TAB 2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re	:	U. S. Patent 6,087,380
Issued	:	July 11, 2000
Inventors	:	Hauel *et al.*
For	:	DISUBSTITUTED BICYCLIC HETEROCYCLES, THE PREPARATIONS AND THE USE THEREOF AS PHARMACEUTICAL COMPOSITIONS

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Sir:

Boehringer Ingelheim Pharma GmbH & Co. KG, a corporation of the Federal Republic of Germany (hereinafter called "the Applicant") and the owner of record of U. S. Patent No. 6,087,380 hereby applies for an extension of the term of U. S. Patent No. 6,087,380 pursuant to the provisions of 35 U.S.C. § 156 and 37 C. F. R. §§ 1.710 – 1.791.

The Applicant seeks extension of the term of U. S. Patent No. 6,087,380 for a period of 1,469 days, so that the expiration date of the patent would be changed from 18 February 2018 to 26 February 2022.

FDA-2011-E-0117

APP

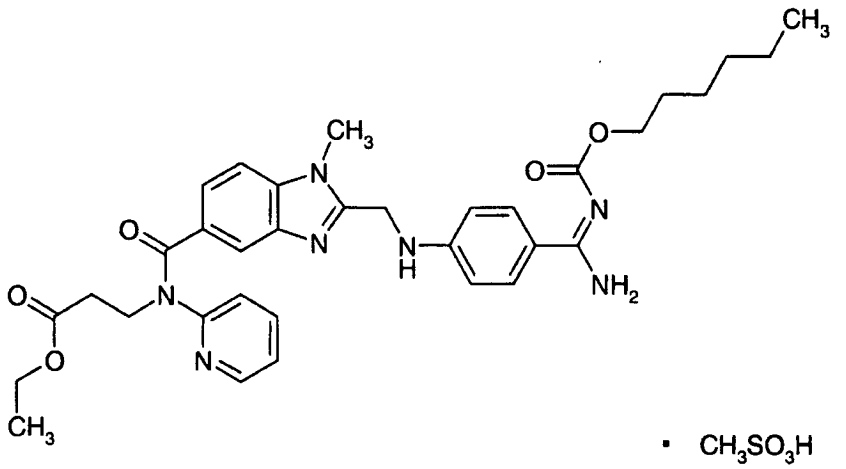
FORMAL REQUIREMENTS FOR APPLICATION FOR EXTENSION OF PATENT TERM

Provided below is the information required by 37 C.F.R. § 1.740(a).

1. A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics

The approved product is dabigatran etexilate mesylate.

Dabigatran etexilate mesylate is the drug substance present in, and thus the active ingredient of, the new drug PRADAXA® (dabigatran etexilate mesylate) Capsules.[1] It has the following structural formula:



Dabigatran etexilate mesylate is the United States Adopted Name (USAN) for the active ingredient.

The active ingredient may also be identified by the following chemical names:

· β-Alanine, *N*-[[2-[[[4-[[[(hexyloxy)carbonyl]amino]iminomethyl]phenyl] amino]methyl]-1-methyl-1*H*-benzimidazol-5-yl]carbonyl]-N-2-pyridinyl-, ethyl ester, methanesulfonate (1:1);

[1] See the text of Package Insert, which is attached hereto as Exhibit A.

· ethyl 3-{[(2-{[(4-{[hexyloxy)carbonyl]carbamimidoyl}phenyl)amino] methyl}-1-methyl-1*H*-benzimidazol-5-yl)carbonyl](pyridin-2-yl)amino}propanoate monomethanesulfonate; and

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

Dabigatran etexilate mesylate is a yellow-white to yellow powder. A saturated solution in pure water has a solubility of 1.8 mg/mL. It is freely soluble in methanol, slightly soluble in ethanol, and sparingly soluble in isopropanol.

2. A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred

The approved product was the subject of regulatory review under the provisions of Section 505 of the Federal Food, Drug & Cosmetic Act (FDCA), as amended (21 U.S.C. § 355). Specifically, the approved product was the subject of regulatory review under section 505(b)(1) of the FDCA.

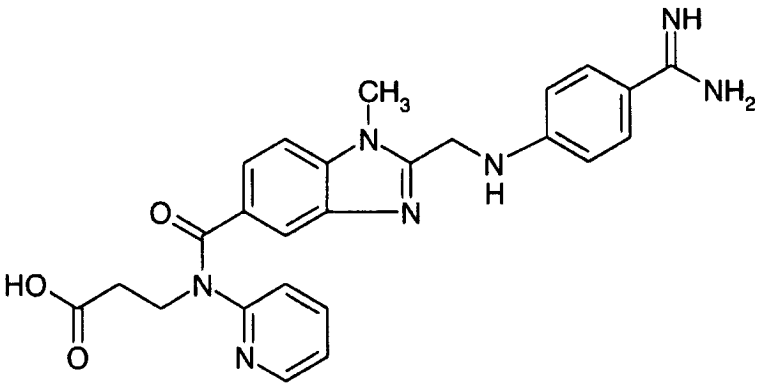
3. An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred

The product received permission for commercial marketing or use under the provisions of Section 505 of the Federal Food, Drug & Cosmetic Act (21 U.S.C. § 355) on 19 October 2010, the date New Drug Application (NDA) No. 22-512 was approved by the United States Food and Drug Administration.

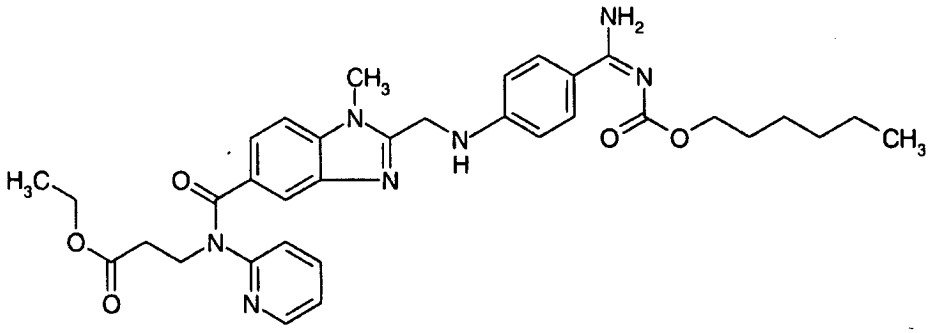
4. An identification of each active ingredient in the drug product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug & Cosmetic Act, the Public Health Service Act, or the Virus-Serum Toxin Act

Dabigatran etexilate mesylate is the active ingredient in PRADAXA® Capsules. 21 C.F.R. § 210.3(b)(7), 54 Fed Reg. 28872, 28881 (July 10, 1989). The chemical names and structural formula of dabigatran etexilate mesylate is as stated and shown, respectively, above.

The active moiety or component of the active ingredient is dabigatran. The chemical name of dabigatran is β-Alanine, *N*-[[2-[[[4-(aminoiminomethyl) phenyl]amino] methyl]-1-methyl-1*H*-benzimidazol-5-yl]carbonyl]-*N*-2-pyridinyl-, or 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide. Dabigatran has the following structural formula:



Dabigatran etexilate is a prodrug of dabigatran. The chemical name of dabigatran etexilate is β-Alanine, *N*-[[2-[[[4-[[[(hexyloxy)carbonyl] amino]iminomethyl]phenyl] amino]methyl]-1-methyl-1*H*-benzimidazol-5-yl]carbonyl]-N-2-pyridinyl-, ethyl ester; ethyl 3-{[(2-{[(4-{[hexyloxy)carbonyl]carbamimidoyl}phenyl)amino] methyl}-1-methyl-1*H*-benzimidazol-5-yl)carbonyl](pyridin-2-yl)amino}propanoate; or 1-Methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)phenyl]aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl) amide. Dabigatran etexilate has the following structural formula:



It is the Applicant's information and belief that none of dabigatran etexilate mesylate, dabigatran etexilate or dabigatran has previously been approved for commercial marketing or use under the Federal Food, Drug & Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

5. A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the date of the last day on which the application could be submitted

This application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f). Such sixty day period will expire on 17 December 2010.

6. A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration

The patent for which an extension is being sought is U. S. Patent No. 6,087,380. It issued on 11 July 2000. Absent any extension which may be granted as a result of the present application, it will expire on 18 February 2018.[2] The inventors named in the patent are Norbert Hauel, of

[2] The term of U. S. Patent No. 6,087,380 was determined in the following manner: It issued on 11 July 2000 and results from Application No. 09/025,690, filed on 18 February 1998. Thus, its term is to be determined in accordance with 35 U.S.C. §154(a)(2), which states, "Subject to the payment of fees under this title, such grant shall be for a term beginning on the date on which the patent issues and ending 20 years from the date on which the application for the patent was filed in the United States or, if the application contains a specific reference to an earlier filed application or applications under section 120, 121, or 365(c) of this title, from the date on which the earliest such application was filed." Thus, its term is 20 years from the earliest filed application under 35

Schemmerhofen in the Federal Republic of Germany, Henning Priepke, of Warthausen in the Federal Republic of Germany, Uwe Ries, of Biberach in the Federal Republic of Germany, Jean Marie Stassen, of Lubbeek in Belgium, and Wolfgang Wienen, of Biberach in the Federal Republic of Germany. At the time the application was filed, Norbert Hauel, Henning Priepke, Uwe Ries and Wolfgang Wienen were citizens of the Federal Republic of Germany, whereas Jean Marie Stassen was a citizen of Belgium.

7. A copy of the patent for which extension is being sought, including the entire specification (including claims) and drawings

A copy of U. S. Patent No. 6,087,380, the patent for which extension is being sought, including the entire specification (including claims) and drawings is attached hereto as Exhibit B.

8. A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent

Copy of the Certificate of Correction (two (2) pages) issued for U. S. Patent No. 6,087,380 is attached hereto as Exhibit C.

Copies of the (1) maintenance fee window dates; (2) maintenance fee statement for 4^{th} year; and (3) maintenance fee statement for 8^{th} year are attached hereto as Exhibit D. The maintenance fee statements indicate timely payment of fees for each window.

9. A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on the approved product or method of using or manufacturing the approved product

USC 120 (18 February 1998) as provided by 35 U.S.C. § 154(a)(2) and the patent will expire on 18 February 2018.

U. S. Patent No. 6,087,380 claims the approved product and a method of using the approved product.

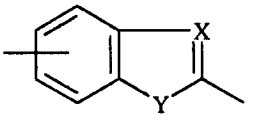
The applicable patent claims which read on the approved product and method of using the approved product are Claims 1-7 and 9-12. The text of these claims, as amended by the Certificate of Correction dated 13 August 2002, is provided in Exhibit E.

Approved Product (Claims 1-7 and 9-10)

Claim 1 reads on the approved product because claim 1 is a genus which encompasses the approved product, dabigatran etexilate (regardless of the salt form). The approved product, dabigatran etexilate mesylate, is a compound of the formula **I**

R_a—A—Het—B—Ar—E (I)

wherein
A is a carbonyl linked to the benzo moiety of the group Het,
B is an ethylene group, wherein a methylene group, linked either to the group Het or Ar, is optionally replaced by a $-NR_1$ group, wherein R_1 is a hydrogen atom,
E is R_bNH—C(=NH)— wherein R_b is a C_{1-9}-alkoxycarbonyl,
Ar is phenylene,
Het denotes a bicyclic heterocycle of formula



wherein,
X is nitrogen,
Y is an imino group optionally substituted by a C_{1-6}-alkyl 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,C_{1-6}-alkyloxycarbonyl,
and
R_3 denotes a pyridinyl group,
or, if E is a group of the formula R_bNH—C—(=NH)—, a physiologically acceptable salt thereof.

Claim 2 reads on the approved product because claim 2 is a subgenus of claim 1, which encompasses the approved product, dabigatran etexilate

(regardless of the salt form). The approved product, dabigatran etexilate mesylate, is a compound of the formula **I**

R_a—A—Het—B—Ar—E **(I)**

wherein the definitions of A, B, R_1, E, R_b, Ar, Het, X, Y, R_a, R_2 and R_3 are the same as in claim 1.

Claims 3-5 read on the approved product because each of claims 3-5 is a subgenus of claim 1, which encompasses the approved product regardless of the salt form. The approved product, dabigatran etexilate mesylate, is a compound of the formula **I**

R_a—A—Het—B—Ar—E **(I)**

wherein
A is a carbonyl group linked to the benzo moiety of the group Het,
B is an ethylene group in which the methylene group linked to the group Ar is optionally replaced by an $-NR_1$ group, wherein
R_1 is a hydrogen atom,
E is an R_bNH—C(=NH)— group wherein
R_b is a C_{1-9}-alkoxycarbonyl,
Ar is a 1,4-phenylene group,
Het is a 1-(C_{1-3}-alkyl) -2,5-benzimidazolylene or 1-methyl-2,5-benzimidazolylene and
R_a is an R_2NR_3– group wherein
R_2 is a C_{1-4}-alkyl or C_{1-3}-alkyl group substituted by a C_{1-6}-alkyloxycarbonyl, and
R_3 is a pyridinyl group,
or a physiologically acceptable salt thereof.

Claim 6 indirectly reads on the approved product, dabigatran etexilate (regardless of the salt form). Part (c) of claim 6 identifies dabigatran, or a pharmaceutically acceptable salt thereof, which is the active moiety of dabigatran etexilate. For example, when a salt of dabigatran etexilate enters the body, the prodrug is cleaved to form dabigatran as an active metabolite.

Claim 7 indirectly reads on the approved product, dabigatran etexilate (regardless of the salt form). Claim 7 is directed to dabigatran, or a pharmaceutically acceptable salt thereof, which is the active moiety of dabigatran etexilate. For example, w

hen a salt of dabigatran etexilate enters the body, the prodrug is cleaved to form dabigatran as an active metabolite.

Claim 9 generally reads on the approved product, dabigatran etexilate mesylate. Claim 9 is directed to dabigatran etexilate or a physiologically acceptable salt thereof, which encompasses the approved product, dabigatran etexilate mesylate.

Claim 10 reads on the approved product because it is directed to a pharmaceutical composition containing dabigatran etexilate or a physiologically accpetable salt thereof.

Method of Using the Approved Product (Claims 11-12)

Claim 11 reads on a method of using the approved product because it is directed to a method for the prophylaxis or treatment of (venous and) arterial thrombotic disease which comprises administering an antithrombotic amount of a compound in accordance with claims 1-7 and 9 or a physiologically acceptable salt thereof. It has already been established above that claims 1-5 and 9 read upon the approved product, dabigatran etexilate (regardless of the salt form). The approved indication for the new drug PRADAXA® (dabigatran extexilate mesylate) Capsules is "to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation." The use recited in claim 11 may fairly be said to correspond to the approved indication for the new drug, or which dabigatran etexilate mesylate is the sole active ingredient.

Claim 12 reads on a method of using the approved product because claim 12 depends from claim 11 and is directed to a thrombotic disease selected from, *inter alia*, stroke. Stroke generically encompasses stroke prevention in patients with atrial fibrillation.

10. A statement, beginning on a new page, of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services or

the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(*Only subparagraph (i) is applicable. Subparaph (i) reads as set forth below.*)

(i) For a patent claiming a human drug, antibiotic, or human biological product:

(A) The effective date of the investigational new drug (IND) application and the IND number;

(B) The date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number; and

(C) The date on which the NDA was approved or the Product License issued.

The required statement appears in Exhibit F.

11. A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities

The required brief description appears in Exhibit G.

12. A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of extension was determined

The required statement appears in Exhibit H.

13. A statement that the applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought

The undersigned attorney for Applicant acknowledges, on behalf of the Applicant, a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services any information that is material to the determination of entitlement to the extension sought.

14. The prescribed fee for receiving and acting upon the application for extension

The prescribed fee of $1,120 pursuant to 37 C.F.R. § 1.20(j)(1) may be charged to Deposit Account No. 02-2955. In addition, the Director is hereby authorized to charge any additional fees necessary, or to refund any overpayment, to Deposit Account 02-2955. A Fee Authorization paper is also submitted herewith.

15. The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed

Direct all correspondence relating to this application to:

Wendy A. Petka
Boehringer Ingelheim Corporation
900 Ridgebury Road, P. O. Box 368
Ridgefield, CT 06877-0368

Phone No. (203) 791-6614
Fax No. (203) 798-4408
E-mail: wendy.petka@boehringer-ingelheim.com

This application is accompanied by two additional copies of such application (for a total of three copies).

Pursuant to 37 C.F.R. § 1.730(b)(2), this application is signed by a registered practitioner on behalf of the patent owner. Proof that this practitioner is authorized to act on behalf of the patent owner is attached hereto as Exhibit I. The revocation of power of attorney and new power of attorney papers were filed in the United States Patent Office on 23 November 2010,

as evidenced by the electronic filing receipt and Notice of Acceptance received from the United States Patent and Trademark Office on 1 December 2010.

BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG

Date: December 10, 2010

Wendy Petka
Attorney for Applicant
Registration No. 53,459

Exhibit A

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PRADAXA safely and effectively. See full prescribing information for PRADAXA.

PRADAXA® (dabigatran etexilate mesylate) capsules for oral use
Initial U.S. Approval: 2010

INDICATIONS AND USAGE

PRADAXA is a direct thrombin inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (1)

DOSAGE AND ADMINISTRATION

- For patients with CrCl >30 mL/min: 150 mg orally, twice daily (2.1)
- For patients with CrCl 15-30 mL/min: 75 mg orally, twice daily (2.1)
- Instruct patients not to chew, break, or open capsules (2.1)
- Review recommendations for converting to or from other oral or parenteral anticoagulants (2.2, 2.3)
- Temporarily discontinue PRADAXA before invasive or surgical procedures when possible, then restart promptly (2.4)

DOSAGE FORMS AND STRENGTHS

Capsules: 75 mg and 150 mg (3)

CONTRAINDICATIONS

- Active pathological bleeding (4)
- History of serious hypersensitivity reaction to PRADAXA (4)

WARNINGS AND PRECAUTIONS

- Risk of bleeding: PRADAXA can cause serious and, sometimes, fatal bleeding. Promptly evaluate signs and symptoms of blood loss. (5.1)
- Temporary discontinuation: Avoid lapses in therapy to minimize risk of stroke (5.2)
- P-gp inducers and inhibitors: Avoid coadministration of rifampin with PRADAXA because of effects on dabigatran exposure (5.3)

ADVERSE REACTIONS

Most common adverse reactions (>15%) are gastritis-like symptoms and bleeding (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at (800) 542-6257 or (800) 459-9906 TTY or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

USE IN SPECIFIC POPULATIONS

Geriatric use: Risk of bleeding increases with age (8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

PRADAXA is indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

For patients with creatinine clearance (CrCl) >30 mL/min, the recommended dose of PRADAXA is 150 mg taken orally, twice daily, with or without food. For patients with CrCl 15-30 mL/min, the recommended dose is 75 mg twice daily *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*. Dosing recommendations for patients with a CrCL < 15 mL/min or on dialysis cannot be provided.

Instruct patients to swallow the capsules whole. Breaking, chewing, or emptying the contents of the capsule can result in increased exposure *[see Clinical Pharmacology (12.3)]*.

