloride

25 Yield: 53 % of theory,

C₂₇H₃₀N₆O₄S x HCl (534.64/571.1)

mass spectrum: (M+H)⁺ = 535

(2) 2-(4-amidinophenylaminomethyl)-1-methyl-5-(N-methyl-phenylcarbonylaminomethyl)]-benzimidazole-hydrochloride

30

Yield: 42 % of theory,

C₂₅H₂₆N₆O x HCl (426.53/462.96)

mass spectrum: (M+H)⁺ = 427

35

Example 10

2- (4-amidinophenylaminomethyl)-1-methyl-5-[(2-methyl-
benzimidazol-1-yl)methyl]-benzimidazole-hydrochloride

5

a. 1-(4-chloro-3-nitrobenzyl)-2-methyl-benzimidazole

Prepared analogously to Example 9a from 2-methyl-
benzimidazole and 4-chloro-3-nitrobenzyl chloride in
dimethylsulphoxide.

10 Yield: 78% of theory,

 $C_{15}H_{12}ClN_3O_2$ (301.7)mass spectrum: M^+ = 301/303

b. 1-(4-methylamino-3-nitrobenzyl)-2-methyl-benzimidazole

15 Prepared analogously to Example 1b from 1-(4-chloro-3-
nitrobenzyl)-2-methyl-benzimidazole and methylamine.

Yield: 96% of theory,

 R_f value: 0.56 (silica gel; methylene chloride/ethanol =
19:1)

20

c. 1-(4-methylamino-3-aminobenzyl)-2-methyl-benzimidazole

Prepared analogously to Example 1c from 1-(4-methylamino-
3-nitrobenzyl)-2-methyl-benzimidazole and hydrogen/Raney
nickel.

25 Yield: 100% of theory,

 R_f value: 0.34 (silica gel; methylene chloride/ethanol =
19:1)

d. 2-(4-cyanophenylaminomethyl)-1-methyl-5-[(2-methyl-
benzimidazol-1-yl)methyl]-benzimidazole

30

A mixture of 1.94 g (11.0 mmol) of N-(4-cyanophenyl)-
glycine and 1.78 g (11.0 mmol) of carbonyldiimidazole is
refluxed in 80 ml of absolute tetrahydrofuran for 15
35 minutes. After the addition of 2.7 g (10.46 mmol) of 1-(4-
methylamino-3-aminobenzyl)-2-methyl-benzimidazole the
mixture is refluxed for a further 16 hours. Then the

solution is evaporated to dryness, the residue is mixed with 80 ml glacial acetic acid and refluxed for 1 hour. It is then evaporated to dryness once more, the residue thus obtained is mixed with 50 ml of water and made alkaline
5 with conc. ammonia (about pH 10). The product which crystallises out is suction filtered, washed with a little water and dried.

Yield: 4.1 g (96% of theory),

R_f value: 0.30 (silica gel; methylene chloride/ethanol =
10 19:1)

$C_{25}H_{22}N_6$ (406.5)

mass spectrum: $M^+ = 406$

e. 2-(4-amidinophenylaminomethyl)-1-methyl-5-[(2-methyl-
15 benzimidazol-1-yl)methyl]-benzimidazole-hydrochloride

Prepared analogously to Example 1g from 2-(4-cyanophenylaminomethyl)-1-methyl-5-[(2-methyl-benzimidazol-1-yl)methyl]-benzimidazole hydrochloric
20 acid/ammonium carbonate.

Yield: 59% of theory,

$C_{25}H_{25}N_7 \times HCl$ (423.5/459.9)

mass spectrum: $(M+H)^+ = 424$
 $(M+2H)^{2+} = 217.7$

25

The following compounds are obtained analogously to Example 10:

(1) 2-(4-amidinophenyloxymethyl)-1-methyl-5-[(imidazol-1-yl)-methyl]-benzimidazole-hydrochloride
30

Yield: 30% of theory,

$C_{20}H_{20}N_6O \times HCl$ (360.4/396.9)

mass spectrum: $(M+H)^+ = 361$
 $(M+2H)^{2+} = 181$

35

(2) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(imidazol-1-yl)-ethyl]-benzimidazole-hydrochloride

Yield: 70% of theory,

$C_{21}H_{23}N_7 \times HCl$ (373.46/410)

mass spectrum: $(M+H)^+ = 374$

$(M+2H)^{2+} = 187.6$

5

(3) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(2-ethyl-4-methyl-imidazol-1-yl)-ethyl]-benzimidazole-dihydrochloride

Yield: 18% of theory,

10 $C_{24}H_{29}N_7 \times 2HCl$ (415.55/488.46)

mass spectrum: $(M+H)^+ = 416$

$(M+2H)^{2+} = 208.7$

(4) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[(2-ethyl-4-methyl-imidazol-1-yl)-methyl]-benzimidazole-dihydrochloride

15

Yield: 36% of theory,

$C_{23}H_{27}N_7 \times 2HCl$ (401.52/437.97)

mass spectrum: $(M+H)^+ = 402$

20 $(M+2H)^{2+} = 201.7$

(5) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[N-(pyridin-2-yl)-N-methyl-aminomethyl]-benzimidazole-dihydrochloride

Yield: 78% of theory,

25 $C_{23}H_{25}N_7 \times 2HCl$ (399.5/435.95)

mass spectrum: $(M+H)^+ = 400$

$(M+2H)^{2+} = 200.6$

(6) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[(2-(2-ethoxycarbonyl-ethyl)-benzimidazol-1-yl)-methyl]-benzimidazole-dihydrochloride

30

Yield: 61% of theory,

$C_{29}H_{31}N_7O_2 \times HCl$ (509.62/546.07)

mass spectrum: $(M+H)^+ = 510$

35 $(M+2H)^{2+} = 255.7$

$(M+H+Na)^{2+} = 266.7$

(7) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[(imidazol-1-yl)-methyl]-benzimidazole-hydrochloride

Yield: 35% of theory,

$C_{20}H_{21}N_7 \times HCl$ (359.44/395.89)

5 mass spectrum: $(M+H)^+ = 360$
 $(M+2H)^{2+} = 180.6$

(8) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[(2-(2-acetyl-amino-ethyl)-4,5-dimethyl-imidazol-1-yl)-methyl]-benzimidazole-dihydrochloride

Yield: 42% of theory,

$C_{26}H_{32}N_8O \times 2HCl$ (472.6/545.51)

10 mass spectrum: $(M+H)^+ = 473$
 $(M+2H)^{2+} = 237$
15 $(M+H+Na)^{2+} = 248$

(9) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[(2-(2-aminocarbonyl-ethyl)-4,5-dimethyl-imidazol-1-yl)-methyl]-benzimidazole-dihydrochloride

20 Yield: 68% of theory,

$C_{25}H_{30}N_8O \times 2HCl$ (458.6/531.51)

mass spectrum: $(M+H)^+ = 459$
 $(M+2H)^{2+} = 230$

25 (10) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[(2-methyl-4-ethoxycarbonyl-imidazol-1-yl)-methyl]-benzimidazole-hydrochloride

Yield: 34% of theory,

$C_{24}H_{27}N_7O_2 \times HCl$ (445.53/481.98)

30 mass spectrum: $(M+H)^+ = 446$
 $(M+2H)^{2+} = 223.5$
 $(M+H+Na)^{2+} = 234.5$

(11) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[(3-(3-ethoxycarbonyl-n-propyl)-benzimidazol-2-on-1-yl)-methyl]-benzimidazole-hydrochloride

Yield: 58% of theory,

$C_{30}H_{33}N_7O_3 \times HCl$ (539.64/576.09)

mass spectrum: $(M+H)^+$ = 540

$(M+H+Na)^{2+}$ = 281.7

- 5 (12) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[(3-(2-ethoxycarbonyl-ethyl)-imidazo[4,5-b]pyridin-2-on-1-yl)-methyl]-benzimidazole-hydrochloride

Yield: 29% of theory,

$C_{28}H_{30}N_8O_3 \times HCl$ (526.6/563.05)

- 10 mass spectrum: $(M+H)^+$ = 527

$(M+2H)^{2+}$ = 264

$(M+H+Na)^{2+}$ = 275

- 15 (13) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[(2-phenyl-imidazol-1-yl)-methyl]-benzimidazole-hydrochloride

Yield: 58% of theory,

$C_{26}H_{25}N_7 \times HCl$ (435.54/472)

mass spectrum: $(M+H)^+$ = 436

$(M+Na)^+$ = 218.6

20

- (14) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[(4,5-dimethyl-2-(2-ethoxycarbonyl-ethyl)-imidazol-1-yl)-methyl]-benzimidazole-dihydrochloride

Yield: 52% of theory,

- 25 $C_{27}H_{33}N_7O_2 \times 2HCl$ (487.61/560.52)

mass spectrum: $(M+H)^+$ = 488

$(M+2H)^{2+}$ = 244.6

Example 11

30

- 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(2-ethoxycarbonyl-azetidin-1-yl)-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole-hydrochloride

35

- a. 2-(4-cyanophenylaminomethyl)-1-methyl-5-[1-(2-tert.butyloxycarbonyl-azetidin-1-yl)-1-(pyrrolidin-1-yl-

carbonyl)-ethyl]-benzimidazole

- 0.8 g (1.86 mmol) of 2-(4-cyanophenylaminomethyl)-1-methyl-5-[1-amino-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole and 1.65 g ((5.5 mmol) of tert.butyl 2,4-dibromobutyrate are dissolved in 5 ml of ethanol, mixed with 0.2 g (1.86 mmol) of sodium carbonate and stirred under nitrogen for 30 hours at 55°C. After cooling, the white precipitate is filtered off and washed with ethanol.
- The filtrate is concentrated by evaporation, the residue is chromatographed on silica gel, eluting with ethyl acetate and ethyl acetate/ethanol/ammonia (20:1:0.01). The desired fractions are combined and concentrated by evaporation.
- Yield: 0.44 g (44% of theory) as a mixture of diastereomers,
 $C_{31}H_{38}N_6O_3$ (542.69)
mass spectrum: $(M+H)^+ = 543$

- b. 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(2-ethoxycarbonyl-azetidin-1-yl)-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole-hydrochloride (mixture of diastereomers)

- Prepared analogously to Example 1g from 2-(4-cyanophenylaminomethyl)-1-methyl-5-[1-(2-tert.butyloxycarbonyl-azetidin-1-yl)-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole and hydrochloric acid/ammonium carbonate in ethanol.
- Yield: 12 % of theory,
- $C_{29}H_{37}N_7O_3 \times HCl$ (531.66/568.12)
mass spectrum: $(M+H)^+ = 532$
 $(M+H+HCl)^{2+} = 568/70$ (Cl)

Example 12

(E/Z)-2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-
[(pyridin-3-yl)-ethoxycarbonylmethylidene)-
5 methylene]cyclopropyl]-benzimidazole-hydrochloride

a. (E/Z)-2-(4-cyanophenylaminomethyl)-1-methyl-5-[1-
[(pyridin-3-yl)-ethoxycarbonylmethylidene)-
10 methylene]cyclopropyl]-benzimidazole

897 mg (4.0 mmol) of triethyl phosphonoacetate are
dissolved in 30 ml tetrahydrofuran under argon. At -15°C
449 mg (4.0 mmol) of potassium tert. butoxide are added.
After 30 minutes 815 mg (2.0 mmol) of 2-(4-
15 cyanophenylaminomethyl)-1-methyl-5-[1-(pyridin-3-yl-
carbonyl)cyclopropyl]-benzimidazole are added batchwise
and the mixture is stirred overnight at ambient
temperature. Then the solution is refluxed for a further 6
hours and concentrated by evaporation. The residue is
20 mixed with sodium chloride solution and extracted 3x with
ethyl acetate. The combined organic phases are dried over
sodium sulphate and concentrated by evaporation. The
residue is dissolved in dichloromethane and
chromatographed on silica gel, eluting with
25 dichloromethane containing 5% ethanol. The desired
fractions are concentrated by evaporation, the residue is
trituated with ether, suction filtered and dried.
Yield: 365 mg (38% of theory).

30 b. ((E/Z)-2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-
[(pyridin-3-yl)-ethoxycarbonylmethylidene)-
methylene]cyclopropyl]-benzimidazole-hydrochloride

Prepared analogously to Example 1g from (E/Z)-2-(4-
35 cyanophenylaminomethyl)-1-methyl-5-[1-[(pyridin-3-yl)-
ethoxycarbonylmethylidene)-methylene]cyclopropyl]-

benzimidazole and hydrochloric acid/ammonium carbonate in ethanol.

Yield: 58 % of theory,

$C_{29}H_{30}N_6O_2 \times HCl$ (494.60/531.05)

5 mass spectrum: $(M+H)^+ = 495$

The following compound is obtained analogously to Example 12:

10 (1) (E/Z)-2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-
[(pyridin-2-yl)-ethoxycarbonylmethylidene)-methylene]-
cyclopropyl]-benzimidazole-hydrochloride

Yield: 72 % of theory,

$C_{29}H_{30}N_6O_2 \times HCl$ (494.60/531.05)

15 mass spectrum: $(M+H)^+ = 495$

Example 13

20 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(2-carboxy-
azetidin-1-yl)-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-
benzimidazole-hydrochloride (mixture of diastereomers)

200 mg (0.35 mmol) of 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(2-ethoxycarbonyl-azetidin-1-yl)-1-
25 (pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole-
hydrochloride are dissolved in 30 ml of 6N hydrochloric acid and stirred for 13 hours at ambient temperature. The reaction mixture is concentrated by evaporation with the addition of toluene, the residue is triturated with
30 acetone/ether, suction filtered, washed with ether and dried.

