

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 21-006

ADMINISTRATIVE DOCUMENTS

Fax

To: Ms. L. Chen **From:** _____
Fax: (301) 594-2859 **Pages:** 3
Phone: (301) 594-5529 **Date:** 04/14/00
Re: Exclusivity Claim **CC:** _____

Urgent For Review Please Comment Please Reply Please Recycle

In response to your request today about the location of the claim for exclusivity for frovatriptan, the following information, in reference to 21 CFR 314.50(j) is provided:

1. The applicant, Vanguard Medica Limited is claiming exclusivity for frovatriptan succinate. Because this is a new chemical entity, the maximum allowable term of 5 years is being requested.
2. This claim for exclusivity is supported by the provisions set forth in 21 CFR 314.108(b)(2).
3. To the best of the applicant's knowledge, this drug is has not previously been approved under section 505(b) of the act. This is supported by the attached patent information and certification, which was submitted in the original application (Volume 1.01 pages 7 and 72). Vanguard Medica Limited signed an exclusive license, with rights to grant sub-licenses, with Smith-Kline Beecham on 21st October 1994, allowing Vanguard Medica Group plc to make develop and sell the product, it has been the sole owner of the product since.

Please let me know if you have further questions or if you need additional information. I will formally submit a copy of the facsimile transmission to the NDA correspondence file.

Yours truly,

NDA 21-006 US Agent

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ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	<u>21006</u>	Trade Name:	<u>MIGUARD(FROVATRIPTAN SUCCINATE) 2.5MG TAB</u>
Supplement Number:		Generic Name:	<u>FROVATRIPTAN SUCCINATE</u>
Supplement Type:		Dosage Form:	<u>TAB</u>
Regulatory Action:	<u>AE</u>	Proposed Indication:	<u>Treatment of Migraine Headache</u>

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

NeoNates (0-30 Days) Children (25 Months-12 years)
 Infants (1-24 Months) Adolescents (13-16 Years)

Label Adequacy Does Not Apply
Formulation Status
Studies Needed
Study Status

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

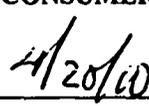
COMMENTS:

Sponsor will be informed in the AE Letter of the need for future pediatric studies.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, LANA CHEN



 Signature



 Date

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CONFIDENTIAL

16.0 DEBARMENT CERTIFICATION

The following is the debarment statement provided by Vanguard Medica Limited.

**APPEARS THIS WAY
ON ORIGINAL**



Vanguard Medica

Vanguard Medica Limited
Chancellor Court, Surrey Research Park
Guildford, Surrey GU2 5SF, UK
Telephone +44 (0)1483-787878
Facsimile +44 (0)1483-787811
e-mail admin@vanguardmedica.com

DEBARMENT CERTIFICATION

On behalf of Vanguard Medica Limited, I hereby certify that we did not and will not use in any capacity the services of an individual, partnership, corporation, or association debarred under subsections (a) or (b) of Section 306 of the Federal Food, Drug and Cosmetic Act in connection with NDA 21-006 for Frovatriptan monosuccinate monohydrate.

Gary Acton, M.D.
Vanguard Medical Limited

APPEARS THIS WAY
ON ORIGINAL



DEPARTMENT OF HEALTH & HUMAN SERVICES

Chen

Food and Drug Administration
Rockville MD 20857

William E. McIntosh, D. O.
3500 Camp Bowie Boulevard
Fort Worth, Texas 76107

MAY 19 2000

Dear Dr. McIntosh:

Between April 20 and 26, 2000, Mr. Phillip D. Waldron representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol VML/96/07) of the investigational drug frovatriptan succinate, performed for Vanguard Medica Limited. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did not adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects, in that you did not conduct some of the protocol-required telephone calls to 14 subjects (0427, 0428, 0432, 0435, 0436, 0579, 0580, 0585, 0727, 0734, 0737, 0931, 0933, and 0941). We do note, however, that you have agreed to implement appropriate procedures to prevent recurrence of this finding in any ongoing or future studies.

We appreciate the cooperation shown Investigator Waldron during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact me at (301) 594-1032.

Sincerely yours,

/S/

for
Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: October 22, 2001	DUE DATE: November 8, 2001	OPDRA CONSULT #: 00-0192-1
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TO: Russell Katz, M.D.
Director, Division of Neuropharmacological Drug Products
HFD-120

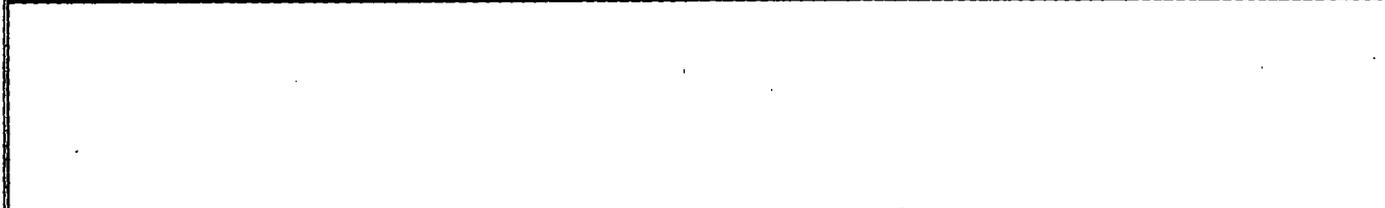
THROUGH: Lana Yan Chen, Project Manager
HFD-120

PRODUCT NAME: _____ (Primary) Frova (Alternate) [Frovatriptan Tablets] 2.5 mg NDA #: 21-006	MANUFACTURED BY: Vanguard Medica Ltd. DISTRIBUTED BY: Elan Pharmaceuticals
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SAFETY EVALUATOR: Carol Holquist, R.Ph.

SUMMARY: In response to a consult from the Division of Neuropharmacological Drug Products (HFD-120), OPDRA conducted a re-review of the proposed proprietary name _____

OPDRA RECOMMENDATION: Following further review, OPDRA reverses its initial decision and does not recommend the use of the proprietary name _____. OPDRA has no objection to the use of the alternate name "Frova". OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.



Jerry Phillips, RPh Associate Director for Medication Error Prevention Office of Post-Marketing Drug Risk Assessment Phone: (301) 827-3242 Fax: (301) 480-8173	Martin Himmel, MD Deputy Director Office of Post-Marketing Drug Risk Assessment Center for Drug Evaluation and Research Food and Drug Administration
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Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: October 30, 2001
NDA NUMBER: 21-006
NAME OF DRUG: _____ or Frova (Frovatriptan Tablets) 2.5 mg
MANUFACTURED BY: Vanguard Medica Ltd.
DISTRIBUTED BY: Elan Pharmaceuticals

I. INTRODUCTION

This consult was written in response to a request from the Division of Neuropharmacological Drug Products (HFD-120) for reassessment of the proposed proprietary name _____ before approval. This is the second proprietary name review for this drug product. OPDRA reviewed and accepted the proprietary name _____ in October of 2000 (see OPDRA consult 00-0192). At that time, we also reviewed container labels, carton labeling, and package insert labeling in which we provided several recommendations that would minimize medication errors. Upon reassessment of the name OPDRA identified several products that posed a potential concern therefore, an analysis was also conducted on the alternate name, Frova.

PRODUCT INFORMATION

_____ tablets contain the active ingredient, frovatriptan succinate. Frovatriptan succinate is a 5-HT receptor agonist indicated for the acute treatment of migraine attacks with or without aura in adults. _____ is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine. The recommended adult dose is 2.5 mg taken orally with fluids at anytime after the onset of a migraine headache. No more than three doses should be taken within 24 hours.

APPEARS THIS WAY
ON ORIGINAL

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts^{i,ii,iii} as well as several FDA databases^{iv} for existing drug names which sound alike or look alike to _____ and "Frova" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's trademark electronic search system (TESS) was conducted^v. The Saegis⁶ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted prescription analysis studies, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary names, _____ and *Frova*. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

With the use of a new database that aids in the detection of phonetic similarity between names, the Expert Panel identified *four* proprietary names that were thought to have the potential for confusion with _____ that were not identified in the first review conducted by OPDRA. These products are listed in table 1 (see page four), along with the dosage forms available and usual FDA-approved dosage. DDMAC did not have concerns about the name with regard to promotional claims.

Additionally, *four* proprietary names were identified as a potential sound-alike/look-alike name to Frova. These products are listed in table 2 (see page four), along with the dosage forms available and usual FDA-approved dosage. DDMAC did not have concerns about Frova with regard to promotional claims.

ⁱ MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

ⁱⁱ American Drug Index, 42nd Edition, online version, Facts and Comparisons, St. Louis, MO.

ⁱⁱⁱ Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.

^{iv} The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

^v WWW location <http://tess.uspto.gov/bin/gate.exe?f=tess&state=k0n826.1.1>

⁶ Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

TABLE 1

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
	Frovatriptan Succinate <i>Tablets</i> 2.5 mg	One 2.5 mg tablet at the onset of a migraine headache. No more than 3 tablets in 24 hours.	
Phrenilin	Acetaminophen and Butalbital <i>Tablets</i> 325 mg/50 mg	One or two tablets every four hours, no more than 6/day. <i>Phrenilin Forte</i> : One capsule every four hours	S/A per OPDRA
Pavulon	Pancuronium Bromide Injection 1 mg/mL and 2 mg/mL	Individualized in each case Initial intravenous dosage range: Adults – 0.04 to 0.1 mg/kg Children – 0.02 mg/kg	S/A, L/A per OPDRA
Novolin	Insulin Human Injection 70/30, 100/mL 10 mL, 1.5 mL cartridges and pen prefill 3 mL	Dosage based on the results of blood and urine glucose determinations, individualized to attain optimum therapeutic effect. Dosage is in units.	S/A per OPDRA
Ovulen	Ethinyl Estradiol and Ethynodiol Diacetate <i>Tablets</i> 1/35 and 1/50	Not marketed in the United States.	S/A, L/A per OPDRA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

TABLE 2

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
Frova	Frovatriptan Succinate <i>Tablets</i> 2.5 mg	One 2.5 mg tablet at the onset of a migraine headache. No more than 3 tablets in 24 hours.	
Acova	Argatroban Injection 100 mg/mL, 2.5 mL vial	2 mcg/kg/min	S/A per OPDRA
Arava	Leflunomide <i>Tablets</i> 10 mg, 20 mg, and 100 mg	Load: 200 mg per day x 3 days Then 20 mg/day.	S/A, L/A per OPDRA
Provera	Medroxyprogesterone Acetate <i>Tablets</i> , 2.5 mg, 5 mg and 10 mg	Secondary Amenorrhea – 5 or 10 mg daily for 5 to 10 days. Abnormal uterine bleeding – 5 or 10 mg daily for 5 to 10 days beginning on the 16 th or 21 st day of the cycle.	S/A per OPDRA
Renova	Tretinoin Cream, 0.02%	Apply to face once a day in the evening.	S/A per OPDRA
Trovan	Trovaflaxacin Mesylate <i>Tablets/Injection</i> 100 mg and 200 mg <i>Tablets</i> 5 mg/mL - 200 mg and 300 mg	100 mg, 200 mg or 300 mg once daily. <i>Tablets and Injections are being distributed only to hospitals and long term nursing care facilities for patient initiating therapy in these facilities.</i>	S/A per OPDRA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology

In the previous consult three separate studies were conducted to determine the degree of confusion of _____ with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The majority of incorrect responses from the verbal and written studies were misspelled/phonetic variations of the drug name and did not identify and overlap with existing approved or not approved drug products. Since the initial review, OPDRA has obtained an additional database that aids in the detection of phonetic similarities between proprietary names. This database was utilized upon this second review and four additional names were identified as potential sound-alikes to _____. Therefore, OPDRA repeated only the verbal portion of our usual proprietary name analysis.

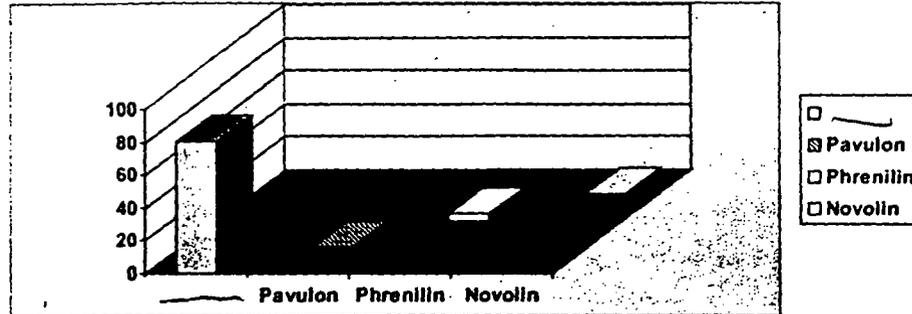
A single study was conducted within FDA to determine the degree of confusion potential of _____ with other U.S. drug names due to similarity in verbal pronunciation of the drug name. This study employed a total of 115 health care professionals (nurses, pharmacists, and physicians). The exercise was conducted in an attempt to simulate the oral prescription ordering process. An OPDRA staff member recorded a verbal prescription that was then delivered to a group of study participants via telephone voicemail. Each participant was requested to listen to the voicemail prescription and determine which drug was heard from a list of four proprietary names (see prescription below). Each participant provided his or her name selection via e-mail.

VERBAL PRESCRIPTION
_____ #15 Use as directed.
Choices: 1. Pavulon 2. Phrenilin 3. _____ 4. Novolin

2. Results

Results of this exercise is summarized below:

Study	No. of participants	# of responses (%)	response	Other response
Verbal: Outpatient	115	87 (77 %)	81 (93 %)	6 (7 %)



Five respondents misinterpreted the proposed name, , as Phrenilin and one as Novolin.

FROVA

1. Methodology

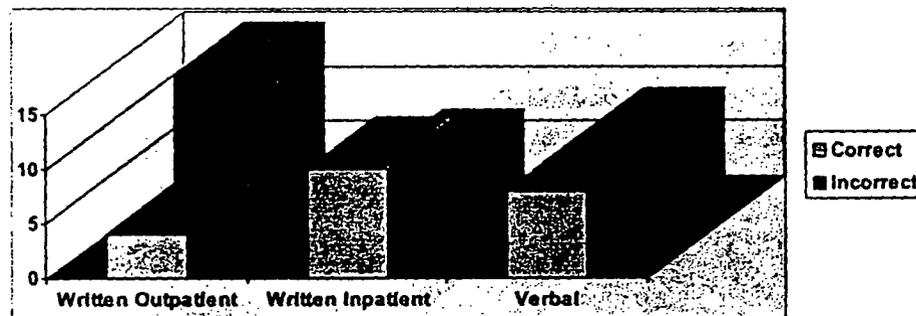
Three separate studies were conducted within FDA for each proposed proprietary name to determine the degree of confusion of Frova with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 90 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote an inpatient order and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for Frova (see page seven). These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
<i>Outpatient:</i> Frova 2.5 mg Take as directed, up to 3 per 24 hrs	Frova 2.5 mg Take as directed, up to 3 in 24 hours
<i>Inpatient:</i> D/C meds Frova 2.5 mg as directed #10	

2. Results

Results of these exercises are summarized below:

Study	No. of participants	# of responses (%)	"Frova" response	Other response
<i>Written:</i> Outpatient	30	18 (60 %)	4 (22 %)	14 (78 %)
Inpatient	29	16 (55 %)	10 (63 %)	6 (37%)
<i>Verbal:</i> Outpatient	31	16 (52 %)	8 (50 %)	8 (50 %)
Total:	90	50 (56 %)	22 (44 %)	28 (56 %)



Among participants in the written prescription studies, 20 of 34 respondents (59%) interpreted the name incorrectly. Most of the incorrect name interpretations were misspelled variations of "Frova". Seven respondents interpreted the name as Freva, misinterpreting the "o" as an "e". Five respondents interpreted the name as Trova substituting the "f" with a "t". Several respondents saw the "f" as an "i" as they interpreted Frova as Inova, Irova, or Irevva. Other responses included Fsrova, Frera, Inerva, Frora and Irova.

Among verbal prescription study respondents, 14 of 18 (78 %) interpreted the name incorrectly. Most of the incorrect name interpretations were phonetic variations of "Frova". Interpretations included: Froid, Frogut, Frofig, Fervid, Frover, Froid and Folage.

C. SAFETY EVALUATOR RISK ASSESSMENT

1. _____

In reviewing the proprietary name, _____ the primary concerns raised by the expert panel were related to three potential sound-alike names that already exist in the US marketplace, Phrenilin, Novolin, and Pavulon. Ovulen was also identified as a potential sound-alike name. However, this product is not marketed in the United States.

We conducted a verbal prescription study to simulate the prescription ordering process. In this case, there was confirmation that _____ could be confused with Phrenilin and Novolin as *five respondents (6%)* misinterpreted _____ as Phrenilin and *one respondent (1%)* misinterpreted _____ as Novolin. Although there are limitations to the predictive value of this study, primarily due to sample size, we have acquired safety concerns due to the positive interpretation with this drug product. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population.

_____]

Phrenilin is used to treat the relief of the symptom complex of tension (or muscle contraction) headache. Phrenilin is a combination product that contains 50 mg of butalbital and 325 mg of acetaminophen in an oral tablet formulation. The usual daily dose is one or two tablets every four hours, not to exceed six tablets per day. Although, there is no overlap in the dosage strength or dosing intervals, both _____ and Phrenilin are available as oral tablets and have similar indications for use, and will be prescribed by general practitioners, increasing the likelihood of confusion. It is highly likely that a prescriber would exclude the strength from a prescription for both are only available in one strength essentially eliminating the need to designate a particular strength. Therefore, the differences in product strength minimally help to distinguish these two products. In addition, since _____ usual dosage is "a single tablet anytime after the onset of a migraine headache" it is most likely that prescriptions will have a SIG of "as directed". If a patient received Phrenilin in error, the patient's symptoms of nausea and vomiting may be exacerbated, as one of the most frequently observed adverse reactions associated with the use of Phrenilin is nausea and vomiting. This could be quite debilitating in this patient population.