If a dose of PRADAXA is not taken at the scheduled time, the dose should be taken as soon as possible on the same day; the missed dose should be skipped if it cannot be taken at least 6 hours before the next scheduled dose. The dose of PRADAXA should not be doubled to make up for a missed dose.

2.2 Converting from or to Warfarin

When converting patients from warfarin therapy to PRADAXA, discontinue warfarin and start PRADAXA when the international normalized ratio (INR) is below 2.0.

When converting from PRADAXA to warfarin, adjust the starting time of warfarin based on creatinine clearance as follows:

- For CrCl >50 mL/min, start warfarin 3 days before discontinuing PRADAXA.
- For CrCl 31-50 mL/min, start warfarin 2 days before discontinuing PRADAXA.
- For CrCl 15-30 mL/min, start warfarin 1 day before discontinuing PRADAXA.
- For CrCl <15 mL/min, no recommendations can be made.

Because PRADAXA can contribute to an elevated INR, the INR will better reflect warfarin's effect after PRADAXA has been stopped for at least 2 days.

2.3 Converting from or to Parenteral Anticoagulants

For patients currently receiving a parenteral anticoagulant, start PRADAXA 0 to 2 hours before the time that the next dose of the parenteral drug was to have been administered or at the time of discontinuation of a continuously administered parenteral drug (e.g., intravenous unfractionated heparin).

For patients currently taking PRADAXA, wait 12 hours (CrCl ≥30 mL/min) or 24 hours (CrCl <30 mL/min) after the last dose of PRADAXA before initiating treatment with a parenteral anticoagulant *[see Clinical Pharmacology (12.3)]*.

2.4 Surgery and Interventions

If possible, discontinue PRADAXA 1 to 2 days (CrCl ≥50 mL/min) or 3 - 5 days (CrCl <50 mL/min) before invasive or surgical procedures because of the increased risk of bleeding. Consider longer times for patients undergoing major surgery, spinal puncture, or placement of a spinal or epidural catheter or port, in whom complete hemostasis may be required *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

If surgery cannot be delayed, there is an increased risk of bleeding *[see Warnings and Precautions (5.1)]*. This risk of bleeding should be weighed against the urgency of intervention *[see Warnings and Precautions (5.2)]*. Bleeding risk can be assessed by the ecarin clotting time (ECT). This test is a better marker of the anticoagulant activity of dabigatran than activated partial thromboplastin time (aPTT), prothrombin time (PT)/INR, or thrombin time (TT). If ECT is not available, the aPTT test provides an approximation of PRADAXA's anticoagulant activity *[see Clinical Pharmacology (12.2)]*.

3 DOSAGE FORMS AND STRENGTHS

Capsules with a light blue opaque cap imprinted in black with the Boehringer Ingelheim company symbol and a cream-colored opaque body imprinted in black with "R150" (150 mg) or "R75" (75 mg).

4 CONTRAINDICATIONS

PRADAXA is contraindicated in patients with:

- Active pathological bleeding *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.
- History of a serious hypersensitivity reaction to PRADAXA (e.g., anaphylactic reaction or anaphylactic shock) *[see Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Bleeding

PRADAXA increases the risk of bleeding and can cause significant and, sometimes, fatal bleeding. Risk factors for bleeding include the use of drugs that increase the risk of bleeding in general (e.g., anti-platelet agents, heparin, fibrinolytic therapy, and chronic use of NSAIDs) and labor and delivery. Promptly evaluate any signs or symptoms of blood loss (e.g., a drop in hemoglobin and/or hematocrit or hypotension). Discontinue PRADAXA in patients with active pathological bleeding.

In the RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy) study, a life-threatening bleed (bleeding that met one or more of the following criteria: fatal, symptomatic intracranial, reduction in hemoglobin of at least 5 grams per deciliter, transfusion of at least 4 units of blood, associated with hypotension requiring the use of intravenous inotropic agents, or necessitating surgical intervention) occurred at an annualized rate of 1.5% and 1.8% for PRADAXA 150 mg and warfarin, respectively *[see Adverse Reactions (6.1)]*.

5. 2 Temporary Discontinuation of PRADAXA

Discontinuing anticoagulants, including PRADAXA, for active bleeding, elective surgery, or invasive procedures places patients at an increased risk of stroke. Lapses in therapy should be avoided, and if anticoagulation with PRADAXA must be temporarily discontinued for any reason, therapy should be restarted as soon as possible.

5.3 Effect of P-gp Inducers and Inhibitors on Dabigatran Exposure

The concomitant use of PRADAXA with P-gp inducers (e.g., rifampin) reduces exposure to dabigatran and should generally be avoided *[see Clinical Pharmacology (12.3)]*.

P-gp inhibitors ketoconazole, verapamil, amiodarone, quinidine, and clarithromycin, do not require dose adjustments. These results should not be extrapolated to other P-gp inhibitors *[see Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The RE-LY study provided safety information on the use of two doses of PRADAXA and warfarin *[see Clinical Studies (14)]*. The numbers of patients and their exposures are described in Table 1. Limited information is presented on the 110 mg dosing arm because this dose is not approved.

Table 1 Summary of Treatment Exposure in RE-LY

	PRADAXA 110 mg twice daily	PRADAXA 150 mg twice daily	Warfarin
Total number treated	5983	6059	5998
Exposure			
> 12 months	4936	4939	5193
> 24 months	2387	2405	2470
Mean exposure (months)	20.5	20.3	21.3
Total patient-years	10,242	10,261	10,659

Because clinical studies are conducted under widely varying conditions and over varying lengths of time, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Drug Discontinuation in RE-LY

The rates of adverse reactions leading to treatment discontinuation were 21% for PRADAXA 150 mg and 16% for warfarin. The most frequent adverse reactions leading to discontinuation of PRADAXA were bleeding and gastrointestinal events (i.e., dyspepsia, nausea, upper abdominal pain, gastrointestinal hemorrhage, and diarrhea).

Bleeding [see Warnings and Precautions (5.1)]

Table 2 shows the number of patients experiencing serious bleeding during the treatment period in the RE-LY study, with the bleeding rate per 100 patient-years (%). Major bleeds fulfilled one or more of the following criteria: bleeding associated with a reduction in hemoglobin of at least 2 grams per deciliter or leading to a transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ (intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding, or pericardial bleeding). A life-threatening bleed met one or more of the following criteria: fatal, symptomatic intracranial bleed, reduction in hemoglobin of at least 5 grams per deciliter, transfusion of at least 4 units of blood, associated with hypotension requiring the use of intravenous inotropic agents, or necessitating surgical intervention. Intracranial hemorrhage included intracerebral (hemorrhagic stroke), subarachnoid, and subdural bleeds.

Table 2 Bleeding Events* (per 100 Patient-Years)

	PRADAXA 150 mg twice daily N (%)	Warfarin N (%)	Hazard Ratio (95% CI**)
Randomized patients	6076	6022	
Patient-years	12,033	11,794	
Intracranial hemorrhage	38 (0.3)	90 (0.8)	0.41 (0.28, 0.60)
Life-threatening bleed	179 (1.5)	218 (1.9)	0.80 (0.66, 0.98)
Major bleed	399 (3.3)	421 (3.6)	0.93 (0.81, 1.07)
Any bleed	1993 (16.6)	2166 (18.4)	0.91 (0.85, 0.96)

*Patients contributed multiple events and events were counted in multiple categories.
**Confidence interval

The risk of major bleeds was similar with PRADAXA 150 mg and warfarin across major subgroups defined by baseline characteristics, with the exception of age, where there was a trend towards a higher incidence of major bleeding on PRADAXA (HR 1.2, 95% CI: 1.0 to 1.4) for patients ≥75 years of age.

There was a higher rate of major gastrointestinal bleeds in patients receiving PRADAXA 150 mg than in patients receiving warfarin (1.6% vs. 1.1%, respectively, with a hazard ratio vs. warfarin of 1.5, 95% CI, 1.2 to 1.9), and a higher rate of any gastrointestinal bleeds (6.1% vs. 4.0%, respectively).

Gastrointestinal Adverse Reactions

Patients on PRADAXA 150 mg had an increased incidence of gastrointestinal adverse reactions (35% vs. 24% on warfarin). These were commonly dyspepsia (including abdominal pain upper, abdominal pain, abdominal discomfort, and epigastric discomfort) and gastritis-like symptoms (including GERD, esophagitis, erosive gastritis, gastric hemorrhage, hemorrhagic gastritis, hemorrhagic erosive gastritis, and gastrointestinal ulcer).

Hypersensitivity Reactions

In the RE-LY study, drug hypersensitivity (including urticaria, rash, and pruritus), allergic edema, anaphylactic reaction, and anaphylactic shock were reported in <0.1% of patients receiving PRADAXA.

7 DRUG INTERACTIONS

The concomitant use of PRADAXA with P-gp inducers (e.g., rifampin) reduces exposure to dabigatran and should generally be avoided *[see Clinical Pharmacology (12.3)]*.

P-gp inhibitors ketoconazole, verapamil, amiodarone, quinidine, and clarithromycin do not require dose adjustments. These results should not be extrapolated to other P-gp inhibitors *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women.

Dabigatran has been shown to decrease the number of implantations when male and female rats were treated at a dosage of 70 mg/kg (about 2.6 to 3.0 times the human exposure at maximum recommended human dose [MRHD] of 300 mg/day based on area under the curve [AUC] comparisons) prior to mating and up to implantation (gestation Day 6). Treatment of pregnant rats after implantation with dabigatran at the same dose increased the number of dead offspring and caused excess vaginal/uterine bleeding close to parturition. Although dabigatran increased the incidence of delayed or irregular ossification of fetal skull bones and vertebrae in the rat, it did not induce major malformations in rats or rabbits.

8.2 Labor and Delivery

Safety and effectiveness of PRADAXA during labor and delivery have not been studied in clinical trials. Consider the risks of bleeding and of stroke in using PRADAXA in this setting *[see Warnings and Precautions (5.1)]*.

Death of offspring and mother rats during labor in association with uterine bleeding occurred during treatment of pregnant rats from implantation (gestation Day 7) to weaning (lactation Day 21) with dabigatran at a dose of 70 mg/kg (about 2.6 times the human exposure at MRHD of 300 mg/day based on AUC comparisons).

8.3 Nursing Mothers

It is not known whether dabigatran is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PRADAXA is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of PRADAXA in pediatric patients has not been established.

8.5 Geriatric Use

Of the total number of patients in the RE-LY study, 82% were 65 and over, while 40% were 75 and over. The risk of stroke and bleeding increase with age, but the risk-benefit profile is favorable in all age groups *[see Warnings and Precautions (5.3), Adverse Reactions (6.1), and Clinical Studies (14)]*.

8.6 Renal Impairment

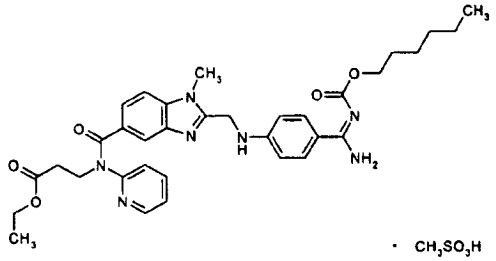
No dose adjustment of PRADAXA is recommended in patients with mild or moderate renal impairment. Reduce the dose of PRADAXA in patients with severe renal impairment (CrCl 15-30 mL/min) *[see Dosage and Administration (2.1)]*. Dosing recommendations for patients with CrCl < 15 mL/min or on dialysis cannot be provided.

10 OVERDOSAGE

Accidental overdose may lead to hemorrhagic complications. There is no antidote to dabigatran etexilate or dabigatran. In the event of hemorrhagic complications, initiate appropriate clinical support, discontinue treatment with PRADAXA, and investigate the source of bleeding. Dabigatran is primarily excreted in the urine; therefore, maintain adequate diuresis. Dabigatran can be dialyzed (protein binding is low), with the removal of about 60% of drug over 2-3 hours; however, data supporting this approach are limited. Consider surgical hemostasis or the transfusion of fresh frozen plasma or red blood cells. There is some experimental evidence to support the role of activated prothrombin complex concentrates (e.g., FEIBA), or recombinant Factor VIIa, or concentrates of coagulation factors II, IX or X; however, their usefulness in clinical settings has not been established. Consider administration of platelet concentrates in cases where thrombocytopenia is present or long-acting antiplatelet drugs have been used. Measurement of aPTT or ECT may help guide therapy *[see Clinical Pharmacology (12.2)]*.

11 DESCRIPTION

The chemical name for dabigatran etexilate mesylate, a direct thrombin inhibitor, is β-Alanine, N-[[2-[[[4-[[[(hexyloxy)carbonyl]amino]iminomethyl] phenyl]amino]methyl]-1-methyl-1H-benzimidazol-5-yl]carbonyl]-N-2-pyridinyl-,ethyl ester, methanesulfonate. The empirical formula is $C_{34}H_{41}N_7O_5 \cdot CH_4O_3S$ and the molecular weight is 723.86 (mesylate salt), 627.75 (free base). The structural formula is:



Dabigatran etexilate mesylate is a yellow-white to yellow powder. A saturated solution in pure water has a solubility of 1.8 mg/mL. It is freely soluble in methanol, slightly soluble in ethanol, and sparingly soluble in isopropanol.

The 150 mg capsule for oral administration contains 172.95 mg dabigatran etexilate mesylate, which is equivalent to 150 mg of dabigatran etexilate, and the following inactive ingredients: acacia, dimethicone, hypromellose, hydroxypropyl cellulose, talc, and tartaric acid. The capsule shell is composed of carageenan, FD&C Blue No. 2, FD&C Yellow No. 6, hypromellose, potassium chloride, titanium dioxide, and black edible ink. The 75 mg capsule contains 86.48 mg dabigatran etexilate mesylate, equivalent to 75 mg dabigatran etexilate, and is otherwise similar to the 150 mg capsule.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dabigatran and its acyl glucuronides are competitive, direct thrombin inhibitors. Because thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of a thrombus. Both free and clot-bound thrombin, and thrombin-induced platelet aggregation are inhibited by the active moieties.

12.2 Pharmacodynamics

At recommended therapeutic doses, dabigatran etexilate prolongs the aPTT, ECT, and TT. With an oral dose of 150 mg twice daily the median peak aPTT is approximately 2x control. Twelve hours after the last dose the median aPTT is 1.5x control, with less than 10% of patients exceeding 2x control. In the RE-LY trial, the median (10^{th} – 90^{th} percentile) trough aPTT in patients receiving the 150 mg dose was 52 (40 – 76) seconds. The median (10^{th} – 90^{th} percentile) trough ECT in patients receiving the 150 mg dose was 63 (44 – 103) seconds. The INR test is relatively insensitive to the activity of dabigatran and may or may not be elevated in patients on PRADAXA. When converting a patient from PRADAXA to warfarin therapy, the INR is unlikely to be useful until at least 2 days after discontinuation of PRADAXA.

Cardiac Electrophysiology

No prolongation of the QTc interval was observed with dabigatran etexilate at doses up to 600 mg.

12.3 Pharmacokinetics

Dabigatran etexilate mesylate is absorbed as the dabigatran etexilate ester. The ester is then hydrolyzed, forming dabigatran, the active moeity. Dabigatran is metabolized to four different acyl glucuronides and both the glucuronides and dabigatran have similar pharmacological activity. Pharmacokinetics described here refer to the sum of dabigatran and its glucuronides. Dabigatran displays dose-proportional pharmacokinetics in healthy subjects and patients in the range of doses from 10 to 400 mg.

Absorption

The absolute bioavailability of dabigatran following oral administration of dabigatran etexilate is approximately 3 to 7%. Dabigatran etexilate is a substrate of the efflux transporter P-gp. After oral administration of dabigatran etexilate in healthy volunteers, C_{max} occurs at 1 hour post-administration in the fasted state. Coadministration of PRADAXA with a high-fat meal delays the time to C_{max} by approximately 2 hours but has no effect on the bioavailability of dabigatran; PRADAXA may be administered with or without food.

The oral bioavailability of dabigatran etexilate increases by 75% when the pellets are taken without the capsule shell compared to the intact capsule formulation. PRADAXA capsules should therefore not be broken, chewed, or opened before administration.

Distribution

Dabigatran is approximately 35% bound to human plasma proteins. The red blood cell to plasma partitioning of dabigatran measured as total radioactivity is less than 0.3. The volume of distribution of dabigatran is 50-70 L. Dabigatran pharmacokinetics are dose proportional after single doses of 10-400 mg. Given twice daily, dabigatran's accumulation factor is approximately two.

Elimination

Dabigatran is eliminated primarily in the urine. Renal clearance of dabigatran is 80% of total clearance after intravenous administration. After oral administration of radiolabeled dabigatran, 7% of radioactivity is recovered in urine and 86% in feces. The half-life of dabigatran in healthy subjects is 12 to 17 hours.

Metabolism

After oral administration, dabigatran etexilate is converted to dabigatran. The cleavage of the dabigatran etexilate by esterase-catalyzed hydrolysis to the active principal dabigatran is the predominant metabolic reaction. Dabigatran is not a substrate, inhibitor or inducer of CYP450 enzymes. Dabigatran is subject to conjugation forming pharmacologically active acyl glucuronides. Four positional isomers, 1-O, 2-O, 3-O and 4-O-acylglucuronide exist, and each accounts for less than 10% of total dabigatran in plasma.

Renal Impairment

An open, parallel-group single-center study compared dabigatran pharmacokinetics in healthy subjects and patients with mild to moderate renal impairment receiving a single dose of PRADAXA 150 mg. Based on pharmacokinetic modeling, estimated exposure to dabigatran increases with the severity of renal function impairment (Table 3). Similar findings were observed in the RE-LY trial.

Table 3 Estimated Pharmacokinetic Parameters of Dabigatran by Renal Function

Renal Function	CrCl (mL/min)	Increase in AUC	Increase in Cmax	$t_{1/2}$ (h)
Normal	80	1x	1x	13
Mild	50	1.5x	1.1x	15
Moderate	30	3.2x	1.7x	18

Hepatic Impairment

Administration of PRADAXA in patients with moderate hepatic impairment (Child-Pugh B) showed a large inter-subject variability, but no evidence of a consistent change in exposure or pharmacodynamics.

Drug Interactions

Impact of Other Drugs on Dabigatran

P-gp Inducers

Rifampin: Rifampin 600 mg once daily for 7 days followed by a single dose of dabigatran decreased its AUC and C_{max} by 66% and 67%, respectively. By Day 7 after cessation of rifampin treatment, dabigatran exposure was close to normal *[see Warnings and Precautions (5.3) and Drug Interactions (7)]*.

P-gp Inhibitors

In studies with the P-gp inhibitors ketoconazole, amiodarone, verapamil and quinidine, the time to peak, terminal half-life, and mean residence time of dabigatran were not affected. Any observed changes in C_{max} and AUC are described below.

Ketoconazole: Ketoconazole increased dabigatran $AUC_{0-\infty}$ and C_{max} values by 138% and 135%, respectively, after a single dose of 400 mg, and 153% and 149%, respectively, after multiple daily doses of 400 mg.

