UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Danielle L. Herritt
McCarter & English LLP
265 Franklin Street
Boston, MA 02110

In Re: Patent Term Extension
Application for
U.S. Patent No. 5,532,241

JUL 30 2014

Dear Ms. Herritt:

A certificate under 35 U.S.C. § 156 is enclosed extending the term of U.S. Patent No. 5,532,241 for a period of 5 years. While a courtesy copy of this letter is being forwarded to the Food and Drug Administration (FDA), you should directly correspond with the FDA regarding any required changes to the patent expiration dates set forth in the Patent and Exclusivity Data Appendix of the Orange Book (Approved Drug Products with Therapeutic Equivalence Evaluations) or in the Patent Information set forth in the Green Book (FDA Approved Animal Drug Products). Effective August 18, 2003, patent submissions for publication in the Orange Book and Docket *95S-0117 need to be submitted on form FDA-3542 which may be downloaded from FDA's Electronic Forms Download Website: http://www.fda.gov/opacom/morechoices/fdaforms/default.html (http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3542.pdf).

Inquiries regarding this communication should be directed to the undersigned by telephone at (571) 272-7755, or by e-mail at mary.till@uspto.gov.

Mary C. Till
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Associate Commissioner
for Patent Examination Policy

cc: Office of Regulatory Policy
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 6284
Silver Spring, MD 20993-0002

RE: VIIBRYD® (vilozodone hydrochloride)
Docket No.: FDA-2011-E-

Attention: Beverly Friedman

UNITED STATES PATENT AND TRADEMARK OFFICE

(12) CERTIFICATE EXTENDING PATENT TERM
UNDER 35 U.S.C. § 156

(68)	PATENT NO.	:	5,532,241
(45)	ISSUED	:	July 2, 1996
(75)	INVENTOR	:	Henning Böttcher et al.
(73)	PATENT OWNER	:	Merck Patent Gesellschaft Mit Beschrankter Haftung
(95)	PRODUCT	:	VIIBRYD® (vilozodone hydrochloride)

This is to certify that an application under 35 U.S.C. § 156 has been filed in the United States Patent and Trademark Office, requesting extension of the term of U.S. Patent No. 5,532,241 based upon the regulatory review of the product VIIBRYD® (vilozodone hydrochloride) by the Food and Drug Administration. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

(94) 5 years

from September 29, 2014, the original expiration date of the patent, subject to the payment of maintenance fees as provided by law, with all rights pertaining thereto as provided by 35 U.S.C. § 156.

I have caused the seal of the United States Patent and Trademark Office to be affixed this 24th day of July 2014.

Michelle K. Lee

Michelle K. Lee
Deputy Under Secretary of Commerce for Intellectual Property and
Deputy Director of the United States Patent and Trademark Office

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Danielle L. Herritt
McCarter & English LLP
265 Franklin Street
Boston, MA 02110

In Re: Patent Term Extension
Application for
U.S. Patent No. 5,532,241

APR 29 2014

NOTICE OF FINAL DETERMINATION

A determination has been made that U.S. Patent No. 5,532,241, which claims the human drug product VIIBRYD® (vilozodone hydrochloride), is eligible for patent term extension under 35 U.S.C. § 156. The period of extension has been determined to be 5 years.

A single request for reconsideration of this final determination as to the length of extension of the term of the patent may be made if filed within one month of the date of this notice. Extensions of time under 37 CFR § 1.136(a) are not applicable to this time period. In the absence of such request for reconsideration, the Director will issue a certificate of extension, under seal, for a period of 5 years.

The period of extension, if calculated using the Food and Drug Administration determination of the length of the regulatory review period published in the Federal Register of April 6, 2012, (77 Fed. Reg. 20830), would be 2,542 days. Under 35 U.S.C. § 156(c):

Period of Extension	=	RRP - PGRRP - DD - ½ (TP - PGTP)[1]
	=	4,778 - 0 - 0 - ½ (4472 - 0)
	=	2,542 (7.0 years)

Since the regulatory review period began December 24, 1997, after the patent issued (July 2, 1996), the entire regulatory review period has been considered in the above determination of the length of the extension period 35 U.S.C. § 156(c). No determination of a lack of due diligence under 35 U.S.C. § 156(c)(1) was made.

The five year limitation of 35 U.S.C. § 156(g)(6)(A) applies in the present situation because the patent was issued after the date of enactment of 35 U.S.C. § 156. Since the period of extension calculated under 35 U.S.C. § 156(c) for the patent cannot exceed five years under 35 U.S.C. § 156(g)(6)(A), the period of extension will be for five years.

---

[1] Consistent with 35 U.S.C. § 156(c), "RRP" is the total number of days in the regulatory review period, "PGRRP" is the number of days of the RRP which were on and before the date on which the patent issued, "DD" is the number of days of the RRP that the applicant did not act with due diligence, "TP" is the testing phase period described in paragraphs (1)(B)(i), (2)(B)(i), (3)(B)(i), (4)(B)(i), and (5)(B)(i) of subsection (g) of 35 U.S.C. § 156, and "PGTP" is the number of days of the TP which were on and before the date on which the patent issued, wherein half days are ignored for purposes of the subtraction of ½ (TP - PGTP).

The 14 year limitation of 35 U.S.C. § 156(c)(3) does not operate to further reduce the period of extension determined above.

Upon issuance of the certificate of extension, the following information will be published in the Official Gazette:

U.S. Patent No.:	5,532,241
Granted:	July 2, 1996
Original Expiration Date[2]:	September 29, 2014
Applicant:	Henning Böttcher et al.
Owner of Record:	Merck Patentgesellschaft Mit Beschrankter Haftung
Title:	Piperidines and Piperazines
Product Trade Name:	VIIBRYD® (vilozodone hydrochloride)
Term Extended:	5 years
Expiration Date of Extension:	September 29, 2019

[2]Subject to the provisions of 35 U.S.C. § 41(b).

Any correspondence from applicant with respect to this matter should be submitted via the USPTO's EFS Web system and should be addressed as follows:

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

Telephone inquiries related to this determination should be directed to the undersigned at (571) 272-7755.

Mary C. Till
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: Office of Regulatory Policy
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 6284
Silver Spring, MD 20993-0002

Attention: Beverly Friedman

RE: VIIBRYD® (vilozodone hydrochloride)
Docket No.: FDA-2011-E-0380

Department of Health and Human Services Public Health Service

Food and Drug Administration
Rockville, MD 20857

DEC 18 2012

Re: VIIBRYD
U.S. Patent Nos. 5,532,241 and 7,834,020
Docket Nos. FDA-2011-E-0380
FDA-2011-E-0389

The Honorable David J. Kappos
Under Secretary of Commerce for Intellectual Property
Director of the United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Director Kappos:

This is in regard to the patent term extension applications for U.S. Patent Nos. 5,532,241 and 7,834,020 filed by Merck Patent GmbH under 35 U.S.C. § 156. The patents claim VIIBRYD, which was assigned new drug application 22-567.

In the April 6, 2012, issue of the Federal Register (77 Fed. Reg. 20830), the Food and Drug Administration published its determination of this product's regulatory review period, as required under 35 U.S.C. § 156(d)(2)(A). The notice provided that on or before October 3, 2012, 180 days after the publication of the determination, any interested person could file a petition with FDA under 35 U.S.C. § 156(d)(2)(B)(i) for a determination of whether the patent term extension applicant acted with due diligence during the regulatory review period.

The 180-day period for filing a due diligence petition pursuant to this notice has expired and FDA has received no such petition. Therefore, FDA considers the regulatory review period determination to be final.

Please let me know if we can provide further assistance.

Sincerely yours,

Jane A. Axelrad

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

cc: Danielle L. Herritt
McCarter & English LLP
265 Franklin Street
Boston, MA 02110

DATSCAN and is publishing this notice of that determination as required by law. FDA has made the determination because of the submission of an application to the Director of Patents and Trademarks, Department of Commerce, for the extension of a patent which claims that human drug product.

ADDRESSES: Submit electronic comments to *http://www.regulations.gov*. Submit written petitions along with three copies and written comments to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Beverly Friedman, Office of Regulatory Policy, Food and Drug Administration, 10903 New Hampshire Ave. Bldg. 51, rm. 6222, Silver Spring, MD 20993–0002, (301) 796–3602.

SUPPLEMENTARY INFORMATION: The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417) and the Generic Animal Drug and Patent Term Restoration Act (Pub. L. 100–670) generally provide that a patent may be extended for a period of up to 5 years so long as the patented item (human drug product, animal drug product, medical device, food additive, or color additive) was subject to regulatory review by FDA before the item was marketed. Under these acts, a product's regulatory review period forms the basis for determining the amount of extension an applicant may receive.

A regulatory review period consists of two periods of time: A testing phase and an approval phase. For human drug products, the testing phase begins when the exemption to permit the clinical investigations of the drug becomes effective and runs until the approval phase begins. The approval phase starts with the initial submission of an application to market the human drug product and continues until FDA grants permission to market the drug product. Although only a portion of a regulatory review period may count toward the actual amount of extension that the Director of Patents and Trademarks may award (for example, half the testing phase must be subtracted as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for a human drug product will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(1)(B).

FDA recently approved for marketing the human drug product DATSCAN (Ioflupane I–123 injection). DATSCAN is indicated for striatal dopamine transporter visualization using single photon emission computed tomography brain imaging to assist in the evaluation of adult patients with suspected Parkinsonian syndromes. Subsequent to this approval, the Patent and Trademark Office received a patent term restoration application for DATSCAN (U.S. Patent No. 5,310,912) from GE Healthcare Limited, and the Patent and Trademark Office requested FDA's assistance in determining this patent's eligibility for patent term restoration. In a letter dated June 22, 2011, FDA advised the Patent and Trademark Office that this human drug product had undergone a regulatory review period and that the approval of DATSCAN represented the first permitted commercial marketing or use of the product. Thereafter, the Patent and Trademark Office requested that FDA determine the product's regulatory review period.

FDA has determined that the applicable regulatory review period for DATSCAN is 677 days. Of this time, 0 days occurred during the testing phase of the regulatory review period, while 677 days occurred during the approval phase. These periods of time were derived from the following dates:

1. *The date an exemption under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the FFD&C Act) (21 U.S.C. 355(i)) became effective:* not applicable. The applicant claims June 19, 1997, as the date the investigational new drug application (IND) became effective. However, FDA records indicate that no IND was submitted under subsection 505(i) of the FFD&C Act for this human drug product.

2. *The date the application was initially submitted with respect to the human drug product under section 505(b) of the FFD&C Act:* March 9, 2009. The applicant claims March 6, 2009, as the date the new drug application (NDA) for DATSCAN (NDA 22–454) was initially submitted. However, FDA records indicate that NDA 22–454 was submitted on March 9, 2009.

3. *The date the application was approved:* January 14, 2011. FDA has verified the applicant's claim that NDA 22–454 was approved on January 14, 2011.

This determination of the regulatory review period establishes the maximum potential length of a patent extension. However, the U.S. Patent and Trademark Office applies several statutory limitations in its calculations of the actual period for patent extension. In its application for patent extension, this applicant seeks 5 years of patent term extension.

Anyone with knowledge that any of the dates as published are incorrect may submit to the Division of Dockets Management (see **ADDRESSES**) either electronic or written comments and ask for a redetermination by June 5, 2012. Furthermore, any interested person may petition FDA for a determination regarding whether the applicant for extension acted with due diligence during the regulatory review period by October 3, 2012. To meet its burden, the petition must contain sufficient facts to merit an FDA investigation. (See H. Rept. 857, part 1, 98th Cong., 2d sess., pp. 41–42, 1984.) Petitions should be in the format specified in 21 CFR 10.30.

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) electronic or written comments and written petitions. It is only necessary to send one set of comments. However, if you submit a written petition, you must submit three copies of the petition. Identify comments with the docket number found in brackets in the heading of this document.

Comments and petitions that have not been made publicly available on regulations.gov may be viewed in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

Dated: March 19, 2012.

Jane A. Axelrad,

Associate Director for Policy, Center for Drug Evaluation and Research.

[FR Doc. 2012–8340 Filed 4–5–12; 8:45 am]

BILLING CODE 4160–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket Nos. FDA–2011–E–0380 and FDA–2011–E–0389]

Determination of Regulatory Review Period for Purposes of Patent Extension; VIIBRYD

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined the regulatory review period for VIIBRYD and is publishing this notice of that determination as required by law. FDA has made the determination because of the submission of applications to the Director of Patents and Trademarks, Department of Commerce, for the extension of patents which claim that human drug product.

ADDRESSES: Submit electronic comments to *http://www.regulations.gov*. Submit written

petitions along with three copies and written comments to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Beverly Friedman, Office of Regulatory Policy, Food and Drug Administration, 10903 New Hampshire Ave. Bldg. 51, rm. 6222, Silver Spring, MD 20993–0002, 301–796–3602.

SUPPLEMENTARY INFORMATION: The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417) and the Generic Animal Drug and Patent Term Restoration Act (Pub. L. 100–670) generally provide that a patent may be extended for a period of up to 5 years so long as the patented item (human drug product, animal drug product, medical device, food additive, or color additive) was subject to regulatory review by FDA before the item was marketed. Under these acts, a product's regulatory review period forms the basis for determining the amount of extension an applicant may receive.

A regulatory review period consists of two periods of time: A testing phase and an approval phase. For human drug products, the testing phase begins when the exemption to permit the clinical investigations of the drug becomes effective and runs until the approval phase begins. The approval phase starts with the initial submission of an application to market the human drug product and continues until FDA grants permission to market the drug product. Although only a portion of a regulatory review period may count toward the actual amount of extension that the Director of Patents and Trademarks may award (for example, half the testing phase must be subtracted as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for a human drug product will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(1)(B).

FDA recently approved for marketing the human drug product VIIBRYD (vilazodone hydrochloride). VIIBRYD is indicated for the treatment of major depressive disorder. Subsequent to this approval, the Patent and Trademark Office received a patent term restoration application for VIIBRYD (U.S. Patent Nos. 5,532,241 and 7,834,020) from Merck Patent GmbH, and the Patent and Trademark Office requested FDA's assistance in determining this patent's eligibility for patent term restoration. In a letter dated June 22, 2011, FDA advised the Patent and Trademark Office that this human drug product had undergone a regulatory review period and that the approval of VIIBRYD represented the first permitted commercial marketing or use of the product. Thereafter, the Patent and Trademark Office requested that FDA determine the product's regulatory review period.

FDA has determined that the applicable regulatory review period for VIIBRYD is 4,778 days. Of this time, 4,472 days occurred during the testing phase of the regulatory review period, while 306 days occurred during the approval phase. These periods of time were derived from the following dates:

1. *The date an exemption under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(i)) became effective:* December 24, 1997. FDA has verified the applicant's claim that the date the investigational new drug application became effective was on December 24, 1997.

2. *The date the application was initially submitted with respect to the human drug product under section 505(b) of the FD&C Act:* March 22, 2010. FDA has verified the applicant's claim that the new drug application (NDA) for VIIBRYD (NDA 22–567) was submitted on March 22, 2010.

3. *The date the application was approved:* January 21, 2011. FDA has verified the applicant's claim that NDA 22–567 was approved on January 21, 2011.

This determination of the regulatory review period establishes the maximum potential length of a patent extension. However, the U.S. Patent and Trademark Office applies several statutory limitations in its calculations of the actual period for patent extension. In its applications for patent extension, this applicant seeks either 67 days or 5 years of patent term extension.

Anyone with knowledge that any of the dates as published are incorrect may submit to the Division of Dockets Management (see **ADDRESSES**) either electronic or written comments and ask for a redetermination by June 5, 2012. Furthermore, any interested person may petition FDA for a determination regarding whether the applicant for extension acted with due diligence during the regulatory review period by October 3, 2012. To meet its burden, the petition must contain sufficient facts to merit an FDA investigation. (See H. Rept. 857, part 1, 98th Cong., 2d sess., pp. 41–42, 1984.) Petitions should be in the format specified in 21 CFR 10.30.

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) electronic or written comments and written petitions. It is only necessary to send one set of comments. However, if you submit a written petition, you must submit three copies of the petition. Identify comments with the docket number found in brackets in the heading of this document.

Comments and petitions that have not been made publicly available on regulations.gov may be viewed in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

Dated: March 19, 2012.

Jane A. Axelrad,

Associate Director for Policy, Center for Drug Evaluation and Research.

[FR Doc. 2012–8341 Filed 4–5–12; 8:45 am]

BILLING CODE 4160–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute; Notice of Closed Meeting

Pursuant to section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. App.), notice is hereby given of the following meeting.

The meeting will be closed to the public in accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C., as amended. The grant applications and the discussions could disclose confidential trade secrets or commercial property such as patentable material, and personal information concerning individuals associated with the grant applications, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Name of Committee: National Cancer Institute Initial Review Group; Subcommittee A—Cancer Centers.

Date: May 3, 2012

Time: 8 a.m. to 5:20 p.m.

Agenda: To review and evaluate grant applications.

Place: Courtyard by Marriott, 5520 Wisconsin Avenue, Chevy Chase, MD 20815.

Contact Person: Gail J Bryant, MD, Medical Officer, Resources and Training Review Branch, Division of Extramural Activities, National Cancer Institute, 6116 Executive Blvd., Room 8107, MSC 8328, Bethesda, MD 20892–8328, (301) 402–0801, *gb30t@nih.gov.*

Information is also available on the Institute's/Center's home page: *http://deainfo.nci.nih.gov/advisory/irg/irg.htm,* where an agenda and any additional information for the meeting will be posted when available.

(Catalogue of Federal Domestic Assistance Program Nos. 93.392, Cancer Construction; 93.393, Cancer Cause and Prevention Research; 93.394, Cancer Detection and

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

APR 3 2012

Re: VIIBRYD
Patent Nos. 5,532,241 and 7,834,020
Docket Nos. FDA-2011-E-0380 and
FDA-2011-E-0389

The Honorable David J. Kappos
Undersecretary of Commerce for Intellectual Property
Director of the United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Director Kappos:

This is in regard to the applications for patent term extension for U.S. Patent Nos. 5,532,241 and 7,834,020, filed by Merck Patent GmbH, under 35 U.S.C. section 156 et seq. We have reviewed the dates contained in the applications and have determined the regulatory review period for VIIBRYD (vilazodone hydrochloride), the human drug product claimed by the patents.

The total length of the regulatory review period for VIIBRYD (vilazodone hydrochloride) is 4,778 days. Of this time, 4,472 days occurred during the testing phase and 306 days occurred during the approval phase. These periods of time were derived from the following dates:

1. The date an exemption under subsection 505(i) of the Federal Food, Drug, and Cosmetic Act involving this drug product became effective: December 24, 1997.

   FDA has verified the applicant's claim that the date the investigational new drug application became effective was on December 24, 1997

2. The date the application was initially submitted with respect to the human drug product under section 505 of the Federal Food, Drug, and Cosmetic Act: March 22, 2010.

   FDA has verified the applicant's claim that the new drug application (NDA) for VIIBRYD (NDA 22-567) was submitted on March 22, 2010.

3. The date the application was approved: January 21, 2011.

   FDA has verified the applicant's claim that NDA 22-567 was approved on January 21, 2011.

This determination of the regulatory review period by FDA does not take into account the effective date of the patent, nor does it exclude one-half of the testing phase as required by 35 U.S.C. section 156(c)(2).

Please let me know if we can be of further assistance.

Sincerely yours,

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

cc: Danielle L. Herritt
McCarter & English LLP
265 Franklin Street
Boston, MA 02110

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

NOV 29 2011

Office of Regulatory Policy
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 6222
Silver Spring, MD 20993-0002

Attention: Beverly Friedman

Dear Ms. Axelrad:

Transmitted herewith is a copy of the application for patent term extension of U.S. Patent No. 5,532,241. The application was filed on March 17, 2011, under 35 U.S.C. § 156. Please note that a patent term extension application for U.S. Patent No. 7,834,020 for NDA 22-567 for the human drug product VIIBRYD® (vilozodone hydrochloride) was filed concurrently, pursuant to the provisions of 37 C.F.R. § 1.785.

The patent claims a product that was subject to regulatory review under the Federal Food, Drug and Cosmetic Act. Subject to final review, the subject patent is considered to be eligible for patent term extension. Thus, a determination by your office of the applicable regulatory review period is necessary. Accordingly, notice and a copy of the application are provided pursuant to 35 U.S.C. § 156(d)(2)(A).

Inquiries regarding this communication should be directed to the undersigned at (571) 272-7755 (telephone) or (571) 273-7755 (facsimile).

Mary C. Till
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Associate Commissioner
for Patent Examination Policy

cc: Danielle L. Herritt
McCarter & English LLP
265 Franklin Street
Boston, MA 02110

RE: VIIBRYD® (vilozodone hydrochloride)
Docket No. FDA-2011-E-389

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JUN 22 2011

Re: VIIBRYD
Patent Nos. 5,532,241 and 7,834,020
Docket Nos. FDA-2011-E-0389
FDA-2011-E-0380

The Honorable David J. Kappos
Under Secretary of Commerce for Intellectual Property
Director of the United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Director Kappos:

This is in regard to the applications for patent term extension for U.S. Patent Nos. 5,532,241 and 7,834,020 filed by Merck Patent GmbH, under 35 U.S.C. § 156. The human drug product claimed by the patents is VIIBRYD (vilazodone hydrochloride), which was assigned new drug application (NDA) No. 22-567.

A review of the Food and Drug Administration's official records indicates that this product was subject to a regulatory review period before its commercial marketing or use, as required under 35 U.S.C. § 156(a)(4). Our records also indicate that it represents the first permitted commercial marketing or use of the product, as defined under 35 U.S.C. § 156(f)(1).

The NDA was approved on January 21, 2011, which makes the submission of the patent term extension applications on March 17, 2011, timely within the meaning of 35 U.S.C. § 156(d)(1).

Should you conclude that the subject patent is eligible for patent term extension, please advise us accordingly. As required by 35 U.S.C. § 156(d)(2)(A) we will then determine the applicable regulatory review period, publish the determination in the *Federal Register*, and notify you of our determination.

Please let me know if we can be of further assistance.

Sincerely yours,

Jane A. Axelrad

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

cc: Danielle L. Herritt
McCarter & English LLP
265 Franklin Street
Boston, MA 02110

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
08/314,734	09/29/1994	HENNING BOTTCHER	MERCK1617

CONFIRMATION NO. 3429

MILLEN WHITE ZELANO AND BRANIGAN
ARLINGTON COURTHOUSE PLAZA I SUITE 1400
2200 CLARENDON BOULEVARD
ARLINGTON, VA 22201

POWER OF ATTORNEY NOTICE

OC000000046925667

Date Mailed: 04/27/2011

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 04/03/2011.

- 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

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
08/314,734	09/29/1994	HENNING BOTTCHER	120140-00201

CONFIRMATION NO. 3429

86736
VideoMining Corporation
403 South Allen Street, Suite 101
State College, PA 16801

POA ACCEPTANCE LETTER

OC000000047391030

Date Mailed: 04/27/2011

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 03/21/2011.

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.

/dtvernon/

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
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
08/314,734	09/29/1994	HENNING BOTTCHER	120140-00201

CONFIRMATION NO. 3429

86738
MCCARTER & ENGLISH, LLP BOSTON
265 Franklin Street
Boston, MA 02110

POA ACCEPTANCE LETTER

OC000000047391125

Date Mailed: 04/27/2011

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 03/21/2011.

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.

/dtvernon/

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

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

APR 18 2011

Office of Regulatory Policy
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 6222
Silver Spring, MD 20993-0002

Attention: Beverly Friedman

The attached application for patent term extension of U.S. Patent No. 5,532,241 was filed on March 17, 2011, under 35 U.S.C. § 156. Please note that a patent term extension application for U.S. Patent No. 7,834,020 for NDA 22-567 for the human drug product VIIBRYD™ (vilozodone hydrochloride) was filed concurrently, pursuant to the provisions of 37 C.F.R. § 1.785.

The assistance of your Office is requested in confirming that the product identified in the application, VIIBRYD™ (vilozodone hydrochloride), has been subject to a regulatory review period within the meaning of 35 U.S.C. § 156(g) before its first commercial marketing or use and that the application for patent term extension was filed within the sixty-day period beginning on the date the product was approved. Since a determination has not been made whether the patent in question claims a product which has been subject to the Federal Food, Drug and Cosmetic Act, or a method of manufacturing or use of such a product, this communication is NOT to be considered as notice which may be made in the future pursuant to 35 U.S.C. § 156(d)(2)(A).

Our review of the application to date indicates that the subject patent would be eligible for extension of the patent term under 35 U.S.C. § 156.

Inquiries regarding this communication should be directed to the undersigned at (571) 272-7755 (telephone) or (571) 273-7755 (facsimile).

Mary C. Till
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Associate Commissioner
for Patent Examination Policy

cc: Danielle L. Herritt
McCarter & English LLP
265 Franklin Street
Boston, MA 02110

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	5532241
Issue Date	July 2, 1996
First Named Inventor	Henning Böttcher
Title	Piperidines and Piperazines
Attorney Docket Number	120140-00201

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: 86736

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	Hartmann	Date	March 13, 2011
Name	Dr. Hartmann	Telephone	
Title and Company	Head of Patents Pharmaceuticals Authorized Employee		

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 _____ 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/96 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
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.

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Henning Bottcher et al.

Application No./Patent No.: 5532241 Filed/Issue Date: July 2, 1996

Titled: Piperidines and Piperazines

Merck Patent GmbH, a Corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. [X] 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. [X] 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 007210, Frame 0397, 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: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

2. 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.

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.

Dr. Arno Hartmann — Dr. Bottcher — March 14, 2011
Signature — Date

Head of Patents Pharmaceuticals — Authorized Employee
Printed or Typed Name — Title

Electronic Acknowledgement Receipt

EFS ID:	9704035
Application Number:	08314734
International Application Number:	
Confirmation Number:	3429
Title of Invention:	PIPERIDINES AND PIPERAZINES
First Named Inventor/Applicant Name:	HENNING BOTTCHER
Correspondence Address:	MILLEN WHITE ZELANO AND BRANIGAN ARLINGTON COURTHOUSE PLAZA I SUITE 1400 2200 CLARENDON BOULEVARD - ARLINGTON VA 22201 US - -
Filer:	Danielle L. Herritt/Maureen Tierney
Filer Authorized By:	Danielle L. Herritt
Attorney Docket Number:	MERCK1617
Receipt Date:	21-MAR-2011
Filing Date:	29-SEP-1994
Time Stamp:	17:54:17
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	Power of Attorney	120140_00201_Patent_POA.pdf	474676 978f535ecab959b7df4f04a466b4347df1ff64bc	no	1
Warnings:					
Information:					
2	Assignee showing of ownership per 37 CFR 3.73(b).	120140_00201_373_b.pdf	477881 5a4cccbbd713ff49721d20e666fda14422a6819d	no	1
Warnings:					
Information:					
		Total Files Size (in bytes):	952557		

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.

Attorney Docket No. 119027-00901
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent of:
Böttcher *et al.*

Patent No.: 5,532,241

Issued: July 2, 1996

For: PIPERIDINES AND PIPERAZINES

Mail Stop: Hatch-Waxman PTE
U.S. Patent and Trademark Office
Office of Patent Legal Administration
Room MDW7D55
600 Dulany Street (Madison Building)
Alexandria, VA 22314

INFORMATION DISCLOSURE STATEMENT

Dear Madam:

In accordance with the duty of disclosure as described in 37 C.F.R. §1.765 and acknowledged under 37 C.F.R. §1.740(13), Marketing Applicant, Trovis Pharmaceuticals LLC, as agent for Applicant, Merck Patent GmbH, wishes to formally inform the Office that two patent term extension applications have been filed concurrently with respect to the regulatory review period for VIIBRYD™ (vilazodone hydrochloride) Tablets. Such patent term extension applications are now pending before the Office and pertain to U.S. Patent Nos. 5,532,241 (*i.e.*, the present application) and 7,834,020. It is requested that the Office examine these applications concurrently so that a meaningful election can be made upon the receipt of a Notice of Final Determination and Requirement of Election as to which patent to ultimately extend in accordance with 37 C.F.R. §1.785.

It is believed that no fee is required for the filing of this Information Disclosure Statement. However, should a fee be required with the filing of this paper (or with any paper hereafter filed in this patent term extension application by this firm), the Director is hereby

authorized to charge our Deposit Account No. 50-4876, under Docket No. 119027-00901. A duplicate copy of this paper is enclosed.

Dated: March 17, 2011

Respectfully submitted,

By _____

Scott A.M. Chambers, Ph.D.
Registration No.: 37,573
PATTON BOGGS LLP
8484 Westpark Drive, 9th Floor
McLean, Virginia 22102
(703) 744-8085
(703-744-8001 (Fax)

Attorney Docket No. 119027-00901
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent of:
Böttcher *et al.*

Patent No.: 5,532,241

Issued: July 2, 1996

For: PIPERIDINES AND PIPERAZINES

Mail Stop: Hatch-Waxman PTE
U.S. Patent and Trademark Office
Office of Patent Legal Administration
Room MDW7D55
600 Dulany Street (Madison Building)
Alexandria, VA 22314

TRANSMITTAL LETTER

Dear Madam:

Enclosed are the following items for filing in connection with the above-referenced Patent:

1. Fee Transmittal;

2. Request for Extension of Patent Term under 35 U.S.C. §156 (original plus two copies) together with Exhibits 1-11 (original plus two copies);

3. Information Disclosure Statement (original plus one copy);

4. Credit Card Payment Form; and

5. Return receipt postcard.

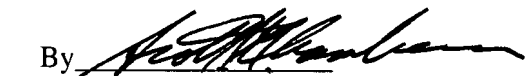
Payment is submitted by Credit Card in the amount of $1,120.00 covering the fee set forth in 37 CFR 1.20(j) (1). The Director is hereby authorized to charge any deficiency in the

fees filed, asserted to be filed or which should have been filed herewith (or with any other paper hereafter filed in this application by this firm) to our Deposit Account No. 50-4876, under Docket No. 119025-00901. A duplicate copy of this paper is enclosed.

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. §1.136(a), and any fees required therefore (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 50-4876.

Dated: March 17, 2011

Respectfully submitted,

By 

Scott A.M. Chambers, Ph.D.
Registration No.: 37,573
PATTON BOGGS LLP
8484 Westpark Drive, 9th Floor
McLean, Virginia 22102
(703) 744-8085
(703-744-8001 (Fax)

PTO/SB/17 (10-08)
Approved for use through 09/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no person are required to respond to a collection of information unless it displays a valid OMB control number

Effective on 12/08/2004.
Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL
For FY 2009

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT	($) 1,120.00

Complete if Known	
Application Number	Patent No. 5532241
Filing Date	Issued: July 2, 1996
First Named Inventor	Henning Bottcher
Examiner Name	N/A
Art Unit	N/A
Attorney Docket No.	119027-00901

METHOD OF PAYMENT (check all that apply)

☐ Check ☒ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☐ Deposit Account Deposit Account Number: 50-4876 Deposit Account Name: McCarter & English LLP

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☐ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☒ Charge any additional fee(s) or underpayments of fee(s) under 37 CFR 1.16 and 1.17 ☒ Credit any overpayments

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
Application Type	Fee ($)	Small Entity Fee ($)	Fee ($)	Small Entity Fee ($)	Fee ($)	Small Entity Fee ($)	Fees Paid ($)
Utility	330	165	540	270	220	110	
Design	220	110	100	50	140	70	
Plant	220	110	330	165	170	85	
Reissue	330	165	540	270	650	325	
Provisional	220	110	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	52	26
Each independent claim over 3 (including Reissues)	220	110
Multiple dependent claims	390	195

Total Claims	- 20 or HP =	Extra Claims	x Fee ($)	= Fee Paid ($)

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims	- 3 or HP =	Extra Claims	x	= Fee Paid ($)

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims — Fee ($): _____ Fee Paid ($): _____

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $270 ($135 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	- 100 =	Extra Sheets	/50 =	Number of each additional 50 or fraction thereof (round up to a whole number)	x Fee ($)	= Fee Paid ($)

4. OTHER FEE(S) Fees Paid ($)

Non-English Specification, $130 fee (no small entity discount) _____

Other (e.g., late filing surcharge): 1457 Extension of term patent $1,120.00

SUBMITTED BY

Signature		Registration No. (Attorney/Agent) 37,573	Telephone (703) 744-8085
Name (Print/Type)	Scott A.M. Chambers, Ph.D.		Date March 17, 2011

RECEIVED
MAR 17 2011
PATENT EXTENSION
OPLA

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent of:
Böttcher *et al.*

Patent No.: 5,532,241

Issued: July 2, 1996

For: PIPERIDINES AND PIPERAZINES

Mail Stop: Hatch-Waxman PTE
Office of Patent Legal Administration
Room MDW7D55
600 Dulany Street (Madison Building)
Alexandria, VA 22314

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

Sir:

Pursuant to 35 U.S.C. §156 and 37 C.F.R. §§1.710-1.791, Applicant, Merck Patent GmbH, the address of which is Frankfurter Strasse 250, 64293 Darmstadt, Germany, represents that it is the owner and assignee of the entire interest in and to Letters Patent of the United States No. 5,532,241 (attached as Exhibit 1, "the '241 patent") granted to Henning Böttcher, Christoph Seyfried, Gerd Bartoszyk and Hartmut Greiner on the 2nd day of July, 1996, for "Piperidines and Piperazines," by virtue of an assignment from Henning Böttcher, Christoph Seyfried, Gerd Bartoszyk and Hartmut Greiner to Merck Patent GmbH, recorded on November 14, 1994 at Reel 007210, Frame 0397 (attached as Exhibit 2). The '241 patent matured from United States Patent Application No. 08/314,734 (hereinafter "the '734 application"), filed September 29, 1994.

The approved product that is relevant to this application is VIIBRYD™ (vilazodone hydrochloride) Tablets, referred to herein as "VIIBRYD" or "Approved Product."

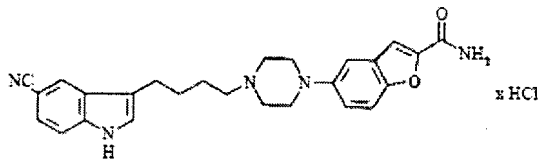
The Marketing Applicant for VIIBRYD is Trovis Pharmaceuticals LLC, a subsidiary of Clinical Data, Inc., of One Gateway Center, Suite 702, Newton, MA 02458. A letter on behalf of the Marketing Applicant authorizing the patent owner to rely upon the activities of the Marketing Applicant, its predecessors and affiliates, is attached as Exhibit 3.

The following information is submitted by Trovis Pharmaceuticals LLC through its duly authorized attorney, on behalf of Applicant (Power of Attorney attached as Exhibit 4), in accordance with 35 U.S.C. §156(d) and the rules for extension of patent term issued by the USPTO at 37 C.F.R. Subpart F, §§1.710 to 1.791 and follows the numerical format set forth in 37 C.F.R. §1.740.

(1) A COMPLETE IDENTIFICATION OF THE APPROVED PRODUCT AS BY APPROPRIATE CHEMICAL AND GENERIC NAME, PHYSICAL STRUCTURE OR CHARACTERISTICS:

The approved product is VIIBRYD Tablets, a formulation with 10, 20 or 40 mg of active ingredient polymorph Form IV vilazodone hydrochloride (HCl). VIIBRYD has been approved for the treatment of major depressive disorder (MDD) (The insert for the approved product is attached as Exhibit 5).

The chemical name of vilazodone hydrochloride is 2-benzofurancarboxamide, 5-[4-[4-(5-cyano-1*H*-indol-3-yl)butyl]-1-piperazinyl]-, hydrochloride, with the chemical structure:



(2) A COMPLETE IDENTIFICATION OF THE FEDERAL STATUTE INCLUDING THE APPLICABLE PROVISION OF LAW UNDER WHICH THE REGULATORY REVIEW OCCURRED:

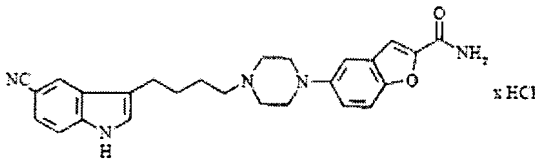
The regulatory review occurred under Section 505(b) of Federal Food, Drug, and Cosmetic Act ("FFDCA") (21 U.S.C. §355(b) and §355(i)). Section 505(b) provides for the submission and approval of new drug applications ("NDAs").

(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 Approved Product received permission for commercial marketing or use by the Food and Drug Administration ("FDA") pursuant to Section 505(b) of the FFDCA in a letter dated January 21, 2011. A copy of the approval letter is attached as Exhibit 6.

(4) IN THE CASE OF A DRUG PRODUCT, AN IDENTIFICATION OF EACH ACTIVE INGREDIENT IN THE PRODUCT AND AS TO EACH ACTIVE INGREDIENT, A STATEMENT THAT IT HAS NOT BEEN PREVIOUSLY APPROVED FOR COMMERCIAL MARKETING OR USE UNDER THE FFDCA, THE PUBLIC HEALTH SERVICE ACT, OR THE VIRUS-SERUM-TOXIN ACT OR A STATEMENT OF WHEN THE ACTIVE INGREDIENT WAS APPROVED FOR COMMERCIAL MARKETING OR USE (EITHER ALONE OR IN COMBINATION WITH OTHER ACTIVE INGREDIENTS), THE USE FOR WHICH IT WAS APPROVED AND THE PROVISION OF LAW UNDER WHICH IT WAS APPROVED: (37 C.F.R. §1.740(a)(4))

VIIBRYD has been approved under section 505(b) of the FFDCA for treatment of major depressive disorder (MDD). The active ingredient in VIIBRYD is vilazodone hydrochloride, with the chemical structure:



Neither vilazodone hydrochloride, nor any salt or ester of that active ingredient, have been previously approved for commercial marketing or use under the FFDCA, the Public Health Service Act, or the Virus-Serum-Toxin Act, and the FDA has determined that VIIBRYD is a New Molecular Entity.

(5) A STATEMENT THAT THE APPLICATION IS BEING SUBMITTED WITHIN THE 60 DAY PERIOD PERMITTED FOR SUBMISSION PURSUANT TO SECTION 1.720(f) AND AN IDENTIFICATION OF THE DATE OF THE LAST DAY ON WHICH THE APPLICATION COULD BE SUBMITTED.

This Application is timely filed, pursuant to 35 U.S.C. §156(d)(1), within the permitted sixty (60) day period that began on January 21, 2011 when the product received permission under 21 U.S.C. §355(b) and that will expire on March 22, 2011. Applicant understands that, pursuant to 37 C.F.R. §1.720(f), the USPTO may deem this period to expire one day earlier, on March 21, 2011.

(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:

United States Patent No.	5,532,241
Inventors:	Böttcher *et al.*
Date of Issue:	July 2, 1996
Expiration Date:	September 29, 2014

The Expiration of the '241 patent is September 29, 2014 based on the following: The patent application (the '734 application) that issued as the '241 patent was filed on September 29, 1994. Because the '734 application was filed prior to June 8, 1995, the expiration date of the '241 patent is the greater of either seventeen (17) years from the issue date of the '241 patent (*e.g.*, July 2, 2013) or twenty (20) years from the filing date of the '734 application (*e.g.*, September 29, 2014). The term expiring twenty (20) years from the filing date of the '734 application is the greater of the two terms. Therefore, the Expiration Date of the '241 patent is September 29, 2014.

(7) A COPY OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT, INCLUDING THE ENTIRE SPECIFICATION (INCLUDING CLAIMS) AND DRAWINGS:

A complete copy of U.S. Patent No. 5,532,241 is attached as Exhibit 1.

(8) A COPY OF ANY DISCLAIMER, CERTIFICATE OF CORRECTION, RECEIPT OF MAINTENANCE FEE PAYMENT, OR RE-EXAMINATION CERTIFICATE ISSUED IN THE U.S. PATENT:

U.S. Patent No. 5,532,241 is not subject to any disclaimer.

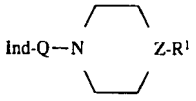
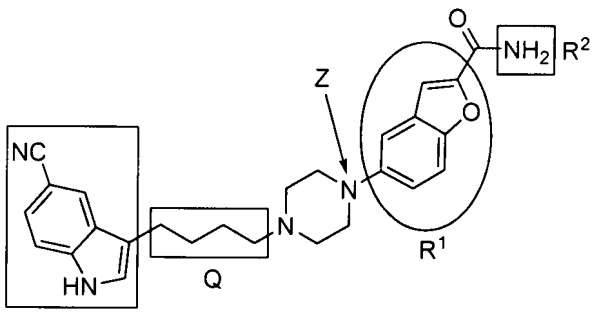
U.S. Patent No. 5,532,241 has not been re-examined, and so no re-examination certificate has been issued.

A Certificate of Correction for U.S. Patent No. 5,532,241 was signed and sealed on November 10, 2009. A copy of the Certificate of Correction is attached as Exhibit 7.

The fourth, eighth and twelve year maintenance fees for U.S. Patent No. 5,532,241 have been paid, as shown by the Patent Bibliographic Data Sheet dated February 8, 2011 (attached as Exhibit 8). Accordingly, there are no unpaid maintenance fees for this patent.

(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 A METHOD OF USING OR MANUFACTURING THE APPROVED PRODUCT:

U.S. Patent No. 5,532,241 claims the Approved Product. Specifically, claims 1-4, 7, 8, 10, 11, 16 and 17 read on the Approved Product. Pursuant to 37 C.F.R. §1.740(a)(9), 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 is set forth below.

CLAIMS	ELEMENTS
1. A compound according to formula I  wherein Ind is unsubstituted indol-3-yl, indol-3-yl monosubstituted by OH, OA, CN, Hal, COR^2 or CH_2R^2, or indol-3-yl polysubstituted by OH, OA, CN, Hal, COR^2, CH_2R^2 or combinations thereof;R^1 is benzofuran-5-yl, chroman-4-on-6-yl, 3-chromen-6-yl or chromen-4-on-6-yl, which in each case is unsubstituted or monosubstituted by CN, CH_2OH, CH_2OA or COR^2; Q is C_mH_{2m}; Z is N; A is alkyl having 1-6 C atoms; Hal is F, Cl, Br or I; R^2 is OH, OA, NH_2, NHA or NA_2; and m is 2, 3, or 4; or a physiologically acceptable salt thereof.	The active ingredient in VIIBRYD is vilazodone HCl which has the structure:  Ind having ▪ an indol-3-yl moiety monosubstituted with a cyano moiety (*i.e.*, Ind is indol-3-yl monosubstituted by CN) ▪ an n-butyl chain (*i.e.*, Q is C_mH_{2m}, m is 4) ▪ a piperazine moiety (*i.e.*, Z is N) ▪ a benzofuran-5-yl moiety that is monosubstituted with an amido moiety (*i.e.*, R^1 is benzofuran-5-yl monosubstituted by COR^2, R^2 is NH_2).
2. A compound according to claim 1, wherein said compound is: (a) 1-[4-(5-methoxyindol-3-yl)butyl]-4-(2-hydroxymethylbenzofuran-5-yl)piperazine or a physiologically acceptable salt thereof; (b) 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-ethoxycarbonyl-benzofuran-5-yl)piperazine or a physiologically acceptable salt thereof; or (c) 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoylbenzofuran-5-yl)piperazine or a physiologically acceptable salt thereof.	An alternative chemical name for vilazodone is 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoylbenzofuran-5-yl)piperazine.
3. A compound according to claim 1, wherein Ind is unsubstituted indol-3-yl, indol-3-yl monosubstituted by OH, OA, CN, Hal, COR^2 or CH_2R^2, or indol-3-yl disubstituted by OH, OA, CN, Hal, COR^2 or CH_2R^2.	The indol-3-yl moiety of vilazodone is monosubstituted with a cyano moiety (*i.e.*, Ind is indol-3-yl monosubstituted by CN).
4. A compound according to claim 1, wherein Ind is indol-3-yl monosubstituted in the 5-position by OH, OA, CN, Hal, COR^2 or CH_2R^2.	The indol-3-yl moiety of vilazodone is monosubstituted at the 5-position with a cyano moiety (*i.e.*, Ind is indol-3-yl monosubstituted in the 5-position by CN).

7. A compound according to claim 1, wherein R^1 is benzofuran-5-yl, or chroman-4-on-6-yl which, in each case is unsubstituted or monosubstituted by $-CH_2OH$, $-CONH_2$, $-CO_2A$ or $-CO_2NHA$.	The benzofuran-5-yl moiety of vilazodone is monosubstituted with $-CONH_2$ (*i.e.*, R^1 is benzofuran-5-yl monosubstituted by $-CONH_2$).
8. A compound according to claim 1, wherein Q is $-(CH_2)_4-$.	The alkyl linker between the indol-3-yl moiety and the piperazine moiety of vilazodone is an n-butyl moiety (*i.e.*, Q is $-(CH_2)_4-$).
10. A compound according to claim 1, wherein Ind is indol-3-yl substituted in the 5-position by $CONH_2$ or CN.	The indol-3-yl moiety of vilazodone is monosubstituted at the 5-position with a cyano moiety (*i.e.*, Ind is indol-3-yl substituted in the 5-position by CN).
11. A compound according to claim 1, wherein R^1 is unsubstituted benzofuran-5-yl or benzofuran-5-yl substituted by CN, CH_2OH, CH_2OA or COR^2.	The benzofuran-5-yl moiety of vilazodone is substituted with $-COR^2$, wherein R^2 is NH_2 (*i.e.*, R^1 is benzofuran-5-yl substituted by COR^2).
16. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.	The Approved Product is a pharmaceutical composition comprising vilazodone hydrochloride and a pharmaceutically acceptable carrier.
17. A composition according to claim 16, wherein said compound is present in an amount of 0.2-500 mg.	The Approved Product comprises 10, 20 or 40 mg of vilazodone hydrochloride.

(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:

(i) FOR A PATENT CLAIMING A HUMAN DRUG, ANTIBIOTIC OR HUMAN BIOLOGICAL PRODUCT, THE EFFECTIVE DATE OF THE INVESTIGATIONAL NEW DRUG APPLICATION (IND) AND THE IND NUMBER; 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 THE DATE ON WHICH THE NDA WAS APPROVED OR THE PRODUCT LICENSE ISSUED:

An original investigational new drug application ("IND") was filed on November 21, 1997 and assigned IND No. 54,613. A copy of the letter acknowledging receipt of the IND is attached as Exhibit 9. The IND became effective December 24, 1997 (*e.g.*, 30 days from receipt of the IND).

A new drug application ("NDA") was submitted on March 22, 2010 and acknowledged as received on March 22, 2010, in a letter from the FDA dated March 24, 2010 (attached as Exhibit 10). The NDA number assigned to the application for vilazodone hydrochloride was 22-567. Accordingly, the NDA was initially submitted on March 22, 2010. The NDA was approved on January 21, 2011 (Approval Letter attached as Exhibit 6).

(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:

In accordance with 37 C.F.R. §1.740(a)(11), a list of significant activities undertaken by the Marketing Applicant, its predecessors, and affiliates, in IND No. 54,613 and NDA No. 22-567 during the applicable regulatory review period with respect to the Approved Product is attached as Exhibit 11.

(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:

(a) Statement of the eligibility of U.S. Patent No. 5,532,241 for extension under 35 U.S.C. § 156(a):

Section 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted; (2) the term of the patent has never been extended under 35 U.S.C. §156(e)(1); (3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. §156(d); (4) the product has been subject to a regulatory review period before its commercial marketing or use; and (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product using the provision of law under which such regulatory review period occurred.

As described below by corresponding number, each of these elements is satisfied here:

(1) Pursuant to 35 U.S.C. §154, the term of U.S. Patent No. 5,532,241 is currently set to expire on September 29, 2014, for reasons discussed above. This application is, therefore, being submitted prior to the expiration of the term of U.S. Patent No. 5,532,241.

(2) The term of this patent has never been extended under 35 U.S.C. §156(e)(1).

(3) This application is being submitted by Trovis Pharmaceuticals LLC, as agent for Applicant, Merck Patent GmbH, the owners of record of U.S. Patent No. 5,532,241 (see Exhibit 3 and Exhibit 4). Merck Patent GmbH is this owner of record by virtue of the duly recorded assignments discussed above (see Exhibit 2). This application is submitted in accordance with 35 U.S.C. §156(d) in that it is submitted within the sixty (60) day period beginning on January 21, 2011, the date the product received permission for marketing under Section 505(b) of the FFDCA (21 U.S.C. §355), and ending on March 22, 2011. Moreover, this application contains the information required under 35 U.S.C. §156(d).

(4) As evidenced by the January 21, 2011 letter from the FDA to Trovis Pharmaceuticals LLC, attached as Exhibit 6, the Approved Product was subject to a regulatory review period under Section 505(b) of the FFDCA before its commercial marketing or use.

(5) The permission for the commercial marketing of the VIIBRYD product is the first permitted commercial marketing and use under Section 505 of the FFDCA (21 U.S.C. §355) of the product, as defined in 35 U.S.C. §156(f) (see Section 4, above).

(b) Statement as to length of extension claimed.

The term of U.S. Patent No. 5,532,241, currently expiring September 29, 2014 should be extended for five (5) years, or to September 29, 2019, in accordance with 35 U.S.C. §156.

As set forth in 35 U.S.C. §156(g)(1), the regulatory review period equals the sum of the number of days in the period beginning on the effective date of IND No. 54,613, which is December 24, 1997, and ending on the date of submission of NDA No. 22-567, which is March 22, 2010 (*e.g.*, the "Testing Phase"), and the number of days in the period beginning on the date of submission of NDA No. 22-567, which is March 22, 2010, and ending on the date of NDA approval, which is January 21, 2011 (*e.g.*, the "Approval Phase"). Including the starting and the ending date, this Testing Phase is a period of four-thousand, four-hundred, seventy-two (4,472) days as calculated at http://www.timeanddate.com/date/duration.html. This is added to the Approval Phase, which--including the starting and the ending date--is a period of three-hundred, six (306) days, as calculated at http://www.timeanddate.com/date/duration.html. The sum of these two periods is the regulatory review period which equals four-thousand, seven-hundred, seventy-eight (4,778) days.

Pursuant to 37 C.F.R. §1.775(d), the term of the patent as extended is determined by subtracting from the four-thousand, seven-hundred, seventy-eight (4,778) day regulatory review period the following:

(i) zero (0) days, which is the number of days in the IND and NDA periods on or before the issuance of U.S. Patent No. 5,532,241 on July 2, 1996; and

(ii) two-thousand, two-hundred, thirty-six (2,236) dayswhich is one-half the number of days in the Testing Phase, as provided by 37 C.F.R. 1.775(d)(1)(iii).

From the foregoing calculation, an extension of two-thousand, five-hundred, forty-two (2,542) days results (*e.g.*, four-thousand, seven-hundred, seventy-eight(4,778) days minus the two-thousand, two-hundred, thirty-six (2,236) days). This length of an extension would provide a new expiration date for U.S. Patent No. 5,532,241 of September 14, 2021. However, this extension period is subject to two further potential limitations under 35 U.S.C. §156.

First, under 35 U.S.C. §156(g)(6)(A), a maximum extension of five (5) years is permitted. In this case, since the current expiry date of U.S. Patent No. 5,532,241 is September 29, 2014, no patent term extension may extend the term of this patent beyond September 29, 2019. This provision thus limits the patent term extension available to the '241 patent to five (5) years, or to September 29, 2019.

Second, under 35 U.S.C. §156(c)(3), if the calculated extension period would lead to a patent term that would result in a patent term exceeding fourteen (14) years after the approval date (*e.g.*, a patent term expiring after January 21, 2026), the period of extension would be limited so that this period does not exceed fourteen (14) years. In this case, this provision does not operate to limit the possible extension available to U.S. Patent No. 5,532,241.

Accordingly, U.S. Patent No. 5,532,241 is eligible for a patent term extension of five (5) years.

(13) A STATEMENT THAT APPLICANT ACKNOWLEDGES A DUTY TO DISCLOSE TO THE DIRECTOR OF THE UNITED STATES PATENTS AND TRADEMARK OFFICE AND THE SECRETARY OF HEALTH AND HUMAN SERVICES ANY INFORMATION WHICH IS MATERIAL TO THE DETERMINATION OF ENTITLEMENT TO THE EXTENSION SOUGHT (SEE 37 C.F.R. §1.765):

Merck Patent GmbH and Trovis Pharmaceuticals LLC acknowledge a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

(14) THE PRESCRIBED FEE FOR RECEIVING AND ACTING UPON THE APPLICATION FOR EXTENSION (SEE 37 C.F.R. §1.20(j)):

Payment is submitted by Credit Card in the amount of $1,120.00 covering the fee set forth in 37 CFR 1.20(j) (1). The Director is hereby authorized to charge our Deposit Account No. 50-4876, under Docket No. 119027-00901, for any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm), to prevent this application from being inadvertently abandoned.

(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:

Danielle L. Herritt
McCarter & English LLP
265 Franklin Street
Boston, MA 02110
Telephone No. 617.449.6500
Direct Dial No. 617.449.6513
Facsimile No. 617.607.9200

Pursuant to 37 C.F.R. § 1.740(b), this Request for Extension of Patent Term under 35 U.S.C. § 156, including Exhibits 1-11, is accompanied by two additional copies, for a total submission of three copies.

Dated: March 17, 2011

Respectfully submitted,

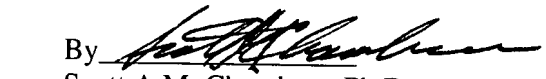
By 
Scott A.M. Chambers, Ph.D.
Registration No.: 37,573
PATTON BOGGS LLP
8484 Westpark Drive, 9th Floor
McLean, Virginia 22102
(703) 744-8085
(703) 744-8001 (Fax)

Exhibit List for Application for PTE for U.S. Patent No. 5,532,241

Exhibit 1:	U.S. Patent No. 5,532,241
Exhibit 2:	Executed Assignment
Exhibit 3:	Letter on Behalf of the Marketing Applicant Authorizing the Patent Owner to Rely upon the Activities of the Marketing Applicant
Exhibit 4:	Power of Attorney
Exhibit 5:	Approved Label
Exhibit 6:	NDA Approval Letter
Exhibit 7:	Certificate of Correction
Exhibit 8:	Patent Bibliographic Data
Exhibit 9:	Letter Acknowledging Receipt of the IND
Exhibit 10:	Letter Acknowledging Receipt of NDA
Exhibit 11:	List of Significant Activities Undertaken during Regulatory Review Period

EXHIBIT 1

U.S. Patent No. 5,532,241

US005532241A

United States Patent [19]

Böttcher et al.

[11] **Patent Number: 5,532,241**

[45] **Date of Patent: Jul. 2, 1996**

[54] **PIPERIDINES AND PIPERAZINES**

[75] Inventors: **Henning Böttcher**, Darmstadt; **Christoph Seyfried**, Seeheim-Jugenheim; **Gerd Bartoszyk**; **Hartmut Greiner**, both of Darmstadt, all of Germany

[73] Assignee: **Merck Patent Gesellschaft mit beschrankter Haftung**, Darmstadt, Germany

[21] Appl. No.: **314,734**

[22] Filed: **Sep. 29, 1994**

[30] **Foreign Application Priority Data**

Sep. 30, 1993 [DE] Germany 43 33 254.4

[51] **Int. Cl.**[6] **A61K 31/495**; A61K 31/445; C07D 405/10

[52] **U.S. Cl.** **514/254**; 544/373; 546/201; 514/323

[58] **Field of Search** 544/373; 514/254

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,002,948	3/1991	Perregaard et al.	544/373
5,242,925	9/1993	Böttcher et al.	514/254
5,418,237	5/1995	Böttcher et al.	514/253

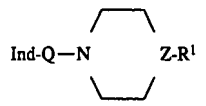
FOREIGN PATENT DOCUMENTS

0490772	6/1992	European Pat. Off. .
4127849	2/1993	Germany .
94/13659	6/1994	WIPO .

Primary Examiner—Emily Bernhardt
Attorney, Agent, or Firm—Millen, White, Zelano & Branigan

[57] **ABSTRACT**

Piperidine and piperazine derivatives of the formula I



I

wherein

Ind is an indol-3-yl radical which is unsubstituted or mono- or polysubstituted by OH, OA, CN, Hal, COR^2 or CH_2R^2,

R^1 is benzofuran-5-yl or 2,3-dihydrobenzofuran-5-yl, chroman-6-yl, chroman-4-on-6-yl, 3-chromen-6-yl or chromen-4-on-6-yl, which is unsubstituted or monosubstituted by CN, CH_2OH, CH_2OA or COR^2,

Q is C_mH_{2m},

N or CR^3,

A is alkyl having 1–6 C atoms,

Hal is F, Cl, Br or I,

R^2 is OH, OA, NH_2, NHA or NA_2,

$R^3$is H, OH or OA and

m is 2, 3 or 4,

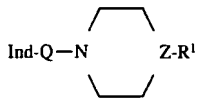
and their physiologically acceptable salts, are active on the central nervous system.

17 Claims, No Drawings

PIPERIDINES AND PIPERAZINES

SUMMARY OF THE INVENTION

The invention relates to novel piperidine and piperazine derivatives of the formula I



I

wherein

Ind is an indol-3-yl radical which is unsubstituted or mono- or polysubstituted by OH, OA, CN, Hal, COR^2 or CH_2R^2,

R^1 is benzofuran-5-yl or 2,3-dihydrobenzofuran-5-yl, chroman-6-yl, chroman-4-on-6-yl, 3-chromen-6-yl or chromen-4-on-6-yl, which is unsubstituted or monosubstituted by CN, CH_2OH, CH_2OA or COR^2,

Q is C_mH_{2m},

Z is N or CR^3,

A is alkyl having 1–6 C atoms,

Hal is F, Cl, Br or I,

R^2 is OH, OA, NH_2, NHA or NA_2,

R^3 is H, OH or OA and

m 2, 3 or 4,

and to their physiologically acceptable salts.

An object of the invention is to provide novel compounds capable of being used for the preparation of drugs.

Upon further study of the specification and appended claims, further objects and advantages of this invention will become apparent to those skilled in the art.

It has been found that the compounds of the formula I and their physiologically acceptable acid addition salts possess valuable pharmacological properties. Thus, in particular, they are active on the central nervous system, especially in terms of 5-HT_{1A}-agonist and 5-HT-reuptake inhibition. The compounds are furthermore active as serotonin agonists and antagonists. They inhibit the binding of tritiated serotonin ligands to hippocampal receptors (Cossery et al., European J. Pharmacol., 140:143–155 (1987)). They also modify the accumulation of DOPA in the corpus striatum and the accumulation of 5-HTP in the nuclei raphes (Seyfried et al., European J. Pharmacol., 160:31–41 (1989)). They also have analgesic and hypotensive effects; thus, in catheterized, conscious, spontaneously hypertensive rats (strain: SHR/Okamoto/NIH-MO-CHB-Kisslegg; method: q.v. Weeks and Jones, Proc. Soc. Exptl. Biol. Med., 104:646–648 (1960)), the directly measured blood pressure is lowered after oral administration of the compounds. They are also useful for prophylaxis and control of the sequelae of cerebral infarction (apoplexia cerebri) such as stroke and cerebral ischaemia.

Compounds of the formula I and their physiologically acceptable acid addition salts can, therefore, be used as active ingredients for anxiolytics, antidepressants, antipsychotics, neuroleptics, and/or antihypertensives, and also as intermediates for the preparation of other pharmaceutical active ingredients.

The invention relates to the piperidine and piperazine derivatives of the formula I and to their physiologically acceptable acid addition salts.

The radical A is alkyl having 1, 2, 3, 4, 5 or 6 C atoms, especially 1 or 2 C atoms, preferably methyl and also ethyl, n-propyl, isopropyl, n-butyl, sec-butyl or tert-butyl. OA is

preferably methoxy and also ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy or tert-butoxy. NHA is preferably methylamino and also ethylamino, isopropylamino, n-butylamino, isobutylamino, sec-butylamino or tert-butylamino. NA_2 is preferably dimethylamino and also N-ethyl-N-methylamino, diethylamino, di-n-propylamino, diisopropylamino or di-n-butylamino.

Analogously, CO—NHA is preferably N-methylcarbamoyl or N-ethylcarbamoyl; CO—NA_2 is preferably N,N-dimethylcarbamoyl or N,N-diethylcarbamoyl.

The radical Ind is an indol-3-yl radical which is unsubstituted or mono- or, for example, disubstituted by the radicals indicated. Preferably, it is substituted in the 5-position. Substitution in the 4-, 6- or 7-position is also suitable. Furthermore, substitution in the 1- or 2-position is possible. Preferred substituents on the indol-3-yl radical are OH, OA, CN, $CONH_2$, CH_2OH, but also CO_2H, F, Cl, Br, I, CH_2NH_2, CONHA or $CONA_2$, where A preferably corresponds to methyl or ethyl.

The radical R^1 is preferably benzofuran-5-yl, 2,3-dihydrobenzofuran-5-yl, chroman-6-yl or chromen-4-on-6-yl, which is unsubstituted or monosubstituted by —CH_2OH, —$CONH_2$, —CO_2A or —CO_2NHA.

Q is preferably —$(CH_2)_4$—, but also —$(CH_2)_2$— or —$(CH_2)_3$—, while Z is preferably —N—, —C (OH)— or —CH—.

Accordingly, the invention relates particularly to those compounds of the formula I in which at least one of said radicals has one of the meanings indicated above, especially one of the preferred meanings indicated above. Some preferred groups of compounds can be expressed by the following partial formulae Ia to Ig, which correspond to formula I and in which the radicals and parameters not described in greater detail are as defined for formula I, but in which:

in Ia, Ind is an indol-3-yl radical substituted in the 5-position by OH or OA;

in Ib, Ind is an indol-3-yl radical substituted in the 5-position by $CONH_2$ or by CN;

in Ic, Z is N and R^1 is substituted or unsubstituted benzofuran-5-yl;

in Id, Z is —C(OH)— and R^1 is substituted or unsubstituted benzofuran-5-yl;

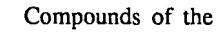
in Ie, Z is N and R^1 is 2,3-dihydrobenzofuran-5-yl;

in If, Z is N and R^1 is chroman-6-yl;

in Ig, Z is N and R^1 is chromen-4-on-6-yl.

Especially preferred compounds are those of partial formulae Ih and Iah to Igh, which correspond to partial formulae I and Ia to Ig, but in which additionally: Q is —$(CH_2)_4$—.

The invention further relates to a process for the preparation of indole derivatives of the formula I and their salts, characterized in that a compound of the formula II



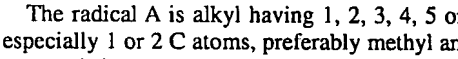
II

wherein

X^1 is X or NH_2,

X is Cl, Br, I, OH or an OH group functionally modified to form a reactive group, and

Ind and Q are as defined, is reacted with a compound of the formula III



III

wherein

X^2 and X^3 can be identical or different and are each X if X^1=NH_2 or are together NH in other cases, and

Z and R^1 are as defined, or in that to prepare a compound of the formula I in which Z is N, a compound of the formula IV

$$Ind—Q—N(CH_2—CH_2—X)_2 \quad IV$$

wherein

X, Q and Ind are as defined, is reacted with a compound of the formula V

$$R^1—NH_2 \quad V$$

wherein

R^1 is as defined, or in that a compound which has formula I except that one or more hydrogen atoms have been replaced by one or more reducible groups and/or one or more additional C—C and/or C—N bonds are treated with a reducing agent,

or in that a compound which has formula I except that one or more hydrogen atoms have been replaced by one or more solvolyzable groups is treated with a solvolyzing agent, and/or in that an OA group is optionally cleaved to form an OH group, and/or an Ind group and/or an Ar group is converted into another Ind and/or Ar group, and/or in that a resulting base or acid of the formula I is converted into one of its salts by treatment with an acid or base.

The compounds of the formula I are otherwise prepared by methods known per se, such as those described in the literature (e.g. in the standard works such as Houben-Weyl, Methoden der Organischen Chemie (Methods of Organic Chemistry), Georg-Thieme-Verlag, Stuttgart; Organic Reactions, John Wiley & Sons, Inc., New York; German Offenlegungsschrift 41 01 686), namely under reaction conditions such as those which are known and suitable for said reactions. It is also possible to make use of variants known per se, which are not mentioned in greater detail here.

If desired, the starting materials for the claimed process can also be formed in situ in such a way that they are not isolated from the reaction mixture but are immediately reacted further to give the compounds of the formula I.

In the compounds of the formula II, X^1 is preferably X; accordingly, in the compounds of the formula III, X^2 and X^3 are together preferably NH. The radical X is preferably Cl or Br, but it can also be I, OH or an OH group functionally modified to form a reactive group, especially alkylsulfonyloxy having 1–6 C atoms (e.g., methanesulfonyloxy) or arylsulfonyloxy having 6–10 C atoms (e.g., benzenesulfonyloxy, p-toluenesulfonyloxy, naphthalene-1- or -2-sulfonyloxy).

Accordingly, the indole derivatives of the formula I can be obtained especially by reacting compounds of the formula Ind—Q—Cl or Ind—Q—Br with piperidine/piperazine derivatives of the formula III in which X^2 and X^3 together are an NH group (designated as IIIa hereafter).

Some of the compounds of the formulae II and, in particular, III are known; the unknown compounds of the formulae II and III can easily be prepared analogously to the known compounds.

Primary alcohols of the formula Ind—Q—OH can be obtained, e.g., by reducing the appropriate carboxylic acids or their esters. Treatment with thionyl chloride, hydrogen bromide, phosphorus tribromide or similar halogen compounds yields the corresponding halides of the formula Ind—Q—Hal. The corresponding sulfonyloxy compounds can be obtained from the alcohols Ind—Q—OH by reaction with the appropriate sulfonyl chlorides.

The iodine compounds of the formula Ind—Q—I can be obtained, e.g., by reacting potassium iodide with the appropriate p-toluenesulfonic acid esters. The amines of the formula Ind—Q—N_2 can be prepared, e.g., from the halides with potassium phthalimide or by reducing the appropriate nitriles.

Most of the piperazine derivatives IIIa are known and can be obtained, e.g., by reacting bis(2-chloroethyl)amine or bis(2-chloroethyl)ammonium chloride with 5-aminobenzofuran, 2,3-dihydro-5-aminobenzofuran, 6-aminochroman or 6-aminochromen-4-one or an appropriately substituted derivative of the compounds mentioned. Compounds of the formula III (X^2 and X^3=X in each case) can be prepared., e.g., by reducing diesters of the formula alky 100C—CH_2—ZR^1—CH_2—COO—alkyl to give compounds of the formula HO—CH_2—CH_2—ZR^1—CH_2-CH_2OH (III, X^2=X^3=OH), this being followed, if desired, by reaction with $SOCl_2$ or PBr_3.

The reaction of the compounds of formulae II and III proceeds according to methods such as those known from the literature for the alkylation of amines. The components can be melted together in the absence of a solvent, in a sealed tube or an autoclave if necessary. It is also possible, however, to react the compounds in the presence of an inert solvent. Examples of suitable solvents are hydrocarbons such as benzene, toluene or xylene; ketones such as acetone or butanone; alcohols such as methanol, ethanol, isopropanol or n-butanol; ethers such as tetrahydrofuran (THF) or dioxane; amides such as dimethylformamide (DMF) or N-methylpyrrolidone; or nitriles such as acetonitrile, or else, if desired, mixtures of these solvents with one another or mixtures with water. It can be favorable to add an acid-binding agent, for example an alkali metal or alkaline earth metal hydroxide, carbonate or bicarbonate or another alkali metal or alkaline earth metal salt of a weak acid, preferably a potassium, sodium or calcium salt, or to add an organic base such as triethylamine, dimethylaniline, pyridine or quinoline, or an excess of the amine component Ind—Q—NH_2 or of the piperidine or piperazine derivative of the formula IIIa. The reaction time is between about a few minutes and 14 days, depending on the conditions used, and the reaction temperature is preferably about 0°–150°, normally 20°–130°.

It is also possible to obtain a compound of the formula I by reacting a compound of the formula Ind—Q—$N(CH_2$—CH_2—$X)_2$ (IV) with a compound of the formula R^1—NH_2 (V).

Most of the compounds of the formula V are known; the unknown compounds can easily be prepared analogously to the known compounds. For example, starting from the appropriately substituted nitro compounds, they can be converted into the amines of the formula V by reduction. The compounds of the formula IV can be prepared by reaction of Ind—Q—Cl, Ind—Q—Br or Ind—Q—I with secondary amines of the formula $HN(CH_2$—CH_2—$X)_2$.

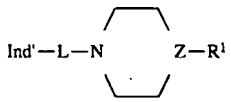
The reaction of compounds IV and V proceeds according to methods which are known from the literature and were given above for the alkylation of amines.

A compound of the formula I can also be obtained by treating a precursor, in which hydrogen atoms have been replaced by one or more reducible groups and/or one or more additional C—C and/or C—N bonds, with a reducing agent, preferably at temperatures of about −80 to 250°, in the presence of at least one inert solvent.

Reducible groups (groups replaceable by hydrogen) are, in particular, oxygen in a carbonyl group, hydroxyl, arylsulfonyloxy (e.g. p-toluenesulfonyloxy), N-benzenesulfonyl, N-benzyl or O-benzyl.

In principle, compounds containing only one of the above-mentioned groups or additional bonds, or compounds containing two or more of the above-mentioned groups or additional bonds adjacent to one another, can be converted into a compound of the formula I by reduction, it being possible simultaneously to reduce substituents in the Ind group which are present in the starting compound. This is preferably carried out using nascent hydrogen or complex metal hydrides or by means of a Wolff-Kishner reduction or the reductions with hydrogen gas under transition metal catalysis.

Preferred starting materials for the reduction have formula VI



VI

wherein

Ind' is an Ind radical which can additionally be substituted in the 1-position by an arylsulfonyl group or an alkyloxycarbonyl group,

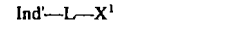
L is Q or a chain which corresponds to the radical Q except that one or more $-CH_2-$ groups have been replaced by —CO— and/or one or more hydrogen atoms have been replaced by one or more OH groups or a double bond, and

R^1 has the meaning given,

but wherein the following meanings cannot apply simultaneously: Ind'=Ind and L=Q.

In the compounds of the formula VI, L is preferably $-CO-(CH_2)_{n-2}-CO-$, wherein n is 2, 3 or 4[specifically —COCO—, $-COCH_2CO-$, $-CO-(CH_2)_2-CO-$, $-CO-(CH_2)_3-CO-$], $-(CH_2)_{n-1}-CO-$, wherein n is 2, 3 or 4 [specifically $-CH_2-CO-$, $-CH_2CH_2-CO-$, $-(CH_2)_3-CO$ —or $-(CH_2)_4-CO-$], further examples being $-CO-CH_2CH_2-$, $-CO-(CH_2)_3-$, $-CH_2-CO-CH_2CH_2-$ or $-CH_2CH_2-CO-CH_2-$.

Compounds of the formula VI can be prepared, e.g., by reacting 4-R^1-piperazine or 4-R^1-piperidine with a compound of the formula VII



VII

wherein

R^1 Ind', L and X^1 are as defined above, under the conditions indicated above for the reaction of II with III.

If nascent hydrogen is used as the reducing agent, this can be produced, e.g., by treating metals with weak acids or with bases. Thus, it is possible, e.g., to use a mixture of zinc with an alkali metal hydroxide solution or a mixture of iron with acetic acid. It is also appropriate to use sodium or another alkali metal dissolved in an alcohol such as ethanol, isopropanol, butanol, amyl or isoamyl alcohol or phenol. It is also possible to use an aluminum-nickel alloy in aqueous-alkaline solution, ethanol being added if necessary. Sodium amalgam or aluminum amalgam in aqueous-alcoholic or aqueous solution is also suitable for producing the nascent hydrogen. The reaction can also be carried out in the heterogeneous phase, in which case it is convenient to use an aqueous phase and a benzene or toluene phase.

Other reducing agents which can be used to particular advantage are complex metal hydrides such as $LiAlH_4$, $NaBH_4$, diisobutylaluminum hydride or $NaAl(OCH_2CH_2OCH_3)_2H_2$, and diborane, catalysts such as BF_3, $AlCl_3$ or LiBr being added if desired. Solvents which are suitable for this purpose are, in particular, ethers such as diethyl ether, di-n-butyl ether, THF, dioxane, diglyme or 1,2-dimethoxyethane, and hydrocarbons such as benzene. Solvents which are suitable for a reduction with $NaBH_4$ are primarily alcohols such as methanol or ethanol, as well as water and aqueous alcohols. Reduction by these methods is preferably carried out at temperatures of about −80 to +150°, especially about 0°–100°.

The reduction of —CO— groups in acid amides (e.g., those of the formula VI in which L is a $-(CH_2)_{n-1}-CO-$ group) to CH_2 groups can be carried out to particular advantage with $LiAlH_4$ in THF at temperatures of preferably about 0°–66°. Arylsulfonyl protecting groups located in the 1-position of the indole ring can be simultaneously eliminated by reduction. N-Benzyl groups can be eliminated by reduction with sodium in liquid ammonia.

It is also possible to reduce one or more carbonyl groups to CH_2 groups according to the Wolff-Kishner method, e.g., by treatment with anhydrous hydrazine in absolute ethanol, under pressure, at temperatures of preferably about 150°–250°. A sodium alcoholate is advantageously used as the catalyst. The reduction can also be varied according to the Huang-Minlon method by carrying out the reaction with hydrazine hydrate in a high-boiling water-miscible solvent such as diethylene glycol or triethylene glycol, in the presence of an alkali such as sodium hydroxide. The reaction mixture is normally boiled for about 3–4 hours. The water is then distilled off and the hydrazone formed is decomposed at temperatures of up to about 200°. The Wolff-Kishner reduction can also be carried out with hydrazine in dimethyl sulfoxide at room temperature.

Moreover, it is possible to carry out certain reductions by using H_2 gas under the catalytic action of transition metals, such as, e.g., Raney Ni or Pd. In this way, e.g., Cl, Br, I, SH or, in certain cases, even OH groups can be replaced by hydrogen. Nitro groups can also be converted into NH_2 groups by catalytic hydrogenation with Pd/H_2 in methanol.

Compounds which have formula I except that one or more H atoms have been replaced by one or more solvolyzable groups can be solvolyzed, especially hydrolyzed, to give the compounds of the formula I.

The starting materials for the solvolysis can be obtained for example by reacting IIIa with compounds which have formula II (X^1=X) except that one or more H atoms have been replaced by one or more solvolyzable groups. Thus, in particular, 1-acylindole derivatives (which have formula I except that, in the 1-position of the Ind radical, they contain an acyl group, preferably an alkoxycarbonyl, alkanoyl, alkylsulfonyl or arylsulfonyl group having up to 10 C atoms in each case, such as methanesulfonyl, benzenesulfonyl or p-toluenesulfonyl) can be hydrolyzed to give the corresponding indole derivatives unsubstituted in the 1-position of the indole ring, e.g. in an acidic or, preferably, neutral or alkaline medium at temperatures of preferably about 0°–200°. Sodium, potassium or calcium hydroxide, sodium or potassium carbonate, or ammonia, is conveniently used as the base. The chosen solvents are preferably water; lower alcohols such as methanol or ethanol; ethers such as THF or dioxane; sulfones such as tetramethylene sulfone; or mixtures thereof, especially mixtures containing water. Hydrolysis can also be carried out simply by treatment with water alone, especially at the boiling point.

A compound of the formula I can furthermore be converted to another compound of the formula I by methods known per se.

Compounds of the formula I in which Ind is an indol- 3-yl radical substituted by CO-R^1 can be obtained by derivatizing

appropriate carboxyindol-3-yl compounds. It is possible, e.g., to esterify the acids with appropriate alcohols or alcoholates, using methods known per se. It is also possible to amidate acids or esters with primary or secondary amines. It is preferred to react the free carboxylic acid with the amine under the conditions of a peptide synthesis. This reaction is preferably carried out in the presence of a dehydrating agent, e.g., a carbodiimide such as dicyclohexylcarbodiimide or else N-(3-dimethylaminopropyl)-N-ethylcarbodiimide, or propanephosphonic anhydride (q.v. Angew. Chem. 92, 129 (1980)), diphenylphosphoryl azide or 2-ethoxy-N-ethoxycarbonyl-1,2-dihydroquinoline, in an inert solvent, e.g., a halogenated hydrocarbon such as methylene chloride, an ether such as THF or dioxane, an amide such as DMF or dimethylacetamide, or a nitrile such as acetonitrile, at temperatures of preferably about −10 to 40, preferably about 0°–30°. Instead of the acid or amide, it is also possible to use reactive derivatives of these substances in the reaction, e.g., those in which reactive groups are blocked by protecting groups in an intermediate step. The acids can also be used in the form of their activated esters, which are conveniently formed in situ, e.g., by the addition of 1-hydroxybenztriazole or N-hydroxysuccinimide.

Furthermore, cyano-substituted indol-3-yl radicals can be hydrolyzed to give carboxy-indol-3-yl or carbamido-indol-3-yl radicals.

Conversely, however, it is particularly convenient to prepare the nitriles by elimination of water, starting from the amides, e.g., by means of trichloroacetyl chloride/Et_3N [Synthesis (2), 184, (1985)] or with $POCl_3$ (J. Org. Chem. 26, 1003 (1961)).

A base of the formula I can be converted with an acid into the corresponding acid addition salt. Acids which produce physiologically acceptable salts are suitable for this reaction. Thus, it is possible to use inorganic acids, e.g., sulfuric acid, hydrohalic acids such as hydrochloric acid or hydrobromic acid, phosphoric acids such as orthophosphoric acid, nitric acid and sulfamic acid, as well as organic acids, i.e., specifically aliphatic, alicyclic, araliphatic, aromatic or heterocyclic monobasic or polybasic carboxylic, sulfonic or sulfuric acids, such as formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, benzoic acid, salicylic acid, 2-phenylpropionic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methanesulfonic or ethanesulfonic acid, ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenemonosulfonic and naphthalenedisulfonic acids and laurylsulfuric acid.

If desired, the free bases of the formula I can be liberated from their salts by treatment with strong bases such as sodium or potassium hydroxide or sodium or potassium carbonate provided there are no other acid groups in the molecule. In those cases where the compounds of the formula I have free acid groups, salt formation can also be achieved by treatment with bases. Suitable bases are alkali metal hydroxides, alkaline earth metal hydroxides or organic bases in the form of primary, secondary or tertiary amines.

The invention further relates to the use of the compounds of the formula I and their physiologically acceptable salts for the manufacture of pharmaceutical preparations, especially by a non-chemical route. For this purpose, they can be converted into a suitable dosage form together with at least one excipient or adjunct and, if appropriate, in combination with one or more additional active ingredients.

The invention further relates to compositions, especially pharmaceutical preparations, containing at least one compound of the formula I and/or one of their physiologically acceptable salts. These preparations can be used as drugs in human or veterinary medicine. Possible excipients are organic or inorganic substances which are suitable for enteral (e.g.,oral), parenteral or topical administration and which do not react with the novel compounds, examples of such excipients being water, vegetable oils, benzyl alcohols, polyethylene glycols, gelatin, carbohydrates such as lactose or starch, magnesium stearate, talc and petroleum jelly. Tablets, coated tablets, capsules, syrups, juices, drops or suppositories are used in particular for enteral administration, solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions or implants are used for parenteral administration, and ointments, creams or powders are used for topical administration. The novel compounds can also be lyophilized and the resulting lyophilizates used, e.g., to manufacture injectable preparations.

The preparations indicated can be sterilized and/or can contain adjuncts such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for influencing the osmotic pressure, buffer substances, colorants, taste correctors and/or flavorings. If desired, they can also contain one or more additional active ingredients, e.g. one or more vitamins.

The compounds of the formula I and their physiologically acceptable salts can be used for the therapeutic treatment of the human or animal body and for controlling diseases. They can be used for treating disorders of the central nervous system, such as tension, depressions and/or psychoses, and side-effects in the treatment of hypertension (e.g., with α-methyldopa). The compounds can also be used in endocrinology and gynecology, e.g., for the therapeutic treatment of acromegaly, hypogonadism, secondary amenorrhea, premenstrual syndrome and undesired puerperal lactation, and also for the prophylaxis and therapy of cerebral disorders (e.g., migraine), especially in geriatrics in a manner similar to certain ergot alkaloids and for controlling the sequelae of cerebral infarction (apoplexia cerebri), such as stroke and cerebral ischemia.

In these treatments, the substances of the invention are normally administered analogously to known, commercially available preparations (e.g., bromocriptine, dihydroergocornine), preferably in dosages of about 0.2–500 mg, especially 0.2–50 mg per dosage unit. The daily dosage is preferably about 0.001–10 mg/kg of body weight. The low dosages (about 0.2–1 mg per dosage unit; about 0.001–0.005 mg/kg of body weight) are particularly suitable for use as antimigraine preparations; dosages of about 10–50 mg per dosage unit are preferred for the other indications. However, the particular dose for each individual patient depends on a very wide variety of factors, for example, the activity of the particular compound used, age, body weight, general state of health, sex, diet, time and method of administration, rate of excretion, drug combination and severity of the particular disease to which the therapy is applied. Oral administration is preferred.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

In the foregoing and in the following examples, all temperatures are set forth uncorrected in degrees Celsius and unless otherwise indicated, all parts and percentages are by weight.

The entire disclosure of all applications, patents and publications, cited above and below, and of corresponding

German application P 43 33 254.4, filed Sep. 30, 1993, are hereby incorporated by reference.

In the following Examples, "working-up in conventional manner" means: Water is added if necessary, extraction is carried out with methylene chloride, the organic phase is separated off, dried over sodium sulfate and filtered, the filtrate is evaporated and the residue is purified by chromatography on silica gel and/or by crystallization. Temperatures are given in ° C. Rf values were obtained by thin layer chromatography on silica gel.

EXAMPLES

Example 1

1.8 g of 3-(4-chlorobutyl)-5-methoxyindole [obtainable by diazotization of p-methoxyaniline, reaction with ethyl cyclohexanone-2-carboxylate according to Japp-Klingemann to give 4-(2-carbethoxyindol-3-yl)butyric acid, alkaline hydrolysis, decarboxylation, reduction with $LiAlH_4$ and reaction with $SOCl_2$] and 1.9 g of 1-(2-hydroxymethylbenzofuran-5-yl)piperazine [obtainable by reaction of N,N-bis(2-chloroethyl)amine with 2-hydroxymethyl-5-aminobenzofuran] are dissolved in 200 ml of acetonitrile and the mixture is stirred at room temperature for 10 hours. Customary working up gives 1-[4-(5-methoxyindol-3-yl)butyl] -4-(2-hydroxymethylbenzofuran- 5-yl)piperazine, m.p. 159°.

The following are obtained analogously by reaction of 3-(4-chlorobutyl)-5-methoxyindole with 1-(2,3-dihydrobenzofuran- 5-yl)piperazine:

1-[4-(5-methoxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)piperazine, m.p. 111°–112°;

of 3-(4-chlorobutyl)-5-hydroxyindole with 1-(chroman-6-yl)piperazine:

1-[4-(5-hydroxyindol-3-yl)butyl]-4-(chroman-6-yl)piperazine, m.p. 220°–222°;

of 3-(4-chlorobutyl)-5-methoxyindole with 1-(chroman-6-yl)piperazine:

1-[4-(5-methoxyindol-3-yl)butyl]-4-(chroman-6-yl)piperazine, m.p. 129°–130°;

of methyl 3-(4-chlorobutyl)-5-indolecarboxylate with 1-(chroman-6-yl)piperazine:

1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(chroman-6-yl)piperazine;

of ethyl 3-(4-chlorobutyl)-5-indolecarboxylate with 1-(benzofuran-5-yl)piperazine:

1-[4-(5-ethoxycarbonylindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine;

of 3-(4-chlorobutyl)-5-methoxyindole with 1-(benzofuran-5-yl)piperazine:

1-[4-(5-methoxyindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine;

of 3-(4-chlorobutyl)-5-methoxycarbonylindole with 1-(chromen-4-on-6-yl)piperazine:

1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(chromen-4-on-6-yl)piperazine;

of 3-(4-chlorobutyl)-5-cyanoindole with 1-(chromen-4-on-6-yl)piperazine:

1-[4-(5-cyanoindol-3-yl)butyl]-4-(chromen-4-on 6-yl)piperazine;

of 3-(4-chlorobutyl)-5-chloroindole with 1-(2,3-dihydrobenzofuran- 5-yl)piperazine:

1-[4-(5-chloroindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)piperazine;

of 3-(4-chlorobutyl)-5-methoxycarbonylindole with 1-(2,3-dihydrobenzofuran-5-yl)piperazine:

1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)piperazine;

of 3-(4-chlorobutyl)-5-methoxycarbonylindole with 4-(2,3-dihydrobenzofuran-5-yl)piperidine:

1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)piperidine;

of 3-(4-chlorobutyl)-5-methoxycarbonylindole with 4-(2,3-dihydrobenzofuran-5-yl)-4-hydroxypiperidine:

1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)-4-hydroxypiperidine;

of 3-(4-chlorobutyl)-5,6-dimethoxyindole with 1-(chroman-6-yl)piperazine:

1-[4-(5,6-dimethoxyindol-3-yl)butyl]-4-(chroman-6-yl)piperazine;

of 3-(4-chlorobutyl)-5-cyanoindole with 1-(2-carboxybenzofuran- 5-yl)piperazine:

1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carboxybenzofuran-5-yl)piperazine;

of 3-(4-chlorobutyl)-6-fluoroindole with 1-(2,3-dihydrobenzofuran- 5-yl)piperazine:

1-[4-(6-fluoroindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)piperazine.

Example 2

1.8 g of 1-[4-(5-methoxycarbonylindol-3-yl)-butyl]-4-(chroman-6-yl)piperazine [obtainable according to Example 1] are boiled for 0.5 hours with 100 ml of 2N ethanolic KOH, worked up in the customary manner and give 1-[4-(5-carboxyindol-3-yl)butyl]-4-(chreman-6-yl)piperazine.

The following are obtained analogously by alkaline hydrolysis of the corresponding esters starting from 1-[4-(5-ethoxycarbonylindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine:

1-[4-(5-carboxyindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine:

from 1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(chromen-4-on-6-yl)piperazine:

1-[4-(5-carboxyindol-3-yl)butyl]-4-(chromen-4-on-6-yl)piperazine;

from 1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)piperazine:

1-[4-(5-carboxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)piperazine;

from 1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)-4-hydroxypiperidine;

1-[4-(5-carboxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)-4-hydroxypiperidine.

Example 3

2.8 g of 1-[4-(5-carboxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine are suspended in 100 ml of N-methylpyrrolidine. 3.2 g of 2-chloro-1-methylpyridinium methanesulfonate are then added and the mixture is stirred at room temperature for 12 hours. Dried NH_3 gas is then passed into the resulting solution until it is saturated and the mixture is stirred again for 10 hours. Customary working up gives 1-[4-(5-carbamoylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)-piperazine.

The following are obtained analogously by amidation of the following carboxylic acids with 2-chloro-1-methylpyridinium methanesulfonate:

from 1-[4-(5-carboxyindol-3-yl)butyl]-4-(2,3-dihydrobinzofuran- 5-yl)piperidine

1-[4-(5-carbamoylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)piperidine, m.p. 155–157°;

from 1-[4-(5-carboxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)-4-hydroxypiperidine

1-[4-(5-carbamoylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)-4-hydroxypiperidine, m.p. 69° (dec.);

from 1-[4-(5-carboxyindol-3-yl)butyl]-4-(chroman-6-yl)-piperazine

1-[4-(5-carbamoylindol-3-yl)butyl]-4-(chroman-6-yl)-piperazine.

Example 4

Analogously to Example 3, starting from 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carboxybenzofuran-5-yl)piperazine reaction with 2-chloro-l-methylpyridinium methanesulfonate gives 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoylbenzofuran-5-yl)piperazine, m.p. 269–272° (hydrochloride).

Example 5

A mixture of 2.6 g of 3-(2-aminoethyl)-5-cyanoindole [obtainable by reaction of 5-cyanoindole with 2-chloroacetyl chloride to give 3-(2-chloroacetyl)-5-cyanoindole, subsequent reduction with diborane, reaction with phthalimide and hydrolysis]and one equivalent of 5-[N,N-bis(2-chloroethyl)amino]benzofuran [obtainable by reaction of 2-chloroacetyl chloride with 5-aminobenzofuran and subsequent reduction with diborane] in 40 ml of acetone and 40 ml of water is boiled for 20 hours and then worked up in the customary manner. 1-[2-(5-Cyanoindol-3-yl)ethyl]-4-(benzofuran-5-yl)piperazine is obtained.

The following are obtained analogously by reaction of 5-[N,N-bis(2-chloroethyl)amino]benzofuran with 3-(4-aminobutyl)-5-methoxymethylindole:

1-[4-(5-methoxymethylindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine; with 3-(3-aminopropyl) -5-hydroxyindole:

1-[3-(5-hydroxyindol-3-yl)propyl]-4-(benzofuran-5-yl)piperazine;

with 3-(2-aminoethyl)-5-methoxyindole:

1-[2-(5-methoxyindol-3-yl)ethyl]-4-(benzofuran-5-yl)piperazine;

with methyl 3-(3-aminopropyl)-5-indolecarboxylate:

1-[3-(5-methoxycarbonylindol-3-yl)propyl]-4-(benzofuran- 5-yl)piperazine;

with ethyl 3-(2-aminoethyl)-5-indolecarboxylate:

1-[2-(5-ethoxycarbonylindol-3-yl)ethyl]-4-(benzofuran-5-yl)piperazine;

with 3-(4-aminobutyl)-5-fluoroindole:

1-[4-(5-fluoroindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine;

with 3-(3-aminopropyl)-5-cyanoindole:

1-[3-(5-cyanoindol-3-yl)propyl]-4-(benzofuran- 5-yl)piperazine.

Example 6

Analogously to Example 5, reaction of 3.2 g of 3-(2-aminoethyl)-5-methoxyindole with 1.3 equivalents of 6-[N,N-bis(2-chloroethyl)amino]chroman [obtainable by reaction of 2-chloroacetyl chloride with 6-aminochroman and subsequent reduction with diborane] gives 1-[2-(5-methoxyindol-3-yl)ethyl]-4-(chroman-6-yl)piperazine.

The following are obtained analogously by reaction of 6-[N,N-bis(2-chloroethyl)amino]chroman with 3-(4-aminobutyl)-5-methoxymethylindole:

1-[4-(5-methoxymethylindol-3-yl)butyl]-4-(chroman-6-yl)piperazine;

with 3-(3-aminopropyl)-5-hydroxyindole:

1-[3-(5-hydroxyindol-3-yl)propyl]-4-(chroman-6-yl)-piperazine;

with 3-(2-aminoethyl)-5-methoxyindole:

1-[2-(5-methoxyindol-3-yl)ethyl]-4-(chroman-6-yl)piperazine;

with methyl 3-(3-aminopropyl)-5-indolecarboxylate:

1-[3-(5-methoxycarbonylindol-3-yl)propyl]-4-(chroman-6-yl)piperazine;

with ethyl 3-(2-aminoethyl)-5-indolecarboxylate:

1-[2-(5-ethoxycarbonylindol-3-yl)ethyl]-4-(chroman-6-yl)piperazine;

with 3-(4-aminobutyl)-5-fluoroindole:

1-[4-(5-fluoroindol-3-yl)butyl]-4-(chroman-6-yl)-piperazine;

with 3-(3-aminopropyl) -5-cyanoindole:

1-[3-(5-cyanoindol-3-yl) propyl]-4-(chroman-6-yl)piperazine.

Example 7

A solution of 3.9 g of 1-[4-(5-carboxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine in 250 ml of DMF is treated with 1 g of N-methylmorpholine. A solution of one equivalent of tert-butylamine in 5 ml of DMF, 1.3 g of 1-hydroxybenzotriazole and a solution of 1.9 g of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in 20 ml of DMF are added with stirring. The mixture is stirred at room temperature for 16 hours and the filtrate is evaporated. Customary working up gives 1-[4-(5-N-tert-butylcarbamoylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine.

The following are obtained analogously by reaction with tert-butylamine starting

from 1-[4-(5-carboxyindol-3-yl)butyl]-4-(chroman-6-yl)-piperazine:

1-[4-(5-N-tert-butylcarbamoylindol-3-yl)butyl]-4-(chroman-6-yl)piperazine:

from 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carboxybenzofuran- 5-yl)piperazine:

1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-N-tert-butyl-carbamoylbenzofuran- 5-yl)piperazine.

