

Charles M. Lizza
William C. Baton
SAUL EWING LLP
One Riverfront Plaza, Suite 1520
Newark, NJ 07102-5426
(973) 286-6700

OF COUNSEL:
Bruce M. Wexler
Joseph M. O'Malley, Jr.
Eric W. Dittmann
Isaac S. Ashkenazi
Leonard A. Monfredo
PAUL HASTINGS LLP
75 East 55th Street
New York, NY 10022
(212) 318-6000

*Attorneys for Plaintiffs
Boehringer Ingelheim Pharma GmbH & Co. KG,
Boehringer Ingelheim International GmbH, and
Boehringer Ingelheim Pharmaceuticals, Inc.*

**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

BOEHRINGER INGELHEIM PHARMA GMBH
& CO. KG, BOEHRINGER INGELHEIM
INTERNATIONAL GMBH, and BOEHRINGER
INGELHEIM PHARMACEUTICALS, INC.,

Plaintiffs,

v.

BRECKENRIDGE PHARMACEUTICAL, INC.

Defendant.

Civil Action No. _____

**COMPLAINT FOR
PATENT INFRINGEMENT**

(Filed Electronically)

Plaintiffs *Boehringer Ingelheim Pharma GmbH & Co. KG, *Boehringer Ingelheim International GmbH, and *Boehringer Ingelheim Pharmaceuticals, Inc.** (collectively, “*Boehringer*” or “*Plaintiffs*”), by their undersigned attorneys, for their Complaint against*

Defendant Breckenridge Pharmaceutical, Inc. (“Breckenridge”) hereby allege as follows:

THE PARTIES

1. Plaintiff Boehringer Ingelheim Pharma GmbH & Co. KG (“BIPKG”) is a limited partnership organized and existing under the laws of Germany, having a principal place of business at Binger Strasse 173, 55216 Ingelheim, Germany.

2. Plaintiff Boehringer Ingelheim International GmbH (“BII”) is a private limited liability company organized and existing under the laws of Germany, having a principal place of business at Binger Strasse 173, 55216 Ingelheim, Germany.

3. Plaintiff Boehringer Ingelheim Pharmaceuticals, Inc. (“BIPI”) is a corporation organized and existing under the laws of the state of Delaware, having a principal place of business at 900 Ridgebury Road, Ridgefield, Connecticut 06877.

4. Defendant Breckenridge is a corporation organized and existing under the laws of the state of Florida, having a principal place of business at 6111 Broken Sound Parkway, NW, Suite 170, Boca Raton, Florida 33487.

5. Defendant Breckenridge maintains its sales and marketing office at 1 Passaic Ave. Fairfield, New Jersey 07004.

NATURE OF THE ACTION

6. This is a civil action concerning United States Patent No. 6,087,380 (“the ’380 patent”). This action arises under the Patent Laws of the United States, 35 U.S.C. § 100, *et seq.* and the Declaratory Judgment Act, 28 U.S.C. §§ 2201-02.

JURISDICTION AND VENUE

7. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

8. Venue is proper in this Court under 28 U.S.C. §§ 1391(c) and 1400(b).

PERSONAL JURISDICTION OVER BRECKENRIDGE

9. Defendant Breckenridge develops, manufactures, and/or distributes generic drugs for sale and use throughout the United States, including in this Judicial District.

10. This Court has personal jurisdiction over Breckenridge because, *inter alia*, Breckenridge: (1) has substantial, continuous, and systematic contacts with this State; (2) intends to market, sell, and/or distribute Breckenridge's infringing Abbreviated New Drug Application ("ANDA") products ("Breckenridge's ANDA products," as defined in paragraph 15 *infra*) to residents of this State; (3) maintains its sales and marketing office in this State; (4) maintains a broad distributorship network within this State; and (5) enjoys substantial income from sales of its generic pharmaceutical products in this State.

11. Breckenridge has initiated at least one lawsuit in this Judicial District: *Breckenridge Pharm., Inc. v. Sonar Prods., Inc.*, No 10-3921 (WHW)(MCA) (D.N.J. Aug. 2, 2010).

PATENT-IN-SUIT

12. BIPI is the holder of New Drug Application ("NDA") No. 22-512, by which the United States Food and Drug Administration ("FDA") first granted approval for 75 mg and 150 mg dabigatran etexilate mesylate capsules. The dabigatran etexilate mesylate capsules described in BIPI's NDA are prescribed, *inter alia*, to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation. Boehringer sells these capsules in the United States under the trade name "PRADAXA[®]."

13. BIPKG owns the '380 patent, which was duly and legally issued on July 11, 2000, and is titled "Disubstituted Bicyclic Heterocycles, the Preparations and the Use Thereof as

Pharmaceutical Compositions.” BII and BIPI have an exclusive license under the ’380 patent in the United States from BIPKG. A copy of the ’380 patent is attached as Exhibit A.

ACTS GIVING RISE TO THIS ACTION

COUNT I – INFRINGEMENT OF THE ’380 PATENT BY BRECKENRIDGE

14. Plaintiffs reallege paragraphs 1-13 as if fully set forth herein.

15. Defendant Breckenridge filed with the FDA ANDA No. 207922, which included a certification with respect to the ’380 patent under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355(j)(2)(A)(vii)(IV), seeking approval to engage in the manufacture, use, sale, offer for sale, and/or importation of 75 mg and 150 mg dabigatran etexilate mesylate capsules (“Breckenridge’s ANDA products”) prior to the expiration of that patent.

16. On or about February 5, 2015, Breckenridge sent a letter (“Breckenridge’s Notice Letter”) to BIPKG and Boehringer Ingelheim Corp. in which Breckenridge represented that it had filed an ANDA for Breckenridge’s ANDA products, including the certification with respect to the ’380 patent, and that it sought approval of its ANDA prior to the expiration of that patent.

17. Breckenridge’s Notice Letter did not provide complete and effective notice under 21 U.S.C. § 355(j)(2)(B)(iii) because Breckenridge has not served notice to BIPI.

18. This action was commenced within 45 days of the receipt of Breckenridge’s Notice Letter.

19. Because Breckenridge seeks approval of its ANDA to engage in the commercial manufacture, use, sale, offer for sale, and/or importation of a drug claimed in the ’380 patent, and a drug the use of which is claimed in the ’380 patent, before its expiration, Breckenridge has infringed the ’380 patent pursuant to 35 U.S.C. § 271(e)(2)(A).

20. Plaintiffs are entitled to a declaration that, if Breckenridge commercially

manufactures, uses, sells, offers to sell, and/or imports any of Breckenridge's ANDA products, or induces or contributes to any such conduct, it would further infringe the '380 patent pursuant to 35 U.S.C. § 271(a), (b), and/or (c).

21. The commercial manufacture, use, sale, offer to sell, and/or importation of Breckenridge's ANDA products, if approved by the FDA, prior to the expiration of the '380 patent, for use in accordance with its proposed labeling would infringe and/or induce and/or contribute to the infringement of the '380 patent. Boehringer is entitled to relief provided by 35 U.S.C. § 271(e)(4), including an Order of this Court that the effective date of the approval of Breckenridge's ANDA No. 207922 be a date that is not earlier than the expiration date of the '380 patent, or any later expiration of exclusivity for the '380 patent to which Boehringer is or may become entitled.

22. Upon information and belief, Breckenridge was aware of the existence of the '380 patent, and was aware that the filing of its ANDA and certification with respect to the '380 patent constituted an act of infringement of that patent.

23. Plaintiffs will be irreparably harmed by Breckenridge's infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request the following relief:

A. A Judgment be entered that Defendant Breckenridge has infringed the '380 patent by submitting Breckenridge's ANDA No. 207922;

B. A Judgment be entered that this case is exceptional, and that Plaintiffs are entitled to their reasonable attorneys' fees pursuant to 35 U.S.C. § 285;

C. A permanent injunction be issued, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Defendant Breckenridge, and its officers, agents, attorneys, and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of the drugs or methods of administering drugs claimed in the '380 patent, including any exclusivities or extensions;

D. An Order be issued pursuant to 35 U.S.C. § 271(e)(4)(A) that the effective date of any approval of Breckenridge's ANDA No. 207922 be a date that is not earlier than the expiration date of the '380 patent, or any later expiration of exclusivity of the '380 patent to which Plaintiffs are or may become entitled; and

E. Such other and further relief as the Court may deem just and proper.

Dated: March 5, 2015

By: s/ Charles M. Lizza
Charles M. Lizza
William C. Baton
SAUL EWING LLP
One Riverfront Plaza, Suite 1520
Newark, NJ 07102-5426
(973) 286-6700
clizza@saul.com
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CERTIFICATION PURSUANT TO LOCAL CIVIL RULES 11.2 & 40.1

I hereby certify that the matter captioned *Boehringer Ingelheim Pharma GmbH & Co. KG, et al. v. Teva Pharm. USA, Inc., et al.*, Civil Action No. 14-7811 (MLC)(TJB), is related to the matter in controversy because the matter in controversy involves the same plaintiffs, the same patent, and defendants seeking FDA approval to market a generic version of the same pharmaceutical product.

I further certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court, or of any pending arbitration or administrative proceeding.

Dated: March 5, 2015

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One Riverfront Plaza, Suite 1520
Newark, NJ 07102-5426
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clizza@saul.com
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EXHIBIT A



US006087380A

United States Patent [19]
Hael et al.

[11] **Patent Number:** **6,087,380**
 [45] **Date of Patent:** ***Jul. 11, 2000**

[54] **DISUBSTITUTED BICYCLIC HETEROCYCLES, THE PREPARATIONS AND THE USE THEREOF AS PHARMACEUTICAL COMPOSITIONS**

[75] Inventors: **Norbert Hael**, Schemmerhofen; **Henning Priepke**, Warthausen; **Uwe Ries**, Biberach; **Jean Marie Stassen**, Warthausen; **Wolfgang Wienen**, Biberach, all of Germany

[73] Assignee: **Boehringer Ingelheim Pharma KG**, Ingelheim, Germany

[*] Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

[21] Appl. No.: **09/025,690**

[22] Filed: **Feb. 18, 1998**

Related U.S. Application Data

[60] Provisional application No. 60/044,421, Apr. 29, 1997.

Foreign Application Priority Data

Nov. 24, 1949 [DE] Germany 197 51 939
 Feb. 18, 1997 [DE] Germany 197 06 229

[51] **Int. Cl.**⁷ **C07D 401/06**; C07D 401/14; A61K 31/4427

[52] **U.S. Cl.** **514/336**; 514/338; 546/268.4; 546/273.4

[58] **Field of Search** 546/273.4, 268.4; 514/338, 336

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,675,405 6/1987 Musser et al. 546/172
 5,416,099 5/1995 Hartman et al. 514/323

FOREIGN PATENT DOCUMENTS

0 540 051 A1 5/1993 European Pat. Off. .
 0 623 596 A1 11/1994 European Pat. Off. .
 0 655 439 A2 5/1995 European Pat. Off. .
 41 29 603 A1 3/1993 Germany .

OTHER PUBLICATIONS

Takayasu Nagahara; Dibasic (amidinoaryl) propanoic Acid Derivatives as Novel Blood Coagulation Factor Xa Inhibitors, *J. Med. Chem.* 1994, 37, 1200-1207-XP000608128.

