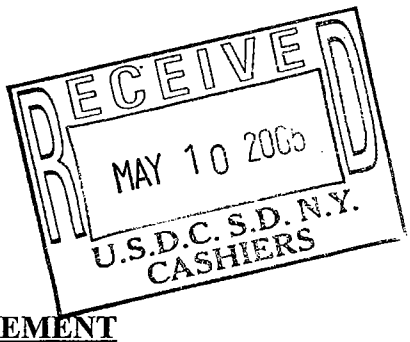
IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

In re Rivastigmine Patent Litigation	:	Civil Action No. 1:05-md-1661 (HB) (JCF)
NOVARTIS PHARMACEUTICALS CORPORATION, NOVARTIS AG, NOVARTIS PHARMA AG NOVARTIS INTERNATIONAL PHARMACEUTICAL LTD., and PROTERRA AG, Plaintiffs, v. DR. REDDY'S LABORATORIES, LTD., and DR. REDDY'S LABORATORIES, INC., Defendants.	:	Civil Action No. 04-CV-06045 (HB) (JCF)



AMENDED COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs Novartis Pharmaceuticals Corporation, Novartis AG, Novartis Pharma AG, Novartis International Pharmaceutical Ltd. and Proterra AG (hereinafter "Plaintiffs"), for their Amended Complaint herein against defendants Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. allege as follows:

NATURE OF ACTION

1. This is an action for patent infringement.

PARTIES

2. Plaintiff Novartis Pharmaceuticals Corporation ("NPC") is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 59 Route 10, East Hanover, New Jersey 07936.

3. Plaintiff Novartis AG ("Novartis AG") is a corporation organized and existing under the laws of Switzerland, having an office and place of business at Lichtstrasse 35, CH-4056 Basel, Switzerland.

4. Plaintiff Novartis Pharma AG ("Pharma AG") is a corporation organized and existing under the laws of Switzerland, having an office and place of business at Lichtstrasse 35, CH-4056 Basel, Switzerland.

5. Plaintiff Novartis International Pharmaceuticals Ltd. ("NIP") is a corporation organized and existing under the laws of Bermuda, having an office and place of business at Hurst Holme, 12 Trott Road, Hamilton HM LX, Bermuda.

6. Plaintiff Proterra AG is a corporation organized and existing under the laws of Switzerland, having an office and place of business at Poststrasse 9, CH-6300 Zug, Switzerland.

7. On information and belief, Dr. Reddy's Laboratories, Ltd. is a public limited liability company incorporated and existing under the laws of India and having a principal place of business at 7-1-27, Ameerpet, Hyderabad 500 016, India.

8. On information and belief, Dr. Reddy's Laboratories, Inc. is a corporation organized and existing under the laws of the State of New Jersey, having its principal place of business at One Park Way #3, Upper Saddle River, New Jersey 07458.

9. On information and belief, Dr. Reddy's Laboratories, Inc. is a subsidiary of Dr. Reddy's Laboratories, Ltd.

10. On information and belief, Dr. Reddy's Laboratories, Inc. is the exclusive agent in North America for Dr. Reddy's Laboratories, Ltd.

11. On information and belief, the acts of Dr. Reddy's Laboratories, Inc. complained of herein, were done at the direction of, with the authorization of, and with the cooperation, participation, and assistance of Dr. Reddy's Laboratories, Ltd.

12. Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. are referred to hereinafter, collectively as "Dr. Reddy's."

JURISDICTION AND VENUE

13. This action arises under the patent laws of the United States of America. This Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331 and 1338(a).

14. Dr. Reddy's sells various products and does business throughout the United States, including within this district.

15. Venue is proper in this Court pursuant to 28 U.S.C. §§ 1391(b) and (c), and 28 U.S.C. § 1400(b).

CLAIM FOR RELIEF - PATENT INFRINGEMENT

16. Plaintiff NPC holds an approved new drug application ("NDA") No. 20-823 for Exelon® capsules (1.5 mg, 3 mg, 4.5 mg and 6 mg), which capsules contain the active

ingredient rivastigmine tartrate (also known as rivastigmine hydrogen tartrate). Exelon® capsules (1.5 mg, 3 mg, 4.5 mg and 6 mg) were approved by the United States Food and Drug Administration ("FDA") on April 21, 2000, for the treatment of mild to moderate dementia of the Alzheimer's type, and are sold in the United States by Plaintiff NPC.

17. The active ingredient in the Exelon® capsules, rivastigmine tartrate, is known chemically as (S)-[N-ethyl-3[(1-dimethylamino)ethyl]-N-methyl-phenyl-carbamate] tartrate and as (S)-N-ethyl-N-methyl-3-[1-(dimethylamino)ethyl]-phenyl carbamate hydrogen-(2R, 3R)-tartrate.