Verapamil: When dabigatran etexilate was co-administered with oral verapamil, the C_{max} and AUC of dabigatran were increased. The extent of increase depends on the formulation of verapamil and timing of administration. If verapamil is present in the gut when dabigatran is taken, it will increase exposure to dabigatran with the greatest increase observed when a single dose of immediate-release verapamil is given one hour prior to dabigatran (AUC increased by a factor of 2.4). If verapamil is given 2 hours after dabigatran, the increase in AUC is negligible. In the population pharmacokinetics study from RE-LY, no important changes in dabigatran trough levels were observed in patients who received verapamil.

Amiodarone: When dabigatran etexilate was co-administered with a single 600 mg oral dose of amiodarone, the dabigatran AUC and C_{max} increased by 58% and 50%, respectively. The increase in exposure was mitigated by a 65% increase in the renal clearance of dabigatran in the presence of amiodarone. The increase in renal clearance may persist after amiodarone is discontinued because of amiodarone's long half-life. In the population pharmacokinetics study from RE-LY, no important changes in dabigatran trough levels were observed in patients who received amiodarone.

Quinidine: Quinidine was given as 200 mg dose every 2 hours up to a total dose of 1000 mg. Dabigatran etexilate was given over 3 consecutive days, the last evening dose on Day 3 with or without quinidine pre-dosing. Concomitant quinidine administration increased dabigatran's AUC and C_{max} by 53% and 56%, respectively.

Clarithromycin: Coadministered clarithromycin had no impact on the exposure to dabigatran.

Other Drugs
Clopidogrel: When dabigatran etexilate was given concomitantly with a loading dose of 300 mg or 600 mg clopidogrel, the dabigatran AUC and C_{max} increased by approximately 30% and 40%, respectively. The concomitant administration of dabigatran etexilate and clopidogrel resulted in no further prolongation of capillary bleeding times compared to clopidogrel monotherapy. When comparing combined treatment and the respective mono-treatments, the coagulation measures for dabigatran's effect (aPTT, ECT and TT) remained unchanged, and inhibition of platelet aggregation (IPA), a measurement of clopidogrel's effect, remained unchanged.

Enoxaparin: Enoxaparin 40 mg given subcutaneously for 3 days with the last dose given 24 hours before a single dose of PRADAXA had no impact on the exposure to dabigatran or the coagulation measures aPTT, ECT, or TT.

Diclofenac, Ranitidine, and Digoxin: None of these drugs alters exposure to dabigatran.

In RE-LY, dabigatran plasma samples were also collected. The concomitant use of proton pump inhibitors, H2 antagonists and digoxin did not appreciably change the trough concentration of dabigatran.

Impact of Dabigatran on Other Drugs
In clinical studies exploring CYP3A4, CYP2C9, P-gp and other pathways, dabigatran did not meaningfully alter the pharmacokinetics of amiodarone, atorvastatin, clarithromycin, diclofenac, clopidogrel, digoxin, pantoprazole, or ranitidine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Dabigatran was not carcinogenic when administered by oral gavage to mice and rats for up to 2 years. The highest doses tested (200 mg/kg/day) in mice and rats were approximately 3.6 and 6 times, respectively, the human exposure at MRHD of 300 mg/day based on AUC comparisons.

Dabigatran was not mutagenic in *in vitro* tests, including bacterial reversion tests, mouse lymphoma assay and chromosomal aberration assay in human lymphocytes, and the *in vivo* micronucleus assay in rats.

In the rat fertility study with oral gavage doses of 15, 70, and 200 mg/kg, males were treated for 29 days prior to mating, during mating up to scheduled termination, and females were treated 15 days prior to mating through gestation Day 6. No adverse effects on male or female fertility were observed at 200 mg/kg or 9 to 12 times the human exposure at MRHD of 300 mg/day based on AUC comparisons. However, the number of implantations decreased in females receiving 70 mg/kg, or 3 times the human exposure at MRHD based on AUC comparisons.

14 CLINICAL STUDIES

The clinical evidence for the efficacy of PRADAXA was derived from RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy), a multi-center, multi-national, randomized parallel group trial comparing two blinded doses of PRADAXA (110 mg twice daily and 150 mg twice daily) with open-label warfarin (dosed to target INR of 2 to 3) in patients with non-valvular, persistent, paroxysmal, or permanent atrial fibrillation and one or more of the following additional risk factors:

- Previous stroke, transient ischemic attack (TIA), or systemic embolism
- Left ventricular ejection fraction <40%
- Symptomatic heart failure, ≥ New York Heart Association Class 2
- Age ≥75 years
- Age ≥65 years and one of the following: diabetes mellitus, coronary artery disease (CAD), or hypertension

The primary objective of this study was to determine if PRADAXA was non-inferior to warfarin in reducing the occurrence of the composite endpoint, stroke (ischemic and hemorrhagic) and systemic embolism. The study was designed to ensure that PRADAXA preserved more than 50% of warfarin's effect as established by previous randomized, placebo-controlled trials of warfarin in atrial fibrillation. Statistical superiority was also analyzed.

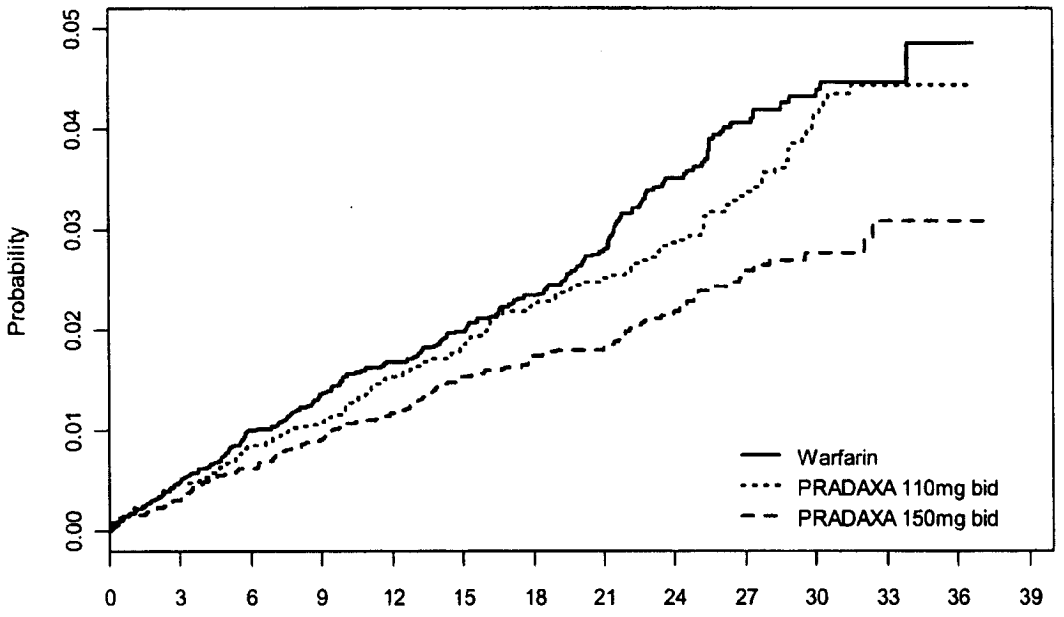
A total of 18,113 patients were randomized and followed for a median of 2 years. The patient's mean age was 71.5 years and the mean $CHADS_2$ score was 2.1. The patient population was 64% male, 70% Caucasian, 16% Asian, and 1% black. Twenty percent of patients had a history of a stroke or TIA and 50% were Vitamin K antagonist (VKA) naïve, defined as less than 2 months total lifetime exposure to a VKA. Thirty-two percent of the population had never been exposed to a VKA. Concomitant diseases of patients in this trial included hypertension 79%, diabetes 23% and CAD 28%. At baseline, 40% of patients were on aspirin and 6% were on clopidogrel. For patients randomized to warfarin, the mean percentage of time in therapeutic range (INR 2-3) was 64%; the mean percentages of time INR measurements were greater than 4 or less than 1.5 were 2% and 5%, respectively.

Relative to warfarin and to PRADAXA 110 mg twice daily, PRADAXA 150 mg twice daily significantly reduced the primary composite endpoint of stroke and systemic embolism (see Table 4 and Figure 1).

Table 4 First Occurrence of Stroke or Systemic Embolism in the RE-LY Study

	PRADAXA 150 mg twice daily	PRADAXA 110 mg twice daily	Warfarin
Patients randomized	6076	6015	6022
Patients (%) with events	134 (2.2%)	183 (3%)	202 (3.4%)
Hazard ratio vs. warfarin (95% CI)	0.65 (0.52, 0.81)	0.90 (0.74,1.10)	
P-value for superiority	0.0001	0.3	
Hazard ratio vs. PRADAXA 110 mg (95% CI)	0.72 (0.58, 0.90)		
P-value for superiority	0.004		

Figure 1 Kaplan-Meier Curve Estimate of Time to First Stroke or Systemic Embolism



Patients at risk

PRAD 110	6015	5927	5862	5797	5713	5481	4615	3778	3132	2383	1446	495	87
PRAD 150	6076	6010	5940	5861	5782	5555	4700	3847	3238	2428	1481	494	90
Warfarin	6022	5937	5862	5782	5719	5438	4615	3702	3092	2338	1364	383	76

The contributions of the components of the composite endpoint, including stroke by subtype, are shown in Table 5. The treatment effect was primarily a reduction in stroke. PRADAXA 150 mg twice daily significantly reduced both ischemic and hemorrhagic strokes relative to warfarin.

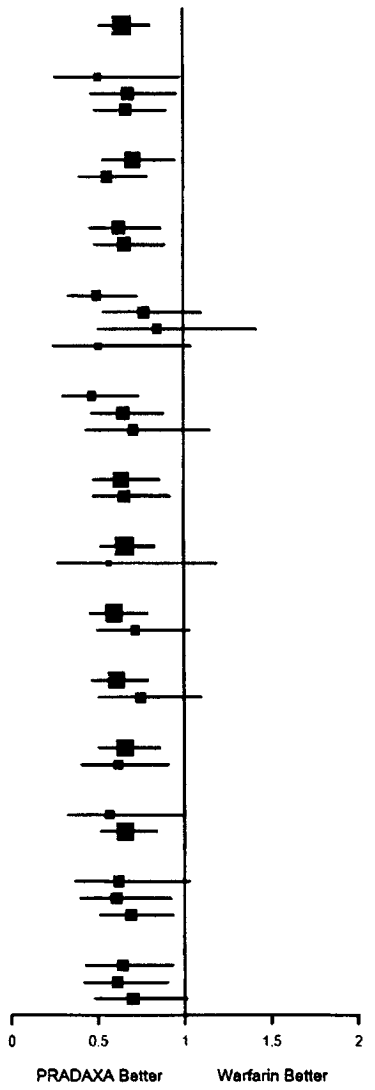
Table 5 Strokes and Systemic Embolism in the RE-LY Study

	PRADAXA 150 mg twice daily	**Warfarin**	**Hazard ratio vs. warfarin (95% CI)**
Patients randomized	6076	6022	
Stroke	122	186	0.64 (0.51, 0.81)
Ischemic stroke	103	134	0.75 (0.58, 0.97)
Hemorrhagic stroke	12	45	0.26 (0.14, 0.49)
Systemic embolism	13	21	0.61 (0.30, 1.21)

The efficacy of PRADAXA 150 mg twice daily was generally consistent across major subgroups (see Figure 2).

Figure 2 Stroke and Systemic Embolism Hazard Ratios by Baseline Characteristics

Subgroup	Patients Total no.	PRADAXA 150 % per yr	Warfarin % per yr	P-value Interaction
All patients	18113	1.11	1.71	
Age (years)				0.62
<65	2981	0.69	1.35	
65<= and <75	7894	0.98	1.45	
>=75	7238	1.43	2.15	
Gender				0.29
Male	11514	1.10	1.53	
Female	6598	1.14	2.03	
VKA use at entry				0.84
Naive	9126	1.07	1.69	
Experienced	8984	1.15	1.74	
BMI (kg/m2)				0.23
<25	4697	1.33	2.65	
25<= and <30	7111	1.16	1.49	
30<= and <35	4038	0.99	1.16	
>=35	2241	0.76	1.49	
CrCL (mL/min)				0.37
30<= and <50	3343	1.27	2.69	
50<= and <80	8297	1.21	1.87	
>=80	5658	0.73	1.03	
ASA use at baseline				0.88
No	10960	1.01	1.57	
Yes	7153	1.29	1.93	
Clopidogrel at baseline				0.71
No	17093	1.08	1.64	
Yes	1020	1.66	2.95	
Stroke/SEE/TIA				0.45
No	14159	0.88	1.46	
Yes	3953	1.91	2.66	
Heart Failure				0.39
No	13203	1.00	1.64	
Yes	4904	1.44	1.92	
Diabetes				0.75
No	13891	1.01	1.52	
Yes	4221	1.46	2.35	
Hypertension				0.62
No	3829	0.78	1.36	
Yes	14283	1.20	1.81	
CHADS2 score				0.91
1	5331	0.68	1.09	
2	6453	0.84	1.38	
3+	5876	1.89	2.73	
AF type				0.88
Persistent	5789	1.14	1.80	
Paroxysmal	5943	1.09	1.77	
Permanent	6375	1.11	1.58	



Centers were ranked post hoc by the percentage of time that warfarin-treated patients were in therapeutic range (INR 2-3). Findings for stroke/systemic embolism, all-cause mortality, and major bleeds are shown for centers above and below the median level of INR control in Table 6. The benefits of PRADAXA 150 mg relative to warfarin were most apparent in patients enrolled at centers with INR control below the median.

Table 6 Center INR Control in the RE-LY Study

	Centers with INR control below the median of 67%	**Centers with INR control above the median of 67%**
Stroke/systemic embolism	0.57 (0.42, 0.76)	0.76 (0.55, 1.05)
All-cause mortality	0.78 (0.66, 0.93)	1.01 (0.84,1.23)
Major bleed	0.82 (0.68, 0.99)	1.08 (0.89, 1.31)

The risk of myocardial infarction was numerically greater in patients who received PRADAXA (1.5% for 150 mg dose) than in those who received warfarin (1.1%).

16 HOW SUPPLIED/STORAGE AND HANDLING

PRADAXA 75 mg capsules have a light blue opaque cap imprinted with the Boehringer Ingelheim company symbol and a cream-colored opaque body imprinted with "R75." The color of the imprinting is black. The capsules are supplied in the packages listed:

- NDC 0597-0107-54 Unit of use bottle of 60 capsules
- NDC 0597-0107-60 Blister package containing 60 capsules (10 x 6 capsule blister cards)

PRADAXA 150 mg capsules have a light blue opaque cap imprinted with the Boehringer Ingelheim company symbol and a cream-colored opaque body imprinted with "R150." The color of the imprinting is black. The capsules are supplied in the packages listed:

- NDC 0597-0135-54 Unit of use bottle of 60 capsules
- NDC 0597-0135-60 Blister package containing 60 capsules (10 x 6 capsule blister cards)

Bottles

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). Once opened, the product must be used within 30 days. Keep the bottle tightly closed. Store in the original package to protect from moisture.

Blisters
Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). Store in the original package to protect from moisture.

Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION

See Medication Guide

17.1 Instructions for Patients

- Tell patients to take PRADAXA exactly as prescribed.
- Remind patients not to discontinue PRADAXA without talking to the health care provider who prescribed it.
- Advise patients not to chew or break the capsules before swallowing them and not to open the capsules and take the pellets alone (e.g., sprinkled over food or into beverages).

17.2 Bleeding

Inform patients that they may bleed more easily, may bleed longer, and should call their health care provider for any signs or symptoms of bleeding.

Instruct patients to seek emergency care right away if they have any of the following, which may be a sign or symptom of serious bleeding:

- Unusual bruising (bruises that appear without known cause or that get bigger)
- Pink or brown urine
- Red or black, tarry stools
- Coughing up blood
- Vomiting blood, or vomit that looks like coffee grounds

Instruct patients to call their health care provider or to get prompt medical attention if they experience any signs or symptoms of bleeding:

- Pain, swelling or discomfort in a joint
- Headaches, dizziness, or weakness
- Reoccurring nose bleeds
- Unusual bleeding from gums
- Bleeding from a cut that takes a long time to stop
- Menstrual bleeding or vaginal bleeding that is heavier than normal

17.3 Gastrointestinal Adverse Reactions

Instruct patients to call their health care provider if they experience any signs or symptoms of dyspepsia or gastritis:

- Dyspepsia (upset stomach), burning, or nausea
- Abdominal pain or discomfort
- Epigastric discomfort, GERD (gastric indigestion)

17.4 Invasive or Surgical Procedures

Instruct patients to inform their health care provider that they are taking PRADAXA before any invasive procedure (including dental procedures) is scheduled.

17.5 Concomitant Medications

Ask patients to list all prescription medications, over-the-counter medications, or dietary supplements they are taking or plan to take so their health care provider knows about other treatments that may affect bleeding risk (e.g., aspirin or NSAIDs) or dabigatran exposure.

Distributed by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA

Resource number here
Component number here

MEDICATION GUIDE

PRADAXA (pra dax' a)
(dabigatran etexilate mesylate)
capsules

Read this Medication Guide before you start taking PRADAXA and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about PRADAXA?

- PRADAXA can cause bleeding which can be serious, and sometimes lead to death. This is because PRADAXA is a blood thinner medicine that lowers the chance of blood clots forming in your body.
- **You may have a higher risk of bleeding if you take PRADAXA and**:
  - are over 75 years old
  - have kidney problems
  - have stomach or intestine bleeding that is recent or keeps coming back, or you have a stomach ulcer
  - take other medicines that increase your risk of bleeding, including:
    - aspirin or aspirin containing products
    - long-term (chronic) use of non-steroidal anti-inflammatory drugs (NSAIDs)
    - warfarin sodium (Coumadin®, Jantoven®)
    - a medicine that contains heparin
    - clopidogrel (Plavix®)
    - prasugrel (Effient®)

    Tell your doctor if you take any of these medicines. Ask your doctor or pharmacist if you are not sure if your medicine is one listed above.

- PRADAXA can increase your risk of bleeding because it lessens the ability of your blood to clot. While you take PRADAXA:
  - you may bruise more easily
  - it may take longer for any bleeding to stop

Call your doctor or get medical help right away if you have any of these signs or symptoms of bleeding:

- unexpected bleeding or bleeding that lasts a long time, such as:
  - unusual bleeding from the gums
  - nose bleeds that happen often
  - menstrual bleed or vaginal bleeding that is heavier than normal
- bleeding that is severe or you cannot control
- pink or brown urine
- red or black stools (looks like tar)
- bruises that happen without a known cause or get larger
- cough up blood or blood clots
- vomit blood or your vomit looks like "coffee grounds"
- unexpected pain, swelling, or joint pain
- headaches, feeling dizzy or weak

Take PRADAXA exactly as prescribed. Do not stop taking PRADAXA without first talking to the doctor who prescribes it for you. Stopping PRADAXA may increase your risk of a stroke.

PRADAXA may need to be stopped, if possible, for one or more days before any surgery, or medical or dental procedure. If you need to stop taking PRADAXA for **any reason**, talk to the doctor who prescribed PRADAXA for you to find out when you should stop taking it. Your doctor will tell you when to start taking PRADAXA again after your surgery or procedure.