_____]

Novolin is available as an intravenous injection for the management of diabetes mellitus. The two share no overlapping strength, indications for use, and dosage form. The two products will be stored in separated areas in a pharmacy as insulin is generally stored under refrigeration. Although the names are similar, the clinical context of use decreases the likelihood for confusion between Novolin and _____

[Pavulon is a nondepolarizing neuromuscular blocking agent indicated for use as an adjunct to general anesthesia, to facilitate tracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation. It is supplied as a nonpyrogenic solution for injection containing 1 mg/mL or 2 mg/mL. The intravenous dosage range is 0.04 to 0.1 mg/kg. Although the names are similar, the clinical context of use decreases the likelihood for confusion between Pavulon and _____]

2. FROVA

In reviewing the proprietary name "Frova", the products considered to have the greatest potential for name confusion are *Acova*, *Arava*, *Renova*, *Provera* and *Trovan*.

Acova is a synthetic direct thrombin inhibitor indicated as an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia. *Acova* and *Frova* sound similar when spoken. However, there are no similarities in the product strength, dosage form, dosing interval, daily dose or indications for use. The two products will be stored in the different areas of the pharmacy and nursing units as well. Although the names are similar, the differences outlined above decrease the likelihood for confusion between *Frova* and *Acova*.

According to the Expert Panel *Arava* and *Frova* can sound similar. *Arava* is a pyrimidine synthesis inhibitor indicated for the treatment of active rheumatoid arthritis to reduce signs and symptoms and to retard structural damage as evidenced by x-ray erosions and joint space narrowing. *Arava* is available as a 10 mg, 20 mg and 100 mg tablet and is dosed daily. Although, *Arava* and *Frova* have overlapping dosage forms (tablets) they share no other commonalities. The potential for confusion among these two products is low.

Provera and *Frova* can look and sound similar according to the panel of experts. *Provera* is a derivative of progesterone indicated for secondary amenorrhea and for abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology. It is also indicated to reduce the incidence of endometrial hyperplasia in nonhysterectomized postmenopausal women receiving conjugated estrogen. *Provera* and *Frova* share an overlapping strength (2.5 mg) and dosage form (tablet). Despite these similarities they differ in dosing intervals, indications of use and daily dosage. The usual daily dose of *Provera* is 5 or 10 mg daily. Additionally, *Provera* and *Frova* differ in the number of syllables. When scripted *Frova* appears much shorter in length. Although the names are similar, the clinical context of use and other differences decrease the likelihood for confusion between *Provera* and *Frova*.

Trovan differs in strength, dosing intervals, and most notably, *Trovan* has limited distribution to hospitals and long term nursing care facilities. The potential for confusion among these products is low.

Renova is a topical cream that contains the active ingredient tretinoin. *Renova* and *Frova* can sound similar when spoken. However, they differ in strength, dosage form, indications for use and dosing interval. Additionally, post-marketing experience has *not* demonstrated much confusion between solid oral dosage forms and topical drug products. Therefore, the potential for confusion is low.

We conducted prescription studies to simulate the prescription ordering process. The study did not confirm confusion between Frova and any of the products identified by the Expert Panel. The majority of the incorrect responses from the verbal and written studies were misspelled/phonetic variations of the drug name. These responses did not overlap with any existing approved drug products. Although a negative finding in a study with such a small sample size does limit its predicative value, OPDRA believes the potential for confusion is low due to the differences in the distribution and administration of these drug products.

III. COMMENTS TO BE PROVIDED TO THE SPONSOR:

OPDRA does not recommend the use of the proprietary name, — Upon a second review of this proprietary name, OPDRA identified several medication names that have potential for verbal confusion with — The primary concerns are related to three potential sound-alike names that already exist in the US marketplace, Phrenilin, Novolin, and Pavulon. Phrenilin is the most concerning of all to OPDRA for the following reasons.

[In a study conducted by OPDRA, there was confirmation of verbal confusion between "Frovelan" and "Phrenilin".]

Phrenilin is used to treat the relief of the symptom complex of tension (or muscle contraction) headache. Phrenilin is a combination product that contains 50 mg of butalbital and 325 mg of acetaminophen in an oral tablet formulation. The usual daily dose is one or two tablets every four hours, not to exceed six tablets per day. Although, there is no overlap in the dosage strength or dosing intervals, both — and Phrenilin are available as oral tablets and have similar indications for use, and will be prescribed by general practitioners, increasing the likelihood of confusion. It is highly likely that a prescriber would exclude the strength from a prescription for both are only available in one strength essentially eliminating the need to designate a particular strength. Therefore, the differences in product strength minimally help to distinguish these two products. In addition, since — usual dosage is "a single tablet anytime after the onset of a migraine headache" it is most likely that prescriptions will have a SIG of "as directed". If a patient received Phrenilin in error, the patient's symptoms of nausea and vomiting may be exacerbated, as one of the most frequently observed adverse reactions associated with the use of Phrenilin is nausea and vomiting. This could be quite debilitating in this patient population.

Based on these findings, OPDRA conducted an analysis of the alternate name, Frova. OPDRA has no objections to the use of the proprietary name Frova.

IV. RECOMMENDATIONS

OPDRA does not recommend the use of the proprietary name _____ However, OPDRA has no objections to the use of the proprietary name Frova.

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3231.

Carol Holquist, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

**APPEARS THIS WAY
ON ORIGINAL**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Carol Holquist
11/7/01 10:22:45 AM
PHARMACIST

Jerry Phillips
11/7/01 11:09:45 AM
DIRECTOR

APPEARS THIS WAY
ON ORIGINAL

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: October 17, 2000
NDA NUMBER: 21-006
NAME OF DRUG: Frovelan (Frovatriptan Tablets) 2.5 mg
MANUFACTURED BY: Vanguard Medica Ltd.
DISTRIBUTED BY: Elan Pharmaceuticals

I. INTRODUCTION

This consult was written in response to a request from the Division of Neuropharmacological Drug Products (HFD-120) for assessment of the tradename _____ regarding potential name confusion with other proprietary/generic drug names. The container labels, carton labeling, and package insert were reviewed for possible interventions in minimizing medication errors.

The sponsor initially submitted the proprietary name, Miguard. The Division informed the sponsor that the name was unacceptable on April 28, 2000. OPDRA did not review this proposed name.

PRODUCT INFORMATION

_____ tablets contain the active ingredient, frovatriptan succinate. Frovatriptan succinate is a 5-HT receptor agonist indicated for the acute treatment of migraine attacks with or without aura in adults. _____ is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine. The recommended adult dose is 2.5 mg taken orally with fluids at anytime after the onset of a migraine headache. No more than three doses should be taken within 24 hours. _____ will be available as a 2.5 mg tablet in bottles of 100 and blister cards containing _____ tablets.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts^{i,ii,iii} as well as several FDA databases^{iv} for existing drug names which

ⁱ MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2000).

ⁱⁱ American Drug index, 42nd Edition, 1999, Facts and Comparisons, St. Louis, MO.

ⁱⁱⁱ Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.

^{iv} COMIS, The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and online version of the FDA Orange Book.

sound alike or look alike to _____ to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted*. An Expert Panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies, to simulate the prescription ordering process.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name, _____. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

Several products were identified in the Expert Panel Discussion that were thought to have potential for confusion with _____. These products are listed in Table 1, along with the dosage forms available and usual FDA-approved dosage.

DDMAC did not have any concerns about the names with regard to promotional claims

TABLE 1

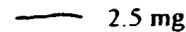
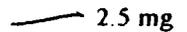
Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
_____	Frovatriptan Succinate Tablets 2.5 mg	One 2.5 mg tablet at the onset of a migraine headache. No more than 3 tablets in 24 hours.	
Trofalgon	Cyanocobalamin	Used as a tonic in Madariaga Spain	S/A, L/A per OPDRA
Trovan	Trovasfloxacin mesylate Tablets/Injection 100 mg and 200 mg Tablets 5 mg/mL - 200 mg and 300 mg	100 mg, 200 mg or 300 mg once daily. Tablets and Injections are being distributed only to hospitals and long term nursing care facilities for patient initiating therapy in these facilities.	S/A, L/A per OPDRA
Trofan	Tryptophan	Withdrawn from the market on 10/23/87 No dosing information available.	S/A, L/A per OPDRA
		*Frequently used, not all-inclusive.	**L/A (look-alike), S/A (sound-alike)

* WWW location <http://www.uspto.gov/tmdb/index.html>.

B. STUDY CONDUCTED BY OPDRA

1. Methodology

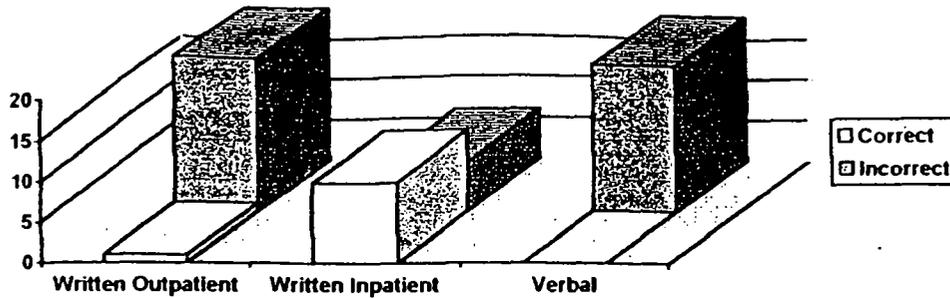
A separate study was conducted within FDA for each proposed proprietary name to determine the degree of confusion of _____ with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 90 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote an inpatient order and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for _____ (see below). These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
<i>Outpatient:</i>  2.5 mg Take as directed, up to 3 daily #10	 2.5 mg Take as directed, up to 3 daily #10
<i>Inpatient:</i>  i po qd	

2. Results

Results of these exercises are summarized below:

Study	No. of participants	# of responses (%)	_____ response	Other response
<i>Written:</i> Outpatient	29	20 (69%)	1 (5%)	19 (95%)
Inpatient	31	16 (52%)	10 (63%)	6 (37%)
<i>Verbal:</i> Inpatient	30	18 (60%)	0 (0%)	18 (100%)
Total:	90	54 (60%)	11 (20%)	43 (80%)



Among participants in the written prescription studies, 25 of 36 respondents (69%) interpreted the name incorrectly. Most of the incorrect name interpretations were misspelled variations of _____ . Three respondents interpreted the name as _____ misinterpreting the "o" as either an "a" or "u". Other responses were: _____

Among verbal prescription study participants, 18 of 18 (100%) of the study participants interpreted the name incorrectly. Most of the incorrect name interpretations were phonetic variations of _____ Interpretations include:

C. SAFETY EVALUATOR RISK ASSESSMENT

1. In reviewing the proprietary name _____ , the three products considered to have the greatest potential for name confusion are *Trofalgon*, *Trofan* and *Trovan*. Trofalgon is the tradename for cyanocobalamin and is only marketed in Europe. Trofan is the proprietary name for Tryptophan, however this application has been withdrawn from the U.S. market since October of 1987. The last name identified as a possible conflict is Trovan. Although Trovan and _____ have overlapping dosage forms they share no other commonalties. They differ in strength, dosing intervals, and most notably, Trovan has limited distribution to hospitals and long term nursing care facilities. The potential for confusion among these products is low.

The currently marketed drug product, *Flolan*, which was not discussed when the expert panel convened, was identified through an independent search of FDA's databases.

This product is listed in the table on page 6 of this review, along with the dosage forms available and usual FDA-approved dosage.

APPEARS THIS WAY
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Product Name	Dosage form(s), Generic name	Usual adult dose*
—	Frovatriptan Succinate Tablets 2.5 mg	One 2.5 mg tablet at the onset of a migraine headache. No more than 3 tablets in 24 hours.
Flolan	Epoprostenol Sodium for Injection 0.5 mg and 1.5 mg vials	2 ng/kg/min and increased in increments of 2 ng/kg/min every 15 minutes or longer until dose-limiting effects are elicited or until a tolerance limit to the drug is established.
		*Frequently used, not all-inclusive.

Flolan is indicated for the long-term intravenous treatment of primary pulmonary hypertension and pulmonary hypertension associated with the scleroderma spectrum of disease in NYHA Class III and Class IV patients who do not respond adequately to conventional therapy. A central line must be established prior to administration of Flolan and the product and is administered by continuous intravenous infusion using an ambulatory infusion pump. Flolan therapy is needed for prolonged periods, possible years, and patients have to accept and care for a permanent intravenous catheter and infusion pump. The patient population would be limited and extensive education on the proper care of the catheter and administration of drug product would need to be completed prior to initiation of therapy. Therefore, the potential for confusion seems low given these constraints.

We conducted prescription studies to simulate the prescription ordering process. The study did not confirm confusion between — and Flolan or Trovan. The majority of the incorrect responses from the verbal and written studies were misspelled/phonetic variations of the drug name. These responses did not overlap with any existing approved drug products. Although a negative finding in a study with such a small sample size does limit its predicative value, OPDRA believes the potential for confusion is low due to the significant differences in the distribution and administration of these drug products.

**APPEARS THIS WAY
ON ORIGINAL**

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

In the review of the container labels, carton labeling, and draft package insert for _____ OPDRA has attempted to focus on safety issues relating to possible medication errors. We have identified several areas of possible improvement, in the interest of minimizing potential user error.

A. GENERAL COMMENTS

1. The current expression of the established name and strength is misleading and incorrect since each tablet contains 2.5 mg of frovatriptan, not 2.5 mg of frovatriptan succinate. The strength must be qualified to reflect it is based on the active moiety. This can be accomplished by expressing the established name and strength in one of the following three manners:

a.

(Frovatriptan) Tablets
2.5 mg

b.

(Frovatriptan Succinate) Tablets
equivalent to
2.5 mg Frovatriptan

c.

(Frovatriptan Succinate) Tablets
2.5 mg*

*Each tablet contains frovatriptan succinate equivalent to 2.5 mg of frovatriptan.

OPDRA prefers the first example as an option because this nomenclature is consistent with USP recommendations on "labeling of salts of drugs" (General Notices, pg. 12).

2. Revise the established name to include the dosage form "Tablets".
3. A space should be placed between the "number" and "mg" in the strength (2.5 mg).

B. UNIT DOSE BLISTER

1. See GENERAL COMMENTS 1 and 3 above.
2. The name of the manufacturer and/or distributor must be on the label.

C. UNIT DOSE CARTON

1. See GENERAL COMMENTS 1-3.
2. We recommend the net quantity statement be relocated nearer the bottom of the label so it does not appear in conjunction with the product strength.
3. The manufacturer's address listed on the carton labeling differs from that listed in the package insert. Revise the "Distributed By" statement to be consistent with the statement in the package insert labeling.
3. Post-marketing experience has demonstrated medication errors resulting from patients administering the entire contents of unit-of-use packages due to the lack of a "Usual Dosage" statement on the labels and labeling. No more than three tablets of this drug product may be administered within 24 hours. Rather than including the statement "Refer to package insert for prescribing information" a "Usual Dosage" statement should be added to provide the patient specific dosing recommendations. For example, Usual Dosage: Take one tablet after the onset of a migraine headache. No more than 3 tablets should be taken within 24 hours. See package insert.

D. PACKAGE INSERT LABELING

OPDRA has the following two concerns with the directions for use outlined in the DOSAGE AND ADMINISTRATION section.

1. The first sentence of this paragraph states "the recommended — dose is a single tablet of — taken orally with fluids —". The third sentence of this paragraph states "The directions to not specify the length of time between administration of the first and second dose."
2. The last sentence should be — so that the important information of "no more than 3 doses should be taken within 24 hours" has greater prominence and is not lost within the text.
3. The "Manufactured By" statement is not in accordance with 21 CFR 201.1(h)(5). There is no provision for a "Supplied by" statement and therefore should be revised accordingly.

IV. RECOMMENDATIONS

- A. OPDRA has no objections to the use of the proprietary name _____
- B. We have made recommendations for labeling revisions to minimize potential errors with the use of this product.

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Carol Holquist, R.Ph. at 301-827-3244.

/S/

10-24-00

Carol Holquist, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

/S/

10/30/2000

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

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DRAFT

Labeling

CONFIDENTIAL

13.0 PATENT INFORMATION

As required under 21 CFR. 314.53(c), the following information is provided:

P30104

Generically covers the use of frovatriptan in the treatment of migraine; the corresponding racemate is exemplified and claimed.

Claim categories:

Use in treatment of migraine ("second medical use")/USA – method of treatment

Compound *per se* (not limited to enantiomeric form)

Pharmaceutical compositions

Country	Application No	Application Date	Patent No	Grant Date	Expiry Date	Status F = pending G = granted
USA	08/167846	23 Dec 1993	5,464,864	07 Nov 1995	07 Nov 2012	G
USA C1	08/442720	15 May 1995*	5,827,871	27 Oct 1998	27 Oct 2015	G
USA C2	08/442719	15 May 1995	5,637,611	10 Jun 1997	10 Jun 2014	G

* Application date recorded at the US Patent Office as 17 May 1995.

P30566

Specifically exemplifies and claims the enantiomer frovatriptan.

Claim categories:

Compound *per se* (including specific claim to succinate salt)

Synthetic process for preparing enantiomer

Use in treatment of migraine/USA – method of treatment

Pharmaceutical compositions

Country	Application No	Application Date	Patent No	Grant Date	Expiry Date	Status F = pending G = granted
USA	08/446655	18 July 1995	5,618,947	08 April 1997	08 April 2014	G
USA C1	08/451846	26 May 1995	5,618,948	08 April 1997	08 April 2014	G
USA C3	08/451898	26 May 1995	5,616,603	01 April 1997	01 April 2014	G



US005464864A

United States Patent [19]

King et al.