18. Proterra AG is the owner of United States Letters Patent No. 4,948,807 ("the '807 patent"). The '807 patent was duly and legally issued on August 14, 1990.

19. The '807 patent claims N-ethyl, N-methyl-3-[1-(dimethylamino)ethyl]phenyl carbamate and pharmaceutically acceptable salts thereof, as well as methods of treating patients that have Alzheimer's disease. A true copy of the '807 patent is attached hereto as Exhibit A.

20. Novartis AG is the owner of United States Letters Patent No. 5,602,176 ("the '176 patent"). The '176 patent was duly and legally issued on February 11, 1997.

21. Novartis AG was formed as a result of the merger of Ciba-Geigy AG and Sandoz Ltd., both of Basel, Switzerland. The '176 patent was initially assigned to Sandoz Ltd. on January 29, 1988, which subsequently became Novartis AG after the merger.

22. The '176 patent claims the (S)-[N-ethyl-3-[(1-dimethylamino)ethyl]-N-methyl-phenyl-carbamate] enantiomer substantially free of its (R) isomer, including the tartrate

salt thereof, as well as pharmaceutical compositions and methods of treating conditions such as Alzheimer's disease. A true copy of the '176 patent is attached hereto as Exhibit B.

23. On information and belief, Dr. Reddy's submitted to the FDA an abbreviated new drug application ("ANDA") under the provisions of 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use, and sale of rivastigmine tartrate 1.5 mg, 3 mg, 4.5 mg and 6 mg capsules (hereinafter referred to as "Dr. Reddy's Rivastigmine Tartrate Products").

24. On information and belief, Dr. Reddy's submitted its ANDA to the FDA for the purpose of obtaining approval to engage in the commercial manufacture, use, or sale of Dr. Reddy's Rivastigmine Tartrate Products before the expiration of the '807 and '176 patents.

25. By filing the ANDA under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use, or sale of Dr. Reddy's Rivastigmine Tartrate Products before the expiration of the '807 and '176 patents, Dr. Reddy's has committed an act of infringement under 35 U.S.C. § 271(e)(2). Further, the commercial manufacture, use, offer for sale, sale and/or importation of Dr. Reddy's Rivastigmine Tartrate Products for which Dr. Reddy's seeks approval in its ANDA will also infringe one or more claims of the '807 and '176 patents.

26. On information and belief, Dr. Reddy's Rivastigmine Tartrate Products if approved, will be administered to human patients in a therapeutically effective amount for treatment of mild to moderate dementia of the Alzheimer's type, which administration constitutes direct infringement of the '807 and '176 patents. On information and belief, this will occur at Dr. Reddy's active behest, and with its intent, knowledge and encouragement. On information and belief, Dr. Reddy will actively induce, encourage, aid and abet this

administration with knowledge that it is in contravention of Plaintiff's rights under the '807 and '176 patents.

27. On information and belief, Dr. Reddy's made, and included in its ANDA, a certification under 21 U.S.C. § 355(j)(2)(vii)(IV) that, in its opinion and to the best of its knowledge, the '807 and '176 patents are invalid, unenforceable or will not be infringed.

28. On information and belief, Dr. Reddy's ANDA seeks approval to manufacture and sell Dr. Reddy's Rivastigmine Tartrate Products, which infringe the '807 and '176 patents.

29. Plaintiffs are entitled to the relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of any approval of the aforementioned ANDA relating to Dr. Reddy's Rivastigmine Tartrate Products be a date which is not earlier than August 14, 2007, the current expiration date of the '807 patent,[1/] and not earlier than February 11, 2014, the expiration date of the '176 patent, and an award of damages for any commercial sale or use of Dr. Reddy's Rivastigmine Tartrate Products, and any act committed by Dr. Reddy's with respect to the subject matter claimed in the '807 and '176 patents, which act is not within the limited exclusions of 35 U.S.C. § 271(e)(1).

30. On information and belief, when Dr. Reddy's filed its ANDA, it was aware of the '807 and '176 patents and that the filing of its ANDA with the request for its approval prior to the expiration of the '807 and '176 patents was an act of infringement of these patents.

[1/] Pursuant to 35 U.S.C. § 155 an extension of the patent term is being sought.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request the following relief:

A. Judgment that Dr. Reddy's has infringed one or more claims of the '807 and '176 patents by filing the aforesaid ANDA relating to Dr. Reddy's Rivastigmine Tartrate Products;

B. A permanent injunction restraining and enjoining Dr. Reddy's and its officers, agents, attorneys and employees, and those acting in privity or concert with it, from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of Dr. Reddy's Rivastigmine Tartrate Products as claimed in the '807 and '176 patents;

C. An order that the effective date of any approval of the aforementioned ANDA relating to Dr. Reddy's Rivastigmine Tartrate Products be a date which is not earlier than the expiration of the right of exclusivity under the '807 and '176 patents;

