

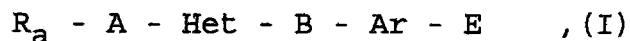
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WO 98/37075

PCT/EP98/00865

- 5 Disubstituted bicyclic heterocycles, the preparation and
the use thereof as pharmaceutical compositions
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10 The present invention relates to new disubstituted bicyclic
heterocycles of general formula



15 the tautomers, stereoisomers and mixtures thereof and the
salts thereof, particularly the physiologically acceptable
salts thereof with organic or inorganic acids or bases
which have valuable properties.

20 The compounds of general formula I above wherein E denotes
a cyano group are valuable intermediates for preparing the
other compounds of general formula I, and the compounds of
general formula I above wherein E denotes an $R_b\text{NH}-\text{C}(=\text{NH})-$
group, and the tautomers and stereoisomers thereof have
25 useful pharmacological properties, particularly a thrombin-
inhibiting activity and the effect of extending thrombin
time.

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

In the above general formula

35 A denotes a carbonyl or sulphonyl group linked to the
benzo, pyrido, pyrimido, pyrazino, pyridazino or thieno

moiety of the group Het, whilst moreover the abovementioned moieties may not contain an R_1 group,

B denotes an ethylene group, wherein a methylene group,
5 linked either to the group Het or Ar, may be replaced by an oxygen or sulphur atom or by a sulphinyl, sulphonyl, carbonyl or $-NR_1$ group, wherein

R_1 denotes a hydrogen atom or a C_{1-6} -alkyl group,
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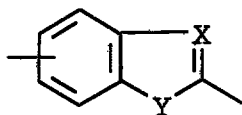
E denotes a cyano or $R_bNH-C(=NH)-$ group wherein

R_b denotes a hydrogen atom, a hydroxy group, a
 C_{1-3} -alkyl group or a group which may be cleaved *in vivo*,
15

Ar denotes a phenylene or naphthylene group optionally substituted by a fluorine, chlorine or bromine atom or by a trifluoromethyl, C_{1-3} -alkyl or C_{1-3} -alkoxy group,
20

a thienylene, thiazolylene, pyridinylene, pyrimidinylene, pyrazinylene or pyridazinylene group optionally substituted in the carbon skeleton by a C_{1-3} -alkyl group,

25 Het denotes a bicyclic heterocycle of formula



, wherein

X is a nitrogen atom and
30

Y is an oxygen or sulphur atom or a nitrogen atom optionally substituted by a C_{1-6} -alkyl or C_{3-7} -cycloalkyl group, whilst additionally one or two non-angular methyne groups in the phenyl moiety of the

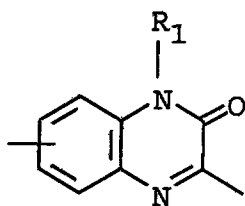
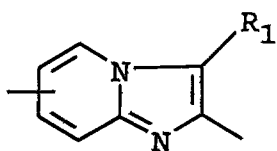
above-mentioned bicyclic heterocycle may each be replaced by a nitrogen atom,

5 or X denotes a methyne group optionally substituted by the group R_1 , wherein R_1 is as hereinbefore defined, and

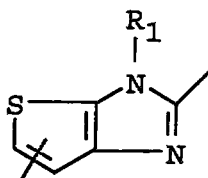
Y denotes a nitrogen atom optionally substituted by a C_{1-6} -alkyl or C_{3-7} -cycloalkyl group,

10

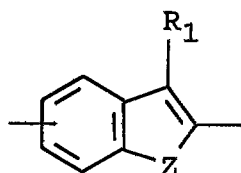
or Het denotes a group of the formula

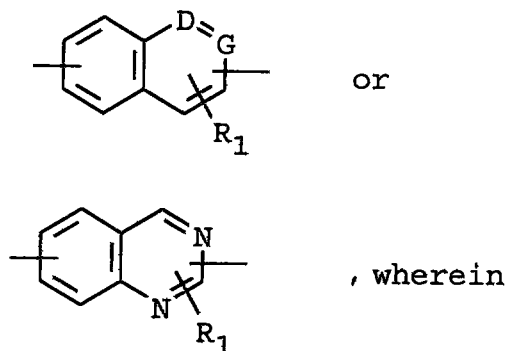


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R_1 is as hereinbefore defined,

Z denotes an oxygen or sulphur atom,

10 one of the groups D or G denotes a nitrogen atom and the other group D or G denotes a methyne group,

and R_2 denotes a C_{1-6} -alkyl group, a C_{3-7} -cycloalkyl group optionally substituted by a C_{1-3} -alkyl group, wherein the
 15 C_{1-3} -alkyl group may additionally be substituted by a carboxyl group or by a group which may be converted *in vivo* into a carboxy group,

or an R_2NR_3 - group wherein

20

R_2 denotes a C_{1-4} -alkyl group, which may be substituted by a carboxy, C_{1-6} -alkyloxycarbonyl, benzyloxycarbonyl, C_{1-3} -alkylsulphonylaminocarbonyl, phenylsulphonylaminocarbonyl, trifluorosulphonylamino, trifluorosulphonylaminocarbonyl or 1H-tetrazolyl
 25 group,

30

a C_{2-4} -alkyl group substituted by a hydroxy, phenyl- C_{1-3} -alkoxy, carboxy- C_{1-3} -alkylamino, C_{1-3} -alkoxycarbonyl- C_{1-3} -alkylamino, N-(C_{1-3} -alkyl)-carboxy- C_{1-3} -alkylamino or N-(C_{1-3} -alkyl)- C_{1-3} -alkoxycarbonyl- C_{1-3} -alkylamino group, whilst in the abovementioned groups

the carbon atom in the α -position relative to the adjacent nitrogen atom may not be substituted, or

5 a piperidinyl group optionally substituted by a C_{1-3} -alkyl group and

R_3 denotes a hydrogen atom, a C_{1-6} -alkyl group, a C_{3-7} -cycloalkyl group optionally substituted by a C_{1-3} -alkyl group, a C_{3-6} -alkenyl or alkynyl group,
10 wherein the unsaturated part may not be linked directly to the nitrogen atom of the R_2NR_3 - group,

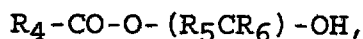
a phenyl group optionally substituted by a fluorine, chlorine or bromine atom or by a C_{1-3} -alkyl or
15 C_{1-3} -alkoxy group, a benzyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, thienyl or imidazolyl group or

20 R_2 and R_3 together with the nitrogen atom between them denote a 5- to 7-membered cycloalkyleneimino group, optionally substituted by a ~~carboxymethyl~~ or C_{1-4} -alkoxycarbonyl group, onto which a phenyl ring may additionally be fused.

25 The compounds of the above general formula I which contain a group capable of being cleaved *in vivo* are thus prodrugs and compounds of general formula I which contain two groups capable of being cleaved *in vivo* are so-called double
30 prodrugs.

The phrase "a group which may be converted *in vivo* into a carboxy group" denotes, for example, a hydroxymethyl group, a carboxy group esterified with an alcohol, in which the
35 alcoholic moiety is preferably a C_{1-6} -alkanol, a phenyl- C_{1-3} -alkanol, a C_{3-9} -cycloalkanol, wherein a C_{5-8} -cycloalkanol may additionally be substituted by one or

two C₁₋₃-alkyl groups, a C₅₋₈-cycloalkanol, in which 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
5 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 emanates from a carbon atom which
10 carries a double or triple bond, a C₃₋₈-cycloalkyl-C₁₋₃-alkanol, a bicycloalkanol having 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
15 an alcohol of formula



wherein

20 R₄ denotes a C₁₋₈-alkyl, C₅₋₇-cycloalkyl, phenyl or phenyl-C₁₋₃-alkyl group,

R₅ denotes a hydrogen atom, a C₁₋₃-alkyl, C₅₋₇-cycloalkyl or phenyl group and

25

R₆ denotes a hydrogen atom or a C₁₋₃-alkyl group,

or the phrase "a group which may be cleaved *in vivo* from an imino or amino group" denotes for example a hydroxy group,
30 an acyl group such as a benzoyl- or pyridinoyl group or a C₁₋₁₆-alkanoyl group such as the formyl-, acetyl-, propionyl-, butanoyl-, pentanoyl- or hexanoyl group, an allyloxycarbonyl group, a C₁₋₁₆-alkoxycarbonyl group such as the methoxycarbonyl-, ethoxycarbonyl-, propoxycarbonyl-,
35 isopropoxycarbonyl-, butoxycarbonyl-, tert.-butoxycarbonyl-, pentoxycarbonyl-, hexoxycarbonyl-, octyloxycarbonyl-, nonyloxycarbonyl-, decyloxycarbonyl-,

- undecyloxy carbonyl-, dodecyloxy carbonyl- or hexadecyloxy carbonyl group, a phenyl- C_{1-6} -alkoxy carbonyl group such as the benzyloxy carbonyl-, phenylethoxy carbonyl- or phenylpropoxy carbonyl group, a C_{1-3} -alkylsulphonyl-
5 C_{2-4} -alkoxy carbonyl-, C_{1-3} -alkoxy- C_{2-4} -alkoxy- C_{2-4} -alkoxy carbonyl- or $R_4CO-O-(R_5CR_6)-O-CO$ -group, wherein R_4 to R_6 are as hereinbefore defined.

- Examples of preferred prodrug groups for a carboxy group
10 include a C_{1-6} -alkoxy carbonyl group such as the methoxy carbonyl, ethoxy carbonyl, n-propyloxy carbonyl, isopropyloxy carbonyl, n-butyloxy carbonyl, n-pentyloxy carbonyl, n-hexyloxy carbonyl or cyclohexyloxy carbonyl group or phenyl- C_{1-3} -alkoxy carbonyl
15 group such as the benzyloxy carbonyl group and

- for an imino or amino group a C_{1-9} -alkoxy carbonyl group such as the methoxy carbonyl, ethoxy carbonyl, n-propyloxy carbonyl, isopropyloxy carbonyl,
20 n-butyloxy carbonyl, n-pentyloxy carbonyl, n-hexyloxy carbonyl, cyclohexyloxy carbonyl, n-heptyloxy carbonyl, n-octyloxy carbonyl or n-nonyloxy carbonyl group, a phenyl- C_{1-3} -alkoxy carbonyl group such as the benzyloxy carbonyl group, a phenyl carbonyl
25 group optionally substituted by a C_{1-3} -alkyl group such as the benzoyl or 4-ethyl-benzoyl group, a pyridinoyl group such as the nicotinoyl group, a C_{1-3} -alkylsulphonyl- $n-C_{2-3}$ -alkoxy carbonyl or C_{1-3} -alkoxy- C_{2-3} -alkoxy- C_{2-4} -alkoxy carbonyl group such as the
30 2-methylsulphonylethoxy carbonyl or 2-(2-ethoxy)-ethoxy carbonyl group.

- Moreover, the saturated alkyl and alkoxy moieties containing more than 2 carbon atoms as well as alkanoyl and
35 unsaturated alkyl moieties containing more than 3 carbon

atoms as mentioned in the foregoing definitions also include the branched isomers thereof such as for example the isopropyl, tert.-butyl and isobutyl group, etc.

- 5 Preferred compounds of the above general formula I, however, are those wherein

A denotes a carbonyl or sulphonyl group linked to the benzo, pyrido, pyrimido, pyrazino, pyridazino or thieno
10 moiety of the group Het, whilst moreover the abovementioned moieties may not contain an R_1 group,

B denotes an ethylene group, in which a methylene group, linked either to the group Het or Ar, may be replaced by an
15 oxygen or sulphur atom or by a sulphinyl, sulphonyl, carbonyl or $-NR_1-$ group, wherein

R_1 denotes a hydrogen atom or a C_{1-5} -alkyl group,

- 20 E denotes an $R_bNH-C(=NH)-$ group wherein

R_b denotes a hydrogen atom, a hydroxy group, a C_{1-3} -alkyl group or a group which may be cleaved *in vivo*,

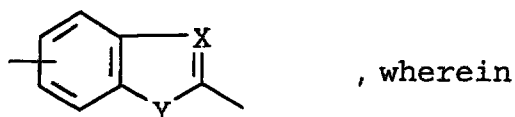
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Ar denotes a phenylene group optionally substituted by a fluorine, chlorine or bromine atom or by a trifluoromethyl, C_{1-3} -alkyl or C_{1-3} -alkoxy group,

- 30 a thienylene, thiazolylene, pyridinylen, pyrimidinylene, pyrazinylen or pyridazinylene group optionally substituted in the carbon skeleton by a C_{1-3} -alkyl group,

Het denotes a bicyclic heterocycle of formula

35



X is a nitrogen atom and

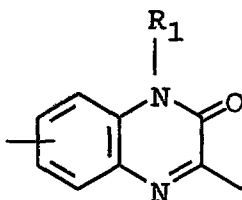
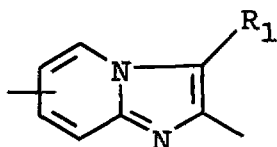
5 Y is an oxygen or sulphur atom or a nitrogen atom optionally substituted by a C₁₋₆-alkyl or C₃₋₇-cycloalkyl group, whilst additionally one or two non-angular methyne groups in the phenyl moiety of the above-mentioned bicyclic heterocycle may each be
10 replaced by a nitrogen atom,

or X denotes a methyne group optionally substituted by the group R₁, wherein R₁ is as hereinbefore defined, and

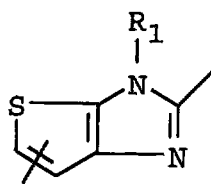
15 Y denotes a nitrogen atom optionally substituted by a C₁₋₆-alkyl or C₃₋₇-cycloalkyl group,

or Het denotes a group of the formulae

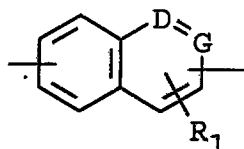
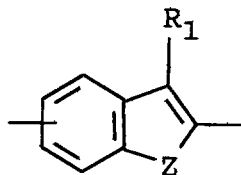
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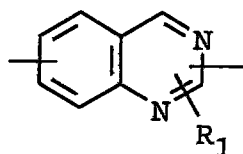
25



5



or



, wherein

10

R_1 is as hereinbefore defined,

15

Z denotes an oxygen or sulphur atom,

one of the groups D or G denotes a nitrogen atom and
the other group D or G denotes a methyne group,

and R_a denotes a C_{1-6} -alkyl group, a C_{3-7} -cycloalkyl group
optionally substituted by a C_{1-3} -alkyl group, wherein the
 C_{1-3} -alkyl group may additionally be substituted by a
carboxyl group or by a group which may be converted *in vivo*
into a carboxy group,

25 or a R_2NR_3 - group wherein

R_2 denotes a C_{1-4} -alkyl group, which may be substituted by a carboxy, C_{1-6} -alkyloxycarbonyl, benzyloxycarbonyl, C_{1-3} -alkylsulphonylaminocarbonyl, phenylsulphonylaminocarbonyl, trifluorosulphonylamino, trifluorosulphonylaminocarbonyl or 1H-tetrazolyl group,

a C_{2-4} -alkyl group substituted by a hydroxy, phenyl- C_{1-3} -alkoxy, carboxy- C_{1-3} -alkylamino, C_{1-3} -alkoxycarbonyl- C_{1-3} -alkylamino, N-(C_{1-3} -alkyl)-carboxy- C_{1-3} -alkylamino or N-(C_{1-3} -alkyl)- C_{1-3} -alkoxycarbonyl- C_{1-3} -alkylamino group, whilst in the abovementioned groups the carbon atom in the α -position relative to the adjacent nitrogen atom may not be substituted, or a piperidinyl group optionally substituted by a C_{1-3} -alkyl group and

R_3 denotes a hydrogen atom, a C_{1-6} -alkyl group, a C_{3-7} -cycloalkyl group optionally substituted by a C_{1-3} -alkyl group, a C_{3-6} -alkenyl or alkynyl group, wherein the unsaturated part may not be linked directly to the nitrogen atom of the R_2NR_3 - group,

a phenyl group optionally substituted by a fluorine, chlorine or bromine atom or by a C_{1-3} -alkyl or C_{1-3} -alkoxy group, a benzyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, imidazolyl or piperidinyl group or

R_2 and R_3 together with the nitrogen atom between them denote a 5- to 7-membered cycloalkyleneimino group, optionally substituted by a carboxy or C_{1-4} -alkoxycarbonyl group, onto which a phenyl ring may additionally be fused, particularly those compounds wherein

Het denotes one of the abovementioned benzimidazolylene, benzothiazolylene, benzoxazolylene, indolylene, quinazolinylene, quinoxazolinonylene, imidazo[4,5-b]pyridinylene, imidazo[1,2-a]pyridinylene, 5 thiazolo[5,4-b]pyridinylene or thieno[2,3-d]imidazolylene groups,

10 the tautomers, the prodrugs, the double prodrugs, the stereoisomers and the salts thereof.

Particularly preferred compounds of general formula I above are those wherein

15

A denotes a carbonyl or sulphonyl group linked to the benzo, pyrido, pyrimido, pyrazino, pyridazino or thieno moiety of the group Het, whilst moreover the abovementioned moieties may not contain an R_1 group,

20

B denotes an ethylene group in which the methylene group linked to the group Ar may be replaced by an oxygen or sulphur atom or by an $-NR_1-$ group, wherein

25

R_1 denotes a hydrogen atom or a C_{1-4} -alkyl group,

E denotes an $R_bNH-C(=NH)-$ group wherein

30

R_b denotes a hydrogen atom, a hydroxy, C_{1-9} -alkoxycarbonyl, cyclohexyloxycarbonyl, phenyl- C_{1-3} -alkoxycarbonyl, benzoyl, p- C_{1-3} -alkyl-benzoyl or pyridinoyl group, whilst the ethoxy moiety in the 2-position of the abovementioned C_{1-9} -alkoxycarbonyl group may additionally be substituted by a C_{1-3} -alkyl-sulfonyl or 2-(C_{1-3} -alkoxy)-ethyl group,

35

Ar denotes a 1,4-phenylene group optionally substituted by a chlorine atom or by a methyl, ethyl or methoxy group or it denotes a 2,5-thienylene group,

- 5 Het denotes a 1-(C₁₋₃-alkyl)-2,5-benzimidazolylene, 1-cyclopropyl-2,5-benzimidazolylene, 2,5-benzothiazolylene, 1-(C₁₋₃-alkyl)-2,5-indolylene, 1-(C₁₋₃-alkyl)-2,5-imidazo[4,5-b]pyridinylene, 3-(C₁₋₃-alkyl)-2,7-imidazo[1,2-a]pyridinylen or 1-(C₁₋₃-alkyl)-
10 2,5-thieno[2,3-d]imidazolylene group and

R_a denotes an R₂NR₃- group wherein

- 15 R₂ is a C₁₋₄-alkyl group substituted by a carboxy, C₁₋₆-alkyloxycarbonyl, benzyloxycarbonyl, C₁₋₃-alkylsulphonylaminocarbonyl or 1H-tetrazol-5-yl group,

- 20 a C₂₋₄-alkyl group substituted by a hydroxy, benzyloxy, carboxy-C₁₋₃-alkylamino, C₁₋₃-alkoxycarbonyl-C₁₋₃-alkylamino, N-(C₁₋₃-alkyl)-carboxy-C₁₋₃-alkylamino or N-(C₁₋₃-alkyl)-C₁₋₃-alkoxycarbonyl-C₁₋₃-alkylamino group, whilst in the abovementioned groups the carbon atom in the α -position to the adjacent nitrogen atom
25 may not be substituted,

- 30 R₃ denotes a C₃₋₇-cycloalkyl group, a propargyl group, wherein the unsaturated part may not be linked directly to the nitrogen atom of the R₂NR₃ group, a phenyl group optionally substituted by a fluorine or chlorine atom, or by a methyl or methoxy group, a pyrazolyl, pyridazolyl or pyridinyl group optionally substituted by a methyl group or

R_2 and R_3 together with the nitrogen atom between them denote a 5- to 7-membered cycloalkyleneimino group, optionally substituted by a carboxy or C_{1-4} -alkoxycarbonyl group, to which a phenyl ring may additionally be fused,

the tautomers, the stereoisomers and the salts thereof.

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

A denotes a carbonyl or sulphonyl group linked to the benzo, pyrido or thieno moiety of the group Het, whilst moreover the abovementioned moieties may not contain an R_1 group,

B denotes an ethylene group in which the methylene group linked to the group Ar may be replaced by an oxygen or sulphur atom or by an $-NR_1-$ group, wherein

R_1 denotes a hydrogen atom or a methyl group,

E denotes an $R_bNH-C(=NH)-$ group, wherein

R_b denotes a hydrogen atom or a hydroxy, C_{1-3} -alkoxycarbonyl, cyclohexyloxycarbonyl, benzyloxycarbonyl, benzoyl, p- C_{1-3} -alkyl-benzoyl or nicotinoyl group, whilst the ethoxy moiety in the 2-position of the abovementioned C_{1-3} -alkoxycarbonyl group may additionally be substituted by a C_{1-3} -alkylsulphonyl or 2-(C_{1-3} -alkoxy)-ethyl group,

Ar denotes a 1,4-phenylene group optionally substituted by a chlorine atom or by a methyl, ethyl or methoxy group, or it denotes a 2,5-thienylene group,

Het denotes a 1-methyl-2,5-benzimidazolylene, 1-cyclopropyl-2,5-benzimidazolylene, 2,5-benzothiazolylene, 1-methyl-2,5-indolylene, 1-methyl-2,5-imidazo[4,5-b]pyridinylene, 3-methyl-
5 2,7-imidazo[1,2-a]pyridinylene or 1-methyl-2,5-thieno[2,3-d]imidazolylene group and

R_a denotes a R_2NR_3 - group wherein

10 R_2 denotes a C_{1-3} -alkyl group which may be substituted by a carboxy, C_{1-6} -alkyloxycarbonyl, benzyloxycarbonyl, methylsulphonylaminocarbonyl or 1H-tetrazol-5-yl group,

a C_{2-3} -alkyl group substituted by a hydroxy, benzyloxy,
15 carboxy- C_{1-3} -alkylamino, C_{1-3} -alkoxycarbonyl- C_{1-3} -alkylamino, N-(C_{1-3} -alkyl)-carboxy- C_{1-3} -alkylamino or N-(C_{1-3} -alkyl)- C_{1-3} -alkoxycarbonyl- C_{1-3} -alkylamino group, whilst in the abovementioned groups the carbon atom in the α -position to the adjacent nitrogen atom
20 may not be substituted, and

R_3 denotes a propargyl group, wherein the unsaturated moiety may not be linked directly to the nitrogen atom of the R_2NR_3 group, a phenyl group optionally
25 substituted by a fluorine or chlorine atom, or by a methyl or methoxy group, or denotes a pyridinyl group,

particularly those wherein

30 A denotes a carbonyl group linked to the benzo or thieno moiety of the group Het,

B denotes an ethylene group wherein the methylene group attached to the group Ar may be replaced by an $-NR_1$ group,
35 wherein

R_1 denotes a hydrogen atom or a methyl group,

E denotes an $R_b\text{NH-C(=NH)-}$ group wherein

5

R_b is a hydrogen atom, a hydroxy, C_{1-9} -alkoxycarbonyl, cyclohexyloxycarbonyl, benzyloxycarbonyl, benzoyl, $p\text{-}C_{1-3}$ -alkyl-benzoyl or nicotinoyl group, whilst the ethoxy moiety in the 2-position of the abovementioned C_{1-9} -alkoxycarbonyl group may additionally be substituted by a methylsulfonyl or 2-ethoxy-ethyl group,

10

Ar denotes a 1,4-phenylene group optionally substituted by a methoxy group, or denotes a 2,5-thienylene group,

15

Het denotes a 1-methyl-2,5-benzimidazolylenes, 2,5-benzothiazolylenes, 1-methyl-2,5-indolylenes or 1-methyl-2,5-thieno[2,3-d]imidazolylenes group and

20

R_a denotes an $R_2\text{NR}_3\text{-}$ group wherein

R_2 denotes a C_{1-3} -alkyl group which may be substituted by a carboxy, C_{1-6} -alkyloxycarbonyl, benzyloxycarbonyl, methylsulfonylaminocarbonyl or 1H-tetrazol-5-yl group,

25

a C_{2-3} -alkyl group substituted by a hydroxy, benzyloxy, carboxy- C_{1-3} -alkylamino, C_{1-3} -alkoxycarbonyl- C_{1-3} -alkylamino, N-(C_{1-3} -alkyl)-carboxy- C_{1-3} -alkylamino or N-(C_{1-3} -alkyl)- C_{1-3} -alkoxycarbonyl- C_{1-3} -alkylamino group, whilst in the abovementioned groups the carbon atom in the α -position to the adjacent nitrogen atom may not be substituted, and

30

R₃ denotes a phenyl group optionally substituted by a fluorine atom, or denotes a 2-pyridinyl group,

the tautomers, stereoisomers and the salts thereof.

5

The following are mentioned as examples of particularly preferred compounds:

10 (a) 2- [N- (4-amidinophenyl) -aminomethyl] -benzthiazole-5-carboxylic acid-N-phenyl-N- (2-carboxyethyl) -amide,

(b) 2- [N- (4-midinophenyl) -N-methyl-aminomethyl] -benzthiazol-5-yl-carboxylic acid-N-phenyl-N- (2-
15 hydroxycarbonylethyl) -amide,

(c) 1-Methyl-2- [N- (4-amidinophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic acid-N-phenyl-N- (2-
20 hydroxycarbonylethyl) -amide,

(d) 1-Methyl-2- [N- (4-amidinophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic acid-N-phenyl-N- (3-hydroxycarbonylpropyl) -amide,

25 (e) 1-Methyl-2- [N- (4-amidinophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic acid-N- (2-pyridyl) -N- (hydroxycarbonylmethyl) -amide,

(f) 1-Methyl-2- [2- (2-amidinothiophen-5-yl) ethyl] -benzimidazol-5-yl-carboxylic acid-N- (2-pyridyl) -N- (2-
30 hydroxycarbonylethyl) -amide,

(g) 1-Methyl-2- [N- (4-amidinophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic acid-N- (2-pyridyl) -N- (2-
35 hydroxycarbonylethyl) -amide,

- (h) 1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide,
- 5 (i) 1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide,
- (j) 1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-[2-(1H-tetrazol-5-yl)ethyl]-amide,
- 10 (k) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-[2-(1H-tetrazol-5-yl)ethyl]-amide,
- 15 (l) 1-Methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide,
- 20 (m) 1-Methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-pyridyl)-N-(2-hydroxycarbonylethyl)-amide,
- (n) 1-Methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide,
- 25 (o) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-[(N-hydroxycarbonylethyl-N-methyl)-2-aminoethyl]-amide,
- 30 (p) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-fluorophenyl)-N-(2-hydroxycarbonylethyl)-amide,
- 35

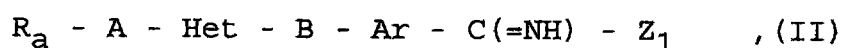
- (q) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(4-fluorophenyl)-N-(2-hydroxycarbonylethyl)-amide,
- 5 (r) 1-Methyl-2-[N-(4-amidino-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide,
- (s) 1-Methyl-2-[N-(4-amidino-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide,
- 10 (t) 1-Methyl-2-[N-(4-amidinophenyl)aminomethyl]-indol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide
- 15 and
- (u) 1-Methyl-2-[N-(4-amidinophenyl)aminomethyl]-thieno[2.3-d]imidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide,
- 20

the tautomers, prodrugs, double prodrugs, stereoisomers and the salts thereof.

- 25 The new compounds may be prepared by methods known *per se*, for example by the following methods:

- a. In order to prepare a compound of general formula I, wherein E denotes an $R_b\text{NH-C(=NH)-}$ group, wherein R_b is a
- 30 hydrogen atom, a hydroxy or C_{1-3} -alkyl group:

By reacting a compound of general formula

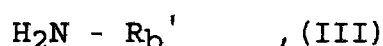


35

optionally formed in the reaction mixture,

wherein

A, B, Ar, Het and R_a are as hereinbefore defined and
Z₁ denotes an alkoxy or aralkoxy group such as the methoxy,
ethoxy, n-propoxy, isopropoxy or benzyloxy group or an
5 alkylthio or aralkylthio group such as the methylthio,
ethylthio, n-propylthio or benzylthio group, with an amine
of general formula



10

wherein

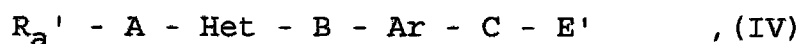
R_b' denotes a hydrogen atom or a hydroxy or C₁₋₃-alkyl
group.

15 The reaction is conveniently carried out in a solvent such
as methanol, ethanol, n-propanol, water, methanol/water,
tetrahydrofuran or dioxane at temperatures between 0 and
150°C, preferably at temperatures between 20 and 120°C,
with a compound of general formula III or with a
20 corresponding acid addition salt such as ammonium
carbonate, for example.

A compound of general formula II may be obtained, for
example, by reacting a compound of general formula I
25 wherein E denotes a cyano group, 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 triethyloxonium-
30 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, appropriately in a solvent such as
pyridine or dimethylformamide and in the presence of a base
35 such as triethylamine and subsequent alkylation of the
resulting thioamide with a corresponding alkyl or aralkyl
halide.

b. In order to prepare a compound of general formula I wherein the R_a -A- group and E are as hereinbefore defined, with the proviso that the R_a -A- group contains a carboxy group and E as hereinbefore defined or that the R_a -A- group is as hereinbefore defined and E denotes an $NH_2-C(=NH)-$ group, or that the R_a -A- group contains a carboxy group and E denotes an $NH_2-C(=NH)-$ group:

10 Converting a compound of general formula



wherein

A, B, Ar and Het are as hereinbefore defined and
15 the R_a' -A- group and E' have the meanings given for the R_a -A- group and E hereinbefore, with the proviso that the R_a' -A- group contains a group which may be converted into a carboxyl group by hydrolysis, treatment with an acid or base, thermolysis or hydrogenolysis and E is as
20 hereinbefore defined or E' denotes a group which may be converted into an $NH_2-C(=NH)-$ group by hydrolysis, treatment with an acid or base, thermolysis or hydrogenolysis and the R_a' -A- group has the meanings given for the R_a -A- group hereinbefore or the R_a' -A- group
25 contains a group which may be converted into a carboxyl group by hydrolysis, treatment with an acid or base, thermolysis or hydrogenolysis and E' denotes a group which may be converted into an $NH_2-C(=NH)-$ group by hydrolysis, treatment with an acid or base, thermolysis or
30 hydrogenolysis,

is converted by hydrolysis, treatment with an acid or base, thermolysis or hydrogenolysis into a compound of general formula I, wherein the R_a -A- group and E are as
35 hereinbefore defined, with the proviso that the R_a -A- group contains a carboxy group and E is as hereinbefore defined or the R_a -A- group has the meanings given above and E

denotes an $\text{NH}_2\text{-C(=NH)-}$ group or the $\text{R}_\text{a}\text{-A-}$ group contains a carboxy group and E denotes an $\text{NH}_2\text{-C(=NH)-}$ group.

5 Examples of groups which may be converted into a carboxy group include a carboxyl group protected by a protecting group and the functional derivatives thereof, e.g. the unsubstituted or substituted amides, esters, thioesters, trimethylsilylesters, orthoesters or iminoesters which may conveniently be converted into a carboxyl group by
10 hydrolysis,

the esters thereof with tertiary alcohols, e.g. the tert.butylester, which are conveniently converted into a carboxyl group by treatment with an acid or by thermolysis,
15 and

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

20 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 mixtures thereof or in the presence
25 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 between -10 and 120°C , e.g. at temperatures
30 between room temperature and the boiling temperature of the reaction mixture.

If the $\text{R}_\text{a}'\text{-A-}$ group and/or E' in a compound of formula IV contains the tert.-butyl or tert.-butyloxycarbonyl group,
35 for example, these may also be cleaved by treating 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 as methylene chloride, chloroform, benzene, toluene, diethylether, tetrahydrofuran or dioxane, preferably at temperatures between -10 and 120°C, e.g. at
5 temperatures between 0 and 60°C, or thermally optionally in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran or dioxane and preferably in the presence of a catalytic quantity of an acid such as p-toluenesulphonic acid, sulphuric acid, phosphoric acid or
10 polyphosphoric acid, preferably at the boiling temperature of the solvent used, e.g. at temperatures between 40 and 120°C.

If the R_a' -A- group and/or E' in a compound of formula IV
15 contains the benzyloxy or benzyloxycarbonyl group, for example, these may also be cleaved by hydrogenolysis 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,
20 dioxane or dimethylformamide, preferably at temperatures between 0 and 50°C, e.g. at room temperature, under a hydrogen pressure of 1 to 5 bar.

c. In order to prepare a compound of general formula I
25 wherein the R_a -A- group contains one of the ester groups mentioned in the definition of the R_a -A- group hereinbefore:

Reaction of a compound of general formula

30

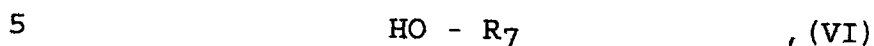


wherein

B, E, Ar and Het are as hereinbefore defined and
35 the R_a'' -A- group has the meanings given for the R_a -A- group hereinbefore, with the proviso that the R_a'' -A- group



contains a carboxyl group or a group which may be converted into a corresponding ester group by means of an alcohol, with an alcohol of general formula



wherein

R_7 is the alkyl moiety of one of the above-mentioned groups which may be cleaved *in vivo*, with the exception of the $\text{R}_6\text{-CO-O-(R}_5\text{CR}_6\text{)}$ - group for a carboxyl group, or with the
10 formamide acetals thereof.

or with a compound of general formula

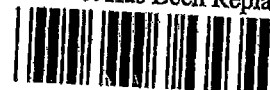


15

wherein

R_8 denotes the alkyl moiety of one of the above-mentioned groups which may be cleaved *in vivo*, with the exception of the $\text{R}_6\text{-CO-O-(R}_5\text{CR}_6\text{)}$ - group for a carboxyl group and
20 Z_2 denotes a leaving group such as a halogen atom, e.g. a chlorine or bromine atom.

The reaction with an alcohol of general formula VI is conveniently carried out in a solvent or mixture of
25 solvents such as methylene chloride, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane, but preferably in an alcohol of general formula VI, optionally in the presence of an acid such as hydrochloric acid or in the presence of a dehydrating
30 agent, e.g. in the presence of isobutylchloroformate, thionyl chloride, trimethylchlorosilane, hydrochloric acid, sulphuric acid, methanesulphonic acid, p-toluenesulphonic acid, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-
35 hydroxysuccinimide, N,N'-carbonyldiimidazole or N,N'-thionyl diimidazole, triphenylphosphine/carbon tetrachloride or triphenylphosphine/diethylazodicarboxylate, optionally



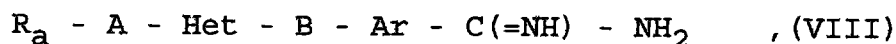
in the presence of a base such as potassium carbonate, N-ethyl-diisopropylamine or N,N-dimethylamino-pyridine, conveniently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C.

5

With a compound of general formula VII the reaction is usefully carried out in a solvent such as methylene chloride, tetrahydrofuran, dioxane, dimethylsulphoxide, dimethylformamide or acetone, optionally in the presence of
10 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 act as solvent at the same
15 time, 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.

d. In order to prepare a compound of general formula I
20 wherein R_b denotes a group which may be cleaved *in vivo*:

Reacting a compound of general formula



25

wherein

R_a , A, Het, B and Ar are as hereinbefore defined, with a compound of general formula

30



wherein

R_5 denotes a group which may be cleaved *in vivo* and

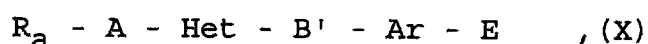
Z_2 denotes a nucleofugic leaving group such as a halogen
35 atom, e.g. a chlorine, bromine or iodine atom.

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

With a compound of general formula IX, wherein Z_2 denotes a nucleofugic leaving group, the reaction is preferably carried out in a solvent such as methylene chloride, acetonitrile, tetrahydrofuran, toluene, dimethylformamide or dimethylsulphoxide, optionally in the presence of a base such as sodium hydride, potassium carbonate, potassium tert.-butoxide or N-ethyl-diisopropylamine at temperatures between 0 and 60°C.

e. In order to prepare a compound of general formula I wherein B denotes an ethylene group, in which a methylene group is replaced by a sulphinyl or sulphonyl group:

Oxidation of a compound of general formula



25

wherein

A, E, Ar, Het and R_a are as hereinbefore defined and B' denotes an ethylene group, wherein a methylene group is replaced by a sulphenyl or sulphinyl group.

30

The oxidation is preferably carried out in a solvent or mixture of solvents, e.g. in water, water/pyridine, acetone, methylene chloride, glacial acetic acid, glacial acetic acid/acetic anhydride, dilute sulphuric acid or trifluoroacetic acid, and depending on the oxidising agent used, at temperatures between -80 and 100°C.