Primary Examiner—Alan L. Rotman
Attorney, Agent, or Firm—Robert P. Raymond; Alan R. Stempel; Mary-Ellen M. Devlin

[57] **ABSTRACT**

New disubstituted bicyclic heterocycles of general formula



Compounds of the above general formula I, wherein E denotes an $R_bNH-C(=NH)-$ group, have valuable pharmacological properties, particularly a thrombin-inhibiting effect and the effect of prolonging thrombin time, and those wherein E denotes a cyano group, are valuable intermediates for preparing the other compounds of general formula I. Exemplary compounds of formula I are:

- (a) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide,
- (b) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(hydroxycarbonylmethyl)-amide,
- (c) 1-Methyl-2-[N-(4-amidino-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(hydroxycarbonylmethyl)-amide, and
- (d) 1-Methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)phenyl]aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl) amide.

13 Claims, No Drawings

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**DISUBSTITUTED BICYCLIC
HETEROCYCLES, THE PREPARATIONS
AND THE USE THEREOF AS
PHARMACEUTICAL COMPOSITIONS**

REFERENCE TO PRIOR PROVISIONAL
APPLICATION

Benefit of prior filed and copending U.S. provisional application Ser. No. 60/044,421, filed on Apr. 29, 1997, is hereby claimed.

DESCRIPTION OF THE INVENTION

The present invention relates to new disubstituted bicyclic heterocycles of general formula



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.

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 $R_bNH-C(=NH)-$ group, and the tautomers and stereoisomers thereof have 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, pharmaceutical compositions containing the pharmacologically active compounds and the use thereof.

In the above general formula

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, 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,

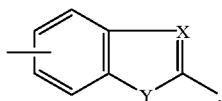
E denotes a cyano or $R_bNH-C(=NH)-$ group wherein

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

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,

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

Het denotes a bicyclic heterocycle of formula



wherein

X is a nitrogen atom and

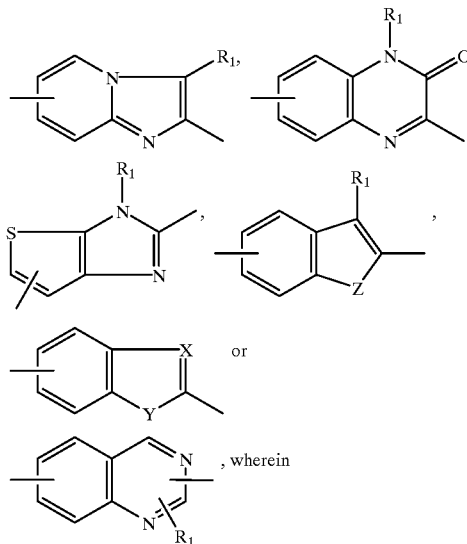
Y is an oxygen or sulphur atom or a nitrogen atom optionally substituted by a C_{1-6} -alkyl or C_{3-7} -cycloalkyl group, whilst additionally one or two non-angular methyne groups in the phenyl moiety of the above-mentioned bicyclic heterocycle may each be replaced by a nitrogen atom,

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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,

or Het denotes a group of the formula



wherein

R_1 is as hereinbefore defined,

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,

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, 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, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, thienyl or imidazolyl group or

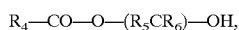
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R_2 and R_3 together with the nitrogen atom between them denote a 5- to 7-membered cycloalkyleneimino group, optionally substituted by a carboxymethyl or C_{1-4} -alkoxycarbonyl group, onto which a phenyl ring may additionally be fused.

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 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 alcoholic moiety is preferably a C_{1-6} -alkanol, a phenyl- C_{1-3} -alkanol, a C_{3-6} -cycloalkanol, wherein a C_{5-8} -cycloalkanol may additionally be substituted by one or two C_{1-3} -alkyl groups, a C_{5-8} -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 C_{1-3} -alkyl, phenyl- C_{1-3} -alkyl, phenyl- C_{1-3} -alkoxycarbonyl or C_{2-6} -alkanoyl group, and the cycloalkanol moiety may additionally be substituted by one or two C_{1-3} -alkyl groups, a C_{4-7} -cycloalkenol, a C_{3-5} -alkenol, a phenyl- C_{3-5} -alkenol, a C_{3-5} -alkynol or phenyl- C_{3-5} -alkynol, with the proviso that no bond to the oxygen atom emanates from a carbon atom which carries a double or triple bond, a C_{3-8} -cycloalkyl- C_{1-3} -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 C_{1-3} -alkyl groups, a 1,3-dihydro-3-oxo-1-isobenzofuranol or an alcohol of formula



wherein

R_4 denotes a C_{1-8} -alkyl, C_{5-7} -cycloalkyl, phenyl or phenyl- C_{1-3} -alkyl group,

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

R_6 denotes a hydrogen atom or a C_{1-3} -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, an acyl group such as a benzoyl- or pyridinoyl group or a C_{1-16} -alkanoyl group such as the formyl-, acetyl-, propionyl-, butanoyl-, pentanoyl- or hexanoyl group, an allyloxycarbonyl group, a C_{1-16} -alkoxycarbonyl group such as the methoxycarbonyl-, ethoxycarbonyl-, propoxycarbonyl-, isopropoxycarbonyl-, butoxycarbonyl-, tert.-butoxycarbonyl-, pentoxycarbonyl-, hexoxycarbonyl-, octyloxycarbonyl-, nonyloxycarbonyl-, decyloxycarbonyl-, undecyloxycarbonyl-, dodecyloxycarbonyl- or hexadecyloxycarbonyl group, a phenyl- C_{1-6} -alkoxycarbonyl group such as the benzyloxycarbonyl-, phenylethoxycarbonyl- or phenylpropoxycarbonyl group, a C_{1-3} -alkylsulphonyl- C_{2-4} -alkoxycarbonyl-, C_{1-3} -alkoxy- C_{2-4} -alkoxy- C_{2-4} -alkoxycarbonyl- 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 include a C_{1-6} -alkoxycarbonyl group such as the methoxycarbonyl, ethoxycarbonyl, n-propyloxycarbonyl, isopropyloxycarbonyl, n-butyloxycarbonyl, n-pentyloxycarbonyl, n-hexyloxycarbonyl or cyclohexyloxycarbonyl group or phenyl- C_{1-3} -alkoxycarbonyl group such as the benzyloxycarbonyl group and

for an imino or amino group a C_{1-9} -alkoxycarbonyl group such as the methoxycarbonyl, ethoxycarbonyl, n-propyloxycarbonyl, isopropyloxycarbonyl,

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n-butyloxycarbonyl, n-pentyloxycarbonyl, n-hexyloxycarbonyl, cyclohexyloxycarbonyl, n-heptyloxycarbonyl, n-octyloxycarbonyl or n-nonyloxycarbonyl group, a phenyl- C_{1-3} -alkoxycarbonyl group such as the benzyloxycarbonyl group, a phenylcarbonyl 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- C_{2-3} -alkoxycarbonyl or C_{1-3} -alkoxy- C_{2-3} -alkoxy- C_{2-4} -alkoxycarbonyl group such as the 2-methylsulphonylethoxycarbonyl or 2-(2-ethoxy)-ethoxycarbonyl group.

Moreover, the saturated alkyl and alkoxy moieties containing more than 2 carbon atoms as well as alkanoyl and 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.

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 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 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,

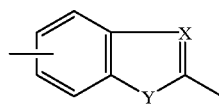
E denotes an $R_bNH-C(=NH)-$ group wherein

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

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,

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

Het denotes a bicyclic heterocycle of formula



wherein

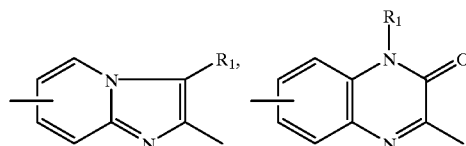
X is a nitrogen atom and

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,

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

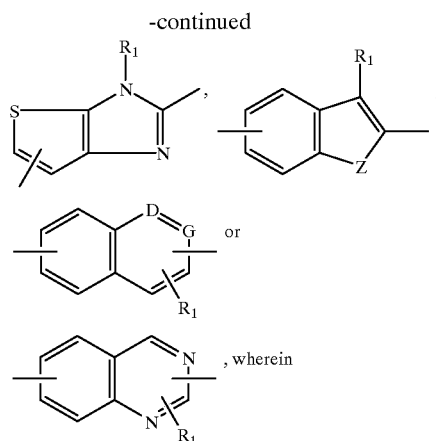
Y denotes a nitrogen atom optionally substituted by a C_{1-6} -alkyl or C_{3-7} -cycloalkyl group,

or Het denotes a group of the formulae



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R_1 is as hereinbefore defined,

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,

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} -alkylsulphonylamino carbonyl, phenylsulphonylamino carbonyl, trifluorosulphonylamino, trifluorosulphonylamino carbonyl 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, quinazolinylenes, quinoxalinylenes, imidazo[4,5-b]pyridinylene, imidazo[1,2-a]pyridinylene, thiazolo[5,4-b]pyridinylene or thieno[2,3-d]imidazolylene groups, the tautomers, the prodrugs, the double prodrugs, the stereoisomers and the salts thereof.

Particularly preferred compounds of general formula I above are those wherein

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

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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 C_{1-4} -alkyl group, 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 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,

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-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

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, C_{1-3} -alkylsulphonylamino carbonyl 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- 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,

R_3 denotes a C_{3-7} -cycloalkyl group, a propargyl 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 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, pyrindo 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_{1-9} -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 C_{1-3} -alkylsulphonyl or 2-(C_{1-3} -alkoxy)-ethyl group,

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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-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

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

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

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 denotes a pyridinyl group, particularly those 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, wherein

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 denotes a 2,5-thienylene group,

Het denotes a 1-methyl-2,5-benzimidazolylene, 2,5-benzothiazolylene, 1-methyl-2,5-indolylene or 1-methyl-2,5-thieno[2,3-d]imidazolylene group and

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, methylsulfonylamino carbonyl or 1H-tetrazol-5-yl group,

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

R_3 denotes a phenyl group optionally substituted by a fluorine atom, or denotes a 2-pyridinyl group, the tautomers, stereoisomers and the salts thereof.

The following are mentioned as examples of particularly preferred compounds:

(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-hydroxycarbonylethyl)-amide,

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

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

(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-hydroxycarbonylethyl)-amide,

(g) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-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-hydroxycarbonylethyl)-amide,

(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,

(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]-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,

(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,

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

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

(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,

(t) 1-Methyl-2-[N-(4-amidinophenyl)aminomethyl]-indol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide and

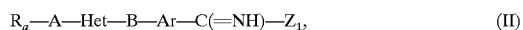
(u) 1-Methyl-2-[N-(4-amidinophenyl)aminomethyl]-thieno[2,3-d]imidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide,

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

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 $R_bNH—C(=NH)—$ group, wherein R_b is a hydrogen atom, a hydroxy or C_{1-3} -alkyl group:

By reacting a compound of general formula



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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 alkylthio or aralkylthio group such as the methylthio, ethylthio, n-propylthio or benzylthio group, with an amine of general formula



wherein

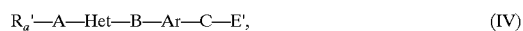
R_b' denotes a hydrogen atom or a hydroxy or C₁₋₃-alkyl group.