See "What are the possible side effects of PRADAXA?" for more information about side effects.

What is PRADAXA?

PRADAXA is a prescription medicine used to reduce the risk of stroke and blood clots in people who have a medical condition called atrial fibrillation. With atrial fibrillation, part of the heart does not beat the way it should. This can lead to blood clots forming and increase your risk of a stroke. PRADAXA is a blood thinner medicine that lowers the chance of blood clots forming in your body.

It is not known if PRADAXA is safe and works in children.

Who should not take PRADAXA?

Do not take PRADAXA if you:

- currently have certain types of abnormal bleeding. Talk to your doctor, before taking PRADAXA if you currently have unusual bleeding.
- have had an serious allergic reaction to PRADAXA. Ask your doctor if you are not sure.

What should I tell my doctor before taking PRADAXA?

Before you take PRADAXA, tell your doctor if you:

- have kidney problems
- have ever had bleeding problems
- have ever had stomach ulcers
- have any other medical condition
- are pregnant or plan to become pregnant. It is not known if PRADAXA will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if PRADAXA passes into your breast milk.

Tell all of your doctors and dentists that you are taking PRADAXA. They should talk to the doctor who prescribed PRADAXA for you, before you have **any** surgery, or medical or dental procedure.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some of your other medicines may affect the way PRADAXA works. Certain medicines may increase your risk of bleeding. See "**What is the most important information I should know about PRADAXA**?"

Especially tell your doctor if you take:

- rifampin (Rifater, Rifamate, Rimactane, Rifadin)

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

How should I take PRADAXA?

- **Take PRADAXA exactly as prescribed by your doctor.**
- Do not take PRADAXA more often than your doctor tells you to.

- You can take PRADAXA with or without food.
- Swallow PRADAXA capsules whole. Do not break, chew, or empty the pellets from the capsule.
- If you miss a dose of PRADAXA, take it as soon as you remember. If your next dose is less than 6 hours away, skip the missed dose. Do not take two doses of PRADAXA at the same time.
- Your doctor will decide how long you should take PRADAXA. **Do not stop taking PRADAXA without first talking with your doctor. Stopping PRADAXA may increase your risk of stroke.**
- Do not run out of PRADAXA. Refill your prescription before you run out. If you plan to have surgery, or a medical or a dental procedure, tell your doctor and dentist that you are taking PRADAXA. You may have to stop taking PRADAXA for a short time. See "What is the most important information I should know about PRADAXA?"
- If you take too much PRADAXA, go to the nearest hospital emergency room or call your doctor or the Poison Control Center right away.

What are the possible side effects of PRADAXA?

PRADAXA can cause serious side effects.

- See "What is the most important information I should know about PRADAXA?"
- Allergic Reactions. In some people, PRADAXA can cause symptoms of an allergic reaction, including hives, rash, and itching. Tell your doctor or get medical help right away if you get any of the following symptoms of a serious allergic reaction with PRADAXA:
    - chest pain or chest tightness
    - swelling of your face or tongue
    - trouble breathing or wheezing
    - feeling dizzy or faint

Common side effects of PRADAXA include:

- indigestion, upset stomach, or burning
- stomach pain

Tell your doctor if you have any side effect that bothers your or that does not go away.

These are not all of the possible side effects of PRADAXA. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store PRADAXA?

- Store PRADAXA at room temperature between 59°F to 86°F (15°C to 30°C). After opening the bottle, use PRADAXA within 30 days. Safely throw away any unused PRADAXA after 30 days.
- Store PRADAXA in the original package to keep it dry. Keep the bottle tightly closed.

Keep PRADAXA and all medicines out of the reach of children.

General information about PRADAXA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use PRADAXA for a condition for which it was not prescribed. Do not give your PRADAXA to other people, even if they have the same symptoms. It may harm them.

This Medication Guide summarizes the most important information about PRADAXA. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about PRADAXA that is written for health professionals.

For more information, go to www.PRADAXA.com or call 1-800-542-6257 or (TTY) 1-800-459-9906.

What are the ingredients in PRADAXA?

Active ingredient: dabigatran etexilate mesylate

Inactive ingredients: acacia, dimethicone, hypromellose, hydroxypropyl cellulose, talc, and tartaric acid. The capsule shell is composed of carageenan, FD&C Blue No. 2, FD&C Yellow No. 6, hypromellose, potassium chloride, titanium dioxide, and black edible ink.

Distributed by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA

Issued Month Year
This Medication Guide has been approved by the U.S. Food and Drug Administration.

Resource number here
Component number here

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Exhibit B

US006087380A

United States Patent [19]

Hauel 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

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[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.

[30] **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**

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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

$$R_a—A—Het—B—Ar—E \quad (I)$$

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

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

$$R_a—A—Het—B—Ar—E\,, \qquad (I)$$

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,

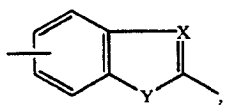
E denotes a cyano or $R_bNH–C(=NH)—$ group wherein

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

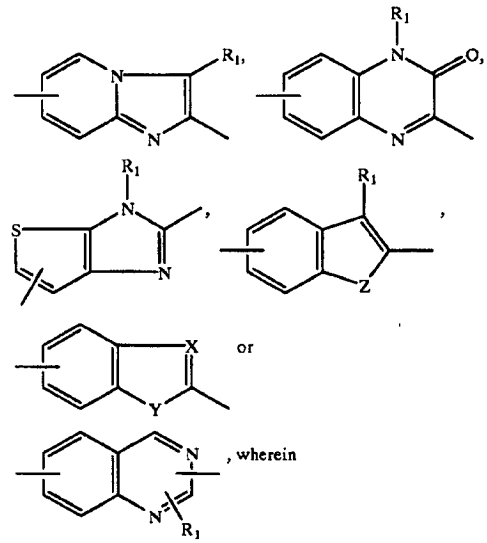
X is a nitrogen atom and

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,

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, trifluorosulphonylamino, trifluorosulphonylaminocarbonyl or 1H-tetrazolyl group,

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

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

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

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

R_2 and R_3 together with the nitrogen atom between them denote a 5- to 7-membered cycloalkyleneimino group, optionally substituted by a carboxymethyl or 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_{3-9}-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

$$R_4—CO—O—(R_5CR_6)—OH,$$

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, 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-n-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,

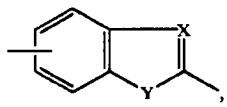
E denotes an $R_bNH—C(=NH)—$ group wherein

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

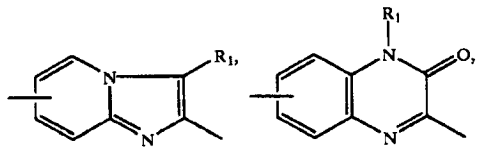
X is a nitrogen atom and

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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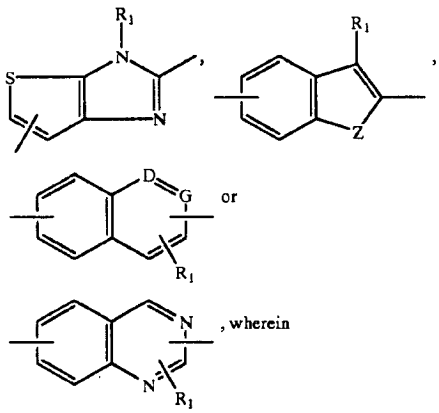


R_1 is as hereinbefore defined,

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}-alkylsulphonylaminocarbonyl, phenylsulphonylaminocarbonyl, trifluorosulphonylamino, trifluorosulphonylaminocarbonyl or 1H-tetrazolyl group,

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

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

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

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

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

Het denotes one of the abovementioned benzimidazolylene, benzothiazolylene, benzoxazolylene, indolylene, quinazolinylene, quinoxazolinonylene, imidazo[4,5-b]pyridinylene, imidazo[1,2-a]pyridinylene, 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, 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 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]pyridinylen 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}-alkylsulphonylaminocarbonyl or 1H-tetrazol-5-yl group,

a C_{2-4}-alkyl group substituted by a hydroxy, benzyloxy, carboxy-C_{1-3}-alkylamino, C_{1-3}-alkoxycarbonyl-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, pyrido or thieno moiety of the group Het, whilst moreover the abovementioned moieties may not contain an R_1 group,

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

R_1 denotes a hydrogen atom or a methyl group,

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

R_b denotes a hydrogen atom or a hydroxy, C_{1-9}-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,

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, methylsulphonylaminocarbonyl 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, methylsulfonylaminocarbonyl 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,

(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

$$R_a—A—Het—B—Ar—C(=NH)—Z_1, \quad (II)$$

optionally formed in the reaction mixture,

wherein

A, B, Ar, Het and R_a are as hereinbefore defined and Z_1 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

$$H_2N—R_b', \quad (III)$$

wherein

R_b' denotes a hydrogen atom or a hydroxy or C_{1-3}-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 NH_2—C(=NH)— group, or that the R_a—A— group contains a carboxy group and E denotes an NH_2—C(=NH)— group:

Converting a compound of general formula

$$R_a'—A—Het—B—Ar—C—E', \quad (IV)$$

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 NH_2—C(=NH)— group by hydrolysis, treatment with an acid or base, thermolysis or hydrogenolysis and the R_a'—A— group has the meanings given for the R_a—A— group hereinbefore or the R_a'—A— group contains a group which may be converted into a carboxyl group by hydrolysis, treatment with an acid or base, thermolysis or hydrogenolysis and E' denotes a group which may be converted into an $NH_2 \cong C(=NH)$— 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 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 NH_2—C(=NH)— group or the R_a—A— group contains a carboxy group and E denotes an NH_2—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, trimethylsilylesters, 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 benzylester, 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, acetic acid, trichloroacetic acid, trifluoroacetic acid or mixtures thereof or in the presence of a base such as lithium hydroxide, sodium hydroxide or potassium hydroxide in a suitable solvent such as water, water/methanol, water/ethanol, water/isopropanol, methanol, ethanol, water/tetrahydrofuran or water/dioxane 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.

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

Reaction of a compound of general formula

$$R_a''—A—Het—B—Ar-E, \quad (V)$$

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—

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

$$HO—R_7, \quad (VI)$$

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 $R_6—CO—O—(R_5CR_6)—$ group for a carboxyl group, or with the formamide acetals thereof.

or with a compound of general formula

$$Z_2—R_8, \quad (VII)$$

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 $R_6—CO—O—(R_5CR_6)—$ group for a carboxyl group and Z_2 denotes a leaving group such as a halogen atom, e.g. a chlorine or bromine atom.

The reaction with an alcohol of general formula VI is conveniently carried out in a solvent or mixture of 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, methanesulphonic acid, p-toluenesulphonic acid, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, N,N'-carbonyldiimidazole or N,N'-thionyldiimidazole, 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.

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.

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

$$R_a—A—Het—B—Ar—C(=NH)—NH_2, \quad (VIII)$$

wherein

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

$$Z_2—R_5, \quad (IX)$$

wherein

R_5 denotes a group which may be cleaved in vivo and

Z_2 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 tertiary organic base, preferably at temperatures between 20° C. and the boiling temperature of the solvent used.

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

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

Oxidation of a compound of general formula

$$R_a—A—Het—B'—Ar—E, \quad (X)$$

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.

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.

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.

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

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 sulphinyl compound.

f. In order to prepare a compound of general formula I wherein E is a cyano group and B is an ethylene group in which a methylene group linked either to group Het or to Ar is replaced by an oxygen or sulphur atom or by a sulphinyl, sulphonyl, carbonyl or —NR_1— group:

Reacting a compound of general formula

$$R_a—A—Het—U, \quad (XI)$$

with a compound of general formula

$$V—Ar—CN, \quad (XII)$$

wherein

R_a, A, Ar and Het are as hereinbefore defined, one of the groups U or V denotes an HO—, HS—, HOSO—, $HOSO_2$— or HNR_1— group and the other group denotes a Z_3CH_2— group, wherein R_1 is as hereinbefore defined and Z_3 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 R_2NR_3— group:

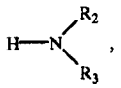
Reacting a compound of general formula

$$H—A—Het—B—Ar—CN, \quad (XIII)$$

wherein

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

(XIV)



wherein

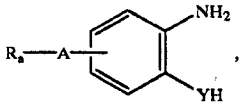
R_2 and R_3 are as hereinbefore defined, or with the reactive derivatives thereof.

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, tetraethylorthocarbonate, 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-tetramethyluronium-tetrafluoroborate/1-hydroxy-benzotriazole, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride and optionally with the addition of a base such as pyridine, 4-dimethylamino-pyridine, N-methyl-morpholine or triethylamine, 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

$$HO—CO—CH_2CH_2—Ar—E, \quad (XVI)$$

wherein

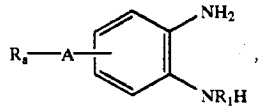
Ar and E are as hereinbefore defined, or with the reactive derivatives thereof.

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, tetraethylorthocarbonate, 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 triphenyl-phosphine/carbon tetrachloride, and optionally with the addition of a base such as pyridine, 4-dimethylamino-pyridine, N-methyl-morpholine or triethylamine, appropriately at temperatures between 0 and 150° C., preferably at temperatures between 0 and 100° C.

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

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

(XVII)



wherein

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

$$HO—CO—COCH_2—Ar—E, \quad (XVIII)$$

wherein

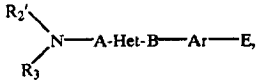
Ar and E are as hereinbefore defined, or with the reactive derivatives thereof.

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:

(IXX)



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

$$C_{1-3}\text{-Alkyl-}SO_2—NH_2. \quad (XX)$$

The reaction is preferably carried out with a corresponding reactive compound of general formula IXX such as the esters, imidazolides or halides thereof with a salt of a compound of general formula XX, preferably with an alkali metal salt thereof such as a sodium salt, in a solvent such as methylene chloride, ether, ethanol, tetrahydrofuran or dimethylformamide at temperatures between 0 and 150° C., preferably at temperatures of between 50 and 100° C.

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.butyloxycarbonyl 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-

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

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

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

As already mentioned, the new compounds of general formula I and the salts thereof have valuable properties. Thus, the compounds of general formula I wherein E denotes a cyano group are valuable intermediate products for 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-hydroxycarbonylethyl)-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-hydroxycarbonylethyl)-amide

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

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

The Examples which follow are intended to illustrate the invention:

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 imidazolide was mixed with a solution of 2.3 g (13 mMol) of methyl 5-amino-6-methylamino-nicotinate in 25 ml of dimethylformamide and heated for 3 hours to 100° C. After the removal of the solvent in vacuo the crude product obtained was taken up in ethyl acetate, the organic phase was washed with water and after drying over sodium sulphate it was again freed from solvent. The residue obtained was purified by flash chromatography (silica gel; gradient: dichloromethane to dichloromethane/ethanol=19:1). Yield: 2.1 g (50% of theory) of beige solid R_f value: 0.54 (silica gel; ethyl acetate/ethanol/ammonia=90:10:1)

d) Methylyl 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

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-ethoxycarbonylethyl)-amide

1.8 g (3.7 mmol) of 3-methyl-2-[2-(4-cyanophenyl) ethyl]-imidazo[4,5-b]pyridine-6-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide were stirred into 100 l of ethanol saturated with hydrogen chloride for 16 hours first at 0° C. and then at room temperature until no more starting material could be detected by thin layer chromatography. Then the solvent was distilled off, the oily residue was taken up in 50 ml of absolute ethanol and mixed with 3.6 g (37 mMol) of ammonium carbonate. After 4 hours the solvent was distilled off in vacuo, the crude product obtained was purified by flash chromatography (silica gel; gradient:dichloromethane/ethanol 19:1 to 4:1) and evaporated down again. Yield: 1.6 g of beige solid (80% of theory), R_f value: 0.30 (silica gel; ethyl acetate/ethanol/ammonia=90:5:5)

EXAMPLE 2

3-Methyl-2-[2-(4-amidinophenyl)ethyl]-imidazo[4,5-b]-pyridine-6-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-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-ethoxycarbonylethyl)-amide in 10 ml ethanol was mixed with 5 ml of 2N sodium hydroxide solution and stirred for 2 hours at room temperature. Then the mixture was diluted with 10 ml water, the alcohol was distilled off, the aqueous phase was washed with 20 ml ethyl acetate and acidified with concentrated hydrochloric acid, whereupon the desired compound was precipitated in the form of white crystals. Yield: 375 mg (74% of theory), R_f value: 0.23 (silica gel; ethyl acetate/ethanol/ammonia=90:5:5) $C_{26}H_{26}N_6O_3$ (470.54) Mass spectrum: $(M+H)^+$=471

EXAMPLE 3

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

EKA mass spectrum:	$(M + H)^+ = 469$ $(M + Na)^+ = 491$

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-nitro-pyridine (Heterocycles 38, 529 (1994)) were dissolved in 300 l 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. $C_7H_{11}N_3$ (137.20) Melting point: 112–113° C.

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

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. $C_{16}H_{14}N_4O$ (278.32) Mass spectrum: M^+=278

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

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), $C_{16}H_{14}N_4O_2$ (294.30) Mass spectrum: M^+=294

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

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), $C_{16}H_{14}N_4O_2$ (294.30) Melting point: 172° C.

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

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), $C_{16}H_{12}N_4O_2$ (292.30) Melting point: 231–234° C.

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

1.25 g (4.3 mMol) of 1-methyl-2-[(4-cyanophenyl) oxymethyl]-imidazo[4,5-b]pyridine-5-carbaldehyde were dissolved in 10 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), $C_{16}H_{12}N_4O_3$ (308.7)

g) 1-Methyl-2-[(4-cyanophenyl)oxymethyl]-imidazo[4,5-b]pyridin-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-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'-tetramethyl-uronium 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), $C_{25}H_{12}N_6O_4$ (407.50) Melting point: 139–140° C.