Example 8

A mixture of 2.1 g of 1-[4-(5-methoxyindol-3-yl)butyl]-4-(chroman-6-yl)piperazine [can be prepared according to Example 1], 1.8 g of pyridine hydrochloride and 50 ml of pyridine is boiled for 3 hours. It is cooled and evaporated, and the residue is worked up in the customary manner and gives 1-[4-(5-hydroxyindol-3-yl)-butyl]-4-(chroman-6-yl)piperazine, m.p. 220°–222°.

The following are obtained analogously

from 1-[4-(5-methoxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)piperazine:

1-[4-(5-hydroxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)piperazine;

from 1-[4-(5-methoxyindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine:

1-[4-(5-hydroxyindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine;

from 1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(chromen-4-on-6-yl)piperazine:

1-[4-(5-hydroxycarbonylindol-3-yl) butyl]-4-(chromen-4-on-6-yl) piperazine;

from 1-[4-(5-methoxymethylindol-3-yl)butyl]-4-(benzofuran- 5-yl)piperazine:

1-[4-(5-hydroxymethylindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine;

from 1-[2-(5-methoxyindol-3-yl)ethyl]-4-(benzofuran-5-yl)piperazine:

1-[2-(5-hydroxyindol-3-yl)ethyl]-4-(benzofuran-5-yl)piperazine;

from 1-[2-(5-methoxyindol-3-yl)ethyl]-4-(benzofuran-5-yl)piperazine:

1-[2-(5-hydroxyindol-3-yl)ethyl]-4-(benzofuran-5-yl)piperazine.

Example 9

Analogously to Example 1, starting from 3-(4-chlorobutyl)-5-cyanoindole [obtainable by reaction of 5-cyanoindole with 4-chlorobutyryl chloride to give 3-(4-chlorobutyryl)-5-methoxyindole and subsequent reduction with $NaAlH_2(OCH_2CH_2OCH_3)_2$] by reaction with 1-(2-ethoxycarbonylbenzofuran-5-yl)piperazine [obtainable by reaction of N,N-bis(2-chloroethyl)amine with 2-ethoxy-carbonyl-5-aminobenzofuran] gives, after customary working up, 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-ethoxy-carbonylbenzofuran- 5-yl)piperazine, m.p. 221°–223° (dihydrochloride).

The following are obtained analogously by reaction of 3-(4-chlorobutyl)-5-methoxyindole with 1-(2-cyano-benzofuran- 5-yl)piperazine:

1-[4-(5-methoxyindol-3-yl)butyl]-4-(2-cyanobenzofuran-5-yl)piperazine;

of 3-(4-chlorobutyl)-5,6-dimethoxyindole with 1-(chroman-6-yl) piperazine:

1-[4-(5,6-dimethoxyindol-3-yl)butyl]-4-(chroman-6-yl)piperazine;

of 3-(4-chlorobutyl)-5,6-difluoroindole with 1-(chroman-6-yl)piperazine:

1-[4-(5,6-difluoroindol-3-yl)butyl]-4-(chroman-6-yl)piperazine;

of methyl 3-(4-chlorobutyl)-6-indolecarboxylate with 1-(chroman-6-yl)piperazine:

1-[4-(6-methoycarbonylindol-3-yl)butyl]-4-(chroman-6-yl)piperazine;

of ethyl 3-(3-chloropropyl)-6-indolecarboxylate with 1-(2-cyanobenzofuran-5-yl)piperazine:

1-[3-(6-ethoxycarbonylindol-3-yl)propyl]-4-(2-cyanobenzofuran- 5-yl)piperazine;

of 3-(4-chlorobutyl)-5-methoxyindole with 1-(2-N-methylcarbamoylbenzofuran- 5-yl)piperazine:

1-[4-(5-methoxyindol-3-yl)butyl]-4-(2-N-methylcarbamoylbenzofuran- 5-yl)piperazine;

of 3-(4-chlorobutyl)-6-chloroindole with 1-(chromen-4-on-6-yl)piperazine:

1-[4-(6-chloroindol-3-yl)butyl]-4-(chromen-4-on-6-yl)piperazine;

of 3-(2-chloroethyl)-5-cyanoindole with 1-(chromen-4-on-6-yl)piperazine:

1-[2-(5-cyanoindol-3-yl)ethyl]-4-(chromen-4-on-6-yl)piperazine;

of 3-(2-chloroethyl)-5,6-dichloroindole with 1-(2,3-dihydrobenzofuran- 5-yl)piperazine:

1-[2-(5,6-dichloroindol-3-yl)ethyl]-4-(2,3-dihydrobenzofuran- 5-yl)piperazine;

of 3-(4-chlorobutyl)-5-methoxycarbonylindole with 1-(2-carboxybenzofuran-5-yl)piperazine:

1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(2-carboxybenzofuran- 5-yl)piperazine;

of 3-(2-chloroethyl)-5-methoxycarbonylindole with 4-(2-carboxybenzofuran-5-yl)piperidine:

1-[2-(5-methoxycarbonylindol-3-yl)ethyl]-4-(2-carboxybenzofuran- 5-yl)piperazine;

of 3-(4-chlorobutyl)-6-methoxycarbonylindole with 4-(3-carboxybenzofuran-5-yl)-4-hydroxypiperidine:

1-(4-(6-methoxycarbonylindol-3-yl)butyl]-4-(3-carboxybenzofuran- 5-yl)-4-hydroxypiperidine;

of 3-(4-chlorobutyl)-7-methoxycarbonylindole with 4-(3-carboxybenzofuran-5-yl)-4-hydroxypiperidine;

1-[4-(7-methoxycarbonylindol-3-yl)butyl]-4-(3-carboxybenzofuran- 5-yl)-4-hydroxypiperidine;

of 3-(4-chlorobutyl)-5,6-dimethoxyindole with 1-(2-carboxybenzofuran- 5-yl)piperazine:

1-[4-(5,6-dimethoxyindol-3-yl)butyl]-4-(2-carboxybenzofuran- 5-yl)piperazine.

Example 10

A solution of 3.6 g of 1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(chromen-4-on-6-yl)piperazine in 40 ml of THF is added dropwise with stirring at room temperature to a suspension of 0.6 g of lithium aluminum hyride in 20 ml of THF. The mixture is then stirred for a further hour at 25° C., 20 ml of dilute sodium hydroxide solution are added, the mixture is filtered and the filtrate is worked up in the customary manner. 1-[4-(5-Hydroxymethylindol-3-yl)butyl] -4-(chromen-4-on-6-yl)piperazine is obtained.

The following are obtained analagously by reduction of 1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(chroman-6-yl)piperazine

1-[4-(5-hydroxymethylindol-3-yl)butyl]-4-(chroman-6-yl)piperazine;

of 1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-benzofuran-5yl)piperazine

1-[4-(5-hydroxymethylindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine;

of 1-[3-(5-methoxycarbonylindol-3-yl)propyl]-4-(chroman-6-yl) piperidine

1-[3-(5-hydroxymethylindol-3-yl)propyl]-4-(chroman-6-yl)piperidine

of 1-[2-(5-methoxycarbonylindol-3-yl)ethyl]-4-chroman-6-yl) piperidine

1-[2-(5-hydroxymethylindol-3-yl)ethyl]-4-(chroman-6-yl)piperidine.

Example 11

HCl gas is passed into a boiling solution of 2.5 g of 1-[4-(5-carboxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)piperazine in 50 ml of absolute methanol for 2 hours. The mixture is then boiled for a further hour, worked up in the customary manner and gives 1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)piperazine.

The following are obtained analagously by esterification of 1-[4-(5-carboxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)-4-hydroxypiperidine:

1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)-4-hydroxypiperidine;

of 1-[4-(5-carboxyindol-3-yl)butyl]-4-(chroman-6-yl)-piperazine:

1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(chroman-6-yl)piperazine;

of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carboxybenzofuran-5-yl)piperazine:

1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-methoxycarbonylbenzofuran- 5-yl)piperazine.

Example A

Injection vials

A solution of 100 g of an active ingredient of the formula I and 5 g of disodium hydrogen phosphate in 3 l of double-distilled water is adjusted to pH 6.5 with 2N hydrochloric acid, sterile-filtered, filled into injection vials, lyophilized and sterile-sealed. Each injection vial contains 5 mg of active ingredient.

Example B

Suppositories

A mixture of 20 mg of an active ingredient of the formula I is melted with 100 g of soya lecithin and 1,400 g of cocoa butter, poured into moulds and allowed to cool. Each suppository contains 20 mg of active ingredient.

Example C

Solution

A solution of 1 g of an active ingredient of the formula I, 9.38 g of $NaH_2PO_4 \times 2H_2O$, 28.48 g $Na_2HPO_4 \times 12\ H_2O$ and 0.1 g of benzalkonium chloride is prepared in 940 ml of double-distilled water. The pH is adjusted to 6.8, and the solution is made up to 1 l and sterilized by irradiation. This solution can be used in the form of eyedrops.

Example D

Ointment

500 mg of an active ingredient of the formula I are mixed with 99.5 g of petroleum jelly under aseptic conditions.

Example E

Tablets

A mixture of 1 kg of active ingredient of the formula I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is compressed to tablets in conventional manner so that each tablet contains 10 mg of active ingredient.

Example F

Coated tablets

Tablets are formed by compression analogously to Example E and then covered in conventional manner with a coating of sucrose, potato starch, talc, tragacanth and colorant.

Example G

Capsules

2 kg of active ingredient of the formula I are filled into hard gelatin capsules in conventional manner so that each capsule contains 20 mg of the active ingredient.

Example H

Ampoules

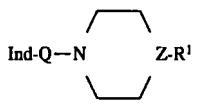
A solution of 1 kg of active ingredient of the formula I in 60 l of double-distilled water is filled into ampoules and lyophilized under aseptic conditions and the ampoules are sealed under sterile conditions. Each ampoule contains 10 mg of active ingredient.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

What is claimed is:

1. A compound according to formula I



I

wherein

Ind is unsubstituted indol-3-yl, indol-3-yl monosubstituted by OH, OA, CN, Hal, COR^2 or CH_2R^2, or indol-3-yl polysubstituted by OH, OA, CN, Hal, COR^2, CH_2R^2 or combinations thereof;

R^1 is benzofuran-5-yl, chroman-4-on-6-yl, 3-chromen-6-yl or chromen-4-on-6-yl, which in each case is unsubstituted or monosubstituted by CN, CH_2OH, CH_2OA or COR^2;

Q is C_mH_{2m};

Z is N;

A is alkyl having 1–6 C atoms;

Hal is F, Cl, Br or I;

R^2 is OH, OA, NH_2, NHA or NA_2;

$R^3$is H, OH or OA; and

m is 2, 3 or 4; or

a physiologically acceptable salt thereof.

2. A compound according to claim **1**, wherein said compound is:

(a) 1-[4-(5-methoxyindol-3-yl)butyl]-4-(2-hydroxymethylbenzofuran- 5-yl)piperazine or a physiologically acceptable salt thereof;

(b) 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-ethoxycarbonylbenzofuran- 5-yl) piperazine or a physiologically acceptable salt thereof; or

(c) 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoylbenzofuran- 5-yl) piperazine or a physiologically acceptable salt thereof.

3. A compound according to claim **1**, wherein Ind is unsubstituted indol-3-yl, indol-3-yl monosubstituted by OH, OA, CN, Hal, COR^2 or CH_2R^2, or indol-3-yl disubstituted by OH, OA, CN, Hal, COR^2 or CH_2R^2.

4. A compound according to claim **1**, wherein Ind is indol-3-yl monosubstituted in the 5-position by OH, OA, CN, Hal, COR^2 or CH_2R^2.

5. A compound according to claim 1, wherein Ind is indol-3-yl monosubstituted in the 4-, 6- or 7-position by OH, OA, CN, Hal, COR^2 or CH_2R^2.

6. A compound according to claim 1, wherein A is methyl or ethyl.

7. A compound according to claim 1, wherein R^1 is benzofuran-5-yl, or chroman-4-on-6-yl which, in each case is unsubstituted or monosubstituted by $—CH_2OH$, $—CONH_2$, $—CO_2A$ or $—CO_2NHA$.

8. A compound according to claim 1, wherein Q is $—(CH_2)_4—$.

9. A compound according to claim 1, wherein Ind is indol-3-yl substituted in the 5-position by OH or OA.

10. A compound according to claim 1, wherein Ind is indol-3-yl substituted in the 5-position by $CONH_2$ or CN.

11. A compound according to claim 1, wherein R^1 is unsubstituted benzofuran-5-yl or benzofuran-5-yl substituted by CN, CH_2OH, CH_2OA or COR^2.

12. A compound according to claim 1, wherein R^1 is chromen-4-on-6-yl.

13. A compound according to claim 1, wherein R^1 is unsubstituted 3-chromen-6-yl or 3-chromen-6-yl substituted by CN, CH_2OH, CH_2OA or COR^2.

14. A compound according to claim 1, wherein R^1 is unsubstituted chroman-4-on-6-yl or chroman-4-on-6-yl substituted by CN, CH_2OH, CH_2OA or COR^2.

15. A compound according to claim 1, wherein R^1 is unsubstituted chromen-4-on-6-yl or chromen-4-on-6-yl substituted by CN, CH_2OH, CH_2OA or COR^2.

16. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

17. A composition according to claim 16, wherein said compound is present in an amount of 0.2–500 mg.

* * * * *

EXHIBIT 2

Executed Assignment

MERCK 1617

ASSIGNMENT

WHEREAS the below named inventor (if only one inventor is named below) or inventors (if plural inventors are named below) hereinafter referred to as the ASSIGNOR invented a certain improvement relating to

PIPERIDINES AND PIPERAZINES

☒ for which an application for Letters Patent to be filed in the United States Patent and Trademark Office was executed on even date.

☒ for which U.S. Application Serial No. 08/314,734 for Letters Patent was filed in the U.S. Patent and Trademark Office on _____

☐ for which an International Application was filed on _____ PCT/ /
designating the United States

AND WHEREAS

MERCK PATENT GESELLSCHAFT MIT BESCHRÄNKTER HAFTUNG,
D-64271 Darmstadt, Fed. Rep. of Germany

hereinafter referred to as the ASSIGNEE, is desirous of acquiring the entire right, title, and interest in and to said invention and application, including any and all divisions and continuations thereof, and any and all Letters Patent which may be granted thereon, including any and all renewals, reissues, and prolongations thereof.

NOW, THIS WITNESSETH that for good and valuable consideration, the receipt whereof is hereby acknowledged, ASSIGNOR hereby assigns, sells, and transfers to ASSIGNEE, its assigns and legal representatives, the entire and exclusive right, title, and interest in and to said invention and application, including any and all divisions and continuations thereof, and any and all Letters Patent which may be granted therefor, including any and all renewals, reissues, and prolongations thereof, ASSIGNEE, its assigns and legal representatives to have, hold, exercise, and enjoy said invention and application, including any and all divisions and continuations thereof, and any and all Letters Patent which may be granted therefor, including any and all renewals, reissues, and prolongations thereof, with all the rights, powers, privileges and advantages in anywise arising from or appertaining thereto, for and during the term or terms of any and all such Letters Patent when granted, including any and all renewals, reissues, prolongations thereof, for the use and benefit of ASSIGNEE and its assigns and legal representatives, in as ample and beneficial a manner to all intents and purposes as the ASSIGNOR might or could have held and enjoyed the same, if the assignment had not been made.

AND ASSIGNOR hereby agrees to execute all papers that may be necessary to file applications in the United States for said invention and to assign the same to said ASSIGNEE, its assigns and legal representatives and to execute any other papers that may be needed in connection with filing said application and securing a Letters Patent thereon.

AND ASSIGNOR authorizes and requests the Commissioner of Patents and Trademarks to issue a Letters Patent on said application, and on any and all divisions and continuations thereof, to ASSIGNEE, its assigns and legal representatives, in accordance herewith.

The undersigned hereby grant(s) the law firm of Millen, White, Zelano & Branigan, P.C. the power to insert on this assignment any further identification which may be necessary or desirable in order to comply with the rules of the United States Patent and Trademark Office for recordation of this document.

IN TESTIMONY WHEREOF this assignment is executed by ASSIGNOR.

	FULL NAME OF SOLE OR FIRST NAMED INVENTOR	INVENTOR'S SIGNATURE	DATE
201	Henning BÖTTCHER		September 20, 1994
202	FULL NAME OF SECOND JOINT INVENTOR, IF ANY Christoph SEYFRIED	INVENTOR'S SIGNATURE	DATE September 20, 1994
203	FULL NAME OF THIRD JOINT INVENTOR, IF ANY Gerd BARTOSZYK	INVENTOR'S SIGNATURE	DATE September 20, 1994
204	FULL NAME OF FOURTH JOINT INVENTOR, IF ANY Hartmut GREINER	INVENTOR'S SIGNATURE	DATE September 20, 1994
205	FULL NAME OF FIFTH JOINT INVENTOR, IF ANY	INVENTOR'S SIGNATURE	DATE
206	FULL NAME OF SIXTH JOINT INVENTOR, IF ANY	INVENTOR'S SIGNATURE	DATE
207	FULL NAME OF SEVENTH JOINT INVENTOR, IF ANY	INVENTOR'S SIGNATURE	DATE
208	FULL NAME OF EIGHTH JOINT INVENTOR, IF ANY	INVENTOR'S SIGNATURE	DATE
209	FULL NAME OF NINTH JOINT INVENTOR, IF ANY	INVENTOR'S SIGNATURE	DATE
210	FULL NAME OF TENTH JOINT INVENTOR, IF ANY	INVENTOR'S SIGNATURE	DATE
211	FULL NAME OF ELEVENTH JOINT INVENTOR, IF ANY	INVENTOR'S SIGNATURE	DATE
212	FULL NAME OF TWELFTH JOINT INVENTOR, IF ANY	INVENTOR'S SIGNATURE	DATE

MWZ 16a

EXHIBIT 3

Letter on Behalf of the Marketing Applicant Authorizing the Patent Owner to Rely upon the Activities of the Marketing Applicant

TROVIS PHARMACEUTICALS
Uncovering the possibilities.

One Gateway Center, Suite 702
Newton, MA 02458

TEL 617 527 9933
FAX 617 965 0445

WWW.TROVISPHARMA.COM

March 14, 2011

VIA HAND DELIVERY

Mary C. Till
Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
For Patent Examination Policy
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Re: *Patent Term Extension for U.S. Patent No. 5,532,241*

Dear Ms. Till:

On behalf of Trovis Pharmaceuticals LLC, Marketing Applicant for New Drug Application No. 22-567 for VIIBRYD™ (vilazodone hydrochloride), its predecessors and affiliates, I hereby authorize the patent owner of record, Merck Patent GmbH, in connection with its application for extension of U.S. Patent No. 5,532,241 to rely upon the activities of Trovis Pharmaceuticals LLC, its predecessors and affiliates, undertaken in connection with seeking approval by the Food and Drug Administration of NDA No. 22-567. Trovis Pharmaceuticals LLC is a licensee of Merck KGaA, of which Merck Patent GmbH is the trustee with respect to patent matters, under this patent.

Respectfully Submitted,

Caesar J. Belbel
EVP & Chief Legal Officer

EXHIBIT 4

Power of Attorney

MERCK

Merck Patent GmbH · Germany · Frankfurter Str. 250 · 64293 Darmstadt

Mary C. Till
Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
For Patent Examination Policy
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
USA

Date	March 16, 2011
Division/Dept.	Patents Pharmaceuticals
Care of	Dr. Bauer
Phone	+ 49 6151 72-21 04
Fax	+ 49 6151 72-71 91
E-Mail	patent@merck.de
Your letter	
Your ref.	

VIA HAND DELIVERY

Re: Patent Term Extension for U.S. Patent No. 5,532,241

Dear Ms. Till:

This is to advise you that, as authorized representatives of Merck Patent GmbH ("Merck"), owner of U.S. Patent No. 5,532,241 ("the '241 patent"), we hereby authorize Trovis Pharmaceuticals LLC, a subsidiary of Clinical Data, Inc., of One Gateway Center, Suite 702, Newton, MA ("Trovis") to file and prosecute the patent term extension application pursuant to 35 U.S.C. §156 for the '241 patent ("the Application") on behalf of Merck, pursuant to 37 CFR §1.730(c). We understand that counsel for McCarter & English, 265 Franklin Street, Boston, MA, and Scott A.M. Chambers, counsel for Patton Boggs LLP, 8484 Westpark Drive, 9th Floor, McLean, Virginia 22102 will file and prosecute the Application as Trovis' representative, pursuant to 37 CFR §1.730(c), and hereby grant McCarter & English and Patton Boggs LLP any authorizations from Merck necessary for McCarter and English and Patton Boggs LLP to act in this capacity.

Respectfully Submitted,

Merck Patent GmbH

i.V.
Dr. Bauer

i.V.
Dr. Wodopia

Merck Patent GmbH
Postfach · 64271 Darmstadt
Frankfurter Straße 250 · 64293 Darmstadt
Telefon 06151/72-0
Telefax 06151/72-7191

Bankkonto:
103648 Deutsche Bank AG,
Filiale Darmstadt (BLZ 508 700 05)

Geschäftsführer:
Dr. Wolfgang Losert
Sitz der Gesellschaft: Darmstadt

EXHIBIT 5

Approved Label

VIIBRYD™ (vilazodone hydrochloride) Tablets

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

VIIBRYD (vilazodone HCl) Tablets for oral administration
Initial U.S. Approval: 2011

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

See full prescribing information for complete boxed warning.
Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders (5.1).
VIIBRYD is not approved for use in pediatric patients (8.4).

INDICATIONS AND USAGE

VIIBRYD is indicated for the treatment of major depressive disorder (MDD). The efficacy of VIIBRYD was established in two 8-week, placebo-controlled trials in adult patients with MDD (1, 14).

DOSAGE AND ADMINISTRATION

- The recommended dose for VIIBRYD is 40 mg once daily (2).
- VIIBRYD should be titrated to the 40 mg dose, starting with an initial dose of 10 mg once daily for 7 days, followed by 20 mg once daily for an additional 7 days, and then increased to 40 mg once daily (2).
- VIIBRYD should be taken with food. Administration without food can result in inadequate drug concentrations and may diminish effectiveness (2, 12.3).
- When discontinuing treatment, reduce the dose gradually (2.4).

DOSAGE FORMS AND STRENGTHS

VIIBRYD is available as 10 mg, 20 mg and 40 mg tablets (3).

CONTRAINDICATIONS

- **Monoamine Oxidase Inhibitors**: Do not use VIIBRYD concomitantly with an MAOI or within 14 days of stopping or starting an MAOI (4.1).

WARNINGS AND PRECAUTIONS

Clinical Worsening/Suicide Risk: Monitor patients for clinical worsening and suicidal thinking or behavior (5.1).
Serotonin Syndrome or Neuroleptic Malignant (NMS)-like Syndrome: Can occur with treatment. Discontinue and initiate supportive treatment (5.2).
Seizures: Can occur with treatment. Use with caution in patients with a seizure disorder (5.3).
Abnormal Bleeding: Treatment can increase the risk of bleeding. Use with caution in association with nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, or other drugs that affect coagulation (5.4).
Activation of Mania/Hypomania: Can occur with treatment. Screen patients for bipolar disorder (5.5).
Discontinuation of Treatment with VIIBRYD: A gradual reduction in dose is recommended rather than an abrupt cessation (5.6).
Hyponatremia: Can occur in association with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) (5.7).

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥ 5% and at least twice the rate of placebo) are: diarrhea, nausea, vomiting, and insomnia (6).
To report SUSPECTED ADVERSE REACTIONS, contact Trovis Pharmaceuticals at 1-877-878-7200 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

MAOIs: Do not use VIIBRYD concomitantly with an MAOI or within 14 days of stopping or starting an MAOI (4.1, 7.1).
CYP3A4 inhibitors: The VIIBRYD dose should be reduced to 20 mg when co-administered with CYP3A4 strong inhibitors (7.3).
CYP3A4 inducers: Concomitant use of VIIBRYD with inducers of CYP3A4 can result in inadequate drug concentrations and may diminish effectiveness. The effect of CYP3A4 inducers on systemic exposure of vilazodone has not been evaluated (7.3).

USE IN SPECIFIC POPULATIONS

Pregnancy: There are no controlled human data regarding VIIBRYD use during pregnancy. Use only if the potential benefits outweigh the potential risks (2.3, 8.1).
Nursing Mothers: There are no human data regarding VIIBRYD concentrations in breast milk. Women should breast feed only if the potential benefits outweigh the potential risks (8.3, 2.3).
Pediatric Use: The safety and efficacy of VIIBRYD in pediatric patients have not been studied (8.4).
Geriatric Use: No dose adjustment is recommended on the basis of age (8.5).
Hepatic Impairment: No dose adjustment is recommended in patients with mild or moderate hepatic impairment. VIIBRYD has not been studied in patients with severe hepatic impairment (8.6).
Renal Impairment: No dose adjustment is recommended in patients with mild, moderate, or severe renal impairment. (8.7).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: January 2010

FULL PRESCRIBING INFORMATION: CONTENTS*

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

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of VIIBRYD or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. VIIBRYD is not approved for use in pediatric patients [*see Warnings and Precautions (5.1), Use in Specific Populations (8.4), and Patient Counseling Information (17.1)*]

1 INDICATIONS AND USAGE

VIIBRYD is indicated for the treatment of major depressive disorder (MDD). The efficacy of VIIBRYD was established in two 8-week, randomized, double-blind, placebo-controlled trials in adult patients with a diagnosis of MDD *[see Clinical Studies (14)]*.

Major depressive disorder consists of one or more major depressive episodes. A major depressive episode (DSM-IV-TR) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, or a suicide attempt or suicidal ideation.

2 DOSAGE AND ADMINISTRATION

2.1 Initial Treatment of Major Depressive Disorder

The recommended dose for VIIBRYD is 40 mg once daily. VIIBRYD should be titrated, starting with an initial dose of 10 mg once daily for 7 days, followed by 20 mg once daily for an additional 7 days, and then an increase to 40 mg once daily. VIIBRYD should be taken with food. VIIBRYD blood concentrations (AUC) in the fasted state can be decreased by approximately 50% compared to the fed state, and may result in diminished effectiveness in some patients *[see Pharmacokinetics (12.3)]*.

2.2 Maintenance/Continuation/Extended Treatment

The efficacy of VIIBRYD has not been systematically studied beyond 8 weeks. It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Patients should be reassessed periodically to determine the need for maintenance treatment and the appropriate dose for treatment.

2.3 Dosing in Special Populations

Pregnant Women: Neonates exposed to serotonergic antidepressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. When treating pregnant women with VIIBRYD, consider whether the potential benefits outweigh the potential risks of treatment *[see Pregnancy (8.1)]*.

Nursing Mothers: There are no clinical data regarding the effect of VIIBRYD on lactation and nursing *[see Nursing Mothers (8.3)]*. Breastfeeding in women treated with VIIBRYD should be considered only if the potential benefit outweighs the potential risk.

Pediatric Patients: The safety and efficacy of VIIBRYD have not been studied in pediatric patients *[see Pediatric Use (8.4)]*.

Geriatric Patients: No dose adjustment is recommended on the basis of age *[see Geriatric Use (8.5)]*.

Hepatic Impairment: No dose adjustment is recommended in patients with mild or moderate hepatic impairment. VIIBRYD has not been studied in severe hepatic impairment *[see Hepatic Impairment (8.6)]*.

Renal Impairment: No dose adjustment is recommended in patients with mild, moderate, or severe renal impairment. *[see Renal Impairment (8.7)]*.

Gender: No dose adjustment is recommended on the basis of gender *[see Gender Effect (8.8)]*.

2.4 Discontinuing Treatment

Discontinuation symptoms have been reported with discontinuation of serotonergic drugs such as VIIBRYD. Gradual dose reduction is recommended, instead of abrupt discontinuation, whenever possible. Monitor patients for these symptoms when discontinuing VIIBRYD. If intolerable symptoms occur following a dose decrease or upon discontinuation of treatment, consider resuming the previously prescribed dose and decreasing the dose at a more gradual rate *[see Warnings and Precautions (5.6)]*.

2.5 Monoamine Oxidase Inhibitors (MAOI)

At least 14 days must elapse between discontinuation of an MAOI and initiation of therapy with VIIBRYD. In addition, at least 14 days must be allowed after stopping VIIBRYD before starting an MAOI *[see Contraindications (4.1)]*.

3 DOSAGE FORMS AND STRENGTHS

VIIBRYD Tablets are available as 10 mg, 20 mg and 40 mg immediate-release, film-coated tablets.
10 mg pink, oval tablet, debossed with 10 on one side
20 mg orange, oval tablet, debossed with 20 on one side
40 mg blue, oval tablet, debossed with 40 on one side

4 CONTRAINDICATIONS

4.1 Monoamine Oxidase Inhibitors

VIIBRYD must not be used concomitantly in patients taking MAOIs or in patients who have taken MAOIs within the preceding 14 days due to the risk of serious, sometimes fatal, drug interactions with serotonergic drugs. These interactions have been associated with symptoms that include tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, rigidity, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Allow at least 14 days after stopping VIIBRYD before starting an MAOI *[see Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled studies of antidepressant drugs (selective serotonin reuptake inhibitors [SSRIs] and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with MDD and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled studies in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term studies of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled studies in adults with MDD or other psychiatric disorders included a total of 295 short-term studies (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric studies. There were suicides in the adult studies, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms [*see Warnings and Precautions (5.6) and Dosage and Administration (2.4)*].

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as

the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for VIIBRYD should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose *[see also Patient Counseling Information (17.1)]*.

Screening patients for bipolar disorder
A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled studies) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that VIIBRYD is not approved for use in treating bipolar depression.

5.2 Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions
The development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions has been reported with antidepressants alone, but particularly with concomitant use of serotonergic drugs (including triptans) with drugs that impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. Symptoms of serotonin syndrome were noted in 0.1% of patients treated with VIIBRYD. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome, in its most severe form can resemble NMS, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.

The concomitant use of VIIBRYD with MAOIs intended to treat depression is contraindicated. *[see Contraindications (4.1)]*.

If concomitant treatment of VIIBRYD with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases *[see Drug Interactions (7.1)]*.

The concomitant use of VIIBRYD with serotonin precursors (such as tryptophan) is not recommended *[see Drug Interactions (7.1)]*.

Treatment with VIIBRYD and any concomitant serotonergic (SSRI, serotonin–norepinephrine reuptake inhibitor [SNRI], triptan, buspirone, tramadol, etc.) or antidopaminergic drugs, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

5.3 Seizures
VIIBRYD has not been systematically evaluated in patients with a seizure disorder. Patients with a history of seizures were excluded from clinical studies. Like other antidepressants, VIIBRYD should be prescribed with caution in patients with a seizure disorder.

5.4 Abnormal Bleeding
The use of drugs that interfere with serotonin reuptake inhibition, including VIIBRYD, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDS), warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of VIIBRYD and NSAIDs, aspirin, or other drugs that affect coagulation or bleeding.

5.5 Activation of Mania/Hypomania
Symptoms of mania/hypomania were reported in 0.1% of patients treated with VIIBRYD in clinical studies. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other antidepressants. As with all antidepressants, use VIIBRYD cautiously in patients with a history or family history of bipolar disorder, mania, or hypomania.

5.6 Discontinuation of Treatment with VIIBRYD
There have been reports of adverse events occurring upon discontinuation of serotonergic antidepressants, particularly when discontinuation is abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesia, such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Monitor patients for these symptoms when discontinuing VIIBRYD. Reduce the dose gradually whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, consider resuming the previously prescribed dose. Subsequently, the dose may be decreased, but at a more gradual rate *[see Dosage and Administration, (2.4)]*.

5.7 Hyponatremia
Although no cases of hyponatremia resulting from VIIBRYD treatment were reported in the clinical studies, hyponatremia has occurred as a result of treatment with SSRIs and SNRIs. In many cases, hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs. Also, patients taking diuretics or who are otherwise volume depleted can be at greater risk. Discontinuation of VIIBRYD in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which can lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience
The most commonly observed adverse reactions in VIIBRYD-treated MDD patients in placebo-controlled studies (incidence ≥ 5% and at least twice the rate of placebo) were: diarrhea, nausea, vomiting, and insomnia.

Patient Exposure

The safety of VIIBRYD was evaluated in 2,177 patients (18-70 years of age) diagnosed with MDD who participated in clinical studies, representing 552 patient-years of exposure. In an open-label 52 week study at 40 mg daily, 599 patients were exposed to VIIBRYD for a total of 348 patient-years.

The information presented in these sections was derived from studies of VIIBRYD 40 mg daily in major depressive disorder including: 1) 2 placebo-controlled 8-week studies in 861 patients, including 436 receiving vilazodone; and 2) an open-label 52-week study of 599 patients. These studies included a titration period of 10 mg daily for 7 days followed by 20 mg daily for 7 days. In these clinical trials, VIIBRYD was administered with food.

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

Adverse reactions reported as reasons for discontinuation of treatment
In the placebo-controlled studies of MDD there was no single adverse reaction leading to discontinuation in > 1% of the patients. Overall, 7.1% of the patients who received VIIBRYD discontinued treatment due to an adverse reaction, compared with 3.2% of placebo-treated patients in these studies.

Common adverse reactions in placebo-controlled MDD studies
Table 2 shows the incidence of common adverse reactions that occurred in ≥ 2% of VIIBRYD-treated MDD patients (and greater than in placebo-treated patients) in the placebo-controlled studies.

Table 2: Common Adverse Reactions Occurring in ≥2% of VIIBRYD-treated Patients and > Placebo-treated Patients

System Organ Class Preferred Term	VIIBRYD 40 mg/day N = 436	Placebo N = 433
Gastrointestinal disorders		
Diarrhea	28	9
Nausea	23	5
Dry mouth	8	5
Vomiting	5	1
Dyspepsia	3	2
Flatulence	3	2
Gastroenteritis	3	<1
Nervous system disorders		
Dizziness	9	5
Somnolence	3	2
Paresthesia	3	1
Tremor	2	0
Psychiatric disorders		
Insomnia	6	2
Abnormal dreams	4	1
Libido decreased	4	<1
Restlessness *	3	<1
Orgasm abnormal**	3	0
General disorders		
Fatigue	4	3
Feeling jittery	2	<1
Cardiac disorders		
Palpitations	2	<1
Musculoskeletal and connective tissue disorders		
Arthralgia	3	2
Reproductive system and breast disorders		
Delayed ejaculation***	2	0
Erectile dysfunction***	2	1
Metabolism and nutrition disorders		

Increased appetite	2	1

*Includes restlessness, akathisia, and restless legs syndrome

**Includes orgasm abnormal and anorgasmia

***Male patients only (Placebo n=182; VIIBRYD n=170)

Table 3: Sexual Adverse Reactions: Percentage in the Placebo-Controlled Studies

	Males		Females	
Preferred Term	VIIBRYD N= 170	Placebo N= 182	VIIBRYD N=266	Placebo N=251
Decreased libido	5	0	3	<1
Abnormal orgasm*	4	0	2	0
Delayed ejaculation	2	0	–	–
Erectile dysfunction	2	1	–	–
Sexual dysfunction	2	0	<1	<1

– Not applicable
*Includes anorgasmia

Laboratory Tests
VIIBRYD has not been associated with any clinically important changes in laboratory test parameters in serum chemistry (including liver function tests), hematology and urinalysis, as measured in placebo-controlled studies. These studies include analysis of (1) mean change from baseline and (2) the proportion of patients meeting criteria for potentially clinically significant changes from baseline. Results from a 52-week open-label study were consistent with the findings from the placebo-controlled studies.

ECG
VIIBRYD has not been associated with any clinically significant effect on ECG parameters, including QT, QTc, PR and QRS intervals, or with any arrhythmogenic potential. ECGs were evaluated in a thorough QTc study at doses up to 80 mg daily with food and in the placebo-controlled studies *[see Pharmacodynamics (12.2)]*.

Vital Signs
VIIBRYD has not been associated with any clinically significant effect on vital signs, including systolic and diastolic blood pressure and heart rate, as measured in placebo-controlled studies. These studies included analyses of (1) change from baseline, and (2) the proportion of patients meeting criteria for potentially clinically significant changes from baseline. Results from a 52-week open-label study were consistent with the findings from the placebo-controlled studies.

Weight
VIIBRYD had no effect on body weight as measured by the mean change from baseline in the 8-week, placebo-controlled studies. The mean changes in weight were +0.16 kg in the VIIBRYD group and +0.18 kg in the placebo group. The proportions of patients with a weight gain $\geq$ 7% were 0.9% in the VIIBRYD group and 1.2% in the placebo group. The proportions of patients with a weight decrease $\geq$ 7% were 1.4% in the VIIBRYD group and 1.4% in the placebo group.

Other adverse reactions observed in clinical studies
The following listing does not include reactions: 1) already listed in previous tables or elsewhere in labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, 4) which were not considered to have significant clinical implications, or 5) which occurred at a rate equal to or less than placebo.

Reactions are categorized by body system according to the following definitions: *frequent* adverse reactions are those occurring in at least 1/100 patients; *infrequent* adverse reactions are those occurring in 1/100 to 1/1000 patients; *rare* reactions are those occurring in fewer than 1/1000 patients:

Cardiac disorders: *infrequent*: ventricular extrasystoles

Eye disorders: *frequent:* vision blurred, dry eye; *infrequent:* cataracts

General disorders: *infrequent*: feeling abnormal

Metabolism and nutrition disorders: *frequent*: decreased appetite

Nervous System: *frequent*: sedation, migraine; *infrequent*: dysgeusia

Psychiatric disorders: *infrequent*: panic attack, mania

Renal and Urinary disorder: *infrequent*: pollakiuria

Skin and subcutaneous tissue disorders: *frequent*: hyperhidrosis, night sweats

7 DRUG INTERACTIONS

7.1 Central Nervous System (CNS)-Active Agents
The risk of using VIIBRYD in combination with other CNS-active drugs has not been systematically evaluated. Consequently, use caution when VIIBRYD is prescribed in combination with other CNS-active drugs.

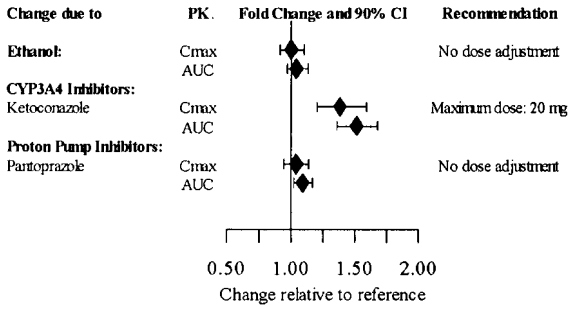
Monoamine Oxidase Inhibitors (MAOI)
Adverse reactions, some of which are serious or fatal, can develop in patients who use MAOIs or who have recently been discontinued from a MAOI and started on antidepressant(s) with pharmacological properties similar to VIIBRYD (e.g. SSRIs), or who have recently had SSRI therapy discontinued prior to initiation of an MAOI. Do not prescribe VIIBRYD concomitantly with an MAOI or within 14 days of discontinuing or starting an MAOI *[see Contraindications (4.1)]*.

Serotonergic Drugs
Based on the mechanism of action of VIIBRYD and the potential for serotonin toxicity, also known as serotonin syndrome, caution is advised when VIIBRYD is coadministered with other drugs that may affect the serotonergic neurotransmitter systems (e.g., MAOI, SSRIs, SNRIs, triptans, buspirone, tramadol, and tryptophan products etc.) *[see Warnings and Precautions (5.2)]*.

7.2 Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)
Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of case-control and cohort design have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when VIIBRYD is initiated or discontinued *[see Abnormal Bleeding (5.4)]*.

7.3 Potential for Other Drugs to Affect Vilazodone

Figure 1. Impact of other drugs on Vilazodone PK



Inhibitors of CYP3A4
Metabolism by CYP3A4 is a major elimination pathway for vilazodone. Concomitant use of VIIBRYD and strong inhibitors of CYP3A4 (e.g., ketoconazole) can increase vilazodone plasma concentrations by approximately 50% (see Figure 1). The VIIBRYD dose should be reduced to 20 mg if co-administered with a strong inhibitor of CYP3A4. During co-administration with moderate inhibitors of CYP3A4 (e.g., erythromycin), the VIIBRYD dose should be reduced to 20 mg for patients with intolerable adverse events. No dose adjustment is recommended when VIIBRYD is co-administered with mild inhibitors of CYP3A4 (e.g., cimetidine).

Inducers of CYP3A4
Concomitant use of VIIBRYD with inducers of CYP3A4 has the potential to reduce vilazodone systemic exposure. However, the effect of CYP3A4 inducers on vilazodone plasma concentrations has not been evaluated.

Inhibitors of other CYP enzymes
Concomitant administration of VIIBRYD with inhibitors of CYP2C19 and CYP2D6 is not expected to alter plasma concentrations of vilazodone. These isoforms are minor elimination pathways in the metabolism of vilazodone. *In vitro* studies have shown that CYP1A2, CYP2A6, CYP2C9 and CYP2E1 have minimal contribution to the metabolism of vilazodone.

7.4 Potential for Vilazodone to Affect Other Drugs

Drugs metabolized by CYP1A2, CYP2C9, CYP2D6, CYP3A4 or CYP2C19.
Coadministration of VIIBRYD with substrates for CYP1A2, CYP2C9, CYP3A4, or CYP2D6 is unlikely to result in clinically significant changes in the concentrations of the CYP substrates. A study in healthy subjects found that VIIBRYD (20 mg/day for 8-10 days) had no effect on the pharmacokinetics of caffeine, flurbiprofen, nifedipine or debrisoquine, probes for CYP1A2, CYP2C9, CYP3A4, and CYP2D6, respectively. VIIBRYD coadministration with mephenytoin to healthy subjects resulted in a small (11%) increase in mephenytoin biotransformation, suggestive of a minor induction of CYP2C19. *In vitro* studies have shown that VIIBRYD is a moderate inhibitor of CYP2C19 and CYP2D6.

Drugs metabolized by CYP2C8
Coadministration of VIIBRYD with a CYP2C8 substrate may lead to an increase in concentration of the other drug. *In vitro* studies suggest that VIIBRYD may inhibit the biotransformation of substrates of CYP2C8. The effect of VIIBRYD on CYP2C8 activity has not been tested *in vivo*.

Induction of CYP isoforms
VIIBRYD did not induce CYP1A1, 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, 3A4 or 3A5 in an *in vitro* study in cultured human hepatocytes. Chronic administration of vilazodone is unlikely to induce the metabolism of drugs metabolized by these major CYP isoforms.

7.5 Drugs Highly Bound to Plasma Protein
The interaction between vilazodone and other highly protein-bound drugs has not been evaluated. Because vilazodone is highly bound to plasma protein, administration of VIIBRYD to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects
Pregnancy Category C

Vilazodone caused some developmental toxicity in rats, but was not teratogenic in rats or rabbits. There are no adequate and well-controlled studies of VIIBRYD in pregnant women. When treating pregnant women with VIIBRYD, carefully consider whether the potential benefits outweigh the potential risks of treatment.

No teratogenic effects were observed when vilazodone was given to pregnant rats or rabbits during the period of organogenesis at oral doses up to 200 and 36 mg/kg/day, respectively. These doses are 48 and 17 times, in rats and rabbits, respectively, the maximum recommended human dose (MRHD) of 40 mg on a mg/m^2 basis. Fetal body weight gain was reduced, and skeletal ossification was delayed in both rats and rabbits at these doses; these effects were not observed at doses up to 10 times the MRHD in rats or 4 times the MRHD in rabbits.

When vilazodone was administered to pregnant rats at an oral dose of 30 times the MRHD during the period of organogenesis and throughout pregnancy and lactation, the number of live born pups was decreased. There was an increase in early postnatal pup mortality, and among surviving pups there was decreased body weight, delayed maturation, and decreased fertility in adulthood. There was some maternal toxicity at this dose. These effects were not seen at 6 times the MRHD.

Nonteratogenic Effects
Neonates exposed to serotonergic antidepressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of serotonergic antidepressants or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome *[see Warnings and Precautions (5.2)]*.

8.2 Labor and Delivery
The effect of VIIBRYD on labor and delivery in humans is unknown. VIIBRYD should be used during labor and delivery only if the potential benefit outweighs the potential risk.

8.3 Nursing Mothers
Vilazodone is excreted into the milk of lactating rats. The effect of VIIBRYD on lactation and nursing in humans is unknown. Breast feeding in women treated with VIIBRYD should be considered only if the potential benefit outweighs the potential risk to the child.

8.4 Pediatric Use
Clinical studies on the use of VIIBRYD in pediatric patients have not been conducted; therefore, the safety and effectiveness of VIIBRYD in the pediatric population have not been established. VIIBRYD is not approved for use in pediatric patients *[see Box Warning and Warnings and Precautions (5.1)]*.

8.5 Geriatric Use
No dose adjustment is recommended on the basis of age (see Figure 2). Results from a single-dose (20 mg) pharmacokinetic study in elderly (> 65 years-old) vs. young (24-55 years-old) subjects demonstrated that the pharmacokinetics were generally similar between the two age groups.

Of the 2177 patients in clinical studies with VIIBRYD, 37 (1.7%) were 65 years of age or older, and 272 (12.5%) were 55 to 64 years of age.

Greater sensitivity of some older individuals cannot be ruled out *[see Dosage and Administration (2.3)]*.

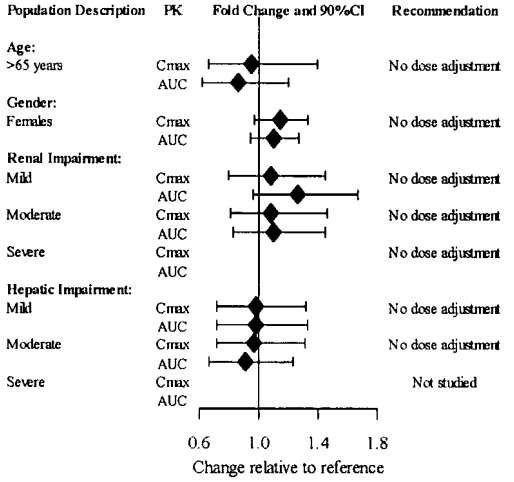
Serotonergic antidepressants have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event *[see Warnings and Precautions (5.7)]*.

8.6 Hepatic Impairment
Vilazodone is eliminated primarily by hepatic metabolism. In mild and moderate hepatic impairment, no dose adjustment is necessary (see Figure 2). VIIBRYD has not been studied in patients with severe hepatic impairment *[see Dosage and Administration (2.3)]*.

8.7 Renal Impairment
In mild, moderate, and severe renal impairment, no dose adjustment is necessary (see Figure 2 below) *[see Dosage and Administration (2.3)]*.

8.8 Gender Effect
After adjustment for body weight, the systemic exposures between males and females are similar (see Figure 2).

Figure 2. Impact of Intrinsic Factors on Vilazodone PK



The data shown for elderly subjects (>65 years) are relative to younger subjects (24-55 y
The data shown for female subjects are relative to male subjects.
The data shown for renal and hepatic impairment are relative to subjects with normal renal and hepatic function, respectively.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance
VIIBRYD is not a controlled substance.

9.2 Abuse and Dependence
VIIBRYD has been systematically studied in animals and did not demonstrate abuse or dependence potential. While VIIBRYD has not been systematically studied in humans for its potential for abuse, there was no suggested evidence of drug-seeking behavior in the clinical studies. However, it is not possible to predict on the basis of clinical experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of VIIBRYD (e.g., development of tolerance, drug-seeking behavior, increases in dose).

10 OVERDOSAGE

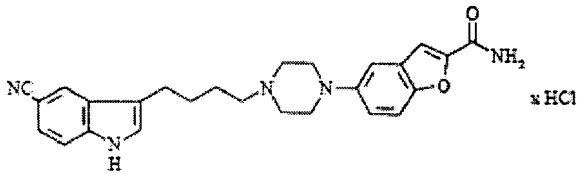
10.1 Human Experience
There is limited clinical experience regarding human overdosage with VIIBRYD. Four patients and 1 patient's child experienced an overdose of VIIBRYD; all recovered. The adverse reactions associated with overdose of VIIBRYD at doses of 200-280 mg as observed in clinical trials included serotonin syndrome, lethargy, restlessness, hallucinations, and disorientation.

10.2 Management of Overdose

Consult a Certified Poison Control Center for up-to-date guidance and advice. Telephone numbers for certified poison control centers are listed in the Physicians' Desk Reference® (PDR). No specific antidotes for vilazodone are known. In case of an overdose, provide supportive care, including close medical supervision and monitoring. Treatment should consist of those general measures employed in the management of overdosage with any drug. Consider the possibility of multiple drug overdose. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be considered. Removal of vilazodone by dialysis has not been studied; however, the high volume of distribution of vilazodone suggests that dialysis will not be effective in reducing vilazodone plasma concentrations.

11 DESCRIPTION
VIIBRYD Tablets for oral administration contain polymorph Form IV vilazodone hydrochloride (HCl), a selective serotonin reuptake inhibitor and a $5HT_{1A}$ receptor partial agonist.

Vilazodone HCl is 2-benzofurancarboxamide, 5-[4-[4-(5-cyano-1*H*-indol-3-yl)butyl]-1-piperazinyl]-, hydrochloride (1:1). Its molecular weight is 477.99. The structural formula is:



In addition to the active ingredient, VIIBRYD Tablets contain lactose monohydrate, microcrystalline cellulose, magnesium stearate, colloidal silicon dioxide, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, FD&C Blue #1 (40 mg only), FD&C Yellow #6 (20 mg only) and FD&C Red #40 (10 mg only).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of action
The mechanism of the antidepressant effect of vilazodone is not fully understood but is thought to be related to its enhancement of serotonergic activity in the CNS through selective inhibition of serotonin reuptake. Vilazodone is also a partial agonist at serotonergic $5\text{-}HT_{1A}$ receptors; however, the net result of this action on serotonergic transmission and its role in vilazodone's antidepressant effect are unknown.

12.2 Pharmacodynamics
Vilazodone binds with high affinity to the serotonin reuptake site (Ki= 0.1 nM), but not to the norepinephrine (Ki=56 nM) or dopamine (Ki=37 nM) reuptake sites. Vilazodone potently and selectively inhibits reuptake of serotonin (IC_{50}= 1.6 nM). Vilazodone also binds selectively with high affinity to $5\text{-}HT_{1A}$ receptors (IC_{50}=2.1 nM) and is a $5\text{-}HT_{1A}$ receptor partial agonist.

Thorough QT Study: Treatment with VIIBRYD did not prolong the QTc interval. The effect of vilazodone (20, 40, 60, and 80 mg) on the QTc interval was evaluated in a randomized, placebo-, and active-controlled (moxifloxacin 400 mg), parallel-group, thorough QTc study in 157 healthy subjects. The study demonstrated an ability to detect small effects. The upper bound of the 90% confidence interval for the largest placebo-adjusted, baseline-corrected QTc interval was below 10 msec, based on the individual correction method (QTcI). This is below the threshold for clinical concern. However, it is unknown whether 80 mg is adequate to represent a high clinical exposure condition.

12.3 Pharmacokinetics
Vilazodone activity is due primarily to the parent drug. The pharmacokinetics of vilazodone (5 mg – 80 mg) are dose-proportional. Accumulation of vilazodone is predictable from single dose data, does not vary with dose, and steady-state is achieved in about 3 days. Elimination of vilazodone is primarily by hepatic metabolism with a terminal half-life of approximately 25 hours. At steady-state, after daily dosing of VIIBRYD 40 mg under fed conditions, the mean C_{max} value is 156 ng/mL, and the mean AUC ($_{0\text{-}24\ hours}$) value is 1645 ng·h/mL.

Absorption
Vilazodone concentrations peak at a median of 4-5 hours (T_{max}) after administration and decline with a terminal half-life of approximately 25 hours. The absolute bioavailability of vilazodone is 72% with food. Administration of VIIBRYD with food (high fat or light meal) increases oral bioavailability (C_{max} increased by approximately 147-160%, and AUC increased by approximately 64-85%).

Coadministration of VIIBRYD with ethanol or with a proton pump inhibitor (pantoprazole) did not affect the rate or extent of vilazodone absorption [*see Drug Interactions (7.3, Figure 1)*]. In addition, neither the T_{max} nor terminal elimination rate of vilazodone was altered by coadministration with either pantoprazole or ethanol.

Absorption is decreased by approximately 25% if vomiting occurs within 7 hours of ingestion; no replacement dose is needed.

Distribution
Vilazodone is widely distributed and approximately 96-99% protein-bound

Metabolism and Elimination
VIIBRYD is extensively metabolized through CYP and non-CYP pathways (possibly by carboxylesterase), with only 1% of the dose recovered in the urine and 2% of the dose recovered in the feces as unchanged vilazodone. CYP3A4 is primarily responsible for its metabolism among CYP pathways, with minor contributions from CYP2C19 and CYP2D6. *In vitro* studies with human microsomes and human hepatocytes indicate that vilazodone is unlikely to inhibit or induce the metabolism of other CYP (except for CYP2C8) substrates; and an *in vivo* study with probe substrates for CYP2C19, 2D6 and 3A4 showed vilazodone did not alter the pharmacokinetics of the probe substrates. However, an *in vivo* study with probe substrate for CYP2C19 demonstrated a minor induction of CYP2C19. Strong inhibitors of CYP3A4 (e.g., ketoconazole) can reduce the metabolism of vilazodone *in vivo* and increase exposure. Conversely, inducers of CYP3A4 can decrease vilazodone exposure *[see Drug Interactions (7.3)]*.

The presence of mild or moderate renal impairment, or mild or moderate hepatic impairment did not affect the apparent clearance of vilazodone.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Carcinogenicity studies were conducted in which B6C3F1mice and Wistar rats were given oral doses of vilazodone up to 135 and 150 mg/kg/day, respectively, for 2 years. These doses are approximately 16.5 and 36 times the maximum recommended human dose (MRHD) of 40 mg, respectively, on a mg/m^2 basis.

In mice, the incidence of hepatocellular carcinomas was increased in males at 16.5 times the MRHD; this finding was not observed at 5.5 times the MRHD. The incidence of malignant mammary gland tumors was numerically increased in females at 5.5 and 16.5 times the MRHD, with statistical significance at 16.5 the MHRD; this finding was not observed at 1.8 times the MRHD. Elevated prolactin levels were observed in a 2-week study of vilazodone administered at 5.5 and 33 times the MRHD. Increases in prolactin levels are known to cause mammary tumors in rodents.

In the rat study, vilazodone was not carcinogenic in either sex at doses up to 36 times the MRHD.

Mutagenesis
Vilazodone was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test). Vilazodone was negative in the *in vitro* V79/HGRPT mammalian cell forward mutation assay. Vilazodone was clastogenic in two *in vitro* mammalian cell chromosome aberration assays. However, vilazodone was negative for clastogenic activity in both an *in vivo* rat bone marrow chromosome aberration assay and a micronucleus test. Vilazodone was also negative in an *in vivo/in vitro* unscheduled DNA synthesis assay in rats.

Impairment of Fertility
Treatment of rats with vilazodone at a dose of 125 mg/kg, which is 30 times the maximum recommended human dose (MRHD) of 40 mg on a mg/m^2 basis, caused impairment of male fertility with no effect on female fertility. Impaired male fertility was not observed at 6 times the MRHD.

14 CLINICAL STUDIES
The efficacy of VIIBRYD as a treatment for major depressive disorder was established in two 8-week, multicenter, randomized, double-blind, placebo-controlled studies in adult (18-70 years of age) outpatients who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria for MDD. In these studies, patients were titrated over 2 weeks to a dose of 40 mg of VIIBRYD with food (n=436) or placebo (n = 433) once daily. VIIBRYD was superior to placebo in the improvement of depressive symptoms as measured by the mean change from baseline to Week 8 in the Montgomery-Asberg Depression Rating Scale (MADRS) total score. Examination of population subgroups based on age (there were few patients over 65), gender, and race did not reveal any clear evidence of differential responsiveness.

Table 4. Summary of Results for the Primary Efficacy Endpoint

Study Number	Primary Endpoint	LS Mean (95% CI) [a] difference from placebo in change from baseline
1	MADRS	-3.2 (-5.2, -1.3)
2	MADRS	-2.5 (-4.4, -0.6)

[a] Least Squares Mean (95% Confidence Interval)

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied
VIIBRYD (vilazodone HCl) Tablets are supplied in the following configurations:
10 mg, pink, oval tablet, debossed with 10 on one side
75838-110-30: 30-count bottles
75838-110-90: 90-count bottles
75838-110-52: 500-count bottles
75838-110-12: 10 blisters cards each containing 10 tablets (HUD)

20 mg, orange, oval tablet, debossed with 20 on one side
75838-120-30: 30-count bottles
75838-120-90: 90-count bottles

75838-120-52: 500-count bottles
75838-120-12: 10 blisters cards each containing 10 tablets (HUD)

40 mg, blue, oval tablet, debossed with 40 on one side
75838-140-30: 30-count bottles
75838-140-90: 90-count bottles
75838-140-52: 500-count bottles
75838-140-12: 10 blisters cards each containing 10 tablets (HUD)

Patient Starter Kit
75838-179-30: blister card containing 30 tablets:
10 mg, pink, oval, debossed with 10 on one side: 7 tablets
20 mg, orange, oval, debossed with 20 on one side: 7 tablets
40 mg, blue, oval, debossed with 40 on one side: 16 tablets

16.2 Storage
VIIBRYD (vilazodone HCl) Tablets should be stored at 25°C (77°F) with excursions permitted to 15°C - 30°C (59°F - 86°F) [*see USP Controlled Room Temperature*].

17 PATIENT COUNSELING INFORMATION
See Medication Guide (17.2).

17.1 Information for Patients
Advise patients and their caregivers about the benefits and risks associated with treatment with VIIBRYD and counsel them in its appropriate use. Advise patients and their caregivers to read the Medication Guide and assist them in understanding its contents. The complete text of the Medication Guide is reprinted at the end of this document.

Suicide Risk
Advise patients and caregivers to look for the emergence of suicidality, especially early during treatment and when the dose is adjusted up or down [*see Box Warning and Warnings and Precautions (5.1)*].

Dosing and Administration
Instruct patients to take VIIBRYD with food. When initiating treatment with VIIBRYD the dose should be titrated, starting with a dose of 10 mg once daily for 7 days, followed by 20 mg once daily for an additional 7 days, and then increased to 40 mg once daily.

Concomitant Medication
Instruct patients not to take VIIBRYD with an MAOI or within 14 days of stopping an MAOI and to allow 14 days after stopping VIIBRYD before starting an MAOI [*see Contraindications (4.1)*].

Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions
Caution patients about the risk of serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions, particularly with the concomitant use of VIIBRYD and triptans, tramadol, tryptophan supplements, other serotonergic agents, or antipsychotic drugs [*see Warnings and Precautions (5.2) and Drug Interactions (7.1)*].

Seizures
Caution patients about using VIIBRYD if they have a history of a seizure disorder [*see Warnings and Precautions (5.3)*]. Patients with a history of seizures were excluded from clinical studies.

Abnormal Bleeding
Caution patients about the concomitant use of VIIBRYD and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of abnormal bleeding [*see Warnings and Precautions (5.4)*].

Activation of Mania/Hypomania
Advise patients and their caregivers to observe for signs of activation of mania/hypomania [*see Warnings and Precautions (5.5)*].

Discontinuation
Advise patients not to stop taking VIIBRYD without talking first with their healthcare provider. Patients should be aware that discontinuation effects may occur when suddenly stopping VIIBRYD [*see Warnings and Precautions (5.6)*].

Hyponatremia
Advise patients that if they are treated with diuretics, or are otherwise volume depleted, or are elderly, they may be at greater risk of developing hyponatremia while taking VIIBRYD [*see Warnings and Precautions (5.7)*].

Alcohol
Advise patients to avoid alcohol while taking VIIBRYD [*see Drug Interactions (7.3)*].

Allergic Reactions
Advise patients to notify their healthcare provider if they develop an allergic reaction such as rash, hives, swelling, or difficulty breathing.

Pregnancy
Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during therapy with VIIBRYD [*see Use in Specific Populations (8.1)*].

Nursing Mothers
Advise patients to notify their healthcare provider if they are breastfeeding an infant and would like to continue or start VIIBRYD [*see Use in Specific Populations (8.3)*].

Interference with Cognitive and Motor Performance

Caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain that VIIBRYD therapy does not adversely affect their ability to engage in such activities.

TROVIS PHARMACEUTICALS

Distributed by
Trovis Pharmaceuticals LLC
New Haven, CT 06511

877-878-7200
viibryd.com

Licensed from Merck KGaA,
Darmstadt, Germany

Product protected by U.S. Patent No. 5,532,241 and U.S. Patent No. 7,834,020.

VZ59PI0000
Revised: January 2010

EXHIBIT 6

NDA Approval Letter

NDA 022567

NDA APPROVAL

Trovis Pharmaceuticals LLC
Attention: Kimberly Fabrizio
Vice President, Regulatory Affairs
Five Science Park
New Haven, CT 06511

Dear Ms. Fabrizio:

Please refer to your New Drug Application (NDA) dated March 22, 2010, received March 22, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Viibryd (vilazodone hydrochloride) 10 mg, 20 mg, and 40 mg tablets.

We acknowledge receipt of your amendments dated May 4, 2010, May 7, 2010, May 18, 2010, May 19, 2010, May 25, 2010, June 3, 2010, June 8, 2010, June 30, 2010, August 4, 2010, August 19, 2010, August 23, 2010, August 31, 2010, September 27, 2010, November 4, 2010, November 18, 2010, November 30, 2010, December 3, 2010, December 13, 2010, December 15, 2010, December 23, 2010, December 29, 2010, January 4, 2011, January 6, 2011, January 7, 2011, January 11, 2011, and January 13, 2011.

This new drug application provides for the use of Viibryd (vilazodone hydrochloride) for the treatment of Major Depressive Disorder.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.
The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels as agreed upon in our January 14, 2011 communication as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22567**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for vilazodone was not referred to an FDA advisory committee because this drug is not the first in its class, and the safety profile is similar to that of other drugs approved for this indication.

PROPRIETARY NAME

The Division of Medication Error and Prevention and Analysis (DMEPA) and the Division of Psychiatry Products do not object to the use of the proprietary name, Viibryd, for this product.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 6 years old in the treatment of major depressive disorder, because studies are highly impractical due to the low prevalence of this disorder in this age range.

We are deferring submission of your pediatric studies for ages 7 to 17 years old in the treatment of major depressive disorder, because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

1723-1 Deferred pediatric study under PREA for the treatment of major depressive disorder in pediatric patients aged 7 to 17. Conduct a study to obtain pharmacokinetic, safety, and tolerability data and provide information pertinent to dosing of vilazodone in the relevant pediatric population.

Final Protocol Submission Date:	January 31, 2012
Study Completion Date:	February 28, 2013
Final Report Submission:	January 31, 2016

1723-2 Deferred pediatric study under PREA for the treatment of major depressive disorder in pediatric patients aged 7 to 17. Conduct a study to obtain data on the efficacy and safety of vilazodone in the relevant pediatric population. This must be a placebo-controlled and active-controlled (fluoxetine) study. This study must be a fixed-dose study.

Final Protocol Submission Date:	May 31, 2013
Study Completion Date:	July 31, 2015
Final Report Submission:	January 31, 2016

1723-3 Deferred pediatric study under PREA for the treatment of major depressive disorder in pediatric patients aged 7 to 17. Conduct a second study to obtain data on the efficacy and safety of vilazodone in the relevant pediatric population. This must be a placebo-controlled and active-controlled (fluoxetine) study. This study may be a fixed-dose study.

Final Protocol Submission Date:	May 31, 2013
Study Completion Date:	July 31, 2015
Final Report Submission:	January 31, 2016

1723-4 To support the use of vilazodone in children less than 13 years of age, you must conduct a study to assess the safety of vilazodone in juvenile rats. This study must include evaluation of neurological/behavioral development and reproductive development. You should submit the protocol for our comments prior to initiating the study.

Final Protocol Submission Date:	January 30, 2012

Study Completion Date:	January 30, 2014
Final Report Submission:	January 30, 2015

Submit final reports to this NDA. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated "**Required Pediatric Assessment(s).**"

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

The major human metabolite of vilazodone, M17, was not demonstrated to be present in plasma of either rats or rabbits. Therefore the embryo-fetal reproductive toxicity studies with vilazodone did not adequately assess the potential reproductive toxicity of M17.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the reproductive toxicity of the major human metabolite M17.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA is not yet sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1723-5 Assess the reproductive toxicity of metabolite M17 by conducting an embryo-fetal study in either rats or rabbits in which M17 is administered by a route that will produce systemic exposure equal to or greater than the exposure in humans at the maximum recommended human dose (MRHD).

The timetable, as agreed upon on a January 19, 2011 communication, states that you will conduct this study according to the following schedule:

Final Protocol Submission Date:	Not applicable
Study Completion Date:	November 30, 2012
Final Report Submission:	January 31, 2013

1723-6 Assess the reproductive toxicity of metabolite M17 by demonstrating that the original rabbit study was adequate to assess the embryo-fetal toxicity of M17. This will require data demonstrating that the systemic exposure to M17 in rabbits in that study was equal to or greater than that in humans at the MRHD.

The timetable, as agreed upon on a January 19, 2011 communication, states that you will conduct this study according to the following schedule:

Final Protocol Submission Date:	Not applicable
Study Completion Date:	November 30, 2012
Final Report Submission:	January 31, 2013

If you are able to address postmarketing study 1723-6 adequately through analyses of existing data, FDA may release you from postmarketing study 1723-5.

Submit the protocol to your IND 54613, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)," "Required Postmarketing Final Report Under 505(o)," "Required Postmarketing Correspondence Under 505(o)."**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii), requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments agreed upon in your communications dated January 19, 2011:

1723-7 A controlled trial to evaluate the longer-term (i.e., maintenance) efficacy of vilazodone in the treatment of adults with major depressive disorder. This trial must be placebo-controlled, utilize a randomized withdrawal design, and include an adequate period of stabilization with open-label treatment of vilazodone prior to double-blind randomization.

Final Protocol Submission:	September 30, 2011
Trial Completion Date:	January 31, 2015
Final Report Submission:	January 31, 2016

1723-8 It is not apparent from the trials you have conducted in major depressive disorder that the lowest effective dose of vilazodone has been identified, because only one dose (40 mg/day) was studied. However, there are suggestions that 20 mg/day may be effective at least in some subjects. In one of the trials, those who did not tolerate 40 mg/day could continue in the trial on a dose of 20 mg/day, and some may have had a significant treatment effect. In addition, data from the phase 2 fixed-dose trials suggest that there may have been a signal of efficacy with the 20 mg/day dose, as measured by the secondary efficacy measure (MADRS). Moreover, some important adverse reactions are dose-related. Thus, we request that you further characterize the efficacy and safety of vilazodone in the treatment of adults with MDD using fixed doses of vilazodone (20 mg and 40 mg), an active control (for assay sensitivity), and placebo in an adequate and well controlled trial.

Final Protocol Submission:	October 31, 2011
Trial Completion:	January 31, 2013
Final Report Submission:	January 31, 2014

1723-9 Vilazodone is metabolized primarily by CYP3A4. You have not submitted information on the potential effect of CYP3A4 induction on vilazodone exposure. We request that you conduct a drug-drug interaction trial of vilazodone using a CYP3A4 inducer (carbamazepine) in healthy subjects.

Final Protocol Submission:	July 31, 2011
Trial Completion:	July 31, 2012
Final Report Submission:	January 31, 2013

1723-10 Vilazodone is extensively metabolized; however, the pharmacokinetics of vilazodone in patients with severe hepatic impairment has not been assessed. We request that you conduct a Phase 1 trial to evaluate the pharmacokinetics of vilazodone in patients with severe hepatic impairment.

Final Protocol Submission:	July 31, 2011
Trial Completion:	July 31, 2012
Final Report Submission:	February 28, 2013

1723-11 Information on the effect of PgP on the pharmacokinetics of vilazodone and the effect of vilazodone on PgP was not submitted. We request that you conduct an *in vitro* study to evaluate whether vilazodone is a substrate or inhibitor of PgP.

Final Protocol Submission:	July 31, 2011
Study Completion:	September 30, 2011
Final Report Submission:	December 31, 2011

Submit clinical protocols to your IND 54613 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under

21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. The details of the REMS requirement were outlined in our REMS notification letter dated November 1, 2010.

Your proposed REMS, submitted on December 15, 2010, and appended to this letter, is approved. The REMS consists of a Medication Guide and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include, but is not limited to, the following:

a. An evaluation of patients' understanding of the serious risks of Viibryd (vilazodone hydrochloride) Tablets.
b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.

Assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to

the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 22567 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 22567
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR NDA 22567
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

Please submit one market package of the drug product when it is available.

DISSOLUTION METHOD AND SPECIFICATIONS

The dissolution method test conditions for all tablet strengths (10 mg, 20 mg, and 40 mg) are as follows:

USP Apparatus: 2 (Paddle) x 60 rpm
Medium: 0.1% Acetic Acid (pH 3.1), 1000 mL at 37°C
Specifications: Q=80% at 30 min

EXPIRY DATE

A 24 month expiry date is granted based on the available stability data.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, email CDR Bill Bender, Senior Regulatory Project Manager, at william.bender@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ellis Unger, M.D.
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
REMS

VIIBRYD™ (vilazodone hydrochloride) Tablets

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

VIIBRYD (vilazodone HCl) Tablets for oral administration
Initial U.S. Approval: 2011

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

See full prescribing information for complete boxed warning.
Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders (5.1).
VIIBRYD is not approved for use in pediatric patients (8.4).

INDICATIONS AND USAGE

VIIBRYD is indicated for the treatment of major depressive disorder (MDD). The efficacy of VIIBRYD was established in two 8-week, placebo-controlled trials in adult patients with MDD (1, 14).

DOSAGE AND ADMINISTRATION

- The recommended dose for VIIBRYD is 40 mg once daily (2).
- VIIBRYD should be titrated to the 40 mg dose, starting with an initial dose of 10 mg once daily for 7 days, followed by 20 mg once daily for an additional 7 days, and then increased to 40 mg once daily (2).
- VIIBRYD should be taken with food. Administration without food can result in inadequate drug concentrations and may diminish effectiveness (2, 12.3).
- When discontinuing treatment, reduce the dose gradually (2.4).

DOSAGE FORMS AND STRENGTHS

VIIBRYD is available as 10 mg, 20 mg and 40 mg tablets (3).

CONTRAINDICATIONS

- **Monoamine Oxidase Inhibitors**: Do not use VIIBRYD concomitantly with an MAOI or within 14 days of stopping or starting an MAOI (4.1).

WARNINGS AND PRECAUTIONS

Clinical Worsening/Suicide Risk: Monitor patients for clinical worsening and suicidal thinking or behavior (5.1).
Serotonin Syndrome or Neuroleptic Malignant (NMS)-like Syndrome: Can occur with treatment. Discontinue and initiate supportive treatment (5.2).
Seizures: Can occur with treatment. Use with caution in patients with a seizure disorder (5.3).
Abnormal Bleeding: Treatment can increase the risk of bleeding. Use with caution in association with nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, or other drugs that affect coagulation (5.4).
Activation of Mania/Hypomania: Can occur with treatment. Screen patients for bipolar disorder (5.5).
Discontinuation of Treatment with VIIBRYD: A gradual reduction in dose is recommended rather than an abrupt cessation (5.6).
Hyponatremia: Can occur in association with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) (5.7).

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥ 5% and at least twice the rate of placebo) are: diarrhea, nausea, vomiting, and insomnia (6).
To report SUSPECTED ADVERSE REACTIONS, contact Trovis Pharmaceuticals at 1-877-878-7200 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

MAOIs: Do not use VIIBRYD concomitantly with an MAOI or within 14 days of stopping or starting an MAOI (4.1, 7.1).
CYP3A4 inhibitors: The VIIBRYD dose should be reduced to 20 mg when co-administered with CYP3A4 strong inhibitors (7.3).
CYP3A4 inducers: Concomitant use of VIIBRYD with inducers of CYP3A4 can result in inadequate drug concentrations and may diminish effectiveness. The effect of CYP3A4 inducers on systemic exposure of vilazodone has not been evaluated (7.3).

USE IN SPECIFIC POPULATIONS

Pregnancy: There are no controlled human data regarding VIIBRYD use during pregnancy. Use only if the potential benefits outweigh the potential risks (2.3, 8.1).
Nursing Mothers: There are no human data regarding VIIBRYD concentrations in breast milk. Women should breast feed only if the potential benefits outweigh the potential risks (8.3, 2.3).
Pediatric Use: The safety and efficacy of VIIBRYD in pediatric patients have not been studied (8.4).
Geriatric Use: No dose adjustment is recommended on the basis of age (8.5).
Hepatic Impairment: No dose adjustment is recommended in patients with mild or moderate hepatic impairment. VIIBRYD has not been studied in patients with severe hepatic impairment (8.6).
Renal Impairment: No dose adjustment is recommended in patients with mild, moderate, or severe renal impairment. (8.7).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: January 2010

FULL PRESCRIBING INFORMATION: CONTENTS*

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

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of VIIBRYD or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. VIIBRYD is not approved for use in pediatric patients [*see Warnings and Precautions (5.1), Use in Specific Populations (8.4), and Patient Counseling Information (17.1)*]

1 INDICATIONS AND USAGE

VIIBRYD is indicated for the treatment of major depressive disorder (MDD). The efficacy of VIIBRYD was established in two 8-week, randomized, double-blind, placebo-controlled trials in adult patients with a diagnosis of MDD *[see Clinical Studies (14)]*.

Major depressive disorder consists of one or more major depressive episodes. A major depressive episode (DSM-IV-TR) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, or a suicide attempt or suicidal ideation.

2 DOSAGE AND ADMINISTRATION

2.1 Initial Treatment of Major Depressive Disorder

The recommended dose for VIIBRYD is 40 mg once daily. VIIBRYD should be titrated, starting with an initial dose of 10 mg once daily for 7 days, followed by 20 mg once daily for an additional 7 days, and then an increase to 40 mg once daily. VIIBRYD should be taken with food. VIIBRYD blood concentrations (AUC) in the fasted state can be decreased by approximately 50% compared to the fed state, and may result in diminished effectiveness in some patients *[see Pharmacokinetics (12.3)]*.

2.2 Maintenance/Continuation/Extended Treatment

The efficacy of VIIBRYD has not been systematically studied beyond 8 weeks. It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Patients should be reassessed periodically to determine the need for maintenance treatment and the appropriate dose for treatment.

2.3 Dosing in Special Populations

Pregnant Women: Neonates exposed to serotonergic antidepressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. When treating pregnant women with VIIBRYD, consider whether the potential benefits outweigh the potential risks of treatment *[see Pregnancy (8.1)]*.

Nursing Mothers: There are no clinical data regarding the effect of VIIBRYD on lactation and nursing *[see Nursing Mothers (8.3)]*. Breastfeeding in women treated with VIIBRYD should be considered only if the potential benefit outweighs the potential risk.

Pediatric Patients: The safety and efficacy of VIIBRYD have not been studied in pediatric patients *[see Pediatric Use (8.4)]*.

Geriatric Patients: No dose adjustment is recommended on the basis of age *[see Geriatric Use (8.5)]*.

Hepatic Impairment: No dose adjustment is recommended in patients with mild or moderate hepatic impairment. VIIBRYD has not been studied in severe hepatic impairment *[see Hepatic Impairment (8.6)]*.

Renal Impairment: No dose adjustment is recommended in patients with mild, moderate, or severe renal impairment. *[see Renal Impairment (8.7)]*.

Gender: No dose adjustment is recommended on the basis of gender *[see Gender Effect (8.8)]*.

2.4 Discontinuing Treatment

Discontinuation symptoms have been reported with discontinuation of serotonergic drugs such as VIIBRYD. Gradual dose reduction is recommended, instead of abrupt discontinuation, whenever possible. Monitor patients for these symptoms when discontinuing VIIBRYD. If intolerable symptoms occur following a dose decrease or upon discontinuation of treatment, consider resuming the previously prescribed dose and decreasing the dose at a more gradual rate *[see Warnings and Precautions (5.6)]*.

2.5 Monoamine Oxidase Inhibitors (MAOI)

At least 14 days must elapse between discontinuation of an MAOI and initiation of therapy with VIIBRYD. In addition, at least 14 days must be allowed after stopping VIIBRYD before starting an MAOI *[see Contraindications (4.1)]*.

3 DOSAGE FORMS AND STRENGTHS

VIIBRYD Tablets are available as 10 mg, 20 mg and 40 mg immediate-release, film-coated tablets.
10 mg pink, oval tablet, debossed with 10 on one side
20 mg orange, oval tablet, debossed with 20 on one side
40 mg blue, oval tablet, debossed with 40 on one side

4 CONTRAINDICATIONS

4.1 Monoamine Oxidase Inhibitors

VIIBRYD must not be used concomitantly in patients taking MAOIs or in patients who have taken MAOIs within the preceding 14 days due to the risk of serious, sometimes fatal, drug interactions with serotonergic drugs. These interactions have been associated with symptoms that include tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, rigidity, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Allow at least 14 days after stopping VIIBRYD before starting an MAOI *[see Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled studies of antidepressant drugs (selective serotonin reuptake inhibitors [SSRIs] and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with MDD and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled studies in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term studies of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled studies in adults with MDD or other psychiatric disorders included a total of 295 short-term studies (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric studies. There were suicides in the adult studies, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms [*see Warnings and Precautions (5.6) and Dosage and Administration (2.4)*].

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as

the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for VIIBRYD should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose *[see also Patient Counseling Information (17.1)]*.

Screening patients for bipolar disorder
A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled studies) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that VIIBRYD is not approved for use in treating bipolar depression.

5.2 Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions
The development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions has been reported with antidepressants alone, but particularly with concomitant use of serotonergic drugs (including triptans) with drugs that impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. Symptoms of serotonin syndrome were noted in 0.1% of patients treated with VIIBRYD. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome, in its most severe form can resemble NMS, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.

The concomitant use of VIIBRYD with MAOIs intended to treat depression is contraindicated. *[see Contraindications (4.1)]*.

If concomitant treatment of VIIBRYD with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases *[see Drug Interactions (7.1)]*.

The concomitant use of VIIBRYD with serotonin precursors (such as tryptophan) is not recommended *[see Drug Interactions (7.1)]*.

Treatment with VIIBRYD and any concomitant serotonergic (SSRI, serotonin–norepinephrine reuptake inhibitor [SNRI], triptan, buspirone, tramadol, etc.) or antidopaminergic drugs, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

5.3 Seizures
VIIBRYD has not been systematically evaluated in patients with a seizure disorder. Patients with a history of seizures were excluded from clinical studies. Like other antidepressants, VIIBRYD should be prescribed with caution in patients with a seizure disorder.

5.4 Abnormal Bleeding
The use of drugs that interfere with serotonin reuptake inhibition, including VIIBRYD, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDS), warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of VIIBRYD and NSAIDs, aspirin, or other drugs that affect coagulation or bleeding.

5.5 Activation of Mania/Hypomania
Symptoms of mania/hypomania were reported in 0.1% of patients treated with VIIBRYD in clinical studies. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other antidepressants. As with all antidepressants, use VIIBRYD cautiously in patients with a history or family history of bipolar disorder, mania, or hypomania.

5.6 Discontinuation of Treatment with VIIBRYD
There have been reports of adverse events occurring upon discontinuation of serotonergic antidepressants, particularly when discontinuation is abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesia, such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Monitor patients for these symptoms when discontinuing VIIBRYD. Reduce the dose gradually whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, consider resuming the previously prescribed dose. Subsequently, the dose may be decreased, but at a more gradual rate *[see Dosage and Administration, (2.4)]*.

5.7 Hyponatremia
Although no cases of hyponatremia resulting from VIIBRYD treatment were reported in the clinical studies, hyponatremia has occurred as a result of treatment with SSRIs and SNRIs. In many cases, hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs. Also, patients taking diuretics or who are otherwise volume depleted can be at greater risk. Discontinuation of VIIBRYD in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which can lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience
The most commonly observed adverse reactions in VIIBRYD-treated MDD patients in placebo-controlled studies (incidence ≥ 5% and at least twice the rate of placebo) were: diarrhea, nausea, vomiting, and insomnia.

Patient Exposure

The safety of VIIBRYD was evaluated in 2,177 patients (18-70 years of age) diagnosed with MDD who participated in clinical studies, representing 552 patient-years of exposure. In an open-label 52 week study at 40 mg daily, 599 patients were exposed to VIIBRYD for a total of 348 patient-years.

The information presented in these sections was derived from studies of VIIBRYD 40 mg daily in major depressive disorder including: 1) 2 placebo-controlled 8-week studies in 861 patients, including 436 receiving vilazodone; and 2) an open-label 52-week study of 599 patients. These studies included a titration period of 10 mg daily for 7 days followed by 20 mg daily for 7 days. In these clinical trials, VIIBRYD was administered with food.

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

Adverse reactions reported as reasons for discontinuation of treatment
In the placebo-controlled studies of MDD there was no single adverse reaction leading to discontinuation in > 1% of the patients. Overall, 7.1% of the patients who received VIIBRYD discontinued treatment due to an adverse reaction, compared with 3.2% of placebo-treated patients in these studies.

Common adverse reactions in placebo-controlled MDD studies
Table 2 shows the incidence of common adverse reactions that occurred in ≥ 2% of VIIBRYD-treated MDD patients (and greater than in placebo-treated patients) in the placebo-controlled studies.

Table 2: Common Adverse Reactions Occurring in ≥2% of VIIBRYD-treated Patients and > Placebo-treated Patients

System Organ Class Preferred Term	VIIBRYD 40 mg/day N = 436	Placebo N = 433
Gastrointestinal disorders		
Diarrhea	28	9
Nausea	23	5
Dry mouth	8	5
Vomiting	5	1
Dyspepsia	3	2
Flatulence	3	2
Gastroenteritis	3	<1
Nervous system disorders		
Dizziness	9	5
Somnolence	3	2
Paresthesia	3	1
Tremor	2	0
Psychiatric disorders		
Insomnia	6	2
Abnormal dreams	4	1
Libido decreased	4	<1
Restlessness *	3	<1
Orgasm abnormal**	3	0
General disorders		
Fatigue	4	3
Feeling jittery	2	<1
Cardiac disorders		
Palpitations	2	<1
Musculoskeletal and connective tissue disorders		
Arthralgia	3	2
Reproductive system and breast disorders		
Delayed ejaculation***	2	0
Erectile dysfunction***	2	1
Metabolism and nutrition disorders		

Increased appetite	2	1

*Includes restlessness, akathisia, and restless legs syndrome

**Includes orgasm abnormal and anorgasmia

***Male patients only (Placebo n=182; VIIBRYD n=170)

Table 3: Sexual Adverse Reactions: Percentage in the Placebo-Controlled Studies

	Males		Females	
Preferred Term	VIIBRYD N= 170	Placebo N= 182	VIIBRYD N=266	Placebo N=251
Decreased libido	5	0	3	<1
Abnormal orgasm*	4	0	2	0
Delayed ejaculation	2	0	–	–
Erectile dysfunction	2	1	–	–
Sexual dysfunction	2	0	<1	<1

– Not applicable
*Includes anorgasmia

Laboratory Tests
VIIBRYD has not been associated with any clinically important changes in laboratory test parameters in serum chemistry (including liver function tests), hematology and urinalysis, as measured in placebo-controlled studies. These studies include analysis of (1) mean change from baseline and (2) the proportion of patients meeting criteria for potentially clinically significant changes from baseline. Results from a 52-week open-label study were consistent with the findings from the placebo-controlled studies.

ECG
VIIBRYD has not been associated with any clinically significant effect on ECG parameters, including QT, QTc, PR and QRS intervals, or with any arrhythmogenic potential. ECGs were evaluated in a thorough QTc study at doses up to 80 mg daily with food and in the placebo-controlled studies *[see Pharmacodynamics (12.2)]*.

Vital Signs
VIIBRYD has not been associated with any clinically significant effect on vital signs, including systolic and diastolic blood pressure and heart rate, as measured in placebo-controlled studies. These studies included analyses of (1) change from baseline, and (2) the proportion of patients meeting criteria for potentially clinically significant changes from baseline. Results from a 52-week open-label study were consistent with the findings from the placebo-controlled studies.

Weight
VIIBRYD had no effect on body weight as measured by the mean change from baseline in the 8-week, placebo-controlled studies. The mean changes in weight were +0.16 kg in the VIIBRYD group and +0.18 kg in the placebo group. The proportions of patients with a weight gain $\geq$ 7% were 0.9% in the VIIBRYD group and 1.2% in the placebo group. The proportions of patients with a weight decrease $\geq$ 7% were 1.4% in the VIIBRYD group and 1.4% in the placebo group.

Other adverse reactions observed in clinical studies
The following listing does not include reactions: 1) already listed in previous tables or elsewhere in labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, 4) which were not considered to have significant clinical implications, or 5) which occurred at a rate equal to or less than placebo.

Reactions are categorized by body system according to the following definitions: *frequent* adverse reactions are those occurring in at least 1/100 patients; *infrequent* adverse reactions are those occurring in 1/100 to 1/1000 patients; *rare* reactions are those occurring in fewer than 1/1000 patients:

Cardiac disorders: *infrequent*: ventricular extrasystoles

Eye disorders: *frequent:* vision blurred, dry eye; *infrequent:* cataracts

General disorders: *infrequent*: feeling abnormal

Metabolism and nutrition disorders: *frequent*: decreased appetite

Nervous System: *frequent*: sedation, migraine; *infrequent*: dysgeusia

Psychiatric disorders: *infrequent*: panic attack, mania

Renal and Urinary disorder: *infrequent*: pollakiuria

Skin and subcutaneous tissue disorders: *frequent*: hyperhidrosis, night sweats

7 DRUG INTERACTIONS

7.1 Central Nervous System (CNS)-Active Agents
The risk of using VIIBRYD in combination with other CNS-active drugs has not been systematically evaluated. Consequently, use caution when VIIBRYD is prescribed in combination with other CNS-active drugs.

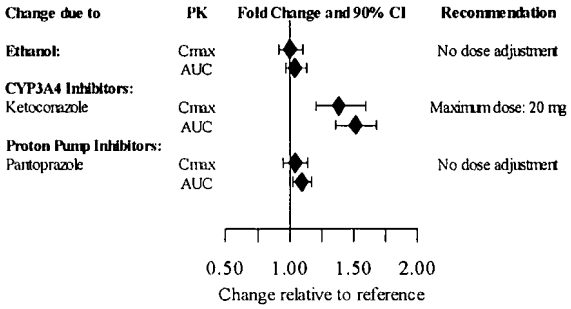
Monoamine Oxidase Inhibitors (MAOI)
Adverse reactions, some of which are serious or fatal, can develop in patients who use MAOIs or who have recently been discontinued from a MAOI and started on antidepressant(s) with pharmacological properties similar to VIIBRYD (e.g. SSRIs), or who have recently had SSRI therapy discontinued prior to initiation of an MAOI. Do not prescribe VIIBRYD concomitantly with an MAOI or within 14 days of discontinuing or starting an MAOI *[see Contraindications (4.1)]*.

Serotonergic Drugs
Based on the mechanism of action of VIIBRYD and the potential for serotonin toxicity, also known as serotonin syndrome, caution is advised when VIIBRYD is coadministered with other drugs that may affect the serotonergic neurotransmitter systems (e.g., MAOI, SSRIs, SNRIs, triptans, buspirone, tramadol, and tryptophan products etc.) *[see Warnings and Precautions (5.2)]*.

7.2 Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)
Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of case-control and cohort design have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when VIIBRYD is initiated or discontinued *[see Abnormal Bleeding (5.4)]*.

7.3 Potential for Other Drugs to Affect Vilazodone

Figure 1. Impact of other drugs on Vilazodone PK



Inhibitors of CYP3A4
Metabolism by CYP3A4 is a major elimination pathway for vilazodone. Concomitant use of VIIBRYD and strong inhibitors of CYP3A4 (e.g., ketoconazole) can increase vilazodone plasma concentrations by approximately 50% (see Figure 1). The VIIBRYD dose should be reduced to 20 mg if co-administered with a strong inhibitor of CYP3A4. During co-administration with moderate inhibitors of CYP3A4 (e.g., erythromycin), the VIIBRYD dose should be reduced to 20 mg for patients with intolerable adverse events. No dose adjustment is recommended when VIIBRYD is co-administered with mild inhibitors of CYP3A4 (e.g., cimetidine).

Inducers of CYP3A4
Concomitant use of VIIBRYD with inducers of CYP3A4 has the potential to reduce vilazodone systemic exposure. However, the effect of CYP3A4 inducers on vilazodone plasma concentrations has not been evaluated.

Inhibitors of other CYP enzymes
Concomitant administration of VIIBRYD with inhibitors of CYP2C19 and CYP2D6 is not expected to alter plasma concentrations of vilazodone. These isoforms are minor elimination pathways in the metabolism of vilazodone. *In vitro* studies have shown that CYP1A2, CYP2A6, CYP2C9 and CYP2E1 have minimal contribution to the metabolism of vilazodone.

7.4 Potential for Vilazodone to Affect Other Drugs

Drugs metabolized by CYP1A2, CYP2C9, CYP2D6, CYP3A4 or CYP2C19.
Coadministration of VIIBRYD with substrates for CYP1A2, CYP2C9, CYP3A4, or CYP2D6 is unlikely to result in clinically significant changes in the concentrations of the CYP substrates. A study in healthy subjects found that VIIBRYD (20 mg/day for 8-10 days) had no effect on the pharmacokinetics of caffeine, flurbiprofen, nifedipine or debrisoquine, probes for CYP1A2, CYP2C9, CYP3A4, and CYP2D6, respectively. VIIBRYD coadministration with mephenytoin to healthy subjects resulted in a small (11%) increase in mephenytoin biotransformation, suggestive of a minor induction of CYP2C19. *In vitro* studies have shown that VIIBRYD is a moderate inhibitor of CYP2C19 and CYP2D6.

Drugs metabolized by CYP2C8
Coadministration of VIIBRYD with a CYP2C8 substrate may lead to an increase in concentration of the other drug. *In vitro* studies suggest that VIIBRYD may inhibit the biotransformation of substrates of CYP2C8. The effect of VIIBRYD on CYP2C8 activity has not been tested *in vivo*.

Induction of CYP isoforms
VIIBRYD did not induce CYP1A1, 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, 3A4 or 3A5 in an *in vitro* study in cultured human hepatocytes. Chronic administration of vilazodone is unlikely to induce the metabolism of drugs metabolized by these major CYP isoforms.

7.5 Drugs Highly Bound to Plasma Protein
The interaction between vilazodone and other highly protein-bound drugs has not been evaluated. Because vilazodone is highly bound to plasma protein, administration of VIIBRYD to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects
Pregnancy Category C

Vilazodone caused some developmental toxicity in rats, but was not teratogenic in rats or rabbits. There are no adequate and well-controlled studies of VIIBRYD in pregnant women. When treating pregnant women with VIIBRYD, carefully consider whether the potential benefits outweigh the potential risks of treatment.

No teratogenic effects were observed when vilazodone was given to pregnant rats or rabbits during the period of organogenesis at oral doses up to 200 and 36 mg/kg/day, respectively. These doses are 48 and 17 times, in rats and rabbits, respectively, the maximum recommended human dose (MRHD) of 40 mg on a mg/m^2 basis. Fetal body weight gain was reduced, and skeletal ossification was delayed in both rats and rabbits at these doses; these effects were not observed at doses up to 10 times the MRHD in rats or 4 times the MRHD in rabbits.

When vilazodone was administered to pregnant rats at an oral dose of 30 times the MRHD during the period of organogenesis and throughout pregnancy and lactation, the number of live born pups was decreased. There was an increase in early postnatal pup mortality, and among surviving pups there was decreased body weight, delayed maturation, and decreased fertility in adulthood. There was some maternal toxicity at this dose. These effects were not seen at 6 times the MRHD.

Nonteratogenic Effects
Neonates exposed to serotonergic antidepressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of serotonergic antidepressants or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome *[see Warnings and Precautions (5.2)]*.

8.2 Labor and Delivery
The effect of VIIBRYD on labor and delivery in humans is unknown. VIIBRYD should be used during labor and delivery only if the potential benefit outweighs the potential risk.