D. Damages from Dr. Reddy's for the infringement of the '807 and '176 patents;

E. The costs and reasonable attorney fees of Plaintiffs in this action; and

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

Dated: May 5, 2005

Robert L. Baechtold (RB 6866)
Nicholas N. Kallas (NK 1084)
Diego Scambia (DS 0296)
Gregory B. Sephton (GS 6416)
FITZPATRICK, CELLA, HARPER & SCINTO
30 Rockefeller Plaza
New York, NY 10112-3801
Phone: (212) 218-2100
Facsimile: (212) 218-2200

Attorneys for Plaintiffs
Novartis Pharmaceuticals Corporation,
Novartis AG,
Novartis Pharma AG,
Novartis International Pharmaceutical Ltd., and
Proterra AG

CERTIFICATE OF SERVICE

I, Diego Scambia, hereby certify that on May 5, 2005, a copy of PLAINTIFFS' AMENDED COMPLIANT FOR PATENT INFRINGEMENT against Reddy was served upon the following attorney in the manner indicated:

BY HAND:

Maurice Ross, Esq.
Attorney for Dr. Reddy's Laboratories, Ltd. and
Dr. Reddy's Laboratories, Inc.
Budd Larner P.C.
150 John F. Kennedy Parkway
Short Hills, NJ 07078-0999

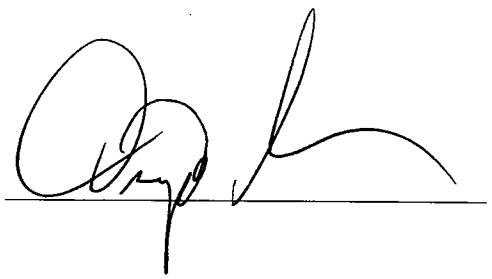


Exhibit A

United States Patent [19]

Rosin et al.

[11] **Patent Number: 4,948,807**

[45] **Date of Patent: Aug. 14, 1990**

[54] PHENYL CARBAMATES

[75] Inventors: **Marta W. Rosin; Michael Chorev; Zeev Tashma**, all of Jerusalem, Israel

[73] Assignee: **Proterra AG**, Zug, Switzerland

[21] Appl. No.: **320,700**

[22] Filed: **Mar. 8, 1989**

Related U.S. Application Data

[63] Continuation of Ser. No. 185,451, Apr. 25, 1988, abandoned, which is a continuation of Ser. No. 835,466, Mar. 3, 1986, abandoned.

[30] **Foreign Application Priority Data**

Mar. 5, 1985 [IL] Israel 74497

[51] **Int. Cl.**[5] **C07C 125/067; A61K 31/27**

[52] **U.S. Cl.** **514/484**; 514/330; 514/487; 514/490; 514/237.5; 544/162; 546/226; 560/32; 560/115; 560/136

[58] **Field of Search** 560/115, 163, 136; 514/484, 490, 487

[56] **References Cited**

U.S. PATENT DOCUMENTS

1,905,990	4/1933	Aeschlimann	560/32
2,208,485	7/1940	Aeschlimann	560/136
2,362,508	11/1944	Stevens	560/136
2,493,710	1/1950	Aeschlimann	560/136

FOREIGN PATENT DOCUMENTS

1037753	7/1956	Fed. Rep. of Germany	560/136

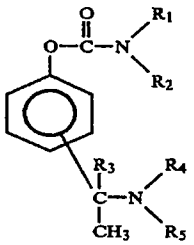
OTHER PUBLICATIONS

Stedman, Biochemical Journal, 20 pp. 719–734 (1926).
Wasserman, Proc. Natl. Acad. Sci., U.S.A., 79 pp. 4810–4814 (1982).
Weiden, J. Agr. Food Chem., 13 pp. 200–204 (1965).
Berry, Biochem. Pharmacol., 20 pp. 3236–3238 (1971).
Weinstock, Advances in Behavioral Biology, 29 pp. 539–549 (1986).
Lange, Haemostasis, 10 pp. 315–347 (1981).
Meltzer, Entomol. Exp. App., 12 pp. 169–182 (1969).

Primary Examiner—Michael L. Shippen
Attorney, Agent, or Firm—Ribis, Graham, Verdon & Curtin

[57] **ABSTRACT**

Phenyl carbamates of the general formula



I

wherein R_1 to R_5 are as defined in the claims, are useful as pharmaceuticals.

4 Claims, No Drawings

PHENYL CARBAMATES

This application is a continuation of application Ser. No. 185,451, filed on 04/25/88, entitled Phenyl Carbamates which in turn was a continuation of application Ser. No. 835,466 filed Mar. 3, 1986, both now abandoned.

The present invention relates to novel phenyl carbamates which are useful as pharmaceutical compositions. The invention further relates to pharmaceutical compositions having anticholinesterase activity.