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

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

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 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

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

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)

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, $C_{24}H_{29}N_5O_3$ (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, $C_{22}H_{25}N_5O_3S$ (439.54) R_f value: 0.14 (silica gel; methylene chloride/ethanol=4:1+a few drops of acetic acid)

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

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

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 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) $C_{28}H_{30}N_6O_3 \times HCl$ (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), $C_{26}H_{26}N_6O_3$ (470.5)

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-chloracetamido-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-chloracetamido-benzoic acid-N-(n-propyl)-N-(2-ethoxycarbonylethyl)-amide were heated to 100° C. in 25 ml of acetic acid for 30 minutes. Then the solvent was distilled off, the crude product was taken up in 40 ml methylene chloride/ethanol (9:1) and 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 value: 0.29 (silica gel; ethyl acetate/ethanol/ammonia =50:45:5) $C_{25}H_{31}N_6O_3S$ (481.62) EKA mass spectrum: $(M+H)^+$=482

EXAMPLE 28

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) $C_{23}H_{27}N_5O_3S$ (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, $C_{25}H_{31}N_6O_3S$ (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, $C_{28}H_{29}N_5O_3S$ (515.64) R_f value:0.24 (silica gel; ethyl acetate/ethanol/ammonia=50:45:5)

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

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

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, $C_{26}H_{25}N_5O_3S$ (487.58) R_f value: 0.31 (silica gel; ethyl acetate/ethanol/ammonia =50:45:5)

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

$(M+Na)^+$ = 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), $C_{13}H_{18}ClN_3O_4S$ (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), $C_{14}H_{22}N_4O_4S$ (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), $C_{14}H_{24}N_4O_2S$ (312.4) R_f value: 0.33 (silica gel; dichloromethane/ethanol=4:1)

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

532 mg (3.0 mMol) of 4-cyanophenyloxyacetic 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), $C_{23}H_{27}N_5O_3S$ (453.6) R_f value: 0.37 (silica gel; dichloromethane/ethanol=4:1)

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

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), $C_{23}H_{30}N_6O_3S$ (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, $C_{23}H_{23}N_5O_3S$ (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, $C_{28}H_{31}N_5O_5S$ (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, $C_{20}H_{23}N_5O_3S$ (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.butyloxycarbonylpropyl)-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) $C_{29}H_{31}N_5O_3$ (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

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.butyloxy-carbonylpropyl)-amide

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

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

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

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

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

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

(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

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)

EKA mass spectrum: $(M+H)^+$ = 459

$(M+Na)^+$ = 481

$(M+2Na)^{++}$ = 252

EXAMPLE 49

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

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

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

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

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

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

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

EXAMPLE 52

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

Prepared analogously to Example 26 from 1-methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(ethoxycarbonylmethyl)-amide-dihydrochloride and sodium hydroxide solution. Yield: 89% of theory, $C_{25}H_{24}N_6O_3$ (456.5)

EKA mass spectrum: $(M+H)^+$ = 457
$(M+Na)^+$ = 479

EXAMPLE 53

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

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide and methanolic hydrochloric acid, methanol and ammonium carbonate. Yield: 87% of theory, R_f value: 0.11 (silica gel; dichloromethane/ethanol=4:1) $C_{27}H_{28}N_6O_3$ (484.6)

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

EXAMPLE 54

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

Prepared analogously to Example 25d from 1-methyl-2-[(4-cyanophenyl)oxymethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate. Yield: 79.5% of theory, $C_{28}H_{29}N_5O_4$ (499.6) R_f value: 0.15 (silica gel; dichloromethane/ethanol=4:1)

EKA mass spectrum: $(M+H)^+$ = 500.0
$(M+H+Na)^{++}$ = 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, $C_{26}H_{25}N_5O_4$ (471.5) R_f value: 0.11 (silica gel; dichloromethane/ethanol=4:1)

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, $C_{26}H_{28}N_6O_3S$ (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, $C_{24}H_{24}N_6O_3S$ (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

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-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-

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-hexyloxycarbonylethyl)-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

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)

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, $C_{27}H_{34}N_6O_3$ (490.6) EKA mass spectrum: $(M+H)^+$=491

EXAMPLE 74

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-cyclopentyl-N-(2-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, $C_{25}H_{30}N_3O_4$ (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, $C_{27}H_{29}N_7O_3$ (499.6)

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

EXAMPLE 76

1-Methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(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, $C_{25}H_{25}N_7O_3$ (471.5)

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, $C_{28}H_{30}N_6O_3$ (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, $C_{27}H_{29}N_7O_3$ (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, $C_{25}H_{25}N_7O_3$ (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, $C_{28}H_{31}N_7O_3$ (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-

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

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)-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-

carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide-hydrochloride and n-octyl chloroformate. Yield: 41% of theory, $C_{36}H_{44}N_6O_5$ (640.8) 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, $C_{28}H_{30}N_6O_4$ (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, $C_{35}H_{42}N_6O_5$ (626.8) R_f value: 0.40 (silica gel; dichloromethane/ethanol=19:1)

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

$(M+H+Na)^{++}$ = 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, $C_{34}H_{32}N_6O_4$ (588.7) R_f value: 0.37 (silica gel; dichloromethane/ethanol=19:1) ^{1}H-NMR spectrum (D_6-DMSO): 2.61 (t,2H), 3.54 (s,3H), 3.76 (s,3H), 4.10 (t,2H), 4.61 (d,2H), 6.83 (d,2H), 7.05 to 7.55 (m,12H),8.03 (d,2H), 8.25 (dd,2H), 8.98 (s,1H), 10.48 (s,1H)

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, $C_{34}H_{40}N_6O_5$ (612.7) R_f value: 0.45 (silica gel; dichloromethane/ethanol=19:1) EKA mass spectrum: $(M+H)^+$=613

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, $C_{36}H_{44}N_6O_5$ (640.8) R_f value: 0.42 (silica gel; dichloromethane/ethanol=19:1)

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

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

$(M+Na)^+$ = 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, $C_{29}H_{31}N_7O_5$ (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, $C_{35}H_{43}N_7O_5$ (641.8) R_f value: 0.60 (silica gel; dichloromethane/methanol=9:1)

EKA mass spectrum: $(M+H)^+$ = 642

$(M+H+Na)^{++}$ = 332.8

$(M+Na)^+$ = 664

EXAMPLE 103

1-Methyl-2-[N-[4-(N-methoxycarbonylamidino)phenyl]-amino-methyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-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 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 vigourously 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-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and 2-(methylsulphonyl)-ethyl chloroformate. Yield: 65% of theory, $C_{31}H_{35}N_7O_7S$ (649.7) 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-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide-hydrochloride and n-butyl chloroformate. Yield: 30% of theory, $C_{31}H_{35}N_7O_5$ (585.7) R_f value: 0.62 (silica gel; dichloromethane/methanol=9:1)

EKA mass spectrum: $(M+H)^+$ = 586
$(M+H+Na)^{++}$ = 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-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide-hydrochloride and n-hexyl chloroformate. Yield: 51% of theory, $C_{33}H_{39}N_7O_5$ (613.7) 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-amidinophenyl)-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-amidinophenyl)-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

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, $C_{36}H_{45}N_7O_5$ (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, $C_{33}H_{31}N_7O_4$ (589.7) R_f value: 0.50 (silica gel; dichloromethane/methanol=9:1)

EKA mass spectrum: $(M+H)^+$ = 590
$(M+Na)^+$ = 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, $C_{32}H_{30}N_8O_4$ (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, $C_{34}H_{41}N_7O_5$ (627.8) R_f value: 0.53 (silica gel; dichloromethane/methanol=9:1)

EKA mass spectrum: $(M+H)^+$ = 628
$(M+H+Na)^{++}$ = 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

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, $C_{36}H_{45}N_7O_5$ (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, $C_{30}H_{33}N_7O_7S$ (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, $C_{32}H_{35}N_7O_5$ (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, $C_{28}H_{29}N_7O_5$ (543.6) R_f value: 0.19 (silica gel; dichloromethane/ethanol=19:1)

EKA mass spectrum: $(M+H)^+$ = 544
$(M+H+Na)^{++}$ = 283.8
$(M+Na)^+$ = 566

EXAMPLE 118

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

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-methoxycarbonylmethyl-amide-hydrochloride and ethyl chloroformate. Yield: 42% of theory, $C_{28}H_{29}N_7O_5$ (543.6) R_f value: 0.20 (silica gel; dichloromethane/ethanol=19:1) EKA mass spectrum: $(M+H)^+$=544

EXAMPLE 119

1-Methyl-2-[N-[4-(N-n-octyloxycarbonyl-amidino)-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, $C36H_{45}N_7O_5$ (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)

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-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-hydroxycarbonyl-methylcyclohex-1-yl)-ketone were added in batches, with stirring, at −5 to −10° 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)

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-Cyanophenyloxyacetylamino)-4-methylaminophenyl-(1-methoxycarbonylmethyl-cyclohex-1-yl)-ketone

620 mg (3.5 mMol) of 4-cyanophenyloxyacetic acid and 570 mg (3.5 mMol) of 1,1'-carbonyl-diimidazole were refluxed in 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-cyanophenyloxyacetylamino)-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-cyanophenyloxymethyl)-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 ^{1}H-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

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-ethoxycarbonylethyl)-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-ethoxycarbonylethyl)-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-ethoxycarbonylethyl)-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-ethoxycarbonylethyl)-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-ethoxycarbonylethyl)-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-ethoxycarbonylethyl)-amide-hydrochloride

a) Methyl 5-amino-6-chloro-nicotinate

A solution of 1.08 g (5.00 mMol) of methyl 6-chloro-5-nitro-nicotinate (see A. H. Berrie, G. T. Newbold, F. S. Spring in J. Chem. Soc., 2590, 1951) in 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

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 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-diisopropyl-ethylamine, 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

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

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

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-octyloxycarbonylamidino)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

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)ethyloxy)-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

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

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-tolylate 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 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]-quinazoline-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]-quinazoline-7-carboxylate were dissolved in 4.7 ml of 1N lithium hydroxide solution and 4 ml of tetrahydrofuran and stirred for 3 hours at ambient temperature. Then 4.7 ml of 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]-quinazoline-7-carboxylic acid and 5 ml of thionyl chloride were stirred for 60 minutes at 50° C. Then the thionyl chloride was distilled off, the residue was dissolved in methylene chloride, mixed with 0.24 g (1.3 mmol) of methyl 3-(N-phenylamino)-propionate and 0.22 ml of (1.3 mmol) of N-ethyldiisopropylamine and stirred for 18 hours at ambient temperature. After evaporation of the solvent in vacuo the residue was chromatographed on silica gel and eluted with methylene chloride containing 1% methanol. Yield: 230 mg (37% of theory), R_f value: 0.64 (silica gel, methylene chloride/methanol=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

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)acetylamino]-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) acetylamino]-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-trifluoracetate

4.81 g (0.10 mol) of 1-methyl-2-(N-tert.butoxycarbonyl-aminomethyl)-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide were dissolved in 25 ml of methylene chloride, mixed with 5 ml of trifluoroacetic acid and stirred for 5 hours at ambient temperature. Then the solvent was evaporated off and the residue was stirred with ether. The crystals thus formed were filtered off, washed with ether and dried. Yield: 3.15 g (68% of theory), $C_{20}H_{23}N_5O_3$ (381.4) R_f value: 0.18 (silica gel; methylene chloride/ethanol=9:1)

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

1.5 g (3.25 mmol) of 1-methyl-2-aminomethyl-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-trifluoracetate 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.

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) $C_{21}H_{22}N_2O_3S$ (382.49) Mass spectrum: $(M)^+$=382

d) 1-tert-Butoxycarbonyl-2-methyl-indol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide

8.9 g (23 mmol) of 2-Methyl-3-thiomethyl-indol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide 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, 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), $C_{28}H_{28}N_4O_3S$ (500.62)

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

$(M+Na)^+$ = 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, $C_{28}H_{29}N_5O_3$ (483.58) R_f value: 0.20 (silica gel; methylene chloride/ethanol=4:1+1 drop of acetic acid) EKA mass spectrum: $(M+H)^+$=484

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 methoxyacetonitrile in 29 ml (23 g, 0.50 mol) of ethanol and 30 ml of absolute diethylether was cooled to 0° C. and over 1 hour 22.5 g (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° 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) $C_6H_{10}N_2O_2$ (142.20) Mass spectrum: $(M)^+$=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

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 (2×6.0 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

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

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/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)

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, $C_{26}H_{28}N_6O_2$ (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, $C_{32}H_{37}N_7O_5$ (599.7) R_f value: 0.22 (silica gel; dichloromethane/methanol=9:1)

EKA mass spectrum: $(M+H)^+$ = 600

$(M+H+Na)^{++}$ = 311.7

$(M+2H)^{++}$ = 300.8

$(M+2Na)^{++}$ = 322.8

EXAMPLE 167

1-Methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-hydroxy-n-propyl)-amide

Prepared analogously to Example 165 from 1-methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)phenyl]-aminomethyl]-benzimidazole-5-yl-carboxylic acid-N-phenyl-N-(3-benzyloxy-n-propyl)-amide by catalytic debenzylation. Yield: 26% of theory, $C_{33}H_{40}N_6O_4$ (584.7) R_f value: 0.39 (silica gel; dichloromethane/ethanol=9:1

EKA mass spectrum: $(M+H)^+$ = 585

$(M+H+Na)^{++}$ = 304

$(M+Na)^+$ = 607

EXAMPLE 168

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

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-fluorophenyl)-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate. Yield: 42% of theory, $C_{28}H_{29}FN_6O_3$ (516.6) R_f value: 0.31 (silica gel; dichloromethane/methanol=5:1)

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

$(M+H+Na)^{++}$ = 270

EXAMPLE 169

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

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(4-fluorophenyl)-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate. Yield: 90% of theory, $C_{28}H_{29}FN_6O_3$ (516.6) R_f value: 0.29 (silica gel; dichloromethane/methanol=5:1)

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

$(M+H+Na)^{++}$ = 270

EXAMPLE 170

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

Prepared analogously to Example 26 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-fluorophenyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution. Yield: 97% of theory, $C_{26}H_{25}FN_6O_3$ (488.5) R_f value: 0.13 (silica gel; dichloromethane/ethanol=4:1)

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

$(M+Na)^+$ = 511

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

EXAMPLE 171

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

Prepared analogously to Example 26 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(4-fluorophenyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution. Yield: 89% of theory, $C_{26}H_{25}FN_6O_3$ (488.5) R_f value: 0.15 (silica gel; dichloromethane/ethanol=4:1)

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

$(M+Na)^+$ = 511

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

EXAMPLE 172

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

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyano-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-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-benzyloxycarbonylamidino)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

-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-benzyloxycarbonylamidino)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-benzyloxycarbonylamidino)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-benzyloxy-n-propyl)-amide-hydrochloride

Prepared analogously to Example 25 from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-benzyloxy-n-propyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate. Yield: 61% of theory, $C_{33}H_{34}N_6O_2$ (546.7) R_f value: 0.19 (silica gel; dichloromethane/ethanol=4:1)

EKA mass spectrum: $(M+H)^+$ = 547

-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, $C_{40}H_{46}N_6O_4$ (674.9) R_f value: 0.46 (silica gel; dichloromethane/ethanol=9:1)

EKA mass spectrum: $(M+H)^+$ = 675

$(M+H+Na)^{++}$ = 349

$(M+Na)^+$ = 697

$(M+K)^+$ = 713

EXAMPLE 181

3-Methyl-2-[2-(4-amidinophenyl)ethyl]-imidazo[1.2-a]pyridin-7-yl-carboxylic acid-N-(2-pyridyl)-N-(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, $C_{28}H_{30}N_6O_3$ (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, $C_{24}H_{24}N_8O_3$ (472.9) R_f value: 0.67 (Reversed Phase silica gel RP-8; methanol/5% saline solution=1:1) 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 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), $C_{26}H_{25}N_7O_4S$ (531.6) R_f value: 0.72 (silica gel; dichloromethane/methanol=9:1)

b. 1-Methyl-2-[N-[4-(N-hydroxylamidino)-phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-[2-(methansulphonylaminocarbonyl)-ethyl]-amide

Prepared analogously to Example 96 from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-[2-(methanesulphonylaminocarbonyl)-ethyl]-amide and hydroxylamine. Yield: 27% of theory, $C_{26}H_{28}N_8O_5S$ (564.6) R_f value: 0.75 (silica gel; dichloromethane/ethanol=7:3+1% glacial acetic acid)

EKA mass spectrum: $(M+H)^+$ = 565

$(M+Na)^+$ = 587

EXAMPLE 184

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

Prepared analogously to Example 25d from 1-methyl-2-[N-(5-cyano-thiazol-2-yl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate. Yield: % of theory, $C_{24}H_{26}N_8O_3S$ (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, $C_{22}H_{22}N_8O_3S$ (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

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)

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

-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
	215.0 mg

Preparation:

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

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
	600.0 mg

(1), (2) and (3) are mixed together and granulated with an aqueous solution of (4). (5) is added to the dried granulated material. From this mixture tablets are pressed, biplanar, faceted on both sides and with a dividing notch on one side. Diameter of the tablets: 12 mm.

EXAMPLE 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
	160.0 mg

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
	430.0 mg

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
	2,000.0 mg

What is claimed is:

1. A compound of the formula I

$$R_a—A—Het—B—Ar—E \quad (I)$$

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

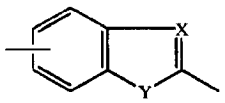
R_1 denotes a hydrogen atom or a C_{1-6}-alkyl group,

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

R_b denotes a hydrogen atom, a hydroxy group, C_{1-9}-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 is optionally, additionally, substituted by a C_{1-3}-alkylsulfonyl or 2-(C_{1-3}-alkoxy)-ethyl group,

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, 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}-alkyloxycarbonyl, benzyloxycarbonyl, C_{1-3}-alkylsulphonylaminocarbonyl, phenylsulphonylaminocarbonyl, trifluorosulphonylamino, trifluorosulphonylaminocarbonyl 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 adjacent nitrogen atom, 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, 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 sulphinyl, sulphonyl, carbonyl or $—NR_1—$ group, wherein

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

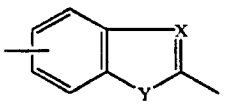
E denotes an $R_bNH—C(=NH)—$ group wherein

R_b denotes a hydrogen atom, a hydroxy group, 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 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 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}-alkyloxycarbonyl, benzyloxycarbonyl, C_{1-3}-alkylsulphonylaminocarbonyl, phenylsulphonylaminocarbonyl, trifluorosulphonylamino, trifluorosulphonylaminocarbonyl 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 adjacent nitrogen atom, 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, 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}-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 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}-alkyloxycarbonyl, benzyloxycarbonyl, 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 adjacent nitrogen atom, by a hydroxy, benzyloxy,

carboxy-C_{1-3}-alkyl-amino, 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, and

R_3 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 —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}-alkylbenzoyl or nicotinoyl group, whilst the ethoxy moiety in the 2-position of the abovementioned C_{1-9}-alkoxycarbonyl group is optionally, additionally, substituted by a C_{1-3}-alkylsulphonyl or 2-(C_{1-3}-alkoxy)-ethyl group,

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

Het denotes a 1-methyl-2,5-benzimidazolylene or 1-cyclopropyl-2,5-benzimidazolylene group and

R_a denotes a R_2NR_3— group wherein

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

a C_{2-3}-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-C_{1-3}-alkyl-amino, 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, and

R_3 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 —NR_1 group, whilst

R_1 denotes a hydrogen atom or a methyl group,

E denotes an R_bNH—C(=NH)— group wherein

R_b is a hydrogen atom, a hydroxy, C_{1-9}-alkoxycarbonyl, cyclohexyloxycarbonyl, benzyloxycarbonyl, benzoyl, p-C_{1-3}-alkyl-benzoyl or nicotinoyl group, whilst the ethoxy moiety in the 2-position of the abovementioned C_{1-9}-alkoxycarbonyl group 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

R_a denotes an R_2NR_3— group wherein R_2 denotes a C_{1-3}-alkyl group which is optionally substituted by a carboxy, C_{1-6}-alkyloxycarbonyl, benzyloxycarbonyl, methylsulfonylaminocarbonyl or 1H-tetrazol-5-yl group, or

a C_{2-3}-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-C_{1-3}-alkyl-amino, 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, and

R_3 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 physiogically 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(C)A), occlusion in peripheral arterial disease, pulmonary embolism, disseminated intravascular

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 denotes an $R_6NH—C(=NH)—$ group, or a compound according to claim 2, 3, 4, 5, 6, 7, 8 or 9, or a physiologically acceptable salt thereof.