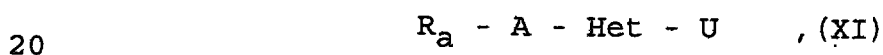
In order to prepare a corresponding sulphonyl compound of general formula I oxidation is conveniently carried out with one equivalent of the oxidising agent used, e.g. with
5 hydrogen peroxide in glacial acetic acid, trifluoroacetic acid or formic acid at 0 to 20°C or in acetone at 0 to 60°C, with a peracid such as performic acid in glacial acetic acid or trifluoroacetic acid at 0 to 50°C or with m-chloroperbenzoic acid in methylene chloride, chloroform or
10 dioxane at -20 to 80°C, with sodium metaperiodate in aqueous methanol or ethanol at -15 to 25°C, with bromine in glacial acetic acid or aqueous acetic acid, optionally in the presence of a weak base such as sodium acetate, with N-bromosuccinimide in ethanol, with tert.-butylhypochlorite
15 in methanol at -80 to -30°C, with iodobenzodichloride in aqueous pyridine at 0 to 50°C, with nitric acid in glacial acetic acid at 0 to 20°C, with chromic acid in glacial acetic acid or in acetone at 0 to 20°C and with sulphuryl chloride in methylene chloride at -70°C, the resulting
20 thioether chlorine complex is conveniently hydrolysed with aqueous ethanol.

In order to prepare a sulphonyl compound of general formula I, oxidation is carried out starting from a corresponding
25 sulphonyl compound, conveniently with one or more equivalents of the oxidising agent used, or starting from a corresponding sulphenyl compound, conveniently with two or more equivalents of the oxidising agent used, e.g. with hydrogen peroxide in glacial acetic acid/acetic anhydride,
30 trifluoroacetic acid or in formic acid at 20 to 100°C or in acetone at 0 to 60°C, with a peracid such as performic acid or with m-chloroperbenzoic acid in glacial acetic acid, trifluoroacetic acid, methylene chloride or chloroform at temperatures between 0 and 60°C, with nitric acid in
35 glacial acetic acid at 0 to 20°C, with chromic acid or

potassium permanganate in glacial acetic acid,
water/sulphuric acid or in acetone at 0 to 20°C. Thus, by
carrying out oxidation, for example, starting from a
corresponding sulphenyl compound, preferably in methylene
5 chloride, by treating with a corresponding amount of m-
chloroperbenzoic acid at temperatures between 20°C and the
reflux temperature of the reaction mixture, a corresponding
sulphonyl compound of general formula I is obtained which
may still contain a small amount of the corresponding
10 sulphinyl compound.

f. In order to prepare a compound of general formula I
wherein E is a cyano group and B is an ethylene group in
which a methylene group linked either to group Het or to Ar
15 is replaced by an oxygen or sulphur atom or by a sulphinyl,
sulphonyl, carbonyl or -NR₁- group:

Reacting a compound of general formula



with a compound of general formula



wherein

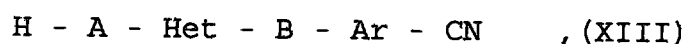
R_a, A, Ar and Het are as hereinbefore defined,
one of the groups U or V denotes an HO-, HS-, HOSO-, HOSO₂-
or HNR₁- group and the other group denotes a Z₃CH₂- group,
30 wherein R₁ is as hereinbefore defined and Z₃ denotes a
nucleofugic leaving group such as a halogen atom, e.g. a
chlorine, bromine or iodine atom.

The reaction is preferably carried out in a solvent such as
35 methanol, ethanol, methylene chloride, tetrahydrofuran,
toluene, dioxane, dimethylsulphoxide or dimethylformamide,
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.

g. In order to prepare a compound of general formula I,
5 wherein E is a cyano group and R_a denotes an R_2NR_3 - group:

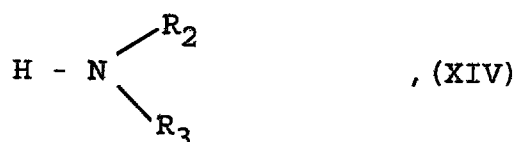
Reacting a compound of general formula



10

wherein

A, B, Het and Ar are as hereinbefore defined, with an amine of general formula



15

wherein

R_2 and R_3 are as hereinbefore defined, or with the reactive derivatives thereof.

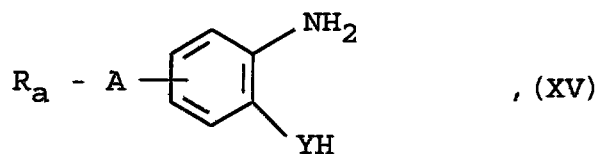
20 The reaction of an acid of general formula XIII is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane or in a corresponding
25 amine of general formula III, optionally in the presence of a dehydrating agent, e.g. in the presence of isobutylchloroformate, tetraethylorthocarbonate, trimethylorthoacetate, 2,2-dimethoxypropane, tetramethoxysilane, thionyl chloride, trimethylchlorosilane, phosphorus trichloride,
30 phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, N,N'-dicyclohexylcarbodiimide/1-hydroxy-benzotriazole, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate/1-hydroxy-

benzotriazole, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride and optionally with the addition of a base such as pyridine, 4-dimethylamino-pyridine, N-methyl-morpholine or triethylamine,
 5 conveniently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 100°C.

The reaction of a corresponding reactive compound of general formula XIII such as the esters, imidazolides or
 10 halides thereof with an amine of general formula XIV is preferably carried out in a corresponding amine as solvent, optionally in the presence of another solvent such as methylene chloride or ether and preferably in the presence of a tertiary organic base such as triethylamine, N-ethyl-diisopropylamine or N-methyl-morpholine at temperatures
 15 between 0 and 150°C, preferably at temperatures between 50 and 100°C.

h. In order to prepare a benzimidazolyl, benzothiazolyl or
 20 benzoxazolyl compound of general formula I wherein B denotes an ethylene group:

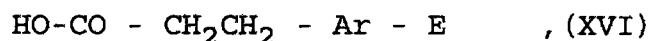
Reacting a compound of general formula



25

wherein

R_a, A and Y are as hereinbefore defined, with a compound of general formula



30

wherein

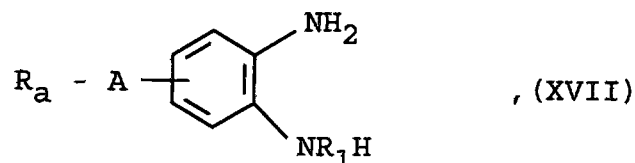
Ar and E are as hereinbefore defined, or with the reactive derivatives thereof.

The reaction is conveniently carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane, optionally in the presence of a dehydrating agent, e.g. in the presence of isobutylchloroformate, tetraethylortho-carbonate, trimethylorthoacetate, 2,2-dimethoxypropane, tetramethoxysilane, thionyl chloride, trimethylchloro-silane, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, N,N'-dicyclohexylcarbodiimide/1-hydroxy-benzotriazole, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate/1-hydroxy-benzotriazole, N,N'-carbonyldiimidazole or triphenyl-phosphine/carbon tetrachloride, and optionally with the addition of a base such as pyridine, 4-dimethylamino-pyridine, N-methyl-morpholine or triethylamine, appropriately at temperatures between 0 and 150°C, preferably at temperatures between 0 and 100°C.

The reaction of a corresponding reactive compound of general formula XVI such as the esters, imidazolides or halides thereof with an amine of general formula XV is preferably carried out in a solvent such as methylene chloride, ether or tetrahydrofuran and preferably in the presence of a tertiary organic base such as triethylamine, N-ethyl-diisopropylamine or N-methyl-morpholine, which may simultaneously be used as solvents, at temperatures between 0 and 150°C, preferably at temperatures between 50 and 100°C.

i. In order to prepare a quinoxalin-2-one compound of the general formula:

Reacting a compound of general formula



wherein

- 5 R_a , R_1 and A are as hereinbefore defined, with a compound of general formula



wherein

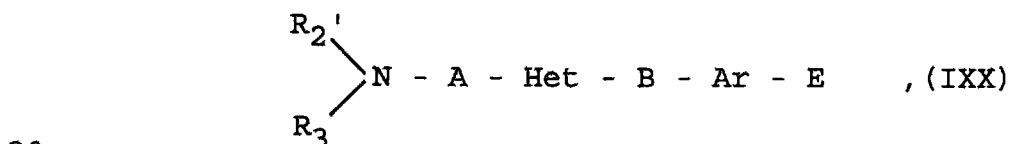
- 10 Ar and E are as hereinbefore defined, or with the reactive derivatives thereof.

- The reaction is conveniently carried out in a solvent or mixture of solvents such as methylene chloride,
- 15 dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran, ethanol or dioxan, optionally in the presence of a dehydrating agent, e.g. in the presence of isobutyl chloroformate, tetraethyl orthocarbonate, trimethyl orthoacetate,
- 20 2,2-dimethoxypropane, tetramethoxysilane, thionyl chloride, trimethylchlorosilane, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, N,N'-dicyclohexylcarbodiimide/1-hydroxy-benzotriazole,
- 25 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate/1-hydroxy-benzotriazole, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, and optionally
- 30 with the addition of a base such as pyridine, 4-dimethylaminopyridine, N-methyl-morpholine or triethylamine, appropriately at temperatures of between 0 and 150°C, preferably at temperatures of between 0 and 100°C.

However, it is particularly preferred to carry out the reaction with a corresponding reactive compound of general formula XVIII such as the esters, imidazolides or halides thereof with an amine of general formula XVII in a solvent such as methylene chloride, ether, ethanol or tetrahydrofuran and optionally in the presence of a tertiary organic base such as triethylamine, N-ethyl-diisopropylamine or N-methyl-morpholine, which may simultaneously serve as solvent, at temperatures of between 0 and 150°C, preferably at temperatures of between 50 and 100°C.

j. In order to prepare a compound of general formula I wherein R_2 denotes a C_{1-4} -alkyl group substituted by an alkylsulphonylaminocarbonyl group:

Reacting a compound of general formula



wherein

R_3 , A, B, E, and Het are as hereinbefore defined and R_2' denotes a C_{1-4} -alkyl group substituted by a carboxy group, or the reactive derivatives thereof, with a salt of a compound of general formula



The reaction is preferably carried out with a corresponding reactive compound of general formula IXX such as the esters, imidazolides or halides thereof with a salt of a compound of general formula XX, preferably with an alkali metal salt thereof such as a sodium salt, in a solvent such as methylene chloride, ether, ethanol, tetrahydrofuran or

dimethylformamide at temperatures between 0 and 150°C, preferably at temperatures of between 50 and 100°C.

5 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 means of conventional protecting groups which are removed by cleaving after the reaction.

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

the protecting group for a carboxyl group may be the
15 trimethylsilyl, methyl, ethyl, tert.butyl, benzyl or tetrahydropyranyl group, and

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

The optional subsequent cleaving of a protecting group may,
25 for example, be carried out hydrolytically in an aqueous solvent, e.g. in water, isopropanol/water, tetrahydrofuran/water or dioxane/water, in the presence of an acid such as trifluoroacetic acid, hydrochloric acid or sulphuric acid or in the presence of an alkali metal base
30 such as lithium hydroxide, sodium hydroxide or potassium hydroxide or by ether cleaving, e.g. in the presence of iodotrimethylsilane, at temperatures between 0 and 100°C, preferably at temperatures between 10 and 50°C.

35 However, a benzyl, methoxybenzyl or benzyloxycarbonyl group may for example be cleaved hydrogenolytically, e.g. using hydrogen in the presence of a catalyst such as

palladium/charcoal in a solvent such as methanol, ethanol, ethyl acetate, dimethylformamide, dimethylformamide/acetone or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid, at temperatures between 0
5 and 50°C, but preferably at room temperature, under a hydrogen pressure of 1 to 7 bar, preferably 3 to 5 bar.

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

However, a 2,4-dimethoxybenzyl group is preferably cleaved
15 in trifluoroacetic acid in the presence of anisole.

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

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,
25 ethanol, isopropanol, toluene/water or dioxane, at temperatures between 20 and 50°C.

An allyloxycarbonyl group is cleaved by treating with a catalytic amount of tetrakis-(triphenylphosphine)-
30 palladium(0), preferably in a solvent such as 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 room temperature and under inert gas, or by treating with a
35 catalytic amount of tris-(triphenylphosphine)-rhodium(I)-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.

5 The compounds of general formulae II to XX used as starting materials, some of which are known from the literature, may be obtained by methods known from the literature and moreover their production is described in the Examples.

10 Thus, for example, a compound of general formula II is obtained by reacting a corresponding nitrile which in turn is conveniently obtained by processes f to h, with a corresponding thio or alcohol in the presence of hydrogen chloride or bromide.

15 A compound of general formulae IV, V, VIII, X and IXX used as starting material is conveniently obtained according to a process of the present invention.

20 A starting compound of general formula XI in which U denotes a halomethyl group is conveniently obtained by cyclisation of a corresponding ester which is substituted in the o-position by a suitable halogen atom and a methoxyacetamido group, to form a corresponding bicyclic 2-alkoxymethyl compound, optionally subsequent hydrolysis and
25 optionally subsequent amidation of a resulting carboxylic acid with a corresponding amine, converting the alkoxymethyl compound thus obtained into the corresponding halomethyl compound, which can if necessary be subsequently converted into the desired compound by means of a suitable
30 compound. If the cyclisation is carried out with a suitable carbonic acid derivative, a starting compound of general formula XI is obtained wherein U denotes a hydroxy, mercapto or amino group.

35 A starting compound of general formula XIII is obtained by cyclisation of a corresponding o-disubstituted ester, followed by saponification of the resulting ester and

subsequent amidation of the carboxylic acid thus obtained with a corresponding amine.

Furthermore, an imidazopyridine substituted in the 5-
5 position by a methyl group and obtained by cyclisation can be converted, via the corresponding N-oxide, into the corresponding hydroxymethyl compound which is converted by oxidation into the desired carboxylic acid of general formula XIII.

10

The compounds of general formulae III, VI, VII, IX and XII used as starting materials are obtained by conventional methods, for example by reducing an aromatic ester substituted in the o-position by an optionally substituted
15 amino group and a nitro group, and optionally subsequent cyclisation of the resulting o-diamino compound with a corresponding carboxylic acid.

Furthermore, the compounds of general formula I obtained
20 may be separated into their enantiomers and/or diastereomers.

Thus, for example, the compounds of general formula I obtained which occur in racemate form may be separated by
25 methods known *per se* (see 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 having at least 2 asymmetric carbon atoms may be separated on the basis of their physical-chemical
30 differences using known methods, e.g. by chromatography and/or fractional crystallisation, into the diastereomers thereof, which, if they occur in racemic form, may subsequently be separated into the enantiomers as mentioned above.

35

The separation of enantiomers is preferably effected by column separation on chiral phases or by recrystallisation

from an optically active solvent or by reacting with an optically active substance, especially acids and the activated derivatives thereof or alcohols, which forms salts or derivatives such as e.g. esters or amides with the racemic compound, and separation of the diastereomeric salt mixture or derivative thus obtained, e.g. on the basis of their different solubilities, whilst the free antipodes may be released from the pure diastereomeric salts or derivatives by the action of suitable agents. Particularly common, optically active acids are, for example, the D- and L-forms of tartaric acid, and dibenzoyltartaric acid, di-o-tolyl tartaric acid, malic acid, mandelic acid, camphorsulphonic acid, glutamic acid, aspartic acid and quinaldic acid. Examples of optically active alcohols include for example (+)- or (-)-menthol and examples of optically active acyl groups in amides include, for example, (+)- or (-)-menthyloxycarbonyl.

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

In addition, the new compounds of formula I thus obtained, if they contain a carboxyl group, may subsequently, if desired, be converted into the salts thereof with inorganic or organic bases, more particularly, for pharmaceutical use, into the physiologically acceptable salts thereof. Examples of suitable bases include for example sodium hydroxide, potassium hydroxide, cyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

As already mentioned, the new compounds of general formula I and the salts thereof have valuable properties. Thus, the compounds of general formula I wherein E denotes a cyano group are valuable intermediate products for
5 preparing the other compounds of general formula I and the compounds of general formula I wherein E denotes an $R_bNH-C(=NH)-$ group and the tautomers, the stereoisomers and the physiologically acceptable salts thereof have valuable pharmacological properties, particularly a thrombin-
10 inhibiting effect, an effect of prolonging the thrombin time and an inhibitory effect on related serine proteases such as e.g. trypsin, urokinase factor VIIa, factor Xa, factor IX, factor XI and factor XII, whilst a few compounds such as for example the compound of Example 16
15 simultaneously also have a slight inhibitory effect on thrombocyte aggregation.

For example, the following compounds:

- 20 A = 2-[N-(4-amidinophenyl)-aminomethyl]-benzthiazole-5-carboxylic acid-N-phenyl-N-(2-carboxyethyl)-amide,
- B = 1-methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-hydroxycarbonyl-propyl)-amide,
25
- C = 1-methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-carboxylic acid -N-phenyl-N-(hydroxycarbonylmethyl)-amide,
30
- D = 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonyl-ethyl)-amide,
- 35 E = 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(hydroxycarbonylmethyl)-amide,

F = 1-methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-[2-(1H-tetrazol-5-yl)ethyl]-amide and

5

G = 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonyl)ethyl)-amide

10 were investigated as follows for their effects on thrombin time: ;

Materials: plasma, from human citrated blood.
Test thrombin (bovine), 30U/ml, Behring Werke,
15 Marburg
Diethylbarbiturate acetate buffer, ORWH 60/61,
Behring Werke, Marburg
Biomatic B10 coagulometer, Sarstedt

20 Method:

The thrombin time was determined using a Biomatic B10 coagulometer made by Messrs. Sarstedt.

25 As the test substance, 0.1 ml of human citrated plasma and 0.1 ml diethylbarbiturate buffer (DBA buffer) were added to the test strip prescribed by the manufacturer. The mixture was incubated for one minute at 37°C. The clotting
reaction was started by the addition of 0.3 U test thrombin
30 in 0.1 ml DBA buffer. The time is measured using the apparatus from the addition of the thrombin up to the clotting of the mixture. Mixtures to which 0.1 ml of DBA buffer were added were used as the controls.

35 According to the definition, a dosage-activity curve was used to determine the effective concentration of the

substance, i.e. the concentration at which the thrombin time is double compared with the control.

The Table which follows contains the results found:

5

Substance	Thrombin time (ED ₂₀₀ in μ M)
A	0.04
B	0.06
C	0.15
D	0.03
E	0.09
F	0.03
G	0.03

By way of example, no acute toxic side effects were observed when compounds A, D, E and G were administered to rats in doses of up to 10 mg/kg i.v. The compounds are thus well tolerated.

10

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 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 or stents. 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.

15

20

25

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
5 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
10 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,
15 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
20 invention:

Preliminary remarks

Unless otherwise specified, the R_f values were always determined using polygram silica gel plates produced by
5 Messrs. E. Merck of Darmstadt.

The EKA mass spectra (electrospray mass spectra of cations) are described, for example, in "Chemie unserer Zeit" 6, 308-316 (1991).

10

Example 1

3-Methyl-2-[2-(4-amidinophenyl)ethyl]-imidazo[4,5-b]-
pyridine-6-carboxylic acid -N-phenyl-N-(2-
15 ethoxycarbonyl)ethyl)-amide

a) Methyl 6-methylamino-5-nitro-nicotinate

1.6 g (7.4 mMol) of methyl 6-chloro-5-nitro-nicotinate (see
Bernie et al. in J. Chem. Soc. 1951, 2590) were stirred in
20 20 ml of 40% aqueous methylamine solution at room
temperature for 30 minutes. The reaction mixture was then
diluted with ice water, the yellow precipitate formed was
filtered off and dried.

Yield: 1.2 g (80 % of theory),

25 R_f value: 0.66 (silica gel; ethyl acetate/ethanol/glacial
acetic acid = 90:5:5)

b) Methyl 5-amino-6-methylamino-nicotinate

To a solution of 3.1 g (15 mMol) of methyl 6-methylamino-
30 5-nitro-nicotinate in 100 ml of ethanol/dichloromethane
(3:1) was added 1 g of palladium on charcoal (10%) and the
resulting suspension was hydrogenated at room temperature
under 5 bar of hydrogen pressure for 1.5 hours. The
catalyst was then filtered off and the solvent was
35 distilled off *in vacuo*. The crude oily product obtained
was further reacted directly.

Yield: 2.4 g (92 % of theory),

R_f value: 0.44 (silica gel; ethyl acetate/ethanol/ammonia = 90:10:1)

5 c) Methyl 5-[2-(4-cyanophenyl)ethylcarbonylamino]-6-methylamino-nicotinate

A solution of 2.6 g (15 mMol) of 3-(4-cyanophenyl)propionic acid in 25 ml of absolute tetrahydrofuran was mixed with 2.4 g (15 mMol) of N,N'-carbonyldiimidazole and stirred for 20 minutes at room temperature. Then the imidazolide was mixed with a solution of 2.3 g (13 mMol) of methyl 5-amino-6-methylamino-nicotinate in 25 ml of dimethylformamide and heated for 3 hours to 100°C. After the removal of the solvent *in vacuo* the crude product obtained was taken up in ethyl acetate, the organic phase was washed with water and after drying over sodium sulphate it was again freed from solvent. The residue obtained was purified by flash chromatography (silica gel; gradient: dichloromethane to dichloromethane/ethanol = 19:1).

Yield: 2.1 g (50 % of theory) of beige solid

20 R_f value: 0.54 (silica gel; ethyl acetate/ethanol/ammonia = 90:10:1)

d) Methyl 3-methyl-2-[2-(4-cyanophenyl)ethyl]-imidazo[4,5-b]pyridine-6-carboxylate

25 A solution of 2.0 g (5.9 mMol) of methyl 5-[2-(4-cyanophenyl)ethylcarbonylamino]-6-methylamino-nicotinate in 50 ml glacial acetic acid was heated to 100°C for one hour. After removal of the solvent the residue was taken up in dichloromethane, washed with sodium hydrogen carbonate solution, dried with sodium sulphate and the solvent was distilled off again.

Yield: 1.7 g brown solid (89 % of theory),

R_f value: 0.50 (silica gel; ethyl acetate/ethanol/ammonia = 90:10:1)

e) 3-Methyl-2-[2-(4-cyanophenyl)ethyl]-imidazo[4,5-b]pyridine-6-carboxylic acid

A solution of 3.2 g (10 mMol) of methyl 3-methyl-2-[2-(4-cyanophenyl)ethyl]-imidazo[4,5-b]pyridine-6-carboxylate in 150 ml methanol was mixed with a solution of 1.5 g lithium hydroxide in 20 ml water and stirred for 24 hours at room temperature. Then the mixture was diluted with 50 ml of water, the alcohol was distilled off and the aqueous phase was washed with ethyl acetate. After acidification with dilute hydrochloric acid the mixture was extracted several times with dichloromethane/methanol (9:1), the organic phase was dried with sodium sulphate and the solvent was distilled off.

Yield: 2.1 g beige solid (70 % of theory),

R_f value: 0.38 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5)

f) 3-Methyl-2-[2-(4-cyanophenyl)ethyl]-imidazo[4,5-b]pyridine-6-carboxylic acid-N-phenyl-N-(2-ethoxycarbonyl-ethyl)-amide

A solution of 2.0 g (6.5 mMol) of 3-methyl-2-[2-(4-cyanophenyl)ethyl]-imidazo[4,5-b]pyridine-6-carboxylic acid in 100 ml dichloromethane was mixed with 20 ml thionyl chloride and refluxed for 2 hours. After the liquid components had been distilled off the crude product was taken up twice more in dichloromethane and the solvent was distilled off each time. The crude acid chloride thus obtained (2 g) was suspended in 100 ml of tetrahydrofuran and mixed with 1.2 g (6.5 mMol) of N-(2-ethoxycarbonyl-ethyl)aniline. Then within 5 minutes 0.73 g (7.2 mMol) of triethylamine were added dropwise. After 1 hour's stirring the solvent was distilled off *in vacuo*, the residue was taken up in ethyl acetate, the organic phase was washed with water and dried with sodium sulphate. After distillation of the solvent and flash chromatography (silica gel; dichloromethane to dichloromethane/ethanol = 49:1) the desired compound was isolated as a brownish oil.

Yield: 1.9 g (65 % of theory),

R_f value: 0.44 (silica gel; ethyl acetate/ethanol/ammonia = 90:10:1)

5 g) 3-Methyl-2-[2-(4-amidinophenyl)ethyl]-imidazo[4,5-b]-pyridine-6-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide

1.8 g (3.7 mMol) of 3-methyl-2-[2-(4-cyanophenyl)ethyl]-imidazo[4,5-b]pyridine-6-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide were stirred into 100 l of ethanol saturated with hydrogen chloride for 16 hours first at 0°C and then at room temperature until no more starting material could be detected by thin layer chromatography. Then the solvent was distilled off, the oily residue was taken up in 50 ml of absolute ethanol and mixed with 3.6 g (37 mMol) of ammonium carbonate. After 4 hours the solvent was distilled off in vacuo, the crude product obtained was purified by flash chromatography (silica gel; gradient: dichloromethane/ethanol 19:1 to 4:1) and evaporated down again.

Yield: 1.6 g of beige solid (80 % of theory),

R_f value: 0.30 (silica gel; ethyl acetate/ethanol/ammonia = 90:5:5)

25 Example 2

3-Methyl-2-[2-(4-amidinophenyl)ethyl]-imidazo[4,5-b]-pyridine-6-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide

30 A solution of 535 mg (1.0 mMol) of 3-methyl-2-[2-(4-amidinophenyl)ethyl]-imidazo[4,5-b]pyridine-6-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide in 10 ml ethanol was mixed with 5 ml of 2N sodium hydroxide solution and stirred for 2 hours at room temperature. Then the mixture was diluted with 10 ml water, the alcohol was distilled off, the aqueous phase was washed with 20 ml

ethyl acetate and acidified with concentrated hydrochloric acid, whereupon the desired compound was precipitated in the form of white crystals.

Yield: 375 mg (74 % of theory),

5 R_f value: 0.23 (silica gel; ethyl acetate/ethanol/ammonia = 90:5:5)

$C_{26}H_{26}N_6O_3$ (470.54)

Mass spectrum: $(M+H)^+ = 471$

10 Example 3

3-Methyl-2-[2-(4-amidinophenyl)ethyl]-imidazo[4,5-b]pyridin-6-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonyl-ethyl)-amide-hydrochloride

15

Prepared analogously to Example 1 from 3-methyl-2-[2-(4-cyanophenyl)ethyl]-imidazo[4,5-b]pyridin-6-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonyl-ethyl)-amide, methanolic hydrochloric acid, methanol and ammonium

20 carbonate.

Yield: 75 % of theory,

$C_{26}H_{27}N_7O_3$ (485.55)

R_f value: 0.31 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5)

25 EKA mass spectrum: $(M+H)^+ = 486$

Example 4

3-Methyl-2-[2-(4-amidinophenyl)ethyl]-imidazo[4,5-b]pyridin-6-yl-carboxylic acid-N-phenyl-N-ethoxycarbonylmethyl-amide-hydrochloride

30

Prepared analogously to Example 1 from 3-methyl-2-[2-(4-cyanophenyl)ethyl]-imidazo[4,5-b]pyridin-6-yl-carboxylic acid-N-phenyl-N-ethoxycarbonylmethyl-amide, ethanolic hydrochloric acid, ethanol and ammonium carbonate.

35

Yield: 84 % of theory,

$C_{27}H_{28}N_6O_3$ (484.56)

R_f value: 0.44 (silica gel; ethyl acetate/ethanol/ammonia
= 50:45:5)

5 EKA mass spectrum: $(M+H)^+ = 485$

Example 5

3-Methyl-2-[2-(4-amidinophenyl)ethyl]-imidazo[4,5-
10 b]pyridin-6-yl-carboxylic acid-N-phenyl-N-
hydroxycarbonylmethyl-amide-hydrochloride

Prepared analogously to Example 2 from 3-methyl-2-[2-(4-
amidinophenyl)ethyl]-imidazo[4,5-b]pyridin-6-yl-carboxylic
15 acid-N-phenyl-N-ethoxycarbonylmethyl-amide-hydrochloride
and sodium hydroxide solution.

Yield: 85 % of theory,

$C_{25}H_{24}N_6O_3$ (456.51)

R_f value: 0.19 (silica gel; ethyl acetate/ethanol/ammonia
20 = 50:45:5)

EKA mass spectrum: $(M+H)^+ = 457$

Example 6

25 2-[2-(4-amidinophenyl)ethyl]-3-methyl-6-(2-methoxycarbonyl-
2,3-dihydroindol-1-yl-carbonyl)-imidazo[4,5-b]pyridine-
hydrochloride

Prepared analogously to Example 1 from 2-[2-(4-
30 cyanophenyl)ethyl]-3-methyl-6-(2-methoxycarbonyl-
2,3-dihydroindol-1-yl-carbonyl)-imidazo[4,5-b]pyridine,
methanolic hydrochloric acid, methanol and ammonium
carbonate.

Yield: 20 % of theory,

35 $C_{27}H_{26}N_6O_3$ (482.54)

R_f value: 0.30 (silica gel; ethyl acetate/ethanol/ammonia

= 50:45:5)

EKA mass spectrum: $(M+H)^+ = 483$

Example 7

5

2-[2-(4-amidinophenyl)ethyl]-3-methyl-6-(2-carboxy-
2,3-dihydroindol-1-yl-carbonyl)-imidazo[4,5-b]pyridine-
hydrochloride

10 Prepared analogously to Example 2 from 2-[2-(4-
amidinophenyl)ethyl]-3-methyl-6-(2-methoxycarbonyl-
2,3-dihydroindol-1-yl-carbonyl)-imidazo[4,5-b]pyridine-
hydrochloride and sodium hydroxide solution.

Yield: 90 % of theory,

15 $C_{26}H_{24}N_6O_3$ (468.52)

R_f value: 0.24 (silica gel; ethyl acetate/ethanol/ammonia
= 50:45:5)

EKA mass spectrum: $(M+H)^+ = 469$

$(M+Na)^+ = 491$

20

Example 8

1-Methyl-2-[(4-amidinophenyl)oxymethyl]-
imidazo[4,5-b]pyridin-5-yl-carboxylic acid-N-(2-pyridyl)-N-
25 (2-ethoxycarbonylethyl)-amide

a) 2-Amino-3-methylamino-6-methyl-pyridine

8.35 g (50 mMol) of 2-Methyl-5-methylamino-6-nitro-pyridine
(Heterocycles 38, 529 (1994)) were dissolved in 300 l ethyl
30 acetate and hydrogenated with 1.5 g Raney nickel for 3.5
hours at room temperature. Then the catalyst was filtered
off and the filtrate was evaporated down. After
crystallisation of the resulting residue from petroleum
ether, 5.75 g (84 % of theory) were obtained as olive-green
35 crystals.

$C_7H_{11}N_3$ (137.20)

Melting point: 112-113°C

b) 1,5-Dimethyl-2-[(4-cyanophenyl)oxymethyl]-imidazo[4,5-b]-pyridine

5 11.4 g (63 mMol) of 4-cyano-phenoxyacetic acid were dissolved in 200 ml of absolute tetrahydrofuran and mixed at room temperature with 10.2 g (63 mMol) of N,N'-carbonyldiimidazole. After 15 minutes at 60°C, 5.70 g (41.5 mMol) of 2-amino-3-methylamino-6-methyl-pyridine were
10 added. After 2 hours at 60°C the solvent was distilled off and the crystalline residue was mixed with water, washed with water and dried. After crystallisation from ethanol 9.95 g (91 % of theory) were obtained in the form of white crystals.

15 $C_{16}H_{14}N_4O$ (278.32)

Mass spectrum: $M^+ = 278$

c) 1,5-Dimethyl-2-[(4-cyanophenyl)oxymethyl]-imidazo[4,5-b]pyridin-4-N-oxide

20 2.62 g (10 mMol) of 1,5-dimethyl-2-[(4-cyanophenyl)-oxymethyl]-imidazo[4,5-b]pyridine were suspended in 125 ml dichloromethane and mixed with 2.62 g (12.7 mMol) of m-chloroperbenzoic acid, whereupon a clear solution was
25 was distilled off and the residue obtained was mixed with a sodium hydrogen carbonate solution. After 30 minutes the white crystalline product obtained was suction filtered, washed with water and dried at 40°C.

Yield: 2.45 g (83 % of theory),

30 $C_{16}H_{14}N_4O_2$ (294.30)

Mass spectrum: $M^+ = 294$

d) 1-Methyl-2-[(4-cyanophenyl)oxymethyl]-5-hydroxymethyl-imidazo[4,5-b]pyridine

35 2.40 g (8.2 mMol) of 1,5-dimethyl-2-[(4-cyanophenyl)-oxymethyl]-imidazo[4,5-b]pyridin-4-N-oxide were suspended in 75 ml dichloromethane and mixed with 2.4 ml of

trifluoroacetic acid anhydride (16.9 mMol), whereupon a clear solution was obtained. After 16 hours at room temperature the solvent was distilled off, the viscous residue obtained was taken up in 50 ml dichloromethane and covered with 50 ml of 2M sodium hydrogen carbonate solution. After 3 hours' vigorous stirring the precipitate formed was suction filtered, washed with water and dried at 40°C.

Yield: 1.85 g white powder (78 % of theory),
10 $C_{16}H_{14}N_4O_2$ (294.30)
Melting point: 172°C

e) 1-Methyl-2-[(4-cyanophenyl)oxymethyl]-imidazo[4,5-b]-pyridine-5-carbaldehyde

15 3.65 g (12.5 mMol) of 1-methyl-2-[(4-cyanophenyl)-oxymethyl]-5-hydroxymethyl-imidazo[4,5-b]pyridine were dissolved in 500 ml dichloromethane and mixed with 15.0 g of manganese dioxide. After 96 hours at room temperature the mixture was filtered through kieselgur and the solvent
20 was distilled off. The filtrate obtained was evaporated down, the crystalline precipitate was triturated with ether, suction filtered and dried.

Yield: 3.05 g white powder (84 % of theory),
 $C_{16}H_{12}N_4O_2$ (292.30)
25 Melting point: 231-234°C

f) 1-Methyl-2-[(4-cyanophenyl)oxymethyl]-5-carboxy-imidazo-[4.5-b]pyridine

1.25 g (4.3 mMol) of 1-methyl-2-[(4-cyanophenyl)oxymethyl]-imidazo[4,5-b]pyridine-5-carbaldehyde were dissolved in 10
30 ml formic acid and mixed at 0°C with 1.0 ml hydrogen peroxide (33% strength). After 12 hours at 4°C the white precipitate formed was suction filtered, washed with water and dried at 40°C.