Acetylcholine is a major neurotransmitter which is found in all parts of the body. Any reduction in its activity, either as a result of neuronal damage, degeneration etc. or as induced by drugs or toxins, causes marked changes in the function of the organism. Acetylcholine itself has an extremely short half life, since it is rapidly hydrolysed at its site of action and in plasma by specific cholinesterase enzymes. Drugs that inhibit acetylcholinesterase, markedly increase and prolong the action of acetylcholine, thereby enhancing cholinergic transmission. Three such agents are used clinically, i.e., physostigmine, a naturally occurring alkaloid, and two synthetic analogues, neostigmine and pyridostigmine. The latter two agents are strongly ionised at physiological pH and therefore are only poorly absorbed from the gastro-intestinal tract, and do not penetrate the central nervous system to any significant extent. Physostigmine is absorbed after oral administration and readily enters the brain. As a therapeutic agent it has several disadvantages. It is chemically unstable and must be prepared in solution with an antioxidant, and protected from light. It has a relatively short half-life (20–40 mins) thereby necessitating frequent administration. The latter is of particular importance when the drug is to be administered chronically. It has a low therapeutic ratio, a value of 3–5 being reported in the majority of studies in laboratory animals, and a small therapeutic window, i.e. small range of dose in which it can be given without the accompaniment of side effects. Although physostigmine is absorbed from the gastrointestinal tract, this is reported to be irregular and unpredictable, and therefore it is usually preferred to administer the drug parenterally. This is a serious drawback if it is to be used chronically on an outpatient basis.

There are a number of clinical and pathological conditions which are associated with cholinergic underactivity which can be improved by the administration of an anticholinesterase agent. These include reduction in cholinergic transmission induced by a variety of exogenous substances acting in the peripheral, or central nervous system. Peripherally acting agents are gallamine, d-tubocurarine and pancuronium, which are used as muscle relaxants. Their action can readily be overcome by an anticholinesterase drug. Drugs which interfere with central cholinergic transmission are numerous, anticholinergic, atropine-like drugs including antiparkinson drugs, tricyclic antidepressants, neuroleptics, opiate analgesics, benzodiazepines and some types of general anaesthetics. So far the only agent that has proved to be of any value in reversing the effects of the latter group of drugs is physostigmine. In all reported cases of drug overdose or lack of recovery when the agent was used peri-operatively, physostigmine is usually administered parenterally, and administration is repeated every 20–30 minutes as required.

Chronic treatment with neuroleptics often results in tardive dyskinesias. The widespread use of agents having anticholinesterase activity for the treatment of schizophrenia makes this side effect an ever increasing possibility. Physostigmine injected intravenously produces a significant but short lived improvement in a proportion of patients.

A number of pathological and degenerative diseases has also been shown to be associated with a reduction or loss of cholinergic transmission. This includes myasthenia gravis and Eaton Lambert syndrome in which there is an interference with neuromuscular transmission.

A selective loss of choline acetyltransferase (the enzyme that synthesises acetylcholine) has been found in specific brain regions of patients with pre-senile dementia of the Alzheimer type. These include the frontal and temporal cortex, hippocampus, amygdala, caudate nucleus, substantia innominata. Degeneration of cholinergic neurons in some of these areas appears to be associated with the aphasia, apraxia, agnosia and loss of short term memory that occurs in Alzheimer's disease. A similar type of dementia is also found in patients with Down's syndrome that survive to the age of 40 years and show similar cholinergic deficits. There is also a loss of cholinergic transmission in the caudate nucleus and putamen of patients with Huntingdon's chorea. Physostigmine injections have also been of some benefit in this condition. Treatment with a centrally acting anticholinesterase should also prove to be beneficial in Friedrich's ataxia.

There are two major classes of potent inhibitors of the enzyme cholinesterase. The first group was modelled primarily on the natural alkaloids physostigmine (a carbamate) and an inhibitor of cholinesterase, and d-tubocurarine, an antagonist of acetylcholine. The second group consists of various organophosphorus compounds, such as diisopropylfluorophosphonate, paraxon etc. The vast majority of the compounds of both these series were designed primarily as insecticides. In the first group of carbamate derivatives, almost all of the potent insecticides are monomethyl carbamates lacking a charged nitrogen function. This enables the molecule to penetrate rapidly the insect cuticle and fatty nerve sheath. The dimethyl derivatives are slightly less potent but are particularly toxic to houseflies and aphids. The monomethyl derivatives tend to be unstable in solution and hydrolyse readily at physiological pH. This greatly limits their biological action in mammals and makes them less suitable as pharmaceutical or therapeutic agents.

The organo-phosphorus group of compounds causes irreversible inhibition of cholinesterase and other serine containing enzymes, which, together with their high relative toxicity, virtually precludes their use in pharmaceutical preparations. The only exception is echothiopate, a quaternary ammonium organophosphorus compound, employed in eye drops for the treatment of glaucoma.