[11] Patent Number: 5,464,864

[45] Date of Patent: Nov. 7, 1995

[54] USE OF TETRAHYDROCARBAZONE DERIVATIVES AS 5HT₁ RECEPTOR AGONISTS

[75] Inventors: Francis D. King; Laramie M. Gaster, both of Harlow; Alberto J. Kaumann, Trumpington; Rodney C. Young, Hertford, all of England

[73] Assignee: SmithKline Beecham P.L.C., Brentford, England

[21] Appl. No.: 167,846

[22] PCT Filed: Jun. 17, 1992

[86] PCT No.: PCT/GB92/01082

§ 371 Date: Dec. 23, 1993

§ 102(e) Date: Dec. 23, 1993

[87] PCT Pub. No.: WO93/00086

PCT Pub. Date: Jan. 7, 1993

[30] Foreign Application Priority Data

Jun. 26, 1991 (GB) United Kingdom 9113802

[51] Int. Cl.⁶ C07D 209/88; A61K 31/40

[52] U.S. Cl. 514/468; 548/439

[58] Field of Search 548/439; 514/468

[56] References Cited

U.S. PATENT DOCUMENTS

3,592,824	7/1971	Schut	260/315
3,642,816	2/1972	Mooradian	260/315
3,959,309	5/1976	Mooradian	260/315
4,062,864	12/1977	Mooradian	260/315
4,172,834	10/1979	Mooradian	260/315
4,257,952	3/1981	Mooradian	260/315

FOREIGN PATENT DOCUMENTS

0004342	10/1979	European Pat. Off.
0115607	8/1984	European Pat. Off.
7211102	8/1972	Netherlands

OTHER PUBLICATIONS

J. Neurochemistry, vol. 35, No. 3, 1981, p. 932, E. Friedman et al.

J. Neurochemistry, vol. 28, No. 5, 1977, pp. 995-1000, E. Meller et al.

J. Chem. Soc., No. 2, 1970, pp. 325-326, G. E. A. Coombes et al.

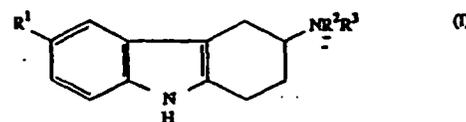
Recenti Progressi in Medicina, vol. 80, No. 12, Dec. 1989, pp. 673-680, J. W. Lance.

J Med Chem, vol. 20, No. 4, 1977, pp. 487-492, Mooradian et al.

Primary Examiner—David B. Springer

Attorney, Agent, or Firm—Nora Stein-Fernandez; Stuart R. Suter; Edward T. Leatz

[57] ABSTRACT



Use of a compound of general formula (I), wherein R¹ represents hydrogen, halogen, trifluoromethyl, nitro, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, arylC₁₋₆alkoxy, —CO₂R⁴, —(CH₂)_nCN, —(CH₂)_nCONR⁵R⁶, —(CH₂)_nSO₂NR⁵R⁶, C₁₋₆alkanoylamino(CH₂)_n, or C₁₋₆alkylsulphonylamino(CH₂)_n; R⁴ represents hydrogen, C₁₋₆alkyl or arylC₁₋₆alkyl; R⁵ and R⁶ each independently represent hydrogen or C₁₋₆alkyl, or R⁵ and R⁶ together with the nitrogen atom to which they are attached form a ring; n represents 0, 1 or 2; and R² and R³ each independently represent hydrogen, C₁₋₆alkyl; or benzyl or together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino or hexahydroazepino ring; or a physiologically acceptable salt thereof, in the manufacture of a medicament for the treatment of a condition where a 5-HT₁-like agonist is indicated, for example migraine. Novel compounds of formula (I), processes for preparing them and pharmaceutical compositions containing them are also described.

6 Claims, No Drawings

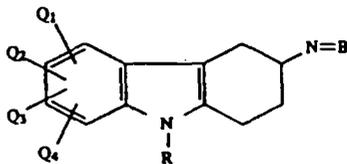
USE OF TETRAHYDROCARBAZONE
DERIVATIVES AS 5HT₁ RECEPTOR
AGONISTS

The present invention relates to certain tetrahydrocarbazole derivatives for use in the treatment of disorders characterized by excessive vasodilatation, in particular the treatment of migraine.

Migraine is a non-lethal disease which has been reported to be suffered by one in ten individuals. The main symptom is headache; other symptoms include vomiting and photophobia. Currently, the most widely used treatment for migraine involves administration of ergotamine, dihydroergotamine or methysergide, which are also used prophylactically. These drugs are *inter alia* agonists of 5HT₁-like receptors but also have other actions; treatment with them is associated with a number of adverse side effects. In addition, some patients experience a "withdrawal headache" following the cessation of treatment with an ergot product, such as ergotamine, causing them to repeat the treatment and resulting in a form of addiction. More recently various tryptamine derivatives have been proposed for potential use in treating migraine.

In view of the foregoing, there is clearly a need for the provision of effective and safe medicaments for the treatment of migraine.

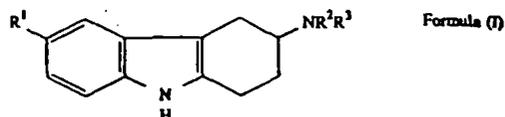
U.S. Pat. Nos. 4,257,952, 4,172,834, 4,062,864 and 3,959,309 disclose a broad class of tetrahydrocarbazoles of the formula:



wherein N=B is *inter alia* —NHR' or —NR'R" where R' and R" are lower alkyl, aryl-lower alkyl or together form a heterocyclic ring; R is *inter alia* hydrogen; Q₁ is *inter alia* hydrogen, halogen, lower alkoxy, cyano, —CO₂R₁ or —CONR₂R₃ (where R₁ may be hydrogen, lower alkyl or —CH₂Ar and R₂ and R₃ are hydrogen, lower alkyl or together form a heterocyclic ring); Q₂ is *inter alia* hydrogen, aryl-(lower alkoxy), hydroxy, trihalomethyl, nitro or alkanoylamino, and Q₃ and Q₄ may each be *inter alia* hydrogen. These compounds are said to have analgetic, psychotropic and antihistaminic activities.

It has now surprisingly been found that certain tetrahydrocarbazoles are agonists and partial agonists at 5HT₁-like receptors and are expected to have utility in the treatment of conditions wherein a 5-HT₁-like agonist or partial agonist is indicated, in particular conditions associated with cephalic pain such as migraine, cluster headache and headache associated with vascular disorders. In this specification the term '5-HT₁-like agonist' will hereinafter be used to include partial agonists at this receptor.

The present invention therefore provides the use of compounds of general formula (I):



wherein:

R¹ represents hydrogen, halogen, trifluoromethyl, nitro, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, arylC₁₋₆alkoxy, —CO₂R⁴, —(CH₂)_nCN, —(CH₂)_nCONR⁵R⁶, —(CH₂)_nSO₂NR⁵R⁶, C₁₋₆alkanoylamino(CH₂)_n, or C₁₋₆alkylsulphonylamino(CH₂)_n;

R⁴ represents hydrogen, C₁₋₆alkyl or arylC₁₋₆alkyl;

R⁵ and R⁶ each independently represent hydrogen or C₁₋₆alkyl, or R⁵ and R⁶ together with the nitrogen atom to which they are attached form a ring;

n represents 0, 1 or 2; and

R² and R³ each independently represent hydrogen, C₁₋₆alkyl or benzyl or together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino or hexahydroazepino ring;

and physiologically acceptable salts thereof, in the manufacture of a medicament for the treatment of a condition where a 5-HT₁-like agonist is indicated, in particular the treatment or prophylaxis of migraine.

The invention also provides a method of treatment of a condition wherein a 5-HT₁-like agonist is indicated, in particular migraine, which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) or a physiologically acceptable salt thereof.

Suitably R¹ represents hydrogen, halogen, cyano, hydroxy, C₁₋₆alkoxy, arylC₁₋₆alkoxy, —CO₂R⁴, —(CH₂)_nCONR⁵R⁶ or —(CH₂)_nSO₂NR⁵R⁶; and R² and R³ each independently represent hydrogen or C₁₋₆alkyl.

It will be appreciated that compounds of formula (I) may contain one or more asymmetric centres, and such compounds will exist as optical isomers (enantiomers). The invention thus includes all such enantiomers and mixtures, including racemic mixtures, thereof.

In the compounds of formula (I) a halogen atom may be a fluorine, chlorine, bromine or iodine atom. An alkyl group or moiety may have a straight or branched chain. Suitable aryl groups include for example unsaturated monocyclic or bicyclic rings and partially saturated bicyclic rings of up to 12 carbon atoms, such as phenyl, naphthyl and tetrahydronaphthyl. When R⁵ and R⁶ together with the nitrogen atom form a ring, this is preferably a 5 to 7-membered saturated heterocyclic ring, which may optionally contain a further heteroatom selected from oxygen, sulphur or nitrogen. Suitable rings thus include pyrrolidino, piperidino, piperazino and morpholino.

In the above compounds R¹ preferably represents halogen (e.g. bromine), CF₃, C₁₋₆alkoxy (e.g. methoxy), (CH₂)_nCN, —(CH₂)_nCONR⁵R⁶, —(CH₂)_nSO₂NR⁵R⁶ or C₁₋₆alkanoylamino. Most preferably R¹ represents a group —(CH₂)_nCONR⁵R⁶ wherein n represents 0 and R⁵ and R⁶ each independently represent hydrogen, methyl, ethyl or propyl. Advantageously, R⁵ and R⁶ independently represent hydrogen or methyl.

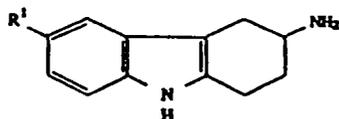
When R¹ represents —CO₂R⁴, then R⁴ preferably represents C₁₋₆alkyl.

R² and R³ each preferably represent hydrogen, methyl or ethyl. Most preferably NR²R³ is —NH₂.

For use according to the present invention the compound of formula (I) is preferably a partial agonist.

Suitable physiologically acceptable salts will be apparent to those skilled in the art and include for example acid

addition salts such as those formed with inorganic acids e.g. hydrochloric, sulphuric or phosphoric acids and organic acids e.g. succinic, maleic, acetic or fumaric acid. Other non-physiologically acceptable salts e.g. oxalates may be used for example in the isolation of compounds of formula (I), and are included within the scope of this invention. Also included within the scope of the invention are solvates and hydrates of compounds of formula (I).



Formula (IA)

wherein R^1 is as hereinbefore defined with the proviso that R^1 is not hydrogen, hydroxy, methoxy or benzyloxy, and salts thereof.

The present invention further provides the following specific compounds which are also believed to be novel:

3-Amino-6-cyano-1,2,3,4-tetrahydrocarbazole hydrochloride, (+)-3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride,

(-)-3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride,

3-amino-6-bromo-1,2,3,4-tetrahydrocarbazole hydrochloride,

3-amino-6-methyl-1,2,3,4-tetrahydrocarbazole oxalate,

3-amino-6-ethoxycarbonyl-1,2,3,4-tetrahydrocarbazole oxalate,

3-amino-6-(N-methyl carboxamido)-1,2,3,4-tetrahydrocarbazole hemioxalate,

3-amino-6-cyanomethyl-1,2,3,4-tetrahydrocarbazole oxalate,

3-amino-6-(N-methylsulphonamidomethyl)-1,2,3,4-tetrahydrocarbazole oxalate,

3-amino-6-chloro-1,2,3,4-tetrahydrocarbazole oxalate,

3-amino-6-trifluoromethyl-1,2,3,4-tetrahydrocarbazole oxalate,

3-amino-6-n-butylloxy-1,2,3,4-tetrahydrocarbazole oxalate,

3-amino-6-sulphonamido-1,2,3,4-tetrahydrocarbazole oxalate,

3-amino-6-nitro-1,2,3,4-tetrahydrocarbazole oxalate,

3-amino-6-(N,N-dimethylcarboxamido)-1,2,3,4-tetrahydrocarbazole hemioxalate,

3-amino-6-nitro-1,2,3,4-tetrahydrocarbazole oxalate,

3-amino-6-(N,N-dimethylcarboxamido)-1,2,3,4-tetrahydrocarbazole hemioxalate,

3-amino-6-(piperidin-1-ylcarbonyl)-1,2,3,4-tetrahydrocarbazole hydrochloride,

3-amino-6-(pyrrolidin-1-ylcarbonyl)-1,2,3,4-tetrahydrocarbazole hydrochloride,

3-amino-6-(N,N-diethylcarboxamido)-1,2,3,4-tetrahydrocarbazole hydrochloride,

3-Amino-6-(acetamido)-1,2,3,4-tetrahydrocarbazole oxalate,

3-amino-6-methanesulphonamido-1,2,3,4-tetrahydrocarbazole oxalate,

3-amino-6-carboxamidomethyl-1,2,3,4-tetrahydrocarbazole hydrochloride,

3-methylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate,

3-ethylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate,

3-n-propylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate,

3-i-propylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate.

3-dimethylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate,

3-benzylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate,

3-pyrrolidinyl-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate, and

3-(N-(methyl)ethylamino)-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate,

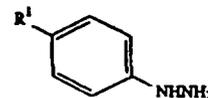
3-amino-6-(2-carboxamidoethyl)-1,2,3,4-tetrahydrocarbazole oxalate.

In a further aspect the present invention provides a novel compound of formula (I) e.g. a compound of formula (IA) or any of the above-named compounds (in free base form or as a physiologically acceptable salt) for use as a therapeutic agent, in particular as a 5-HT₁-like agonist or partial agonist, for example for the treatment of migraine.

The invention also provides a process for the preparation of novel compounds of formula (I).

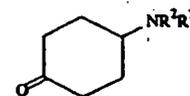
Compounds of formula (I) may be prepared by methods known in the art for the preparation of tetrahydrocarbazoles, for example:

A) Reaction of a compound of formula (II):



Formula (II)

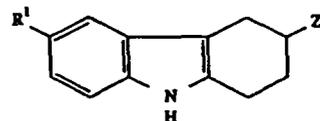
(wherein R^1 is as hereinbefore defined) or an acid addition salt thereof with a compound of formula (III):



Formula (III)

(wherein R^2 and R^3 are as hereinbefore defined) or an N-protected derivative thereof; or

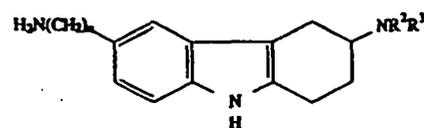
B) Reaction of a compound of formula (IV):



Formula (IV)

(wherein R^1 is as defined for formula (I) and Z is a leaving group) with a compound of formula HNR^2R^3 ;

C) Reacting a compound of formula (V):



Formula (V)

with an acylating or sulphonylating agent;

D) Conversion of one compound of formula (I) into another compound of formula (I) eg.

(i) to prepare a compound of formula (I) wherein R^1 represents $-(CH_2)_nCONH_2$ or C_2R^4 , hydrolysis of a compound of formula (I) wherein R^1 represents $-(CH_2)_nCN$, or an N-protected derivative thereof;

(ii) to prepare a compound of formula (I) wherein R^1 represents $-CONR^5R^6$, amination of a compound of formula (I) wherein R^1 represents $-CO_2H$, or an

N-protected derivative thereof; or

(iii) to prepare a compound of formula (I) wherein one of R^2 and R^3 is hydrogen and the other is C_{1-6} alkyl, alkylation of a compound (I) in which R^2 and R^3 are both hydrogen;

(iv) to prepare a compound of formula (I) wherein R^1 represents hydroxy, cleavage of a compound wherein R^1 represents alkoxy or aralkoxy;

followed if necessary by deprotection of any protected nitrogen atoms and if desired by salt formation.

Process (A), which is a form of the Fischer indole synthesis, may be carried out using methods well known in the art. Thus, the reaction may be effected in a solvent, for example an alcohol such as ethanol or butanol; or acetic acid, and at a temperature in the range 0° to 150° C.

Hydrazines of formula (II), which are usually employed as the hydrochloride salt, are known compounds, or may be prepared by conventional methods.

A cyclohexanone of formula (III) may be prepared by oxidation of the corresponding cyclic alcohol, using an oxidising agent such as pyridinium chlorochromate, pyridinium dichromate, dipyridine Cr (VI) oxide, sodium hypochlorite, calcium hypochlorite or manganese dioxide.

The leaving group Z in the compounds of formula (IV) may be for example a halogen atom, or a sulphonyloxy group eg. p-toluenesulphonyloxy or methanesulphonyloxy. Process (B) may be effected in an inert organic solvent, such as an alcohol eg. methanol or an ether eg. tetrahydrofuran and at a temperature in the range 0° to 150° C. Compounds of formula (IV) may be obtained by reacting a hydrazine of formula (II) with an appropriately substituted cyclohexanone compound. When Z is acyloxy or sulphonyloxy this may be prepared from a compound (IV) wherein Z is hydroxy, using standard procedures.

Suitable acylating and sulphonylating agents which may be used in process (C) include carboxylic and sulphonic acid chlorides (e.g. acetyl chloride or methanesulphonylchloride) alkyl esters, activated esters and symmetrical and mixed anhydrides. The reaction may be carried out in an organic solvent such as haloalkane (e.g. dichloromethane), an amide (e.g. N,N-dimethylformamide; an ether (e.g. tetrahydrofuran) or a tertiary amine such as pyridine. In general a base will also be used, e.g. triethylamine, dimethylaminopyridine, or an alkali metal carbonate or bicarbonate. The reaction may be effected at a temperature in the range of -10° to 100° C.

Compounds of formula (V) may be prepared by methods analogous to processes (A) and (B) hereinbefore described. Alternatively a compound of formula (V) may be obtained by subjecting a compound of formula (I) wherein R^1 is nitro to reduction, e.g. by catalytic hydrogenation.