35 Yield: 0.81 g (61 % of theory),
 $C_{16}H_{12}N_4O_3$ (308.7)

g) 1-Methyl-2-[(4-cyanophenyl)oxymethyl]-imidazo[4,5-b]pyridin-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonyl-ethyl)-amide

308 mg (1.0 mMol) of 1-methyl-2-[(4-cyanophenyl)oxymethyl]-
5 5-carboxy-imidazo[4.5-b]pyridine were suspended in 5 ml of dimethylformamide and mixed with 303 mg (3.0 mMol) of N-methyl-morpholine and 321 mg (1.0 mMol) of O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyl-uronium tetrafluoroborate. After 10 minutes at room temperature a
10 solution of 215 mg (1.2 mMol) of methyl N-(2-pyridyl)-3-amino-propionate in 2 ml of dimethylformamide was added, whereupon a clear solution was obtained. After 12 hours at room temperature the reaction solution was stirred into ice-water. After extracting 3 times with ethyl acetate the
15 combined organic extracts were washed with a saline solution, dried over sodium sulphate and evaporated down. The residue obtained was chromatographed on silica gel with dichloromethane/ethanol (90:1 to 25:1).
Yield: 165 mg of white powder (35 % of theory),
20 $C_{25}H_{12}N_6O_4$ (407.50)
Melting point: 139-140°C

h) 1-Methyl-2-[(4-amidinophenyl)oxymethyl]-imidazo[4.5-b]-pyridin-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonyl-ethyl)-amide

25 Prepared by reacting 140 mg (0.3 mMol) of 1-methyl-2-[(4-cyanophenyl)oxymethyl]-imidazo[4,5-b]pyridin-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonyl-ethyl)-amide with ethanol saturated by hydrogen chloride and with
30 ammonium carbonate/ethanol analogously to Example 1g. The resulting product was purified by chromatography over silica gel with dichloromethane/ethanol (19:1 to 4:1).
Yield: 48 mg of white powder (36 % of theory),
 $C_{26}H_{27}N_7O_4$ (501.57)
35 Mass spectrum: $(M+H)^+ = 502$

Example 9

2- [N- (4-amidinophenyl) -aminomethyl] -benzothiazole-5-
carboxylic acid-N-phenyl-N- (2-ethoxycarbonylethyl) -amide

5

a) Ethyl 4-fluoro-3-methoxyacetamido-benzoate

A solution of 2.8 g (15.3 mMol) of ethyl 3-amino-4-fluoro-
benzoate (cf. L.S. Fosdick, A.F. Dodds in J. Amer. Chem.
Soc. 65, 2305 (1943)) and 1.56 ml (1.85 g = 17.0 mMol) of
10 methoxyacetylchloride in 50 ml chlorobenzene was stirred
for 1 hour at 50°C and then refluxed for 15 minutes. Then
the solvent was distilled off *in vacuo* and the crude
product obtained was purified by flash chromatography
(silica gel; dichloromethane/ethanol = 100:1). The desired
15 compound, initially oily, solidified within a few days.
Yield: 3.8 g (98 % of theory),
R_f value: 0.38 (silica gel; dichloromethane/ethanol = 19:1)

b) Ethyl-2-methoxymethyl-benzothiazole-5-carboxylate

20 A mixture of 3.0 g (11.7 mMol) of 4-fluoro-3-
methoxyacetamido-benzoic acid and 2.1 g (5.2 mMol) of
Lawesson's reagent was refluxed for 6 hours in 90 ml
toluene, mixed with 1.0 g Lawesson's reagent and heated to
120°C for another 6 hours. After the solvent was replaced
25 with xylene the mixture was heated to 180°C for a further 8
hours in a pressurised vessel. Then the solvent was
distilled off *in vacuo*, the crude product obtained was
purified by flash chromatography (silica gel; ethyl
acetate/petroleum ether = 5:95) and evaporated down again.
30 Yield: 2.1 g of yellow crystals (72 % of theory),
R_f value: 0.55 (silica gel; ethyl acetate/petroleum ether =
3:7)

c) 2-Methoxymethyl-benzothiazole-5-carboxylic acid

35 A mixture of 2.1 g (8.36 mMol) of ethyl 2-methoxymethyl-
benzothiazole-5-carboxylate and 16 ml of 2N sodium
hydroxide solution was stirred into 60 ml ethanol for 1

hour at room temperature. Then the alcohol was distilled off, the crude product was taken up in 20 ml water, washed with 50 ml diethylether and the aqueous phase was acidified with concentrated hydrochloric acid whilst being cooled with ice. The pinkish-beige compound thereby precipitated was suction filtered, washed with water and dried.
Yield: 1.6 g (86 % of theory),
R_f value: 0.12 (silica gel; dichloromethane/ethanol = 29:1)

10 d) 2-Methoxymethyl-benzothiazole-5-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide

A suspension of 1.6 g (7.2 mMol) of 2-methoxymethyl-benzothiazole-5-carboxylic acid in 60 ml dichloromethane was mixed with 1.6 ml (22 mMol) of thionyl chloride and refluxed for 1 hour. The solid dissolved after 20 minutes. After distillation of the liquid components the crude product was taken up in dichloromethane twice more and each time the solvent was distilled off. The crude acid chloride thus obtained was taken up in 50 ml of tetrahydrofuran, added dropwise to a mixture of 1.4 g (7.2 mMol) of N-(2-ethoxycarbonylethyl)aniline and 3.0 ml (21 mMol) of triethylamine in 50 ml of tetrahydrofuran and stirred overnight at room temperature. Then the solvent was distilled off *in vacuo*, the residue was taken up in 30 ml of dichloromethane, this solution was washed with water and dried with sodium sulphate. After distillation of the solvent and flash chromatography (silica gel; gradient: dichloromethane/ethanol 98.5:1.5 to 80:20) the desired compound was isolated as a brownish oil.
Yield: 2.05 (72 % of theory),
R_f value: 0.40 (silica gel; ethyl acetate/petroleum ether = 1:1)

e) 2-[N-(4-Cyanophenyl)-aminomethyl]-benzothiazole-5-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide
A mixture of 2.05 g (5.14 mMol) of 2-methoxymethyl-benzothiazole-5-carboxylic acid-N-phenyl-N-(2-

ethoxycarbonylethyl)-amide and 5.7 ml (5.7 mMol) of a 1M solution of boron tribromide in dichloromethane was dissolved in a further 60 ml of dichloromethane and stirred for 16 hours at room temperature. Then the mixture was washed with 40 ml of saturated sodium hydrogen carbonate solution, the organic phase was dried with sodium sulphate and the solvent was distilled off. The crude 2-bromomethyl-benzothiazole-5-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide thus obtained (2.4 g) was taken up in 5.0 ml of N,N-diisopropyl-ethylamine and mixed with 0.64 g (5.4 mMol) of 4-amino-benzonitrile. After 1 hour's heating to 130°C the solvent was distilled off *in vacuo* and the crude product obtained was purified by flash chromatography (silica gel; gradient: ethyl acetate/petroleum ether = 1:3 to 1:1), whilst an orange foam was obtained when the eluates were evaporated down. Yield: 1.1 g (44 % of theory), R_f value: 0.35 (silica gel; ethyl acetate/petroleum ether = 7:3)

f) 2-[N-(4-amidinophenyl)-aminomethyl]-benzothiazole-5-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide 1.1 g (2.27 mMol) of 2-[N-(4-cyanophenyl)-aminomethyl]-benzothiazole-5-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide was stirred in 100 ml of ethanol saturated with hydrogen chloride for 5 hours first at 0°C and then at room temperature until no more starting material could be detected by thin layer chromatography. Then the solvent was distilled off at a maximum bath temperature of 30°C and the oily residue was taken up in 100 ml of absolute ethanol and mixed with 1.6 g (22 mMol) of ammonium carbonate. After 18 hours stirring at room temperature the solvent was distilled off *in vacuo* and the crude product was purified by flash chromatography (silica gel; gradient: water/methanol = 19:1 to 4:1). When the eluates are evaporated down the desired compound is obtained as a white foam.

Yield: 0.77 g (63 % of theory),

R_f value: 0.19 (silica gel; dichloromethane/ethanol = 3:7)

C₂₇H₂₇N₅O₃S (501.60)

Mass spectrum: (M+H)⁺ = 502

5

Example 10

2-[N-(4-amidinophenyl)-aminomethyl]-benzothiazole-
5-carboxylic acid-N-phenyl-N-(2-carboxyethyl)-amide

10

0.45 g (0.84 mMol) of 2-[N-(4-amidinophenyl)-aminomethyl]-
benzothiazole-5-carboxylic acid-N-phenyl-N-(2-
ethoxycarbonyl-ethyl)-amide were dissolved in 15 ml of
ethanol, mixed with 2 ml of 2N sodium hydroxide solution
and stirred for 4 hours at room temperature. Then the
mixture was acidified with 3 ml of 2N hydrochloric acid and
the solvent was distilled off. The crude product obtained
was taken up in 5 ml dichloromethane/ethanol (2:1) and
filtered to remove the insoluble sodium chloride. After
the distillation of the solvent the desired compound was
obtained as a yellow foam.

15

20

Yield: 0.26 g (67 % of theory),

R_f value: 0.47 (silica gel; methanol/5 % aqueous sodium
chloride = 6:4)

25 C₂₅H₂₃N₅O₃S (473.55)

Mass spectrum: (M+H)⁺ = 474

Example 11

2-[N-(4-amidinophenyl)-aminomethyl]benzothiazol-5-yl-
carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonyl-ethyl)-
amide-dihydrochloride

35

Prepared analogously to Example 9 from 2-[N-(4-
cyanophenyl)-aminomethyl]benzothiazol-5-yl-carboxylic acid-
N-(2-pyridyl)-N-(2-methoxycarbonyl-ethyl)-amide, methanolic
hydrochloric acid, methanol and ammonium carbonate.

Yield: 68 % of theory,

$C_{25}H_{24}N_6O_3S$ (488.57)

R_f value: 0.13 (silica gel; methylene chloride/ethanol =
4:1 + a few drops of acetic acid)

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

Example 12

2-[2-(4-amidinophenyl)ethyl]-benzothiazol-5-yl-carboxylic
10 acid-N-(2-pyridyl)-N-(ethoxycarbonylmethyl)-amide-
dihydrochloride

Prepared analogously to Example 9 from 2-[2-(4-
cyanophenyl)ethyl]-benzothiazol-5-yl-carboxylic acid-N-(2-
15 pyridyl)-N-(ethoxycarbonylmethyl)-amide, ethanolic
hydrochloric acid, ethanol and ammonium carbonate.

Yield: 95 % of theory,

$C_{26}H_{25}N_5O_3S$ (487.58)

R_f value: 0.20 (silica gel; methylene chloride/ethanol =
20 4:1 + a few drops of acetic acid)

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

Example 13

25 2-[N-(4-amidinophenyl)-aminomethyl]-benzothiazol-5-yl-
carboxylic acid-N-(2-pyridyl)-N-(ethoxycarbonylmethyl)-
amide-dihydrochloride

Prepared analogously to Example 9 from 2-[N-(4-
30 cyanophenyl)-aminomethyl]-benzothiazol-5-yl-carboxylic
acid-N-(2-pyridyl)-N-(ethoxycarbonylmethyl)-amide,
ethanolic hydrochloric acid, ethanol and ammonium
carbonate.

Yield: 68 % of theory,

35 $C_{25}H_{24}N_6O_3S$ (488.57)

R_f value: 0.14 (silica gel; methylene chloride/ethanol =

4:1 + a few drops of acetic acid)

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

Example 14

5

2- [N- (4-amidinophenyl) -aminomethyl] -benzothiazol-5-yl-
carboxylic acid-N- (2-pyridyl) -N- (hydroxycarbonylmethyl) -
amide-dihydrochloride

10 Prepared analogously to Example 10 from 2- [N- (4-
amidinophenyl) -aminomethyl] -benzothiazol-5-yl-carboxylic
acid-N- (2-pyridyl) -N- (ethoxycarbonylmethyl) -amide-
dihydrochloride and sodium hydroxide solution.

Yield: 90 % of theory,

15 $C_{23}H_{20}N_6O_3S$ (460.52)

R_f value:

EKA mass spectrum: $(M+H)^+ = 461$

$(M+Na)^+ = 483$

$(M+2Na)^{++} = 253$

20

Example 15

2- [N- (4-amidinophenyl) -N-methyl-aminomethyl] -benzothiazol-
5-yl-carboxylic acid-N-phenyl-N- (2-ethoxycarbonylethyl) -
25 amide-hydrochloride

a) 2- [N- (4-Cyanophenyl) -N-methyl-aminomethyl] -benzothiazol-
5-yl-carboxylic acid-N-phenyl-N- (2-ethoxycarbonylethyl) -
amide

30 Prepared analogously to Example 9e from 4-cyano-N-methyl-
aniline and 2-methoxymethyl-benzothiazole-5-carboxylic
acid-N-phenyl-N- (2-ethoxycarbonylethyl) -amide.

Yield: 57 % of theory,

R_f value: 0.46 (silica gel; dichloromethane/ethanol =

35 19:1).

b) 2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzothiazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

Prepared analogously to Example 9 from 2-[N-(4-cyanophenyl)-N-methyl-aminomethyl]-benzothiazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide, ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 73 % of theory,

10 $C_{28}H_{29}N_5O_3S$ (515.64)

R_f value: 0.29 (silica gel; methylene chloride/ethanol = 4:1 + a few drops of acetic acid)

EKA mass spectrum: $(M+H)^+ = 516$

15 Example 16

2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzothiazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide-hydrochloride

20

Prepared analogously to Example 10 from 2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzothiazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.

25 Yield: 96 % of theory,

$C_{26}H_{25}N_5O_3S$ (487.58)

R_f value: 0.48 (Merck RP-8, methanol/5% NaCl solution = 6:4)

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

30

$(M+2Na)^{++} = 266.5$

Example 17

2-[(4-amidinophenyl)thiomethyl]-benzothiazol-5-yl-
carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-
5 hydrochloride

Prepared analogously to Example 9 from 2-[(4-
cyanophenyl)thiomethyl]-benzothiazol-5-yl-carboxylic acid-
N-phenyl-N-(2-ethoxycarbonylethyl)-amide, ethanolic
10 hydrochloric acid, ethanol and ammonium carbonate.
Yield: 61 % of theory,
 $C_{27}H_{26}N_4O_3S_2$ (518.66)
 R_f value: 0.27 (silica gel; methylene chloride/ethanol =
4:1 + a few drops of acetic acid)
15 EKA mass spectrum: $(M+H)^+ = 519$

Example 18

2-[(4-amidinophenyl)thiomethyl]-benzothiazol-5-yl-
20 carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide-
hydrochloride

Prepared analogously to Example 10 from 2-[(4-
amidinophenyl)thio-48- [sic] methyl]-benzothiazol-5-yl-
25 carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-
hydrochloride and sodium hydroxide solution.
Yield: 95 % of theory,
 $C_{25}H_{22}N_4O_3S_2$ (490.61)
 R_f value: 0.25 (Merck RP-8, methanol/5% NaCl solution =
30 6:4)
EKA mass spectrum: $(M+H)^+ = 491$
 $(M+Na)^+ = 513$

Example 19

2- [N- (4-amidinophenyl) -aminomethyl] -benzothiazol-5-yl-
carboxylic acid-N-phenyl-N- (ethoxycarbonylmethyl) -amide-
5 hydrochloride

Prepared analogously to Example 9 from 2- [N- (4-
cyanophenyl) -aminomethyl] -benzothiazol-5-yl-carboxylic
acid-N-phenyl-N- (ethoxycarbonylmethyl) -amide, ethanolic
10 hydrochloric acid, ethanol and ammonium carbonate.

Yield: 82 % of theory,

$C_{26}H_{25}N_5O_3S$ (487.58)

R_f value: 0.21 (silica gel; methylene chloride/ethanol =
4:1 + a few drops of acetic acid)

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

Example 20

2- [N- (4-amidinophenyl) -aminomethyl] -benzothiazol-5-yl-
20 carboxylic acid-N-phenyl-N- (hydroxycarbonylmethyl) -amide-
hydrochloride

Prepared analogously to Example 10 from 2- [N- (4-
amidinophenyl) -aminomethyl] -benzothiazol-5-yl-carboxylic
25 acid-N-phenyl-N- (ethoxycarbonylmethyl) -amide-hydrochloride
and sodium hydroxide solution.

Yield: 75 % of theory,

$C_{24}H_{21}N_5O_3S$ (459.53)

R_f value: 0.14 (silica gel; methylene chloride/ethanol =
30 4:1 + a few drops of acetic acid)

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

$(M+Na)^+ = 482$

Example 21

2-[2-(4-amidinophenyl)ethyl]-benzothiazol-5-yl-carboxylic
acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

5

Prepared analogously to Example 9 from 2-[2-(4-
cyanophenyl)ethyl]-benzothiazol-5-yl-carboxylic acid-N-
phenyl-N-(2-ethoxycarbonylethyl)-amide, ethanolic
hydrochloric acid, ethanol and ammonium carbonate.

10 Yield: 80 % of theory,

$C_{28}H_{28}N_4O_3S$ (500.62)

R_f value: 0.30 (silica gel; methylene chloride/ethanol =
4:1 + a few drops of acetic acid)

EKA mass spectrum: $(M+H)^+ = 501$

15

Example 22

2-[2-(4-amidinophenyl)ethyl]-benzothiazol-5-yl-carboxylic
acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide-
20 hydrochloride

Prepared analogously to Example 10 from 2-[2-(4-
amidinophenyl)ethyl]-benzothiazol-5-yl-carboxylic acid-N-
phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and
25 sodium hydroxide solution.

Yield: 77 % of theory,

$C_{26}H_{24}N_4O_3S$ (472.57)

R_f value: 0.18 (silica gel; methylene chloride/ethanol =
4:1 + a few drops of acetic acid)

30 EKA mass spectrum: $(M+H)^+ = 473$

$(M+Na)^+ = 495$

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

Example 23

2- [N- (4-amidinophenyl) -aminomethyl] -benzothiazol-5-yl-
carboxylic acid-N- (n-propyl) -N- (2-ethoxycarbonylethyl) -
5 amide-hydrochloride

Prepared analogously to Example 9 from 2- [N- (4-
cyanophenyl) -aminomethyl] -benzothiazol-5-yl-carboxylic
acid-N- (n-propyl) -N- (2-ethoxycarbonylethyl) -amide,
10 ethanolic hydrochloric acid, ethanol and ammonium
carbonate.

Yield: 83 % of theory,

$C_{24}H_{29}N_5O_3$ (467.59)

R_f value: 0.31 (silica gel; methylene chloride/ethanol =
15 4:1 + a few drops of acetic acid)

EKA mass spectrum: $(M+H)^+ = 468$

$(2M+H)^+ = 935$

Example 24

20

2- [N- (4-amidinophenyl) -aminomethyl] -benzothiazol-5-yl-
carboxylic acid-N- (n-propyl) -N- (2-hydroxycarbonylethyl) -
amide-hydrochloride

25 Prepared analogously to Example 10 from 2- [N- (4-
amidinophenyl) -aminomethyl] -benzothiazol-5-yl-carboxylic
acid-N- (n-propyl) -N- (2-ethoxycarbonylethyl) -amide-
hydrochloride and sodium hydroxide solution.

Yield: 75 % of theory,

30 $C_{22}H_{25}N_5O_3S$ (439.54)

R_f value: 0.14 (silica gel; methylene chloride/ethanol =
4:1 + a few drops of acetic acid)

EKA mass spectrum: $(M+H)^+ = 440$

$(M+H+Na)^{++} = 231.6$

35

Example 25

1-Methyl-2- [N- (4-amidinophenyl) -aminomethyl] -benzimidazol-
5 5-yl-carboxylic acid-N-phenyl-N- (2-ethoxycarbonylethyl) -
amide-hydrochloride

a) 4-Methylamino-3-nitro-benzoic acid-N-phenyl-N- (2-ethoxy-
carbonylethyl) -amide

10 To a solution of 24.7 g (0.115 mol) of 4-methylamino-3-
nitro-benzoic acid chloride and 22.3 g (0.115 mol) of
N- (2-ethoxy-carbonylethyl) -aniline in 300 ml of
tetrahydrofuran, 13.1 g (0.13 mol) of triethylamine were
added dropwise in 15 minutes, with stirring, at room
15 temperature. After 2 hours stirring the solvent was
distilled off in a water-jet vacuum and the residue was
mixed with 700 ml of water with stirring. The mixture was
extracted 3 times with 200 ml of dichloromethane, the or-
ganic extract was washed twice with 200 ml of 2N
20 hydrochloric acid and twice with 300 ml of water and dried
over sodium sulphate. The solvent was then distilled off
and the oily product thus obtained was purified by column
chromatography (1 kg silica gel; eluant: petroleum
ether/ethyl acetate = 2:1).
25 Yield: 35.0 g (82 % of theory),
R_f value: 0.28 (silica gel; dichloromethane/ethanol = 50:1)

b) 3-Amino-4-methylamino-benzoic acid-N-phenyl-N- (2-ethoxy-
carbonylethyl) -amide

30 12.1 g (0.0326 mol) of 4-methylamino-3-nitro-benzoic acid-
N-phenyl-N- (2-ethoxycarbonylethyl) -amide were hydrogenated
in 300 ml ethanol and 150 ml dichloromethane after the
addition of about 4 g of palladium/charcoal (10%) at room
temperature and under a hydrogen pressure of 5 bar. Then
35 the catalyst was filtered off and the filtrate was
evaporated down. The crude product thus obtained was
reacted without further purification.

Yield: 10.6 g (95 % of theory),

R_f value: 0.19 (silica gel; dichloromethane/ethanol = 50:1)

5 c) 1-Methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide

6.17 g (0.035 mol) of N-(4-cyanophenyl)glycine and 5.68 g (0.035 mol) of N,N'-carbonyldiimidazole were refluxed in 300 ml of tetrahydrofuran for 30 minutes, then 10.6 g (0.032 mol) of 3-amino-4-methylamino-benzoic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide were added and the mixture was refluxed for a further five hours. Then the solvent was distilled off *in vacuo*, the residue was dissolved in 150 ml of glacial acetic acid and refluxed for one hour. 15 Then the glacial acetic acid was distilled off *in vacuo*, the residue was dissolved in about 300 ml of dichloromethane, the solution was washed twice with about 150 ml water and then dried over sodium sulphate. After evaporation of the solvent the crude product thus obtained 20 was purified by column chromatography (800 g silica gel; eluant: dichloromethane with 1-2 % ethanol).

Yield: 8.5 g (57 % of theory),

R_f value: 0.51 (silica gel; dichloromethane/ethanol = 19:1)

25 d) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

1.2 g (2.49 mMol) of 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide were stirred in 100 ml of saturated ethanolic hydrochloric acid for 6 hours at room temperature. Then the mixture was evaporated to dryness *in vacuo*, the residue was dissolved in 100 ml of ethanol, mixed with 2.5 g (26 mMol) of ammonium carbonate and 35 stirred overnight at room temperature. After distillation of the solvent the crude product thus obtained was purified by column chromatography (100 g silica gel; eluant:

dichloromethane/ethanol = 4:1). By concentrating the eluates the desired compound was obtained as a white, amorphous solid.

Yield: 1.10 g (83 % of theory),

5 R_f value: 0.18 (silica gel; dichloromethane/ethanol = 4:1)
 $C_{28}H_{30}N_6O_3 \times HCl$ (498.6)

EKA mass spectrum: $(M+H)^+$ = 499

$(M+2H)^{++}$ = 250

$(M+H+Na)^{++}$ = 261

10

Example 26

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide
15

A mixture of 300 mg (0.56 mMol) of 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-
20 hydrochloride, 15 ml of ethanol, 4 ml of water and 120 mg (3.0 mMol) of sodium hydroxide was stirred for two hours at room temperature. Then the mixture was diluted with about 20 ml of water and made weakly alkaline with glacial acetic acid. The product which crystallised out was suction
25 filtered, washed with water and dried at 60°C *in vacuo*.

Yield: 250 mg (95 % of theory),

$C_{26}H_{26}N_6O_3$ (470.5)

EKA mass spectrum: $(M+H)^+$ = 471

$(M+H+Na)^{++}$ = 247

30

$(M+2Na)^{++}$ = 258

Example 27

1-Methyl-2-[(4-amidinophenyl)thiomethyl]-benzimidazol-5-yl-
carboxylic acid-N-(n-propyl)-N-(2-ethoxycarbonylethyl)-
5 amide-hydrochloride

a) 4-Methylamino-3-chloracetamido-benzoic acid-N-(n-propyl)-N-(2-ethoxycarbonylethyl)-amide

A solution of 1.8 g (5.9 mMol) of 3-amino-4-methylamino-
10 benzoic acid-N-(n-propyl)-N-(2-ethoxycarbonylethyl)-amide
[prepared analogously to 3-amino-4-ethylamino-benzoic acid-
N-phenyl-N-(2-ethoxycarbonylethyl)-amide], 1.1g (6.8 mMol)
of N,N'-carbonyldiimidazole and 0.65 g (6.9 mMol) of
chloroacetic acid in 75 ml tetrahydrofuran was stirred for
15 1 hour at room temperature. Then the solvent was distilled
off *in vacuo*, and the crude product was purified by flash
chromatography (silica gel; methylene chloride/ethanol =
49:1).

Yield: 1.7 g (77% of theory) yellow oil,
20 R_f value: 0.58 (silica gel; ethyl acetate/ethanol/ammonia
= 90:10:1)

b) 2-Chloromethyl-1-methyl-benzimidazol-5-yl-carboxylic acid-N-(n-propyl)-N-(2-ethoxycarbonylethyl)-amide

25 1.6 g (4.3 mMol) of 4-methylamino-3-chloracetamido-benzoic
acid-N-(n-propyl)-N-(2-ethoxycarbonylethyl)-amide were
heated to 100°C in 25 ml of acetic acid for 30 minutes.
Then the solvent was distilled off, the crude product was
taken up in 40 ml methylene chloride/ethanol (9:1) and
30 washed with 20 ml saturated sodium hydrogen carbonate
solution. The organic phase was dried with sodium sulphate
and evaporated down.

Yield: 1.5 g (100% of theory) of brown oil,
 R_f value: 0.63 (silica gel; ethyl acetate/ethanol/ammonia
35 = 90:10:1)

c) 1-Methyl-2-[(4-cyanophenyl)thiomethyl]-benzimidazol-5-yl-carboxylic acid-N-(n-propyl)-N-(2-ethoxycarbonylethyl)-amide

A mixture of 1.5 g (4.1 mMol) of 2-chloromethyl-1-methyl-
5 benzimidazol-5-yl-carboxylic acid-N-(n-propyl)-N-(2-ethoxycarbonylethyl)-amide and 0.65 g (4.8 mMol) of p-cyanothiophenol was heated in 10 ml of dimethylformamide and 10 ml of diisopropylethylamine for 1 hour to 100°C. The solvent was distilled off *in vacuo*, the crude product
10 was dissolved in 30 ml ethyl acetate, washed with 30 ml water, and after concentration purified by flash chromatography (silica gel; methylene chloride/ethanol (49:1 to 19:1)).

Yield: 1.5 g (79% of theory) of brown oil,

15 R_f value: 0.65 (silica gel; ethyl acetate/ethanol/ammonia = 90:10:1)

d) 1-Methyl-2-[(4-amidinophenyl)thiomethyl]-benzimidazol-5-yl-carboxylic acid-N-(n-propyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

1.4 g (3.01 mMol) of 1-methyl-2-[(4-cyanophenyl)-thiomethyl]-benzimidazol-5-yl-carboxylic acid-N-(n-propyl)-N-(2-ethoxycarbonylethyl)-amide were stirred in 50 ml of ethanol saturated with hydrogen chloride for 5 hours first
25 at 0°C, later at room temperature, until no more starting material could be detected by thin layer chromatography. Then the solvent was distilled off at a maximum bath temperature of 30°C, the oily residue was taken up in 40 ml of absolute ethanol and mixed with 2.8 g of ammonium
30 carbonate. After 18 hours the solvent was distilled off *in vacuo* and the crude product was purified by flash chromatography (silica gel; methylene chloride/ethanol = 19:1 to 4:1).

Yield: 1.3 g (83% of theory) as a light beige solid,

35 R_f value: 0.29 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5)

$C_{25}H_{31}N_6O_3S$ (481.62)

EKA mass spectrum: $(M+H)^+ = 482$

Example 28

5

1-Methyl-2-[(4-amidinophenyl)thiomethyl]-benzimidazol-5-yl-carboxylic acid-N-(n-propyl)-N-(2-hydroxycarbonylethyl)-amide-hydrochloride

10 0.52 g (1.0 mMol) of 1-Methyl-2-[(4-amidinophenyl)-thiomethyl]-benzimidazol-5-yl-carboxylic acid-N-(n-propyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride was dissolved in 15 ml ethanol, mixed with 5 ml of 2N sodium hydroxide solution and stirred for 2 hours at room temperature. Then
15 5 ml of water were added, the alcohol was distilled off, and it was acidified with concentrated hydrochloric acid. The water was distilled off in vacuo, and the crude product was taken up in 5 ml of ethanol and filtered to remove the insoluble sodium chloride. After the solvent had been
20 distilled off the title compound was obtained as a white solid.

Yield: 0.43 g (88% of theory),

R_f value: 0.19 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5)

25 $C_{23}H_{27}N_5O_3S$ (453.57)

EKA mass spectrum: $(M+H)^+ = 454$

$(M+Na)^+ = 476$

Example 29

30

1-Methyl-2-[(4-amidinophenyl)thiomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-methylpropyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

35 Prepared analogously to Example 27 from 1-methyl-2-[(4-cyanophenyl)thiomethyl]-benzimidazol-5-yl-carboxylic acid-(N-(2-methylpropyl)-N-(2-ethoxycarbonylethyl)-amide,

ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 83 % of theory,

$C_{25}H_{31}N_6O_3S$ (495.65)

5 R_f value: 0.30 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5) :

EKA mass spectrum: $(M+H)^+ = 496$

Example 30

10

1-Methyl-2-[(4-amidinophenyl)thiomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

15 Prepared analogously to Example 27 from 1-methyl-2-[(4-cyanophenyl)thiomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide, and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 90 % of theory,

20 $C_{28}H_{29}N_5O_3S$ (515.64)

R_f value: 0.24 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5)

EKA mass spectrum: $(M+H)^+ = 516$

$(M+H+Na)^{++} = 269.7$

25

Example 31

1-Methyl-2-[(4-amidinophenyl)thiomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide-hydrochloride

Prepared analogously to Example 28 from 1-methyl-2-[(4-amidinophenyl)thiomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.

35

Yield: 76 % of theory,

$C_{26}H_{25}N_5O_3S$ (487.58)

R_f value: 0.31 (silica gel; ethyl acetate/ethanol/ammonia
= 50:45:5)

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

5 $(M+Na)^+$ = 510

Example 32

10 1-Methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-
sulphonic acid-N-(1-methyl-piperidin-4-yl)-N-methyl-amide-
hydrochloride

a) 4-Chloro-3-nitrobenzenesulphonic acid-N-(1-methyl-
piperidin-4-yl)-N-methyl-amide

15 To a solution of 2.2 ml (15 mMol) of 1-methyl-4-
methylamino-piperidine in 60 ml pyridine, 3.8 g (15 mMol)
of 4-chloro-3-nitro-benzenesulphonic acid chloride were
added, in batches, whilst cooling with ice. The mixture was
then stirred for two hours with cooling, then evaporated to
20 dryness, the residue was mixed with about 50 ml of water
and made alkaline with concentrated ammonia whilst stirring
vigorously. The crude product precipitated was suction
filtered and purified by column chromatography (250 g
silica gel, eluant: dichloromethane with 1.5% ethanol).

25 Yield: 1.6 g (31% of theory),

$C_{13}H_{18}ClN_3O_4S$ (347.8)

R_f value: 0.19 (silica gel; dichloromethane/ethanol = 19:1)

30 b) 4-Methylamino-3-nitrobenzenesulphonic acid-N-methyl-N-
(1-methylpiperidin-4-yl)-amide

1.6 g (4.6 mMol) of 4-chloro-3-nitrobenzenesulphonic acid-
N-methyl-N-(1-methyl-piperidin-4-yl)-amide was mixed with
30 ml of 40% methylamine solution and stirred in a sealed
flask for four hours at room temperature. Then the mixture
35 was diluted with about 40 ml of water, the product
precipitated was suction filtered, washed with water and
dried.

Yield: 1.5 g (95% of theory),

$C_{14}H_{22}N_4O_4S$ (343.4)

R_f value: 0.45 (silica gel; dichloromethane/ethanol = 4:1)

5 c) 3-Amino-4-methylaminobenzenesulphonic acid-N-methyl-N-(1-methylpiperidin-4-yl)-amide

1.5 g (4.4 mMol) of 4-methylamino-3-nitrobenzenesulphonic acid-N-methyl-N-(1-methyl-piperidin-4-yl)-amide were dissolved in 100 ml methanol and catalytically hydrogenated at room temperature and under 5 bar hydrogen pressure (10% palladium on charcoal). Then the catalyst was filtered off and the filtrate was evaporated down. The resulting oily product was further reacted without any purification.

Yield: 1.4 g (100% of theory),

15 $C_{14}H_{24}N_4O_2S$ (312.4)

R_f value: 0.33 (silica gel; dichloromethane/ethanol = 4:1)

d) 1-Methyl-2-[(4-cyanophenyl)oxymethyl]-benzimidazol-5-yl-sulfonic acid-N-methyl-N-(1-methyl-piperidin-4-yl)-amide

20 532 mg (3.0 mMol) of 4-cyanophenylxyacetic acid and 486 mg (3.0 mMol) of 1,1'-carbonyldiimidazole were dissolved in 40 ml of tetrahydrofuran and refluxed for 15 minutes. Then 700 mg (2.24 mMol) of 3-amino-4-methylaminobenzenesulphonic acid-N-methyl-N-(1-methyl-piperidin-4-yl)-amide were added and boiling was continued for a further eight hours. Then the mixture was evaporated down and the resulting oily residue was refluxed in 30 ml of glacial acetic acid for one hour. The glacial acetic acid was distilled off, the residue was mixed with about 30 ml of water and made alkaline with concentrated ammonia, and the solution was extracted three times with about 20 ml of dichloromethane. The organic phases were dried and evaporated down. The resulting product was further reacted without any purification.

35 Yield: 400 mg (39% of theory),

$C_{23}H_{27}N_5O_3S$ (453.6)

R_f value: 0.37 (silica gel; dichloromethane/ethanol = 4:1)

e) 1-Methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-sulphonic acid-N-methyl-N-(1-methylpiperidin-4-yl)-amide-hydrochloride

- 5 Prepared analogously to Example 25d from 400 mg of 1-methyl-2-[(4-cyanophenyl)oxymethyl]-benzimidazol-5-yl-sulphonic acid-N-methyl-N-(1-methylpiperidin-4-yl)-amide with ethanolic hydrochloric acid and ammonium carbonate. Yield: 370 mg (83% of theory),
- 10 $C_{23}H_{30}N_6O_3S$ (470.6)

EKA mass spectrum: $(M+H)^+ = 471$

$(M+2H)^{++} = 236$

Example 33

15

1-Methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-sulphonic acid-N-methyl-N-phenyl-amide-hydrochloride

-
- 20 Prepared analogously to Example 32 from 1-methyl-2-[(4-cyanophenyl)-oxymethyl]-benzimidazol-5-yl-sulphonic acid-N-methyl-N-phenyl-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate. Yield: 46 % of theory, $C_{23}H_{23}N_5O_3S$ (449.5)

25 EKA mass spectrum: $(M+H)^+ = 450$

$(M+H+Methanol)^+ = 482$

$(M+2H)^{++} = 223$

Example 34

30

1-Methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-sulphonic acid-N-(3-ethoxycarbonyl-n-propyl)-N-phenyl-amide-hydrochloride

-
- 35 Prepared analogously to Example 32 from 1-methyl-2-[(4-cyanophenyl)oxymethyl]-benzimidazol-5-yl-sulphonic acid-N-

(3-ethoxycarbonyl-n-propyl)-N-phenyl-amide, ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 57 % of theory,

$C_{28}H_{31}N_5O_5S$ (549.7)

5 EKA mass spectrum: $(M+H)^+ = 550$

Example 35

10 1-Methyl-2-[(3-amidinophenyl)oxymethyl]-benzimidazol-5-yl-sulphonic acid-pyrrolidide-hydrochloride

Prepared analogously to Example 32 from 1-methyl-2-[(3-cyanophenyl)oxymethyl]-benzimidazol-5-yl-sulphonic acid-pyrrolidide, ethanolic hydrochloric acid, ethanol and
15 ammonium carbonate.

Yield: 71 % of theory,

$C_{20}H_{23}N_5O_3S$ (413.5)

EKA mass spectrum: $(M+H)^+ = 414$

20 Example 36

1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-methoxycarbonylpropyl)-amide-dihydrochloride

25 Prepared analogously to Example 25d from 1-methyl-2-[2-(4-cyanophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-tert.butyloxycarbonylpropyl)-amide and methanolic hydrochloric acid, methanol and ammonium
30 carbonate.

Yield: 83.5 % of theory,

R_f value: 0.17 (silica gel; dichloromethane/ethanol = 4:1)

$C_{29}H_{31}N_5O_3$ (497.6)

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

35 $(M+H+Na)^{++} = 260.7$

Example 37

1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-
carboxylic acid-N-phenyl-N-(3-hydroxycarbonylpropyl)-amide-
5 hydrochloride

Prepared analogously to Example 26 from 1-methyl-2-[(4-
amidinophenyl)aminomethyl]-benzimidazol-5-yl-carboxylic
acid-N-phenyl-N-(3-methoxycarbonylpropyl)-amide-
10 dihydrochloride and sodium hydroxide solution.

Yield: 92 % of theory,

R_f value: 0.09 (silica gel; dichloromethane/ethanol = 4:1)

C₂₈H₂₉N₅O₃ (483.6)

EKA mass spectrum: (M+H)⁺ = 484
15 (M+Na)⁺ = 506
(M+H+Na)⁺⁺ = 253.7

Example 38

20 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-
5-yl-carboxylic acid-N-phenyl-N-(3-ethoxycarbonylpropyl)-
amide-dihydrochloride

a) 1-Methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-
25 5-yl-carboxylic acid-N-phenyl-N-(3-tert.butylloxy-
carbonylpropyl)-amide

Prepared analogously to Example 25c from N-(4-cyanophenyl)-
glycine and 3-amino-4-methylamino-benzoic acid-N-phenyl-
N-(3-tert.butylloxycarbonylpropyl)-amide.