8.3 Nursing Mothers
Vilazodone is excreted into the milk of lactating rats. The effect of VIIBRYD on lactation and nursing in humans is unknown. Breast feeding in women treated with VIIBRYD should be considered only if the potential benefit outweighs the potential risk to the child.

8.4 Pediatric Use
Clinical studies on the use of VIIBRYD in pediatric patients have not been conducted; therefore, the safety and effectiveness of VIIBRYD in the pediatric population have not been established. VIIBRYD is not approved for use in pediatric patients *[see Box Warning and Warnings and Precautions (5.1)]*.

8.5 Geriatric Use
No dose adjustment is recommended on the basis of age (see Figure 2). Results from a single-dose (20 mg) pharmacokinetic study in elderly (> 65 years-old) vs. young (24-55 years-old) subjects demonstrated that the pharmacokinetics were generally similar between the two age groups.

Of the 2177 patients in clinical studies with VIIBRYD, 37 (1.7%) were 65 years of age or older, and 272 (12.5%) were 55 to 64 years of age.

Greater sensitivity of some older individuals cannot be ruled out *[see Dosage and Administration (2.3)]*.

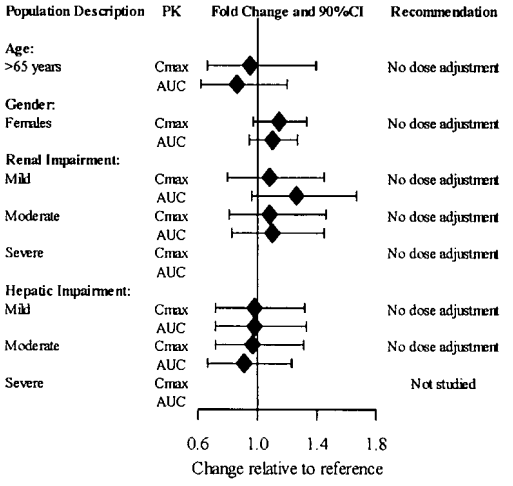
Serotonergic antidepressants have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event *[see Warnings and Precautions (5.7)]*.

8.6 Hepatic Impairment
Vilazodone is eliminated primarily by hepatic metabolism. In mild and moderate hepatic impairment, no dose adjustment is necessary (see Figure 2). VIIBRYD has not been studied in patients with severe hepatic impairment *[see Dosage and Administration (2.3)]*.

8.7 Renal Impairment
In mild, moderate, and severe renal impairment, no dose adjustment is necessary (see Figure 2 below) *[see Dosage and Administration (2.3)]*.

8.8 Gender Effect
After adjustment for body weight, the systemic exposures between males and females are similar (see Figure 2).

Figure 2. Impact of Intrinsic Factors on Vilazodone PK



The data shown for elderly subjects (>65 years) are relative to younger subjects (24-55 y
The data shown for female subjects are relative to male subjects.
The data shown for renal and hepatic impairment are relative to subjects with normal renal and hepatic function, respectively.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance
VIIBRYD is not a controlled substance.

9.2 Abuse and Dependence
VIIBRYD has been systematically studied in animals and did not demonstrate abuse or dependence potential. While VIIBRYD has not been systematically studied in humans for its potential for abuse, there was no suggested evidence of drug-seeking behavior in the clinical studies. However, it is not possible to predict on the basis of clinical experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of VIIBRYD (e.g., development of tolerance, drug-seeking behavior, increases in dose).

10 OVERDOSAGE

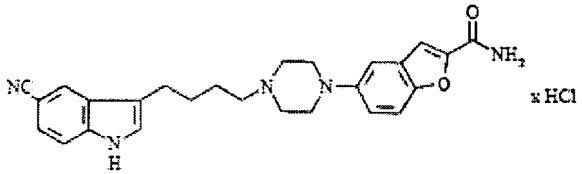
10.1 Human Experience
There is limited clinical experience regarding human overdosage with VIIBRYD. Four patients and 1 patient's child experienced an overdose of VIIBRYD; all recovered. The adverse reactions associated with overdose of VIIBRYD at doses of 200-280 mg as observed in clinical trials included serotonin syndrome, lethargy, restlessness, hallucinations, and disorientation.

10.2 Management of Overdose

Consult a Certified Poison Control Center for up-to-date guidance and advice. Telephone numbers for certified poison control centers are listed in the Physicians' Desk Reference® (PDR). No specific antidotes for vilazodone are known. In case of an overdose, provide supportive care, including close medical supervision and monitoring. Treatment should consist of those general measures employed in the management of overdosage with any drug. Consider the possibility of multiple drug overdose. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be considered. Removal of vilazodone by dialysis has not been studied; however, the high volume of distribution of vilazodone suggests that dialysis will not be effective in reducing vilazodone plasma concentrations.

11 DESCRIPTION
VIIBRYD Tablets for oral administration contain polymorph Form IV vilazodone hydrochloride (HCl), a selective serotonin reuptake inhibitor and a $5HT_{1A}$ receptor partial agonist.

Vilazodone HCl is 2-benzofurancarboxamide, 5-[4-[4-(5-cyano-1*H*-indol-3-yl)butyl]-1-piperazinyl]-, hydrochloride (1:1). Its molecular weight is 477.99. The structural formula is:



In addition to the active ingredient, VIIBRYD Tablets contain lactose monohydrate, microcrystalline cellulose, magnesium stearate, colloidal silicon dioxide, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, FD&C Blue #1 (40 mg only), FD&C Yellow #6 (20 mg only) and FD&C Red #40 (10 mg only).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of action
The mechanism of the antidepressant effect of vilazodone is not fully understood but is thought to be related to its enhancement of serotonergic activity in the CNS through selective inhibition of serotonin reuptake. Vilazodone is also a partial agonist at serotonergic $5\text{-}HT_{1A}$ receptors; however, the net result of this action on serotonergic transmission and its role in vilazodone's antidepressant effect are unknown.

12.2 Pharmacodynamics
Vilazodone binds with high affinity to the serotonin reuptake site (Ki= 0.1 nM), but not to the norepinephrine (Ki=56 nM) or dopamine (Ki=37 nM) reuptake sites. Vilazodone potently and selectively inhibits reuptake of serotonin (IC_{50}= 1.6 nM). Vilazodone also binds selectively with high affinity to $5\text{-}HT_{1A}$ receptors (IC_{50}=2.1 nM) and is a $5\text{-}HT_{1A}$ receptor partial agonist.

Thorough QT Study: Treatment with VIIBRYD did not prolong the QTc interval. The effect of vilazodone (20, 40, 60, and 80 mg) on the QTc interval was evaluated in a randomized, placebo-, and active-controlled (moxifloxacin 400 mg), parallel-group, thorough QTc study in 157 healthy subjects. The study demonstrated an ability to detect small effects. The upper bound of the 90% confidence interval for the largest placebo-adjusted, baseline-corrected QTc interval was below 10 msec, based on the individual correction method (QTcI). This is below the threshold for clinical concern. However, it is unknown whether 80 mg is adequate to represent a high clinical exposure condition.

12.3 Pharmacokinetics
Vilazodone activity is due primarily to the parent drug. The pharmacokinetics of vilazodone (5 mg – 80 mg) are dose-proportional. Accumulation of vilazodone is predictable from single dose data, does not vary with dose, and steady-state is achieved in about 3 days. Elimination of vilazodone is primarily by hepatic metabolism with a terminal half-life of approximately 25 hours. At steady-state, after daily dosing of VIIBRYD 40 mg under fed conditions, the mean C_{max} value is 156 ng/mL, and the mean AUC ($_{0\text{-}24\ hours}$) value is 1645 ng·h/mL.

Absorption
Vilazodone concentrations peak at a median of 4-5 hours (T_{max}) after administration and decline with a terminal half-life of approximately 25 hours. The absolute bioavailability of vilazodone is 72% with food. Administration of VIIBRYD with food (high fat or light meal) increases oral bioavailability (C_{max} increased by approximately 147-160%, and AUC increased by approximately 64-85%).

Coadministration of VIIBRYD with ethanol or with a proton pump inhibitor (pantoprazole) did not affect the rate or extent of vilazodone absorption [*see Drug Interactions (7.3, Figure 1)*]. In addition, neither the T_{max} nor terminal elimination rate of vilazodone was altered by coadministration with either pantoprazole or ethanol.

Absorption is decreased by approximately 25% if vomiting occurs within 7 hours of ingestion; no replacement dose is needed.

Distribution
Vilazodone is widely distributed and approximately 96-99% protein-bound

Metabolism and Elimination
VIIBRYD is extensively metabolized through CYP and non-CYP pathways (possibly by carboxylesterase), with only 1% of the dose recovered in the urine and 2% of the dose recovered in the feces as unchanged vilazodone. CYP3A4 is primarily responsible for its metabolism among CYP pathways, with minor contributions from CYP2C19 and CYP2D6. *In vitro* studies with human microsomes and human hepatocytes indicate that vilazodone is unlikely to inhibit or induce the metabolism of other CYP (except for CYP2C8) substrates; and an *in vivo* study with probe substrates for CYP2C19, 2D6 and 3A4 showed vilazodone did not alter the pharmacokinetics of the probe substrates. However, an *in vivo* study with probe substrate for CYP2C19 demonstrated a minor induction of CYP2C19. Strong inhibitors of CYP3A4 (e.g., ketoconazole) can reduce the metabolism of vilazodone *in vivo* and increase exposure. Conversely, inducers of CYP3A4 can decrease vilazodone exposure *[see Drug Interactions (7.3)]*.

The presence of mild or moderate renal impairment, or mild or moderate hepatic impairment did not affect the apparent clearance of vilazodone.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Carcinogenicity studies were conducted in which B6C3F1mice and Wistar rats were given oral doses of vilazodone up to 135 and 150 mg/kg/day, respectively, for 2 years. These doses are approximately 16.5 and 36 times the maximum recommended human dose (MRHD) of 40 mg, respectively, on a mg/m^2 basis.

In mice, the incidence of hepatocellular carcinomas was increased in males at 16.5 times the MRHD; this finding was not observed at 5.5 times the MRHD. The incidence of malignant mammary gland tumors was numerically increased in females at 5.5 and 16.5 times the MRHD, with statistical significance at 16.5 the MHRD; this finding was not observed at 1.8 times the MRHD. Elevated prolactin levels were observed in a 2-week study of vilazodone administered at 5.5 and 33 times the MRHD. Increases in prolactin levels are known to cause mammary tumors in rodents.

In the rat study, vilazodone was not carcinogenic in either sex at doses up to 36 times the MRHD.

Mutagenesis
Vilazodone was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test). Vilazodone was negative in the *in vitro* V79/HGRPT mammalian cell forward mutation assay. Vilazodone was clastogenic in two *in vitro* mammalian cell chromosome aberration assays. However, vilazodone was negative for clastogenic activity in both an *in vivo* rat bone marrow chromosome aberration assay and a micronucleus test. Vilazodone was also negative in an *in vivo/in vitro* unscheduled DNA synthesis assay in rats.

Impairment of Fertility
Treatment of rats with vilazodone at a dose of 125 mg/kg, which is 30 times the maximum recommended human dose (MRHD) of 40 mg on a mg/m^2 basis, caused impairment of male fertility with no effect on female fertility. Impaired male fertility was not observed at 6 times the MRHD.

14 CLINICAL STUDIES
The efficacy of VIIBRYD as a treatment for major depressive disorder was established in two 8-week, multicenter, randomized, double-blind, placebo-controlled studies in adult (18-70 years of age) outpatients who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria for MDD. In these studies, patients were titrated over 2 weeks to a dose of 40 mg of VIIBRYD with food (n=436) or placebo (n = 433) once daily. VIIBRYD was superior to placebo in the improvement of depressive symptoms as measured by the mean change from baseline to Week 8 in the Montgomery-Asberg Depression Rating Scale (MADRS) total score. Examination of population subgroups based on age (there were few patients over 65), gender, and race did not reveal any clear evidence of differential responsiveness.

Table 4. Summary of Results for the Primary Efficacy Endpoint

Study Number	Primary Endpoint	LS Mean (95% CI) [a] difference from placebo in change from baseline
1	MADRS	-3.2 (-5.2, -1.3)
2	MADRS	-2.5 (-4.4, -0.6)

[a] Least Squares Mean (95% Confidence Interval)

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied
VIIBRYD (vilazodone HCl) Tablets are supplied in the following configurations:

10 mg, pink, oval tablet, debossed with 10 on one side
75838-110-30: 30-count bottles
75838-110-90: 90-count bottles
75838-110-52: 500-count bottles
75838-110-12: 10 blisters cards each containing 10 tablets (HUD)

20 mg, orange, oval tablet, debossed with 20 on one side
75838-120-30: 30-count bottles
75838-120-90: 90-count bottles

75838-120-52: 500-count bottles
75838-120-12: 10 blisters cards each containing 10 tablets (HUD)

40 mg, blue, oval tablet, debossed with 40 on one side
75838-140-30: 30-count bottles
75838-140-90: 90-count bottles
75838-140-52: 500-count bottles
75838-140-12: 10 blisters cards each containing 10 tablets (HUD)

Patient Starter Kit
75838-179-30: blister card containing 30 tablets:
10 mg, pink, oval, debossed with 10 on one side: 7 tablets
20 mg, orange, oval, debossed with 20 on one side: 7 tablets
40 mg, blue, oval, debossed with 40 on one side: 16 tablets

16.2 Storage
VIIBRYD (vilazodone HCl) Tablets should be stored at 25°C (77°F) with excursions permitted to 15°C - 30°C (59°F - 86°F) [*see USP Controlled Room Temperature*].

17 PATIENT COUNSELING INFORMATION
See Medication Guide (17.2).

17.1 Information for Patients
Advise patients and their caregivers about the benefits and risks associated with treatment with VIIBRYD and counsel them in its appropriate use. Advise patients and their caregivers to read the Medication Guide and assist them in understanding its contents. The complete text of the Medication Guide is reprinted at the end of this document.

Suicide Risk
Advise patients and caregivers to look for the emergence of suicidality, especially early during treatment and when the dose is adjusted up or down [*see Box Warning and Warnings and Precautions (5.1)*].

Dosing and Administration
Instruct patients to take VIIBRYD with food. When initiating treatment with VIIBRYD the dose should be titrated, starting with a dose of 10 mg once daily for 7 days, followed by 20 mg once daily for an additional 7 days, and then increased to 40 mg once daily.

Concomitant Medication
Instruct patients not to take VIIBRYD with an MAOI or within 14 days of stopping an MAOI and to allow 14 days after stopping VIIBRYD before starting an MAOI [*see Contraindications (4.1)*].

Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions
Caution patients about the risk of serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions, particularly with the concomitant use of VIIBRYD and triptans, tramadol, tryptophan supplements, other serotonergic agents, or antipsychotic drugs [*see Warnings and Precautions (5.2) and Drug Interactions (7.1)*].

Seizures
Caution patients about using VIIBRYD if they have a history of a seizure disorder [*see Warnings and Precautions (5.3)*]. Patients with a history of seizures were excluded from clinical studies.

Abnormal Bleeding
Caution patients about the concomitant use of VIIBRYD and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of abnormal bleeding [*see Warnings and Precautions (5.4)*].

Activation of Mania/Hypomania
Advise patients and their caregivers to observe for signs of activation of mania/hypomania [*see Warnings and Precautions (5.5)*].

Discontinuation
Advise patients not to stop taking VIIBRYD without talking first with their healthcare provider. Patients should be aware that discontinuation effects may occur when suddenly stopping VIIBRYD [*see Warnings and Precautions (5.6)*].

Hyponatremia
Advise patients that if they are treated with diuretics, or are otherwise volume depleted, or are elderly, they may be at greater risk of developing hyponatremia while taking VIIBRYD [*see Warnings and Precautions (5.7)*].

Alcohol
Advise patients to avoid alcohol while taking VIIBRYD [*see Drug Interactions (7.3)*].

Allergic Reactions
Advise patients to notify their healthcare provider if they develop an allergic reaction such as rash, hives, swelling, or difficulty breathing.

Pregnancy
Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during therapy with VIIBRYD [*see Use in Specific Populations (8.1)*].

Nursing Mothers
Advise patients to notify their healthcare provider if they are breastfeeding an infant and would like to continue or start VIIBRYD [*see Use in Specific Populations (8.3)*].

Interference with Cognitive and Motor Performance

Caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain that VIIBRYD therapy does not adversely affect their ability to engage in such activities.

TROVIS PHARMACEUTICALS

Distributed by
Trovis Pharmaceuticals LLC
New Haven, CT 06511

877-878-7200
viibryd.com

Licensed from Merck KGaA,
Darmstadt, Germany

Product protected by U.S. Patent No. 5,532,241 and U.S. Patent No. 7,834,020.

VZ59PI0000
Revised: January 2010

MEDICATION GUIDE

VIIBRYD *[vi-brid]*
(vilazodone hydrochloride)
Tablets

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

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

VIIBRYD and other antidepressant medicines may cause serious side effects.

Call your healthcare provider right away if you have any of the following symptoms, or call 911 if there is an emergency:

1. Suicidal thoughts or actions:
- **VIIBRYD and other antidepressant medicines may increase suicidal thoughts or actions** in some children, teenagers, or young adults within the **first few months of treatment or when the dose is changed.**
- Depression or other serious mental illnesses are the most important causes of suicidal thoughts or actions.
- Watch for these changes and call your healthcare provider right away if you notice:
- New or sudden changes in mood, behavior, actions, thoughts, or feelings, especially if severe.
- Pay particular attention to such changes when VIIBRYD is started or when the dose is changed.

  Keep all follow-up visits with your healthcare provider and call between visits if you are worried about symptoms.

  Call your healthcare provider right away if you have any of the following symptoms, especially if they are new, worse, or worry you:
  - attempts to commit suicide
  - acting on dangerous impulses
  - acting aggressive or violent
  - thoughts about suicide or dying
  - new or worse depression
  - new or worse anxiety or panic attacks
  - feeling agitated, restless, angry or irritable
  - trouble sleeping
  - an increase in activity or talking more than what is normal for you (mania)
  - other unusual changes in behavior or mood

2. Serotonin Syndrome or Neuroleptic Malignant Syndrome-like reactions:
- agitation, hallucinations, coma or other changes in mental status
- coordination problems or muscle twitching (overactive reflexes)
- fast heartbeat, high or low blood pressure
- sweating or fever
- nausea, vomiting, or diarrhea
- muscle stiffness or tightness

3. Abnormal bleeding: VIIBRYD and other antidepressant medicines may increase your risk of bleeding or bruising, especially if you take the blood thinner warfarin (Coumadin, Jantoven), a non-steroidal anti-inflammatory drug (NSAID), or aspirin.

4. Seizures or convulsions.

5. Manic episodes:
- greatly increased energy
- severe trouble sleeping
- racing thoughts
- reckless behavior
- unusually grand ideas
- excessive happiness or irritability
- talking more or faster than usual

6. Low salt (sodium) levels in the blood.

Elderly people may be at greater risk for this. Symptoms may include:

- headache
- weakness or feeling unsteady
- confusion, problems concentrating or thinking or memory problems

Do not stop VIIBRYD without first talking to your healthcare provider. Stopping VIIBRYD suddenly may cause serious symptoms including:

- anxiety, irritability, high or low mood, feeling restless or sleepy
- headache, sweating, nausea, dizziness
- electric shock-like sensations, tremor, confusion

What is VIIBRYD?

VIIBRYD is a prescription medicine used to treat a certain type of depression called Major Depressive Disorder (MDD). It is important to talk with your healthcare provider about the risks of treating depression and also the risk of not treating it. You should discuss all treatment choices with your healthcare provider.

Talk to your healthcare provider if you do not think that your condition is getting better with VIIBRYD treatment.

It is not known if VIIBRYD is safe and effective in children.

Who should not take VIIBRYD?

Do not take VIIBRYD if you:

- Take an Monoamine Oxidase Inhibitor (MAOI). Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI.
  - Do not take an MAOI within 14 days of stopping VIIBRYD.
  - Do not start VIIBRYD if you stopped taking an MAOI in the last 14 days.

  People who take VIIBRYD close in time to taking an MAOI may have serious or even life-threatening side effects. Get medical help right away if you have any of these symptoms:
  - high fever
  - uncontrolled muscle spasms
  - stiff muscles
  - rapid changes in heart rate or blood pressure
  - confusion
  - loss of consciousness (pass out)

What should I tell my healthcare provider before taking VIIBRYD?

Before starting VIIBRYD, tell your healthcare provider if you:

- have liver problems
- have kidney problems
- have or had seizures or convulsions
- have bipolar disorder (manic depression) or mania
- have low sodium levels in your blood
- have or had bleeding problems
- drink alcohol
- have any other medical conditions
- Are pregnant or plan to become pregnant. It is not known if VIIBRYD will harm your unborn baby. Talk to your healthcare provider about the benefits and risks of treating depression during pregnancy.
- Are breastfeeding or plan to breastfeed. It is not known if VIIBRYD passes into breast milk. You and your healthcare provider should decide if you should take VIIBRYD while breastfeeding.

Tell your healthcare provider about all the medicines that you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. VIIBRYD and some medicines may interact with each other, may not work as well, or may cause serious side effects when taken together.

Especially tell your healthcare provider if you take:

- triptans used to treat migraine headache
- medicines used to treat mood, anxiety, psychotic or thought disorders, including tricyclics, lithium, SSRIs, SNRIs, buspirone, or antipsychotics
- tramadol
- over-the-counter supplements such as tryptophan or St. John's Wort
- nonsteroidal anti-inflammatory drugs (NSAIDS)
- aspirin

- warfarin (Coumadin, Jantoven)
- mephenytoin (Mesantoin)
- diuretics

Your healthcare provider or pharmacist can tell you if it is safe to take VIIBRYD with your other medicines. Do not start or stop any medicine while taking VIIBRYD without talking to your healthcare provider first.

How should I take VIIBRYD?

- Take VIIBRYD exactly as prescribed. Your healthcare provider may need to change the dose of VIIBRYD until it is the right dose for you.
- **Take VIIBRYD with food.** VIIBRYD may not work as well if you take it on an empty stomach.
- If you miss a dose of VIIBRYD, take the missed dose as soon as you remember. If it is almost time for the next dose, skip the missed dose and take your next dose at the regular time. Do not take two doses of VIIBRYD at the same.
- If you take too much VIIBRYD, call your healthcare provider or poison control center right away, or get emergency treatment.

What should I avoid while taking VIIBRYD?

- VIIBRYD can cause sleepiness or may affect your ability to make decisions, think clearly, or react quickly. You should not drive, operate heavy machinery, or do other dangerous activities until you know how VIIBRYD affects you.
- You should avoid drinking alcohol while taking VIIBRYD. See "What should I tell my healthcare provider before taking VIIBRYD?"

What are the possible side effects of VIIBRYD?

VIIBRYD may cause serious side effects, including:

- **See "What is the most important information I should know about VIIBRYD?"**

Common side effects in people who take VIIBRYD include:

- diarrhea
- nausea or vomiting
- trouble sleeping

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of VIIBRYD. For more information, ask your healthcare provider 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 VIIBRYD?

Store VIIBRYD at room temperature (59°F to 86°F or 15°C to 30°C).

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

General information about VIIBRYD.

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

This Medication Guide summarizes the most important information about VIIBRYD. If you would like more information, talk with your healthcare provider. You may ask your healthcare provider or pharmacist for information about VIIBRYD that is written for healthcare professionals.

For more information about VIIBRYD call 1-877-878-7200 or go to www.VIIBRYD.com.

What are the ingredients in VIIBRYD?

Active ingredient: vilazodone hydrochloride
Inactive ingredients: lactose monohydrate, microcrystalline cellulose, magnesium stearate, colloidal silicon dioxide, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and FD&C Blue #1 (40 mg only), FD&C Yellow #6 (20 mg only) and FD&C Red #40 (10 mg only).

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

TROVIS PHARMACEUTICALS

Trovis Pharmaceuticals LLC
5 Science Park
New Haven, CT 06511

Licensed from Merck KGaA, Darmstadt, Germany

Product protected by U.S. Patent No. 5,532,241 and U.S. Patent No. 7,834

VIIBRYD™ is a trademark of Trovis Pharmaceuticals LLC.

Revised January2011

NDA 22-567 vilazodone HCl Tablets

Viibryd™

(*vilazodone hydrochloride*)

Class of Product: Antidepressant

PGxHealth, LLC
5 Science Park
New Haven, CT 06511

Contact Information: PGxHealth, LLC (1-877-878-7200)

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL

The goal of this REMS is to inform patients about the serious risks associated with the use of vilazodone HCl Tablets.

II. REMS ELEMENTS:

A. Medication Guide

PGxHealth, LLC, will ensure that a currently approved Medication Guide will be dispensed with each vilazodone prescription in accordance with 21 CFR 208.24.

B. Timetable for Submission of Assessments

PGxHealth, LLC, will submit REMS Assessments to FDA at 18 months, 3 years, and 7 years from the date of the approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. PGxHealth, LLC will submit each assessment so that it will be received by the FDA on or before the due date.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELLIS F UNGER
01/21/2011

EXHIBIT 7

Certificate of Correction

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,532,241
APPLICATION NO. : 08/314734
DATED : July 2, 1996
INVENTOR(S) : Henning Bottcher et al.

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

Column 16, Line 46, please delete "R^3 is H, OH or OA;"

Signed and Sealed this

Tenth Day of November, 2009

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

EXHIBIT 8

Patent Bibliographic Data

Return To:

USPTO Home Page

Finance Online Shopping Page

United States Patent and Trademark Office

Patent Bibliographic Data				02/08/2011 11:26 AM	
Patent Number:	5532241		**Application Number:**	08314734	
Issue Date:	07/02/1996		**Filing Date:**	09/29/1994	
Title:	PIPERIDINES AND PIPERAZINES				
Status:	4th, 8th and 12th year fees paid			**Entity:**	Large
Window Opens:	N/A	**Surcharge Date:**	N/A	**Expiration:**	N/A
Fee Amt Due:	Window not open	**Surchg Amt Due:**	Window not open	**Total Amt Due:**	Window not open
Fee Code:					
Surcharge Fee Code:					
Most recent events (up to 7):	12/11/2007 12/09/2003 12/29/1999 09/10/1996	Payment of Maintenance Fee, 12th Year, Large Entity. Payment of Maintenance Fee, 8th Year, Large Entity. Payment of Maintenance Fee, 4th Year, Large Entity. Payor Number Assigned. --- End of Maintenance History ---			
Address for fee purposes:	CPA GLOBL LIMITED 2318 Mill Road 12th Floor ALEXANDRIA, VA 22314				

Run Another Query

Return To:

USPTO Home Page

Finance Online Shopping Page

United States Patent and Trademark Office

Patent Maintenance Fees		02/08/2011 03:19 PM EST	
Patent Number:	5532241	**Application Number:**	08314734
Issue Date:	07/02/1996	**Filing Date:**	09/29/1994
Window Opens:		**Surcharge Date:**	
Window Closes:		**Payment Year:**	
Entity Status:	LARGE		

Customer Number:	197
Street Address:	CPA GLOBL LIMITED
City:	ALEXANDRIA
State:	VA
Zip Code:	22314
Phone Number:	(703) 739-2234

Currently there are no fees due.

Need Help? | USPTO Home Page | Finance Online Shopping Page | Alerts Page

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Customer No 197 | ISTMT | DATE PRINTED 02/08/2011

CPA GLOBL LIMITED
2318 Mill Road 12th Floor
ALEXANDRIA VA 22314

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
5,532,241	**$830.00**	**$0.00**	**12/29/99**	**08/314,734**	**07/02/96**	**09/29/94**	**04**	**NO**	**MERCK1617**

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Customer No 197 | ISTMT | DATE PRINTED 02/08/2011

CPA GLOBL LIMITED
2318 Mill Road 12th Floor
ALEXANDRIA VA 22314

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
5,532,241	**$2,090.00**	**$0.00**	**12/09/03**	**08/314,734**	**07/02/96**	**09/29/94**	**08**	**NO**	**MERCK1617**

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Customer No 197 | ISTMT | DATE PRINTED 02/08/2011

CPA GLOBL LIMITED
2318 Mill Road 12th Floor
ALEXANDRIA VA 22314

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
5,532,241	**$3,910.00**	**$0.00**	**12/11/07**	**08/314,734**	**07/02/96**	**09/29/94**	**12**	**NO**	**MERCK1617**

EXHIBIT 9

Letter Acknowledging Receipt of the IND

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 54,613 Date DEC 1 1997

Lipha Pharmaceuticals, Inc.
ATTN: Anita M. Goodman, M.D.
9 West 57th Street, Suite 3825
New York, NY 10019-2701

Dear Sir or Madam:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted pursuant to Section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned:	54,613
Sponsor:	Lipha Pharmaceuticals, Inc.
Name of Drug:	EMD 68 843
Date of Submission:	November 21, 1997
Date of Receipt:	November 24, 1997

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, within the 30-day waiting period, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies until correction, we will notify you immediately that the study may not be initiated ("clinical hold") or that certain restrictions must be placed on it. In the event of such notification, you must continue to withhold, or to restrict, such studies until you have submitted material to correct the deficiencies, and we have notified you that the material you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the regulations implementing that Act (Title 21 of the Code of Federal Regulations). Those responsibilities include reporting any adverse experience associated with use of the drug that is both serious and unexpected to the FDA as soon as possible and in no event later than 10 working days after initial receipt of the information and reporting any unexpected fatal or life-threatening experience to the FDA by telephone no later than 3 working days after receipt of the information (21 CFR 312.32), and submission of annual progress reports (21 CFR 312.33).

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, and addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research (HFD-120)
Attention: Document Control Room
5600 Fishers Lane
Rockville, Maryland 20857

Should you have any questions concerning this IND, please contact: Mr. Paul David
Project Manager
(301) 594-2777

Sincerely yours,

John Purvis
Chief, Project Management Staff
Division of Neuropharmacologic Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc: Original IND - pink
HFD-120 - yellow
HFD-120/CSO - green

IND ACKNOWLEDGEMENT

EXHIBIT 10

Letter Acknowledging Receipt of NDA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-567

NDA ACKNOWLEDGMENT

PgxHealth, LLC
Attention: Kimberly Fabrizio
Vice President, Regulatory Affairs
Five Science Park
New Haven, CT 06511

Dear Ms. Fabrizio:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Vilazodone HCL tablets, 10 mg, 20 mg, and 40 mg

Date of Application: March 22, 2010

Date of Receipt: March 22, 2010

Our Reference Number: NDA 22-567

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 21, 2010 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm

If you have any questions, call me at (301) 796-2145.

Sincerely,

{See appended electronic signature page}

CDR Bill Bender, R.Ph., MS HCA
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22567	ORIG-1	PGX HEALTH LLC	VILAZODONE HCL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM H BENDER
03/24/2010

EXHIBIT 11

List of Significant Activities Undertaken during Regulatory Review Period

LIST OF SIGNIFICANT ACTIVITIES UNDERTAKEN DURING THE REGULATORY REVIEW PERIOD

SUBMISSION DATE	SERIAL NUMBER	DESCRIPTION
11/21/1997	000	IND Submitted to FDA (IND Effective on December 21, 1997)
2/27/1998	004	Draft Rat and Mouse Carcinogenicity Study Protocols for CAC review
8/26/1998	007	Transfer of IND Ownership from Lipha Pharmaceuticals to Merck KGaA
12/1/1998	010	Study Protocol - 15-Day Safety Report
12/31/1998	011	Study Protocol - 15-Day Safety Report
3/5/1999	013	Annual Report 1998 (12 volumes)
6/16/1999	014	Study Protocol - Protocol Amendment
2/21/2000	018	Annual Report 1999 (6 volumes)
12/19/2000	020	FDA Correspondence (toxicology)
2/8/2001	021	Annual Report 2000 (4 volumes)
4/30/2001	022	Submission of Phase 2 Study Reports
1/5/2001	023	Transfer of IND Ownership to GSK
5/15/2001		FDA Correspondence (Clinical)
10/25/2001	027	Protocol Amendment
12/21/2001	032	Protocol Amendment
3/1/2002	037	Protocol Amendment
4/30/2002	039	Protocol Amendment
7/24/2002	044	Protocol Amendment
10/23/2002	047	General Correspondence (Protocol)
1/7/2003	050	Protocol Amendment
2/11/2003	052	Transfer of IND Ownership to Merck KGaA
11/7/2003	053	Information Amendment - General Correspondence
2/20/2004	054	General Correspondence
10/25/2004	055	Transfer of IND Ownership to GNSC
12/22/2004	057	Submission of Carcinogenicity Report
1/19/2005	058	Annual Report 2004
1/5/2005		General Teleconference (FDA) - Outstanding Reports
5/12/2005		FDA Correspondence (Pharm/Tox))
10/10/2005		FDA Type B Meeting Request (End-of-Phase 2 meeting)
11/19/2005	060	FDA Meeting Request Briefing Documents
12/21/2005	061	Protocol Submission
6/22/2006	065	FDA Meeting Request (CMC and Clin Pharm)
7/6/2006	067	FDA Meeting Request Briefing Documents

SUBMISSION DATE	SERIAL NUMBER	DESCRIPTION
1/17/2007	069	Annual Report 2006
3/26/2007	071	Clinical Statistical Analysis Plan
7/20/2007	074	Responses to FDA SAP Comments
8/3/2007		General Correspondence (Drug Substance)
9/27/2007	077	Protocol Submission
1/8/2008	080	Investigator Brochure and Protocol
4/25/2008	091	IND Safety Report
6/8/2008	095	IND Safety Report
8/1/2008	100	Clinical Study Report
10/20/2008	109	Clinical Study Report
12/8/2008	116	Clinical Study Report
1/19/2009	123	Annual Report (2008)
3/11/2009	128	IND Safety Report
6/3/2009	134	CMC Update/Amendment
8/19/2009		FDA Contact Report
1/14/2010		FDA Contact Report
1/24/2010	142	Annual Report (2009)
3/22/2010		NDA No. 22-567 Submission
1/21/2011		NDA No. 22-567 FDA Approval

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,532,241
APPLICATION NO. : 08/314734
DATED : July 2, 1996
INVENTOR(S) : Henning Bottcher et al.

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

Column 16, Line 46, please delete "R^3 is H, OH or OA;"

Signed and Sealed this

Tenth Day of November, 2009

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

SPE RESPONSE FOR CERTIFICATE OF CORRECTION

Paper No.: _____

DATE : 09/14/09

TO SPE OF : ART UNIT 1624

SUBJECT : Request for Certificate of Correction for Appl. No.: 08314734 Patent No.: 5532241

Please respond to this request for a certificate of correction within 7 days.

FOR IFW FILES:

Please review the requested changes/corrections as shown in the **COCIN** document(s) in the IFW application image. No new matter should be introduced, nor should the scope or meaning of the claims be changed.

Please complete the response (see below) and forward the completed response to scanning using document code **COCX**.

FOR PAPER FILES:

Please review the requested changes/corrections as shown in the attached certificate of correction. Please complete this form (see below) and forward it with the file to:

Certificates of Correction Branch (C of C)
Randolph Square 9C62-D
Palm Location 7580

You can fax the Directors/SPE response to 571-270-9990

Lamonte Newsome
Certificates of Correction Branch
703-756-1574

Thank You For Your Assistance

The request for issuing the above-identified correction(s) is hereby:
Note your decision on the appropriate box.

- ☒ **Approved** — **All** changes apply.
- ☐ **Approved in Part** — Specify below which changes **do not** apply.
- ☐ **Denied** — State the reasons for denial below.

Comments: The request to delete R^3 definition is approved since R^3 is extraneous (directed to subject matter not elected/allowed).

EB
10/15/09

1624

SPE RESPONSE FOR CERTIFICATE OF CORRECTION

Paper No.: _____

DATE : 09/14/09

TO SPE OF : ART UNIT 1624

SUBJECT : Request for Certificate of Correction for Appl. No.: 08314734 Patent No.: 5532241

Please respond to this request for a certificate of correction within 7 days.

FOR IFW FILES:

Please review the requested changes/corrections as shown in the **COCIN** document(s) in the IFW application image. No new matter should be introduced, nor should the scope or meaning of the claims be changed.

Please complete the response (see below) and forward the completed response to scanning using document code **COCX**.

FOR PAPER FILES:

Please review the requested changes/corrections as shown in the attached certificate of correction. Please complete this form (see below) and forward it with the file to:

Certificates of Correction Branch (C of C)
Randolph Square 9C62-D
Palm Location 7580

You can fax the Directors/SPE response to 571-270-9990

Lamonte Newsome
Certificates of Correction Branch
703-756-1574

Thank You For Your Assistance

The request for issuing the above-identified correction(s) is hereby:
Note your decision on the appropriate box.

☒ **Approved**	**All** changes apply.
☐ **Approved in Part**	Specify below which changes **do not** apply.
☐ **Denied**	State the reasons for denial below.

Comments: The request to delete R^3 definition is approved since R^3 is extraneous (directed to subject matter not elected/allowed).

EB
10/15/09

1624

PTOL-306 (REV. 7/03) U.S. DEPARTMENT OF COMMERCE Patent and Trademark Office

PTO/SB/ 44 (08-00)
Approved for use through 09/30/2000. OMB 0651-0033
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.
(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO : 5,532,241

DATED: July 2, 1996

INVENTOR (S): Henning Bottcher et al.

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

Column 16, Line 46, please delete "R^3 is H, OH or OA;"

MAILING ADDRESS OF SENDER: Millen, White, Zelano & Branigan, P.C.
2200 Clarendon Blvd, Suite 1400
Arlington, VA 22201

PATENT NO. 5,532,241

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U.S. Patent No.: 5,532,241

Issued : July 2, 1996

Serial No. : 08/314,734

Filed : September 29, 1994

For : **Piperidines And Piperazines**

PETITION FOR CERTIFICATE OF CORRECTION
PURSUANT TO 37 C.F.R. § 1.322 OR § 1.323

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicants hereby request that the above-identified U.S. patent be corrected in accordance with the attached Certificate of Correction.

I. C.F.R. § 1.322

☐ The mistake(s) was/were incurred through the fault of the Patent and Trademark Office and is/are clearly disclosed in the records of the Office. Therefore, no fee is due.

II. C.F.R. § 1.323

☒ The mistake was made by the applicant. Therefore, a payment in the amount of $100.00 for the fee set forth in 37 C.F.R. § 1.20(a) is enclosed herewith.

Enclosed herewith is a Form PTO-1050 listing an error that has been found in the above-identified patent. The error is of a clerical or typographical nature or of minor character and was made in good faith. The requested correction does not constitute new matter or require reexamination.

III. Accordingly, patentees and their assignee respectfully request that the Patent and Trademark Office issue a Certificate of Correction pursuant to 37 C.F.R. § 1.322 or § 1.323, respectively.

Respectfully submitted,

/Brion P. Heaney/

_____

Brion P. Heaney, Reg. No. 32,542
Attorney for Applicants

MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza 1
2200 Clarendon Blvd. Suite 1400
Arlington, Virginia 22201
Telephone: (703) 243-6333
Facsimile: (703) 243-6410

Attorney Docket No.: MERCK-1617

Date: September 1, 2009

Electronic Patent Application Fee Transmittal

Application Number:	08314734
Filing Date:	29-Sep-1994
Title of Invention:	PIPERIDINES AND PIPERAZINES
First Named Inventor/Applicant Name:	HENNING BOTTCHER
Filer:	Brion Patrick Heaney/Ashley Weber
Attorney Docket Number:	MERCK1617

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Certificate of correction	1811	1	100	100
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**100**

Electronic Acknowledgement Receipt

EFS ID:	5991821
Application Number:	08314734
International Application Number:	
Confirmation Number:	3429
Title of Invention:	PIPERIDINES AND PIPERAZINES
First Named Inventor/Applicant Name:	HENNING BOTTCHER
Correspondence Address:	MILLEN WHITE ZELANO AND BRANIGAN ARLINGTON COURTHOUSE PLAZA I SUITE 1400 2200 CLARENDON BOULEVARD - ARLINGTON VA 22201 US - -
Filer:	Brion Patrick Heaney/Ashley Weber
Filer Authorized By:	Brion Patrick Heaney
Attorney Docket Number:	MERCK1617
Receipt Date:	01-SEP-2009
Filing Date:	29-SEP-1994
Time Stamp:	14:22:37
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$100

RAM confirmation Number	505
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Certificate of Correction	pto1050.pdf	12285 166ce8895f13a6cc02d0123b4afeb49f16f6ea61	no	1
Warnings:					
Information:					
2	Request for Certificate of Correction	petforcoc.pdf	18834 d18baa8d808ed388a12fbcb7f084bedf98addb1c	no	2
Warnings:					
Information:					
3	Fee Worksheet (PTO-875)	fee-info.pdf	30243 4d243f53d82bf4194c59257d594e39a513f098b8	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	61362		

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.

#10
L.M.N.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

9/1/9

U.S. Patent No.: 5,532,241

Issued : July 2, 1996

Serial No. : 08/314,734

Filed : September 29, 1994

For : **Piperidines And Piperazines**

PETITION FOR CERTIFICATE OF CORRECTION
PURSUANT TO 37 C.F.R. § 1.322 OR § 1.323

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicants hereby request that the above-identified U.S. patent be corrected in accordance with the attached Certificate of Correction.

I. C.F.R. § 1.322

☐ The mistake(s) was/were incurred through the fault of the Patent and Trademark Office and is/are clearly disclosed in the records of the Office. Therefore, no fee is due.

II. C.F.R. § 1.323

☒ The mistake was made by the applicant. Therefore, a payment in the amount of $100.00 for the fee set forth in 37 C.F.R. § 1.20(a) is enclosed herewith.

Enclosed herewith is a Form PTO-1050 listing an error that has been found in the above-identified patent. The error is of a clerical or typographical nature or of minor character and was made in good faith. The requested correction does not constitute new matter or require reexamination.

III. Accordingly, patentees and their assignee respectfully request that the Patent and Trademark Office issue a Certificate of Correction pursuant to 37 C.F.R. § 1.322 or § 1.323, respectively.

Respectfully submitted,

/Brion P. Heaney/

Brion P. Heaney, Reg. No. 32,542
Attorney for Applicants

MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza I
2200 Clarendon Blvd. Suite 1400
Arlington, Virginia 22201
Telephone: (703) 243-6333
Facsimile: (703) 243-6410

Attorney Docket No.: MERCK-1617

Date: September 1, 2009

PTO/SB/ 44 (08-00)
Approved for use through 09/30/2000. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE

SN: 08/314,734 # CERTIFICATE OF CORRECTION

PATENT NO : 5,532,241

Issue DATED: July 2, 1996

INVENTOR (S): Henning Bottcher et al.

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

Column 16, Line 46, please delete "R^3 is H, OH or OA;"

MAILING ADDRESS OF SENDER: Millen, White, Zelano & Branigan, P.C.
2200 Clarendon Blvd, Suite 1400
Arlington, VA 22201

PATENT NO. 5,532,241

PTO/SB/ 44 (08-00)
Approved for use through 09/30/2000. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO : 5,532,241

DATED: July 2, 1996

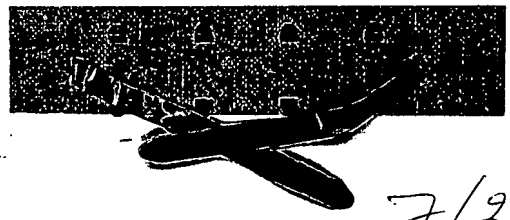
INVENTOR (S): Henning Bottcher et al.

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

Column 16, Line 46, please delete "R^3 is H, OH or OA;"

MAILING ADDRESS OF SENDER: Millen, White, Zelano & Branigan, P.C.
2200 Clarendon Blvd, Suite 1400
Arlington, VA 22201

PATENT NO. 5,532,241



7/2/96

PTO UTILITY GRANT
Paper Number 9

The United States of America

The Commissioner of Patents and Trademarks

Has received an application for a patent for a new and useful invention. The title and description of the invention are enclosed. The requirements of law have been complied with, and it has been determined that a patent on the invention shall be granted under the law.

Therefore, this

United States Patent

Grants to the person or persons having title to this patent the right to exclude others from making, using or selling the invention throughout the United States of America for the term of seventeen years from the date of this patent, subject to the payment of maintenance fees as provided by law.

Bruce Lehman

Commissioner of Patents and Trademarks

Marjorie V. Turner

Attest

PTO-1584

FPI-LDM

(RIGHT INSIDE)

1250-142

B

PART B—ISSUE FEE TRANSMITTAL

MAILING INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE. Blocks 2 through 6 should be completed where appropriate. All further correspondence including the Issue Fee Receipt, the Patent, advance orders and notification of maintenance fees will be mailed to addressee entered in Block 1 unless you direct otherwise, by: (a) specifying a new correspondence address in Block 3 below; or (b) providing the PTO with a separate "FEE ADDRESS" for maintenance fee notifications with the payment of Issue Fee or thereafter. **See reverse for Certificate of Mailing.**

1. CORRESPONDENCE ADDRESS

12M2/0207
MILLEN WHITE ZELANO AND BRANIGAN
ARLINGTON COURTHOUSE PLAZA I, SUITE 1400
2200 CLARENDON BOULEVARD
ARLINGTON VA 22201

C

2. INVENTOR(S) ADDRESS CHANGE (Complete only if there is a change)

INVENTOR'S NAME

Street Address

City, State and ZIP Code

CO-INVENTOR'S NAME

Street Address

City, State and ZIP Code

☐ Check if additional changes are on reverse side

SERIES CODE/SERIAL NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
08/314,734	09/29/94	017	BERNHARDT, E 1202	02/07/96

First Named Applicant: BOTTCHER, HENNING

TITLE OF INVENTION: PIPERIDINES AND PIPERAZINES

	ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
1	MERCK1617	514-254.000	08	UTILITY	NO	$1250.00	05/07/96

3. Correspondence address change (Complete only if there is a change)

4. For printing on the patent front page, list the names of not more than 3 registered patent attorneys or agents OR, alternatively, the name of a firm having as a member a registered attorney or agent. If no name is listed, no name will be printed.

1 Millen, White, Zelano, & Branigan, P.C.

2

3

DO NOT USE THIS SPACE

090 RT 04/19/96 08314734 1142 1250.00 CR

5. ASSIGNMENT DATA TO BE PRINTED ON THE PATENT (print or type)

(1) NAME OF ASSIGNEE: MERCK PATENT GESELLSCHAFT MIT BESCHRANKTER HAFTUNG

(2) ADDRESS: (CITY & STATE OR COUNTRY)
Darmstadt, Germany

A. ☐ This application is NOT assigned.

☒ Assignment previously submitted to the Patent and Trademark Office.

☐ Assignment is being submitted under separate cover. Assignments should be directed to Box ASSIGNMENTS.

PLEASE NOTE: Unless an assignee is identified in Block 5, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the PTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

6a. The following fees are enclosed:
☒ Issue Fee ☐ Advance Order - # of Copies

6b. The following fees should be charged to:
DEPOSIT ACCOUNT NUMBER
(ENCLOSE PART C)
☐ Issue Fee ☐ Advance Order - # of Copies
☒ Any Deficiencies in Enclosed Fees

The COMMISSIONER OF PATENTS AND TRADEMARKS is requested to apply the Issue Fee to the application identified above.

(Authorized Signature) Brion P. Heaney (32,542) (Date) 4/16/96

NOTE: The Issue Fee will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the Patent and Trademark Office.

TRANSMIT THIS FORM WITH FEE-CERTIFICATE OF MAILING ON REVERSE

1250-14

B

PART C—CHARGE TO DEPOSIT ACCOUNT

CORRESPONDENCE ADDRESS

12M2/0207
MILLEN WHITE ZELANO AND BRANIGAN
ARLINGTON COURTHOUSE PLAZA I SUITE 1400
2200 CLARENDON BOULEVARD
ARLINGTON VA 22201

C

SERIES CODE/SERIAL NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
08/314,734	09/29/94	017	BERNHARDT, E 1202	02/07/96

First Named Applicant: BOTTCHER; HENNING

TITLE OF INVENTION: PIPERIDINES AND PIPERAZINES

	ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
1	MERCK1617 D	514-254.000	T58	UTILITY	NO	$1250.00	05/07/96

DO NOT USE THIS SPACE

090 RT 04/19/96 08314734 1 142 1250.00 CK

2a. The following fees are enclosed:
☒ Issue Fee ☐ Advance Order - # of Copies

2b. The following fees should be charged to:
DEPOSIT ACCOUNT NUMBER
☐ Issue Fee ☐ Advance Order - # of Copies
☒ Any Deficiencies in Enclosed Fees

The COMMISSIONER OF PATENTS AND TRADEMARKS is requested to apply the Issue Fee to the application identified above.

(Authorized Signature)

4/16/96

NOTE: The Issue Fee will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the Patent and Trademark Office.

Brion P. Heaney (32,542)

TRANSMIT THIS FORM WITH PART B WHEN AUTHORIZING USE OF A DEPOSIT ACCOUNT

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: Box ISSUE FEE
COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

12M2/0207

MILLEN WHITE ZELANO AND BRANIGAN
ARLINGTON COURTHOUSE PLAZA I SUITE 1400
2200 CLARENDON BOULEVARD
ARLINGTON VA 22201

NOTICE OF ALLOWANCE AND ISSUE FEE DUE

☐ Note attached communication from the Examiner
☐ This notice is issued in view of applicant's communication filed _____

SERIES CODE/SERIAL NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
08/314,734	09/29/94	017	BERNHARDT, E 1202	02/07/96

First Named Applicant: BOTTCHER, HENNING

TITLE OF INVENTION: PIPERIDINES AND PIPERAZINES

	ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
1.	MERCK1617	514-254.000	TS8	UTILITY	NO	$1250.00	05/07/96

THE APPLICATION IDENTIFIES ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED.

THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED.

HOW TO RESPOND TO THIS NOTICE:

I. Review the SMALL ENTITY Status shown above.
If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is changed, pay twice the amount of the FEE DUE shown above and notify the patent and Trademark Office of the change in status, or
B. If the Status is the same, pay the FEE DUE shown above.

If the SMALL ENTITY is shown as NO:
A. Pay FEE DUE shown above, or
B. File verified statement of Small Entity Status before, or with, pay of 1/2 the FEE DUE shown above.

II. Part B of this notice should be completed and returned to the Patent and Trademark Office (PTO) with your ISSUE FEE. Even if the ISSUE FEE has already been paid by charge to deposit account, Part B should be completed and returned. If you are charging the ISSUE FEE to your deposit account, Part C of this notice should also be completed and returned.

III. All communications regarding this application must give series code (or filing date), serial number and batch number. Please direct all communication prior to issuance to Box ISSUE FEE unless advised to contrary.

IMPORTANT REMINDER: Patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PATENT AND TRADEMARK OFFICE COPY

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/314,734	09/29/94	BOTTCHER H	MERCK1617

EXAMINER	
BERNHARDT, E	

12M2/0207
MILLEN WHITE ZELANO AND BRANIGAN
ARLINGTON COURTHOUSE PLAZA I SUITE 1400
2200 CLARENDON BOULEVARD
ARLINGTON VA 22201

ART UNIT	PAPER NUMBER
1202	

DATE MAILED: 02/07/96

NOTICE OF ALLOWABILITY

PART I.

1. ☑ This communication is responsive to 1/24/96.
2. ☑ All the claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice Of Allowance And Issue Fee Due or other appropriate communication will be sent in due course.
3. ☑ The allowed claims are 1-8, 10-12, 16-18, 24-25 and 28.
4. ☐ The drawings filed on _____ are acceptable.
5. ☑ Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has [☑] been received. [_] not been received. [_] been filed in parent application Serial No. _____, filed on _____.
6. ☐ Note the attached Examiner's Amendment.
7. ☐ Note the attached Examiner Interview Summary Record, PTOL-413.
8. ☐ Note the attached Examiner's Statement of Reasons for Allowance.
9. ☐ Note the attached NOTICE OF REFERENCES CITED, PTO-892.
10. ☐ Note the attached INFORMATION DISCLOSURE CITATION, PTO-1449.

PART II.

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE THREE MONTHS FROM THE "DATE MAILED" indicated on this form. Failure to timely comply will result in the ABANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

1. ☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.
2. ☐ APPLICANT MUST MAKE THE DRAWING CHANGES INDICATED BELOW IN THE MANNER SET FORTH ON THE REVERSE SIDE OF THIS PAPER.
   a. ☐ Drawing informalities are indicated on the NOTICE RE PATENT DRAWINGS, PTO-948, attached hereto or to Paper No. _____. CORRECTION IS REQUIRED.
   b. ☐ The proposed drawing correction filed on _____ has been approved by the examiner. CORRECTION IS REQUIRED.
   c. ☐ Approved drawing corrections are described by the examiner in the attached EXAMINER'S AMENDMENT. CORRECTION IS REQUIRED.
   d. ☐ Formal drawings are now REQUIRED.

Any response to this letter should include in the upper right hand corner, the following information from the NOTICE OF ALLOWANCE AND ISSUE FEE DUE: ISSUE BATCH NUMBER, DATE OF THE NOTICE OF ALLOWANCE, AND SERIAL NUMBER.

Attachments:

- _ Examiner's Amendment
- _ Examiner Interview Summary Record, PTOL-413
- _ Reasons for Allowance
- _ Notice of References Cited, PTO-892
- _ Information Disclosure Citation, PTO-1449
- _ Notice of Informal Application, PTO-152
- _ Notice re Patent Drawings, PTO-948
- _ Listing of Bonded Draftsmen
- _ Other

E Bernhardt

EMILY BERNHARDT
PRIMARY EXAMINER
GROUP 1200

PTOL-37 (REV. 4-89) ★

USCOMM-DC 89-3789

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :
Henning BÖTTCHER et al. :
Serial No.: 08/314,734 :
Filed: September 29, 1994 :
For: PIPERIDINES AND PIPERAZINES

Box AF
Group Art Unit: 1202
Examiner: E. Bernhardt

Please Enter Amendment
EB
2/6/96

AMENDMENT UNDER 37 C.F.R. §1.116

Assistant Commissioner for Patents
Washington, D.C. 20231

SIR:

Applicants acknowledge receipt of the Office Action of October 25, 1995. Entry of the following amendments is respectfully requested.

IN THE CLAIMS:

Please **cancel claims 9, 13-15, 19-23, 26 and 27** without prejudice or disclaimer.

Please **amend claims 1, 2, 7, 12, 16, 24, 25 and 28** as follows:

Claim 1, line 9: Delete "2,3-dihydrobenzofuran-5-";
line 10: Delete "yl, chroman-6-yl,"; and
line 15: Change "N or CR^3;" to -- N; --.

Claim 2, lines 6-14: Delete in their entirety;
line 15: Change "(e)" to -- (b) --;
line 17: After "thereof;", insert -- or --;
line 18: Change "(f)" to -- (c) --;
line 20: Change "thereof;" to -- thereof. --; and
lines 21-25: Delete in their entirety.

Claim 7, line 2: Delete "2,3-dihydrobenzofuran-5-yl, chroman-6-yl,".

Claim 12, line 1: Delete "Z is N and".

Claim 16, line 1: Delete "Z is N and".

Claim 24, line 1: Change "23," to -- 1, --.

Claim 25, line 1: Change "23," to -- 1, --.

Claim 28, line 1: Change "23," to -- 1, --.

R E M A R K S

Amendments

The above amendments are submitted for purposes of furthering prosecution and to obtain an early allowance of the instant application. Entry thereof is respectfully requested. Submission of these amendments is not to be construed as an acquiescence to any ground of rejection.

In the Office Action of October 25, 1995, the examiner indicated that claims 16, 24, 25 and 28 recited allowable subject matter. While claim 12 was not indicated as reciting allowable subject matter, it is stated in the Office Action that "R^1 as ... benzofuranyl ... is not suggested by the combined teachings of Boettcher and Perregaard...." See page 4, lines 4-6, of the October 25, 1995, Office Action.

Claim 1, as amended above, corresponds to the combined scope of claims 12, 24, 25 and 28. Therefore, it is respectfully submitted that the above amendments place the application in condition for allowance. Entry of the amendments and allowance of the instant application is again respectfully requested.

Improper Markush Rejection

As noted above, the amendments to the claims is not to be construed as an acquiescence to any ground of rejection. In any

event, the above amendment to claim 1 regarding group Z renders moot the improper Markush group rejection. Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §103

As correctly noted by the examiner, Boettcher et al. (U.S. '925) cannot be eliminated as a reference by perfection of the claim of benefit to foreign priority under 35 U.S.C. §119. Counsel apologizes for the confusion. The rejection in view of U.S. '925 in combination with U.S. '948 was traversed in the Amendment of June 28, 1995.

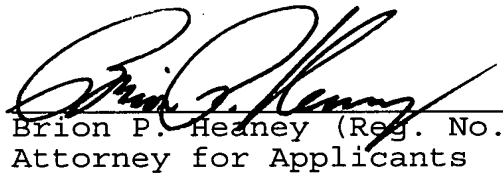
In any event, the above amendment renders moot the rejection under 35 U.S.C. §103. See also the examiner's discussion of what is not suggested by the combined prior art disclosures at page 4, lines 3-6, of the October 25, 1995, Office Action.

Withdrawal of the rejection under 35 U.S.C. §103 is respectfully requested.

Obviousness-Type Double-Patenting Rejection in view of Perregaard (U.S. '925)

For the reasons discussed above with regard to the §103 rejection, the rejection of obviousness-type double patenting in view of U.S. '925 is rendered moot by the above amendment to claim 1. Withdrawal of the rejection is respectfully requested.

Respectfully submitted,



Brion P. Heaney (Reg. No. 32,542)
Attorney for Applicants

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
Arlington Courthouse Plaza I
2200 Clarendon Boulevard, Suite 1400
Arlington, Virginia 22201
(703) 812-5308

Filed: January 24, 1996

BPH:kdp123:merck617.am2

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SAH

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/314,734	09/29/94	BOTTCHER H	MERCK1617

BERNHARD EXAMINER

12M2/1025

MILLEN WHITE ZELANO AND BRANIGAN
ARLINGTON COURTHOUSE PLAZA I SUITE 1400
2200 CLARENDON BOULEVARD
ARLINGTON VA 22201

ART UNIT	PAPER NUMBER
1202	6

DATE MAILED: 10/25/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☐ This application has been examined ☑ Responsive to communication filed on 6/30/95 ☑ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 1-28 are pending in the application.
   Of the above, claims 13, 19-22 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1-12, [redacted] 14-15, 17-18, 23 and 27 are rejected.
5. ☑ Claims 16, 24-25 and 28 are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

In view of applicants' response filed 06/30/95 the following applies.

Applicants' election of Group I subject matter with traverse is acknowledged but is not persuasive for reasons previously set forth-see page 3 of previous office action. The field of search in the U.S. Classification is completely independent for the two Z groups and where multiple uses exist restriction is proper between compounds (and compositions) vs. multiple uses-see MPEP 806.05(h). Different uses raise different issues of patentability over corresponding compound/composition claims. Note In re May 197 USPQ 601; In re Shetty 195 USPQ 753.

For the above reasons the restriction is deemed proper and is therefore made FINAL.

Claims 1-11 and 17-18 are rejected under judicial doctrine as being drawn to an improper Markush group for reasons of record. Unlike Harnisch, 206 USPQ 300 cited by applicants, the pharmaceutical art does not recognize the instant Z moieties ~~on~~ as equivalent. Note Bottcher and Perregaard *dont.* Note that in Harnisch the various substituents defined by NZ^1Z^2 were held to be incidental, the coumarin core responsible for the dye activity. In contrast to Harnisch, there is no evidence of record that either the instant indolyl and/or bicyclic oxygen heteros common to both groups contributes solely to the physiological activity. Clearly if only the former ring system

(indole) and piperazine ~~and~~ are predominately responsible for the activity, Bottcher applied previously and maintained below cannot be overcome. Note In re Milas 71 USPQ 212 in which the structural difference between Vitamin A and Vitamin D was sufficient to uphold the improper Markush rejection. Also see In re Winnek, 73 USPQ 225 and In re Ruzicka, 66 USPQ 226 which structural differences were small yet a similar holding was maintained. All these cases involved compounds in the pharmaceutical art known to be structure-sensitive in general.

This application contains claims drawn to an invention non-elected with traverse in Paper No. 5. A complete response to the final rejection must include cancellation of non-elected claims or other appropriate action (37 C.F.R. § 1.144) M.P.E.P. § 821.01.

Claims 1-12, 14-15, 17-18, 23, 26, and 27 are rejected under 35 U.S.C. § 103 as being unpatentable over Boettcher in view of Perregaard for reasons of record - see previous action.

The issue date of Boettcher is one year earlier than the instant U.S. filing date. Thus Boettcher can't be antedated even if benefit under 35 USC 119 exists. See MPEP 201.13, p. 200-28, left column entitled "Effect on Right of Priority", Rev. January 1995.

Applicant's arguments filed 6/3/95 have been fully considered but they are not deemed to be persuasive.

Contrary to what applicants seem to infer a claim is properly rejected once any part of its instant scope is anticipated or rendered obvious by a competent reference. While R^1 as chromenyl or chromen-4on-6yl or benzofuranyl or chroman-4-on-6-yl is not suggested by the combined teachings of Boettcher and Perregaard, R^1 as dihydro benzofuran-5-yl or chroman-6-yl is. Applicants urge Perregaard is too structurally remote since point of attachment to piperazine ring is at a different location ~~or~~ on benzene ring than is claimed herein. While this is correct, note that Boettcher, the primary reference teaches attachment of fused benzene ring system at the same location as herein. Perregaard was only relied on to show that benzodioxane can be replaced with instant R^1 rings as discussed above in similar compounds and still retain activity disclosed in Boettcher. Furthermore, it is not believed the disclosure of Perregaard is to diffuse since the pertinent rings embraced in Ar is not an infinite Markush group but rather narrow in scope. For the above reasons the rejection is maintained.

Claims 1-12, 14-15, 17-18, 23, and 26-27 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 5242925 in view of Perregaard for reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other because of the same reasons

as discussed previously in the corresponding 103 rejection and discussed above. Note the inclusion of claims 19-22 in this rejection in the previous action was inadvertent.

Claims 16, 24-25, and 28 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant is again reminded that if non-elected subject matter is deleted many claims will be superfluous as well as "Z is N" recitation in various dependent claims.

Böttcher, US '237, recently issued and commonly assigned is cited to show the state of the art.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

A facsimile center has been established in Group 1200, room 3C10. The hours of operation are monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine is (703) 308-4556 or 305-3592.

Any inquiry concerning this communication should be directed to Emily Bernhardt at telephone number (703) 308-4714.

E Bernhardt

EMILY BERNHARDT
PRIMARY EXAMINER
GROUP 120

BERNHARDT:jd
OCTOBER 18, 1995

FORM PTO-892 (REV. 2-92)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	SERIAL NO.	GROUP ART UNIT	ATTACHMENT TO PAPER NUMBER
NOTICE OF REFERENCES CITED		08/314734	1202	6
		APPLICANT(S) BOTTCHER		

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
*	A	5418237	5/23/95	BÖTTCHER et al	514	253	
	B						
	C						
	D						
	E						
	F						
	G						
	H						
	I						
	J						
	K						

FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. DWG	PERTINENT PP. SPEC.
	L								
	M								
	N								
	O								
	P								
	Q								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

	R	
	S	
	T	
	U	

EXAMINER	DATE
F Benhacutt	10/5/95

* A copy of this reference is not being furnished with this office action.
(See Manual of Patent Examining Procedure, section 707.05 (a).)

1302 - 103
4.1202

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :

Henning BÖTTCHER et al. :

Serial No.: 08/314,734 :

Filed: September 29, 1994 :

For: PIPERIDINES AND PIPERAZINES

Group Art Unit: 1202

Examiner: E. Bernhardt

A M E N D M E N T

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

SIR:

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as First Class Mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231 On: June 28, 1995
Name: Brion P. Heaney
Signature:
Date: 6/28/95

In response to the Office Action of March 28, 1995, please amend the above-identified application as follows:

IN THE CLAIMS:

Please amend claim 12 as follows:

Claim 12, line 2: Change "benzo-5-yl" to -- benzofuran-5-yl --.

Please add the following new claims:

23. A compound according to claim 1, wherein Z is N.

~~24.~~ 13. A compound according to claim ~~23~~ 1, wherein R^1 is unsubstituted 3-chromen-6-yl or 3-chromen-6-yl substituted by CN, CH_2OH, CH_2OA or COR^2.

~~25.~~ 14. A compound according to claim ~~23~~ 1, wherein R^1 is unsubstituted chroman-4-on-6-yl or chroman-4-on-6-yl substituted by CN, CH_2OH, CH_2OA or COR^2.

26. A compound according to claim ~~23~~, wherein R^1 is unsubstituted 2,3-dihydrobenzofuran-5-yl or 2,3-dihydrobenzofuran-5-yl substituted by CN, CH_2OH, CH_2OA or COR^2.

MERCK 1617

160 MK 07/24/95 08314734 1 103 132.00 CK

34

27. A compound according to ~~claim~~ 23, wherein R^1 is unsubstituted chroman-6-yl or chroman-6-yl substituted by CN, CH_2OH, CH_2OA or COR^2.

~~28.~~ A compound according to claim ~~23~~, wherein R^1 is unsubstituted chromen-4-on-6-yl or chromen-4-on-6-yl substituted by CN, CH_2OH, CH_2OA or COR^2.

R E M A R K S

Restriction Requirement

With respect to the restriction requirement under 35 U.S.C. §121, applicants hereby affirm election of Group I, i.e., compounds and compositions wherein Z is N. However, this restriction requirement is respectfully traversed.

In the restriction requirement, the claims drawn to the compounds and compositions are split between Groups I and II on the basis of Z being defined as N or CR^3, respectively. Further, it is indicated that the subject matter of these two groups is separately classified. However, the mere assertion that the two groups of subject matter are separately classified within the PTO classification system does not establish justification for a restriction requirement.

Moreover, while group Z differs in each class, the remaining portion of the compounds is the same for both classes. In such a case, there does not appear to be an undue burden imposed upon the examiner to search both classes of subject matter together. As set forth in M.P.E.P. §803, regardless of whether it is asserted that an application contains claims directed to independent and distinct inventions, if the search and examination can be made without serious burden, the examiner must examine the entire application.

Further, the method-of-use claims set forth in Groups III and IV of the restriction requirement are clearly related to the compounds/compositions of Groups I and II. A complete and thorough search of Groups I and II would necessarily overlap with the search required for Groups III and IV, respectively. Thus,

it is respectfully submitted that no serious burden would be imposed upon the examiner in examining Groups III and IV with Groups I and II.

In view of the above remarks, withdrawal of the restriction requirement and examination of all of the pending claims is respectfully requested.

Rejection under 35 U.S.C. §112, second paragraph

Claim 12 is amended above to eliminate a typographical error. It is respectfully submitted that the language of claim 12 is sufficiently definite to one of ordinary skill in the art. Withdrawal of the rejection under 35 U.S.C. §112, second paragraph, is respectfully requested.

Objection/Rejection under 35 U.S.C. §112, first paragraph

Contrary to the assertion in the rejection, applicants' original disclosure does provide sufficient descriptive support for species (e) recited in claim 2. See, for example, the disclosure at page 22, lines 1-2.

Withdrawal of the objection/rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Rejections under 35 U.S.C. §103 and Obviousness-Type Double Patenting

Boettcher et al. (U.S. 5,242,925) has the same inventive entity as the instant application. U.S. '925 issued as a patent on September 7, 1993, less than 1 year prior to the German priority application of the instant application, P 43 33 254.4 (filed September 30, 1993). Enclosed herewith is a certified translation of German application '254.4. Submission of the English translation of the priority document perfects applicants' claim of priority and thus the effective U.S. filing date of the instant application is September 30, 1993.

In light of applicants' perfection of their claim of priority and the fact that U.S. '925 is not a disclosure "by another," U.S. '925 is not an effective prior art reference against appli-

cants' claimed invention. Withdrawal of the rejection under 35 U.S.C. §103 is respectfully requested.

In any event, U.S. '925 discloses a genus of piperazinyl-benzodioxane compounds. These compounds are described as being active on the central nervous system and serotonin agonists and antagonists. The 1,4-benzodioxane derivatives of U.S. '925 do not anticipate or render obvious applicants' claimed genus of compounds. Compare, for example, the description of R^1 with the 1,4-benzodioxane radical of the compounds of U.S. '925.

Perregaard et al. (U.S. 5,002,948) discloses a genus of indoles, indazoles, 2-indolones and 2,3-dihydro derivatives thereof. In the abstract, U.S. '948 indicates that the compounds have central serotonin activity. The piperazinyl compounds are substituted in the para position by the group Ar which can be a substituted phenyl ring or a phenyl ring fused with the structure $-Y-(CH_2)_{1-3}-Z-$. See column 1, lines 40-50. In this fused ring structure, Y is O or S and Z is O, S or CH_2.

This description of the fused ring structure for group Ar does <u>not</u> include benzofuranyl radicals, chroman-4-one radicals, chromene radicals or chromen-4-one radicals. Furthermore, the description of Ar does <u>not</u> include 2,3-dihydrobenzofuran-<u>5-yl</u>, chroman-<u>6-yl</u> or even 1,4-benzodioxan-<u>6-yl</u> radicals.

As can be seen from the description of Ar at column 1, lines 40-50, the point of attachment between this group and the piperazine structure is in the <u>ortho</u> position to Y. Thus, when Y is O, Z is O and subscript n is 2, the resultant fused structure is 1,4-benzodioxan-5-yl, not 1,4-benzodioxan-6-yl. See, for example, the list of preferred Ar groups at column 2, lines 9-11. Thus, U.S. '948 does not disclose the same benzodioxane radical as U.S. '925. Hence, Perregaard et al. do not suggest interchangeability of other radicals for the 1,4-benzodioxan-6-yl radical of the compounds of Boettcher et al.

Even if one of ordinary skill in the art were to modify the compounds of U.S. '925 based on the fused Ar groups of U.S. '948, the resultant modification would still not result in a compound in accordance with applicants' claimed genus. Attention is again

directed to the attachment of the Ar group to the piperazine structure at the ortho position relative to the group Y.

In addition, U.S. '948 specifically defines only Z to possibly by CH_2, not both Y and Z. Even if one were to modify Y to be CH_2 when Z is O and subscript n is 1, the resultant dihydrobenzofuranyl radical would be 2,3-dihydro-4-benzofuranyl and, thus, still would not suggest a compound of applicants' claimed genus.

Further, referring to the specific compounds disclosed by U.S. '948, the only fused Ar substituents exhibited by these compounds are 2,3-dihydro-7-benzofuranyl and 1,4-benzodioxan-5-yl. See, for example, the compounds disclosed at column 7, lines 4-11.

In view of the above, it is respectfully submitted that no suggestion or motivation is provided by the disclosure or the claims of U.S. '948 that would lead one of ordinary skill in the art to modify the compounds of U.S. '925 in such a manner as to arrive at a compound in accordance with applicants' claimed genus. Withdrawal of the obviousness-type double-patenting rejection and the rejection under 35 U.S.C. §103 is respectfully requested.

Improper Markush Rejection

The classical test for an improper Markush group is set forth by the C.C.P.A. in In re Harnisch, 206 U.S.P.Q. 300 (C.C.P.A. 1980). If the compounds of the claimed genus possess a common utility and the grouping of the compounds together in a genus is not repugnant to scientific classification, then a Markush group is proper.

In Harnisch, the claimed genus of compounds were coumarin compounds which were dyes and thus shared at least one common utility. The court also found that the genus of coumarin compounds was not repugnant to scientific classification.

The coumarin base structure exhibited a substituent NZ^1Z^2 in which Z^1 and Z^2 could each be hydrogen, alkyl or cycloalkyl. Z^1 could also be aralkyl or aryl. Further, Z^1 could be a 2- or 3-membered alkylene radical connecting to the 6-position of the

coumarin ring and Z^2 could be a 2- or 3-membered alkylene radical connected to the 8-position of the coumarin ring. Furthermore, Z^1 and Z^2 could, together with the nitrogen atom, be an optionally benz-fused heterocyclic ring.

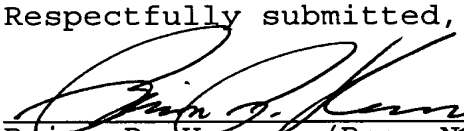
Thus, the NZ^1Z^2 group could either be an amino substituent, a further ring group fused with a coumarin base structure and possessing a nitrogen atom or it could be a nitrogen atom-containing cyclic substituent. Although all of these various structures were included, the court found the genus to not be repugnant to scientific classification.

The variation in the compounds in the Harnisch case is even greater than the variation between Groups I and II of the restriction requirement. The difference between Groups I and II of the restriction requirement is whether the cyclic structure containing group Z is a piperidine or piperazine, i.e., whether the cyclic structure contains one or two nitrogen atoms. In comparison, the NZ^1Z^2 structure in the Harnisch case could have represented no cyclic structure whatsoever, a fused cyclic structure, or a cyclic substituent.

In view of the above, it is respectfully submitted that the grouping of the compounds of Groups I and II identified in the restriction requirement in a genus is not repugnant to scientific classification. Furthermore, the compounds share at least one common utility, e.g., active on the central nervous system.

In view of the above, withdrawal of the improper Markush rejection is respectfully requested.

Respectfully submitted,



Brion P. Heaney (Reg. No. 32,542)
Attorney for Applicants

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
Arlington Courthouse Plaza I
2200 Clarendon Boulevard, Suite 1400
Arlington, Virginia 22201
(703) 243-6333

Filed: June 28, 1995

BPH:kdp112:merck617.am1

#15

IN THE UNITED STATES PATENT OFFICE

I, John William SPICER BSc PhD MRSC CChem, translator to RWS Translations Ltd., of Europa House, Marsham Way, Gerrards Cross, Buckinghamshire, England declare;

1. That I am a citizen of the United Kingdom of Great Britain and Northern Ireland.

2. That I am well acquainted with the German and English languages.

3. That the attached is, to the best of my knowledge and belief, a true translation into the English language of the accompanying copy of the specification filed with the application for a patent in Germany on 30 September 1993 under the number P 43 33 254.4 and the official certificate attached hereto.

4. That I believe that all statements made herein of my own knowledge are true and that all statements made on information and belief are true; and further that these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of the patent application in the United States of America or any patent issuing thereon.

J.W. Spicer

For and on behalf of RWS Translations Ltd.

The 13th day of June 1995

FEDERAL REPUBLIC OF GERMANY

CERTIFICATE

Merck Patent Gesellschaft mit beschränkter Haftung

of

64293 Darmstadt

have filed a Patent Application under the title:

"Piperidines and piperazines"

on 30 September 1993 at the German Patent Office.

The attached document is a correct and accurate reproduction of the original submission for this Patent Application.

The German Patent Office has for the time being given the Application the symbols C 07 D 405/12, C 07 D 405/14, A 61 K 31/495 and A 61 K 31/445 of the International Patent Classification.

Munich, 9 June 1995
President of the German Patent Office
pp Faust

File No: P 43 33 254.4

HA2708TA.DOC1/20

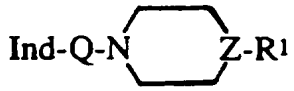
[rubber stamp
of German
Patent Office]

**Merck Patent Gesellschaft
mit beschränkter Haftung
64271 D a r m s t a d t**

Piperidines and piperazines

Piperidines and piperazines

The invention relates to novel piperidine and piperazine derivatives of the formula I



I

wherein

Ind is an indol-3-yl radical which is unsubstituted or mono- or polysubstituted by OH, OA, CN, Hal, COR^2 or CH_2R^2,

R^1 is benzofuran-5-yl or 2,3-dihydrobenzofuran-5-yl, chroman-6-yl, chroman-4-on-6-yl, 3-chromen-6-yl or chromen-4-on-6-yl, which is unsubstituted or monosubstituted by CN, CH_2OH, CH_2OA or COR^2,

Q is C_mH_{2m},

Z is N or CR^3,

A is alkyl having 1-6 C atoms,

Hal is F, Cl, Br or I,

R^2 is OH, OA, NH_2, NHA or NA_2,

R^3 is H, OH or OA and

m is 2, 3 or 4,

and to their physiologically acceptable salts.

The object of the invention was to find novel compounds capable of being used for the preparation of drugs.

It has been found that the compounds of the formula I and their physiologically acceptable acid addition salts possess valuable pharmacological properties. Thus, in particular, they are active on the central nervous system, especially especially in terms of $5\text{-}HT_{1A}$-agonist and 5-HT-reuptake inhibition. The compounds are furthermore active as serotonin agonists and antagonists. They inhibit the binding of tritiated serotonin ligands to hippocampal receptors (Cossery et al., European J. Pharmacol. 140 (1987), 143-155). They also modify the accumulation of DOPA in the corpus striatum and the accumulation of 5-HTP in the nuclei raphes (Seyfried et al., European J. Pharmacol. 160 (1989),

31-41). They also have analgesic and hypotensive effects; thus, in catheterized, conscious, spontaneously hypertensive rats (strain: SHR/Okamoto/NIH-MO-CHB-Kisslegg; method: q.v. Weeks and Jones, Proc. Soc. Exptl. Biol. Med. 104 (1960), 646-648), the directly measured blood pressure is lowered after oral administration of the compounds. They are also useful for prophylaxis and control of the sequelae of cerebral infarction (apoplexia cerebri) such as stroke and cerebral ischaemia.

Compounds of the formula I and their physiologically acceptable acid addition salts can therefore be used as active ingredients for anxiolytics, antidepressants, antipsychotics, neuroleptics, and/or antihypertensives, and also as intermediates for the preparation of other pharmaceutical active ingredients.

The invention relates to the piperidine and piperazine derivatives of the formula I and to their physiologically acceptable acid addition salts.

The radical A is alkyl having 1, 2, 3, 4, 5 or 6 C atoms, especially 1 or 2 C atoms, preferably methyl and also ethyl, n-propyl, isopropyl, n-butyl, sec-butyl or tert-butyl. OA is preferably methoxy and also ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy or tert-butoxy. NHA is preferably methylamino and also ethylamino, isopropylamino, n-butylamino, isobutylamino, sec-butylamino or tert-butylamino. NA_2 is preferably dimethylamino and also N-ethyl-N-methylamino, diethylamino, di-n-propylamino, diisopropylamino or di-n-butylamino.

Analogously, CO-NHA is preferably N-methylcarbamoyl or N-ethylcarbamoyl; $CO\text{-}NA_2$ is preferably N,N-dimethylcarbamoyl or N,N-diethylcarbamoyl.

The radical Ind is an indol-3-yl radical which is unsubstituted or mono- or disubstituted by one of the radicals indicated. Preferably it is substituted in the 5-position, and also in the 4-, 6- or 7-position. Furthermore, substitution in the 1- or 2-position is possible. Preferred substituents on the indol-3-yl radical are OH, OA, CN, $CONH_2$, CH_2OH, but also CO_2H, F,

Cl, Br, I, CH_2NH_2, CONHA or $CONA_2$, where A preferably corresponds to methyl or ethyl.

The radical R^1 is preferably benzofuran-5-yl, 2,3-dihydrobenzofuran-5-yl, chroman-6-yl or chromen-4-on-6-yl, which is unsubstituted or monosubstituted by $-CH_2OH$, $-CONH_2$, $-CO_2A$ or $-CO_2NHA$.

Q is preferably $-(CH_2)_4-$, but also $-(CH_2)_2-$ or $-(CH_2)_3-$, while Z is preferably -N-, -C(OH)- or -CH-.

Accordingly, the invention relates particularly to those compounds of the formula I in which at least one of said radicals has one of the meanings indicated above, especially one of the preferred meanings indicated above. Some preferred groups of compounds can be expressed by the following partial formulae Ia to Ig, which correspond to formula I and in which the radicals and parameters not described in greater detail are as defined for formula I, but in which:

in Ia, Ind is an indol-3-yl radical substituted in the 5-position by OH or OA;

in Ib, Ind is an indol-3-yl radical substituted in the 5-position by $CONH_2$ or by CN;

in Ic, Z is N and R^1 is substituted or unsubstituted benzofuran-5-yl;

in Id, Z is -C(OH)- and R^1 is substituted or unsubstituted benzofuran-5-yl;

in Ie, Z is N and R^1 is 2,3-dihydrobenzofuran-5-yl;

in If, Z is N and R^1 is chroman-6-yl;

in Ig, Z is N and R^1 is chromen-4-on-6-yl.

Especially preferred compounds are those of partial formulae Ih and Iah to Igh, which correspond to partial formulae I and Ia to Ig, but in which additionally:

Q is $-(CH_2)_4-$.

The invention further relates to a process for the preparation of indole derivatives of the formula I and their salts, characterised in that a compound of the formula II

$$Ind\text{-}Q\text{-}X^1 \qquad II$$

wherein

X^1 is X or NH_2,

X is Cl, Br, I, OH or an OH group functionally modified to form a reactive group, and

Ind and Q are as defined,

is reacted with a compound of the formula III

$$X^2-(CH_2)_2-ZR^1-(CH_2)_2-X^3 \qquad III$$

wherein

X^2 and X^3

can be identical or different and are each X if $X^1 = NH_2$ or are together NH in other cases, and

Z and R^1 are as defined,

or in that to prepare a compound of the formula I in which Z is N, a compound of the formula IV

$$Ind-Q-N(CH_2-CH_2-X)_2 \qquad IV$$

wherein

X, Q and Ind are as defined,

is reacted with a compound of the formula V

$$R^1-NH_2 \qquad V$$

wherein

R^1 is as defined,

or in that a compound which has formula I except that one or more hydrogen atoms have been replaced by one or more reducible groups and/or one or more additional C-C and/or C-N bonds are treated with a reducing agent,

or in that a compound which has formula I except that one or more hydrogen atoms have been replaced by one or more solvolysable groups is treated with a solvolysing agent, and/or in that an OA group is optionally cleaved to form an OH group, and/or an Ind group and/or an Ar group is converted into another Ind and/or Ar group, and/or in that a resulting base or acid of the formula I is converted into one of its salts by treatment with an acid or base.

The compounds of the formula I are otherwise prepared by methods known per se, such as those described in the literature (e.g. in the standard works such as Houben- Weyl, Methoden der Organischen Chemie (Methods of Organic Chemistry), Georg-Thieme-Verlag, Stuttgart; Organic Reactions, John Wiley & Sons, Inc., New York; German Offenlegungsschrift 41 01 686), namely under reaction conditions such as those which are known and suitable for said reactions. It is also possible to make use of variants known per se, which are not mentioned in greater detail here.

If desired, the starting materials for the claimed process can also be formed in situ in such a way that they are not isolated from the reaction mixture but are immediately reacted further to give the compounds of the formula I.

In the compounds of the formula II, X^1 is preferably X; accordingly, in the compounds of the formula III, X^2 and X^3 are together preferably NH. The radical X is preferably Cl or Br, but it can also be I, OH or an OH group functionally modified to form a reactive group, especially alkylsulfonyloxy having 1-6 C atoms (e.g. methanesulfonyloxy) or arylsulfonyloxy having 6-10 C atoms (e.g. benzenesulfonyloxy, p-toluenesulfonyloxy, naphthalene-1- or -2-sulfonyloxy).

Accordingly, the indole derivatives of the formula I can be obtained especially by reacting compounds of the formula Ind-Q-Cl or Ind-Q-Br with piperidine/piperazine derivatives of the formula III in which X^2 and X^3 together are an NH group (designated as IIIa hereafter).

Some of the compounds of the formulae II and, in particular, III are known; the unknown compounds of the formulae II and III can easily be prepared analogously to the known compounds.

Primary alcohols of the formula Ind-Q-OH can be obtained e.g. by reducing the appropriate carboxylic acids or their esters. Treatment with thionyl chloride, hydrogen bromide, phosphorus tribromide or similar

halogen compounds yields the corresponding halides of the formula Ind-Q-Hal. The corresponding sulfonyloxy compounds can be obtained from the alcohols Ind-Q-OH by reaction with the appropriate sulfonyl chlorides.

The iodine compounds of the formula Ind-Q-I can be obtained e.g. by reacting potassium iodide with the appropriate p-toluenesulfonic acid esters. The amines of the formula Ind-Q-NH_2 can be prepared e.g. from the halides with potassium phthalimide or by reducing the appropriate nitriles.

Most of the piperazine derivatives IIIa are known and can be obtained e.g. by reacting bis(2-chloroethyl)amine or bis(2-chloroethyl)ammonium chloride with 5-aminobenzofuran, 2,3-dihydro-5-aminobenzofuran, 6-aminochroman or 6-aminochromen-4-one or an appropriately substituted derivative of the compounds mentioned. Compounds of the formula III (X^2 and X^3 = X in each case) can be prepared e.g. by reducing diesters of the formula alkylOOC-CH_2-ZR^1-CH_2-COO-alkyl to give compounds of the formula HO-CH_2-CH_2-ZR^1-CH_2-CH_2OH (III, X^2 = X^3 = OH), this being followed, if desired, by reaction with $SOCl_2$ or PBr_3.

The reaction of the compounds II and III proceeds according to methods such as those known from the literature for the alkylation of amines. The components can be melted together in the absence of a solvent, in a sealed tube or an autoclave if necessary. It is also possible, however, to react the compounds in the countertype [sic] of an inert solvent. Examples of suitable solvents are hydrocarbons such as benzene, toluene or xylene; ketones such as acetone or butanone; alcohols such as methanol, ethanol, isopropanol or n-butanol; ethers such as tetrahydrofuran (THF) or dioxane; amides such as dimethylformamide (DMF) or N-methylpyrrolidone; or nitriles such as acetonitrile, or else, if desired, mixtures of these solvents with one another or mixtures with water. It can be favourable to add an acid-binding agent, for example an alkali metal or alkaline earth metal hydroxide, carbonate or bicarbonate

or another alkali metal or alkaline earth metal salt of a weak acid, preferably a potassium, sodium or calcium salt, or to add an organic base such as triethylamine, dimethylaniline, pyridine or quinoline, or an excess of the amine component Ind-Q-NH_2 or of the piperidine or piperazine derivative of the formula IIIa. The reaction time is between a few minutes and 14 days, depending on the conditions used, and the reaction temperature is between about 0 and 150°, normally between 20 and 130°.

It is also possible to obtain a compound of the formula I by reacting a compound of the formula Ind-Q-$N(CH_2-CH_2-X)_2$ (IV) with a compound of the formula R^1-NH_2 (V).

Most of the compounds of the formulae [sic] V are known; the unknown compounds can easily be prepared analogously to the known compounds. For example, starting from the appropriately substituted nitro compounds, they can be converted into the amines of the formula V by reduction. The compounds of the formula IV can be prepared by reaction of Ind-Q-Cl, Ind-Q-Br or Ind-Q-I with secondary amines of the formula $HN(CH_2-CH_2-X)_2$.

The reaction of compounds IV and V proceeds according to methods which are known from the literature and were given above for the alkylation of amines.

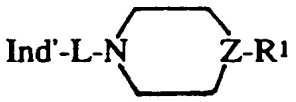
A compound of the formula I can also be obtained by treating a precursor, in which hydrogen atoms have been replaced by one or more reducible groups and/or one or more additional C-C and/or C-N bonds, with a reducing agent, preferably at temperatures of between -80 and +250°, in the presence of at least one inert solvent.

Reducible groups (groups replaceable by hydrogen) are, in particular, oxygen in a carbonyl group, hydroxyl, arylsulfonyloxy (e.g. p-toluenesulfonyloxy), N-benzenesulfonyl, N-benzyl or O-benzyl.

In principle, compounds containing only one of the above-mentioned groups or additional bonds, or compounds containing two or more of the above-mentioned groups or additional bonds adjacent to one another, can be converted into a compound of the formula I by

reduction, it being possible simultaneously to reduce substituents in the Ind group which are present in the starting compound. This is preferably carried out using nascent hydrogen or complex metal hydrides or by means of a Wolff-Kishner reduction or the reductions with hydrogen gas under transition metal catalysis.

Preferred starting materials for the reduction have formula VI



VI

wherein

Ind′ is an Ind radical which can additionally be substituted in the 1-position by an arylsulfonyl group or an alkyloxycarbonyl group,

L is Q or a chain which corresponds to the radical Q except that one or more $-CH_2$ groups have been replaced by -CO- and/or one or more hydrogen atoms have been replaced by one or more OH groups or a double bond, and

R^1 has the meaning given,

but wherein the following meanings cannot apply simultaneously: Ind′ = Ind and L = Q.

In the compounds of the formula VI, L is preferably $-CO-(CH_2)_{n-2}-CO-$ [specifically -COCO-, $-COCH_2CO-$, $-CO-(CH_2)_2-CO-$, $-CO-(CH_2)_3-CO-$], $-(CH_2)_{n-1}-CO-$ [specifically $-CH_2-CO-$, $-CH_2CH_2-CO-$, $-(CH_2)_3-CO-$ or $-(CH_2)_4-CO-$], further examples being $-CO-CH_2CH_2-$, $-CO-(CH_2)_3-$, $-CH_2-CO-CH_2CH_2-$ or $-CH_2CH_2-CO-CH_2-$.

Compounds of the formula VI can be prepared e.g. by reacting 4-R^1-piperazine or 4-R^1-piperidine with a compound of the formula VII

$$Ind'-L-X^1 \qquad VII$$

wherein

R^1, Ind′, L and X^1 are as defined above,

under the conditions indicated above for the reaction of II with III.

If nascent hydrogen is used as the reducing agent, this can be produced e.g. by treating metals with weak acids or with bases. Thus it is possible e.g. to use a mixture of zinc with an alkali metal hydroxide solution or a mixture of iron with acetic acid. It is also appropriate to use sodium or another alkali metal dissolved in an alcohol such as ethanol, isopropanol, butanol, amyl or isoamyl alcohol or phenol. It is also possible to use an aluminium-nickel alloy in aqueous-alkaline solution, ethanol being added if necessary. Sodium amalgam or aluminium amalgam in aqueous-alcoholic or aqueous solution is also suitable for producing the nascent hydrogen. The reaction can also be carried out in the heterogeneous phase, in which case it is convenient to use an aqueous phase and a benzene or toluene phase.

Other reducing agents which can be used to particular advantage are complex metal hydrides such as $LiAlH_4$, $NaBH_4$, diisobutylaluminium hydride or $NaAl(OCH_2CH_2OCH_3)_2H_2$, and diborane, catalysts such as BF_3, $AlCl_3$ or LiBr being added if desired. Solvents which are suitable for this purpose are, in particular, ethers such as diethyl ether, di-n-butyl ether, THF, dioxane, diglyme or 1,2-dimethoxyethane, and hydrocarbons such as benzene. Solvents which are suitable for a reduction with $NaBH_4$ are primarily alcohols such as methanol or ethanol, as well as water and aqueous alcohols. Reduction by these methods is preferably carried out at temperatures of between -80 and +150°, especially of between about 0 and about 100°.

The reduction of -CO groups in acid amides (e.g. those of the formula VI in which L is a $-(CH_2)_{n-1}$-CO group) to CH_2 groups can be carried out to particular advantage with $LiAlH_4$ in THF at temperatures of between about 0 and 66°. Arylsulfonyl protecting groups located in the 1-position of the indole ring can be simultaneously eliminated by reduction. N-Benzyl groups can be eliminated by reduction with sodium in liquid ammonia.

It is also possible to reduce one or more carbonyl groups to CH_2 groups according to the Wolff-Kishner

method, e.g. by treatment with anhydrous hydrazine in absolute ethanol, under pressure, at temperatures of between about 150 and 250°. A sodium alcoholate is advantageously used as the catalyst. The reduction can also be varied according to the Huang-Minlon method by carrying out the reaction with hydrazine hydrate in a high-boiling water-miscible solvent such as diethylene glycol or triethylene glycol, in the presence of an alkali such as sodium hydroxide. The reaction mixture is normally boiled for about 3-4 hours. The water is then distilled off and the hydrazone formed is decomposed at temperatures of up to about 200°. The Wolff-Kishner reduction can also be carried out with hydrazine in dimethyl sulfoxide at room temperature.

Moreover, it is possible to carry out certain reductions by using H_2 gas under the catalytic action of transition metals, such as e.g. Raney Ni or Pd. In this way, e.g. Cl, Br, I, SH or, in certain cases, even OH groups can be replaced by hydrogen. Nitro groups can also be converted into NH_2 groups by catalytic hydrogenation with Pd/H_2 in methanol.

Compounds which have formula I except that one or more H atoms have been replaced by one or more solvolysable groups can be solvolysed, especially hydrolysed, to give the compounds of the formula I.