It is well known in the chemical art that hydrolysis of a nitrile initially results in an amide, which can be further hydrolysed to an acid. It will therefore be appreciated that the precise product of process (Di) will depend upon the reaction conditions chosen for the hydrolysis. To obtain a compound wherein R^1 represents H_2NCO- the hydrolysis is preferably effected using hydrogen peroxide in the presence of an alkali hydroxide e.g. sodium hydroxide, in a solvent such as an alcohol e.g. methanol. Other suitable means of hydrolysis include acetic acid and BF_3 ; or formic acid and hydrobromic or hydrochloric acid. To prepare a compound wherein R^1 represents $-COOH$ acid or base catalysed hydrolysis may be used.

Process (Dii) may be effected by reacting a compound of formula (I) wherein R^1 is $-CO_2H$ with an amine HNR^2R^3 , in the presence of a coupling agent e.g. dicyclohexylcarbo-

diimide or N,N'-carbonyldiimidazole. Alternatively the carboxylic acid starting material may first be reacted to form an activated derivative of the carboxyl group, for example an acid chloride, acid anhydride or activated ester, which is then reacted directly with an amine HNR^2R^3 . The carboxylic acid may also be activated in situ for example by treating with hexamethylphosphorotriamide.

Alkylation according to process (Diii) may be effected by reacting an amine of formula (I) with an acylating agent, for example an anhydride, such as acetic or propionic anhydride, to form an intermediate in which one of R^2 or R^3 is $-C(O)C_{1-6}$ alkyl, followed by reduction of said intermediate to give the desired product. Other reagents and conditions will be apparent to those skilled in the art.

Cleavage according to process (Div) may be effected by reduction, using methods well known in the art.

It will be appreciated that in many of the above reactions it will be necessary to protect the group $-NR^2R^3$ when one or both of the groups R^2 and R^3 represent hydrogen. Suitable N-protecting groups are well-known in the art and include for example acyl groups such as acetyl, trifluoroacetyl, benzoyl, methoxycarbonyl, t-butoxycarbonyl, benzyloxy-carbonyl or phthaloyl; and aralkyl groups such as benzyl, diphenylmethyl or triphenylmethyl. When R^2 and R^3 both represent hydrogen the nitrogen atom is preferably protected as the phthalimide. The protecting groups should be easily removable at the end of the reaction sequence. N-deprotection may be effected by conventional methods, for example a phthaloyl group may be removed by reaction with hydrazine; an acyl group such as benzoyl may be cleaved by hydrolysis and an aralkyl group such as benzyl may be cleaved by hydrogenolysis.

When a compound of formula (I) is obtained as a mixture of enantiomers these may be separated by conventional methods, for example by reaction of the mixture with a suitable optically active acid such as d-tartaric acid, l-malic acid, l-mandelic acid, l-gulonic acid or 2,3:4,6-di-O-isopropylidene-keto-L-gulonic acid to give two diastereoisomeric salts which may be separated eg. by crystallisation. Alternatively mixtures of enantiomers may be separated by chromatography, for example on a chiral HPLC column.

Compounds of formula (I) have been found to be agonists and partial agonists at 5HT₁-like receptors and are expected to have utility in the treatment and/or prophylaxis of migraine, and other conditions associated with cephalic pain.

For use in medicine, the compounds of the present invention are usually administered as a standard pharmaceutical composition. The present invention therefore provides in a further aspect pharmaceutical compositions comprising a novel compound of formula (I) or a physiologically acceptable salt thereof and a physiologically acceptable carrier.

The compounds of formula (I) may be administered by any convenient method, for example by oral, parenteral, buccal, sublingual, nasal, rectal or transdermal administration and the pharmaceutical compositions adapted accordingly.

The compounds of formula (I) and their physiologically acceptable salts which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or physiologically acceptable salt in a suitable liquid carrier(s) for example an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or physiologically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas such as compressed air or an organic propellant such as a fluorochloro-hydrocarbon. The aerosol dosage forms can also take the form of a pump-atomiser.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

Compositions suitable for transdermal administration include ointments, gels and patches.

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the formula (I) or a physiologically acceptable salt thereof calculated as the free base.

The physiologically acceptable compounds of the invention will normally be administered in a daily dosage regimen (for an adult patient) of, for example, an oral dose of between 1 mg and 500 mg, preferably between 10 mg and 400 mg, e.g. between 10 and 250 mg or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 50 mg, e.g. between 1 and 25 mg of the compound of the formula (I) or a physiologically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

BIOLOGICAL DATA

5-HT₁-like Receptor Screen

Dog Saphenous Vein

Helicoids of dog saphenous vein were set up at 37° C. in modified Krebs solution at a resting force of 10 mN. The solution also contained 1 μmol/l each of ketanserin prazosin, atropine and mepyramine, 6 μmol/l cocaine and 200 μmol/l ascorbate. Nearly isometric contractions were measured with force transducers on a polygraph. The tissues were exposed twice to 5-hydroxytryptamine (5-HT) 2 μmol/l followed by washes. A cumulative concentration-effect curve was determined, followed by a curve to 5-HT in the presence of the highest used concentration of test compound. Contractions caused by the test compound were compared with those caused by 5-HT. The intrinsic activity of the test compound was calculated as the ratio of the maximum test compound-induced effect over the effect caused by 2 μmol/l 5-HT. The EC₅₀ of the test compound was estimated from the corresponding effect curve. When appropriate equilibrium dissociation constants K_p were estimated by the method of Marano & Kaumann (1976, *J. Pharmacol. Exp. Ther.* 198, 518-525).

In this screen the compounds of Examples 2, 4, 5, 6, 9, 10, 11, 13, 17, 18, 21 and 24 had EC₅₀'s in the range 0.1 to 15 μmol.

RABBIT BASILAR ARTERY

METHODS

Experiments were performed in intracranial arteries from rabbit isolated basilar artery in a similar method to one described previously (Parsons and Whalley, 1989. *Eur J Pharmacol* 174, 189-196.).

In brief, rabbits were killed by overdose with anaesthetic (sodium pentobarbitone). The whole brain was quickly removed and immersed in ice cold modified Krebs solution and the basilar artery removed with the aid of a dissecting microscope. The Krebs solution was of the following composition (mM) Na⁺ (120); K⁺ (5); Ca²⁺ (2.25); Mg²⁺ (0.5); Cl⁻ (98.5); SO₄²⁻ (1); EDTA (0.04), equilibrated with 95% O₂/5% CO₂. The endothelium was removed by a gentle rubbing of the lumen with a fine metal wire. Arteries were then cut into ring segments (ca 4-5 mm wide) and set up for recording of isometric tension in 50 ml tissue baths in modified Krebs solution with the additional supplement of (mM); Na²⁺ (20); fumarate (10); pyruvate (5); L-glutamate (5) and glucose (10). The arteries were then placed under a resting force of 3-4 mN maintained at 37° C. and the solution bubbled with 95% O₂/5% CO₂.

After tests for initial reactivity with 90 mM KCl depolarising solution and for lack of acetylcholine-induced relaxation of 5-HT (10 mM) precontraction, cumulative concentration-effect curves (2 nM-60 mM) to 5-HT were constructed in the presence of ascorbate 200 mM, cocaine 6 mM, indomethacin 2.8 mM, ketanserin 1 mM and prazosin 1 mM.

Following a 45-60 min wash period, cumulative concentration-effect curves to the test compounds or 5-HT (as a time match control) were constructed in the presence of ascorbate, indomethacin, cocaine, ketanserin and prazosin.

In this screen the compounds of Example 2, 5, 6, 15, 17, 24, 25, 26, 28 and 29 had EC₅₀'s in the range 0.04 to 15.

EXAMPLE 1

3-Amino-6-cyano-1,2,3,4-tetrahydrocarbazole hydrochloride

A solution of 4-aminocyclohexanol hydrochloride (6.08 g, 0.04 mole) in water (60 ml) was brought to pH 8 with aqueous sodium bicarbonate solution. N-carbethoxy-phthalimide (8.76 g, 0.04 mole) was added followed by tetrahydrofuran (until homogenous solution was obtained). The clear solution was stirred at room temperature overnight. During this time a white solid was precipitated. The tetrahydrofuran was removed in vacuo and the remaining aqueous solution was extracted with ethyl acetate until the solution was clear. The ethyl acetate extracts were combined, washed with water, dried (MgSO₄) and concentrated to give 4-phthalimido cyclohexanol as a white solid (7.1 g).

A solution of 4-phthalimido cyclohexanol (7.1 g, 0.029 mole) in dichloromethane (250 ml) was treated with pyridinium chlorochromate (8.6 g, 0.04 mole) and the resulting dark mixture was stirred at room temperature overnight. Diethyl ether (50 ml) was added and the mixture filtered through kieselguhr. The filtrate was concentrated in vacuo and the residue purified by column chromatography (SiO₂; CHCl₃/EtOAc) to give 4-phthalimido cyclohexanone as a white solid (6.4 g).

4-Cyanophenyl hydrazine hydrochloride (4.41 g, 0.026 mole) was dissolved in acetic acid (100 ml) and sodium acetate (2 g) was added. 4-Phthalimido cyclohexanone (6.4 g, 0.026 mole) was added and the mixture heated under reflux overnight. The solvent was removed in vacuo and the residue triturated with methanol to give 3-phthalimido-6-cyano-1,2,3,4-tetrahydrocarbazole as a beige solid, (5.3 g).

A suspension of the above product (1 g) in ethanol (40 ml) was treated with hydrazine in water (10 ml). The reaction mixture was stirred at room temperature overnight during which time the reactants dissolved. The solvent was removed in vacuo and the residue partitioned between aqueous potassium carbonate and ethyl acetate. The ethyl acetate solution was washed with water, dried and concentrated in vacuo to give 3-amino-6-cyano-1,2,3,4-tetrahydrocarbazole as a beige solid (500 mg). This product was converted into the hydrochloride salt to give the title compound, mp 289° C. (dec.).

¹H NMR [250 MHz, CD₃OD] δ 1.98–2.18 (1H, m), 2.25–2.40 (1H, m), 2.77 (1H, dd), 2.98 (2H, m), 3.22 (1H, dd), 3.68 (1H, m), 7.34 (1H, d), 7.43 (1H, d), 7.82 (1H, s).

EXAMPLE 2

3-Amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride

The product of Example 1 (400 mg) was dissolved in tetrahydrofuran, and di-*t*-butyl dicarbonate (500 mg) was added. The mixture was stirred at room temperature overnight. The solvent was removed in vacuo and the residue purified by column chromatography (SiO₂; CHCl₃/EtOAc) to give 3-*t*-butyloxycarbonylamino-6-cyano-1,2,3,4-tetrahydrocarbazole (40 mg).

A mixture of the above product nitrile (440 mg), aqueous hydrogen peroxide (30%, 0.5 ml) and sodium hydroxide (aq) (20%, 0.5 ml) in methanol (25 ml) was stirred at room temperature overnight. Sodium metabisulphite (100 mg) was added and the solvent removed in vacuo. The residue was dissolved in ethyl acetate and the ethyl acetate layer was separated, dried and concentrated in vacuo to give a gummy

solid which was purified by column chromatography (SiO₂; CHCl₃/EtOAc) to give 3-*t*-butyloxycarbonylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole as a white solid (400 mg), mp 270° C. (dec).

The above product (400 mg, 0.0012 mole) was dissolved in dioxan (100 ml) and HCl gas was bubbled through the solution for 20 minutes. During this time a white solid was precipitated. Excess hydrogen chloride was swept from the solution by bubbling through N₂, and the solid product, 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride was collected by filtration, washed with diethyl ether and dried to give the title compound as a white solid (300 mg), m.p. 270 (dec).

¹H NMR [250 MHz, DMSO-*d*⁶] δ 1.96 (1H, m), 2.16–2.30 (1H, m), 2.74 (1H, dd), 2.85 (2H, m), 3.12 (1H, dd), 1 signal obscured by H₂O at ca. 3.6, 7.08 (1H, brd.s), 7.27 (1H, d), 7.61 (1H, d), 7.87 (1H, brd.s), 7.99 (1H, s), 8.39 (3H, brd.s).

EXAMPLE 3

3-Amino-6-methoxy-1,2,3,4-tetrahydrocarbazole hydrochloride

Reaction of 4-methoxyphenyl hydrazine hydrochloride (0.87 g, 5.0 mmol) with 4-phthalimido-cyclohexanone (1.22 g, 5.0 mmol) in ethanol (20 ml) heated under reflux for 2 hr, followed by cooling and removal of the precipitated solid by filtration gave 3-phthalimido-6-methoxy-1,2,3,4-tetrahydrocarbazole (1.62 g).

The above product (1.57 g, 4.5 mmol) was suspended in ethanol (100 ml) and treated with hydrazine hydrate (23 ml) while stirring at room temperature. After 30 min, the solvent was removed in vacuo and the residue was partitioned between K₂CO₃ (aq) and EtOAc. The latter layer was separated, washed with water, dried (MgSO₄) and evaporated to dryness. This residue was dissolved in ethanol and treated with ethereal HCl until cloudy, then left to stand overnight to yield the title compound (0.95 g) mp >250° C. ¹H NMR [250 MHz, DMSO-*d*⁶] δ 1.81–2.02 (1H, m), 2.10–2.28 (1H, m), 2.65 (1H, dd), 2.82 (2H, m), 3.02 (1H, dd), 1 signal obscured by H₂O at ca. 3.5, 3.74 (3H, s), 6.66 (1H, d), 6.84 (1H, d), 7.14 (1H, d), 8.16 (3H, brd.s).

EXAMPLE 4

3-Amino-6-bromo-1,2,3,4-tetrahydrocarbazole hydrochloride

Reaction of 4-bromophenylhydrazine hydrochloride (4.0 g, 18.1 mmol) with 4-phthalimido-cyclohexanone (4.39 g, 18.1 mmol) in refluxing *n*-butanol for 20 min, followed by cooling, filtration, and evaporation of the filtrate to dryness yielded 3-phthalimido-6-bromo-1,2,3,4-tetrahydrocarbazole as an orange solid (7.45 g).

This product (0.33 g, 0.83 mmol) was suspended in ethanol (13 ml) and treated with hydrazine hydrate (3 ml), then left to stir at room temperature overnight. The solid precipitate was filtered off, and the filtrate was evaporated to dryness and partitioned between K₂CO₃ (aq) and ethylacetate. After separation of the organic layer, washing with water, drying (MgSO₄) and evaporation to dryness, the residue was dissolved in MeOH and treated with HCl gas. Solvent was removed in vacuo and the residue was crystallized from ethanol/ethyl acetate to yield the title compound as a cream-coloured solid (0.15 g), mp 308°–310° C. ¹H NMR [250 MHz, DMSO-*d*⁶] δ 1.91 (1H, m), 2.10–2.26 (1H, m), 2.63 (1H, dd), 2.84 (2H, m), 3.04 (1H, dd), 3.50 (1H, m), 7.12 (1H, d), 7.24 (1H, d), 7.55 (1H, s), 8.15 (2H, brd.s).

11

11.12 (1H, s).

EXAMPLE 5

3-Amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole

4-Carboxamidophenylhydrazine hydrochloride (2.87 g) and 4-phthalimidocyclohexanone (3.00 g) were mixed in acetic acid and the mixture was heated under reflux for 2 hr. After cooling, the mixture was neutralized using aq. potassium carbonate solution, and the yellow solid thus obtained was filtered, washed with water, and dried. Purification by column chromatography (SiO_2 ; $\text{CHCl}_3/\text{CH}_3\text{OH}$) gave 3-phthalimido-6-carboxamido-1,2,3,4-tetrahydrocarbazole (2.8 g).

The above product (1.0 g) was suspended in ethanol (10 ml) and hydrazine hydrate (5 ml) was added. A clear solution was obtained, and the mixture was left to stir overnight, to yield a precipitate. The whole mixture was evaporated to dryness, washed with aq. K_2CO_3 solution, and water, to leave the title compound 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (0.44 g), as the monohydrate, top. 146°-148° C.

^1H NMR [250 MHz, $\text{DMSO}-d_6$] δ 1.49-1.77 (1H, m), 1.83-2.03 (1H, m), 2.17-2.40 (1H, m), 2.62-2.80 (2H, m), 2.90 (1H, dd), 1 signal obscured by H_2O at ca. 3.1, 7.03 (1H, brd.s), 7.18 (1H, d), 7.58 (1H, d), 7.83 (1H, brd.s), 7.98 (1H, s).

EXAMPLE 6

(+) and (-)

3-Amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride

Method 1

(\pm)-3-t-Butyloxycarbonylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole was separated into its enantiomers using chiral HPLC: (chiralcel OD 4.6 mm column, eluting with hexane/ethanol 85:15). The (+)-enantiomer was collected first and had mp=150°-152° C. and $[\alpha]_D^{25} = +70.1$ (in methanol, 0.41% w/v). The (-)-enantiomer had mp=150°-152° C. and $[\alpha]_D^{25} = -79.4$ (in methanol, 0.40% w/v). The (+)-enantiomer was converted to the parent amine hydrochloride by treating with HCl gas in dioxane, to furnish the (+)-enantiomer of 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride, mp=248°-251° C., $[\alpha]_D^{25} = +26.2$ (in methanol, 0.50% w/v). The (-)-enantiomer of 3-t-butyloxycarbonylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole was similarly converted into the (-)-enantiomer of 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride, mp=248°-251° C., $[\alpha]_D^{25} = -28.6$ (in methanol, 0.50% w/v).

Method 2

(\pm)-6-carboxamido-3-amino-1,2,3,4-tetrahydrocarbazole was treated with one equivalent of 2,3:4,6-di-O-isopropylidene-2-keto-L-gulonic acid in methanol to give the salt of the (+)-enantiomer, in 38% yield (with respect to racemate) and 84% enantiomeric excess (ee). This material was recrystallized twice from methanol to give the salt of the (+)-enantiomer in 25% overall yield (with respect to racemate), and >98% ee. This product was converted to the hydrochloride salt first by treatment with aqueous alkali, and the precipitated free base treated with 2M aq. HCl in ethanol, to give (+)-3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride.