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 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 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-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 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 NH₂-C(=NH)- group, or that the R_a-A- group contains a carboxy group and E denotes an NH₂-C(=NH)- group:

Converting a compound of general formula



wherein

A, B, Ar and Het are as hereinbefore defined and 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 hereinbefore defined 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 for the R_a-A- group hereinbefore 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, 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 general

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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 is as hereinbefore defined or the R_a-A- group has the meanings given above 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.

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, trimethylsilylestere, orthoesters or iminoesters which may conveniently be converted into a carboxyl group by 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, and

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

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

If the R_a'-A- group and/or E' in a compound of formula IV contains the tert.-butyl or tert.-butyloxycarbonyl group, 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 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 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 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, 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.

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 hereinbefore:

Reaction of a compound of general formula



wherein

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

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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 R_6 —CO—O—(R_5 CR₆)— group for a carboxyl group, or with the formamide acetals thereof. 10
or with a compound of general formula



wherein

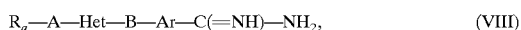
R_8 denotes the alkyl moiety of one of the above-mentioned groups which may be cleaved in vivo, with the exception of the R_6 —CO—O—(R_5 CR₆)— group for a carboxyl group and Z_2 denotes a leaving group such as a 20
halogen atom, e.g. a chlorine or bromine atom.

The reaction with an alcohol of general formula VI is conveniently carried out in a solvent or mixture of 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 agent, e.g. in the presence of isobutylchloroformate, thionyl chloride, trimethylchlorosilane, hydrochloric acid, sulphuric acid, 30
methanesulphonic acid, p-toluenesulphonic acid, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-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. 35

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 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-methylmorpholine, which may act as solvent at the same 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. 40

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

Reacting a compound of general formula 45



wherein

R_a , A, Het, B and Ar are as hereinbefore defined, with a compound of general formula 50



wherein

R_5 denotes a group which may be cleaved in vivo and 55
 Z_2 denotes a nucleofugic leaving group such as a halogen atom, e.g. a chlorine, bromine or iodine atom.

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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. 15

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



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. 25

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 1000° C. 30

In order to prepare a corresponding sulphinyl compound of general formula I oxidation is conveniently carried out with one equivalent of the oxidising agent used, e.g. with 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 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 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 thioether chlorine complex is conveniently hydrolysed with aqueous ethanol. 40

In order to prepare a sulphonyl compound of general formula I, oxidation is carried out starting from a corresponding sulphinyl 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, 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 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 55

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sulphenyl compound, preferably in methylene 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 sulphanyl 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 is replaced by an oxygen or sulphur atom or by a sulphanyl, 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, 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 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.

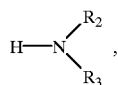
g. In order to prepare a compound of general formula I, wherein E is a cyano group and R_a denotes an R₂NR₃— group:

Reacting a compound of general formula



wherein

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



wherein

R₂ and R₃ are as hereinbefore defined, or with the reactive derivatives thereof.

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 amine of general formula III, optionally in the presence of a dehydrating agent, e.g. in the presence of isobutyl-chloroformate, tetraethylortho-carbonate, trimethylortho-acetate, 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, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate, 2-(1H-benzotriazol-1-yl)-1,1,3,3-

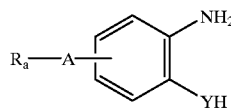
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tetramethyluronium-tetrafluoroborate/1-hydroxy-benzotriazole, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride and optionally with the addition of a base such as pyridine, 4-dimethylaminopyridine, N-methyl-morpholine or triethylamine, 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 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 between 0 and 150° C., preferably at temperatures between 50 and 100° C.

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

(XV)



wherein

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



wherein

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

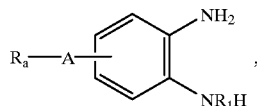
The reaction is conveniently carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane, optionally in the presence of a dehydrating agent, e.g. in the presence of isobutylchloroformate, tetraethylortho-carbonate, trimethylorthoacetate, 2,2-dimethoxypropane, tetramethoxysilane, thionyl chloride, trimethylchlorosilane, 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 triphenylphosphine/carbon tetrachloride, and optionally with the addition of a base such as pyridine, 4-dimethylaminopyridine, 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.

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



wherein

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



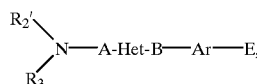
wherein

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, ethanol or dioxan, optionally in the presence of a dehydrating agent, e.g. in the presence of isobutyl chloroformate, tetraethyl orthocarbonate, trimethyl orthoacetate, 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, 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-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:



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



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The reaction is preferably carried out with a corresponding reactive compound of general formula XIX 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.

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.

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 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, 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, 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 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.

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 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 a solvent such as methylene chloride, acetonitrile or acetonitrile/water at temperatures between 0 and 50°, but preferably at room temperature.

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

A tert.butyl or tert.butylloxycarbonyl group is preferably cleaved by treatment with an acid such as trifluoroacetic acid or hydrochloric acid, optionally using a solvent such 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, 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)-palladium (O), 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°, preferably at room temperature and under inert gas, or by treating with a catalytic amount of tris-

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(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.

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.

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.

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.

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 methoxy-acetamido group, to form a corresponding bicyclic 2-alkoxymethyl compound, optionally subsequent hydrolysis and 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 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.

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-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.

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 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 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 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 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.

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

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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 (-)-menthylxycarbonyl.

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 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-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 simultaneously also have a slight inhibitory effect on thrombocyte aggregation.

For example, the following compounds:

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,

C=1-methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(hydroxycarbonyl-methyl)-amide,

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

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

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

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were investigated as follows for their effects on thrombin time:

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

Method:

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

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 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.

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:

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.

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 reclosures 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.

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

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polyethyleneglycol, propyleneglycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof, to produce conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions or suppositories.

The Examples which follow are intended to illustrate the invention:

Preliminary remarks

Unless otherwise specified, the R_f values were always determined using polygram silica gel plates produced by 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).

EXAMPLE 1

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

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 imidazole 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 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

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

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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)

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

EXAMPLE 2

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

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-ethoxycarbonyl-ethyl)-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), R_f

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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

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

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 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) 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

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. 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) EKA mass spectrum: (M+H)⁺=485

EXAMPLE 5

3-Methyl-2-[2-(4-amidinophenyl)ethyl]-imidazo[4,5-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 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=50:45:5) EKA mass spectrum: (M+H)⁺=457

EXAMPLE 6

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-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, $C_{27}H_{26}N_6O_3$ (482.54) R_f value: 0.30 (silica gel; ethyl acetate/ethanol/ammonia=50:45:5) EKA mass spectrum: (M+H)⁺=483

EXAMPLE 7

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

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, $C_{26}H_{24}N_6O_3$ (468.52) R_f value: 0.24 (silica gel; ethyl acetate/ethanol/ammonia =50:45:5)

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EKA mass spectrum:	(M + H) ⁺ = 469 (M + Na) ⁺ = 491
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EXAMPLE 8

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

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

8.35 g (50 mMol) of 2-Methyl-5-methylamino-6-nitropyridine (Heterocycles 38, 529 (1994)) were dissolved in 300 ml ethyl 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 crystals. C₇H₁₁N₃ (137.20) Melting point: 112–113° C.

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

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 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. C₁₆H₁₄N₄O (278.32) Mass spectrum: M⁺=278

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

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 obtained. After 2 hours at room temperature the solvent 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), C₁₆H₁₄N₄O₂ (294.30) Mass spectrum: M⁺=294

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

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), C₁₆H₁₄N₄O₂ (294.30) Melting point: 172° C.

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

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 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), C₁₆H₁₂N₄O₂ (292.30) Melting point: 231–234° C.

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f) 1-Methyl-2-[(4-cyanophenyl)oxymethyl]-5-carboxymidazo[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 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. Yield: 0.81 g (61% of theory), C₁₆H₁₂N₄O₃ (308.7)

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

308 mg (1.0 mMol) of 1-methyl-2-[(4-cyanophenyl)oxymethyl]-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'-tetramethyluronium tetrafluoroborate. After 10 minutes at room temperature a 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 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), C₂₅H₁₂N₆O₄ (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

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-methoxycarbonylethyl)-amide with ethanol saturated by hydrogen chloride and with 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), C₂₆H₂₇N₇O₄ (501.57) Mass spectrum: (M+H)⁺=502

EXAMPLE 9

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

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 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 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

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 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

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purified by flash chromatography (silica gel; ethyl acetate/petroleum ether=5:95) and evaporated down again. 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

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)

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

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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) $C_{27}H_{27}N_5O_3S$ (501.60) Mass spectrum: (M+H)⁺=502

EXAMPLE 10

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

0.45 g (0.84 mMol) of 2-[N-(4-amidinophenyl)-aminomethyl]-benzothiazole-5-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-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. Yield: 0.26 g (67% of theory), R_f value: 0.47 (silica gel; methanol/5% aqueous sodium chloride=6:4) $C_{25}H_{23}N_5O_3S$ (473.55) Mass spectrum: (M+H)⁺=474

EXAMPLE 11

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

Prepared analogously to Example 9 from 2-[N-(4-cyanophenyl)-aminomethyl]benzothiazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-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) EKA mass spectrum: (M+H)⁺=489

EXAMPLE 12

2-[2-(4-amidinophenyl)ethyl]-benzothiazol-5-yl-carboxylic 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-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=4:1+a few drops of acetic acid) EKA mass spectrum: (M+H)⁺=488

EXAMPLE 13

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-cyanophenyl)-aminomethyl]-benzothiazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(ethoxycarbonylmethyl)-amide, ethanolic hydrochloric acid, ethanol and ammonium carbonate. Yield: 68% of theory, $C_{25}H_{24}N_6O_3S$ (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

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

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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, $C_{23}H_{20}N_6O_3S$ (460.52) R_f value:

EKA mass spectrum: (M + H)⁺ = 461
 (M + Na)⁺ = 483
 (M + 2Na)⁺⁺ = 253

EXAMPLE 15

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

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

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=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, $C_{28}H_{29}N_5O_3S$ (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

EXAMPLE 16

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

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. 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
 (M + 2Na)⁺⁺ = 266.5

EXAMPLE 17

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

Prepared analogously to Example 9 from 2-[(4-cyanophenyl)thiomethyl]-benzothiazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide, ethanolic 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) EKA mass spectrum: (M+H)⁺=519

EXAMPLE 18

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

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Prepared analogously to Example 10 from 2-[(4-amidinophenyl)thio-methyl]-benzothiazol-5-yl-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=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-hydrochloride

Prepared analogously to Example 9 from 2-[N-(4-cyanophenyl)-aminomethyl]-benzothiazol-5-yl-carboxylic acid-N-phenyl-N-(ethoxycarbonylmethyl)-amide, ethanolic 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) EKA mass spectrum: (M+H)⁺=488