30 Yield: 65 % of theory,

R_f value: 0.17 (silica gel; dichloromethane/methanol =
19:1)

b) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-
35 benzimidazol-5-yl-carboxylic acid-N-phenyl-
N-(3-ethoxycarbonylpropyl)-amide-dihydrochloride

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-tert.butyloxycarbonylpropyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium

5 carbonate.

Yield: 68 % of theory,

R_f value: 0.12 (silica gel; dichloromethane/ethanol = 4:1)

C₂₉H₃₂N₆O₃ (512.6)

EKA mass spectrum: (M+H)⁺ = 513

10 (M+H+Na)⁺⁺ = 268

Example 39

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-
15 5-yl-carboxylic acid-N-phenyl-N-(3-hydroxycarbonylpropyl)-amide-hydrochloride

Prepared analogously to Example 26 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic
20 acid-N-phenyl-N-(3-ethoxycarbonylpropyl)-amide-dihydrochloride and sodium hydroxide solution.

Yield: 73.5 % of theory,

C₂₇H₂₈N₆O₃ (484.6)

EKA mass spectrum: (M+H)⁺ = 485

25 (M+2H)⁺⁺ = 243

(M+H+Na)⁺⁺ = 254

Example 40

30 1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(ethoxycarbonylmethyl)-amide-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2-[2-(4-cyanophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-

35

phenyl-N-(ethoxycarbonylmethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 73 % of theory,

R_f value: 0.15 (silica gel; dichloromethane/ethanol = 4:1)

5 C₂₈H₂₉N₅O₃ (483.6)

EKA mass spectrum: (M+H)⁺ = 484

(M+H+Na)⁺⁺ = 253.7

Example 41

10

1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(hydroxycarbonylmethyl)-amide-hydrochloride

15 Prepared analogously to Example 26 from 1-methyl-2-[2-(4-amidinophenyl)ethyl]benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(ethoxycarbonylmethyl)-amide-hydrochloride and sodium hydroxide solution.

Yield: 97 % of theory,

20 C₂₆H₂₅N₅O₃ (455.5)

EKA mass spectrum: (M+H)⁺ = 456

(M+Na)⁺ = 478

(M+2Na)⁺⁺ = 250.6

25 Example 42

1-Methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(ethoxycarbonylmethyl)-amide-hydrochloride

30

Prepared analogously to Example 25d from 1-methyl-2-[(4-cyanophenyl)oxymethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(ethoxycarbonylmethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

35 Yield: 76 % of theory,

R_f value: 0.17 (silica gel; dichloromethane/ethanol = 4:1)

$C_{27}H_{27}N_5O_4$ (485.6)

EKA mass spectrum: $(M+H)^+ = 486$
 $(M+H+Na)^{++} = 254.7$

5 Example 43

1-Methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(hydroxycarbonylmethyl)-amide-hydrochloride

10

Prepared analogously to Example 26 from 1-methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(ethoxycarbonylmethyl)-amide-hydrochloride and sodium hydroxide solution.

15 Yield: 58 % of theory,

$C_{25}H_{23}N_5O_4$ (457.5)

EKA mass spectrum: $(M+H)^+ = 458$
 $(M+Na)^+ = 480$
 $(M+2Na)^{++} = 251.6$

20

Example 44

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(ethoxycarbonylmethyl)-amide-hydrochloride

25

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(ethoxycarbonylmethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

30

Yield: 74 % of theory,

R_f value: 0.12 (silica gel; dichloromethane/ethanol = 4:1)

$C_{27}H_{28}N_6O_3$ (484.6)

EKA mass spectrum: $(M+H)^+ = 485$
 $(M+H+Na)^{++} = 254$

35

Example 45

1-Methyl-2- [N- (4-amidinophenyl) -aminomethyl] -benzimidazol-
5-yl-carboxylic acid-N-phenyl-N- (hydroxycarbonylmethyl) -
5 amide-hydrochloride

Prepared analogously to Example 26 from 1-methyl-2- [N- (4-
amidinophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic
acid-N-phenyl-N- (ethoxycarbonylmethyl) -amide-hydrochloride
10 and sodium hydroxide solution.

Yield: 84 % of theory,

$C_{25}H_{24}N_6O_3$ (456.5)

EKA mass spectrum: $(M+H)^+$ = 457

$(M+Na)^+$ = 479

15 $(M+2Na)^{++}$ = 251

Example 46

1-Methyl-2- [(4-amidinophenyl)oxymethyl] -benzimidazol-5-yl-
20 carboxylic acid-N- (4-pyrimidyl) -N- (2-ethoxycarbonylethyl) -
amide-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2-
[(4-cyanophenyl)oxymethyl] -benzimidazol-5-yl-carboxylic
acid-N- (4-pyrimidyl) -N- (2-ethoxycarbonylethyl) -amide and
25 ethanolic hydrochloric acid, ethanol and ammonium
carbonate.

Yield: 14 % of theory,

$C_{26}H_{27}N_7O_4$ (501.6)

30 Mass spectrum: $(M+H)^+$ = 502

Example 47

1-Methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-
carboxylic acid-N-(2-pyridyl)-N-(ethoxycarbonylmethyl)-
5 amide-dihydrochloride

Prepared analogously to Example 25d from 1-methyl-2-
[(4-cyanophenyl)oxymethyl]-benzimidazol-5-yl-carboxylic
acid-N-(2-pyridyl)-N-(ethoxycarbonylmethyl)-amide and
10 ethanolic hydrochloric acid, ethanol and ammonium
carbonate.

Yield: 44 % of theory,

R_f value: 0.12 (silica gel; dichloromethane/ethanol = 4:1)

C₂₆H₂₆N₆O₄ (486.5)

15 EKA mass spectrum: (M+H)⁺ = 487

(M+2H)⁺⁺ = 244

(M+H+Na)⁺⁺ = 255

Example 48

20

1-Methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-
carboxylic acid-N-(2-pyridyl)-N-(hydroxycarbonylmethyl)-
amide-hydrochloride

25 Prepared analogously to Example 26 from 1-methyl-2-[(4-
amidinophenyl)oxymethyl]-benzimidazol-5-yl-carboxylic acid-
N-(2-pyridyl)-N-(ethoxycarbonylmethyl)-amide-
dihydrochloride and sodium hydroxide solution.

Yield: 85 % of theory,

30 C₂₄H₂₂N₆O₄ (458.5)

EKA mass spectrum: (M+H)⁺ = 459

(M+Na)⁺ = 481

(M+2Na)⁺⁺ = 252

Example 49

- 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-
5 N-(ethoxycarbonylmethyl)-amide-dihydrochloride

a) 1-Methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-ethoxycarbonylmethyl-amide

- 10 Prepared analogously to Example 25c from N-(4-cyanophenyl)-glycine and 3-amino-4-methylamino-benzoic acid-N-(2-pyridyl)-N-ethoxycarbonylmethyl-amide.

Yield: 24 % of theory,

R_f value: 0.56 (silica gel; dichloromethane/methanol = 4:1)

15

b) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(ethoxycarbonylmethyl)-amide-dihydrochloride

- Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(ethoxycarbonylmethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 70 % of theory,

- 25 R_f value: 0.16 (silica gel; dichloromethane/ethanol = 4:1)
C₂₆H₂₇N₇O₃ (485.6)

EKA mass spectrum: (M+H)⁺ = 486

(M+2H)⁺⁺ = 243.7

(M+H-Na)⁺⁺ = 254.6

Example 50

- 1-Methyl-2- [N- (4-amidinophenyl) -aminomethyl] -benzimidazol-
5-yl-carboxylic acid-N- (2-pyridyl) -
5 N- (hydroxycarbonylmethyl) -amide-hydrochloride

Prepared analogously to Example 26 from 1-methyl-2- [N- (4-
amidinophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic
acid-N- (2-pyridyl) -N- (ethoxycarbonylmethyl) -amide-
10 dihydrochloride and sodium hydroxide solution.

Yield: 91 % of theory,

$C_{24}H_{23}N_7O_3$ (457.5)

EKA mass spectrum: $(M+H)^+$ = 458
 $(M+Na)^+$ = 480
15 $(M+2Na)^{++}$ = 251.7

Example 51

- 1-Methyl-2- [2- (4-amidinophenyl) ethyl] -benzimidazol-5-yl-
20 carboxylic acid-N- (2-pyridyl) -N- (ethoxycarbonylmethyl) -
amide-dihydrochloride

Prepared analogously to Example 25d from 1-methyl-2- [2- (4-
cyanophenyl) ethyl] -benzimidazol-5-yl-carboxylic acid-N- (2-
25 pyridyl) -N- (ethoxycarbonylmethyl) -amide, ethanolic
hydrochloric acid, ethanol and ammonium carbonate.

Yield: 90 % of theory,

R_f value: 0.17 (silica gel; dichloromethane/ethanol = 4:1)

$C_{27}H_{28}N_6O_3$ (484.6)

30 EKA mass spectrum: $(M+H)^+$ = 485
 $(M+2H)^{++}$ = 243
 $(M+H+Na)^{++}$ = 254

Example 52

1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(hydroxycarbonylmethyl)-amide-hydrochloride

Prepared analogously to Example 26 from 1-methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(ethoxycarbonylmethyl)-amide-dihydrochloride and sodium hydroxide solution.

Yield: 89 % of theory,

$C_{25}H_{24}N_6O_3$ (456.5)

EKA mass spectrum: $(M+H)^+$ = 457

$(M+Na)^+$ = 479

Example 53

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide and methanolic hydrochloric acid, methanol and ammonium carbonate.

Yield: 87 % of theory,

R_f value: 0.11 (silica gel; dichloromethane/ethanol = 4:1)

$C_{27}H_{28}N_6O_3$ (484.6)

EKA mass spectrum: $(M+H)^+$ = 485

$(M+2H)^{++}$ = 243

$(M+H+Na)^{++}$ = 254

Example 54

1-Methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-
carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-
5 hydrochloride

Prepared analogously to Example 25d from 1-methyl-2-
[(4-cyanophenyl)oxymethyl]-benzimidazol-5-yl-carboxylic
acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide and ethanolic
10 hydrochloric acid, ethanol and ammonium carbonate.

Yield: 79.5 % of theory,

$C_{28}H_{29}N_5O_4$ (499.6)

R_f value: 0.15 (silica gel; dichloromethane/ethanol = 4:1)

EKA mass spectrum: $(M+H)^+$ = 500.0

15 $(M+H+Na)^{++}$ = 261.7

Example 55

1-Methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-
20 carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide-
hydrochloride

Prepared analogously to Example 26 from 1-methyl-2-[(4-
amidinophenyl)oxymethyl]-benzimidazol-5-yl-carboxylic acid-
25 N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and
sodium hydroxide solution.

Yield: 82 % of theory,

$C_{26}H_{25}N_5O_4$ (471.5)

R_f value: 0.11 (silica gel; dichloromethane/ethanol = 4:1)

30 EKA mass spectrum: $(M+H)^+$ = 472

$(M+H+Na)^{++}$ = 247.6

$(M+Na)^+$ = 494

$(M+2Na)^{++}$ = 258.6

35

Example 56

1-Methyl-2-[2-(2-amidinothiophen-5-yl)ethyl]-benzimidazol-
5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-
ethoxycarbonylethyl)-amide-hydrochloride

a) 1-Methyl-2-[2-(2-cyanothiophen-5-yl)-ethyl]-
benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-
ethoxycarbonylethyl)-amide

Prepared analogously to Example 25c from 3-(2-
cyanothiophen-5-yl)-propionic acid and 3-amino-
4-methylamino-benzoic acid-N-(2-pyridyl)-
N-(2-ethoxycarbonylethyl)amide.

Yield: 18 % of theory,

R_f value: 0.66 (silica gel; dichloromethane/methanol = 9:1)

b) 1-Methyl-2-[2-(2-amidinothiophen-5-yl)ethyl]-
benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-
ethoxycarbonylethyl)-amide-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2-[2-(2-
cyanothiophen-5-yl)ethyl]-benzimidazol-5-yl-carboxylic
acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide and
ethanolic hydrochloric acid, ethanol and ammonium
carbonate.

Yield: 53 % of theory,

C₂₆H₂₈N₆O₃S (504.6)

R_f value: 0.22 (silica gel; dichloromethane/methanol = 5:1)

EKA mass spectrum: (M+H)⁺ = 505

(M+H+Na)⁺⁺ = 264

Example 57

1-Methyl-2-[2-(2-amidinothiophen-5-yl)ethyl]-benzimidazol-
5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-
5 hydroxycarbonylethyl)-amide

Prepared analogously to Example 26 from 1-methyl-2-[2-(2-
amidinothiophen-5-yl)ethyl]-benzimidazol-5-yl-carboxylic
acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-
10 hydrochloride and sodium hydroxide solution.

Yield: 98 % of theory,

C₂₄H₂₄N₆O₃S (476.6)

EKA mass spectrum: (M+H)⁺ = 477

(M+Na)⁺ = 499

15 (M+2H)⁺⁺ = 239

Example 58

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-
20 5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-
ethoxycarbonylethyl)-amide-hydrochloride

a) 1-Methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-
5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-
25 ethoxycarbonylethyl)-amide

Prepared analogously to Example 25c from N-(4-cyanophenyl)-
glycine and 3-amino-4-methylamino-benzoic acid-N-(2-
pyridyl)-N-(2-ethoxycarbonylethyl)-amide.

Yield: 61 % of theory,

30 R_f value: 0.62 (silica gel; dichloromethane/methanol =
19:1)

b) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-
benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-
35 ethoxycarbonylethyl)-amide-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-
cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic

acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide and
ethanolic hydrochloric acid, ethanol and ammonium
carbonate.

Yield: 71 % of theory,

5 $C_{27}H_{29}N_7O_3$ (499.6)

R_f value: 0.28 (silica gel; dichloromethane/methanol = 5:1)

EKA mass spectrum: $(M+H)^+$ = 500

$(M+H+Na)^{++}$ = 261.8

$(M+2H)^{++}$ = 250.8

10

Example 59

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-
5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-
15 hydroxycarbonylethyl)-amide

Prepared analogously to Example 26 from 1-methyl-2-[N-(4-
amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic
acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-
20 hydrochloride and sodium hydroxide solution.

Yield: 91 % of theory,

$C_{25}H_{25}N_7O_3$ (471.5)

EKA mass spectrum: $(M+H)^+$ = 472

$(M+H+Na)^{++}$ = 247.6

25 $(M+2H)^{++}$ = 236.7

$(M+2Na)^{++}$ = 258.6

Example 60

30 1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-
carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-
amide-hydrochloride

a) 1-Methyl-2-[2-(4-cyanophenyl)-ethyl]-benzimidazol-5-yl-
35 carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-
amide

Prepared analogously to Example 149a from 3-(4-cyanophenyl)-propionic acid and 3-amino-4-methylamino-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide. Yield: 22 % of theory,

5 R_f value: 0.68 (silica gel; dichloromethane/methanol = 19:1)

b) 1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2-[2-(4-cyanophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

15 Yield: 85 % of theory,

$C_{28}H_{30}N_6O_3$ (498.6)

R_f value: 0.30 (silica gel; dichloromethane/methanol = 5:1)

EKA mass spectrum: $(M+H)^+$ = 499

$(M+H+Na)^{++}$ = 261

20

Example 61

1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide

25

Prepared analogously to Example 26 from 1-methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.

30

Yield: 97 % of theory,

$C_{26}H_{26}N_6O_3$ (470.5)

EKA mass spectrum: $(M+H)^+$ = 471

$(M+H+Na)^{++}$ = 247

35

$(M+Na)^+$ = 493

Example 62

1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-
5 carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-
hydrochloride

Prepared analogously to Example 25d from 1-methyl-2-[2-(4-
cyanophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-
10 phenyl-N-(2-ethoxycarbonylethyl)-amide and ethanolic
hydrochloric acid, ethanol and ammonium carbonate.

Yield: 86 % of theory,

$C_{29}H_{31}N_5O_3$ (497.6)

R_f value: 0.11 (silica gel; dichloromethane/ethanol = 4:1)

15 EKA mass spectrum: $(M+H)^+ = 498$
 $(M+2H)^{++} = 249.8$

Example 63

20 1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-
carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide-
hydrochloride

Prepared analogously to Example 26 from 1-methyl-2-[2-(4-
25 amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-
phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and
sodium hydroxide solution.

Yield: 71 % of theory,

$C_{27}H_{27}N_5O_3$ (469.6)

30 EKA mass spectrum: $(M+H)^+ = 470$
 $(M+H+Na)^{++} = 246.6$
 $(M+Na)^+ = 492$
 $(M+2H)^{++} = 235.6$

Example 64

- 1-Methyl-2- [N- (4-amidinophenyl) -aminomethyl] -benzimidazol-
5-yl-carboxylic acid-N- (2-pyridyl) -N-
5 (methoxycarbonylmethyl) -amide-dihydrochloride

Prepared analogously to Example 25d from 1-methyl-2- [N- (4-
cyanophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic
acid-N- (2-pyridyl) -N- (methoxycarbonylmethyl) -amide and
10 methanolic hydrochloric acid, methanol and ammonium
carbonate.

Yield: 73 % of theory,

$C_{25}H_{25}N_7O_3$ (471.5)

R_f value: 0.12 (silica gel; dichloromethane/ethanol = 4:1)

- 15 EKA mass spectrum: $(M+H)^+$ = 472
 $(M+H+Na)^{++}$ = 247.8

Example 65

- 20 1-Methyl-2- [N- (4-amidinophenyl) -aminomethyl] -benzimidazol-
5-yl-carboxylic acid-N- (2-pyridyl) -N- (2-
methoxycarbonylethyl) -amide-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2- [N- (4-
25 cyanophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic
acid-N- (2-pyridyl) -N- (2-methoxycarbonylethyl) -amide and
methanolic hydrochloric acid, methanol and ammonium
carbonate.

Yield: 78 % of theory,

- 30 $C_{26}H_{27}N_7O_3$ (485.6)

R_f value: 0.31 (silica gel; dichloromethane/methanol = 5:1)

EKA mass spectrum: $(M+H)^+$ = 486
 $(M+H+Na)^{++}$ = 254.8

Example 66

1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-
carboxylic acid-N-phenyl-N-[2-(1H-tetrazol-5-yl)ethyl]-
5 amide-hydrochloride

a) 1-Methyl-2-[2-(4-cyanophenyl)ethyl]-benzimidazol-5-yl-
carboxylic acid-N-phenyl-N-[2-(1H-tetrazol-5-yl)ethyl]-
amide

10 Prepared analogously to Example 25c from 3-(4-cyanophenyl)-
propionic acid and 3-amino-4-methylamino-benzoic acid-
N-phenyl-N-[2-(1H-tetrazol-5-yl)ethyl]-amide.

Yield: 67 % of theory,

IR Mass spectrum (KBr): characteristic bands at

15 3439.5 cm^{-1} (N-H); 2235.5 cm^{-1}
C $\equiv$ N);
1631.6 cm^{-1} (C=O)

b) 1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-
20 carboxylic acid-N-phenyl-N-[2-(1H-tetrazol-5-yl)ethyl]-
amide-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2-[2-(4-
cyanophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-
phenyl-N-[2-(1H-tetrazol-5-yl)ethyl]-amide and ethanolic

25 hydrochloric acid, ethanol and ammonium carbonate.

Yield: 92 % of theory,

C₂₇H₂₇N₉O (493.6)

EKA mass spectrum: (M+H)⁺ = 494

(M+Na)⁺ = 516

30 (M+2H)⁺⁺ = 258.7

Example 67

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-[2-(1H-tetrazol-5-yl)ethyl]-amide-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-[2-(1H-tetrazol-5-yl)ethyl]-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 29 % of theory,

$C_{26}H_{26}N_{10}O$ (494.6)

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

Example 68

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-n-hexyloxycarbonyl)ethyl)-amide-hydrochloride

0.60 g (1.1 mMol) of 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonyl)ethyl)-amide-hydrochloride were added to about 30 ml of n-hexanol saturated with hydrogen chloride and the mixture was stirred for 19 hours at room temperature. Then the hexanol was distilled off *in vacuo*, the residue was mixed with about 5 ml of 1N ammonia solution with stirring and evaporated down once more. The crude product thus obtained was purified by column chromatography (silica gel, dichloromethane/methanol = 5:1).

Yield: 53 % of theory,

$C_{31}H_{37}N_7O_3$ (555.7)

R_f value: 0.36 (silica gel; dichloromethane/methanol = 5:1)

EKA mass spectrum: $(M+H)^+ = 556$

Example 69

5 1-Methyl-2- [N- (4-amidinophenyl) -N-methyl-aminomethyl] -
benzimidazol-5-yl-carboxylic acid-N- (2-pyridyl) -N- (2-
ethoxycarbonylethyl) -amide-hydrochloride

10 a) 1-Methyl-2- [N- (4-cyanophenyl) -N-methyl-aminomethyl] -
benzimidazol-5-yl-carboxylic acid-N- (2-pyridyl) -N- (2-
ethoxycarbonylethyl) -amide

Prepared analogously to Example 25c from N- (4-cyanophenyl) -
N-methylglycine and 3-amino-4-methylamino-benzoic acid-N-
(2-pyridyl) -N- (2-ethoxycarbonylethyl) -amide.

15 Yield: 71 % of theory,

R_f value: 0.66 (silica gel; dichloromethane/methanol =
19:1)

b) 1-Methyl-2- [N- (4-amidinophenyl) -N-methyl-aminomethyl] -
20 benzimidazol-5-yl-carboxylic acid-N- (2-pyridyl) -N- (2-
ethoxycarbonylethyl) -amide-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2- [N- (4-
cyanophenyl) -N-methyl-aminomethyl] -benzimidazol-5-yl-
carboxylic acid-N- (2-pyridyl) -N- (2-ethoxycarbonylethyl) -

25 amide and ethanolic hydrochloric acid, ethanol and ammonium
carbonate.

Yield: 77 % of theory,

$C_{28}H_{31}N_7O_3$ (513.6)

EKA mass spectrum: $(M+H)^+ = 514$

30 $(M+H+Na)^{++} = 268.7$

Example 70

1-Methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-
benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-
5 hydroxycarbonylethyl)-amide

Prepared analogously to Example 26 from 1-methyl-2-[N-(4-
amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-
carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-
10 amide-hydrochloride and sodium hydroxide solution.

Yield: 66 % of theory,

$C_{26}H_{27}N_7O_3$ (485.6)

EKA mass spectrum: $(M+H)^+$ = 486

$(M+Na)^+$ = 508

15 $(M+2Na)^{++}$ = 265.6

Example 71

1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-
20 carboxylic acid-N-cyclopentyl-N-(2-ethoxycarbonylethyl)-
amide-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2-[2-(4-
cyanophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-
25 cyclopentyl-N-(2-ethoxycarbonylethyl)-amide and ethanolic
hydrochloric acid, ethanol and ammonium carbonate.

Yield: 65 % of theory,

$C_{28}H_{35}N_5O_3$ (489.6)

EKA mass spectrum: $(M+H)^+$ = 490

Example 72

1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-
carboxylic acid-N-cyclopentyl-N-(2-hydroxycarbonylethyl)-
5 amide

Prepared analogously to Example 26 from 1-methyl-2-[2-(4-
amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-
cyclopentyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride
10 and sodium hydroxide solution.

Yield: 89 % of theory,

$C_{26}H_{31}N_5O_3$ (461.6)

EKA mass spectrum: $(M+H)^+$ = 462
 $(M+H+Na)^{++}$ = 242.6
15 $(M+Na)^+$ = 484
 $(M+2H)^{++}$ = 231.6

Example 73

20 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-
5-yl-carboxylic acid-N-cyclopentyl-N-(2-
ethoxycarbonylethyl)-amide-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-
25 cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic
acid-N-cyclopentyl-N-(2-ethoxycarbonylethyl)-amide and
ethanolic hydrochloric acid, ethanol and ammonium
carbonate.

Yield: 60 % of theory,

30 $C_{27}H_{34}N_6O_3$ (490.6)

EKA mass spectrum: $(M+H)^+$ = 491

Example 74

1-Methyl-2- [N- (4-amidinophenyl) -aminomethyl] -benzimidazol-
5-yl-carboxylic acid-N-cyclopentyl-N- (2-
5 hydroxycarbonylethyl) -amide

Prepared analogously to Example 26 from 1-methyl-2- [N- (4-
amidinophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic
acid-N-cyclopentyl-N- (2-ethoxycarbonylethyl) -amide-
10 hydrochloride and sodium hydroxide solution.

Yield: 45 % of theory,

$C_{25}H_{30}N_3O_4$ (462.6)

EKA mass spectrum: $(M+H)^+$ = 463
 $(M+H+Na)^{++}$ = 243
15 $(M+Na)^+$ = 485
 $(M+2Na)^{++}$ = 254

Example 75

20 1-Methyl-2- [N- (4-amidinophenyl) -N-methyl-aminomethyl] -
benzimidazol-5-yl-carboxylic acid-N- (2-pyridyl) -N-
(ethoxycarbonylmethyl) -amide-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2- [N- (4-
25 cyanophenyl) -N-methyl-aminomethyl] -benzimidazol-5-yl-
carboxylic acid-N- (2-pyridyl) -N- (ethoxycarbonylmethyl) -
amide and ethanolic hydrochloric acid, ethanol and ammonium
carbonate.

Yield: 54 % of theory,

30 $C_{27}H_{29}N_7O_3$ (499.6)

EKA mass spectrum: $(M+H)^+$ = 500
 $(M+2H)^{++}$ = 250.7

Example 76

1-Methyl-2- [N- (4-amidinophenyl) -N-methyl-aminomethyl] -
benzimidazol-5-yl-carboxylic acid-N- (2-pyridyl) -N-
5 (hydroxycarbonylmethyl) -amide

Prepared analogously to Example 26 from 1-methyl-2- [N- (4-
amidinophenyl) -N-methyl-aminomethyl] -benzimidazol-5-yl-
carboxylic acid-N- (2-pyridyl) -N- (ethoxycarbonylmethyl) -
10 amide-hydrochloride and sodium hydroxide solution.

Yield: 68 % of theory,

$C_{25}H_{25}N_7O_3$ (471.5)

EKA mass spectrum: $(M+H)^+$ = 472

$(M+Na)^+$ = 494

15 $(M+2Na)^{++}$ = 258.6

Example 77

1-Methyl-2- [2- (4-amidinophenyl) -ethyl] -benzimidazol-5-yl-
20 carboxylic acid-N- (3-pyridyl) -N- (2-ethoxycarbonylethyl) -
amide-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2- [2- (4-
cyanophenyl) -ethyl] -benzimidazol-5-yl-carboxylic acid-N- (3-
25 pyridyl) -N- (2-ethoxycarbonylethyl) -amide and ethanolic
hydrochloric acid, ethanol and ammonium carbonate.

Yield: 91 % of theory,

$C_{28}H_{30}N_6O_3$ (498.6)

R_f value: 0.19 (silica gel; dichloromethane/ethanol = 4:1)

30 EKA mass spectrum: $(M+H)^+$ = 499

Example 78

1-Methyl-2- [N- (4-amidinophenyl) -aminomethyl] -benzimidazol-
5-yl-carboxylic acid-N- (3-pyridyl) -N- (2-
5 ethoxycarbonylethyl) -amide-dihydrochloride

Prepared analogously to Example 25d from 1-methyl-2- [N- (4-
cyanophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic
acid-N- (3-pyridyl) -N- (2-ethoxycarbonylethyl) -amide and
10 ethanolic hydrochloric acid, ethanol and ammonium
carbonate.

Yield: 86 % of theory,

$C_{27}H_{29}N_7O_3$ (499.6)

R_f value: 0.09 (silica gel; dichloromethane/ethanol = 4:1)

15 EKA mass spectrum: $(M+H)^+ = 500$

Example 79

1-Methyl-2- [N- (4-amidinophenyl) -aminomethyl] -benzimidazol-
20 5-yl-carboxylic acid-N- (3-pyridyl) -N- (2-
hydroxycarbonylethyl) -amide

Prepared analogously to Example 26 from 1-methyl-2- [N- (4-
amidinophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic
25 acid-N- (3-pyridyl) -N- (2-ethoxycarbonylethyl) -amide-
dihydrochloride and sodium hydroxide solution.

Yield: 85 % of theory,

$C_{25}H_{25}N_7O_3$ (471.5)

EKA mass spectrum: $(M+H)^+ = 472$

30 $(M+2H)^{++} = 236.6$

$(M+2Na)^{++} = 258.6$

Example 80

1-Methyl-2- [N- (4-amidinophenyl) -N-methyl-aminomethyl] -
benzimidazol-5-yl-carboxylic acid-N- (3-pyridyl) -N- (2-
5 ethoxycarbonylethyl) -amide-hydrochloride

Prepared analogously to Example 25d from 1-Methyl-2- [N- (4-
cyanophenyl) -N-methyl-aminomethyl] -benzimidazol-5-yl-
carboxylic acid-N- (3-pyridyl) -N- (2-ethoxycarbonylethyl) -
10 amide and ethanolic hydrochloric acid, ethanol and ammonium
carbonate.

Yield: 64 % of theory,

$C_{28}H_{31}N_7O_3$ (513.6)

EKA mass spectrum: $(M+H)^+ = 514$

15

Example 81

1-Methyl-2- [N- (4-amidinophenyl) -N-methyl-aminomethyl] -
benzimidazol-5-yl-carboxylic acid-N- (3-pyridyl) -N- (2-
20 hydroxycarbonylethyl) -amide

Prepared analogously to Example 26 from 1-Methyl-2- [N- (4-
amidinophenyl) -N-methyl-aminomethyl] -benzimidazol-5-yl-
carboxylic acid-N- (3-pyridyl) -N- (2-ethoxycarbonylethyl) -
25 amide-hydrochloride and sodium hydroxide solution.

Yield: 70 % of theory,

$C_{26}H_{27}N_7O_3$ (485.6)

EKA mass spectrum: $(M+H)^+ = 486$

$(M+Na)^+ = 508$

30

$(M+2Na)^{++} = 265.6$

Example 82

1-Methyl-2- [N- (4-amidinophenyl) -N-methyl-aminomethyl] -
benzimidazol-5-yl-carboxylic acid-N-phenyl-N- (2-
5 ethoxycarbonylethyl) -amide-hydrochloride

a) 1-Methyl-2- [N- (4-cyanophenyl) -N-methyl-aminomethyl] -
benzimidazol-5-yl-carboxylic acid-N-phenyl-N- (2-pyridyl) -N-
(2-ethoxycarbonylethyl) -amide

10 Prepared analogously to Example 25c from N- (4-cyanophenyl) -
N-methylglycine and 3-amino-4-methylamino-benzoic acid-
N-phenyl-N- (2-ethoxycarbonylethyl) -amide.

Yield: 71 % of theory,

R_f value: 0.38 (silica gel; dichloromethane/methanol =
15 19:1)

b) 1-Methyl-2- [N- (4-amidinophenyl) -N-methyl-aminomethyl] -
benzimidazol-5-yl-carboxylic acid-N-phenyl-N- (2-
ethoxycarbonylethyl) -amide-hydrochloride

20 Prepared analogously to Example 25d from 1-methyl-2- [N- (4-
cyanophenyl) -N-methyl-aminomethyl] -benzimidazol-5-yl-
carboxylic acid-N-phenyl-N- (2-ethoxycarbonylethyl) -amide
and ethanolic hydrochloric acid, ethanol and ammonium
carbonate.

25 Yield: 74 % of theory,

C₂₉H₃₂N₆O₃ (512.6)

EKA mass spectrum: (M+H)⁺ = 513

(M+H+Na)⁺⁺ = 268

(M+2H)⁺⁺ = 257

Example 83

1-Methyl-2- [N- (4-amidinophenyl) -N-methyl-aminomethyl] -
benzimidazol-5-yl-carboxylic acid-N-phenyl-N- (2-
5 hydroxycarbonylethyl) -amide

Prepared analogously to Example 26 from 1-methyl-2- [N- (4-
amidinophenyl) -N-methyl-aminomethyl] -benzimidazol-5-yl-
carboxylic acid-N-phenyl-N- (2-ethoxycarbonylethyl) -amide-
10 hydrochloride and sodium hydroxide solution.

Yield: 80 % of theory,

$C_{27}H_{28}N_6O_3$ (484.6)

EKA mass spectrum: $(M+H)^+$ = 485
 $(M+H+Na)^{++}$ = 254
15 $(M+Na)^+$ = 507
 $(M+2Na)^+$ = 265

Example 84

20 1-ethyl-2- [N- (4-amidinophenyl) -aminomethyl] -benzimidazol-5-
yl-carboxylic acid-N- (2-pyridyl) -N- (2-ethoxycarbonylethyl) -
amide-hydrochloride

Prepared analogously to Example 25d from 1-ethyl-2- [N- (4-
25 cyanophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic
acid-N- (2-pyridyl) -N- (2-ethoxycarbonylethyl) -amide and
ethanolic hydrochloric acid, ethanol and ammonium
carbonate.

Yield: 85 % of theory,

30 $C_{28}H_{31}N_7O_3$ (513.6)

R_f value: 0.21 (silica gel; dichloromethane/methanol = 5:1)

EKA mass spectrum: $(M+H)^+$ = 514
 $(M+H+Na)^{++}$ = 268.6
35 $(M+2H)^{++}$ = 257.7

Example 85

1-ethyl-2- [N- (4-amidinophenyl) -aminomethyl] -benzimidazol-5-
5 yl-carboxylic acid-N- (2-pyridyl) -N- (2-
hydroxycarbonylethyl) -amide

Prepared analogously to Example 26 from 1-ethyl-2- [N- (4-
amidinophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic
10 acid-N- (2-pyridyl) -N- (2-ethoxycarbonylethyl) -amide-
hydrochloride and 2N sodium hydroxide solution.

Yield: 49 % of theory,

$C_{26}H_{27}N_7O_3$ (485.6)

EKA mass spectrum: $(M+H)^+$ = 486
15 $(M+H+Na)^{++}$ = 254.6
 $(M+2H)^{++}$ = 243.6
 $(M+2Na)^{++}$ = 265.7

Example 86

20

1-Methyl-2- [N- (4-amidinophenyl) -aminomethyl] -benzimidazol-
5-yl-carboxylic acid-N- (2-fluorophenyl) -N- (2-
ethoxycarbonylethyl) -amide-hydrochloride

25 Prepared analogously to Example 25d from 1-methyl-2- [N- (4-
cyanophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic
acid-N- (2-fluorophenyl) -N- (2-ethoxycarbonylethyl) -amide and
ethanolic hydrochloric acid, ethanol and ammonium
carbonate.

30 Yield: 88 % of theory,

$C_{28}H_{29}FN_6O_3$ (516.6)

R_f value: 0.08 (silica gel; dichloromethane/ethanol = 4:1)

EKA mass spectrum: $(M+H)^+$ = 517
 $(M+H+Na)^{++}$ = 270
35 $(M+2H)^{++}$ = 259

Example 87

- 5 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-fluorophenyl)-N-(2-hydroxycarbonylethyl)-amide

10 Prepared analogously to Example 26 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-fluorophenyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.

Yield: 45 % of theory,

$C_{26}H_{25}FN_6O_3$ (488.5)

- 15 R_f value: 0.05 (silica gel; dichloromethane/ethanol = 4:1)

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

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

$(M+2H)^{++}$ = 256

20 Example 88

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-methylphenyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

25

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-methylphenyl)-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

30

Yield: 79 % of theory,

$C_{29}H_{32}N_6O_3$ (512.6)

R_f value: 0.10 (silica gel; dichloromethane/ethanol = 4:1)

EKA mass spectrum: $(M+H)^+$ = 513

35

$(M+H+Na)^{++}$ = 268

Example 89

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-methylphenyl)-N-(2-hydroxycarbonylethyl)-amide

Prepared analogously to Example 26 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-methylphenyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.

Yield: 62 % of theory,

$C_{27}H_{28}N_6O_3$ (484.6)

EKA mass spectrum: $(M+H)^+ = 485$

$(M+H+Na)^{++} = 254$

$(M+Na)^+ = 507$

$(M+2Na)^{++} = 265$

Example 90

1-Methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide

1.1 g (2.06 mMol) of 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride was dissolved in a mixture of 40 ml of tetrahydrofuran and 10 ml of water, then 570 mg (4.12 mMol) of potassium carbonate and 362 mg (2.2 mMol) of n-hexyl chloroformate were added and stirred for two hours at room temperature. The solvent was then distilled off, the residue was mixed with about 50 ml of saturated saline solution and the resulting solution was extracted three times with 20 ml of dichloromethane. The extracts were dried over sodium sulphate and evaporated down. The crude product thus obtained was purified by column chromatography (100 g silica gel; dichloromethane + 5% ethanol).