The starting materials for the solvolysis can be obtained for example by reacting IIIa with compounds which have formula II (X^1 = X) except that one or more H atoms have been replaced by one or more solvolysable groups. Thus, in particular, 1-acylindole derivatives (which have formula I except that, in the 1-position of the Ind radical, they contain an acyl group, preferably an alkoxycarbonyl, alkanoyl, alkylsulfonyl or arylsulfonyl group having up to 10 C atoms in each case, such as methanesulfonyl, benzenesulfonyl or p-toluenesulfonyl) can be hydrolysed to give the corresponding indole derivatives unsubstituted in the 1-position of the indole ring, e.g. in an acidic or, preferably, neutral or alkaline medium at temperatures of between 0 and 200°.

Sodium, potassium or calcium hydroxide, sodium or potassium carbonate, or ammonia, is conveniently used as the base. The chosen solvents are preferably water; lower alcohols such as methanol or ethanol; ethers such as THF or dioxane; sulfones such as tetramethylene sulfone; or mixtures thereof, especially mixtures containing water. Hydrolysis can also be carried out simply by treatment with water alone, especially at the boiling point.

A compound of the formula I can furthermore be converted to another compound of the formula I by methods known per se.

Compounds of the formula I in which Ind is an indol-3-yl radical substituted by CO-R^1 can be obtained by derivatising appropriate carboxyindol-3-yl compounds. It is possible, e.g. to esterify the acids with appropriate alcohols or alcoholates, using methods known per se. It is also possible to amidate acids or esters with primary or secondary amines. It is preferred to react the free carboxylic acid with the amine under the conditions of a peptide synthesis. This reaction is preferably carried out in the presence of a dehydrating agent, e.g. a carbodiimide such as dicyclohexylcarbodiimide or else N-(3-dimethylaminopropyl)-N-ethylcarbodiimide, or propanephosphonic anhydride (q.v. Angew. Chem. 92, 129 (1980)), diphenylphosphoryl azide or 2-ethoxy-N-ethoxycarbonyl-1,2-dihydroquinoline, in an inert solvent, e.g. a halogenated hydrocarbon such as methylene chloride, an ether such as THF or dioxane, an amide such as DMF or dimethylacetamide, or a nitrile such as acetonitrile, at temperatures of between about -10 and 40, preferably of between 0 and 30°. Instead of the acid or amide, it is also possible to use reactive derivatives of these substances in the reaction, e.g. those in which reactive groups are blocked by protecting groups in an intermediate step. The acids can also be used in the form of their activated esters, which are conveniently formed in situ, e.g. by the addition of 1-hydroxybenztriazole or N-hydroxysuccinimide.

Furthermore, cyano-substituted indol-3-yl

radicals can be hydrolysed to give carboxy-indol-3-yl or carbamido-indol-3-yl radicals.

Conversely, however, it is particularly convenient to prepare the nitriles by elimination of water, starting from the amides, e.g. by means of trichloroacetyl chloride/Et_3N [Synthesis (2), 184, (1985)] or with $POCl_3$ (J. Org. Chem. 26, 1003 (1961)).

A base of the formula I can be converted with an acid into the corresponding acid addition salt. Acids which produce physiologically acceptable salts are suitable for this reaction. Thus it is possible to use inorganic acids, e.g. sulfuric acid, hydrohalic acids such as hydrochloric acid or hydrobromic acid, phosphoric acids such as orthophosphoric acid, nitric acid and sulfamic acid, as well as organic acids, i.e. specifically aliphatic, alicyclic, araliphatic, aromatic or heterocyclic monobasic or polybasic carboxylic, sulfonic or sulfuric acids, such as formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, benzoic acid, salicylic acid, 2-phenylpropionic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methanesulfonic or ethanesulfonic acid, ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenemonosulfonic and naphthalenedisulfonic acids and laurylsulfuric acid.

If desired, the free bases of the formula I can be liberated from their salts by treatment with strong bases such as sodium or potassium hydroxide or sodium or potassium carbonate provided there are no other acid groups in the molecule. In those cases where the compounds of the formula I have free acid groups, salt formation can also be achieved by treatment with bases. Suitable bases are alkali metal hydroxides, alkaline earth metal hydroxides or organic bases in the form of primary, secondary or tertiary amines.

The invention further relates to the use of the

compounds of the formula I and their physiologically acceptable salts for the manufacture of pharmaceutical preparations, especially by a non-chemical route. For this purpose, they can be converted into a suitable dosage form together with at least one excipient or adjunct and, if appropriate, in combination with one or more additional active ingredients.

The invention further relates to compositions, especially pharmaceutical preparations, containing at least one compound of the formula I and/or one of their physiologically acceptable salts. These preparations can be used as drugs in human or veterinary medicine. Possible excipients are organic or inorganic substances which are suitable for enteral (e.g. oral), parenteral or topical administration and which do not react with the novel compounds, examples of such excipients being water, vegetable oils, benzyl alcohols, polyethylene glycols, gelatin, carbohydrates such as lactose or starch, magnesium stearate, talc and petroleum jelly. Tablets, coated tablets, capsules, syrups, juices, drops or suppositories are used in particular for enteral administration, solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions or implants are used for parenteral administration, and ointments, creams or powders are used for topical administration. The novel compounds can also be lyophilized and the resulting lyophilizates used e.g. to manufacture injectable preparations.

The preparations indicated can be sterilized and/or can contain adjuncts such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for influencing the osmotic pressure, buffer substances, colourants, taste correctors and/or flavourings. If desired, they can also contain one or more additional active ingredients, e.g. one or more vitamins.

The compounds of the formula I and their physiologically acceptable salts can be used for the therapeutic treatment of the human or animal body and for controlling diseases. They can be used for treating

disorders of the central nervous system, such as tension, depressions and/or psychoses, and side-effects in the treatment of hypertension (e.g. with α-methyldopa). The compounds can also be used in endocrinology and gynaecology, e.g. for the therapeutic treatment of acromegaly, hypogonadism, secondary amenorrhoea, premenstrual syndrome and undesired puerperal lactation, and also for the prophylaxis and therapy of cerebral disorders (e.g. migraine), especially in geriatrics in a manner similar to certain ergot alkaloids and for controlling the sequelae of cerebral infarction (apoplexia cerebri), such as stroke and cerebral ischaemia.

In these treatments, the substances of the invention are normally administered analogously to known, commercially available preparations (e.g. bromocriptine, dihydroergocornine), preferably in dosages of between about 0.2 and 500 mg, especially of between 0.2 and 50 mg per dosage unit. The daily dosage is preferably between about 0.001 and 10 mg/kg of body weight. The low dosages (about 0.2 to 1 mg per dosage unit; about 0.001 to 0.005 mg/kg of body weight) are particularly suitable for use as anti-migraine preparations; dosages of between 10 and 50 mg per dosage unit are preferred for the other indications. However, the particular dose for each individual patient depends on a very wide variety of factors, for example the activity of the particular compound used, age, body weight, general state of health, sex, diet, time and method of administration, rate of excretion, drug combination and severity of the particular disease to which the therapy is applied. Oral administration is preferred.

In the following Examples, "working-up in conventional manner" means: Water is added if necessary, extraction is carried out with methylene chloride, the organic phase is separated off, dried over sodium sulfate and filtered, the filtrate is evaporated and the residue is purified by chromatography on silica gel and/or by crystallization. Temperatures are given in °C. Rf values were obtained by thin layer chromatography on silica gel.

Example 1

1.8 g of 3-(4-chlorobutyl)-5-methoxyindole [obtainable by diazotization of p-methoxyaniline, reaction with ethyl cyclohexanone-2-carboxylate according to Japp-Klingemann to give 4-(2-carbethoxyindol-3-yl)butyric acid, alkaline hydrolysis, decarboxylation, reduction with $LiAlH_4$ and reaction with $SOCl_2$] and 1.9 g of 1-(2-hydroxymethylbenzofuran-5-yl)piperazine [obtainable by reaction of N,N-bis(2-chloroethyl)amine with 2-hydroxymethyl-5-aminobenzofuran] are dissolved in 200 ml of acetonitrile and the mixture is stirred at room temperature for 10 hours. Customary working up gives 1-[4-(5-methoxyindol-3-yl)butyl]-4-(2-hydroxymethylbenzofuran-5-yl)piperazine, m.p. 159°.

The following are obtained analogously by reaction of 3-(4-chlorobutyl)-5-methoxyindole with 1-(2,3-dihydrobenzofuran-5-yl)piperazine:

1-[4-(5-methoxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine, m.p. 111-112°;

of 3-(4-chlorobutyl)-5-hydroxyindole with 1-(chroman-6-yl)piperazine:

1-[4-(5-hydroxyindol-3-yl)butyl]-4-(chroman-6-yl)-piperazine, m.p. 220-222°;

of 3-(4-chlorobutyl)-5-methoxyindole with 1-(chroman-6-yl)piperazine:

1-[4-(5-methoxyindol-3-yl)butyl]-4-(chroman-6-yl)-piperazine, m.p. 129-130°;

of methyl 3-(4-chlorobutyl)-5-indolecarboxylate with 1-(chroman-6-yl)piperazine:

1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(chroman-6-yl)piperazine;

of methyl 3-(4-chlorobutyl)-5-indolecarboxylate with 1-(benzofuran-5-yl)piperazine:

1-[4-(5-ethoxycarbonylindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine;

of 3-(4-chlorobutyl)-5-methoxyindole with 1-(benzofuran-5-yl)piperazine:

1-[4-(5-methoxyindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine;

of 3-(4-chlorobutyl)-5-methoxycarbonylindole with 1-(chromen-4-on-6-yl)piperazine:

1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(chromen-4-on-6-yl)piperazine;

of 3-(4-chlorobutyl)-5-cyanoindole with 1-(chromen-4-on-6-yl)piperazine:

1-[4-(5-cyanoindol-3-yl)butyl]-4-(chromen-4-on-6-yl)piperazine;

of 3-(4-chlorobutyl)-5-chloroindole with 1-(2,3-dihydrobenzofuran-5-yl)piperazine:

1-[4-(5-chloroindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine;

of 3-(4-chlorobutyl)-5-methoxycarbonylindole with 1-(2,3-dihydrobenzofuran-5-yl)piperazine:

1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine;

of 3-(4-chlorobutyl)-5-methoxycarbonylindole with 4-(2,3-dihydrobenzofuran-5-yl)piperidine:

1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperidine;

of 3-(4-chlorobutyl)-5-methoxycarbonylindole with 4-(2,3-dihydrobenzofuran-5-yl)-4-hydroxypiperidine:

1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)-4-hydroxypiperidine;

of 3-(4-chlorobutyl)-5,6-dimethoxyindole with 1-(chroman-6-yl)piperazine:

1-[4-(5,6-dimethoxyindol-3-yl)butyl]-4-(chroman-6-yl)piperazine;

of 3-(4-chlorobutyl)-5-cyanoindole with 1-(2-carboxybenzofuran-5-yl)piperazine:

1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carboxybenzofuran-5-yl)piperazine;

of 3-(4-chlorobutyl)-6-fluoroindole with 1-(2,3-dihydrobenzofuran-5-yl)piperazine:

1-[4-(6-fluoroindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine.

Example 2

1.8 g of 1-[4-(5-methoxycarbonylindol-3-yl)-

butyl]-4-(chroman-6-yl)piperazine [obtainable according to Example 1] are boiled for 0.5 hours with 100 ml of 2N ethanolic KOH, worked up in the customary manner and give 1-[4-(5-carboxyindol-3-yl)butyl]-4-chroman-6-ylpiperazine.

The following are obtained analogously by alkaline hydrolysis of the corresponding esters starting from 1-[4-(5-ethoxycarbonylindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine:

1-[4-(5-carboxyindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine:

from 1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(chromen-4-on-6-yl)piperazine:

1-[4-(5-carboxyindol-3-yl)butyl]-4-(chromen-4-on-6-yl)piperazine;

from 1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine:

1-[4-(5-carboxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl-piperazine [sic];

from 1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine:

1-[4-(5-carboxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl-piperazine [sic];

from 1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)-4-hydroxypiperidine;

1-[4-(5-carboxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)-4-hydroxypiperidine.

Example 3

2.8 g of 1-[4-(5-carboxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine are suspended in 100 ml of N-methylpyrrolidine. 3.2 g of 2-chloro-1-methylpyridinium methanesulfonate are then added and the mixture is stirred at room temperature for 12 hours. Dried NH_3 gas is then passed into the resulting solution until it is saturated and the mixture is stirred again for 10 hours. Customary working up gives 1-[4-(5-carbamoylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)-piperazine.

The following are obtained analogously by amidation of the following carboxylic acids with 2-chloro-1-methylpyridinium methanesulfonate:

from 1-[4-(5-carboxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperidine

1-[4-(5-carbamoylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl-piperidine [sic], m.p. 155-157°;

from 1-[4-(5-carboxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)-4-hydroxypiperidine

1-[4-(5-carbamoylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)-4-hydroxypiperidine, m.p. 69° (dec.);

from 1-[4-(5-carboxyindol-3-yl)butyl]-4-(chroman-6-yl)-piperazine

1-[4-(5-carbamoylindol-3-yl)butyl]-4-(chroman-6-yl)-piperazine.

Example 4

Analogously to Example 3, starting from 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carboxybenzofuran-5-yl)piperazine reaction with 2-chloro-1-methylpyridinium methanesulfonate gives 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoylbenzofuran-5-yl)piperazine, m.p. 269-272° (hydrochloride).

Example 5

A mixture of 2.6 g of 3-(2-aminoethyl)-5-cyanoindole [obtainable by reaction of 5-cyanoindole with 2-chloroacetyl chloride to give 3-(2-chloroacetyl)-5-cyanoindole, subsequent reduction with diborane, reaction with phthalimide and hydrolysis] and one equivalent of 5-[N,N-bis(2-chloroethyl)amino]benzofuran [obtainable by reaction of 2-chloroacetyl chloride with 5-aminobenzofuran and subsequent reduction with diborane] in 40 ml of acetone and 40 ml of water is boiled for 20 hours and then worked up in the customary manner. 1-[2-(5-Cyanoindol-3-yl)ethyl]-4-(benzofuran-5-yl)piperazine is obtained.

The following are obtained analogously by

reaction of 5-[N,N-bis(2-chloroethyl)amino]benzofuran with 3-(4-aminobutyl)-5-methoxymethylindole: 1-[4-(5-methoxymethylindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine;

with 3-(3-aminopropyl)-5-hydroxyindole: 1-[3-(5-hydroxyindol-3-yl)propyl]-4-(benzofuran-5-yl)piperazine;

with 3-(2-aminoethyl)-5-methoxyindole: 1-[2-(5-methoxyindol-3-yl)ethyl]-4-(benzofuran-5-yl)piperazine;

with methyl 3-(3-aminopropyl)-5-indolecarboxylate: 1-[3-(5-methoxycarbonylindol-3-yl)propyl]-4-(benzofuran-5-yl)piperazine;

with ethyl 3-(2-aminoethyl)-5-indolecarboxylate: 1-[2-(5-ethoxycarbonylindol-3-yl)ethyl]-4-(benzofuran-5-yl)piperazine;

with 3-(4-aminobutyl)-5-fluoroindole: 1-[4-(5-fluoroindol-3-yl)butyl]-4-(benzofuran-5-yl)-piperazine;

with 3-(3-aminopropyl)-5-cyanoindole: 1-[3-(5-cyanoindol-3-yl)propyl]-4-(2-carboxybenzofuran-5-yl)piperazine.

Example 6

Analogously to Example 5, reaction of [sic] 3.2 g of 3-(2-aminoethyl)-5-methoxyindole with 1.3 equivalents of 6-[N,N-bis(2-chloroethyl)amino]chroman [obtainable by reaction of 2-chloroacetyl chloride with 6-aminochroman and subsequent reduction with diborane] gives 1-[2-(5-methoxyindol-3-yl)ethyl]-4-(chroman-6-yl)piperazine.

The following are obtained analogously by reaction of 6-[N,N-bis(2-chloroethyl)amino]chroman with 3-(4-aminobutyl)-5-methoxymethylindole: 1-[4-(5-methoxymethylindol-3-yl)butyl]-4-(chroman-6-yl)piperazine;

with 3-(3-aminopropyl)-5-hydroxyindole: 1-[3-(5-hydroxyindol-3-yl)propyl]-4-(chroman-6-yl)-piperazine;

with 3-(2-aminoethyl)-5-methoxyindole:
1-[2-(5-methoxyindol-3-yl)ethyl]-4-(chroman-6-yl)-piperazine;
with methyl 3-(3-aminopropyl)-5-indolecarboxylate:
1-[3-(5-methoxycarbonylindol-3-yl)propyl]-4-(chroman-6-yl)piperazine;
with ethyl 3-(2-aminoethyl)-5-indolecarboxylate:
1-[2-(5-ethoxycarbonylindol-3-yl)ethyl]-4-(chroman-6-yl)piperazine;
with 3-(4-aminobutyl)-5-fluoroindole:
1-[4-(5-fluoroindol-3-yl)butyl]-4-(chroman-6-yl)-piperazine;
with 3-(3-aminopropyl)-5-cyanoindole:
1-[3-(5-cyanoindol-3-yl)propyl]-4-(2-carboxychroman-6-yl)piperazine.

Example 7

A solution of 3.9 g of 1-[4-(5-carboxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine in 250 ml of DMF is treated with 1 g of N-methylmorpholine. A solution of one equivalent of tert-butylamine in 5 ml of DMF, 1.3 g of 1-hydroxybenzotriazole and a solution of 1.9 g of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in 20 ml of DMF are added with stirring. The mixture is stirred at room temperature for 16 hours and the filtrate is evaporated. Customary working up gives 1-[4-(5-N-tert-butylcarbamoylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine.

The following are obtained analogously by reaction with tert-butylamine starting
from 1-[4-(5-carboxyindol-3-yl)butyl]-4-(chroman-6-yl)-piperazine:
1-[4-(5-N-tert-butylcarbamoylindol-3-yl)butyl]-4-(chroman-6-yl)piperazine:
from 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carboxybenzofuran-5-yl)piperazine:
1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-N-tert-butylcarbamoylbenzofuran-5-yl)piperazine.

Example 8

A mixture of 2.1 g of 1-[4-(5-methoxyindol-3-yl)butyl]-4-(chroman-6-yl)piperazine [can be prepared according to Example 1], 1.8 g of pyridine hydrochloride and 50 ml of pyridine is boiled for 3 hours. It is cooled and evaporated, and the residue is worked up in the customary manner and gives 1-[4-(5-hydroxyindol-3-yl)-butyl]-4-(chroman-6-yl)piperazine, m.p. 220-222°.

The following are obtained analogously

from 1-[4-(5-methoxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine:

1-[4-(5-hydroxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine;

from 1-[4-(5-methoxyindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine:

1-[4-(5-hydroxyindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine;

from 1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(chromen-4-on-6-yl)piperazine:

1-[4-(5-hydroxycarbonylindol-3-yl)butyl]-4-(chromen-4-on-6-yl)piperazine;

from 1-[4-(5-methoxymethylindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine:

1-[4-(5-hydroxymethylindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine;

from 1-[2-(5-methoxyindol-3-yl)ethyl]-4-(benzofuran-5-yl)piperazine:

1-[2-(5-hydroxyindol-3-yl)ethyl]-4-(benzofuran-5-yl)piperazine;

from 1-[2-(5-methoxyindol-3-yl)ethyl]-4-(benzofuran-5-yl)piperazine:

1-[2-(5-hydroxyindol-3-yl)ethyl]-4-(benzofuran-5-yl)piperazine [sic].

Example 9

Analogously to Example 1, starting from 3-(4-chlorobutyl)-5-cyanoindole [obtainable by reaction of 5-cyanoindole with 4-chlorobutyryl chloride to give 3-(4-chlorobutyryl)-5-methoxyindole and subsequent

reduction with $NaAlH_2(OCH_2CH_2OCH_3)_2$] by reaction with 1-(2-ethoxycarbonylbenzofuran-5-yl)piperazine [obtainable by reaction of N,N-bis(2-chloroethyl)amine with 2-ethoxycarbonyl-5-aminobenzofuran] gives, after customary working up, 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-ethoxycarbonylbenzofuran-5-yl)piperazine, m.p. 221-223° (dihydrochloride).

The following are obtained analogously by reaction

of 3-(4-chlorobutyl)-5-methoxyindole with 1-(2-cyanobenzofuran-5-yl)piperazine:

1-[4-(5-methoxyindol-3-yl)butyl]-4-(2-cyanobenzofuran-5-yl)piperazine;

of 3-(4-chlorobutyl)-5,6-dimethoxyindole with 1-(chroman-6-yl)piperazine:

1-[4-(5,6-dimethoxyindol-3-yl)butyl]-4-(chroman-6-yl)piperazine;

of 3-(4-chlorobutyl)-5,6-difluoroindole with 1-(chroman-6-yl)piperazine:

1-[4-(5,6-difluoroindol-3-yl)butyl]-4-(chroman-6-yl)piperazine;

of methyl 3-(4-chlorobutyl)-6-indolecarboxylate with 1-(chroman-6-yl)piperazine:

1-[4-(6-methoxycarbonylindol-3-yl)butyl]-4-(chroman-6-yl)piperazine;

of ethyl 3-(3-chloropropyl)-6-indolecarboxylate with 1-(2-cyanobenzofuran-5-yl)piperazine:

1-[3-(6-ethoxycarbonylindol-3-yl)propyl]-4-(2-cyanobenzofuran-5-yl)piperazine;

of 3-(4-chlorobutyl)-5-methoxyindole with 1-(2-N-methylcarbamoylbenzofuran-5-yl)piperazine:

1-[4-(5-methoxyindol-3-yl)butyl]-4-(2-N-methylcarbamoylbenzofuran-5-yl)piperazine;

of 3-(4-chlorobutyl)-6-chloroindole with 1-(chromen-4-on-6-yl)piperazine:

1-[4-(6-chloroindol-3-yl)butyl]-4-(chromen-4-on-6-yl)piperazine;

of 3-(2-chloroethyl)-5-cyanoindole with 1-(chromen-4-on-6-yl)piperazine:

1-[2-(5-cyanoindol-3-yl)ethyl]-4-(chromen-4-on-6-yl)piperazine;

of 3-(2-chloroethyl)-5,6-dichloroindole with 1-(2,3-dihydrobenzofuran-5-yl)piperazine:

1-[2-(5,6-dichloroindol-3-yl)ethyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine;

of 3-(4-chlorobutyl)-5-methoxycarbonylindole with 1-(2-carboxybenzofuran-5-yl)piperazine:

1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(2-carboxybenzofuran-5-yl)piperazine;

of 3-(2-chloroethyl)-5-methoxycarbonylindole with 4-(2-carboxybenzofuran-5-yl)piperidine:

1-[2-(5-methoxycarbonylindol-3-yl)ethyl]-4-(2-carboxybenzofuran-5-yl)piperazine;

of 3-(4-chlorobutyl)-6-methoxycarbonylindole with 4-(3-carboxybenzofuran-5-yl)-4-hydroxypiperidine:

1-(4-(6-methoxycarbonylindol-3-yl)butyl]-4-(3-carboxybenzofuran-5-yl)-4-hydroxypiperidine;

of 3-(4-chlorobutyl)-7-methoxycarbonylindole with 4-(3-carboxybenzofuran-5-yl)-4-hydroxypiperidine;

1-[4-(7-methoxycarbonylindol-3-yl)butyl]-4-(3-carboxybenzofuran-5-yl)-4-hydroxypiperidine;

of 3-(4-chlorobutyl)-5,6-dimethoxyindole with 1-(2-carboxybenzofuran-5-yl)piperazine:

1-[4-(5,6-dimethoxyindol-3-yl)butyl]-4-(2-carboxybenzofuran-5-yl)piperazine.

Example 10

A solution of 3.6 g of 1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(chromen-4-on-6-yl)piperazine in 40 ml of THF is added dropwise with stirring at room temperature to a suspension of 0.6 g of lithium aluminium hyride in 20 ml of THF. The mixture is then stirred for a further hour at 25°C, 20 ml of dilute sodium hydroxide solution are added, the mixture is filtered and the filtrate is worked up in the customary manner. 1-[4-(5-Hydroxymethylindol-3-yl)butyl]-4-(chromen-4-on-6-yl)piperazine is obtained.

The following are obtained analagously by

reduction
of 1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(chroman-6-yl)piperazine
1-[4-(5-hydroxymethylindol-3-yl)butyl]-4-(chroman-6-yl)piperazine;
of 1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-benzofuran-5-yl)piperazine
1-[4-(5-hydroxymethylindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine;
of 1-[3-(5-methoxycarbonylindol-3-yl)propyl]-4-(chroman-6-yl)piperidine
1-[3-(5-hydroxymethylindol-3-yl)propyl]-4-(chroman-6-yl)piperidine
of 1-[2-(5-methoxycarbonylindol-3-yl)ethyl]-4-chroman-6-yl)piperidine
1-[2-(5-hydroxymethylindol-3-yl)ethyl]-4-(chroman-6-yl)piperidine.

Example 11

HCl gas is passed into a boiling solution of 2.5 g of 1-[4-(5-carboxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine in 50 ml of absolute methanol for 2 hours. The mixture is then boiled for a further hour, worked up in the customary manner and gives 1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine.

The following are obtained analagously by esterification
of 1-[4-(5-carboxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)-4-hydroxypiperidine:
1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)-4-hydroxypiperidine;
of 1-[4-(5-carboxyindol-3-yl)butyl]-4-(chroman-6-yl)-piperazine:
1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(chroman-6-yl)piperazine;
of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carboxybenzofuran-5-yl)piperazine:
1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-methoxycarbonyl-

benzofuran-5-yl)piperazine.

Example A: Injection vials

A solution of 100 g of an active ingredient of the formula I and 5 g of disodium hydrogen phosphate in 3 l of double-distilled water is adjusted to pH 6.5 with 2 N hydrochloric acid, sterile-filtered, filled into injection vials, lyophilized and sterile-sealed. Each injection vial contains 5 mg of active ingredient.

Example B: Suppositories

A mixture of 20 mg of an active ingredient of the formula I is melted with 100 g of soya lecithin and 1,400 g of cocoa butter, poured into moulds and allowed to cool. Each suppository contains 20 mg of active ingredient.

Example C: Solution

A solution of 1 g of an active ingredient of the formula I, 9.38 g of $NaH_2PO_4 \times 2\ H_2O$, 28.48 g $Na_2HPO_4 \times 12\ H_2O$ and 0.1 g of benzalkonium chloride is prepared in 940 ml of double-distilled water. The pH is adjusted to 6.8, and the solution is made up to 1 l and sterilized by irradiation. This solution can be used in the form of eyedrops.

Example D: Ointment

500 mg of an active ingredient of the formula I are mixed with 99.5 g of petroleum jelly under aseptic conditions.

Example E: Tablets

A mixture of 1 kg of active ingredient of the formula I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is compressed to tablets in conventional manner so that each tablet contains 10 mg of active ingredient.

Example F: Coated tablets

Tablets are formed by compression analogously to Example E and then covered in conventional manner with a coating of sucrose, potato starch, talc, tragacanth and colourant.

Example G: Capsules

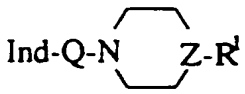
2 kg of active ingredient of the formula I are filled into hard gelatin capsules in conventional manner so that each capsule contains 20 mg of the active ingredient.

Example H: Ampoules

A solution of 1 kg of active ingredient of the formula I in 60 l of double-distilled water is filled into ampoules and lyophilized under aseptic conditions and the ampoules are sealed under sterile conditions. Each ampoule contains 10 mg of active ingredient.

Patent Claims

1. Piperidine and piperazine derivatives of the formula I



I

wherein

Ind is an indol-3-yl radical which is unsubstituted or mono- or polysubstituted by OH, OA, CN, Hal, COR^2 or CH_2R^2

R^1 is benzofuran-5-yl or 2,3-dihydrobenzofuran-5-yl, chroman-6-yl, chroman-4-on-6-yl, 3-chromen-6-yl or chromen-4-on-6-yl, which is unsubstituted or monosubstituted by CN, CH_2OH, CH_2OA or COR^2,

Q is C_mH_{2m},

Z is N or CR^3,

A is alkyl having 1-6 C atoms,

Hal is F, Cl, Br or I,

R^2 is OH, OA, NH_2, NHA or NA_2,

R^3 is H, OH or OA and

m is 2, 3 or 4,

and their physiologically acceptable salts.

2. (a) 1-[4-(5-Methoxyindol-3-yl)butyl]-4-(2-hydroxymethylbenzofuran-5-yl)piperazine;

(b) 1-[4-(5-carbamoylindol-3-yl)butyl]-4-hydroxy-4-(2,3-dihydrobenzofuran-5-yl)piperidine;

(c) 1-[4-(5-carbamoylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperidine;

(d) 1-[4-(5-methoxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine;

(e) 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-ethoxycarbonylbenzofuran-5-yl)piperazine;

(f) 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoylbenzofuran-5-yl)piperazine;

(g) 1-[4-(5-methoxyindol-3-yl)butyl]-4-(chroman-6-yl)piperazine;

(h) 1-[4-(5-hydroxyindol-3-yl)butyl]-4-(chroman-6-yl)piperazine.

3. Process for the preparation of piperazine and

piperidine derivatives of the formula I according to Claim 1, and their salts, characterised in that a compound of the formula II

$$Ind\text{-}Q\text{-}X^1 \qquad II$$

wherein

X^1 is X or NH_2,

X is Cl, Br, I, OH or an OH group functionally modified to form a reactive group, and

Ind and Q are as defined,

is reacted with a compound of the formula III

$$X^2\text{-}(CH_2)_2\text{-}ZR^1\text{-}(CH_2)_2\text{-}X^3 \qquad III$$

wherein

X^2 and X^3 can be identical or different and are each X if $X^1 = NH_2$ or are together NH in other cases, and

Z and R^1 are as defined,

or in that to prepare a compound of the formula I, in which Z is N, a compound of the formula IV

$$Ind\text{-}Q\text{-}N(CH_2\text{-}CH_2\text{-}X)_2 \qquad IV$$

wherein

X, Q and Ind are as defined, is reacted with a compound of the formula V

$$R^1\text{-}NH_2 \qquad V$$

wherein

R^1 is as defined,

or in that a compound which has formula I except that one or more hydrogen atoms have been replaced by one or more reducible groups and/or one or more additional C-C and/or C-N bonds is treated with a reducing agent,

or in that a compound which has formula I except that one or more hydrogen atoms have been replaced by one or more solvolysable groups is treated with a solvolysing agent, and/or in that an OA group is optionally cleaved to form an OH group, and/or an Ind group or an R^1 group is converted into another Ind and/or R^1 group, and/or in that a resulting base or acid of the formula I is converted into one of its salts by treatment with an acid or base.

4. Process for the manufacture of pharmaceutical preparations, characterized in that a compound of the formula I according to Claim 1 and/or one of its

physiologically acceptable salts are converted into a suitable dosage form together with at least one solid, liquid or semiliquid excipient or adjunct.

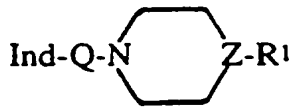
5. Pharmaceutical preparation, characterized in that it contains at least one compound of general formula I according to Claim 1 and/or one of its physiologically acceptable salts.

6. Use of compounds of the formula I according to Claim 1, or their physiologically acceptable salts, for the manufacture of a drug.

7. Use of compounds of the formula I according to Patent Claim 1, or their physiologically acceptable salts, for controlling diseases.

Abstract of the disclosure

Piperidine and piperazine derivatives of the formula I



I

wherein

Ind is an indol-3-yl radical which is unsubstituted or mono- or polysubstituted by OH, OA, CN, Hal, COR^2 or CH_2R^2,

R^1 is benzofuran-5-yl or 2,3-dihydrobenzofuran-5-yl, chroman-6-yl, chroman-4-on-6-yl, 3-chromen-6-yl or chromen-4-on-6-yl, which is unsubstituted or monosubstituted by CN, CH_2OH, CH_2OA or COR^2,

Q is C_mH_{2m},

Z is N or CR^3,

A is alkyl having 1-6 C atoms,

Hal is F, Cl, Br or I,

R^2 is OH, OA, NH_2, NHA or NA_2,

R^3 is H, OH or OA and

m is 2, 3 or 4,

and their physiolocally acceptable salts, are active on the central nervous system.

LAW OFFICES
MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
ARLINGTON COURTHOUSE PLAZA I
SUITE 1400
2200 CLARENDON BOULEVARD
ARLINGTON, VIRGINIA 22201

TELEPHONE: (703) 243-6333
CABLE: USALAW INT'L TELEX: 64191
TELECOPIER: (703) 243-6410

Atty's Docket No. MERCK 1617

In re application of Henning BÖTTCHER et al.
Serial No. 08/314,734
Filed September 29, 1994

THE COMMISSIONER OF PATENTS & TRADEMARKS
Washington, D.C. 20231

Sir:
Transmitted herewith is an amendment in the above-identified application.

- ☐ Small entity status of this application under 37 CFR 1.9 and 1.27 has been established by a verified statement previously submitted.
- ☐ Verified statement(s) to establish small entity status under 37 CFR 1.9 and 1.27 enclosed.
- ☐ No additional fee is required.

The fee has been calculated as shown below.

CLAIMS AS AMENDED						
(1)	(2) CLAIMS REMAINING AFTER AMENDMENT	(3)	(4) HIGHEST NO. PREVIOUSLY PAID FOR	(5) PRESENT EXTRA	(6) RATE	(7) ADDITIONAL FEE
TOTAL CLAIMS	* 28	MINUS	** 22	= 6	x $22	$132.00
INDEP. CLAIMS	* 1	MINUS	*** 3	= 0	x $76	0.00
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM						
			TOTAL ADDITIONAL FEE FOR THIS AMENDMENT			$132.00

* If entry in Col. 2 is less than entry in Col. 4, write "0" in Col. 5.
** If "Highest No. Previously Paid For" in this space is less than 20, write "20" in this space.
*** If "Highest No. Previously Paid For" in this space is less than 3, write "3" in this space.

The "Highest No. Previously Paid For" (total or independent) is the highest number found from the equivalent box in Col. 2 of a prior amendment or the number of claims originally filed.

- ☒ The amount of $ 132.00 is included in the attached check.
- ☐ Please charge my Deposit Account No. 13-3402 in the amount of $_____. Two copies of this sheet are attached for this purpose.

Applicant(s) request(s) that the time for taking action in this case be extended pursuant to 37 C.F.R. §1.136(a).

- ☐ Included in the attached check is the statutory fee of $_____ for an extension of time of _____ month(s).
- ☒ If the box for the sentence immediately above is marked but no check is attached, then charge the statutory fee recited in such sentence for an extension of time of the number of months recited in such sentence to Deposit Account No. 13-3402. Two copies of this sheet are attached for this purpose.
- ☐ Charge the Statutory Fee of $_____ for an extension of time of _____ month(s) to Deposit Account No. 13-3402. Two copies of this sheet are attached for this purpose.

- ☒ The Commissioner is hereby authorized to charge any deficiencies in payment of the following fees associated with this communication or credit any overpayment to Deposit Account No. 13-3402.
  - ☒ Any filing fees under 37 C.F.R. §1.16 for the presentation of extra claims.
  - ☒ Any patent application processing fees under 37 C.F.R. §1.17.

Respectfully submitted,
MILLEN, WHITE, ZELANO & BRANIGAN, P.C.

DATE: June 28, 1995

BY: _____
Brion P. Heaney (Reg. No. 32,542)

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/314,734	09/29/94	BOTTNER	MERCK1617

EXAMINER	
BERNHARDT, E	JA

ART UNIT	PAPER NUMBER
1202	4

1202/0328

MILLEN WHITE ZELANO AND BRANIGAN
ARLINGTON COURTHOUSE PLAZA I SUITE 1400
2200 CLARENDON BOULEVARD
ARLINGTON VA 22201

DATE MAILED: 03/28/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 1-22 are pending in the application.
   Of the above, claims 13, 19-22 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1-12, 14-15, 17-18 are rejected.
5. ☑ Claims 16 are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☑ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☑ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

PTOL-326 (Rev. 2/93) EXAMINER'S ACTION

Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1-12, 14-18, drawn to compounds and compositions where Z=N, classified in Class 544, subclass 373; Class 514, subclass 254.

II. Claims 1-11, 13, 17-18, drawn to compounds and compositions where $Z=CR^3$, classified in Class 546, subclass 201; class 514, subclass 323.

III. Claims 19-22, drawn to multi-methods of use employing group I compounds, classified in Class 514, subclass 254.

IV. Claims 19-22, drawn to multi-methods of use employing group II compounds, classified in Class 514, subclass 323.

If III or IV is elected applicants must further elect a use or related uses associated with a particular physiological activity.

The inventions are distinct, each from the other because of the following reasons:

Compounds of Groups I and II are structurally dissimilar which are thus separately classified, require separate Chemical Abstract searches and would be expected to raise different issues of patentability - see the art applied below directed to the elected invention. Each can support a patent as the compounds of each group are capable of being utilized alone not in combination with other remaining members in the Markush group.

Inventions I/II and III/IV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case the respective products of I and II have more than one distinct use as evidenced by applicants' own disclosure - see p.1 and 2.

During a telephone conversation with Mr. Heaney on [illegible] a provisional election was made with traverse to prosecute the invention of Group I, claims 1-12, 14-18. Affirmation of this election must be made by applicant in responding to this Office action. Claims 13, 19-22 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

Claims 11, 17-18 which link inventions I and II will only be examined with respect to the elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

Claim 12 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. In claim 12 what is intended by "benzo-5-yl"?

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide descriptive support (antecedent basis) for the invention claimed.

The examiner cannot find a description of species (e) in claim 2 in the specification.

Claim 2 is rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-12, 14-15, 17-18 are rejected under 35 U.S.C. § 103 as being unpatentable over Boettcher in view of Perregaard. Boettcher having issued more than a year earlier than the instant filing date teaches similar compounds to that claimed herein and for the same disclosed uses as herein. See formula I compounds in column 1 and exemplified compounds in cols. 11-17. The compounds differ in only one respect to that claimed herein - benzodioxanyl substitution vs. instant R^1 as dihydro benzofuranyl, chromanyl.

Perregaard teaches the interchangeability of the above mentioned rings on similar compounds and for the same uses (as 5HT agonists, antagonists). See definition of Y and Z in col. 1 in the Ar definition. Thus it would have been obvious to one skilled in the art at the time the invention was made to replace the benzodioxane ring system with those taught in Perregaard and thus obtain the instant compounds in view of the equivalency teaching outlined above.

Claims 1-12, 14-15, 17-28 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 5,242,925 in view of Perregaard.

While the conflicting claims are not identical, they are not patentably distinct for the same reasons discussed in the above 103 rejection.

The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. *In re Vogel*, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d).

Claim 16 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Said claim would be allowed as the R^1 moiety recited ~~herein~~ therein is not taught ~~a~~ or suggested by the art of record or from or search in the pertinent art area.

Claims 1-11, 17-18 are rejected under judicial doctrine as being drawn to an improper Markush group. The Markush at Z embraces ~~were~~ more than one ~~insertion~~ invention as discussed in the above restriction requirement. Note if nonelected subject matter is deleted claim 9 would be an improper dependent. Claim and "Z is N" in claims 12, 14-16 would be superfluous.

Any inquiry concerning this communication should be directed to Examiner Emily Bernhardt at telephone number (703) 308-4714.

A facsimile center has been established in Group 1200, room 3C10. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine is (703) 308-4556 or 305-3592.

BERNHARDT:tcj
March 22, 1995

E Bernhardt

EMILY BERNHARDT
PRIMARY EXAMINER
GROUP 120

TO SEPARATE, HOLD TOP AND BOTTOM EDGES, SNAP–APART AND DISCARD CARBON

FORM PTO-892 (REV. 3-78) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	SERIAL NO.	GROUP ART UNIT	ATTACHMENT TO PAPER NUMBER	
NOTICE OF REFERENCES CITED	314734	1202		4
	APPLICANT(S) BOTTCHER et al			

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	A	5002948	3/26/91	PERRE GAALO et al	544	373	
	B						
	C						
	D						
	E						
	F						
	G						
	H						
	I						
	J						
	K						

FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. DWG	PERTINENT PP. SPEC.
	L								
	M								
	N								
	O								
	P								
	Q								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

	R	
	S	
	T	
	U	

EXAMINER	DATE	
F Bernhardt	3/15/95	

* A copy of this reference is not being furnished with this office action.
(See Manual of Patent Examining Procedure, section 707.05 (a).)

Form PTO-1449 U.S. DEPT. OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DKT. NO. MERCK 1617	SERIAL NO. 08/314,734
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use several sheets if necessary)	APPLICANT Henning BÖTTCHER et al.	
	FILING DATE September 29, 1994	GROUP 1202

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date
EB	AA	5,242,925	09/07/93	Böttcher et al.	514	254	08/24/92
	AB						
	AC						
	AD						
	AE						
	AF						
	AG						
	AH						
	AI						
	AJ						
	AK						

FOREIGN PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Country	Class	Subclass	Translation Yes	Translation No
EB	AL	94/13659	06/23/94	PCT			X	
EB	AM	0 490 772	06/17/92	Europe				X
EB	AN	41 27 849	02/25/93	Germany				X
	AO							
	AP							
	AQ							
	AR							
	AS							
	AT							

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

	AU	
	AV	
	AW	
	AX	
	AY	
	AZ	

Examiner	Date Considered
E Benhaddou	3/15/95

PTO-1542 (4-85)

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

John, please

3-12

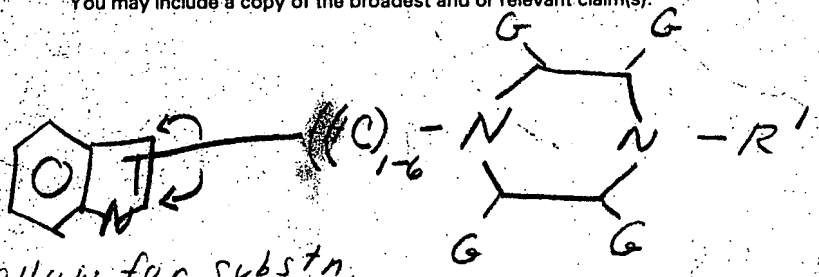
ONLINE SEARCH REQUEST FORM

USER EBernhardt SERIAL NUMBER 314 734

ART UNIT _____ PHONE 308-4714 DATE 3/8/95

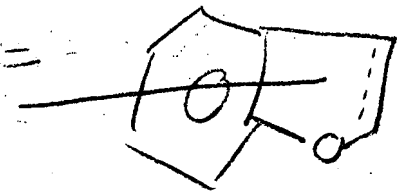
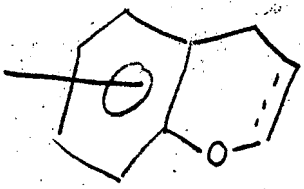
Please give a detailed statement of requirements. Describe as specifically as possible the subject matter to be searched. Define any terms that may have special meaning. Give examples or relevant citations, authors, or keywords, if known.

You may include a copy of the broadest and or relevant claim(s).



allow for substn. on indole ring system

G = H, Me, Et,

R' =  or 

Allow for optional substitution on these ring systems

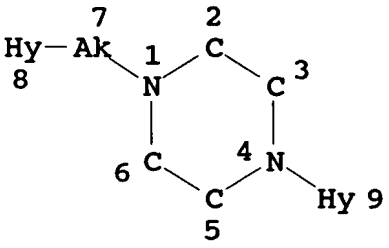
See what you get

STAFF USE ONLY

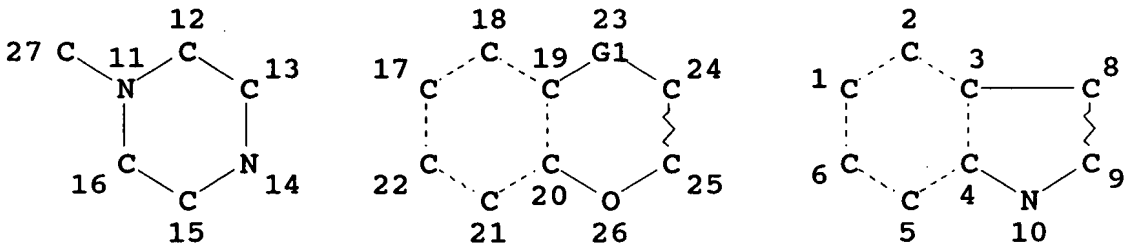
COMPLETED 3-9-95
SEARCHER JOHN O.
ONLINE TIME (in minutes) 10 TOTAL TIME 20
NO. OF DATABASES 3

SYSTEMS
✓ CAS ONLINE
___ DARC/QUESTEL
___ DIALOG
___ SDC
___ OTHER

```
=> fil reg
FILE 'REGISTRY' ENTERED AT 07:55:39 ON 09 MAR 95
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
COPYRIGHT (C) 1995 American Chemical Society (ACS)

STRUCTURE FILE UPDATES:   3 MAR 95   HIGHEST RN 161274-47-1
DICTIONARY FILE UPDATES:  8 MAR 95   HIGHEST RN 161274-47-1

TSCA INFORMATION NOW CURRENT THROUGH MAY 1994

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

=>
=>
=> d que l6
L2                STR
```




```
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
GGCAT   IS PCY  HIC  LOQ  UNS  AT   8
GGCAT   IS PCY  HIC  LOQ  UNS  AT   9
DEFAULT ECLEVEL IS LIMITED
ECOUNT  IS E8 C  E1 N  AT   8
ECOUNT  IS M8 C  E1 O  AT   9

GRAPH ATTRIBUTES:
RSPEC   1
NUMBER OF NODES IS   9

STEREO ATTRIBUTES: NONE
L4                STR
```




```
REP G1=(0-1) C
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
```

RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 26

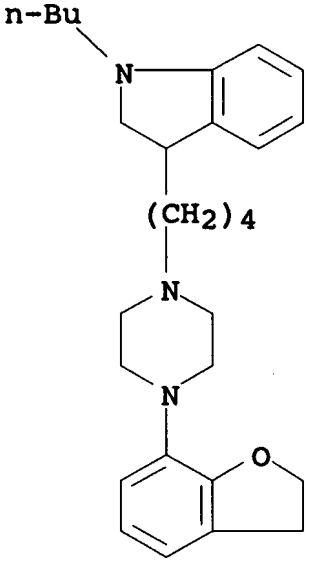
STEREO ATTRIBUTES: NONE
L6 3 SEA FILE=REGISTRY SSS FUL L2 AND L4

=> d 1-3 ide can

L6 ANSWER 1 OF 3 REGISTRY COPYRIGHT 1995 ACS
RN 131084-05-4 REGISTRY
CN 1H-Indole, 1-butyl-3-[4-[4-(2,3-dihydro-7-benzofuranyl)-1-piperazinyl]butyl]-2,3-dihydro-, ethanedioate (1:2) (9CI) (CA INDEX NAME)
MF C28 H39 N3 O . 2 C2 H2 O4
SR CA
LC STN Files: CA, TOXLIT, USPATFULL

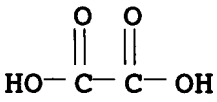
CM 1

CRN 131083-77-7
CMF C28 H39 N3 O



CM 2

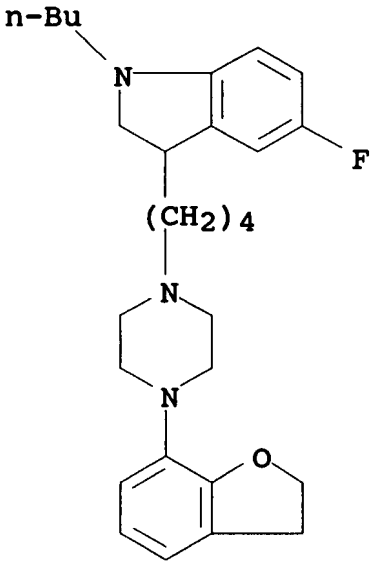
CRN 144-62-7
CMF C2 H2 O4



1 REFERENCES IN FILE CA (1967 TO DATE)

REFERENCE 1: P 114:17582

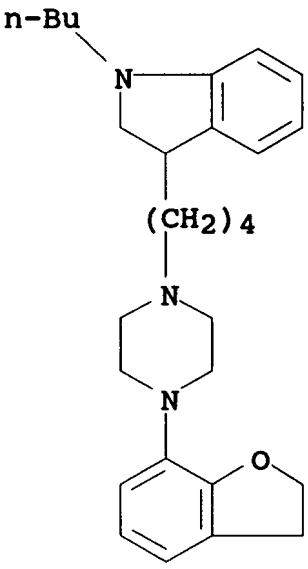
L6 ANSWER 2 OF 3 REGISTRY COPYRIGHT 1995 ACS
RN 131083-92-6 REGISTRY
CN 1H-Indole, 1-butyl-3-[4-[4-(2,3-dihydro-7-benzofuranyl)-1-piperazinyl]butyl]-5-fluoro-2,3-dihydro- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C28 H38 F N3 O
SR CA
LC STN Files: CA, TOXLIT, USPATFULL



1 REFERENCES IN FILE CA (1967 TO DATE)

REFERENCE 1: P 114:17582

L6 ANSWER 3 OF 3 REGISTRY COPYRIGHT 1995 ACS
RN 131083-77-7 REGISTRY
CN 1H-Indole, 1-butyl-3-[4-[4-(2,3-dihydro-7-benzofuranyl)-1-piperazinyl]butyl]-2,3-dihydro- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C28 H39 N3 O
CI COM
SR CA
LC STN Files: CA, TOXLIT, USPATFULL



1 REFERENCES IN FILE CA (1967 TO DATE)

REFERENCE 1: P 114:17582

=> fil ca
FILE 'CA' ENTERED AT 07:55:56 ON 09 MAR 95
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
COPYRIGHT (C) 1995 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1967 - 4 Mar 1995 (950304/ED) VOL 122 ISS 10

To help control your online searching costs, consider using the HCA File when using the FSEARCH command or when conducting SmartSELECT searches with large numbers of terms.

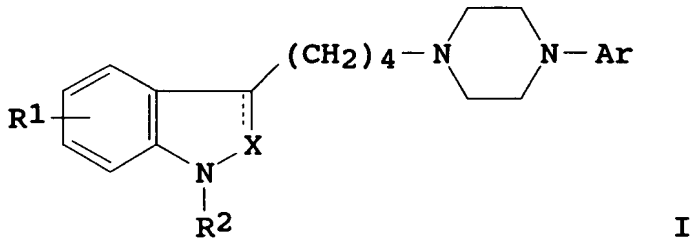
CAPLUS IS NOW ONLINE!

=> s l6
L7 1 L6

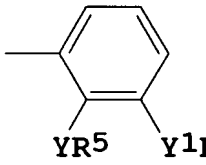
=> d all

L7 ANSWER 1 OF 1 CA COPYRIGHT 1995 ACS
AN 114:17582 CA
TI Preparation of piperazinyl derivatives, and their use as serotoninergic agonists in the treatment of central nervous system disorders
IN Perregaard, Jens; Stenberg, John Willie
PA Lundbeck, H., og Co. A/S, Den.
SO Eur. Pat. Appl., 18 pp.
CODEN: EPXXDW
= US 5002948
PI EP 376607 A1 900704
DS R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE
AI EP 89-313371 891220
PRAI GB 88-30312 881228
DT Patent

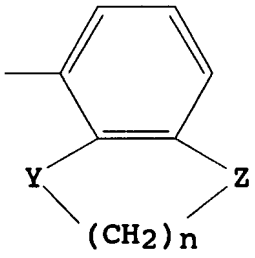
LA English
IC ICM C07D209-14
ICS C07D231-56; C07D231-54; C07D405-12; C07D409-12; C07D411-12; A61K031-40
CC 1-11 (Pharmacology)
Section cross-reference(s): 28, 63
OS MARPAT 114:17582
GI



I



Q1



Q2

AB The title derivs. I [dotted line is optional bond; X = CH, CH2, N(H), C:O; R1 = H, halogen, (un)branched C1-6 alk(en)yl, trifluoromethyl; R2 = H, (un)branched (un)substituted C1-6 alk(en)yl; Ar = Q1, Q2 (Y = O, S; Y1 = H, O, S, CH2; Z = O, S, CH2; n = 1-3; R5 = (un)branched C1-6 alk(en)yl)], and their pharmaceutically acceptable acid addn. salts and stereoisomers, are prepd. for use in treatment of central nervous system disorders, including anxiety, depression, and aggression, or in diseases related to cardiovascular, renal, and gastrointestinal systems. Methods of prepn. of I and pharmaceutical compns. contg. I are also provided. I have central serotonin activity with preference for the 5-HT1A receptor. Thus, 3-[4-(4-(2-methoxyphenyl)-1-piperazinyl)-1-butyl]-1H-2,3-dihydroindole dioxalate (prepn. given) inhibited 5-methoxy-N,N-dimethyltryptamine-induced 5-HT syndrome in rats with ED50 = 1.9 .mu.mole/kg. A tablet formulation contained 3-[4-(4-(1,4-benzodioxan-5-yl)-1-piperazinyl)-1-butyl]-1H-2,3-dihydroindole dioxalate 5, lactose 18, potato starch 27, saccharose 58, sorbitol 3, talcum 5, gelatine 2, povidone 1, and Mg stearate 0.5 mg.

ST piperazine deriv serotoninergic 5HT1A agonist; central nervous system treatment piperazine deriv
IT Pharmaceutical dosage forms
(injections, of piperazine deriv. 5-HT1A agonist, for central nervous system disorders treatment)
IT Neurotransmitter agonists

(serotoninergic S1A, piperazine derivs. as, prepn. of and pharmaceuticals contg.)
IT Pharmaceutical dosage forms
(syrups, of piperazine deriv. 5-HT1A agonist, for central nervous system disorders treatment)
IT Pharmaceutical dosage forms
(tablets, of piperazine deriv. 5-HT1A agonist, for central nervous system disorders treatment)
IT 131083-84-6P 131083-94-8P
(prepn. and reaction of, for serotoninergic 5-HT1A agonist)
IT 131083-83-5P 131083-86-8P 131083-87-9P 131084-17-8P
131084-18-9P 131084-24-7P 131084-25-8P 131084-28-1P
131084-29-2P 131084-30-5P
(prepn. and reaction of, in serotoninergic 5-HT1A agonist prepn.)
IT **131083-77-7P** 131083-89-1P 131083-91-5P
131083-92-6P 131083-96-0P 131083-98-2P 131084-00-9P
131084-01-0P 131084-02-1P 131084-03-2P 131084-04-3P
131084-05-4P 131084-07-6P 131084-09-8P 131084-11-2P
131084-12-3P 131084-14-5P 131084-15-6P 131084-23-6P
131084-27-0P 131084-31-6P 131109-70-1P
(prepn. of, for serotoninergic 5-HT1A agonist)
IT 328-87-0, 2-Chloro-5-trifluoromethylbenzonitrile 928-51-8, 4-Chloro-1-butanol 35386-24-4, 1-(2-Methoxyphenyl)piperazine
131083-82-4 131083-85-7
(reaction of, in serotoninergic 5-HT1A agonist prepn.)
IT 131084-20-3 131084-22-5
(resoln. of, for serotoninergic 5-HT1A agonist)
IT 131083-76-6 **131083-77-7** 131083-78-8 131083-79-9
131083-81-3 131084-16-7
(serotoninergic 5-HT1A agonist)
IT 110-85-0D, Piperazine, derivs.
(serotoninergic 5-HT1a agonists)

=> fil caold caprev
FILE 'CAOLD' ENTERED AT 07:56:17 ON 09 MAR 95
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
COPYRIGHT (C) 1995 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'CAPREVIEWS' ENTERED AT 07:56:17 ON 09 MAR 95
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
COPYRIGHT (C) 1995 American Chemical Society (ACS)

=> s l6
FILE 'CAOLD'
L8 0 L6

FILE 'CAPREVIEWS'
L9 0 L6

TOTAL FOR ALL FILES
L10 0 L6

=> fil hom
FILE 'HOME' ENTERED AT 07:56:26 ON 09 MAR 95

Bernhart 2/25/95

U. 3/13/95

#3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :

Henning BÖTTCHER et al. :

Serial No.: 08/314,734 KdP :

Filed: September 29, 1994 :

For: PIPERIDINES AND PIPERAZINES

Group Art Unit: 1202

Examiner: Bernhardt

INFORMATION DISCLOSURE STATEMENT

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

SIR:

Enclosed is the search report which issued in corresponding European application No. 94114798.5. The following documents were cited in the search report:

WO 94/13659
EP 0 490 772
DE 41 27 849
DE 41 01 686
GB 1,075,156
FR 1,551,082

The following is an English translation of the comments in the search report.

WO-A-94 13659 (LUNDBECK) 23 June 1994
Page 3, line 28 - line 30

EP-A-0 490 772 (ADIR ET COMPAGNIE) 17 June 1992
Page 2, line 41; Claim 1

DE-A-41 27 849 (MERCK PATENT GMBH) 25 February 1993
Page 2, line 28; Claim 1

DE-A-41 01 686 (MERCK PATENT GMBH) 23 July 1992
Claim 1

GB-A-1 075 156 (FARMACO D'ITALIA) 12 July 1967
Claim 1

FR-A-1 551 082 (STERLING) 27 December 1968
Claim 1

WO '659, EP '772 and DE '849 (copies enclosed) listed as "Y" type references. WO '659 is also indicated as being a "P" reference, i.e., effective date after filing date of application. U.S. 5,242,925 corresponds to DE 41 27 849. A copy of U.S. '925 is also enclosed.

DE '686, GB '156 and FR '082 are cited as "A" type references relating to technological background. DE '686 is also indicated as being a "D" type reference, i.e., cited in the application. U.S. Serial No. 08/262,256 (now allowed) lists DE '686 for purposes of priority. Copies of these documents are not enclosed.

This Information Disclosure Statement is being submitted prior to receipt of the first action on the merits. Therefore, it is believed that no fee is required. See 37 C.F.R. §1.97(b)(3).

Respectfully submitted,

Brion P. Heaney (Reg. No. 32,542)
Attorney for Applicants

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
Arlington Courthouse Plaza I
2200 Clarendon Boulevard, Suite 1400
Arlington, Virginia 22201
(703) 243-6333

Filed: March 8, 1995

BPH:kdp104:merck617.ids

(19) BUNDESREPUBLIK DEUTSCHLAND

DEUTSCHES PATENTAMT

(12) **Offenlegungsschrift**

(10) **DE 41 27 849 A1**

(51) Int. Cl.[5]:
C 07 D 405/12
A 61 K 31/495
// (C07D 405/12, 319:18,233:61,209:14)

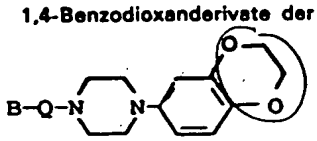
(21) Aktenzeichen: P 41 27 849.6
(22) Anmeldetag: 22. 8. 91
(43) Offenlegungstag: 25. 2. 93

(71) Anmelder:
Merck Patent GmbH, 6100 Darmstadt, DE

(72) Erfinder:
Böttcher, Henning, Dr., 6100 Darmstadt, DE;
Seyfried, Christoph, Dr., 6104 Jugenheim, DE;
Greiner, Hartmut, Dr.; Bartoszyk, Gerd, 6100 Darmstadt, DE

(54) **Benzodioxanderivate**

(57) 1,4-Benzodioxanderivate der Formel I



I,

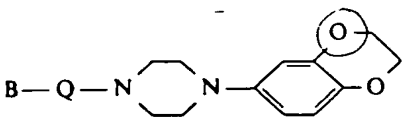
worin B und Q die in Patentanspruch 1 angegebenen Bedeutungen haben, sowie deren Salze, zeigen Wirkungen auf das Zentralnervensystem.

bioequiv. Same activity

DE 41 27 849 A1

Beschreibung

Die Erfindung betrifft neue 1,4-Benzodioxanderivate der Formel I



(I)

worin
B einen unsubstituierten oder einfach durch CN, $CO-R^1$, $C_nH_{2n}-R^1$, Hal, OH, OA, $O-C_nH_{2n}-COR^1$ oder NHR_2 substitituierten Indol-3-yl- oder Benzimidazol-1-yl-rest,
R^1 OH, OA, NH_2, NHA oder NA_2,
R^2 H, A, $CO-A$, $CO-Ar$, $CO-NH_2$, $CO-NHA$, SO_2-Ar oder SO_2-A,
Q C_nH_{2n},
n 1, 2, 3, 4, 5 oder 6,
A Alkyl mit 1—6 C-Atomen,
Ar einen unsubstituierten oder einen ein- oder zweifach durch A, Hal, CN, OH und/oder OA substituierten Phenylrest, und
Hal F, Cl, Br oder I
bedeuten
sowie deren Salze.

Der Erfindung lag die Aufgabe zugrunde, neue Verbindungen aufzufinden, die zur Herstellung von Arzneimitteln verwendet werden können.

Es wurde gefunden, daß die Verbindungen der Formel I und ihre physiologisch unbedenklichen Säureadditionssalze wertvolle pharmakologische Eigenschaften besitzen. So zeigen sie insbesondere Wirkungen auf das Zentralnervensystem, vor allem serotonin-agonistische und -antagonistische Wirkungen. Sie hemmen die Bindung von tritiierten Serotoninliganden an hippocampale Rezeptoren (Cossery et al., European J. Pharmacol. 140 (1987), 143—155). Außerdem treten Veränderungen der DOPA-Akkumulation im Stratium und der 5-HTP-Akkumulation in N.raphe auf (Scyfried et al., European J. Pharmacol. 160 (1989), 31—41). Weiterhin treten analgetische und blutdrucksenkende Wirkungen auf; so wird bei kathetertragenden wachen, spontan hypertonen Ratten (Stamm SHR/Okamoto/NIH-MO-CHB-Kisslegg; Methode vgl. Weeks und Jones, Proc. Soc. Exptl. Biol. Med. 104 (1960), 646—648) der direkt gemessene Blutdruck nach peroraler Gabe der Verbindungen gesenkt. Ebenso eignen sie sich als Prophylaxe und zur Bekämpfung der Folgen cerebraler Infarktgeschehen (Apoplexia cerebri), wie Schlaganfall und cerebraler Ischämien.

Verbindungen der Formel I und ihre physiologisch unbedenklichen Säureadditionssalze können daher als Arzneimittelwirkstoffe für Anxiolytika, Antidepressiva, Neuroleptika und/oder Antihypertonika, ferner zur Cerebroprotektion nach Schlaganfall bzw. zur Prophylaxe, bei Morbus Alzheimer und auch als Zwischenprodukte zur Herstellung anderer Arzneimittelwirkstoffe verwendet werden.

Gegenstand der Erfindung sind die 1,4-Benzodioxanderivate der Formel I sowie ihre physiologisch unbedenklichen Säureadditionssalze.

Der Rest A bedeutet Alkyl mit 1, 2, 3, 4, 5 oder 6, insbesondere 1 oder 2 C-Atome, vorzugsweise Methyl, ferner auch Ethyl, n-Propyl, Isopropyl, n-Butyl, Isobutyl, sek.-Butyl oder tert.-Butyl. OA ist vorzugsweise Methoxy, ferner auch Ethoxy, n-Propoxy, Isopropoxy, n-Butoxy, Isobutoxy, sek.-Butoxy oder tert.-Butoxy. NHA ist vorzugsweise Methylamino, ferner Ethylamino, n-Propylamino, Isopropylamino, n-Butylamino, Isobutylamino, sek.-Butylamino oder tert.-Butylamino. NA_2 bedeutet vorzugsweise Dimethylamino, ferner N-Ethyl-N-methylamino, Diethylamino, Di-n-propylamino, Diisopropylamino oder Di-n-butylamino.

Analog bedeutet $CO-NHA$ vorzugsweise N-Methylcarbamoyl oder N-Ethylcarbamoyl; $CO-NA_2$ vorzugsweise N,N-Dimethylcarbamoyl oder N,N-Diethylcarbamoyl und SO_2-A vorzugsweise Methylsulfonyl oder Ethylsulfonyl.

Der Rest Ar bedeutet vorzugsweise unsubstituiertes Phenyl, aber auch ein- oder zweifach substituiertes Phenyl. Falls der Phenylrest zweifach substituiert ist, können die Substituenten gleich oder verschieden sein. Bevorzugte Substituenten an der Phenylgruppe sind F, Cl, Methoxy, CN, CF_3 oder Methyl. Die Substituenten befinden sich im Fall der substituierten Phenylrest in ortho-, meta- und/oder para-Position, wobei zweifach substituierte Phenylreste bevorzugt ortho- und para-substituiert sind. Im einzelnen ist Ar bevorzugt Phenyl, o-, m- oder p-Trifluormethylphenyl, o-, m- oder p-Methoxyphenyl, o-, m- oder p-Fluorphenyl, o-, m- oder p-Methylphenyl, o-, m- oder p-Cyanphenyl oder 2,4-Dimethoxyphenyl, aber auch o-, m- oder p-Ethoxyphenyl, o-, m- oder p-Bromphenyl, 2,3-, 2,5-, 2,6-, 3,4- oder 3,5-Dimethoxyphenyl, 2,3- oder 3,4-Methylendioxyphenyl.

Der Rest B bedeutet einen unsubstituierten oder einfach durch einen der angegebenen Reste substituierten Indol-3-yl- oder Benzimidazol-1-yl-rest. Vorzugsweise sind sie in 5-Stellung, ferner auch in der 4-, 6- oder 7-Stellung substituiert. Bevorzugte Substituenten am Indol-3-yl-rest sind CO_2CH_3, CO_2H, CN, $CONH_2$, CH_2OH, $H_2N-CO-NH$, CH_3-SO_2-NH und $CH_3-CO-NH$, aber auch OH, Methoxy, Ethoxy, NH_2 oder NHA, wobei A bevorzugt Methyl oder Ethyl entspricht.

Der Benzimidazolyl-1-rest ist vorzugsweise unsubstituiert, sofern er substituiert ist, sind die gleichen Substituenten besonders bevorzugt, die für den Indol-3-yl-rest angegeben sind.

Der Parameter n kann 1, 2, 3, 4, 5 oder 6 sein, vorzugsweise ist er 1, 2 oder 4.

Der Rest Q ist vorzugsweise $-(CH_2)_4-$, weiterhin $-CH_2-$, $-(CH_2)_2-$ oder $-(CH_2)_3-$.

R^1 ist bevorzugt OH, Methoxy oder NH_2, ferner bevorzugt Ethoxy, $NH-CH_3$ oder $N(CH_3)_2$.

R^2 ist vorzugsweise $CO-CH_3$, $CO-NH_2$ oder SO_2-CH_3, ferner $CO-NH-CH_3$ oder $CO-N(CH_3)_2$, aber auch CO-Phenyl oder SO_2-Methyl.

Dementsprechend sind Gegenstand der Erfindung insbesondere diejenigen Verbindungen der Formel I, in denen mindestens einer der genannten Reste eine der vorstehend angegebenen, insbesondere der vorstehend angegebenen bevorzugten Bedeutungen hat. Einige bevorzugte Gruppen von Verbindungen können durch die folgenden Teilformeln Ia bis Ij ausgedrückt werden, die der Formel I entsprechen und worin die nicht näher bezeichneten Reste und Parameter die bei der Formel I angegebene Bedeutung haben, worin jedoch

in Ia B einen in 5-Stellung durch $CO-R^1$ substituierten Indol-3-yl-rest bedeutet;
in Ib B einen in 5-Stellung durch NHR^2 substituierten Indol-3-yl-rest bedeutet;
in Ic B einen in 5-Stellung durch COOH substituierten Indol-3-yl-rest bedeutet;
in Id B einen in 5-Stellung durch $COOCH_3$ substituierten Indol-3-yl-rest bedeutet;
in Ie B einen in 5-Stellung durch $CONH_2$ substituierten Indol-3-yl-rest bedeutet;
in If B einen in 5-Stellung durch CN substituierten Indol-3-yl-rest bedeutet;
in Ig B einen in 5-Stellung durch CH_2OH substituierten Indol-3-yl-rest bedeutet;
in Ih B einen in 5-Stellung durch OA substituierten Indol-3-yl-rest bedeutet;
in Ii B einen unsubstituierten Benzimidazol-1-yl-rest bedeutet;
in Ij B einen in 5-Stellung durch $CO-R^1$ substituierten Benzimidazol-1-yl-rest bedeutet.

Insbesondere sind bevorzugt Verbindungen der Teilformeln Ik sowie Iak bis Iik, die den Teilformeln I sowie Ia bis Ij entsprechen, worin jedoch zusätzlich

$Q-(CH_2)_4-$

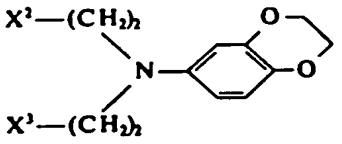
bedeutet.

Gegenstand der Erfindung ist ferner ein Verfahren zur Herstellung von 1,4-Benzodioxanderivaten der Formel I sowie von deren Salzen, dadurch gekennzeichnet, daß man eine Verbindung der Formel II

$B-Q-X^1$ (II)

worin

X^1 X oder NH und
X Cl, Br, I, OH oder eine reaktionsfähig funktionell abgewandelte OH-Gruppe bedeuten und
B und Q die angegebenen Bedeutungen haben,
mit einer Verbindung der Formel III



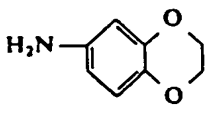
(III)

worin

X^2 und X^3 gleich oder verschieden sein können und, falls $X^1 = NH_2$ ist, jeweils X, andernfalls zusammen NH bedeuten,
umsetzt
oder daß man eine Verbindung der Formel IV

$B-Q-N(CH_2-CH_2-X)_2$ (IV)

worin
X, Q und B die angegebenen Bedeutungen haben, mit einer Verbindung der Formel V



(V)

umsetzt
oder daß man eine sonst der Formel I entsprechende Verbindung, die jedoch anstelle der 1,4-Benzodioxangruppe eine 3,4-Dihydroxyphenylgruppe, wobei aber auch die beiden Hydroxygruppen zur Erhöhung der Reaktionsbereitschaft in entsprechend aktivierter Form vorliegen können, mit Ethandiol oder einem entsprechenden reaktiveren Derivat zu einer Verbindung der Formel I umsetzt

oder daß man eine sonst der Formel I entsprechende Verbindung, die jedoch anstelle eines oder mehrerer Wasserstoffatome eine oder mehrere reduzierbare Gruppe(n) und/oder eine oder mehrere zusätzliche C—C- und/oder C—N-Bindung(en) enthält, mit einem reduzierenden Mittel behandelt

oder daß man eine sonst der Formel I entsprechende Verbindung, die jedoch anstelle eines oder mehrerer Wasserstoffatome eine oder mehrere solvolysierbare Gruppe(n) enthält, mit einem solvolysierenden Mittel behandelt

und/oder daß man gegebenenfalls eine O—A-Gruppe unter Bildung einer OH-Gruppe spaltet und/oder eine Gruppe B in eine andere Gruppe B umwandelt und/oder daß man eine erhaltene Base oder Säure der Formel I durch Behandeln mit einer Säure oder Base in eines ihrer Salze umwandelt.

Die Herstellung der Verbindungen der Formel I erfolgt im übrigen nach an sich bekannten Methoden, wie sie in der Literatur (z. B. in Standardwerken wie Houben-Weyl, Methoden der Organischen Chemie, Georg Thieme Verlag, Stuttgart; Organic Reactions, John Wiley & Sons, Inc., New York; DE-OS 33 42 632) beschrieben sind, und zwar unter Reaktionsbedingungen, wie sie für die genannten Umsetzungen bekannt und geeignet sind. Dabei kann man auch von an sich bekannten, hier nicht näher erwähnten Varianten Gebrauch machen.

Die Ausgangsstoffe für das beanspruchte Verfahren können gewünschtenfalls auch in situ gebildet werden, derart, daß am sie aus dem Reaktionsgemisch nicht isoliert, sondern sofort weiter zu den Verbindungen der Formel I umsetzt.

In den 1,4-Benzodioxanderivaten der Formel II ist X^1 vorzugsweise X; dementsprechend sind in den Verbindungen der Formel III X^2 und X^3 vorzugsweise zusammen NH. Der Rest X ist vorzugsweise Cl oder Br; er kann jedoch auch I, OH oder eine reaktionsfähig funktionell abgewandelte OH-Gruppe bedeuten, insbesondere Alkylsulfonyloxy mit 1—6 (z. B. Methansulfonyloxy) oder Arylsulfonyloxy mit 6—10 C-Atomen (z. B. Benzolsulfonyloxy, p-Toluolsulfonyloxy, 1- oder 2-Naphthalin-sulfonyloxy).

Dementsprechend sind die 1,4-Benzodioxanderivate der Formel I insbesondere durch Umsetzung von Verbindungen der Formel B—Q—Cl oder B—Q—Br mit 6-Piperazino-1,4-benzodioxan (Formel III, worin X^2 und X^3 zusammen eine NH-Gruppe bedeuten; nachstehend als IIIa bezeichnet) erhältlich.

Die Verbindungen der Formeln II und insbesondere III sind zum Teil bekannt; die nicht bekannten Verbindungen der Formeln II und III können leicht analog zu den bekannten Verbindungen hergestellt werden.

Primäre Alkohole der Formel B—Q—OH sind z. B. durch Reduktion der entsprechenden Carbonsäuren oder ihrer Ester erhältlich. Behandeln mit Thionylchlorid, Bromwasserstoff, Phosphortribromid oder ähnlichen Halogenverbindungen liefert die entsprecheden Halogenide der Formel B—Q—Hal. Die entsprechenden Sulfonyloxyverbindungen sind erhältlich aus den Alkoholen B—Q—OH durch Umsetzung mit den entsprechenden Sulfonsäurechloriden.

Die Iodverbindungen der Formel B—Q—I sind z. B. durch Einwirkung von Kaliumiodid auf die zugehörigen p-Toluolsulfonsäureester erhältlich. Die Amine der Formel B—Q—NH_2 sind z. B. aus den Halogeniden mit Phthalimidkalium oder durch Reduktion der entsprechenden Nitrile herstellbar.

Das Piperazinderivat IIIa ist z. B. erhältlich durch Umsetzung von Di-(2-chlorethyl)-amin mit 6-Amino-1,4-benzodioxan. Verbindungen der Formel III (X^2 und X^3 = jeweils X) sind z. B. herstellbar durch Reduktion von 1,4-Benzodioxanen, die in 6-Stellung eine —$N(CH_2CO_2A)_2$-Gruppe besitzen, zu den entsprechenden 1,4-Benzodioxanderivaten, die in Position 6 eine —$N(CH_2CH_2—OH)_2$-Gruppe aufweisen und gegebenenfalls anschließende Umsetzung mit $SOCl_2$ bzw. PBr_3.

Die Umsetzung der Verbindungen II und III verläuft nach Methoden, wie sie für die Alkylierung von Aminen aus der Literatur bekannt sind. Man kann ohne Gegenwart eines Lösungsmittels die Komponenten miteinander verschmelzen, gegebenenfalls im geschlossenen Rohr oder im Autoklaven. Es ist aber auch möglich, die Verbindungen in Gegenwart eines indifferenten Lösungsmittels umzusetzen. Als Lösungsmittel eignen sich z. B. Kohlenwasserstoffe, wie Benzol, Toluol, Xylol; Ketone wie Aceton, Butanon; Alkohole wie Methanol, Ethanol, Isopropanol, n-Butanol; Ether wie Tetrahydrofuran (THF) oder Dioxan; Amide wie Dimethylformamid (DMF) oder N-Methyl-pyrrolidon; Nitrile wie Acetonitril, gegebenenfalls auch Gemische dieser Lösungsmittel untereinander oder Gemische mit Wasser. Der Zusatz eines säurebindenden Mittels, beispielsweise eines Alkali- oder Erdalkalimetall-hydroxids, -carbonats oder -bicarbonats oder eines anderen Salzes einer schwachen Säure der Alkali- oder Erdalkalimetalle, vorzugsweise des Kaliums, Natriums oder Calciums, oder der Zusatz einer organischen Base wie Triethylamin, Dimethylanilin, Pyridin oder Chinolin oder eines Überschusses der Aminkomponente B—Q—NH_2 bzw. des Piperazinderivates der Formel IIIa kann günstig sein. Die Reaktionszeit liegt je nach den angewendeten Bedingungen zwischen einigen Minuten und 14 Tagen, die Reaktionstemperatur zwischen etwa 0 und 150°, normalerweise zwischen 20 und 130°.

Ferner ist es möglich, eine Verbindung der Formel I zu erhalten, indem man eine Verbindung der Formel B—Q—$N(CH_2—CH_2—X)_2$ (IV) mit 6-Amino-1,4-benzodioxan (V) umsetzt.

Die Verbindungen der Formeln IV sind zum Teil bekannt; die nicht bekannten Verbindungen können leicht in Analogie zu den bekannten hergestellt werden. So lassen sich Verbindungen der Formel IV leicht durch Umsetzung von B—Q—NH_2 mit 1,2-Dihalogenethan, wobei Halogen bevorzugt für Chlor oder Brom steht, herstellen. Ebenso ist es möglich, Verbindungen des Typs IV durch Umsetzung von B—Q—Cl, B—Q—Br oder B-Q-I mit sekundären Aminen der Formel $HN(CH_2—CH_2—X)_2$ zu erhalten.

Das primäre Amin der Formel V läßt sich beispielsweise ausgehend von Anilin durch die diversen, an sich bekannten Möglichkeiten der elektrophilen Substitution am Aromaten herstellen. Ferner ist es möglich, entsprechend substituierte Nitroverbindungen durch Reduktion in die Amine der Formel V zu überführen.

Die Umsetzung der Verbindungen IV und V verläuft nach Methoden, wie sie für die Alkylierung von Aminen aus der Literatur bekannt sind. Die Komponenten können direkt, ohne Gegenwart eines Lösungsmittels, miteinander verschmolzen werden, gegebenenfalls im geschlossenen Rohr oder im Autoklaven, unter Normaldruck oder unter erhöhtem Druck, wobei ein Inertgas wie z. B. N_2 zur Druckerhöhung zugeführt wird. Es ist aber

auch möglich, die Verbindungen in Gegenwart eines inerten Lösungsmittels umzusetzen. Als Lösungsmittel eignen sich die zuvor bei der Umsetzung von II mit III genannten. Ebenso kann sich der Zusatz eines säurebindenden Mittels zur Reaktionsmischung begünstigend auswirken. Es kommen die gleichen Basen, wie zuvor bei der Umsetzung der Verbindungen II und III beschrieben, in Frage.

Die optimale Reaktionszeit liegt, je nach den gewählten Reaktionsbedingungen, zwischen einigen Minuten und 14 Tagen, die Reaktionstemperatur zwischen etwa 0° und 150°, üblicherweise zwischen 20° und 130°.

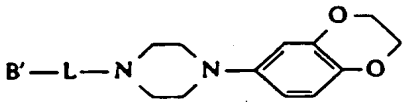
Eine weitere Möglichkeit, Verbindungen der Formel I herzustellen, besteht darin, daß man ein Vorprodukt, welches jedoch anstelle der 1,4-Benzodioxangruppe eine 3,4-Dihydroxyphenylgruppe enthält, mit Ethandiol umsetzt. Besonders bevorzugt sind allerdings Varianten dieser Methode, wie sie beispielsweise zur Ether-Darstellung eingesetzt werden, bei denen die Hydroxidgruppen der Reaktionspartner in an sich bekannter Weise aktiviert sind.

Es ist ferner möglich, eine Verbindung der Formel I zu erhalten, indem man ein Vorprodukt, das anstelle von Wasserstoffatomen eine oder mehrere reduzierbare Gruppe(n) und/oder eine oder mehrere zusätzliche C—C- und/oder C—N-Bindung(en) enthält, mit einem reduzierenden Mittel behandelt, vorzugsweise bei Temperaturen zwischen —80 und +250° in Gegenwart mindestens eines inerten Lösungsmittels.

Reduzierbare (durch Wasserstoff ersetzbare) Gruppen sind insbesondere Sauerstoff in einer Carbonylgruppe, Hydroxyl, Arylsulfonyloxy (z. B. p-Toluolsulfonyloxy), N-Benzolsulfonyl, N-Benzyl oder O-Benzyl.

Es ist grundsätzlich möglich, Verbindungen, die nur eine, oder solche, die nebeneinander zwei oder mehr der oben angeführten Gruppen bzw. zusätzlichen Bindungen enthalten, reduktiv in eine Verbindung der Formel I überzuführen; dabei können gleichzeitig Substituenten in der Gruppe B, die in der Ausgangsverbindung enthalten sind, reduziert werden. Vorzugsweise bedient man sich hierzu des nascierenden Wasserstoffs oder komplexer Metallhydride, ferner der Reduktion nach Wolff-Kishner sowie der Reduktion mit Wasserstoffgas unter Übergangsmetallkatalyse.

Bevorzugte Ausgangsstoffe für die Reduktion entsprechen der Formel VI



(VI)

worin

B' einen Indol-3-yl-rest, der zusätzlich durch eine Arylsulfonylgruppe oder eine Benzylgruppe in 1-Stellung substituiert sein kann oder einem unsubstituierten Benzimidazol-1-yl-rest entspricht und

L Q oder eine dem Rest Q entsprechende Kette, worin jedoch eine oder mehrere $-CH_2$-Gruppe(n) durch —CO— und/oder ein oder mehrere Wasserstoffatome durch Cl, Br, F, SH- oder OH-Gruppen ersetzt sind,

worin jedoch nicht gleichzeitig B' = B und L = Q sein können.

In den Verbindungen der Formel VI ist L bevorzugt $-CO-(CH_2)_{n-2}-CO-$ [im einzelnen —COCO—, $-COCH_2CO-$, $-CO-(CH_2)_2-CO-$, $-CO-(CH_2)_3-CO-$] $-(CH_2)_{n-1}-CO-$ [im einzelnen $-CH_2-CO-$, $-CH_2CH_2-CO-$, $-(CH_2)_3-CO-$ oder $-(CH_2)_4-CO-$] ferner z. B. $-CO-CH_2CH_2-$, $-CO-(CH_2)_3-$, $-CH_2-CO-CH_2CH_2-$, $-CH_2CH_2-CO-CH_2-$, $-CO-(CH_2)_4-$, $-CH_2-CO-(CH_2)_3-$, $-CH_2CH_2CO-CH_2CH_2-$ oder $-(CH_2)_3-CO-CH_2-$.

Verbindungen der Formel VI sind z. B. herstellbar durch Umsetzung von 6-Piperazino-benzo-1,4-dioxan mit einer Verbindung der Formel VII

$$B'-L-X^1 \quad \text{(VII)}$$

worin

B', L und X^1 die oben angegebenen Bedeutungen haben, unter den Bedingungen, die zuvor für die Umsetzung von II mit III angegeben sind.

Wird als Reduktionsmittel nascierender Wasserstoff verwendet, so kann man diesen z. B. durch Behandlung von Metallen mit schwachen Säuren oder mit Basen erzeugen. So kann man z. B. ein Gemisch von Zink mit Alkalilauge oder von Eisen mit Essigsäure verwenden. Geeignet ist auch die Verwendung von Natrium oder einem anderen Alkalimetall ein einem Alkohol wie Ethanol, Isopropanol, Butanol, Amyl- oder Isoamylalkohol oder Phenol. Man kann ferner eine Aluminium-Nickel-Legierung in alkalisch-wäßriger Lösung, gegebenenfalls unter Zusatz von Ethanol, verwenden. Auch Natrium- oder Aluminiumamalgam in wäßrig-alkoholischer oder wäßriger Lösung sind zur Erzeugung des nascierenden Wasserstoffs geeignet. Die Umsetzung kann auch in heterogener Phase durchgeführt werden, wobei man zweckmäßig eine wäßrige und eine Benzol- oder Toluol-Phase verwendet.

Als Reduktionsmittel können ferner besonders vorteilhaft komplexe Metallhydride, wie $LiAlH_4$, $NaBH_4$, Diisobutylaluminiumhydrid oder $NaAl(OCH_2CH_2OCH_3)_2H_2$ sowie Diboran eingesetzt werden, falls erwünscht unter Zusatz von Katalysatoren wie BF_3, $AlCl_3$ oder $LiBr$. Als Lösungsmittel eignen sich hierfür insbesondere Ether wie Diethylether, Di-n-butylether, THF, Dioxan, Diglyme oder 1,2-Dimethoxyethan sowie Kohlenwasserstoffe wie Benzol. Für eine Reduktion mit $NaBH_4$ sind in erster Linie Alkohole wie Methanol oder Ethanol, ferner Wasser sowie wäßrige Alkohole als Lösungsmittel geeignet. Nach diesen Methoden reduziert man vorzugsweise bei Temperaturen zwischen —80 und +150°, insbesondere zwischen etwa 0 und etwa 100°.

Besonders vorteilhaft lassen sich —CO-Gruppen in Säureamiden (z. B. solchen der Formel VI, worin L eine $-(CH_2)_{n-1}$-CO-Gruppe bedeutet) mit $LiAlH_4$ in THF bei Temperaturen zwischen etwa 0 und 66° zu CH_2-Gruppen reduzieren. Dabei können in 1-Stellung des Indolrings befindliche Arylsulfonyl-Schutzgruppen gleichzeitig reduktiv abgespalten werden. N-Benzylgruppen können reduktiv mit Natrium in flüssigem Ammoniak abgespalten werden.

Es ist ferner möglich, eine oder mehrere Carbonylgruppen nach der Methode von Wolff-Kishner zu CH_2-Gruppen zu reduzieren, z. B. durch Behandlung mit wasserfreiem Hydrazin in absolutem Ethanol unter Druck bei Temperaturen zwischen etwa 150 und 250°. Als Katalysator wird vorteilhaft Natriumalkoholat verwendet. Die Reduktion kann auch nach der Methode von Huang-Minlon variiert werden, indem man mit Hydrazinhydrat in einem hochsiedenden, mit Wasser mischbaren Lösungsmittel, wie Diethylenglykol oder Tiethylenglykol, in Gegenwart von Alkali, wie Natriumhydroxid, umsetzt. Das Reaktionsgemisch wird in der Regel etwa 3—4 Stunden gekocht. Anschließend wird das Wasser abdestilliert und das gebildete Hydrazon bei Temperaturen bis zu etwa 200° zersetzt. Die Wolff-Kishner-Reduktion kann auch bei Raumtemperatur in Dimethylsulfoxid mit Hydrazin ausgeführt werden.

Darüber hinaus ist es möglich, bestimmte Reduktionen durch Verwendung von H_2-Gas unter katalytischer Wirkung von Übergangsmetallen, wie z. B. Raney-Ni oder Pd durchzuführen. Man kann auf diese Weise z. B. Cl, Br, I, SH oder in bestimmten Fällen auch OH-Gruppen durch Wasserstoff ersetzen. Ebenso können Nitrogruppen durch katalytische Hydrierung mit Pd/H_2 in Methanol oder THF in NH_2-Gruppen umgewandelt werden.

Verbindungen, die sonst der Formel I entsprechen, aber anstelle eines oder mehrerer H-Atome eine oder mehrere solvolysierbare Gruppe(n) enthalten, können zu den Verbindungen der Formel I solvolysiert, insbesondere hydrolysiert werden.

Die Ausgangsstoffe für die Solvolyse sind beispielsweise erhältlich durch Reaktion von IIIa mit Verbindungen, die der Formel II ($X^1 = X$) entsprechen, aber anstelle eines oder mehrerer H-Atome eine oder mehrere solvolysierbare Gruppe(n) enthalten. So können insbesondere 1-Acylindolderivate (entsprechend der Formel I, aber in 1-Stellung des Ind-Rests eine Acylgruppe enthaltend, vorzugsweise eine Alkanoyl-, Alkylsulfonyl- oder Arylsulfonylgruppe mit jeweils bis zu 10 C-Atomen, wie Methan-, Benzol- oder p-Toluolsulfonyl) zu den entsprechenden in der 1-Stellung des Indolringes unsubstituierten Indolderivaten hydrolysiert werden, z. B. in saurem, besser in neutralem oder alkalischem Medium bei Temperaturen zwischen 0 und 200°. Als Basen verwendet man zweckmäßig Natrium-, Kalium- oder Calciumhydroxid, Natrium- oder Kaliumcarbonat, oder Ammoniak. Als Lösungsmittel wählt man vorzugsweise Wasser; niedere Alkohole wie Methanol, Ethanol; Ether wie THF, Dioxan; Sulfone wie Tetramethylsulfon; oder deren Gemische, besonders die Wasser enthaltenden Gemische. Eine Hydrolyse kann auch bereits beim Behandeln mit Wasser allein erfolgen, insbesondere in der Siedehitze.

Weiterhin kann man eine Verbindung der Formel I nach an sich bekannten Methoden in eine andere Verbindung der Formel I umwandeln.

Verbindungen der Formel I, worin B einen durch CO—R^1 substituierten Benzimidazol-1-yl- oder Indol-3-yl-rest bedeutet, können durch Derivatisierung entsprechender Carboxy-benzimidazol-1-yl- oder Carboxy-indol-3-yl-Verbindungen erhalten werden. Man kann z. B. die Säuren oder ihre reaktionsfähigen Derivate, wie z. B. ihre Säurehalogenide oder Anhydride mit entsprechenden Alkoholen oder Alkoholaten, unter Verwendung der an sich bekannten Methodik oder einer der zahlreichen Varianten, verestern. Ferner ist es möglich, Säuren, Säurehalogenide, Anhydride oder Ester mit primäre oder sekundären, aliphatischen oder cyclischen Aminen zu amidieren. Bevorzugt ist die Umsetzung der freien Carbonsäure mit dem Amin unter den Bedingungen einer Peptidsynthese. Diese Reaktion gelingt vorzugsweise in Gegenwart eines Dehydratisierungsmittels, z. B. eines Carbodiimids wie Dicyclohexylcarbodiimid oder N-(3-Dimethylaminopropyl)-N-ethyl-carbodiimid, ferner Propanphosphonsäuren-hydrid (vgl. Angew. Chem. 92, 129 (1980)), Diphenylphosphoryl azid oder 2-Ethoxy-N-ethoxycarbonyl-1,2-dihydrochinolin, in einem inerten Lösungsmittel, z. B. einem halogenierten Kohlenwasserstoff wie Dichlormethan, einem Ether wie THF oder Dioxan, einem Amid wie DMF oder Dimethylacetamid, einem Nitril wie Acetonitril, bei Temperaturen zwischen etwa —10 und 40, vorzugsweise zwischen 0 und 30°. Anstelle der Säure bzw. des Amids können auch reaktionsfähige Derivate dieser Stoffe in die Reaktion eingesetzt werden, z. B. solche, in denen reaktive Gruppen intermediär durch Schutzgruppen blockiert sind. Die Säuren können auch in Form ihrer aktivierten Ester verwendet werden, die zweckmäßig in situ gebildet werden, z. B. durch Zusatz von 1-Hydroxybenztriazol oder N-Hydroxysuccinimid.

Weiterhin kann man cyan-substituierte Reste B zu Carboxy-indol-3-yl- oder Carboxybenzimidazol-1-yl-resten oder Carbamido-in-dol-3-yl- bzw. Carbamidobenzimidazol-1-yl-resten hydrolysieren.

Verbindungen der Formel I, die durch O-Alkyl substituiert sind, können durch Etherspaltung in die entsprechenden Hydroxyderivate überführt werden. Z. B. kann man die Ether spalten durch Behandeln mit Dimethylsulfid-Bortribromid-Komplex, z. B. in Toluol, Ethern wie THF oder Dimethylsulfoxid, oder durch Verschmelzen mit Pyridin- oder Anilin-hydrohalogeniden, vorzugsweise Pyridinhydrochlorid, bei etwa 150—250°.