The synthetic anticholinesterase agents currently employed as pharmaceuticals all contain a charged nitrogen function and can be broadly classified into 3 groups.

(1) Reversible inhibitors which contain a charged nitrogen function attached to an aromatic ring, e.g. edrophonium.

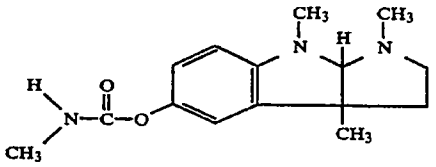
(2) Dimethyl carbamates with an aromatic or heterocyclic ring containing a charged nitrogen, neostigmine, pyridostigmine.

(3) Bisquaternary structures, e.g. Demacarium, Ambenonium. These agents tend to be more selective inhibitors of acetylcholinesterase than butyrylcholinesterase, compared with the monoquaternary molecules.

The pharmaceutical application of the quaternary anticholinesterase agents is limited because of their poor penetration through cell membranes. They are therefore used for actions outside the central nervous system, and are usually given parenterally, since they are not reliably absorbed from the gastrointestinal tract. Edrophonium, neostigmine and pyridostigmine and the bisquaternary analogues are used in anesthetic practice for the reversal of the action of muscle relaxants. They are also used for the treatment of myasthenia gravis, and paralytic ileus.

Physostigmine is the only potent anti-cholinesterase agent which has been used clinically to treat conditions in which an elevation of brain acetylcholine activity is desired. These include, Alzheimer's disease, tardive dyskinesia, Down's syndrome and Huntingdon's chorea. Physostigmine is also used to reverse the effects of overdose of anticholinergic agents, anti-Parkinson drugs, benzodiazepines and opiate analgesics.

Physostigmine is a natural alkaloid extracted from calabar beans and the seeds of the vine Physostigma venenosum and has the formula



There is a need to provide new carbamate derivatives which show greater chemical stability than physostigmine.

Furthermore there is a need to provide new compounds which inhibit acetylcholinesterase in the brain for periods exceeding 3 hours but not more than 12 hours after a single administration.

There is also a need to provide new compounds which will be completely and reliably absorbed after oral administration.

There is also a need to provide new compounds which will be relatively less toxic than physostigmine. This means that the therapeutic ratio, defined as

$$\frac{\text{dose to produce therapeutic effect}}{\text{dose to produce mortality in 50\% of animals}}$$

should be significantly higher than those of physostigmine and that the incidence and severity of side effects should be less than those of physostigmine at therapeutic doses.

There is also a need to provide new compounds which can be given orally or parenterally to treat chronic conditions in which it is desired to raise cholinergic activity in the central nervous system. These include, Alzheimer's disease, Down's syndrome, Huntingdon's chorea, Friedrich's ataxia.

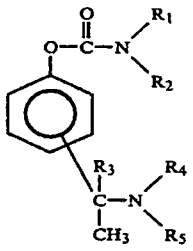
There is also a need to provide compounds that can be given parenterally at the end of operations, and anesthetic procedures, to restore wakefulness, respiration and cardiovascular parameters to normal, after the use of anticholinergic, opiates, benzodiazepines, neuroleptics and general anaesthetics, thereby shortening the stay of patients in the recovery room.

There is also a need to provide compounds that can be given together with narcotic analgesics to patients suffering from severe pain, e.g. traumatic, post-operative, or due to carcinomatosis etc. in order to reduce the side effects (respiratory depression, somnolence, constipation and urinary retention) commonly encountered with narcotics, without impairing their analgesic potency.

There is also a need to provide compounds that can be given to patients receiving antipsychotic drugs, which have developed tardive dyskinesias, in order to diminish or abolish the latter syndrome, without exascerbating the psychosis.

According to the present invention it has now been surprisingly found that certain novel and known phenyl carbamates also inhibit acetylcholinesterase in the mammalian brain after administration to provide systemic activity, e.g. oral or parenteral administration.

Thus according to the present invention there is now provided a pharmaceutical composition adapted to produce anticholinesterase activity in the central nervous system of mammals comprising a compound of the general formula I



wherein

R_1 is hydrogen, lower alkyl, cyclohexyl, allyl or benzyl,

R_2 is hydrogen, methyl, ethyl or propyl, or

R_1 and R_2 together with the nitrogen to which they are attached form a morpholino or piperidino radical,

R_3 is hydrogen or lower alkyl,

R_4 and R_5 are the same dr different and each is a lower alkyl, and the dialkylaminoalkyl group is in the meta, ortho or para position,

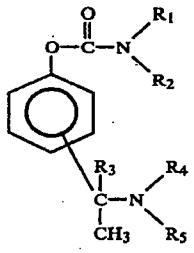
or a pharmacologically acceptable salt thereof and a physiologically acceptable carrier therefor. Hereinafter these compounds are called compounds of the invention.