12

EXAMPLE 7

3-Amino-6-methyl-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of 4-phthalimidocyclohexanone (2.16 g) with 4-tolylhydrazine hydrochloride (1.41 g), and subsequent deprotection of the product by the method described in example 3, gave the title compound free base, which was converted to the oxalate salt (0.23 g), mp 272°-5° C.

EXAMPLE 8

3-Amino-6-ethoxycarbonyl-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of 4-phthalimidocyclohexanone (0.37 g) with 4-ethoxycarbonylphenylhydrazine hydrochloride (0.33 g), and subsequent deprotection by the method described in example 3, gave the title compound free base. This was converted to the oxalate salt (0.11 g), mp 230°-240° C. dec.

EXAMPLE 9

3-Amino-6-(N-methylcarboxamido)-1,2,3,4-tetrahydrocarbazole hemioxalate

Reaction of 4-phthalimidocyclohexanone (1.20 g) with 4-(N-methylcarboxamido)-phenylhydrazine hydrochloride (1.00 g), and subsequent deprotection by the method described in example 3, gave the title compound free base. This was converted to the hemioxalate salt (0.22 g), mp 227° C. dec.

EXAMPLE 10

3-Amino-6-cyanomethyl-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of 4-phthalimidocyclohexanone (1.05 g) with 4-cyanomethylphenylhydrazine hydrochloride (0.79 g), and subsequent deprotection by the method described in example 3, gave the title compound free base, which was treated with oxalic acid to give the oxalate salt (0.49 g), mp 219°-224° C. dec.

EXAMPLE 11

3-Amino-6-(N-methylsulphonamidomethyl)-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of 4-phthalimidocyclohexanone (0.42 g) with 4-(N-methylsulphonamidomethyl) phenyl hydrazine hydrochloride (0.44 g), and subsequent deprotection by the method described in example 3, gave the title compound free base. This was treated with oxalic acid to give the oxalate salt (0.15 g), mp 218°-222° C. dec.

EXAMPLE 12

3-Amino-6-chloro-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of 4-phthalimidocyclohexanone (6.7 g) with 4-chlorophenyl hydrazine hydrochloride (4.93 g), and subsequent deprotection by the method described in example 3, gave the title compound free base, which was treated with oxalic acid to give the oxalate salt (2.77 g), dec >220° C.

13

EXAMPLE 13

3-Amino-6-trifluoromethyl-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of 4-phthalimidocyclohexanone (1.14 g) with 4-trifluoromethyl phenyl hydrazine hydrochloride (1.00 g), and subsequent deprotection by the method described in example 3, gave the title compound free base (0.40 g). This was treated with oxalic acid to give the oxalate salt, mp 212°-213° C.

EXAMPLE 14

3-Amino-6-n-butyloxy-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of 4-phthalimidocyclohexanone (1.12 g) with 4-n-butyloxyphenyl hydrazine hydrochloride (1.00 g) and subsequent deprotection by the method described in example 3, gave the title compound free base. This was treated with oxalic acid to give the oxalate salt (0.47 g), mp 227°-229° C.

EXAMPLE 15

3-Amino-6-sulphonamido-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of 4-phthalimidocyclohexanone (1.00 g) with 4-sulphonamido phenyl hydrazine hydrochloride (1.08 g), and subsequent deprotection by the method described in example 3, gave the title compound free base. This was converted to the oxalate salt (0.090 g), dec >200° C.

EXAMPLE 16

3-Amino-6-Nitro-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of 4-phthalimidocyclohexanone (1.28 g) with 4-nitrophenyl hydrazine hydrochloride (1.00 g), and subsequent deprotection by the method described in example 3, gave the title compound free base, which was converted to the oxalate salt (0.25 g), mp 275°-277° C.

EXAMPLE 17

3-Amino-6-(N,N-dimethyl carboxamido)-1,2,3,4-tetrahydrocarbazole hemioxalate

3-Amino-6-ethoxycarbonyl-1,2,3,4-tetrahydrocarbazole (260 mg, 1.0 mmol) was suspended in dry THF (5 ml), and di-tert butyl dicarbonate (320 mg, 1.5 mmol) was added. A clear solution was obtained after 10 min. The mixture was left to stir for 20 hr, then the solvent was removed, and the residue was dissolved in ethyl acetate, washed with aqueous sodium bicarbonate solution, and dried (MgSO₄). After removal of ethyl acetate, the residue was triturated with ether and hexane to give 3-t-butyloxycarbonylamino-6-ethoxycarbonyl-1,2,3,4-tetrahydrocarbazole (310 mg).

The above product (556 mg, 1.55 mmol) was suspended in ethanol (5 ml) and 2M NaOH (3 ml) was added. The mixture was heated under reflux for 1 hr and evaporated to dryness. The residue was dissolved in water and neutralized with acetic acid, when 3-t-butyloxycarbonylamino-6-carboxy-1,2,3,4-tetrahydrocarbazole precipitated out as a white solid (425 mg). A solution of the above product (400 mg, 1.2 mmol) in dry DMF (8 ml) was treated with hexamethyl

14

phosphorous triamide (198 mg, 1.2 mmol), and cooled to -10° C. Dimethylamine gas was bubbled into the mixture for 10 min at this temperature, then carbon tetrachloride (185 mg, 1.2 mmol) was added dropwise, under an atmosphere of nitrogen. The mixture was left to stir at room temperature for 1 hr, then the DMF was removed in vacuo. The residue was partitioned between ethyl acetate and water, and the organic layer was washed with saturated aqueous sodium bicarbonate solution, then brine, and dried (MgSO₄). The solvent was removed in vacuo, and the residual oil was triturated with ether and hexane and the solid recrystallized from toluene to give 3-t-butyloxycarbonylamino-6-(N,N-dimethyl carboxamido)-1,2,3,4-tetrahydrocarbazole (198 mg).

This product (180 mg, 0.53 mmol) was dissolved in dioxane (5 ml) and HCl gas was bubbled through, to precipitate an oil. The solvent was removed in vacuo, and the oil was dissolved in water, and treated with K₂CO₃ solution to bring the pH to 12. The amine free base was then extracted with ethyl acetate, dried (MgSO₄) and evaporated to dryness. The resulting oil was dissolved in methanol and treated with oxalic acid to provide the title compound as a pale pink solid (140 mg) mp=190°-195° C.

EXAMPLE 18

3-Amino-6-(piperidin-1-yl carbonyl)-1,2,3,4-tetrahydrocarbazole hydrochloride

Reaction of 3-t-butyloxycarbonylamino-6-carboxy-1,2,3,4-tetrahydrocarbazole (175 mg) with piperidine and the product subsequently deprotected by the method described for Example 17, gave the title compound, mp=246°-249° C. (55 mg).

EXAMPLE 19

3-Amino-6-(pyrrolidin-1-yl carbonyl)-1,2,3,4-tetrahydrocarbazole hydrochloride

Reaction of 3-t-butyloxycarbonylamino-6-carboxy-1,2,3,4-tetrahydrocarbazole (140 mg) with pyrrolidine, and the product subsequently deprotected as described for Example 17, gave the title compound, mp=201°-212° C. (81 mg).

EXAMPLE 20

3-Amino-6-(N,N-diethyl carboxamido)-1,2,3,4-tetrahydrocarbazole hydrochloride

Reaction of 3-t-butyloxycarbonylamino-6-carboxy-1,2,3,4-tetrahydrocarbazole (105 mg) with diethylamine, and deprotection of the product, as described for Example 17, gave the title compound, mp 200°-205° C. (50 mg).

EXAMPLE 21

3-Amino-6-(acetamido)-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of 4-phthalimido cyclohexanone (1.2 g) with 4-(acetamido)-phenyl hydrazine hydrochloride (1.0 g), and subsequent deprotection of the product by the method described in example 3, gave the title compound free base (570 mg). A portion of this product (50 mg) was treated with oxalic acid in methanol to give the oxalate salt, which softens >170° C. (38 mg).

15

EXAMPLE 22

3-Amino-6-methanesulphonamido-1,2,3,4-tetrahydrocarbazole oxalate

3-phthalimido-6-nitro-1,2,3,4-tetrahydrocarbazole (4.00 g) was dissolved in hot ethyl acetate (130 ml). To the cooled solution was added raney nickel, and the mixture was hydrogenated at an initial pressure of 39 psi at room temperature for 4 hr. After filtering off the insoluble materials, the filtrate was evaporated to dryness, and extracted twice into 20% aqueous methanol and the extracts combined and reduced in volume to give 3-phthalimido-6-amino-1,2,3,4-tetrahydrocarbazole (0.31 g).

The above product (0.50 g) was dissolved in freshly distilled pyridine (30 ml), and methanesulphonyl chloride (0.28 g) and 4-dimethylaminopyridine (46 mg) were added. The mixture was heated with stirring at 50° C. for 5 hr, and then evaporated to dryness. The residue was dissolved in chloroform, washed with water, brine and aqueous sodium bicarbonate, then dried (MgSO₄), and evaporated to dryness to give a pale yellow solid, which was recrystallized from aqueous ethanol to give 3-phthalimido-6-methanesulphonamido-1,2,3,4-tetrahydrocarbazole (0.27 g).

The above compound was suspended in ethanol (15 ml) and hydrazine hydrate (2.72 g) was added. After stirring for 25 min at room temperature, the mixture was evaporated to dryness, partitioned between water and ethyl acetate, and the aqueous layer re-extracted with ethyl acetate. The organic extracts were combined, washed with water, dried (MgSO₄) and evaporated to give a pale yellow solid. This was dissolved in methanol and treated with oxalic acid (89 mg). Addition of ether resulted in crystallization of the title compound (50 mg), mp 230°-233° C.

EXAMPLE 23

3-Amino-6-carboxamidomethyl-1,2,3,4-tetrahydrocarbazole hydrochloride

3-Amino-6-cyanomethyl-1,2,3,4-tetrahydrocarbazole (2.5 g) and di-*t*-butyl dicarbonate (3.63 g) were stirred in THF (56 ml) for 2 hr. The THF was evaporated, and the residue was partitioned between aqueous sodium bicarbonate solution and ethyl acetate. The aqueous phase was re-extracted with ethyl acetate, and the combined organic extracts were washed with water, dried (MgSO₄), and evaporated to dryness to leave a solid which was triturated with ether/hexane (20%) to give 3-*t*-butyloxycarbonylamino-6-cyanomethyl-1,2,3,4-tetrahydrocarbazole as an off-white solid (3.44 g).

The above product (7.0 g) was dissolved in DMSO (70 ml), and hydrogen peroxide (100 volume, 3.5 ml) was added. After stirring for an hour, further peroxide (8.5 ml) was added, and the mixture was stirred for 2 hr at room temperature. Potassium carbonate (0.84 g) was added, and the mixture was stirred overnight and for a further 20 hr. The reaction mixture was poured into water (500 ml) and the resulting white solid was filtered off, and recrystallized from methanol to give 3-*t*-butyloxycarbonylamino-6-carboxamidomethyl-1,2,3,4-tetrahydrocarbazole (5.42 g).

The above product (500 mg) was dissolved in dry dioxane (30 ml), and HCl gas was bubbled through for 20 min. The resulting solution and deposited gum were evaporated to dryness, and treated with aqueous potassium carbonate solution. This was extracted with ethyl acetate, and the extracts were combined, dried (MgSO₄) and evaporated to

16

dryness. The residue was dissolved in methanol and treated with excess oxalic acid. Addition of ether led to crystallization of the title compound (250 mg), mp 257°-260° C.

EXAMPLE 24

3-Methylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride

4-Cyanophenyl hydrazine hydrochloride (20.2 g) and 4-benzoyloxycyclohexanone (25.9 g) were dissolved in glacial acetic acid (400 ml) and the mixture was heated under reflux for 1.5 hr. After allowing to cool, the mixture was filtered, and the filtrate was evaporated to dryness, and neutralized with aqueous sodium bicarbonate solution to give a solid precipitate, which was purified by chromatography (SiO₂; hexane/ethyl acetate) to give 3-benzoyloxy-6-cyano-1,2,3,4-tetrahydrocarbazole (18 g). This product (11.6 g) was suspended in ethanol (230 ml) and treated with 2.5% aqueous potassium hydroxide solution (120 ml), and heated under reflux for 1 hr. The cooled mixture was neutralized with glacial acetic acid and evaporated to a solid residue, which was washed with water, and dried to give 3-hydroxy-6-cyano-1,2,3,4-tetrahydrocarbazole (6.6 g).

The above product (3.57 g) was dissolved in dry pyridine (35 ml) and treated with tosyl chloride (3.51 g) in dry pyridine (35 ml), and the mixture was stirred at 100° C. for 2 hr. After cooling, the solution was poured into water (500 ml), extracted with ethyl acetate, and the latter extract was washed with 2M HCl, dried (MgSO₄) and evaporated to dryness. Purification by chromatography (SiO₂; hexane/ethyl acetate) gave 3-tosyloxy-6-cyano-1,2,3,4-tetrahydrocarbazole (0.53 g).

This product (0.40 g) was dissolved in 33% methylamine in alcohol (25 ml) and heated at 100° C. in a sealed steel vessel for 1.5 hr. After cooling, the mixture was evaporated to dryness and purified by chromatography (SiO₂; chloroform/methanol) to give 3-methylamino-6-cyano-1,2,3,4-tetrahydrocarbazole (0.13 g).

The above product (0.12 g) was dissolved in THF (10 ml) and reacted with di-*tert*-butyl dicarbonate (0.36 g) in THF (3 ml) at room temperature overnight. The reaction mixture was evaporated to dryness, partitioned between 2M sodium bicarbonate solution and ethyl acetate, and the organic extract dried and evaporated to give a white solid. This was triturated with ether/hexane to give 3-*t*-butyloxycarbonylmethyl amino-6-cyano-1,2,3,4-tetrahydrocarbazole (0.14 g).

This product (0.14 g) was dissolved in methanol (15 ml) and treated with a mixture of 20% aqueous sodium hydroxide (0.20 ml) and 30% hydrogen peroxide (0.20 ml), and the whole mixture was stirred at room temperature overnight. Sodium metabisulphite (38 mg) was added, and the solution was evaporated to dryness, and chromatographed (SiO₂; chloroform/10% NH₄OH in methanol) to give 3-methylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (0.12 g). The above compound (0.11 g) was dissolved in methanol (10 ml), and treated with 3M hydrochloric acid at room temperature. The mixture was evaporated to dryness, azeotroping with ethanol to give a solid, which was recrystallized from methanol/ether to give the title compound, mp 327°-328° C. (80 mg).

¹H NMR [250 MHz, MeOH-d₄] δ 1.98-2.20 (1H, m), 2.29-2.49 (1H, m), 2.75-2.90 (5H, s+m), 2.90-3.09 (2H, m), 3.52-3.69 (1H, m), 7.31 (1H, d), 7.63 (1H, d), 8.05 (1H, s).

17
EXAMPLE 25

3-Ethylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate

1,4-Cyclohexanedione mono-2',2'-dimethyl trimethylene ketal (2.00 g) was mixed with anhydrous ethylamine (10.0 g) and benzene (10 ml), and the mixture was cooled to 5° C. A solution of titanium tetrachloride (0.95 g) in benzene (10 ml) was added, dropwise, then the mixture was stirred at room temperature for 1 hr. The mixture was filtered, and evaporated to dryness to give an oil, which was dissolved in ethanol (30 ml). To this solution was added palladium-on-carbon catalyst (100 mg), and the mixture was hydrogenated at 50 psi pressure overnight. The catalyst was filtered off and the ethanol evaporated to leave 4-ethylamino-cyclohexanone 2',2'-dimethyl trimethylene ketal as an oil (2.0 g).

This compound (0.80 g) was dissolved in formic acid (20 ml) and the solution was heated to 90° C. for 1 hr. Formic acid was evaporated, and the residue was partitioned between chloroform and 1M hydrochloric acid. The aqueous layer was evaporated to dryness to give 4-ethylaminocyclohexanone (0.40 g).

A mixture of the above product (0.40 g) and 4-carboxamidophenyl hydrazine hydrochloride (0.60 g) in glacial acetic acid (20 ml) was heated under reflux for 1 hr. The acid was evaporated in vacuo to an oil, which was purified by chromatography (SiO₂; CHCl₃/10% NH₃ in MeOH) to give an oil (0.50 g). Part of this product (150 mg) was dissolved in methanol and treated with oxalic acid. The solution was treated with ether to give the title compound as a crystalline solid, mp 165°-170° C. (100 mg).

¹H NMR [250 MHz, DMSO-d₆] δ 1.25 (3H, t), 1.81-2.05 (1H, m), 2.20-2.38 (1H, m), 2.61-2.79 (1H, m), 2.79-2.94 (2H, m), 2.98-3.28 (3H, dd+s), 3.41-3.60 (1H, m), 7.08 (1H, brd. s), 7.28 (1H, d), 7.60 (1H, d), 7.82 (1H, brd. s), 8.00 (1H, s), 11.12 (1H, s).

EXAMPLE 26

3-n-Propylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate

Propylamine (1.81 g) was dissolved in methanol (12.5 ml), and 1.5M HCl in methanol (6.6 ml) was added with cooling. After 1 min, 1,4-cyclohexanedione mono-2',2'-dimethyl trimethylene ketal (1.0 g) was added, followed after a further 10 min by sodium cyanoborohydride (0.23 g). The mixture was stirred at room temperature for 3 days. The resulting mixture was filtered, and the filtrate was evaporated and treated with 1M HCl (10 ml) with cooling. The residue was digested to form a solution, which was washed with ether, basified to pH 12 with aqueous sodium hydroxide, and extracted with dichloromethane. This extract was washed with saturated aqueous sodium bicarbonate solution, dried (MgSO₄), and evaporated to dryness. Chromatography (SiO₂; chloroform/methanol/ammonia) gave 4-n-propylamino cyclohexanone 2',2'-dimethyl trimethylene ketal (0.72 g).