* * * * *

Exhibit C

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,087,380
DATED : July 11, 2000
INVENTOR(S) : Norbert Hauel, 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:

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
DATED : July 11, 2000
INVENTOR(S) : Norbert Hauel, 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, "physiogically" should read -- physiologically --

Signed and Sealed this

Thirteenth Day of August, 2002

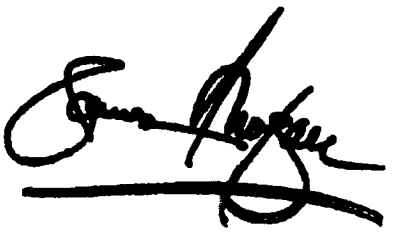


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Exhibit D

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Maintenance Fees Window Dates

10/20/2010 11:57 AM EDT

Patent Number: 6087380

Application Number: 09025690

	4th Year	8th Year	12th Year
Open Date	07/11/2003	07/11/2007	07/11/2011
Surcharge Date	01/13/2004	01/12/2008	01/12/2012
Close Date	07/12/2004	07/11/2008	07/11/2012

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MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
6,087,380	**$910.00**	**$0.00**	**12/22/03**	**09/025,690**	**07/11/00**	**02/18/98**	**04**	**NO**	**05-1213**

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MAINTENANCE FEE STATEMENT

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The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
6,087,380	**$2,360.00**	**$0.00**	**01/07/08**	**09/025,690**	**07/11/00**	**02/18/98**	**08**	**NO**	**05-1213**

Exhibit E

1. A compound of the formula **I**

$$R_a—A—Het—B—Ar—E \qquad (I)$$

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

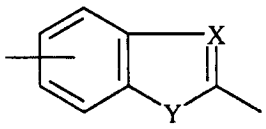
R_1 denotes a hydrogen atom or a C_{1-6}-alkyl group,

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

R_b denotes a hydrogen atom, a hydroxy group, C_{1-9}-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 is optionally, additionally, substituted by a C_{1-3}-alkylsulfonyl or 2-(C_{1-3}-alkoxy)-ethyl group,

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, 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}-alkyloxycarbonyl, benzyloxycarbonyl, C_{1-3}-alkylsulphonylaminocarbonyl, phenylsulphonylaminocarbonyl, trifluorosulphonylamino, trifluorosulphonylaminocarbonyl 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 adjacent nitrogen atom, 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, 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 sulphinyl, sulphonyl, carbonyl or –NR_1— group, wherein

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

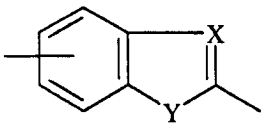
E denotes an R_bNH—C(=NH)— group wherein

R_b denotes a hydrogen atom, a hydroxy group, 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 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 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}-alkyloxycarbonyl, benzyloxycarbonyl, C_{1-3}-alkylsulphonylaminocarbonyl, phenylsulphonylaminocarbonyl, trifluorosulphonylamino, trifluorosulphonylaminocarbonyl 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 adjacent nitrogen atom, 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, 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}-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 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}-alkyloxycarbonyl, benzyloxycarbonyl, 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 adjacent nitrogen atom, by a hydroxy, benzyloxy, carboxy-C_{1-3}-alkyl-amino, 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, and

R_3 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 –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}-alkylbenzoyl

or nicotinoyl group, whilst the ethoxy moiety in the 2-position of the abovementioned C_{1-9}-alkoxycarbonyl group is optionally, additionally, substituted by a C_{1-3}-alkylsulphonyl or 2-(C_{1-3}-alkoxy)-ethyl group,

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

Het denotes a 1-methyl-2,5-benzimidazolylene or 1-cyclopropyl-2,5-benzimidazolylene group and

R_a denotes a R_2NR_3— group wherein

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

a C_{2-3}-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-C_{1-3}-alkyl-amino, 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, and

R_3 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 $-NR_1$ group, whilst

R_1 denotes a hydrogen atom or a methyl group,

E denotes an R_bNH—C(=NH)— group wherein

R_b is a hydrogen atom, a hydroxy, C_{1-9}-alkoxycarbonyl, cyclohexyloxycarbonyl, benzyloxycarbonyl, benzoyl, p-C_{1-3}-alkyl-benzoyl or nicotinoyl group, whilst the ethoxy moiety in the 2-position of the abovementioned C_{1-9}-alkoxycarbonyl group 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

R_a denotes an R_2NR_3— group wherein R_2 denotes a C_{1-3}-alkyl group which is optionally substituted by a carboxy, C_{1-6}-alkyloxycarbonyl, benzyloxycarbonyl, methylsulfonylaminocarbonyl or 1H-tetrazol-5-yl group, or

a C_{2-3}-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-C_{1-3}-alkyl-amino, 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, and

R_3 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)-aminomethy l]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethy l)-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(C)A), occlusion in peripheral arterial disease, pulmonary embolism, disseminated intravascular coagulation, coronary thrombosis, stroke, and the occlusion of a shunt or stent.

Exhibit F

Exhibit F

RELEVANT DATES AND INFORMATION PURSUANT TO 35 U.S.C. 156(g) IN ORDER TO ENABLE THE SECRETARY OF HEALTH AND HUMAN SERVICES TO DETERMINE THE APPLICABLE REGULATORY REVIEW PERIOD

(A) The relevant investigational new drug (IND) application, No. 65,813, became effective on 7 August 2003.

(B) The relevant new drug application (NDA), No. 22-512, had the following NDA submission dates:

1. Presubmission[1] of nonclinical data under rolling review began on 17 September 2009;
2. Complete NDA was initially submitted on 15 December 2009; and
3. NDA resubmission[2] was made on 19 April 2010.

Applicant takes the position that NDA No. 22-512 was initially submitted on 15 December 2009 for the following reasons. Under 21 C.F.R. § 60.22(f), "an application for agency review is considered to be 'initially submitted' if the applicant has made a deliberate effort to submit an application containing all information necessary for agency review to begin." Additionally, "[I]f the agency requires additional information after beginning its review, the application will nevertheless be considered to have been 'initially submitted' for patent extension purposes," as long as the additional information is not critical information that led to the refusal-to-file. FDA, *Final Rule, Patent Term Restoration Regulations*, 53 Fed. Reg. 7298, 7301-02 (March 7, 1988). Applicant takes the position that there

[1] The FDA requested that the relevant investigational new drug (NDA) application, No. 22-512, be submitted under rolling review. NDA No. 22-512 was not designated as a fast tract drug development program (Section 506 (21 U.S.C. § 356) of the Federal Food, Drug, and Cosmetic Act). However, under current "FDA Guidance for Industry: Fast Track Drug Development Programs – Designation, Development, and Application Review, January 2006," the review clock will not begin until the applicant informs the FDA that a complete NDA has been submitted. The applicant completed submission of the original application on 15 December 2009 for NDA No. 22-512. At that time, applicant requested and was granted priority review.

[2] A refusal-to-file action letter was received from the FDA on 12 February 2010. In that letter, the FDA commented that the application was not sufficiently complete to permit a substantive review and discussed the data quality as an issue. However, the Agency acknowledged the priority application/rolling review and commented it would continue to review parts of the application which were complete and reviewable, for example, the chemistry and pharmacology toxicology sections. The application was not withdrawn during this time.

was not an omission of critical information in the original filing but a re-evaluation of the data originally submitted. Therefore, applicant views 15 December 2009 as the initial submission date and not the re-submission date.

(C) The relevant new drug application (NDA), No. 22-512, was approved on 19 October 2010.

Exhibit G

Exhibit G

SIGNIFICANT ACTIVITIES UNDERTAKEN BY THE MARKETING APPLICANT DURING THE IND PHASE AND NDA PHASE OF THE REGULATORY REVIEW PERIOD

Date	Type of communication	Abstract
3-Jul-03	Submission SN 000	Original IND
15-Jul-03	Submission SN 001	Response to FDA Request for Information
29-Jul-03	Submission SN 002	Information Amendment: CMC
1-Aug-03	Submission SN 003	Information Amendment: CMC
4-Aug-03	Submission SN 004	Information Amendment: CMC
6-Aug-03	Submission SN 005	Response to FDA Request for Information, PETRO informed consent forms
11-Aug-03	Submission SN 006	Response to FDA Request for Information
18-Aug-03	Submission SN 007	Information Amendment: CMC
3-Sep-03	Submission SN 008	Protocol Amendment: Change in Protocol 1160.20
29-Sep-03	Submission SN 012	Information Amendment: CMC
7-Oct-03	Submission SN 014	General Correspondence: Safety reporting of 1160.19
9-Oct-03	Submission SN 015	Protocol Amendment: New Investigators 1160.20
14-Oct-03	Submission SN 016	Information Amendment: Clinical
14-Oct-03	Submission SN 017	Response to FDA Request for Information
27-Oct-03	Submission SN 018	Protocol Amendment: New Protocol 1160.42
14-Nov-03	Submission SN 020	Protocol Amendment: New Investigators 1160.20
24-Nov-03	Submission SN 021	Information Amendment: CMC
11-Dec-03	Submission SN 023	Protocol Amendment: Change in Protocol 1160.20
15-Dec-03	Submission SN 024	Protocol Amendment: New Investigators 1160.20
6-Jan-04	Submission SN 025	Protocol Amendment: New Investigator 1160.42
15-Jan-04	Submission SN 026	General Correspondence: Special Protocol Assessment
6-Feb-04	Submission SN 027	Protocol Amendment: New Investigators 1160.20 and 1160.42
18-Feb-04	Submission SN 028	Special Protocol Assessment: Mouse Carcinogenicity Study Protocol
18-Feb-04	Submission SN 029	Special Protocol Assessment: Rat Carcinogenicity Study Protocol
3-Mar-04	Submission SN 030	Response to FDA Request for Information 205.276
3-Mar-04	Submission SN 031	Response to FDA Request for Information 205.277
8-Mar-04	Submission SN 032	Protocol Amendment New Investigators 1160.42
9-Mar-04	Submission SN 033	Protocol Amendment: Change in Protocol 1160.42 Amendment 1
16-Mar-04	FDA letter	Comments on carcinogenicity study
20-Apr-04	Submission SN 034	Protocol Amendment: New Investigators 1160.42
21-Apr-04	Submission SN 035	Protocol Amendment: Change in Protocol 1160.20 Amendment 3 and 4
14-May-04	Submission SN 036	Protocol Amendment: New Investigators 1160.20 and 1160.42
2-Jun-04	Submission SN 037	Protocol Amendment: Change in Protocol 1160.42 Amendment 2
9-Jun-04	Submission SN 038	Protocol Amendment: New Investigator 1160.42
23-Jul-04	Submission SN 041	Protocol Amendment: New Investigators 1160.20
18-Aug-04	Submission SN 045	IND Annual Report for reporting period 7 Aug 2003 to 29 May 2004
30-Sep-04	Submission SN 048	Protocol Amendment: New Investigator 1160.42
8-Oct-04	Submission SN 049	Information Amendment: Clinical U04-1195
5-Nov-04	Submission SN 052	Protocol Amendment: Change in Protocol
15-Nov-04	Submission SN 054	Meeting Request Type C Meeting: Phase 3 development
27-Dec-04	Submission SN 058	Information Amendment: Clinical IB U98-3208
7-Jan-05	Submission SN 060	Protocol Amendment New Investigators 1160.42
14-Jan-05	Submission SN 061	Information Amendment Pharmacology and Toxicology

25-Feb-05	Submission SN 065	General Correspondence: Type C Pre Meeting Package: Phase 3 development
9-Mar-05	Submission SN 067	Information Amendment: Clinical
10-Mar-05	Submission SN 068	Information Amendment: Pharmacology/Toxicology
24-Mar-05	FDA letter	Type C meeting minutes on RE-LY dosing, blinding, non-inferiority margin, etc.
17-May-05	Submission SN 070	Information Amendment: Pharmacology/Toxicology
26-May-05	Submission SN 073	Request for Special Protocol Assessment Clinical Protocol 1160.47
24-Jun-05	Submission SN 077	Request for Type C Meeting - QT Study
15-Jul-05	FDA letter	RE-LY Special Protocol Assessment (open label, warfarin control, adjudication, sample size, etc.)
29-Jul-05	Submission SN 078	General Correspondence: Type C Pre Meeting Package QT Study
5-Aug-05	Submission SN 079	Information Amendment: Revised IB Version 6 and CTR 1160.28 (U05-3052)
17-Aug-05	Submission SN 083	Information Amendment: Pharmacology/Toxicology
19-Aug-05	Submission SN 084	Information Amendment : CMC
30-Aug-05	FDA letter	Type C meeting minutes on QTc study
22-Sep-05	Submission SN 085	IND Annual Report for reportig period 30 May 2004 to 29 May 2005
5-Oct-05	Submission SN 0087	Information Amendment: Pharmacology/Toxicology
6-Oct-05	Submission SN 0089	Response to FDA Request for Information - CRF's for Rely Trial Final
6-Oct-05	Submission SN 0088	Protocol Amendment : New Protocol 1160.26
4-Nov-05	Submission SN 0102	Response to FDA Request for Information Informed Consent
13-Dec-05	Submission SN 0107	Protocol Amendment: New Investigators 1160.42
13-Jan-06	Submission SN 0109	Response to FDA Request for Information - Regarding 1160.26 SPA
27-Jan-06	Submission SN 0111	Protocol Amendment: New Investigators 1160.26
24-Feb-06	Submission SN 0121	General Correspondence: SAE Proposal
28-Feb-06	Submission SN 0123	Protocol Amendment: New Investigators 1160.26
7-Mar-06	Submission SN 0124	General Correspondence: Mesylate Exposure Proposal
7-Mar-06	Submission SN 0125	Response to FDA Request for Information Pharmacological Activity
8-Mar-06	Submission SN 0126	Complete response to FDA request: acyl-glucuronide
14-Mar-06	Submission SN 0129	General Correspondence CAC
16-Mar-06	Submission SN 0132	Protocol Amendment New Investigators 1160.26
20-Mar-06	FDA letter	RE-LY safety reporting
27-Mar-06	Submission SN 0136	General Correspondence Non US Investigator Proposal
6-Apr-06	Submission SN 0141	Information Amendment CMC
14-Apr-06	Submission SN 0145	Protocol Amendment New Investigators 1160.26
21-Apr-06	Submission SN 0150	Information Amendment: Clinical/Transfer of Obligations 1160.26 (RELY)
25-Apr-06	Submission SN 0151	Response to FDA Request for Information - CRF's for Rely Trial Final
12-May-06	Submission SN 0160	Type C Meeting Request and Package: non-clinical and CMC
19-May-06	Submission SN 0164	Protocol Amendment New Investigators 1160.26
12-Jun-06	FDA letter	Type C meeting minutes on CMC and acylglucuronides
23-Jun-06	Submission SN 0168	Protocol Amendment New Investigators 1160.26
19-Jul-06	Submission SN 0179	Protocol Amendment New Investigators 1160.26
21-Jul-06	Submission SN 0181	Response to FDA Request for Information 1160.47 and 1160.53
18-Aug-06	Submission SN 0192	CMC AMENDMENT
25-Aug-06	Submission SN 0194	Response to request for information Clinical
12-Sep-06	FDA letter	Warfarin INR
29-Sep-06	Submission SN 0202	Response to FDA Request for Information: CMC
6-Oct-06	Submission SN 0204	IND Annual Report

11-Oct-06	Submission SN 0205	General Correspondence (Site Closure 0128)
16-Oct-06	Submission SN 0208	Protocol Amendment: Change in Protocol 1160.26 A1
17-Oct-06	Submission SN 0209	Protocol Amendment :New Investigators 1160.26
20-Oct-06	Submission SN 0213	Protocol Amendment: New Protocol 1160.26(Platelet sub-study) Information Amendment: Transfer of Obligations
16-Nov-06	Submission SN 0221	Information Amendment Clinical 1160.26 DSMB
29-Nov-06	Submission SN 0227	General correspondence Other (Site closure 0265)
29-Nov-06	Submission SN 0228	Response to FDA Request for Information (U06-2130 1160.26 PK analysis and U06-1996 1160.20 PK)
1-Dec-06	Submission SN 0231	Protocol Amendment New Investigators 1160.26
11-Dec-06	Submission SN 0235	Response to FDA Request for Information: PK
10-Jan-07	Submission SN 0249	Protocol Amendment New Investigators 1160.26
12-Jan-07	Submission SN 0251	Protocol Amendment Change in Protocol (Genomics sub-study) Transfer of Obligations
15-Jan-07	Submission SN 0252	Information Amendment Pharmacology and Toxicology
2-Feb-07	Submission SN 0259	Protocol Amendment New Investigators 1160.26
9-Mar-07	Submission SN 0274	Information Amendment Clinical IB U98-3208 Version 8
14-Mar-07	Submission SN 0277	Protocol Amendment Change in Protocol (Quality of Life sub-study) TORO
29-Mar-07	Submission SN 0281	Protocol Amendment New Investigators 1160.26 and Information Amendment Clinical Updated TORO (QOL)
6-Apr-07	Submission SN 0285	General Correspondence – Reporting Bleeding Events Proposal
14-May-07	Submission SN 300	Information Amendment Clinical (1160.24, 1160.25, 1160.48)
14-May-07	Submission SN 0301	Protocol Amendment New Investigators 1160.26
18-May-07	FDA letter	Bleeding can be listed as "expected"
5-Jun-07	Submission SN 0312	Protocol Amendment Change in Protocol Amendment #2 to Genomics Sub study
19-Jun-07	Submission SN 0318	Protocol Amendment Change in Protocol Amendment #2 to 1160.26
22-Jun-07	Submission SN 0322	Protocol Amendment New Investigators 1160.26 and 1160.42
6-Jul-07	Submission SN 0328	Information Amendment Pharmacology and Toxicology
6-Jul-07	Submission SN 0329	Information Amendment with request for comments and advice (LFT Proposal
20-Jul-07	Submission SN 0335	Information Amendment Clinical
20-Jul-07	Submission SN 0336	Response to FDA Request for Information - Clinical LFT Proposal 1160.26
27-Jul-07	Submission SN 0340	Information Amendment CMC
27-Jul-07	Submission SN 0339	Protocol Amendment: New Investigators 1160.26
20-Aug-07	Submission SN 0351	Information Amendment Clinical Updated IB Version 9
23-Aug-07	Submission SN 0354	Response to FDA Request for Information - Clinical LFT Proposal 1160.26
31-Aug-07	FDA letter	accepted decreased liver function monitoring
5-Oct-07	Submission SN 0368	IND ANNUAL REPORT 2007
16-Oct-07	Submission SN 0371	Protocol Amendment New Investigators 1160.26
3-Dec-07	Submission SN 0429	Information Amendment Pharm/Tox Carci studies Mouse and Rat
14-Dec-07	Submission SN 0434	Information Amendment Clinical Safety Data 1160.75
17-Dec-07	Submission SN 0436	Information Amendment Clinical Patient Narratives and Informed consent 1160.75
17-Dec-07	Submission SN 0435	Information Amendment Clinical Safety Data 1160.75 Suporting Reports
20-Dec-07	Submission SN 0438	Information Amendment Clinical
11-Jan-08	Submission SN 0448	Protocol Amendment Change in Protocol Amendments 3,4,5,6 1160.42