Yield: 200 mg (>100 % of theory, contains ammonium chloride),

$C_{27}H_{33}N_7O_3 \times HCl$ (503.62/540.07)

35 mass spectrum: $(M+H)^+ = 504$

The following compounds are obtained analogously to Example 13:

(1) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(2-carboxyethylamino)-1-(dimethylaminocarbonyl)-ethyl]-benzimidazole-hydrochloride

Yield: 91% of theory,

R_f value: 0.75 (Reversed phase; 5% saline solution/methanol = 1:1)

10 C₂₄H₃₁N₇O₃ x HCl (465.56/502.01)

mass spectrum: (M+H)⁺ = 466
(M-H+2HCl)⁻ = 537/539 (Cl₂)

(2) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(carboxymethylamino)-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole-dihydrochloride

Yield: 70 % of theory,

R_f value: 0.51 (Reversed phase; 5% saline solution/methanol = 3:2)

20 C₂₅H₃₁N₇O₃ x 2 HCl (477.57/550.48)

mass spectrum: (M+H)⁺ = 478

(3) (E/Z)-2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-[(pyridin-2-yl)-carboxymethylidene)-methylene]-cyclopropyl]-benzimidazole-hydrochloride

Yield: 65 % of theory,

C₂₇H₂₆N₆O₂ x HCl (466.55/503.0)

mass spectrum: (M+H)⁺ = 467
(M+Cl)⁺ = 501/503 (Cl)

30

(4) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(N-methyl-carboxymethylcarbonylamino)-2-(pyrrolidinocarbonyl)-prop-2-yl]-benzimidazole-dihydrochloride

35 Yield: 99 % of theory,

R_f value: 0.55 (Reversed phase RP 8; methanol/5% saline solution = 1:1)

$C_{28}H_{35}N_7O_4 \times 2 HCl$ (533.64/606.64)

mass spectrum: $(M+H)^+ = 534$
 $(M-H)^- = 532$
 $(M-H+HCl)^- = 568/70 (Cl)$

5

(5) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(2-carboxyethyl-amino)-1-(N-ethyl-N-methylaminocarbonyl)-ethyl]-benzimidazole-dihydrochloride

Yield: 75 % of theory,

10 R_f value: 0.54 (Reversed phase RP 8; methanol/5% saline solution = 1:1)

$C_{25}H_{33}N_7O_3 \times 2 HCl$ (479.59/552.59)

mass spectrum: $(M+H)^+ = 480$

15 Example 14

2-[4-(N-hexyloxycarbonylamidino)-phenylaminomethyl]-1-methyl-5-[1-(2-ethoxycarbonylethylamino)-1-(dimethylaminocarbonyl)-ethyl]-benzimidazole

20

1.5 g (2.8 mmol) of 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(2-ethoxycarbonylethylamino)-1-(dimethylaminocarbonyl)-ethyl]-benzimidazole-hydrochloride are dissolved in 14 ml water and 55 ml tetrahydrofuran, mixed with 2.0 g potassium carbonate and 1.0 ml (6 mmol) of hexyl chloroformate and stirred for 4 hours at ambient temperature. After removal of the solvent *in vacuo* the residue is mixed with saline solution and extracted 3 x with methylene chloride. The combined organic phases are washed with a little water, dried over magnesium sulphate and concentrated by evaporation. The crude product is purified on silica gel, eluting with methylene chloride plus 2 to 7.5% ethanol. The uniform fractions are combined, concentrated by evaporation, dissolved in a little ethyl acetate and mixed with petroleum ether. The solid form is suction filtered, washed with petroleum ether and dried.

30

35

Yield: 0.8 g (43 % of theory),

$C_{33}H_{47}N_7O_5$ (621.79)

R_f value: 0.50 (silica gel; methylene chloride/ethanol = 19:1)

- 5 mass spectrum: $(M+H)^+ = 622$
 $(M+Na)^+ = 644$

Example 15

- 10 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(N-ethoxycarbonylmethylcarbonyl-methylamino)-2-(pyrrolidinocarbonyl)-prop-2-yl]-benzimidazole-hydrochloride

- 15 a. Methyl 2-(4-chloro-phenyl)-3-hydroxy-2-methyl-propionate

35 ml of a 1.6 molar solution of n-butyllithium in hexane (61 mmol) are added dropwise to a solution of 8.1 ml of
20 diisopropylamine (85 mmol) in 20 ml tetrahydrofuran at -78°C. Then a solution of 10.0 g (50 mmol) of methyl 2-(4-chloro-phenyl)-propionate in 30 ml tetrahydrofuran is added dropwise at -78°C. Formaldehyde gas is then piped into the reaction mixture at -20°C for 30 minutes. After
25 the addition of 5% citric acid and glacial acetic acid the mixture is extracted with ethyl acetate. The organic phases are washed with 1N sulphuric acid, water, saturated sodium bicarbonate solution and saline solution and dried over magnesium sulphate. The crude product is purified on
30 silica gel, eluting with cyclohexane/ethyl acetate (19:1; 9:1; 4:1; 1:1 and 0:1). The uniform fractions are combined and concentrated by evaporation.

Yield: 9.7 g (84% of theory) yellow oil,

- 35 R_f value: 0.25 (silica gel; petroleum ether/ethyl acetate 4:1)

b. 2-(4-chloro-phenyl)-3-hydroxy-2-methyl-propionic acid

Prepared analogously to Example 4 from methyl 2-(4-chloro-phenyl)-3-hydroxy-2-methyl-propionate and sodium hydroxide solution in ethanol.

5 Yield: 83% of theory,

R_F value: 0.55 (silica gel; ethyl acetate/cyclohexane 2:1 + glacial acetic acid)

10 c. 2-(4-chloro-3-nitro-phenyl)-2-methyl-3-nitroxy-propionic acid

Prepared analogously to Example 1a from 2-(4-chloro-phenyl)-3-hydroxy-2-methyl-propionic acid and nitric acid.

Yield: 90% of theory,

melting point: 129-132°C

15 C₁₀H₉ClN₂O₇ (304.64)

d. 2-(4-chloro-3-nitro-phenyl)-2-methyl-3-hydroxy-propionic acid

Prepared analogously to Example 6 from 2-(4-chloro-3-

20 nitro-phenyl)-3-nitrooxy-2-methyl-propionic acid and 6N hydrochloric acid in dioxane.

Yield: 98% of theory,

C₁₀H₁₀ClNO₅ (259.65)

mass spectrum: (M-H)⁻ = 258/60 (Cl)

25 (2M-H)⁻ = 517/9 (Cl₂)

e. 2-[4-(N-benzyl-methylamino)-3-nitro-phenyl]-2-methyl-3-hydroxy-propionic acid

30 Prepared analogously to Example 1b from 2-(4-chloro-3-nitro-phenyl)-3-hydroxy-2-methyl-propionic acid and N-methyl-benzylamine.

Yield: 81% of theory,

C₁₈H₂₀ClN₂O₅ (344.37)

35 mass spectrum: M⁺ = 344

f. 2-[4-(N-benzyl-methylamino)-3-nitro-phenyl]-2-methyl-3-hydroxy-1-pyrrolidin-1-yl-propan-1-one

Prepared analogously to Example 1c from 2-[4-(N-benzyl-methylamino)-3-nitro-phenyl]-3-hydroxy-2-methyl-propionic acid and N-methyl-benzylamine.

Yield: 96% of theory,

$C_{22}H_{27}N_3O_4$ (397.48)

mass spectrum: M^+ = 398

10 $(M+Na)^+ = 420$

g. 2-[4-(N-benzyl-methylamino)-3-nitro-phenyl]-2-methyl-3-methanesulphonyloxy-1-pyrrolidin-1-yl-propan-1-one

15 A solution of 1.2 g (3.0 mmol) of 2-[4-(N-benzyl-methylamino)-3-nitro-phenyl]-2-methyl-3-hydroxy-1-pyrrolidin-1-yl-propan-1-one in 20 ml tetrahydrofuran is mixed at ambient temperature with 1.3 ml (9.3 mmol) of triethylamine. Then 0.27 ml (3.5 mmol) of methanesulphonyl chloride are added dropwise at 2-5°C. After 2 hours at ambient temperature the precipitate formed is suction filtered and the filtrate is concentrated by evaporation. The crude product is further reacted without being purified.

25 Yield: 1.4 g (98% of theory)

h. 2-[4-(N-benzyl-methylamino)-3-nitro-phenyl]-2-methyl-3-methylamino-1-pyrrolidin-1-yl-propan-1-one

30 A solution of 1.4 g (2.9 mmol) of 2-[4-(N-benzyl-methylamino)-3-nitro-phenyl]-2-methyl-3-methanesulphonyloxy-1-pyrrolidin-1-yl-propan-1-one in 10 ml dimethylformamide is combined with 20 ml of a 40% aqueous methylamine solution and heated to 100°C for 70 minutes. After cooling the reaction mixture is combined with ice water and extracted with ethyl acetate. The organic phases are washed with water and with saline

solution, dried over magnesium sulphate and concentrated by evaporation. The crude product is purified on silica gel, eluting with ethyl acetate/ethanol (10:1, 9:1, 4:1 + 1% conc. ammonia). The uniform fractions are combined and
5 concentrated by evaporation.

Yield: 740 mg (61% of theory),

R_F value: 0.45 (silica gel; methylene chloride/ethanol 9:1 + 1% conc. ammonia)

- 10 i. 2-[4-(benzyl-methylamino)-3-nitro-phenyl]-2-methyl-3-(N-methoxycarbonylmethylcarbonyl-methylamino)-1-pyrrolidin-1-yl-propan-1-one
-

Prepared analogously to Example 7d from 2-[4-(N-benzyl-methylamino)-3-nitro-phenyl]-2-methyl-3-methylamino-1-pyrrolidin-1-yl-propan-1-one and methyl malonate chloride.

Yield: 84% of theory,

R_F value: 0.65 (silica gel; ethyl acetate/ethanol 9:1 + ammonia)

- 20 C₂₇H₃₄N₄O₆ (510.60)
mass spectrum: (M-H)⁻ = 509
(M+Na)⁺ = 533

- j. 2-(4-methylamino-3-amino-phenyl)-2-methyl-3-(N-methoxycarbonylmethylcarbonyl-methylamino)-1-pyrrolidin-1-yl-propan-1-one
-

Prepared analogously to Example 1d from 2-[4-(N-benzyl-methylamino)-3-nitro-phenyl]-2-methyl-3-(N-methoxycarbonylmethylcarbonyl-methylamino)-1-pyrrolidin-1-yl-propan-1-one and hydrogen/palladium on activated charcoal.

Yield: 100% of theory,

- 35 R_F value: 0.40 (silica gel; ethyl acetate/ethanol 9:1 + 1% conc. ammonia)

C₂₀H₃₀N₄O₄ (390.49)

mass spectrum: M⁺ = 390

k. 4-[2-(3-(N-methoxycarbonylmethylcarbonyl-methylamino))-2-methyl-1-pyrrolidin-1-yl-propan-1-on-2-yl]-2-(4-cyanophenyl)-aminomethylcarbonylamino-N-methyl-aniline

5

Prepared analogously to Example 1e from 2-(4-methylamino-3-amino-phenyl)-2-methyl-3-(N-methoxycarbonylmethylcarbonyl-methylamino)-1-pyrrolidin-1-yl-propan-1-one and O-(benzotriazol-1-yl)-N,N,N'-

10 tetramethyluronium tetrafluoroborate, 4-cyanophenylglycine and triethylamine in dimethylformamide.

Yield: 95% of theory,

R_F value: 0.35 (silica gel; ethyl acetate/ethanol 9:1 + 1% conc. ammonia)

15

l. 2-(4-cyanophenylaminomethyl)-1-methyl-5-[1-(N-ethoxycarbonylmethylcarbonyl-methylamino)-2-(pyrrolidinocarbonyl)-prop-2-yl]-benzimidazole

20 Prepared analogously to Example 1f from 4-[2-(3-(N-methoxycarbonylmethylcarbonyl-methylamino))-2-methyl-1-pyrrolidin-1-yl-propan-1-on-2-yl]-2-(4-cyanophenyl)-aminomethylcarbonylamino-N-methyl-aniline in glacial acetic acid.

25 Yield: 47 % of theory,

R_F value: 0.20 (silica gel; ethyl acetate/ethanol = 9:1)

C₂₉H₃₄N₆O₄ (530.63)

mass spectrum: (M+H)⁺ = 531

(M+Na)⁺ = 553

30

m. 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(N-ethoxycarbonylmethylcarbonyl-methylamino)-2-(pyrrolidinocarbonyl)-prop-2-yl]-benzimidazole-hydrochloride

35 Prepared analogously to Example 1g from 2-(4-cyanophenylaminomethyl)-1-methyl-5-[1-(N-ethoxycarbonylmethylcarbonyl-methylamino)-2-

(pyrrolidinocarbonyl)-prop-2-yl]-benzimidazole and hydrochloric acid/ammonium carbonate in ethanol.