Yield: 78 % of theory,

$C_{35}H_{42}N_6O_5$ (626.8)

R_f value: 0.49 (silica gel; dichloromethane/ethanol = 19:1)

EKA mass spectrum: $(M+H)^+$ = 627

5 $(M+H+Na)^{++}$ = 325

$(M+2H)^{++}$ = 314

Example 91

10 1-Methyl-2-[N-[4-(N-methoxycarbonylamidino)phenyl]-amino-
methyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-
ethoxycarbonylethyl)-amide

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-
15 amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic
acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride
and methyl chloroformate.

Yield: 41 % of theory,

$C_{30}H_{32}N_6O_5$ (556.6)

20 R_f value: 0.85 (silica gel; dichloromethane/ethanol = 4:1)

EKA mass spectrum: $(M+H)^+$ = 557

$(M+H+Na)^{++}$ = 290

$(M+Na)^+$ = 579

25 Example 92

1-Methyl-2-[N-[4-(N-ethoxycarbonylamidino)phenyl]-
aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-
30 (2-methoxycarbonylethyl)-amide

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-
amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic
acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide-
hydrochloride and ethyl chloroformate.

35 Yield: 62 % of theory,

$C_{30}H_{32}N_6O_5$ (556.6)

R_f value: 0.51 (silica gel; dichloromethane/ethanol = 19:1)

EKA mass spectrum: (M+H)⁺ = 557

(M+H+Na)⁺⁺ = 290

(M+2H)⁺⁺ = 279

5

Example 93

1-Methyl-2- [N- [4- (N-cyclohexyloxycarbonylamidino)phenyl] -
aminomethyl] -benzimidazol-5-yl-carboxylic acid-N-phenyl-N-
10 (2-methoxycarbonylethyl) -amide

Prepared analogously to Example 90 from 1-methyl-2- [N- (4-
amidinophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic
acid-N-phenyl-N- (2-methoxycarbonylethyl) -amide-
15 hydrochloride and cyclohexyl chloroformate.

Yield: 25 % of theory,

C₃₄H₃₈N₆O₅ (610.7)

R_f value: 0.44 (silica gel; dichloromethane/ethanol = 19:1)

EKA mass spectrum: (M+H)⁺ = 611

20 (M+2H)⁺⁺ = 306

Example 94

1-Methyl-2- [N- [4- [N- [2- (methylsulphonyl) ethyloxycarbonyl] -
amidino]phenyl] -aminomethyl] -benzimidazol-5-yl-carboxylic
25 acid-N-phenyl-N- (2-ethoxycarbonylethyl) -amide

Prepared analogously to Example 90 from 1-methyl-2- [N- (4-
amidinophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic
30 acid-N-phenyl-N- (2-ethoxycarbonylethyl) -amide-hydrochloride
and 2- (methylsulphonyl) -ethyl chloroformate.

Yield: 66 % of theory,

C₃₂H₃₆N₆O₇S (648.8)

R_f value: 0.44 (silica gel; dichloromethane/ethanol = 19:1)

35 EKA mass spectrum: (M+H)⁺ = 649

(M+H+Na)⁺⁺ = 336

$$(M+2H)^{++} = 325$$

Example 95

- 5 1-Methyl-2- [N- [4- (N-n-octyloxycarbonylamidino)phenyl] -
aminomethyl] -benzimidazol-5-yl-carboxylic acid-N-phenyl-N-
(2-methoxycarbonylethyl) -amide

10 Prepared analogously to Example 90 from 1-methyl-2- [N- (4-
amidinophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic
acid-N-phenyl-N- (2-methoxycarbonylethyl) -amide-
hydrochloride and n-octyl chloroformate.

Yield: 41 % of theory,

$C_{36}H_{44}N_6O_5$ (640.8)

- 15 R_f value: 0.43 (silica gel; dichloromethane/ethanol = 19:1)
EKA mass spectrum: $(M+H)^+ = 641$
 $(M+Na)^+ = 663$

Example 96

20

1-Methyl-2- [N- [4- (N-hydroxylamidino)phenyl] -aminomethyl] -
benzimidazol-5-yl-carboxylic acid-N-phenyl-N- (2-
ethoxycarbonylethyl) -amide

-
- 25 1.44 g (3.0 mMol) of 1-methyl-2- [N- (4-cyanophenyl) -
aminomethyl] -benzimidazol-5-yl-carboxylic acid-N-phenyl-N-
(2-ethoxycarbonylethyl) -amide, 0.625 g (9.0 mMol) of
hydroxylamine hydrochloride and 0.425 g (4.0 mMol) of
sodium carbonate were dissolved in 80 ml of ethanol and
30 refluxed for 7 hours. Then a further 210 mg of
hydroxylamine hydrochloride and 170 mg of sodium carbonate
were added, the mixture was boiled for a further 5 hours
and then evaporated down in vacuo. The residue was
dissolved in about 30 ml of dichloromethane, the solution
35 obtained was washed with 20 ml of water, the organic phase
was dried and evaporated down. The crude product thus

obtained was purified by column chromatography (200 g silica gel, dichloromethane + 4% ethanol).

Yield: 39 % of theory,

$C_{28}H_{30}N_6O_4$ (514.6)

5 R_f value: 0.15 (silica gel; dichloromethane/ethanol = 19:1)

EKA mass spectrum: $(M+H)^+$ = 515

$(M+Na)^+$ = 537

$(2M+H)^+$ = 1029

$(2M+Na)^+$ = 1051

10

Example 97

1-Methyl-2- [N- [4- (N-n-heptyloxycarbonylamidino)phenyl] -aminomethyl] -benzimidazol-5-yl-carboxylic acid-N-phenyl-N-
15 (2-methoxycarbonylethyl) -amide

Prepared analogously to Example 90 from 1-methyl-2- [N- (4-amidinophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic acid-N-phenyl-N- (2-methoxycarbonylethyl) -amide-
20 hydrochloride and n-heptyl chloroformate.

Yield: 43 % of theory,

$C_{35}H_{42}N_6O_5$ (626.8)

R_f value: 0.40 (silica gel; dichloromethane/ethanol = 19:1)

EKA mass spectrum: $(M+H)^+$ = 627

25 $(M+H+Na)^{++}$ = 325

$(M+Na)^+$ = 649

Example 98

30 1-Methyl-2- [N- [4- (N-benzoylamidino)phenyl] -aminomethyl] -benzimidazol-5-yl-carboxylic acid-N-phenyl-N- (2-methoxycarbonylethyl) -amide

Prepared analogously to Example 90 from 1-methyl-2- [N- (4-amidinophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic
35

acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide-
hydrochloride and benzoyl chloride.

Yield: 88 % of theory,

$C_{34}H_{32}N_6O_4$ (588.7)

- 5 R_f value: 0.37 (silica gel; dichloromethane/ethanol = 19:1)
 1H -NMR spectrum (D_6 -DMSO): 2.61 (t,2H), 3.54 (s,3H), 3.76
(s,3H), 4.10 (t,2H), 4.61 (d,2H), 6.83 (d,2H), 7.05 to 7.55
(m,12H), 8.03 (d,2H), 8.25 (dd,2H), 8.98 (s,1H), 10.48
(s,1H)

10

Example 99

- 1-Methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)phenyl]-
aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-
15 (2-methoxycarbonylethyl)-amide

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-
amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic
acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide-

- 20 hydrochloride and n-hexyl chloroformate.

Yield: 54 % of theory,

$C_{34}H_{40}N_6O_5$ (612.7)

R_f value: 0.45 (silica gel; dichloromethane/ethanol = 19:1)

EKA mass spectrum: $(M+H)^+ = 613$

25

Example 100

- 1-Methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)phenyl]-
aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-
30 (2-n-propyloxycarbonylethyl)-amide

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-
amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic
acid-N-phenyl-N-(2-n-propyloxycarbonylethyl)-amide-

- 35 hydrochloride and n-hexyl chloroformate.

Yield: 31 % of theory,

$C_{36}H_{44}N_6O_5$ (640.8)

R_f value: 0.42 (silica gel; dichloromethane/ethanol = 19:1)

EKA mass spectrum: $(M+H)^+$ = 641

$(M+H+Na)^{++}$ = 332

5 $(M+Na)^+$ = 663

Example 101

1-Methyl-2-[N-[4-(N-ethoxycarbonylamidino)phenyl]-
10 aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-
pyridyl)-N-(2-methoxycarbonylethyl)-amide

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-
amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic
15 acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide-
hydrochloride and ethyl chloroformate.

Yield: 72 % of theory,

$C_{29}H_{31}N_7O_5$ (557.6)

20 R_f value: 0.58 (silica gel; dichloromethane/methanol =
9:1)

EKA mass spectrum: $(M+H)^+$ = 558

$(M+H+Na)^{++}$ = 290.8

$(M+Na)^+$ = 580

25 Example 102

1-Methyl-2-[N-[4-(N-n-octyloxycarbonylamidino)phenyl]-
aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-
30 pyridyl)-N-(2-methoxycarbonylethyl)-amide

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-
amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic
acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide-
hydrochloride and n-octyl chloroformate.

35 Yield: 57 % of theory,

$C_{35}H_{43}N_7O_5$ (641.8)

R_f value: 0.60 (silica gel; dichloromethane/methanol = 9:1)

EKA mass spectrum: (M+H)⁺ = 642

(M+H+Na)⁺⁺ = 332.8

(M+Na)⁺ = 664

Example 103

1-Methyl-2- [N- [4- (N-methoxycarbonylamidino) phenyl] -amino-
methyl] -benzimidazol-5-yl-carboxylic acid-N- (2-pyridyl) -
5 N- (2-ethoxycarbonylethyl) -amide

Prepared analogously to Example 90 from 1-methyl-2- [N- (4-
amidinophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic
acid-N- (2-pyridyl) -N- (2-ethoxycarbonylethyl) -amide-
10 hydrochloride and methyl chloroformate.

Yield: 48 % of theory,

$C_{29}H_{31}N_7O_5$ (557.6)

R_f value: 0.62 (silica gel; dichloromethane/methanol = 9:1)

EKA mass spectrum: $(M+H)^+$ = 558

15 $(M+H+Na)^{++}$ = 290.7

$(M+Na)^+$ = 580

Example 104

20 1-Methyl-2- [N- [4- (N-n-octyloxycarbonylamidino) phenyl] -
aminomethyl] -benzimidazol-5-yl-carboxylic acid-N- (2-
pyridyl) -N- (2-hydroxycarbonylethyl) -amide

0.7 g (1.1 mMol) of 1-methyl-2- [N- [4- (N-n-
25 octyloxycarbonylamidino) -phenyl] -aminomethyl] -benzimidazol-
5-yl-carboxylic acid-N- (2-pyridyl) -N- (2-
methoxycarbonylethyl) -amide was stirred in a mixture of
0.12 g (3.0 mMol) of sodium hydroxide, 5 ml of water and
10 ml of methanol for one hour at room temperature. Then
30 the mixture was diluted with 20 ml of water and adjusted to
pH 6 with glacial acetic acid. Then about 5 ml of
diethylether were added and the mixture was vigorously
stirred for one hour. The product thus precipitated was
suction filtered, washed with a little water, then with
35 diethylether and dried.

Yield: 80 % of theory,

$C_{34}H_{41}N_7O_5$ (627.8)

EKA mass spectrum: $(M+H)^+ = 628$

$(M+H+Na)^{++} = 325.7$

$(M+Na)^+ = 650$

5 $(M+2Na)^{++} = 337.7$

Example 105

1-Methyl-2-[N-[4-[N-(2-methylsulphonyl-
10 ethyloxycarbonyl)amidino]-phenyl]-aminomethyl]-
benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-
N-(2-ethoxycarbonylethyl)-amide

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-
15 amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic
acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-
hydrochloride and 2-(methylsulphonyl)-ethyl chloroformate.
Yield: 65 % of theory,

$C_{31}H_{35}N_7O_7S$ (649.7)

20 R_f value: 0.54 (silica gel; dichloromethane/methanol = 9:1)

EKA mass spectrum: $(M+H)^+ = 650$

$(M+H+Na)^{++} = 336.6$

$(M+Na)^+ = 672$

$(M+2Na)^{++} = 347.6$

25

Example 106

1-Methyl-2-[N-[4-(N-n-butyloxycarbonylamidino)phenyl]-
aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-
30 pyridyl)-N-(2-methoxycarbonylethyl)-amide

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-
amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic
acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide-
35 hydrochloride and n-butyl chloroformate.

Yield: 30 % of theory,

$C_{31}H_{35}N_7O_5$ (585.7)

R_f value: 0.62 (silica gel; dichloromethane/methanol = 9:1)

EKA mass spectrum: $(M+H)^+$ = 586

5 $(M+H+Na)^{++}$ = 304.7

$(M+2H)^{++}$ = 293.7

Example 107

10 1-Methyl-2- [N- [4- (N-n-hexyloxycarbonylamidino) phenyl] -
aminomethyl] -benzimidazol-5-yl-carboxylic acid-N- (2-
pyridyl) -N- (2-methoxycarbonylethyl) -amide

Prepared analogously to Example 90 from 1-methyl-2- [N- (4-
15 amidinophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic
acid-N- (2-pyridyl) -N- (2-methoxycarbonylethyl) -amide-
hydrochloride and n-hexyl chloroformate.

Yield: 51 % of theory,

$C_{33}H_{39}N_7O_5$ (613.7)

20 R_f value: 0.56 (silica gel; dichloromethane/methanol = 9:1)

EKA mass spectrum: $(M+H)^+$ = 614

$(M+H+Na)^{++}$ = 318.7

$(M+2H)^{++}$ = 307.6

25 Example 108

1-Methyl-2- [N- [4- (N-n-heptyloxycarbonylamidino) -phenyl] -
aminomethyl] -benzimidazol-5-yl-carboxylic acid-N- (2-
pyridyl) -N- (2-methoxycarbonylethyl) -amide

30 Prepared analogously to Example 90 from 1-methyl-2- [N- (4-
amidinophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic
acid-N- (2-pyridyl) -N- (2-methoxycarbonylethyl) -amide-
hydrochloride and n-heptyl chloroformate.

35 Yield: 21 % of theory,

$C_{34}H_{41}N_7O_5$ (627.8)

R_f value: 0.60 (silica gel; dichloromethane/methanol = 9:1)

EKA mass spectrum: (M+H)⁺ = 628

(M+H+Na)⁺⁺ = 325.7

(M+2H)⁺⁺ = 314.7

5

Example 109

1-Methyl-2-[N-[4-(N-n-pentyloxycarbonylamidino)-phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide-hydrochloride and n-pentyl chloroformate.

Yield: 66 % of theory,

C₃₂H₃₇N₇O₅ (599.7)

R_f value: 0.58 (silica gel; dichloromethane/methanol = 9:1)

EKA mass spectrum: (M+H)⁺ = 600

(M+H+Na)⁺⁺ = 311.7

(M+Na)⁺ = 622

Example 110

1-Methyl-2-[N-[4-(N-n-nonyloxycarbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide-hydrochloride and n-nonyl chloroformate.

Yield: 60 % of theory,

C₃₆H₄₅N₇O₅ (655.8)

R_f value: 0.48 (silica gel; dichloromethane/methanol = 9:1)

EKA mass spectrum: (M+H)⁺ = 656

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$$(M+H+Na)^{++} = 339.8$$

$$(M+Na)^{+} = 678$$

;



Example 111

1-Methyl-2- [N- [4- (N-benzoylamidino) phenyl] -aminomethyl] -
benzimidazol-5-yl-carboxylic acid-N- (2-pyridyl) -N- (2-
5 methoxycarbonylethyl) -amide

Prepared analogously to Example 90 from 1-methyl-2- [N- (4-
amidinophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic
acid-N- (2-pyridyl) -N- (2-methoxycarbonylethyl) -amide-
10 hydrochloride and benzoyl chloride.
Yield: 62 % of theory,
 $C_{33}H_{31}N_7O_4$ (589.7)
 R_f value: 0.50 (silica gel; dichloromethane/methanol = 9:1)
EKA mass spectrum: $(M+H)^+$ = 590
15 $(M+Na)^+$ = 612

Example 112

1-Methyl-2- [N- [4- (N-nicotinoylamidino) phenyl] aminomethyl] -
20 benzimidazol-5-yl-carboxylic acid-N- (2-pyridyl) -N- (2-
methoxycarbonylethyl) -amide

Prepared analogously to Example 90 from 1-methyl-2- [N- (4-
amidinophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic
acid-N- (2-pyridyl) -N- (2-methoxycarbonylethyl) -amide-
25 hydrochloride and nicotinic acid chloride.
Yield: 40 % of theory,
 $C_{32}H_{30}N_8O_4$ (590.7)
 R_f value: 0.47 (silica gel; dichloromethane/methanol = 9:1)
30 EKA mass spectrum: $(M+H)^+$ = 591
 $(M+H+Na)^{++}$ = 307
 $(M+Na)^+$ = 613

Example 113

1-Methyl-2- [N- [4- (N-n-hexyloxycarbonylamidino) phenyl] -
aminomethyl] -benzimidazol-5-yl-carboxylic acid-N- (2-
5 pyridyl) -N- (2-ethoxycarbonylethyl) -amide

Prepared analogously to Example 90 from 1-methyl-2- [N- (4-
amidinophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic
acid-N- (2-pyridyl) -N- (2-ethoxycarbonylethyl) -amide-
10 hydrochloride and n-hexyl chloroformate.

Yield: 51 % of theory,

$C_{34}H_{41}N_7O_5$ (627.8)

R_f value: 0.53 (silica gel; dichloromethane/methanol = 9:1)

EKA mass spectrum: $(M+H)^+$ = 628
15 $(M+H+Na)^{++}$ = 325.7
 $(M+2H)^{++}$ = 314.7

Example 114

20 1-Methyl-2- [N- [4- (N-n-octyloxycarbonylamidino) phenyl] -
aminomethyl] -benzimidazol-5-yl-carboxylic acid-N- (2-
pyridyl) -N- (2-ethoxycarbonylethyl) -amide

Prepared analogously to Example 90 from 1-methyl-2- [N- (4-
25 amidinophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic
acid-N- (2-pyridyl) -N- (2-ethoxycarbonylethyl) -amide-
hydrochloride and n-octyl chloroformate.

Yield: 57 % of theory,

$C_{36}H_{45}N_7O_5$ (655.8)

30 R_f value: 0.46 (silica gel; dichloromethane/methanol
= 9:1)

EKA mass spectrum: $(M+H)^+$ = 656
 $(M+H+Na)^{++}$ = 339.7
 $(M+2H)^{++}$ = 328.7

Example 115

- 1-Methyl-2-[N-[4-[N-(2-methylsulphonyl-
ethyloxycarbonyl)amidino]-phenyl]-aminomethyl]-
5 benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-
ethoxycarbonylmethyl-amide

-
- Prepared analogously to Example 90 from 1-methyl-2-[N-(4-
amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic
10 acid-N-(2-pyridyl)-N-ethoxycarbonylmethyl-amide-
hydrochloride and 2-(methylsulphonyl)-ethyl chloroformate.
Yield: 72 % of theory,
 $C_{30}H_{33}N_7O_7S$ (635.7)
 R_f value: 0.23 (silica gel; dichloromethane/ethanol = 19:1)
15 EKA mass spectrum: $(M+H)^+$ = 636
 $(M+H+Na)^{++}$ = 329.8

Example 116

- 20 1-Methyl-2-[N-[4-(N-cyclohexyloxycarbonylamidino)-
phenyl]aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-
pyridyl)-N-methoxycarbonylmethyl-amide

-
- Prepared analogously to Example 90 from 1-methyl-2-[N-(4-
25 amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic
acid-N-(2-pyridyl)-N-methoxycarbonylmethyl-amide-
hydrochloride and cyclohexyl chloroformate.
Yield: 40 % of theory,
 $C_{32}H_{35}N_7O_5$ (597.7)
30 R_f value: 0.26 (silica gel; dichloromethane/ethanol = 19:1)
EKA mass spectrum: $(M+H)^+$ = 598
 $(M+Na)^+$ = 620

Example 117

1-Methyl-2-[N-[4-(N-methoxycarbonylamidino)-phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-ethoxycarbonylmethyl-amide

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-ethoxycarbonylmethyl-amide-hydrochloride and methyl chloroformate.

Yield: 62 % of theory,

$C_{28}H_{29}N_7O_5$ (543.6)

R_f value: 0.19 (silica gel; dichloromethane/ethanol = 19:1)

EKA mass spectrum: $(M+H)^+$ = 544

$(M+H+Na)^{++}$ = 283.8

$(M+Na)^+$ = 566

Example 118

1-Methyl-2-[N-[4-(N-ethoxycarbonylamidino)-phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-methoxycarbonylmethyl-amide

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-methoxycarbonylmethyl-amide-hydrochloride and ethyl chloroformate.

Yield: 42 % of theory,

$C_{28}H_{29}N_7O_5$ (543.6)

R_f value: 0.20 (silica gel; dichloromethane/ethanol = 19:1)

EKA mass spectrum: $(M+H)^+$ = 544

Example 121

1-Methyl-2- [N- [4- (N-n-octyloxycarbonylamidino) -phenyl] -
N-methyl-aminomethyl] -benzimidazol-5-yl-carboxylic acid-
5 N- (2-pyridyl) -N- (2-ethoxycarbonylethyl) -amide

Prepared analogously to Example 90 from 1-methyl-2- [N- (4-
amidinophenyl) -N-methyl-aminomethyl] -benzimidazol-5-yl-
carboxylic acid-N- (2-pyridyl) -N- (2-ethoxycarbonylethyl) -
10 amide-hydrochloride and n-octyl chloroformate.

Yield: 36 % of theory,

$C_{37}H_{47}N_7O_5$ (669.8)

EKA mass spectrum: $(M+H)^+$ = 670

$(M+H+Na)^{++}$ = 346.8

15 $(M+2H)^{++}$ = 335.6

Example 122

1-Methyl-2- [N- [4- (N-n-butyloxycarbonylamidino) -phenyl] -
20 N-methyl-aminomethyl] -benzimidazol-5-yl-carboxylic acid-
N- (2-pyridyl) -N- (2-ethoxycarbonylethyl) -amide

Prepared analogously to Example 90 from 1-methyl-2- [N- (4-
amidinophenyl) -N-methyl-aminomethyl] -benzimidazol-5-yl-
25 carboxylic acid-N- (2-pyridyl) -N- (2-ethoxycarbonylethyl) -
amide-hydrochloride and n-butyl chloroformate.

Yield: 34 % of theory,

$C_{33}H_{39}N_7O_5$ (613.7)

EKA mass spectrum: $(M+H)^+$ = 614

30 $(M+H+Na)^{++}$ = 318.7

$(M+Na)^+$ = 636

Example 123

1-Methyl-2-[N-[4-(N-benzoylamidino)phenyl]-N-methyl-amino-
methyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-
5 N-(2-ethoxycarbonylethyl)-amide

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-
amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-
carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-
10 amide-hydrochloride and benzoyl chloride.

Yield: 63 % of theory,

C₃₅H₃₅N₇O₄ (617.7)

EKA mass spectrum: (M+H)⁺ = 618

(M+H+Na)⁺⁺ = 320.7

15 (M+Na)⁺ = 640

Example 124

1-Methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-
20 (1-ethoxycarbonylmethyl-cyclohex-1-yl)-ketone-hydrochloride

a) 4-Chlorophenyl-(1-hydroxycarbonylmethyl-cyclohex-1-yl)-
ketone

8.4 g (40 mMol) of 3-(4-chlorobenzoyl)-propionic acid were
25 dissolved in 300 ml of tetrahydrofuran and 5.8 g (120 mMol)
of sodium hydride (50-60% suspension in paraffin oil) were
added in batches. Then the mixture was refluxed for 1.5
hours with stirring, after which 8.9 ml (60 mMol) of 1,5-
diiodopentane were added dropwise and boiling was continued
30 for a further three hours. After cooling the solution was
stirred into 200 ml of ice-water, then the tetrahydrofuran
was distilled off in vacuo, the resulting aqueous solution
was acidified with 2N hydrochloric acid and extracted three
times with 150 ml of dichloromethane. The organic phase
35 was dried and evaporated down, the crude product thus
obtained was purified by column chromatography (500 g
silica gel; eluant: dichloromethane with 1-2% ethanol).

Example 119

1-Methyl-2-[N-[4-(N-n-octyloxycarbonyl-amidino)-
phenyl]aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-
5 pyridyl)-N-(2-ethoxycarbonylethyl)-amide

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-
amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic
acid-N-(3-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-
10 hydrochloride and n-octyl chloroformate.

Yield: 35 % of theory,

$C_{36}H_{45}N_7O_5$ (655.8)

R_f value: 0.28 (silica gel; dichloromethane/ethanol = 19:1)

EKA mass spectrum: $(M+H)^+$ = 656

15 $(M+2H)^{++}$ = 328.7

Example 120

1-Methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)-phenyl]-
20 N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-
N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-
amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-
25 carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-
amide-hydrochloride and n-hexyl chloroformate.

Yield: 58 % of theory,

$C_{35}H_{43}N_7O_5$ (641.2)

R_f value: 0.42 (silica gel; dichloromethane/ethanol = 19:1)

30 EKA mass spectrum: $(M+H)^+$ = 642

$(M+H+Na)^{++}$ = 332.7

Yield: 6.2 g (55% of theory) of oily product,

$C_{15}H_{17}ClO_3$ (280.8)

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

5 b) 4-Chloro-3-nitrophenyl-(1-hydroxycarbonylmethyl-cyclohex-1-yl)-ketone

7.0 g (25 mMol) of 4-chlorophenyl-(1-hydroxycarbonylmethylcyclohex-1-yl)-ketone were added in batches, with stirring, at -5 to -10°C, to 80 ml of fuming nitric acid.

10 The solution was then stirred for a further 10 minutes, then stirred into 200 ml of ice-water, the precipitated product was then washed with water and dried.

Yield: 7.8 g (96% of theory),

$C_{15}H_{16}ClNO_5$ (325.8)

15 R_f value: 0.41 (silica gel; petroleum ether/ethyl acetate 4:6)

c) 4-Methylamino-3-nitrophenyl-(1-hydroxycarbonylmethyl-cyclohex-1-yl)-ketone

20 7.8 g (23.9 mMol) of 4-chloro-3-nitrophenyl-(1-hydroxycarbonylmethyl-cyclohex-1-yl)-ketone were stirred in 100 ml of a 40% aqueous methylamine solution at room temperature for 14 hours, then diluted with about 150 ml of water and made slightly acidic with glacial acetic acid.

25 The precipitated product was suction filtered, washed with water and dried.

Yield: 7.1 g (93% of theory),

$C_{16}H_{20}N_2O_5$ (320.4)

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

30

d) 4-Methylamino-3-nitrophenyl-(1-methoxycarbonylmethyl-cyclohex-1-yl)-ketone

4.9 g (15 mMol) of 4-methylamino-3-nitrophenyl-(1-hydroxycarbonylmethyl-cyclohex-1-yl)-ketone were dissolved
35 in 100 ml of tetrahydrofuran, 2.4 g (15 mMol) of 1,1'-carbonyl-diimidazole were added and the mixture was refluxed for 15 minutes. Then the solvent was evaporated

off, 30 ml of methanol were added and the mixture was
boiled for three hours with stirring. After the methanol
had been distilled off the crude product thus obtained was
purified by column chromatography (250 g silica gel,
5 eluant: dichloromethane with 1 to 5% ethanol).
Yield: 2.4 g (48% of theory),
 $C_{17}H_{22}N_2O_5$ (334.4)
 R_f value: 0.76 (silica gel; dichloromethane/ethanol = 19:1)

10 e) 3-Amino-4-methylaminophenyl-(1-methoxycarbonylmethyl-
cyclohex-1-yl)-ketone

2.4 g (7.2 mMol) of 4-methylamino-3-nitrophenyl-(1-
methoxycarbonylmethyl-cyclohex-1-yl)-ketone were
catalytically hydrogenated in 100 ml of methanol at room
15 temperature under 5 bar hydrogen pressure (10% palladium on
charcoal). The crude product thus obtained was further
reacted without purification.
Yield: 2.1 g (96% of theory),
 R_f value: 0.34 (silica gel; dichloromethane/ethanol = 19:1)

20

f) 3-(4-Cyanophenyloxyacetyl-amino)-4-methylaminophenyl-
(1-methoxycarbonylmethyl-cyclohex-1-yl)-ketone

620 mg (3.5 mMol) of 4-cyanophenyloxyacetic acid and 570 mg
(3.5 mMol) of 1,1'-carbonyl-diimidazole were refluxed in
25 50 ml of tetrahydrofuran for 15 minutes. Then 1.0 g (3.28
mMol) of 3-amino-4-methylaminophenyl-(1-methoxycarbonylme-
thyl-cyclohex-1-yl)-ketone were added and the mixture was
boiled for a further 4 hours. Then the solvent was
evaporated off and the crude product thus obtained was
30 purified by column chromatography (150 g silica gel;
eluant: dichloromethane with 0 to 2% ethanol).
Yield: 1.4 g (93% of theory),
 $C_{26}H_{29}N_3O_5$ (463.5)
 R_f value: 0.44 (silica gel; dichloromethane/ethanol = 19:1)

35

g) 1-Methyl-2-[(4-cyanophenyl)oxymethyl]-benzimidazol-5-yl-(1-methoxycarbonylmethyl-cyclohex-1-yl)-ketone

1.4 g (3.02 mMol) of 3-(4-cyanophenyloxyacetyl amino)-4-methylaminophenyl-(1-methoxycarbonylmethyl-cyclohex-1-yl)-ketone were refluxed in 50 ml of glacial acetic acid for one hour. Then the glacial acetic acid was distilled off, the residue was mixed with 20 ml of water and made alkaline with concentrated ammonia. This solution was extracted three times with 20 ml of dichloromethane, the organic extracts were dried and evaporated down. The crude product thus obtained was purified by column chromatography (100 g silica gel; eluant: dichloromethane with 0 to 2% ethanol). Yield: 700 mg (52% of theory),
 $C_{26}H_{27}N_3O_4$ (445.5)

15

h) 1-Methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-(1-ethoxycarbonylmethyl-cyclohex-1-yl)-ketone-hydrochloride

Prepared analogously to Example 25d from 700 mg (1.57 mMol) of 1-methyl-2-(4-cyanophenyloxy methyl)-benzimidazol-5-yl-(1-methoxycarbonylmethyl-cyclohex-1-yl)-ketone with ethanolic hydrochloric acid and ammonium carbonate. Yield: 390 mg (50% of theory),
 $C_{27}H_{32}N_4O_4$ (476.6)

25 EKA mass spectrum: $(M+H)^+ = 477$

1H -NMR spectrum(d_6 -DMSO): 1.10 (t, 3H); 1.0-2.15 (m, 10H); 3.36 (s, 3H); 3.90 (s, 2H); 3.94 (q, 2H); 5.60 (s, 2H); 7.25-7.40 (m, 3H); 7.56-7.75 (m, 2H); 7.90 (d, 2H); 9.20 (broad s, 4H) ppm.

Example 125

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-tert.butyl-ketone-hydrochloride

5

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-tert.butyl-ketone, ethanolic hydrochloric acid, ethanol and ammonium carbonate.

10 Yield: 59 % of theory,

$C_{21}H_{25}N_5O$ (363.5)

EKA mass spectrum: $(M+H)^+ = 364$

Example 126

15

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-(1-methylcyclopent-1-yl)-ketone-hydrochloride

20

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-(1-methylcyclopent-1-yl)-ketone, ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 63.5 % of theory,

$C_{23}H_{27}N_5O$ (389.5)

25 EKA mass spectrum: $(M+H)^+ = 390$

Example 127

2-[(4-amidinophenyl)sulphinylmethyl]-benzothiazol-5-yl-
carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-
5 hydrochloride

A solution of 0.15 g (0.27 mMol) of 2-[(4-
amidinophenyl)thiomethyl]-benzothiazol-5-yl-carboxylic
acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride
10 in 10 ml of acetic acid was mixed with 0. [sic] ml (about
0.81 mMol) of 30% hydrogen peroxide solution and stirred at
room temperature. After 4 days a further 0.18 ml of
hydrogen peroxide solution was added and the resulting
mixture was stirred for a further two days. After removal
15 of the solvent *in vacuo* the crude product obtained was
purified by flash chromatography (silica gel; methylene
chloride/ethanol = 10:1 to 4:1).

Yield: 58 % of theory,

$C_{27}H_{26}N_4O_4S_2$ (534.66)

20 R_f value: 0.24 (silica gel; methylene chloride/ethanol
= 4:1
+ a few drops of acetic acid)

EKA mass spectrum: $(M+H)^+ = 535$

25 Example 128

1-Methyl-2-[(4-amidinophenyl)sulphonylmethyl]-benzimidazol-
5-yl-carboxylic acid-N-(n-propyl)-N-(2-
ethoxycarbonylethyl)-amide-hydrochloride
30

A solution of 0.40 g (0.70 mMol) of 1-methyl-2-[(4-
amidinophenyl)thiomethyl]-benzimidazol-5-yl-carboxylic
acid-N-(n-propyl)-N-(2-ethoxycarbonylethyl)-amide-
hydrochloride in 10 ml of formic acid was mixed with 2 ml
35 of 30% hydrogen peroxide solution and the mixture was
stirred for 16 hours at room temperature. Then the solvent
was distilled off *in vacuo*, whereupon the desired compound

was obtained as a beige solid (contaminated with some 1-methyl-2-[(4-amidinophenyl)sulfinylmethyl]-benzimidazol-5-yl-carboxylic acid-N-(n-propyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride).

5 Yield: 95 % of theory,

$C_{25}H_{31}N_6O_5S$ (513.62)

R_f value: 0.50 (silica gel; ethyl acetate/ethanol/1N hydrochloric acid

= 50:45:5)

10 EKA mass spectrum: $(M+H)^+ = 514$

Example 129

2-[N-(4-amidinophenyl)-aminomethyl]-thiazolo[5,4-b]pyridin-
15 6-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

a) Methyl 5-amino-6-chloro-nicotinate

A solution of 1.08 g (5.00 mMol) of methyl 6-chloro-5-nitro-nicotinate (see A.H. Berrie, G.T. Newbold, F.S. Spring in J. Chem. Soc., 2590, 1951) in [sic] ml of absolute ethanol was mixed successively with 0.53 ml (29 mMol) of water, 3.2 g (57 mMol) of iron powder and 0.030 ml of concentrated hydrochloric acid and heated to boiling for
25 one hour. Then equal quantities of water, iron powder and hydrochloric acid were added and the mixture was heated to boiling for 30 minutes. The precipitate formed on cooling was filtered off and washed with ethanol and the solvent was distilled off *in vacuo*.

30 Yield: 0.75 g (81% of theory) of greenish-yellow solid,
 R_f value: 0.31 (silica gel;ethyl acetate/petroleum ether = 1:4)

$C_7H_7ClN_2O_2$ (186.60)

YEF- Mass spectrum: $M^+ = 186$ and 188 (chlorine isotopes).

b) Methyl 6-chloro-5-methoxyacetamido-nicotinate

A solution of 0.75 g (4.02 mMol) of methyl 5-amino-6-chloro-nicotinate and 0.43 g = 0.35 ml (4.5 mMol) of methoxyacetylchloride in 20 ml of chlorobenzene was stirred for one hour at 110°C. After the solvent had been removed *in vacuo* the crude product obtained was purified by flash chromatography (silica gel; methylene chloride/ethanol = 100:1), evaporated down again *in vacuo* and then digested with petroleum ether.

Yield: 0.55 g (53% of theory) light yellow amorphous solid, R_f value: 0.33 (silica gel; ethyl acetate/petroleum ether = 1:4)

c) Methyl 2-methoxymethyl-thiazolo[5,4-b]pyridin-6-yl-carboxylate

A mixture of 0.53 g (2.05 mMol) of methyl 6-chloro-5-methoxyacetamido-nicotinate and 0.42 g (1.0 mMol) of Lawessons reagent was refluxed for 16 hours in 25 ml of xylene. After the solvent had been removed *in vacuo* the crude product obtained was purified by flash chromatography (silica gel; methylene chloride/ethanol = 100:1) and evaporated down again *in vacuo*.

Yield: 0.33 g (67% of theory) of yellow amorphous solid, R_f value: 0.52 (silica gel; ethyl acetate/petroleum ether = 1:4)

d) 2-Methoxymethyl-thiazolo[5,4-b]pyridin-6-yl-carboxylic acid

A mixture of 1.1 g (4.62 mMol) of methyl 2-methoxymethyl-thiazolo[5,4-b]pyridine-6-carboxylate and 9.2 ml of 2N sodium hydroxide solution were stirred into 50 ml of ethanol for one hour at room temperature. Then 9.2 ml of 2N hydrochloric acid were added, the alcohol was distilled off, and it was diluted with 20 ml of water. The aqueous phase was acidified with concentrated hydrochloric acid

whilst cooling with ice, the beige precipitate formed was filtered off, then washed with water and dried.

