593051

APPLICATION ACCEPTED AND AMENDMENTS ALLOWED 15-1-89

FORM 1
REGULATION 9

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952-1973

APPLICATION FOR A PATENT

I/We BONNIE DAVIS

of 17 Seacrest Drive, Huntington, New York, U.S.A.

hereby apply for the grant of a Patent for an invention entitled:

METHOD OF TREATING ALZHEIMER'S DISEASE

which is described in the accompanying complete specification. This Application is a Convention Application and is based on the Application(s) numbered: 819,141 for a Patent or similar protection made in U.S.A. on 15 January 1986

My/Our address for service is:

GRIFFITH HASSEL & FRAZER
71 YORK STREET
SYDNEY N.S.W. 2000
AUSTRALIA

DATED this 15th day of January, 1987.

BONNIE DAVIS

By his/their Patent Attorneys

GRIFFITH HASSEL & FRAZER

TO: THE COMMISSIONER OF PATENTS
COMMONWEALTH OF AUSTRALIA

LODGED AT SUB-OFFICE
15 JAN 1987
Sydney

2361A:rk

FORM 7
CONVENTION

COMMONWEALTH OF AUSTRALIA

US 819,141

PATENTS ACT 1952-1969

- - - - - - - -

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT ~~OR A PATENT OF ADDITION~~

In support of the Convention application made by

Bonnie Davis, a citizen of the United States of America, of 17 Seacrest Drive, Huntington, State of New York, United States of America

for a patent / ~~patent of addition~~ / for an invention entitled:

METHOD OF TREATING ALZHEIMER'S DISEASE

I, Bonnie Davis

~~of~~

do solemnly and sincerely declare as follows:

~~1.~~ I am the applicant for the patent. / ~~patent of addition.~~
~~(or in the case of an application by a body corporate)~~
~~I am authorized by~~

~~the applicant for the patent / patent of addition / to make this declaration on its behalf.~~

2. The basic application as defined by Section 141 of the Act was made in the United States of America on the 15 day of January 1986, by Bonnie Davis

3. I am / ~~We are~~ the actual inventor of the invention referred to in the basic application.
~~(or, where a person other than inventor is applicant)~~

~~I, are the actual inventor of the invention and the facts upon which I am / the said Company is entitled to make the application are as follows: The Applicant Company is the assignee of the said invention from the actual inventor~~

4. The basic application referred to in paragraph 2 of this Declaration was the first application made in a convention country in respect of the invention the subject of the application.

Declared at New York, U.S.A. this 7th day of January 1987

TO:
THE COMMISSIONER OF PATENTS
COMMONWEALTH OF AUSTRALIA.

Bonnie Davis
(Full signature of Declarant-no initials)

(12) PATENT ABRIDGMENT (11) Document No. AU-B-67609/87
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 593051

(54) Title
METHOD OF TREATMENT OF ALZHEIMER'S DISEASE USING GALANTHAMINE

International Patent Classification(s)
(51)[4] A61K 031/55

(21) Application No. : 67609/87 (22) Application Date : 15.01.87

(30) Priority Data

(31) Number (32) Date (33) Country
819141 15.01.86 US UNITED STATES OF AMERICA

(43) Publication Date : 16.07.87

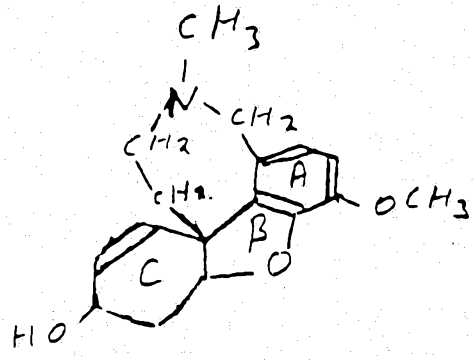
(44) Publication Date of Accepted Application : 01.02.90

(71) Applicant(s)
BONNIE DAVIS

(72) Inventor(s)
BONNIE DAVIS

(74) Attorney or Agent
GRIFFITH HACK & CO. SYDNEY

(57) Galanthamine is generally regarded as having the structure:



Compounds of a similar structure wherein the hydroxy is replaced by methoxy, ethoxy, lower alkanoyl oxy such as acetyloxy or oxy, the methoxy group is replaced by hydrogen, methoxy, ethoxy, or lower alkanoyloxy such as acetyloxy and the methyl group substituted on the nitrogen atom is replaced by other straight or branch chain lower alkyl groups such as ethyl, cyclopropylmethyl or cyclobutylmethyl, allyl, lower alkyl phenyl or substituted lower alkyl phenyl wherein

the substituents are fluoro, chloro, bromo, lower alkoxy, hydroxy, nitro, amino lower alkyl or acylamino of from 1 to 5 carbon atoms, heteroaryl lower alkyl in which the heteroaryl group is thienyl, furyl, pyridyl pyrrolyl, or pyrazinyl, or a cyano radical; or unsubstituted and halogen substituted benzoyl lower alkyl in which the substituents are on the phenyl ring, and compounds wherein hydrogen atoms in the "core" structure have been replaced by fluoro or chloro groups or the carbon to carbon single bond between the carbons common to the B and C rings is replaced by a double bond are likely to have similar properties to galanthamine. When used herein the term "galanthamine or its analogues" means galanthamine and galanthamine derivatives which one or more of the above mentioned replacements of hydrogen, methoxy or methyl groups or replacement of a single bond by a double bond have been effected.

CLAIM

1. A method of treating Alzheimer's disease and related dementias which comprises administering to a patient suffering from such a disease a therapeutically effective amount of galanthamine or an analogue as hereinbefore defined or a pharmaceutically-acceptable acid addition salt thereof.

593051

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952 Form 10

COMPLETE SPECIFICATION

FOR OFFICE USE

Short Title:

Int. Cl:

67609/87

Application Number:
Lodged:

Complete Specification-Lodged:
Accepted:
Lapsed:
Published:

This document contains the amendments made under Section 49 and is correct for printing.

Priority:

Related Art:

TO BE COMPLETED BY APPLICANT

Name of Applicant: BONNIE DAVIS

Address of Applicant: 17 Seacrest Drive, Huntington, New York, U.S.A.

Actual Inventor: Bonnie Davis

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71 YORK STREET
SYDNEY NSW 2000
AUSTRALIA

Complete Specification for the invention entitled:

METHOD OF TREATING ALZHEIMER'S DISEASE

The following statement is a full description of this invention, including the best method of performing it known to me/us:-

2361A:rk

PREPARATION OF MEDICANT FOR TREATING AD

General Field of the Invention

The present invention relates to a novel method of treating Alzheimer's disease and more particularly to a treatment using galanthamine, and its analogues.

Background Art

Galanthamine and acid addition salts thereof have, for many years, been known to have anticholinesterase properties. Cozanitis in Anaesthesia 29 163-8 (1974) describes the effect of galanthamine hydrobromide on plasma cortisol of patients receiving relaxant anaesthesia and Cozanitis et al in Acta Anesth. Scand. 24:166-168 (1980) describe the effect of galanthamine on plasma ACTH values during anaethesia. These studies showed an increase in both plasma cortisol and plasma ACTH when galanthamine was administered to patients together with atropine.

Il'yuchenok et al (Chemical Abstracts 70 36296K describe the appearance of θ-rhythm on an electroencephalogram when galanthamine is administered intravenously to rabbits.

Increase in short-term memory in dogs by use of galanthamine is described by Krauz in Chemical Abstracts 81 72615z.

The antagonistic effect of galanthamine to scopolamine-induced amnesia in rats is described by Chaplygina et al in Chemical Abstracts 86 115157z, and

in Zhurnal Vysshei Nervnoi Deiatelnosti imeni P. Pavlova (MOSKVA) 26:1091-3, 1976.

Alzheimer's disease, presenile dementia, causes much distress not only to those suffering from the disease, but also those who are close to them. The custodial care of advanced victims of the disease is a tremendous expense to society. At present, there is no effective means of improving the functional status of persons with the disease.