Die Verbindungen der Formel I können ein oder mehrere Asymmetriezentren besitzen. Sie können daher bei ihrer Herstellung als Racemate oder, falls optisch aktive Ausgangsstoffe verwendet werden, auch in optisch aktiver Form erhalten werden. Weisen die Verbindungen zwei oder mehr Asymmetriezentren auf, dann fallen sie bei der Synthese im allgemeinen als Gemische von Racematen an, aus denen man die einzelnen Racemate, beispielsweise durch Umkristallisieren aus inerten Lösungsmitteln, in reiner Form isolieren kann. Erhaltene Racemate können, falls erwünscht, nach an sich bekannten Methoden mechanisch oder chemisch in ihre optischen Antipoden getrennt werden. Vorzugsweise werden aus dem Racemat durch Umsetzung mit einem optisch aktiven Trennmittel Diastereomere gebildet. Als Trennmittel eignen sich z. B. optisch aktive Säuren, wie die D- und L-Formen von Weinsäuren, Dibenzoylweinsäure, Diacetylweinsäure, Camphersulfonsäuren, Mandelsäure, Äpfelsäure oder Milchsäure. Die verschiedenen Formen der Diastereomeren können in an sich bekannter Weise, z. B. durch fraktionierte Kristallisation, getrennt, und die optisch aktiven Verbindungen der Formel I können in

an sich bekannter Weise aus den Diastereomeren in Freiheit gesetzt werden.

Eine erhaltene Base der Formel I kann mit einer Säure in das zugehörige Säureadditionssalz übergeführt werden. Für diese Umsetzung eignen sich Säuren, die physiologisch unbedenkliche Salze liefern. So können anorganische Säuren verwendet werden, z. B. Schwefelsäure, Halogenwasserstoffsäuren wie Chlorwasserstoffsäure oder Bromwasserstoffsäure, Phosphorsäuren wie Orthophosphorsäure, Salpetersäure, Sulfaminsäure, ferner organische Säuren, im einzelnen aliphatische, alicyclische, araliphatische, aromatische oder heterocyclische ein- oder mehrbasige Carbon-, Sulfon- oder Schwefelsäuren, wie Ameisensäure, Essigsäure, Propionsäure, Pivalinsäure, Diethylessigsäure, Malonsäure, Bernsteinsäure, Pimelinsäure, Fumarsäure, Maleinsäure, Michsäure, Weinsäure, Äpfelsäure, Benzoesäure, Salicylsäure, 2-Phenylpropionsäure, Citronensäure, Gluconsäure, Ascorbinsäure, Nicotinsäure, Isonicotinsäure, Methan- oder Ethansulfonsäure, Ethandisulfonsäure, 2-Hydroxyethansulfonsäure, Benzolsulfonsäure, p-Toluolsulfonsäure, Naphthalin-mono- und -disulfonsäuren, Laurylschwefelsäure.

Die freien Basen der Formel I können, falls gewünscht, aus ihren Salzen durch Behandlung mit starken Basen wie Natrium- oder Kaliumhydroxid, Natrium- oder Kaliumcarbonat in Freiheit gesetzt werden, sofern keine weiteren aciden Gruppen im Molekül vorliegen. In jenen Fällen, wo die Verbindungen der Formel I über freie Säuregruppen verfügen, kann durch Behandlung mit Basen ebenfalls eine Salzbildung erreicht werden. Als Basen eignen sich Alkalimetallhydroxide, Erdalkalimetallhydroxide oder organische Basen in Form von primären, sekundären oder tertiären Aminen.

Gegenstand der Erfindung ist ferner die Verwendung der Verbindungen der Formel I und ihrer physiologisch unbedenklichen Salze zur Herstellung pharmazeutischer Zubereitungen, insbesondere auf nicht-chemischem Wege. Hierbei können sie zusammen mit mindestens einem Träger- oder Hilfsstoff und gegebenenfalls in Kombination mit einem oder mehreren weiteren Wirkstoffe(en) in eine geeignete Dosierungsform gebracht werden.

Gegenstand der Erfindung sind ferner Mittel, insbesondere pharmazeutische Zubereitungen, enthaltend mindestens eine Verbindung der Formel I und/oder eines ihrer physiologisch unbedenklichen Salze. Diese Zubereitungen können als Arzneimittel in der Human- und Veterinärmedizin eingesetzt werden. Als Trägersubstanzen kommen organische oder anorganische Stoffe in Frage, die sich für die enterale (z. B. orale), parenterale oder topische Applikation eignen und mit den neuen Verbindungen nicht reagieren, beispielsweise Wasser, pflanzliche Öle, Benzylalkohole, Polyethylenglykole, Gelatine, Kohlehydrate wie Lactose oder Stärke, Magnesiumstearat, Talk Vaseline. Zur enteralen Applikation dienen insbesondere Tabletten, Dragees, Kapseln, Sirupe, Säfte, Tropfen oder Suppositorien, zur parenteralen Applikation Lösungen, vorzugsweise ölige oder wäßrige Lösungen, ferner Suspensionen, Emulsionen oder Implantate, für die topische Anwendung Salben, Cremes oder Puder. Die neuen Verbindungen können auch lyophilisiert und die erhaltenen Lyophilisate z. B. zur Herstellung von Injektionspräparaten verwendet werden.

Die angegebenen Zubereitungen können sterilisiert sein und/oder Hilfsstoffe wie Gleit-, Konservierungs-, Stabilisierungs- und/oder Netzmittel, Emulgatoren, Salze zur Beeinflussung des osmotischen Druckes, Puffersubstanzen, Farb-, Geschmacks- und/oder Aromastoffe enthalten. Sie können, falls erwünscht, auch einen oder mehrere weitere Wirkstoffe enthalten, z. B. ein oder mehrere Vitamine.

Die Verbindungen der Formel I und ihre physiologisch unbedenklichen Salze können bei der therapeutischen Behandlung des menschlichen oder tierischen Körpern und bei der Bekämpfung von Krankheiten verwendet werden. Sie eignen sich zur Behandlung von Erkrankungen des Zentralnervensystems wie Spannungszuständen, Depressionen und/oder Psychosen und von Nebenwirkungen bei der Behandlung der Hypertonie (z. B. mit α-Methyldopa). Ferner können die Verbindungen in der Endokrinologie und Gynäkologie Verwendung finden, z. B. zur Therapie von Akromegalie, Hypogonadismus, sekundärer Amenorrhoe, prämenstruellem Syndrom, unerwünschter puerperaler Laktation, weiterhin zur Prophylaxe und Therapie cerebraler Störungen (z. B. Migräne), insbesondere in der Geriatrie ähnlich wie gewisse Ergot-Alkaloide und zur Bekämpfung der Folgen cerebraler Infarktgeschehen (Apoplexia cerebri), wie Schlaganfall und cerebraler Ischämien.

Dabei werden die erfindungsgemäßen Substanzen in der Regel in Analogie zu bekannten, im Handel befindlichen Präparaten (z. B. Bromocriptin, Dihydroergocornin) verabreicht, vorzugsweise in Dosierungen zwischen etwa 0,2 und 500 mg, insbesondere zwischen 0,2 und 50 mg pro Dosierungseinheit. Die tägliche Dosierung liegt vorzugsweise zwischen etwa 0,001 und 10 mg/kg Körpergewicht. Die niedrigen Dosierungen (etwa 0,2 bis 1 mg pro Dosierungseinheit; etwa 0,001 bis 0,005 mg/kg Körpergewicht) kommen dabei insbesondere für die Verwendung als Migränemittel in Betracht; für die übrigen Indikationen werden Dosierungen zwischen 10 und 50 mg pro Dosierungseinheit bevorzugt. Die spezielle Dosis für jeden bestimmten Patienten hängt jedoch von den verschiedensten Faktoren ab, beispielsweise von der Wirksamkeit der eingesetzten speziellen Verbindung, vom Alter, Körpergewicht, allgemeinen Gesundheitszustand, Geschlecht, von der Kost, vom Verabfolgungszeitpunkt und -weg, von der Ausscheidungsgeschwindigkeit, Arzneistoffkombination und Schwere der jeweiligen Erkrankung, welcher die Therapie gilt. Die orale Applikation ist bevorzugt.

In den nachstehenden Beispielen bedeutet "übliche Aufarbeitung": Man gibt, falls erforderlich, Wasser hinzu, extrahiert mit Dichlormethan, trennt ab, trocknet die organische Phase über Natriumsulfat, filtriert, dampft ein und reinigt durch Chromatographie an Kieselgel und/oder durch Kristallisation. Temperaturen sind in °C angegeben. Rf-Werte wurden dünnschichtchromatographisch an Kieselgel erhalten.

Beispiel 1

Man rührt eine Lösung von 3,6 g 3-(4-Chlorbutyl)-5-methoxycarbonyl-indol [erhältlich durch Umsetzung von 5-Methoxycarbonylindol mit 4-Chlorbutyrylchlorid zu 3-(4-Chlorbutyryl)-5-methoxy-indol und anschließender Reduktion mit Diboran zu 3-(4-Chlorbutyl)-5-methoxycarbonyl-indol] und 3,4 g 6-Piperazino-1,4-benzodioxan

("A") in 200 ml Acetonitril 14 Std. bei Raumtemperatur, arbeitet wie üblich auf und erhält 6-[4-(4-(5-Methoxycarbonyl-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan, F. 177—179° (Dihydrochlorid).

Analog erhält man durch Umsetzung von "A"

mit 3-(4-Chlorbutyl)-5-fluor-indol
6-[4-(4-(5-Fluor-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan, F. 227—228°C (Hydrochlorid);
mit 3-(4-Brombutyl)-5-brom-indol
6-[4-(4-(5-Brom-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan;
mit 3-(4-Chlorbutyl)-5-cyan-indol
6-[4-(4-(5-Cyan-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan;
mit 3-(4-Chlorbutyl)-5-chlor-indol
6-[4-(4-(5-Chlor-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan, F. 205—207° (Hydrochlorid);
mit 3-(4-Chlorbutyl)-5-indol-carbonsäure
6-[4-(4-(5-Carboxy-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan, F. 241—243° (Hydrochlorid);
mit 3-(4-Chlorbutyl)-6-indol-carbonsäuremethylester
6-[4-(4-(6-Methoxycarbonyl-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan;
mit 3-(3-Chlorpropyl)-5-fluor-indol
6-[4-(3-(5-Fluor-indol-3-yl)-propyl)-piperazino]-1,4-benzodioxan;
mit 3-(3-Brompropyl)-5-brom-indol
6-[4-(3-(5-Brom-indol-3-yl)-propyl)-piperazino]-1,4-benzodioxan;
mit 3-(3-Chlorpropyl)-5-cyan-indol
6-[4-(3-(5-Cyan-indol-3-yl)-propyl)-piperazino]-1,4-benzodioxan;
mit 3-(3-Chlorpropyl)-6-cyan-indol
6-[4-(3-(6-Cyan-indol-3-yl)-propyl)-piperazino]-1,4-benzodioxan;
mit 3-(3-Chlorpropyl)-indol-5-carbonsäure
6-[4-(3-(5-Carboxy-indol-3-yl)-propyl)-piperazino]-1,4-benzodioxan;
mit 3-(2-Chlorethyl)-5-fluor-indol
6-[4-(2-(5-Fluor-indol-3-yl)-ethyl)-piperazino]-1,4-benzodioxan.

Beispiel 2

Analog Beispiel 1 erhält man durch Umsetzung von 1-(4-Brom-butyl)-benzimidazol mit 6-Piperazino-1,4-benzodioxan ("A") in 200 ml Acetonitril 6-[4-(4-Benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan, F. 247—248°.

Analog erhält man durch Umsetzung von "A"

mit 1-(4-Chlorbutyl)-5-fluor-benzimidazol
6-[4-(4-(5-Fluor-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan;
mit 1-(4-Brombutyl)-5-brom-benzimidazol
6-[4-(4-(5-Brom-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan;
mit 1-(4-Chlorbutyl)-5-cyan-benzimidazol
6-[4-(4-(5-Cyan-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan;
mit 1-(4-Chlorbutyl)-5-benzimidazol-carbonsäureamid
6-[4-(4-(5-Carbamoyl-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan;
mit 1-(4-Chlorbutyl)-5-benzimidazol-carbonsäure
6-[4-(4-(5-Carboxy-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan;
mit 1-(4-Chlorbutyl)-5-benzimidazol-carbonsäuremethylester
6-[4-(4-(5-Methylcarboxy-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan;
mit 1-(3-Chlorpropyl)-5-fluor-benzimidazol
6-[4-(3-(5-Fluor-benzimidazol-1-yl)-propyl)-piperazino]-1,4-benzodioxan;
mit 1-(3-Brompropyl)-5-brom-benzimidazol
6-[4-(3-(5-Brom-benzimidazol-1-yl)-propyl)-piperazino]-1,4-benzodioxan;
mit 1-(3-Chlorpropyl)-5-cyan-benzimidazol
6-[4-(3-(5-Cyan-benzimidazol-1-yl)-propyl)-piperazino]-1,4-benzodioxan;
mit 1-(3-Chlorpropyl)-5-benzimidazol-carbonsäureamid
6-[4-(3-(5-Carbamoyl-benzimidazol-1-yl)-propyl)-piperazino]-1,4-benzodioxan;
mit 1-(3-Chlorpropyl)-5-benzimidazol-carbonsäure
6-[4-(3-(5-Carboxy-benzimidazol-1-yl)-propyl)-piperazino]-1,4-benzodioxan;
mit 1-(2-Chlorethyl)-5-fluor-benzimidazol
6-[4-(2-(5-Fluor-benzimidazol-1-yl)-ethyl)-piperazino]-1,4-benzodioxan;
mit 1-(2-Bromethyl)-5-brom-benzimidazol
6-[4-(2-(5-Brom-benzimidazol-1-yl)-ethyl)-piperazino]-1,4-benzodioxan;
mit 1-(2-Chlorethyl)-5-cyan-benzimidazol
6-[4-(2-(5-Cyan-benzimidazol-1-yl)-ethyl)-piperazino]-1,4-benzodioxan;
mit 1-(2-Chlorethyl)-5-benzimidazol-carbonsäureamid
6-[4-(2-(5-Carbamoyl-benzimidazol-1-yl)-ethyl)-piperazino]-1,4-benzodioxan;
mit 1-(2-Chlorethyl)-5-benzimidazol-carbonsäure
6-[4-(2-(5-Carboxy-benzimidazol-1-yl)-ethyl)-piperazino]-1,4-benzodioxan.

Beispiel 3

Ein Gemisch von 2,18 g 3-(4-Aminobutyl)-5-ethoxycarbonyl-indol [erhältlich aus 5-Fthoxycarbonyl-indol durch Umsetzung mit 4-Chlorbutyrylchlorid, Reduktion des Produktes zu 3-(4-Chlorbutyl)-5-ethoxycarbonyl-indol und Überführung in 3-(4-Phthal-imido-butyl)-5-ethoxycarbonyl-indol] und einem Äquivalent 6-(N,N-Bis-(2-chlorethyl)-amino)-1,4-benzodioxan ("B") in 40 ml Aceton und 40 ml Wasser wird 24 Std. gekocht und wie üblich aufgearbeitet. Man erhält 6-[4-(4-(5-Ethoxycarbonyl-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan.

Analog erhält man durch Umsetzung von "B"

mit 3-(4-Aminobutyl)-5-N-methyl-carbamoyl-indol
6-[4-(4-(5-N-Methyl-carbamoyl-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan;
mit 3-(4-Aminobutyl)-5-N,N-dimethyl-carbamoyl-indol
6-[4-(4-(5-N,N-dimethyl-carbamoyl-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan;
mit 3-(4-Aminobutyl)-6-cyan-indol
6-[4-(4-(6-Cyan-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan;
mit 3-(4-Aminobutyl)-6-brom-indol
6-[4-(4-(6-Brom-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan;
mit 3-(4-Aminobutyl)-5-indolyl-N-methyl-harnstoff
6-[4-(4-(5-N-Methyl-ureido-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan;
mit 3-(4-Aminobutyl)-5-indolyl-N,N-dimethyl-harnstoff
6-[4-(4-(5-N,N-Dimethyl-ureido-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan;
mit 3-(3-Aminopropyl)-5-methoxy-indol
6-[4-(3-(5-Methoxy-indol-3-yl)-propyl)-piperazino]-1,4-benzodioxan;
mit 3-(3-Aminopropyl)-6-brom-indol
6-[4-(3-(6-Brom-indol-3-yl)-propyl)-piperazino]-1,4-benzodioxan;
mit 3-(3-Aminopropyl)-6-methoxy-indol
6-[4-(3-(6-Methoxy-indol-3-yl)-propyl)-piperazino]-1,4-benzodioxan;
mit 3-(3-Aminopropyl)-4-methoxy-indol
6-[4-(3-(4-Methoxy-indol-3-yl)-propyl)-piperazino]-1,4-benzodioxan;
mit 3-(3-Aminopropyl)-4-cyan-indol
6-[4-(3-(4-Cyan-indol-3-yl)-propyl)-piperazino]-1,4-benzodioxan;
mit 3-(3-Aminopropyl)-5-ethoxy-indol
6-[4-(3-(5-Ethoxy-indol-3-yl)-propyl)-piperazino]-1,4-benzodioxan;
mit 3-(3-Aminopropyl)-indol-6-carbonsäuremethylester
6-[4-(3-(6-Methoxycarbonyl-indol-3-yl)-propyl)-piperazino]-1,4-benzodioxan;
mit 3-(2-Aminoethyl)-4-fluor-indol
6-[4-(2-(4-Fluor-indol-3-yl)-ethyl)-piperazino]-1,4-benzodioxan.

Beispiel 4

Analog Beispiel 3 erhält man durch Umsetzung von 1-(4-Aminobutyl)-5-ethoxycarbonyl-benzimidazol mit 6-(N,N-Bis-(2-chlorethyl)-amino)-1,4-benzodioxan ("B") 6-[4-(4-(5-Ethoxycarbonyl-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan.

Analog erhält man durch Umsetzung von "B"

mit 1-(4-Aminobutyl)-5-N-methyl-carbamoyl-benzimidazol
6-[4-(4-(5-N-Methyl-carbamoyl-benzimidazol-1-yl)-butyl-piperazino]-1,4-benzodioxan;
mit 1-(4-Aminobutyl)-5-N,N-dimethyl-carbamoyl-benzimidazol
6-[4-(4-(5-N,N-dimethyl-carbamoyl-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan;
mit 1-(4-Aminobutyl)-6-cyan-benzimidazol
6-[4-(4-(6-Cyan-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan;
mit 1-(4-Aminobutyl)-6-brom-benzimidazol
6-[4-(4-(6-Brom-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan;
mit 1-(4-Aminobutyl)-5-benzimidazolyl-N-methyl-harnstoff
6-[4-(4-(5-N-Methyl-ureido-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan;
mit 1-(4-Aminobutyl)-5-benzimidazolyl-N,N-dimethyl-harnstoff
6-[4-(4-(5-N,N-Dimethyl-ureido-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan;
mit 1-(3-Aminopropyl)-5-methoxy-benzimidazol
6-[4-(3-(5-Methoxy-benzimidazol-1-yl)-propyl)-piperazino]-1,4-benzodioxan;
mit 1-(3-Aminopropyl)-6-brom-benzimidazol
6-[4-(3-(6-Brom-benzimidazol-1-yl)-propyl)-piperazino]-1,4-benzodioxan;
mit 1-(3-Aminopropyl)-6-methoxy-benzimidazol
6-[4-(3-(6-Methoxy-benzimidazol-1-yl)-propyl)-piperazino]-1,4-benzodioxan;
mit 1-(3-Aminopropyl)-4-methoxy-benzimidazol
6-[4-(3-(6-Methoxy-benzimidazol-1-yl)-propyl)-piperazino]-1,4-benzodioxan;
mit 1-(3-Aminopropyl)-4-cyan-benzimidazol
6-[4-(3-(4-Cyan-benzimidazol-1-yl)-propyl)-piperazino]-1,4-benzodioxan;
mit 1-(3-Aminopropyl)-5-ethoxy-benzimidazol

6-[4-(3-(5-Ethoxy-benzimidazol-1-yl)-propyl)-piperazino]-1,4-benzodioxan;
mit 1-(3-Aminopropyl)-6-benzimidazol-carbonsäuremethylester
6-[4-(3-(6-Methoxy-carbonyl-benzimidazol-1-yl)-propyl)-piperazino]-1,4-benzodioxan;
mit 1-(2-Aminoethyl)-4-fluor-benzimidazol
6-[4-(2-(4-Fluor-benzimidazol-1-yl)-ethyl)-piperazino]-1,4-benzodioxan.

Beispiel 5

Analog Beispiel 1 erhält man durch Umsetzung von 3-(4-Chlorbutyl)-5-nitro-indol mit "A" 6-[4-(4-(5-Nitro-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan.

Beispiel 6

Eine Lösung von 4,21 g 6-[4-(4-(5-Amino-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan ("C") [erhältlich gemäß Beispiel 5] in 35 ml THF wird mit einer Lösung von 0,9 g Acetylchlorid in 10 ml THF versetzt, 2 Std. bei 50° gerührt, eingedampft und wie üblich aufgearbeitet. Man erhält 6-[4-(4-(5-Acetamido-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan.
Analog erhält man durch Umsetzung von "C"

mit Benzoylchlorid
6-[4-(4-(5-Benzamido-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan;
mit Methansulfonylchlorid
6-[4-(4-(5-Methansulfonylamino-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan;
mit N,N-Dimethylcarbamoylchlorid
6-[4-(4-(5-N,N-dimethyl-ureido-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan;
mit N,N-Diethylcarbamoylchlorid
6-[4-(4-(5-N,N-diethyl-ureido-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan.

Beispiel 7

Analog Beispiel 6 erhält man durch Umsetzung von 6-[4-(4-(6-Aminobenzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan ("D") mit Acetylchlorid das 6-[4-(4-(6-Acetamido-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan.
Analog erhält man durch Umsetzung von "D"

mit Benzoylchlorid
6-[4-(4-(6-Benzamido-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan;
mit Methansulfonylchlorid
6-[4-(4-(6-Methansulfonylamido-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan;
mit N,N-Dimethylcarbamoylchlorid
6-[4-(4-(6-N,N-dimethyl-ureido-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan;
mit N,N-Diethylcarbamoylchlorid
6-[4-(4-(6-N,N-diethyl-ureido-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan.

Beispiel 8

Analog Beispiel 7 erhält man durch Umsetzung von 6-[4-(4-(Aminobenzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan ("E") mit Acetylchlorid das 6-[4-(4-(5-Acetamido-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan.
Analog erhält man durch Umsetzung von "E"

mit Benzoylchlorid
6-[4-(4-(5-Benzamido-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan;
mit Methansulfonylchlorid
6-[4-(4-(5-Methansulfonylamino-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan;
mit N,N-Dimethylcarbamoylchlorid
6-[4-(4-(5-N,N-dimethyl-ureido-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan;
mit N,N-Diethylcarbamoylchlorid
6-[4-(4-(5-N,N-diethyl-ureido-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan.

Beispiel 9

Eine Suspension von 3,8 g 6-[4-(4-(5-Nitro-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan in 45 ml Methanol wird unter Rühren an 0,1%iger Pd--C bei 20° und 1 bar bis zum Ende der H_2-Aufnahme hydriert. Man gießt auf Eiswasser, arbeitet wie üblich auf und erhält 6-[4-(4-(5-Amino-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan.
Analog erhält man

aus 6-[4-(4-(4-Nitro-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan

Beispiel 16

Man kocht 4,7 g 6-[4-(4-(1-Benzolsulfonyl-5-brom-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan mit 1,5 g KOH in wäßriger Ethanollösung über 16 Std., arbeitet wie üblich auf und erhält 6-[4-(4-(5-Bromindol-3-yl)-butyl)-piperazino]-1,4-benzodioxan.

Beispiel 17

Analog Beispiel 9 erhält man durch katalytische Reduktion (Pd—C/H₂)

aus 6-[4-(4-(6-Nitro-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan
6-[4-(4-(6-Amino-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan
aus 6-[4-(4-(7-Nitro-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan
6-[4-(4-(7-Amino-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan.

Beispiel 18

Eine Mischung von 3,1 g 6-[4-(3-(5-Cyan-indol-3-yl)-propyl)-piperazino]-1,4-benzodioxan, 2,7 g NaOH, 100 ml Wasser und 50 ml Diethylenglykolmonoethylether wird 3 Std. bei 140° Badtemperatur gerührt. Man kühlt ab, arbeitet wie üblich auf und erhält 6-4-(3-(5-Carbamoyl-indol-3-yl)-propyl)-piperazino]-1,4-benzodioxan.

Analog erhält man durch partielle Hydrolyse der entsprechenden Cyanindole:

6-[4-(4-(5-Carbamoyl-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan, F. 215° (Zers.);
6-[4-(4-(5-Carbamoyl-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan;
6-[4-(4-(7-Carbamoyl-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan.

Die nachstehenden Beispiele betreffen pharmazeutische Zubereitungen, die Amine der Formel I oder ihre Säureadditionssalze enthalten:

Beispiel A

Tabletten

Ein Gemisch von 1 kg 6-[4-(4-Benzimidazol-1-yl)-butyl-piperazino]-1,4-benzodioxan, 4 kg Lactose, 1,2 kg Kartoffelstärke, 0,2 kg Talk und 0,1 kg Magnesiumstearat wird in üblicher Weise zu Tabletten verpreßt, derart, daß jede Tablette 10 mg Wirkstoff enthält.

Beispiel B

Dragees

Analog Beispiel A werden Tabletten gepreßt, die anschließend in üblicher Weise mit einem Überzug aus Saccharose, Kartoffelstärke, Talk, Tragant und Farbstoff überzogen werden.

Beispiel C

Kapseln

2 kg 6-[4-(4-(5-Methoxy-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan werden in üblicher Weise in Hartgelatinekapseln gefüllt, so daß jede Kapsel 20 mg des Wirkstoffs enthält.

Beispiel D

Ampullen

Eine Lösung von 1 kg 6-[4-(4-(5-Methoxy-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan in 60 l zweifach destilliertem Wasser wird steril filtriert, in Ampullen abgefüllt, unter sterilen Bedingungen lyophilisiert und steril verschlossen. Jede Ampulle enthält 10 mg Wirkstoff.

Analog sind Tabletten, Dragees, Kapseln und Ampullen erhältlich, die einen oder mehrere der übrigen Wirkstoffe der Formel I und/oder ihre physiologisch unbedenklichen Säureadditionssalze enthalten.

Patentansprüche

1. 1,4-Benzodioxanderivate der Formel I

6-[4-(4-(4-Amino-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan;
aus 6-[4-(4-(6-Nitro-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan
6-[4-(4-(6-Amino-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan;
aus 6-[4-(4-(5-Nitro-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan
6-[4-(4-(5-Amino-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan;
aus 6-[4-(4-(4-Nitro-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan
6-[4-(4-(4-Amino-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan.

Beispiel 10

Eine Mischung von 4,16 g 6-[4-(4-(5-Cyan-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan, 2,4 g NaOH, 50 ml H_2O und 40 ml Diethylenglykolmonoethylether wird 3 Std. bei 140° Badtemperatur gerührt. Anschließend kühlt man auf Raumtemperatur ab, arbeitet wie üblich auf und erhält 6-[4-(4-(5-Carbamoyl-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan.

Analog erhält man durch partielle Hydrolyse der entsprechenden Nitrile:

6-[4-(4-(6-Carbamoyl-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan;
6-[4-(4-(5-Carbamoyl-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan;
6-[4-(4-(6-Carbamoyl-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan.

Beispiel 11

Zu einer Suspension von 0,6 g Lithiumaluminiumhydrid in 20 ml THF wird unter Rühren in einer N_2-Atmosphäre bei 20° eine Lösung von 4,4 g 6-[4-(4-(5-Methoxycarbonyl-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan in 40 ml THF zugetropft. Man rührt 1 Std. bei 20°, zersetzt mit verdünnter Natronlauge, filtriert, arbeitet das Filtrat wie üblich auf und erhält 6-[4-(4-(5-Hydroxymethyl-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan.

Beispiel 12

In eine siedende Lösung von 3,1 g 6-[4-(4-(5-Carboxyl-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan in 50 ml absolutem Methanol wird 2 Std. HCl-Gas eingeleitet. Anschließend kocht man eine weitere Stunde, arbeitet wie üblich auf und erhält 6-[4-(4-(5-Methoxycarbonyl-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan.

Beispiel 13

In eine siedende Lösung von 3,1 g 6-[4-(4-(5-Carboxyl-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan in 50 ml absolutem Methanol wird 2 Std. HCl-Gas eingeleitet. Anschließend kocht man eine weitere Stunde, arbeitet wie üblich auf und erhält 6-[4-(4-(5-Methoxycarbonyl-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan.

Beispiel 14

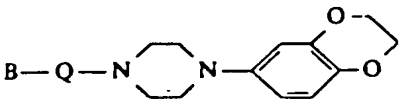
Man kocht 4,7 g 6-[4-(4-(5-Methoxycarbonyl-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan 0,5 Std. mit 100 ml 2n ethanolischer KOH, arbeitet wie üblich auf und erhält 6-[4-(4-(5-Carboxy-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan, F. 241—243° (Hydrochlorid).

Beispiel 15

Man rührt eine Lösung von 7,4 g 3-[4-(N,N-Bis-(2-chlorethyl)-aminobutyl)-5-ethoxy-indol und einem Äquivalent 6-Amino-1,4-benzodioxan in 200 ml Acetonitril über eine Zeitdauer von 12 Std. bei Raumtemperatur, arbeitet wie üblich auf und erhält 6-[4-(4-(5-Ethoxy-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan.

Analog erhält man durch Umsetzung von 6-Amino-1,4-benzodioxan

mit 3-[4-(N,N-Bis-(2-chlorethyl)-amino-butyl)-4-ethoxy-indol
6-[4-(4-(4-Ethoxy-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan;
mit 1-[4-(N,N-Bis-(2-chlorethyl)-amino-butyl)-5-ethoxy-benzimidazol
6-[4-(4-(5-Ethoxy-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan;
mit 1-[4-(N,N-Bis-(2-chlorethyl)-amino-butyl)-6-ethoxy-benzimidazol
6-[4-(4-(6-Ethoxy-benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan;
mit 1-[3-(N,N-Bis-(2-chlorethyl)-amino-propyl)-5-ethoxy-benzimidazol
6-[4-(3-(5-Ethoxy-benzimidazol-1-yl)-propyl)-piperazino]-1,4-benzodioxan;
mit 3-[2-(N,N-Bis-(2-chlorethyl)-amino-ethyl)-4-ethoxy-indol
6-[4-(2-(4-Ethoxy-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan;
mit 3-[2-(N,N-Bis-(2-chlorethyl)-amino-ethyl)-5-methoxy-indol
6-[4-(2-(5-Methoxy-indol-3-yl)-butyl)-piperazino] 1,4-benzodioxan.



(I)

worin
B einen unsubstituierten oder einfach durch CN, CO—R^1, C_nH_{2n}—R^1, Hal, OH, OA, O—C_nH_{2n}—CO—R^1, oder NHR^2 substituierten Indol-3-yl- oder Benzimidazol-1-yl-rest,
R^1 OH, OA, NH_2, NHA oder NA_2,
R^2 H, A, CO—A, CO—Ar, CO—NH_2, CO—NHA, CO—NA_2, SO_2—Ar oder SO_2—A,
Q C_nH_{2n},
n 1, 2, 3, 4, 5 oder 6,
A Alkyl mit 1—6 C-Atomen,
Ar einen unsubstituierten oder einen ein- oder zweifach durch A, Hal, CN, OH und/oder OA substituierten Phenylrest,
Hal F, Cl, Br oder I
bedeuten
sowie deren Salze.

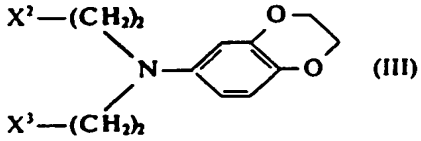
2. a) 6-[4-(4-Benzimidazol-1-yl)-butyl)-piperazino]-1,4-benzodioxan;
b) 6-[4-(4-(5-Methoxy-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan;
c) 6-[4-(4-(5-Carbamoyl-indol-3-yl)-butyl)-piperazino]-1,4-benzodioxan

sowie die Säureadditionssalze der genannten Verbindungen.

3. Verfahren zur Herstellung von 1,4 Benzodioxanderivaten der Formel I nach Anspruch 1 sowie von deren Salzen, dadurch gekennzeichnet, daß man eine Verbindung der Formel II

B—Q—X^1 (II)

worin
X^1 X oder NH_2 und
X Cl, Br, I, OH oder eine reaktionsfähig funktionell abgewandelte OH-Gruppe bedeuten und
B und Q die angegebenen Bedeutungen haben,
mit einer Verbindung der Formel III

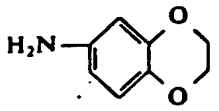


(III)

worin
X^2 und X^3 gleich oder verschieden sein können und, falls $X^1 = NH_2$ ist, jeweils X, andernfalls zusammen NH bedeuten,
umsetzt oder daß man eine Verbindung der Formel IV

B—Q—$N(CH_2—CH_2—X)_2$ (IV)

worin
X, Q und B die angegebenen Bedeutungen haben, mit einer Verbindung der Formel V



(V)

umsetzt
oder daß man eine sonst der Formel I entsprechende Verbindung, die jedoch anstelle der 1,4-Benzodioxan-gruppe eine 3,4-Dihydroxyphenylgruppe, wobei aber auch die beiden Hydroxygruppen zur Erhöhung der Reaktionsbereitschaft in entsprechend aktivierter Form vorliegen können, mit Ethandiol oder einem entsprechenden reaktiveren Derivat zu einer Verbindung I umsetzt
oder daß man eine sonst der Formel I entsprechende Verbindung, die jedoch anstelle eines oder mehrerer Wasserstoffatome eine oder mehrere reduzierbare Gruppe(n) und/oder eine oder mehrere zusätzliche C-C- und/oder C-N-Bindung(en) enthält, mit einem reduzierenden Mittel behandelt,
oder daß man eine sonst der Formel I entsprechende Verbindung, die jedoch anstelle eines oder mehrerer Wasserstoffatome eine oder mehrere solvolysierbare Gruppe(n) enthält, mit einem solvolysierenden Mittel behandelt,

und/oder daß man gegebenenfalls eine OA-Gruppe unter Bildung einer OH-Gruppe spaltet und/oder eine Gruppe B in eine andere Gruppe B und/oder daß man eine erhaltene Base oder Säure der Formel I durch Behandeln mit einer Säure oder Base in eines ihrer Salze umwandelt.

4. Verfahren zur Herstellung pharmazeutischer Zubereitungen, dadurch gekennzeichnet, daß man eine Verbindung der Formel I nach Patentanspruch 1 und/oder eines ihrer physiologisch unbedenklichen Salze zusammen mit mindestens einem festen, flüssigen oder halbflüssigen Träger- oder Hilfsstoff in eine geeignete Dosierungsform bringt.

5. Pharmazeutische Zubereitung, gekennzeichnet durch einen Gehalt an mindestens eine Verbindung der allgemeinen Formel I nach Patentanspruch 1 und/oder einem ihrer physiologisch unbedenklichen Salze.

6. Verwendung von Verbindungen der Formel I nach Patentanspruch 1 oder von deren physiologisch unbedenklichen Salzen zur Herstellung eines Arzneimittels.

7. Verwendung von Verbindungen der Formel I nach Patentanspruch 1 oder von deren physiologisch unbedenklichen Salzen bei der Bekämpfung von Krankheiten.

D3 P doc

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07D 319/18, 307/18, 405/12, 405/14, 417/12, 401/12, 233/36, 409/12, A61K 31/495, 31/54 — A1

(11) International Publication Number: WO 94/13659

(43) International Publication Date: 23 June 1994 (23.06.94)

(21) International Application Number: PCT/DK93/00414

(22) International Filing Date: 8 December 1993 (08.12.93)

(30) Priority Data:
1483/92 9 December 1992 (09.12.92) DK

(71) Applicant *(for all designated States except US)*: H. LUNDBECK A/S [DK/DK]; Ottiliavej 9, DK-2500 Copenhagen-Valby (DK).

(72) Inventors; and

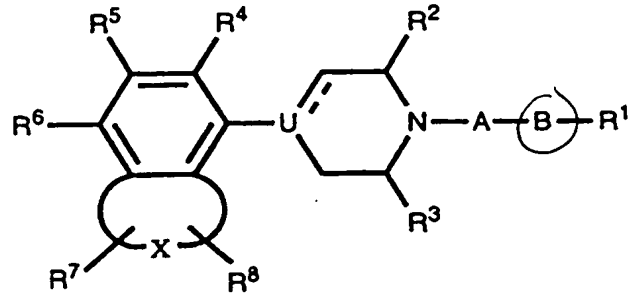
(75) Inventors/Applicants *(for US only)*: MOLTZEN, Ejner, K. [DK/DK]; Howitzvej 46, DK-2000 Frederiksberg C (DK). PERREGAARD, Jens, Kristian [DK/DK]; Thyrasvej 22, DK-3630 Jægerspris (DK). PEDERSEN, Henrik [DK/DK]; Mellemvangen 63, DK-2700 Broenhoej (DK).

(74) Agent: MEIDAHL , Petersen, John; H. Lundbeck A/S, Ottiliavej 9, DK-2500 Copenhagen-Valby (DK).

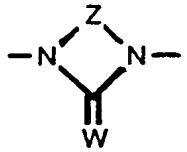
(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: FUSED BENZO COMPOUNDS



(I)



(a)

(57) Abstract

Fused benzo compounds of formula (I), wherein A is a 2 to 6 membered hydrocarbon spacer group, B is a polar divalent group selected from SO, SO_2, and a group (a); U is C, N or CH; X is a divalent 3-4 membered chain optionally comprising one or more heteroatoms; R^1 is an aliphatic hydrocarbon group, arylalkyl or diphenylalkyl; R^2 and R^3 are hydrogen or alkyl or together form an ethylene or propylene bridge; R^4, R^5, and R^6 are hydrogen or substituents; R^7 and R^8 are hydrogen or substituents including, a group $-COOR^9$ and a group $-CONR^{10}R^{11}$; are 5-HT_{1A} receptor ligands useful in the treatment of CNS disorders. Pharmaceutical compositions comprising the compounds and their use for the manufacture of a pharmaceutical preparation are also disclosed.

see P3

5-HT1A

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria
AU	Australia
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CS	Czechoslovakia
CZ	Czech Republic
DE	Germany
DK	Denmark
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgystan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakhstan
LI	Liechtenstein
LK	Sri Lanka
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SI	Slovenia
SK	Slovakia
SN	Senegal
TD	Chad
TG	Togo
TJ	Tajikistan
TT	Trinidad and Tobago
UA	Ukraine
US	United States of America
UZ	Uzbekistan
VN	Viet Nam

FUSED BENZO COMPOUNDS

Field of the invention.

The present invention relates to a class of fused benzoderivatives potently binding to the 5-HT_{1A} receptor and having central serotonergic 5-HT_{1A} activity. These fused benzoderivatives are, therefore, useful in the treatment of certain psychic and neurological disorders.

Background of the invention.

A number of compounds structurally related to the compounds of the invention are known from the prior art.

So, EP patents Nos. 0 138 280 and 0 185 429 disclose an extremely broad class of piperazinyl compounds having a bicyclic hetero aryl radical in the 4-position and a heteroaryl-, aryl- or alkyl substituted carbamoylethyl or carbamoylpropyl group in the 1-position. Said compounds are alleged to show blood pressure lowering effect through a central mechanism. EP 0 372 657 discloses similar derivatives differing only in that they have slightly different substituents on the bicyclic heteroaryl radical. These latter derivatives are said to exert anxiolytic effects in animal models without showing effect on the blood pressure. One of the compounds covered by EP patent No. 0 138 280, i.e. the compound 4-fluoro-N-[2-(4-(2-hydroxymethyl-1,4-benzodioxan-5-yl)piperazine-1-yl)ethyl]benzamide, which is known as flesinoxan has recently been reported to be a high efficacy 5-HT_{1A} agonist having antidepressant and anxiolytic effects (Schipper et al, *Human Psychopharm.*, **1991**, *6*, S53).

EP patent No 0 364 327 discloses a class of 4-[2-(4-(naphthyl- or isoquinolyl)piperazine-1-yl)ethyl]-2-quinolone derivatives having 5-HT_{1A} and 5-HT_2 receptor activity. The compounds are said to be agonists, partial agonists or antagonists *in vivo* . EP 0 343 050 describes a group of 6-phenyl-3-[(4-(naphthyl or isoquinolyl)piperazine-1-yl)alkyl(2-4)]-1H,3H-pyrimidine-2,4-dione compounds said to posses 5-HT_{1A} and 5-HT_2 receptor activity. Again, with respect to the 5-HT_{1A} receptor, the

compounds are said to be agonists, partial agonists or antagonists *in vivo* .

In International patent publication No. WO 92/03426 a class of piperazine derivatives having naphtyl or quinolyl in the 4-position and a N-aryl substituted carbamoyl alkyl group or a N-aryl substituted ureido alkyl group in the 1-position is described. Said compounds are claimed to exhibit affinity for various receptors, including 5-HT_2, 5-HT_{1A}, alpha and dopamine receptors.

EP patent No 0 466 585 relates to 1-(benzamidoalkyl)-4-(naphthyl- or quinolyl)piperidines or -tetrahydropyridines having 5-HT_{1A} receptor affinity and found to exhibit potent antihypertensive effect in animals.

Finally, EP 0 490 772 A1 discloses a class of 1,4-disubstituted piperazine derivatives alleged to show 5-HT_{1A} antagonistic activitivities. Said derivatives have a 5-benzodioxanyl or 7-isobenzofuranyl radical in the 4-position and a lower alkyl chain substituted with a bicyclic carbo ring system in the 1-position.

Compounds having central serotonergic 5-HT_{1A} activity may according to well known and recognized pharmacological principles be devided into full agonists, partial agonists and antagonists.

Clinical studies of known 5-HT_{1A} partial agonists such as e.g. buspirone (8-[4-[4-(2-pyrimidyl)-1-piperazinyl]butyl]-8-azaspiro[4,5]decane-7,9-dione), ipsapirone (4,4-dimethyl-1-[4-[4-(2-pyrimidyl)-1-piperazinyl]butyl]-2,6-piperidinedione), and gepirone (2-[4-[4-(2-pyrimidyl)-1-piperazinyl]butyl]-1,2-benzothiazol-3(2*H*)-one-1,1-dioxide), have shown that 5-HT_{1A} partial agonists are useful in the treatment of anxiety disorders such as generalised anxiety disorder, panic disorder, and obsessive compulsive disorder (Glitz, D. A., Pohl, R., *Drugs* **1991**, *41*, 11). Preclinical studies indicate that full agonists also are useful in the treatment of the above mentioned anxiety related disorders (Schipper, *Human Psychopharm.*, **1991**, *6*, S53).

There is also evidence, both clinical and preclinical, in support of the beneficial effect of 5-HT_{1A} partial agonists in the treatment of depression as well as impulse

control disorders and alcohol abuse (van Hest , *Psychopharm.*, 1992, *107*, 474; Schipper et al, *Human Psychopharm.*, 1991, *6*, S53; Cervo et al, *Eur. J. Pharm.*, 1988, *158*, 53; Glitz, D. A., Pohl, R., *Drugs* 1991, *41*, 11).

5-HT_{1A} agonists and partial agonists inhibit isolation-induced aggresion in male mice indicating that these compounds are useful in the treatment of aggression (Sanchéz et al, *Psychopharmacology*, 1993, *110*, 53-59).

Furthermore, recent studies also indicate that 5-HT_{1A} receptors are important in the serotonergic modulation of haloperidol-induced catalepsy (Hicks, *Life Science* 1990, *47*, 1609) suggesting that 5-HT_{1A} agonists are useful in the treatment of the side effects induced by conventional antipsychotic agents such as e.g. haloperidol.

5-HT_{1A} agonists have shown neuroprotective properties in rodent models of focal and global cerebral ischaemia and may, therefore, be useful in the treatment of ischaemic disease states (Prehn , *Eur. J. Pharm.* 1991, *203*, 213).

Pharmacological studies have been presented which indicates that 5-HT_{1A} antagonists are useful in the treatment of senile dementia (Bowen et al, Trends Neur. Sci. 1992, *15*, 84).

Both in animal models and in clinical trials it has been shown that 5-HT_{1A} agonists exert antihypertensive effects via a central mechanism (Saxena and Villalón, *Trends Pharm. Sci.* 1990, *11*, 95; Gillis *et al*, *J. Pharm. Exp. Ther.* 1989, *248*, 851. 5-HT_{1A} ligands may, therefore, be beneficial in the treatment of cardiovascular disorders.

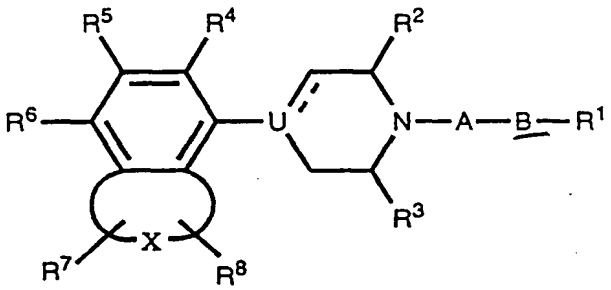
Accordingly, agents acting on the 5-HT_{1A} receptor, both agonists and antagonists, are believed to be of potential use in the therapy of such conditions and thus being highly desired.

It has now been found that compounds of a certain class of fused benzoderivatives bind to the 5-HT_{1A} receptor with high affinities. Furthermore, it has been found that

the compounds cover a broad range of selectivities for the 5-HT_{1A} receptor vs. the dopamine D_2 receptor and the alpha$_1$ adrenoceptor and a broad range of the efficacy scale.

Summary of the invention.

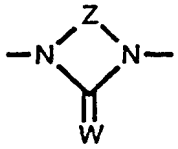
Accordingly, the present invention provides a novel class of fused benzo compounds of the general Formula I



I

wherein A is a 2 to 6 membered spacer group selected from alkylene, alkenylene, and alkynylene each of which may be branched or straight chain, or a 3-7 membered cycloalkylene group, said spacer group being optionally substituted with aryl or hydroxy;

B is a polar divalent group selected from SO, SO_2, and a group of Formula II,

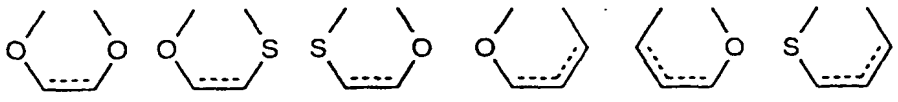


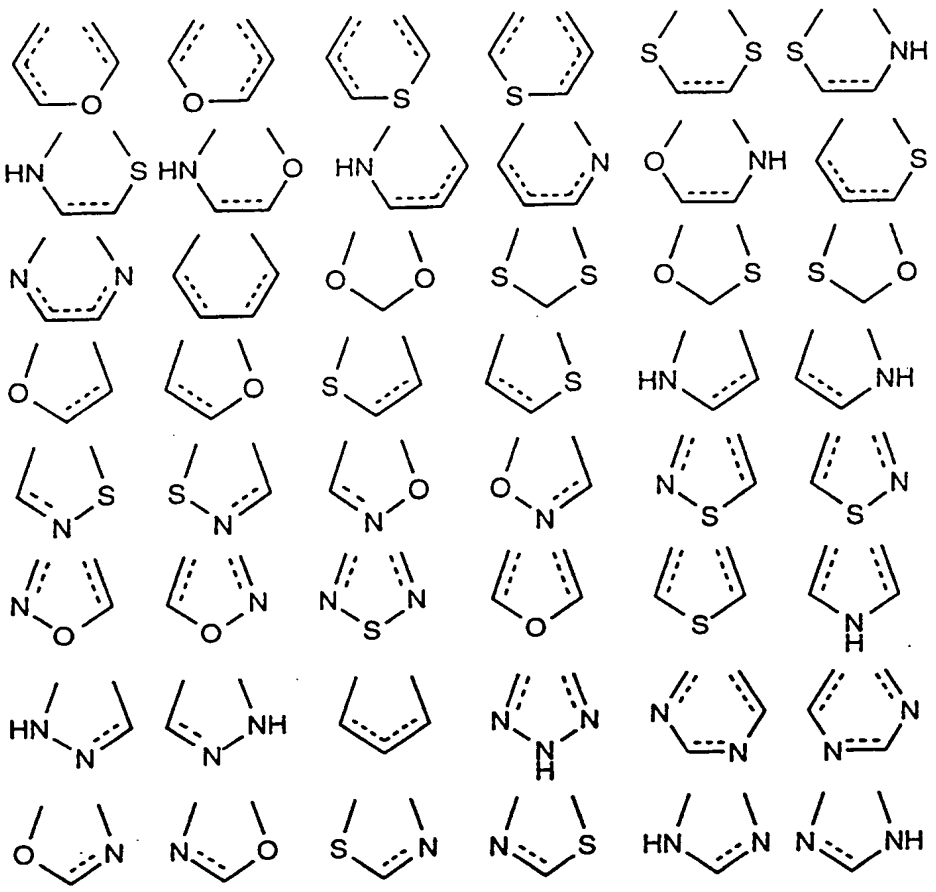
II

wherein W is O or S, and Z is selected from $-(CH_2)_n-$ n being 2 or 3, –CH=CH–, $-COCH_2-$, $-CSCH_2-$, or 1,2-phenylene optionally substituted with halogen or trifluoromethyl;

U is N or CH; the dotted line designates an optional bond, and if it designates a bond U is C;

X is selected from the group of divalent 3 – 4 membered groups consisting of





wherein the dotted lines indicate optional bonds; thereby forming a carbocyclic or heterocyclic ring fused with the benzene ring ;

R^1 is alkyl, alkenyl, cycloalk(en)yl, aryl, cycloalk(en)ylalk(en/yn)yl, arylalkyl, diphenylalkyl, any alkylgroup optionally being substituted with one or two hydroxy groups, with the proviso that if Z is 1,2-phenylene and U is N, then R^1 is selected from aryl and substituted aryl;

R^2 and R^3 are independently hydrogen, lower alkyl or they may be linked together, thereby forming an ethylene or propylene bridge;

R^4, R^5, and R^6 are independently selected from the group consisting of hydrogen, halogen, lower alkyl, lower alkoxy, hydroxy, lower alkylthio, lower alkylamino or di-lower-alkylamino, cyano, nitro, trifluoromethyl and trifluoromethylthio;

R^7 and R^8 are independently selected from the group consisting of hydrogen, halogen, trifluoromethyl, lower alkyl, lower alkyl substituted with one or more hydroxy groups, aryl, cyano, a group $-COOR^9$ and a group $-CONR^{10}R^{11}$, R^9, R^{10}, and R^{11} being hydrogen or lower alkyl; any aryl group present being optionally substituted with one or more substituents selected from halogen, lower alkyl, lower

alkoxy, hydroxy, lower alkylthio, lower alkylsulfonyl, lower alkyl- or dialkylamino, cyano, trifluoromethyl, or trifluoromethylthio;
and pharmaceutically acceptable acid addition salts thereof.

In a second aspect the present invention provides a pharmaceutical composition comprising at least one novel fused benzoderivative according to the invention as defined above or a pharmaceutically acceptable acid addition salt thereof or prodrug thereof in a therapeutically effective amount and in combination with one or more pharmaceutically acceptable carriers or diluents.

In a further aspect the present invention provides the use of fused benzoderivatives having the above defined general Formula I or acid addition salts or prodrugs thereof for the manufacture of a pharmaceutical preparation for the treatment of anxiety disorders, depression, psychosis, impulse control disorders, alcohol abuse, ischaemic diseases, cardiovascular disorders, side effects induced by conventional antipsychotic agents and senile dementia.

The compounds of the invention have been found to displace tritiated 8-hydroxy-2-dipropylaminotetralin (8-OH-DPAT) from 5-HT_{1A} receptors *in vitro*, the majority of the compounds showing affinities higher than 50 nM. Furthermore, the present compounds have proven to cover a broad range of selectivities for 5-HT_{1A} receptors as compared to α_1 adrenoceptors and D_2 receptors. Some of the compounds of the present invention are highly selective for the 5-HT_{1A} receptors, while other compounds of the present invention have affinities to some of the above mentioned binding sites. The present compounds have also been shown to cover a wide range of efficacies.

An especially interesting group of compounds show high affinity to both 5-HT_{1A} and D_2 receptors. In view of the fact that dopamine D_2 antagonists are effective in the treatment of schizophrenic disorders (see *e.g.* Lowe *et al*, *Med. Res. Rev.*, **1988**, *8*, 475) and since 5-HT_{1A} agonists, as mentioned above, can alleviate neuroleptica induced side effects, such compounds are useful in the treatment of schizophrenic disorders.

Accordingly, the compounds of the invention have proven to be useful for the treatment of anxiety disorders, depression, psychosis, impulse control disorders, alcohol abuse, ischaemic diseases, cardiovascular disorders, side effects induced by conventional antipsychotic agents and senile dementia.

Detailed description of the invention.

Some of the compounds of general Formula I may exist as optical isomers thereof and such optical isomers are also embraced by the invention.

As used herein the term alkyl refers to a C_1-C_{20} straight chain or branched alkyl group and similarly alkenyl and alkynyl mean a C_2-C_{20} straight chain or branched hydrocarbon group having one or more double bonds or triple bonds, respectively. The term cycloalkyl designates a carbocyclic ring having 3-8 carbon atoms, inclusive, or a bicyclic or tricyclic carbocycle, such as adamantyl.

In the formulas included in the definition of X, the dotted lines indicate optional bonds, i.e. in case a dotted line represents a bond, the bond in question is a double bond. Of course double bonds may not be present in adjacent positions and the arrangement of the bonds may not be in conflict with the conventional rules as readily understood by a person skilled in the art.

The expression alk(en/yn)yl means that the group may be an alkyl, alkenyl or alkynyl group.

The terms lower alkyl, lower alkoxy, lower alkylthio, etc. designate such branched or unbranched groups having from one to six carbon atoms inclusive. Exemplary of such groups are methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl, 2-methyl-1-propyl, methoxy, ethoxy, 1-propoxy, methylthio, ethylthio, 1-propylthio, 2-propylthio, methylsulfonyl, ethylsulfonyl, or the like.

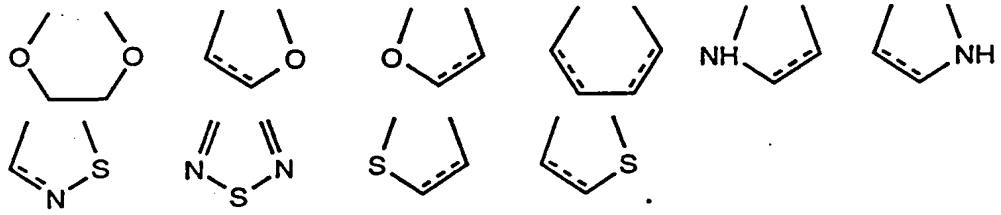
The term aryl is intended to mean a carbocyclic or heterocyclic aromatic monocyc-

lic or fused bicyclic group or a biphenyl group. Examples of groups are: thienyl, furyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, benzofuranyl, benzothienyl, benzisothiazolyl, benzisoxazolyl, indolyl, phenyl, pyridyl, pyrimidinyl, pyridazinyl, naphthyl, quinolinyl, and quinazolinyl, in particular phenyl, thienyl, naphtyl, or furanyl.

In Formula I, A is preferably a 2 to 6 membered alkylene group.

B is preferably SO, SO_2 or a group of Formula II, as defined above wherein W is O and Z is selected from $-(CH_2)_n-$ n being 2 or 3, –CH=CH– or 1,2-phenylene optionally substituted with halogen or trifluoromethyl.

X is preferably selected from the group of divalent 3 – 4 membered groups consisting of



R^1 is preferably lower alkyl, aryl, cycloalkyl or aryl-lower alkyl, most preferably lower alkyl, phenyl, phenyl substituted with one of the substituents as defined above, C_5-C_6 cycloalkyl, adamantyl, phenyl-lower alkyl optionally substituted with one of the substituents as defined above or naphthyl.

R^2 and R^3 are preferably both hydrogen.

R^4, R^5, and R^6 are preferably independently selected from the group consisting of hydrogen and halogen.

R^7 and R^8 are preferably independently selected from the group consisting of hydrogen, lower alkyl, aryl, a group $-COOR^9$ R^9 being hydrogen or lower alkyl and a group $-CONH_2$. Most preferably R^7 and R^8 are independently selected from hydrogen, lower alkyl, phenyl optionally substituted with one of the substituents as

defined above, a group $-COOR^9$ R^9 being hydrogen or lower alkyl and a group $-CONH_2$.

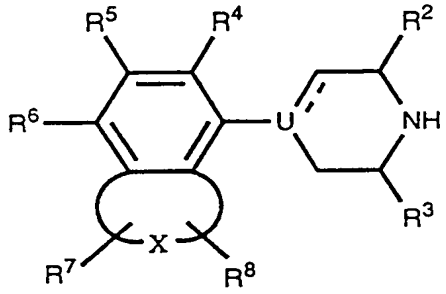
The acid addition salts of the invention are pharmaceutically acceptable salts of the compounds of Formula I formed with non-toxic acids. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, embonic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, and theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric acids.

The pharmaceutical compositions of this invention or those which are manufactured in accordance with this invention may be administered by any suitable route, for example orally in the form of tablets, capsules, powders, syrups, etc., or parenterally in the form of solutions for injection. For preparing such compositions methods well known in the art may be used, and any pharmaceutically acceptable carriers, diluents, exipients, or other additive usually used in the art may be used.

Conveniently, the compounds of the invention are administered in unit dosage form containing said compounds in an amount of about 0.01 to 50 mg.
The total daily dose usually ranges of about 0.05 - 500 mg, and most preferably about 0.1 to 20 mg of the active compound of the invention.

The compounds of Formula I are prepared by:

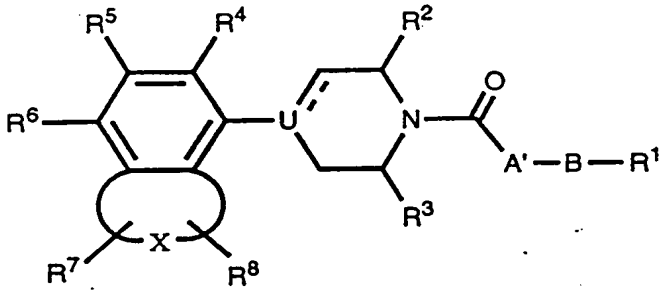
a) reacting a compound of Formula III



III

wherein R^2 - R^8, U, X, and the dotted line are as previously defined, with a reagent of the formula R^1-B-A-V wherein R^1, A, and B are as previously defined and V is a suitable leaving group such as halogen, mesylate or tosylate;

b) reducing the amide carbonyl of a compound of Formula IV

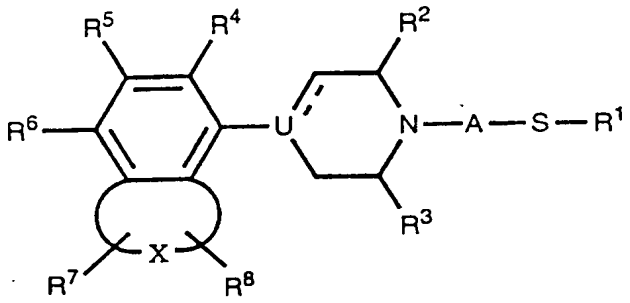


IV

wherein R^1-R^8, B, U, X, and the dotted line are as previously defined and A' is such a group that CH_2-A' is a 2 to 6 membered branched or straight chain alkylene, alkenylene or alkynylene group which is optionally substituted with aryl or hydroxy as comprised by the definition of A;

c) reductive alkylation of an amine of Formula III as previously defined with an aldehyde of the formula R^1-B-A'-CHO, a carboxylic acid of the formula R^1-B-A'-COOH or a ketone of the formula R^1-B-A"-CO-A"' wherein R^1, B and A' are as previously defined and A" and A"' are such groups that A"-CH-A"' is a 2 to 6 membered branched or straight chain alkylene, alkenylene or alkynylene group optionally substituted with aryl or hydroxy as comprised by the definition of A;

d) oxidation of the sulfide sulfur atom in a compound of Formula V

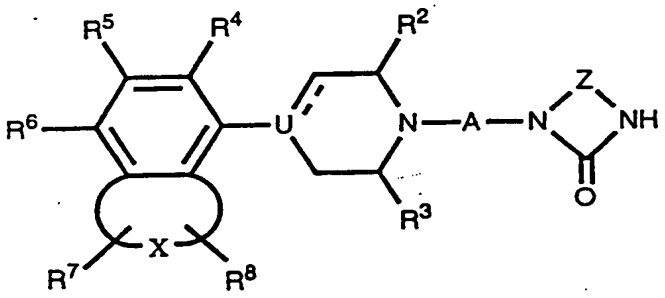


V

wherein R^1-R^8, A, U, X, and the dotted line are as previously defined, to the corresponding sulfoxide or sulfone;

e) 1,4-addition of an amine of general Formula III as previously defined to a α,β-unsaturated compound of formula $R^{12}R^{13}C=CR^{14}$-B-R^1, wherein R^1 and B are as previously defined and R^{12}, R^{13}, and R^{14} are such groups that $R^{12}R^{13}C=CR^{14}$ is a 2-6 membered branched or straight chain alkenylene group optionally substituted with aryl or hydroxy as comprised by the definition of A;

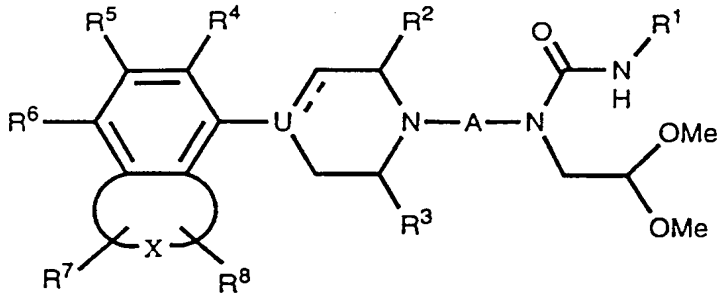
f) reductive alkylation of the NH group of a compound of general Formula VI



VI

wherein R^2-R^8, A, U, X, Z, and the dotted line are as previously defined, with an aldehyde of the formula $R^{1'}$-CHO, a carboxylic acid of the formula $R^{1'}$-COOH or a ketone of the formula $R^{1''}$-CO-$R^{1'''}$ wherein $R^{1'}$, $R^{1''}$, and $R^{1'''}$ are such groups that $R^{1'}$-CH_2 and $R^{1''}$-CH_2-$R^{1'''}$, respectively, are groups comprised by the above definition of R^1;

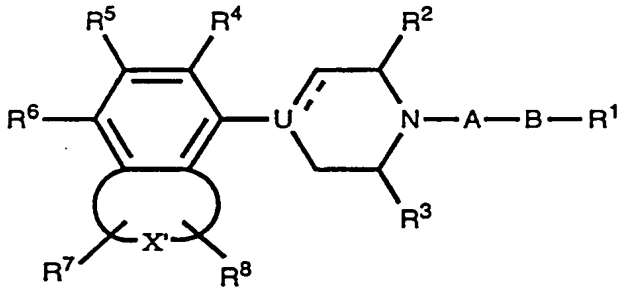
g) cyclization of a compounds of general Formula VII



VII

wherein R1-R8, A, U, X, and the dotted line are as previously defined;

h) arylation of the NH group of a compound of general Formula VIII



VIII

wherein A, B, R1-R8, the dotted line and U is as previously defined and X' is defined as X with the proviso that X' designates a heteroaromatic ring system containing a NH functionality, with an arylating agent of the formula Ar-hal wherein Ar is aryl as previously defined and hal is halogen;

i) transformation of a compound of general Formula I wherein R7 or R8 designates a group -COOR9 to the corresponding compound wherein R7 or R8 designates a group -CONR10R11 in which formulas R7-R11 is as previously defined;

j) treating a compound of general Formula I in which the ring system defined by X comprises one or more double bonds in order to reduce one or more of said double bonds thereby obtaining a corresponding partially or completely reduced ring system;

k) reductive removal of one or more of the substituents R4-R8 in a compound of general Formula I in which one or more of these substituents are selected from the group consisting of chloro, bromo, or iodo;

l) reducing the double bond in the tetrahydropyridine ring of a compound of general Formula I in which U is C and the dotted line represents a bond in order to obtain the corresponding piperidine derivative;

whereupon the compound of Formula I is isolated as the free base or a pharmaceutically acceptable acid addition salt thereof.

The reaction of the compound of Formula III according to method a) is conveniently performed in an inert organic solvent such as a suitably boiling alcohol or ketone, preferably in the presence of a base (potassium carbonate or triethylamine) at reflux temperature.

The reagents of formula R^1-B-A-V wherein B is SO or SO_2 are obtained by oxidation of the corresponding sulfides according to methods well known in the art. The starting sulfides are prepared by standard literature methods.

Such reagents in which B represents a group of Formula II wherein Z is $-(CH_2)_2-$ and W is O are prepared by the method disclosed in DE-OS No 2,035,370. Preparation of such reagents wherein Z is -CH=CH- or 1,2-phenylene is described in EXAMPLES 5 and 12-13, respectively.

Arylpiperazine derivatives of Formula III are conveniently prepared from the corresponding arylamines according to the method described by Martin *et al*, *J. Med. Chem.*, **1989**, *32*, 1052, or the method described by Kruse *et al*, *Rec. Trav. Chim Pays-Bas*, **1988**, *107*, 303.

The starting arylamines are either commercially available or are described in the literature as follows:

The synthesis of 5-amino-1,4-benzodioxane is described by Dauksas *et al*, *Zh. Org. Khim.*, **1967**, *3*, 1121.

The synthesis of 7-amino-2,3-dihydrobenzofuran is described in US Pat. Appl. No. 4302592.

The synthesis of ethyl 7-amino-2-indolyl carboxylate is described by Scriven *et al*,

J. Chem. Soc., Perkin Trans. I, **1979**, 53.

The synthesis of 7-aminobenzofuran is described by Van Wijngaarden *et al, J. Med. Chem.*, **1988**, *31*, 1934.

The synthesis of 7-amino-2,3-dihydro-2,2-dimethylbenzofuran is described in Ger. Offen. DE 3526510.

The synthesis of 7-amino-benzo[b]thiophene is described by Boswell *et al, J. Heterocycl. Chem.* **1968**, *5*, 69.

The synthesis of 7-aminoindole is described in US Pat. Appl. No. 4506078.

The synthesis of 7-amino-1,2-benzisothiazole is described by Ricci *et al, Ann. Chim. (Rome)*, **1963**, *53*, 1860.

The synthesis of 4-aminoindole is described by Melhado *et al, J. Org. Chem.*, **1983**, *48*, 5130.

4-Aminobenzofuran and ethyl 4-amino-2-benzofuranyl carboxylate are obtained by conventional reduction of the corresponding nitro compounds (Andrisano *et al, Gazz. Chim. Ital.*, **1956**, *86*, 1257).

7-Amino-2-phenylbenzofuran is obtained from 2-phenyl-7-benzofuranyl carboxylic acid (Eur. Pat. Appl. No. EP 147044 A2) *via* the Curtius rearrangement.

Substituted derivatives of various ring systems are obtained by analogy methods to the above mentioned methods.

Piperidine and 1,2,5,6-tetrahydropyridine derivatives of Formula **III** are prepared by known methods, cf. *e.g.* US Pat. No. 2,891,066; McElvain *et al, J. Amer. Chem. Soc.* **1950**, *72*, 3134, or are prepared as described in EXAMPLES 10 and 11.

The reduction according to method b) is preferably carried out in an inert organic solvent such as diethyl ether or tetrahydrofuran in the presence of lithium aluminium hydride at reflux temperature.

The amides of Formula **IV** are conveniently prepared by treating compounds of general Formula **III** with suitable carboxylic acid chlorides of formula R^1-B-A'-COCl in the presence of base (potassium carbonate or triethylamine). The carboxylic acid chlorides are prepared according to standard methods.

The reductive alkylation of the amines of Formula **III** according to method c) is

performed by standard literature methods (see EXAMPLE 4). The aldehydes, carboxylic acids, and ketones of formulas R^1-B-A'-CHO, R^1-B-A'-COOH, and R^1-B-A"-CO-A"', respectively, are prepared according to standard methods.

The oxidation of sulfur according to method d) is performed by applying a well known oxidation agent, for example m-chloroperbenzoic acid, hydrogen peroxide, or potassium peroxymonosulfate. Sulfoxides are preferably prepared using m-chloroperbenzoic acid according to standard methods. Sulfones are preferably prepared using hydrogen peroxide in glacial acetic acid according to standard methods.

Sulfides of Formula **V** are prepared either by method a) using reagents of formula R^1-S-A-V, or by method b) using compounds of Formula **IV** where B is defined as S, or by method c) using aldehydes of formula R^1-S-A'-CHO or carboxylic acids of formula R^1-S-A'-COOH or ketones of formula R^1-S-A"-CO-A"'. All sulfide reagents mentioned are prepared according to standard methods.

The addition of amines to α,β-unsaturated compounds according to method e) is conveniently performed in an inert solvent such as methylene chloride at room temperature. Unsaturated compounds of formula $R^{12}R^{13}C{=}CR^{14}$-B-R are prepared by standard methods.

The reductive alkylation according to method f) is performed in glacial acetic acid using sodium borohydride as reducing agent. The starting compounds of Formula **VI** are prepared by methods analogous to methods a), b), and c).

The cyclization according to method g) is performed in ethanol in the presence of hydrochloric acid. The starting compounds of general Formula **VII** are prepared by alkylating amines of Formula **III** with chloroacetonitrile followed by alane reduction of the cyano group to the corresponding primary amine. Monoalkylation with 2-bromoacetaldehyde dimethyl acetal and subsequent addition of isocyanates give **VII**.

The arylation according to method h) is most conveniently performed by applying the well known Ullmann reacton. The arylating reagents, Ar-hal, are commercially

available and the transformation of esters according to method i) is well-described in the literature.

The reduction of double bonds according to method j) is conveniently performed by catalytic hydrogenation in an alcohol with a platinum catalyst or by treatment with sodium cyanoborohydride in trifluoroacetic acid (see EXAMPLE 9) or by hydrogenation with diborane or a diborane precursor such as trimethylamine or dimethyl sulfide complex in tetrahydrofuran or dioxan from 0 °C to reflux temperature followed by acid catalyzed hydrolysis of the intermediate borane derivative.

The removal of halogen substituents according to method k) and reduction of the double bond according to method l) are conveniently performed by catalytic hydrogenation in an alcohol in the presence of a palladium catalyst or by treatment with ammonium formate in an alcohol at elevated temperatures in the presence of a palladium catalyst.

whereupon the compound of Formula I is isolated as the free base or a pharmaceutically acceptable acid addition salt thereof.

Examples.

In the following the invention is further illustrated by examples which, however, may not be construed as limiting.

EXAMPLE 1

1-(1,4-Benzodioxan-5-yl)-4-(3-cyclohexylsulfonyl-1-propyl)piperazine, oxalate, **1a**.

To a suspension of potassium tert-butoxide (100 g) in toluene (600 ml) cyclohexylthiol (100 g) was added dropwise. After stirring for half an hour at room temperature 3-bromo-1-propanol (100 g) was added dropwise. The mixture was stirred at 60 °C for 3 hours. The mixture was poured into 2 M sodium hydroxide solution (1 l). The phases were separated and the organic phase washed with 2 M sodium hydroxide (500 ml). Removal of solvent *in vacuo* left a colorless oil (120 g) of 3-cyclohexylthio-1-propanol which was sufficiently pure for use in the next step.

To a solution of 3-cyclohexylthio-1-propanol (60 g) in glacial acetic acid (250 ml) hydrogen peroxide (35% in water, 210 ml) was added at 10 °C followed by reflux for 2 h. After cooling the mixture was poured onto ice followed by extraction with ethyl acetate (1 l). The organic phase was washed several times with 1 M sodium hydroxide. Removal of solvent gave an oil which was treated at reflux temperature with 1 M sodium hydroxide (600 ml) for 1 h. Extraction with ethyl acetate, drying of the organic phase over magnesium sulfate, and removal of solvent *in vacuo* gave a colorless oil (37 g) of 3-cyclohexylsulfonyl-1-propanol which was used without further purification in the next step.

A solution of 3-cyclohexylsulfonyl-1-propanol (37 g) and triethylamine (30 ml) in methylene chloride (400 ml) was treated dropwise at -5 °C with methanesulfonyl chloride (15 ml). After stirring for 2 h at room temperature the mixture was washed with water and dried over magnesium sulfate. Removal of solvent *in vacuo* gave a viscous oil (49 g) of 3-cyclohexylsulfonyl-1-propyl methanesulfonate.

A mixture of 3-cyclohexylsulfonyl-1-propyl methanesulfonate (8.5 g), 1-(1,4-benzodioxan-5-yl)-piperazine (5.4 g), and potassium carbonate in methyl isobutyl ketone (200 ml) was refluxed for 20 h. Filtration and removal of solvent *in vacuo* gave an oil which was purified by column chromatography (silica gel, eluent: ether/methanol/triethylamine = 96:2:2). The title compound crystallized as the oxalate salt from acetone by addition of oxalic acid. Yield: 8.1 g, mp: 162-64 °C.

^{1}H NMR (δ, DMSO): 1.05-1.45 (m, 6H), 1.60-1.90 (m, 2H), 1.95-2.10 (m, 4H), 2.90-3.20 (m, 13 H), 4.15-4.30 (m, 4H), 6.45-6.60 (m, 2H), 6.75 (d, 1H).

In a similar manner were also prepared:

1-(1,4-Benzodioxan-5-yl)-4-(3-phenylsulfonyl-1-propyl)piperazine, hydrochloride, **1b**, mp: 184-96 °C. ^{1}H NMR (δ, DMSO): 2.00-2.20 (m, 2H), 3.00-3.25 (m, 6H), 3.30-3.60 (m, 6H), 4.15-4.30 (m, 4H), 6.45-6.60 (m, 2H), 6.75 (t, 1H), 7.60-7.80 (m, 3H), 7.95 (d, 2H), 8.00 (b, 2H).

1-(3-Cyclohexylsulfonyl-1-propyl)-4-(2,3-dihydrobenzofuran-7-yl)piperazine, maleate, **1c**, mp: 166-68 °C. ^{1}H NMR (δ, DMSO): 1.05-1.50 (m, 5H), 1.60-1.70 (m, 1H), 1.75-1.90 (m, 2H), 1.95-2.20 (m, 4H), 3.00-3.40 (m, 17H), 4.50 (t, 2H), 6.05 (s, 2H), 6.65-6.80 (m, 2H), 6.90 (d, 1H).

1-(2,3-Dihydrobenzofuran-7-yl)-4-(3-methylsulfonyl-1-propyl)piperazine, maleate,

1d, mp: 150-51 °C. ^{1}H NMR (δ, DMSO): 2.00-2.20 (m, 2H), 3.05 (s, 3H), 3.00-3.50 (m, 16H), 4.55 (t, 3H), 6.10 (s, 2H), 6.65-6.85 (m, 2H), 6.90 (d, 1H).

1-(1,4-Benzodioxan-5-yl)-4-(3-isopropylsulfonyl-1-propyl)piperazine, fumarate, **1e**, mp: 166-67 °C. ^{1}H NMR (δ, DMSO): 1.25 (d, 6H), 1.80-2.00 (m, 2H), 2.50-2.65 (m, 6H), 2.90-3.05 (m, 4H), 3.05-3.15 (m, 2H), 3.30 (h, 1H), 4.15-4.30 (m, 4H), 6.50 (t, 2H), 6.60 (s, 2H), 6.70 (t, 1H).

1-[3-(1-Adamantyl)sulfonyl-1-propyl]-4-(1,4-benzodioxan-5-yl)piperazine, **1f**, mp: 143-44 °C. ^{1}H NMR (δ, $CDCL_3$): 1.65-1.85 (m, 6H), 2.00-2.25 (m, 11H), 2.55 (t, 2H), 2.60-2.70 (m, 4H), 2.90-3.00 (m, 2H), 3.00-3.15 (m, 4H), 4.20-4.25 (m, 2H), 4.25-4.35 (m, 2H), 6.50-6.60 (m, 2H), 6.80 (t, 1H).

EXAMPLE 2

1-[3-[4-(1,4-Benzodioxan-5-yl)-1-piperazinyl]-1-propyl]-3-phenyl-2-imidazolidinone, hydrochloride, **2a**.

A mixture of 1-(1,4-benzodioxan-5-yl)-piperazine (1.5 g), 1-(3-chloro-1-propyl)-3-phenyl-2-imidazolidinone (1.4 g), potassium carbonate (3 g), and potassium iodide (0.1 g) in methyl isobutyl ketone was refluxed for 20 h. Filtration and removal of solvent *in vacuo* gave a viscous oil which was separated by column chromatography (silica gel; eluent: ethyl acetate/methanol/triethylamine = 15:4:1). The title compound was isolated as an oil which crystallized as the hydrochloride salt from acetone by addition of hydrochloric acid. Yield: 1.9 g, mp: 229-32 °C. ^{1}H NMR (δ, DMSO): 1.95-2.15 (m, 2H), 3.00-3.25 (m, 6H), 3.30 (t, 2H), 3.40-3.65 (m, 4H), 3.70-4.00 (m, 4H), 4.15-4.30 (m, 4H), 6.45-6.70 (m, 2H), 6.75 (t, 1H), 7.00 (t, 1H), 7.30 (t, 2H), 7.60 (d, 2H), 11.30 (b, 1H).

In a similar manner were also prepared:

1-[2-[4-(1,4-Benzodioxan-5-yl)-1-piperazinyl]ethyl]-3-cyclopentyl-2-imidazolidinone, hydrochloride, **2b**, mp: 266-68 °C. ^{1}H NMR (δ, $CDCl_3$): 1.45-1.95 (m, 8H), 3.00-3.30 (m, 4H), 3.35-3.60 (m, 8H), 3.60-3.85 (m, 4H), 4.15-4.35 (m, 5H), 6.50 (d, 1H), 6.65 (d, 1H), 6.80 (t, 1H), 12.30 (b, 1H).

1-[2-[4-(1,4-Benzodioxan-5-yl)-1-piperazinyl]ethyl]-3-phenyl-2-imidazolidinone,

hydrochloride, **2c**, mp: 288-90 °C. ^{1}H NMR (δ, DMSO): 3.00-3.75 (m, 10H), 3.85 (t, 2H), 4.10-4.35 (m, 4H), 4.50-4.75 (m, 4H), 6.45-6.70 (m, 2H), 6.75 (t, 1H), 7.00 (t, 1H), 7.35 (t, 2H), 7.60 (d, 2H).10.95 (b, 1H).

1-[2-[4-(1,4-Benzodioxan-5-yl)-1-piperazinyl]ethyl]-3-cyclohexyl-2-imidazolidinone, fumarate, **2d**, mp: 103-14 °C. ^{1}H NMR (δ, DMSO): 0.95-1.15 (m, 1H), 1.15-1.45 (m, 4H), 1.45-1.65 (m, 3H), 1.65-1.80 (m, 2H), 2.60 (t, 2H), 2.65-2.80 (m, 4H), 2.90-3.05 (m, 4H), 3.15-3.35 (m, 6H), 3.40-3.55 (m, 1H), 4.15-4.30 (m, 4H), 6.4-6.55 (m, 2H), 6.60 (s, 2H), 6.70 (t, 1H), 7.90 (b, 1H).

1-[4-[4-(1,4-Benzodioxan-5-yl)-1-piperazinyl]-1-butyl]-3-cyclohexyl-2-imidazolidinone, hydrochloride, **2e**, mp: 212-22 °C. ^{1}H NMR (δ, DMSO): 0.95-1.15 (m, 1H), 1.15-1.40 (m, 4H), 1.40-1.65 (m, 5H), 1.65-1.85 (m, 4H), 3.00-3.25 (m, 8H), 3.25 (2, 4H), 3.40-3.60 (m, 5H), 4.15-4.30 (m, 4H), 6.45-6.60 (m, 2H), 6.75 (t, 1H), 8.00 (b, 1H), 11.40 (b, 1H).

1-Cyclopentyl-3-[2-[4-(2,3-dihydrobenzofuran-7-yl)-1-piperazinyl]ethyl]-2-imidazolidinone, hydrochloride, **2f**, mp: 200-2 °C. ^{1}H NMR (δ, DMSO): 1.40-1.80 (m, 8H), 3.00-3.80 (m, 18H), 4.00-4.15 (m, 1H), 4.50 (t, 2H), 6.65-6.85 (m, 2H), 6.90 (t, 1H), 11.05 (b, 1H).

1-[3-[4-(2,3-Dihydrobenzofuran-7-yl)-1-piperazinyl]-1-propyl]-3-phenyl-2-imidazolidinone, hydrochloride, **2g**, mp: 225-28 °C. ^{1}H NMR (δ, DMSO): 1.95-2.10 (m, 2H), 2.95-3.40 (m, 12H), 3.40-3.70 (m, 6H), 3.80 (t, 2H), 4.50 (t, 2H), 6.65-6.80 (m, 2H), 6.90 (d, 1H), 7.00 (t, 1H), 7.35 (t, 2H), 7.60 (d, 2H), 11.20 (b, 1H).

4-[4-[2-(3-Phenylimidazolidin-2-on-1-yl)ethyl]-1-piperazinyl]-2,1,3-benzothiadiazole, maleate, **2h**, mp: 182-83 °C. ^{1}H NMR (δ, DMSO): 3.20-3.95 (m, 18H), 6.10 (s, 2H), 6.90-7.10 (m, 2H), 7.35 (t, 2H), 7.55-7.70 (m, 4H).

1-[2-[4-(2,3-Dihydrobenzofuran-7-yl)-1-piperazinyl]ethyl]-3-(4-fluorophenyl)-2-imidazolidinone, fumarate, **2i**, mp: 188-90 °C. ^{1}H NMR (δ, DMSO): 2.55-2.70 (m, 6H), 2.95-3.15 (m, 4H), 3.10 (t, 2H), 3.35 (t, 2H), 3.55 (t, 2H), 3.80 (t, 2H), 4.50 (t, 2H), 5.10 (b, 2H), 6.60 (s, 2H), 6.65 (d, 1H), 6.75 (t, 1H), 6.80 (d, 1H), 7.15 (t, 2H), 7.50-7.60 (m, 2H).

Ethyl 7-[4-[2-(3-phenyl-2-imidazolidin-2-on-1-yl)ethyl]-1-piperazinyl]-2-indolyl carboxylate, fumarate, **2j**, mp: 202-4 °C. ^{1}H NMR (δ, DMSO): 1.35 (t, 3H), 2.70 (t, 2H),

2.75-2.90 (m, 4H), 2.95-3.15 (m, 4H), 3.40 (t, 2H), 3.60 (t, 2H), 3.80 (t, 2H), 4.35 (q, 2H), 6.60 (s, 2H), 6.80 (d, 1H), 6.95-7.05 (m, 2H), 7.15 (d, 1H), 7.25-7.40 (m, 2H), 7.60 (d, 2H).

1-[2-[4-(1-Naphtyl)-1-piperazinyl]ethyl]-3-phenyl-2-imidazolidinone, fumarate, **2k**, mp: 176-80 °C. ^{1}H NMR (δ, DMSO): 2.70 (t, 2H), 2.65-2.90 (m, 4H), 2.95-3.15 (m, 4H), 3.40 (t, 2H), 3.55 (t, 2H), 3.80 (t, 2H), 6.60 (s, 2H), 7.00 (t, 1H), 7.10 (d, 1H), 7.30 (t, 2H), 7.40 (t, 1H), 7.45-7.65 (m, 5H), 7.85-7.95 (m, 1H), 8.05-8.20 (m, 1H).

1-[2-[4-(1,4-Benzodioxan-5-yl)-1-piperazinyl]ethyl]-3-ethyl-2-imidazolidinone, hydrochloride, **2l**, mp: 250-52 °C. ^{1}H NMR (δ, DMSO): 1.05 (t, 3H), 2.95-3.70 (m, 18H), 4.15-4.30 (m, 4H), 6.50 (d, 1H), 6.55 (d, 1H), 6.25 (t, 1H), 10.65 (b, 1H).

1-[2-[4-Benzofuran-7-yl-1-piperazinyl]ethyl]-3-phenyl-2-imidazolidinone, hemifumarate, **2m**, mp: 175-76 °C. ^{1}H NMR (δ, DMSO): 2.60 (t, 2H), 2.65-2.75 (m, 4H), 3.20-3.35 (m, 4H), 3.40 (t, 2H), 3-60 (t, 2H), 3.80 (t, 2H), 6.75 (s, 1H), 6.75 (d, 1H), 6.90 (s, 1H), 7.00 (t, 1H), 7.05-7.25 (m, 2H), 7.30 (t, 2H), 7.60 (d, 1H), 7.95 (s, 1H).

1-[2-[4-(2,3-Dihydro-2,2-dimethylbenzofuran-7-yl)-1-piperazinyl]ethyl]-3-phenyl-2-imidazolidinone, dihydrochloride, **2n**, mp: 220-30 °C. ^{1}H NMR (δ, DMSO): 1.40 (s, 6H), 3.00 (s, 2H), 3.10-3.45 (m, 6H), 3.50-3.75 (m, 8H), 3.85 (t, 2H), 6.65-6.80 (m, 2H), 6.85 (d, 1H), 7.00 (t, 1H), 7.35 (t, 2H), 7.60 (d, 2H), 9.35 (b, 1H), 11.30 (b, 1H).

1-[2-[4-(1,4-Benzodioxan-5-yl)-1-piperazinyl]ethyl]-3-isopropyl-2-imidazolidinone, hydrochloride, **2o**, mp: 228-30 °C. ^{1}H NMR (δ, DMSO): 1.05 (d, 6H), 2.95-3.65 (m, 16H), 3.90 (h, 1H), 4.15-4.30 (m, 4H), 6.50 (d, 1H), 6.60 (d, 1H), 6.25 (d, 1H), 10.95 (b, 1H).

1-Cyclopentyl-3-[2-[4-(2,3-dihydro-2,2-dimethylbenzofuran-7-yl)-1-piperazinyl]ethyl]-2-imidazolidinone, dihydrochloride, **2p**, mp: 185-95 °C. ^{1}H NMR (δ, DMSO): 1.45 (s, 6H), 1.45-1.75 (m, 8H), 3.00 (s, 2H), 3.10-3.40 (m, 10H), 3.50 (t, 2H), 3.55-3.70 (m, 4H), 4.00-4.15 (m, 1H), 6.70-6.80 (m, 2H), 6.35 (d, 1H), 7.35 (b, 1H), 11.30 (b, 1H).

1-Adamantyl-3-[2-[4-(1,4-benzodioxan-5-yl)-1-piperazinyl]ethyl]-2-imidazolidinone, hydrochloride, **2q**, mp: 246-48 °C. ^{1}H NMR (δ, DMSO): 1.55-1.65 (m, 6H), 1.90-2.10 (m, 9H), 2.96-3.60 (m, 16H), 4.15-4.30 (m, 4H), 6.50 (d, 1H), 6.55 (d, 1H), 6.75 (t, 1H), 10.85 (b, 1H).

1-[2-(4-Benzofuran-4-yl-1-piperazinyl)ethyl]-3-phenyl-2-imidazolidinone, sesquifumarate, **2r**, mp: 207-9 °C. ^{1}H NMR (δ, DMSO): 2.65 (t, 2H), 2.70-2.80 (m, 4H), 3.10-3.20 (m, 4H), 3.40 (t, 2H), 3.55 (t, 2H), 3.80 (t, 2H), 6.60 (s, 3H), 6.65-6.70 (m, 1H), 6.95-7.05 (m, 2H), 7.10-7,20 (m, 2H), 7.30 (t, 2H), 7.55 (d, 2H), 7.90 (s, 1H).

1-[2-(4-Benzofuran-4-yl-1-piperazinyl)ethyl]-3-cyclopentyl-2-imidazolidinone, dihydrochloride, **2s**, mp: 237-39 °C. ^{1}H NMR (δ, DMSO): 1.40-1.80 (m, 8H), 3.15-3.45 (m, 10H), 3.55 (t, 2H), 3.55-3.75 (m, 4H), 4.00-4.20 (m, 1H), 4.45 (b, 1H), 6.75 (dd, 1H), 7.10 (d, 1H), 7.20-7.30 (m, 2H), 8.00 (s, 1H), 11.20 (b, 1H).

1-[2-(4-Benzo[b]thiophen-7-yl-1-piperazinyl)ethyl]-3-phenyl-2-imidazolidinone, **2t**, mp: 136-38 °C. ^{1}H NMR (δ, $CDCl_3$): 2.70 (t, 2H), 2.70-2.85 (m, 4H), 3.15-3.35 (m, 4H), 3.50 (t, 2H), 3.55 (t, 2H), 3.80j (t, 2H), 6.90 (d, 1H), 7.00 (t, 1H), 7.20-7.45 (m, 5H), 7.45-7.65 (m, 3H).

1-Cyclopentyl-3-[2-[4-(7-indolyl)-1-piperazinyl]ethyl]-2-imidazolidinone, **2u**, mp: 188-89 °C. ^{1}H NMR (δ, $CDCl_3$): 1.40-1.90 (m, 8H), 2.60 (t, 2H), 2.65-2.75 (m, 4H), 3.05-3.15 (m, 4H), 3.20-3.45 (m, 6H), 4.25 (p, 1H), 6.50-6.55 (m, 1H), 6.80 (d, 1H), 7.05 (t, 1H), 7.10-7.20 (m, 1H), 7.35 (d, 1H), 8.40 (b, 1H).

1-[2-[4-(7-Indolyl)-1-piperazinyl]ethyl]-3-phenyl-2-imidazolidinone, fumarate, **2v**, mp: 215-16 °C. ^{1}H NMR (δ, DMSO): 2.70 (t, 2H), 2.75-2.85 (m, 4H), 3.00-3.15 (m, 4H), 3.40 (t, 2H), 3.55 (t, 2H), 3.80 (t, 2H), 6.35-6.40 (m, 1H), 6.60 (s, 2H), 6.65 (d, 1H), 6.90 (t, 1H), 7.00 (t, 1H), 7.15-7.35 (m, 4H), 7.60 (d, 2H).

1-[2-[4-(1,2-Benzisothiazol-7-yl)-1-piperazinyl]ethyl]-3-phenyl-2-imidazolidinone, hydrochloride, **2x**, mp: 237-44 °C. ^{1}H NMR (δ, DMSO): 3.10-3.80 (m, 14H), 3.85 (t, 2H), 7.00 (t, 1H), 7.20 (d, 1H), 7.30 (t, 2H), 7.50 (t, 1H), 7.60 (d, 2H), 7.90 (d, 1H), 9.15 (s, 1H), 11.25 (b, 1H).

1-Cyclopentyl-3-[2-[4-(4-indolyl)-1-piperazinyl]ethyl]-2-imidazolidinone, dihydrochloride, **2y**, mp: 214-20°C. ^{1}H NMR (δ, DMSO): 1.50-1.80 (m, 8H), 3.20-3.60 (m, 12H), 3.60-3.80 (m, 4H), 3.95-4.20 (m, 1H), 6.60j (s, 1H), 6.70 (d, 1H), 7,00 (t, 1H), 7.20 (d, 1H), 7.35 (s, 1H), 11.30 (b, 1H).

1-[2-[4-(4-Indolyl)-1-piperazinyl]ethyl]-3-phenyl-2-imidazolidinone, dihydrochloride, **2z**, mp: 233-38°C. ^{1}H NMR (δ, DMSO): 3.25-3.50 (m, 8H), 3.60 (t, 2H), 3.60-3.75 (m, 4H), 3.85 (t, 2H), 5.00 (b, 2H), 6.50 (2, 1H), 6.60 (d, 1H), 6.95-7.00 (m, 2H),

7.15 (d, 1H), 7.25-7.40 (m, 3H), 7.60 (d, 2H), 11.20 (b, 1H).

1-[2-[4-Benzo[b]thiophen-7-yl-1-piperazinyl]ethyl]-3-cyclopentyl-2-imidazolidinone, hydrochloride, **2aa**, mp: 264-67 °C. ^{1}H NMR (δ, DMSO): 1.40-1.75 (m, 8H), 3.20-3.45 (m, 10H), 3.50 (t, 2H), 3.60-3.75 (m, 4H), 4.10 (p, 1H), 7.05 (d, 1H), 7.40 (t, 1H), 7.50 (d, 1H), 7.60 (d, 1H), 7.75 (d, 1H), 11.30 (b, 1H).