Yield: 65 % of theory,

R_f value: 0.30 (silica gel; methylene chloride/methanol = 4:1 + glacial acetic acid)

$C_{30}H_{39}N_7O_4 \times HCl$ (561.69/598.19)

mass spectrum: $(M+H)^+ = 562$

$(M+Cl)^- = 596/8$ (Cl)

10 The following compounds are obtained analogously to Example 15:

(1) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(N-methoxycarbonylmethyl-methylamino)-2-(pyrrolidinocarbonyl)-prop-2-yl]-benzimidazole-hydrochloride

Yield: 89 % of theory,

R_f value: 0.35 (Reversed phase RP 8; methanol/5% saline solution = 3:2)

20 $C_{28}H_{37}N_7O_3 \times HCl$ (519.66/556.11)

mass spectrum: $(M+H)^+ = 520$

$(M-H+HCl)^- = 554/6$ (Cl)

(2) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(N-ethoxycarbonylmethylcarbonylamino)-2-(pyrrolidinocarbonyl)-prop-2-yl]-benzimidazole-acetate

Yield: 45% of theory,

R_f value: 0.20 (silica gel; methylene chloride/ethanol = 8:2 + 1 % ethyl acetate)

30 $C_{29}H_{37}N_7O_4 \times CH_3COOH$ (547.66/607.71)

mass spectrum: $(M+H)^+ = 548$

$(M-H)^- = 546$

$(M-H+CH_3COOH)^- = 606$

35 (3) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(N-ethoxycarbonylmethylcarbonyl-methylamino)-2-(N-methyl-ethylaminocarbonyl)-prop-2-yl]-benzimidazole-hydrochloride

(4) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(N-ethoxycarbonylmethyl-methylamino)-2-(N-methyl-N-ethylaminocarbonyl)-prop-2-yl]-benzimidazole-hydrochloride

5

(5) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(N-ethoxycarbonylmethylcarbonyl-methylamino)-2-(piperidinocarbonyl)-prop-2-yl]-benzimidazole-hydrochloride

10

(6) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(N-ethoxycarbonylmethylsulphonyl-methylamino)-2-(piperidinocarbonyl)-prop-2-yl]-benzimidazole-hydrochloride

15

(7) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(N-methoxycarbonylmethylcarbonyl-methylamino)-2-(pyrrolidinocarbonyl)-prop-2-yl]-benzimidazole-acetate
Yield: 72% of theory,

20 R_f value: 0.20 (silica gel; methylene chloride/ethanol = 8:2 + 1 % glacial acetic acid)

$C_{29}H_{37}N_7O_4 \times CH_3COOH$ (547.66/607.71)

mass spectrum: $(M+H)^+ = 548$

$(M-H)^- = 546$

25

(8) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(2-ethoxycarbonyl-ethylcarbonylamino)-2-(pyrrolidinocarbonyl)-prop-2-yl]-benzimidazole-hydrochloride

30

(9) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(ethoxycarbonylmethylsulphonylamino)-2-(pyrrolidinocarbonyl)-prop-2-yl]-benzimidazole-hydrochloride

35 Yield: 14% of theory,

R_f value: 0.20 (silica gel; methylene chloride/ethanol = 8:2)

$C_{28}H_{37}N_7O_5S \times HCl$ (583.65/620.17)

mass spectrum: $(M+H)^+ = 584$

$(M+Na)^+ = 606$

5

(10) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(1H-tetrazol-5-yl)-methylcarbonylamino]-2-(pyrrolidinocarbonyl)-prop-2-yl]-benzimidazole-hydrochloride

10

(11) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(ethoxycarbonylmethylamino)-2-(pyrrolidinocarbonyl)-prop-2-yl]-benzimidazole-dihydrochloride

Yield: 40% of theory,

15 $C_{28}H_{37}N_7O_3 \times 2 HCl$ (519.65/592.56)

mass spectrum: $(M+H)^+ = 520$

$(M+Na)^+ = 542$

$(M+HCOO)^- = 564$

$(M+Cl)^- = 554$

20

Example 16

25 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(carboxymethylamino)-1-(isoxazolidin-1-yl-carbonyl)-ethyl]-benzimidazole-hydrochloride

Prepared by hydrolysis of 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(ethoxycarbonylmethylamino)-1-(isoxazolidin-1-yl-carbonyl)-ethyl]-benzimidazole-hydrochloride with sodium hydroxide solution in ethanol.

30 Yield: 90 % of theory,

R_f value: 0.65 (Reversed phase RP 8; methanol/5% saline solution = 3:2)

35 $C_{24}H_{29}N_7O_4 \times HCl$ (479.54/515.99)

mass spectrum: $(M+H)^+ = 480$

The following compounds are prepared analogously to Example 16:

(1) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(2-carboxyethylamino)-1-(isoxazolidin-1-yl-carbonyl)-ethyl]-benzimidazole-hydrochloride

(2) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(carboxymethylamino)-1-(N-methyl-N-ethylaminocarbonyl)-ethyl]-benzimidazole-hydrochloride

Yield: 93% of theory,

R_f value: 0.40 (Reversed phase RP 8; methanol/5% saline solution = 1:1)

C₂₄H₃₁N₇O₃ x HCl (465.57/502.02)

mass spectrum: (M+H)⁺ = 466
(M+Cl-H)⁻ = 500/2 (Cl)

(3) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(N-carboxymethyl-methylamino)-2-(pyrrolidinocarbonyl)-prop-2-yl]-benzimidazole-dihydrochloride

Yield: 89% of theory,

R_f value: 0.57 (Reversed phase RP 8; methanol/5% saline solution = 4:3)

C₂₇H₃₅N₇O₃ x 2 HCl (505.63/578.54)

mass spectrum: (M+H)⁺ = 506
(M+2H)⁺⁺ = 253
(M+H+Na)⁺⁺ = 264.5

(4) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(carboxymethylcarbonylamino)-2-(pyrrolidinocarbonyl)-prop-2-yl]-benzimidazole-hydrochloride

Yield: 90% of theory,

R_f value: 0.55 (Reversed phase RP 8; methanol/5% saline solution = 4:6)

C₂₇H₃₃N₇O₄ x HCl (519.61/556.06)

mass spectrum: (M+H)⁺ = 520
(M-H)⁻ = 518

(5) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(N-carboxymethyl-methylamino)-2-(N-ethyl-methylaminocarbonyl)-prop-2-yl]-benzimidazole-
5 hydrochloride

(6) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(N-carboxymethylcarbonyl-methylamino)-2-(N-ethyl-methylaminocarbonyl)-prop-2-yl]-benzimidazole-
10 hydrochloride

(7) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(N-carboxymethylcarbonyl-methylamino)-2-(piperidinocarbonyl)-prop-2-yl]-benzimidazole-
15 hydrochloride

(8) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(N-carboxymethylsulphonyl-methylamino)-2-(piperidinocarbonyl)-prop-2-yl]-benzimidazole-
20 hydrochloride

(9) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(carboxymethylamino)-1-(piperidinocarbonyl)-ethyl]-benzimidazole-hydrochloride

25 Yield: 81% of theory,

R_f value: 0.40 (Reversed phase RP 8; methanol/5% saline solution = 1:1)

C₂₆H₃₃N₇O₃ (491.60/528.05)

mass spectrum: (M+H)⁺ = 492

30 (M-H)⁻ = 490

(10) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(2-carboxyethylcarbonylamino)-2-(pyrrolidinocarbonyl)-prop-2-yl]-benzimidazole-hydrochloride

35

(11) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(carboxymethylsulphonylamino)-2-(pyrrolidinocarbonyl)-prop-2-yl]-benzimidazole-hydrochloride

5 (12) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(carboxymethylamino)-1-(diethylaminocarbonyl)-ethyl]-benzimidazole-hydrochloride

Yield: 70% of theory,

10 R_f value: 0.50 (Reversed phase RP 8; methanol/5% saline solution = 1:1)

$C_{25}H_{33}N_7O_3$ (479.59/516.05)

mass spectrum: $(M+H)^+$ = 480

$(M-H)^-$ = 478

$(M-H+HCl)^-$ = 514/516 (Cl)

15

(13) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(carboxymethylamino)-2-(pyrrolidinocarbonyl)-prop-2-yl]-benzimidazole-dihydrochloride

20 Yield: 22 % of theory,

R_f value: 0.50 (Reversed phase RP 8; 5% saline solution/methanol = 1:1)

$C_{26}H_{33}N_7O_3 \times 2 HCl$ (491.60/564.51)

mass spectrum: $(M+H)^+$ = 492

25 $(M-H)^-$ = 490

(14) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(N-carboxymethyl-methylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole-dihydrochloride

30 R_f value: 0.48 (Reversed phase RP 8; 5% saline solution/methanol = 3:2)

$C_{26}H_{33}N_7O_3 \times 2 HCl$ (491.60/564.51)

mass spectrum: $(M+H)^+$ = 492

35 $(M-H)^-$ = 490

(15) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(3-carboxy-propylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole-dihydrochloride

5 Yield: 82 % of theory,

R_f value: 0.73 (Reversed phase; 5% sodium chloride solution/ methanol = 1:1)

$C_{27}H_{35}N_7O_3 \times 2 HCl$ (505.63/578.54)

mass spectrum: $(M+H)^+ = 506$

10

Example 17

2-[4-(N-phenylcarbonylamidino)-phenylaminomethyl]-1-methyl-5-[1-(ethoxycarbonylmethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole

15

A suspension of 1.4 g (2.4 mmol) of 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(ethoxycarbonylmethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole-dihydrochloride in 5 ml of N-ethyl-diisopropylamine and 2 ml dimethylformamide is combined with 1.5 g (6 mmol) of 4-nitrophenyl benzoate, whilst a clear solution is formed by heating. After 2 hours at 120°C the solution is concentrated by evaporation in vacuo, after cooling the residue is dissolved in dichloromethane and purified on silica gel, eluting first with dichloromethane, later with dichloromethane/ethanol (50:1, 25:1, 18:1). The uniform fractions are combined, concentrated by evaporation, triturated with water, suction filtered and dried.

20

25

30

Yield: 0.7 g (49% of theory),

R_f value: 0.40 (silica gel; methylene chloride/ethanol = 19:1)

$C_{34}H_{39}N_7O_4$ (609.73)

35 mass spectrum: $(M+H)^+ = 610$

$(M+Na)^+ = 632$

$$(M-H)^- = 608$$

The following compounds are obtained analogously to Examples 14 and 17:

5

(1) 2-[4-(N-n-hexyloxycarbonylamidino)-phenylaminomethyl]-1-methyl-5-[1-(ethoxycarbonylmethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole

Yield: 53% of theory,

10 R_f value: 0.35 (silica gel; methylene chloride/ethanol = 9:1)

$C_{34}H_{47}N_7O_5$ (633.79)

mass spectrum: $(M+Na)^+ = 656$

$$(M-H)^- = 632$$

15

(2) 2-[4-(N-n-octyloxycarbonylamidino)-phenylaminomethyl]-1-methyl-5-[1-(ethoxycarbonylmethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole

Yield: 46% of theory,

20 R_f value: 0.43 (silica gel; methylene chloride/ethanol = 9:1)

$C_{36}H_{51}N_7O_5$ (661.84)

mass spectrum: $(M+Na)^+ = 684$

$$(M-H)^- = 660$$

25

(3) 2-[4-(N-n-hexyloxycarbonyl-amidino)-phenylaminomethyl]-1-methyl-5-[1-(methoxycarbonylmethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole

30

(4) 2-[4-(N-n-octyloxycarbonylamidino)-phenylaminomethyl]-1-methyl-5-[1-(methoxycarbonylmethylamino)-1-(pyrrolidinocarbonyl)ethyl]-benzimidazole

Yield: 32% of theory,

35 R_f value: 0.27 (silica gel; methylene chloride/ethanol = 9:1)

$C_{35}H_{49}N_7O_5$ (647.82)

mass spectrum: $(M+Na)^+ = 670$

$(M-H)^- = 646$

5 (5) 2-[4-(N-n-hexyloxycarbonylamidino)-phenylaminomethyl]-
1-methyl-5-[1-(N-ethoxycarbonylmethylcarbonyl-
methylamino)-2-(pyrrolidinocarbonyl)-prop-2-yl]-
benzimidazole

Yield: 52% of theory,

10 R_f value: 0.60 (silica gel; methylene chloride/ethanol =
9:1)

$C_{37}H_{51}N_7O_6$ (689.85)

mass spectrum: $(M+H)^+ = 690$

$(M-H)^- = 688$

15 $(M+Na)^+ = 712$

$(M+HCl-H)^- = 724/26$ (Cl)

(6) 2-[4-(N-n-octyloxycarbonyl-amidino)-
phenylaminomethyl]-1-methyl-5-[1-
20 (N-ethoxycarbonylmethylcarbonyl-methylamino)-
2-(pyrrolidinocarbonyl)-prop-2-yl]-benzimidazole

(7) 2-[4-(N-n-hexyloxycarbonylamidino)-phenylaminomethyl]-
1-methyl-5-[1-(N-methoxycarbonylmethylcarbonyl-
25 methylamino)-2-(pyrrolidinocarbonyl)-prop-2-yl]-
benzimidazole

Yield: 21% of theory,

R_f value: 0.55 (silica gel; methylene chloride/ethanol =
9:1)

30 $C_{36}H_{49}N_7O_6$ (675.83)

mass spectrum: $(M+H)^+ = 676$

$(M+Na)^+ = 698$

$(M+HCl-H)^- = 724/26$ (Cl)

35 (8) 2-[4-(N-n-octyloxycarbonyl-amidino)-
phenylaminomethyl]-1-methyl-5-[1-(N-

methoxycarbonylmethylcarbonyl-methylamino) -
2- (pyrrolidinocarbonyl) -prop-2-yl] -benzimidazole

(9) 2- [4- (N-phenylcarbonylamidino) -phenylaminomethyl] -1-
5 methyl-5- [1- (methoxycarbonylmethylamino) -1-
(pyrrolidinocarbonyl) -ethyl] -benzimidazole

Yield: 34% of theory.

R_f value: 0.55 (silica gel; methylene chloride/ethanol =
9:1 + 1 % ammonia)

10 C₃₃H₃₇N₇O₄ (595.70)

mass spectrum: (M-H)⁻ = 594

(M+Na)⁺ = 618

(10) 2- [4- (N-isopropoxyloxycarbonylamidino) -
15 phenylaminomethyl] -1-methyl-5- [1- (N-
ethoxycarbonylmethylcarbonyl-methylamino) -
2- (pyrrolidinocarbonyl) -prop-2-yl] -benzimidazole

Yield: 66% of theory,

20 R_f value: 0.45 (silica gel; methylene chloride/ethanol =
9:1)

C₃₄H₄₅N₇O₆ (647.77)

mass spectrum: (M+H)⁺ = 648

(M-H)⁻ = 646

(M+Na)⁺ = 670

25

(11) 2- [4- (N-phenylcarbonylamidino) -phenylaminomethyl] -1-
methyl-5- [1- (N-ethoxycarbonylmethylcarbonyl-methylamino) -
2- (pyrrolidinocarbonyl) -prop-2-yl] -benzimidazole

Yield: 23% of theory,

30 R_f value: 0.45 (silica gel; methylene chloride/ethanol =
9:1)

C₃₇H₄₃N₇O₅ (665.79)

mass spectrum: (M+H)⁺ = 666

(M-H)⁻ = 664

35 (M+Na)⁺ = 688

(M+H+Cl)⁺ = 700/2 (Cl)

(12) 2-[4-(N-phenylcarbonylamidino)-phenylaminomethyl]-
1-methyl-5-[1-(N-methoxycarbonylmethylcarbonyl-
methylamino)-2-(pyrrolidinocarbonyl)-prop-2-yl]-
5 benzimidazole
Yield: 67% of theory,
R_f value: 0.60 (silica gel; methylene chloride/ethanol =
9:1)
C₃₆H₄₁N₇O₅ (651.76)
10 mass spectrum: (M+H)⁺ = 652
(M-H)⁻ = 650
(M+Na)⁺ = 674