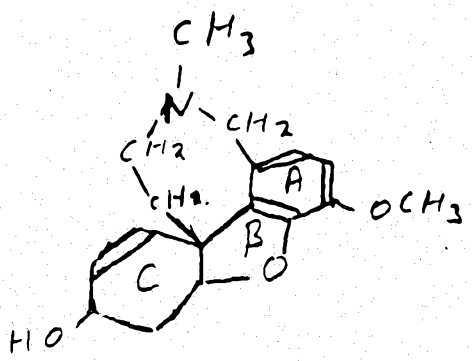
It is an object of the present invention to improve the cognitive function of patients with Alzheimer's disease.

Summary of the Invention

A method for treating Alzheimer's disease and related dementias which comprises administering to mammals, including humans, an effective Alzheimer's disease cognitively-enhancing amount of galanthamine or an analogue thereof or a pharmaceutically-acceptable acid addition salt thereof. A radioactively-labelled form of the molecule may also serve as a diagnostic test for Alzheimer's disease.

Detailed Description of the Invention

Galanthamine is generally regarded as having the structure:



Compounds of a similar structure wherein the hydroxy is replaced by methoxy, ethoxy, lower alkanoyl oxy such as acetyloxy or oxy, the methoxy group is replaced by hydrogen, methoxy, ethoxy, or lower alkanoyloxy such as acetyloxy and the methyl group substituted on the nitrogen atom is replaced by other straight or branch chain lower alkyl groups such as ethyl, cyclopropylmethyl or cyclobutylmethyl, allyl, lower alkyl phenyl or substituted lower alkyl phenyl wherein the substituents are fluoro, chloro, bromo, lower alkoxy, hydroxy, nitro, amino lower alkyl or acylamino of from 1 to 5 carbon atoms, heteroaryl lower alkyl in which the heteroaryl group is thienyl, furyl, pyridyl pyrrolyl, or pyrazinyl, or a cyano radical; or unsubstituted and halogen substituted benzoyl lower alkyl in which the substituents are on the phenyl ring, and compounds wherein hydrogen atoms in the "core" structure have been replaced by fluoro or chloro groups or the carbon to carbon single bond between the carbons common to the B and C rings is replaced by a double bond are likely to have similar properties to galanthamine. When used herein the term "galanthamine or its analogues" means galanthamine and galanthamine derivatives which one or more of the above mentioned replacements of hydrogen, methoxy or methyl groups or replacement of a single bond by a double bond have been effected. Conversion of galanthamine to its analogues can be accomplished by steps well known to those skilled in the art, for example, converting the hydroxy groups to an alkyl group by use of a dehydrating catalyst in a reaction with an alcohol or by a Williamson reaction, oxidizing a hydroxy group to an oxy group by use of a suitable mild oxidizing agent such as Jones reagent or by the Oppenauer reaction and by esterifying a hydroxy group to form an alkanoyloxy group, for example, by use of acetic anhydride. Alternatively, many of these compounds may be synthesized by normal chemical techniques.

Galanthamine or an analogue can be administered in any convenient chemical or physical form. For example, it may be administered as its hydrobromide, hydrochloride, methylsulfate or methiodide.

Galanthamine or an analogue or its pharmaceutically-acceptable acid addition salts may be administered to a patient suffering from Alzheimer's disease orally or by subcutaneous or intravenous, injection, or intracerebroventricularly by means of an implanted reservoir. It may be necessary to begin at lower doses than are ultimately effective.