EXAMPLE 20

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

Prepared analogously to Example 10 from 2-[N-(4-amidinophenyl)-aminomethyl]-benzothiazol-5-yl-carboxylic 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=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

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. 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

EXAMPLE 22

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

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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)-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, ethanolic hydrochloric acid, ethanol and ammonium carbonate. Yield: 83% of theory, C₂₄H₂₉N₅O₃ (467.59) R_f value: 0.31 (silica gel; methylene chloride/ethanol=4:1+a few drops of acetic acid)

EKA mass spectrum: (M + H) ⁺	= 468
(2M + H) ⁺	= 935

EXAMPLE 24

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

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, C₂₂H₂₅N₅O₃S (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

EXAMPLE 25

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-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

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 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 organic extract was washed twice with 200 ml of 2N 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). 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

12.1 g (0.0326 mol) of 4-methylamino-3-nitro-benzoic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide were

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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 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)

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. 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 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)

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 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), R_f value: 0.18 (silica gel; dichloromethane/ethanol=4:1) C₂₈H₃₀N₆O₃·xHCl (498.6)

EKA mass spectrum: (M + H) ⁺	= 499
(M + 2H) ⁺⁺	= 250
(M + H + Na) ⁺⁺	= 261

EXAMPLE 26

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

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-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 filtered, washed with water and dried at 60° C. in vacuo. Yield: 250 mg (95% of theory), C₂₆H₂₆N₆O₃ (470.5)

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EKA mass spectrum: (M + H)⁺ = 471
 (M + H + Na)⁺ = 247
 (M + 2Na)⁺⁺ = 258

EXAMPLE 27

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

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

A solution of 1.8 g (5.9 mMol) of 3-amino-4-methylamino-benzoic acid-N-(n-propyl)-N-(2-ethoxycarbonylethyl)-amide [prepared analogously to 3-amino-4-ethylamino-benzoic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide], 1.1 g (6.8 mMol) of N,N'-carbonyldiimidazole and 0.65 g (6.9 mMol) of chloroacetic acid in 75 ml tetrahydrofuran was stirred for 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, 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

1.6 g (4.3 mMol) of 4-methylamino-3-chloroacetamido-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 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 =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-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 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, 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 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 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, R_f

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value: 0.29 (silica gel; ethyl acetate/ethanol/ammonia =50:45:5) C₂₅H₃₁N₆O₃S (481.62) EKA mass spectrum: (M+H)⁺=482

EXAMPLE 28

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

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 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 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) C₂₃H₂₇N₅O₃S (453.57)

EKA mass spectrum: (M + H)⁺ = 454

(M + Na)⁺ = 476

EXAMPLE 29

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

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, C₂₅H₃₁N₆O₃S (495.65) R_f value: 0.30 (silica gel; ethyl acetate/ethanol/ammonia =50:45:5); EKA mass spectrum: (M+H)⁺=496

EXAMPLE 30

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

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, C₂₈H₂₉N₅O₃S (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

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. Yield: 76% of theory, C₂₆H₂₅N₅O₃S (487.58) R_f value: 0.31 (silica gel; ethyl acetate/ethanol/ammonia =50:45:5)

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33EKA mass spectrum: (M + H)⁺ = 488(M + Na)⁺ = 510**EXAMPLE 32**

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

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 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). Yield: 1.6 g (31% of theory), C₁₃H₁₈ClN₃O₄S (347.8) R_f value: 0.19 (silica gel; dichloromethane/ethanol=19:1)

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 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), C₁₄H₂₂N₄O₄S (343.4) R_f value: 0.45 (silica gel; dichloromethane/ethanol=4:1)

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), C₁₄H₂₄N₄O₂S (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

532 mg (3.0 mMol) of 4-cyanophenylacetic 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. Yield: 400 mg (39% of theory), C₂₃H₂₇N₅O₃S (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

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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), C₂₃H₃₀N₆O₃S (470.6)

EKA mass spectrum: (M + H)⁺ = 471(M + 2H)⁺⁺ = 236**EXAMPLE 33**

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

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, C₂₃H₂₃N₅O₃S (449.5)

EKA mass spectrum: (M + H)⁺ = 450(M + H + Methanol)⁺ = 482(M + 2H)⁺⁺ = 223**EXAMPLE 34**

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

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, C₂₈H₃₁N₅O₅S (549.7) EKA mass spectrum: (M+H)⁺=550

EXAMPLE 35

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 ammonium carbonate. Yield: 71% of theory, C₂₀H₂₃N₅O₃S (413.5) EKA mass spectrum: (M+H)⁺=414

EXAMPLE 36

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

Prepared analogously to Example 25d from 1-methyl-2-[2-(4-cyanophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-tert.butylloxycarbonylpropyl)-amide and methanolic hydrochloric acid, methanol and ammonium carbonate. Yield: 83.5% of theory, R_f value: 0.17 (silica gel; dichloromethane/ethanol=4:1) C₂₉H₃₁N₅O₃ (497.6)

EKA mass spectrum: (M + H)⁺ = 498(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-hydrochloride

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Prepared analogously to Example 26 from 1-methyl-2-[(4-amidinophenyl)aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-methoxycarbonylpropyl)-amide-dihydrochloride and sodium hydroxide solution. Yield: 92% of theory, R_f value: 0.09 (silica gel; dichloromethane/ethanol=4:1) $C_{28}H_{29}N_5O_3$ (483.6)

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

EXAMPLE 38

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-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.butylloxy-carbonylpropyl)-amide. Yield: 65% of theory, R_f value: 0.17 (silica gel; dichloromethane/methanol=19:1)

b) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-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.butylloxy-carbonylpropyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate. Yield: 68% of theory, R_f value: 0.12 (silica gel; dichloromethane/ethanol=4:1) $C_{29}H_{32}N_6O_3$ (512.6)

EKA mass spectrum: (M + H)⁺ = 513
(M + H + Na)⁺⁺ = 268

EXAMPLE 39

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-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 acid-N-phenyl-N-(3-ethoxycarbonylpropyl)-amide-dihydrochloride and sodium hydroxide solution. Yield: 73.5% of theory, $C_{27}H_{28}N_6O_3$ (484.6)

EKA mass spectrum: (M + H)⁺ = 485
(M + 2H)⁺⁺ = 243
(M + H + Na)⁺⁺ = 254

EXAMPLE 40

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

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Yield: 73% of theory, R_f value: 0.15 (silica gel; dichloromethane/ethanol=4:1) $C_{28}H_{29}N_5O_3$ (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, $C_{26}H_{25}N_5O_3$ (455.5)

EKA mass spectrum: (M + H)⁺ = 456
(M + Na)⁺ = 478
(M + 2Na)⁺⁺ = 250.6

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. 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

EXAMPLE 43

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

45 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. 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

EXAMPLE 44

60 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(ethoxycarbonylmethyl)-amide-hydrochloride

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. Yield: 74% of theory, R_f value: 0.12

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(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

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EXAMPLE 45

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(hydroxycarbonylmethyl)-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 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
(M + 2Na)⁺⁺ = 251

EXAMPLE 46

1-Methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-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 ethanolic hydrochloric acid, ethanol and ammonium carbonate. Yield: 14% of theory, $C_{26}H_{27}N_7O_4$ (501.6) Mass spectrum: (M+H)⁺=502

EXAMPLE 47

1-Methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(ethoxycarbonylmethyl)-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 ethanolic hydrochloric acid, ethanol and ammonium carbonate. Yield: 44% of theory, R_f value: 0.12 (silica gel; dichloromethane/ethanol=4:1) $C_{26}H_{26}N_6O_4$ (486.5)EKA mass spectrum: (M + H)⁺ = 487
(M + 2H)⁺⁺ = 244
(M + H + Na)⁺⁺ = 255

EXAMPLE 48

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

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, $C_{24}H_{22}N_6O_4$ (458.5)

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EKA mass spectrum: (M + H)⁺ = 459
(M + Na)⁺ = 481
(M + 2Na)⁺⁺ = 252

EXAMPLE 49

10 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(ethoxycarbonylmethyl)-amide-dihydrochloride

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

15 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)

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

25 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, R_f value: 0.16 (silica gel; dichloromethane/ethanol=4:1) $C_{26}H_{27}N_7O_3$ (485.6)EKA mass spectrum: (M + H)⁺ = 486
(M + 2H)⁺⁺ = 243.7
(M + H - Na)⁺⁺ = 254.6

EXAMPLE 50

40 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(hydroxycarbonylmethyl)-amide-hydrochloride

45 Prepared analogously to Example 26 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(ethoxycarbonylmethyl)-amide-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
(M + 2Na)⁺⁺ = 251.7

EXAMPLE 51

1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-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-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)

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EKA mass spectrum: (M + H)⁺ = 485
 (M + 2H)⁺⁺ = 243
 (M + H + Na)⁺⁺ = 254

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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, C₂₅H₂₄N₆O₃ (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) C₂₇H₂₈N₆O₃
 (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-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 etha-
 nolic hydrochloric acid, ethanol and ammonium carbonate.
 Yield: 79.5% of theory, C₂₈H₂₉N₅O₄ (499.6) R_f value: 0.15
 (silica gel; dichloromethane/ethanol=4:1)

EKA mass spectrum: (M + H)⁺ = 500.0
 (M + H + Na)⁺⁺ = 261.7

EXAMPLE 55

1-Methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-
 5-yl-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-N-phenyl-N-(2-ethoxycarbonylethyl)-
 amide-hydrochloride and sodium hydroxide solution. Yield:
 82% of theory, C₂₆H₂₅N₅O₄ (471.5) R_f value: 0.11 (silica
 gel; dichloromethane/ethanol=4:1)

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EKA mass spectrum: (M + H)⁺ = 472
 (M + H + Na)⁺⁺ = 247.6
 (M + Na)⁺ = 494
 (M + 2Na)⁺⁺ = 258.6

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-
 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-hydrochloride and sodium hydroxide solution. Yield:
 98% of theory, C₂₄H₂₄N₆O₃S (476.6)

EKA mass spectrum: (M + H)⁺ = 477
 (M + Na)⁺ = 499
 (M + 2H)⁺⁺ = 239

EXAMPLE 58

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-
 benzimidazol-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-
 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, 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-
 ethoxycarbonylethyl)-amide-hydrochloride

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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, $C_{27}H_{29}N_7O_3$ (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

EXAMPLE 59

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-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-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
(M + 2H)⁺⁺ = 236.7
(M + 2Na)⁺⁺ = 258.6

EXAMPLE 60

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-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, 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. 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

EXAMPLE 61

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

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-

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hydrochloride and sodium hydroxide solution. Yield: 97% of theory, $C_{26}H_{26}N_6O_3$ (470.5)

EKA mass spectrum: (M + H)⁺ = 471
(M + H + Na)⁺⁺ = 247
(M + Na)⁺ = 493

EXAMPLE 62

1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-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-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)

EKA mass spectrum: (M + H)⁺ = 498
(M + 2H)⁺⁺ = 249.8

EXAMPLE 63

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-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)

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-(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 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)

EKA mass spectrum: (M + H)⁺ = 472
(M + H + Na)⁺⁺ = 247.8

EXAMPLE 65

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-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-