(13) 2-[4-(N-n-butyloxycarbonylamidino)-
15 phenylaminomethyl]-1-methyl-5-[1-(N-
methoxycarbonylmethylcarbonyl-methylamino)-
2-(pyrrolidinocarbonyl)-prop-2-yl]-benzimidazole
Yield: 45% of theory,
R_f value: 0.50 (silica gel; methylene chloride/ethanol =
20 9:1)
C₃₄H₄₅N₇O₆ (647.77)
mass spectrum: (M+H)⁺ = 648
(M-H)⁻ = 646
(M+Na)⁺ = 670
25 (M-H+HCl)⁻ = 682/4 (Cl)

(14) 2-[4-(N-ethyloxycarbonylamidino)-phenylaminomethyl]-
1-methyl-5-[1-(N-ethoxycarbonylmethylcarbonyl-
methylamino)-2-(pyrrolidinocarbonyl)-prop-2-yl]-
30 benzimidazole
Yield: 54% of theory,
R_f value: 0.40 (silica gel; methylene chloride/ethanol =
9:1)
C₃₃H₄₃N₇O₆ (633.75)
35 mass spectrum: (M+H)⁺ = 634
(M-H)⁻ = 632
(M+Na)⁺ = 656

(15) 2-[4-(N-ethyloxycarbonylamidino)-phenylaminomethyl]-
1-methyl-5-[1-(N-methoxycarbonylmethylcarbonyl-
methylamino)-2-(pyrrolidinocarbonyl)-prop-2-yl]-

5 benzimidazole

Yield: 53% of theory,

R_f value: 0.45 (silica gel; methylene chloride/ethanol =
9:1)

C₃₂H₄₁N₇O₆ (619.72)

10 mass spectrum: (M+H)⁺ = 620

(M-H)⁻ = 618

(M+Na)⁺ = 642

(16) 2-[4-(N-pyridin-3-yl-carbonylamidino)-

15 phenylaminomethyl]-1-methyl-5-[1-(N-
ethoxycarbonylmethylcarbonyl-methylamino)-
2-(pyrrolidinocarbonyl)-prop-2-yl]-benzimidazole

Yield: 16% of theory,

R_f value: 0.45 (silica gel; methylene chloride/ethanol =
20 9:1)

C₃₆H₄₂N₈O₅ (666.78)

mass spectrum: (M-H)⁻ = 665

(M+Na)⁺ = 689

25 (17) 2-[4-(N-n-butyloxycarbonylamidino)-

phenylaminomethyl]-1-methyl-5-[1-
(ethoxycarbonylmethylamino)-1-(pyrrolidinocarbonyl)-
ethyl]-benzimidazole

Yield: 52% of theory,

30 R_f value: 0.42 (silica gel; methylene chloride/ethanol =
9:1)

C₃₂H₄₃N₇O₅ (605.74)

mass spectrum: (M+H)⁺ = 606

(M+Na)⁺ = 628

35 (M-H)⁻ = 604

(18) 2-[4-(N-ethyloxycarbonylamidino)-phenylaminomethyl]-
1-methyl-5-[1-(ethoxycarbonylmethylamino)-1-
(pyrrolidinocarbonyl)-ethyl]-benzimidazole

Yield: 30% of theory,

5 R_f value: 0.44 (silica gel; methylene chloride/ethanol =
9:1)

$C_{30}H_{39}N_7O_5$ (577.68)

mass spectrum: $(M+H)^+$ = 578

$(M+Na)^+$ = 600

10 $(M-H)^-$ = 576

(19) 2-[4-(N-benzyloxycarbonylamidino)-phenylaminomethyl]-
1-methyl-5-[1-(ethoxycarbonylmethylamino)-1-
(pyrrolidinocarbonyl)-ethyl]-benzimidazole

15 Yield: 51% of theory,

R_f value: 0.50 (silica gel; methylene chloride/ethanol =
9:1)

$C_{35}H_{41}N_7O_5$ (639.75)

mass spectrum: $(M+Na)^+$ = 662

20 $(M-H)^-$ = 638

(20) 2-[4-(N-pyridin-3-yl-carbonylamidino)-
phenylaminomethyl]-1-methyl-5-[1-
(ethoxycarbonylmethylamino)-1-(pyrrolidinocarbonyl)-
25 ethyl]-benzimidazole

Yield: 84% of theory,

R_f value: 0.20 (silica gel; ethyl acetate/ethanol = 4:1)

$C_{33}H_{38}N_8O_4$ (610.72)

mass spectrum: $(M+H)^+$ = 611

30 $(M-H)^-$ = 609

$(M-HCOO)^-$ = 611

(21) 2-[4-(N-acetoxymethyloxycarbonylamidino)-
phenylaminomethyl]-1-methyl-5-[1-

35 (ethoxycarbonylmethylamino)-1-(pyrrolidinocarbonyl)-
ethyl]-benzimidazole

Yield: 42% of theory,

R_f value: 0.44 (silica gel; methylene chloride/ethanol = 9:1)

C₃₁H₃₉N₇O₇ (621.09)

mass spectrum: (M+Na)⁺ = 644

5 (M-H)⁻ = 620

(22) 2-[4-(N-(2,2,2-trichloroethyloxycarbonyl)-amidino)-phenylaminomethyl]-1-methyl-5-[1-(ethoxycarbonylmethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole

Yield: 73% of theory,

R_f value: 0.54 (silica gel; methylene chloride/ethanol = 9:1)

C₃₀H₃₆Cl₃N₇O₅ (681)

15 mass spectrum: M⁺ = 679/81/3 (Cl₃)

(M+Na)⁺ = 702/4/6 (Cl₃)

(M-H)⁻ = 678/80/2 (Cl₃)

Example 18

20

2-[4-(N-n-octyloxycarbonylamidino)-phenylaminomethyl]-1-methyl-5-[1-(carboxymethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole

25 A solution of 0.2 g (0.3 mmol) of 2-[4-(N-n-octyloxycarbonylamidino)-phenylaminomethyl]-1-methyl-5-[1-(ethoxycarbonylmethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole in 3 ml tetrahydrofuran and 2.5 ml ethanol is mixed with 1.1 ml of 1N sodium hydroxide

30 solution and stirred for 4 hours at ambient temperature. The reaction mixture is concentrated by evaporation and combined with 1 ml of 1N hydrochloric acid. After 12 hours at ambient temperature (pH 4) 2 drops of ammonia (33%) are added, whereupon a bright yellow precipitate is formed.

35 After the solid formed has been suction filtered the filtrate is combined with 1 ml of 1 N hydrochloric acid and concentrated by evaporation with the addition of

toluene. The residue is triturated with acetone, suction filtered, washed with diethylether and dried.

Yield: 0.1 g (50% of theory),

R_f value: 0.35 (Reversed phase RP 8; methanol/5% saline
5 solution = 2:1)

C₃₄H₄₇N₇O₅ (633.79)

mass spectrum: (M+H)⁺ = 634

(M+H+Na)⁺⁺ = 328.5

10 Example 19

2-[4-(N-hydroxyamidino)-phenylaminomethyl]-1-methyl-5-[1-(ethoxycarbonylmethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole

15

A suspension of 0.6 g (1.2 mmol) of 2-(4-cyanophenylaminomethyl)-1-methyl-5-[1-(ethoxycarbonylmethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole in 50 ml ethanol is mixed with 0.47 g
20 (7.8 mmol) of hydroxylamine hydrochloride and 0.35 g (3.5 mmol) of sodium carbonate and refluxed for 17 hours. After cooling, the residue is filtered off, the filtrate is concentrated by evaporation and taken up in water. After extracting twice with dichloromethane, the combined
25 organic phases are dried and concentrated by evaporation. The crude product is purified on silica gel, eluting with dichloromethane/ethanol (19/1 and 7/1). The uniform fractions are combined, concentrated by evaporation, triturated with diisopropylether and dried.

30 Yield: 0.025 g (4% of theory),

R_f value: 0.68 (silica gel; methylene chloride/ethanol = 4:1)

C₂₇H₃₅N₇O₄ (521.62)

mass spectrum: (M-H)⁻ = 520

35 (M+Na)⁺ = 544

Example 20

2-[4-(N-phenylcarbonylamidino)-phenylaminomethyl]-1-methyl-5-[1-(isopropoxyloxycarbonylmethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole

a. Ethyl 4-(5-methyl-1,2,4-oxadiazol-3-yl)-phenylamino-acetate

10 Prepared analogously to Example 9a from 4-(5-methyl-1,2,4-oxadiazol-3-yl)-aniline and ethyl bromoacetate in N-ethyl-diisopropylamine.

Yield: 78% of theory,

R_f value: 0.60 (silica gel; ethyl acetate/petroleum ether
15 = 1:1)

b. 4-(5-methyl-1,2,4-oxadiazol-3-yl)-phenylamino-acetic acid

Prepared analogously to Example 4 from ethyl 4-(5-methyl-1,2,4-oxadiazol-3-yl)-phenylamino-acetate and sodium
20 hydroxide solution in ethanol.

Yield: 75% of theory,

R_f value: 0.15 (silica gel; methylene chloride/ethanol =
25 9:1)

c. 2-[4-(5-methyl-1,2,4-oxadiazol-3-yl)-phenylaminomethyl]-1-methyl-5-[1-amino-(pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole

30 Prepared analogously to Example 1e/f from 2-(4-methylamino-3-amino-phenyl)-2-tert.butyloxycarbonyl-amino-1-pyrrolidin-1-yl-propanone, 4-(5-methyl-1,2,4-oxadiazol-3-yl)-phenylamino-acetic acid and carbonyldiimidazole in tetrahydrofuran and subsequent treatment with glacial
35 acetic acid.

Yield: 34% of theory,

R_f value: 0.10 (silica gel; methylene chloride/ethanol = 9:1)

d. 2-[4-(5-methyl-1,2,4-oxadiazol-3-yl)-phenylaminomethyl]-1-methyl-5-[1-(isopropoxyloxycarbonylmethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole

Prepared analogously to Example 11 from 2-[4-(5-methyl-1,2,4-oxadiazol-3-yl)-phenylaminomethyl]-1-methyl-5-[1-amino-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole, isopropyl bromoacetate and potassium carbonate in isopropanol/methylene chloride.

Yield: 42% of theory,

R_f value: 0.60 (silica gel; methylene chloride/ethanol = 9:1)

e. 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(isopropoxyloxycarbonylmethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole-acetate

Prepared analogously to Example 1d from 2-[4-(5-methyl-1,2,4-oxadiazol-3-yl)-phenylaminomethyl]-1-methyl-5-[1-(isopropoxyloxycarbonylmethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole and hydrogen/palladium (10% on activated charcoal) in ethanol/glacial acetic acid.

Yield: 69% of theory,

R_f value: 0.30 (silica gel; methylene chloride/ethanol = 7:3)

f. 2-[4-(N-phenylcarbonylamidino)-phenylaminomethyl]-1-methyl-5-[1-(isopropoxyloxycarbonylmethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole

Prepared analogously to Example 17 from 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(isopropoxyloxycarbonylmethylamino)-1-(pyrrolidinocarbonyl)-

ethyl]-benzimidazole-acetate and 4-nitrophenyl benzoate in N-ethyl-diisopropylamine/dimethylformamide.

Yield: 26% of theory,

R_f value: 0.50 (silica gel; methylene chloride/ethanol = 9:1)

C₃₅H₄₁N₇O₄ (623.75)

mass spectrum: (M+Na)⁺ = 646

(M-H)⁻ = 622

10 The following compounds are prepared analogously to Example 20:

(1) 2-[4-(N-phenylcarbonylamidino)-phenylaminomethyl]-1-methyl-5-[1-(n-butyloxycarbonylmethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole

(2) 2-[4-(N-phenylcarbonylamidino)-phenylaminomethyl]-1-methyl-5-[1-(2-phenylethyloxycarbonylmethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole

20

(3) 2-[4-(N-n-hexyloxycarbonylamidino)-phenylaminomethyl]-1-methyl-5-[1-(isopropyloxycarbonylmethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole

Yield: 40 % of theory,

25 R_f value: 0.45 (silica gel: methylene chloride/ethanol = 9:1)

C₃₅H₄₉N₇O₅ (647.82)

mass spectrum: (M+H)⁺ = 648

(M-H)⁻ = 646

30

(M+Na)⁺ = 670

(4) 2-[4-(N-n-octyloxycarbonylamidino)-phenylaminomethyl]-1-methyl-5-[1-(isopropyloxycarbonylmethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole

35 Yield: 31% of theory,

R_f value: 0.48 (silica gel: methylene chloride/ethanol = 9:1)

$C_{37}H_{53}N_7O_5$ (675.88)

mass spectrum: $(M+H)^+$ = 674

$(M+Na)^+$ = 698

- 5 (5) 2-[4-(N-(2,2,2-trichloroethyloxycarbonyl)-amidino)-phenylaminomethyl]-1-methyl-5-[1-(isopropyloxycarbonylmethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole
Yield: 43% of theory,
Rf value: 0.50 (silica gel: methylene chloride/ethanol =
10 9:1)

$C_{31}H_{38}Cl_3N_7O_5$ (695.05)

mass spectrum: $(M-H)^-$ = 692/694/696/698 (Cl_3)

- (6) 2-[4-(N-phenylcarbonylamidino)-phenylaminomethyl]-
15 1-methyl-5-[1-(n-propyloxycarbonylmethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole

Yield: 79% of theory

Rf value: 0.35 (silica gel; ethyl acetate/ethanol = 9:1)

$C_{35}H_{41}N_7O_4$ (623.76)

- 20 mass spectrum: $(M+H)^+$ = 624

$(M-H)^-$ = 622

$(M+HCOO)^-$ = 668

- (7) 2-[4-(N-n-octyloxycarbonylamidino)-
25 phenylaminomethyl]-1-methyl-5-[1-(n-propyloxycarbonylmethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole
Yield: 53% of theory

Rf value: 0.39 (silica gel; ethyl acetate/ethanol = 9:1)

$C_{37}H_{53}N_7O_5$ (675.88)

- 30 mass spectrum: $(M+H)^+$ = 676

$(M+Na)^+$ = 698

$(M-H)^-$ = 674

Example 21

(R)-2-(4-Amidinophenylaminomethyl)-1-methyl-5-[1-
(carboxymethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-
5 benzimidazole hydrochloride

a. Ethyl 2-amino-2-(4-chloro-3-nitrophenyl)-propionate

A mixture of 28 g (0.11 mol) of 2-amino-2-(4-chloro-3-nitrophenyl)-propionic acid in 200 ml of 5.6 N ethanolic
10 hydrochloric acid is refluxed for 36 hours. After the solvent has been evaporated off the residue is suspended in 300 ml of ethyl acetate and combined with 300 ml of saturated sodium hydrogen carbonate solution. The organic phase is washed twice with saturated sodium hydrogen
15 carbonate solution and once with water, dried over sodium sulphate and evaporated down.