Yield: 1.03 g (100% of theory),

R_f value: 0.10 (silica gel; ethyl acetate/petroleum ether =
5 3:7)

e) 2-Methoxymethyl-thiazolo[5,4-b]pyridin-6-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide

A suspension of 1.03 g (4.62 mMol) of 2-methoxymethyl-
10 thiazolo[5,4-b]pyridin-6-yl-carboxylic acid in 40 ml of methylene chloride was mixed with 1.6 g = 1.0 ml (13.5 mMol) of thionyl chloride and refluxed for 90 minutes, during which time the solid gradually dissolved. After the liquid components had been distilled off the crude product
15 was taken up twice more in methylene chloride and concentrated again. The resulting crude acid chloride (1.2 g) was taken up in 40 ml of tetrahydrofuran, added dropwise to a mixture of 0.94 g (4.86 mMol) of N-(2-ethoxycarbonylethyl)aniline and 2.1 ml (13.8 mMol) of
20 triethylamine in 30 ml of tetrahydrofuran and stirred for 2 hours at room temperature. Then it was diluted with 200 ml of ethyl acetate, washed with 100 ml of 14% saline solution and the organic phase was dried with sodium sulphate. After the solvent had been removed *in vacuo* the crude
25 product obtained was purified by flash chromatography (silica gel; methylene chloride/ethanol = 100:1).

Yield: 1.57 g (87% of theory) of yellow oil,

R_f value: 0.55 (silica gel; methylene chloride/ethanol =
19:1)

30

f) 2-[N-(4-Cyanophenyl)-aminomethyl]-thiazolo[5,4-b]-pyridin-6-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide

A mixture of 1.54 g (3.85 mMol) of 2-methoxymethyl-
35 thiazolo[5,4-b]pyridin-6-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide and 4.3 ml (4.3 mMol) of a 1 molar solution of boron tribromide in methylene chloride

was dissolved in a further 30 ml of methylene chloride and stirred for 5 hours at room temperature. Then the mixture was washed with 40 ml of saturated sodium hydrogen carbonate solution, the organic phase was dried with sodium sulphate and the solvent was distilled off. The crude product (1.9 g) was taken up in 15.0 ml of N,N-diisopropylethylamine, mixed with 0.50 g (4.2 mMol) of 4-aminobenzonitrile and heated to boiling for one hour. Then the solvent was distilled off *in vacuo*, the crude product was taken up in 100 ml of methylene chloride, the organic phase was washed with 100 ml of water and dried with sodium sulphate. After the solvent had been removed *in vacuo* the crude product obtained was purified by flash chromatography (silica gel; ethyl acetate/petroleum ether = 35:65 to 1:1) and evaporated down again *in vacuo*.

Yield: 0.45 g (24% of theory) of yellow amorphous solid, R_f value: 0.34 (silica gel; ethyl acetate/petroleum ether = 1:1)

g) 2-[N-(4-amidinophenyl)-aminomethyl]-thiazolo[5,4-b]-pyridin-6-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride
0.39 g (0.803 mMol) of 2-[N-(4-cyanophenyl)-aminomethyl]-thiazolo[5,4-b]pyridin-6-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide were stirred in 40 ml of ethanol saturated with hydrogen chloride for 5 hours first at 0°C and then at room temperature, until no more starting material could be detected by thin layer chromatography. Then the solvent was distilled off at a maximum bath temperature of 30°C, the oily residue was taken up in 40 ml of absolute ethanol and mixed with 0.5 g ammonium carbonate. After 18 hours the solvent was removed *in vacuo* and the crude product obtained was purified by flash chromatography (silica gel; methylene chloride/ethanol = 9:1 to 4:1).

Yield: 78 % of theory of yellow foam,

$C_{26}H_{26}N_6O_3S$ (502.60)

R_f value: 0.19 (silica gel; methylene chloride/ethanol
= 4:1
+ a few drops of acetic acid)

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

Example 130

1-Methyl-2-[(4-amidinophenyl)methylthio]-benzimidazol-5-yl-
10 carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-
hydrochloride

a) 1-Methyl-2-mercapto-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide

15 A solution of 6.5 g (19 mMol) of 3-amino-4-methylamino-
benzoic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide and
4.5 g (22.8 mMol) of N,N'-thiocarbonyldiimidazole were
dissolved in 100 ml of tetrahydrofuran under a nitrogen
atmsphere, the solution was heated to 90°C for 4 hours and
20 left to stand for 16 hours at room temperature. After
removal of the solvent *in vacuo* the crude product obtained
was purified by flash chromatography (silica gel; petroleum
ether/ethyl acetate = 100:0 to 65:35).

Yield: 6.8 g (93 % of theory) of beige crystalline solid,

25 R_f value: 0.55 (silica gel; ethyl acetate)

b) 1-Methyl-2-[(4-cyanophenyl)methylthio]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide

A solution of 1.30 g (3.4 mMol) of 1-methyl-2-mercapto-
30 benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-
ethoxycarbonylethyl)-amide, 0.52 g (3.74 mMol) of potassium
carbonate and 0.66 g (3.4 mMol) of 4-bromo-
methylbenzonitrile were dissolved in 40 ml of absolute
ethanol, stirred for 4 hours at 60°C and 16 hours at room
35 temperature. Then the solvent was distilled off *in vacuo*,
the crude product was taken up in 30 ml of methylene
chloride, washed with 40 ml of water and dried with sodium

sulphate. After filtration and distillation of the solvent the desired compound was obtained as a beige-white solid.

Yield: 1.8 g (100 % of theory),

R_f value: 0.64 (silica gel; ethyl acetate)

5

c) 1-Methyl-2-[(4-amidinophenyl)methylthio]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

1.5 g (3.0 mMol) of 1-methyl-2-[(4-cyanophenyl)methylthio]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide were stirred in 80 ml of ethanol saturated with hydrogen chloride for 6.5 hours first at 0°C, then at room temperature, until no more starting material could be detected by thin layer chromatography.

15 Then the solvent was distilled off at a maximum bath temperature of 30°C, the oily residue taken up in 80 ml of absolute ethanol and mixed with 1.0 g (10.5 mMol) of ammonium carbonate. After 18 hours the solvent was distilled off in vacuo and the crude product obtained was purified by flash chromatography (silica gel; methylene chloride/ethanol = 19:1 to 10:1).

Yield: 78 % of theory of light beige solid,

C₂₈H₂₉N₅O₃S (515.63)

R_f value: 0.19 (silica gel; methylene chloride/ethanol = 4:1)

EKA mass spectrum: (M+H)⁺ = 516

(M+H+Na)⁺⁺ = 269.7

(M+2H)⁺⁺ = 258.7

30 Example 131

1-Methyl-2-[(4-amidinophenyl)methylthio]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide-hydrochloride

35

Prepared analogously to Example 10 from 1-methyl-2-[(4-amidinophenyl)methylthio]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.

5 Yield: 57 % of theory,

$C_{26}H_{25}N_5O_3S$ (487.58)

R_f value: 0.23 (Reversed Phase silica gel RP-8; Methanol/5% saline solution = 6:4)

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

10 $(M+Na)^+$ = 510

$(M+Na+H)^{++}$ = 255.6

Example 132

15 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-propargyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-propargyl-N-(2-ethoxycarbonylethyl)-amide, ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 81 % of theory,

$C_{25}H_{28}N_6O_3$ (460.6)

25 R_f value: 0.094 (silica gel; dichloromethane/ethanol = 4:1)

EKA mass spectrum: $(M+H)^+$ = 461

$(M+H+Na)^{++}$ = 242

$(M+2H)^{++}$ = 231

30 Example 133

1-Methyl-2-[2-[4-(N-n-hexyloxycarbonylamidino)phenyl]ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

35

Prepared analogously to Example 90 from 1-methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and n-hexyl chloroformate.

5 Yield: 72 % of theory,

$C_{35}H_{42}N_6O_5$ (626.8)

R_f value: 0.54 (silica gel; dichloromethane/methanol = 9:1)

EKA mass spectrum: $(M+H)^+ = 627$

$(M+Na)^+ = 649$

10

Example 134

1-Methyl-2-[2-[4-(N-benzoylamidino)phenyl]ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

15

Prepared analogously to Example 90 from 1-methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and benzoyl chloride.

20

Yield: 79 % of theory,

$C_{35}H_{34}N_6O_4$ (602.7)

R_f value: 0.52 (silica gel; dichloromethane/methanol = 9:1)

EKA mass spectrum: $(M+H)^+ = 603$

25

$(M+Na)^+ = 625$

Example 135

1-Methyl-2-[2-[4-(N-nicotinoylamidino)phenyl]ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

30

Prepared analogously to Example 90 from 1-methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and nicotinic acid chloride.

35

Yield: 56 % of theory,

$C_{34}H_{33}N_7O_4$ (603.7)

R_f value: 0.52 (silica gel; dichloromethane/methanol = 9:1)

EKA mass spectrum: $(M+H)^+ = 604$

5 $(M+Na)^+ = 626$

Example 136

10 1-Cyclopropyl-2-[N-(4-amidinophenyl)-aminomethyl]-
benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-
ethoxycarbonylethyl)-amide-hydrochloride

Prepared analogously to Example 25d from 1-Cyclopropyl-2-
15 [N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-
carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide,
ethanolic hydrochloric acid, ethanol and ammonium
carbonate.

Yield: 31 % of theory,

20 $C_{30}H_{33}N_6O_3$ (524.6)

R_f value: 0.40 (silica gel; dichloromethane/methanol = 5:1)

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

$(M+H+Na)^{++} = 274$

$(M+2H)^{++} = 263$

25

Example 137

1-Cyclopropyl-2-[N-(4-amidinophenyl)-aminomethyl]-
benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-
30 hydroxycarbonylethyl)-amide

Prepared analogously to Example 26 from 1-cyclopropyl-2-[N-
(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic
acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride
35 and sodium hydroxide solution.

Yield: 64 % of theory,

$C_{28}H_{28}N_6O_3$ (496.6)

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

$(M+H+Na)^{++}$ = 260

$(M+Na)^+$ = 519

5

$(M+2Na)^{++}$ = 271

Example 138

1-Methyl-2- [N- (4-amidinophenyl) -N- (n-butyl) -aminomethyl] -
benzimidazol-5-yl-carboxylic acid-N-phenyl-N- (2-
5 ethoxycarbonylethyl) -amide-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2- [N- (4-
cyanophenyl) -N- (n-butyl) -aminomethyl] -benzimidazol-5-yl-
carboxylic acid-N-phenyl-N- (2-ethoxycarbonylethyl) -amide,
10 ethanolic hydrochloric acid, ethanol and ammonium
carbonate.

Yield: 62 % of theory,

$C_{32}H_{38}N_6O_3$ (554.7)

EKA mass spectrum: $(M+H)^+$ = 555
15 $(M+H+Na)^{++}$ = 289
 $(M+2H)^{++}$ = 278

Example 139

20 1-Methyl-2- [N- (4-amidino-2-chloro-phenyl) -aminomethyl] -
benzimidazol-5-yl-carboxylic acid-N-phenyl-N- (2-
ethoxycarbonylethyl) -amide-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2- [N- (4-
25 cyano-2-chloro-phenyl) -aminomethyl] -benzimidazol-5-yl-
carboxylic acid-N-phenyl-N- (2-ethoxycarbonylethyl) -amide,
ethanolic hydrochloric acid, ethanol and ammonium
carbonate.

Yield: 82 % of theory,

30 $C_{28}H_{29}ClN_6O_3$ (533.1)

EKA mass spectrum: $(M+H)^+$ = 533/5
 $(M+H+Na)^{++}$ = 278/9

Example 140

1-Methyl-2- [N- [4- (n-octyloxycarbonylamidino)phenyl] -
aminomethyl] -benzimidazol-5-yl-carboxylic acid-N-phenyl-N-
5 (2-ethoxycarbonylethyl) -amide

Prepared analogously to Example 90 from 1-methyl-2- [N- (4-
amidinophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic
acid-N-phenyl-N- (2-ethoxycarbonylethyl) -amide-hydrochloride
10 and n-octyl chloroformate.

Yield: 34 % of theory,

$C_{37}H_{46}N_6O_5$ (654.8)

R_f value: 0.15 (silica gel; dichloromethane/ethanol = 19:1)

EKA mass spectrum: $(M+H)^+$ = 655
15 $(M+H+Na)^{++}$ = 339
 $(M+Na)^+$ = 677

Example 141

20 1-Methyl-2- [N- (4-amidino-2-ethyl-phenyl) -aminomethyl] -
benzimidazol-5-yl-carboxylic acid-N-phenyl-N- (2-
ethoxycarbonylethyl) -amide-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2- [N- (4-
25 cyano-2-ethyl-phenyl) -aminomethyl] -benzimidazol-5-yl-
carboxylic acid-N-phenyl-N- (2-ethoxycarbonylethyl) -amide,
ethanolic hydrochloric acid, ethanol and ammonium
carbonate.

Yield: 61 % of theory

30 $C_{30}H_{34}N_6O_3$ (526.6)

EKA mass spectrum: $(M+H)^+$ = 527
 $(M+H+Na)^{++}$ = 275
 $(M+2H)^{++}$ = 264

Example 142

1-Methyl-2- [N- (4-amidinophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic acid-benzylamide-hydrochloride

5

Prepared analogously to Example 25d from 1-methyl-2- [N- (4-cyanophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic acid-benzylamide, ethanolic hydrochloric acid, ethanol and ammonium carbonate.

10 Yield: 63 % of theory,

$C_{24}H_{24}N_6O$ (412.5)

R_f value: 0.76 (silica gel; dichloromethane/ethanol = 4:1)

EKA mass spectrum: $(M+H)^+ = 413$

15 Example 143

1-Methyl-2- [N- [4- (N- (2- (2-ethoxyethoxy) ethyloxy) -carbonylamidino) -phenyl] -aminomethyl] -benzimidazol-5-yl-carboxylic acid-N- (2-pyridyl) -N- (2-ethoxycarbonylethyl) -amide

20

Prepared analogously to Example 90 from 1-methyl-2- [N- (4-amidinophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic acid-N- (2-pyridyl) -N- (2-ethoxycarbonylethyl) -amide-hydrochloride and diethyleneglycolmonoethylether chloroformate.

25

Yield: 43 % of theory,

$C_{34}H_{41}N_7O_7$ (659.8)

R_f value: 0.56 (silica gel; dichloromethane/methanol = 9:1)

30 EKA mass spectrum: $(M+H)^+ = 660$

$(M+H+Na)^{++} = 341.7$

Example 144

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(1-methylpyrazol-4-yl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide, ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 60 % of theory,

$C_{26}H_{30}N_8O_3$ (502.6)

R_f value: 0.13 (silica gel; dichloromethane/ethanol = 4:1)

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

$(M+H+Na)^{++}$ = 263

$(M+2H)^{++}$ = 252

Example 145

20

3-Methyl-2-[(4-amidinophenyl)-thiomethyl]-imidazo[4,5-b]-pyridin-6-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

Prepared analogously to Example 1 from 3-methyl-2-[(4-cyanophenyl)thiomethyl]-imidazo[4,5-b]pyridin-6-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide, ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 88 % of theory,

$C_{27}H_{28}N_6O_3S$ (516.63)

R_f value: 0.23 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5)

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

$(M+H+Na)^{++}$ = 270

Example 146

3-Methyl-2- [N- (4-amidinophenyl) -aminomethyl] -
5 imidazo[4,5-b]pyridin-6-yl-carboxylic acid-N-phenyl-N-
(2-ethoxycarbonylethyl) -amide-hydrochloride

Prepared analogously to Example 1 from 3-methyl-2- [N- (4-
cyanophenyl) -aminomethyl] -imidazo[4,5-b]pyridin-6-yl-
10 carboxylic acid-N-phenyl-N- (2-methoxycarbonylethyl) -amide,
ethanolic hydrochloric acid, ethanol and ammonium
carbonate.

Yield: 82 % of theory,

$C_{27}H_{29}N_7O_3$ (499.58)

15 R_f value: 0.20 (silica gel; ethyl acetate/ethanol/ammonia =
50:45:5)

EKA mass spectrum: $(M+H)^+$ = 500

$(M+H+Na)^{++}$ = 261.7

20 Example 147

3-Methyl-2- [(4-amidinophenyl) -thiomethyl] -
imidazo[4,5-b]pyridin-6-yl-carboxylic acid-N-phenyl-N-
(2-hydroxycarbonylethyl) -amide-hydrochloride

25 Prepared analogously to Example 2 from 3-methyl-2- [(4-
amidinophenyl) -thiomethyl] -imidazo[4,5-b]pyridin-6-yl-
carboxylic acid-N-phenyl-N- (2-ethoxycarbonylethyl) -amide-
hydrochloride and sodium hydroxide solution.

30 Yield: 88 % of theory,

$C_{25}H_{24}N_6O_3S$ (488.56)

R_f value: 0.21 (silica gel; ethyl acetate/ethanol/ammonia =
50:45:5)

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

35 $(M+Na)^+$ = 511

Example 148

- 5 3-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-
imidazo[4,5-b]pyridin-6-yl-carboxylic acid-N-phenyl-N-
(2-hydroxycarbonylethyl)-amide-hydrochloride

10 Prepared analogously to Example 2 from 3-methyl-2-[N-(4-
amidinophenyl)-aminomethyl]-imidazo[4,5-b]pyridin-6-yl-
carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-
hydrochloride and sodium hydroxide solution.

Yield: 80 % of theory,

$C_{25}H_{25}N_7O_3$ (471.52)

- 15 R_f value: 0.19 (silica gel; ethyl acetate/ethanol/ammonia =
50:45:5)

EKA mass spectrum: $(M+H)^+$ = 472

$(M+Na)^+$ = 494

$(M+2Na)^{++}$ = 258.6

20

Example 149

- 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-
5-yl-sulphonic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-
25 amide-hydrochloride

a) 1-Methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-
5-yl-sulphonic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-
amide

- 30 2.54 g (6,2 mMol) of 3-nitro-4-methylamino-benzenesulphonic
acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide were
hydrogenated at room temperature under 5 bar hydrogen
pressure over palladium/charcoal (10%) in a mixture of
75 ml of ethanol and 75 ml of dichloromethane. The
35 resulting crude 3-amino-4-methylamino-benzenesulphonic
acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide was taken up
in 30 ml of phosphorus oxychloride, without purification,

- then 1.1 g (6,2 mMol) of N-(4-cyanophenyl)-glycine were added and the mixture was refluxed for two hours. After cooling to room temperature the reaction mixture was added to about 70 ml of water with cooling and in this way the excess phosphorus oxychloride was destroyed. The resulting solution was neutralised with solid sodium carbonate and extracted three times with 30 ml of ethyl acetate. After evaporation of the solvent the crude product was purified by column chromatography (100 g silica gel; eluant: cyclohexane/ethyl acetate = 2:3).
- Yield: 860 mg (26.8 % of theory),
Melting point: 188-191°C
 $C_{27}H_{27}N_5O_3S$ (517.6)
 R_f value: 0.52 (silica gel; dichloromethane/methanol = 9:1)
- EKA mass spectrum: $(M+H)^+ = 518$
 $(M+Na)^+ = 540$

- b) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-sulphonic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride
- Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-sulphonic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide, ethanolic hydrochloric acid, ethanol and ammonium carbonate.
- Yield: 87 % of theory,
 $C_{27}H_{30}N_6O_4S$ (534.6)
 R_f value: 0.13 (silica gel; dichloromethane/ethanol = 9:1)
EKA mass spectrum: $(M+H)^+ = 535$
 $(M+H+Na)^{++} = 279$

Example 150

- 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-sulphonic acid-N-(1-methylpyrazol-4-yl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride
-

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-sulphonic acid-N-(1-methylpyrazol-4-yl)-N-(2-ethoxycarbonylethyl)-amide, ethanolic hydrochloric acid, ethanol and ammonium

5 carbonate.

Yield: 38 % of theory,

$C_{25}H_{30}N_8O_4S$ (538.6)

R_f value: 0.09 (silica gel; dichloromethane/ethanol = 9:1)

EKA mass spectrum: $(M+H)^+ = 539$

10

Example 151 ;

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-
5-(2.3-dihydroindol-1-yl-sulphonyl)-benzimidazole-
15 hydrochloride

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-5-(2.3-dihydroindol-1-yl-sulphonyl)-benzimidazole and ethanolic hydrochloric acid,

20 ethanol and ammonium carbonate.

Yield: 15 % of theory,

R_f value: 0.36 (silica gel; dichloromethane/methanol = 4:1)

$C_{24}H_{24}N_6O_2S$ (460.6)

EKA mass spectrum: $(M+H)^+ = 461$

25

Example 152

1-Methyl-2- [N- (4-amidinophenyl) -aminomethyl] -benzimidazole-
5-yl-sulphonic acid-N-phenyl-N- (2-hydroxycarbonylethyl) -
5 amide

Prepared analogously to Example 26 from 1-methyl-
2- [N- (4-amidinophenyl) -aminomethyl] -benzimidazol-5-yl-
sulphonic acid-N-phenyl-N- (2-ethoxycarbonylethyl) -amide-
10 hydrochloride and sodium hydroxide solution.

Yield: 24 % of theory,

R_f value: 0.55 (Reverse-Phase RP-18 silica gel; methanol/5%
saline solution = 3:2)

C₂₅H₂₆N₆O₄S (506.6)

15 EKA mass spectrum: (M+H)⁺ = 507
(M+Na)⁺ = 529
(M+2Na)⁺⁺ = 276

Example 153

20

1-Methyl-2- [N- (4-amidinophenyl) -aminomethyl] -5- (isoindolin-
2-yl-sulphonyl) -benzimidazol-hydrochloride

Prepared analogously to Example 25d from 1-methyl-
25 2- [N- (4-cyanophenyl) -aminomethyl] -5- (isoindolin-2-yl-
sulphonyl) -benzimidazole and ethanolic hydrochloric acid,
ethanol and ammonium carbonate.

Yield: 33 % of theory,

R_f value: 0.32 (silica gel; dichloromethane/methanol = 4:1)

30 C₂₄H₂₄N₆O₂S (460.6)

EKA mass spectrum: (M+H)⁺ = 461

Example 154

2-[2-(4-Amidinophenyl)-ethyl]-quinazolin-7-yl-carboxylic
acid-N-phenyl-N-(2-ethoxycarbonyl-ethyl)-amide-hydrochloride

5

a. Ethyl 4-methyl-3-nitro-benzoate

To a solution of 3 ml of concentrated hydrochloric acid and
4 ml of concentrated sulphuric acid, 4.9 g (0.03 mol) of
ethyl p-tolylate were added dropwise with stirring at 5°C
10 and stirred for 1 hour whilst cooling in an ice-bath. After
heating to ambient temperature the mixture was poured onto
ice-water and extracted with ethyl acetate. The organic
extracts were washed with sodium hydrogen carbonate
solution, dried and evaporated down.

15 Yield: 5.7 g (90 % of theory),

R_f value: 0.81 (silica gel, ethyl acetate/cyclohexane =
1:1)

b. Methyl 4-(2-dimethylaminovinyl)-3-nitro-benzoate

20 1.0 g (4.8 mmol) of ethyl 4-methyl-3-nitro-benzoate, 0.74 g
(6.2 mmol) of dimethylformamide dimethylacetal and 2 ml of
dimethylformamide were heated to 140°C with stirring for 3
hours. Then the solvent was distilled off and the crude
product thus obtained was reacted without any further
25 purification.

Yield: 1.2 g (100 % of theory),

R_f value: 0.54 (silica gel, ethyl acetate/cyclohexane =
1:1)

30 c. Methyl 4-formyl-3-nitro-benzoate

1.2 g (4.8 mmol) of methyl 4-(2-dimethylaminovinyl)-3-
nitro-benzoate were dissolved in 120 ml of
tetrahydrofuran/water (1:1) and after the addition of 3.0 g
(14.3 mmol) of sodium metaperiodate the mixture was
35 stirred for 20 hours at ambient temperature. The suspension
was then diluted with water and methylene chloride and
extracted with methylene chloride. The combined organic

extracts were washed with sodium hydrogen carbonate solution, dried and evaporated down. The residue was chromatographed on silica gel and eluted with ethyl acetate/cyclohexane (1:3).

- 5 Yield: 0.6 g (63 % of theory),
R_f value: 0.63 (silica gel, ethyl acetate/cyclohexane = 1:1)

d. Methyl 3-Amino-4-formyl-benzoate

- 10 To a solution of 25 ml of ethanol/glacial acetic acid/water (2:2:1) were added 0.6 g (2.9 mmol) of methyl 4-formyl-3-nitro-benzoate, 1.2 g (21.4 mmol) of iron powder and 0.01 ml of concentrated hydrochloric acid and the mixture was refluxed with stirring for 15 minutes. Then the iron
15 was separated off, the solution was diluted with water and extracted with methylene chloride. The combined organic extracts were washed with water, dried and evaporated down.

Yield: 0.3 g (58 % of theory),

- 20 R_f value: 0.74 (silica gel, methylene chloride/methanol = 9.5:0.5)

e. Methyl 3-[3-(4-cyanophenyl)-propionylamino]-4-formyl-benzoate

- 25 1.0 g (5.6 mmol) of methyl 3-amino-4-formyl-benzoate and 1.1 g (5.6 mmol) of 4-cyanophenylpropionic acid chloride were dissolved in 50 ml of methylene chloride and after the addition of 0.7 g (5.6 mmol) of N-ethyl-diisopropylamine the mixture was stirred for 24 hours at ambient
30 temperature. Then it was extracted with sodium hydrogen carbonate solution, the combined organic extracts were dried and evaporated down. The residue was chromatographed on silica gel and eluted with ethyl acetate/cyclohexane (1:3).
35 Yield: 0.6 g (32 % of theory),
R_f value: 0.60 (silica gel, ethyl acetate/cyclohexane = 1:1)

f. Methyl 2-[2-(4-cyanophenyl)-ethyl]-quinazoline-7-carboxylate

5 0.6 g (1.8 mmol) of ethyl 3-[3-(4-cyanophenyl)-propionylamino]-4-formyl-benzoate and 10 ml of methanolic ammonia solution were agitated in a pressure vessel for 36 hours. Then the solvent was distilled off, the residue was chromatographed on silica gel and eluted with methylene
10 chloride containing 0 to 1 % methanol.
Yield: 0.35 g (62 % of theory),
R_f value: 0.38 (silica gel, ethyl acetate/cyclohexane = 1:1)

15 g. 2-[2-(4-Cyanophenyl)-ethyl]-quinazolin-7-carboxylic acid
0.3 g (0.94 mmol) of methyl 2-[2-(4-cyanophenyl)-ethyl]-quinazoline-7-carboxylate were dissolved in 4.7 ml of 1N lithium hydroxide solution and 4 ml of tetrahydrofuran and stirred for 3 hours at ambient temperature. Then 4.7 ml of
20 1N hydrochloric acid were added and the mixture was stirred for 30 minutes. The product precipitated was suction filtered, washed with water and dried.
Yield: 0.30 g (100 % of theory),
R_f value: 0.1 (silica gel, ethyl acetate/cyclohexane = 1:1)

25 h. 2-[2-(4-Cyanophenyl)-ethyl]-quinazolin-7-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide

0.4 g (1.3 mmol) of 2-[2-(4-cyanophenyl)-ethyl]-
30 quinazoline-7-carboxylic acid and 5 ml of thionyl chloride were stirred for 60 minutes at 50°C. Then the thionyl chloride was distilled off, the residue was dissolved in methylene chloride, mixed with 0.24 g (1.3 mmol) of methyl
3-(N-phenylamino)-propionate and 0.22 ml of (1.3 mmol) of
35 N-ethyldiisopropylamine and stirred for 18 hours at ambient temperature. After evaporation of the solvent *in vacuo* the

residue was chromatographed on silica gel and eluted with methylene chloride containing 1 % methanol.

Yield: 230 mg (37 % of theory),

R_f value: 0.64 (silica gel, methylene chloride/methanol =
5 9:1)

i. 2-[2-(4-Amidinophenyl)-ethyl]-quinazolin-7-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

10 230 mg (0.5 mmol) of 2-[2-(4-cyanophenyl)-ethyl]-
quinazolin-7-yl-carboxylic acid-N-phenyl-
N-(2-methoxycarbonylethyl)-amide were stirred in 30 ml of
saturated ethanolic hydrochloric acid for 8 hours at
ambient temperature. Then the mixture was evaporated to
15 dryness *in vacuo*, the residue was taken up in 20 ml of
ethanol, combined with 0.5 g (5.0 mmol) of ammonium
carbonate and stirred overnight at ambient temperature.
After evaporation of the solvent the crude product was
chromatographed on silica gel and eluted with methylene
20 chloride/ethanol (4:1).
Yield: 100 mg (39 % of theory),
R_f value: 0.5 (silica gel, methylene chloride/ethanol =
4:1)

C₂₉H₂₉N₅O₃ (495.59)

25 Mass spectrum: (M+H)⁺ = 496

Example 155

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-
30 5-yl-sulphonic acid-N-(1-methylpyrazol-4-yl)-N-(2-
hydroxycarbonylethyl)-amide

Prepared analogously to Example 26 from 1-methyl-2-[N-(4-
35 amidinophenyl)-aminomethyl]-benzimidazol-5-yl-sulphonic
acid-N-(1-methylpyrazol-4-yl)-N-(2-ethoxycarbonylethyl)-
amide-hydrochloride and sodium hydroxide solution.

Yield: 95 % of theory,

$C_{23}H_{26}N_8O_4S$ (510.6)

R_f value: 0.53 (Reversed Phase silica gel RP-18, methanol + 5% saline solution)

5 EKA mass spectrum: $(M+H)^+$ = 511
 $(M+Na)^+$ = 533
 $(M+2Na)^{++}$ = 278

Example 156

10

1-Methyl-2- [N- (3-amidino-pyridin-6-yl) -aminomethyl] -
benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl) -
N- (2-ethoxycarbonylethyl) -amide-hydrochloride

15

a) 3- [(N-tert.Butoxycarbonyl-amino) acetyl amino] -
4-methylamino-benzoic acid-N-(2-pyridyl) -
N-(2-ethoxycarbonylethyl) -amide

20 19.2 g (0.11 mol) of N-tert.butyloxycarbonylglycine were
dissolved in 175 ml of dimethylformamide, mixed with 35.2 g
(0.11 mol) of O-benzotriazol-1-yl) -N,N,N',N' -
tetramethyluronium tetrafluoroborate, 11.0 g of
triethylamine and 34.2 g (0.10 mol) of 3-amino-4-methyl-
25 amino-benzoic acid-N-(2-pyridyl) -N-(2-ethoxycarbonylethyl) -
amide and stirred for 2.5 hours at ambient temperature.
Then the reaction solution was mixed with 5 l of ice water
and stirred for 2 hours. The grey precipitate formed was
filtered off, washed with water, dried and recrystallised
30 from ethyl acetate with the addition of activated charcoal.
Yield: 39.85 g (80 % of theory),
 $C_{25}H_{33}N_5O_6$ (499.6)
 R_f value: 0.55 (silica gel; methylene chloride/ethanol =
19:1)

35

b) 1-Methyl-2-(N-tert.butoxycarbonyl-aminomethyl)-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

10.0 g (0.02 mol) of 3-[(N-tert.butoxycarbonyl-amino)acetyl-amino]-4-methylamino-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide were dissolved in 50 ml of glacial acetic acid and refluxed for one hour. Then the solvent was distilled off, the residue was mixed with ice water and adjusted to pH 8 by the addition of 2N ammonia. After extraction three times with ethyl acetate the combined organic phases were washed with saline solution and dried over sodium sulphate. After evaporation of the solvent the crude product was chromatographed on silica gel, eluting first with methylene chloride, then with methylene chloride/ethanol (50:1) and (25:1). The desired fractions were combined and evaporated down.

Yield: 5.85 g (61 % of theory),

$C_{25}H_{31}N_5O_5$ (481.6)

R_f value: 0.70 (silica gel; methylene chloride/ethanol = 9:1)

c) 1-Methyl-2-aminomethyl-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-trifluoroacetate

4.81 g (0.10 mol) of 1-methyl-2-(N-tert.butoxycarbonyl-aminomethyl)-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide were dissolved in 25 ml of methylene chloride, mixed with 5 ml of trifluoroacetic acid and stirred for 5 hours at ambient temperature. Then the solvent was evaporated off and the residue was stirred with ether. The crystals thus formed were filtered off, washed with ether and dried.

Yield: 3.15 g (68 % of theory),

$C_{20}H_{23}N_5O_3$ (381.4)

R_f value: 0.18 (silica gel; methylene chloride/ethanol = 9:1)

d) 1-Methyl-2-[N-(3-cyano-pyridin-6-yl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

5

1.5 g (3.25 mmol) of 1-methyl-2-aminomethyl-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-trifluoroacetate were stirred into 10 ml of N-ethyl-diisopropylamine and heated to 100°C for 15 minutes. After the addition of 720 mg (5.25 mmol) of 2-chloro-5-cyano-pyridine the reaction mixture was heated to 125°C for 2 hours. After cooling to ambient temperature and stirring with about 20 ml of water, the pH was adjusted to 4 by the addition of 1N hydrochloric acid and the mixture was extracted 3 times with ethyl acetate. The combined organic phases were washed with saline solution and dried over sodium sulphate. After evaporation of the solvent the crude product was chromatographed on silica gel, eluting first with methylene chloride, later with methylene chloride/ethanol (25:1) and (19:1). The desired fractions were combined and evaporated down.

Yield: 1.05 g (67 % of theory),

$C_{26}H_{25}N_7O$ (483.6)

25 Mass spectrum: $(M+H)^+ = 484$

e) 1-Methyl-2-[N-(3-amidino-pyridin-6-yl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

30 Prepared analogously to Example 25d from 1-Methyl-2-[N-(3-cyano-pyridin-6-yl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

35 Yield: 38 % of theory,

$C_{28}H_{28}N_8O_3$ (500.6)

Mass spectrum: $(M+H)^+ = 501$

Example 157

- 5 1-Methyl-2-[N-(4-amidinophenyl)aminomethyl]-indol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide-hydroiodide

-
- a) 4-Nitro-benzoic acid-N-phenyl-N-(2-methoxycarbonylethyl)amide
- 10 16.7 g (0.1 mol) of 4-nitrobenzoic acid were refluxed in 50 ml of thionyl chloride and 3 drops of dimethylformamide for 1 hour. After the solvent had been distilled off in vacuo the crude product was dissolved in 150 ml of
- 15 tetrahydrofuran and added dropwise to a solution of 18 g (0.1 mol) of N-(2-methoxycarbonylethyl)aniline in 250 ml of tetrahydrofuran and 42 ml 0.3 mol) of triethylamine. After being stirred for one hour at ambient temperature the reaction mixture was diluted with 250 ml of ethyl acetate
- 20 and washed 2x with 200 ml of 14% saline solution. After the solvent had been distilled off and the residue chromatographed (silica gel; methylene chloride) a yellow oil was obtained which slowly solidified.
- Yield: 32.6 g (100 % of theory),
- 25 R_f value: 0.37 (silica gel; methylene chloride/methanol = 50:1)

- b) 4-Amino-benzoic acid-N-phenyl-N-(2-methoxycarbonylethyl)amide
- 30 22 g (67 mmol) of 4-nitro-benzoic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide were hydrogenated in 500 ml of methanol with 2 g of 10% palladium on charcoal at 3 bar hydrogen pressure for 3 hours. After filtration and distillation of the solvent the reaction mixture was washed
- 35 with 100 ml of ether and the white crystalline product was further reacted directly.