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carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide and methanolic hydrochloric acid, methanol and ammonium carbonate. Yield: 78% of theory, $C_{26}H_{27}N_7O_3$ (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]-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

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 3439.5 cm^{-1} (N-H); 2235.5 cm^{-1} (C≡N); 1631.6 cm^{-1} (C=O)

b) 1-Methyl-2-[2-(4-amidinophenyl)ethyl]-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-[2-(4-cyanophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-(1H-tetrazol-5-yl)ethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate. Yield: 92% of theory, $C_{27}H_{27}N_9O$ (493.6)

EKA mass spectrum: (M+H)⁺ = 494
(M+Na)⁺ = 516
(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-hexyloxy-carbonylethyl)-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-ethoxycarbonylethyl)-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

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EXAMPLE 69

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

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. 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]-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)-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
(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-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)-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
(M+2Na)⁺⁺ = 265.6

EXAMPLE 71

1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-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-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)-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 and sodium hydroxide solution. Yield: 89% of theory, $C_{26}H_{31}N_5O_3$ (461.6)

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EKA mass spectrum: (M + H)⁺ = 462
 (M + H + Na)⁺⁺ = 242.6
 (M + Na)⁺ = 484
 (M + 2H)⁺⁺ = 231.6

EXAMPLE 73

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-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, C₂₇H₃₄N₆O₃ (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-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-hydrochloride and sodium hydroxide solution. Yield: 45% of theory, C₂₅H₃₀N₃O₄ (462.6)

EKA mass spectrum: (M + H)⁺ = 463
 (M + H + Na)⁺⁺ = 243
 (M + Na)⁺ = 485
 (M + 2Na)⁺⁺ = 254

EXAMPLE 75

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-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, C₂₇H₂₉N₇O₃ (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-(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)-amide-hydrochloride and sodium hydroxide solution. Yield: 68% of theory, C₂₅H₂₅N₇O₃ (471.5)

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EKA mass spectrum: (M + H)⁺ = 472
 (M + Na)⁺ = 494
 (M + 2Na)⁺⁺ = 258.6

EXAMPLE 77

1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-benzimidazol-5-yl-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-pyridyl)-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate. Yield: 91% of theory, C₂₈H₃₀N₆O₃ (498.6) R_f value: 0.19 (silica gel; dichloromethane/ethanol=4:1) 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-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 ethanolic hydrochloric acid, ethanol and ammonium carbonate. Yield: 86% of theory, C₂₇H₂₉N₇O₃ (499.6) R_f value: 0.09 (silica gel; dichloromethane/ethanol=4:1) EKA mass spectrum: (M+H)⁺=500

EXAMPLE 79

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-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 acid-N-(3-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-dihydrochloride and sodium hydroxide solution. Yield: 85% of theory, C₂₅H₂₅N₇O₃ (471.5)

EKA mass spectrum: (M + H)⁺ = 472
 (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-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)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate. Yield: 64% of theory, C₂₈H₃₁N₇O₃ (513.6) EKA mass spectrum: (M+H)⁺=514

EXAMPLE 81

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

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ethoxycarbonylethyl)-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
(M + 2Na)⁺⁺ = 265.6

EXAMPLE 82

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

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=19:1)

b) 1-Methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-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-phenyl-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate. Yield: 74% of theory, $C_{29}H_{32}N_6O_3$ (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-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-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
(M + Na)⁺ = 507
(M + 2Na)⁺ = 265

EXAMPLE 84

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-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, $C_{28}H_{31}N_7O_3$

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

EKA mass spectrum: (M + H)⁺ = 514
(M + H + Na)⁺⁺ = 268.6
(M + 2H)⁺⁺ = 257.7

EXAMPLE 85

1-ethyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-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 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
(M + H + Na)⁺⁺ = 254.6
(M + 2H)⁺⁺ = 243.6
(M + 2Na)⁺⁺ = 265.7

EXAMPLE 86

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-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-(2-fluorophenyl)-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate. 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
(M + 2H)⁺⁺ = 259

EXAMPLE 87

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

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

EKA mass spectrum: (M + H)⁺ = 489
(M + H + Na)⁺⁺ = 267
(M + 2H)⁺⁺ = 256

EXAMPLE 88

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

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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. 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
(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
(M + H + Na)⁺⁺ = 325
(M + 2H)⁺⁺ = 314

EXAMPLE 91

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-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-

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amide-hydrochloride and methyl chloroformate. Yield: 41% of theory, $C_{30}H_{32}N_6O_5$ (556.6) R_f value: 0.85 (silica gel; dichloromethane/ethanol=4:1)

EKA mass spectrum: (M + H)⁺ = 557
(M + H + Na)⁺⁺ = 290
(M + Na)⁺ = 579

EXAMPLE 92

1-Methyl-2-[N-[4-(N-ethoxycarbonylamidino)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 acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide-hydrochloride and ethyl chloroformate. 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

EXAMPLE 93

1-Methyl-2-[N-[4-(N-cyclohexyloxycarbonylamidino)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 acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide-hydrochloride and cyclohexyl chloroformate. Yield: 25% of theory, $C_{34}H_{38}N_6O_5$ (610.7) R_f value: 0.44 (silica gel; dichloromethane/ethanol=19:1)

EKA mass spectrum: (M + H)⁺ = 611
(M + 2H)⁺⁺ = 306

EXAMPLE 94

1-Methyl-2-[N-[4-[N-[2-(methylsulphonyl)ethyloxycarbonyl]-amidino]phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(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 and 2-(methylsulphonyl)-ethyl chloroformate. Yield: 66% of theory, $C_{32}H_{36}N_6O_7S$ (648.8) R_f value: 0.44 (silica gel; dichloromethane/ethanol=19:1)

EKA mass spectrum: (M + H)⁺ = 649
(M + H + Na)⁺⁺ = 336

EXAMPLE 95

1-Methyl-2-[N-[4-(N-n-octyloxycarbonylamidino)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-

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carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide-hydrochloride and n-octyl chloroformate. Yield: 41% of theory, C₃₆H₄₄N₆O₅ (640.8) R_f value: 0.43 (silica gel; dichloromethane/ethanol=19:1)

EKA mass spectrum: (M + H)⁺ = 641
(M + Na)⁺ = 663

EXAMPLE 96

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

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 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 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, C₂₈H₃₀N₆O₄ (514.6) 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

EXAMPLE 97

1-Methyl-2-[N-[4-(N-n-heptyloxycarbonylamidino)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 acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide-hydrochloride and n-heptyl chloroformate. Yield: 43% of theory, C₃₅H₄₂N₆O₅ (626.8) R_f value: 0.40 (silica gel; dichloromethane/ethanol=19:1)

EKA mass spectrum: (M + H)⁺ = 627
(M + H + Na)⁺⁺ = 325
(M + Na)⁺ = 649

EXAMPLE 98

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 acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide-hydrochloride and benzoyl chloride. Yield: 88% of theory, C₃₄H₃₂N₆O₄ (588.7) R_f value: 0.37 (silica gel; dichloromethane/ethanol=19:1) ¹H-NMR spectrum (D₆-DMSO): 2.61 (t,2H), 3.54 (s,3H), 3.76 (s,3H), 4.10 (t,2H),

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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)

EXAMPLE 99

1-Methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)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 acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide-hydrochloride and n-hexyl chloroformate. Yield: 54% of theory, C₃₄H₄₀N₆O₅ (612.7) R_f value: 0.45 (silica gel; dichloromethane/ethanol=19:1) EKA mass spectrum: (M+H)⁺=613

EXAMPLE 100

1-Methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(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-hydrochloride and n-hexyl chloroformate. Yield: 31% of theory, C₃₆H₄₄N₆O₅ (640.8) R_f value: 0.42 (silica gel; dichloromethane/ethanol=19:1)

EKA mass spectrum: (M + H)⁺ = 641
(M + H + Na)⁺⁺ = 332
(M + Na)⁺ = 663

EXAMPLE 101

1-Methyl-2-[N-[4-(N-ethoxycarbonylamidino)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 ethyl chloroformate. Yield: 72% of theory, C₂₉H₃₁N₇O₅ (557.6) 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

EXAMPLE 102

1-Methyl-2-[N-[4-(N-n-octyloxycarbonylamidino)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-octyl chloroformate. Yield: 57% of theory, C₃₅H₄₃N₇O₅ (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)-N-(2-ethoxycarbonylethyl)-amide

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Prepared analogously to Example 90 from 1-methyl-2-[N-(4-aminophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-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
(M + H + Na)⁺⁺ = 290.7
(M + Na)⁺ = 580

EXAMPLE 104

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-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 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 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
(M + 2Na)⁺⁺ = 337.7

EXAMPLE 105

1-Methyl-2-[N-[4-[N-(2-methylsulphonyl-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-aminophenyl)-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) 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

EXAMPLE 106

1-Methyl-2-[N-[4-(N-n-butyloxycarbonylamidino)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-aminophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide-hydrochloride and n-butyl

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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
(M + H + Na)⁺⁺ = 304.7
(M + 2H)⁺⁺ = 293.7

EXAMPLE 107

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-aminophenyl)-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) 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

EXAMPLE 108

1-Methyl-2-[N-[4-(N-n-heptyloxycarbonylamidino)-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-aminophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide-hydrochloride and n-heptyl chloroformate. 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

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-aminophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide-hydrochloride and n-pentyl chloroformate. Yield: 66% of theory, $C_{32}H_{37}N_7O_5$ (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

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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
(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-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 benzoyl chloride. Yield: 62% of theory, C₃₃H₃₁N₇O₄ (589.7) R_f value: 0.50 (silica gel; dichloromethane/methanol=9:1)

EKA mass spectrum: (M + H)⁺ = 590
(M + Na)⁺ = 612

EXAMPLE 112

1-Methyl-2-[N-[4-(N-nicotinoylamidino)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 nicotinic acid chloride. Yield: 40% of theory, C₃₂H₃₀N₈O₄ (590.7) R_f value: 0.47 (silica gel; dichloromethane/methanol=9:1)

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-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 n-hexyl chloroformate. Yield: 51% of theory, C₃₄H₄₁N₇O₅ (627.8) R_f value: 0.53 (silica gel; dichloromethane/methanol=9:1)

EKA mass spectrum: (M + H)⁺ = 628
(M + H + Na)⁺⁺ = 325.7
(M + 2H)⁺⁺ = 314.7

EXAMPLE 114

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

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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 n-octyl chloroformate. Yield: 57% of theory, C₃₆H₄₅N₇O₅ (655.8) 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]-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 2-(methylsulphonyl)-ethyl chloroformate. Yield: 72% of theory, C₃₀H₃₃N₇O₇S (635.7) R_f value: 0.23 (silica gel; dichloromethane/ethanol=19:1)

EKA mass spectrum: (M + H)⁺ = 636
(M + H + Na)⁺⁺ = 329.8

EXAMPLE 116

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-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-methoxycarbonylmethyl-amide-hydrochloride and cyclohexyl chloroformate. Yield: 40% of theory, C₃₂H₃₅N₇O₅ (597.7) 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, C₂₈H₂₉N₇O₅ (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]-amino-methyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-methoxycarbonylmethyl-amide