1-Cyclohexyl-3-[4-[4-(2,3-dihydro-2,2-dimethylbenzofuran-7-yl)-1-piperazinyl]-1-butyl]-2-imidazolidinone, dihydrochloride, **2bb**, mp: 196-203 °C. ^{1}H NMR (δ, DMSO): 1.20-1.65 (m, 10H), 1.40 (s, 6H), 1.65-1.80 (m, 4H), 3.00 (s, 2H), 3.00-3.20 (m, 8H), 3.20-3.25 (m, 6H), 3.40-3.55 (m, 2H), 3.60-3.65 (m, 1H), 6.70-6.80 (m, 2H), 6.85 (d, 1H), 7.60 (b, 1H), 11.30 (b, 1H).

Ethyl [4-[4-[2-(3-cyclopentyl-2-imidazolidinon-1-yl)ethyl]-1-piperazinyl]-2-benzofuranyl] carboxylate, hydrochloride **2cc**, mp: 198-201 °C. ^{1}H NMR (δ, DMSO): 1.35 (t, 3 H), 1.40-1.75 (m, 8H), 3.25-3.75 (m, 16H), 4.00-4.15 (m, 1H), 4.35 (q, 2H), 6.80 (d, 1H), 7.30 (d, 1H), 7.40 (t, 1H), 7.95 (s, 1H).

1-[4-[4-(2,3-Dihydro-2,2-dimethylbenzofuran-7-yl)-1-piperazinyl]-1-butyl]-3-(4-fluorophenyl)-2-imidazolidinone, **2dd**, mp: 158-60 °C. ^{1}H NMR (δ, $CDCl_3$): 1.50 (s, 6H), 1.55-1.65 (m, 4H), 2.45 (t, 2H), 2.55-2.70 (m, 4H), 3.00 (s, 2H), 3.10-3.20 (m, 4H), 3.30 (t, 2H), 3.45 (t, 2H), 3.80 (t, 2H), 6.65-6.70 (m, 1H), 6.75 (d, 2H), 7.00 (t, 2H), 7.40-7.55 (m, 2H).

1-[2-[4-(1,4-Benzodioxan-5-yl)-1-piperazinyl]ethyl]-3-*t*-butyl-2-imidazolidinone, hydrochloride, **2ee**, mp: 229-31 °C. ^{1}H NMR (δ, DMSO): 1.30 (s, 9H), 3.00-3.60 (m, 16H), 4.20-4.30 (m, 4H), 6.45-6.60 (m, 2H), 6.75 (t, 1H).

1-[3-[4-(2,3-Dihydro-2,2-dimethylbenzofuran-7-yl)-1-piperazinyl]-1-propyl]-3-phenyl-2-imidazolidinone, fumarate, **2ff**, mp: 183-85 °C. ^{1}H NMR (δ, DMSO): 1.40 (s, 6H), 1.75 (hep, 2H), 2.50 (t, 2H), 2.60-2.70 (m, 4H), 2.95 (s, 2H), 3.00-3.15 (m, 4H), 3.25 (t, 2H), 3.45 (t, 2H), 3.80 (t, 2H), 6.60 (s, 2H), 6.65 (d, 1H), 6.70 (t, 1H), 6.75 (d, 1H), 7.00 (t, 1H), 7.30 (t, 2H), 7.55 (d, 2H).

1-Adamantyl-3-[4-[4-(2,3-dihydro-2,2-dimethylbenzofuran-7-yl)-1-piperazinyl]-1-butyl]-2-imidazolidinone, **2gg**, mp: 125-27 °C. ^{1}H NMR (δ, $CDCl_3$): 1.50 (s, 6H), 1.50-1.55 (m, 3H), 1.65-1.70 (m, 6H), 2.00-2.10 (m, 9H), 2.40 (t, 2H), 2.55-2.65 (m, 4H), 3.00 (s, 2H), 3.10-3.20 (m, 8H), 3.30 (t, 2H), 6.70 (t, 1H), 6.75 (d, 2H).

1-[4-[4-(5-Chloro-2-phenylbenzofuran-7-yl)-1-piperazinyl]-1-butyl]-3-cyclohexyl-2-imidazolidinone, dihydrochloride, **2hh**, mp: 198-200 °C. ^{1}H NMR (δ, DMSO): 1.00-1.85 (m, 14H), 3.10 (t, 2H), 3.15-3.70 (m, 14H), 4.00-4.10 (m, 1H), 4.65 (b, 2H), 6.85 (s, 1H), 7.30 (s, 1H), 7.40 (s, 1H), 7.45 (t, 1H), 7.50 (t, 2H), 7.95 (d, 2H).

1-[2-[4-(5-Chloro-2-phenylbenzofuran-7-yl)-1-piperazinyl]ethyl]-3-cyclopentyl-2-imidazolidinone, fumarate, **2ii**, mp: 155-57 °C. ^{1}H NMR (δ, DMSO): 1.40-1.70 (m, 8H), 2.55 (t, 2H), 2.65-2.75 (m, 4H), 3.20-3.45 (m, 10H), 4.00-4.15 (m, 1H), 6.60 (s, 2H), 6.70 (s, 1H), 7.20 (s, 1H), 7.35 (s, 1H), 7.45 (t, 1H), 7.50 (t, 2H), 7.90 (d, 2H).

1-[4-[4-(2,3-Dihydro-2,2-dimethylbenzofuran-7-yl)-1-piperazinyl]-1-butyl]-3-(1-naphtyl)-2-imidazolidinone, fumarate, **2jj**, mp: 220-21 °C. ^{1}H NMR (δ, DMSO): 1.40 (s, 6H), 1.50-1.65 (m, 4H), 2.55 (t, 2H), 2.65-2.75 (m, 4H), 2.95 (s, 2H), 3.05-3.15 (m, 4H), 3.25 (t, 2H), 3.60 (t, 2H), 3.80 (t, 2H), 6.60 (s, 2H), 6.65 (d, 1H), 6.70 (t, 1H), 6-80 (d, 1H), 7.45 (d, 1H), 7.45-7.60 (m, 3H), 7.85-8.00 (m, 3H).

1-Cyclohexyl-3-[3-[4-(2,3-dihydro-2,2-dimethylbenzofuran-7-yl)-1-piperazinyl]-1-propyl]-2-imidazolidinone,oxalate, **2kk**, mp: 191-92 °C. ^{1}H NMR (δ, DMSO): 1.00-1.90 (m, 10H), 1.40 (s, 6H), 2.90-3.00 (m, 4H), 3.10 (t, 2H), 3.15-3.30 (m, 10H), 3.40-3.50 (m, 1H), 4.10 (b, 2H), 6.65 (d, 1H), 6.70 (t, 1H), 6.80 (d, 1H).

1-[4-[4-(2,3-Dihydro-2,2-dimethyl-5-fluorobenzofuran-7-yl)-1-piperazinyl]-1-butyl]-3-(4-fluorophenyl)-2-imidazolidinone,oxalate, **2ll**, mp: 126-27 °C. ^{1}H NMR (δ, DMSO): 1.45 (s, 6H), 1.50-1.65 (m, 4H), 2.40 (t, 2H), 2.55-2.65 (m, 4H), 2.95 (s, 2H), 3.05-3.20 (m, 4H), 3.30 (t, 2H), 3.95 (t, 2H), 3.80 (t, 2H), 6.30-6.50 (m, 2H), 7.00 (t, 2H), 7.40-7.55 (m, 2H).

1-Cyclohexyl-3-[4-[4-(2,3-dihydro-2,2-dimethyl-5-fluorobenzofuran-7-yl)-1-piperazinyl]-1-butyl]-2-imidazolidinone,oxalate, **2mm**, mp: 125-35 °C. ^{1}H NMR (δ, DMSO): 1.00-1.80 (m, 14H), 1.40 (s, 6H), 2.95 (s, 2H), 3.00-3.50 (m, 17H), 6.50 (dd, 1H), 6.65 (dd, 1H).

1-Cyclopentyl-3-[6-[4-(2,3-dihydro-2,2-dimethylbenzofuran-7-yl)-1-piperazinyl]-1-hexyl]-2-imidazolidinone,oxalate, **2nn**, mp: 132-34 °C. ^{1}H NMR (δ, DMSO): 1.15-1.75 (m, 14H), 1.40 (s, 6H), 2.95 (s, 2H), 2.95-3.10 (m, 4H), 3.15-3.45 (m, 12H), 4.00-4.15 (m, 1H), 6.65 (d, 1H), 6.75 (t, 1H), 6.85 (d, 1H).

1-[2-[4-(5-Chloro-2,3-dihydro-3,3-dimethyl)-7-benzofuranyl)-1-piperazinyl]ethyl]-3-

cyclopentyl-2-imidazolidinone, oxalate, **2oo**, mp: 104-7 °C. ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 6H), 1.40-1.75 (m, 8H), 3.00 (t, 2H), 3.05-3.15 (m, 4H), 3.20-3.35 (m, 8H), 3.40 (t, 2H), 4.00-4.15 (m, 1H), 4.25 (s, 2H), 6.70 (d, 1H), 6.90 (d, 1H).

1-[6-[4-(5-Chloro-2,3-dihydro-3,3-dimethyl)-7-benzofuranyl)-1-piperazinyl]-1-hexyl]-3-cyclopentyl-2-imidazolidinone, oxalate, **2pp**, mp: 125-27 °C. ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 6H), 1.20-1.75 (m, 16H), 2.95 (t, 2H), 3.00 (t, 2H), 3.10-3.40 (m, 12H), 4.00-4.15 (m, 1H), 4.25 (s, 2H), 6.70 (d, 1H), 6.90 (d, 1H).

1-[3-[4-(7-Chloro-2,3-dihydro-2,2-dimethyl)-4-benzofuranyl)-1-piperazinyl]-1-propyl]-3-cyclohexyl-2-imidazolidinone, oxalate, **2qq**, mp: 123-33 °C. ^{1}H NMR ($CDCl_3$) δ 0.95-1.50 (m, 5H), 1.45 (s, 6H), 1.50-1.65 (m, 3H), 1.65-1.90 (m, 4H), 2.85-3.30 (m, 18H), 3.35-3.50 (m, 1H), 6.45 (d, 1H), 7.10 (d, 1H).

EXAMPLE 3

1-(1,4-Benzodioxan-5-yl)-4-(3-cyclohexylthio-1-propyl)piperazine *S*-oxide, oxalate, **3a**

A solution of 1-(1,4-benzodioxan-5-yl)-4-(3-cyclohexylthio-1-propyl)piperazin (7 g) in tetrahydrofuran (70 ml) was cooled to 0 °C followed by portionwise addition of m-chloroperbenzoic acid (6.4 g) keeping the temperature at 0 °C. After stirring for 3 h at 0 °C aqueous sodium carbonate (20% solution, 100 ml) was added. The phases were separated and the aqueous phase was extracted with methylene chloride. The combined organic phases was concentrated *in vacuo* and the resulting oil applied to a silica gel column (eluent: ethyl acetat/methanol/diethylamine = 88:8:4). The title compound crystallized as the oxalate salt from an acetone/methanol mixture by addition of oxalic acid. Yield: 1.5 g, mp: 113-15 °C. ^{1}H NMR (δ, DMSO): 1.00-1.50 (m, 6H), 1.55-2.20 (m, 7H), 2.55-2.95 (m, 4H), 2.95-3.35 (m, 8H), 4.15-4.35 (m, 4H), 6.50 (d, 1H), 6.55 (d, 1H), 6.75 (t, 1H).

EXAMPLE 4

1-[3-[4-(1,4-Benzodioxan-5-yl)-1-piperazinyl]-1-propyl]-3-benzyl-2-imidazolidinone, hydrochloride, **4a**.

filtered, and concentrated *in vacuo*. The product, 1-(1,4-benzodioxan-5-yl)-4-cyanomethylpiperazine, was obtained as an oil (17.4 g) which was sufficiently pure for use in the next step.

A suspension of lithium aluminium chloride (8.2 g) in dry ether (170 ml) was treated dropwise with a solution of aluminium chloride (8.2 g) in ether (170 ml) under cooling. After stirring for half an hour at room temperature a solution of 1-(1,4-benzodioxan-5-yl)-4-cyanomethylpiperazine (9.4 g) in dry tetrahydrofuran (250 ml) was added dropwise at 15 °C. After reflux for 1.5 h the mixture was cooled and conc. sodium hydroxide solution (40 ml) was added dropwise. Filtration and removal of solvent *in vacuo* gave an oil which was dissolved in methylene chloride and dried over magnesium sulfate. Removal of solvent *in vacuo* gave 1-(2-amino-1-ethyl)-4-(1,4-benzodioxan-5-yl)piperazine (9.1 g) as a viscous oil.

A mixture of 1-(2-amino-1-ethyl)-4-(1,4-benzodioxan-5-yl)piperazine (9.1 g), bromoacetaldehyde dimethylacetale (6.5 g), potassium iodide (0.5 g), and potassium carbonate (4.8 g) in 1,4-dioxan (200 ml) was refluxed for 16 h. Water was added followed by extraction with ethyl acetate. The organic phase was concentrated *in vacuo* leaving an oil which was applied to a silica gel column (eluent: ethyl acetate/methanol = 1:3). The product, 1-(1,4-benzodioxan-5-yl)-4-[2-(2,2-dimethoxy-1-ethylamino)-1-ethyl]piperazine, was obtained as an oil (4.7 g).

A solution of 1-(1,4-benzodioxan-5-yl)-4-(2-(2,2-dimethoxy-1-ethylamino)-1-ethyl)piperazine (2.3 g) and 4-fluorophenyl isocyanate (0.9 g) in methylene chloride (100 ml) was refluxed for 2 h. Removal of solvent *in vacuo* gave an oil which was purified on a silica gel column (eluent: ethyl acetate/methanol = 3:1). The product, 1-(1,4-benzodioxan-5-yl)-4-(2-(*N*-(2,2-dimethoxy-1-ethyl)-*N*-(4-fluorophenylaminocarbonyl)amino)-1-ethyl)piperazine, was obtained as a solid (2.5 g).

A solution of 1-(1,4-benzodioxan-5-yl)-4-(2-(*N*-(2,2-dimethoxy-1-ethyl)-*N*-(4-fluorophenylaminocarbonyl)amino)-1-ethyl)piperazine (2.5 g) and 3 M hydrochloric acid (2.5 ml) in ethanol (50 ml) was stirred at room temperature for 72 h. The title compound was collected by filtration as the hydrochloride. Yield: 1.2 g, mp: 301-5 °C. ^{1}H NMR (δ, DMSO): 3.00-3.60 (m, 10H), 4.05 (t, 2H), 4.20-4.35 (m, 4H), 6.55 (t, 2H), 6.75 (t, 1H), 6.80 (d, 1H), 7.00 (d, 1H), 7.25 (t, 2H), 7.65-7.80 (m, 2H).

In a similar manner was also prepared:

A solution of 1-[3-[4-(1,4-benzodioxan-5-yl)-1-piperazinyl]-1-propyl]-2-imidazolidinone (prepared from 1-(1,4-benzodioxan-5-yl)piperazin and 1-(3-chloro-1-propyl)-2-imidazolidinone by the method described in EXAMPLE 2) (2.5 g) and benzaldehyde (2.3 g) in glacial acetic acid (30 ml) was treated portionwise with sodium borohydride (0.6 g) keeping the temperature at 10 °C. After stirring for 40 min. at room temperature additional benzaldehyde (2.3 g) and sodium borohydride (0.6 g) was added and the mixture stirred for 16 h at room temperature. Removal of solvent *in vacuo* gave a heavy oil which was applied to a silica gel column (eluent: ethyl acetate/ethanol/triethylamine = 10:1:1). The title compound was isolated as a viscous oil which crystallized as the hydrochloride from an acetone/ether mixture by addition of an ether solution of dry HCl. Yield: 2.8 g, mp: 181-91 °C. ^{1}H NMR (δ, DMSO): 1.90-2.10 (m, 2H), 3.00-3.25 (m, 10H), 3.30 (t, 2H), 3.35-3.65 (m, 4H), 4.20 (s, 4H), 4.25 (s, 2H), 6.50 (d, 1H), 6.55 (d, 1H), 6.75 (t, 1H), 7.00 (b, 2H), 7.20-7.40 (m, 5H).

In a similar manner were also prepared:

1-[3-[4-(1,4-Benzodioxan-5-yl)-1-piperazinyl]-1-propyl]-3-ethyl-2-imidazolidinone, hydrochloride, **4b**, mp: 240-43 °C. ^{1}H NMR (δ, DMSO): 1.00 (t, 3H), 1.85-2.05 (m, 2H), 2.95-3.35 (m, 14H), 3.35-3.65 (m, 4H), 4.25 (s, 4H), 6.35 (b, 2H), 6.50 (d, 1H), 6.55 (d, 1H), 6.75 (t, 1H).

1-[3-[4-(1,4-Benzodioxan-5-yl)-1-piperazinyl]-1-propyl]-3-cyclohexyl-2-imidazolidinone, hydrochloride, **4c**, mp: 189-200 °C. ^{1}H NMR (δ, DMSO): 0.95-1.50 (m, 5H), 1.50-1.65 (m, 3H), 1.65-1,85 (m, 2H), 1.90-2.10 (hep, 2H), 3.00-3.35 (m, 12H), 3.35-3.60 (m, 5H), 4.15-4.30 (m, 4H), 6.45-6.60 (m, 2H), 6.75 (t, 1H).

EXAMPLE 5

1-[3-[4-(1,4-Benzodioxan-5-yl)-1-piperazinyl]-1ethyl]-1,3-dihydro-3-(4-fluorophenyl)-2-imidazolone, hydrochloride, **5a**.

A solution of 1-(1,4-benzodioxan-5-yl)piperazin (11 g) and triethylamine (7 ml) in N-methyl-2-pyrrolidinone was treated dropwise with chloroacetonitrile (4.5 g). After stirring for 2 h at 100 °C the mixture was poured onto ice and extracted with ethyl acetate. The organic phase was washed with water, dried over magnesium sulfate,

1-[3-[4-(1,4-Benzodioxan-5-yl)-1-piperazinyl]-ethyl]-1,3-dihydro-3-phenyl-2-imidazolone, hydrochloride, **5b**, mp: 295-300 °C. ^{1}H NMR (δ, DMSO): 3.00-3.60 (m, 10H), 4.05 (t, 2H), 4.20-4.30 (m, 4H), 6.50 (t, 2H), 6.70 (t, 1H), 6.80 (d, 1H), 7.00 (d, 1H), 7.20 (t, 1H), 7.45 (t, 2H), 7.70 (d, 2H).

EXAMPLE 6

1-(2-Cyclohexylsulfonyl-1-ethyl)-4-(2,3-dihydrobenzofuran-7-yl)piperazine, maleate, **6a**.

A solution of 2-cyclohexylsulfonylethanol (22 g) and triethylamine (30 ml) in methylene chloride (200 ml) was treated dropwise with a solution of methanesulfonyl chloride (15 ml) in methylene chloride (100 ml) at 10 °C. After stirring for 2 h at room temperature the mixture was washed with water, dried over magnesium sulfate and concentrated *in vacuo* leaving the product, cyclohexyl vinyl sulfone, as an oil (19 g).

A solution of cyclohexyl vinyl sulfone (2.4 g) and 1-(2,3-dihydrobenzofuran-7-yl)piperazine (2.5 g) in methylene chloride (50 ml) was stirred at room temperature for 16 h. Removal of solvent *in vacuo* left an oil which was applied to a silica gel column (eluent: ethyl acetate/methanol/diethylamine = 97:2:1). The title compound was obtained as an oil which crystallized as the maleate salt from acetone by addition of maleic acid. Yield: 3.4 g, mp: 178-79 °C. ^{1}H NMR (δ, DMSO): 1.00-1.50 (m, 5H), 1.60-1.70 (m, 1H), 1.75-1.90 (m, 2H), 2.00-2.15 (m, 2H), 3.00-3.35 (m, 13H), 3.45 (t, 2H), 4.50 (t, 2H), 6.10 (s, 2H), 6.65 (d, 1H), 6.75 (t, 1H), 6.85 (d, 1H).

EXAMPLE 7

1-Cyclopentyl-3-[2-[4-[1-(4-fluorophenyl)-4-indolyl]-1-piperazinyl]ethyl]-2-imidazolidinone, oxalate, **7a**.

A mixture of **2y** (1.3 g), 4-fluoroiodobenzene (2.0 g), cupper powder (0.2 g), potassium carbonate (0.8 g) in N-methyl-pyrrolidinone (20 ml) was kept at 170 °C under stirring for 5 h. After cooling the reaction mixture was filtered and water (200 ml) added followed by extraction with dichloromethane (2 x 100 ml). Removal of solvent *in vacuo* and purification by flash chromatography (silica gel, ethyl acetate/

triethylamine 95:5) gave the free base as a solid (0.8 g). The title oxalate salt crystallized by addition of oxalic acid to an ethanol solution of the base. Yield: 0.7 g, mp: 210-12 °C. ^{1}H NMR (δ, DMSO): 1.40-1.75 (m, 8H), 3.10 (t, 2H), 3.20-3.45 (m, 16H), 4.05-4.15 (m, 1H), 6.65 (d, 1H), 6.70 (dd, 1H), 7.05-7.15 (m, 2H), 7.40 (t, 2H), 7.55-7.65 (m, 3H).

EXAMPLE 8

4-[4-[2-(3-Cyclopentyl-2-imidazolidinon-1-yl)ethyl]-1-piperazinyl]-2-benzofuranyl-carboxamide, hydrochloride, monohydrate, **8a**.

A solution of **2cc** (1.0 g) in a mixture of conc. ammonia (50 ml) and tetrahydrofuran (25 ml) was kept at 50 °C for 48 h. Extraction with ether (3 x 50 ml), drying over magnesium sulfate, and removal of solvent *in vacuo* gave the free base as an oil. Addition of an etheral solution of HCl to an ethanol/heptane solution of the base gave the title hydrochloride salt. Yield: 0.5 g, mp: 166-70 °C. ^{1}H NMR (δ, DMSO): 1.40-1.75 (m, 8H), 3.20-3.85 (m, 16H), 4.05-4.15 (m, 1H), 6.80 (d, 1H), 7.25 (d, 1H), 7.35 (t, 1H), 7.65 (b, 1H), 7.80 (s, 1H), 8.10 (b, 1H), 11.15 (b, 1H).

EXAMPLE 9

1-Cyclopentyl-3-[2-[4-(7-indolinyl)-1-piperazinyl]ethyl]-2-imidazolidinone, **9a**.

A solution of **2u** (1.3 g) in trifluoroacetic acid was treated portionwise over 3 h with sodium cyanoborohydride (0.6 g) at room temperature. After additional stirring for 0.5 h the mixture was poured onto ice followed by extraction with ethyl acetate (3 x 100 ml). Removal of solvent *in vacuo* and purification by chromatography (silica gel, ethyl acetate/triethylamine 96:4) gave the title compound as a crystalline material. Yield: 0.2 g, mp: 130-32 °C. ^{1}H NMR (δ, $CDCl_3$): 1.40-1.85 (m, 8H), 2.55 (t, 2H), 2.55-2.70 (m, 4H), 2.95-3.05 (m, 4H), 3.05 (t, 2H), 3.20-3.45 (m, 6H), 3.55 (t, 2H), 4.25 (hep, 1H), 6.65-6.75 (m, 2H), 6.80-6.90 (m, 1H).

EXAMPLE 10

1-Cyclohexyl-3-[4-[4-(2,3-dihydro-2,2-dimethylbenzofuran-7-yl)-1,2,3,6-tetrahydro-pyrid-1-yl]-1-butyl]-2-imidazolidinone, oxalate, **10a**.

A mixture of 2,3-dihydro-2,2-dimethylbenzofuran (25 g) and tetramethylethylenediamine (46 g) in heptane (250 ml) was treated dropwise at room temperature with 1.6 M BuLi in hexane (250 ml). After stirring for 1.5 h at 30-40 °C the mixture was cooled to -40 °C and 1-benzyl-4-piperidinone (32 g) was added dropwise at -40 °C. The reaction mixture was allowed to warm to room temperature during 3 h followed by quench with water. After concentrating the reaction mixture *in vacuo* dichloromethane (500 ml) was added followed by wash with water (3 x 500 ml). Removal of solvent *in vacuo* gave an oil which was purified by flash chromatography (silica gel, heptane/ethyl acetate/triethylamine 50:48:2) giving an oil. Addition of heptane gave the product, 7-(1-benzyl-4-hydroxy-4-piperidinyl)-2,3-dihydro-2,2-dimethylbenzofuran as a solid (11 g).

The obtained solid was dissolved in trifluoroacetic acid (150 ml) and refluxed for 1 h. The mixture was poured onto ice followed by basification with conc. NaOH. Extraction with dichloromethane (3 x 100 ml) and removal of solvent *in vacuo* gave an oil which was applied to a silica gel flash column (eluent: ethyl acetate/heptane/triethylamine 50:48:2) giving 7-(1-benzyl-1,2,3,6-tetrahydropyrid-4-yl)-2,3-dihydro-2,2-dimethylbenzofuran as an oil (5.0 g).

The product was dissolved in trichloroethane (15 ml) and added dropwise to ethyl chloroformate (20 ml) at reflux temperature. After reflux for 1 h the volatiles were removed *in vacuo* leaving crude 7-(1-ethoxycarbonyl-1,2,3,6-tetrahydropyrid-4-yl)-2,3-dihydro-2,2-dimethylbenzofuran as an oil (4.5 g). The crude product was dissolved in ethanol (50 ml) and solid KOH (3 g) was added. After reflux for 20 h the mixture was poured into water followed by extraction with ethyl acetate. The organic phase was dried over magnesium sulfate and the solvent removed *in vacuo* leaving crude 2,3-dihydro-2,2-dimethyl-7-(1,2,3,6-tetrahydropyrid-4-yl)-benzofuran as an oil (2.9 g). The crude product was sufficiently pure for use in the final step.

The obtained product was alkylated with 1-cyclohexyl-3-(4-chloro-1-butyl)-2-imidazolidinone (4.5 g) according to the method described in EXAMPLE 2 giving the free base of the title compound as an oil (2.7 g). The oxalate salt crystallized by addition of oxalic acid to an acetone solution of the base. Mp: 132-35 °C. ^{1}H NMR (δ, DMSO): 0.95-1.80 (m, 14H), 1.40 (s, 6H), 2.65-2.75 (m, 2H), 2.95 (s, 2H), 3.00-3.10 (m, 5H), 3.20-3.25 (m, 4H), 3.25-3.35 (m, 3H), 3.40-3.50 (m, 1H), 6.30 (m, 1H), 6.80 (t, 1H), 7.10 (t, 2H).

EXAMPLE 11

1-Cyclohexyl-3-[4-[4-(2,3-dihydro-2,2-dimethylbenzofuran-7-yl)-1-piperidinyl]-1-butyl]-2-imidazolidinone, oxalate, **11a**.

A mixture of **10a**, oxalate (1.0 g) and 5% Pd/C (0.2 g) in ethanol (20 ml) was kept under a hydrogen atmosphere at 4 atm. of pressure for 36 h. Filtration, removal of solvent *in vacuo* and addition of acetone/ether gave the title compound as a crystalline solid. Yield: 0.5 g, mp: 150-54 °C. ^{1}H NMR (δ, DMSO): 0.95-2.05 (m, 18H), 1.40 (s, 6H), 2.80-3.10 (m, 8H), 3.15-3.25 (m, 4H), 3.35-3.50 (m, 3H), 6.75 (t, 1H), 6.90 (d, 1H), 7.05 (d, 1H).

EXAMPLE 12

1-[2-[4-(1,4-Benzodioxan-5-yl)-1-piperazinyl]ethyl]-3-(4-fluorophenyl)-2(3*H*)-benzimidazolone, **12a**.

A mixture of 1-(2-hydroxyethyl)benzimidazolone (J. Davoll, *J. Chem. Soc.*, **1960**, 308) (9 g), 4-fluoroiodobenzene (23 g), potassium carbonate (8.0 g), cupper(I) iodide (1 g), and zinc oxide (0.5 g) in N-methyl-2(3*H*)-pyrrolidinone (100 ml) was kept at 155 °C for 4.5 h. After cooling water (500 ml) was added followed by extraction with ethyl acetate (3 x 200 ml). The organic phase was washed with water and saturated calcium chloride solution and dried over magnesium sulfate. Removal of solvent *in vacuo* gave an oil which was purified by chromatography (silica gel, ethyl acetate) giving 1-(4-fluorophenyl)-3-(2-hydroxyethyl)-2(3*H*)-benzimidazolone (2 g) as a solid, mp: 124-26 °C.

The oil was dissolved in dichloromethane (60 ml) and thionyl chloride (10 ml) and dimethylformamide (0.5 ml) was added followed by reflux for 16 h. Removal of volatiles *in vacuo* gave 1-(2-chloroethyl)-3-(4-fluorophenyl)-2(3*H*)-benzimidazolone (2 g) as an oil.

The obtained chloride was treated with 1-(1,4-benzodioxan-5-yl)piperazine (2.4 g) according to the method described in EXAMPLE 2 giving the title compound as a crystalline material. Yield: 1.7 g, mp: 161-62 °C. ^{1}H NMR (δ, $CDCl_3$): 2.55-2.65 (m, 4H), 2.70 (t, 2H), 2.85-2.95 (m, 4H), 4.05 (t, 2H), 4.15-4.25 (m, 4H), 6.35-6.50 (m, 2H), 6.70 (t, 1H), 6.95-7.20 (m, 3H), 7.30 (d, 1H), 7.40 (t, 2H), 7.55-7.65 (m, 2H).

EXAMPLE 13

1-[4-[4-(1,4-Benzodioxan-5-yl)-1-piperazinyl]-1-butyl]-3-(4-fluorophenyl)-2(3*H*)-benzimidazolone, **13a**.

A solution of 1-(4-fluorophenyl)-3-(1-propen-2-yl)-2(3*H*)-benzimidazolone (prepared by arylation of 1-(1-propen-2-yl)-2(3*H*)-benzimidazolone (J. Davoll, *J. Chem. Soc.*, **1960**, 308) according to the method described in EXAMPLE 12) (5 g) in ethanol (100 ml) was treated with conc. hydrochloric acid (50 ml) at room temperature. After stirring for 1.5 h water (150 ml) was added. The resulting precipitate was collected by filtration and dried. Yield: 4 g of 1-(4-fluorophenyl)-2(3*H*)-benzimidazolone, mp: 209-10 °C.

The 4 g of product was dissolved in tetrahydrofuran (100 ml) followed by addition of potassium *tert*-butoxide (3.0 g) during 5-10 min. After stirring for 10 min 1,4-dibromobutane (15 ml) was added followed by heating to 50 °C for 5 h. After filtration and removal of solvent the remaining oil was purified by column chromatography (silica gel, heptane, heptane/ethyl acetate 1:1). The product, 1-(4-bromo-1-butyl)-3-(4-fluorophenyl)-2-imidazolidinone, (5.0 g) was obtained as an oil.

Treatment of the oil (2.5 g) with 1-(1,4-benzodioxan-5-yl)piperazine (2.5 g) according to the method described in EXAMPLE 2 gave the title compound as a crystalline material. Yield: 1.9 g, mp: 145-47 °C. ^{1}H NMR (δ, $CDCl_3$): 1.55-1.75 (m, 2H), 1.80-1.95 (m, 2H), 2.45 (t, 2H), 2.55-2.70 (m, 4H), 3.00-3.15 (m, 4H), 4.00 (t, 2H), 4.20-4.40 (m, 4H), 6.45-6.60 (m, 2H), 6.75 (t, 1H), 7.00-7.30 (m, 6H), 7.45-7.55 (m, 2H).

EXAMPLE 14

1-Cyclopentyl-3-[2-[4-(2-phenylbenzofuran-7-yl)-1-piperazinyl]ethyl]-2-imidazolidinone, oxalate, **14a**.

A mixture of **2ii** (1.1 g), 5% Pd/C, glacial acetic acid (2 ml) and ethanol (100 ml) was kept under a hydrogen atmosphere at 4 atm. of pressure for 72 h. Filtration and removal of solvent *in vacuo* gave an oil which was dissolved in ethyl acetate (15 ml). Addition of oxalic acid gave the title compound. Yield: 0.5 g, mp: 182-83

°C. ^{1}H NMR (δ, DMSO): 0.95-1.80 (m, 8H), 2.95-3.15 (m, 4H), 3.15-3.35 (m, 8H), 3.40-3.60 (m, 4H), 6.80 (d, 1H), 7.15 (t, 1H), 7.25 (d, 1H), 7.35-7.45 (m, 2H), 7.50 (t, 2H), 7.95 (d, 2H).

1-Cyclopentyl-3-[2-[4-(2,3-dihydro-3,3-dimethyl)-7-benzofuranyl)-1-piperazinyl]ethyl]-2-imidazolidinone, oxalate, **14b**, mp: 94-98 °C. ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 6H), 1.40-1.75 (m, 8H), 3.00 (t, 2H), 3.05-3.35 (m, 12H), 3.40 (t, 2H), 4.00-4.15 (m, 1H), 4.20 (s, 2H), 6.65-6.75 (m, 1H), 6.75-6.85 (m, 2H).

1-Cyclopentyl-3-[6-[4-(2,3-dihydro-3,3-dimethyl)-7-benzofuranyl)-1-piperazinyl]-1-hexyl]-2-imidazolidinone, oxalate, **14c**, mp: 128-31 °C. ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 6H), 1.20-1.75 (m, 16H), 2.95-3.10 (m, 4H), 3.15-3.40 (m, 12H), 3.95-4.10 (m, 1H), 4.20 (s, 2H), 6.65-6.75 (m, 1H), 6.75-6.90 (m, 2H).

1-Cyclohexyl-3-[3-[4-(2,3-dihydro-2,2-dimethyl)-4-benzofuranyl)-1-piperazinyl]-1-propyl]-2-imidazolidinone, oxalate, **14d**, mp: 181-83 °C. ^{1}H NMR ($CDCl_3$) δ 0.95-1.45 (m, 5H), 1.35 (s, 6H), 1.50-1.65 (m, 3H), 1.65-1.90 (m, 4H), 2.80-3.00 (m, 4H), 3.00-3.30 (m, 14H), 3.40-3.55 (m, 1H), 6.35 (d, 1H), 6.40 (d, 1H), 7.00 (t, 1H).

Pharmacology

The compounds of Formula I have been tested according to established and reliable pharmacological methods for determination of the affinity to the 5-HT_{1A} receptor and for detemination of the efficacy of the compounds with respect to said receptor. The tests were as descibed in the following.

Inhibition of ^{3}H-8-OH-DPAT Binding to Serotonin 5-HT_{1A} Receptors in Rat Brain *in vitro*.

By this method the inhibition by drugs of the binding of the 5-HT_{1A} agonist ^{3}H-8-OH-DPAT (1 nM) to 5-HT_{1A} receptors in membranes from rat brain minus cerebellum is determined *in vitro* . Accordingly, this is a test for affinity for the 5-HT_{1A} receptor. The assay was performed as described by Hyttel et al., *Drug Dev. Res.* **1988**, *15*, 389-404.

Antagonism of the Discriminative Stimulus Properties Induced by 8-OH-DPAT in Rats.

This test is used to determine the 5-HT_{1A} receptor antagonistic effect of a test compound *in vivo*. A related method is described by Tricklebank, M. D., *et al*, *Eur. J. Pharmacol*, **1987**, *133*, 47-56; Amt, J. *Pharmacology & Toxicology*, **1989**, *64*, 165.

PROCEDURE

Male Wistar rats are trained to discriminate between 8-OH-DPAT (0.4 mg/kg, i.p., 15 min pretreatment) and physiological saline in operant chambers equipped with two response levers. Between the levers a dipper is placed, where water rewards (0.1 ml) are presented. The rats are water deprived for at least 24 h and work in a fixed ratio (FR) schedule (final FR=32).

Following 8-OH-DPAT administration, responding is reinforced only on a designated (drug) lever, whereas responding on the opposite lever has no consequences. Following saline administration, responding is reinforced on the lever opposite to the drug lever. Drug and saline trials alternate randomly between days. The level of discrimination accuracy is expressed as the per cent drug responses and is calculated as the number of correct responses x100 divided by the sum of the correct and incorrect responses before the first reward. The time to the first reward is also recorded as a measure of reaction time. When stable accuracy (mean correct responding = 90%; individual rats at least 75% correct responding) is obtained test sessions are included between training days. Test compound is injected s.c. or p.o. at appropriate time before 8-OH-DPAT and the test begins 15 min after 8-OH-DPAT injection. The test trial is terminated when a total of 32 responses are made on either lever or when 20 min have elapsed. No reward is given and the rats have free access to water for 20-30 min after the test. The effects are expressed as per cent inhibition of drug responding. Only results from rats making at least 10 responses on one lever are included in data analysis. Furthermore, only test sessions in which at least half of the rats respond are included.

The per cent inhibition of drug response obtained for each dose of test compound is used to calculate ED_{50} values by log-probit analysis.

Generalization to the Discriminative Stimulus Properties Induced by 8-OH-DPAT in Rats

This test is used to determine the 5-HT_{1A} receptor agonistic effect of a test compound *in vivo.* A related method is described by Tricklebank, M. D., *supra*; Arnt, J. *Pharmacology & Toxicology*, **1989**, *64*, 165.

PROCEDURE

The procedure is the same as for the antagonism test mentioned above, except that the test compound is substituted for 8-OH-DPAT and injected s.c. usually 30 min or 45 min, respectively, before beginning of the test.

The per cent drug responce obtained for each dose of test compound is used to calculate ED_{50} values by log-probit analysis.

Inhibition of 5-MeO-DMT-Induced 5-HT Syndrome in Rats

The so-called 5-HT syndrome is a characteristic pattern of behaviours which are induced by 5-HT agonists with effects on 5-HT, possibly 5-HT_{1A} receptors (Smith, L.M. and Peroutka, S.J., *Pharmacol. Biochem. & Behaviour,* **1986**, *24*, 1513; Tricklebank, M. *et al, Eur. J. Pharmacol.* **1985**, *117*, 15). This test is a test for determining the antagonist effects of a test compound on 5-HT_{1A} receptors *in vivo* by measuring the ability to inhibit 5-MeO-DMT induced 5-HT syndrome.

PROCEDURE

Male Wistar rats (Mol:Wist) weighing 170-240 g are used. Test substance is injected s.c. before 5-MeO-DMT 5 mg/kg, s.c. Four rats are used for each dose. A control group pretreated with saline is included each test day. 10, 15 and 20 min later the rats are observed for presence of serotonin (5-HT) syndrome. The following symptoms are recorded: 1) forepaw treading ("piano playing"), 2) head weaving and 3) hindleg abduction. Furthermore, flat motility is scored. Each part of the syndrome is scored as follows: marked effect (score 2), weak syndrome (score 1) and no effect (score 0). The scores of the three observation periods are added. Thus the maximum obtainable score for four rats is 24. The effect of the test substance is expressed as percent inhibition relative to the control group.

The percent inhibition of the piano playing syndrome is used as the response and

ED_{50} value are calculated by log-probit analysis.

The test results are shown in the following Tables 1 - 3:

TABLE 1: ^{3}H 8-OH-DPAT BINDING DATA (IC_{50} values in nM)

Compound No.	IC_{50}	Compound No.	IC_{50}
1a	2.6	2ee	43
1b	7.8	2ff	6.6
1c	2.6	2gg	2.8
1d	190	2hh	130
1e	23	2ii	300
1f	1.1	2jj	1.1
2a	16	2kk	5.7
2b	18	2ll	10
2c	13	2mm	1.7
2d	17	2nn	5.4
2e	0.45	2oo	44
2f	54	2pp	20
2g	37	2qq	300
2h	28	3a	1.8
2i	30	4a	18
2j	53	4b	40
2k	15	4c	19
2l	72	5a	11
2m	12	5b	12
2n	3.2	6a	220
2o	51	7a	51000
2p	3.7	8a	3.9
2q	13	9a	230
2r	23	10a	1.2
2s	32	11a	3.5
2t	15	12a	36
2u	110	13a	22
2v	71	14a	9.7
2x	75	14b	38
2y	28	14c	7.5
2z	34	14d	22
2aa	11	Buspirone	41
2bb	0.92	Gepirone	310
2cc	83	Ipsapirone	17
2dd	0.5	Flesinoxane	4

It is seen from Table 1 that most of the compounds of the present invention bind to the 5-HT_{1A} receptor with affinities comparable to reference compounds such as buspirone, gepirone, and flesinoxane.

TABLE 2: 8-OH-DPAT CUE DATA (ED_{50} values in µmol/kg, s.c.)

Compound No.	Antagonism	Agonism
1a	>0.62	0.034
1b	NT	0.099
1c	NT	0.069
1e	>10	see note a)
1f	NT	0.052
2a	>11	3.1
2b	2.7	>11
2c	>2.6	0.76
2d	6.3	see note b)
2e	6.1	see note c)
2f	NT	40
2g	>11	1.6
2m	NT	2.3
2n	NT	0.13
2o	23	27
2p	NT	1.1
2y	1.9	NT
2bb	NT	0.036
3a	NT	0.020
5a	NT	1.8
Buspirone	NT	0.62
Gepirone	NT	0.81
Ipsapirone	NT	1.6
Flesinoxane	NT	0.38

note a): partial agonist, 30 - 75% response at 0.04 - 10 µmol/kg
note b): partial agonist, 30 - 50% response at 0.08 - 19 µmol/kg
note c): partial agonist, 20 - 60% response at 0.6 - 2.4 µmol/kg

It is seen from Table 2 that the compounds of the present invention both include agonists and antagonists as determined in the 8-OH-DPAT cue model.

TABLE 3: INHIBITION OF 5-MeO-DMT INDUCED 5-HT SYNDROME (ED_{50} values in μmol/kg, s.c.)

Compound No.	ED_{50}
1a	2.3
1b	9.5
1c	12
1e	5.1
1f	0.47
2a	6.6
2b	8.9
2c	15
2d	10
2e	4.7
2f	28
2g	10
2o	9.0
2p	4.2
2y	2.7
2bb	0.78
3a	5.2
5a	12
Buspirone	4.3
Gepirone	32
Ipsapirone	26
Flesinoxane	>44

It is seen from Table 3 that the compounds of the present invention are antagonists in the 5-MeO-DMT inhibition test.

Furthermore, the compounds of the invention were tested with respect to affinity for the α_1 adrenoceptors and for the dopamine D_2 receptor by determining their ability to inhibit the binding of ^{3}H-prazosin to α_1 adrenoceptors (Hyttel, J. *et al*, *J. Neurochem.*, **1985**, *44*, 1615; Skarsfeldt, T. *et al*, *Eur. J. Pharmacol.*, **1986**, *125*, 323) and the binding of ^{3}H-spiroperidol to D_2 receptors (Hyttel *et al*, *J. Neurochem.*, **1985**, *44*, 1615).

Some of the compounds of the present invention showed high selectivity for the 5-

HT_{1A} receptor, while other compounds of the invention showed mixed binding profiles. A certain class of compounds within this invention showed high affinity to both 5-HT_{1A} receptors and D_2 receptors. All the mentioned types of compounds are beneficial in the treatments of various diseases.

It is seen from the above tables 1, 2 and 3 that the present compounds have high affinities for the 5-HT_{1A} receptor. Furthermore, it is seen that this series comprises compounds showing effects as partial agonists with medium to low efficacies. In particular, it is noted that some of the compounds show antagonistic effects in the 5-MeO-DMT test and very low efficacies in the 8-OH-DPAT cue test. Furthermore, some of the compounds show both high affinity to 5-HT_{1A} and dopamine D_2 receptors and show high efficacy effects in the 8-OH-DPAT cue test.

Formulation Examples

The pharmaceutical formulations of the invention may be prepared by conventional methods in the art.

For example: Tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a conventional tabletting machine. Examples of adjuvants or diluents comprise: corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvants or additives usually used for such purposes such as colourings, flavourings, preservatives etc. may be used provided that they are compatible with the active ingredients.

Solutions for injections may be prepared by dissolving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to desired volume, sterilization of the solution and filling in suitable ampules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

Typical examples of recipes for the formulation of the invention are as follows:

1) Tablets containing 5.0 mg of Compound **1a** calculated as the free base:

Compound 1a	5.0 mg
Lactose	60 mg
Maize starch	30 mg
Hydroxypropylcellulose	2.4 mg
Microcrystalline cellulose	19.2 mg
Croscarmellose Sodium Type A	2.4 mg
Magnesium stearate	0.84 mg

2) Tablets containing 0.5 mg of Compound **1f** calculated as the free base:

Compound **1f**	0.5 mg
Lactose	46.9 mg
Maize starch	23.5 mg
Povidone	1.8 mg
Microcrystalline cellulose	14.4 mg
Croscarmellose Sodium Type A	1.8 mg
Magnesium stearate	0.63 mg

3) Syrup containing per millilitre:

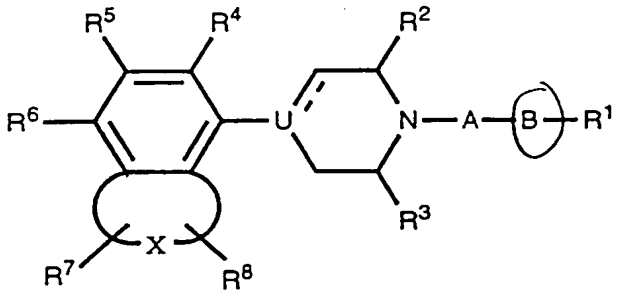
Compound **2bb**	2.5 mg
Sorbitol	500 mg
Hydroxypropylcellulose	15 mg
Glycerol	50 mg
Methyl-paraben	1 mg
Propyl-paraben	0.1 mg
Ethanol	0.005 ml
Flavour	0.05 mg
Saccharin natrium	0.5 mg
Water	ad 1 ml

4) Solution for injection containing per millilitre:

Compound **2e**	0.5 mg
Sorbitol	5.1 mg
Acetic acid	0.08 mg
Water for injection	ad 1 ml

CLAIMS

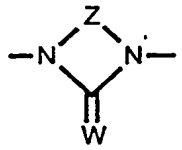
1. A fused benzo compound characterised in that it is a compound of the general Formula I



I

wherein A is a 2 to 6 membered spacer group selected from alkylene, alkenylene, and alkynylene each of which may be branched or straight chain, or a 3-7 membered cycloalkylene group, said spacer group being optionally substituted with aryl or hydroxy;

B is a polar divalent group selected from SO, SO_2, and a group of Formula II,

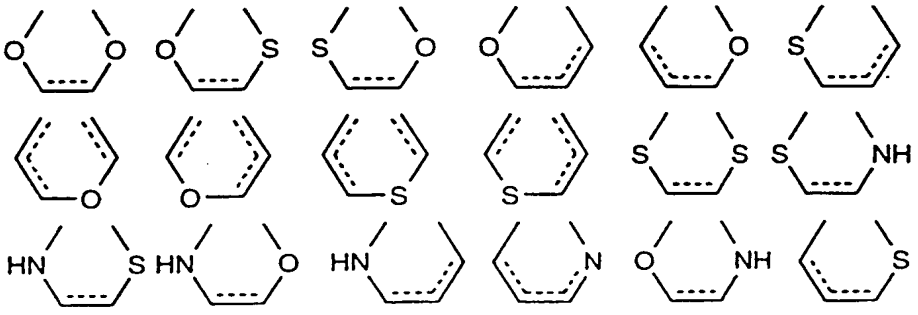


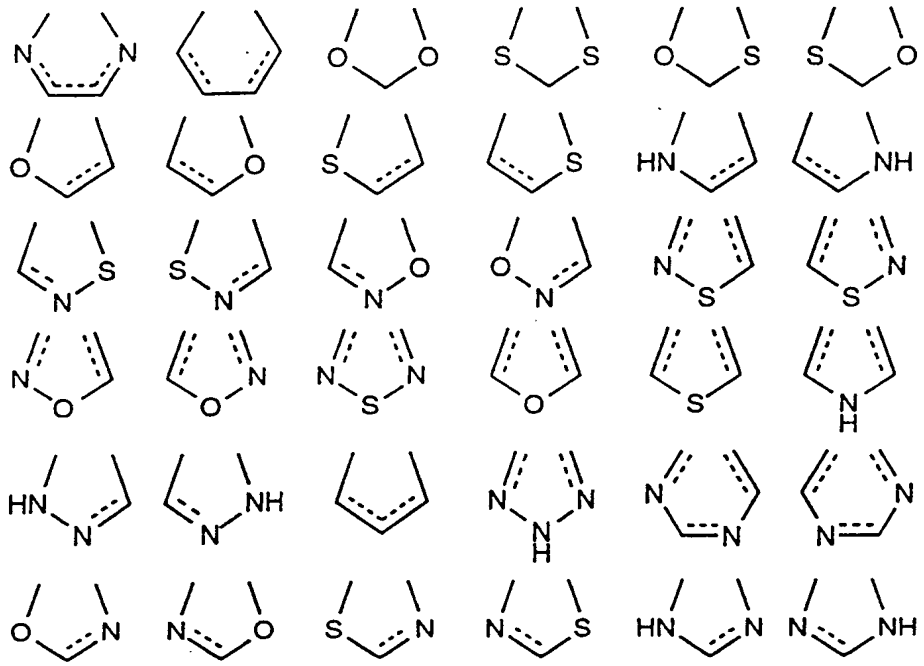
II

wherein W is O or S, and Z is selected from $-(CH_2)_n-$ n being 2 or 3, –CH=CH–, $-COCH_2-$, $-CSCH_2-$, or 1,2-phenylene optionally substituted with halogen or trifluoromethyl;

U is N or CH; the dotted line designates an optional bond, and if it designates a bond U is C;

X is selected from the group of divalent 3 – 4 membered groups consisting of





wherein the dotted lines indicate optional bonds; thereby forming a carbocyclic or heterocyclic ring fused with the benzene ring ;

R^1 is alkyl, alkenyl, cycloalk(en)yl, aryl, cycloalk(en)ylalk(en/yn)yl, arylalkyl, diphenylalkyl, any alkylgroup optionally being substituted with one or two hydroxy groups, with the proviso that if Z is 1,2-phenylene and U is N, then R^1 is selected from aryl and substituted aryl;

R^2 and R^3 are independently hydrogen, lower alkyl or they may be linked together, thereby forming an ethylene or propylene bridge;

R^4, R^5, and R^6 are independently selected from the group consisting of hydrogen, halogen, lower alkyl, lower alkoxy, hydroxy, lower alkylthio, lower alkylamino or di-lower-alkylamino, cyano, nitro, trifluoromethyl and trifluoromethylthio;

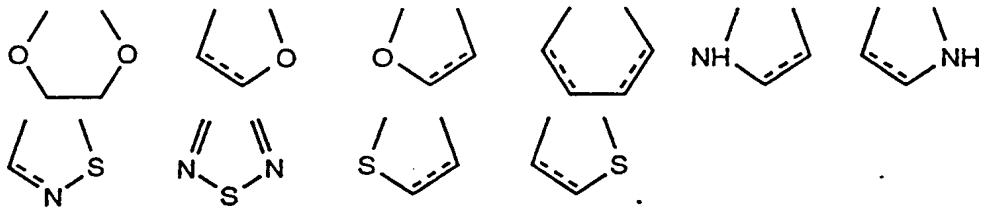
R^7 and R^8 are independently selected from the group consisting of hydrogen, halogen, trifluoromethyl, lower alkyl, lower alkyl substituted with one or more hydroxy groups, aryl, cyano, a group $-COOR^9$ and a group $-CONR^{10}R^{11}$, R^9, R^{10}, and R^{11} being hydrogen or lower alkyl; any aryl group present being optionally substituted with one or more substituents selected from halogen, lower alkyl, lower alkoxy, hydroxy, lower alkylthio, lower alkylsulfonyl, lower alkyl- or dialkylamino, cyano, trifluoromethyl, or trifluoromethylthio;

and pharmaceutically acceptable acid addition salts thereof.

2. A compound according to Claim 1, **characterised in** that A is a 2 to 6 membered alkylene group.

3. A compound according to Claim 1, **characterised in** that B is SO, SO_2 or a group of Formula II, as defined in Claim 1 wherein W is O and Z is selected from $-(CH_2)_n-$ n being 2 or 3, –CH=CH– and 1,2-phenylene optionally substituted with halogen or trifluoromethyl.

4. A compound according to Claim 1, **characterised in** that X is selected from the group of divalent 3 – 4 membered groups consisting of



5. A compound according to Claim 1, **characterised in** that R^1 is lower alkyl, aryl, cycloalkyl or aryl-lower alkyl.

6. A compound according to Claim 5, **characterised in** that R^1 is lower alkyl, phenyl, phenyl substituted with one of the substituents as defined in Claim 1, C_5-C_6 cycloalkyl, adamantyl, phenyl-lower alkyl optionally substituted with one of the substituents as defined in Claim 1 or naphthyl.

7. A compound according to Claim 1, **characterised in** that R^2 and R^3 are both hydrogen.

8. A compound according to Claim 1, **characterised in** that R^4, R^5, and R^6 are each selected from the group consisting of hydrogen and halogen.

9. A compound according to Claim 1, **characterised in** that R^7 and R^8 independently selected from the group consisting of hydrogen, lower alkyl, aryl, a group $-COOR^9$, R^9 being hydrogen or lower alkyl and a group $-CONH_2$.

10. A compound according to Claim 9, **characterised in** that R^7 and R^8 are independently selected from the group consisting of hydrogen, lower alkyl, phenyl optionally substituted with one of the substituents as defined in Claim 1, a group $-COOR^9$ R^9 being hydrogen or lower alkyl and a group $-CONH_2$.

11. A pharmaceutical composition **characterised in** that it comprises at least one novel fused benzoderivative according to any of Claims 1-10 or a pharmaceutically acceptable acid addition salt thereof in a therapeutically effective amount and in combination with one or more pharmaceutically acceptable carriers or diluents.

12. Use of a fused benzoderivative according to Claim 1 or an acid addition salt thereof for the manufacture of a pharmaceutical preparation for the treatment of anxiety disorders, depression, psychosis, impulse control disorders, alcohol abuse, ischaemic diseases, cardiovascular disorders, side effects induced by conventional antipsychotic agents and senile dementia.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 93/00414

A. CLASSIFICATION OF SUBJECT MATTER

IPC5: C07D 319/18, C07D 307/18, C07D 405/12, C07D 405/14, C07D 417/12, C07D 401/12, C07D 233/36, C07D 409/12, A61K 31/495, A61K 31/54

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	EP, A1, 0526434 (BOEHRINGER INGELHEIM ITALIA S.P.A.), 3 February 1993 (03.02.93), see especially compound 20, 22 and 29 --	1-12
A	EP, A1, 0343050 (SYNTHELABO), 23 November 1989 (23.11.89), see the whole document --	1-12
A	Chemical Abstracts, Volume 116, No. 25, 22 June 1992 (22.06.92), (Columbus, Ohio, USA), Boddeke Hendrikus W.G.M. et al: "Agonist/antagonist interactions with cloned human 5-HT1A receptors: variations in intrinsic activity studied in transfected HeLa cells", THE ABSTRACT No 249160s, Naunyn-Schmiedeberg's Arch. Pharmacol. 1992, 345(3), 257-63, see reg.number 141533-35-9 --	1-12

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" erlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 February 1994	11-03-1994
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 93/00414

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Chemical Abstracts, Volume 109, No. 15, 10 October 1988 (10.10.88), (Columbus, Ohio, USA), Glennon Richard A. et al: "Arylpiperazine derivatives as high-affinity 5-HT1A serotonin ligands", THE ABSTRACT No 128953z, J. Med. Chem. 1988, 31(10), 1968-71, see reg.numbers 115 338-25-5 and 115 338-33-5	1-12
	--	
A	GB, A, 1456253 (BOEHRINGER INGELHEIM GMBH), 24 November 1976 (24.11.76), see especially compound 41 and 61	1-12
	--	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 93/00414

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-2
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claims 1-2 are so broadly formulated, including long lists of variable substituents, that a complete search is impossible. The search has thus been confined to the scope covered by synthesized examples.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

28/01/94

International application No.
PCT/DK 93/00414

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A1- 0526434	03/02/93	AU-A- 2427592	02/03/93
		WO-A- 9303016	18/02/93
EP-A1- 0343050	23/11/89	SE-T3- 0343050	
		AU-B- 614135	22/08/91
		AU-A- 3484389	23/11/89
		DE-U- 6890368	14/01/93
		FR-A,B- 2631625	24/11/89
		JP-A- 2138266	28/05/90
		US-A- 4950670	21/08/90
GB-A- 1456253	24/11/76	AT-B- 338271	10/08/77
		AT-A,B- 338801	12/09/77
		AT-A,B- 338802	12/09/77
		AT-A,B- 338803	12/09/77
		AT-A,B- 338804	12/09/77
		AT-A,B- 338805	12/09/77
		AT-A,B- 338806	12/09/77
		AT-A,B- 338807	12/09/77
		AT-A,B- 338808	12/09/77
		AT-B- 339320	10/10/77
		AU-A- 6397773	03/07/75
		BE-A- 809041	21/06/74
		CH-A- 605872	13/10/78
		CH-A- 616667	15/04/80
		CH-A- 616668	15/04/80
		CH-A- 616669	15/04/80
		CH-A- 616670	15/04/80
		CH-A- 616673	15/04/80
		CH-A- 616674	15/04/80
		CH-A- 616675	15/04/80
		CH-A- 616676	15/04/80
		CH-A- 616677	15/04/80
		DE-A- 2263211	04/07/74
		FR-A,B- 2211252	19/07/74
		JP-A- 49094688	09/09/74
		JP-A- 59076067	28/04/84
		JP-A- 59076070	28/04/84
		JP-A- 59076074	28/04/84
		LU-A- 69064	20/08/75
		NL-A- 7317469	25/06/74
		SE-B,C- 417516	23/03/81
		US-A- 3941789	02/03/76
		US-A- 4000274	28/12/76
		US-A- 4038279	26/07/77
		US-A- 4100282	11/07/78
		US-A- 4136185	23/01/79

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Numéro de publication : **0 490 772 A1**

(12) **DEMANDE DE BREVET EUROPEEN**

(21) Numéro de dépôt : **91403378.2**

(22) Date de dépôt : **13.12.91**

(51) Int. Cl.[5] : **C07D 319/18**, C07D 321/10, C07D 307/79, A61K 31/495

(30) Priorité : **14.12.90 FR 9015631**

(43) Date de publication de la demande : **17.06.92 Bulletin 92/25**

(84) Etats contractants désignés : **AT BE CH DE DK ES FR GB GR IT LI LU NL SE**

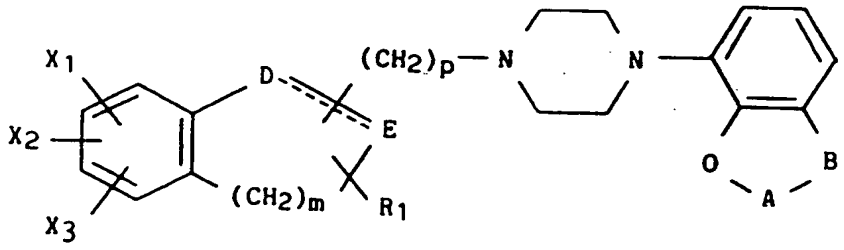
(71) Demandeur : **ADIR ET COMPAGNIE**
1 rue Carle Hébert
F-92415 Courbevoie Cédex (FR)

(72) Inventeur : **Peglion, Jean-Louis**
5 Allée des Bégonias
F-78110 Le Vesinet (FR)
Inventeur : **Millan, Mark**
179 Bld. Malesherbes
F-75017 Paris (FR)
Inventeur : **Rivet, Jean-Michel**
160 Rue de la Source
F-92000 Nanterre (FR)

(74) Mandataire : **Reverbori, Marcelle**
Adir et Compagnie, 1, rue Carle Hébert
F-92415 Courbevoie Cédex (FR)

(54) **Piperazines 1,4-disubstiuées, leur procédé de préparation et les compositions pharmaceutiques les renfermant.**

(57) Nouvelles pipérazines 1,4-disubsituées, utilisables comme médicament et répondant à la formule :



dans laquelle :

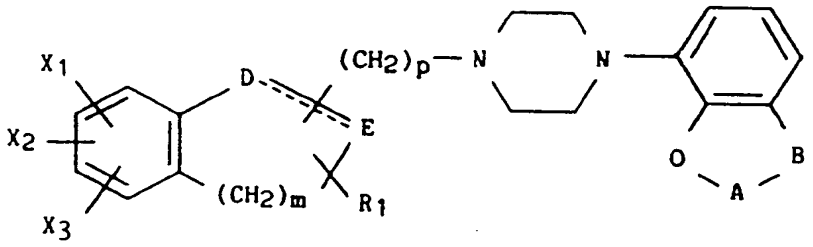
X_1, X_2, X_3, R_1, $\overline{\overline{\quad}}$ E -,
m, p et -A-B- ont les significations définies dans la description,
sous formes racémiques et optiquement actives ;
Ces dérivés et leurs sels physiologiquement tolérables peuvent être utilisés en thérapeutique notamment dans le traitement des maladies du système nerveux central et des maladies neuroendocriniennes.

EP 0 490 772 A1

5HT$_{1A}$ antagonist p1
+
app is agonist

La présente invention a pour objet de nouvelles pipérazines 1,4-disubstituées, leur procédé de préparation et les compositions pharmaceutiques les renfermant.

Elle concerne particulièrement les pipérazines 1,4-disubstituées de formule générale I :

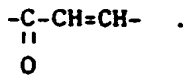


(I)

dans laquelle :

- X_1, X_2 et X_3 :
  - identiques ou différents, représentent chacun : un atome d'hydrogène ou d'halogène, un radical alkyle en chaine droite ou ramifiée contenant de 1 à 5 atomes de carbone, un radical hydroxy, un radical alcoxy ou alkylthio contenant chacun de 1 à 5 atomes de carbone en chaine droite ou ramifiée, un radical trifluorométhyle, un radical nitro, un radical amino, ou un radical acétamido, ou
  - deux d'entre eux pris en position adjacente forment ensemble un radical méthylènedioxy ou un radical éthylènedioxy ;
- R_1 représente un atome d'hydrogène ou un radical alkyle en chaine droite ou ramifiée contenant de 1 à 5 atomes de carbone ;
- -D ⩬ E- représente : $-(CH_2)_n-(CH_2)-$ ou -CH=CH-
- m et n représentent chacun les valeurs zéro, un, deux ou trois à condition que m + n soit ≧ 1.
- p représente zéro ou un nombre entier de 1 à 6, et
- -A-B- représente un des radicaux de formule :

$-(CH_2)_2-O-$; $-(CH_2)_3-O-$; -CH=CH- ; $-CH_2-CH_2-$ et



.

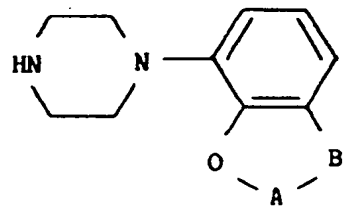
Certains dérivés de formule générale I renferment un atome de carbone asymétrique et de ce fait peuvent être dédoublés en isomères optiques lesquels sont également inclus dans la présente invention.

L'état antérieur de la technique dans ce domaine est illustré notamment par les demandes de brevet européen publiées sous les N° 138.280 ; 185.429 ; 189.612 ; 307.061 et 376.607.

Aucune de ces demandes ne décrit ni suggère les dérivés objet de la présente invention, lesquels dérivés ont une activité pharmacologique du type antagoniste 5 HT_1 A, ce qui n'est pas le cas des dérivés de l'état antérieur de la technique ci-dessus cité.

La présente invention a également pour objet le procédé de préparation des dérivés de formule générale I, caractérisé en ce que l'on condense :

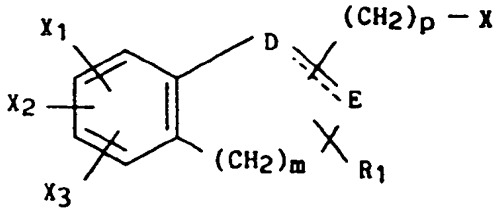
- une pipérazine N-monosubstituée de formule générale II :



(II)

dans laquelle le groupe -A-B- a la signification précédemment définie, avec :

- un dérivé de formule générale III :



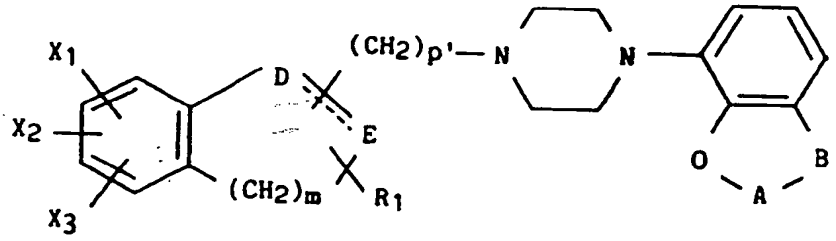
(III)

dans laquelle

– X_1, X_2, X_3, R_1, -D ⩵ E -, m et p ont les significations précédemment définies
et
– X représente un atome d'halogène, ou un radical mésyloxy ou tosyloxy.

La condensation s'effectue de façon particulièrement adéquate en opérant dans un solvant approprié tel que , par exemple, la méthyléthylcétone, la méthylisobutylcétone, le toluène, ou le diméthylformamide en présence d'un accepteur de l'acide formé au cours de la réaction, à une température de 20 à 150°C. Comme accepteur, on peut employer par exemple un carbonate de métaux alcalins comme le carbonate de sodium ou une amine tertiaire comme la triéthylamine.

De plus, les dérivés de formule générale I dans laquelle p prend les significations autre que zéro, c'est à dire les dérivés répondant plus précisément à la formule générale I' :



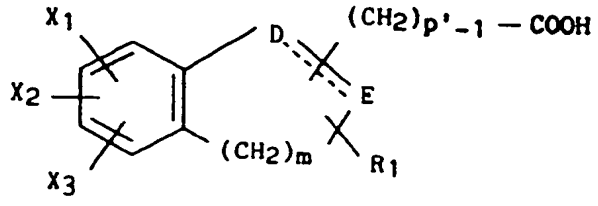
(I')

dans laquelle :

– X_1, X_2, X_3, R_1, - D ⩵ E - , m et -A-B- ont les significations précédemment définies et
– p' représente un nombre entier de 1 à 6, ont également été préparés selon une variante du procédé précédent caractérisée en ce que :

l'on condense :

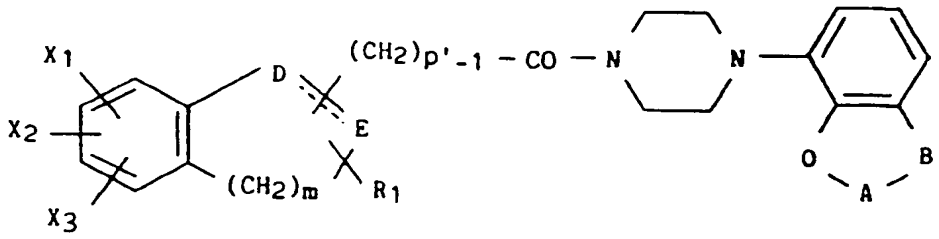
– la pipérazine N-monosubstituée de formule générale II précédemment définie, avec
– un dérivé de formule générale IV :



(IV)

dans laquelle :

– X_1, X_2, X_3, R_1, - D ⩵ E - , m et p' ont les significations précédemment définies ; et
– l'on réduit l'amide ainsi obtenue de formule générale V :



(V)

dans laquelle :

- X_1, X_2, X_3, R_1, - D ⎯ E - , m, p' et -A-B- ont les significations précédemment définies .

La condensation des dérivés II et IV s'effectue de façon particulièrement adéquate en opérant dans un solvant approprié comme par exemple le chlorure de méthylène, en présence de carbonyldiimidazole.

La réduction de l'amide V s'effectue avantageusement au moyen d'un hydrure double de lithium-aluminium dans un solvant adéquat comme par exemple l'éther ou le tétrahydrofurane.

Ce dernier procédé de préparation des dérivés I' est également inclus dans la présente invention.

De plus, les amides de formule générale V sont des produits intermédiaires nouveaux qui font, à ce titre, partie de la présente invention.

Les matières premières de formules II, III et IV sont soit des produits connus, soit des produits préparés à partir de composés connus selon des procédés connus, comme précisé dans les exemples ci-après.

Les dérivés de formule générale I donnent des sels avec les acides physiologiquement tolérables. Ces sels sont également inclus dans la présente invention.

Les dérivés de la présente invention possèdent des propriétés pharmacologiques et thérapeutiques intéressantes. En effet, les essais pharmacologiques ont démontré que les composés de l'invention se comportent, in vitro et in vivo, comme des ligands très puissants et très sélectifs des récepteurs de la sérotonine $5HT_{1A}$ avec une activité antagoniste de ce neurotransmetteur au niveau du système nerveux central, démontrée par l'étude pharmacologique ci-après exemplifiée.

Cette activité permet l'utilisation des dérivés de la présente invention dans le traitement des maladies du système nerveux central, notamment de l'anxiété, la douleur, la dépression, la psychose, la schizophrénie, la migraine, les troubles de la cognition, le stress et l'anorexie et des maladies neuroendocriniennes comme le diabète.

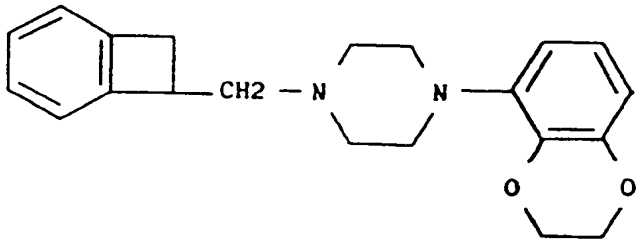
La présente invention a également pour objet les compositions pharmaceutiques contenant comme principe actif un dérivé de formule générale I ou un de ses sels physiologiquement tolérables, mélangé ou associé à un excipient pharmaceutique approprié, comme par exemple, le glucose, le lactose, le talc, l'éthylcellulose, le stéarate de magnésium ou le beurre de cacao.

Les compositions pharmaceutiques ainsi obtenues se présentent généralement sous forme dosée et peuvent contenir de 0,1 à 100 mg de principe actif. Elles peuvent revêtir, par exemple, la forme de comprimés, dragées, gélules, suppositoires, solutions injectables ou buvables et être selon les cas, administrées par voie orale, rectale ou parentérale à la dose de 0,1 à 100 mg de principe actif 1 à 3 fois par jour.

Les exemples suivants illustrent la présente invention, les points de fusion étant déterminés à la platine chauffante de Kofler (K) éventuellement sous microscope (M.K).

Exemple 1 :

4-(Benzodioxan-5-yl)-1-[(benzocyclobutan-1-yl)méthyl]-pipérazine (R,S) :



On mélange 4 g ($16,4.10^{-3}$ mole) d'iodure de (benzocyclobutan-1-yl)méthyle, 3,61 g ($16,4.10^{-3}$ mole) de N-(benzodioxan-5-yl)- piperazine, 6,95 g ($65,5.10^{-3}$ mole) de Na_2CO_3 et 100 ml de méthylisobutylcétone ; et chauffe le tout à reflux que l'on maintient pendant 24 heures sous agitation. On concentre le mélange réactionnel à l'évaporateur rotatif, reprend le concentrat par CH_2Cl_2. Après lavage à l'eau, on extrait la phase organique avec une solution normale d'acide chlorhydrique. On alcalinise la phase aqueuse puis l'extrait au CH_2Cl_2. Après séchage et concentration on obtient 4,4 g d'une huile que l'on cristallise dans l'éther. Le solide obtenu est recristallisé dans 15 ml d'éther isopropylique. On obtient 1,6 g de 4-(benzodioxan-5-yl)-1-[(benzocyclobutan-1-yl)méthyl] pipérazine (R,S), P.F.(M.K) : 91-95°C, Rendement : 29 %, qui a été chromatographié sur couche mince (solvants : chlorure de méthylène-méthanol 90-10).

- RMN (solvant : $CDCl_3$)

4H (m) 7,3-7,0 ppm ; 1H (t) 6,8 ppm ; 2H (m) 6,6 ppm ; 4H (m) 4,3 ppm ;
1H (m) 3,7 ppm ; 1H (dd) 3,4 ppm ; 4H (m) 3,10 ppm ; 2H (m) 2,85 ppm ;
4H (m) 2,7 ppm ; 1H (dd) 2,65 ppm.

La N-(benzodioxan-5-yl)-pipérazine de départ a été préparée selon la méthode décrite dans J. Med. Chem (1988) 31, 1934, à partir du 1-nitro-2,3-dihydroxybenzène, lui-même décrit dans J.A.C.S (1953), 3277.

De la même façon, ont été préparés les dérivés objets des exemples 2 à 5.

Exemples 2-5 :

2) La 4-(benzodioxan-5-yl)-1[2-(benzocyclobutan-1-yl)éthyl]pipérazine (R,S) et son dichlorhydrate P.F. (M.K) : 215-226°c (avec sublimation à partir de 192°C) (Rendement : 56 %), à partir du bromure de 2-(benzocyclobutan-1-yl)éthyle (lui-même préparé à partir de l'alcool correspondant comme décrit dans la demande de brevet français déposée le 7 novembre 1989 sous le n° 89.14571) et de la N-(benzodioxan-5-yl) pipérazine, en présence de Na_2CO_3 par chauffage à reflux dans la méthylisobutylcétone pendant 8 heures.

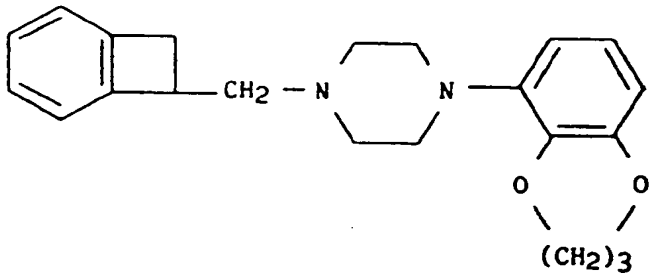
3) La 4-[benzo(1,5)dioxépin-6-yl]-1-[2-(benzocyclobutan-1-yl) éthyl] pipérazine (R,S) et son chlorhydrate, P.F. (M.K) : 170-210°C (avec sublimation), Rendement : 51 %, à partir du bromure de 2-(benzocyclobutan-1-yl)éthyle et de la N-(benzo(1,5)dioxépin-6-yl)pipérazine, elle-même décrite dans J. med. Chem. (1988) 31, 1934.

4) La 4-(benzofuran-7-yl)-1-[2-(benzocyclobutan-1-yl)éthyl] pipérazine (R,S), et son chlorhydrate P.F. (M.K) : 192-195 °C (isopropanol) (Rendement : 47%), à partir du bromure de 2-(benzocyclobutan-1-yl) éthyle et de la N-(benzofuran-7-yl) pipérazine, elle-même préparée, avec un rendement de 49 %, selon la méthode décrite dans J. med. Chem (1988) 31, 1934 à partir du chlorhydrate de di-(2-chloroéthyl)amine et du chlorhydrate de 7-aminobenzofurane lui-même obtenu par réduction du 7-nitrobenzofurane.
Ce dernier a été préparé à partir du 2-éthoxycarbonyl-7-nitrobenzofurane lui-même obtenu à partir du 2-hydroxy-3-nitro benzaldéhyde lui-même formé par nitration du 2- hydroxybenzaldéhyde.

5) La 4-(benzodioxan-5-yl)-1-[2-(3-chlorobenzocyclobutan-1-yl)éthyl] pipérazine (R,S) et son dichlorhydrate P.F.(M.K) : 207-211 °C (cyanure de méthyle) à partir du bromure de 2-(3-chlorobenzocyclobutan-1-yl) éthyle (huile $Eb/_{0,1}$ mmHg : 80 °C) et de la N-(benzodioxan-5-yl) pipérazine (Rendement : 54 %).
Le bromure de 2-(3-chlorobenzocyclobutan-1-yl)éthyle a été préparé à partir de l'acide (3-chlorobenzocyclobutan-1-yl) carboxylique, qui, traité par $LiAlH_4$ puis le chlorure de tosyle, donne le tosylate de (3-chlorobenzocyclobutan-1-yl)méthyle P.F (K) : 60-62 °C (Rendement : 84 %), lequel traité par le cyanure de sodium dans le diméthylsulfoxyde, puis par l'hydroxyde de potassium dans une solution aqueuse d'éthanol et enfin réduit en acide (3-chlorobenzocyclobutan-1-yl) méthyl carboxylique, P.F (K) : 94-96 °C, lequel est alors traité par $LiAlH_4$ puis PBr_3 dans le benzène pour donner le bromure attendu, avec un rendement de 41 %.

Exemple 6 :

4-[Benzo(1,5)dioxépin-6-yl]-1-[(benzocyclobutan-1-yl)méthyl] pipérazine (R,S) :



On mélange 4 g ($13,8.10^{-3}$ mole) de tosylate de (benzocyclobutan-1-yl)méthyle, 3,3 g ($13,8.10^{-3}$ mole) de N-benzo(1,5)dioxépin-6-yl)pipérazine, 3,9 ml ($27,6.10^{-3}$ mole) de triéthylamine et 50 ml de toluène ; et chauffe le tout à reflux que l'on maintient pendant 24 heures. On concentre le mélange réactionnel à l'évaporateur rotatif et reprend le concentrat par H_2O et CH_2Cl_2. On extrait la phase organique avec une solution normale d'acide chlorhydrique. On alcalinise la phase aqueuse puis l'extrait au CH_2Cl_2. Après séchage, on obtient 2,1 g d'un solide que l'on dissout dans 20 ml d'éthanol. A cette solution éthanolique on ajoute 1,7 ml d'éther chlorhydrique 3,5 N et abandonne le tout au réfrigérateur pendant 48 heures. Le précipité formé est filtré, séché. On recueille 2 g de chlorhydrate de 4-[benzo(1,5)dioxépine-6-yl]-1-[(benzocyclobutan-1-yl)méthyl] pipérazine (R,S), P.F. (M.K) : 248-252°C (avec sublimation à partir de 190°C), Rendement : 37 %, qui a été chromatographié sur couche mince (solvants : chlorure de méthylène-méthanol, 95-5).
De la même façon ont été préparés les dérivés objets des exemples 7 à 10.

Exemple 7-10 :

7) La 4-(benzodioxan-5-yl)-1-(indan-2-yl)pipérazine, P.F. (M.K.) : 168-171°C, à partir du tosylate d'indan-2-yle [cf. Bull. Soc. Chem. (1962) p 51] et de N-(benzodioxan-5-yl)pipérazine. (Rendement : 11 %).

8) La 4-(benzodioxan-5-yl)-1-[4-(benzocyclobutan-1-yl)butyl] pipérazine (R,S) et son fumarate P.F (M.K) : 180-183 °C (éthanol), à partir du mésylate de 4-(benzocyclobutan-1-yl)butyle (huile) et du dichlorhydrate de N-(benzodioxan-5-yl)pipérazine. (Rendement : 44 %).

Le mésylate de 4-(benzocyclobutan-1-yl) butyle a lui-même été préparé, avec un rendement de 96 %, en traitant le 4-(benzocyclobutan-1-yl)butanol (huile) par CH_3SO_2Cl en présence de triéthylamine dans le chlorure de méthylène.

9) La 4-[benzo(1,5)dioxépin-6-yl]-1-(indan-2-yl)pipérazine, P.F (M.K) : 138-140 °C, à partir du tosylate d'indan-2 yle et de N-[benzo(1,5)dioxépin-6-yl] pipérazine [cf. J. Med. Chem. (1988) p 1935] (Rendement : 20 %).

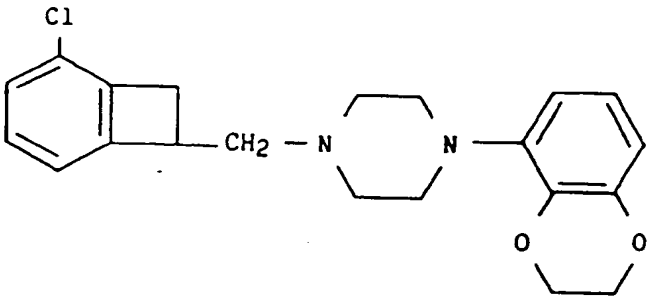
10) La 4-(coumarin-8-yl)-1-(indan-2-yl)pipérazine, P.F (M.K) : 162-163 °C (acétonitrile) à partir du tosylate d'indan-2 yle et de N-(coumarin-8-yl) pipérazine P.F (K)>260 °C (sublimation). Rendement : 28 %.

La N-(coumarin-8-yl) pipérazine a été préparée en faisant réagir la 8-amino coumarine avec un excès de chlorhydrate de bis (2-chloroéthyl) amine en présence de carbonate de potassium puis d'iodure de potassium, en opérant à reflux dans le chlorobenzène.

La 8-aminocoumarine a été obtenue à partir du dérivé nitré correspondant selon Archiv. der Parmazie, (1963), 296 (6), 365-369 ;
lequel dérivé nitré a lui-même été préparé à partir de l'o-hydroxybenzaldéhyde, selon Fort. Hase Papers (1975), 6 (2), 109-118.

Exemple 11 :

4-(Benzodioxan-5-yl)-1-[(3-chlorobenzocyclobutan-1-yl)méthyl] pipérazine (R,S)



a) première étape :

A 0,1 mole d'acide (3-chlorobenzocyclobutan-1-yl) carboxylique dans 200 ml de chlorure de méthylène on ajoute en une fois, sous atmosphère d'azote, 0,1 mole de N,N-carbonyldiimidazole, et on laisse en contact pendant 2 heures. On ajoute ensuite, en un goutte à goutte rapide, 0,1 mole de N-(benzodioxan-5-yl)pipérazine en solution dans 50 ml de chlorure de méthylène. On laisse en contact sous agitation durant une nuit. Puis on évapore, reprend le résidu à l'éther, extrait la phase organique avec une solution normale d'acide chlorhydrique, puis alcalinise les phases aqueuses à froid.

Après évaporation et chromatographie de l'huile résiduelle (solvants : chlorure de méthylène-acétate d'éthyle, 90-10), on obtient la 4-(benzodioxan-5-yl)-1-[(3-chlorobenzocyclobutan-1-yl)carbonyl] pipérazine (R,S), P.F. (K) : 182-184°C, Rendement : 40 %.

- RMN (solvant : $CDCl_3$) :

3H, 7,25 et 7,05 ppm (m) ; 1H, 6,8 ppm (t) ; 2H 6,7 à 6,5 ppm (d) ;
1H, 4,5 ppm (m) ; 4H, 4,25 à 4 ppm (m) ; 4H, 3,85 ppm ;
2H, 3,65 et 3,45 ppm (dd) ; 4H, 3,05 ppm (t+t).

L'acide (3-chlorobenzocyclobutan-1-yl)carboxylique de départ a été préparé, comme décrit dans la demande de brevet européen déposée par la demanderesse sous le n° 90.403145.7, à partir du 3-chloro-1-cyanobenzocyclobutane lui-même décrit dans le brevet européen 119.107.

b) deuxième étape

A une suspension de 0,1 mole d'hydrure de lithium aluminium dans 50 ml de tétrahydrofurane, on coule goutte à goutte, sous atmosphère d'azote, 0,1 mole de 4-(benzodioxan-5-yl)-1-[(3-chlorobenzocyclobutan-1-yl)carbonyl] pipérazine (R,S), préparée comme ci-dessus décrit, dans 100 ml de tétrahydrofurane. On laisse, une nuit, sous agitation, à température ambiante. On décompose, au bain de glace, par H_2O : 2,6 ml, NaOH à 20 % : 2,1 ml et H_2O : 9,5 ml.

On filtre le précipité, évapore le filtrat. On chromatographie l'huile résiduelle sur silice fine en éluant avec le système : CH_2Cl_2-CH_3OH (95-5) pour obtenir la 4-(benzodioxan-5-yl)-1-[(3-chlorobenzocyclobutan-1-yl)méthyl] pipérazine (R,S), avec un rendement de 72 %.

- RMN (solvant : $CDCl_3$) :

3H, 7,2 à 6,95 ppm (m) ; 1H, 6,8 ppm (t) ; 2H, 6,55 ppm (m) ;
4H, 4,25 ppm (m) ; 1H, 3,7 ppm (m) ; 2H, 3,5 à 3,25 ppm (m) ;
4H, 3,1 ppm (m) ; 6H, 3 à 2,7 ppm (m).

Une solution de 0,05 mole de la base ainsi obtenue dans 20 ml d'éther est maintenue sous agitation pendant 15 minutes avec 10 ml d'acide chlorhydrique normal. Puis on filtre, rince à l'éther et recristallise de l'eau le chlorhydrate de 4-(benzodioxan-5-yl)-1-[(3-chlorobenzocyclobutan-1-yl)méthyl] pipérazine (R,S), P.F. (K) : > 260°C avec sublimation. (Rendement : 30 %).

Exemples 12 à 29 :

En opérant comme décrit dans l'exemple 11, ont été préparés les dérivés objets des exemples ci-après :

12) La 4-(benzodioxan-5-yl)-1-[(3-fluorobenzocyclobutan-1-yl)méthyl] pipérazine (R,S) et son chlorhydrate

P.F. (K) : 254-256°C avec sublimation, par réduction de la 4(benzodioxan-5-yl)-1-[(3-fluorobenzocyclobutan-1-yl)carbonyl] pipérazine (R,S), (Rendement : 48 %), elle-même préparée avec un rendement de 40 %, à partir de l'acide (3-fluorobenzocyclobutan-1-yl)carboxylique [lui-même préparé selon la méthode décrite dans Tetrahedron (1974), 30, 1053, à partir de la 3-fluorobenzaldéhyde] et de la N-(benzodioxan-5-yl)pipérazine.

13) La 4-(benzodioxan-5-yl)-1-[3-(benzocyclobutan-1-yl)propyl] pipérazine (R,S) et son chlorhydrate P.F. (K) : 206-208°C, par réduction de la 4-(benzodioxan-5-yl)-1-[3-(benzocyclobutan-1-yl) propionyl] pipérazine (Rendement : 65 %), elle-même préparée avec un rendement de 37 %, à partir de l'acide 3-(benzocyclobutan-1-yl)propionique (décrit dans la demande de brevet européen déposée par la demanderesse sous le n° 90.403145.7) et de la N-(benzodioxan-5-yl)-pipérazine.

14) La 4-(benzodioxan-5-yl)-1-[(indan-2-yl)méthyl] pipérazine et son chlorhydrate P.F. (K) : 232-234°C, par réduction de la 4-(benzodioxan-5-yl)-1-[(indan-2-yl)carbonyl] pipérazine, P.F. (K) : 160-162°C (Rendement : 43 %), elle-même préparée avec un rendement de 37 %, à partir de l'acide (indan-2-yl)carboxylique [décrit dans J.A.C.S. (1975), 97 vol. 2, 347-353] et de la N-(benzodioxan-5-yl) pipérazine.

15) La 4-(benzodioxan-5-yl)-1-[(indan-1-yl)méthyl] pipérazine (H,S), P.F. (MK) : 87-90°C, par réduction de la 4-(benzodioxan-5-yl)-1-[(indan-1-yl)carbonyl] pipérazine (Rendement : 70 %), elle-même préparée avec un rendement de 41 %, à partir de l'acide (indan-1-yl) carboxylique [décrit dans Synthesis (1987), 845] et de la N-(benzodioxan-5-yl)pipérazine.

16) La 4-(benzodioxan-5-yl)-1-[2-(5-méthoxybenzocyclobutan-1-yl)éthyl] pipérazine (R,S) (produit huileux) et son chlorhydrate P.F. (K) : 192-194°C, par réduction de la 4-(benzodioxan-5-yl)-1-[2-(5-méthoxybenzocyclobutan-1-yl)acétyl] pipérazine (produit huileux) (Rendement : 62 %), elle-même préparée, avec un rendement de 72 %, à partir de l'acide 2-(5-méthoxybenzocyclobutan-1-yl)acétique, et de la N-(benzodioxan-5-yl)pipérazine.

L'acide 2-(5-méthoxybenzocyclobutan-1-yl)acétique a été préparé selon la méthode décrite dans J.A.C.S. (1975), 347, avec un rendement de 54 %, à partir du nitrile correspondant, lequel est obtenu, avec un rendement de 97 % à partir du tosylate correspondant, lui-même préparé, avec un rendement de 76 %, à partir de l'alcool correspondant et de paratoluène sulfochlorure, en milieu pyridine.

17) La 4-(benzodioxan-5-yl)-1-[2-(4,5-diméthoxybenzocyclobutan-1-yl)éthyl] pipérazine (R,S), (huile) et son chlorhydrate P.F. (K) : 232-234°C, par réduction de la 4-(benzodioxan-5-yl)-1-[2-(4,5-diméthoxy-benzocyclobutan-1-yl)acétyl] pipérazine (huile), (Rendement : 59 %), elle-même préparée, avec un rendement de 51,5 %, à partir de l'acide 2-(4,5-diméthoxybenzocyclobutan-1-yl)acétique, et de la N-(benzodioxan-5-yl)pipérazine.

L'acide 2-(4,5-diméthoxybenzocyclobutan-1-yl) acétique, P.F. (K) : 136-139°C, a lui-même été obtenu, avec un rendement de 96 %, selon la méthode décrite dans J.A.C.S. (1975), 347, à partir du nitrile correspondant, P.F. (K) : 110-112°C.

18) La 4-(benzodioxan-5-yl)-1-[2-(ind-1-én-1-yl)éthyl]pipérazine et son chlorhydrate P.F (K) : 254-256 °C, par réduction de la 4-(benzodioxan-5-yl)-1-[2-(ind-1-én-1-yl)acétyl]pipérazine (Rendemnt : 30 %) elle-même préparée avec un rendement de 66 %, à partir de l'acide 2-(ind-1-én-1-yl)acétique [P.F (K) : 92-94 °C] et de la N-(benzodioxan-5-yl)pipérazine.

L'acide 2-(ind-1-én-1-yl)acétique a été préparé selon la méthode de H. Ahmed et N. Campbell J.C.S. (1960), 4115-4120, avec un rendement de 90 %, à partir du 2-(indan-1-ylidène)acétate d'éthyle, lui-même préparé avec un rendement de 48 % à partir d'indan-1-one et de $(C_6H_5)_3$ P=CH-$COOC_2H_5$ dans le toluène.

19) La 4-(benzodioxan-5-yl)-1-[2-(5,6-diméthoxyindan-1-yl)éthyl] pipérazine (R,S) et son chlorhydrate P.F (K) : 225-226 °C (méthanol), par réduction de la 4-(benzodioxan-5-yl)-1-[2-(5,6-diméthoxyindan-1-yl)acétyl]pipérazine (Rendement : 25 %), elle-même préparée, avec un rendement de 98 %, à partir de l'acide 2-(5,6-diméthoxyindan-1-yl)acétique, P.F (K) : 151-153 °C, et de la N-(benzodioxan-5-yl)pipérazine.

L'acide 2-(5,6-diméthoxyindan-1-yl)acétique a été préparé avec un rendement de 79 % à partir de l'ester éthylique correspondant (huile) lequel a été obtenu avec un rendement de 97 % à partir du 2-(5,6-diméthoxyindan-1-ylidène)acétate d'éthyle, lui-même préparé avec un rendement de 25 % à partir de 5,6-diméthoxyindan-1-one et de $(C_6H_5)_3$ P=CH-$COOC_2H_5$ dans le toluène.

20) La 4-(benzodioxan-5-yl)-1-[2-(indan-2-yl)éthyl]pipérazine P.F (MK) : 121-123 °C, par réduction de la 4-(benzodioxan-5-yl)-1-[2-(indan-2-yl)acétyl]pipérazine (huile) (Rendement : 64 %) elle-même préparée, avec un rendement de 90 % à partir de l'acide 2-(indan-2-yl)acétique P.F (M.K) : 91-93 °C et de la N-(benzodioxan-5-yl)pipérazine.

L'acide 2-(indan-2-yl)acétique a été préparé à partir de l'ester éthylique correspondant (huile) lequel a été obtenu avec un rendement de 98 % par hydrogénation du 2-(indan-2-ylidène)acétate d'éthyle (huile), lui-même préparé avec un rendement de 74 % à partir d'indan-2-one et de $(C_6H_5)_3$ P=CH-$COOC_2H_5$ dans le toluène.

21) La 4-(benzofuran-7-yl)-1-[3-(benzocyclobutan-1-yl)propyl]pipérazine (R,S) et son fumarate P.F (M.K) : 197-200 °C (méthanol), par réduction de la 4-(benzofuran-7-yl)-1-[3-(benzocyclobutan-1-yl)propionyl]pipérazine (huile) (Rendement : 47 %), elle-même préparée, avec un rendement de 57 %, à partir de l'acide 3-(benzocyclobutan-1-yl)propionique et de la N-(benzofuran-7-yl)pipérazine, préparée selon J. Med. Chem. (1988), 31, 1934-1940.