Especially preferred are pharmaceutical compositions having anticholinesterase activity in the central nervous system of mammals, wherein the dialkylaminoalkyl group is in the meta position, and R_4 and R_5 are both methyl.

Certain compounds falling within the above formula have previously been described i.e. the m disubstituted compound in which R_1 and R_3=H and R_2, R_4 and R_5=methyl which is known as Miotine(R) was claimed to be an insecticide and a myopic agent for use in eye drops. The m disubstituted compound in which R_1 and R_2 are methyl, R_3 is H and R_4 and R_5 are methyl has been described as an insecticide. The p and o disubstituted derivatives in which R_1 and R_3=H and R_2, R_4 and R_5=CH_3 have been shown to inhibit a preparation of

liver cholinesterase. The m disubstituted derivative in which R_1=H and R_2, R_3, R_4 and R_5=CH_3 has also been shown to inhibit liver cholinesterase.

The remaining compounds are believed to be novel and thus the present invention also provides novel phenyl carbamate derivatives of the general formula I'



I'

wherein

R_1 is hydrogen, lower alkyl, cyclohexyl, allyl or benzyl,

R_2 is hydrogen, methyl, ethyl or propyl, or

R_1 and R_2 together with the nitrogen to which they are attached form a morpholino or piperidino radical,

R_3 is hydrogen or lower alkyl,

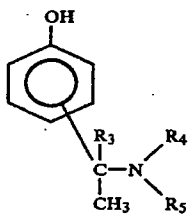
R_4 and R_5 are the same or different and each is a lower alkyl, and the dialkylaminoalkyl group is in the meta, ortho or para position,

and pharmacologically acceptable salts thereof, provided that for compounds wherein R_4 and R_5 are both methyl and having the dialkylamino group in the meta position, when R_2 is methyl and R_3 is hydrogen, R_1 is neither hydrogen nor methyl, and when R_2 and R_3 are methyl, R_1 is not hydrogen, and for compounds wherein R_4 and R_5 are both methyl and having the dialkylamino group in the ortho or para position when R_1 and R_3 are both hydrogen R_2 is not methyl.

Preferred compounds of the above formula are N-ethyl-3-[1-(dimethylamino)ethyl]phenyl carbamate, N-propyl-3[1-(dimethylamino)ethyl]phenyl carbamate, N-allyl-3-[1-(dimethylamino)ethyl]phenyl carbamate, N-ethyl, N-methyl-3[1-(dimethylamino)ethyl]phenyl carbamate, N,N-diethyl-3[1-(dimethylamino)ethyl]phenyl carbamate, N-butyl-3-[1-(dimethylamino)ethyl]phenyl carbamate, N-methyl, N-propyl-3[1-(dimethylamino)ethyl]phenyl carbamate and N-ethyl, N-methyl-3[1-(dimethylamino)isopropyl]phenyl carbamate.

As indicated, the invention also includes the pharmacologically acceptable salts of these compounds such as the acetate, salicylate, fumarate, phosphate, sulphate, maleate, succinate, citrate, tartrate, propionate and butyrate salts thereof.

The compounds of formula I can be prepared by amidating a compound of formula II

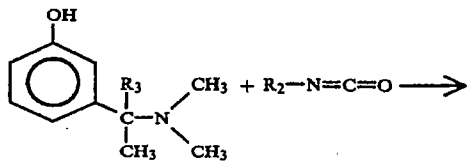


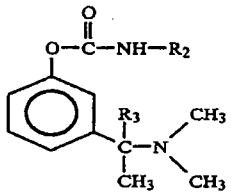
II

wherein R_3, R_4 and R_5 are as defined above.

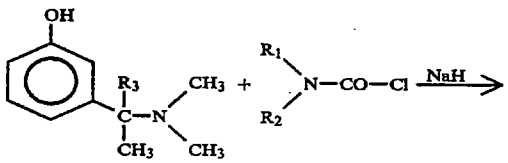
The process can be effected in conventional manner, e.g. by reacting the compound of formula II with an appropriate isocyanate if a compound wherein R_1 is hydrogen is desired, or with an appropriate carbamoyl halogenide, e.g. as described below in processes A and B.

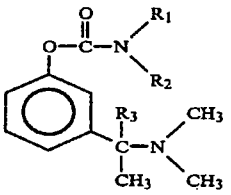
PROCESS A





PROCESS B





PROCESS A

A stirred suspension of α-m-Hydroxyphenylethyldimethylamine or α-m-hydroxyphenylisopropyldimethylamine in benzene (0.2–0.3 g/ml) is treated with 2.5–3 fold molar excess of the isocyanate. After stirring for 15–24 hours at ambient temperature the reaction mixture is connected to a rotovaporator (20 mm Hg). The residue obtained is dissolved in dry ether (25 ml) and the solution, which is ice cooled, is saturated with dry HCl (g). The formed precipitate (the anticipated carbamate) is filtered off, washed with dry ether (25 ml) and dried to constant weight in a dessicator over KOH pellets under high vacuum (0.1 mm Hg).