Yield: 21.1 g (68% of theory) of light brown oil.

20 b. ethyl (R)-(+)-2-amino-2-(4-chloro-3-nitrophenyl)-propionate

17.33 g (63.6 mmol) of ethyl 2-amino-2-(4-chloro-3-nitrophenyl)-propionate are dissolved in 247 ml of isopropanol and 207 ml of methanol and mixed with 9.54 g
25 (63.6 mmol) of L-(+)-tartaric acid. The reaction mixture is heated to 100°C, whereupon a clear solution is formed. The solution is cooled to 27°C within 3 hours, the precipitate formed is suction filtered, washed with ethanol and dried. Then the solid formed (21.5 g) is
30 suspended in 400 ml of ethyl acetate and combined with 400 ml of saturated sodium hydrogen carbonate solution. After extraction and phase separation, the organic phase is washed with water, dried and evaporated down.

Yield: 7.68 g (44.4% of theory) of light yellow oil,

35 $[\alpha]^{20} = +4.38^\circ$ (ethyl acetate)

HPLC analysis: ee value > 98.6%

c. (R)-(-)-2-amino-2-(4-chloro-3-nitrophenyl)-propionic acid

5 Prepared analogously to Example 4 from ethyl (R)-(+)-2-amino-2-(4-chloro-3-nitrophenyl)-propionate and sodium hydroxide solution in tetrahydrofuran.

Yield: 63% of theory,

$[\alpha]^{20} = -59.6^\circ$ (methanol/water 1:1)

10

d. (R)-2-tert.butyloxycarbonylamino-2-(4-chloro-3-nitrophenyl)-propionic acid

Prepared analogously to Example 5d from (R)-(-)-2-amino-2-(4-chloro-3-nitrophenyl)-propionic acid and pyrocarbonic acid di-tert.butyldicarbonate and triethylamine in dioxan.
15 Yield: 100% of theory.

e. (R)-2-tert.butyloxycarbonylamino-2-(4-methylamino-3-nitrophenyl)-propionic acid

20

Prepared analogously to Example 1b from (R)-2-tert.butyloxycarbonylamino-2-(4-chloro-3-nitrophenyl)-propionic acid and methylamine.

25 Yield: 69% of theory.

f. (R)-2-(4-methylamino-3-nitrophenyl)-2-tert.butyloxycarbonylamino-1-pyrrolidino-propanone

30 Prepared analogously to Example 1c from (R)-2-tert.butyloxycarbonylamino-2-(4-methylamino-3-nitrophenyl)-propionic acid, pyrrolidine and carbonyldiimidazole in tetrahydrofuran.
Yield: 96% of theory.

35

g. (R)-2-(4-methylamino-3-aminophenyl)-2-tert.butylloxycarbonylamino-1-pyrrolidino-propanone

Prepared analogously to Example 1c from (R)-2-(4-methylamino-3-nitrophenyl)-2-tert.butylloxycarbonylamino-1-pyrrolidino-propanone and hydrogen/palladium on activated charcoal in methanol.
Yield: 99% of theory.

10 h. (R)-2-(4-cyanophenylaminomethyl)-1-methyl-5-[1-(N-tert.butylloxycarbonylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole

Prepared analogously to Example 1c/1f from (R)-2-(4-methylamino-3-aminophenyl)-2-tert.butylloxycarbonylamino-1-pyrrolidino-propanone, 4-cyanophenylglycine, carbonyldiimidazole in tetrahydrofuran and subsequent cyclisation in glacial acetic acid.
Yield: 100% of theory.

20 i. (R)-2-(4-cyanophenylaminomethyl)-1-methyl-5-[1-amino-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole

Prepared analogously to Example 6i from (R)-2-(4-cyanophenylaminomethyl)-1-methyl-5-[1-(N-tert.butylloxycarbonylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole and 6N hydrochloric acid in dioxan.
Yield: 76% of theory.

30 k. (R)-2-(4-cyanophenylaminomethyl)-1-methyl-5-[1-(ethoxycarbonylmethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole

Prepared analogously to Example 6k from (R)-2-(4-cyanophenylaminomethyl)-1-methyl-5-[1-amino-1-(pyrrolidino-carbonyl)-ethyl]-benzimidazole and ethyl iodoacetate/potassium carbonate in acetone.

Yield: 75% of theory.

1. (R)-2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-
(ethoxycarbonylmethylamino)-1-(pyrrolidinocarbonyl)-
5 ethyl]-benzimidazole hydrochloride

Prepared analogously to Example 1g from (R)-2-(4-cyanophenylaminomethyl)-1-methyl-5-[1-(ethoxycarbonylmethylamino)-1-(pyrrolidino-carbonyl)-
10 ethyl]-benzimidazole and hydrochloric acid/ammonium carbonate in ethanol.
Yield: 95% of theory.

m. (R)-2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-
15 (carbonylmethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-
benzimidazole hydrochloride

Prepared analogously to Example 4 from (R)-2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(ethoxycarbonylmethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole
20 and sodium hydroxide solution in ethanol.

Yield: 100% of theory,

$C_{25}H_{31}N_7O_3 \times 2HCl$ (477.57/550.5)

Mass spectrum: $(M+H)^+ = 478$
25 $(M-H+HCl)^- = 512/514$ (Cl)
 $(M-H+2HCl)^- = 448/550/552$ (Cl₂)

Example 22

30 Dry ampoule containing 75 mg of active substance per 10 ml

Composition:

Active substance	75.0 mg
35 Mannitol	50.0 mg
water for injections	ad 10.0 ml

Preparation:

Active substance and mannitol are dissolved in water.
After packaging the solution is freeze-dried. To produce
the solution ready for use, the product is dissolved in
5 water for injections.

Example 23

10 Dry ampoule containing 35 mg of active substance per 2 ml

Composition:

Active substance	35.0 mg
Mannitol	100.0 mg
15 water for injections	ad 2.0 ml

Preparation:

Active substance and mannitol are dissolved in water.
After packaging, the solution is freeze-dried.

20 To produce the solution ready for use, the product is
dissolved in water for injections.

Example 24

25 Tablet containing 50 mg of active substance

Composition:

30 (1) Active substance	50.0 mg
(2) Lactose	98.0 mg
(3) Maize starch	50.0 mg
(4) Polyvinylpyrrolidone	15.0 mg
(5) Magnesium stearate	<u>2.0 mg</u>
35	215.0 mg

Preparation:

(1), (2) and (3) are mixed together and granulated with an aqueous solution of (4). (5) is added to the dried granulated material. From this mixture tablets are pressed, biplanar, faceted on both sides and with a dividing notch on one side.

Diameter of the tablets: 9 mm.

10 Example 25

Tablet containing 350 mg of active substance

15 Preparation:

(1) Active substance	350.0 mg
(2) Lactose	136.0 mg
(3) Maize starch	80.0 mg
20 (4) Polyvinylpyrrolidone	30.0 mg
(5) Magnesium stearate	<u>4.0 mg</u>
	600.0 mg

(1), (2) and (3) are mixed together and granulated with an aqueous solution of (4). (5) is added to the dried granulated material. From this mixture tablets are pressed, biplanar, faceted on both sides and with a dividing notch on one side.

Diameter of the tablets: 12 mm.

Example 26

Capsules containing 50 mg of active substance

5 Composition:

	(1) Active substance	50.0 mg
	(2) Dried maize starch	58.0 mg
	(3) Powdered lactose	50.0 mg
10	(4) Magnesium stearate	<u>2.0 mg</u>
		160.0 mg

Preparation:

(1) is triturated with (3). This trituration is added to
15 the mixture of (2) and (4) with vigorous mixing.

This powder mixture is packed into size 3 hard gelatin capsules in a capsule filling machine.

20 Example 27

Capsules containing 350 mg of active substance

Composition:

25

	(1) Active substance	350.0 mg
	(2) Dried maize starch	46.0 mg
	(3) Powdered lactose	30.0 mg
	(4) Magnesium stearate	<u>4.0 mg</u>
30		430.0 mg

Preparation:

(1) is triturated with (3). This trituration is added to
the mixture of (2) and (4) with vigorous mixing.

35

This powder mixture is packed into size 0 hard gelatin capsules in a capsule filling machine.

Example 28

5

Suppositories containing 100 mg of active substance

1 suppository contains:

10	Active substance	100.0 mg
	Polyethyleneglycol (M.W. 1500)	600.0 mg
	Polyethyleneglycol (M.W. 6000)	460.0 mg
	Polyethylenesorbitan monostearate	<u>840.0 mg</u>
		2,000.0 mg

15

Method:

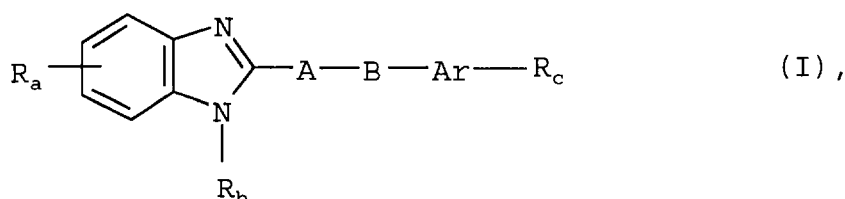
The polyethyleneglycol is melted together with polyethylene sorbitan monostearate. At 40°C the ground active substance is homogeneously dispersed in the melt.

20 It is cooled to 38°C and poured into slightly chilled suppository moulds.

Patent Claims

1. Benzimidazoles of general formula

5



wherein

Ar denotes a phenylene or naphthylene group optionally
10 substituted by a fluorine, chlorine or bromine atom, by a
trifluoromethyl, C₁₋₃-alkyl or C₁₋₃-alkoxy group,

a thienylene, thiazolylene, pyridinylen, pyrimidinylene,
pyrazinylen or pyridazinylene group optionally
15 substituted in the carbon skeleton by a C₁₋₃-alkyl group,

A denotes a C₁₋₃-alkylene group,

B denotes an oxygen or sulphur atom, a methylene,
20 carbonyl, sulphinyl or sulphonyl group, an imino group
optionally substituted by a C₁₋₃-alkyl group wherein the
alkyl moiety may be mono- or disubstituted by a carboxy
group,

25 R_a denotes an R₁-CO-C₃₋₅-cycloalkyl group wherein

R₁ denotes a C₁₋₃-alkoxy, amino, C₁₋₄-alkylamino or di-
(C₁₋₄-alkyl)-amino group wherein each alkyl moiety may be
substituted by a carboxy group,

30

a 4- to 7-membered cycloalkyleneimino or
cycloalkenyleneimino group which may be substituted by a
hydroxy group or by one or two C₁₋₃-alkyl groups, whilst

an alkyl substituent may simultaneously be substituted by a hydroxy, C₁₋₃-alkoxy, carboxy, carboxy-C₁₋₃-alkoxy, carboxy-C₁₋₃-alkylamino, N-(C₁₋₃-alkyl)-N-(carboxy-C₁₋₃-alkyl)-amino, carboxy-C₁₋₃-alkylaminocarbonyl, N-(C₁₋₃-alkyl)-N-(carboxy-C₁₋₃-alkyl)-aminocarbonyl, carboxy-C₁₋₃-alkylaminocarbonylamino, 1-(C₁₋₃-alkyl)-3-(carboxy-C₁₋₃-alkyl)-aminocarbonylamino, 3-(C₁₋₃-alkyl)-3-(carboxy-C₁₋₃-alkyl)-aminocarbonylamino or 1,3-di-(C₁₋₃-alkyl)-3-(carboxy-C₁₋₃-alkyl)-aminocarbonylamino group,

a 4- to 7-membered cycloalkenyleneimino group substituted by a hydroxy group,

a 5- to 7-membered cycloalkyleneimino group optionally substituted by a C₁₋₃-alkyl group, to which a phenyl ring is fused via two adjacent carbon atoms,

a morpholino, piperazino, N-(C₁₋₃-alkyl)-piperazino, pyrrolino, 3,4-dehydro-piperidino or pyrrol-1-yl group,

an R₂-CX-C₃₋₅-cycloalkyl group wherein

R₂ denotes a phenyl, naphthyl or monocyclic 5- or 6-membered heteroaryl group optionally substituted by a C₁₋₃-alkyl group, wherein the 6-membered heteroaryl group contains one, two or three nitrogen atoms and the 5-membered heteroaryl group contains an imino group optionally substituted by a C₁₋₃-alkyl group, an oxygen or sulphur atom or an imino group optionally substituted by a C₁₋₃-alkyl group and an oxygen or sulphur atom or one or two nitrogen atoms and the abovementioned alkyl substituent may be substituted by a carboxy, carboxy-C₁₋₃-alkoxy, carboxy-C₁₋₃-alkylamino or N-(C₁₋₃-alkyl)-carboxy-C₁₋₃-alkylamino group, and