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Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-methoxycarbonylmethylamide-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 119

1-Methyl-2-[N-[4-(N-n-octyloxycarbonylamidino)-phenyl]aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-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-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: $(M+H)^+ = 656$
 $(M+2H)^{++} = 328.7$

EXAMPLE 120

1-Methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)-phenyl]-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-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)

EKA mass spectrum: $(M+H)^+ = 642$
 $(M+H+Na)^{++} = 332.7$

EXAMPLE 121

1-Methyl-2-[N-[4-(N-n-octyloxycarbonylamidino)-phenyl]-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-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and n-octyl chloroformate. Yield: 36% of theory, $C_{37}H_{47}N_7O_5$ (669.8)

EKA mass spectrum: $(M+H)^+ = 670$
 $(M+H+Na)^{++} = 346.8$
 $(M+2H)^{++} = 335.6$

EXAMPLE 122

1-Methyl-2-[N-[4-(N-n-butyloxycarbonylamidino)-phenyl]-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-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)

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EKA mass spectrum: $(M+H)^+ = 614$
 $(M+H+Na)^{++} = 318.7$
 $(M+Na)^+ = 636$

EXAMPLE 123

1-Methyl-2-[N-[4-(N-benzoylamidino)phenyl]-N-methyl-amino-methyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-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)-amide-hydrochloride and benzoyl chloride. Yield: 63% of theory, $C_{35}H_{35}N_7O_4$ (617.7)

EKA mass spectrum: $(M+H)^+ = 618$
 $(M+H+Na)^{++} = 320.7$
 $(M+Na)^+ = 640$

EXAMPLE 124

1-Methyl-2-[4-(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-(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 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 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 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). 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)

b) 4-Chloro-3-nitrophenyl-(1-hydroxycarbonylmethyl-cyclohex-1-yl)-ketone

7.0 g (25 mMol) of 4-chlorophenyl-(1-hydroxycarbonylmethyl-cyclohex-1-yl)-ketone were added in batches, with stirring, at -5 to $-10^\circ C.$, to 80 ml of fuming nitric acid. 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) R_f value: 0.41 (silica gel; petroleum ether/ethyl acetate 4:6)

c) 4-Methylamino-3-nitrophenyl-(1-hydroxycarbonylmethyl-cyclohex-1-yl)-ketone

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. 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)

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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 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, 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)

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 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)

f) 3-(4-Cyanophenyl)oxyacetyl-amino-4-methylaminophenyl-(1-methoxycarbonylmethyl-cyclohex-1-yl)-ketone

620 mg (3.5 mMol) of 4-cyanophenylacetic acid and 570 mg (3.5 mMol) of 1,1'-carbonyl-diimidazole were refluxed in 50 ml of tetrahydrofuran for 15 minutes. Then 1.0 g (3.28 mMol) of 3-amino-4-methylaminophenyl-(1-methoxycarbonylmethyl-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 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)

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-cyanophenyl)oxyacetyl-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)

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-cyanophenyl)oxymethyl-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) 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

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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. Yield: 59% of theory, $C_{21}H_{25}N_5O$ (363.5) EKA mass spectrum: $(M+H)^+=364$

EXAMPLE 126

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-(1-methylcyclopent-1-yl)-ketone-hydrochloride

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) EKA mass spectrum: $(M+H)^+=390$

EXAMPLE 127

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

A solution of 0.15 g (0.27 mMol) of 2-[(4-amidinophenyl)thiomethyl]-benzothiazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonyl)ethyl)-amide-hydrochloride in 10 ml of acetic acid was mixed with 0.09 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 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) R_f value: 0.24 (silica gel; methylene chloride/ethanol =4:1+a few drops of acetic acid) EKA mass spectrum: $(M+H)^+=535$

EXAMPLE 128

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

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-ethoxycarbonyl)ethyl)-amide-hydrochloride in 10 ml of formic acid was mixed with 2 ml 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-ethoxycarbonyl)ethyl)-amide-hydrochloride). 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) EKA mass spectrum: $(M+H)^+=514$

EXAMPLE 129

2-[N-(4-amidinophenyl)-aminomethyl]-thiazolo[5,4-b]pyridin-6-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonyl)ethyl)-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 25 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 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

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distilled off in vacuo. 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=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-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 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 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 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)

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-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

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

EXAMPLE 130

1-Methyl-2-[(4-amidinophenyl)methylthio]-benzimidazol-5-yl-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

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 atmosphere, the solution was heated to 90° C. for 4 hours and 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, 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-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-bromomethylbenzonitrile were dissolved in 40 ml of absolute ethanol, stirred for 4 hours at 60° C. and 16 hours at room 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

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compound was obtained as a beige-white solid. Yield: 1.8 g (100% of theory), R_f value: 0.64 (silica gel; ethyl acetate)
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. 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, $C_{28}H_{29}N_5O_3S$ (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

EXAMPLE 131

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

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. 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
(M + Na)⁺ = 510
(M + Na + H)⁺⁺ = 255.6

EXAMPLE 132

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) R_f value: 0.094 (silica gel; dichloromethane/ethanol=4:1)

EKA mass spectrum: (M + H)⁺ = 461
(M + H + Na)⁺⁺ = 242
(M + 2H)⁺⁺ = 231

EXAMPLE 133

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

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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. 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

EXAMPLE 134

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

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. 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
(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

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. 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
(M + Na)⁺ = 626

EXAMPLE 136

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-[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, $C_{30}H_{33}N_6O_3$ (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

EXAMPLE 137

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

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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 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
(M + 2Na) ⁺⁺	= 271

EXAMPLE 138

1-Methyl-2-[N-(4-amidinophenyl)-N-(n-butyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-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, 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
(M + H + Na) ⁺⁺	= 289
(M + 2H) ⁺⁺	= 278

EXAMPLE 139

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-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, $C_{28}H_{29}ClN_6O_3$ (533.1)

EKA mass spectrum: (M + H) ⁺	= 533/5
(M + H + Na) ⁺⁺	= 278/9

EXAMPLE 140

1-Methyl-2-[N-[4-(n-octyloxy-carbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(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 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
(M + H + Na) ⁺⁺	= 339
(M + Na) ⁺	= 677

EXAMPLE 141

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

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Prepared analogously to Example 25d from 1-methyl-2-[N-(4-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 $C_{30}H_{34}N_6O_3$ (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

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. 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

EXAMPLE 143

1-Methyl-2-[N-[4-(N-(2-(2-ethoxyethoxy)ethoxy)-carbonylamidino)-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 diethyleneglycolmonoethylether chloroformate. Yield: 43% of theory, $C_{34}H_{41}N_7O_7$ (659.8) R_f value: 0.56 (silica gel; dichloromethane/methanol=9:1)

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

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

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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]-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-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide, ethanolic hydrochloric acid, ethanol and ammonium carbonate. Yield: 82% of theory, $C_{27}H_{26}N_7O_3$ (499.58) 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

EXAMPLE 147

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

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. 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

$(M+Na)^+$ = 511

EXAMPLE 148

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

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

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

$(M+Na)^+$ = 494

EXAMPLE 149

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

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

2.54 g (6.2 mMol) of 3-nitro-4-methylamino-benzenesulphonic acid-N-phenyl-N-(2-

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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 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 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

EXAMPLE 151

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-5-(2,3-dihydroindol-1-yl-sulphonyl)-benzimidazole-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, 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

EXAMPLE 152

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazole-5-yl-sulphonic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide

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Prepared analogously to Example 26 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-sulphonic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-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) $C_{25}H_{26}N_6O_4S$ (506.6)

EKA mass spectrum: (M + H)⁺ = 507

(M + Na)⁺ = 529

(M + 2Na)⁺⁺ = 276

EXAMPLE 153

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-5-(isoindolin-2-yl-sulphonyl)-benzimidazol-hydrochloride

Prepared analogously to Example 25d from 1-methyl-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) $C_{24}H_{24}N_6O_2S$ (460.6) EKA mass spectrum: (M+H)⁺=461

EXAMPLE 154

2-[2-(4-Amidinophenyl)-ethyl]-quinazolin-7-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

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-tolate were added dropwise with stirring at 5° C. 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. 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

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 purification. Yield: 1.2 g (100% of theory), R_f value: 0.54 (silica gel, ethyl acetate/cyclohexane=1:1)

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 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). 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

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 was separated off, the solution was diluted with water and

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extracted with methylene chloride. The combined organic extracts were washed with water, dried and evaporated down. Yield: 0.3 g (58% of theory), R_f value: 0.74 (silica gel, methylene chloride/methanol=9.5:0.5)

e. Methyl 3-[3-(4-cyanophenyl)-propionylamino]-4-formyl-benzoate

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 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). 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]-quinazolin-7-carboxylate

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 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)

g. 2-[2-(4-Cyanophenyl)-ethyl]-quinazolin-7-carboxylic acid

0.3 g (0.94 mmol) of methyl 2-[2-(4-cyanophenyl)-ethyl]-quinazolin-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 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)

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]-quinazolin-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 N-ethyl-diisopropylamine 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=9:1)

i. 2-[2-(4-Amidinophenyl)-ethyl]-quinazolin-7-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

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 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 chloride/ethanol (4:1). Yield: 100 mg (39% of theory), R_f value: 0.5 (silica gel, methylene chloride/ethanol=4:1) $C_{29}H_{29}N_5O_3$ (495.59) Mass spectrum: (M+H)⁺=496

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EXAMPLE 155

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

Prepared analogously to Example 26 from 1-methyl-2-[N-(4-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)

EKA mass spectrum: $(M+H)^+$ = 511

$(M+Na)^{++}$ = 533

$(M+2Na)^{++}$ = 278

EXAMPLE 156

1-Methyl-2-[N-(3-amidino-pyridin-6-yl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

a) 3-[(N-tert.Butoxycarbonyl-amino)acetyl-amino]-4-methylamino-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

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-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 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)

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%

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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

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) 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

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. Yield: 38% of theory, $C_{28}H_{28}N_8O_3$ (500.6) Mass spectrum: $(M+H)^+=501$

EXAMPLE 157

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

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 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 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), R_f value: 0.37 (silica gel; methylene chloride/methanol=50:1)

b) 4-Amino-benzoic acid-N-phenyl-N-(2-methoxycarbonylethyl)amide

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 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)

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 minutes with freshly prepared tert.butylhypochlorite (M.