Galanthamine and its acid addition salts form crystals. They are in general only sparingly soluble in water at room temperature and so injectible compositions are normally in the form of an aqueous suspension. If necessary, pharmaceutically-acceptable suspension aids may be employed. Typically, such a suspension will be employed at a concentration of 1-50 mg/ml more commonly 5-40 mg/ml, for example, 5-30 mg/ml or 10-40 mg/ml, typically 20-30 mg/ml of galanthamine. Typical dosage rates when administering galanthamine or an analogue will depend upon the exact nature of the compound used and the condition of the patient. Thus for treatment with galanthamine itself or a salt thereof typical dosage rates by injection are in the range 5-1,000 mg per day depending upon the patient. In some cases even lower dosages, as low as 0.5 or 1 mg per day may be helpful. For example, divided doses in the range 0.5-5 mg/kg body weight per day may prove useful. Typically, one might administer a dosage of 50-300 mg per day to a patient of a body weight of 40-100 kg, although in appropriate cases such dosages may prove useful for patients having a body weight outside this range. In other cases, dosages as low as 10 mg and as high as 500 mg may be appropriate for persons in this body weight range.

Galanthamine or an analogue or its pharmaceutically-acceptable acid addition salts may also be administer-

ed orally, for example, as an aqueous suspension or a solution in aqueous ethanol or as a solid such as a tablet or capsule. Suspensions or solutions for oral administration are typically of about the same concentration as those used for injections. However, it may be desirable when administering the drug orally to use a higher dosage rate than when administering it by injection. For example, dosages up to 2000 mg per day may be used, such as dosages in the range 100-600 mg per day. In preparing such tablets or capsules, standard tablet or capsule-making techniques may be employed. The dosage rate of galanthamine or its pharmaceutically-acceptable salt will normally be in the same range as for oral administration of a liquid. If desired, a pharmaceutically-acceptable carrier such as starch or lactose may be used in preparing galanthamine tablets. Capsules may be prepared using soft gelatine as the encapsulating agent. If desired, such capsules may be in the form of sustained release capsules wherein the main capsule contains microcapsules of galanthamine which release the contents over a period of several hours thereby maintaining a constant level of galanthamine in the patient's blood stream.

The following test provides a good animal model for Alzheimer's disease in humans: A selective lesion is placed in a subcortical nucleus (nucleus basalis of Meynert) with a resultant cortical cholinergic deficiency, similar in magnitude to that seen in early to moderate stage Alzheimer's disease. Numerous behavioral deficits, including the inability to learn and retain new information, characterizes this lesion. Drugs that can normalize these abnormalities would have a reasonable expectation of efficacy in Alzheimer's disease. Haroutunian, V, Kanof P, Davis, KL: Pharmacological alleviations of cholinergic-lesion-induced memory defects in rats.

Life Sciences 37:945-952, 1985.

The following specific formulations may find use in treatment of Alzheimer's disease:

Tablets or capsules containing 5, 10 and 25 mg galanthamine hydrobromide to be taken four times a day, or a sustained-release preparation delivering an equivalent daily dose.

Parenteral solution containing 5 mg/ml.

Liquid formulation for oral administration available in 5mg/5ml and 25mg/5ml concentration.

There have been reports that galanthamine can cause cardiac arrythmias. In such cases, it may be desirable to administer galanthamine in conjunction with another drug such as propanthelinbromide to control such arrythmias.

The claims defining the invention are as follows:

1. A method of treating Alzheimer's disease and related dementias which comprises administering to a patient suffering from such a disease a therapeutically effective amount of galanthamine or an analogue as hereinbefore defined or a pharmaceutically-acceptable acid addition salt thereof.

2. A method according to claim 1, wherein the administration is parenteral at a daily dosage of 5-1,000 mg of galanthamine or a pharmaceutically-acceptable acid addition salt thereof.

3. A method according to claim 2, wherein said dosage rate is 50-300 mg per day.

4. A method according to claim 1, wherein said administration is oral and is in the range 10-2000 mg per day.

5. A method according to claim 4, wherein said dosage rate of 100-600 mg per day.

6. A method according to claim 1, wherein galanthamine is administered at a dasage rate of 0.1 to 4 mg/kg body weight of a patient, parenterally.

7. A method according to claim 1, wherein galanthamine is administered intracerebroventricularly via an implanted reservoir at a dosage rate of 0.01 to 5.0 mg/kg/day.

8. A method of treating Alzeimer's disease and related dementias substantially as disclosed herein.

Dated this 31st day of October 1989

BONNIE DAVIS

By their Patent Attorney

GRIFFITH HACK & CO.