X denotes an oxygen atom, a C₁₋₃-alkylimino, C₁₋₃-alkoxyimino, C₁₋₃-alkylhydrazino, di-(C₁₋₃-alkyl)-hydrazino, C₂₋₄-alkanoylhydrazino, N-(C₁₋₃-alkyl)-C₂₋₄-alkanoylhydrazino or C₁₋₃-alkylidene group each of which may be substituted in the alkyl or alkanoyl moiety or in the alkyl and alkanoyl moieties by a carboxy group,

a C₁₋₃-alkyl or C₃₋₅-cycloalkyl group substituted by an imidazole or imidazolone group wherein

the imidazole ring may be substituted by a phenyl or carboxy group and by one or two C₁₋₃-alkyl groups or by one, two or three C₁₋₃-alkyl groups, wherein the substituents may be identical or different and one of the abovementioned alkyl substituents may simultaneously be substituted by a carboxy group or may be substituted in the 2 or 3 position by an amino, C₂₋₄-alkanoylamino, C₁₋₃-alkylamino, N-(C₂₋₄-alkanoyl)-C₁₋₃-alkylamino or di-(C₁₋₃-alkyl)-amino group, and

the imidazolone ring may be substituted by a C₁₋₃-alkyl group, whilst the alkyl substituent may be substituted by a carboxy group or in the 2 or 3 position by an amino, C₂₋₄-alkanoylamino, C₁₋₃-alkylamino, N-(C₂₋₄-alkanoyl)-C₁₋₃-alkylamino or di-(C₁₋₃-alkyl)-amino group, and

additionally a phenyl or pyridine ring may be fused to the abovementioned imidazole or imidazolone rings via two adjacent carbon atoms,

an imidazolidine-2,4-dione-5-yl group which may be substituted by one or two C₁₋₃-alkyl groups, whilst at the same time an alkyl substituent may be substituted by a carboxy group,

a C₁₋₄-alkyl group which is substituted

by a C₁₋₃-alkyl-Y₁-C₁₋₃-alkyl, HOOC-C₁₋₃-alkyl-Y₁-C₁₋₃-alkyl,
tetrazolyl-C₁₋₃-alkyl-Y₂, R₃NR₄- or R₃NR₄-C₁₋₃-alkyl group
5 and

by an isoxazolidinylcarbonyl group optionally
substituted by a C₁₋₃-alkyl group, by a pyrrolino-
carbonyl, 3,4-dehydro-piperidinocarbonyl, pyrrol-1-yl-
10 carbonyl, carboxy, aminocarbonyl,
C₁₋₃-alkylaminocarbonyl, di-(C₁₋₃-alkyl)-aminocarbonyl or
4- to 7-membered cycloalkyleneiminocarbonyl group,
whilst in the abovementioned groups the
cycloalkyleneimino moiety may be substituted by one or
15 two C₁₋₃-alkyl groups and at the same time each alkyl
moiety or alkyl substituent in the abovementioned
C₁₋₃-alkylaminocarbonyl, di-(C₁₋₃-alkyl)-aminocarbonyl or
cycloalkyleneiminocarbonyl groups may be substituted by
a carboxy group, and the remaining hydrogen atoms of the
20 C₁₋₄-alkyl group may be wholly or partially replaced by
fluorine atoms wherein

R₃ denotes a hydrogen atom or a C₁₋₃-alkyl group
optionally substituted by a carboxy group and

25

R₄ denotes a hydrogen atom, a C₁₋₃-alkyl-
Y₁-C₁₋₃-alkyl-Y₂, carboxy-C₁₋₃-alkyl-Y₁-C₁₋₃-alkyl-Y₂,
C₁₋₃-alkyl-Y₂ or carboxy-C₁₋₃-alkyl-Y₂ group or

30

R₃ and R₄ together with the nitrogen atom between them
denote an 4- to 7-membered cycloalkyleneimino group
optionally substituted by a carboxy, C₁₋₃-alkyl or
carboxy-C₁₋₃-alkyl group wherein

35

Y₁ denotes a carbon-carbon bond, an oxygen atom, a
sulphenyl, sulphinyl, sulphonyl, -NH-, -NH-CO- or
-NH-CO-NH- group and

Y₂ denotes a carbon-nitrogen bond or a carbonyl, sulphonyl, imino or -NH-CO- group, wherein the carbonylgroup of the -NH-CO- group is linked to the nitrogen atom of the R₃NR₄- group, and the imino groups occurring in the definition of the groups Y₁ and Y₂ may each additionally be substituted by a C₁₋₃-alkyl or carboxy-C₁₋₃-alkyl group,

10 a C₁₋₃-alkyl or C₃₋₅-cycloalkyl group substituted by a R₅NR₆-group wherein

R₅ denotes a hydrogen atom, a C₁₋₃-alkyl, C₅₋₇-cycloalkyl, phenylcarbonyl, phenylsulphonyl or pyridinyl group and

15

R₆ denotes a C₁₋₃-alkyl, carboxy-C₁₋₃-alkyl or carboxy-C₁₋₃-alkylcarbonyl group,

a C₁₋₃-alkyl group which is substituted by a C₂₋₄-alkanoyl or C₅₋₇-cycloalkanoyl group and by a C₁₋₃-alkyl group substituted by a chlorine, bromine or iodine atom,

20

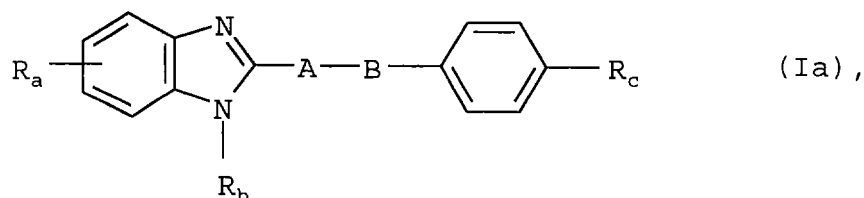
R_b denotes a hydrogen atom or a C₁₋₃-alkyl group and

25 R_c denotes a cyano group or an amidino group optionally substituted by one or two C₁₋₃-alkyl groups,

the tautomers, stereoisomers, mixtures thereof, the prodrugs thereof, the derivatives thereof which contain, instead of a carboxy group, a group which is negatively charged under physiological conditions, and the salts thereof.

30

2. Benzimidazoles of general formula



wherein

5

A denotes a C₁₋₃-alkylene group,

B denotes an oxygen or sulphur atom, a methylene,
 carbonyl, sulphinyl or sulphonyl group, an imino group
 10 optionally substituted by a C₁₋₃-alkyl group wherein the
 alkyl moiety may be mono- or disubstituted by a carboxy
 group,

R_a denotes an R₁-CO-C₃₋₅-cycloalkyl group wherein
 15

R₁ denotes a C₁₋₃-alkoxy, amino, C₁₋₄-alkylamino or di-
 (C₁₋₄-alkyl)-amino group wherein each alkyl moiety may be
 substituted by a carboxy group,

20 a 4- to 7-membered cycloalkyleneimino or
 cycloalkenyleneimino group which may be substituted by
 one or two C₁₋₃-alkyl groups, whilst an alkyl substituent
 may simultaneously be substituted by a hydroxy,
 C₁₋₃-alkoxy, carboxy, carboxy-C₁₋₃-alkoxy, carboxy-
 25 C₁₋₃-alkylamino, N-(C₁₋₃-alkyl)-N-(carboxy-C₁₋₃-alkyl)-
 amino, carboxy-C₁₋₃-alkylaminocarbonyl, N-(C₁₋₃-alkyl)-
 N-(carboxy-C₁₋₃-alkyl)-aminocarbonyl, carboxy-
 C₁₋₃-alkylaminocarbonylamino, 1-(C₁₋₃-alkyl)-3-(carboxy-
 C₁₋₃-alkyl)-aminocarbonylamino, 3-(C₁₋₃-alkyl)-3-(carboxy-
 30 C₁₋₃-alkyl)-aminocarbonylamino or 1,3-di-(C₁₋₃-alkyl)-
 3-(carboxy-C₁₋₃-alkyl)-aminocarbonylamino group,

a 4- to 7-membered cycloalkenyleneimino group
substituted by a hydroxy group,

5 a 5- to 7-membered cycloalkyleneimino group optionally
substituted by a C₁₋₃-alkyl group, to which a phenyl ring
is fused via two adjacent carbon atoms,

a morpholino, piperazino, N-(C₁₋₃-alkyl)-piperazino,
pyrrolino, 3,4-dehydro-piperidino or pyrrol-1-yl group,
10 an R₂-CX-C₃₋₅-cycloalkyl group wherein

R₂ denotes a phenyl, naphthyl or monocyclic 5- or
6-membered heteroaryl group optionally substituted by a
15 C₁₋₃-alkyl group, wherein the 6-membered heteroaryl group
contains one, two or three nitrogen atoms and the
5-membered heteroaryl group contains an imino group
optionally substituted by a C₁₋₃-alkyl group, an oxygen
or sulphur atom or an imino group optionally substituted
20 by a C₁₋₃-alkyl group and an oxygen or sulphur atom or
one or two nitrogen atoms and the abovementioned alkyl
substituent may be substituted by a carboxy, carboxy-
C₁₋₃-alkoxy, carboxy-C₁₋₃-alkylamino or N-(C₁₋₃-alkyl)-
carboxy-C₁₋₃-alkylamino group, and

25 X denotes an oxygen atom, a C₁₋₃-alkylimino,
C₁₋₃-alkoxyimino, C₁₋₃-alkylhydrazino, di-(C₁₋₃-alkyl)-
hydrazino, C₂₋₄-alkanoylhydrazino, N-(C₁₋₃-alkyl)-
C₂₋₄-alkanoylhydrazino or C₁₋₃-alkylidene group each of
30 which may be substituted in the alkyl or alkanoyl moiety
or in the alkyl and alkanoyl moieties by a carboxy
group,

a C₁₋₃-alkyl or C₃₋₅-cycloalkyl group substituted by an
35 imidazole or imidazolone group wherein

the imidazole ring may be substituted by a phenyl or carboxy group and by one or two C₁₋₃-alkyl groups or by one, two or three C₁₋₃-alkyl groups, wherein the substituents may be identical or different and one of the abovementioned alkyl substituents may simultaneously be substituted by a carboxy group or may be substituted in the 2 or 3 position by an amino, C₂₋₄-alkanoylamino, C₁₋₃-alkylamino, N-(C₂₋₄-alkanoyl)-C₁₋₃-alkylamino or di-(C₁₋₃-alkyl)-amino group, and

the imidazolone ring may be substituted by a C₁₋₃-alkyl group, whilst the alkyl substituent may be substituted by a carboxy group or in the 2 or 3 position by an amino, C₂₋₄-alkanoylamino, C₁₋₃-alkylamino, N-(C₂₋₄-alkanoyl)-C₁₋₃-alkylamino or di-(C₁₋₃-alkyl)-amino group, and

additionally a phenyl or pyridine ring may be fused to the abovementioned imidazole or imidazolone rings via two adjacent carbon atoms,

an imidazolidine-2,4-dione-5-yl group which may be substituted by one or two C₁₋₃-alkyl groups, whilst at the same time an alkyl substituent may be substituted by a carboxy group,

a C₁₋₄-alkyl group which is substituted

by a C₁₋₃-alkyl-Y₁-C₁₋₃-alkyl, HOOC-C₁₋₃-alkyl-Y₁-C₁₋₃-alkyl, tetrazolyl-C₁₋₃-alkyl-Y₂, R₃NR₄- or R₃NR₄-C₁₋₃-alkyl group and

by an isoxazolidinylcarbonyl group optionally substituted by a C₁₋₃-alkyl group, by a pyrrolinocarbonyl, 3,4-dehydro-piperidinocarbonyl, pyrrol-1-yl-carbonyl, carboxy, aminocarbonyl, C₁₋₃-alkylaminocarbonyl, di-(C₁₋₃-alkyl)-aminocarbonyl or

4- to 7-membered cycloalkyleneiminocarbonyl group,
whilst in the abovementioned groups the
cycloalkyleneimino moiety may be substituted by one or
two C₁₋₃-alkyl groups and at the same time each alkyl
5 moiety or alkyl substituent in the abovementioned
C₁₋₃-alkylaminocarbonyl, di-(C₁₋₃-alkyl)-aminocarbonyl or
cycloalkyleneiminocarbonyl groups may be substituted by
a carboxy group, and the remaining hydrogen atoms of the
C₁₋₄-alkyl group may be wholly or partially replaced by
10 fluorine atoms wherein

R₃ denotes a hydrogen atom or a C₁₋₃-alkyl group
optionally substituted by a carboxy group and

15 R₄ denotes a hydrogen atom, a C₁₋₃-alkyl-
Y₁-C₁₋₃-alkyl-Y₂, carboxy-C₁₋₃-alkyl-Y₁-C₁₋₃-alkyl-Y₂,
C₁₋₃-alkyl-Y₂ or carboxy-C₁₋₃-alkyl-Y₂ group or

R₃ and R₄ together with the nitrogen atom between them
20 denote an 4- to 7-membered cycloalkyleneimino group
optionally substituted by a carboxy, C₁₋₃-alkyl or
carboxy-C₁₋₃-alkyl group wherein

Y₁ denotes a carbon-carbon bond, an oxygen atom, a
25 sulphenyl, sulphinyl, sulphonyl, -NH-, -NH-CO- or
-NH-CO-NH- group and

Y₂ denotes a carbon-nitrogen bond or a carbonyl,
sulphonyl, imino or -NH-CO- group, wherein the carbonyl
30 group of the -NH-CO- group is linked to the nitrogen
atom of the R₃NR₄- group, and the imino groups occurring
in the definition of the groups Y₁ and Y₂ may each
additionally be substituted by a C₁₋₃-alkyl or carboxy-
C₁₋₃-alkyl group,

35 a C₁₋₃-alkyl or C₃₋₅-cycloalkyl group substituted by a R₅NR₆-
group wherein

R₅ denotes a hydrogen atom, a C₁₋₃-alkyl, C₅₋₇-cycloalkyl, phenylcarbonyl, phenylsulphonyl or pyridinyl group and

5 R₆ denotes a C₁₋₃-alkyl, carboxy-C₁₋₃-alkyl or carboxy-C₁₋₃-alkylcarbonyl group,

a C₁₋₃-alkyl group which is substituted by a C₂₋₄-alkanoyl or C₅₋₇-cycloalkanoyl group and by a C₁₋₃-alkyl group
10 substituted by a chlorine, bromine or iodine atom,

R_b denotes a hydrogen atom or a C₁₋₃-alkyl group and

R_c denotes a cyano group or an amidino group which may be
15 substituted by a hydroxy group, by one or two C₁₋₃-alkyl groups, or by one or two C₁₋₈-alkoxycarbonyl groups,

wherein the carboxy, amino and imino groups mentioned in the definition of the abovementioned groups may also be
20 substituted by a group which can be cleaved *in vivo*,

the tautomers, stereoisomers and salts thereof.