This product (0.66 g) was hydrolyzed to the ketone, which was reacted with 4-carboxamidophenyl hydrazine hydrochloride and converted to the oxalate salt as described for Example 25, to give the title compound (0.44 g), mp >168° C. dec.

18
EXAMPLE 27

3-i-Propylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of isopropylamine (9.54 g) with 1,4-cyclohexanedione mono-2',2'-dimethyl trimethylene ketal (2.0 g) by the method described for Example 25 gave 4-i-propylamino cyclohexanone 2',2'-dimethyl trimethylene ketal (2.38 g). This product (0.66 g) was hydrolyzed and reacted with 4-carboxamidophenyl hydrazine hydrochloride (0.45 g), and the mixture worked up as described above to give the title compound free base (0.34 g). This was converted to the oxalate, mp >235° C. dec.

EXAMPLE 28

3-Dimethylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate

Dimethylamine (10.0 g) was reacted with 1,4-cyclohexanedione mono-2',2'-dimethyl trimethylene ketal (2.0 g) by the method described for Example 25 to give 4-dimethylaminocyclohexanone 2',2'-dimethyl trimethylene ketal (0.72 g). This product (0.72 g) was hydrolyzed and reacted with 4-carboxamidophenyl hydrazine hydrochloride (0.47 g) and the product converted to the oxalate salt as described above to give the title compound (0.20 g), mp 99°-101° C.

¹H NMR [250 MHz, DMSO-d₆] δ 1.83-2.05 (1H, m), 2.27-2.40 (1H, m), 2.72-3.00 (9H, 2m+s), 3.07-3.22 (1H, dd), 3.50-3.68 (1H, m), 7.05 (1H, brd. s), 7.27 (1H, d), 7.60 (1H, d), 7.81 (1H, brd. s), 8.00 (1H, s), 11.11 (1H, s).

EXAMPLE 29

3-Benzylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of benzylamine (0.59 g) with 1,4-cyclohexanedione mono-2',2'-dimethyl trimethylene ketal (10 g) and subsequent reduction of the imine with sodium cyanoborohydride by the method described for Example 26 gave 4-benzylaminocyclohexanone 2',2'-dimethyl trimethylene ketal (0.54 g). This product (0.52 g) was reacted with 4-carboxamidophenyl hydrazine hydrochloride (0.34 g) and the product treated with oxalic acid to give the title compound, mp >190° C. dec (0.11 g).

EXAMPLE 30

3-Pyrrolidinyl-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of pyrrolidine (15.6 g) with 1,4-cyclohexanedione mono-2',2'-dimethyl trimethylene ketal (2.0 g) by the method described for Example 25 gave 4-pyrrolidinyl-cyclohexanone 2',2'-dimethyl trimethylene ketal (1.74 g). This product (1.70 g) was hydrolyzed and reacted with 4-carboxamidophenyl hydrazine hydrochloride (1.70 g) and the product treated with oxalic acid as described above to give the title compound (32 mg), mp >190° C. dec.

19

EXAMPLE 31

3-(N-methyl
ethylamino)-6-carboxamido-1,2,3,4-tetrahydrocarbazole
oxalate

Reaction of N-methyl ethylamine (13.0 g) with 1,4-cyclohexanedione mono-2',2'-dimethyl trimethylene ketal (2.0 g) by the method described for Example 25 gave 4-(N-methyl ethylamino)-cyclohexanone-2',2'-dimethyl trimethylene ketal (1.71 g). This product (0.86 g) was hydrolyzed and reacted with 4-carboxamidophenyl hydrazine hydrochloride (0.52 g) and worked up as described above to give the title compound (76 mg), mp >130° C. dec.

EXAMPLE 32

3-Amino-6-(2-carboxamidoethyl)-1,2,3,4-
Tetrahydrocarbazole oxalate

A mixture of 4-nitrocinnamic acid (22.5 g) and thionyl chloride (20.8 g) in benzene (160 ml) was heated under reflux for 4 h. The resulting orange mixture was filtered and evaporated to give the acid chloride (22.9 g). This was dissolved in dichloromethane (1 l), and ammonia gas was bubbled through, with cooling to below 20° C. and stirring. Solvent was removed in vacuo, and the residue was dissolved in hot ethyl acetate and the solution was shaken with 1M sodium hydroxide solution. The resulting organic phase was dried, filtered and evaporated to leave a residue which was slurried with ethyl acetate to give 4-nitro cinnamamide as a crystalline solid (18.6 g). This product (18.6 g) was suspended in ethanol (1 l) and hydrogenated using Pd—C catalyst (6.6 g) at 50 psi for 1 h. The resulting mixture was filtered and evaporated to dryness, providing 4-aminophenyl propionamide (17.1 g).

Concentrated hydrochloric acid (4 ml) was added slowly, with cooling and stirring to 4-aminophenyl propionamide (0.80 g), maintaining the temperature below 5° C. To this slurry was added a solution of sodium nitrite (0.37 g) in water (2 ml), dropwise over 15 min, followed by stirring for a further 15 min. The turbid solution thus formed was added portionwise to a cooled, stirred solution of stannous chloride (2.19 g) in conclusion. HCl (4 ml), and the resulting mixture was stirred for 1 h. After filtering, the solution was reduced in volume until an inorganic precipitate formed. This was filtered off, and the filtrate was evaporated to dryness. The residual gum was crystallized from acetic acid to give crude 4-hydrazinophenyl propionamide hydrochloride (1.05 g).

A mixture of the above product (1.05 g) and 4-phthalimidocyclohexanone (1.18 g) in acetic acid (40 ml) was heated under reflux for 40 min. The solvent was removed in vacuo and the residue was partitioned between aqueous potassium carbonate solution and ethyl acetate. The organic phase was dried (MgSO₄) and evaporated to dryness, and the residue was chromatographed (SiO₂; CH₂Cl₂/MeOH) to give 3-phthalimido-6-carboxamidoethyl-1,2,3,4-tetrahydrocarbazole (0.70 g).

This product (0.70 g) was dissolved in methanol (50 ml), treated with hydrazine hydrate (1.0 ml), and heated under reflux for 30 min. The mixture was evaporated to dryness then partitioned between ethyl acetate and aqueous potas-

20

sium carbonate solution. The organic phase was dried (MgSO₄) and evaporated to dryness, and the residue was dissolved in ethanol to dryness, and the residue was dissolved in ethanol and treated with oxalic acid (83 mg) in ethanol. A solid was formed, which was recrystallized from ethanol to give the title compound (110 mg), mp 232°-5° C.

Pharmaceutical formulations

Example A

A tablet for oral administration is prepared by combining

	Mg/Tablet
Compound of formula (I)	100
lactose	153
starch	33
croscopolidone	12
microcrystalline cellulose	30
magnesium stearate	2
	330 mg

into a 9 mm tablet.

Example B

An injection for parenteral administration is prepared from the following

	% w/w
Compound of formula (I)	0.50% (w/v)
1M citric acid	30% (v/v)
sodium hydroxide (qs)	to pH 3.2
water for injection BP	to 100 ml

The compound of formula (I) is dissolved in the citric acid and the pH slowly adjusted to pH 3.2 with the sodium hydroxide solution. The solution is then made up to 100 ml with water, sterilized by filtration and sealed into appropriately sized ampoules and vials.

We claim:

1. A compound of formula (I) which is 3-methylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole, or a salt, solvate or hydrate thereof.
2. A method of treatment of a condition wherein a 5-HT₁-like agonist is indicated, which comprises administering to a subject in need thereof an effective amount of a compound of claim 1.
3. The method according to claim 1 wherein the condition is migraine.
4. The method according to claim 1 wherein the condition is cluster headache.
5. The method according to claim 1 wherein the condition is headache associated with vascular disorders.
6. A pharmaceutical composition comprising the compound according to claim 1, or a physiologically acceptable salt thereof and a physiologically acceptable carrier.

* * * * *



US005827871A

United States Patent [19]
King et al.

[11] Patent Number: **5,827,871**
 [45] Date of Patent: **Oct. 27, 1998**

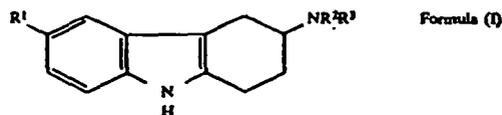
- [54] **MEDICAMENTS 1,2,3,4-TETRAHYDROCARBAZOLES AND 5-HT₁ AGONIST USE THEREOF**
- [75] Inventors: **Francis David King; Laramie Mary Gaster, both of Harlow; Alberto Jullo Kaumann, Trumpington; Rodney Christopher Young, Hertford, all of England**
- [73] Assignee: **Smithkline Beecham plc, England**
- [21] Appl. No.: **442,720**
- [22] Filed: **May 17, 1995**
- Related U.S. Application Data**
- [63] Continuation-in-part of Ser. No. 167,846, filed as PCT/GB92/01082, Jun. 17, 1992, Pat. No. 5,464,864.
- [30] **Foreign Application Priority Data**
- Jun. 26, 1991 [GB] United Kingdom 9113802
- [51] Int. Cl.⁶ **A61K 31/40; C07D 209/82**
- [52] U.S. Cl. **514/411; 514/212; 514/323; 540/602; 546/200; 548/448; 548/449**
- [58] Field of Search **514/411, 212, 514/323; 540/602; 546/200; 548/448, 440, 449**

- [56] **References Cited**
- FOREIGN PATENT DOCUMENTS**
- 0 242 518 10/1997 European Pat. Off. .
- Primary Examiner—Jacqueline Haley*

Attorney, Agent, or Firm—Nora Stein-Fernandez; Janice E. Williams

[57] **ABSTRACT**

Use of a compound of general formula (I):



wherein

- R¹** represents hydrogen, halogen, trifluoromethyl, nitro, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, arylC₁₋₆alkoxy, —CO₂R⁴, —(CH₂)_nCN, —(CH₂)_nCONR²R³, —(CH₂)_nSO₂NR²R³, C₁₋₆alkanoylamino(CH₂)_n, or C₁₋₆alkylsulphonylamino(CH₂)_n;
- R⁴** represents hydrogen, C₁₋₆alkyl or arylC₁₋₆alkyl;
- R²** and **R³** each independently represent hydrogen or C₁₋₆alkyl, or **R²** and **R³** together with the nitrogen atom to which they are attached form a ring;
- n** represents 0, 1 or 2; and
- R²** and **R³** each independently represent hydrogen, C₁₋₆alkyl or benzyl or together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino or hexahydroazepino ring;
- or a physiologically acceptable salt thereof, in the manufacture of a medicament for the treatment of a condition where a 5-HT₁-like agonist is indicated, for example migraine. Novel compounds of formula (I), processes for preparing them and pharmaceutical compositions containing them are also described.

17 Claims, No Drawings

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**MEDICAMENTS 1,2,3,4-
 TETRAHYDROCARBAZOLES AND 5-HT₁
 AGONIST USE THEREOF**

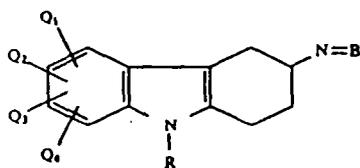
This is a continuation-in-part application of application Ser. No. 08/167,846, filed Dec. 23, 1993, now U.S. Pat. No. 5,464,864, which is a U.S. national phase application of PCT/GB92/01082, filed Jun. 17, 1992, claiming priority from GB 9113802, filed Jun. 26, 1991.

The present invention relates to certain tetrahydrocarbazole derivatives for use in the treatment of disorders characterised by excessive vasodilatation, in particular the treatment of migraine.

Migraine is a non-lethal disease which has been reported to be suffered by one in ten individuals. The main symptom is headache; other symptoms include vomiting and photophobia. Currently, the most widely used treatment for migraine involves administration of ergotamine, dihydroergotamine or methysergide, which are also used prophylactically. These drugs are inter alia agonists of 5HT₁-like receptors but also have other actions; treatment with them is associated with a number of adverse side effects. In addition, some patients experience a "withdrawal headache" following the cessation of treatment with an ergot product, such as ergotamine, causing them to repeat the treatment and resulting in a form of addiction. More recently various tryptamine derivatives have been proposed for potential use in treating migraine.

In view of the foregoing, there is clearly a need for the provision of effective and safe medicaments for the treatment of migraine.

U.S. Pat. Nos. 4,257,952, 4,172,834, 4,062,864 and 3,959,309 disclose a broad class of tetrahydrocarbazoles of the formula:

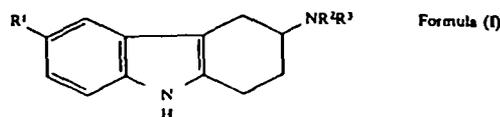


wherein N=B is inter alia —NHR' or —NR'R* where R' and R* are lower alkyl, aryl-lower alkyl or together form a heterocyclic ring; R is inter alia hydrogen; Q₁ is inter alia hydrogen, halogen, lower alkoxy, cyano, —CO₂R₁ or —CONR₂R₃ (where R₁ may be hydrogen, lower alkyl or —CH₂Ar and R₂ and R₃ are hydrogen, lower alkyl or together form a heterocyclic ring); Q₂ is inter alia hydrogen, aryl-(lower alkoxy), hydroxy, trihalomethyl, nitro or alkanoylamino, and Q₃ and Q₄ may each be inter alia hydrogen. These compounds are said to have analgetic, psychotropic and antihistaminic activities.

It has now surprisingly been found that certain tetrahydrocarbazoles are agonists and partial agonists at 5HT₁-like receptors and are expected to have utility in the treatment of conditions wherein a 5-HT₁-like agonist or partial agonist is indicated, in particular conditions associated with cephalic pain such as migraine, cluster headache and headache associated with vascular disorders. In this specification the term '5-HT₁-like agonist' will hereinafter be used to include partial agonists at this receptor.

The present invention therefore provides the use of compounds of general formula (I):

2



Formula (I)

wherein:

R¹ represents hydrogen, halogen, trifluoromethyl, nitro, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, arylC₁₋₆alkoxy, —CO₂R⁴, —(CH₂)_nCN, —(CH₂)_nCONR⁵R⁶, —(CH₂)_nSO₂NR⁵R⁶, C₁₋₆alkanoylamino(CH₂)_n, or C₁₋₆alkylsulphonylamino(CH₂)_n;

R⁴ represents hydrogen, C₁₋₆alkyl or arylC₁₋₆alkyl;

R⁵ and R⁶ each independently represent hydrogen or C₁₋₆alkyl, or R⁵ and R⁶ together with the nitrogen atom to which they are attached form a ring;

n represents 0, 1 or 2; and

R² and R³ each independently represent hydrogen, C₁₋₆alkyl or benzyl or together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino or hexahydroazepino ring;

and physiologically acceptable salts thereof, in the manufacture of a medicament for the treatment of a condition where a 5-HT₁-like agonist is indicated, in particular the treatment or prophylaxis of migraine.

The invention also provides a method of treatment of a condition wherein a 5-HT₁-like agonist is indicated, in particular migraine, which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) or a physiologically acceptable salt thereof.

Suitably R¹ represents hydrogen, halogen, cyano, hydroxy, C₁₋₆alkoxy, arylC₁₋₆alkoxy, —CO₂R⁴, —(CH₂)_nCONR⁵R⁶ or —(CH₂)_nSO₂NR⁵R⁶; and R² and R³ each independently represent hydrogen or C₁₋₆alkyl.

It will be appreciated that compounds of formula (I) may contain one or more asymmetric centres, and such compounds will exist as optical isomers (enantiomers). The invention thus includes all such enantiomers and mixtures, including racemic mixtures, thereof.

In the compounds of formula (I) a halogen atom may be a fluorine, chlorine, bromine or iodine atom. An alkyl group or moiety may have a straight or branched chain. Suitable aryl groups include for example unsaturated monocyclic or bicyclic rings and partially saturated bicyclic rings of up to 12 carbon atoms, such as phenyl, naphthyl and tetrahydronaphthyl. When R⁵ and R⁶ together with the nitrogen atom form a ring, this is preferably a 5 to 7-membered saturated heterocyclic ring, which may optionally contain a further heteroatom selected from oxygen, sulphur or nitrogen. Suitable rings thus include pyrrolidino, piperidino, piperazino and morpholino.

In the above compounds R¹ preferably represents halogen (e.g. bromine), CF₃, C₁₋₆alkoxy (e.g. methoxy), (CH₂)_nCN, —(CH₂)_nCONR⁵R⁶, —(CH₂)_nSO₂NR⁵R⁶ or C₁₋₆alkanoylamino. Most preferably R¹ represents a group —(CH₂)_nCONR⁵R⁶ wherein n represents 0 and R⁵ and R⁶ each independently represent hydrogen, methyl, ethyl or propyl. Advantageously, R⁵ and R⁶ independently represent hydrogen or methyl.

When R⁴ represents —CO₂R⁴, then R⁴ preferably represents C₁₋₆alkyl.

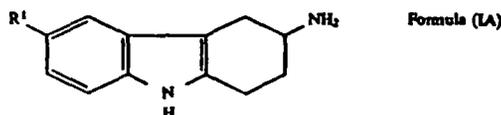
R² and R³ each preferably represent hydrogen, methyl or ethyl. Most preferably NR²R³ is —NH₂.

For use according to the present invention the compound of formula (I) is preferably a partial agonist.

Suitable physiologically acceptable salts will be apparent to those skilled in the art and include for example acid

addition salts such as those formed with inorganic acids e.g. hydrochloric, sulphuric or phosphoric acids and organic acids e.g. succinic, maleic, acetic or fumaric acid. Other non-physiologically acceptable salts e.g. oxalates may be used for example in the isolation of compounds of formula (I), and are included within the scope of this invention. Also included within the scope of the invention are solvates and hydrates of compounds of formula (I).

It is believed that compounds of formula (I) wherein R^2 and R^3 both represent hydrogen are novel. Thus in a further aspect the present invention provides compounds of formula (IA):



wherein R^1 is as hereinbefore defined, and salts thereof.