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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 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 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), R_f value: 0.58 (silica gel; ethyl acetate/petroleum ether=1:1) $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_3\text{S}$ (382.49) Mass spectrum: $(\text{M})^+=382$

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 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 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 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)

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)-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 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 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)

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,

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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), $\text{C}_{28}\text{H}_{28}\text{N}_4\text{O}_3\text{S}$ (500.62)

EKA mass spectrum: $(\text{M} + \text{H})^+ = 501$

$(\text{M} + \text{Na})^+ = 523$

g) 1-Methyl-2-[N-(4-amidinophenyl)aminomethyl]-indol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide-hydroiodide

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 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, $\text{C}_{28}\text{H}_{29}\text{N}_5\text{O}_3$ (483.58) R_f value: 0.20 (silica gel; methylene chloride/ethanol=4:1+1 drop of acetic acid) EKA mass spectrum: $(\text{M}+\text{H})^+=484$

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

a) Iminoethyl methoxyacetate hydrochloride

A solution of 35.5 g (0.50 mol) of methoxyacetone nitrile 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 (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. Yield: 66.4 g (86% of theory), Melting point: $117-118^{\circ}\text{C}$.

b) 4-Hydroxymethyl-2-methoxymethyl-imidazole

A mixture of 30.6 g (0.20 mol) of iminoethyl 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 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=9:1) $\text{C}_6\text{H}_{10}\text{N}_2\text{O}_2$ (142.20) Mass spectrum: $(\text{M})^+=142$

c) 4-Hydroxymethyl-2-methoxymethyl-1-methyl-imidazole as a 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 was heated to 50°C . in 100 ml of dimethylformamide

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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 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)

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-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. 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

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 (2x6.0 g, a total of 0.14 mol). After 4 hours the inorganic component was filtered off, the solvent 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 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., 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 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=50:1) $C_{11}H_{14}N_2O_3S$ (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 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. 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) $C_9H_{10}N_2O_3S$ (226.26) Mass spectrum: (M)⁺=226

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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 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 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' 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=19:1)

i) 1-Methyl-2-(N-4-cyanophenylaminomethyl)-thieno[2.3-d]imidazol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide

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 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 obtained was heated to 5° 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. 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]-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 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 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). Yield: 57% of theory $C_{26}H_{28}N_6O_3S$ (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

(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-hydroxycarbonylethyl)-amide-hydrochloride

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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-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)

EKA mass spectrum: (M + H)⁺ = 477

(M + Na)⁺ = 499

(M + 2Na)⁺⁺ = 250

EXAMPLE 160

1-Methyl-3-[N-(4-amidinophenyl)thiomethyl]-quinoxalin-2-on-6-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

a) 1-Methyl-3-[N-(4-cyanophenyl)thiomethyl]1-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 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). 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

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, $C_{28}H_{27}N_5O_4S$ (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

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

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 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)-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/

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ethanol=0 to 2%) a brown oil was obtained. Yield: 1.48 g (64% of theory), 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-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-phenyl-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate. 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

EXAMPLE 162

3-Methyl-2-[2-(4-amidinophenyl)ethyl]-imidazo[1.2-a]pyridin-7-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-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-ethoxycarbonylethyl)-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)

EKA mass spectrum: (M + H)⁺ = 470

(M + Na)⁺ = 492

(M + 2H)⁺⁺ = 235.7

(M + H + Na)⁺⁺ = 246.7

(M + 2Na)⁺⁺ = 257.7

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

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. 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

(M + H + Na)⁺⁺ = 289.8

(M + 2H)⁺⁺ = 278.8

EXAMPLE 164

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

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, $C_{29}H_{33}N_7O_3$ (527.6) R_f value: 0.43 (Reversed Phase silica gel RP-18; methanol/5% aqueous saline solution=6:4)

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EKA mass spectrum: (M + H)⁺ = 528
 (M + H + Na)⁺⁺ = 275.6
 (M + 2H)⁺⁺ = 264.6

EXAMPLE 165

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-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-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) 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, C₃₂H₃₇N₇O₅ (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]-benzimidazole-5-yl-carboxylic acid-N-phenyl-N-(3-benzyloxy-n-propyl)-amide by catalytic debenzylation. Yield: 26% of theory, C₃₃H₄₀N₆O₄ (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

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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, C₂₈H₂₉FN₆O₃ (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, C₂₈H₂₉FN₆O₃ (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, C₂₆H₂₅FN₆O₃ (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, C₂₆H₂₅FN₆O₃ (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]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

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Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyano-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-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) R_f value: 0.13 (silica gel; dichloromethane/ethanol=4:1)

EKA mass spectrum: (M + H) ⁺	= 529
(M + H + Na) ⁺⁺	= 276
(M + 2H) ⁺⁺	= 265

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. 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
(M + Na) ⁺	= 654

EXAMPLE 174

1-Methyl-2-[N-[4-(N-benzoyloxycarbonylamidino)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 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
(M + H + Na) ⁺⁺	= 328.8
(M + Na) ⁺	= 656

EXAMPLE 175

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

EKA mass spectrum: (M + H) ⁺	= 501
(M + Na) ⁺	= 523

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-continued

(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-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)-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) 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-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)-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

EXAMPLE 178

1-Methyl-2-[N-[4-(N-benzoyloxycarbonylamidino)phenyl]-amino-methyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide

Prepared analogously to Example 104 from 1-methyl-2-[N-[4-(N-benzoyloxycarbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-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
(M + Na) ⁺	= 628
(M - H + 2Na) ⁺	= 650
(M + 2H) ⁺⁺	= 303.8
(M + H + Na) ⁺⁺	= 314.8
(M + 2Na) ⁺⁺	= 325.7

EXAMPLE 179

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-benzoyloxy-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-benzoyloxy-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
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-continued
(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, C₄₀H₄₆N₆O₄ (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-(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-hydrochloride and ethanolic hydrochloric acid, ethanol and ammonium carbonate. Yield: 53% of theory, C₂₈H₃₀N₆O₃ (498.59) R_f value: 0.42 (silica gel; ethyl acetate/ethanol/ammonia =50:45:5)

EKA mass spectrum: (M + H)⁺ = 499
(M + 2Na)⁺⁺ = 272
(M + H + Na)⁺⁺ = 261
(M + 2H)⁺⁺ = 250

EXAMPLE 182

1-Methyl-2-[N-(3-amidino-pyridin-6-yl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-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)-amide and sodium hydroxide solution. Yield: 40% of theory, C₂₄H₂₄N₈O₃ (472.9) R_f value: 0.67 (Reversed Phase silica gel RP-8; methanol/5% saline solution=1:1) 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-(methansulphonylaminocarbonyl)-ethyl]-amide

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

2.0 g (4.5 mmol) of 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide and 0.73 g (4.7

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mmol) of carbonyldiimidazole were dissolved in 80 ml of tetrahydrofuran and 5 ml of dimethylformamide and 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 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 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), C₂₆H₂₅N₇O₄S (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, C₂₆H₂₈N₈O₅S (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. Yield: % of theory, C₂₄H₂₆N₈O₃S (506.6) R_f value: (silica gel; dichloromethane/methanol=4:1)

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. Yield: % of theory, C₂₂H₂₂N₈O₃S (478.5) R_f value: (silica gel; dichloromethane/methanol=4:1)

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

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. Yield: 19% of

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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)

EKA mass spectrum: $(M + H)^+$ = 502

$(M + H + Na)^+$ = 262.5

EXAMPLE 187

1-Methyl-2-[N-(2-amidino-pyrazin-5-yl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide

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, $C_{23}H_{23}N_9O_3$ (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

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. Yield: % of theory, $C_{34}H_{39}N_9O_3$ (621.7) R_f value: (silica gel; dichloromethane/methanol=4:1)

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, $C_{35}H_{42}N_6O_6$ (642.7) R_f value: 0.54 (silica gel; dichloromethane/ethanol=9:1)

EKA mass spectrum: $(M + H)^+$ = 643

$(M + H + Na)^{++}$ = 333.4

EXAMPLE 190

1-Methyl-2-[N-(4-n-heptyloxycarbonylamidino-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)

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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-(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 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

$(M + H + Na)^{++}$ = 333.9

EXAMPLE 193

1-Methyl-2-[N-(2-methoxy-4-n-heptyloxycarbonylamidino-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 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

$(M + H + Na)^{++}$ = 347.9

EXAMPLE 194

Dry ampoule containing 75 mg of active substance per 10 ml

Composition:

Active substance	75.0 mg
Mannitol	50.0 mg

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-continued

Dry ampoule containing 75 mg of active substance per 10 ml

Composition:

water for injections ad 10.0 ml

Preparation:

Active substance and mannitol are dissolved in water. After packaging the solution is freeze-dried. To produce the solution ready for use, the product is dissolved in water for injections.

EXAMPLE 195

Dry ampoule containing 35 mg of active substance per 2 ml

Composition:

Active substance	35.0 mg
Mannitol	100.0 mg
water for injections	ad 2.0 ml

Preparation:

Active substance and mannitol are dissolved in water. After packaging, the solution is freeze-dried.

To produce the solution ready for use, the product is dissolved in water for injections.

EXAMPLE 196

Tablet containing 50 mg of active substance

Composition:

(1) Active substance	50.0 mg
(2) Lactose	98.0 mg
(3) Maize starch	50.0 mg
(4) Polyvinylpyrrolidone	15.0 mg
(5) Magnesium stearate	2.0 mg
	<u>215.0 mg</u>

Preparation:

(1), (2) and (3) are mixed together and granulated with an aqueous solution of (4). (5) is added to the dried granulated material. From this mixture tablets are pressed, biplanar, faceted on both sides and with a dividing notch on one side. Diameter of the tablets: 9 mm.

EXAMPLE 197

Tablet containing 350 mg of active substance

Preparation:

(1) Active substance	350.0 mg
(2) Lactose	136.0 mg
(3) Maize starch	80.0 mg
(4) Polyvinylpyrrolidone	30.0 mg
(5) Magnesium stearate	4.0 mg
	<u>600.0 mg</u>

(1), (2) and (3) are mixed together and granulated with an aqueous solution of (4). (5) is added to the dried granulated

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material. From this mixture tablets are pressed, biplanar, faceted on both sides and with a dividing notch on one side. Diameter of the tablets: 12 mm.

EXAMPLE 198

Capsules containing 50 mg of active substance

Composition:

(1) Active substance	50.0 mg
(2) Dried maize starch	58.0 mg
(3) Powdered lactose	50.0 mg
(4) Magnesium stearate	2.0 mg
	<u>160.0 mg</u>

Preparation:

(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous mixing.

This powder mixture is packed into size 3 hard gelatin capsules in a capsule filling machine.

EXAMPLE 199

Capsules containing 350 mg of active substance

Composition:

(1) Active substance	350.0 mg
(2) Dried maize starch	46.0 mg
(3) Powdered lactose	30.0 mg
(4) Magnesium stearate	4.0 mg
	<u>430.0 mg</u>

Preparation:

(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous mixing.