3. Benzimidazoles of general formula Ia according to claim
25 2, wherein

A denotes a C₁₋₃-alkylene group,

B denotes an oxygen atom, a methylene, imino or N-(C₁₋₃-alkyl)-imino group wherein the alkyl moiety may be
30 substituted by a carboxy group,

R_a denotes an C₃₋₅-cycloalkyl group substituted by the R₁-CO group in the 1 position wherein
35

R_1 denotes a C_{1-3} -alkoxy, amino, C_{1-4} -alkylamino or di-
(C_{1-4} -alkyl)-amino group wherein each alkyl moiety may be
substituted by a carboxy group,

5 a 4- to 7-membered cycloalkyleneimino group which may be
substituted by a hydroxy group or by one or two
 C_{1-3} -alkyl groups, whilst an alkyl substituent may
simultaneously be substituted by a hydroxy, C_{1-3} -alkoxy,
carboxy, carboxy- C_{1-3} -alkoxy, carboxy- C_{1-3} -alkylamino,
10 N-(C_{1-3} -alkyl)-N-(carboxy- C_{1-3} -alkyl)-amino, carboxy-
 C_{1-3} -alkylaminocarbonyl, N-(C_{1-3} -alkyl)-N-(carboxy-
 C_{1-3} -alkyl)-aminocarbonyl, carboxy-
 C_{1-3} -alkylaminocarbonylamino, 1-(C_{1-3} -alkyl)-3-(carboxy-
 C_{1-3} -alkyl)-aminocarbonylamino, 3-(C_{1-3} -alkyl)-3-(carboxy-
15 C_{1-3} -alkyl)-aminocarbonylamino or 1,3-di-(C_{1-3} -alkyl)-
3-(carboxy- C_{1-3} -alkyl)-aminocarbonylamino group,

a 5- to 7-membered cycloalkyleneimino group optionally
substituted by a C_{1-3} -alkyl group, to which a phenyl ring
20 is fused via two adjacent carbon atoms,

a morpholino, piperazino, N-(C_{1-3} -alkyl)-piperazino,
pyrrolino, 3,4-dehydro-piperidino or pyrrol-1-yl group,

25 a C_{3-5} -cycloalkyl group substituted in the 1 position by
the R_2 -CX- group, wherein

R_2 denotes a phenyl, naphthyl or monocyclic 5- or
6-membered heteroaryl group optionally substituted by a
30 C_{1-3} -alkyl group, wherein the 6-membered heteroaryl group
contains one, two or three nitrogen atoms and the
5-membered heteroaryl group contains an imino group
optionally substituted by a C_{1-3} -alkyl group, an oxygen
or sulphur atom or an imino group optionally substituted
35 by a C_{1-3} -alkyl group and an oxygen or sulphur atom or
one or two nitrogen atoms and the abovementioned alkyl
substituent may be substituted by a carboxy, carboxy-

C₁₋₃-alkoxy, carboxy-C₁₋₃-alkylamino or N-(C₁₋₃-alkyl)-carboxy-C₁₋₃-alkylamino group, and

5 X denotes an oxygen atom, a C₁₋₃-alkylimino, C₁₋₃-alkoxyimino or C₁₋₃-alkylidene group, each of which may be substituted in the alkyl or alkanoyl moiety by a carboxy group,

10 a C₁₋₃-alkyl group substituted in the 1 position by an imidazole or imidazolone group wherein

the imidazole ring may be substituted by a phenyl or carboxy group and by one or two C₁₋₃-alkyl groups or by one, two or three C₁₋₃-alkyl groups, wherein the
15 substituents may be identical or different and one of the abovementioned alkyl substituents may simultaneously be substituted by a carboxy group or may be substituted in the 2 or 3 position by an amino, C₂₋₄-alkanoylamino, C₁₋₃-alkylamino, N-(C₂₋₄-alkanoyl)-C₁₋₃-alkylamino or di-
20 (C₁₋₃-alkyl)-amino group, and

the imidazolone ring may be substituted by a C₁₋₃-alkyl group, whilst the alkyl substituent may be substituted by a carboxy group or in the 2 or 3 position by an
25 amino, C₂₋₄-alkanoylamino, C₁₋₃-alkylamino, N-(C₂₋₄-alkanoyl)-C₁₋₃-alkylamino or di-(C₁₋₃-alkyl)-amino group, and

30 additionally a phenyl or pyridine ring may be fused to the abovementioned imidazole or imidazolone rings via two adjacent carbon atoms,

an imidazolidine-2,4-dione-5-yl group which may be substituted by one or two C₁₋₃-alkyl groups, whilst at the
35 same time an alkyl substituent may be substituted by a carboxy group,

a C₁₋₄-alkyl group which is substituted in the 1 position

by an R₃NR₄- or R₃NR₄-C₁₋₃-alkyl group and

5 by a pyrrolinocarbonyl, 2,3-dehydro-piperidinocarbonyl, imidazol-1-yl-carbonyl, carboxy, aminocarbonyl, C₁₋₃-alkylaminocarbonyl, di-(C₁₋₃-alkyl)-aminocarbonyl, isoxazolidin-1-ylcarbonyl or 4- to 7-membered cyclo-alkyleneiminocarbonyl group, whilst in the
10 abovementioned groups the cycloalkyleneimino moiety may be substituted by one or two C₁₋₃-alkyl groups and at the same time each alkyl moiety or alkyl substituent in the abovementioned C₁₋₃-alkylaminocarbonyl, di-(C₁₋₃-alkyl)-aminocarbonyl or cycloalkyleneiminocarbonyl groups may
15 be substituted by a carboxy group, and the remaining hydrogen atoms of the C₁₋₄-alkyl group may be wholly or partially replaced by fluorine atoms, wherein

20 R₃ denotes a hydrogen atom or a C₁₋₃-alkyl group optionally substituted by a carboxy group and

R₄ denotes a hydrogen atom, a C₁₋₃-alkyl-Y₂ or carboxy-C₁₋₃-alkyl-Y₂ group or

25 R₃ and R₄ together with the nitrogen atom between them denote a 4- to 7-membered cycloalkyleneimino group optionally substituted in the 1 position by a carboxy, C₁₋₃-alkyl or carboxy-C₁₋₃-alkyl group, wherein

30 Y₂ denotes a carbon-nitrogen bond or a carbonyl, imino or -NH-CO- group, wherein the carbonyl group of the -NH-CO- group is linked to the nitrogen atom of the R₃NR₄- group, and the imino group occurring in the definition of the groups Y₂ may additionally be
35 substituted by a C₁₋₃-alkyl or carboxy-C₁₋₃-alkyl group,

a C₁₋₃-alkyl or C₃₋₅-cycloalkyl group substituted in the 1 position by an R₅NR₆- group, wherein

5 R₅ denotes a hydrogen atom, a C₁₋₃-alkyl, C₅₋₇-cycloalkyl, phenylcarbonyl, phenylsulphonyl or pyridinyl group and

R₆ denotes a C₁₋₃-alkyl, carboxy-C₁₋₃-alkyl or carboxy-C₁₋₃-alkylcarbonyl group,

10 a C₁₋₃-alkyl group which is substituted by a C₂₋₄-alkanoyl or C₅₋₇-cycloalkanoyl group and by a C₁₋₃-alkyl group substituted by a chlorine, bromine or iodine atom,

15 R_b denotes a C₁₋₃-alkyl group and

R_c denotes an amidino group which may optionally be substituted by a 2,2,2-trichloroethoxycarbonyl, C₁₋₈-alkoxycarbonyl, acetoxymethyloxycarbonyl, benzyloxycarbonyl or benzoyl group, whilst the benzoyl moiety may be mono- or disubstituted by fluorine, chlorine, bromine or iodine atoms, by C₁₋₃-alkyl or C₁₋₃-alkoxy groups and the substituents may be identical or different,

25 the C₁₋₃-alcohol esters, the tautomers, stereoisomers and salts thereof.

4. Benzimidazoles of general formula Ia according to claim 2, wherein

30

A denotes a methylene group,

B denotes an oxygen atom or an imino group,

35 R_a denotes a cyclopropyl group substituted by the R₁-CO-group in the 1 position, wherein

R_1 denotes a pyrrolidino or piperidino group optionally substituted by a methyl or ethyl group wherein each methyl or ethyl moiety may be substituted by a carboxy, carboxy- C_{1-3} -alkoxy, carboxy- C_{1-3} -alkylamino or
5 N-(C_{1-3} -alkyl)-carboxy- C_{1-3} -alkylamino group,

a cyclopropyl group substituted in the 1 position by the R_2 -CX- group, wherein

10

R_2 denotes a phenyl, pyridyl, pyrazolyl group optionally substituted by a C_{1-3} -alkyl group and

X denotes an oxygen atom, a C_{1-3} -alkoxyimino or
15 C_{1-3} -alkylidene group, each of which is substituted in the alkyl or alkoxy moiety by a carboxy group,

a C_{1-2} -alkyl group substituted in the 1 position by an imidazole group wherein the imidazole ring may be
20 substituted by a phenyl or carboxy group and by one or two C_{1-3} -alkyl groups or by one, two or three C_{1-3} -alkyl groups, wherein the substituents may be identical or different and one of the abovementioned alkyl substituents may simultaneously be substituted by a
25 carboxy group or may be substituted in the 2 or 3 position by an amino, C_{2-4} -alkanoylamino, C_{1-3} -alkylamino, N-(C_{2-4} -alkanoyl)- C_{1-3} -alkylamino or di-(C_{1-3} -alkyl)-amino group, whilst additionally a phenyl or pyridine ring may be fused to the abovementioned imidazole rings via two
30 adjacent carbon atoms,

a C_{1-2} -alkyl substituted in the 1 position by a benzimidazolone-1-yl group, whilst the imidazolone ring may be substituted by a methyl or ethyl group optionally
35 substituted by a carboxy group,

a methyl or ethyl group which is substituted in the 1 position

by an R_3NR_4 or R_3NR_4 - C_{1-3} -alkyl group and

5 by a di- (C_{1-3} -alkyl)-aminocarbonyl group, by a isoxazolidin-1-ylcarbonyl group, by a pyrrolidino-carbonyl or piperidinocarbonyl group substituted by a C_{1-3} -alkyl group, whilst in the abovementioned groups
10 each alkyl moiety or alkyl substituent in the abovementioned groups may be substituted by a carboxy group, wherein

15 R_3 denotes a hydrogen atom or a C_{1-3} -alkyl group optionally substituted by a carboxy group and

R_4 denotes a hydrogen atom, a C_{1-3} -alkyl- Y_2 or carboxy- C_{1-3} -alkyl- Y_2 group or

20 R_3 and R_4 together with the nitrogen atom between them denote a 4- to 7-membered cycloalkyleneimino group optionally substituted by a carboxy group, wherein

25 Y_2 denotes a carbon-nitrogen bond, a carbonyl group or an imino group optionally substituted by a C_{1-3} -alkyl group,

a C_{1-2} -alkyl group substituted in the 1 position by an R_5NR_6 - group, wherein

30 R_5 denotes a pyridinyl, phenylcarbonyl or phenylsulphonyl group and

35 R_6 denotes a C_{1-3} -alkyl or carboxy- C_{1-3} -alkyl group,

an n-propyl group substituted in the 3 position by a chlorine atom, which is substituted in the 1 position by a cyclopentylcarbonyl group,

- 5 a cyclopropyl group substituted in the 1 position by a cyclopentylamino group, which is substituted at the nitrogen atom by a carboxy- C_{1-3} -alkylcarbonyl group,

R_b denotes a methyl group and

10

R_c denotes an amidino group which may optionally be substituted by a C_{1-8} -alkoxycarbonyl, acetoxymethyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, benzyloxycarbonyl or benzoyl group,

15

the C_{1-3} -alkanol esters thereof, the tautomers, stereoisomers and salts thereof.

- 20 5. Benzimidazoles of general formula Ia according to claim 2, wherein

A denotes a methylene group,

B denotes an imino group,

25

R_a denotes a cyclopropyl group substituted by the R_1 -CO-group in the 1 position, wherein

- 30 R_1 denotes a pyrrolidino or piperidino group optionally substituted by a methyl or ethyl group wherein each methyl or ethyl moiety may be substituted by a carboxy, carboxy- C_{1-3} -alkoxy, carboxy- C_{1-3} -alkylamino or N-(C_{1-3} -alkyl)-carboxy- C_{1-3} -alkylamino group,

- 35 a cyclopropyl group substituted in the 1 position by the R_2 -CX group, wherein

R_2 denotes a phenyl, pyridyl, pyrazolyl group optionally substituted by a C_{1-3} -alkyl group and

5 X denotes an oxygen atom, a C_{1-3} -alkoxyimino or C_{1-3} -alkylidene group, each of which is substituted in the alkyl or alkoxy moiety by a carboxy group,

10 a C_{1-2} -alkyl group substituted in the 1 position by an imidazole group wherein the imidazole ring may be substituted by one to three methyl groups or by two methyl groups and an ethyl group, whilst additionally one of the abovementioned methyl or ethyl substituents may simultaneously be substituted by a carboxy group,

15 a methyl or ethyl group which is substituted in the 1 position

by an R_3NR_4 - or $R_3NR_4-CH_2$ - group and

20 by a di- (C_{1-3} -alkyl)-aminocarbonyl, by a pyrrolidinocarbonyl or piperidinocarbonyl group optionally substituted by a C_{1-3} -alkyl group, whilst in the abovementioned groups each alkyl moiety or alkyl

25 substituent may be substituted by a carboxy group, wherein

30 R_3 denotes a hydrogen atom or a C_{1-3} -alkyl group optionally substituted by a carboxy group and

R_4 denotes a C_{1-3} -alkyl- Y_2 or carboxy- C_{1-3} -alkyl- Y_2 group wherein

35 Y_2 denotes a carbon-nitrogen bond, a carbonyl group or an imino group optionally substituted by a C_{1-3} -alkyl group,

R_b denotes a methyl group and

R_c denotes an amidino group which may optionally be substituted by a C₁₋₈-alkoxycarbonyl,
5 acetoxymethyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, benzyloxycarbonyl or benzoyl group,

the C₁₋₃-alkanol esters thereof, the tautomers, stereoisomers and salts thereof.

10

6. Benzimidazoles of general formula I according to at least one of claims 1 to 5 wherein the group R_a is in the 5 position,

15 the tautomers, stereoisomers and salts thereof.