The present invention further provides the following 20 specific compounds which are also believed to be novel:

- 3-Amino-6-cyano-1,2,3,4-tetrahydrocarbazole hydrochloride,
- (+)-3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride,
- (-)-3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride,
- 3-amino-6-methoxy-1,2,3,4-tetrahydrocarbazole hydrochloride,
- 3-amino-6-bromo-1,2,3,4-tetrahydrocarbazole hydrochloride,
- 3-amino-6-methyl-1,2,3,4-tetrahydrocarbazole oxalate,
- 3-amino-6-ethoxycarbonyl-1,2,3,4-tetrahydrocarbazole oxalate,
- 3-amino-6-(N-methyl carboxamido)-1,2,3,4- 35 tetrahydrocarbazole hemioxalate,
- 3-amino-6-cyanomethyl-1,2,3,4-tetrahydrocarbazole oxalate,
- 3-amino-6-(N-methylsulphonamidomethyl)-1,2,3,4-tetrahydrocarbazole oxalate,
- 3-amino-6-chloro-1,2,3,4-tetrahydrocarbazole oxalate,
- 3-amino-6-trifluoromethyl-1,2,3,4-tetrahydrocarbazole oxalate,
- 3-amino-6-n-butylloxy-1,2,3,4-tetrahydrocarbazole oxalate,
- 3-amino-6-sulphonamido-1,2,3,4-tetrahydrocarbazole oxalate,
- 3-amino-6-nitro-1,2,3,4-tetrahydrocarbazole oxalate,
- 3-amino-6-(N,N-dimethylcarboxamido)-1,2,3,4-tetrahydrocarbazole hemioxalate,
- 3-amino-6-(piperidin-1-ylcarbonyl)-1,2,3,4- 50 tetrahydrocarbazole hydrochloride,
- 3-amino-6-(pyrrolidin-1-ylcarbonyl)-1,2,3,4-tetrahydrocarbazole hydrochloride,
- 3-amino-6-(N,N-diethylcarboxamido)-1,2,3,4-tetrahydrocarbazole hydrochloride,
- 3-Amino-6-(acetamido)-1,2,3,4-tetrahydrocarbazole oxalate,
- 3-amino-6-methanesulphonamido-1,2,3,4-tetrahydrocarbazole oxalate,
- 3-amino-6-carboxamidomethyl-1,2,3,4-tetrahydrocarbazole hydrochloride,
- 3-methylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate,
- 3-cethylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate,
- 3-n-propylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate,

- 3-i-propylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate,
- 3-dimethylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate,
- 3-benzylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate,
- 3-pyrrolidinyl-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate, and
- 3-(N-(methyl)ethylamino)-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate,
- 3-amino-6-(2-carboxamidoethyl)-1,2,3,4-tetrahydrocarbazole oxalate.

In a further aspect the present invention provides a novel compound of formula (I) e.g. a compound of formula (IA) or any of the above-named compounds (in free base form or as a physiologically acceptable salt) for use as a therapeutic agent, in particular as a 5-HT₁-like agonist or partial agonist, for example for the treatment of migraine.

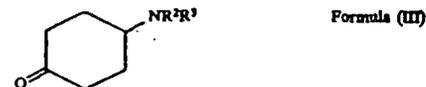
The invention also provides a process for the preparation of novel compounds of formula (I).

Compounds of formula (I) may be prepared by methods known in the art for the preparation of tetrahydrocarbazoles, for example:

A) Reaction of a compound of formula (II):

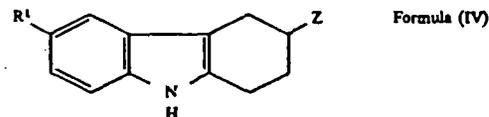


(wherein R^1 is as hereinbefore defined) or an acid addition salt thereof with a compound of formula (III):



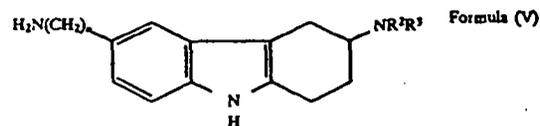
(wherein R^2 and R^3 are as hereinbefore defined) or an N-protected derivative thereof; or

B) Reaction of a compound of formula (IV):



(wherein R^1 is as defined for formula (I) and Z is a leaving group) with a compound of formula HNR^2R^3 ;

C) Reacting a compound of formula (V):



with an acylating or sulphonylating agent;

D) Conversion of one compound of formula (I) into another compound of formula (I) eg.

(i) to prepare a compound of formula (I) wherein R^1 represents $-(CH_2)_nCONH_2$ or CO_2R^4 , hydrolysis of a compound of formula (I) wherein R^1 represents $-(CH_2)_nCN$, or an N-protected derivative thereof;

(ii) to prepare a compound of formula (I) wherein R^1 represents $-CONR^5R^6$, amination of a compound of formula (I) wherein R^1 represents $-CO_2H$, or an N-protected derivative thereof; or

(iii) to prepare a compound of formula (I) wherein one of R^2 and R^3 is hydrogen and the other is C_{1-6} alkyl, alkylation of a compound (I) in which R^2 and R^3 are both hydrogen;

5

(iv) to prepare a compound of formula (I) wherein R^1 represents hydroxy, cleavage of a compound wherein R^2 represents alkoxy or aralkoxy;

followed if necessary by deprotection of any protected nitrogen atoms and if desired by salt formation.

Process (A), which is a form of the Fischer indole synthesis, may be carried out using methods well known in the art. Thus, the reaction may be effected in a solvent, for example an alcohol such as ethanol or butanol; or acetic acid, and at a temperature in the range 0° to 150° C.

Hydrazines of formula (II), which are usually employed as the hydrochloride salt, are known compounds, or may be prepared by conventional methods.

A cyclohexanone of formula (III) may be prepared by oxidation of the corresponding cyclic alcohol, using an oxidising agent such as pyridinium chlorochromate, pyridinium dichromate, dipyridine Cr (VI) oxide, sodium hypochlorite, calcium hypochlorite or manganese dioxide.

The leaving group Z in the compounds of formula (IV) may be for example a halogen atom, or a sulphonyloxy group eg. p-toluenesulphonyloxy or methanesulphonyloxy. Process (B) may be effected in an inert organic solvent, such as an alcohol eg. methanol or an ether eg. tetrahydrofuran and at a temperature in the range 0° to 150° C. Compounds of formula (IV) may be obtained by reacting a hydrazine of formula (II) with an appropriately substituted cyclohexanone compound. When Z is acyloxy or sulphonyloxy this may be prepared from a compound (IV) wherein Z is hydroxy, using standard procedures. Suitable acylating and sulphonylating agents which may be used in process (C) include carboxylic and sulphonic acid chlorides (e.g. acetyl chloride or methanesulphonylchloride) alkyl esters, activated esters and symmetrical and mixed anhydrides. The reaction may be carried out in an organic solvent such as a haloalkane (e.g. dichloromethane), an amide (e.g. N,N-dimethylformamide; an ether (e.g. tetrahydrofuran) or a tertiary amine such as pyridine. In general a base will also be used, e.g. triethylamine, dimethylaminopyridine, or an alkali metal carbonate or bicarbonate. The reaction may be effected at a temperature in the range of -10° to 100° C.

Compounds of formula (V) may be prepared by methods analogous to processes (A) and (B) hereinbefore described. Alternatively a compound of formula (V) may be obtained by subjecting a compound of formula (I) wherein R^1 is nitro to reduction, e.g. by catalytic hydrogenation.

It is well known in the chemical art that hydrolysis of a nitrile initially results in an amide, which can be further hydrolysed to an acid. It will therefore be appreciated that the precise product of process (Di) will depend upon the reaction conditions chosen for the hydrolysis. To obtain a compound wherein R^1 represents H_2NCO- the hydrolysis is preferably effected using hydrogen peroxide in the presence of an alkali hydroxide e.g. sodium hydroxide, in a solvent such as an alcohol e.g. methanol. Other suitable means of hydrolysis include acetic acid and BF_3 ; or formic acid and hydrobromic or hydrochloric acid. To prepare a compound wherein R^1 represents $-COOH$ acid or base catalysed hydrolysis may be used.

Process (Dii) may be effected by reacting a compound of formula (I) wherein R^1 is $-CO_2H$ with an amine HNR^2R^3 , in the presence of a coupling agent e.g. dicyclohexylcarbodiimide or N,N'-carbonyldiimidazole. Alternatively the carboxylic acid starting material may first be reacted to form an activated derivative of the carboxyl group, for example an acid chloride, acid anhydride or activated ester, which is then reacted directly with an amine HNR^2R^3 . The carboxylic acid may also be activated in situ for example by treating with hexamethylphosphorotriamide.

6

Alkylation according to process (Diii) may be effected by reacting an amine of formula (I) with an acylating agent, for example an anhydride, such as acetic or propionic anhydride, to form an intermediate in which one of R^2 or R^3 is $-C(O)C_{1-6}alkyl$, followed by reduction of said intermediate to give the desired product. Other reagents and conditions will be apparent to those skilled in the art.

Cleavage according to process (Div) may be effected by reduction, using methods well known in the art.

It will be appreciated that in many of the above reactions it will be necessary to protect the group $-NR^2R^3$ when one or both of the groups R^2 and R^3 represent hydrogen. Suitable N-protecting groups are well-known in the art and include for example acyl groups such as acetyl, trifluoroacetyl, benzoyl, methoxycarbonyl, t-butoxycarbonyl, benzyloxy-carbonyl or phthaloyl; and aralkyl groups such as benzyl, diphenylmethyl or triphenylmethyl. When R^2 and R^3 both represent hydrogen the nitrogen atom is preferably protected as the phthalimide. The protecting groups should be easily removable at the end of the reaction sequence. N-deprotection may be effected by conventional methods, for example a phthaloyl group may be removed by reaction with hydrazine; an acyl group such as benzoyl may be cleaved by hydrolysis and an aralkyl group such as benzyl may be cleaved by hydrogenolysis.

When a compound of formula (I) is obtained as a mixture of enantiomers these may be separated by conventional methods, for example by reaction of the mixture with a suitable optically active acid such as d-tartaric acid, l-malic acid, l-mandelic acid, l-gulonic acid or 2,3,4,6-di-O-isopropylidene-keto-L-gulonic acid to give two diastereoisomeric salts which may be separated e.g. by crystallisation. Alternatively mixtures of enantiomers may be separated by chromatography, for example on a chiral HPLC column.

Compounds of formula (I) have been found to be agonists and partial agonists at $5HT_1$ -like receptors and are expected to have utility in the treatment and/or prophylaxis of migraine, and other conditions associated with cephalic pain.

For use in medicine, the compounds of the present invention are usually administered as a standard pharmaceutical composition. The present invention therefore provides in a further aspect pharmaceutical compositions comprising a novel compound of formula (I) or a physiologically acceptable salt thereof and a physiologically acceptable carrier.

The compounds of formula (I) may be administered by any convenient method, for example by oral, parenteral, buccal, sublingual, nasal, rectal or transdermal administration and the pharmaceutical compositions adapted accordingly.

The compounds of formula (I) and their physiologically acceptable salts which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or physiologically acceptable salt in a suitable liquid carrier(s) for example an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets

containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or physiologically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas such as compressed air or an organic propellant such as a fluorochlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomiser.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

Compositions suitable for transdermal administration include ointments, gels and patches.

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the formula (I) or a physiologically acceptable salt thereof calculated as the free base.

The physiologically acceptable compounds of the invention will normally be administered in a daily dosage regimen (for an adult patient) of, for example, an oral dose of between 1 mg and 500 mg, preferably between 10 mg and 400 mg, e.g. between 10 and 250 mg or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 50 mg, e.g. between 1 and 25 mg of the compound of the formula (I) or a physiologically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

BIOLOGICAL DATA

5-HT₁-like Receptor Screen

Dog Saphenous Vein

Helicoids of dog saphenous vein were set up at 37° C. in modified Krebs solution at a resting force of 10 mN. The solution also contained 1 μmol/l each of ketanserin prazosin, atropine and mepyramine, 6 μmol/l cocaine and 200 μmol/l ascorbate. Nearly isometric contractions were measured with

force transducers on a polygraph. The tissues were exposed twice to 5-hydroxytryptamine (5-HT) 2 μmol/l followed by washes. A cumulative concentration-effect curve was determined, followed by a curve to 5-HT in the presence of the highest used concentration of test compound. Contractions caused by the test compound were compared with those caused by 5-HT. The intrinsic activity of the test compound was calculated as the ratio of the maximum test compound-induced effect over the effect caused by 2 μmol/l 5-HT. The EC₅₀ of the test compound was estimated from the corresponding effect curve. When appropriate equilibrium dissociation constants K_p were estimated by the method of Marano & Kaumann (1976, *J. Pharmacol. Exp. Ther.* 198, 518-525).

In this screen the compounds of Examples 2, 4, 5, 6, 9, 10, 11, 13, 17, 18, 21 and 24 had EC₅₀'s in the range 0.1 to 15 μmol.

RABBIT BASILAR ARTERY

METHODS

Experiments were performed in intracranial arteries from rabbit isolated basilar artery in a similar method to one described previously (Parsons and Whalley, 1989. *Eur J Pharmacol* 174, 189-196.).

In brief, rabbits were killed by overdose with anaesthetic (sodium pentobarbitone). The whole brain was quickly removed and immersed in ice cold modified Krebs's solution and the basilar artery removed with the aid of a dissecting microscope. The Krebs solution was of the following composition (mM) Na⁺ (120); K⁺ (5); Ca²⁺ (2.25); Mg²⁺ (0.5); Cl⁻ (98.5); SO₄²⁻ (1); EDTA (0.04), equilibrated with 95% O₂/5% CO₂. The endothelium was removed by a gentle rubbing of the lumen with a fine metal wire. Arteries were then cut into ring segments (ca 4-5 mm wide) and set up for recording of isometric tension in 50 ml tissue baths in modified Krebs solution with the additional supplement of (mM); Na²⁺ (20); fumarate (10); pyruvate (5); L-glutamate (5) and glucose (10). The arteries were then placed under a resting force of 3-4 mN maintained at 37° C. and the solution bubbled with 95% O₂/5% CO₂.

After tests for initial reactivity with 90 mM KCl depolarising solution and for lack of acetylcholine-induced relaxation of 5-HT (10 mM) precontraction, cumulative concentration-effect curves (2 nM-60 mM) to 5-HT were constructed in the presence of ascorbate 200 mM, cocaine 6 mM, indomethacin 2.8 mM, ketanserin 1 mM and prazosin 1 mM.

Following a 45-60 min wash period, cumulative concentration-effect curves to the test compounds or 5-HT (as a time match control) were constructed in the presence of ascorbate, indomethacin, cocaine, ketanserin and prazosin.

In this screen the compounds of Example 2, 5, 6, 15, 17, 24, 25, 26, 28 and 29 had EC₅₀'s in the range 0.04 to 15.

Example 1

3-Amino-6-cyano-1,2,3,4-tetrahydrocarbazole hydrochloride

A solution of 4-aminocyclohexanol hydrochloride (6.08 g, 0.04 mole) in water (60 ml) was brought to pH 8 with aqueous sodium bicarbonate solution. N-carbomethoxyphthalimide (8.76 g, 0.04 mole) was added followed by tetrahydrofuran (until homogenous solution was obtained). The clear solution was stirred at room temperature overnight. During this time a white solid was precipitated. The tetrahydrofuran was removed in vacuo and the remaining

aqueous solution was extracted with ethyl acetate until the solution was clear. The ethyl acetate extracts were combined, washed with water, dried ($MgSO_4$) and concentrated to give 4-phthalimido cyclohexanol as a white solid (7.1 g).

A solution of 4-phthalimido cyclohexanol (7.1 g, 0.029 mole) in dichloromethane (250 ml) was treated with pyridinium chlorochromate (8.6 g, 0.04 mole) and the resulting dark mixture was stirred at room temperature overnight. Diethyl ether (50 ml) was added and the mixture filtered through keiseliguhr. The filtrate was concentrated in vacuo and the residue purified by column chromatography (SiO_2 ; $CHCl_3/EtOAc$) to give 4-phthalimido cyclohexanone as a white solid (6.4 g).

4-Cyanophenyl hydrazine hydrochloride (4.41 g, 0.026 mole) was dissolved in acetic acid (100 ml) and sodium acetate (2 g) was added. 4-Phthalimido cyclohexanone (6.4 g, 0.026 mole) was added and the mixture heated under reflux overnight. The solvent was removed in vacuo and the residue triturated with methanol to give 3-phthalimido-6-cyano-1,2,3,4-tetrahydrocarbazole as a beige solid, (5.3 g).

A suspension of the above product (1 g) in ethanol (40 ml) was treated with hydrazine in water (10 ml). The reaction mixture was stirred at room temperature overnight during which time the reactants dissolved. The solvent was removed in vacuo and the residue partitioned between aqueous potassium carbonate and ethyl acetate. The ethyl acetate solution was washed with water, dried and concentrated in vacuo to give 3-amino-6-cyano-1,2,3,4-tetrahydrocarbazole as a beige solid (500 mg). This product was converted into the hydrochloride salt to give the title compound, mp 289° C. (dec).

1H NMR [250 MHz, CD_3OD] δ 1.98–2.18 (1H, m), 2.25–2.40 (1H, m), 2.77 (1H, dd), 2.98 (2H, m), 3.22 (1H, dd), 3.68 (1H, m), 7.34 (1H, d), 7.43 (1H, d), 7.82 (1H, s).

Example 2

3-Amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride

The product of Example 1 (400 mg) was dissolved in tetrahydrofuran, and di-t-butyl dicarbonate (500 mg) was added. The mixture was stirred at room temperature overnight. The solvent was removed in vacuo and the residue purified by column chromatography (SiO_2 ; $CHCl_3/EtOAc$) to give 3-t-butyloxycarbonylamino-6-cyano-1,2,3,4-tetrahydrocarbazole (40 mg).