23-Jan-08	Submission SN 0453	Information amendment Clinical DSMB 1160.26
23-Jan-08	Submission SN 0452	Protocol Amendment New Investigators 1160.26
31-Jan-08	Submission SN 0456	Information Amendment CMC
4-Feb-08	Submission SN 0460	Partial Request to FDA 1160.75
6-Feb-08	Submission SN 0463	Information Amendment Pharmacology and Toxicology
11-Feb-08	Submission SN 0467	General Correspondence - Reporting Proposal
11-Feb-08	Submission SN 0469	Information Amendment Pharmacology and Toxicology
11-Feb-08	Submission SN 0468	Response to FDA Request 1160.75 Feb 1st Phone call
19-Feb-08	Submission SN 0473	Request for Type A Meeting: regarding 1160.75
26-Feb-08	Submission SN 0476	Protocol Amendment Change in Protocol 1160.26 Amendment 4
11-Mar-08	Submission SN 0478	Protocol Amendment Change in protocol 1160.42 A 7
17-Mar-08	Submission SN 0479	Type A Meeting Package: regarding 1160.75
19-Mar-08	Submission SN 0481	Protocol Amendment Change in Protocol Quality of life substudy 1160.26 Amendment 1
26-Mar-08	Submission SN 0484	Response to FDA Request Carci Datasets
28-Mar-08	FDA letter	accepted an EU safety reporting proposal
2-Apr-08	Submission SN 0487	Response to FDA Request RELY DSMB
11-Apr-08	FDA letter	Type A meeting minutes (quinidine study results)
18-Apr-08	Submission SN 0491	Response to Request - European SmPC
25-Apr-08	Submission SN 0495	Information Amendment Clinical CTR 1160.75
2-May-08	Submission SN 0496	Request for Type C Meeting CMC: starting materials
5-May-08	Submission SN 0498	Response to FDA Request for Information Site Closures
6-May-08	Submission SN 0500	General Correspondence Site Closures for RELY
6-May-08	Submission SN 0499	Information Amendment Clinical Updated TORO for RELY
12-May-08	Submission SN 0502	General Corresponse Site Closure for RELY
12-May-08	Submission SN 0501	Protocol Amendment New Investigators 1160.26
6-Jun-08	Submission SN 0508	Meeting Request and Information Package for Type C Meeting [Biowaiver]
16-Jun-08	Submission SN 0511	Request and Information Package for Type A Meeting TSAP 1160.26
30-Jun-08	Submission SN 0516	Response to FDA Request - April 11th type A Meeting Response 1160.75
2-Jul-08	Submission SN 0517	Information Amendment Clinical 1160.56
10-Jul-08	Submission SN 0520	Response to FDA CMC
28-Jul-08	FDA letter	Accepted biowaiver for the warfarin BE study
11-Aug-08	Submission SN 0534	Information Amendment CMC 1160.68
12-Aug-08	Submission SN 0535	Protocol Amendment - New Investigators 1160.26
14-Aug-08	Submission SN 0536	Written Response to FDA's preliminary response to TSAP Meeting
18-Aug-08	FDA letter	Type C meeting minutes (changes in RE-LY statistical analysis plan)
20-Aug-08	Submission SN 0540	Protocol amendment - Amendment #5 1160.26
27-Aug-08	Submission SN 0542	Response to FDA Request Population PK for 1160.19
29-Aug-08	Submission SN 0544	Protocol Amendment New Protocol 1160.68 and TORO
3-Sep-08	FDA letter	Drug interaction studies
3-Sep-08	Submission SN 0546	Information Amendment Pharmacology and Toxicology
23-Sep-08	Submission SN 0551	Information Amendment - Clinical Updated IB Version 10 05 Sept 2008
23-Sep-08	Submission SN 0550	Site Closure Dr. Lader for RELY 1160.26 Site 0251
24-Sep-08	Submission SN 0552	Protocol Amendment Change in Protocol Amendment #1 1160.68
25-Sep-08	Submission SN 0553	Complete Response to FDA - TSAP
26-Sep-08	Submission SN 0558	Complete Response to FDA - QTc
26-Sep-08	Submission SN 0557	IND ANNUAL REPORT 2008

26-Sep-08	Submission SN 0555	Information Amendment Clinical CTRs 1160.61, 1160.49, 1160.50 and U07-3471
3-Oct-08	Submission SN 0562	Complete Response to Request Quinidine Protocol
3-Oct-08	Submission SN 0563	Response to FDA Requset Safety
7-Oct-08	Submission SN 0564	Response to FDA Request Updated Tables
10-Oct-08	Submission SN 0566	Information Amendment CMC to Support 1160.71
16-Oct-08	Submission SN 0568	Information Amendment Pharmacology and Toxicology U07-1334-02, U08-1941-01
21-Oct-08	Submission SN 0571	Complete Response to Request 1160.75 CRFs
28-Oct-08	Submission SN 0573	Resposne to FDA Request Nonclinical Quinidine
5-Nov-08	Submission SN 0576	Other site Closure for 1160.26 Dr. Mckay
5-Nov-08	Submission SN 0577	Response to FDA Request for Information Quinidine Protocol 1160.90
12-Nov-08	Submission SN 0580	Information amendment Clinical DSMB 1160.26
21-Nov-08	Submission SN 0583	Information Amendment Pharm/Tox U07-1722 and U07-1731
21-Nov-08	Submission SN 0582	Protocol Amendment New Protocol, TORO, New Investigators 1160.71
3-Dec-08	Submission SN 0589	Information Amendment Clinical PSUR
5-Dec-08	Submission SN 0591	Information Amendment CMC to Support 1160.90
9-Dec-08	Submission SN 0595	Protocol Amendment New Investigators 1160.26
15-Jan-09	Submission SN 0604	Safety Proposal 1160.71
21-Jan-09	Submission SN 0605	Protocol Amendment - New Investigator 1160.71
21-Jan-09	Submission SN 0606	Protocol Amendment Change in Protocol Substudies Thrombin Clotting and Echocardiography
28-Jan-09	Submission SN 0609	Protocol Amendment Change in Protocol Amendment #8 1160.42
17-Feb-09	Submission SN 0615	Protocol Amendment New Protocol 1160.90
23-Feb-09	Submission SN 0619	Protocol Amendment - New Investigator 1160.71
24-Feb-09	Submission SN 0622	Information Amendment Clinical 1160.74
25-Feb-09	Submission SN 0623	Information Amendment Clinical 1160.82
13-Mar-09	Submission SN 0627	General Correspondence Pre-NDA Meeting Request
25-Mar-09	Submission SN 0633	Protocol Amendment Change in Protocol 1160.71 A1
25-Mar-09	Submission SN 0634	Response to FDA Request Verapamil
26-Mar-09	Submission SN 0637	Response to FDA Request DDI Proposal 1160.100 and 1160.101
26-Mar-09	Submission SN 0636	Response to FDA Request Draft CTR 1160.74 verapamil
27-Mar-09	Submission SN 0638	Protocol Amendment - New Investigator 1160.26 1160.71
7-Apr-09	Submission SN 0642	Information Amendment - Clinical 1160.74
10-Apr-09	Submission SN 0645	Other Site Closure for 1160.26 Mexico site 01312
10-Apr-09	Submission SN 0646	Other Site Closure for 1160.26 site 0108 (arnold)
15-Apr-09	Submission SN 0650	Pre NDA Meeting Package SPAF
20-Apr-09	Submission SN 0653	Information Amendment Clinical 1160.78
30-Apr-09	Submission SN 0655	Protocol Amendment - New Investigator 1160.26 1160.71
1-May-09	Submission SN 0656	Response to FDA Request RELY CRF
7-May-09	Submission SN 0658	Information Amendment Pharm/tox U09-1126-01
7-May-09	Submission SN 0659	Request for Type C Meeting RELY topline results
12-May-09	Submission SN 0661	Response to FDA Request Final TSAP T08-3024-01
18-May-09	FDA letter	Type B pre-NDA meeting minutes
22-May-09	Submission SN 0664	Information Amendment Clinical Updated IB V11 dated 18 May 2009
29-May-09	Submission SN 0666	Information Amendment Clinical PSUR U09-0098-01
8-Jun-09	Submission SN 0673	Protocol amendment New Investigators 1160.71
12-Jun-09	Submission SN 0674	Information amendment Clinical DSMB 1160.26
17-Jun-09	Submission SN 0677	Other Site Closure Site 0006 Patrick Simpson RELY 1160.26
17-Jun-09	Submission SN 0676	Other Site Closure Site 0006 Patrick Simpson RELY-ABLE 1160.71

22-Jun-09	Submission SN 0681	Information Amendment Clinical CTRs 1160.66 and 1160.68
15-Jul-09	Submission SN 0687	RELY Topline Results Information Package
21-Jul-09	Submission SN 0689	Information Amendment Pharmacology and Toxicology U09-1332-01
28-Jul-09	Submission SN 0694	Information Amendment Pharmacology/Toxicology U08-2317-01, U08-2155-01, U08-2324-01, U09-1024-01 and Clinical CTR 1160.70
4-Aug-09	FDA letter	Accepted proposal of drug interaction studies
17-Aug-09	FDA letter	Type C meeting minutes (RE-LY topline results)
21-Aug-09	Submission SN 0701	IND Annual report 2009
28-Aug-09	Submission SN 0704	Information Amendment - Pharmacology/Toxicology, Clinical (U09-1126-01, U09-1125-01 and CTR 1160.42
31-Aug-09	Submission SN 0705	General Correspondence Press Release and Journal Articles
1-Sep-09	Submission SN 0706	Protocol Amendment New Investigators 1160.71 and 1160.26
6-Oct-09	Submission SN 0719	Information Amendment Clinical U09-1909-01, U09-1985-01
19-Oct-09	Submission SN B2490722	Information Amendment Clinical Content final Draft Reports 1160.100 and 1160.101
27-Oct-09	Submission SN 0725	Information Amendment Clinical Site 01055 RELY and RELYABLE Eric Bolster
13-Nov-09	Submission SN 0728	General Correspondence - Slides
19-Nov-09	Submission SN 0731	Information Amendment Clinical CTRs 1160.87 and 1160.83
20-Nov-09	Submission SN 0732	Information Amendment Clinical PSUR
24-Nov-09	Submission SN 0734	General Correspondence: 1160.53 presentation in ASH
1-Dec-09	Submission SN 0738	General Correspondence: 1160.53 manuscript
3-Dec-09	Submission SN 0741	Other Site Closure Bolster Site 01055
3-Dec-09	Submission SN 0740	Protocol Amendment - New Investigator 1160.71
4-Dec-09	Submission SN 0743	Information Amendment Clinical CTR 1160.53
14-Jan-10	Submission SN 0759	Protocol Amendment New Investigators 1160.71
5-Feb-10	Submission SN 0767	Protocol Amendment Change in Protocol 1160.71 A2
17-Feb-10	Submission SN 0770	Other Site Closure Walker Site 0095
18-Feb-10	Submission SN 0772	Information Amendment - Clinical DSMB 1160.71
25-Feb-10	Submission SN 0775	Information Amendment Pharmacology/Toxicology and Clinical CTR 1160.26
12-Mar-10	Submission SN 0783	General Correspodence RELY Abstracts for American College of Cardiology Annual Scientific Session
12-Mar-10	Submission SN 0784	Protocol Amendment New Investigators 1160.71
1-Apr-10	Submission SN 0793	General Correspondence Abstract RENOVATE II
14-Apr-10	Submission SN 0798	Protocol Amendment New Investigators 1160.71
20-Apr-10	Submission SN 0804	Protocol Amendment Change in Protocol RELY Genomics substudy A3
27-Apr-10	Submission SN 0810	Infomration Amendment Pharmacology/Toxicology and Clinical CTRs 1160.64 and 1160.67
4-Jun-10	Submission SN 0831	Protocol Amendment New Investigators 1160.71
9-Jun-10	Submission SN 0835	Information Amendment Pharmacology/Toxicology U07-3554-02
1-Jul-10	Submission SN 0846	Information Amendment Clinical CTR 1160.81
16-Jul-10	Submission SN 0853	Response to FDA Request Hepatic Search
21-Jul-10	Submission SN 0855	Information Amendment Clinical RELY Substudy Risk/Coagulation Markers U10-3449-01
5-Aug-10	Submission SN 0861	IND annual Report
11-Aug-10	Submission SN 0865	Site Closure Dr. Anil Kumar Site 0246
8-Sep-10	Submission SN 0880	Information Amendment Clinical CTR 1160.90 U09-3246-02
9-Sep-10	Submission SN 0882	Protocol Amendment New Investigators 1160.71
28-Sep-10	Submission SN 0892	Infomration Amendment Clinical IB Version 12

12-Oct-10	Submission SN 0903	Information Amendment Kumar GCP

ADDITIONAL SIGNIFICANT ACTIVITIES UNDERTAKEN BY THE MARKETING APPLICANT DURING THE NDA PHASE OF THE REGULATORY REVIEW PERIOD

Date	Regulatory Correspondence	Key Content Description
17-Sep-09	Presubmission	Nonclinical information (Modules 2.4, 2.6, and complete Module 4)
30-Sep-09	Presubmission	Biopharmaceutic and clinical pharmacokinetic information (Modules 2.7.1(draft), 2.7.2 (draft) and available Module 5 reports)
30-Sep-09	Presubmission	Chemistry, manufacturing, and controls (CMC) information (complete Module 3)
13-Oct-09	Presubmission	CMC information (Module 2.3)
27-Oct-09	Presubmission	Clinical study information (available Module 5 reports and datasets)
4-Nov-09	Presubmission	Clinical pharmacokinetic and clinical study information (available Module 5 reports and datasets)
9-Nov-09	Presubmission	Clinical study information (available Module 5 documentation, including clinical study report for RE-LY and associated CRFs)
13-Nov-09	Presubmission	Proposed tradename and labeling information
30-Nov-09	Presubmission	Clinical study information (Module 5, additional RE-LY datasets in response to FDA requests)
8-Dec-09	Presubmission	Revised draft labeling information
15-Dec-09	Original Application	Original eCTD NDA complete Submission included: Module 1 documentation (e.g., waiver requests, priority review requests, proposed REMS, etc); Modules 2.2, 2.5, 2.7; Module 3 response to FDA request; Module 5 newly available reports, responses to FDA requests for additional datasets)
22-Dec-09	Amendment	Clinical study information (response to request for new/replacement datasets)
6-Jan-10	Amendment	Clinical study information (response to request for additional CRFs for RELY, new dataset for financial disclosure)
7-Jan-10	Amendment	Clinical study information (response to request for new CRFs for 1160.83, new PK datasets)
12-Jan-10	Amendment	Clinical study information (response to request, replace 1160.1 CTR)
13-Jan-10	Amendment	Clinical study information (response to request, replaced dataset for financial disclosure (sent Jan. 6) for 1160.26, new dataset for financial disclosure for 1160.49 and 1160.50)

20-Jan-10	Amendment	Clinical study information (response to request for SAS code used to generate primary efficacy dataset sent Nov 30)
22-Jan-10	Amendment	Response to request for samples of 75mg, 110mg, 150mg capsules and associated carton/container labeling
28-Jan-10	Amendment	Clinical study information (response to request for primary and secondary analyses using FDA censoring rules, submission of post-database lock events using protocol specified and FDA censoring rules)
1-Feb-10	Amendment	Clinical study information (response to request for CRF raw dataset)
3-Feb-10	Amendment	Clinical study information (response to request for CRF for patient 1160-0026-01361033)
4-Feb-10	Amendment	Clinical study information (response to request related to patient 1160-0026-00855030)
4-Feb-10	Amendment	Clinical study information (response to request for SAS file of all subjects for whom CRF or narrative was submitted)
5-Feb-10	Amendment	Response to request to describe quality checks for datasets, clarify what datasets contributed to specific analyses, and explain query rules
11-Feb-10	Amendment	Clinical study information (response to request for list/dataset of subjects on warfarin whose dose decreased with subsequent INR increases or whose dose increased with subsequent INR decreases)
11-Feb-10	Amendment	Clinical study information (updated 1160.90 CTR)
11-Feb-10	Amendment	Response to request for availability of dataset that indicates each adjudication date; for clarification of process for investigator verification of positive responses to stroke and bleeding questionnaire; and for clarification of determination of "adjudicated non-CNS embolic events"
11-Feb-10	Amendment	Clinical study information (response to request for specific 1160.26 CRFs)
11-Feb-10	Amendment	**Clinical study information** (response to request for new dataset with sites that randomized at least one subject and at least one investigator that did not provide financial disclosure information)
11-Feb-10	Amendment	Clinical study information (response to request related to INR.xpt file)
11-Feb-10	Amendment	Response to request for rationale for the applicability of foreign data to the U.S. population
12-Feb-10	Amendment	Response to questions regarding data quality
12-Feb-10	Amendment	Response to request for a detailed description of processes to capture potential endpoint events and a list by subject with procedure used to identify the event (hospitalization report, adverse event report or laboratory result), event identified (potential stroke, TIA, major bleed, etc) and date of endpoint event

12-Feb-10	Amendment	Response to request related to DQRM Excel file
12-Feb-10	Amendment	Response to request to describe quality checks for datasets, clarify what datasets contributed to specific analyses
12-Feb-10	Amendment	Additional information to respond to request for a detailed description of processes to capture potential endpoint events and a list by subject with procedure used to identify the event (hospitalization report, adverse event report or laboratory result), event identified (potential stroke, TIA, major bleed, etc) and date of endpoint event
12-Feb-10	FDA letter	Communication outlining FDA's refusal to file original new drug application
16-Feb-10	Amendment	Additional information to respond to request regarding data quality
16-Feb-10	Amendment	Information for discussion at face to face meeting
19-Feb-10	Amendment	Clinical study information (response to request for specific 1160.26 CRFs)
19-Feb-10	Amendment	Response to request for details related to completion of CRF 122 and reporting outcome events
22-Feb-10	Amendment	Response to request for EMA letter
22-Feb-10	Amendment	Clinical study information (response to request for information related to liver data)
24-Feb-10	Amendment	Follow-up to face to face meeting outlining planned activities
24-Feb-10	Amendment	Clinical study information (response to request resulting in replacement of program file)
24-Feb-10	Amendment	Clinical study information (response to DSI request)
15-Mar-10	Amendment	Clinical study information (response to request related to CSRULE variable in the LABDATA dataset)
19-Mar-10	Other	CMC proposal to amend NDA with information to support capsule color change
30-Mar-10	Amendment	Response to request related to adjudication
19-Apr-10	Original Application	Original new drug application addressing issues outlined in refusal to file letter
19-Apr-10	Amendment	Clinical study information (amendment to QC document)
19-Apr-10	Amendment	Clinical study information (response to request for 1160.71 protocol)
20-Apr-10	Amendment	Clinical study information (response to request for additional datasets)
20-Apr-10	Amendment	Clinical study information (replacement of 1160.71 protocol)
28-Apr-10	Amendment	CMC information (amendment to support color change in capsule change)