PROCESS B

A solution of α-m-hydroxyphenylethyldimethylamine or α-m-hydroxyphenylisopropyldimethylamine in dry acetonitrile (0.1–0.5M) is reacted with 50–70% molar excess of the corresponding carbamoyl chloride in the presence of 200% molar excess of NaH dispersion (50–80% in mineral oil). The reaction mixture is left to

stir at ambient temperature for 15–24 hours. Removal of the acetonitrile under reduced pressure (20 mm Hg) is followed by the addition of water (10–25 ml). The pH of the aqueous solution is adjusted to pH=11 by the addition of the appropriate amount of NaOH 0.1N followed by extraction with ether (3×25 ml). The combined organic phases are washed with brine (25 ml) dried over $MgSO_4$ anhydride which is then filtered off. The ice cooled etheral filtrate is saturated with a stream of HCl (g) resulting in the formation of a heavy precipitate (the anticipated carbamate) which is collected by filtration, washed with dry ether (20 ml) and dried to constant weight in a desiccator under high vacuum (0.1 mm Hg) over KOH pellets.

The compounds of the invention e.g. in free form or salt form can be utilized by formulating one or more of them in compositions such as tablets, capsules or elixirs for oral administration or in sterile solutions or suspensions for parenteral administration. A compound or mixture of compounds of formula (I) or physiologically acceptable salt(s) thereof is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in these compositions or preparations is such that a suitable dosage is obtained.

Illustrative of the adjuvants which may be incorporated in tablets, capsules and the like are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; a sweetening agent such as sucrose, lactose or saccharin; a flavoring agent such as peppermint, oil of wintergreen or cherry. When the dosage unit form is a capsule, it may contain in addition to materials of the above type a liquid carrier such as a fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange flavour.

Sterile compositions for injection can be formulated according to conventional pharmaceutical practice by dissolving or suspending the active substance in a vehicle such as water for injection. Buffers, preservatives, antioxidants and the like can be incorporated as required.

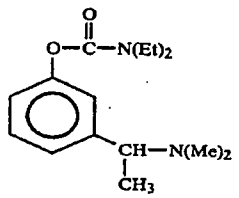
Preferred antioxidants for use with the compounds of the present invention include sodium metabisulphite and ascorbic acid.

While the invention will now be described in connection with certain preferred embodiments in the following examples, it will be understood that it is not intended to limit the invention to these particular embodiments. On the contrary, it is intended to cover all alternatives, modifications and equivalents as may be included within the scope of the invention as defined by the appended claims. Thus, the following examples which include preferred embodiments will serve to illustrate the practice of this invention, it being understood that the particulars described are by way of example and for purposes of illustrative discussion of preferred embodiments of the present invention only and are presented in the cause of providing what is believed to be the most useful and readily understood description of procedures as well as of the principles and conceptual aspects of the invention.

EXAMPLE 1

0.5 g (3.03 mmole) of α-m-hydroxyphenylethyldimethylamine are dissolved in 15 ml of dry acetonitrile and 0.70 g (5.2 mmole) of diethylcarbamoylchloride are added to the mixture with stirring. This is followed by NaH 150 mg (50%) of dispersion. The reaction mixture is stirred overnight at 25°–30° C. Removal of acetonitrile under reduced pressure is followed by addition of water (10 ml) and adjustment of the pH to 11. The product is extracted in ether, which is washed by brine, dried over $MgSO_4$ and filtered. Upon addition of HCl (g) precipitation occurs immediately, the product is filtered off, washed by dry ether and dried in a desiccator under high vacuum over KOH pellets.

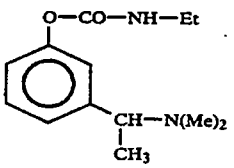
The carbamate is obtained as a white powder 640 mg (80%) mp. 137°–138° and identified as N,N-diethyl-3-[1-(dimethylamino)ethyl]phenyl carbamate, having the formula



EXAMPLE 2

0.75 g (4.55 mmol) of α-m-hydroxyphenylethyldimethylamine are suspended in benzene (3 ml) and 0.898 g of ethylisocyanate are added to the mixture with stirring. After stirring 12 hours at room temperature the solvent is removed under reduced pressure.

The residue obtained was dissolved in dry ether. Introduction of dry HCl gas into the reaction mixture causes a heavy precipitation. The product is filtered off, washed with ether and dried in a desiccator over KOH pellets. The carbamate is obtained as a white powder 800 mg (75%) mp. 177°–179° C. and identified as N-ethyl-3[1-(dimethylamino)ethyl]phenyl carbamate having the formula



The compounds of the present invention are useful as pharmaceuticals. In particular they show the following activities in vitro and in vivo in the tests specified below.