A mixture of the above product nitrile (440 mg), aqueous hydrogen peroxide (30%, 0.5 ml) and sodium hydroxide (aq) (20%, 0.5 ml) in methanol (25 ml) was stirred at room temperature overnight. Sodium metabisulphite (100 mg) was added and the solvent removed in vacuo. The residue was dissolved in ethyl acetate and the ethyl acetate layer was separated, dried and concentrated in vacuo to give a gummy solid which was purified by column chromatography (SiO_2 ; $CHCl_3/EtOAc$) to give 3-t-butyloxycarbonylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole as a white solid (400 mg), mp 270° C. (dec).

The above product (400 mg, 0.0012 mole) was dissolved in dioxan (100 ml) and HCl gas was bubbled through the solution for 20 minutes. During this time a white solid was precipitated. Excess hydrogen chloride was swept from the solution by bubbling through N_2 , and the solid product, 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride was collected by filtration, washed with diethyl ether and dried to give the title compound as a white solid (300 mg), m.p. 270 (dec).

1H NMR [250 MHz, $DMSO-d_6$] δ 1.96 (1H, m), 2.16–2.30 (1H, m), 2.74 (1H, dd), 2.85 (2H, m), 3.12 (1H,

dd), 1 signal obscured by H_2O at ca. 3.6, 7.08 (1H, brd.s), 7.27 (1H, d), 7.61 (1H, d), 7.87 (1H, brd.s), 7.99 (1H, s), 8.39 (3H, brd.s).

Example 3

3-Amino-6-methoxy-1,2,3,4-tetrahydrocarbazole hydrochloride

Reaction of 4-methoxyphenyl hydrazine hydrochloride (0.87 g, 5.0 mmol) with 4-phthalimido-cyclohexanone (1.22 g, 5.0 mmol) in ethanol (20 ml) heated under reflux for 2 hr, followed by cooling and removal of the precipitated solid by filtration gave 3-phthalimido-6-methoxy-1,2,3,4-tetrahydrocarbazole (1.62 g).

The above product (1.57 g, 4.5 mmol) was suspended in ethanol (100 ml) and treated with hydrazine hydrate (23 ml) while stirring at room temperature. After 30 min, the solvent was removed in vacuo and the residue was partitioned between K_2CO_3 (aq) and $EtOAc$. The latter layer was separated, washed with water, dried ($MgSO_4$) and evaporated to dryness. This residue was dissolved in ethanol and treated with ethereal HCl until cloudy, then left to stand overnight to yield the title compound (0.95 g) mp >250° C. 1H NMR [250 MHz, $DMSO-d_6$] δ 1.81–2.02 (1H, m), 2.10–2.28 (1H, m), 2.65 (1H, dd), 2.82 (2H, m), 3.02 (1H, dd), 1 signal obscured by H_2O at ca. 3.5, 3.74 (3H, s), 6.66 (1H, d), 6.84 (1H, d), 7.14 (1H, d), 8.16 (3H, brd.s)

Example 4

3-Amino-6-bromo-1,2,3,4-tetrahydrocarbazole hydrochloride

Reaction of 4-bromophenylhydrazine hydrochloride (4.0g, 18.1 mmol) with 4-phthalimido-cyclohexanone (4.39g, 18.1 mmol) in refluxing n-butanol for 20 min, followed by cooling, filtration, and evaporation of the filtrate to dryness yielded 3-phthalimido-6-bromo-1,2,3,4-tetrahydrocarbazole as an orange solid (7.45g).

This product (0.33g, 0.83 mmol) was suspended in ethanol (13 ml) and treated with hydrazine hydrate (3 ml), then left to stir at room temperature overnight. The solid precipitate was filtered off, and the filtrate was evaporated to dryness and partitioned between K_2CO_3 (aq) and ethylacetate. After separation of the organic layer, washing with water, drying ($MgSO_4$) and evaporation to dryness, the residue was dissolved in MeOH and treated with HCl gas. Solvent was removed in vacuo and the residue was crystallized from ethanol/ethyl acetate to yield the title compound as a cream-coloured solid (0.15g), mp 308°–310° C. 1H NMR [250 MHz, $DMSO-d_6$] δ 1.91 (1H, m), 2.10–2.26 (1H, m), 2.63 (1H, dd), 2.84 (2H, m), 3.04 (1H, dd), 3.50 (1H, m), 7.12 (1H, d), 7.24 (1H, d), 7.55 (1H, s), 8.15 (2H, brd.s), 11.12 (1H, s).

Example 5

3-Amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole

4-Carboxamidophenylhydrazine hydrochloride (2.87 g) and 4-phthalimidocyclohexanone (3.00 g) were mixed in acetic acid and the mixture was heated under reflux for 2 hr. After cooling, the mixture was neutralized using aq. potassium carbonate solution, and the yellow solid thus obtained was filtered, washed with water, and dried. Purification by column chromatography (SiO_2 ; $CHCl_3/CH_3OH$) gave 3-phthalimido-6-carboxamido-1,2,3,4-tetrahydrocarbazole (2.8 g).

The above product (1.0 g) was suspended in ethanol (10 ml) and hydrazine hydrate (5 ml) was added. A clear solution was obtained, and the mixture was left to stir overnight, to

11

yield a precipitate. The whole mixture was evaporated to dryness, washed with aq. K_2CO_3 solution, and water, to leave the title compound 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (0.44 g), as the monohydrate, mp. 146°-148° C. 1H NMR [250 MHz, DMSO- d_6] δ 1.49-1.77 (1H,m), 1.83-2.03 (1H,m), 2.17-2.40 (1H,m), 2.62-2.80 (2H,m), 2.90 (1H,dd), 1 signal obscured by H_2O at ca. 3.1, 7.03 (1H,brd.s), 7.18 (1H,d), 7.58 (1H,d), 7.83 (1H,brd.s), 7.98 (1H,s).

Example 6

(+)- and (-)- 3-Amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride

Method 1

(±)-3-t-Butyloxycarbonylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole was separated into its enantiomers using chiral HPLC: (chiralcel OD 4.6 mm column, eluting with hexane/ethanol 85:15). The (+)-enantiomer was collected first and had mp =150°-152° C. and $[\alpha]_D^{25} = +70.1$ (in methanol, 0.41% w/v). The (-)-enantiomer had mp =150°-152° C. and $[\alpha]_D^{25} = -79.4$ (in methanol, 0.40% w/v). The (+)-enantiomer was converted to the parent amine hydrochloride by treating with HCl gas in dioxane, to furnish the (+)-enantiomer of 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride, mp =248°-251° C., $[\alpha]_D^{25} = +26.2$ (in methanol, 0.50% w/v). The (-)-enantiomer of 3-t-butylloxycarbonylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole was similarly converted into the (-)-enantiomer of 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride, mp =248°-251° C., $[\alpha]_D^{25} = -28.6$ (in methanol, 0.50% w/v).

Method 2

(±)-6-carboxamido-3-amino-1,2,3,4-tetrahydrocarbazole was treated with one equivalent of 2,3:4,6-di-O-isopropylidene-2-keto-L-gulonic acid in methanol to give the salt of the (+)-enantiomer, in 38% yield (with respect to racemate) and 84% enantiomeric excess (ee). This material was recrystallized twice from methanol to give the salt of the (+)-enantiomer in 25% overall yield (with respect to racemate), and >98% ee. This product was converted to the hydrochloride salt first by treatment with aqueous alkali, and the precipitated free base treated with 2M aq. HCl in ethanol, to give (+)- 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride.

Example 7

3-Amino-6-methyl-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of 4-phthalimidocyclohexanone (2.16 g) with 4-tolylhydrazine hydrochloride (1.41 g), and subsequent deprotection of the product by the method described in example 3, gave the title compound free base, which was converted to the oxalate salt (0.23 g), mp 272°-5° C.

Example 8

3-Amino-6-ethoxycarbonyl-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of 4-phthalimidocyclohexanone (0.37 g) with 4-ethoxycarbonylphenylhydrazine hydrochloride (0.33 g), and subsequent deprotection by the method described in example 3, gave the title compound free base. This was converted to the oxalate salt (0.11 g), mp 230°-240° C. dec.

Example 9

3-Amino-6-(N-methyl carboxamido)-1,2,3,4-tetrahydrocarbazole hemioxalate

Reaction of 4-phthalimidocyclohexanone (1.20 g) with 4-(N-methylcarboxamido)-phenylhydrazine hydrochloride

12

(1.00 g), and subsequent deprotection by the method described in example 3, gave the title compound free base. This was converted to the hemioxalate salt (0.22 g), mp 227° C. dec.

Example 10

3-Amino-6-cyanomethyl-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of 4-phthalimidocyclohexanone (1.05 g) with 4-cyanomethylphenylhydrazine hydrochloride (0.79 g), and subsequent deprotection by the method described in example 3, gave the title compound free base, which was treated with oxalic acid to give the oxalate salt (0.49 g), mp 219°-224° C. dec.

Example 11

3-Amino-6-(N-methylsulphonamidomethyl)-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of 4-phthalimidocyclohexanone (0.42 g) with 4-(N-methylsulphonamidomethyl) phenyl hydrazine hydrochloride (0.44 g), and subsequent deprotection by the method described in example 3, gave the title compound free base. This was treated with oxalic acid to give the oxalate salt (0.15 g), mp 218°-222° C. dec.

Example 12

3-Amino-6-chloro-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of 4-phthalimidocyclohexanone (6.7 g) with 4-chlorophenyl hydrazine hydrochloride (4.93 g), and subsequent deprotection by the method described in example 3, gave the title compound free base, which was treated with oxalic acid to give the oxalate salt (2.77 g), dec >220° C.

Example 13

3-Amino-6-trifluoromethyl-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of 4-phthalimidocyclohexanone (1.14 g) with 4-trifluoromethyl phenyl hydrazine hydrochloride (1.00 g), and subsequent deprotection by the method described in example 3, gave the title compound free base (0.40 g). This was treated with oxalic acid to give the oxalate salt, mp 212°-213° C.

Example 14

3-Amino-6-n-butyloxy-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of 4-phthalimidocyclohexanone (1.12 g) with 4-n-butyloxyphenyl hydrazine hydrochloride (1.00 g) and subsequent deprotection by the method described in example 3, gave the title compound free base. This was treated with oxalic acid to give the oxalate salt (0.47 g), mp 227°-229° C.

Example 15

3-Amino-6-sulphonamido-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of 4-phthalimidocyclohexanone (1.00 g) with 4-sulphonamido phenyl hydrazine hydrochloride (1.08 g), and subsequent deprotection by the method described in example 3, gave the title compound free base. This was converted to the oxalate salt (0.090 g), dec >200° C.

Example 16

3-Amino-6-Nitro-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of 4-phthalimidocyclohexanone (1.28 g) with 4-nitrophenyl hydrazine hydrochloride (1.00 g), and subse-

13

quent deprotection by the method described in example 3, gave the title compound free base, which was converted to the oxalate salt (0.25 g), mp 275°-277° C.

Example 17

3-Amino-6-(N,N-dimethyl carboxamido)-1,2,3,4-tetrahydrocarbazole hemioxalate

3-Amino-6-ethoxycarbonyl-1,2,3,4-tetrahydrocarbazole (260 mg, 1.0 mmol) was suspended in dry THF (5 ml), and di-tert butyl dicarbonate (320 mg, 1.5 mmol) was added. A clear solution was obtained after 10 min. The mixture was left to stir for 20 hr. then the solvent was removed, and the residue was dissolved in ethyl acetate, washed with aqueous sodium bicarbonate solution, and dried (MgSO₄). After removal of ethyl acetate, the residue was triturated with ether and hexane to give 3-t-butylloxycarbonylamino-6-ethoxycarbonyl-1,2,3,4-tetrahydrocarbazole (310 mg).

The above product (556 mg, 1.55 mmol) was suspended in ethanol (5 ml) and 2M NaOH (3 ml) was added. The mixture was heated under reflux for 1 hr and evaporated to dryness. The residue was dissolved in water and neutralized with acetic acid, when 3-t-butylloxycarbonylamino-6-carboxy-1,2,3,4-tetrahydrocarbazole precipitated out as a white solid (425 mg). A solution of the above product (400 mg, 1.2 mmol) in dry DMF (8 ml) was treated with hexamethyl phosphorous triamide (198 mg, 1.2 mmol), and cooled to -10° C. Dimethylamine gas was bubbled into the mixture for 10 min at this temperature, then carbon tetrachloride (185 mg, 1.2 mmol) was added dropwise, under an atmosphere of nitrogen. The mixture was left to stir at room temperature for 1 hr, then the DMF was removed in vacuo. The residue was partitioned between ethyl acetate and water, and the organic layer was washed with saturated aqueous sodium bicarbonate solution, then brine, and dried (MgSO₄). The solvent was removed in vacuo, and the residual oil was triturated with ether and hexane and the solid recrystallized from toluene to give 3-t-butylloxycarbonylamino-6-(N,N-dimethyl carboxamido)-1,2,3,4-tetrahydrocarbazole (198 mg).

This product (180 mg, 0.53 mmol) was dissolved in dioxane (5 ml) and HCl gas was bubbled through, to precipitate an oil. The solvent was removed in vacuo, and the oil was dissolved in water, and treated with K₂CO₃ solution to bring the pH to 12. The amine free base was then extracted with ethyl acetate, dried (MgSO₄) and evaporated to dryness. The resulting oil was dissolved in methanol and treated with oxalic acid to provide the title compound as a pale pink solid (140 mg) mp=190°-195° C.

Example 18

3-Amino-6-(piperidin-1-yl carbonyl)-1,2,3,4-tetrahydrocarbazole hydrochloride

Reaction of 3-t-butylloxycarbonylamino-6-carboxy-1,2,3,4-tetrahydrocarbazole (175 mg) with piperidine and the product subsequently deprotected by the method described for Example 17, gave the title compound, mp =246°-249° C. (55 mg).

Example 19

3-Amino-6-(pyrrolidin-1-yl carbonyl)-1,2,3,4-tetrahydrocarbazole hydrochloride

Reaction of 3-t-butylloxycarbonylamino-6-carboxy-1,2,3,4-tetrahydrocarbazole (140 mg) with pyrrolidine, and the product subsequently deprotected as described for Example 17, gave the title compound, mp=201°-212° C. (81 mg).

Example 20

3-Amino-6-(N,N-diethyl carboxamido)-1,2,3,4-tetrahydrocarbazole hydrochloride

14

Reaction of 3-t-butylloxycarbonylamino-6-carboxy-1,2,3,4-tetrahydrocarbazole (105 mg) with diethylamine, and deprotection of the product, as described for Example 17, gave the title compound, mp 200°-205° C. (50 mg).

Example 21

3-Amino-6-(acetamido)-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of 4-phthalimido cyclohexanone (1.2 g) with 4-(acetamido)-phenyl hydrazine hydrochloride (1.0 g), and subsequent deprotection of the product by the method described in example 3, gave the title compound free base (570 mg). A portion of this product (50 mg) was treated with oxalic acid in methanol to give the oxalate salt, which softens >170° C. (38 mg).

Example 22

3-Amino-6-methanesulphonamido-1,2,3,4-tetrahydrocarbazole oxalate

3-phthalimido-6-nitro-1,2,3,4-tetrahydrocarbazole (4.00 g) was dissolved in hot ethyl acetate (130 ml). To the cooled solution was added raney nickel, and the mixture was hydrogenated at an initial pressure of 39-psi at room temperature for 4 hr. After filtering off the insoluble materials, the filtrate was evaporated to dryness, and extracted twice into 20% aqueous methanol and the extracts combined and reduced in volume to give 3-phthalimido-6-amino-1,2,3,4-tetrahydrocarbazole (0.31 g).

The above product (0.50 g) was dissolved in freshly distilled pyridine (30 ml), and methanesulphonyl chloride (0.28 g) and 4-dimethylaminopyridine (46 mg) were added. The mixture was heated with stirring at 50° C. for 5 hr, and then evaporated to dryness. The residue was dissolved in chloroform, washed with water, brine and aqueous sodium bicarbonate, then dried (MgSO₄), and evaporated to dryness to give a pale yellow solid, which was recrystallized from aqueous ethanol to give 3-phthalimido-6-methanesulphonamido-1,2,3,4-tetrahydrocarbazole (0.27 g).

The above compound was suspended in ethanol (15 ml) and hydrazine hydrate (2.72 g) was added. After stirring for 25 min at room temperature, the mixture was evaporated to dryness, partitioned between water and ethyl acetate, and the aqueous layer re-extracted with ethyl acetate. The organic extracts were combined, washed with water, dried (MgSO₄) and evaporated to give a pale yellow solid. This was dissolved in methanol and treated with oxalic acid (89 mg). Addition of ether resulted in crystallization of the title compound (50 mg), mp 230°-233° C.

Example 23

3-Amino-6-carboxamidomethyl-1,2,3,4-tetrahydrocarbazole hydrochloride

3-Amino-6-cyanomethyl-1,2,3,4-tetrahydrocarbazole (2.5 g) and di-t-butyl dicarbonate (3.63 g) were stirred in THF (56 ml) for 2 hr. The THF was evaporated, and the residue was partitioned between aqueous sodium bicarbonate solution and ethyl acetate. The aqueous phase was re-extracted with ethyl acetate, and the combined organic extracts were washed with water, dried (MgSO₄), and evaporated to dryness to leave a solid which was triturated with ether/hexane (20%) to give 3-t-butylloxycarbonylamino-6-cyanomethyl-1,2,3,4-tetrahydrocarbazole as an off-white solid (3.44 g).

The above product (7.0 g) was dissolved in DMSO (70 ml), and hydrogen peroxide (100 volume, 3.5 ml) was added. After stirring for an hour, further peroxide (8.5 ml) was added, and the mixture was stirred for 2 hr at room