22) La 4-(benzodioxan-5-yl)-1-[2-(indan-1-yl)éthyl]pipérazine (R,S) et son chlorhydrate P.F (K) : 220-222 °C, par réduction de la 4-(benzodioxan-5-yl) 1-[2-(indan-1-yl)acétyl]pipérazine (Rendement : 44 %), elle-même préparée, avec un rendement de 75 %, à partir de l'acide 2-(indan-1-yl)acétique et de la N-(benzodioxan-5-yl)pipérazine.

23) La 4-(benzodioxan-5-yl)-1-[3-(indan-1-yl)propyl]pipérazine (R,S) et son dichlorhydrate P.F (K) : 175-185 °C, par réduction de la 4-(benzodioxan-5-yl)-1-[3-indan-1-yl)propionyl]pipérazine (huile) (rendement : 71,5 %), elle-même préparée, avec un rendement de 85 %, à partir de l'acide 3-(indan-1-yl)propionique (huile) et de la N-(benzodioxan-5-yl)pipérazine.

L'acide 3-(indan-1-yl)propionique a été préparé comme suit : 27 g d'ester méthylique de l'acide 1-indane carboxylique [obtenu selon la méthode de F.M Nongrun et B. Myrboh, Synthesis (1987) 9, 845-846], dans 200 ml d'hydroxyde de sodium et 200 ml d'éthanol, sont agités une nuit à température ambiante. Après acidification à l'acide chlorhydrique concentré, on obtient 8 g d'acide 1-indane carboxylique P.F (K) 65 °C (Rendement : 30 %).

8 g de l'acide ainsi obtenu dans 200 ml de tétrahydrofurane sont ajoutés à une suspension de 1,55 g d'hydrure de lithium aluminium dans 40 ml de tétrahydrofurane et agités une nuit à température ambiante. Après hydrolyse par 1,07 ml d'eau puis 0,86 ml d'hydroxyde de sodium à 20 %, et enfin 4 ml d'eau, évaporation du solvant, le résidu est distillé au Kügelrohr. On obtient 4,3 g de 1-indane méthanol (huile-$Eb/_{0,05}$ mmHg : 70-75 °C) (Rendement : 58 %).

10 g de cet alcool et 19 g de p-toluène sulfochlorure sont agités dans 80 ml de pyridine pendant 18 heures. Après évaporation du solvant, le milieu est lavé à l'eau et extrait à CH_2Cl_2. On obtient 14 g de tosylate de 1-indane méthanol sous forme d'huile, avec un rendement de 70 %.

5 g du tosylate ainsi obtenu dissous dans 5 ml d'éthanol sont ajoutés au mélange de 3,2 g de malonate de diéthyle lui-même ajouté goutte à goutte à une solution d'éthylate de sodium obtenue à partir de 0,46 g de sodium dans 10 ml d'éthanol. Le milieu réactionnel est alors amené et maintenu au reflux pendant 18 heures. Après dilution à l'acide chlorhydrique, on extrait le produit à l'acétate d'éthyle et le purifie sur colonne de silice en éluant avec CH_2Cl_2/cyclohexane (40/60). On obtient ainsi, avec un rendement de 56 %, l'ester éthylique de l'acide 3-(indan-1-yl)-2-éthoxycarbonyl propionique.

On porte à reflux 2,3 g de cet ester dans 5 ml d'eau et 2,5 g d'hydroxyde de potassium pendant 2 heures. Après acidification par HCl, on obtient 1,8 g d'acide 3-(indan-1-yl)-2-carboxy propionique, P.F (K) : 150-152 °C, (Rendement : 96 %).

1,8 g de ce diacide ainsi obtenu sont portés à reflux dans la N,N-diméthylacétamide pendant 2 heures 30. On obtient, après dilution à l'eau et extraction à l'éther, 1,3 g d'acide 3-(indan-1-yl)propionique sous forme d'huile, avec un rendement de 89 %.

24) La 4-[benzo(1,5)dioxépin-6-yl]-1-[3-(benzocyclobutan-1-yl)propyl] pipérazine (R,S) et son chlorhydrate P.F (M.K) : 262-265 °C, par réduction de la 4-[benzo(1,5)dioxépin-6-yl]-1-[3-(benzocyclobutan-1-yl)propionyl]pipérazine (huile) (Rendement : 37 %), elle-même préparée avec un rendement de 30 % à partir de l'acide 3-(benzocyclobutan-1-yl)propionique et de la N-[benzo(1,5)dioxépin-6-yl]pipérazine.

25) La 4-(benzodioxan-5-yl)-1-[3-(indan-2-yl)propyl]pipérazine et son chlorhydrate P.F (K) : 210 °C, par réduction de la 4-(benzodioxan-5-yl)-1-[3-(indan-2-yl)propionyl]pipérazine (Rendement : 50 %), elle-même préparée avec un rendement de 86 % à partir de l'acide 3-(indan-2-yl)propionique, P.F (K) : 75-78 °C, et de la N-(benzodioxan-5-yl) pipérazine.

L'acide 3-(indan-2-yl)propionique a été préparé avec un rendement de 68 % à partir de l'acide 3-(indan-2-yl)-2-carboxy propionique, lequel a été préparé, avec un rendement de 44 %, à partir du diéthyl ester correspondant, qui est lui-même obtenu, avec un rendement de 69 %, à partir du mésylate d'(indan-2-yl-)éthyle et du di(éthoxycarbonyl)méthane.

26) La 4-(benzodioxan-5-yl)-1-[3-(3-chlorobenzocyclobutan-1-yl) propyl] piperazine (R,S) et son dichlorhydrate P.F (M.K) : 223-226 °C, par réduction de la 4-(benzodioxan-5-yl)-1-[3-(3-chlorobenzocyclobutan-1-yl)propionyl]pipérazine P.F (K) : 135-140 °C (Rendement : 84 %) elle-même préparée, avec un rendement de 74 %, à partir de l'acide 3-(3-chlorobenzocyclobutan-1-yl)propionique (huile) et de la N-(benzodioxan-5-yl)pipérazine.

L'acide 3-(3-chlorobenzocyclobutan-1-yl)propionique a été préparé, avec un rendement de 61 %, à partir de l'acide 3-(3-chlorobenzocyclobutan-1-yl)-2-carboxy propionique P.F (K) : 190-192 °C, lequel a été préparé, avec un rendement de 100 %, à partir du diéthylester correspondant lui-même obtenu, avec un ren-

dement de 30 %, à partir du tosylate de (3-chlorobenzocyclobutan-1-yl)méthyle et du di(éthoxycarbonyl)méthane.

27) La 4-(benzodioxan-5-yl)-1-[2-(1,2,3,4-tétrahydronaphtalén-1-yl)éthyl] pipérazine (R,S) et son chlorhydrate P.F instantané : 250-252 °C (acétonitrile) par réduction de la 4-(benzodioxan-5-yl)-1-[2-(1,2,3,4-tétrahydronaphtalén-1-yl)acétyl]pipérazine elle-même préparée à partir de l'acide (1,2,3,4-tétrahydronaphtalén-1-yl)acétique et de la N-(benzodioxan-5-yl)pipérazine.

L'acide (1,2,3,4-tétrahydronaphtalén-1-yl)acétique a lui-même été préparé à partir du 1-éthoxycarbonylméthyl 1,2,3,4-tétrahydronaphtalène lequel est obtenu à partir du 1-éthoxycarbonylméthyl 3,4-dihydronaphtalène [cf. J. Chem. Soc. (1960), 4115-4120], lui-même préparé à partir de 1,2,3,4-tétrahydronaphtalén-1-one.

28) La 4-(benzodioxan-5-yl)-1-[2-(benzocycloheptan-1-yl)éthyl]pipérazine (R,S) et son dichlorhydrate P.F (M.K) : 179-186 °C, par réduction de la 4-(benzodioxan-5-yl)-1-(2-(benzocycloheptan-1-yl)acétyl]pipérazine, elle-même préparée à partir de l'acide (benzocycloheptan-1-yl)acétique et de la N-(benzodioxan-5-yl)pipérazine.

L'acide (benzocycloheptan-1-yl)acétique a été préparé à partir de 1-éthoxycarbonylméthyl benzocycloheptane, lui-même préparé à partir de benzocycloheptan-1-one.

29) La 4-(benzodioxan-5-yl)-1-[2-(benzocyclohept-1-én-1-yl)éthyl] pipérazine et son chlorhydrate P.F (M.K) : 233-236 °C par réduction de la 4-(benzodioxan-5-yl)-1-[(benzocyclohept-1-én-1-yl)acétyl]pipérazine, elle-même préparée à partir de l'acide (benzocyclohept-1-én-1-yl)acétique et de la N-(benzodioxan-5-yl)pipérazine.

L'acide (benzocyclohept-1-én-1-yl)acétique a été préparé à partir du 1-éthoxycarbonylméthyl benzocyclohept-1-ène, lui-même préparé à partir de benzocycloheptan-1-one traité par

et NaH dans le tétrahydrofurane, puis séparation des deux isomères exocycliques insaturés cis et trans également formés, en opérant par chromato-flash sur silice en éluant avec le toluène.

Exemple 30 :

ETUDE PHARMACOLOGIQUE

Les dérivés de la présente invention ont été étudiés comparativement à la Buspirone, produit de référence connu à titre de ligand des récepteurs sérotoninergiques 5 HT_{1A}.

A) Méthodologie :

Les essais ont été réalisés sur des rats Wistar mâles de 200 à 220 g ayant libre accès à leur nourriture et à leur eau de boisson, dans des cages standards.

Les animaux sont isolés individuellement pour les essais d'hypothermie, de secrétion de corticostérone et de position affaissée du corps (Flat Body Posture) ou réunis par goupes de trois pour le test des battements de la queue (Tail-Flicks).

La température du laboratoire est maintenue à 21 ± 1 °C sous une humidité de 60 ± 5 %. Ils sont soumis à un cycle lumière/obscurité de 12 heures/12 heures (le cycle lumière commençant à 7 h 30 du matin).

1) Etude in vitro - Test de Binding;

L'hippocampe issu des cerveaux de rats décapités a été immédiatement congélé sur glace carbonique puis conservé à - 80 °C jusqu'à la préparation des membranes. Le tissus a été homogénéisé à 4 °C dans le tampon approprié en utilisant un Polytron (Instruments Brinkman-Lucerne - Suisse) et centrifugé à 20.000 tours/mn.

L'incubation a été faite à 25 °C pendant 30 mn. La liaison non spécifique a été définie par 10 µmole de 5 HT. Les essais ont été terminés par filtration rapide à l'aide d'un collecteur de Brandel sur des filtres en fibre de verre prétraités avec 0,1 % de polyéthylène imine.

Pour chaque ligand froid, on a pris en compte un minimum de 3 valeurs produisant une inhibition entre 20 et 80 % de la liaison du ligand chaud. Les valeurs de concentrations inhibitrices 50 (IC_{50}) ont été déterminées

selon le procédé 8 de Tallarida R.J et Murray R.B., Manual of Pharmacological calculations with computer programs, Springer Cerlag, New York, (1987).

Le pKi a été calculé selon la formule :

$$pKi = - \log \left(\frac{IC_{50}}{1+[L]/Kd} \right)$$

dans laquelle [L] est la concentration du ligand chaud ([13]H-8-OH-DPAT, 0,4 nM) et Kd est la constante de dissociation apparente déterminée à partir des expériences de saturation.

Les substances étudiées ont été solubilisées dans le tampon d'incubation.

2) Etude in vivo

a/ Processus général concernant les tests d'activités agonistes et antagonistes sur les récepteurs $5HT_{1A}$.

Les composés à étudier ont été administrés par voie sous-cutanée (s.c) 60 minutes avant le début du test c'est à dire 30 minutes avant le solvant (réponses agonistes) ou le 8-OH-DPAT (réponses antagonistes).

Dans tous les essais le solvant est utilisé en parallèle comme contrôle. Les animaux ont été laissés au repos dans leur cage pendant le temps compris entre les injections et l'évaluation. Pour les études agonistes, le solvant a été administré à 1 ml/kg s.c. 30 minutes avant le début du test. Pour les études antagonistes, on a choisi des doses de 8-OH-DPAT induisant des réponses sous-maximales soit des doses de 0,63-0,16-0,16 et 0,16 mg/kg s.c. respectivement pour les tests de Tail-Flicks, Flat Body Posture, Sécrétion de Corticostérone et d'Hypothermie.

b/ Position affaissée du corps (Flat Body Posture ou FBP) et Sécrétion de Corticostérone (CS).

Les mêmes animaux ont été employés pour évaluer l'influence des composés étudiés sur le FBP et sur la détermination de la concentration plasmatique de CS. Tous les essais ont été réalisés le matin entre 10 h 30 et 12 h 30, soit lorsque les taux circadien de CS sont les plus faibles.

25 minutes après le traitement (soit 5 minutes avant la décapitation) les animaux sont observés dans leurs cages et on note la présence ou non de FBP.

La présence de FBP est définie par une position caractéristique de l'animal. Celui-ci est alors en position de decubitus ventral avec les membres postérieurs nettement en extension. 5 minutes après l'observation de FBP, les animaux sont décapités et le sang du tronc est recueilli dans des tubes refroidis contenant 50 µl d'une solution de EDTA à 10 % . Après centrifugation à 4000 tours/mn, le plasma est prélevé et conservé à - 30 °C jusqu'au dosage.

La CS a été déterminée en utilisant un dosage radio-compétitif pour une protéine plasmatique fixant la CS : la trancortine. Celle-ci est obtenue à partir d'un sérum de singe. La séparation des complexes CS-transcortine de la CS libre a été réalisée au moyen d'une solution de Dextran et de charbon actif. La limite de détection était de 50 pg/tube. Les variations de dosage intra- et inter-expériences étaient respectivement de 5 et 15 % [cf Rivet J.M. et al, Eur. J. Pharmacol., 183, 634-635 (1990)].

Les taux de base de CS dans le plasma n'étant jamais zéro, on a utilisé, pour calculer le pourcentage d'inhibition de CS plasmatique induite par 8-OH-DPAT, la formule suivante :

$$\% \text{ d'inhibition} = 100 \times \frac{(\text{Antagoniste} + \text{Agoniste}) - \text{Antagoniste seul}}{(\text{Solvant} + \text{Agoniste}) - \text{Solvant seul}}$$

c/ Température corporelle (CT)

Les rats sont immobilisés et un thermomètre digital lubrifié (Thermistoprobe de Testotherm, Bale, suisse) est inséré dans le rectum à une profondeur de 5 cm. 30 secondes après l'insertion, la température est lue sur une échelle digitale. Le pourcentage d'inhibition est calculé à l'aide de la formule citée précédemment.

d/ Test spontané de Tail Flicks : (STF)

Les battements de la queue on été déterminés sur des animaux maintenus dans des cylindres en plastique opaque horizontaux, la queue des animaux pendant librement sur le bord de la paillasse de laboratoire. Après 5 minutes d'adaptation, on enregistre le nombre de mouvements émis en 5 minutes. Un STF est défini comme étant une élévation de la queue à un niveau supérieur à celui de l'axe du corps [Millan M.J. et al., J. Pharmacol. Exp. Ther., 256, 973-982 (1990)].

e/ Analyse des résultats in vivo

- En général, après analyse de variance, les résultats sont soumis au test de Dunett. Les résultats sont tenus pour significatifs si $p<0,05$.
- Pour l'analyse des courbes dose-réponse concernant l'induction des STF, CS et Hypothermie, on a déterminé la dose efficace minimale (M.E.D) en mg/kg, c'est à dire la dose qui induit une réponse significativement différente de celle produite par le solvant.
- Pour l'analyse des courbes dose-réponse concernant l'inhibition de STF, CS, et Hypothermie, les valeurs ID_{50} -en mg/kg (dose réduisant de 50 % l'action de 8-OH-DPAT) ont été calculées ainsi que les limites de confiance à 95 % en utilisant une méthode inspirée de la méthode de Finney (1964).
- Pour la dose-réponse d'induction et d'inhibition du FBP, les doses efficaces 50 (ED_{50}) (doses pour lesquelles 50 % des animaux montrent une réponse) ont été calculées par la méthode de Litchfield et Wilcoxon.

f/ Composés étudiés

Les doses des composés testés sont toutes exprimées en terme de base. Sauf mention contraire, tous les composés ont été dissous dans de l'eau stérile (additionnée si nécessaire de quelques gouttes d'acide lactique) et administrés à un volume de 1 ml/kg s.c.

B) Résultats :

Les résultats sont regroupés dans les tableaux 1 et 2 ci-après.

Tableau 1

Binding des récepteurs 5 HT_{1A}

MOLECULE	AFFINITE (pKi)
Produit de référence BUSPIRONE	7,93
Exemple 1	8,74
Exemple 2	9,21
Exemple 3	8,94
Exemple 4	8,85
Exemple 5	8,65
Exemple 7	8,75
Exemple 8	8,80
Exemple 9	8,42
Exemple 12	8,75
Exemple 13	9,35
Exemple 14	8,47
Exemple 15	8,70
Exemple 16	8,85
Exemple 17	8,46
Exemple 18	9,09
Exemple 19	8,83
Exemple 20	9,18
Exemple 21	8,55
Exemple 22	8,80
Exemple 23	9,21
Exemple 24	9,10

TABLEAU 2 : ACTIVITE (IN VIVO) AGONISTE ET ANTAGONISTE DES RECEPTEURS 5 HT_{1A}

MOLECULE	SPONTANEOUS TAIL-FLICKS		FLAT BODY POSTURE ED_{50} (95 % C.L)		CORTICO-STERONE SECRETION		HYPOTHERMIE	
	M.E.D.	ID_{50} (95 % C.L)	REPONSE AGONISTE	ANTAGONISME DE 8-OH-DPAT	M.E.D.	ID_{50} (95 % C.L)	M.E.D.	ID_{50} (95 % C.L)
Produit de réf. Buspirone	> 10,0	3,71 (1,40-9,84)	7,4 (2,16-25,57)	>10,0	>2,5	>10,0	2,5	-
Exemple 1	> 10,0	0,09 (0,02-0,32)	>10,0	0,71 (0,09-5,34)	>2,5	<2,5	10,0	0,5 (0,2-1,24)
Exemple 2	>10,0	0,085 (0,025-0,28)	>20,0	0,76 (0,23-2,58)	10,0	0,66 (0,35-1,24)	40,0	0,65 (0,36-1,14)
Exemple 3	>10,0	0,32 (0,077-1,38)	>10,0	1,55 (0,76-3,17)	>10,0	2,15 (1,21-3,84)	>20,0	1,64 (0,83-3,25)
Exemple 7	>10,0	0,74 (0,28-1,93)	>10,0	0,52 (0,18-1,48)	>10,0	2,5	20,0	1,60 (0,80-3,20)
Exemple 9	>10,0	1,59 (0,77-3,3)	>2,5	<2,5	>2,5	>2,5	5,0	4,36 (1,67-11,42)
Exemple 13	>10,0	0,13 (0,054-0,32)	>10,0	0,57 (0,17-1,87)	10,0	1,27 (0,59-2,73)	10,0	0,21 (0,04-0,97)
Exemple 14		0,19 (0,05-0,74)	>2,5	≥2,5	>2,5	>2,5	>10,0	<2,5
Exemple 15		0,085 (0,03-0,22)	>2,5	≥2,5	>2,5	>2,5	10,0	1,53 (0,57-4,06)
Exemple 20		0,18 (0,03-1,03)	>2,5	<2,5	>2,5	<2,5	10,0	0,58 (0,22-1,49)
Exemple 22	>10,0	0,74 (0,28-1,91)	>10,0	1,03 (0,52-2,03)	>10,0	1,92 (1,08-3,43)	>40,0	1,19 (0,59-2,42)
Exemple 23		0,56 (0,17-1,81)	10,0	0,29 (0,06-1,55)	>2,5	<2,5	5,0	0,40 (0,12-1,37)

ID_{50}=Dose inhibitrice 50 ; ED_{50}=Dose efficace 50 ; CL=limite de confiance ; MED=Dose efficace minimale

EP 0 490 772 A1

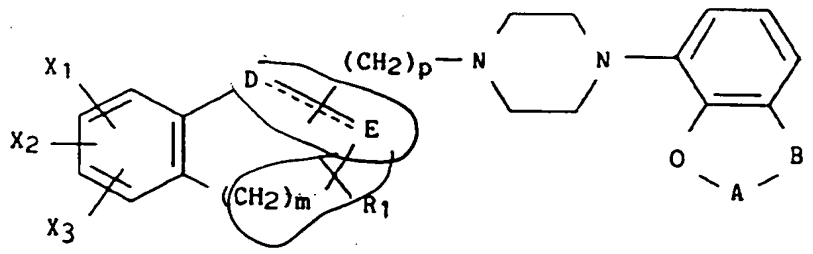
C) Conclusion :

L'examen des résultats repertoriés dans les tableaux 1 et 2 montre que les composés de la présente invention ont un comportement antagoniste des récepteurs $5HT_{1A}$ contrairement à la buspirone qui, bien que se fixant également sur les récepteurs 5HT1A, a un comportement agoniste.

D'où l'intérêt des composés de la présente invention dans le traitement des maladies du système nerveux central et des maladies neuroendocriniennes.

Revendications

1) Les pipérazines 1,4-disubstituées de formule générale I : bioequiv

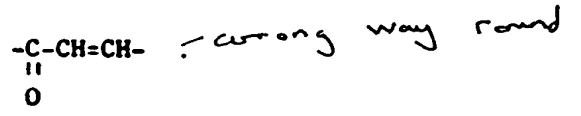


(I)

dans laquelle :

- X_1, X_2 et X_3 :
  - identiques ou différents, représentent chacun : un atome d'hydrogène ou d'halogène, un radical alkyle en chaine droite ou ramifiée contenant de 1 à 5 atomes de carbone, un radical hydroxy, un radical alcoxy ou alkylthio contenant chacun de 1 à 5 atomes de carbone en chaine droite ou ramifiée, un radical trifluorométhyle, un radical nitro, un radical amino, ou un radical acétamido, ou
  - deux d'entre eux pris en position adjacente forment ensemble un radical méthylènedioxy ou un radical éthylènedioxy ;
- R_1 représente un atome d'hydrogène ou un radical alkyle en chaine droite ou ramifiée contenant de 1 à 5 atomes de carbone ;
- -D ⋯ E- représente : $-(CH_2)_n-(CH_2)-$ ou -CH=CH-
- m et n représentent chacun les valeurs zéro, un, deux ou trois à condition que m + n soit ≧ 1.
- p représente zéro ou un nombre entier de 1 à 6, et
- -A-B- représente un des radicaux de formule :

$-(CH_2)_2-O-$; $-(CH_2)_3-O-$; -CH=CH- ; $-CH_2-CH_2-$ et



wrong way round

sous formes racémiques et optiquement actives.

2) Les sels physiologiquement tolérables des dérivés de la revendication 1 avec des acides appropriés.

3) La 4-(benzodioxan-5-yl)-1-(2-(benzocyclobutan-1-yl)éthylpipérazine (R,S) et son dichlorhydrate.

4) La 4-(benzodioxan-5-yl)-1-(2-(3-chlorobenzocyclobutan-1-yl)éthyl] pipérazine (R,S) et son dichlorhydrate.

5) La 4-(benzodioxan-5-yl)-1-(indan-2-yl)pipérazine.

6) La 4-(benzodioxan-5-yl)-1-(4-(benzocyclobutan-1-yl)butylpipérazine (R,S) et son fumarate.

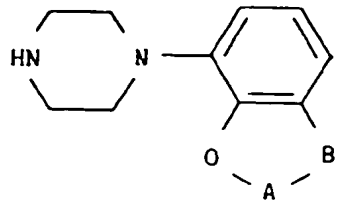
7) La 4-[benzo (1,5) dioxépin-6-yl]-1-(indan-2-yl)pipérazine.

8) La 4-[benzodioxan-5-yl)-1-(2-(ind-1-én-1-yl)éthyl]pipérazine et son chlorhydrate.

9) La 4-[benzodioxan-5-yl)-1-(2-(indan-1-yl)éthyl]pipérazine (R,S) et son chlorhydrate.

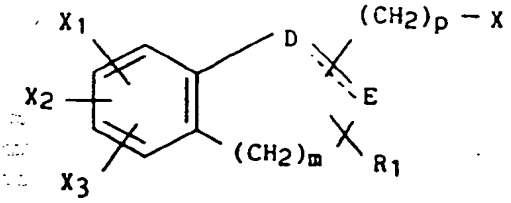
10) Le procédé de préparation des dérivés de la revendication 1 caractérisé en ce que l'on condense :

- une pipérazine N-monosubstituée de formule générale II :



(II)

dans laquelle le groupe -A-B- a la signification définie dans la revendication 1,
– avec un dérivé de formule générale III :

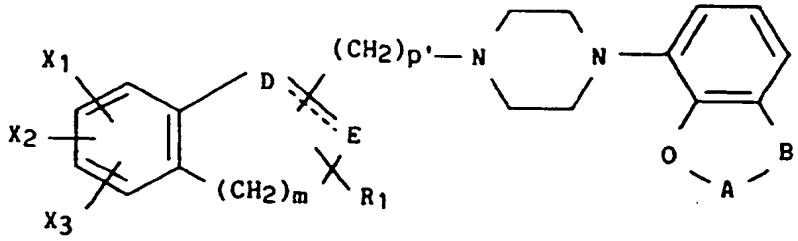


(III)

dans laquelle :
– X_1, X_2, X_3, R_1, - D ⎓ E-, m et p ont les significations définies dans la revendication 1,
et
– X représente un atome d'halogène, ou un radical mésyloxy ou tosyloxy.

11) Le procédé de préparation selon la revendication 10 caractérisé en ce que l'on effectue la condensation des dérivés II et III dans un solvant approprié, à une température comprise entre 20 et 150°C, en présence d'un accepteur de l'acide formé au cours de la réaction.

12) Le procédé de préparation des dérivés de la revendication 1 répondant à la formule générale I' :

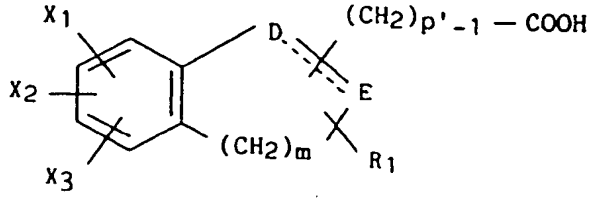


(I')

dans laquelle :

– X_1, X_2, X_3, R_1, - D ⎓ E - , m et -A-B- ont les significations définies dans la revendication 1, et
– p' représente un nombre entier de 1 à 6,

caractérisé en ce que :
– l'on condense :
– la pipérazine N-monosubsituée de formule générale II définie dans la revendication 10, avec
– un dérivé de formule générale IV :

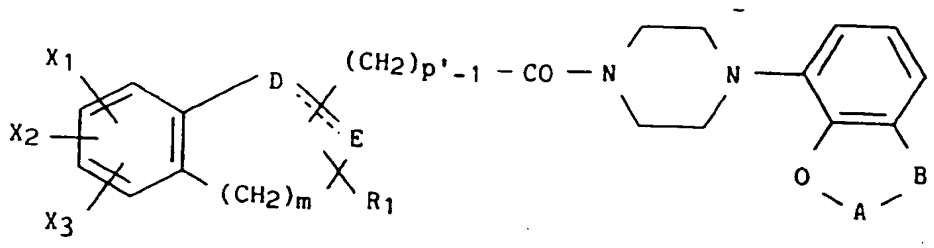


(IV)

dans laquelle :

– X_1, X_2, X_3, R_1, - D ⎓ E - , m et p' ont les significations précédemment définies ; et

– l'on réduit l'amide ainsi obtenue de formule générale V :



(V)

dans laquelle

– X_1, X_2, X_3, R_1, - D ⎓ E - , m, p' et -A-B- ont les significations précédemment définies.

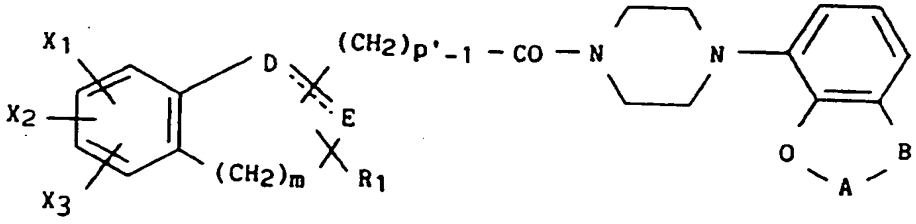
13) Le procédé de préparation selon la revendication 12 caractérisé en ce que l'on effectue la condensation des dérivés II et IV dans le chlorure de méthylène en présence de carbonyldiimidazole.

14) Le procédé de préparation selon la revendication 12 caractérisé en ce que l'on effectue la réduction de l'amide V au moyen d'un hydrure double de lithium-aluminium dans un solvant approprié.

15) Les compositions pharmaceutiques contenant comme principe actif un dérivé selon une des revendications 1 à 9 avec des excipients pharmaceutiques appropriés.

16) Les compositions pharmaceutiques selon la revendication 15, présentées sous une forme convenant notamment pour le traitement des maladies du système nerveux central et des maladies neuroendocriniennes.

17) A titre de produits intermédiaires nouveaux utilisables dans la synthèse des dérivés I', les amides de formule générale V :



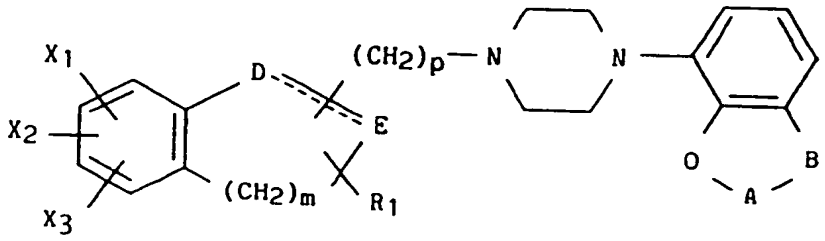
(V)

dans laquelle :

– X_1, X_2, X_3, R_1, - D ⎓ E - , m, p' et -A-B- ont les significations définies dans la revendication 12.

Revendications pour l'Etat contractant suivant : ES

1) Le procédé de préparation des pipérazines 1,4-disubstituées de formule générale I :



(I)

dans laquelle :

– X_1, X_2 et X_3 :

– identiques ou différents, représentent chacun : un atome d'hydrogène ou d'halogène, un radical alkyle en chaine droite ou ramifiée contenant de 1 à 5 atomes de carbone, un radical hydroxy, un radical alcoxy ou alkylthio contenant chacun de 1 à 5 atomes de carbone en chaine droite ou ramifiée, un radical trifluorométhyle, un radical nitro, un radical amino, ou un radical acétamido, ou

– deux d'entre eux pris en position adjacente forment ensemble un radical méthylènedioxy ou un radical éthylènedioxy ;

– R_1 représente un atome d'hydrogène ou un radical allyle en chaine droite ou ramifiée contenant de 1 à 5 atomes de carbone ;

– - D ⎓ E - représente : $-(CH_2)_n-(CH_2)-$ ou -CH=CH-

– m et n représentent chacun les valeurs zéro, un, deux ou trois à condition que m + n soit ≧ 1.

– p représente zéro ou un nombre entier de 1 à 6, et

– -A-B- représente un des radicaux de formule :

$-(CH_2)_2-O-$; $-(CH_2)_3-O-$; -CH=CH- ; $-CH_2-CH_2-$ et

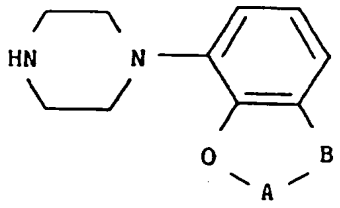
$$-\overset{\overset{O}{\|}}{C}-CH=CH- \quad .$$

sous formes racémiques et optiquement actives,

ainsi que leurs sels physiologiquement tolérables avec des acides appropriés,

caractérisé en ce que l'on condense :

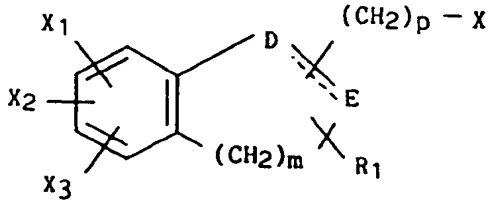
– une pipérazine N-monosubstituée de formule générale II :



(II)

dans laquelle le groupe -A-B- a la signification précédemment définie ,

– avec un dérivé de formule générale III :



(III)

dans laquelle :

– X_1, X_2, X_3, R_1, - D ⎓ E -, m et p ont les significations précédemment définies ,

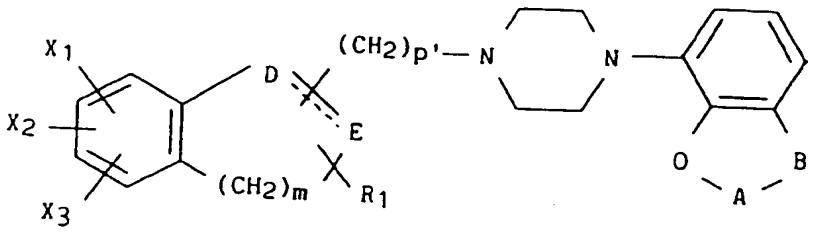
et

– X représente un atome d'halogène, ou un radical mésyloxy ou tosyloxy ;

– et si on le désire, on traite les dérivés I ainsi obtenus avec des acides appropriés pour donner les sels d'addition acides correspondants.

2) Le procédé de préparation selon la revendication 1 caractérisé en ce que l'on effectue la condensation des dérivés II et III dans un solvant approprié, à une température comprise entre 20 et 150°C, en présence d'un accepteur de l'acide formé au cours de la réaction.

3) Le procédé de préparation des dérivés (I) répondant à la formule générale I' :



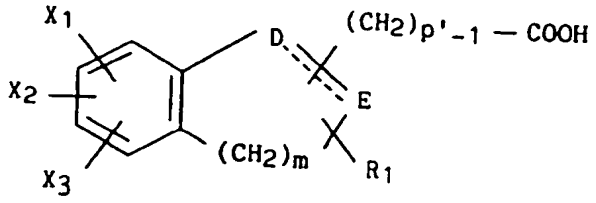
(I')

dans laquelle :

- X_1, X_2, X_3, R_1, - D ⋍ E -, m et -A-B- ont les significations définies dans la revendication 1, et
- p' représente un nombre entier de 1 à 6,

caractérisé en ce que :

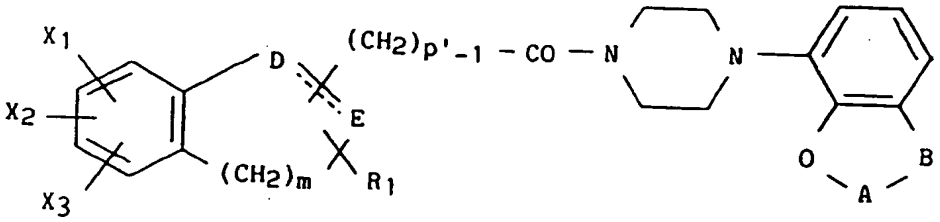
- l'on condense :
  - la pipérazine N-monosubsituée de formule générale II définie dans la revendication 1, avec
  - un dérivé de formule générale IV :



(IV)

dans laquelle :

- X_1, X_2, X_3, R_1, - D ⋍ E -, m et p' ont les significations précédemment définies ; et
- l'on réduit l'amide ainsi obtenue de formule générale V :



(V)

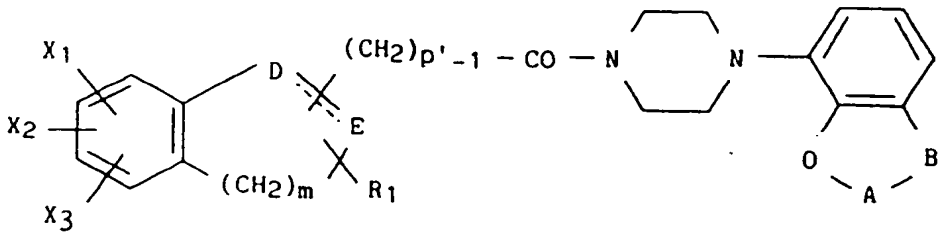
dans laquelle :

- X_1, X_2, X_3, R_1, - D ⋍ E -, m, p' et -A-B- ont les significations précédemment définies ;
- et si on le désire, on traite les dérivés I' ainsi obtenus avec des acides appropriés pour donner les sels d'addition acides correspondants.

4) Le procédé de préparation selon la revendication 3 caractérisé en ce que l'on effectue la condensation des dérivés II et IV dans le chlorure de méthylène en présence de carbonyldiimidazole.

5) Le procédé de préparation selon la revendication 3 caractérisé en ce que l'on effectue la réduction de l'amide V au moyen d'un hydrure double de lithium-aluminium dans un solvant approprié.

6) Le procédé de préparation des amides de formule générale V :



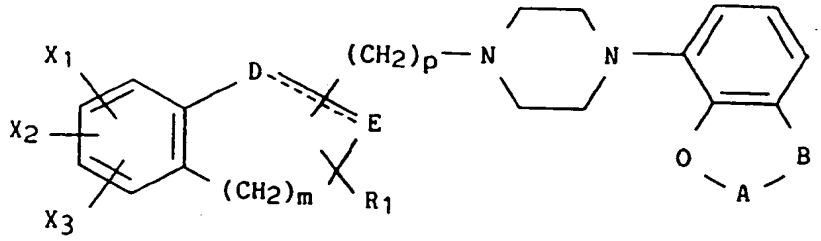
(V)

dans laquelle

– X_1, X_2, X_3, R_1, - D ⎓ E - , m, p' et -A-B- ont les significations définies dans la revendication 3, caractérisé en ce que l'on condense les dérivés II et III comme inclus dans la revendication 3.

Revendications pour l'Etat contractant suivant : GR

1) Le procédé de préparation des pipérazines 1,4-disubstituées de formule générale I :



(I)

dans laquelle :

– X_1, X_2 et X_3 :

– identiques ou différents, représentent chacun : un atome d'hydrogène ou d'halogène, un radical alkyle en chaine droite ou ramifiée contenant de 1 à 5 atomes de carbone, un radical hydroxy, un radical alcoxy ou alkylthio contenant chacun de 1 à 5 atomes de carbone en chaine droite ou ramifiée, un radical trifluorométhyle, un radical nitro, un radical amino, ou un radical acétamido, ou

– deux d'entre eux pris en position adjacente forment ensemble un radical méthylènedioxy ou un radical éthylènedioxy ;

– R_1 représente un atome d'hydrogène ou un radical alkyle en chaine droite ou ramifiée contenant de 1 à 5 atomes de carbone ;

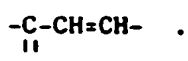
– - D ⎓ E - représente : $-(CH_2)_n-(CH_2)-$ ou -CH=CH-

– m et n représentent chacun les valeurs zéro, un, deux ou trois à condition que m + n soit ≧ 1.

– p représente zéro ou un nombre entier de 1 à 6, et

– -A-B- représente un des radicaux de formule :

$-(CH_2)_2-O-$; $-(CH_2)_3-O-$; -CH=CH- ; $-CH_2-CH_2-$ et

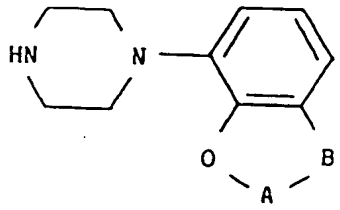


sous formes racémiques et optiquement actives,

ainsi que leurs sels physiologiquement tolérables avec des acides appropriés,

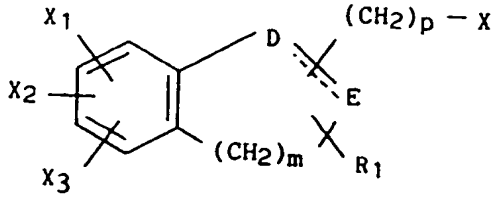
caractérisé en ce que l'on condense :

– une pipérazine N-monosubstituée de formule générale II :



(II)

dans laquelle le groupe -A-B- a la signification précédemment définie ,
– avec un dérivé de formule générale III :

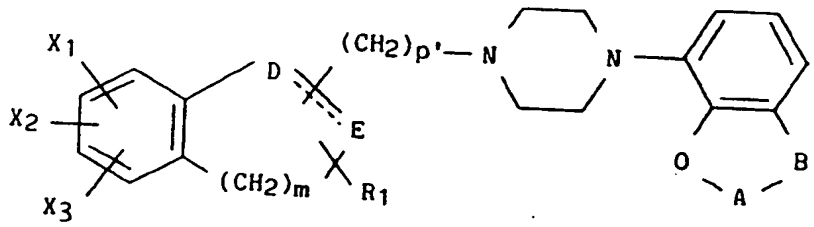


(III)

dans laquelle :
– X_1, X_2, X_3, R_1, - D = E -, m et p ont les significations précédemment définies ,
et
– X représente un atome d'halogène, ou un radical mésyloxy ou tosyloxy ;
– et si on le désire, on traite les dérivés I ainsi obtenus avec des acides appropriés pour donner les sels d'addition acides correspondants.

2) Le procédé de préparation selon la revendication 1 caractérisé en ce que l'on effectue la condensation des dérivés II et III dans un solvant approprié, à une température comprise entre 20 et 150°C, en présence d'un accepteur de l'acide formé au cours de la réaction.

3) Le procédé de préparation des dérivés (I) répondant à la formule générale I' :

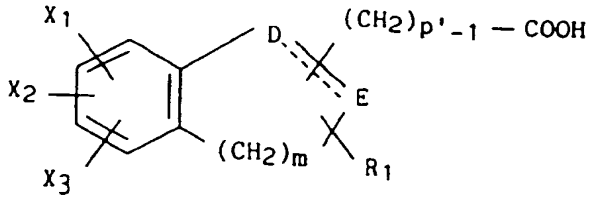


(I')

dans laquelle :

– X_1, X_2, X_3, R_1, - D = E -, m et -A-B- ont les significations définies dans la revendication 1, et
– p' représente un nombre entier de 1 à 6,

caractérisé en ce que :
– l'on condense :
– la pipérazine N-monosubsituée de formule générale II définie dans la revendication 1, avec
– un dérivé de formule générale IV :

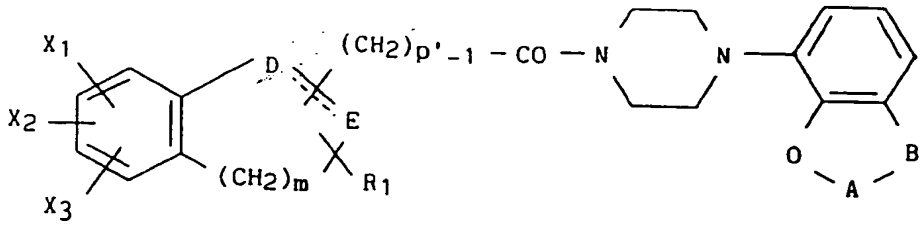


(IV)

dans laquelle :

– X_1, X_2, X_3, R_1, - D ⩬ E - , m et p' ont les significations précédemment définies ; et

– l'on réduit l'amide ainsi obtenue de formule générale V :



(V)

dans laquelle :

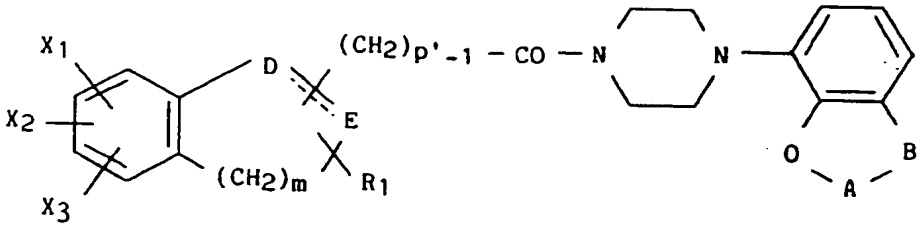
– X_1, X_2, X_3, R_1, - D ⩬ E - , m, p' et -A-B- ont les significations précédemment définies ;

– et si on le désire, on traite les dérivés I' ainsi obtenus avec des acides appropriés pour donner les sels d'addition acides correspondants.

4) Le procédé de préparation selon la revendication 3 caractérisé en ce que l'on effectue la condensation des dérivés II et IV dans le chlorure de méthylène en présence de carbonyldiimidazole.

5) Le procédé de préparation selon la revendication 3 caractérisé en ce que l'on effectue la réduction de l'amide V au moyen d'un hydrure double de lithium-aluminium dans un solvant approprié.

6) Le procédé de préparation des amides de formule générale V :



(V)

dans laquelle

– X_1, X_2, X_3, R_1, - D ⩬ E -, m, p' et -A-B- ont les significations définies dans la revendication 3, caractérisé en ce que l'on condense les dérivés II et III comme inclus dans la revendication 3.

Office européen des brevets

RAPPORT DE RECHERCHE EUROPEENNE

Numero de la demande

EP 91 40 3378

DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie	Citation du document avec indication, en cas de besoin, des parties pertinentes	Revendication concernée	CLASSEMENT DE LA DEMANDE (Int. Cl.5)
A	EP-A-0 376 607 (LUNDBECK) * page 1 - page 6; revendications * -----	1,10-17	C07D319/18 C07D321/10 C07D307/79 A61K31/495
			DOMAINES TECHNIQUES RECHERCHES (Int. Cl.5)
			C07D

Le présent rapport a été établi pour toutes les revendications

Lieu de la recherche	Date d'achèvement de la recherche	Examinateur
LA HAYE	11 MARS 1992	FRANCOIS J.C.

CATEGORIE DES DOCUMENTS CITES

X : particulièrement pertinent à lui seul
Y : particulièrement pertinent en combinaison avec un autre document de la même catégorie
A : arrière-plan technologique
O : divulgation non-écrite
P : document intercalaire

T : théorie ou principe à la base de l'invention
E : document de brevet antérieur, mais publié à la date de dépôt ou après cette date
D : cité dans la demande
L : cité pour d'autres raisons

& : membre de la même famille, document correspondant

EPO FORM 1503 03.82 (P0402)

08/314734

LAW OFFICES
MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
ARLINGTON COURTHOUSE PLAZA 1
SUITE 1400
2200 CLARENDON BOULEVARD
ARLINGTON, VIRGINIA 22201

TELEPHONE: (703) 243-6333
CABLE: USALAW
INT'L. TELEX: 64191
TELECOPIER: (703) 243-6410

Atty's Docket No. MERCK-1617

Applicant(s) : Henning BOTTCHER ET AL.

For : PIPERIDINES AND PIPERAZINES

THE COMMISSIONER OF PATENTS & TRADEMARKS
Washington, D.C. 20231

Sir:

Herewith is the above-identified application for Letters Patent including:

- ☒ Specification and claims
- ☐ _____ Sheets Drawings
  - ☐ Formal ☐ Informal
- ☒ Declaration and Power of Attorney
- ☐ Preliminary Amendment
- ☒ Charge Dollars ($) to Deposit Acct. 13-3402
  to cover the filing fee calculated as follows:
- ☐ Verified statement(s) to establish small entity status under 37 CFR 1.9 and 37 CFR 1.27
- ☐ Information Disclosure
- ☐

CLAIMS AS FILED				
FOR	NUMBER FILED	NUMBER EXTRA	RATE	BASIC FEE $710.00
TOTAL CLAIMS	22 -20 =	2	x$22	44.00
INDEPENDENT CLAIMS	1 - 3 =	0	x	0.00
☐ Multiple Dependent Claim Presented				
		TOTAL FILING FEE		$754.00

☒ The benefit under 35 USC 119 is claimed of the filing date of:

GERMAN APPLICATION NO. P 43 33 254.4, filed September 30, 1993

☒ A certified copy of the priority document(s) is attached.

☒ The Commissioner is hereby authorized to charge payment of the following fees associated with this communication or credit any overpayments to Deposit Account No. 13-3402, two copies of this sheet are being enclosed.

- ☒ Any additional filing fees required under 37 CFR 1.16.
- ☒ Any patent application processing fees under 37 CFR 1.17.

☒ The Commissioner is hereby authorized to charge payment of the following fees during the pendency of this application or credit any overpayments to Deposit Account No. 13-3402, two copies of this sheet are being enclosed.

- ☒ Any patent application processing fees under 37 CFR 1.17.
- ☐ The issue fee set in 37 CFR 1.18 at or before mailing of the Notice of Allowance, pursuant to 37 CFR 1.311(b).
- ☒ Any filing fees under 37 CFR 1.16 for presentation of extra claims.

Respectfully submitted,

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.

DATE: September 29, 1994

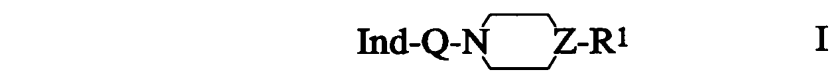
BY: _____
Brion P. Heaney (32,542)
Attorney for Applicants

MWZ-10, Revised 5/93

PIPERIDINES AND PIPERAZINES

Summary of the Invention

The invention relates to novel piperidine and piperazine derivatives of the formula I



wherein

Ind is an indol-3-yl radical which is unsubstituted or mono- or polysubstituted by OH, OA, CN, Hal, COR^2 or CH_2R^2,

R^1 is benzofuran-5-yl or 2,3-dihydrobenzofuran-5-yl, chroman-6-yl, chroman-4-on-6-yl, 3-chromen-6-yl or chromen-4-on-6-yl, which is unsubstituted or monosubstituted by CN, CH_2OH, CH_2OA or COR^2,

Q is C_mH_{2m},

Z is N or CR^3,

A is alkyl having 1-6 C atoms,

Hal is F, Cl, Br or I,

R^2 is OH, OA, NH_2, NHA or NA_2,

R^3 is H, OH or OA and

m is 2, 3 or 4,

and to their physiologically acceptable salts.

An object of the invention is to provide novel compounds capable of being used for the preparation of drugs.

Upon further study of the specification and appended claims, further objects and advantages of this invention will become apparent to those skilled in the art.

It has been found that the compounds of the formula I and their physiologically acceptable acid addition salts possess valuable pharmacological properties. Thus, in particular, they are active on the central nervous system, especially in terms of 5-HT_{1A}-agonist and 5-HT-reuptake inhibition. The compounds are furthermore active as serotonin agonists and antagonists. They inhibit the binding of tritiated serotonin ligands to hippocampal receptors (Cossery et al., European J. Pharmacol., 140:143-155 (1987)). They also modify the accumulation of DOPA in the corpus striatum and the accumulation of 5-HTP in the nuclei raphes (Seyfried et al., European J. Pharmacol., 160:31-41 (1989)). They also

have analgesic and hypotensive effects; thus, in catheterized, conscious, spontaneously hypertensive rats (strain: SHR/Okamoto/NIH-MO-CHB-Kisslegg; method: q.v. Weeks and Jones, Proc. Soc. Exptl. Biol. Med., 104:646-648 (1960)), the directly measured blood pressure is lowered after oral administration of the compounds. They are also useful for prophylaxis and control of the sequelae of cerebral infarction (apoplexia cerebri) such as stroke and cerebral ischaemia.

Compounds of the formula I and their physiologically acceptable acid addition salts can, therefore, be used as active ingredients for anxiolytics, antidepressants, antipsychotics, neuroleptics, and/or antihypertensives, and also as intermediates for the preparation of other pharmaceutical active ingredients.

The invention relates to the piperidine and piperazine derivatives of the formula I and to their physiologically acceptable acid addition salts.

The radical A is alkyl having 1, 2, 3, 4, 5 or 6 C atoms, especially 1 or 2 C atoms, preferably methyl and also ethyl, n-propyl, isopropyl, n-butyl, sec-butyl or tert-butyl. OA is preferably methoxy and also ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy or tert-butoxy. NHA is preferably methylamino and also ethylamino, isopropylamino, n-butylamino, isobutylamino, sec-butylamino or tert-butylamino. NA_2 is preferably dimethylamino and also N-ethyl-N-methylamino, diethylamino, di-n-propylamino, diisopropylamino or di-n-butylamino.

Analogously, CO-NHA is preferably N-methylcarbamoyl or N-ethylcarbamoyl; CO-NA_2 is preferably N,N-dimethylcarbamoyl or N,N-diethylcarbamoyl.

The radical Ind is an indol-3-yl radical which is unsubstituted or mono- or, for example, disubstituted by the radicals indicated. Preferably, it is substituted in the 5-position. Substitution in the 4-, 6- or 7-position is also suitable. Furthermore, substitution in the 1- or 2-position is possible. Preferred substituents on the indol-3-yl radical are OH, OA, CN, $CONH_2$, CH_2OH, but also CO_2H, F, Cl, Br, I, CH_2NH_2, CONHA or $CONA_2$, where A preferably

3

corresponds to methyl or ethyl.

The radical R^1 is preferably benzofuran-5-yl, 2,3-dihydrobenzofuran-5-yl, chroman-6-yl or chromen-4-on-6-yl, which is unsubstituted or monosubstituted by $-CH_2OH$, $-CONH_2$, $-CO_2A$ or $-CO_2NHA$.

Q is preferably $-(CH_2)_4-$, but also $-(CH_2)_2-$ or $-(CH_2)_3-$, while Z is preferably -N-, -C(OH)- or -CH-.

Accordingly, the invention relates particularly to those compounds of the formula I in which at least one of said radicals has one of the meanings indicated above, especially one of the preferred meanings indicated above. Some preferred groups of compounds can be expressed by the following partial formulae Ia to Ig, which correspond to formula I and in which the radicals and parameters not described in greater detail are as defined for formula I, but in which:

in Ia, Ind is an indol-3-yl radical substituted in the 5-position by OH or OA;

in Ib, Ind is an indol-3-yl radical substituted in the 5-position by $CONH_2$ or by CN;

in Ic, Z is N and R^1 is substituted or unsubstituted benzofuran-5-yl;

in Id, Z is -C(OH)- and R^1 is substituted or unsubstituted benzofuran-5-yl;

in Ie, Z is N and R^1 is 2,3-dihydrobenzofuran-5-yl;

in If, Z is N and R^1 is chroman-6-yl;

in Ig, Z is N and R^1 is chromen-4-on-6-yl.

Especially preferred compounds are those of partial formulae Ih and Iah to Igh, which correspond to partial formulae I and Ia to Ig, but in which additionally:

Q is $-(CH_2)_4-$.

The invention further relates to a process for the preparation of indole derivatives of the formula I and their salts, characterized in that a compound of the formula II

$$Ind\text{-}Q\text{-}X^1 \qquad II$$

4

wherein

X^1 is X or NH_2,

X is Cl, Br, I, OH or an OH group functionally modified to form a reactive group, and

Ind and Q are as defined,

is reacted with a compound of the formula III

$$X^2-(CH_2)_2-ZR^1-(CH_2)_2-X^3 \qquad III$$

wherein

X^2 and X^3

can be identical or different and are each X if $X^1 = NH_2$ or are together NH in other cases, and

Z and R^1 are as defined,

or in that to prepare a compound of the formula I in which Z is N, a compound of the formula IV

$$Ind-Q-N(CH_2-CH_2-X)_2 \qquad IV$$

wherein

X, Q and Ind are as defined,

is reacted with a compound of the formula V

$$R^1-NH_2 \qquad V$$

wherein

R^1 is as defined,

or in that a compound which has formula I except that one or more hydrogen atoms have been replaced by one or more reducible groups and/or one or more additional C-C and/or C-N bonds are treated with a reducing agent,

or in that a compound which has formula I except that one or more hydrogen atoms have been replaced by one or more solvolyzable groups is treated with a solvolyzing agent,

and/or in that an OA group is optionally cleaved to form an OH group, and/or an Ind group and/or an Ar group is converted into another Ind and/or Ar group, and/or in that a resulting base or acid of the formula I is converted into one of its salts by treatment with an acid or base.

5

The compounds of the formula I are otherwise prepared by methods known per se, such as those described in the literature (e.g. in the standard works such as Houben- Weyl, Methoden der Organischen Chemie (Methods of Organic Chemistry), Georg-Thieme-Verlag, Stuttgart; Organic Reactions, John Wiley & Sons, Inc., New York; German Offenlegungsschrift 41 01 686), namely under reaction conditions such as those which are known and suitable for said reactions. It is also possible to make use of variants known per se, which are not mentioned in greater detail here.

If desired, the starting materials for the claimed process can also be formed in situ in such a way that they are not isolated from the reaction mixture but are immediately reacted further to give the compounds of the formula I.

In the compounds of the formula II, X^1 is preferably X; accordingly, in the compounds of the formula III, X^2 and X^3 are together preferably NH. The radical X is preferably Cl or Br, but it can also be I, OH or an OH group functionally modified to form a reactive group, especially alkylsulfonyloxy having 1-6 C atoms (e.g., methanesulfonyloxy) or arylsulfonyloxy having 6-10 C atoms (e.g., benzenesulfonyloxy, p-toluenesulfonyloxy, naphthalene-1- or -2-sulfonyloxy).

Accordingly, the indole derivatives of the formula I can be obtained especially by reacting compounds of the formula Ind-Q-Cl or Ind-Q-Br with piperidine/piperazine derivatives of the formula III in which X^2 and X^3 together are an NH group (designated as IIIa hereafter).

Some of the compounds of the formulae II and, in particular, III are known; the unknown compounds of the formulae II and III can easily be prepared analogously to the known compounds.

Primary alcohols of the formula Ind-Q-OH can be obtained, e.g., by reducing the appropriate carboxylic acids or their esters. Treatment with thionyl chloride, hydrogen bromide, phosphorus tribromide or similar

6

halogen compounds yields the corresponding halides of the formula Ind-Q-Hal. The corresponding sulfonyloxy compounds can be obtained from the alcohols Ind-Q-OH by reaction with the appropriate sulfonyl chlorides.

The iodine compounds of the formula Ind-Q-I can be obtained, e.g., by reacting potassium iodide with the appropriate p-toluenesulfonic acid esters. The amines of the formula Ind-Q-NH_2 can be prepared, e.g., from the halides with potassium phthalimide or by reducing the appropriate nitriles.

Most of the piperazine derivatives IIIa are known and can be obtained, e.g., by reacting bis(2-chloroethyl)amine or bis(2-chloroethyl)ammonium chloride with 5-aminobenzofuran, 2,3-dihydro-5-aminobenzofuran, 6-aminochroman or 6-aminochromen-4-one or an appropriately substituted derivative of the compounds mentioned. Compounds of the formula III (X^2 and X^3 = X in each case) can be prepared, e.g., by reducing diesters of the formula alkylOOC-CH_2-ZR^1-CH_2-COO-alkyl to give compounds of the formula HO-CH_2-CH_2-ZR^1-CH_2-CH_2OH (III, X^2 = X^3 = OH), this being followed, if desired, by reaction with $SOCl_2$ or PBr_3.

The reaction of the compounds of formulae II and III proceeds according to methods such as those known from the literature for the alkylation of amines. The components can be melted together in the absence of a solvent, in a sealed tube or an autoclave if necessary. It is also possible, however, to react the compounds in the presence of an inert solvent. Examples of suitable solvents are hydrocarbons such as benzene, toluene or xylene; ketones such as acetone or butanone; alcohols such as methanol, ethanol, isopropanol or n-butanol; ethers such as tetrahydrofuran (THF) or dioxane; amides such as dimethylformamide (DMF) or N-methylpyrrolidone; or nitriles such as acetonitrile, or else, if desired, mixtures of these solvents with one another or mixtures with water. It can be favorable to add an acid-binding agent, for example an alkali metal or alkaline earth metal hydroxide, carbonate or bicarbonate or another

alkali metal or alkaline earth metal salt of a weak acid, preferably a potassium, sodium or calcium salt, or to add an organic base such as triethylamine, dimethylaniline, pyridine or quinoline, or an excess of the amine component Ind-Q-NH_2 or of the piperidine or piperazine derivative of the formula IIIa. The reaction time is between about a few minutes and 14 days, depending on the conditions used, and the reaction temperature is preferably about 0-150°, normally 20-130°.

It is also possible to obtain a compound of the formula I by reacting a compound of the formula Ind-Q-$N(CH_2-CH_2-X)_2$ (IV) with a compound of the formula R^1-NH_2 (V).

Most of the compounds of the formula V are known; the unknown compounds can easily be prepared analogously to the known compounds. For example, starting from the appropriately substituted nitro compounds, they can be converted into the amines of the formula V by reduction. The compounds of the formula IV can be prepared by reaction of Ind-Q-Cl, Ind-Q-Br or Ind-Q-I with secondary amines of the formula $HN(CH_2-CH_2-X)_2$.

The reaction of compounds IV and V proceeds according to methods which are known from the literature and were given above for the alkylation of amines.

A compound of the formula I can also be obtained by treating a precursor, in which hydrogen atoms have been replaced by one or more reducible groups and/or one or more additional C-C and/or C-N bonds, with a reducing agent, preferably at temperatures of about -80 to +250°, in the presence of at least one inert solvent.

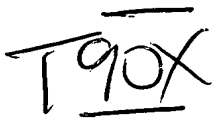
Reducible groups (groups replaceable by hydrogen) are, in particular, oxygen in a carbonyl group, hydroxyl, arylsulfonyloxy (e.g. p-toluenesulfonyloxy), N-benzenesulfonyl, N-benzyl or O-benzyl.

In principle, compounds containing only one of the above-mentioned groups or additional bonds, or compounds containing two or more of the above-mentioned groups or additional bonds adjacent to one another, can be converted into a compound of the formula I by

8

reduction, it being possible simultaneously to reduce substituents in the Ind group which are present in the starting compound. This is preferably carried out using nascent hydrogen or complex metal hydrides or by means of a Wolff-Kishner reduction or the reductions with hydrogen gas under transition metal catalysis.

Preferred starting materials for the reduction have formula VI



VI

wherein

Ind' is an Ind radical which can additionally be substituted in the 1-position by an arylsulfonyl group or an alkyloxycarbonyl group,

L is Q or a chain which corresponds to the radical Q except that one or more $-CH_2-$ groups have been replaced by -CO- and/or one or more hydrogen atoms have been replaced by one or more OH groups or a double bond, and

R^1 has the meaning given,

but wherein the following meanings cannot apply simultaneously: Ind' = Ind and L = Q.

In the compounds of the formula VI, L is preferably $-CO-(CH_2)_{n-2}-CO-$, wherein n is 2, 3 or 4 [specifically -COCO-, $-COCH_2CO-$, $-CO-(CH_2)_2-CO-$, $-CO-(CH_2)_3-CO-$], $-(CH_2)_{n-1}-CO-$, wherein n is 2, 3 or 4 [specifically $-CH_2-CO-$, $-CH_2CH_2-CO-$, $-(CH_2)_3-CO-$ or $-(CH_2)_4-CO-$], further examples being $-CO-CH_2CH_2-$, $-CO-(CH_2)_3-$, $-CH_2-CO-CH_2CH_2-$ or $-CH_2CH_2-CO-CH_2-$.

Compounds of the formula VI can be prepared, e.g., by reacting 4-R^1-piperazine or 4-R^1-piperidine with a compound of the formula VII

$$Ind'-L-X^1 \qquad VII$$

wherein

R^1, Ind', L and X^1 are as defined above,

under the conditions indicated above for the reaction of II with III.

If nascent hydrogen is used as the reducing agent, this can be produced, e.g., by treating metals with weak acids or with bases. Thus, it is possible, e.g., to use a mixture of zinc with an alkali metal hydroxide solution or a mixture of iron with acetic acid. It is also appropriate to use sodium or another alkali metal dissolved in an alcohol such as ethanol, isopropanol, butanol, amyl or isoamyl alcohol or phenol. It is also possible to use an aluminum-nickel alloy in aqueous-alkaline solution, ethanol being added if necessary. Sodium amalgam or aluminum amalgam in aqueous-alcoholic or aqueous solution is also suitable for producing the nascent hydrogen. The reaction can also be carried out in the heterogeneous phase, in which case it is convenient to use an aqueous phase and a benzene or toluene phase.

Other reducing agents which can be used to particular advantage are complex metal hydrides such as $LiAlH_4$, $NaBH_4$, diisobutylaluminum hydride or $NaAl(OCH_2CH_2OCH_3)_2H_2$, and diborane, catalysts such as BF_3, $AlCl_3$ or LiBr being added if desired. Solvents which are suitable for this purpose are, in particular, ethers such as diethyl ether, di-n-butyl ether, THF, dioxane, diglyme or 1,2-dimethoxyethane, and hydrocarbons such as benzene. Solvents which are suitable for a reduction with $NaBH_4$ are primarily alcohols such as methanol or ethanol, as well as water and aqueous alcohols. Reduction by these methods is preferably carried out at temperatures of about -80 to +150°, especially about 0-100°.

The reduction of -CO- groups in acid amides (e.g., those of the formula VI in which L is a $-(CH_2)_{n-1}-CO-$ group) to CH_2 groups can be carried out to particular advantage with $LiAlH_4$ in THF at temperatures of preferably about 0-66°. Arylsulfonyl protecting groups located in the 1-position of the indole ring can be simultaneously eliminated by reduction. N-Benzyl groups can be eliminated by reduction with sodium in liquid ammonia.

It is also possible to reduce one or more carbonyl groups to CH_2 groups according to the Wolff-Kishner

10

method, e.g., by treatment with anhydrous hydrazine in absolute ethanol, under pressure, at temperatures of preferably about 150-250°. A sodium alcoholate is advantageously used as the catalyst. The reduction can also be varied according to the Huang-Minlon method by carrying out the reaction with hydrazine hydrate in a high-boiling water-miscible solvent such as diethylene glycol or triethylene glycol, in the presence of an alkali such as sodium hydroxide. The reaction mixture is normally boiled for about 3-4 hours. The water is then distilled off and the hydrazone formed is decomposed at temperatures of up to about 200°. The Wolff-Kishner reduction can also be carried out with hydrazine in dimethyl sulfoxide at room temperature.

Moreover, it is possible to carry out certain reductions by using H_2 gas under the catalytic action of transition metals, such as, e.g., Raney Ni or Pd. In this way, e.g., Cl, Br, I, SH or, in certain cases, even OH groups can be replaced by hydrogen. Nitro groups can also be converted into NH_2 groups by catalytic hydrogenation with Pd/H_2 in methanol.

Compounds which have formula I except that one or more H atoms have been replaced by one or more solvolyzable groups can be solvolyzed, especially hydrolyzed, to give the compounds of the formula I.

The starting materials for the solvolysis can be obtained for example by reacting IIIa with compounds which have formula II (X^1 = X) except that one or more H atoms have been replaced by one or more solvolyzable groups. Thus, in particular, 1-acylindole derivatives (which have formula I except that, in the 1-position of the Ind radical, they contain an acyl group, preferably an alkoxycarbonyl, alkanoyl, alkylsulfonyl or arylsulfonyl group having up to 10 C atoms in each case, such as methanesulfonyl, benzenesulfonyl or p-toluenesulfonyl) can be hydrolyzed to give the corresponding indole derivatives unsubstituted in the 1-position of the indole ring, e.g. in an acidic or, preferably, neutral or alkaline medium at temperatures of preferably about 0-200°.

Sodium, potassium or calcium hydroxide, sodium or potassium carbonate, or ammonia, is conveniently used as the base. The chosen solvents are preferably water; lower alcohols such as methanol or ethanol; ethers such as THF or dioxane; sulfones such as tetramethylene sulfone; or mixtures thereof, especially mixtures containing water. Hydrolysis can also be carried out simply by treatment with water alone, especially at the boiling point.

A compound of the formula I can furthermore be converted to another compound of the formula I by methods known per se.

Compounds of the formula I in which Ind is an indol- 3-yl radical substituted by CO-R^1 can be obtained by derivatizing appropriate carboxyindol-3-yl compounds. It is possible, e.g., to esterify the acids with appropriate alcohols or alcoholates, using methods known per se. It is also possible to amidate acids or esters with primary or secondary amines. It is preferred to react the free carboxylic acid with the amine under the conditions of a peptide synthesis. This reaction is preferably carried out in the presence of a dehydrating agent, e.g., a carbodiimide such as dicyclohexylcarbodiimide or else N-(3-dimethylaminopropyl)-N-ethylcarbodiimide, or propanephosphonic anhydride (q.v. Angew. Chem. 92, 129 (1980)), diphenylphosphoryl azide or 2-ethoxy-N-ethoxycarbonyl-1,2-dihydroquinoline, in an inert solvent, e.g., a halogenated hydrocarbon such as methylene chloride, an ether such as THF or dioxane, an amide such as DMF or dimethylacetamide, or a nitrile such as acetonitrile, at temperatures of preferably about -10 to 40, preferably about 0-30°. Instead of the acid or amide, it is also possible to use reactive derivatives of these substances in the reaction, e.g., those in which reactive groups are blocked by protecting groups in an intermediate step. The acids can also be used in the form of their activated esters, which are conveniently formed in situ, e.g., by the addition of 1-hydroxybenztriazole or N-hydroxysuccinimide.

Furthermore, cyano-substituted indol-3-yl

radicals can be hydrolyzed to give carboxy-indol-3-yl or carbamido-indol-3-yl radicals.

Conversely, however, it is particularly convenient to prepare the nitriles by elimination of water, starting from the amides, e.g., by means of trichloroacetyl chloride/Et_3N [Synthesis (2), 184, (1985)] or with $POCl_3$ (J. Org. Chem. 26, 1003 (1961)).

A base of the formula I can be converted with an acid into the corresponding acid addition salt. Acids which produce physiologically acceptable salts are suitable for this reaction. Thus, it is possible to use inorganic acids, e.g., sulfuric acid, hydrohalic acids such as hydrochloric acid or hydrobromic acid, phosphoric acids such as orthophosphoric acid, nitric acid and sulfamic acid, as well as organic acids, i.e., specifically aliphatic, alicyclic, araliphatic, aromatic or heterocyclic monobasic or polybasic carboxylic, sulfonic or sulfuric acids, such as formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, benzoic acid, salicylic acid, 2-phenylpropionic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methanesulfonic or ethanesulfonic acid, ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenemonosulfonic and naphthalenedisulfonic acids and laurylsulfuric acid.

If desired, the free bases of the formula I can be liberated from their salts by treatment with strong bases such as sodium or potassium hydroxide or sodium or potassium carbonate provided there are no other acid groups in the molecule. In those cases where the compounds of the formula I have free acid groups, salt formation can also be achieved by treatment with bases. Suitable bases are alkali metal hydroxides, alkaline earth metal hydroxides or organic bases in the form of primary, secondary or tertiary amines.

The invention further relates to the use of the

compounds of the formula I and their physiologically acceptable salts for the manufacture of pharmaceutical preparations, especially by a non-chemical route. For this purpose, they can be converted into a suitable dosage form together with at least one excipient or adjunct and, if appropriate, in combination with one or more additional active ingredients.

The invention further relates to compositions, especially pharmaceutical preparations, containing at least one compound of the formula I and/or one of their physiologically acceptable salts. These preparations can be used as drugs in human or veterinary medicine. Possible excipients are organic or inorganic substances which are suitable for enteral (e.g., oral), parenteral or topical administration and which do not react with the novel compounds, examples of such excipients being water, vegetable oils, benzyl alcohols, polyethylene glycols, gelatin, carbohydrates such as lactose or starch, magnesium stearate, talc and petroleum jelly. Tablets, coated tablets, capsules, syrups, juices, drops or suppositories are used in particular for enteral administration, solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions or implants are used for parenteral administration, and ointments, creams or powders are used for topical administration. The novel compounds can also be lyophilized and the resulting lyophilizates used, e.g., to manufacture injectable preparations.

The preparations indicated can be sterilized and/or can contain adjuncts such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for influencing the osmotic pressure, buffer substances, colorants, taste correctors and/or flavorings. If desired, they can also contain one or more additional active ingredients, e.g. one or more vitamins.

The compounds of the formula I and their physiologically acceptable salts can be used for the therapeutic treatment of the human or animal body and for controlling diseases. They can be used for treating

disorders of the central nervous system, such as tension, depressions and/or psychoses, and side-effects in the treatment of hypertension (e.g., with α-methyldopa). The compounds can also be used in endocrinology and gynecology, e.g., for the therapeutic treatment of acromegaly, hypogonadism, secondary amenorrhea, premenstrual syndrome and undesired puerperal lactation, and also for the prophylaxis and therapy of cerebral disorders (e.g., migraine), especially in geriatrics in a manner similar to certain ergot alkaloids and for controlling the sequelae of cerebral infarction (apoplexia cerebri), such as stroke and cerebral ischemia.

In these treatments, the substances of the invention are normally administered analogously to known, commercially available preparations (e.g., bromocriptine, dihydroergocornine), preferably in dosages of about 0.2-500 mg, especially 0.2-50 mg per dosage unit. The daily dosage is preferably about 0.001-10 mg/kg of body weight. The low dosages (about 0.2-1 mg per dosage unit; about 0.001-0.005 mg/kg of body weight) are particularly suitable for use as anti-migraine preparations; dosages of about 10-50 mg per dosage unit are preferred for the other indications. However, the particular dose for each individual patient depends on a very wide variety of factors, for example, the activity of the particular compound used, age, body weight, general state of health, sex, diet, time and method of administration, rate of excretion, drug combination and severity of the particular disease to which the therapy is applied. Oral administration is preferred.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

In the foregoing and in the following examples, all temperatures are set forth uncorrected in degrees Celsius and unless otherwise indicated, all parts and percentages are by weight.

15

The entire disclosure of all applications, patents and publications, cited above and below, and of corresponding German application P 43 33 254.4, filed September 30, 1993, are hereby incorporated by reference.

In the following Examples, "working-up in conventional manner" means: Water is added if necessary, extraction is carried out with methylene chloride, the organic phase is separated off, dried over sodium sulfate and filtered, the filtrate is evaporated and the residue is purified by chromatography on silica gel and/or by crystallization. Temperatures are given in °C. Rf values were obtained by thin layer chromatography on silica gel.

16

EXAMPLES

Example 1

1.8 g of 3-(4-chlorobutyl)-5-methoxyindole [obtainable by diazotization of p-methoxyaniline, reaction with ethyl cyclohexanone-2-carboxylate according to Japp-Klingemann to give 4-(2-carbethoxyindol-3-yl)butyric acid, alkaline hydrolysis, decarboxylation, reduction with $LiAlH_4$ and reaction with $SOCl_2$] and 1.9 g of 1-(2-hydroxymethylbenzofuran-5-yl)piperazine [obtainable by reaction of N,N-bis(2-chloroethyl)amine with 2-hydroxymethyl-5-aminobenzofuran] are dissolved in 200 ml of acetonitrile and the mixture is stirred at room temperature for 10 hours. Customary working up gives 1-[4-(5-methoxyindol-3-yl)butyl]-4-(2-hydroxymethyl-benzofuran-5-yl)piperazine, m.p. 159°.

The following are obtained analogously by reaction of 3-(4-chlorobutyl)-5-methoxyindole with 1-(2,3-dihydro-benzofuran-5-yl)piperazine:

1-[4-(5-methoxyindol-3-yl)butyl]-4-(2,3-dihydro-benzofuran-5-yl)piperazine, m.p. 111-112°;

of 3-(4-chlorobutyl)-5-hydroxyindole with 1-(chroman-6-yl)piperazine:

1-[4-(5-hydroxyindol-3-yl)butyl]-4-(chroman-6-yl)-piperazine, m.p. 220-222°;

of 3-(4-chlorobutyl)-5-methoxyindole with 1-(chroman-6-yl)piperazine:

1-[4-(5-methoxyindol-3-yl)butyl]-4-(chroman-6-yl)-piperazine, m.p. 129-130°;

of methyl 3-(4-chlorobutyl)-5-indolecarboxylate with 1-(chroman-6-yl)piperazine:

1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(chroman-6-yl)piperazine;

of ethyl 3-(4-chlorobutyl)-5-indolecarboxylate with 1-(benzofuran-5-yl)piperazine:

1-[4-(5-ethoxycarbonylindol-3-yl)butyl]-4-(benzo-furan-5-yl)piperazine;

of 3-(4-chlorobutyl)-5-methoxyindole with 1-(benzofuran-5-yl)piperazine:

1-[4-(5-methoxyindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine;

17

of 3-(4-chlorobutyl)-5-methoxycarbonylindole with 1-(chromen-4-on-6-yl)piperazine:

1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(chromen-4-on-6-yl)piperazine;

of 3-(4-chlorobutyl)-5-cyanoindole with 1-(chromen-4-on-6-yl)piperazine:

1-[4-(5-cyanoindol-3-yl)butyl]-4-(chromen-4-on-6-yl)piperazine;

of 3-(4-chlorobutyl)-5-chloroindole with 1-(2,3-dihydrobenzofuran-5-yl)piperazine:

1-[4-(5-chloroindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine;

of 3-(4-chlorobutyl)-5-methoxycarbonylindole with 1-(2,3-dihydrobenzofuran-5-yl)piperazine:

1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine;

of 3-(4-chlorobutyl)-5-methoxycarbonylindole with 4-(2,3-dihydrobenzofuran-5-yl)piperidine:

1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperidine;

of 3-(4-chlorobutyl)-5-methoxycarbonylindole with 4-(2,3-dihydrobenzofuran-5-yl)-4-hydroxypiperidine:

1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)-4-hydroxypiperidine;

of 3-(4-chlorobutyl)-5,6-dimethoxyindole with 1-(chroman-6-yl)piperazine:

1-[4-(5,6-dimethoxyindol-3-yl)butyl]-4-(chroman-6-yl)piperazine;

of 3-(4-chlorobutyl)-5-cyanoindole with 1-(2-carboxybenzofuran-5-yl)piperazine:

1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carboxybenzofuran-5-yl)piperazine;

of 3-(4-chlorobutyl)-6-fluoroindole with 1-(2,3-dihydrobenzofuran-5-yl)piperazine:

1-[4-(6-fluoroindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine.

Example 2

1.8 g of 1-[4-(5-methoxycarbonylindol-3-yl)-

18

butyl]-4-(chroman-6-yl)piperazine [obtainable according to Example 1] are boiled for 0.5 hours with 100 ml of 2N ethanolic KOH, worked up in the customary manner and give 1-[4-(5-carboxyindol-3-yl)butyl]-4-(chroman-6-yl)piperazine.

The following are obtained analogously by alkaline hydrolysis of the corresponding esters starting from 1-[4-(5-ethoxycarbonylindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine:

1-[4-(5-carboxyindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine:

from 1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(chromen-4-on-6-yl)piperazine:

1-[4-(5-carboxyindol-3-yl)butyl]-4-(chromen-4-on-6-yl)piperazine;

from 1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine:

1-[4-(5-carboxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine;

from 1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)-4-hydroxypiperidine;

1-[4-(5-carboxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)-4-hydroxypiperidine.

Example 3

2.8 g of 1-[4-(5-carboxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine are suspended in 100 ml of N-methylpyrrolidine. 3.2 g of 2-chloro-1-methylpyridinium methanesulfonate are then added and the mixture is stirred at room temperature for 12 hours. Dried NH_3 gas is then passed into the resulting solution until it is saturated and the mixture is stirred again for 10 hours. Customary working up gives 1-[4-(5-carbamoylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)-piperazine.

The following are obtained analogously by amidation of the following carboxylic acids with 2-chloro-1-methylpyridinium methanesulfonate:

from 1-[4-(5-carboxyindol-3-yl)butyl]-4-(2,3-dihydro-

benzofuran-5-yl)piperidine

1-[4-(5-carbamoylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperidine, m.p. 155-157°;

from 1-[4-(5-carboxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)-4-hydroxypiperidine

1-[4-(5-carbamoylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)-4-hydroxypiperidine, m.p. 69° (dec.);

from 1-[4-(5-carboxyindol-3-yl)butyl]-4-(chroman-6-yl)-piperazine

1-[4-(5-carbamoylindol-3-yl)butyl]-4-(chroman-6-yl)-piperazine.

Example 4

Analogously to Example 3, starting from 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carboxybenzofuran-5-yl)piperazine reaction with 2-chloro-1-methylpyridinium methanesulfonate gives 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoylbenzofuran-5-yl)piperazine, m.p. 269-272° (hydrochloride).

Example 5

A mixture of 2.6 g of 3-(2-aminoethyl)-5-cyanoindole [obtainable by reaction of 5-cyanoindole with 2-chloroacetyl chloride to give 3-(2-chloroacetyl)-5-cyanoindole, subsequent reduction with diborane, reaction with phthalimide and hydrolysis] and one equivalent of 5-[N,N-bis(2-chloroethyl)amino]benzofuran [obtainable by reaction of 2-chloroacetyl chloride with 5-aminobenzofuran and subsequent reduction with diborane] in 40 ml of acetone and 40 ml of water is boiled for 20 hours and then worked up in the customary manner. 1-[2-(5-Cyanoindol-3-yl)ethyl]-4-(benzofuran-5-yl)piperazine is obtained.

The following are obtained analogously by reaction of 5-[N,N-bis(2-chloroethyl)amino]benzofuran with 3-(4-aminobutyl)-5-methoxymethylindole:

1-[4-(5-methoxymethylindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine;

20

with 3-(3-aminopropyl)-5-hydroxyindole:
1-[3-(5-hydroxyindol-3-yl)propyl]-4-(benzofuran-5-yl)piperazine;
with 3-(2-aminoethyl)-5-methoxyindole:
1-[2-(5-methoxyindol-3-yl)ethyl]-4-(benzofuran-5-yl)piperazine;
with methyl 3-(3-aminopropyl)-5-indolecarboxylate:
1-[3-(5-methoxycarbonylindol-3-yl)propyl]-4-(benzofuran-5-yl)piperazine;
with ethyl 3-(2-aminoethyl)-5-indolecarboxylate:
1-[2-(5-ethoxycarbonylindol-3-yl)ethyl]-4-(benzofuran-5-yl)piperazine;
with 3-(4-aminobutyl)-5-fluoroindole:
1-[4-(5-fluoroindol-3-yl)butyl]-4-(benzofuran-5-yl)-piperazine;
with 3-(3-aminopropyl)-5-cyanoindole:
1-[3-(5-cyanoindol-3-yl)propyl]-4-(benzofuran-5-yl)piperazine.

Example 6

Analogously to Example 5, reaction of 3.2 g of 3-(2-aminoethyl)-5-methoxyindole with 1.3 equivalents of 6-[N,N-bis(2-chloroethyl)amino]chroman [obtainable by reaction of 2-chloroacetyl chloride with 6-aminochroman and subsequent reduction with diborane] gives 1-[2-(5-methoxyindol-3-yl)ethyl]-4-(chroman-6-yl)piperazine.

The following are obtained analogously by reaction of 6-[N,N-bis(2-chloroethyl)amino]chroman
with 3-(4-aminobutyl)-5-methoxymethylindole:
1-[4-(5-methoxymethylindol-3-yl)butyl]-4-(chroman-6-yl)piperazine;
with 3-(3-aminopropyl)-5-hydroxyindole:
1-[3-(5-hydroxyindol-3-yl)propyl]-4-(chroman-6-yl)-piperazine;
with 3-(2-aminoethyl)-5-methoxyindole:
1-[2-(5-methoxyindol-3-yl)ethyl]-4-(chroman-6-yl)-piperazine;
with methyl 3-(3-aminopropyl)-5-indolecarboxylate:

1-[3-(5-methoxycarbonylindol-3-yl)propyl]-4-(chroman-6-yl)piperazine;

with ethyl 3-(2-aminoethyl)-5-indolecarboxylate:

1-[2-(5-ethoxycarbonylindol-3-yl)ethyl]-4-(chroman-6-yl)piperazine;

with 3-(4-aminobutyl)-5-fluoroindole:

1-[4-(5-fluoroindol-3-yl)butyl]-4-(chroman-6-yl)-piperazine;

with 3-(3-aminopropyl)-5-cyanoindole:

1-[3-(5-cyanoindol-3-yl)propyl]-4-(chroman-6-yl)piperazine.

Example 7

A solution of 3.9 g of 1-[4-(5-carboxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine in 250 ml of DMF is treated with 1 g of N-methylmorpholine. A solution of one equivalent of tert-butylamine in 5 ml of DMF, 1.3 g of 1-hydroxybenzotriazole and a solution of 1.9 g of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in 20 ml of DMF are added with stirring. The mixture is stirred at room temperature for 16 hours and the filtrate is evaporated. Customary working up gives 1-[4-(5-N-tert-butylcarbamoylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine.

The following are obtained analogously by reaction with tert-butylamine starting

from 1-[4-(5-carboxyindol-3-yl)butyl]-4-(chroman-6-yl)-piperazine:

1-[4-(5-N-tert-butylcarbamoylindol-3-yl)butyl]-4-(chroman-6-yl)piperazine:

from 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carboxybenzofuran-5-yl)piperazine:

1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-N-tert-butylcarbamoylbenzofuran-5-yl)piperazine.

Example 8

A mixture of 2.1 g of 1-[4-(5-methoxyindol-3-yl)butyl]-4-(chroman-6-yl)piperazine [can be prepared according to Example 1], 1.8 g of pyridine hydrochloride

22

and 50 ml of pyridine is boiled for 3 hours. It is cooled and evaporated, and the residue is worked up in the customary manner and gives 1-[4-(5-hydroxyindol-3-yl)-butyl]-4-(chroman-6-yl)piperazine, m.p. 220-222°.

The following are obtained analogously

from 1-[4-(5-methoxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine:

1-[4-(5-hydroxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine;

from 1-[4-(5-methoxyindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine:

1-[4-(5-hydroxyindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine;

from 1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(chromen-4-on-6-yl)piperazine:

1-[4-(5-hydroxycarbonylindol-3-yl)butyl]-4-(chromen-4-on-6-yl)piperazine;

from 1-[4-(5-methoxymethylindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine:

1-[4-(5-hydroxymethylindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine;

from 1-[2-(5-methoxyindol-3-yl)ethyl]-4-(benzofuran-5-yl)piperazine:

1-[2-(5-hydroxyindol-3-yl)ethyl]-4-(benzofuran-5-yl)piperazine;

from 1-[2-(5-methoxyindol-3-yl)ethyl]-4-(benzofuran-5-yl)piperazine:

1-[2-(5-hydroxyindol-3-yl)ethyl]-4-(benzofuran-5-yl)piperazine.

Example 9

Analogously to Example 1, starting from 3-(4-chlorobutyl)-5-cyanoindole [obtainable by reaction of 5-cyanoindole with 4-chlorobutyryl chloride to give 3-(4-chlorobutyryl)-5-methoxyindole and subsequent reduction with $NaAlH_2(OCH_2CH_2OCH_3)_2$] by reaction with 1-(2-ethoxycarbonylbenzofuran-5-yl)piperazine [obtainable by reaction of N,N-bis(2-chloroethyl)amine with 2-ethoxycarbonyl-5-aminobenzofuran] gives, after customary

23

working up, 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-ethoxycarbonylbenzofuran-5-yl)piperazine, m.p. 221-223° (dihydrochloride).

The following are obtained analogously by reaction

of 3-(4-chlorobutyl)-5-methoxyindole with 1-(2-cyanobenzofuran-5-yl)piperazine:

1-[4-(5-methoxyindol-3-yl)butyl]-4-(2-cyanobenzofuran-5-yl)piperazine;

of 3-(4-chlorobutyl)-5,6-dimethoxyindole with 1-(chroman-6-yl)piperazine:

1-[4-(5,6-dimethoxyindol-3-yl)butyl]-4-(chroman-6-yl)piperazine;

of 3-(4-chlorobutyl)-5,6-difluoroindole with 1-(chroman-6-yl)piperazine:

1-[4-(5,6-difluoroindol-3-yl)butyl]-4-(chroman-6-yl)piperazine;

of methyl 3-(4-chlorobutyl)-6-indolecarboxylate with 1-(chroman-6-yl)piperazine:

1-[4-(6-methoxycarbonylindol-3-yl)butyl]-4-(chroman-6-yl)piperazine;

of ethyl 3-(3-chloropropyl)-6-indolecarboxylate with 1-(2-cyanobenzofuran-5-yl)piperazine:

1-[3-(6-ethoxycarbonylindol-3-yl)propyl]-4-(2-cyanobenzofuran-5-yl)piperazine;

of 3-(4-chlorobutyl)-5-methoxyindole with 1-(2-N-methylcarbamoylbenzofuran-5-yl)piperazine:

1-[4-(5-methoxyindol-3-yl)butyl]-4-(2-N-methylcarbamoylbenzofuran-5-yl)piperazine;

of 3-(4-chlorobutyl)-6-chloroindole with 1-(chromen-4-on-6-yl)piperazine:

1-[4-(6-chloroindol-3-yl)butyl]-4-(chromen-4-on-6-yl)piperazine;

of 3-(2-chloroethyl)-5-cyanoindole with 1-(chromen-4-on-6-yl)piperazine:

1-[2-(5-cyanoindol-3-yl)ethyl]-4-(chromen-4-on-6-yl)piperazine;

of 3-(2-chloroethyl)-5,6-dichloroindole with 1-(2,3-dihydrobenzofuran-5-yl)piperazine:

24

1-[2-(5,6-dichloroindol-3-yl)ethyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine;

of 3-(4-chlorobutyl)-5-methoxycarbonylindole with 1-(2-carboxybenzofuran-5-yl)piperazine:

1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(2-carboxybenzofuran-5-yl)piperazine;

of 3-(2-chloroethyl)-5-methoxycarbonylindole with 4-(2-carboxybenzofuran-5-yl)piperidine:

1-[2-(5-methoxycarbonylindol-3-yl)ethyl]-4-(2-carboxybenzofuran-5-yl)piperazine;

of 3-(4-chlorobutyl)-6-methoxycarbonylindole with 4-(3-carboxybenzofuran-5-yl)-4-hydroxypiperidine:

1-(4-(6-methoxycarbonylindol-3-yl)butyl]-4-(3-carboxybenzofuran-5-yl)-4-hydroxypiperidine;

of 3-(4-chlorobutyl)-7-methoxycarbonylindole with 4-(3-carboxybenzofuran-5-yl)-4-hydroxypiperidine;

1-[4-(7-methoxycarbonylindol-3-yl)butyl]-4-(3-carboxybenzofuran-5-yl)-4-hydroxypiperidine;

of 3-(4-chlorobutyl)-5,6-dimethoxyindole with 1-(2-carboxybenzofuran-5-yl)piperazine:

1-[4-(5,6-dimethoxyindol-3-yl)butyl]-4-(2-carboxybenzofuran-5-yl)piperazine.

Example 10

A solution of 3.6 g of 1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(chromen-4-on-6-yl)piperazine in 40 ml of THF is added dropwise with stirring at room temperature to a suspension of 0.6 g of lithium aluminum hyride in 20 ml of THF. The mixture is then stirred for a further hour at 25°C, 20 ml of dilute sodium hydroxide solution are added, the mixture is filtered and the filtrate is worked up in the customary manner. 1-[4-(5-Hydroxymethylindol-3-yl)butyl]-4-(chromen-4-on-6-yl)piperazine is obtained.

The following are obtained analagously by reduction

of 1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(chroman-6-yl)piperazine

1-[4-(5-hydroxymethylindol-3-yl)butyl]-4-(chroman-

25

6-yl)piperazine;
of 1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-benzofuran-5-yl)piperazine
1-[4-(5-hydroxymethylindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine;
of 1-[3-(5-methoxycarbonylindol-3-yl)propyl]-4-(chroman-6-yl)piperidine
1-[3-(5-hydroxymethylindol-3-yl)propyl]-4-(chroman-6-yl)piperidine
of 1-[2-(5-methoxycarbonylindol-3-yl)ethyl]-4-chroman-6-yl)piperidine
1-[2-(5-hydroxymethylindol-3-yl)ethyl]-4-(chroman-6-yl)piperidine.

Example 11

HCl gas is passed into a boiling solution of 2.5 g of 1-[4-(5-carboxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine in 50 ml of absolute methanol for 2 hours. The mixture is then boiled for a further hour, worked up in the customary manner and gives 1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine.

The following are obtained analagously by esterification
of 1-[4-(5-carboxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)-4-hydroxypiperidine:
1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)-4-hydroxypiperidine;
of 1-[4-(5-carboxyindol-3-yl)butyl]-4-(chroman-6-yl)-piperazine:
1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(chroman-6-yl)piperazine;
of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carboxybenzofuran-5-yl)piperazine:
1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-methoxycarbonyl-benzofuran-5-yl)piperazine.