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

1 suppository contains:

Active substance	100.0 mg
Polyethyleneglycol (M.W. 1500)	600.0 mg
Polyethyleneglycol (M.W. 6000)	460.0 mg
Polyethylenesorbitan monostearate	840.0 mg
	<u>2,000.0 mg</u>

What is claimed is:

1. A compound of the formula I



wherein

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

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

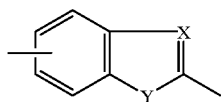
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R_1 denotes a hydrogen atom or a C_{1-6} -alkyl group,
 E denotes a cyano or $R_bNH-C(=NH)-$ group wherein
 R_b denotes a hydrogen atom, a hydroxy group, C_{1-9} -
 alkoxy carbonyl, cyclohexyloxy carbonyl,
 phenyl- C_{1-3} -alkoxy carbonyl, benzoyl, p- C_{1-3} -alkyl-
 benzoyl or pyridinoyl group, whilst the ethoxy moi-
 ety in the 2-position of the abovementioned C_{1-9} -
 alkoxy carbonyl group is optionally, additionally,
 substituted by a C_{1-3} -alkylsulfonyl or 2-(C_{1-3} -
 alkoxy)-ethyl group,

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,
 or a thienylene group optionally substituted in the
 carbon skeleton by a C_{1-3} -alkyl group,

Het denotes a bicyclic heterocycle of formula



wherein,

X is a nitrogen atom and

Y is an imino group optionally substituted by a C_{1-6} -
 alkyl or C_{3-7} -cycloalkyl group

and R_a denotes an R_2NR_3- group wherein

R_2 denotes a C_{1-4} -alkyl group, which is optionally
 substituted by a carboxy, C_{1-6} -alkyloxy carbonyl,
 benzyloxy carbonyl, C_{1-3} -
 alkylsulphonylaminocarbonyl,
 phenylsulphonylaminocarbonyl,
 trifluorosulphonylamino, trifluorosulphonylami-
 nocarbonyl or 1H-tetrazolyl group, or

a C_{2-4} -alkyl group substituted, at a carbon which is
 other the one in the α -position relative to the adja-
 cent nitrogen atom, by a hydroxy, phenyl- C_{1-3} -
 alkoxy, carboxy- C_{1-3} -alkylamino, C_{1-3} -
 alkoxy carbonyl- C_{1-3} -alkylamino, N-(C_{1-3} -alkyl)-
 carboxy- C_{1-3} -alkylamino or N-(C_{1-3} -alkyl)- C_{1-3} -
 alkoxy carbonyl- C_{1-3} -alkylamino group, and

R_3 denotes a pyridinyl group optionally substituted by
 a methyl group,

or, if E is a group of the formula $R_bNH-C(=NH)-$,
 a physiologically acceptable salt thereof or, if E is a
 cyano group, a salt thereof.

2. A compound of the formula I according to claim 1,
 wherein

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

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

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

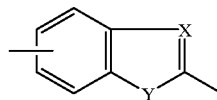
E denotes an $R_bNH-C(=NH)-$ group wherein

R_b denotes a hydrogen atom, a hydroxy group, C_{1-9} -
 alkoxy carbonyl, cyclohexyloxy carbonyl,
 phenyl- C_{1-3} -alkoxy carbonyl, benzoyl, p- C_{1-3} -alkyl-
 benzoyl or pyridinoyl group, whilst the ethoxy moi-
 ety in the 2-position of the abovementioned C_{1-9} -
 alkoxy carbonyl group is optionally, additionally,
 substituted by a C_{1-3} -alkylsulfonyl or 2-(C_{1-3} -
 alkoxy)-ethyl group,

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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,
 or a thienylene group optionally substituted in the carbon
 skeleton by a C_{1-3} -alkyl group,

Het denotes a bicyclic heterocycle of formula



wherein,

X is a nitrogen atom and

Y is an imino group optionally substituted by a C_{1-6} -
 alkyl or C_{3-7} -cycloalkyl group

and R_a denotes a R_2NR_3- group wherein

R_2 denotes a C_{1-4} -alkyl group, which is optionally
 substituted by a carboxy, C_{1-6} -alkyloxy carbonyl,
 benzyloxy carbonyl, C_{1-3} -
 alkylsulphonylaminocarbonyl,
 phenylsulphonylaminocarbonyl,
 trifluorosulphonylamino, trifluorosulphonylami-
 nocarbonyl or 1H-tetrazolyl group, or

a C_{2-4} -alkyl group substituted, at a carbon which is
 other the one in the α -position relative to the adja-
 cent nitrogen atom, by a hydroxy, phenyl- C_{1-3} -
 alkoxy, carboxy- C_{1-3} -alkylamino, C_{1-3} -
 alkoxy carbonyl- C_{1-3} -alkylamino, N-(C_{1-3} -alkyl)-
 carboxy- C_{1-3} -alkylamino or N-(C_{1-3} -alkyl)- C_{1-3} -
 alkoxy carbonyl- C_{1-3} -alkylamino group, and

R_3 denotes pyridinyl group optionally substituted by a
 methyl group,

or a physiologically acceptable salt thereof.

3. A compound of the formula I according to claim 1,
 wherein

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

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

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

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

R_b denotes a hydrogen atom, a hydroxy, C_{1-9} -
 alkoxy carbonyl, cyclohexyloxy carbonyl,
 phenyl- C_{1-3} -alkoxy carbonyl, benzoyl, p- C_{1-3} -alkyl-
 benzoyl or pyridinoyl group, whilst the ethoxy moi-
 ety in the 2-position of the abovementioned C_{1-9} -
 alkoxy carbonyl group is optionally, additionally,
 substituted by a C_{1-3} -alkyl-sulfonyl 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-(C_{1-3} -alkyl)-2,5-benzimidazolylene or
 1-cyclopropyl-2,5-benzimidazolylene group and

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} -alkyloxy carbonyl, benzyloxy carbonyl, C_{1-3} -
 alkylsulphonylaminocarbonyl or 1H-tetrazol-5-yl
 group, or

a C_{2-4} -alkyl group substituted, at a carbon which is
 other the one in the α -position relative to the adja-
 cent nitrogen atom, by a hydroxy, benzyloxy,

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carboxy-C₁₋₃-alkyl-amino, 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, and

R₃ denotes a pyridinyl group optionally substituted by a methyl group,

or a physiologically acceptable salt thereof.

4. A compound of the formula I according to claim 1, wherein

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

B denotes an ethylene group in which the methylene group linked to the group Ar is optionally replaced by an oxygen or sulphur atom or by an —NR₁— group, wherein

R₁ 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, C₁₋₉-alkoxycarbonyl, cyclohexyloxycarbonyl, benzyloxycarbonyl, benzoyl, p-C₁₋₃-alkylbenzoyl or nicotinoyl group, whilst the ethoxy moiety in the 2-position of the abovementioned C₁₋₉-alkoxycarbonyl group is optionally, additionally, substituted by a C₁₋₃-alkylsulphonyl or 2-(C₁₋₃-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 or 1-cyclopropyl-2,5-benzimidazolylene group and

R_a denotes a R₂NR₃— group wherein

R₂ denotes a C₁₋₃-alkyl group which is optionally substituted by a carboxy, C₁₋₆-alkyloxycarbonyl, benzyloxycarbonyl, methylsulphonylaminocarbonyl or 1H-tetrazol-5-yl group, or

a C₂₋₃-alkyl group substituted, at a carbon which is other the one in the α-position relative to the adjacent nitrogen atom, by a hydroxy, benzyloxy, carboxy-C₁₋₃-alkyl-amino, 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, and

R₃ denotes a pyridinyl group,

or a physiologically acceptable salt thereof.

5. A compound of the formula I according to claim 1, wherein

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

B denotes an ethylene group wherein the methylene group attached to the group Ar is optionally replaced by an —NR₁— group, whilst

R₁ 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, C₁₋₉-alkoxycarbonyl, cyclohexyloxycarbonyl, benzyloxycarbonyl, benzoyl, p-C₁₋₃-alkyl-benzoyl or nicotinoyl group, whilst the ethoxy moiety in the 2-position of the abovementioned C₁₋₉-alkoxycarbonyl group is optionally, additionally, 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-benzimidazolylene group and

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R_a denotes an R₂NR₃— group wherein R₂ denotes a C₁₋₃-alkyl group which is optionally substituted by a carboxy, C₁₋₆-alkyloxycarbonyl, benzyloxycarbonyl, methylsulphonylaminocarbonyl or 1H-tetrazol-5-yl group, or

a C₂₋₃-alkyl group substituted, at a carbon which is other the one in the α-position relative to the adjacent nitrogen atom, by a hydroxy, benzyloxy, carboxy-C₁₋₃-alkyl-amino, 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, and

R₃ denotes a 2-pyridinyl group,

or a physiologically acceptable salt thereof.

6. A compound selected from the group consisting of:

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

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

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

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

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

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

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

or a physiologically acceptable salt thereof.

7. 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide or a physiologically acceptable salt thereof.

8. 1-Methyl-2-[N-(4-amidino-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide or a physiologically acceptable salt thereof.

9. 1-Methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)phenyl]aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl) amide or a physiologically acceptable salt thereof.

10. A pharmaceutical composition containing a compound according to claim 1, wherein E denotes an R_bNH—C(=NH)— group, or a compound according to claim 2, 3, 4, 5, 6, 7, 8 or 9, or a physiologically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent.

11. A method for the prophylaxis or treatment of venous and arterial thrombotic disease which comprises administering an antithrombotic amount of a compound according claim 1, wherein E denotes an R_bNH—C(=NH)— group, or a compound according to claim 2, 3, 4, 5, 6, 7, 8 or 9, or a physiologically acceptable salt thereof.

12. The method of claim 11 wherein said thrombotic disease is selected from the group consisting of deep leg vein thrombosis, reocclusion after a bypass operation or angioplasty (PT(CA)), occlusion in peripheral arterial disease, pulmonary embolism, disseminated intravascular

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coagulation, coronary thrombosis, stroke, and the occlusion of a shunt or stent.

13. A method for providing antithrombotic support in thrombolytic treatment utilizing rt-PA or streptokinase, which comprises administering a therapeutically effective amount of a compound according claim **1**, wherein E

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denotes an $R_bNH-C(=NH)-$ group, or a compound according to claim **2, 3, 4, 5, 6, 7, 8** or **9**, or a physiologically acceptable salt thereof.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,087,380 Page 1 of 2
DATED : July 11, 2000
INVENTOR(S) : Norbert Hael, Henning Pripke, Uwe Ries, Jean Marie Stassen and Wolfgang Wienen

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page.

Item [30], **Foreign Application Priority Data** the date "Nov. 24, 1949", should read -- Nov. 24, 1997 --.

Column 6.

Line 22, "pyridinylen" should read -- pyridinylene --.

Column 20.

Line 55, "Methyly" should read -- Methyl --

Column 23.

Line 63, "kieselgur" should read -- Kieselguhr --.

Column 71.

Line 59, "trifluoracetate" should read -- trifluoroacetate --.

Column 72.

Line 8, "trifluoracetate" should read -- trifluoroacetate --.

Column 83.

Line 60, "methansulphonylaminocarbonyl" should read -- methanesulphonylaminocarbonyl --.

Column 84.

Line 20, "methansulphonylaminocarbonyl" should read -- methanesulphonylaminocarbonyl --.

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,087,380 Page 2 of 2
DATED : July 11, 2000
INVENTOR(S) : Norbert Huel, Henning Priepke, Uwe Ries, Jean Marie Stassen and Wolfgang Wienen

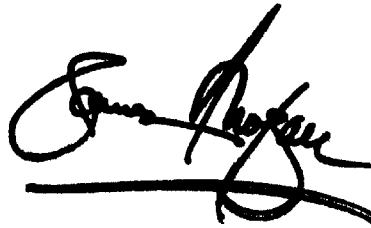
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 92,
Line 62, "physiologically" should read -- physiologically --

Signed and Sealed this

Thirteenth Day of August, 2002

Attest:



Attesting Officer

JAMES E. ROGAN
Director of the United States Patent and Trademark Office