Yield: 18.6 g (94 % of theory),

R_f value: 0.70 (silica gel; methylene chloride/ethanol = 19:1)

- 5 c) 2-Methyl-3-thiomethyl-indol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide
26.8 g (91 mmol) of 4-amino-benzoic acid-N-phenyl-N-(2-methoxycarbonylethyl)amide were dissolved in 500 ml of methylene chloride, cooled to -70°C and mixed within 30
10 minutes with freshly prepared tert.butylhypochlorite (M. J. Mintz et al., Organic Synthesis, Coll. Vol. 5, page 184). The mixture was stirred for 2 hours at -70°C, then 9.46 g (91 mmol) of methylthioacetone in 40 ml of methylene chloride were added dropwise within 10 minutes and stirring
15 was continued for a further 1.5 hours. Then 12.7 ml (9.1 g, 91 mmol) of triethylamine in 25 ml of methylene chloride were added. The mixture was left for 30 minutes at -78°C and then slowly warmed to ambient temperature overnight. After washing twice with 50 ml of water the organic phase
20 was separated off and dried with sodium sulphate. After removal of the solvent in vacuo a white amorphous substance is obtained after purification by chromatography (silica gel; ethyl acetate/petroleum ether = 2:8 to 3:7).
Yield: 24.1 g (69 % of theory),
25 R_f value: 0.58 (silica gel; ethyl acetate/petroleum ether = 1:1)
C21H22N2O3S (382.49)
Mass spectrum: (M)⁺ = 382

d) 1-tert-Butoxycarbonyl-2-methyl-indol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide

8.9 g (23 mmol) of 2-Methyl-3-thiomethyl-indol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide
5 were dissolved in 600 ml of ethanol, mixed with about 150 mg of Raney nickel and stirred for 2 hours at ambient temperature (analogously to P.G. Gassman et al., Organic Synthesis Coll. Vol. 6, page 601). Then the mixture was filtered and the solvent eliminated *in vacuo*. The crude
10 product thus obtained (8 g) was dissolved in 200 ml of absolute tetrahydrofuran, mixed with 150 mg of dimethylaminopyridine and 6.84 g (32 mmol) of di-tert.butyl pyrocarbonate and stirred for 2.5 hours at 50°C. Then the solvent was distilled off *in vacuo* and the crude product
15 was purified by chromatography (silica gel, ethyl acetate/petroleum ether = 1:4).
Yield: 10.0 g (98 % of theory),
R_f value: 0.40 (silica gel; ethyl acetate/petroleum ether = 3:7)

20

e) 2-[N-(4-Cyanophenyl)aminomethyl]-indol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide

3.5 g (8 mmol) of 1-tert.butoxycarbonyl-2-methyl-indol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-
25 amide were dissolved in 80 ml of carbon tetrachloride, mixed with 1.5 g (8.4 mmol) of N-bromo-succinimide and 20 mg of azobisisobutyronitrile and refluxed for 2.5 hours. Then the still warm solution was filtered, the filtrate obtained was washed with saturated sodium hydrogen
30 carbonate solution and dried with sodium sulphate. After distillation of the solvent the crude product was dissolved in 30 ml of N-ethyl-diisopropylamine, mixed with 1.0 g (8 mmol) of 4-aminobenzonitrile and refluxed for 2.5 hours. The solvent was distilled off *in vacuo* and the residue
35 obtained was purified by chromatography (silica gel; ethyl acetate/petroleum ether = 1:4 to 1:1).

Yield: 1.1 g (30 % of theory),

R_f value: 0.21 (silica gel; ethyl acetate/petroleum ether = 1:1)

5 f. 1-Methyl-2-[N-(4-thiocarbamoyl-phenyl)aminomethyl]-indol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide

1.5 g (3.3 mmol) of 2-[N-(4-cyanophenyl)aminomethyl]-indol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide were dissolved in 60 ml of xylene, mixed with 0.45 g (3.3 mmol) of potassium carbonate and 0.5 ml of (3.3 mmol) of methyl p-toluenesulphonate and refluxed for 4 hours. Then the same amounts of potassium carbonate and methyl toluenesulphonate were added a second time and the mixture was refluxed overnight. It was filtered and washed with acetone. After concentration of the filtrate thus obtained, the residue obtained was purified by chromatography (silica gel; ethyl acetate/petroleum ether = 1:4 to 2:3). The N-methylated indole obtained (yield: 0.64 g, 41 % of theory) was dissolved in 20 ml of pyridine and mixed with 0.67 ml (1.37 mmol) of triethylamine. Then hydrogen sulphide gas was introduced into the solution thus obtained. After 4.5 days nitrogen was passed through the reaction solution for 30 minutes, the solvent was distilled off and the residue obtained was purified by chromatography (silica gel; methylene chloride/ethanol 99:1 to 98:2).

Yield: 0.30 g (43 % of theory),

C₂₈H₂₈N₄O₃S (500.62)

EKA mass spectrum: (M+H)⁺ = 501

30 (M+Na)⁺ = 523

g) 1-Methyl-2-[N-(4-amidinophenyl)aminomethyl]-indol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide-hydroiodide

35 0.30 g (0.60 mmol) of 1-methyl-2-[N-(4-thiocarbamoyl)-phenyl)aminomethyl]-indol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide were dissolved in 20 ml of

acetone together with 0.75 ml (12 mmol) of methyl iodide and stirred for 2 hours at ambient temperature. Then the solvent was distilled off and the crude product was stirred together with 1.0 g of ammonium acetate in 12 ml of ethanol
5 and 5 ml of methylene chloride for 20 hours at 40°C. The solvent was distilled off *in vacuo* and the residue obtained was purified by chromatography (silica gel; methylene chloride/ethanol = 9:1 to 4:1).

Yield: 55 % of theory,

10 $C_{28}H_{29}N_5O_3$ (483.58)

R_f value: 0.20 (silica gel; methylene chloride/ethanol = 4:1 + 1 drop of acetic acid)

EKA mass spectrum: (M+H)⁺ = 484

15 Example 158

1-Methyl-2-[N-(4-amidinophenyl)aminomethyl]-thieno[2.3-d]imidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

20

a) Iminoethyl methoxyacetate hydrochloride

A solution of 35.5 g (0.50 mol) of methoxyacetonitrile in 29 ml (23 g, 0.50 mol) of ethanol and 30 ml of absolute diethylether was cooled to 0°C and over 1 hour 22.5 g

25 (0.62 mol) of hydrogen chloride gas was introduced, whilst towards the end of the introduction of gas the reaction product crystallised out. To complete the precipitation 130 ml of diethylether were added and the colourless needles were filtered off.

30 Yield: 66.4 g (86 % of theory),

Melting point: 117-118°C.

b) 4-Hydroxymethyl-2-methoxymethyl-imidazole

A mixture of 30.6 g (0.20 mol) of iminoethyl

35 methoxyacetate-hydrochloride, 18 g (0.20 mol) of 1,3-dihydroxyacetone and 200 ml of liquid ammonia was heated to 68°C for 3 hours in a stirred autoclave at a pressure of 27

bar (analogously to: P. Dziuron et al. Arch. Pharm. 307, 1974, p.470). Then the ammonia was eliminated and 200 ml of methylene chloride were added. The white precipitate formed was filtered off and washed with methylene chloride. The
5 filtrate was evaporated down and the residue obtained was purified by chromatography (aluminium oxide; methylene chloride/ethanol = 90:10 to 85:15).

Yield: 26.7 g (94 % of theory),

R_f value: 0.43 (silica gel; methylene chloride/ethanol =
10 9:1)

C₆H₁₀N₂O₂ (142.20)

Mass spectrum: (M)⁺ = 142

c) 4-Hydroxymethyl-2-methoxymethyl-1-methyl-imidazole as a
15 1:1 mixture with 5-hydroxymethyl-2-methoxymethyl-1-methyl-
imidazole

A mixture of 7.1 g (50 mmol) of 4-hydroxymethyl-2-methoxymethylimidazole, 3.0 g (53 mmol) of powdered potassium hydroxide and 3.4 ml (0.55 mmol) of methyl iodide
20 was heated to 50°C in 100 ml of dimethylformamide for 4 hours (analogously to I. Sinclair et al., J. Med. Chem., 29, 1986, 261). Then the solvent was distilled off *in vacuo* and the crude product purified by column chromatography (aluminium oxide; methylene chloride/ethanol = 99:1 to
25 95:5).

Yield: 6.1 g (78 % of theory; 1:1 mixture of the two regioisomers)

R_f value: 0.32 (silica gel; methylene chloride/ethanol =
19:1)

30

d) 5-Chloro-4-hydroxymethyl-2-methoxymethyl-1-methyl-
imidazole

A 1:1 mixture of 7.7 g (49 mmol) of 4-hydroxymethyl-2-methoxymethyl-1-methyl-imidazole and 5-hydroxymethyl-
35 2-methoxymethyl-1-methyl-imidazole and 7.3 g (55 mmol) of N-chloro-succinimide was heated to 50°C in 48 ml of ethylene glycol monoethylether and 70 ml of dioxan for 10

hours. Then the solvent was distilled off *in vacuo* and the crude product purified by chromatography (silica gel; methylene chloride/ethanol = 99:1 to 90:10) to obtain the isomerically pure title compound.

- 5 Yield: 3.4 g (36 % of theory),
R_f value: 0.40 (silica gel; methylene chloride/ethanol = 19:1)

e) 5-chloro-4-formyl-2-methoxymethyl-1-methyl-imidazole

- 10 3.4 g (18 mmol) of 5-chloro-4-hydroxymethyl-2-methoxymethyl-1-methyl-imidazole were dissolved in 100 ml of methylene chloride and at two-hour intervals manganese dioxide was added (2 x 6.0 g, a total of 0.14 mol). After 4 hours the inorganic component was filtered off, the solvent
15 was eliminated and the crude product obtained was further reacted without any further purification.

Yield: 3.0 g (89 % of theory),
R_f value: 0.44 (silica gel; methylene chloride/ethanol = 50:1)

f) Ethyl 1-methyl-2-methoxymethyl-thieno[2.3-d]imidazol-5-yl-carboxylate

To a freshly prepared sodium ethoxide solution (from 391 mg, 17 mMol of sodium) in 15 ml of ethanol were added
5 dropwise 1.9 ml (2.1 g, 17 mmol) of ethyl thioglycolate. After 1 hour stirring at ambient temperature 1.6 g (8.5 mmol) of 5-chloro-4-formyl-2-methoxymethyl-1-methyl-imidazole in 20 ml of absolute ethanol were added and the mixture was heated to 80°C (analogously to B. Iddon et al.,
10 J. Chem. Soc. Perkin Trans. I, 1987, 1457). After 5 hours the solvent was distilled off, the residue was taken up in 50 ml of methylene chloride and washed with 20 ml of water. The aqueous phase was washed again with 20 ml of methylene chloride and then the combined organic phases were dried
15 with sodium sulphate. After removal of the solvent *in vacuo* the crude product obtained was purified by column chromatography (aluminium oxide; methylene chloride). Yield: 1.0 g (46 % of theory),
R_f value: 0.48 (silica gel; methylene chloride/ethanol =
20 50:1)
C11H14N2O3S (254.31)
EKA mass spectrum: (M+H)⁺ = 255
(M+Na)⁺ = 277

g) 1-Methyl-2-methoxymethyl-thieno[2.3-d]imidazol-5-yl-carboxylic acid

To a solution of 0.90 g (3.54 mmol) of ethyl 1-methyl-2-methoxymethyl-thieno[2.3-d]imidazol-5-yl-carboxylate in 30 ml of ethanol were added dropwise 5 ml of 2 N sodium
30 hydroxide solution and the mixture was stirred for 2 hours at ambient temperature. Then the solvent was distilled off *in vacuo*, the residue was taken up in 5 ml of water and washed with 10 ml of diethylether. The aqueous phase was acidified with 6 ml of 2N hydrochloric acid, cooled to 0°C
35 and the precipitated crystals are filtered off.
Yield: 0.50 g (63% of theory)

R_f value: 0.21 (silica gel; methylene chloride/ethanol = 9:1 + a few drops of acetic acid)

C₉H₁₀N₂O₃S (226.26)

Mass spectrum: (M)⁺ = 226

5

h) 1-Methyl-2-methoxymethyl-thieno[2.3-d]imidazol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide

A suspension of 0.50 g (2.2 mmol) of 1-methyl-2-methoxymethyl-thieno[2.3-d]imidazol-5-yl-carboxylic acid in
10 20 ml of methylene chloride was mixed with 2.0 ml (3.2 g, 27 mmol) of thionyl chloride and refluxed for 60 minutes, during which time the solid gradually dissolved. After distillation of the liquid components the crude product was taken up twice more in methylene chloride. After the
15 solvent had been eliminated once more the crude acid chloride was taken up in 20 ml of tetrahydrofuran and added dropwise to a mixture of 0.42 g (2.3 mmol) of N-(2-methoxycarbonylethyl)aniline and 0.92 ml (6.6 mmol) of triethylamine in 30 ml of tetrahydrofuran. After 16 hours'
20 stirring at 50°C the solvent was eliminated and the crude product obtained was purified by chromatography (silica gel; methylene chloride/ethanol = 100:1).

Yield: 0.66 g (77% of theory),

R_f value: 0.47 (silica gel; methylene chloride/ethanol =
25 19:1)

i) 1-Methyl-2-(N-4-cyanophenylaminomethyl)-thieno[2.3-d]imidazol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide

30 To a solution of 0.73 g (1.88 mmol) of 1-methyl-2-methoxymethyl-thieno[2.3-d]imidazol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide in 30 ml of methylene chloride were added dropwise at 5°C 2.9 ml (2.9 mmol) of a 1-molar solution of boron tribromide in
35 methylene chloride. After 16 hours' stirring at ambient temperature the mixture was washed with 20 ml of saturated sodium hydrogen carbonate solution, the organic phase was

separated off, dried with sodium sulphate and filtered. The filtrate was mixed with 14 ml of N-ethyl-diisopropylamine and 0.43 g (3.64 mmol) of 4-aminobenzonitrile. Then the methylene chloride was distilled off *in vacuo*, the residue
5 obtained was heated to 50°C for 1 hour and then the residual solvent was distilled off *in vacuo*. After chromatography (silica gel; methylene chloride/ethanol = 99:1 to 97:3) a yellow oil was obtained which slowly solidified.
10 Yield: 0.37 g (42% of theory),
R_f value: 0.29 (silica gel; methylene chloride/ethanol = 50:1 + a few drops of ammonia)

j) 1-Methyl-2-[N-(4-amidinophenyl)aminomethyl]-
15 thieno[2.3-d]imidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride
0.38 g (0.80 mmol) of 1-methyl-2-(N-4-cyanophenylaminomethyl)-thieno[2.3-d]imidazol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide
20 were stirred in 40 ml of ethanol saturated with hydrogen chloride for 5 hours first at 0°C, then later at ambient temperature until no more starting material could be detected by thin layer chromatography. Then the solvent was distilled off at a maximum 28°C bath temperature, the oily
25 residue was taken up in 40 ml of absolute ethanol and mixed with 1.1 g of ammonium carbonate. After 18 hours the solvent was distilled off *in vacuo* and the crude product was purified by chromatography (silica gel; methylene chloride/ethanol = 9:1 to 4:1).
30 Yield : 57 % of theory
C₂₆H₂₈N₆O₃S (504.62)
R_f value: 0.21 (silica gel; methylene chloride/ethanol = 4:1 + a few drops of acetic acid)
EKA mass spectrum: (M+H)⁺ = 505
35 (M+H+Na)⁺⁺ = 264

Example 159

1-Methyl-2-[N-(4-amidinophenyl)aminomethyl]-
thieno[2.3-d]imidazol-5-yl-carboxylic acid-N-phenyl-N-(2-
5 hydroxycarbonylethyl)-amide-hydrochloride

Prepared analogously to Example 2 from 1-methyl-2-[N-(4-
amidinophenyl)aminomethyl]-thieno[2.3-d]imidazol-5-yl-
carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-
10 hydrochloride and sodium hydroxide solution.

Yield: 85 % of theory,

$C_{24}H_{24}N_6O_3S$ (476.56)

R_f value: 0.36 (Reversed Phase silica gel RP-8; methanol
+ 5 % saline solution)

15 EKA mass spectrum: $(M+H)^+ = 477$
 $(M+Na)^+ = 499$
 $(M+2Na)^{++} = 250$

Example 160

20

1-Methyl-3-[N-(4-amidinophenyl)thiomethyl]-quinoxalin-2-on-
6-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-
amide-hydrochloride

25 a) 1-Methyl-3-[N-(4-cyanophenyl)thiomethyl]-quinoxalin-2-
on-6-yl-carboxylic acid-N-phenyl-N-(2-
methoxycarbonylethyl)-amide

A solution of 2.5 g (7.6 mmol) of 3-amino-4-methylamino-
benzoic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide and
30 2.4 g (9.6 mmol) of ethyl 3-(4-cyanophenyl)thio-2-oxo-
propionate were heated to boiling in 50 ml of ethanol for
30 minutes. After removal of the solvent the crude product
obtained was purified by chromatography (silica gel;
methylene chloride).

35 Yield: 1.6 g (40 % of theory),

R_f value: 0.63 (silica gel; EtOAc/EtOH/ammonia = 90:10:1)

b) 1-Methyl-3-[N-(4-amidinophenyl)thiomethyl]-quinoxalin-2-on-6-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

- 5 Prepared analogously to Example 1 from 1-methyl-3-[N-(4-cyanophenyl)thiomethyl]-quinoxalin-2-on-6-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.
Yield: 23 % of theory,
10 $C_{28}H_{27}N_5O_4S$ (543.64)
 R_f value: 0.25 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5)
EKA mass spectrum: $(M+H)^+ = 544$
 $(M+Na)^+ = 566$

15

Example 161

3-Methyl-2-[2-(4-amidinophenyl)ethyl]-imidazo[1.2-a]pyridin-7-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

- a) 3-Methyl-2-[2-(4-cyanophenyl)ethyl]-imidazo[1.2-a]pyridin-7-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide
- 25 1.4 g (4.6 mmol) of 3-methyl-2-[2-(4-cyanophenyl)ethyl]-imidazo[1.2-a]pyridin-7-yl-carboxylic acid (prepared from 4-bromo-1-(4-cyanophenyl)-1-penten-3-one and methyl 2-aminopyridine-4-carboxylate analogously to Y. Katsura et al. Chem. Pharm. Bull. 1992, 40, 1424-1438) were suspended
30 in 15 ml of thionyl chloride and heated to boiling for 1 hour until fully dissolved. After the thionyl chloride had been distilled off the acid chloride was dissolved in 15 ml of pyridine without any further purification and at 0°C mixed with 1.0 g (5.2 mmol) of N-(2-ethoxycarbonylethyl)-
35 aniline. After 1 hour the solvent was distilled off, the residue was taken up in 30 ml of methylene chloride, washed with 15 ml of 1N hydrochloric acid and dried with sodium

sulphate. After distillation of the solvent and chromatography (silica gel; methylene chloride/ethanol = 0 to 2 %) a brown oil was obtained.

Yield: 1.48 g (64 % of theory),

5 R_f value: 0.73 (silica gel; ethyl acetate/ethanol/ammonia = 90:10:1)

b) 3-Methyl-2-[2-(4-amidinophenyl)ethyl]-imidazo[1.2-a]pyridin-7-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonyl-ethyl)-amide-hydrochloride

Prepared analogously to Example 1 from 3-methyl-2-[2-(4-cyanophenyl)ethyl]-imidazo[1.2-a]pyridin-7-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonyl-ethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

15 Yield: 62 % of theory,

$C_{29}H_{31}N_5O_3$ (497.60)

R_f value: 0.23 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5)

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

20

Example 162

3-Methyl-2-[2-(4-amidinophenyl)ethyl]-imidazo[1.2-a]pyridin-7-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonyl-ethyl)-amide-hydrochloride

Prepared analogously to Example 2 from 3-methyl-2-[2-(4-amidinophenyl)ethyl]-imidazo[1.2-a]pyridin-7-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonyl-ethyl)-amide-hydrochloride and sodium hydroxide solution.

Yield: 92 % of theory,

$C_{27}H_{27}N_5O_3$ (469.55)

R_f value: 0.19 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5)

35 EKA mass spectrum: $(M+H)^+ = 470$

$(M+Na)^+ = 492$

$$(M+2H)^{++} = 235.7$$

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

$$(M+2Na)^{++} = 257.7$$

5 Example 163

1-Methyl-2- [N- (4-amidinophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic acid-N-phenyl-N- [(N-ethoxycarbonylethyl-N-methyl) -2-aminoethyl] -amide-dihydrochloride

10

Prepared analogously to Example 25d from 1-methyl-2- [N- (4-cyanophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic acid-N-phenyl-N- [(N-ethoxycarbonylethyl-N-methyl) -2-aminoethyl] -amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

15

Yield: 80 % of theory,

$C_{31}H_{37}N_7O_3$ (555.7)

R_f value: 0.24 (silica gel; dichloromethane/methanol = 4:1)

EKA mass spectrum: $(M+H)^+ = 556$

20

$(M+H+Na)^{++} = 289.8$

$(M+2H)^{++} = 278.8$

Example 164

25 1-Methyl-2- [N- (4-amidinophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic acid-N-phenyl-N- [(N-hydroxycarbonylethyl-N-methyl) -2-aminoethyl] -amide-hydrochloride

30

Prepared analogously to Example 26 from 1-methyl-2- [N- (4-amidinophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic acid-N-phenyl-N- [(N-ethoxycarbonylethyl-N-methyl) -2-aminoethyl] -amide-dihydrochloride and sodium hydroxide solution.

Yield: 79 % of theory,

35

$C_{29}H_{33}N_7O_3$ (527.6)

R_f value: 0.43 (Reversed Phase silica gel RP-18;
methanol/5% aqueous saline solution = 6:4)

EKA mass spectrum: (M+H)⁺ = 528
(M+H+Na)⁺⁺ = 275.6
5 (M+2H)⁺⁺ = 264.6

Example 165

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-
10 5-yl-carboxylic acid-N-phenyl-N-(3-hydroxy-n-propyl)-amide-
hydrochloride

Prepared from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-
benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-benzyloxy-
15 n-propyl)-amide-hydrochloride by hydrogenation over
palladium/charcoal (10%) at 5 bar hydrogen pressure and at
ambient temperature.

Yield: 61 % of theory,

C₂₆H₂₈N₆O₂ (456.6)

20 R_f value: 0.70 (Reversed Phase silica gel RP-18;
methanol/5% aqueous saline solution = 9:1)

EKA mass spectrum: (M+H)⁺ = 457
(M+H+Na)⁺⁺ = 240

Example 166

1-Methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide

Prepared analogously to Example 26 from 1-methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide and sodium hydroxide solution.
Yield: 97 % of theory,
 $C_{32}H_{37}N_7O_5$ (599.7)
 R_f value: 0.22 (silica gel; dichloromethane/methanol = 9:1)
EKA mass spectrum: $(M+H)^+ = 600$
 $(M+H+Na)^{++} = 311.7$
 $(M+2H)^{++} = 300.8$
 $(M+2Na)^{++} = 322.8$

Example 167

1-Methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-hydroxy-n-propyl)-amide

Prepared analogously to Example 165 from 1-methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-benzyloxy-n-propyl)-amide by catalytic debenzylation.
Yield: 26 % of theory,
 $C_{33}H_{40}N_6O_4$ (584.7)
 R_f value: 0.39 (silica gel; dichloromethane/ethanol = 9:1)
EKA mass spectrum: $(M+H)^+ = 585$
 $(M+H+Na)^{++} = 304$
 $(M+Na)^+ = 607$

Example 168

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-fluorophenyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-fluorophenyl)-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 42 % of theory,

$C_{28}H_{29}FN_6O_3$ (516.6)

R_f value: 0.31 (silica gel; dichloromethane/methanol = 5:1)

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

$(M+H+Na)^{++} = 270$

Example 169

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(4-fluorophenyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(4-fluorophenyl)-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 90 % of theory,

$C_{28}H_{29}FN_6O_3$ (516.6)

R_f value: 0.29 (silica gel; dichloromethane/methanol = 5:1)

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

$(M+H+Na)^{++} = 270$

Example 170

1-Methyl-2- [N- (4-amidinophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic acid-N- (3-fluorophenyl) -N- (2-hydroxycarbonylethyl) -amide

Prepared analogously to Example 26 from 1-methyl-2- [N- (4-amidinophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic acid-N- (3-fluorophenyl) -N- (2-ethoxycarbonylethyl) -amide-hydrochloride and sodium hydroxide solution.

Yield: 97 % of theory,

$C_{26}H_{25}FN_6O_3$ (488.5)

R_f value: 0.13 (silica gel; dichloromethane/ethanol = 4:1)

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

$(M+Na)^+$ = 511

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

Example 171

1-Methyl-2- [N- (4-amidinophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic acid-N- (4-fluorophenyl) -N- (2-hydroxycarbonylethyl) -amide

Prepared analogously to Example 26 from 1-methyl-2- [N- (4-amidinophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic acid-N- (4-fluorophenyl) -N- (2-ethoxycarbonylethyl) -amide-hydrochloride and sodium hydroxide solution.

Yield: 89 % of theory,

$C_{26}H_{25}FN_6O_3$ (488.5)

R_f value: 0.15 (silica gel; dichloromethane/ethanol = 4:1)

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

$(M+Na)^+$ = 511

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

Example 172

1-Methyl-2-[N-(4-amidino-2-methoxy-phenyl)-aminomethyl]-
5 benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-
ethoxycarbonylethyl)-amide-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-
cyano-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-
10 carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide
and ethanolic hydrochloric acid, ethanol and ammonium
carbonate.

Yield: 89 % of theory,

$C_{29}H_{32}N_6O_4$ (528.6)

15 R_f value: 0.13 (silica gel; dichloromethane/ethanol = 4:1)

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

$(M+H+Na)^{++}$ = 276

$(M+2H)^{++}$ = 265

20 Example 173

1-Methyl-2-[N-[4-(N-4-ethylbenzoylamidino)phenyl]-
aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-
pyridyl)-N-(2-ethoxycarbonylethyl)-amide

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-
amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic
acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-
hydrochloride and 4-ethylbenzoylchloride.

30 Yield: 64 % of theory,

$C_{36}H_{37}N_7O_4$ (631.7)

R_f value: 0.78 (silica gel; dichloromethane/methanol = 9:1)

EKA mass spectrum: $(M+H)^+$ = 632

$(M+H+Na)^{++}$ = 327.8

35 $(M+Na)^+$ = 654

Example 174

1-Methyl-2- [N- [4- (N-benzyloxycarbonylamidino)phenyl] -
aminomethyl] -benzimidazol-5-yl-carboxylic acid-N- (2-
5 pyridyl) -N- (2-ethoxycarbonylethyl) -amide

Prepared analogously to Example 90 from 1-methyl-2- [N- (4-
amidinophenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic
acid-N- (2-pyridyl) -N- (2-ethoxycarbonylethyl) -amide-
10 hydrochloride and benzyl chloroformate.
Yield: 64 % of theory,
 $C_{35}H_{35}N_7O_5$ (633.6)
 R_f value: 0.60 (silica gel; dichloromethane/methanol = 9:1)
EKA mass spectrum: $(M+H)^+$ = 634
15 $(M+H+Na)^{++}$ = 328.8
 $(M+Na)^+$ = 656

Example 175

20 1-Methyl-2- [N- (4-amidino-2-methoxy-phenyl) -aminomethyl] -
benzimidazol-5-yl-carboxylic acid-N-phenyl-N- (2-
hydroxycarbonylethyl) -amide

Prepared analogously to Example 26 from 1-methyl-2- [N- (4-
25 amidino-2-methoxy-phenyl) -aminomethyl] -benzimidazol-5-yl-
carboxylic acid-N-phenyl-N- (2-ethoxycarbonylethyl) -amide-
hydrochloride and sodium hydroxide solution.
Yield: 71 % of theory,
 $C_{27}H_{28}N_6O_4$ (500.6)
30 R_f value: 0.15 (silica gel; dichloromethane/ethanol = 4:1)
EKA mass spectrum: $(M+H)^+$ = 501
 $(M+Na)^+$ = 523
 $(M+2Na)^{++}$ = 273

Example 176

1-Methyl-2-[N-(4-amidino-2-methoxy-phenyl)-aminomethyl]-
benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-
5 ethoxycarbonylethyl)-amide-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-
cyano-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-
carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-
10 amide and ethanolic hydrochloric acid, ethanol and ammonium
carbonate.

Yield: 67 % of theory,

$C_{28}H_{31}N_7O_4$ (529.6)

R_f value: 0.16 (silica gel; dichloromethane/ethanol = 4:1)

15 EKA mass spectrum: $(M+H)^+ = 530$

Example 177

1-Methyl-2- [N- (4-amidino-2-methoxy-phenyl) -aminomethyl] -
benzimidazol-5-yl-carboxylic acid-N- (2-pyridyl) -N- (2-
5 hydroxycarbonylethyl) -amide

Prepared analogously to Example 26 from 1-methyl-2- [N- (4-
amidino-2-methoxy-phenyl) -aminomethyl] -benzimidazol-5-yl-
carboxylic acid-N- (2-pyridyl) -N- (2-ethoxycarbonylethyl) -
10 amide-hydrochloride and sodium hydroxide solution.

Yield: 78 % of theory,

$C_{26}H_{27}N_7O_4$ (501.6)

R_f value: 0.12 (silica gel; dichloromethane/ethanol = 4:1)

EKA mass spectrum: $(M+H)^+ = 502$

15

Example 178

1-Methyl-2- [N- [4- (N-benzyloxycarbonylamidino)phenyl] -amino-
methyl] -benzimidazol-5-yl-carboxylic acid-N- (2-pyridyl) -N-
20 (2-hydroxycarbonylethyl) -amide

Prepared analogously to Example 104 from 1-methyl-2- [N- [4-
(N-benzyloxycarbonylamidino)phenyl] -aminomethyl] -
benzimidazol-5-yl-carboxylic acid-N- (2-pyridyl) -N- (2-
25 ethoxycarbonylethyl) -amide and sodium hydroxide solution.

Yield: 62 % of theory,

$C_{33}H_{31}N_7O_5$ (605.7)

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

EKA mass spectrum: $(M+H)^+ = 606$

30 $(M+Na)^+ = 628$

$(M-H+2Na)^+ = 650$

$(M+2H)^{++} = 303.8$

$(M+H+Na)^{++} = 314.8$

$(M+2Na)^{++} = 325.7$

35

Example 179

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-benzyloxy-n-propyl)-amide-hydrochloride

Prepared analogously to Example 25 from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-benzyloxy-n-propyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 61 % of theory,

$C_{33}H_{34}N_6O_2$ (546.7)

R_f value: 0.19 (silica gel; dichloromethane/ethanol = 4:1)

EKA mass spectrum: $(M+H)^+$ = 547

$(M+H+Na)^{++}$ = 285

Example 180

1-Methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-benzyloxy-n-propyl)-amide

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-benzyloxy-n-propyl)-amide-hydrochloride and n-hexyl chloroformate.

Yield: 73 % of theory,

$C_{40}H_{46}N_6O_4$ (674.9)

R_f value: 0.46 (silica gel; dichloromethane/ethanol = 9:1)

EKA mass spectrum: $(M+H)^+$ = 675

$(M+H+Na)^{++}$ = 349

$(M+Na)^+$ = 697

$(M+K)^+$ = 713

Example 181

3-Methyl-2-[2-(4-amidinophenyl)ethyl]-
imidazo[1.2-a]pyridin-7-yl-carboxylic acid-N-(2-pyridyl)-N-
5 (2-ethoxycarbonylethyl)-amide-hydrochloride

Prepared analogously to Example 1 from 3-methyl-2-[2-(4-
cyanophenyl)ethyl]-imidazo[1.2-a]pyridin-7-yl-carboxylic
acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide-
10 hydrochloride and ethanolic hydrochloric acid, ethanol and
ammonium carbonate.

Yield: 53 % of theory,

$C_{28}H_{30}N_6O_3$ (498.59)

R_f value: 0.42 (silica gel; ethyl acetate/ethanol/ammonia
15 = 50:45:5)

EKA mass spectrum: $(M+H)^+$ = 499

$(M+2Na)^{++}$ = 272

$(M+H+Na)^{++}$ = 261

$(M+2H)^{++}$ = 250

20

Example 182

1-Methyl-2-[N-(3-amidino-pyridin-6-yl)-aminomethyl]-
benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-
25 hydroxycarbonylethyl)-amide

Prepared analogously to Example 26 from 1-methyl-
2-[N-(3-cyanopyridin-6-yl)-aminomethyl]-benzimidazol-5-yl-
carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-
30 amide and sodium hydroxide solution.

Yield: 40 % of theory,

$C_{24}H_{24}N_8O_3$ (472.9)

R_f value: 0.67 (Reversed Phase silica gel RP-8; methanol/5%
saline solution = 1:1)

35 EKA mass spectrum: $(M+H)^+$ = 473

Example 183

1-Methyl-2-[N-[4-(N-hydroxylamidino)phenyl]-aminomethyl]-
benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-[2-
5 (methansulphonylaminocarbonyl)-ethyl]-amide

a. 1-Methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-[2-(methanesulphonylaminocarbonyl)-ethyl]-amide

- 10 2.0 g (4.5 mmol) of 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonyl-ethyl)-amide and 0.73 g (4.7 mmol) of carbonyldiimidazole were dissolved in 80 ml of tetrahydrofuran and 5 ml of dimethylformamide and
15 stirred for 30 minutes at ambient temperature and for 2 hours at 90°C. In parallel 0.55 g (5.8 mmol) of methansulphonic acid amide and 0.28 g (5.8 mmol) of sodium hydride were suspended in 15 ml of dimethylformamide and stirred for 2 hours at ambient temperature. Then this
20 suspension was added at ambient temperature to the tetrahydrofuran solution. After 12 hours at ambient temperature 50 ml of water were added and the pH value was adjusted to 6.8. The solution was extracted 4x with methylene chloride, the combined organic phases were dried
25 over sodium sulphate and evaporated down. The crude product was chromatographed on silica gel (methylene chloride/ethanol (40:1)). The desired fractions were combined and evaporated down. Yield: 1.05 g (44 % of theory),
30 $C_{26}H_{25}N_7O_4S$ (531.6)
 R_f value: 0.72 (silica gel; dichloromethane/methanol = 9:1)

b. 1-Methyl-2-[N-[4-(N-hydroxylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-[2-(methansulphonylaminocarbonyl)-ethyl]-amide

Prepared analogously to Example 96 from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-[2-(methanesulphonylaminocarbonyl)-ethyl]-amide and hydroxylamine.

Yield: 27% of theory,

$C_{26}H_{28}N_8O_5S$ (564.6)

R_f value: 0.75 (silica gel; dichloromethane/ethanol = 7:3 + 1% glacial acetic acid)

EKA mass spectrum: $(M+H)^+ = 565$
 $(M+Na)^+ = 587$

Example 184

1-Methyl-2-[N-(5-amidino-thiazol-2-yl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2-[N-(5-cyano-thiazol-2-yl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Example 185

1-Methyl-2-[N-(5-amidino-thiazol-2-yl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide

Prepared analogously to Example 26 from 1-methyl-2-[N-(5-amidino-thiazol-2-yl)-aminomethyl]-benzimidazol-

5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.

5 Example 186

1-Methyl-2-[N-(2-amidino-pyrazin-5-yl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

10

Prepared analogously to Example 25d from 1-methyl-2-[N-(2-cyano-pyrazin-5-yl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

15

Yield: 19 % of theory,

$C_{25}H_{27}N_9O_3$ (501.6)

R_f value: 0.28 (silica gel; dichloromethane/methanol = 4:1 + 1% glacial acetic acid)

20

EKA mass spectrum: $(M+H)^+ = 502$

$(M+H+Na)^+ = 262.5$

Example 187

25

1-Methyl-2-[N-(2-amidino-pyrazin-5-yl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide

30

Prepared analogously to Example 26 from 1-methyl-2-[N-(2-amidino-pyrazin-5-yl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.

Yield: 11 % of theory,

35

$C_{23}H_{23}N_9O_3$ (473.5)

R_f value: 0.55 (Reversed Phase silica gel RP-8; 5% saline solution/methanol = 6:4)

EKA mass spectrum: (M+H)⁺ = 474
(M+H+Na)⁺ = 496.6

5

Example 188

1-Methyl-2-[2-[4-(N-n-hexyloxycarbonylamidino)phenyl]-ethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-[2-(1H-tetrazol-5-yl)-ethyl]-amide

Prepared analogously to Example 90 from 1-methyl-2-[2-(4-amidinophenyl)-ethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-[2-(1H-tetrazol-5-yl)-ethyl]-amide and n-hexyl chloroformate.

Example 189

1-Methyl-2-[N-(2-methoxy-4-n-pentoxycarbonylamidino-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidino-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and n-pentyl chloroformate.

Yield: 53 % of theory,

C₃₅H₄₂N₆O₆ (642.7)

R_f value: 0.54 (silica gel; dichloromethane/ethanol = 9:1)

EKA mass spectrum: (M+H)⁺ = 643
(M+H+Na)⁺⁺ = 333.4

30

Example 190

1-Methyl-2- [N- (4-n-heptyloxy-carbonylamidino-2-methoxy-phenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic acid-N-phenyl-N- (2-ethoxycarbonylethyl) -amide

Prepared analogously to Example 90 from 1-methyl-2- [N- (4-amidino-2-methoxy-phenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic acid-N-phenyl-N- (2-ethoxycarbonylethyl) -amide-hydrochloride and n-heptyl chloroformate.