30-Apr-10	Amendment	Clinical study information (amendment with CTR 1160.67)
3-May-10	Amendment	Clinical study information (response to request to replace 8 datasets)
4-May-10	Amendment	Request for proprietary name review
5-May-10	Amendment	Clinical study information (response to request for new liver dataset)
6-May-10	Amendment	Clinical study information (response to request related to clinical pharmacology)
7-May-10	Amendment	Clinical study information (response to request resulting in replaced dataset clinsite.xpt)
10-May-10	Amendment	Clinical study information (response to request for PSUR)
10-May-10	Amendment	Clinical study information (response to request related to liver case)
10-May-10	Amendment	Nonclinical study information (response to request related to tox study)
13-May-10	Amendment	Clinical study information (response to request for additional dataset)
13-May-10	Amendment	Nonclinical study information (response to request related to tox study)
13-May-10	Amendment	Clinical study information (response to request for specific 1160.26 CRFs)
14-May-10	Amendment	Clinical study information (amendment - CTR 1160.64)
17-May-10	Amendment	Response to request for inventory of changes as a result of data QC
21-May-10	Amendment	CMC information (amendment with new stability data)
24-May-10	Amendment	Clinical study information (response to request related to liver case)
26-May-10	Amendment	Clinical study information (response to request for LB data)
26-May-10	Amendment	Clinical study information (response to request related to plt062n in Table 4.2.4)
26-May-10	Amendment	Clinical study information (response to request related to plt062n in Table 15.1.1:3 and 15.1.1:4)
27-May-10	Amendment	Response to request for updated PI
27-May-10	Amendment	Clinical study information (response to request related to site closure)
27-May-10	Amendment	Clinical study information (response to request for clarification on outcome event terms)
28-May-10	Amendment	Clinical study information (response to request for additional liver data)
28-May-10	Amendment	Clinical study information (response to request related to site closure)

28-May-10	Amendment	Clinical study information (response to DSI request)
28-May-10	Amendment	Clinical study information (response to request related to early term patients)
28-May-10	Amendment	Clinical study information (response to request related to clin pharm report)
1-Jun-10	Amendment	Clinical study information (response to request for additional information regarding the RELY Probe report)
7-Jun-10	Amendment	Clinical study information (response to request for additional information regarding liver data)
16-Jun-10	Amendment	Clinical study information (information amendment updated Pgp report)
18-Jun-10	Amendment	Clinical study information (response to request for RELY monitoring manuals)
18-Jun-10	Amendment	Clinical study information (response to request for clarification regarding the adverse event database)
22-Jun-10	Amendment	Clinical study information (response to request related to early term patients)
23-Jun-10	Amendment	Clinical study information (response to request related to vital status)
25-Jun-10	Amendment	Clinical study information (response to request related to data monitoring)
25-Jun-10	Amendment	Clinical study information (response to request regarding PK studies in Japanese and Caucasians)
25-Jun-10	Amendment	Clinical study information (response to request regarding safety report)
29-Jun-10	Amendment	Response to request related to GCP site inspections
29-Jun-10	Amendment	Clinical study information (response to request for a telecon and additional dataset on vital status)
30-Jun-10	Amendment	Clinical study information (new CTR 1160.81 and expert statement)
30-Jun-10	Amendment	Clinical study information (response to request for additional dataset or table on potential Hy's law cases)
30-Jun-10	Amendment	Response to request related to GCP site inspections
1-Jul-10	Amendment	Response to request related to REMS
1-Jul-10	Amendment	Response to request related to GCP site inspections
1-Jul-10	Amendment	Clinical study information (response to request for additional liver information)
1-Jul-10	Amendment	Response to request related to GCP site inspections
2-Jul-10	Amendment	Clinical study information (response to request for additional discontinuation, dataset)
3-Jul-10	FDA letter	Communication that new drug application is filed, priority review granted

6-Jul-10	Amendment	Clinical study information (response to request for manuscript)
6-Jul-10	Amendment	Clinical study information (response to request for additional liver information)
7-Jul-10	Amendment	Clinical study information (follow-up response to request for additional liver information)
7-Jul-10	Amendment	Clinical study information (response to request related to DSMB)
9-Jul-10	Amendment	Clinical study information (response to request for additional CRFs)
9-Jul-10	Amendment	Clinical study information (response to request to provide programs for number of LFT tests)
9-Jul-10	Amendment	Clinical study information (response to request related to four patients)
12-Jul-10	Amendment	Clinical study information (response to request related to genomics substudy)
12-Jul-10	Amendment	Clinical study information (response to request for additional liver information)
12-Jul-10	Amendment	Clinical study information (information amendment with source documentation reclassifying a case as not related to liver)
15-Jul-10	Amendment	Clinical study information (response to request for RELY PopPK information)
15-Jul-10	Amendment	CMC information (response to request for CMC information)
15-Jul-10	Amendment	Clinical study information (information amendment with source documents for patient 0528-006)
15-Jul-10	Amendment	Clinical study information (response to request for a "days off medication" dataset)
15-Jul-10	Amendment	Clinical study information (response to request for liver information)
15-Jul-10	Amendment	Response to request for description of process for review of Hy's law cases
16-Jul-10	Amendment	Clinical study information (response to request for information on RELY substudy on risk and coagulation markers)
20-Jul-10	Amendment	Response to request related to REMS documents
21-Jul-10	Amendment	CMC information (response to request for CMC information)
21-Jul-10	Amendment	Clinical study information (response to request for data monitoring plan.)
22-Jul-10	Amendment	CMC information (stability reports)
22-Jul-10	Amendment	Response to request related to submission dated April 19, 2010

23-Jul-10	Amendment	Response to request related to RELY administrative documentation
25-Jul-10	Amendment	Clinical study information (response to request for data management plan)
25-Jul-10	Amendment	Clinical study information (response to request for information on bleeding events)
26-Jul-10	Amendment	Response to request related to RELY administrative documentation
27-Jul-10	Amendment	Clinical study information (response to request for information on bleeding events)
27-Jul-10	Amendment	Response to request to revise proposed indication statement
29-Jul-10	Amendment	CMC information (response to request for CMC information)
29-Jul-10	Amendment	Clinical study information (response to request for data and CRFs)
29-Jul-10	Amendment	Clinical study information (response to request for data and CRFs)
30-Jul-10	Amendment	Clinical study information (response to request for special data analyses)
30-Jul-10	Amendment	Clinical study information (response to request for CRFs)
3-Aug-10	Amendment	Clinical study information (response to request for patient source documentation)
4-Aug-10	Amendment	Clinical study information (response to request for adjudication dataset)
4-Aug-10	Amendment	Clinical study information (response to request for information on specific patient and specific dataset)
4-Aug-10	Amendment	Clinical study information (response to request for bleeding/outcome dataset)
4-Aug-10	Amendment	Clinical study information (response to request for source documentation on specific patients)
4-Aug-10	Amendment	Clinical study information (response to request for information on adjudication and disposition datasets)
5-Aug-10	Amendment	Clinical study information (response to request for information on DISCO datasets)
5-Aug-10	Amendment	Clinical study information (response to request for source documentation on specific patient)
5-Aug-10	Amendment	Clinical study information (response to request for new specific dataset)
6-Aug-10	Amendment	Clinical study information (response to request for information on specific datasets and request for new dataset)
10-Aug-10	Amendment	CMC information (response to request for CMC information)

10-Aug-10	Amendment	Clinical study information (response to request for clarification and new dataset)
11-Aug-10	Amendment	Clinical study information (response to request for information and for replacement dataset)
11-Aug-10	Amendment	Clinical study information (response to request for clarification of vascular mortality)
11-Aug-10	Amendment	Clinical study information (response to request for new analyses related to INR)
11-Aug-10	Amendment	Clinical study information (response to request for new analyses related to liver and MI data)
11-Aug-10	Amendment	Clinical study information (response to request for replacement of source documentation for specific patient)
13-Aug-10	Amendment	Clinical study information (response to request for disposition tables)
16-Aug-10	Amendment	Clinical study information (response to request for exposure-response analysis)
16-Aug-10	Amendment	Clinical study information (response to request for clarification on the number of patients with no medication interruptions)
17-Aug-10	Amendment	Clinical study information (Four Month Safety Update)
17-Aug-10	Amendment	Clinical study information (response to request for additional analyses)
17-Aug-10	Amendment	Response to request for changes to the proposed medication guide
17-Aug-10	Amendment	Clinical study information (background materials for September 20, 2010 Advisory Committee meeting)
18-Aug-10	Amendment	Clinical study information (response to request for clarification of adverse event table and specific dataset)
23-Aug-10	Amendment	Clinical study information (response to request related to adjucation, TIMI major, and major bleeds
24-Aug-10	Amendment	Response to request related to REMS
24-Aug-10	Amendment	Clinical study information (response to request related to RELY net clinical benefit)
24-Aug-10	Amendment	Clinical study information (response to request related to sensitivity analyses)
2-Sep-10	Amendment	Clinical study information (replacement background materials for September 20, 2010 Advisory Committee meeting)
3-Sep-10	Amendment	CMC information (response to request for CMC information)
14-Sep-10	Amendment	Clinical study information (response to request related to sensitivity and post-hoc analyses for presentation at Advisory Committee)

4-Oct-10	Amendment	Request for proprietary name review
5-Oct-10	Amendment	Response to request related to proprietary name review
12-Oct-10	Amendment	Clinical study information (GCP information regarding investigator site)
18-Oct-10	Amendment	Response to request related to proprietary name review
18-Oct-10	Amendment	Response to request related to REMS
19-Oct-10	Amendment	CMC information (response to request to support 75 mg capsule)
19-Oct-10	Amendment	Clinical study information (response to request related to bleeding response)
19-Oct-10	FDA letter	Approval of NDA 22-512

Exhibit H

Exhibit H

STATEMENT ASSERTING ELIGIBILITY OF U.S. PATENT NO. 6,087,380 FOR EXTENSION

In the opinion of the Applicant, U.S. Patent No. 6,087,380 is eligible for extension under the provisions of 35 U.S.C. § 156.

(1) The term of this patent has not expired before this application is being submitted to the Director.

(2) The term of this patent has never been extended.

(3) An application for extension is submitted by an agent of the record owner, Boehringer Ingelheim Pharma GmbH & Co. KG, of the subject patent.

(4) The product has been subject to a regulatory review period before its commercial marketing or use as evident from the information set forth in numbered paragraph 11 of the application for patent term extension.

(5) The permission for commercial marketing or use of the product after the regulatory review period is the first commercial marketing or use permission for the product under the provisions of the Federal Food, Drug and Cosmetic Act.

(6) Applicant believes that the subject patent is entitled to **1,469 days** of extension.

The claimed extension has been calculated in the manner set forth in 37 C.F.R. § 1.775.

Initially, the length of the regulatory review period was determine as set forth in 37 C.F.R. § 1.775(c). It is **2,630 days**, which is the sum of:

/(1) **2,322 days**, the number of days in the period beginning on **7 August 2003**, the date the exemption under subsection (i) of section 505 of the Federal Food, Drug, and Cosmetic Act became effective for the approved product (IND 65,813) and ending on **15 December 2009**, the date the application (NDA 22-512) was initially submitted for such product under section 505(b) of the Federal Food, Drug and Cosmetic Act; and

(2) **308 days**, the number of days in the period beginning on **15 December 2009**, the date the application (NDA 22-512) was initially submitted for the approved product under subsection (b) of section 505 and ending on **19 October 2010**, the date such application was approved under such section.

Next, the term of the patent as extended was determined in accordance with 37 C.F.R. §1.775(d), by:

(1) subtracting from **2,360 days**, the number of days calculated above to be in the regulatory review period, **1,161 days**, which is the sum of the periods set forth in 37 C.F.R. § 1.775 (d)(1)(i), (ii) and (iii), as set forth in the following **Table 1** below,

Table 1

Provision of 37 C.F.R § 1.775 (d)(1)		**Number of Days**
(i)	the number of days in the periods of paragraphs (c)(1) and (c)(2) of 37 C.F.R. §1.775 which were on and before the date on which the patent issued	**0 days**
(ii)	the number of days in the periods of paragraphs (c)(1) and (c)(2) of this section during which it is determined under 35 U.S.C. § 156(d)(2)(B) by the Secretary of Health and Human Services that applicant did not act with due diligence	**0 days**
(iii)	one-half the number of days remaining in the period defined by paragraph (c)(1) of this section after that period is reduced in accordance with paragraphs (d)(1)(i) and (ii) of 37 C.F.R. §1.775	**1,161 days**

Which calculation yields **1,469 days** as its result;

(2) adding the number of days determined in accordance with 37 C.F.R. § 1.775 (d)(1), **1,469 days**, to the original term of the patent as shortened by any terminal disclaimer (which term will expire on 18 February 2018), which calculation yields **26 February 2022** as a result;

(3) adding 14 years to 19 October 2010, the date of the approval of the application under subsection (b) of section 505 of the Federal Food, Drug, and Cosmetic Act, which calculation yields **19 October 2024** as a result;

(4) comparing **26 February 2022** and **19 October 2024**, the dates for the end of the periods obtained pursuant to 37 C.F.R. § 1.775 (d)(2) and (d)(3), respectively, with each other and selecting the earlier date, which comparison yields **26 February 2022** as its result; and

(5) as the original patent was issued after September 24, 1984,

(i) by adding five (5) years to **18 February 2018**, the original expriation date of the patent or any earlier date set by terminal disclaimer, which calculation yields **18 February 2023** as its result; and

(ii) by comparing **26 February 2022** and **18 February 2023**, the dates obtained pursuant to paragraphs (d)(4) and (d)(5)(i) of this section with each other and selecting the earlier date, which comparison yields **26 February 2022** as its result (the new expiration date after extension).

The difference between **18 February 2018**, the original expiration date of the patent, and **26 February 2022**, the new expiration date of the patent, is **1,469 days**.

Exhibit I

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
09/025,690	02/18/1998	NORBERT HAUEL	05-1213

CONFIRMATION NO. 9875

28505
MICHAEL P. MORRIS
BOEHRINGER INGELHEIM USA CORPORATION
900 RIDGEBURY ROAD
P. O. BOX 368
RIDGEFIELD, CT 06877-0368

POA ACCEPTANCE LETTER

OC000000044739794

Patent Dept. Rec'd 12/1/2010
Attorney - WP

Date Mailed: 12/01/2010

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 11/30/2010.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/dolipscomb/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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09/025,690	02/18/1998	NORBERT HAUEL	05-1213

CONFIRMATION NO. 9875

POWER OF ATTORNEY NOTICE

23703
MICHAEL P. MORRIS
BOEHRINGER INGELHEIM USA CORPORATION
900 RIDGEBURY ROAD
P O BOX 368
RIDGEFIELD, CT 06877-0368

OC000000044739787

Date Mailed: 12/01/2010

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 11/30/2010.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

/dolipscomb/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

Electronic Acknowledgement Receipt

EFS ID:	8895838
Application Number:	09025690
International Application Number:	
Confirmation Number:	9875
Title of Invention:	DISUBSTITUTED BICYCLIC HETEROCYCLES, THE PREPARATIONS AND THE USE THEREOF AS PHARMACEUTICAL COMPOSITIONS
First Named Inventor/Applicant Name:	NORBERT HAUEL
Customer Number:	23703
Filer:	Wendy Ann Petka/Beatriz Guerra
Filer Authorized By:	Wendy Ann Petka
Attorney Docket Number:	05-1213
Receipt Date:	23-NOV-2010
Filing Date:	18-FEB-1998
Time Stamp:	10:32:32
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Assignee showing of ownership per 37 CFR 3.73(b).	05-1213-2010-11-04-StatementUnder37CFR373.pdf	150530 b2875988d2c0640295e262ccfc441719cff14bc2	no	1

Warnings:	
Information:	

2	Power of Attorney	05-1213-2010-11-04-POA-signed.pdf	312256 e55df687bdba190a82013611ac03c4270e757e29	no	2

Warnings:	
Information:	
Total Files Size (in bytes):	462786

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/96 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Boehringer Ingelheim Pharma GmbH & Co. KG

Application No./Patent No.: 6,087,380 Filed/Issue Date: July 11, 2000

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

Boehringer Ingelheim Pharma GmbH & Co. KG , a Corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. ☒ the assignee of the entire right, title, and interest in;

2. ☐ an assignee of less than the entire right, title, and interest in (The extent (by percentage) of its ownership interest is _____ %); or

3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made) the patent application/patent identified above, by virtue of either:

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy therefore is attached.

OR

B. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Inventors To: Boehringer Ingelheim Pharma KG

The document was recorded in the United States Patent and Trademark Office at
Reel 009039, Frame 0359, or for which a copy thereof is attached.

2. From: Boehringer Ingelheim Pharma KG To: Boehringer Ingelheim Pharma GmbH & Co. KG

The document was recorded in the United States Patent and Trademark Office at
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3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☒ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

ppa Signature	November 4th, 2010 Date	ppa Signature	Nov 3, 2010 Date
Printed or typed name:	Dr. Heinz Hammann	Printed or typed name:	Dr. Hans-Michael Kompter
Telephone number:	011-49-6132-77-98898	Telephone number:	011-49-6132-77-8884
Title:	Corporate Director Patents	Title:	Authorized Signatory

PTO/SB/81A (12-08)
Approved for use through 11/30/2011. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT - POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Patent Number	6,087,380
Issue Date	July 11, 2000
First Named Inventor	Norbert HAUEL
Title	Dibsubstituted Bicyclic heterocycles, the Preparations and the Use Thereof
Attorney Docket Number	05-1213

I hereby revoke all previous powers of attorney given in the above-identified patent.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith: 28505

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified patent to:

☒ The address associated with the above-mentioned Customer Number.

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the:

☐ Inventor, having ownership of the patent.

OR

☒ Patent owner.

Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____.

SIGNATURE of Inventor or Patent Owner

Signature		Date	November 4th, 2010
Name	Dr. Heinz Hammann	Telephone	011-49-6132-77-98898
Title and Company	Corporate Director Patents		

NOTE: Signatures of all the inventors or patent owners of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 3 forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/SB/81A (12-08)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT - POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Patent Number	6,087,380
Issue Date	July 11, 2000
First Named Inventor	Norbert HAUEL
Title	Dibsubstituted Bicyclic heterocycles, the Preparations and the Use Thereof
Attorney Docket Number	05-1213

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☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith: 28505

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number

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☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the:

☐ Inventor, having ownership of the patent.

OR

☒ Patent owner.
Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____.

SIGNATURE of Inventor or Patent Owner

Signature		Date	Nov. 3/2010
Name	Dr. Hans Michael Kompter	Telephone	011-49-6132-77-8884
Title and Company	Authorized Signatory		

NOTE: Signatures of all the inventors or patent owners of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 3 forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: **Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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