Example A: Injection vials

A solution of 100 g of an active ingredient of

26

the formula I and 5 g of disodium hydrogen phosphate in 3 l of double-distilled water is adjusted to pH 6.5 with 2 N hydrochloric acid, sterile-filtered, filled into injection vials, lyophilized and sterile-sealed. Each injection vial contains 5 mg of active ingredient.

Example B: Suppositories

A mixture of 20 mg of an active ingredient of the formula I is melted with 100 g of soya lecithin and 1,400 g of cocoa butter, poured into moulds and allowed to cool. Each suppository contains 20 mg of active ingredient.

Example C: Solution

A solution of 1 g of an active ingredient of the formula I, 9.38 g of $NaH_2PO_4 \times 2\ H_2O$, 28.48 g $Na_2HPO_4 \times 12\ H_2O$ and 0.1 g of benzalkonium chloride is prepared in 940 ml of double-distilled water. The pH is adjusted to 6.8, and the solution is made up to 1 l and sterilized by irradiation. This solution can be used in the form of eyedrops.

Example D: Ointment

500 mg of an active ingredient of the formula I are mixed with 99.5 g of petroleum jelly under aseptic conditions.

Example E: Tablets

A mixture of 1 kg of active ingredient of the formula I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is compressed to tablets in conventional manner so that each tablet contains 10 mg of active ingredient.

Example F: Coated tablets

Tablets are formed by compression analogously to Example E and then covered in conventional manner with a coating of sucrose, potato starch, talc, tragacanth and colorant.

27

Example G: Capsules

2 kg of active ingredient of the formula I are filled into hard gelatin capsules in conventional manner so that each capsule contains 20 mg of the active ingredient.

Example H: Ampoules

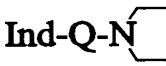
A solution of 1 kg of active ingredient of the formula I in 60 l of double-distilled water is filled into ampoules and lyophilized under aseptic conditions and the ampoules are sealed under sterile conditions. Each ampoule contains 10 mg of active ingredient.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

WHAT IS CLAIMED IS:

1. A compound according to formula I



I

wherein

Ind is unsubstituted indol-3-yl, indol-3-yl monosubstituted by OH, OA, CN, Hal, COR^2 or CH_2R^2, or indol-3-yl polysubstituted by OH, OA, CN, Hal, COR^2, CH_2R^2 or combinations thereof;

R^1 is benzofuran-5-yl, ~~2,3-dihydrobenzofuran-5-yl, chroman-6-yl,~~ chroman-4-on-6-yl, 3-chromen-6-yl or chromen-4-on-6-yl, which in each case is unsubstituted or monosubstituted by CN, CH_2OH, CH_2OA or COR^2;

Q is C_mH_{2m};

Z is ~~N or CR³~~;

A is alkyl having 1-6 C atoms;

Hal is F, Cl, Br or I;

R^2 is OH, OA, NH_2, NHA or NA_2;

R^3 is H, OH or OA; and

m is 2, 3 or 4; or

a physiologically acceptable salt thereof.

2. A compound according to claim 1, wherein said compound is:

(a) 1-[4-(5-methoxyindol-3-yl)butyl]-4-(2-hydroxymethylbenzofuran-5-yl)piperazine or a physiologically acceptable salt thereof;

~~(b) 1-[4-(5-carbamoylindol-3-yl)butyl]-4-hydroxy-4-(2,3-dihydrobenzofuran-5-yl)piperidine or a physiologically acceptable salt thereof;~~

~~(c) 1-[4-(5-carbamoylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperidine or a physiologically acceptable salt thereof;~~

~~(d) 1-[4-(5-methoxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine or a physiologically acceptable salt thereof;~~

(e) 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-ethoxycarbonylbenzofuran-5-yl)piperazine or a physiologically acceptable salt thereof;

(f) 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoylbenzofuran-5-yl)piperazine or a physiologically acceptable salt thereof;

~~(g) 1-[4-(5-methoxyindol-3-yl)butyl]-4-(chroman-6-yl)piperazine or a physiologically acceptable salt thereof;~~

~~or~~

~~(h) 1-[4-(5-hydroxyindol-3-yl)butyl]-4-(chroman-6-yl)piperazine or a physiologically acceptable salt thereof.~~

3. A compound according to claim 1, wherein Ind is unsubstituted indol-3-yl, indol-3-yl monosubstituted by OH, OA, CN, Hal, COR^2 or CH_2R^2, or indol-3-yl disubstituted by OH, OA, CN, Hal, COR^2 or CH_2R^2.

4. A compound according to claim 1, wherein Ind is indol-3-yl monosubstituted in the 5-position by OH, OA, CN, Hal, COR^2 or CH_2R^2.

5. A compound according to claim 1, wherein Ind is indol-3-yl monosubstituted in the 4-, 6- or 7-position by OH, OA, CN, Hal, COR^2 or CH_2R^2.

6. A compound according to claim 1, wherein A is methyl or ethyl.

31

7. A compound according to claim 1, wherein R^1 is benzofuran-5-yl, ~~2,3-dihydrobenzofuran-5-yl, chroman-6-yl~~ or chroman-4-on-6-yl which, in each case is unsubstituted or monosubstituted by $-CH_2OH$, $-CONH_2$, $-CO_2A$ or $-CO_2NHA$.

8. A compound according to claim 1, wherein Q is $-(CH_2)_4-$.

9. A compound according to claim 1, wherein Z is -N-, -C(OH)- or -CH-.

~~10~~ 9. A compound according to claim 1, wherein Ind is indol-3-yl substituted in the 5-position by OH or OA.

~~11~~ 10. A compound according to claim 1, wherein Ind is indol-3-yl substituted in the 5-position by $CONH_2$ or CN.

~~12~~ 11. A compound according to claim 1, wherein ~~Z is N and~~ R^1 is unsubstituted benzofuran-5-yl or ~~benzo-5-yl~~ benzofuran-5-yl substituted by CN, CH_2OH, CH_2OA or COR^2.

13. A compound according to claim 1, wherein Z is -CH(OH)-.

14. A compound according to claim 1, wherein Z is N and R^1 is 2,3-dihydrobenzofuran-5-yl.

15. A compound according to claim 1, wherein Z is N and R^1 is chroman-6-yl.

~~16~~ 12. A compound according to claim 1, wherein ~~Z is N and~~ R^1 is chromen-4-on-6-yl.

~~17~~ 13. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

32

18. A composition according to claim 17, wherein said compound is present in an amount of 0.2-500 mg.

19. A method of treating tension, depression, psychosis or side effects associated with the treatment of hypertension, comprising administering a compound according to claim 1.

20. A method of treating acromegaly, hypogonadism, secondary amenorrhea, premenstrual syndrome, undesired puerperal lactation, or cerebral disorders, comprising administering a compound according to claim 1.

21. A method of treating migraines, comprising administering a compound according to claim 1.

22. A method according to claim 21, wherein said compound is administered in a daily dosage of 0.001-0.005 mg/kg of body weight.

ABSTRACT OF THE DISCLOSURE

Piperidine and piperazine derivatives of the formula I

I

wherein

Ind is an indol-3-yl radical which is unsubstituted or mono- or polysubstituted by OH, OA, CN, Hal, COR^2 or CH_2R^2,

R^1 is benzofuran-5-yl or 2,3-dihydrobenzofuran-5-yl, chroman-6-yl, chroman-4-on-6-yl, 3-chromen-6-yl or chromen-4-on-6-yl, which is unsubstituted or monosubstituted by CN, CH_2OH, CH_2OA or COR^2,

Q is C_mH_{2m},

Z is N or CR^3,

A is alkyl having 1-6 C atoms,

Hal is F, Cl, Br or I,

R^2 is OH, OA, NH_2, NHA or NA_2,

R^3 is H, OH or OA and

m is 2, 3 or 4,

and their physiologically acceptable salts, are active on the central nervous system.

PTO

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY
(Includes Reference to PCT International Applications)

ATTORNEY'S DOCKET NUMBER
MERCK 1617

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

PIPERIDINES AND PIPERAZINES

the specification of which (check only one item below):

☐ is attached hereto.

☐ was filed as United States application

Serial No. _____

on _____,

and was amended

on _____ (if applicable).

☐ was filed as PCT international application

Number _____

on _____,

and was amended under PCT Article 19

on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowlege the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (if PCT, indicate "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
Germany	P 43 33 254.4	30 September 1993	☒ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO

Combined Declaration For Patent Application and Power of Attorney (Continued)
(Includes Reference to PCT International Applications)

ATTORNEY'S DOCKET NUMBER: MERCK 1617

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED

PCT APPLICATION NO.	PCT FILING DATE	U.S. SERIAL NUMBERS ASSIGNED *(if any)*			

POWER OF ATTORNEY: As a named inventor, I hereby appoint I. William Millen (19,544); John L. White (17,746); Anthony J. Zelano (27,969); Alan E. J. Branigan (20,565); John R. Moses (24,983); Harry B. Shubin (32,004); Brion P. Heaney (32,542); Diana Hamlet-King (33,302); Richard J. Traverso (30,595); Richard E. Kurtz (33,936); John A. Sopp (33,103) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

Send Correspondence to: MILLEN, WHITE, ZELANO AND BRANIGAN, P.C.
Arlington Courthouse Plaza I, Suite 1400
2200 Clarendon Boulevard
Arlington, Virginia 22201

Telephone No. 703-243-6333

Direct Telephone Calls to: Brion P. Heaney

201	FULL NAME OF INVENTOR	FAMILY NAME: BOTTCHER	FIRST GIVEN NAME: Henning	SECOND GIVEN NAME:
	RESIDENCE & CITIZENSHIP	CITY: 64287 Darmstadt	STATE OR FOREIGN COUNTRY: Germany	COUNTRY OF CITIZENSHIP: Germany
	POST OFFICE ADDRESS	STREET: c/o E. MERCK	CITY: 64271 Darmstadt	STATE & ZIP CODE/COUNTRY: Germany
202	FULL NAME OF INVENTOR	FAMILY NAME: SEYFRIED	FIRST GIVEN NAME: Christoph	SECOND GIVEN NAME:
	RESIDENCE & CITIZENSHIP	CITY: 64342 Seeheim-Jugenheim	STATE OR FOREIGN COUNTRY: Germany	COUNTRY OF CITIZENSHIP: Germany
	POST OFFICE ADDRESS	STREET: c/o E. MERCK	CITY: 64271 Darmstadt	STATE & ZIP CODE/COUNTRY: Germany
203	FULL NAME OF INVENTOR	FAMILY NAME: BARTOSZYK	FIRST GIVEN NAME: Gerd	SECOND GIVEN NAME:
	RESIDENCE & CITIZENSHIP	CITY: 64289 Darmstadt	STATE OR FOREIGN COUNTRY: Germany	COUNTRY OF CITIZENSHIP: Germany
	POST OFFICE ADDRESS	STREET: c/o E. MERCK	CITY: 64271 Darmstadt	STATE & ZIP CODE/COUNTRY: Germany
204	FULL NAME OF INVENTOR	FAMILY NAME: GREINER	FIRST GIVEN NAME: Hartmut	SECOND GIVEN NAME:
	RESIDENCE & CITIZENSHIP	CITY: 64287 Darmstadt	STATE OR FOREIGN COUNTRY: Germany	COUNTRY OF CITIZENSHIP: Germany
	POST OFFICE ADDRESS	STREET: c/o E. MERCK	CITY: 64271 Darmstadt	STATE & ZIP CODE/COUNTRY: Germany
205	FULL NAME OF INVENTOR	FAMILY NAME:	FIRST GIVEN NAME:	SECOND GIVEN NAME:
	RESIDENCE & CITIZENSHIP	CITY:	STATE OR FOREIGN COUNTRY:	COUNTRY OF CITIZENSHIP:
	POST OFFICE ADDRESS	STREET:	CITY:	STATE & ZIP CODE/COUNTRY:
206	FULL NAME OF INVENTOR	FAMILY NAME:	FIRST GIVEN NAME:	SECOND GIVEN NAME:
	RESIDENCE & CITIZENSHIP	CITY:	STATE OR FOREIGN COUNTRY:	COUNTRY OF CITIZENSHIP:
	POST OFFICE ADDRESS	STREET:	CITY:	STATE & ZIP CODE/COUNTRY:

Combined Declaration For Patent Application and Power of Attorney (Continued)

(Includes Reference to PCT International Applications)

ATTORNEY'S DOCKET NUMBER: MERCK 1617

207	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
208	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
209	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
210	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
211	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
212	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 201	DATE	SIGNATURE OF INVENTOR 207	DATE
Henry Bither	Sept. 20, 94		
SIGNATURE OF INVENTOR 202	DATE	SIGNATURE OF INVENTOR 208	DATE
Christopher Saywell	Sept. 20, 94		
SIGNATURE OF INVENTOR 203	DATE	SIGNATURE OF INVENTOR 209	DATE
Ed Barry	Sept. 20, 94		
SIGNATURE OF INVENTOR 204	DATE	SIGNATURE OF INVENTOR 210	DATE
Hartmut Jeromin	Sept. 20, 94		
SIGNATURE OF INVENTOR 205	DATE	SIGNATURE OF INVENTOR 211	DATE
SIGNATURE OF INVENTOR 206	DATE	SIGNATURE OF INVENTOR 212	DATE

MWZ PTO 1391-3

BAR CODE LABEL

U.S. PATENT APPLICATION

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT
08/314,734	09/29/94	546	1203

APPLICANT

HENNING BOTTCHER, DARMSTADT, FED REP GERMANY; CHRISTOPH SEYFRIED, SEEHEIM-JUGENHE, FED REP GERMANY; GERD BARTOSZYK, DARMSTADT, FED REP GERMANY; HARTMUT GREINER, DARMSTADT, FED REP GERMANY.

CONTINUING DATA********
VERIFIED

_____

FOREIGN/PCT APPLICATIONS********
VERIFIED FED REP GERMANY P 43 33 254.4 09/30/93

_____

STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS	FILING FEE RECEIVED	ATTORNEY DOCKET NO.
DEX	0	22	1	$754.00	MERCK1617

ADDRESS

MILLEN WHITE ZELANO AND BRANIGAN
ARLINGTON COURTHOUSE PLAZA I SUITE 1400
2200 CLARENDON BOULEVARD
ARLINGTON VA 22201

TITLE

PIPERIDINES AND PIPERAZINES

This is to certify that annexed hereto is a true copy from the records of the United States Patent and Trademark Office of the application which is identified above.

By authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

Date Certifying Officer

PATENT APPLICATION SERIAL NO. 08/314734

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

SC13204 10/11/94 08314734 13-3402 130 101 754.00CH MERCK-1617

PTO-1556
(5/87)

PATENT APPLICATION FEE DETERMINATION RECORD

Effective October 1, 1992

Application or Docket Number: 314734

CLAIMS AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE	SMALL ENTITY FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY FEE
BASIC FEE				$355.00	OR		$710.00
TOTAL CLAIMS	22 minus 20 =	* 2	x$11=		OR	x$22=	44
INDEPENDENT CLAIMS	1 minus 3 =	*	x 37=		OR	x 74=	
MULTIPLE DEPENDENT CLAIM PRESENT			+115=		OR	+230=	
			TOTAL		OR	TOTAL	754

* If the difference in column 1 is less then zero, enter "0" in column 2

CLAIMS AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE	SMALL ENTITY ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY ADDITIONAL FEE
AMENDMENT A	Total	* 38	Minus	** 22	= 6	x$11=		OR	x$22=	132.
	Independent	*	Minus	***	=	x 37=		OR	x 74=	
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM					+ 115=		OR	+230=	
						TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	132.
AMENDMENT B	Total	*	Minus	**	=	x$11=		OR	x$22=	
	Independent	*	Minus	***	=	x 37=		OR	x 74=	
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM					+ 115=		OR	+ 230=	
						TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	
AMENDMENT C	Total	*	Minus	**	=	x$11=		OR	x$22=	
	Independent	*	Minus	***	=	x 37=		OR	x 74=	
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM					+115=		OR	+230=	
						TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

BUNDESREPUBLIK DEUTSCHLAND

Bescheinigung

Die Merck Patent GmbH in 64293 Darmstadt hat eine Patentanmeldung unter der Bezeichnung

"Piperidine und Piperazine"

am 30. September 1993 beim Deutschen Patentamt eingereicht.

Das angeheftete Stück ist eine richtige und genaue Wiedergabe der ursprünglichen Unterlage dieser Patentanmeldung.

Die Anmeldung hat im Deutschen Patentamt vorläufig die Symbole C 07 D 405/12, C 07 D 405/14, A 61 K 31/495 und A 61 K 31/445 der Internationalen Patentklassifikation erhalten.

München, den 15. April 1994
Der Präsident des Deutschen Patentamts
Im Auftrag

Röske

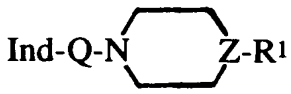
: P 43 33 254.4

Merck Patent Gesellschaft
mit beschränkter Haftung
64271 D a r m s t a d t

Piperidine und Piperazine

Piperidine und Piperazine

Die Erfindung betrifft neue Piperidin- und Piperazinderivate der Formel I



I,

worin

Ind	einen unsubstituierten oder einen ein- oder zweifach durch OH, OA, CN, Hal, COR^2 oder CH_2R^2 substituierten Indol-3-yl-rest,
R^1	unsubstituiertes oder einfach durch CN, CH_2OH, CH_2OA oder COR^2 substituiertes Benzofuran-5-yl bzw. 2,3-Dihydrobenzofuran-5-yl, Chroman-6-yl, Chroman-4-on-6-yl, 3-Chromen-6-yl oder Chromen-4-on-6-yl,
Q	C_mH_{2m},
Z	N oder CR^3,
A	Alkyl mit 1-6 C-Atomen,
Hal	F, Cl, Br oder I,
R^2	OH, OA, NH_2, NHA oder NA_2,
R^3	H, OH oder OA und
m	2, 3 oder 4

bedeuten,

sowie deren physiologisch unbedenkliche Salze.

Der Erfindung lag die Aufgabe zugrunde, neue Verbindungen aufzufinden, die zur Herstellung von Arzneimitteln verwendet werden können.

Es wurde gefunden, daß die Verbindungen der Formel I und ihre physiologisch unbedenklichen Säureadditionssalze wertvolle pharmakologische Eigenschaften besitzen. So zeigen sie insbesondere Wirkungen auf das Zentralnervensystem, vor allem 5-HT_{1A}-agonistische und 5-HT-Reuptake hemmende Wirkungen. Die Verbindungen zeigen ferner serotonin-agonistische und -antagonistische Eigenschaften. Sie hemmen die Bindung von tritiierten Serotoninliganden an hippocampale Rezeptoren (Cossery et al., European J. Pharmacol. 140 (1987), 143-155). Außerdem treten Veränderungen der DOPA-Akkumulation im Striatum und der 5-HTP-Akkumulation in N. raphe auf (Seyfried et al., European J. Pharmacol. 160 (1989), 31-41). Weiterhin treten analgetische und blutdrucksenkende Wirkungen auf; so wird bei kathetertragenden wachen, spontan hypertonen Ratten (Stamm SHR/ Okamoto/NIH-MO-CHB-Kisslegg; Methode vgl. Weeks und Jones, Proc. Soc. Exptl. Biol. Med. 104 (1960), 646-648) der direkt gemessene Blutdruck nach peroraler Gabe der Verbindungen gesenkt. Ebenso eignen sie sich zur Prophylaxe und zur Bekämpfung der Folgen cerebraler Infarktgeschehen (apoplexia cerebri) wie Schlaganfall und cerebraler Ischämien.

Verbindungen der Formel I und ihre physiologisch unbenklichen Säureadditionssalze können daher als Arzneimittelwirkstoffe für Anxiolytika, Antidepressiva, Antipsychotika, Neuroleptika und/oder Antihypertonika und auch als Zwischenprodukte zur Herstellung anderer Arzneimittelwirkstoffe verwendet werden.

Gegenstand der Erfindung sind die Piperidin- und Piperazinderivate der Formel I sowie ihre physiologisch unbedenklichen Säureadditionssalze.

Der Rest A bedeutet Alkyl mit 1, 2, 3, 4, 5 oder 6, insbesondere 1 oder 2 C-Atomen, vorzugsweise Methyl, ferner auch Ethyl, n-Propyl, Isopropyl, n-Butyl, sek.-Butyl oder tert.-Butyl. OA ist vorzugsweise Methoxy, ferner auch Ethoxy, n-Propoxy, Isopropoxy, n-Butoxy, Isobutoxy, sek.-Butoxy

oder tert.-Butoxy. NHA ist vorzugsweise Methylamino, ferner Ethylamino, Isopropylamino, n-Butylamino, Isobutylamino, sek.-Butylamino oder tert.-Butylamino. NA_2 bedeutet vorzugsweise Dimethylamino, ferner N-Ethyl-N-methylamino, Diethylamino, Di-n-propylamino, Diisopropylamino oder Di-n-butylamino.

Analog bedeutet CO-NHA vorzugsweise N-Methylcarbamoyl oder N-Ethylcarbamoyl; $CO\text{-}NA_2$ vorzugsweise N,N-Dimethylcarbamoyl oder N,N-Diethylcarbamoyl.

Der Rest Ind bedeutet einen unsubstituierten oder ein- oder zweifach durch einen der angegebenen Reste substituierten Indol-3-ylrest. Vorzugsweise ist er in 5-Stellung, ferner auch in der 4-, 6- oder 7-Stellung substituiert. Weiterhin ist eine Substitution in 1- oder 2-Stellung möglich. Bevorzugte Substituenten am Indol-3-ylrest sind OH, OA, CN, $CONH_2$, CH_2OH, aber auch CO_2H, F, Cl, Br, I, CH_2NH_2, CONHA oder $CONA_2$, wobei A bevorzugt Methyl oder Ethyl entspricht.

Der Rest R^1 bedeutet vorzugsweise unsubstituiertes oder einfach durch $-CH_2OH$, $-CONH_2$, $-CO_2A$ oder $-CO_2NHA$ substituiertes Benzofuran-5-yl, 2,3-Dihydrobenzofuran-5-yl, Chroman-6-yl oder Chromen-4-on-6-yl.

Q ist vorzugsweise $-(CH_2)_4-$, aber auch $-(CH_2)_2-$ oder $-(CH_2)_3-$, während Z bevorzugt -N-, -C(OH)- oder -CH- bedeutet.

Dementsprechend sind Gegenstand der Erfindung insbesondere diejenigen Verbindungen der Formel I, in denen mindestens einer der genannten Reste eine der vorstehend angegebenen, insbesondere der vorstehend angegebenen bevorzugten Bedeutungen hat. Einige bevorzugte Gruppen von Verbindungen können durch die folgenden Teilformeln Ia bis Ig ausgedrückt werden, die der Formel I entsprechen und worin die nicht näher bezeichneten Reste und Parameter die bei der Formel I angegebene Bedeutung haben, worin jedoch

in Ia	Ind	einen in 5-Stellung durch OH oder OA substituierten Indol-3-yl-rest bedeutet;
in Ib	Ind	einen in 5-Stellung durch $CONH_2$ oder durch CN substituierten Indol-3-yl-rest bedeutet;
in Ic		Z gleich N ist und R^1 substituiertes oder unsubstituiertes Benzofuran-5-yl bedeutet;
in Id		Z gleich -C(OH)- ist und R^1 substituiertes oder unsubstituiertes Benzofuran-5-yl bedeutet;
in Ie		Z gleich N ist und R^1 2,3-Dihydrobenzofuran-5-yl bedeutet;
in If		Z gleich N ist und R^1 Chroman-6-yl bedeutet;
in Ig		Z gleich N ist und R^1 Chromen-4-on-6-yl bedeutet.

Insbesondere sind bevorzugt Verbindungen der Teilformeln Ih sowie Iah bis Igh, die den Teilformeln I sowie Ia bis Ig entsprechen, worin jedoch zusätzlich

Q	$-(CH_2)_4-$

bedeutet.

Gegenstand der Erfindung ist ferner ein Verfahren zur Herstellung von Indolderivaten der Formel I sowie von deren Salzen, dadurch gekennzeichnet, daß man eine Verbindung der Formel II

$$Ind\text{-}Q\text{-}X^1 \qquad II$$

worin

X^1	X oder NH_2 und

X Cl, Br, I, OH oder eine reaktionsfähig funktionell abgewandelte OH-Gruppe bedeuten und

Ind und Q die angegebenen Bedeutungen haben, mit einer Verbindung der Formel III

$$X^2\text{-}(CH_2)_2\text{-}ZR^1\text{-}(CH_2)_2\text{-}X^3 \qquad III$$

worin

X^2 und X^3 gleich oder verschieden sein können und, falls $X^1 = NH_2$ ist, jeweils X, andernfalls zusammen NH bedeuten und

Z und R^1 die angegebenen Bedeutungen haben,

umsetzt

oder daß man zur Herstellung einer Verbindung der Formel I, worin Z gleich N ist, eine Verbindung der Formel IV

$$Ind\text{-}Q\text{-}N(CH_2\text{-}CH_2\text{-}X)_2 \qquad IV$$

worin

X, Q und Ind die angegebenen Bedeutungen haben, mit einer Verbindung der Formel V

$$R^1\text{-}NH_2 \qquad V$$

worin

R^1 die angegebene Bedeutung hat,

umsetzt

oder daß man eine sonst der Formel I entsprechende Verbindung, die jedoch anstelle eines oder mehrerer Wasserstoffatome eine oder mehrere reduzierbare Gruppe(n) und/oder eine oder mehrere zusätzliche C-C- und/oder C-N-Bindungen(en) enthält, mit einem reduzierenden Mittel behandelt

oder daß man eine sonst der Formel I entsprechende Verbindung, die jedoch anstelle eines oder mehrerer Wasserstoffatome eine oder mehrere solvolysierbare Gruppe(n) enthält, mit einem solvolysierenden Mittel behandelt.

und/oder daß man gegebenenfalls eine OA-Gruppe unter Bildung einer OH-Gruppe spaltet und/oder eine Gruppe Ind und/oder eine Gruppe Ar in eine andere Gruppe Ind und/oder Ar umwandelt und/oder daß man eine erhaltene Base oder Säure der Formel I durch Behandeln mit einer Säure oder Base in eines ihrer Salze umwandelt.

Die Herstellung der Verbindungen der Formel I erfolgt im übrigen nach an sich bekannten Methoden, wie sie in der Literatur (z.B. in Standardwerken wie Houben-Weyl, Methoden der Organischen Chemie, Georg Thieme Verlag, Stuttgart; Organic Reactions, John Wiley & Sons, Inc., New York; DE-OS 41 01 686) beschrieben sind, und zwar unter Reaktionsbedingungen, wie sie für die genannten Umsetzungen bekannt und geeignet sind. Dabei kann man auch von an sich bekannten, hier nicht näher erwähnten Varianten Gebrauch machen.

Die Ausgangsstoffe für das beanspruchte Verfahren können gewünschtenfalls auch in situ gebildet werden, derart, daß man sie aus dem Reaktionsgemisch nicht isoliert, sondern sofort weiter zu den Verbindungen der Formel I umsetzt.

In den Verbindungen der Formel II ist X^1 vorzugsweise X; dementsprechend sind in der Verbindungen der Formel III X^2 und X^3 vorzugsweise zusammen NH. Der Rest X ist vorzugsweise Cl oder Br; er kann jedoch auch I, OH oder eine reaktionsfähig funktionell abgewandelte OH-Gruppe bedeuten, insbesondere Alkylsulfonyloxy mit 1-6 (z.B. Methansulfonyloxy) oder Arylsulfonyloxy mit 6-10 C-Atomen (z.B. Benzolsulfonyloxy, p-Toluolsulfonyloxy, 1- oder 2-Naphthalinsulfonyloxy).

Dementsprechend sind die Indolderivate der Formel I insbesondere durch Umsetzung von Verbindungen der Formel Ind-Q-Cl oder Ind-Q-Br mit Piperidin/Piperazinderivaten der Formel III, worin X^2 und X^3 zusammen eine NH-Gruppe bedeuten (nachstehend als IIIa bezeichnet) erhältlich.

Die Verbindungen der Formel II und insbesondere III sind zum Teil bekannt; die nicht bekannten Verbindungen der Formeln II und III können leicht analog zu den bekannten Verbindungen hergestellt werden.

Primäre Alkohole der Formel Ind-Q-OH sind z.B. durch Reduktion der entsprechenden Carbonsäuren oder ihrer Ester erhältlich. Behandeln mit Thionylchlorid, Bromwasserstoff, Phosphortribromid oder ähnlichen Halogenverbindungen liefert die entsprechenden Halogenide der Formel Ind-Q-Hal. Die entsprechenden Sulfonyloxyverbindungen sind erhältlich aus den Alkoholen Ind-Q-OH durch Umsetzung mit den entsprechenden Sulfonsäurechloriden.

Die Iodverbindungen der Formel Ind-Q-I sind z.B. durch Einwirkung von Kaliumiodid auf die zugehörigen p-Toluolsulfonsäureester erhältlich. Die Amine der Formel Ind-Q-NH_2 sind z.B. aus den Halogeniden mit Phthalimidkalium oder durch Reduktion der entsprechenden Nitrile herstellbar.

Die Piperazinderivate IIIa sind größtenteils bekannt und z.B. erhältlich durch Umsetzung von Bis-(2-chlorethyl)-amin oder Bis-(2-chlorethyl)-ammoniumchlorid mit 5-Amino-benzofuran, 2,3-Dihydro-5-aminobenzofuran, 6-Aminochroman oder 6-Amino-chromen-4-on oder einem entsprechend substituierten Derivat der genannten Verbindungen. Verbindungen der Formel III (X^2 und X^3 = jeweils X) sind z.B. herstellbar durch Reduktion von Diestern der Formel AlkylOOC-CH_2-ZR^1-CH_2-COOalkyl zu Verbindungen der Formel HO-CH_2-CH_2-ZR^1-CH_2-CH_2OH (III, $X^2 = X^3$ = OH) und gegebenenfalls anschließende Umsetzung mit $SOCl_2$ bzw. PBr_3.

Die Umsetzung der Verbindungen II und III verläuft nach Methoden, wie sie für die Alkylierung von Aminen aus der Literatur bekannt sind. Man kann ohne Gegenwart eines Lösungsmittels die Komponenten miteinander verschmelzen, gegebenenfalls im geschlossenen Rohr oder im Autoklaven. Es

ist aber auch möglich, die Verbindungen in Gegenart eines indifferenten Lösungsmittels umzusetzen. Als Lösungsmittel eigenen sich z.B. Kohlenwasserstoffe, wie Benzol, Toluol, Xylol; Ketone wie Aceton, Butanon; Alkohole wie Methanol, Ethanol, Isopropanol, n-Butanol; Ether wie Tetrahydrofuran (THF) oder Dioxan; Amide wie Dimethylformamid (DMF) oder N-Methyl-pyrrolidon; Nitrile wie Acetonitril, gegebenenfalls auch Gemische dieser Lösungsmittel untereinander oder Gemische mit Wasser. Der Zusatz eines säurebindenden Mittels, beispielsweise eines Alkali- oder Erdalkalimetall-hydroxids, -carbonats oder -bicarbonats oder eines anderen Salzes einer schwachen Säure der Alkali- oder Erdalkalimetalle, vorzugsweise des Kaliums, Natriums oder Calciums, oder der Zusatz einer organischen Base wie Triethylamin, Dimethylanilin, Pyridin oder Chinolin oder eines Überschusses der Aminkomponente Ind-Q-NH_2 bzw. des Piperidin- oder Piperazinderivates der Formel IIIa kann günstig sein. Die Reaktionszeit liegt je nach den angewendeten Bedingungen zwischen einigen Minuten und 14 Tagen, die Reaktionstemperatur zwischen etwa 0 und 150°, normalerweise zwischen 20 und 130°.

Ferner ist es möglich, eine Verbindung der Formel I zu erhalten, indem man eine Verbindung der Formel Ind-Q-$N(CH_2\text{-}CH_2\text{-}X)_2$ (IV) mit einer Verbindung der Formel $R^1\text{-}NH_2$ (V) umsetzt.

Die Verbindungen der Formeln V sind zum größten Teil bekannt; die nicht bekannten Verbindungen können leicht in Analogie zu den bekannten hergestellt werden. Sie lassen sich beispielsweise ausgehend von den entsprechend substituierten Nitroverbindungen durch Reduktion in die Amine der Formel V überführen. Die Verbindungen der Formel IV lassen sich durch Umsetzung von Ind-Q-Cl, Ind-Q-Br oder Ind-Q-I mit sekundären Aminen der Formel $HN(CH_2\text{-}CH_2\text{-}X)_2$ herstellen.

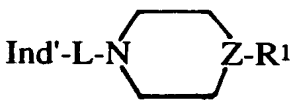
Die Umsetzung der Verbindungen IV und V verläuft nach Methoden wie sie für die Alkylierung von Aminen aus der Literatur bekannt sind und bereits oben angegeben werden.

Es ist ferner möglich, eine Verbindung der Formel I zu erhalten, indem man ein Vorprodukt, das anstelle von Wasserstoffatomen eine oder mehrere reduzierbare Gruppe(n) und/oder eine oder mehrere zusätzliche C-C- und/oder C-N-Bindungen(en) enthält, mit einem reduzierenden Mittel behandelt, vorzugsweise bei Temperaturen zwischen -80 und +250° in Gegenwart mindestens eines inerten Lösungsmittels.

Reduzierbare (durch Wasserstoff ersetzbare) Gruppen sind insbesondere Sauerstoff in einer Carbonylgruppe, Hydroxyl, Arylsulfonyloxy (z.B. p-Toluolsulfonyloxy), N-Benzolsulfonyl, N-Benzyl oder O-Benzyl.

Es ist grundsätzlich möglich, Verbindungen, die nur eine, oder solche, die nebeneinander zwei oder mehr der oben angeführten Gruppen bzw. zusätzlichen Bindungen enthalten, reduktiv in eine Verbindung der Formel I überzuführen; dabei können gleichzeitig Substituenten in der Gruppe Ind, die in der Ausgangsverbindung enthalten sind, reduziert werden. Vorzugsweise bedient man sich hierzu des nascierenden Wasserstoffs oder komplexer Metallhydride, ferner der Reduktion nach Wolff-Kishner sowie der Reduktionen mit Wasserstoffgas unter Übergangsmetallkatalyse.

Bevorzugte Ausgangsstoffe für die Reduktion entsprechen beispielsweise der Formel VI



VI

worin

Ind' einen Rest Ind, der zusätzlich durch eine Arylsulfonylgruppe oder eine Alkyloxycarbonylgruppe in 1-Stellung substituiert sein kann,

L Q oder eine dem Rest Q entsprechende Kette, worin jedoch eine oder mehrere -CH_2-Gruppe(n) durch -CO- und/oder ein oder mehrere Wasserstoffatome durch eine oder mehrere OH-Gruppe(n) oder eine Doppelbindung ersetzt sind, bedeuten und

R^1 die angegebene Bedeutung besitzt

worin jedoch nicht gleichzeitig Ind' = Ind und L = Q sein können.

In den Verbindungen der Formel VI ist L bevorzugt -CO-$(CH_2)_{n-2}$-CO- [im einzelnen -COCO-, -$COCH_2CO$-, -CO-$(CH_2)_2$-CO-, -CO-$(CH_2)_3$-CO-], -$(CH_2)_{n-1}$-CO- [im einzelnen -CH_2-CO-, -CH_2CH_2-CO-, -$(CH_2)_3$-CO- oder -$(CH_2)_4$-CO-], ferner z.B. -CO-CH_2CH_2-, -CO-$(CH_2)_3$-, -CH_2-CO-CH_2CH_2- oder -CH_2CH_2-CO-CH_2-.

Verbindungen der Formel VI sind z.B. herstellbar durch Umsetzung von 4-R^1-piperazin oder -piperidin mit einer Verbindung der Formel VII

Ind'-L-X^1 VII

worin

R^1, Ind', L und X^1 die oben angegebenen Bedeutungen haben, unter den Bedingungen, die zuvor für die Umsetzung von II mit III angegeben sind.

Wird als Reduktionsmittel nascierender Wasserstoff verwendet, so kann man diesen z.B. durch Behandlung von Metallen mit schwachen Säuren oder mit Basen erzeugen. So kann man z.B. ein Gemisch von Zink mit Alkalilauge oder von Eisen mit Essigsäure verwenden. Geeignet ist auch die Verwendung von Natrium oder einem anderen Alkalimetall gelöst in einem Alkohol wie Ethanol, Isopropanol, Butanol, Amyl- oder Isoamylalkohol oder Phenol. Man kann ferner eine Aluminium-Nickel-Legierung in alkalisch-wässeriger Lösung, gegebenenfalls unter Zusatz von Ethanol, verwenden. Auch Natrium- oder Aluminiumamalgam in wässerig-alkoholischer oder

wässeriger Lösung sind zur Erzeugung des nascierenden Wasserstoffs geeignet. Die Umsetzung kann auch in heterogener Phase durchgeführt werden, wobei man zweckmäßig eine wässerige und eine Benzol- oder Toluol-Phase verwendet.

Als Reduktionsmittel können ferner besonders vorteilhaft komplexe Metallhydride, wie $LiAlH_4$, $NaBH_4$, Diisobutylaluminiumhydrid oder $NaAl(OCH_2CH_2OCH_3)_2H_2$ sowie Diboran eingesetzt werden, falls erwünscht unter Zusatz von Katalysatoren wie BF_3, $AlCl_3$ oder LiBr. Als Lösungsmittel eigenen sich hierfür insbesondere Ether wie Diethylether, Di-n-butylether, THF, Dioxan, Diglyme oder 1,2-Dimethoxyethan sowie Kohlenwasserstoffe wie Benzol. Für eine Reduktion mit $NaBH_4$ sind in erster Linie Alkohole wie Methanol oder Ethanol, ferner Wasser sowie wässerige Alkohole als Lösungsmittel geeignet. Nach diesen Methoden reduziert man vorzugsweise bei Temperaturen zwischen -80 und +150°, insbesondere zwischen etwa 0 und etwa 100°.

Besonders vorteilhaft lassen sich -CO-Gruppen in Säureamiden (z.B. solchen der Formel VI, worin L eine $-(CH_2)_{n-1}$ -CO-Gruppe bedeutet) mit $LiAlH_4$ in THF bei Temperaturen zwischen etwa 0 und 66° zu CH_2-Gruppen reduzieren. Dabei können in 1-Stellung des Indolring befindliche Arylsulfonyl-Schutzgruppen gleichzeitig reduktiv abgespalten werden. N-Benzylgruppen können reduktiv mit Natrium im flüssigem Ammoniak abgespalten werden.

Es ist ferner möglich, eine oder mehrere Carbonylgruppen nach der Methode von Wolff-Kishner zu CH_2-Gruppen zu reduzieren, z.B. durch Behandlung mit wasserfreiem Hydrazin in absolutem Ethanol unter Druck bei Temperaturen zwischen etwa 150 und 250°. Als Katalysator wird vorteilhaft Natriumalkoholat verwendet. Die Reduktion kann auch nach der Methode von Huang-Minlon variiert werden, indem man mit Hydrazinhydrat in einem hochsiedenden, mit Wasser mischbaren Lösungsmittel, wie Diethylenglykol oder Triethylenglykol, in Gegenwart von Alkali, wie Natriumhydroxid, umsetzt. Das Reaktionsgemisch wird in der Regel etwa 3-4 Stunden gekocht.

Anschließend wird das Wasser abdestilliert und das gebildete Hydrazon bei Temperaturen bis zu etwa 200° zersetzt. Die Wolff-Kishner-Reduktion kann auch bei Raumtemperatur in Dimethylsulfoxid mit Hydrazin ausgeführt werden.

Darüber hinaus ist es möglich, bestimmte Reduktionen durch Verwendung von H_2-Gas unter katalytischer Wirkung von Übergangsmetallen, wie z.B. Raney-Ni oder Pd durchzuführen. Man kann auf diese Weise z.B. Cl, Br, I, SH oder in bestimmten Fällen auch OH-Gruppen durch Wasserstoff ersetzen. Ebenso können Nitrogruppen durch katalytische Hydrierung mit Pd/H_2 in Methanol in NH_2-Gruppen umgewandelt werden.

Verbindungen, die sonst der Formel I entsprechen, aber anstelle eines oder mehrerer H-Atome eine oder mehrere solvolysierbare Gruppe(n) enthalten, können zu den Verbindungen der Formel I solvolysiert, insbesondere hydrolysiert werden.

Die Ausgangsstoffe für die Solvolyse sind beispielsweise erhältlich durch Reaktion von IIIa mit Verbindungen, die der Formel II (X^1 = X) entsprechen, aber anstelle eines oder mehrerer H-Atome eine oder mehrere solvolysierbare Gruppe(n) enthalten. So können insbesondere 1-Acylindolderivate (entsprechend der Formel I, aber in 1-Stellung des Ind-Rests eine Acylgruppe enthaltend, vorzugsweise eine Alkoxycarbonyl-, Alkanoyl-, Alkylsulfonyl- oder Arylsulfonylgruppe mit jeweils bis zu 10 C-Atomen, wie Methan-, Benzol- oder p-Toluolsulfonyl) zu den entspechenden in der 1-Stellung des Indolringes unsubstituierten Indolderivaten hydrolysiert werden, z.B. in saurem, besser in neutralem oder alkalischem Medium bei Temperaturen zwischen 0 und 200°. Als Basen verwendet man zweckmäßig Natrium-, Kalium- oder Calciumhydroxid, Natrium- oder Kaliumcarbonat, oder Ammoniak. Als Lösungsmittel wählt man vorzugsweise Wasser; niedere Alkohole wie Methanol, Ethanol; Ether wie THF, Dioxan; Sulfone wie Tetramethylensulfon; oder deren Gemische, besonders die Wasser enthaltenden Gemische. Eine Hydrolyse kann auch bereits beim Behandeln mit Wasser allein erfolgen, insbesondere in der Siedehitze.

Weiterhin kann man eine Verbindung der Formel I nach an sich bekannten Methoden in eine andere Verbindung der Formel I umwandeln.

Verbindungen der Formel I, worin Ind einen durch CO-R^1 substituierten Indol-3-yl-rest bedeutet, können durch Derivatisierung entsprechender Carboxy-indol-3-yl-Verbindungen erhalten werden. Man kann z.B. die Säuren mit entsprechenden Alkoholen oder Alkoholaten unter Verwendung an sich bekannter Methoden verestern. Ferner ist es möglich, Säuren oder Ester mit primären oder sekundären Aminen zu amidieren. Bevorzugt ist die Umsetzung der freien Carbonsäure mit dem Amin unter den Bedingungen einer Peptidsynthese. Diese Reaktion gelingt vorzugsweise in Gegenwart eines Dehydratisierungsmittels, z.B. eines Carbodiimids wie Dicyclohexylcarbodiimid oder N-(3-Dimethylaminopropyl)-N-ethyl-carbodiimid, ferner Propanphosphonsäureanhydrid (vgl. Angew. Chem. 92, 129 (1980)), Diphenylphosphorylazid oder 2-Ethoxy-N-ethoxycarbonyl-1,2-dihydrochinolin, in einem inerten Lösungsmittel, z.B. einem halogenierten Kohlenwasserstoff wie Dichlormethan, einem Ether wie THF oder Dioxan, einem Amid wie DMF oder Dimethylacetamid, einem Nitril wie Acetonitril, bei Temperaturen zwischen etwa -10 und 40°, vorzugsweise zwischen 0 und 30°. Anstelle der Säure bzw. des Amids können auch reaktionsfähige Derivate dieser Stoffe in die Reaktion eingesetzt werden, z.B. solche, in denen reaktive Gruppen intermediär durch Schutzgruppen blockiert sind. Die Säuren können auch in Form ihrer aktivierten Ester verwendet werden, die zweckmäßig in situ gebildet werden, z.B. durch Zusatz von 1-Hydroxybenztriazol oder N-Hydroxysuccinimid.

Weiterhin kann man cyan-substituierte Indol-3-yl-reste zu Carboxy-indol-3-yl- oder Carboxamido-indol-3-yl-resten hydrolysieren.

Besonders günstig ist es aber auch in umgekehrter Weise, durch Wasserabspaltung, ausgehend von den Amiden, z.B. mittels Trichloracetylchlorid/ Et_3N [Synthesis (2), 184, (1985)] oder mit $POCl_3$ (J. Org. Chem. 26, 1003 (1961)), die Nitrile herzustellen.

Eine erhaltene Base der Formel I kann mit einer Säure in das zugehörige Säureadditionssalz übergeführt werden. Für diese Umsetzung eignen sich Säuren, die physiologisch unbedenkliche Salze liefern. So können anorganische Säuren verwendet werden, z.B. Schwefelsäure, Halogenwasserstoffsäuren wie Chlorwasserstoffsäure oder Bromwasserstoffsäure, Phosphorsäuren wie Orthophosphorsäure, Salpetersäure, Sulfaminsäure, ferner organische Säuren, im einzelnen aliphatische, alicyclische, araliphatische, aromatische oder heterocyclische ein- oder mehrbasige Carbon-, Sulfon- oder Schwefelsäuren, wie Ameisensäure, Essigsäure, Propionsäure, Pivalinsäure, Diethylessigsäure, Malonsäure, Bernsteinsäure, Pimelinsäure, Fumarsäure, Maleinsäure, Milchsäure, Weinsäure, Äpfelsäure, Benzoesäure, Salicylsäure, 2-Phenylpropionsäure, Citronensäure, Gluconsäure, Ascorbinsäure, Nicotinsäure, Isonicotinsäure, Methan- oder Ethansulfonsäure, Ethandisulfonsäure, 2-Hydroxyethansulfonsäure, Benzolsulfonsäure, p-Toluolsulfonsäure, Naphthalin-mono- und -disulfonsäuren, Laurylschwefelsäure.

Die freien Basen der Formel I können, falls gewünscht, aus ihren Salzen durch Behandlung mit starken Basen wie Natrium- oder Kaliumhydroxid, Natrium- oder Kaliumcarbonat in Freiheit gesetzt werden, sofern keine weiteren aciden Gruppen im Molekül vorliegen. In jenen Fällen, wo die Verbindungen der Formel I über freie Säuregruppen verfügen, kann durch Behandlung mit Basen ebenfalls eine Salzbildung erreicht werden. Als Basen eignen sich Alkalimetallhydroxide, Erdalkalimetallhydroxide oder organische Basen in Form von primären, sekundären oder tertiären Aminen.

Gegenstand der Erfindung ist ferner die Verwendung der Verbindungen der Formel I und ihrer physiologisch unbedenklichen Salze zur Herstellung pharmazeutischer Zubereitungen, insbesondere auf nicht-chemischem Wege. Hierbei können sie zusammen mit mindestens einem Träger- oder Hilfsstoff und gegebenenfalls in Kombination mit einem oder mehreren weiteren Wirkstoffe(n) in eine geeignete Dosierungsform gebracht werden.

Gegenstand der Erfindung sind ferner Mittel, insbesondere pharmazeutische Zubereitungen, enthaltend mindestens eine Verbindung der Formel I und/ oder eines ihrer physiologisch unbedenklichen Salze. Diese Zubereitungen

können als Arzneimittel in der Human- und Veterinärmedizin eingesetzt werden. Als Trägersubstanzen kommen organische oder anorganische Stoffe in Frage, die sich für die enterale (z.B. orale), parenterale oder topische Applikation eignen und mit den neuen Verbindungen nicht reagieren, beispielsweise Wasser, pflanzliche Öle, Benzylalkohole, Polyethylenglykole, Gelatine, Kohlehydrate wie Lactose oder Stärke, Magnesiumstearat, Talk, Vaseline. Zur enteralen Applikation dienen insbesondere Tabletten, Dragees, Kapseln, Sirupe, Säfte, Tropfen oder Suppositorien, zur parenteralen Applikation Lösungen, vorzugsweise ölige oder wässerige Lösungen, ferner Suspensionen, Emulsionen oder Implantate, für die topische Anwendung Salben, Cremes oder Puder. Die neuen Verbindungen können auch lyophilisiert und die erhaltenden Lyophilisate z.B. zur Herstellung von Injektionspräparaten verwendet werden.

Die angegebenen Zubereitungen können sterilisiert sein und/oder Hilfsstoffe wie Gleit-, Konservierungs-, Stabilisierung- und/oder Netzmittel, Emulgatoren, Salze zur Beeinflussung des osmotischen Druckes, Puffersubstanzen, Farb-, Geschmacks- und/oder Aromastoffe enthalten. Sie können, falls erwünscht, auch einen oder mehrere weitere Wirkstoffe enthalten, z.B. ein oder mehrere Vitamine.

Die Verbindungen der Formel I und ihre physiologisch unbedenklichen Salze können bei der therapeutischen Behandlung des menschlichen oder tierischen Körpers und bei der Bekämpfung von Krankheiten verwendet werden. Sie eignen sich zur Behandlung von Erkrankungen des Zentralnervensystems wie Spannungszuständen, Depressionen und/oder Psychosen und von Nebenwirkungen bei der Behandlung der Hypertonie (z.B. mit α-Methyldopa). Ferner können die Verbindungen in der Endokrinologie und Gynäkologie Verwendung finden, z.B. zur Therapie von Akromegalie, Hypogonadismus, sekundärer Amenorrhoe, prämenstruellem Syndrom, unerwünschter puerperaler Laktation, weiterhin zur Prophylaxe und Therapie cerebraler Störungen (z.B. Migräne), insbesondere in der Geriatrie ähnlich wie gewisse Ergot-Alkaloide und zur Bekämpfung der Folgen cerebraler Infarktgeschehen (Apoplexia cerebri), wie Schlaganfall und cerebraler Ischämien.

Dabei werden die erfindungsgemäßen Substanzen in der Regel in Analogie zu bekannten, im Handel befindlichen Präparaten (z.B. Bromocriptin, Dihydroergocornin) verabreicht, vorzugsweise in Dosierungen zwischen etwa 0,2 und 500 mg, insbesondere zwischen 0,2 und 50 mg pro Dosierungseinheit. Die tägliche Dosierung liegt vorzugsweise zwischen etwa 0,001 und 10 mg/kg Körpergewicht. Die niedrigen Dosierungen (etwa 0,2 bis 1 mg pro Dosierungseinheit; etwa 0,001 bis 0,005 mg/kg Körpergewicht) kommen dabei insbesondere für die Verwendung als Migränemittel in Betracht; für die übrigen Indikationen werden Dosierungen zwischen 10 und 50 mg pro Dosierungseinheit bevorzugt. Die spezielle Dosis für jeden bestimmten Patienten hängt jedoch von den verschiedensten Faktoren ab, beispielsweise von der Wirksamkeit der eingesetzten speziellen Verbindung, vom Alter, Körpergewicht, allgemeinen Gesundheitszustand, Geschlecht, von der Kost, vom Verabfolgungszeitpunkt und -weg, von der Ausscheidungsgeschwindigkeit, Arzneistoffkombination und Schwere der jeweiligen Erkrankung, welcher die Therapie gilt. Die orale Applikation ist bevorzugt.

In den nachstehenden Beispielen bedeutet "übliche Aufarbeitung": Man gibt, falls erforderlich, Wasser hinzu, extrahiert mit Dichlormethan, trennt ab, trocknet die organische Phase über Natriumsulfat, filtriert, dampft ein und reinigt durch Chromatographie an Kieselgel und/oder durch Kristallisation. Temperaturen sind in °C angegeben. Rf-Werte wurden dünnschichtchromatographisch an Kieselgel erhalten.

Beispiel 1

Man löst 1,8 g 3-(4-Chlorbutyl)-5-methoxy-indol [erhältlich durch Diazotierung von p-Methoxyanilin, Umsetzung mit Cyclohexanon-2-carbonsäureethylester nach Japp-Klingemann zu 4-(2-Carbethoxy-indol-3-yl)-buttersäure, Verseifung, Decarboxylierung, Reduktion mit $LiAlH_4$ und Reaktion mit $SOCl_2$] sowie 1,9 g 1-(2-Hydroxymethyl-benzofuran-5-yl)-piperazin [erhältlich durch Umsetzung von N,N-Bis-(2-chlorethyl)-amin mit 2-Hydroxymethyl-5-amino-benzofuran] in 200 ml Acetonitril und rührt 10 Stunden bei Raumtemperatur. Nach üblicher Aufarbeitung erhält man 1-[4-(5-Methoxy-indol-3-yl)-butyl]-4-(2-hydroxymethyl-benzofuran-5-yl)-piperazin, F. 159°.

Analog erhält man durch Umsetzung

von 3-(4-Chlorbutyl)-5-methoxy-indol mit 1-(2,3-Dihydrobenzofuran-5-yl)-piperazin:
1-[4-(5-Methoxy-indol-3-yl)-butyl]-4-(2,3-dihydrobenzofuran-5-yl)-piperazin, F. 111-112°;

von 3-(4-Chlorbutyl)-5-hydroxy-indol mit 1-(Chroman-6-yl)-piperazin:
1-[4-(5-Hydroxy-indol-3-yl)-butyl]-4-(chroman-6-yl)-piperazin, F. 220-222°;

von 3-(4-Chlorbutyl)-5-methoxy-indol mit 1-(Chroman-6-yl)-piperazin:
1-[4-(5-Methoxy-indol-3-yl)-butyl]-4-(chroman-6-yl)-piperazin, F. 129-130°;

von 3-(4-Chlorbutyl)-5-indolcarbonsäuremethylester mit 1-(Chroman-6-yl)-piperazin:
1-[4-(5-Methoxycarbonyl-indol-3-yl)-butyl]-4-(chroman-6-yl)-piperazin;

von 3-(4-Chlorbutyl)-5-indolcarbonsäureethylester mit 1-(Benzo-furan-5-yl)-piperazin:
1-[4-(5-Ethoxycarbonyl-indol-3-yl)-butyl]-4-(benzofuran-5-yl)-piperazin;

von 3-(4-Chlorbutyl)-5-methoxy-indol mit 1-(Benzofuran-5-yl)-piperazin:
1-[4-(5-Methoxy-indol-3-yl)-butyl]-4-(benzofuran-5-yl)-piperazin;

von 3-(4-Chlorbutyl)-5-methoxycarbonyl-indol mit 1-(Chromen-4-on-6-yl)-piperazin:
1-[4-(5-Methoxycarbonyl-indol-3-yl)-butyl]-4-(chromen-4-on-6-yl)-piperazin;

von 3-(4-Chlorbutyl)-5-cyan-indol mit 1-(Chromen-4-on-6-yl)-piperazin:
1-[4-(5-Cyan-indol-3-yl)-butyl]-4-(chromen-4-on-6-yl)-piperazin;

von 3-(4-Chlorbutyl)-5-chlor-indol mit 1-(2,3-Dihydrobenzofuran-5-yl)-piperazin:

1-[4-(5-Chlor-indol-3-yl)-butyl]-4-(2,3-dihydrobenzofuran-5-yl)-piperazin;

von 3-(4-Chlorbutyl)-5-methoxycarbonyl-indol mit 1-(2,3-Dihydrobenzofuran-5-yl)-piperazin:

1-[4-(5-Methoxycarbonyl-indol-3-yl)-butyl]-4-(2,3-dihydrobenzofuran-5-yl)-piperazin;

von 3-(4-Chlorbutyl)-5-methoxycarbonyl-indol mit 4-(2,3-Dihydrobenzofuran-5-yl)-piperidin:

1-[4-(5-Methoxycarbonyl-indol-3-yl)-butyl]-4-(2,3-dihydrobenzofuran-5-yl)-piperidin;

von 3-(4-Chlorbutyl)-5-methoxycarbonyl-indol mit 4-(2,3-Dihydrobenzofuran-5-yl)-4-hydroxy-piperidin:

1-[4-(5-Methoxycarbonyl-indol-3-yl)-butyl]-4-(2,3-dihydrobenzofuran-5-yl)-4-hydroxy-piperidin;

von 3-(4-Chlorbutyl)-5,6-dimethoxy-indol mit 1-(Chroman-6-yl)-piperazin:

1-[4-(5,6-Dimethoxy-indol-3-yl)-butyl]-4-(chroman-6-yl)-piperazin;

von 3-(4-Chlorbutyl)-5-cyan-indol mit 1-(2-Carboxy-benzofuran-5-yl)-piperazin:

1-[4-(5-Cyan-indol-3-yl)-butyl]-4-(2-carboxy-benzofuran-5-yl)-piperazin;

von 3-(4-Chlorbutyl)-6-fluor-indol mit 1-(2,3-Dihydrobenzofuran-5-yl)-piperazin:

1-[4-(6-Fluor-indol-3-yl)-butyl]-4-(2,3-dihydrobenzofuran-5-yl)-piperazin.

Beispiel 2

Man kocht 1,8 g 1-[4-(5-Methoxycarbonyl-indol-3-yl)-butyl]-4-(chroman-6-yl)-piperazin [erhältlich nach Beispiel 1] 0,5 Std. mit 100 ml 2n ethanolischer KOH, arbeitet wie üblich auf und erhält 1-[4-(5-Carboxy-indol-3-yl)-butyl]-4-chroman-6-yl-piperazin.

Analog erhält man durch Verseifung der entsprechenden Ester ausgehend

von 1-[4-(5-Ethoxycarbonyl-indol-3-yl)-butyl]-4-(benzofuran-5-yl)-piperazin:
1-[4-(5-Carboxy-indol-3-yl)-butyl]-4-(benzofuran-5-yl)-piperazin;

von 1-[4-(5-Methoxycarbonyl-indol-3-yl)-butyl]-4-(chromen-4-on-6-yl)-piperazin:
1-[4-(5-Carboxy-indol-3-yl)-butyl]-4-(chromen-4-on-6-yl)-piperazin;

von 1-[4-(5-Methoxycarbonyl-indol-3-yl)-butyl]-4-(2,3-dihydrobenzofuran-5-yl)-piperazin:
1-[4-(5-Carboxy-indol-3-yl)-butyl]-4-(2,3-dihydrobenzofuran-5-yl-piperazin;

von 1-[4-(5-Methoxycarbonyl-indol-3-yl)-butyl]-4-(2,3-dihydrobenzofuran-5-yl)-piperazin:
1-[4-(5-Carboxy-indol-3-yl)-butyl]-4-(2,3-dihydrobenzofuran-5-yl-piperazin;

von 1-[4-(5-Methoxycarbonyl-indol-3-yl)-butyl]-4-(2,3-dihydrobenzofuran-5-yl)-4-hydroxy-piperidin:
1-[4-(5-Carboxy-indol-3-yl)-butyl]-4-(2,3-dihydrobenzofuran-5-yl)-4-hydroxy-piperidin.

Beispiel 3

2,8 g 1-[4-(5-Carboxy-indol-3-yl)-butyl]-4-(2,3-dihydrobenzo-furan-5-yl)-piperazin werden in 100 ml N-Methylpyrrolidin suspendiert. Anschließend fügt man 3,2 g 2-Chlor-1-methyl-pyridiniummethansulfonat hinzu und rührt bei Raumtemperatur 12 Stunden. In die entstandene Lösung leitet man bis zur Sättigung getrocknetes NH_3-Gas ein und rührt erneut 10 Stunden. Nach üblicher Aufarbeitung erhält man 1-[4-(5-Carbamoyl-indol-3-yl)-butyl]-4-(2,3-dihydrobenzofuran-5-yl)-piperazin.

Analog erhält man durch Amidierung der nachfolgenden Carbonsäuren mit 2-Chlor-1-methyl-pyridiniummethansulfonat:

aus 1-[4-(5-Carboxy-indol-3-yl)-butyl]-4-(2,3-dihydrobenzofuran-5-yl)-piperidin das
1-[4-(5-Carbamoyl-indol-3-yl)-butyl]-4-(2,3-dihydrobenzofuran-5-yl-piperidin, F. 155-157°;

aus 1-[4-(5-Carboxy-indol-3-yl)-butyl]-4-(2,3-dihydrobenzofuran-5-yl)-4-hydroxy-piperidin das
1-[4-(5-Carbamoyl-indol-3-yl)-butyl]-4-(2,3-dihydrobenzofuran-5-yl-4-hydroxy-piperidin, F. 69° (Zers.);

aus 1-[4-(5-Carboxy-indol-3-yl)-butyl]-4-(chroman-6-yl)-piperazin das
1-[4-(5-Carbamoyl-indol-3-yl)-butyl]-4-(chroman-6-yl)-piperazin.

Beispiel 4

Analog Beispiel 3 erhält man ausgehend von 1-[4-(5-Cyan-indol-3-yl)-butyl]-4-(2-carboxy-benzofuran-5-yl)-piperazin durch Umsetzung mit 2-Chlor-1-methyl-pyridiniummethansulfonat das 1-[4-(5-Cyan-indol-3-yl)-butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazin, F. 269-272° (Hydrochlorid).

Beispiel 5

Ein Gemisch von 2,6 g 3-(2-Aminoethyl)-5-cyan-indol [erhältlich durch Umsetzung von 5-Cyanindol mit 2-Chloracetylchlorid zu 3-(2-Chloracetyl)-5-cyanindol, anschließende Reduktion mit Diboran, Umsetzung mit Phthalimid und Hydrolyse] und einem Äquivalent 5-[N,N-Bis-(2-chlorethyl)-amino]-benzofuran [erhältlich durch Umsetzung von 2-Chloracetylchlorid mit 5-Aminobenzofuran und anschließende Reduktion mit Diboran] in 40 ml Aceton und 40 ml Wasser wird 20 Stunden gekocht und danach wie üblich aufgearbeitet. Man erhält 1-[2-(5-Cyan-indol-3-yl)-ethyl]-4-(benzofuran-5-yl)-piperazin.

Analog erhält man durch Umsetzung von 5-[N,N-Bis-(2-chlorethyl)-amino]-benzofuran

mit 3-(4-Aminobutyl)-5-methoxymethyl-indol:
1-[4-(5-Methoxymethyl-indol-3-yl)-butyl]-4-(benzofuran-5-yl)-piperazin;

mit 3-(3-Aminopropyl)-5-hydroxy-indol:
1-[3-(5-Hydroxy-indol-3-yl)-propyl]-4-(benzofuran-5-yl)-piperazin;

mit 3-(2-Aminoethyl)-5-methoxy-indol:
1-[2-(5-Methoxy-indol-3-yl)-ethyl]-4-(benzofuran-5-yl)-piperazin;

mit 3-(3-Aminopropyl)-5-indolcarbonsäuremethylester:
1-[3-(5-Methoxycarbonyl-indol-3-yl)-propyl]-4-(benzofuran-5-yl)-piperazin;

mit 3-(2-Aminoethyl)-5-indolcarbonsäureethylester:
1-[2-(5-Ethoxycarbonyl-indol-3-yl)-ethyl]-4-(benzofuran-5-yl)-piperazin;

mit 3-(4-Aminobutyl)-5-fluor-indol:
1-[4-(5-Fluor-indol-3-yl)-butyl]-4-(benzofuran-5-yl)-piperazin.

mit 3-(3-Aminopropyl)-5-cyan-indol:
1-[3-(5-Cyan-indol-3-yl)-propyl]-4-(2-carboxy-benzofuran-5-yl)-piperazin.

Beispiel 6

Analog Beispiel 5 erhält man durch Umsetzung von von 3,2 g 3-(2-Aminoethyl)-5-methoxy-indol mit 1,3 Äquivalenten 6-[N,N-Bis-(2-chlorethyl)-amino]-chroman [erhältlich durch Umsetzung von 2-Chloracetyl-chlorid mit 6-Aminochroman und anschließende Reduktion mit Diboran] das 1-[2-(5-Methoxy-indol-3-yl)-ethyl]-4-(chroman-6-yl)-piperazin.

Analog erhält man durch Umsetzung von 6-[N,N-Bis-(2-chlorethyl)-amino]-chroman

mit 3-(4-Aminobutyl)-5-methoxymethyl-indol:
1-[4-(5-Methoxymethyl-indol-3-yl)-butyl]-4-(chroman-6-yl)-piperazin;

mit 3-(3-Aminopropyl)-5-hydroxy-indol:
1-[3-(5-Hydroxy-indol-3-yl)-propyl]-4-(chroman-6-yl)-piperazin;

mit 3-(2-Aminoethyl)-5-methoxy-indol:
1-[2-(5-Methoxy-indol-3-yl)-ethyl]-4-(chroman-6-yl)-piperazin;

mit 3-(3-Aminopropyl)-5-indolcarbonsäuremethylester:
1-[3-(5-Methoxycarbonyl-indol-3-yl)-propyl]-4-(chroman-6-yl)-piperazin;

mit 3-(2-Aminoethyl)-5-indolcarbonsäureethylester:
1-[2-(5-Ethoxycarbonyl-indol-3-yl)-ethyl]-4-(chroman-6-yl)-piperazin;

mit 3-(4-Aminobutyl)-5-fluor-indol:
1-[4-(5-Fluor-indol-3-yl)-butyl]-4-(chroman-6-yl)-piperazin.

mit 3-(3-Aminopropyl)-5-cyan-indol:
1-[3-(5-Cyan-indol-3-yl)-propyl]-4-(2-carboxy-chroman-6-yl)-piperazin.

Beispiel 7

Eine Lösung von 3,9 g 1-[4-(5-Carboxy-indol-3-yl)-butyl]-4-(2,3-dihydrobenzofuran-5-yl)-piperazin in 250 ml DMF wird mit 1 g N-Methylmorpholin versetzt. Unter Rühren gibt man eine Lösung von einem Äquivalent tert.-Butylamin in 5 ml DMF, 1,3 g 1-Hydroxybenztriazol sowie eine Lösung von 1,9 g N-(3-Dimethylaminopropyl)-N'-ethyl-carbodiimid-hydrochlorid in 20 ml DMF hinzu. Man rührt 16 Stunden bei Raumtemperatur und dampft das Filtrat ein. Nach üblicher Aufarbeitung erhält man 1-[4-(5-N-tert.-Butylcarbamoyl-indol-3-yl)-butyl]-4-(2,3-dihydrobenzofuran-5-yl)-piperazin.

Analog erhält man durch Umsetzung mit tert.-Butylamin ausgehend

von 1-[4-(5-Carboxy-indol-3-yl)-butyl]-4-(chroman-6-yl)-piperazin:
1-[4-(5-N-tert.-Butylcarbamoyl-indol-3-yl)-butyl]-4-(chroman-6-yl)-piperazin;

von 1-[4-(5-Cyan-indol-3-yl)-butyl]-4-(2-carboxy-benzofuran-5-yl)-piperazin:
1-[4-(5-Cyan-indol-3-yl)-butyl]-4-(2-N-tert.-butyl-carbamoyl-benzofuran-5-yl)-piperazin.

Beispiel 8

Eine Gemisch von 2,1 g 1-[4-(5-Methoxy-indol-3-yl)-butyl]-4-(chroman-6-yl)-piperazin [herstellbar nach Beispiel 1], 1,8 g Pyridinhydrochlorid sowie 50 ml Pyridin wird 3 Stunden gekocht. Man kühlt ab, dampft ein, arbeitet wie üblich auf und erhält 1-[4-(5-Hydroxy-indol-3-yl)-butyl]-4-(chroman-6-yl)-piperazin, F. 220-222°.

Analog erhält man

aus 1-[4-(5-Methoxy-indol-3-yl)-butyl]-4-(2,3-dihydrobenzofuran-5-yl)-piperazin:
1-[4-(5-Hydroxy-indol-3-yl)-butyl]-4-(2,3-dihydrobenzofuran-5-yl)-piperazin;

aus 1-[4-(5-Methoxy-indol-3-yl)-butyl]-4-(benzofuran-5-yl)-piperazin:
1-[4-(5-Hydroxy-indol-3-yl)-butyl]-4-(benzofuran-5-yl)-piperazin;

aus 1-[4-(5-Methoxycarbonyl-indol-3-yl)-butyl]-4-(chromen-4-on-6-yl)-piperazin:
1-[4-(5-Hydroxycarbonyl-indol-3-yl)-butyl]-4-(chromen-4-on-6-yl)-piperazin;

aus
1-[4-(5-Methoxymethyl-indol-3-yl)-butyl]-4-(benzofuran-5-yl)-piperazin:
1-[4-(5-Hydroxymethyl-indol-3-yl)-butyl]-4-(benzofuran-5-yl)-piperazin;

aus 1-[2-(5-Methoxy-indol-3-yl)-ethyl]-4-(benzofuran-5-yl)-piperazin:
1-[2-(5-Hydroxy-indol-3-yl)-ethyl]-4-(benzofuran-5-yl)-piperazin;

aus 1-[2-(5-Methoxy-indol-3-yl)-ethyl]-4-(benzofuran-5-yl)-piperazin:
1-[2-(5-Hydroxy-indol-3-yl)-ethyl]-4-(benzofuran-5-yl)-piperazin.

Beispiel 9

Analog Beispiel 1 erhält man ausgehend von 3-(4-Chlorbutyl)-5-cyan-indol [erhältlich durch Umsetzung von 5-Cyanindol mit 4-Chlorbutyrylchlorid zu 3-(4-Chlorbutyryl)-5-methoxyindol und anschließende Reduktion mit $NaAlH_2(OCH_2CH_2OCH_3)_2$] durch Umsetzung mit 1-(2-Ethoxycarbonyl-benzofuran-5-yl)-piperazin [erhältlich durch Umsetzung von N,N-Bis-(2-chlorethyl)-amin mit 2-Ethoxycarbonyl-5-amino-benzofuran] nach

üblicher Aufarbeitung das 1-[4-(5-Cyan-indol-3-yl)-butyl]-4-(2-ethoxy-carbonyl-benzofuran-5-yl)-piperazin, F. 221-223° (Dihydrochlorid).

Analog erhält man durch Umsetzung

von 3-(4-Chlorbutyl)-5-methoxy-indol mit 1-(2-Cyanbenzofuran-5-yl)-piperazin:
1-[4-(5-Methoxy-indol-3-yl)-butyl]-4-(2-cyanbenzofuran-5-yl)-piperazin;

von 3-(4-Chlorbutyl)-5,6-dimethoxy-indol mit 1-(Chroman-6-yl)-piperazin:
1-[4-(5,6-Dimethoxy-indol-3-yl)-butyl]-4-(chroman-6-yl)-piperazin;

von 3-(4-Chlorbutyl)-5,6-difluor-indol mit 1-(Chroman-6-yl)-piperazin:
1-[4-(5,6-Difluor-indol-3-yl)-butyl]-4-(chroman-6-yl)-piperazin;

von 3-(4-Chlorbutyl)-6-indolcarbonsäuremethylester mit 1-(Chroman-6-yl)-piperazin:
1-[4-(6-Methoxycarbonyl-indol-3-yl)-butyl]-4-(chroman-6-yl)-piperazin;

von 3-(3-Chlorpropyl)-6-indolcarbonsäureethylester mit 1-(2-Cyan-benzofuran-5-yl-piperazin:
1-[3-(6-Ethoxycarbonyl-indol-3-yl)-propyl]-4-(2-cyan-benzofuran-5-yl)-piperazin;

von 3-(4-Chlorbutyl)-5-methoxy-indol mit 1-(2-N-Methylcarbamoyl-benzofuran-5-yl)-piperazin:
1-[4-(5-Methoxy-indol-3-yl)-butyl]-4-(2-N-methylcarbamoyl-benzofuran-5-yl)-piperazin;

von 3-(4-Chlorbutyl)-6-chlor-indol mit 1-(Chromen-4-on-6-yl)-piperazin:
1-[4-(6-Chlor-indol-3-yl)-butyl]-4-(chromen-4-on-6-yl)-piperazin;

von 3-(2-Chlorethyl)-5-cyan-indol mit 1-(Chromen-4-on-6-yl)-piperazin: 1-[2-(5-Cyan-indol-3-yl)-ethyl]-4-(chromen-4-on-6-yl)-piperazin;

von 3-(2-Chlorethyl)-5,6-dichlor-indol mit 1-(2,3-Dihydrobenzofuran-5-yl)-piperazin:
1-[2-(5,6-Dichlor-indol-3-yl)-ethyl]-4-(2,3-dihydrobenzofuran-5-yl)-piperazin;

von 3-(4-Chlorbutyl)-5-methoxycarbonyl-indol mit 1-(2-Carboxy-benzofuran-5-yl)-piperazin:
1-[4-(5-Methoxycarbonyl-indol-3-yl)-butyl]-4-(2-carboxy-benzofuran-5-yl)-piperazin;

von 3-(2-Chlorethyl)-5-methoxycarbonyl-indol mit 4-(2-Carboxy-benzofuran-5-yl)-4-piperidin:
1-[2-(5-Methoxycarbonyl-indol-3-yl)-ethyl]-4-(2-carboxy-benzofuran-5-yl)-piperazin;

von 3-(4-Chlorbutyl)-6-methoxycarbonyl-indol mit 4-(3-Carboxy-benzofuran-5-yl)-4-hydroxy-piperidin:
1-[4-(6-Methoxycarbonyl-indol-3-yl)-butyl]-4-(3-carboxy-benzofuran-5-yl)-4-hydroxy-piperidin;

von 3-(4-Chlorbutyl)-7-methoxycarbonyl-indol mit 4-(3-Carboxy-benzofuran-5-yl)-4-hydroxy-piperidin:
1-[4-(7-Methoxycarbonyl-indol-3-yl)-butyl]-4-(3-carboxy-benzofuran-5-yl)-4-hydroxy-piperidin;

von 3-(4-Chlorbutyl)-5,6-dimethoxy-indol mit 1-(2-Carboxy-benzofuran-5-yl)-piperazin:
1-[4-(5,6-Dimethoxy-indol-3-yl)-butyl]-4-(2-carboxy-benzofuran-5-yl)-piperazin.

Beispiel 10

Zu einer Suspension von 0,6 g Lithiumaluminiumhydrid in 20 ml THF wird unter Rühren bei Raumtemperatur eine Lösung von 3,6 g 1-[4-(5-Methoxycarbonyl-indol-3-yl)-butyl]-4-(chromen-4-on-6-yl)-piperazin in 40 ml THF tropfenweise zugegeben. Anschließend rührt man eine weitere Stunde bei 25°, fügt 20 ml verdünnte Natronlauge hinzu, filtriert und arbeitet das Filtrat wie üblich auf. Man erhält 1-[4-(5-Hydroxymethyl-indol-3-yl)-butyl]-4-(chromen-4-on-6-yl)-piperazin.

Analog erhält man durch Reduktion

von 1-[4-(5-Methoxycarbonyl-indol-3-yl)-butyl]-4-(chroman-6-yl)-piperazin das
1-[4-(5-Hydroxymethyl-indol-3-yl)-butyl]-4-(chroman-6-yl)-piperazin;

von 1-[4-(5-Methoxycarbonyl-indol-3-yl)-butyl]-4-(benzofuran-5-yl)-piperazin das
1-[4-(5-Hydroxymethyl-indol-3-yl)-butyl]-4-(benzofuran-5-yl)-piperazin;

von 1-[3-(5-Methoxycarbonyl-indol-3-yl)-propyl]-4-(chroman-6-yl)-piperidin das
1-[3-(5-Hydroxymethyl-indol-3-yl)-propyl]-4-(chroman-6-yl)-piperidin;

von 1-[2-(5-Methoxycarbonyl-indol-3-yl)-ethyl]-4-(chroman-6-yl)-piperidin das
1-[2-(5-Hydroxymethyl-indol-3-yl)-ethyl]-4-(chroman-6-yl)-piperidin.

Beispiel 11

In eine siedende Lösung von 2,5 g 1-[4-(5-Carboxy-indol-3-yl)-butyl]-4-(2,3-dihydrobenzofuran-5-yl)-piperazin in 50 ml absolutem Methanol wird

2 Stunden HCl-Gas eingeleitet. Anschließend kocht man eine weitere Stunde, arbeitet wie üblich auf und erhält 1-[4-(5-Methoxycarbonyl-indol-3-yl)-butyl]-4-(2,3-dihydrobenzofuran-5-yl)-piperazin.

Analog erhält man durch Veresterung

von 1-[4-(5-Carboxy-indol-3-yl)-butyl]-4-(2,3-dihydrobenzofuran-5-yl)-4-hydroxy-piperidin:
1-[4-(5-Methoxycarbonyl-indol-3-yl)-butyl]-4-(2,3-dihydrobenzofuran-5-yl)-4-hydroxy-piperidin;

von 1-[4-(5-Carboxy-indol-3-yl)-butyl]-4-(chroman-6-yl)-piperazin:
1-[4-(5-Methoxycarbonyl-indol-3-yl)-butyl]-4-(chroman-6-yl)-piperazin;

von 1-[4-(5-Cyan-indol-3-yl)-butyl]-4-(2-carboxy-benzofuran-5-yl)-piperazin:
1-[4-(5-Cyan-indol-3-yl)-butyl]-4-(2-methoxycarbonyl-benzofuran-5-yl)-piperazin.

Beispiel A: Injektionsgläser

Eine Lösung von 100 g eines Wirkstoffes der Formel I und 5 g Dinatriumhydrogenphosphat in 3 l zweifach destilliertem Wasser wird mit 2 n Salzsäure auf pH 6,5 eingestellt, steril filtriert, in Injektionsgläser abgefüllt, lyophilisiert und steril verschlossen. Jedes Injektionsglas enthält 5 mg Wirkstoff.

Beispiel B: Suppositorien

Man schmilzt ein Gemisch von 20 mg eines Wirkstoffes der Formel I mit 100 g Sojalecithin und 1400 g Kakaobutter, gießt in Formen und läßt erkalten. Jedes Suppositorium enthält 20 mg Wirkstoff.

Beispiel C: Lösung

Man bereitet eine Lösung aus 1 g eines Wirkstoffes der Formel I, 9,38 g NaH_2PO_4 x 2 H_2O, 28,48 g $Na_2HPO_4 \times 12\ H_2O$ und 0,1 g Benzalkoniumchlorid in 940 ml zweifach destilliertem Wasser. Man stellt auf pH 6,8 ein, füllt auf 1 l auf und sterilisiert durch Bestrahlung. Diese Lösung kann in Form von Augentropfen verwendet werden.

Beispiel D: Salbe

Man mischt 500 mg eines Wirkstoffes der Formel I mit 99,5 g Vaseline unter aseptischen Bedinungen.

Beispiel E: Tabletten

Ein Gemisch von 1 kg Wirkstoff der Formel I, 4 kg Lactose, 1,2 kg Kartoffelstärke, 0,2 kg Talk und 0,1 kg Magnesiumstearat wird in üblicher Weise zu Tabletten verpreßt, derart, daß jede Tablette 10 mg Wirkstoff enthält.

Beispiel F: Dragees

Analog Beispiel E werden Tabletten gepreßt, die anschließend in üblicher Weise mit einem Überzug aus Saccharose, Kartoffelstärke, Talk, Tragant und Farbstoff überzogen werden.

Beispiel G: Kapseln

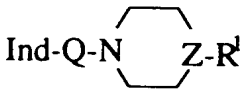
2 kg Wirkstoff der Formel I werden in üblicher Weise in Hartgelatinekapseln gefüllt, so daß jede Kapsel 20 mg des Wirkstoffs enthält.

Beispiel H: Ampullen

Eine Lösung von 1 kg Wirkstoff der Formel I in 60 l zweifach destilliertem Wasser wird in Ampullen abgefüllt, unter aseptischen Bedingungen lyophilisiert und steril verschlossen. Jede Ampulle enthält 10 mg Wirkstoff.

Patentansprüche

1. Piperidin- und Piperazinderivate der Formel I



I,

worin

Ind	einen unsubstituierten oder einen ein- oder zweifach durch OH, OA, CN, Hal, COR^2 oder CH_2R^2 substituierten Indol-3-yl-rest,
R^1	unsubstituiertes oder einfach durch CN, CH_2OH, CH_2OA oder COR^2 substituiertes Benzofuran-5-yl bzw. 2,3-Dihydrobenzofuran-5-yl, Chroman-6-yl, Chroman-4-on-6-yl, 3-Chromen-6-yl oder Chromen-4-on-6-yl,
Q	C_mH_{2m},
Z	N oder CR^3,
A	Alkyl mit 1-6 C-Atomen,
Hal	F, Cl, Br oder I,
R^2	OH, OA, NH_2, NHA oder NA_2,
R^3	H, OH oder OA und
m	2, 3 oder 4

bedeuten,

sowie deren physiologisch unbedenkliche Salze.

2. (a) 1-[4-(5-Methoxy-indol-3-yl)-butyl]-4-(2-hydroxymethylbenzofuran-5-yl)-piperazin;

(b) 1-[4-(5-Carbamoyl-indol-3-yl)-butyl]-4-hydroxy-4-(2,3-dihydrobenzofuran-5-yl)-piperidin;

(c) 1-[4-(5-Carbamoyl-indol-3-yl)-butyl]-4-(2,3-dihydrobenzofuran-5-yl)-piperidin;

(d) 1-[4-(5-Methoxy-indol-3-yl)-butyl]-4-(2,3-dihydrobenzofuran-5-yl)-piperazin;

(e) 1-[4-(5-Cyan-indol-3-yl)-butyl]-4-(2-ethoxycarbonylbenzofuran-5-yl)-piperazin;

(f) 1-[4-(5-Cyan-indol-3-yl)-butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazin;

(g) 1-[4-(5-Methoxy-indol-3-yl)-butyl]-4-(chroman-6-yl)-piperazin;

(h) 1-[4-(5-Hydroxy-indol-3-yl)-butyl]-4-(chroman-6-yl)-piperazin.

3. Verfahren zur Herstellung von Piperazin- und Piperidinderivaten der Formel I nach Anspruch 1 sowie von deren Salzen, dadurch gekennzeichnet, daß man eine Verbindung der Formel II

$$Ind\text{-}Q\text{-}X^1 \qquad II,$$

worin

X^1 X oder NH_2 und

X Cl, Br, I, OH oder eine reaktionsfähig funktionell abgewandelte OH-Gruppe bedeuten und

Ind und Q die angegebenen Bedeutungen haben.

mit einer Verbindung der Formel III

$$X^2\text{-}(CH_2)_2\text{-}ZR^1\text{-}(CH_2)_2\text{-}X^3 \qquad \text{III},$$

worin

X^2 und X^3 gleich oder verschieden sein können und, falls $X^1 = NH_2$ ist, jeweils X, andernfalls zusammen NH bedeuten und

Z und R^1 die angegebenen Bedeutungen haben,

umsetzt,

oder daß man zur Herstellung einer Verbindung der Formel I, worin Z gleich N bedeutet, eine Verbindung der Formel IV

$$Ind\text{-}Q\text{-}N(CH_2\text{-}CH_2\text{-}X)_2 \qquad \text{IV},$$

worin X, Q und Ind die angegebenen Bedeutungen haben, mit einer Verbindung der Formel V

$$R^1\text{-}NH_2 \qquad \text{V},$$

worin R^1 die angegebene Bedeutung hat,

umsetzt

oder daß man eine sonst der Formel I entsprechende Verbindung, die jedoch anstelle eines oder mehrerer Wasserstoffatome eine oder mehrere reduzierbare Gruppe(n) und/oder eine oder mehrere zusätzliche C-C- und/oder C-N-Bindung(en) enthält, mit einem reduzierenden Mittel behandelt

oder daß man eine sonst der Formel I entsprechende Verbindung, die jedoch anstelle eines oder mehrerer Wasserstoffatome eine oder mehrere solvolysierbare Gruppe(n) enthält, mit einem solvolysierenden Mittel behandelt

und/oder daß man gegebenenfalls eine OA-Gruppe unter Bildung einer OH-Gruppe spaltet und/oder eine Gruppe Ind und/oder eine Gruppe R^1 in eine andere Gruppe Ind und/oder R^1 umwandelt und/oder daß man eine erhaltene Base oder Säure der Formel I durch Behandeln mit einer Säure oder Base in eines ihrer Salze umwandelt.

4. Verfahren zur Herstellung pharmazeutischer Zubereitungen, dadurch gekennzeichnet, daß man eine Verbindung der Formel I gemäß Anspruch 1 und/oder eines ihrer physiologisch unbedenklichen Salze zusammen mit mindestens einem festen, flüssigen oder halbflüssigen Träger- oder Hilfsstoff in eine geeignete Dosierungsform bringt.

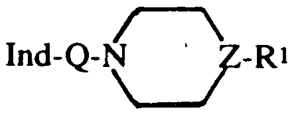
5. Pharmazeutische Zubereitung, gekennzeichnet durch einen Gehalt an mindestens einer Verbindung der allgemeinen Formel I gemäß Anspruch 1 und/oder einem ihrer physiologisch unbedenklichen Salze.

6. Verwendung von Verbindungen der Formel I nach Anspruch 1 oder von deren physiologisch unbedenklichen Salzen zur Herstellung eines Arzneimittels.

7. Verwendung von Verbindungen der Formel I nach Patentanspruch 1 oder von deren physiologisch unbedenklichen Salzen bei der Bekämpfung von Krankheiten.

Zusammenfassung

Piperidin- und Piperazinderivate der Formel I



I,

worin

Ind einen unsubstituierten oder einen ein- oder zweifach durch OH, OA, CN, Hal, COR^2 oder CH_2R^2 substituierten Indol-3-yl-rest,

R^1 unsubstituiertes oder einfach durch CN, CH_2OH, CH_2OA oder COR^2 substituiertes Benzofuran-5-yl bzw. 2,3-Dihydrobenzofuran-5-yl, Chroman-6-yl, Chroman-4-on-6-yl, 3-Chromen-6-yl oder Chromen-4-on-6-yl,

Q C_mH_{2m},

Z N oder CR^3,

A Alkyl mit 1-6 C-Atomen,

Hal F, Cl, Br oder I,

R^2 OH, OA, NH_2, NHA oder NA_2,

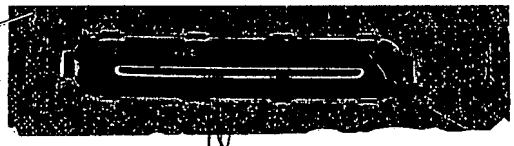
R^3 H, OH oder OA und

m 2, 3 oder 4

bedeuten,

sowie deren physiologisch unbedenkliche Salze, zeigen Wirkungen auf das Zentralnervensystem.

08/314734 | 514 | 254 | Class | Subclass | ISSUE CLASSIFICATION



5532241

UTILITY SERIAL NUMBER	PATENT DATE	PATENT NUMBER
08/314734	JUL 02 1996	5532241

SERIAL NUMBER	FILING DATE	CLASS	SUBCLASS	GROUP ART UNIT	EXAMINER
08/314,734	09/29/94	~~546~~ 514	254	~~1203~~ 1202	

APPLICANTS

HENNING BOTTCHER, DARMSTADT, FED REP GERMANY; CHRISTOPH SEYFRIED, SEEHEIM-JUGENHE, FED REP GERMANY; GERD BARTOSZYK, DARMSTADT, FED REP GERMANY; HARTMUT GREINER, DARMSTADT, FED REP GERMANY.

CONTINUING DATA******** NONE
VERIFIED
EB

FOREIGN/PCT APPLICATIONS********
VERIFIED FED REP GERMANY P 43 33 254.4 09/30/93
EB

Foreign priority claimed / 35 USC 119 conditions met / Verified and Acknowledged	Examiner's initials	AS FILED	STATE OR COUNTRY	SHEETS DRWGS.	TOTAL CLAIMS	INDEP. CLAIMS	FILING FEE RECEIVED	ATTORNEY'S DOCKET NO.
☑ yes ☐ no / ☑ yes ☐ no	EB	→	DEX	0	22	1	$754.00	MERCK1617

ADDRESS

MILLEN WHITE ZELAND AND BRANIGAN
ARLINGTON COURTHOUSE PLAZA I SUITE 1400
2200 CLARENDON BOULEVARD
ARLINGTON VA 22201

TITLE

PIPERIDINES AND PIPERAZINES

ISSUE FEE IN FILE

U.S. DEPT. of COMM./Pat. & TM Office — PTO-436L (rev. 10-78)

2-22-96
Renee Petters
Applications Examiner

PARTS OF APPLICATION FILED SEPARATELY

NOTICE OF ALLOWANCE MAILED		CLAIMS ALLOWED	
2-7-96	Assistant Examiner	Total Claims: 17	Print Claim: 1

ISSUE FEE		DRAWING		
Amount Due	Date Paid	Sheets Drwg.	Figs. Drwg.	Print Fig.
$1250.00	4-10-96	0	0	—

E Bernhardt
EMILY BERNHARDT
PRIMARY EXAMINER
GROUP 1200 1202
Primary Examiner

ISSUE BATCH NUMBER: T58

PREPARED FOR ISSUE

Label Area

WARNING: The information disclosed herein may be restricted. Unauthorized disclosure may be prohibited by the United States Code Title 35, Sections 122, 181 and 368. Possession outside the U.S. Patent & Trademark Office is restricted to authorized employees and contractors only.

Form PTO-436A
(Rev. 8/92)

(FACE)

PATENT NUMBER

APPLICATION SERIAL NUMBER
08/314734

APPLICANT'S NAME (PLEASE PRINT)
BOTCHER et al

IF REISSUE, ORIGINAL PATENT NUMBER

ORIGINAL CLASSIFICATION

CLASS	SUBCLASS
514	254

CROSS REFERENCE(S)

CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)			
544	373			
546	201			
514	323			

INTERNATIONAL CLASSIFICATION

A	61	K		31	495
A	61	K		31	495
C	07	D		405	10

GROUP ART UNIT: 1202

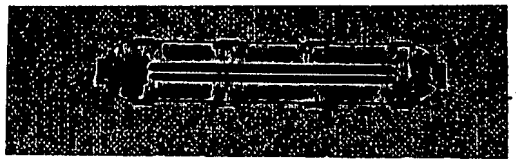
ASSISTANT EXAMINER (PLEASE STAMP OR PRINT FULL NAME)

PRIMARY EXAMINER (PLEASE STAMP OR PRINT FULL NAME)
L. Bernhardt

PTO 270
(REV. 5-91)

ISSUE CLASSIFICATION SLIP

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE



SEARCHED

Class	Sub.	Date	Exmr.
544	373	3/15/95	EB
514	254	"	"
Updated	Above	10/5/95	EB
Updated	Above	2/6/96	EB

INTERFERENCE SEARCHED

Class	Sub.	Date	Exmr.
544	373	2/6/96	EB
514	254	"	"

SEARCH NOTES

	Date	Exmr.
CAS ONLINE	3/95	EB

(RIGHT OUTSIDE)

Staple Issue Slip Here

POSITION		ID NO.	DATE
CLASSIFIER		399	10/17/94
EXAMINER		299	10-24
TYPIST		324	108594
VERIFIER		204	10 27 94
CORPS CORR.			
SPEC. HAND			
FILE MAINT.			
DRAFTING			

INDEX OF CLAIMS

Claim Final	Claim Original	Date 3/15/95	Date 12/5/95	Date 2/6/96
1	(1)	✓	✓	=
2	2			
3	3			
4	4			
5	5			
6	6			
7	7			
8	8			↓
	~~9~~			
9	10			=
10	11			=
11	12	↓	↓	=
	~~13~~	N	N	
	~~14~~	✓	✓	
	~~15~~	✓	✓	
12	16	O	O	=
16	17	✓	✓	=
17	18	✓	✓	=
	~~19~~	N	N	
	~~20~~	N	N	
	~~21~~	N	N	
	~~22~~	N	N	
	~~23~~		✓	
13	24		O	=
14	25		Ø	=
	~~26~~		✓	
	~~27~~		✓	
a 15	28		O	=
	29			
	30			
	31			
	32			
	33			
	34			
	35			
	36			
	37			
	38			
	39			
	40			
	41			
	42			
	43			
	44			
	45			
	46			
	47			
	48			
	49			
	50			

SYMBOLS

- ✓ ..... Rejected
- = ... Allowed
- - (Through numberal) Canceled
- + ... Restricted
- N ..... Non-elected
- I ..... Interference
- A ..... Appeal
- O ..... Objected

Claim Final	Claim Original	Date
	51	
	52	
	53	
	54	
	55	
	56	
	57	
	58	
	59	
	60	
	61	
	62	
	63	
	64	
	65	
	66	
	67	
	68	
	69	
	70	
	71	
	72	
	73	
	74	
	75	
	76	
	77	
	78	
	79	
	80	
	81	
	82	
	83	
	84	
	85	
	86	
	87	
	88	
	89	
	90	
	91	
	92	
	93	
	94	
	95	
	96	
	97	
	98	
	99	
	100	

(LEFT INSIDE)