Yield: 68 % of theory,

$C_{37}H_{46}N_6O_6$ (670.8)

R_f value: 0.56 (silica gel; dichloromethane/ethanol = 9:1)

EKA mass spectrum: $(M+H)^+$ = 671

$(M+H+Na)^{++}$ = 347.4

Example 191

1-Methyl-2- [N- (4-ethoxycarbonylamidino-2-methoxy-phenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic acid-N- (2-pyridyl) -N- (2-ethoxycarbonylethyl) -amide

Prepared analogously to Example 90 from 1-methyl-2- [N- (4-amidino-2-methoxy-phenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic acid-N- (2-pyridyl) -N- (2-ethoxycarbonylethyl) -amide-hydrochloride and ethyl chloroformate.

Yield: 43 % of theory,

$C_{31}H_{35}N_7O_6$ (601.7)

R_f value: 0.44 (silica gel; dichloromethane/ethanol = 9:1)

EKA mass spectrum: $(M+H)^+$ = 602

$(M+H+Na)^{++}$ = 312.8

Example 192

1-Methyl-2- [N- (2-methoxy-4-n-pentoxycarbonylamidino-
phenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic acid-N-
5 (2-pyridyl) -N- (2-ethoxycarbonylethyl) -amide

Prepared analogously to Example 90 from 1-methyl-2- [N- (4-
amidino-2-methoxy-phenyl) -aminomethyl] -benzimidazol-5-yl-
carboxylic acid-N- (2-pyridyl) -N- (2-ethoxycarbonylethyl) -
10 amide-hydrochloride and n-pentyl chloroformate.

Yield: 72 % of theory,

$C_{34}H_{41}N_7O_6$ (643.7)

R_f value: 0.49 (silica gel; dichloromethane/ethanol = 9:1)

EKA mass spectrum: $(M+H)^+$ = 644
15 $(M+H+Na)^{++}$ = 333.9

Example 193

1-Methyl-2- [N- (2-methoxy-4-n-heptyloxycarbonylamidino-
20 phenyl) -aminomethyl] -benzimidazol-5-yl-carboxylic acid-N-
(2-pyridyl) -N- (2-ethoxycarbonylethyl) -amide

Prepared analogously to Example 90 from 1-methyl-2- [N- (4-
amidino-2-methoxy-phenyl) -aminomethyl] -benzimidazol-5-yl-
25 carboxylic acid-N- (2-pyridyl) -N- (2-ethoxycarbonylethyl) -
amide-hydrochloride and n-heptyl chloroformate.

Yield: 55 % of theory,

$C_{36}H_{45}N_7O_6$ (671.8)

R_f value: 0.54 (silica gel; dichloromethane/ethanol = 9:1)

EKA mass spectrum: $(M+H)^+$ = 672
30 $(M+H+Na)^{++}$ = 347.9

Example 194

Dry ampoule containing 75 mg of active substance per 10 ml

5

Composition:

	Active substance	75.0 mg
	Mannitol	50.0 mg
10	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
15 the solution ready for use, the product is dissolved in
water for injections.

Example 195

Dry ampoule containing 35 mg of active substance per 2 ml

5

Composition:

Active substance	35.0 mg
Mannitol	100.0 mg
10 water for injections	ad 2.0 ml

Preparation:

Active substance and mannitol are dissolved in water. After packaging, the solution is freeze-dried.

15

To produce the solution ready for use, the product is dissolved in water for injections.

20 Example 196

Tablet containing 50 mg of active substance

25 Composition:

(1) Active substance	50.0 mg
(2) Lactose	98.0 mg
(3) Maize starch	50.0 mg
30 (4) Polyvinylpyrrolidone	15.0 mg
(5) Magnesium stearate	<u>2.0 mg</u>
	215.0 mg

Preparation:

35 (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.

5 Example 197

Tablet containing 350 mg of active substance

10 Preparation:

	(1) Active substance	350.0 mg
	(2) Lactose	136.0 mg
	(3) Maize starch	80.0 mg
15	(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.

25

Example 198

Capsules containing 50 mg of active substance

30 Composition:

	(1) Active substance	50.0 mg
	(2) Dried maize starch	58.0 mg
	(3) Powdered lactose	50.0 mg
35	(4) Magnesium stearate	<u>2.0 mg</u>
		160.0 mg

Preparation:

(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous mixing.

- 5 This powder mixture is packed into size 3 hard gelatin capsules in a capsule filling machine.

Example 199

- 10 Capsules containing 350 mg of active substance
-

Composition:

15	(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>
		430.0 mg

- 20 Preparation:

(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous mixing.

- 25 This powder mixture is packed into size 0 hard gelatin capsules in a capsule filling machine.

Example 200

Suppositories containing 100 mg of active substance

30

- 1 suppository contains:

	Active substance	100.0 mg
	Polyethyleneglycol (M.W. 1500)	600.0 mg
35	Polyethyleneglycol (M.W. 6000)	460.0 mg
	Polyethylenesorbitan monostearate	<u>840.0 mg</u>
		2,000.0 mg

Patent Claims

1. Disubstituted bicyclic heterocycles of general formula

5 $R_a - A - \text{Het} - B - \text{Ar} - E$, (I)
wherein

A denotes a carbonyl or sulphonyl group linked to the
benzo, pyrido, pyrimido, pyrazino, pyridazino or thieno
10 moiety of the group Het, whilst moreover the abovementioned
moieties may not contain an R_1 group,

B denotes an ethylene group, wherein a methylene group,
linked either to the group Het or Ar, may be replaced by an
15 oxygen or sulphur atom or by a sulphinyl, sulphonyl,
carbonyl or $-NR_1$ group, wherein

R_1 denotes a hydrogen atom or a C_{1-6} -alkyl group,

20 E denotes a cyano or $R_b\text{NH}-C(=\text{NH})-$ group wherein

R_b denotes a hydrogen atom, a hydroxy group, a
 C_{1-3} -alkyl group or a group which may be cleaved in
vivo,

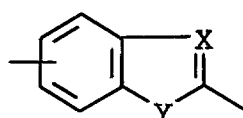
25

Ar denotes a phenylene or naphthylene group optionally
substituted by a fluorine, chlorine or bromine atom or by a
trifluoromethyl, C_{1-3} -alkyl or C_{1-3} -alkoxy group,

30 a thienylene, thiazolylene, pyridinylen, pyrimidinylene,
pyrazinylen or pyridazinylene group optionally substituted
in the carbon skeleton by a C_{1-3} -alkyl group,

Het denotes a bicyclic heterocycle of formula
35





, wherein

X is a nitrogen atom and

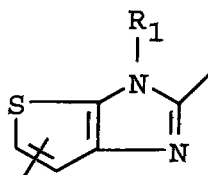
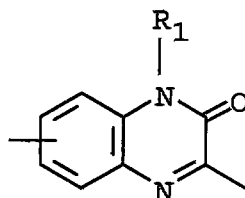
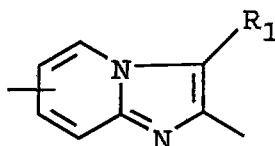
5 Y is an oxygen or sulphur atom or a nitrogen atom optionally substituted by a C₁₋₆-alkyl or C₃₋₇-cycloalkyl group, whilst additionally one or two non-angular methyne groups in the phenyl moiety of the above-mentioned bicyclic heterocycle may each be
10 replaced by a nitrogen atom,

or X denotes a methyne group optionally substituted by the group R₁, wherein R₁ is as hereinbefore defined, and

15 Y denotes a nitrogen atom optionally substituted by a C₁₋₆-alkyl or C₃₋₇-cycloalkyl group,

or Het denotes a group of the formula

20

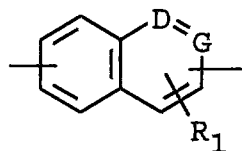
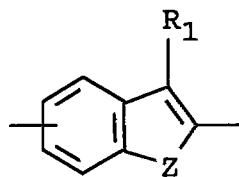


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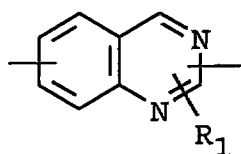


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or



wherein

5

R_1 is as hereinbefore defined,

10

Z denotes an oxygen or sulphur atom,

one of the groups D or G denotes a nitrogen atom and
the other group D or G denotes a methyne group,

15

and R_a denotes a C_{1-6} -alkyl group, a C_{3-7} -cycloalkyl group
optionally substituted by a C_{1-3} -alkyl group, wherein the
 C_{1-3} -alkyl group may additionally be substituted by a
carboxyl group or by a group which may be converted *in vivo*
into a carboxy group,

20

or an R_2NR_3 - group wherein

R_2 denotes a C_{1-4} -alkyl group, which may be substituted
by a carboxy, C_{1-6} -alkyloxycarbonyl, benzyloxycarbonyl,
 C_{1-3} -alkylsulphonylaminocarbonyl,
phenylsulphonylaminocarbonyl, trifluorosulphonylamino,
trifluorosulphonylaminocarbonyl or 1H-tetrazolyl
group,

30





- 5 a C₂₋₄-alkyl group substituted by a hydroxy, phenyl-C₁₋₃-alkoxy, carboxy-C₁₋₃-alkylamino, C₁₋₃-alkoxycarbonyl-C₁₋₃-alkylamino, N-(C₁₋₃-alkyl)-carboxy-C₁₋₃-alkylamino or N-(C₁₋₃-alkyl)-C₁₋₃-alkoxycarbonyl-C₁₋₃-alkylamino group, whilst in the abovementioned groups the carbon atom in the α -position relative to the adjacent nitrogen atom may not be substituted, or
- 10 a piperidinyl group optionally substituted by a C₁₋₃-alkyl group and
- 15 R₃ denotes a hydrogen atom, a C₁₋₆-alkyl group, a C₃₋₇-cycloalkyl group optionally substituted by a C₁₋₃-alkyl group, a C₃₋₆-alkenyl or alkynyl group, wherein the unsaturated part may not be linked directly to the nitrogen atom of the R₂NR₃- group, a phenyl group optionally substituted by a fluorine, chlorine or bromine atom or by a C₁₋₃-alkyl or
- 20 C₁₋₃-alkoxy group, a benzyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, thienyl or imidazolyl group or
- 25 R₂ and R₃ together with the nitrogen atom between them denote a 5- to 7-membered cycloalkyleneimino group, optionally substituted by a carboxymethyl or C₁₋₄-alkoxycarbonyl group, onto which a phenyl ring may additionally be fused,
- 30 the tautomers, the stereoisomers, the mixtures thereof and the salts thereof.

2. Disubstituted bicyclic heterocycles of general formula I according to claim 1, wherein

35

A denotes a carbonyl or sulphonyl group linked to the benzo, pyrido, pyrimido, pyrazino, pyridazino or thieno





moiety of the group Het, whilst moreover the abovementioned moieties may not contain an R_1 group,

B denotes an ethylene group, in which a methylene group,
5 linked either to the group Het or Ar, may be replaced by an oxygen or sulphur atom or by a sulphinyl, sulphonyl, carbonyl or $-NR_1-$ group, wherein

R_1 denotes a hydrogen atom or a C_{1-5} -alkyl group,
10

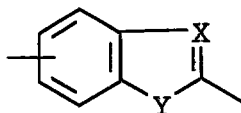
E denotes an $R_bNH-C(=NH)-$ group wherein

R_b denotes a hydrogen atom, a hydroxy group, a
 C_{1-3} -alkyl group or a group which may be cleaved in
15 vivo,

Ar denotes a phenylene group optionally substituted by a fluorine, chlorine or bromine atom or by a trifluoromethyl,
 C_{1-3} -alkyl or C_{1-3} -alkoxy group,
20

a thienylene, thiazolylene, pyridinylene, pyrimidinylene, pyrazinylene or pyridazinylene group optionally substituted in the carbon skeleton by a C_{1-3} -alkyl group,

25 Het denotes a bicyclic heterocycle of formula



, wherein

X is a nitrogen atom and
30

Y is an oxygen or sulphur atom or a nitrogen atom optionally substituted by a C_{1-6} -alkyl or C_{3-7} -cycloalkyl group, whilst additionally one or two non-angular methyne groups in the phenyl moiety of the





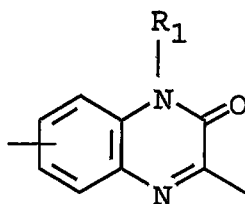
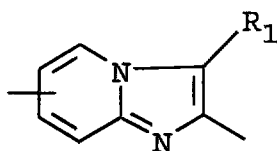
above-mentioned bicyclic heterocycle may each be replaced by a nitrogen atom,

5 or X denotes a methyne group optionally substituted by the group R_1 , wherein R_1 is as hereinbefore defined, and

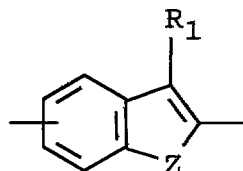
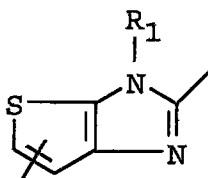
Y denotes a nitrogen atom optionally substituted by a C_{1-6} -alkyl or C_{3-7} -cycloalkyl group,

10

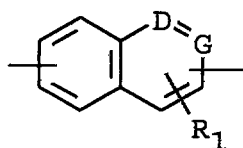
or Het denotes a group of the formulae



15



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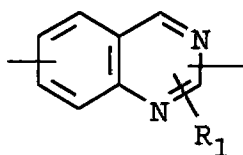


or



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wherein

5 wherein R_1 is as hereinbefore defined,

Z denotes an oxygen or sulphur atom

10 one of the groups D or G denotes a nitrogen atom and
the other group D or G denotes a methyne group,

and R_a denotes a C_{1-6} -alkyl group, a C_{3-7} -cycloalkyl group
optionally substituted by a C_{1-3} -alkyl group, wherein the
 C_{1-3} -alkyl group may additionally be substituted by a
15 carboxyl group or by a group which may be converted *in vivo*
into a carboxy group,

or a R_2NR_3 - group wherein

20 R_2 denotes a C_{1-4} -alkyl group, which may be substituted
by a carboxy, C_{1-6} -alkyloxycarbonyl, benzyloxycarbonyl,
 C_{1-3} -alkylsulphonylaminocarbonyl,
phenylsulphonylaminocarbonyl, trifluorosulphonylamino,
trifluorosulphonylaminocarbonyl or 1H-tetrazolyl
25 group,

a C_{2-4} -alkyl group substituted by a hydroxy, phenyl-
 C_{1-3} -alkoxy, carboxy- C_{1-3} -alkylamino, C_{1-3} -
alkoxycarbonyl- C_{1-3} -alkylamino, N-(C_{1-3} -alkyl)-carboxy-
30 C_{1-3} -alkylamino or N-(C_{1-3} -alkyl)- C_{1-3} -alkoxycarbonyl- C_{1-3} -
alkylamino group, whilst in the abovementioned groups
the carbon atom in the α -position relative to the
adjacent nitrogen atom may not be substituted, or





a piperidinyl group optionally substituted by a C_{1-3} -alkyl group and

5 R_3 denotes a hydrogen atom, a C_{1-6} -alkyl group, a C_{3-7} -cycloalkyl group optionally substituted by a C_{1-3} -alkyl group, a C_{3-6} -alkenyl or alkynyl group, wherein the unsaturated part may not be linked directly to the nitrogen atom of the R_2NR_3 - group,

10 a phenyl group optionally substituted by a fluorine, chlorine or bromine atom or by a C_{1-3} -alkyl or C_{1-3} -alkoxy group, a benzyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl,
15 imidazolyl or piperidinyl group or

R_2 and R_3 together with the nitrogen atom between them denote a 5- to 7-membered cycloalkyleneimino group, optionally substituted by a carboxymethyl or
20 C_{1-4} -alkoxycarbonyl group, onto which additionally a phenyl ring may be fused,

the tautomers, the stereoisomers and the salts thereof.

25 3. Disubstituted bicyclic heterocycles of general formula I according to claim 1, wherein

A denotes a carbonyl or sulphonyl group linked to the benzo, pyrido, pyrimido, pyrazino, pyridazino or thieno
30 moiety of the group Het, whilst moreover the abovementioned moieties may not contain an R_1 group,

B denotes an ethylene group in which the methylene group linked to the group Ar may be replaced by an oxygen or
35 sulphur atom or by an $-NR_1$ - group, wherein





R_1 denotes a hydrogen atom or a C_{1-4} -alkyl group,

5 E denotes an $R_bNH-C(=NH)-$ group wherein

R_b denotes a hydrogen atom, a hydroxy,
 C_{1-9} -alkoxycarbonyl, cyclohexyloxycarbonyl, phenyl-
 C_{1-3} -alkoxycarbonyl, benzoyl, p- C_{1-3} -alkyl-benzoyl or
10 pyridinoyl group, whilst the ethoxy moiety in the
2-position of the abovementioned C_{1-9} -alkoxycarbonyl
group may additionally be substituted by a C_{1-3} -alkyl-
sulfonyl or 2-(C_{1-3} -alkoxy)-ethyl group,

15 Ar denotes a 1,4-phenylene group optionally substituted by
a chlorine atom or by a methyl, ethyl or methoxy group or
it denotes a 2,5-thienylene group,

Het denotes a 1-(C_{1-3} -alkyl)-2,5-benzimidazolylene, 1-
20 cyclopropyl-2,5-benzimidazolylene, 2,5-benzothiazolylene,
1-(C_{1-3} -alkyl)-2,5-indolylene, 1-(C_{1-3} -alkyl)-
2,5-imidazo[4,5-b]pyridinylene, 3-(C_{1-3} -alkyl)-
2,7-imidazo[1,2-a]pyridinylene or 1-(C_{1-3} -alkyl)-
2,5-thieno[2,3-d]imidazolylene group and

25

R_a denotes an R_2NR_3- group wherein

R_2 is a C_{1-4} -alkyl group substituted by a carboxy,
 C_{1-6} -alkyloxycarbonyl, benzyloxycarbonyl,
30 C_{1-3} -alkylsulphonylaminocarbonyl or 1H-tetrazol-5-yl
group,

a C_{2-4} -alkyl group substituted by a hydroxy, benzyloxy,
carboxy- C_{1-3} -alkylamino, C_{1-3} -alkoxycarbonyl-
35 C_{1-3} -alkylamino, N-(C_{1-3} -alkyl)-carboxy- C_{1-3} -alkylamino





or N-(C₁₋₃-alkyl)-C₁₋₃-alkoxycarbonyl-C₁₋₃-alkylamino group, whilst in the abovementioned groups the carbon atom in the α -position to the adjacent nitrogen atom may not be substituted,

5

R₃ denotes a C₃₋₇-cycloalkyl group, a propargyl group, wherein the unsaturated part may not be linked directly to the nitrogen atom of the R₂NR₃ group, a phenyl group optionally substituted by a fluorine or chlorine atom, or by a methyl or methoxy group, a pyrazolyl, pyridazolyl or pyridinyl group optionally substituted by a methyl group or

10

R₂ and R₃ together with the nitrogen atom between them denote a 5- to 7-membered cycloalkyleneimino group, optionally substituted by a carboxy or C₁₋₄-alkoxycarbonyl group, to which a phenyl ring may additionally be fused,

15

the tautomers, the stereoisomers and the salts thereof.

20

4. Disubstituted bicyclic heterocycles of general formula I according to claim 1, wherein

A denotes a carbonyl or sulphonyl group linked to the benzo, pyrido or thieno moiety of the group Het, whilst moreover the abovementioned moieties may not contain an R₁ group,

25

B denotes an ethylene group in which the methylene group linked to the group Ar may be replaced by an oxygen or sulphur atom or by an -NR₁- group, wherein

30

R₁ denotes a hydrogen atom or a methyl group,

35

E denotes an R_bNH-C(=NH)- group, wherein





- 5 R_b denotes a hydrogen atom or a hydroxy,
 C_{1-9} -alkoxycarbonyl, cyclohexyloxycarbonyl,
benzyloxycarbonyl, benzoyl, p- C_{1-3} -alkylbenzoyl or
nicotinoyl group, whilst the ethoxy moiety in the 2-
position of the abovementioned C_{1-9} -alkoxycarbonyl
group may additionally be substituted by a C_{1-3} -
alkylsulphonyl or 2-(C_{1-3} -alkoxy)-ethyl group,
- 10 Ar denotes a 1,4-phenylene group optionally substituted by
a chlorine atom or by a methyl, ethyl or methoxy group, or
it denotes a 2,5-thienylene group,
- 15 Het denotes a 1-methyl-2,5-benzimidazolylenes, 1-
cyclopropyl-2,5-benzimidazolylenes, 2,5-benzothiazolylenes,
1-methyl-2,5-indolylenes, 1-methyl-
2,5-imidazo[4,5-b]pyridinylenes, 3-methyl-
2,7-imidazo[1,2-a]pyridinylenes or 1-methyl-
20 2,5-thieno[2,3-d]imidazolylenes group and
- R_a denotes a R_2NR_3 - group wherein
- 25 R_2 denotes a C_{1-3} -alkyl group which may be substituted
by a carboxy, C_{1-6} -alkyloxycarbonyl, benzyloxycarbonyl,
methylsulphonylaminocarbonyl or 1H-tetrazol-5-yl group,
- 30 a C_{2-3} -alkyl group substituted by a hydroxy, benzyloxy,
carboxy- C_{1-3} -alkylamino, C_{1-3} -alkoxycarbonyl-
 C_{1-3} -alkylamino, N-(C_{1-3} -alkyl)-carboxy- C_{1-3} -alkylamino
or N-(C_{1-3} -alkyl)- C_{1-3} -alkoxycarbonyl- C_{1-3} -alkylamino
group, whilst in the abovementioned groups the carbon
atom in the α -position to the adjacent nitrogen atom
may not be substituted, and
- 35





R_3 denotes a propargyl group, wherein the unsaturated moiety may not be linked directly to the nitrogen atom of the R_2NR_3 group, a phenyl group optionally substituted by a fluorine or chlorine atom, or by a methyl or methoxy group or it denotes a pyridinyl group,

the tautomers, the stereoisomers and the salts thereof.

5. Disubstituted bicyclic heterocycles of general formula I according to claim 1, wherein

A denotes a carbonyl group linked to the benzo or thieno moiety of the group Het,

B denotes an ethylene group wherein the methylene group attached to the group Ar may be replaced by an $-NR_1$ group, whilst

R_1 denotes a hydrogen atom or a methyl group,

E denotes an $R_bNH-C(=NH)-$ group wherein

R_b is a hydrogen atom, a hydroxy, C_{1-9} -alkoxycarbonyl, cyclohexyloxycarbonyl, benzyloxycarbonyl, benzoyl, p- C_{1-3} -alkyl-benzoyl or nicotinoyl group, whilst the ethoxy moiety in the 2-position of the abovementioned C_{1-9} -alkoxycarbonyl group may additionally be substituted by a methylsulfonyl or 2-ethoxy-ethyl group,

Ar denotes a 1,4-phenylene group optionally substituted by a methoxy group or it denotes a 2,5-thienylene group,





Het denotes a 1-methyl-2,5-benzimidazolylylene, 2,5-benzothiazolylylene, 1-methyl-2,5-indolylylene or 1-methyl-2,5-thieno[2,3-d]imidazolylylene group and

5 R_a denotes an R_2NR_3 - group wherein

R_2 denotes a C_{1-3} -alkyl group which may be substituted by a carboxy, C_{1-6} -alkyloxycarbonyl, benzyloxycarbonyl, methylsulfonylaminocarbonyl or 1H-tetrazol-5-yl group,

10

a C_{2-3} -alkyl group substituted by a hydroxy, benzyloxy, carboxy- C_{1-3} -alkylamino, C_{1-3} -alkoxycarbonyl- C_{1-3} -alkylamino, N-(C_{1-3} -alkyl)-carboxy- C_{1-3} -alkylamino or N-(C_{1-3} -alkyl)- C_{1-3} -alkoxycarbonyl- C_{1-3} -alkylamino group, whilst in the abovementioned groups the carbon atom in the α -position to the adjacent nitrogen atom may not be substituted, and

15

R_3 denotes a phenyl group optionally substituted by a fluorine atom, or it denotes a 2-pyridinyl group,

20

the tautomers, stereoisomers and the salts thereof.

25 6. The following compounds of general formula I:

(a) 2-[N-(4-amidinophenyl)-aminomethyl]-benzthiazole-5-carboxylic acid-N-phenyl-N-(2-carboxyethyl)-amide,

30 (b) 2-[N-(4-midinophenyl)-N-methyl-aminomethyl]-benzthiazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide,

(c) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide,

35





- (d) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-
benzimidazol-5-yl-carboxylic acid-N-phenyl-
N-(3-hydroxycarbonylpropyl)-amide,
5
- (e) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-
benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-
N-(hydroxycarbonylmethyl)-amide,
- 10 (f) 1-Methyl-2-[2-(2-amidinothiophen-5-yl)ethyl]-
benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-
hydroxycarbonylethyl)-amide,
- (g) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-
15 benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-
hydroxycarbonylethyl)-amide,
- (h) 1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-
yl-carboxylic acid-N-(2-pyridyl)-N-(2-
20 hydroxycarbonylethyl)-amide,
- (i) 1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-
yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-
amide,
25
- (j) 1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-
yl-carboxylic acid-N-phenyl-N-[2-(1H-tetrazol-5-yl)ethyl]-
amide,
- 30 (k) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-
benzimidazol-5-yl-carboxylic acid-N-phenyl-N-[2-(1H-
tetrazol-5-yl)ethyl]-amide,
- (l) 1-Methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-
35 benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-
hydroxycarbonylethyl)-amide,





- (m) 1-Methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-pyridyl)-N-(2-hydroxycarbonylethyl)-amide,
- 5 (n) 1-Methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide,
- (o) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-[(N-hydroxycarbonylethyl-N-methyl)-2-aminoethyl]-amide,
- 10 (p) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-fluorophenyl)-N-(2-hydroxycarbonylethyl)-amide,
- 15 (q) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(4-fluorophenyl)-N-(2-hydroxycarbonylethyl)-amide,
- 20 (r) 1-Methyl-2-[N-(4-amidino-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide,
- 25 (s) 1-Methyl-2-[N-(4-amidino-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide,
- (t) 1-Methyl-2-[N-(4-amidinophenyl)aminomethyl]-indol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide and
- 30 (u) 1-Methyl-2-[N-(4-amidinophenyl)aminomethyl]-thieno[2.3-d]imidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide,
- 35





the tautomers, prodrugs, double prodrugs, stereoisomers and the salts thereof.

7. 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benz-
5 imidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxy-carbonylethyl)-amide, the prodrugs, double prodrugs and the salts thereof.
8. 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benz-
10 imidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxy-carbonylethyl)-amide, the prodrugs, double prodrugs and the salts thereof.
9. 1-Methyl-2-[N-(4-amidino-2-methoxy-phenyl)-aminomethyl]-
15 benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide, the prodrugs, double prodrugs and the salts thereof.
10. 1-Methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)phenyl]-
20 aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide and the salts thereof.
11. Physiologically acceptable salts of the compounds according to claims 1 to 10, wherein E denotes an
25 $R_pNH-C(=NH)$ - group.
12. Pharmaceutical compositions containing a compound according to at least one of claims 1 to 10, wherein E denotes an $R_pNH-C(=NH)$ - group, or a salt according to claim
30 11, optionally together with one or more inert carriers and/or diluents.
13. Use of a compound according to at least one of claims 1 to 10, wherein E denotes an $R_pNH-C(=NH)$ - group, or a salt
35 according to claim 11, for preparing a pharmaceutical composition having the effect of prolonging the thrombin





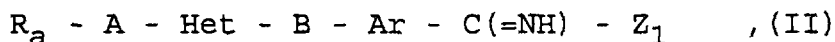
time, a thrombin-inhibiting effect and an inhibiting effect on related serine proteases.

14. Process for preparing a pharmaceutical composition according to claim 123, characterised in that a compound according to at least one of claims 1 to 10, wherein E denotes an $R_b\text{NH-C(=NH)-}$ group, or a salt according to claim 11, is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

10

15. Process for preparing compounds according to claims 1 to 11, characterised in that

- a. in order to prepare a compound of general formula I, wherein E denotes an $R_b\text{NH-C(=NH)-}$ group, wherein R_b is a hydrogen atom or a hydroxy or C_{1-3} -alkyl group, a compound of general formula



20

optionally formed in the reaction mixture, wherein

A, B, Ar, Het and R_a are defined as in claims 1 to 10 and

- 25 Z_1 denotes an alkoxy, aralkoxy, alkylthio or aralkylthio group, is reacted with an amine of general formula



- 30 wherein

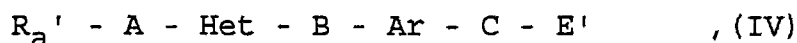
R_b' denotes a hydrogen atom, a hydroxy or C_{1-3} -alkyl group, or

- b. in order to prepare a compound of general formula I, wherein the $R_a\text{-A-}$ group and E are defined as in claims 1 to 10, with the proviso that the $R_a\text{-A-}$ group contains a





carboxy group and E is defined as in claims 1 to 10 or the
R_a-A- group is defined as in claims 1 to 10 and E denotes
an NH₂-C(=NH)- group, or the R_a-A- group contains a carboxy
group and E denotes an NH₂-C(=NH)- group, a compound of
5 general formula



wherein

A, B, Ar and Het are defined as in claims 1 to 10 and

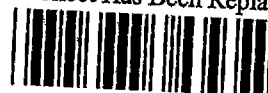
10

the R_a'-A- group and E' have the meanings given for the
R_a-A- group and E in claims 1 to 10, with the proviso that
the R_a'-A- group contains a group which can be converted
into a carboxyl group by hydrolysis, treatment with an acid
15 or base, thermolysis or hydrogenolysis and E is defined as
in claims 1 to 10 or E' denotes a group which may be
converted into an NH₂-C(=NH)- group by hydrolysis,
treatment with an acid or base, thermolysis or
hydrogenolysis and the R_a'-A- group has the meanings given
20 for the R_a-A- group in claims 1 to 10, or the R_a'-A- group
contains a group which may be converted into a carboxyl
group by hydrolysis, treatment with an acid or base,
thermolysis or hydrogenolysis and E' denotes a group which
may be converted into an NH₂-C(=NH)- group by hydrolysis,
25 treatment with an acid or base, thermolysis or
hydrogenolysis,

is converted, by hydrolysis, treatment with an acid or
base, thermolysis or hydrogenolysis, into a compound of
30 general formula I, wherein the R_a-A- group and E are
defined as in claims 1 to 10, with the proviso that the
R_a-A- group contains a carboxy group and E is defined as in
claims 1 to 10 or the R_a-A- group has the meanings given in
claims 1 to 10 and E denotes an NH₂-C(=NH)- group or the
35 R_a-A- group contains a carboxy group and E denotes an
NH₂-C(=NH)- group, or

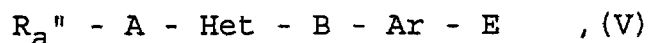


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c. in order to prepare a compound of general formula I wherein the R_a -A- group contains one of the ester groups mentioned in the definition of the R_a -A- group in claims 1 to 10, a compound of general formula

5



wherein

B, E, Ar and Het are defined as in claims 1 to 10 and R_a -A- group has the meanings given for the R_a -A- group in claims 1 to 10, with the proviso that the R_a -A- group contains a carboxyl group or a group which may be converted by means of an alcohol into a corresponding ester group, is reacted with an alcohol of general formula

15



wherein

R_7 denotes the alkyl moiety of one of the groups which may be cleaved *in vivo* mentioned in claims 1 to 10, with the exception of the R_6 -CO-O- (R_5CR_6) - group for a carboxyl group, or with the formamide acetals thereof or with a compound of general formula

20



25

wherein

R_8 denotes the alkyl moiety of one of the groups which may be cleaved *in vivo* mentioned in claims 1 to 10, with the exception of the R_6 -CO-O- (R_5CR_6) - group for a carboxyl group and

30

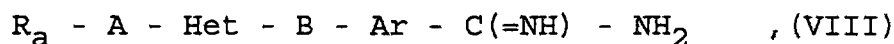
Z_2 denotes a leaving group, or

d. in order to prepare a compound of general formula I wherein R_b denotes a group which may be cleaved *in vivo*, a compound of general formula

35



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wherein

R_a , A, Het, B and Ar are defined as in claims 1 to 10, is reacted with a compound of general formula

5

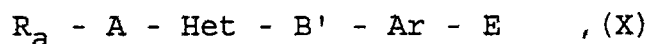


wherein

R_5 denotes a group which may be cleaved *in vivo* and

10 Z_2 denotes a nucleofugic leaving group, or

e. in order to prepare a compound of general formula I wherein B denotes an ethylene group wherein a methylene group is replaced by a sulphinyl or sulphonyl group, a
15 compound of general formula



wherein

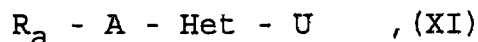
A, E, Ar, Het and R_a are defined as in claims 1 to 10 and

20

B' denotes an ethylene group, in which a methylene group is replaced by a sulphenyl or sulphinyl group, is oxidised or

f. in order to prepare a compound of general formula I, wherein E denotes a cyano group and B is an ethylene group, in which a methylene group, linked either to the group Het or Ar, is replaced by an oxygen or sulphur atom or by a sulphinyl, sulphonyl, carbonyl or $-\text{NR}_1-$ group, a compound
25 of general formula

30



is reacted with a compound of general formula

35



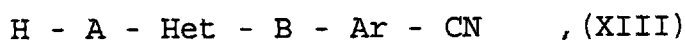
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wherein

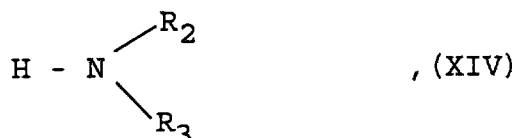
R_a , A, Ar and Het are defined as in claims 1 to 10,
one of the groups U or V denotes an HO-, HS-, HOSO-, HOSO₂-
or HNR₁- group and the other group denotes a Z₃CH₂- group,
5 wherein R₁ is defined as in claims 1 to 10 and Z₃ denotes a
nucleofugic leaving group, or

g. in order to prepare a compound of general formula I,
wherein E is a cyano group and R_a denotes an R₂NR₃- group,
10 a compound of general formula



wherein

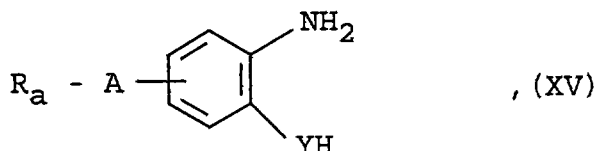
A, B, Het and Ar are defined as in claims 1 to 10, is
15 reacted with an amine of general formula



wherein

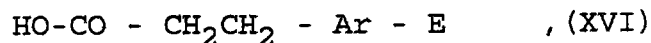
R₂ and R₃ are defined as in claims 1 to 10, or with the
20 reactive derivatives thereof, or

h. in order to prepare a benzimidazolyl, benzothiazolyl or
benzoxazolyl compound of general formula I, wherein B
denotes an ethylene group, a compound of general formula
25



wherein

R_a, A and Y are defined as in claims 1 to 10, is reacted
with a compound of general formula
30



wherein



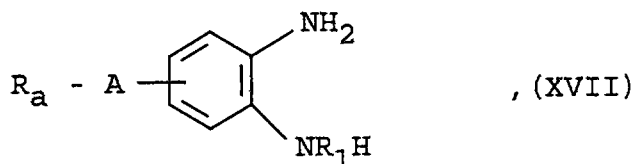
Ar and E are defined as in claims 1 to 10, or with the reactive derivatives thereof and

i. in order to prepare a quinoxalin-2-one compound of the general formula:

5

a compound of general formula

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wherein

10

R_a , R_1 and A are defined as in claims 1 to 10, is reacted with a compound of general formula

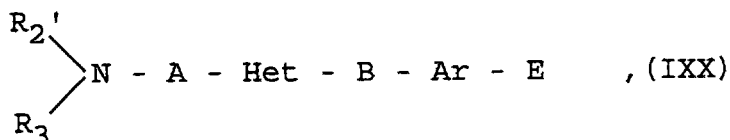


15 wherein

Ar and E are defined as in claims 1 to 10, or with the reactive derivatives thereof, or

j. in order to prepare a compound of general formula I
20 wherein R_2 denotes a C_{1-4} -alkyl group substituted by an alkylsulphonylaminocarbonyl group:

a compound of general formula



25

wherein

R_3 , A, B, E, and Het are defined as in claims 1 to 10 and R_2' denotes a C_{1-4} -alkyl group substituted by a carboxy group, or the reactive derivatives thereof,

30 is reacted with a salt of a compound of general formula



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C_{1-3} -Alkyl-SO₂-NH₂ (XX),

5

and, if necessary, a protecting group used during the reactions in order to protect reactive groups is cleaved and/or

10 subsequently, if desired, a compound of general formula I thus obtained is resolved into the stereoisomers thereof and/or

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



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