7. The following compounds of general formula Ia:

(a) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(pyrrolidin-1-yl-carbonyl)cyclopropyl]-benzimidazole,
20

(b) (E/Z)-2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-[(pyridin-2-yl)-(carboxymethyloxyimino)methylene]-cyclopropyl]-benzimidazole,

25

(c) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(2-carboxyethylamino)-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole,

30 (d) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-[2-(2-carboxyethyl)-pyrrolidin-1-yl-carbonyl]cyclopropyl]-benzimidazole,

35 (e) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[2-(2-carboxyethyl)-4,5-dimethyl-imidazol-1-yl-methyl]-benzimidazole

(f) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(carboxymethylamino)-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole and

5 (g) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(N-methylcarboxymethylcarbonylaminomethyl)-1-methyl-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-benzimidazole

and the C₁₋₃-alkanolesters, the N-(C₁₋₈-alkoxycarbonyl),
10 N-benzyloxycarbonyl and N-benzoyl-amidines thereof, the tautomers, stereoisomers and salts thereof.

8. 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(carboxymethylamino)-1-(pyrrolidin-1-yl-carbonyl)-ethyl]-
15 benzimidazole, the C₁₋₃-alkanolesters thereof, and their N-(C₁₋₈-alkoxycarbonyl), N-benzyloxycarbonyl and N-benzoyl-amidines, tautomers, stereoisomers and salts.

9. Physiologically acceptable salts of the compounds
20 according to claims 1 to 8 wherein R_c denotes one of the amidino groups mentioned in claims 1 to 8.

10. Pharmaceutical compositions containing a compound according to at least one of claims 1 to 8 wherein R_c
25 denotes one of the amidino groups mentioned in claims 1 to 8, or a salt according to claim 9, optionally together with one or more inert carriers and/or diluents.

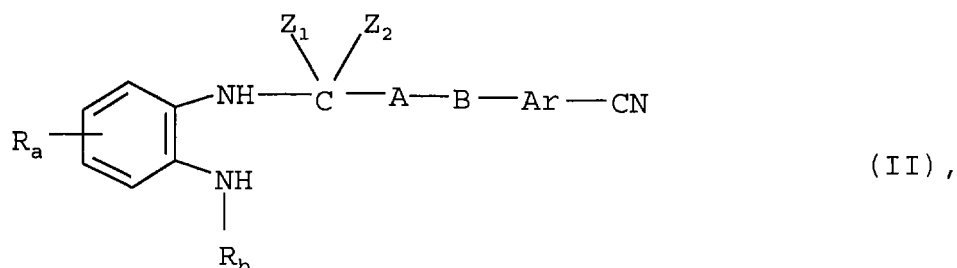
11. Use of a compound according to at least one of claims
30 1 to 8 wherein R_c denotes one of the amidino groups mentioned in claims 1 to 8, or a salt according to claim 9, for preparing a pharmaceutical composition with a thrombin time prolonging effect, a thrombin-inhibiting effect and an inhibiting effect on related serine
35 proteases.

12. Process for preparing a pharmaceutical composition according to claim 10, characterised in that a compound according to at least one of claims 1 to 8 wherein R_c denotes one of the amidino groups mentioned in claims 1 to 8, or a salt according to claim 9, is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

13. Process for preparing the compounds according to claims 1 to 9, characterised in that

a) in order to prepare a compound of general formula I wherein R_c denotes a cyano group:

a compound of general formula



optionally formed in the reaction mixture,
wherein

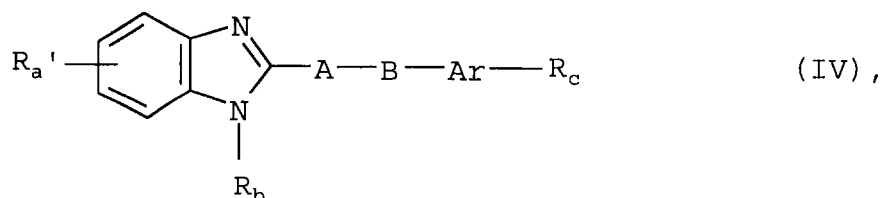
R_a, R_b, Ar, A and B are defined as in claims 1 to 8, Z₁ and Z₂, which may be identical or different, denote amino, hydroxy or mercapto groups optionally substituted by alkyl groups with 1 to 6 carbon atoms or Z₁ and Z₂ together represent an oxygen or sulphur atom, an imino group optionally substituted by an alkyl group with 1 to 3 carbon atoms, an alkylenedioxy or alkylenedithio group with 2 or 3 carbon atoms, is cyclised, or

b) in order to prepare a compound of general formula I wherein R_a denotes an R₂-CX'-C₃₋₅-cycloalkylene group,

wherein R_2 is defined as in claims 1 to 8 and X' denotes one of the imino groups mentioned for X in claims 1 to 8:

a compound of general formula

5



wherein

R_b , Ar , A and B are defined as in claims 1 to 8 and R_a' denotes an R_2 -CO-C₃₋₅-cycloalkylene group, where

10

R_2 is defined as in claims 1 to 8,

is reacted with an amine of general formula

15



wherein

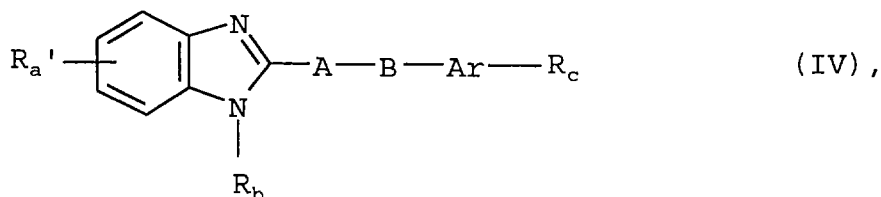
X' denotes one of the imino groups mentioned for X in claims 1 to 8, or

20

c) in order to prepare a compound of general formula I wherein R_a denotes an R_2 -CX"-C₃₋₅-cycloalkylene group, wherein R_2 is defined as in claims 1 to 8 and X'' denotes one of the alkylidene groups mentioned for X in claims 1

25

to 8, a compound of general formula



wherein

R_b , Ar , A and B are defined as in claims 1 to 8 and

R_a' denotes an R_2 -CO-C₃₋₅-cycloalkylene group, where

R_2 is defined as in claims 1 to 8,

5 is reacted with a phosphone of general formula



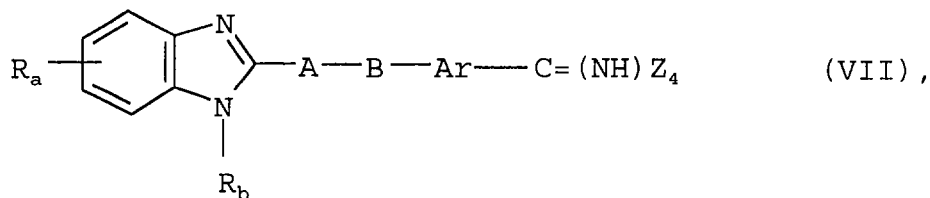
wherein

10 X'' denotes one of the alkylidene groups mentioned for X in claims 1 to 8 and

Z_3 denotes a triphenylphosphono or di-(C₁₋₃-alkoxy)phosphono group, or

15 d) in order to prepare a compound of general formula I wherein R_c denotes an amidino group which may be substituted by one or two C₁₋₃-alkyl groups:

a compound of general formula



20

optionally formed in the reaction mixture

wherein

25 R_a , R_b , Ar , A and B are defined as in claims 1 to 8 and Z_4 denotes an alkoxy, aralkoxy, alkylthio or aralkylthio group, is reacted with an amine of general formula



30

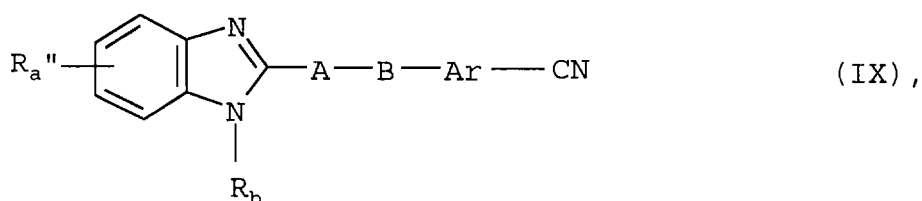
wherein

R_7 and R_8 , which may be identical or different, each denote a hydrogen atom or a C_{1-3} -alkyl group, or with the salts thereof, or

- 5 e) in order to prepare a compound of general formula I wherein R_a denotes an imidazolidin-2,4-dion-5-yl group which may be substituted by one or two C_{1-3} -alkyl groups, whilst at the same time an alkyl substituent may be substituted by a carboxy or C_{1-3} -alkoxycarbonyl group:

10

a compound of general formula



- 15 optionally formed in the reaction mixture

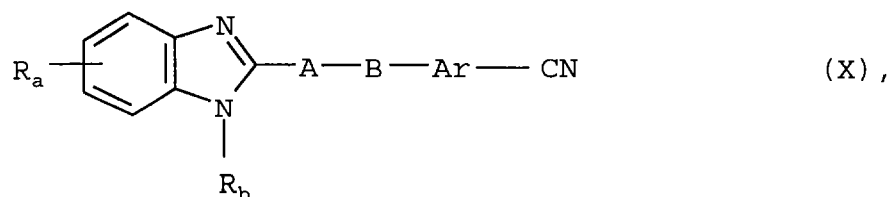
wherein

- R_b , Ar, A and B are defined as in claims 1 to 8 and R_a'' denotes an aminocarbonylamino group, substituted in
20 the 3 position by a C_{1-3} -alkoxycarbonyl- C_{1-3} -alkyl group, is cyclised, or

f) in order to prepare a compound of general formula I wherein R_c denotes a hydroxyamidino group:

25

a nitrile of general formula

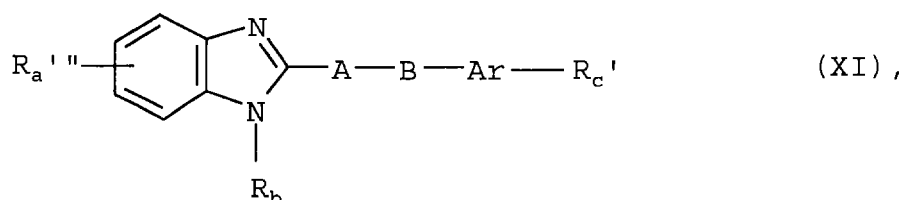


wherein

R_a , R_b , Ar, A and B are defined as in claims 1 to 8, is reacted with hydroxylamine or the salts thereof, or

- g) in order to prepare a compound of general formula I
 5 wherein R_a contains a carboxy group and R_c is defined as in claims 1 to 8 or R_a is defined as in claims 1 to 8 and R_c denotes an amidino group optionally substituted by a hydroxy group or by one or two C_{1-3} -alkyl groups:

- 10 a compound of general formula



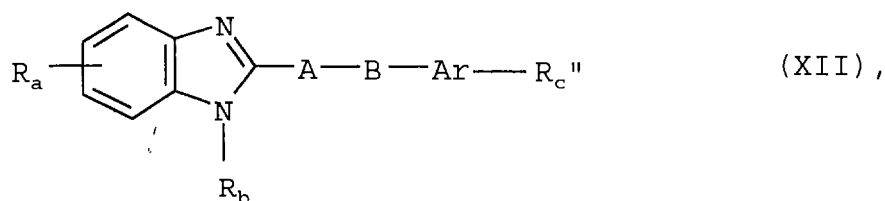
wherein

- R_b , Ar, A and B are defined as in claims 1 to 8 and
 15 R_a' and R_c' have the meanings given for R_a and R_c in claims 1 to 8, with the proviso that R_a contains a group which may be converted into a carboxy group by hydrolysis, treatment with an acid or base, thermolysis or hydrogenolysis and R_c is defined as in claims 1 to 8 or R_c
 20 denotes a group which may optionally be converted by hydrolysis, treatment with an acid or base, thermolysis or hydrogenolysis into an amidino group substituted by a hydroxy group or by one or two C_{1-3} -alkyl groups and R_a is defined as in claims 1 to 8,
 25 is converted by hydrolysis, treatment with an acid or base, thermolysis or hydrogenolysis into a compound of general formula I wherein R_a contains a carboxy group and R_c is defined as in claims 1 to 8 or R_a is defined as in
 30 claims 1 to 8 and R_c denotes an amidino group optionally substituted by a hydroxy group or by one or two C_{1-3} -alkyl groups, or

h) in order to prepare a compound of general formula I wherein R_c denotes an amidino group which is substituted by one or two C_{1-8} -alkoxycarbonyl groups or by a group which can be cleaved *in vivo*:

5

a compound of general formula I



wherein

10 R_a , R_b , Ar, A and B are defined as in claims 1 to 8 and R_c'' denotes an amidino group, is reacted with a compound of general formula



15

wherein

R_9 denotes a C_{1-8} -alkoxycarbonyl group or the acyl group of one of the groups which can be cleaved *in vivo* mentioned hereinbefore and

20 Z_5 denotes a nucleofugic leaving group, and

subsequently if desired a compound of general formula I thus obtained which contains an $(R_3NR_4)-C_{1-3}$ -alkyl group in which at least one of the groups R_3 or R_4 denotes a
 25 hydrogen atom, is converted with a corresponding isocyanate or carbamoyl halide into a corresponding urea compound of general formula I, and/or

a compound of general formula I thus obtained which
 30 contains a NH_2-C_{1-3} -alkyl group is converted with a corresponding acrylic acid ester into a corresponding

2-(C₁₋₃-alkoxycarbonyl)-ethyl compound of general formula I and/or

a compound of general formula I thus obtained which
5 contains an (R₃NR₄)-C₁₋₃-alkyl group in which R₃ and R₄ each denote a hydrogen atom is converted with a corresponding dihaloalkane into a corresponding compound of general formula I wherein R₃ and R₄ together with the nitrogen atom between them denote a corresponding 4- to 7-membered
10 cycloalkyleneimino group and/or

a compound of general formula I thus obtained wherein R_c denotes an amidino group is converted with a haloacetic acid derivative and subsequent hydrolysis and
15 decarboxylation into a corresponding amidino compound substituted by one or two methyl groups and/or

a compound of general formula I thus obtained wherein R_c denotes a hydroxyamidino group is converted by catalytic
20 hydrogenation into a corresponding amidino compound and/or

a compound of general formula I thus obtained wherein R_a contains a carboxy group is converted by esterification into a corresponding ester and/or
25

a protecting group used to protect reactive groups during the reactions is cleaved and/or

a compound of general formula I thus obtained is resolved
30 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
35 salts thereof with an inorganic or organic acid or base.