The values are correct when taken in comparison with the standard drug physostigmine.

IN VITRO EXPERIMENTS

Tests for anticholinesterase activity

A solubilized preparation of acetylcholinesterase was prepared from mouse whole brain (minus cerebellum). The brain was homogenized with (100 mg/ml) phos-

phate buffer; pH 8.0, centrifuged, the supernatant discarded, and the pellet mixed with a similar volume as above of buffer pH 8.0 plus 1% Triton; mixed, centrifuged and the supernatant which contained most of the solubilized enzyme, was used for the subsequent determinations of anticholinesterase activity.

The activity of the enzyme (rate of hydrolysis of substrate, acetylthiocholine) was measured using at least 4 different concentrations of substrate, and at least 3 different concentrations of each inhibitor. The enzyme was incubated with inhibitor for periods ranging for 2–180 mins. at 37° C., substrate was then added, and its rate of hydrolysis measured by the spectrophotometric method of Ellman et al. (1961).

The molar concentration of each agent that inhibited the activity of the enzyme by 50% (IC_{50}) at the peak time of activity (15–60 min) was calculated from this data and recorded in Table 1 hereinafter. The compounds in general produce a significant inhibition from about 10^{-5} to about 10^{-8} molar.

IN VIVO EXPERIMENTS

(a) Assessment of acetylcholinesterase inhibition

The effect of each compound on brain acetylcholinesterase in vivo was measured, after subcutaneous or oral administration to mice. Animals were sacrificed, at different times ranging from 0.25–8 hours after drug administration. The brain was rapidly removed, and the enzyme acetylcholinesterase extracted and solubilized with 0.1% Triton, and its ability to hydrolyse acetylthiocholine assessed as described above (in vitro experiments), in comparison with the enzyme removed from mice injected with normal saline. The compounds have in general a potency of from about 2% to about 90% that of physostigmine.

(b) Assessment of acute toxicity

Mice were given one of at least three different doses of each compound, orally or subcutaneously, a minimum of 10 mice allotted to each dose. The number of animals which died at each dose within 3 hours was determined. From these data, the LD_{50} (dose in mg/kg which was lethal to 50% of the mice) was computed.

This experiment was repeated after the animals had been pretreated with atropine sulphate, which blocks both peripheral and central muscarinic receptors. The data from these experiments enabled the assessment of the relative degrees of toxicity of the carbamates which result from excessive activation of muscarinic receptors, and from respiratory muscle paralysis, which is insensitive to this blocking agent.

The incidence and degree of side effects was noted for each dose of drug, starting with the lowest that caused any significant (>20%) inhibition of whole brain acetylcholinesterase.

(c) Antagonism of the somnolent and respiratory depressant effects of opiates

Different doses of the carbamate compounds were injected intravenously with morphine in rabbits Respiration rate, arterial blood gas tensions and pH were monitored continuously before and after drug administration for 4–5 hours. In another series of experiments the effect of the anticholinesterase drugs was assessed on the analgesic effect of opiates in rabbits after application of a nociceptive stimulus, i.e. electrical stimulation of the sciatic nerve.

All specific examples of formula I' mentioned hereinbefore, e.g. on specification page 10, and after especially Tables 1 to 3, are prepared in analogous manner to Example 1 when R_1 and R_2 are each other than hydrogen and Example 2 when one of R_1 and R_2 are hydrogen. They are thus obtained as hydrochloride salts (except where otherwise specified). The specific compounds have metal substitutions.

TABLE 1

In vitro activity on solubilized mouse brain enzyme

Compound ($R_4 = R_5 = CH_3$)	R_1	R_2	R_3	IC_{50}(M)	Time of peak activity (mins)
Physiostigmine (Salicylate)	H	CH_3	H	1.1×10^{-8}	30
Miotine HCl	H	CH_3	H	1.3×10^{-8}	30
RA_6 HCl	H	C_2H_5	H	4.0×10^{-7}	120
RA_{15} HCl	H	C_3H_7 n-propyl	H	1.1×10^{-7}	120
RA_{14} HCl	H	C_3H_5 allyl	H	4.3×10^{-7}	120
RA_{13} HCl	H	C_3H_7 isopropy	H	1.2×10^{-5}	120
RA_5 HCl	H	C_4H_9 n-butyl	H	7.6×10^{-8}	120
RA_{12}	H	cyclohexyl	H	9.3×10^{-8}	120
RA_{10} HCl	CH_3	CH_3	H	2.7×10^{-8}	120
RA_7 HCl	CH_3	C_2H_5	H	1.3×10^{-6}	90
RA_8 HCl	C_2H_5	C_2H_5	H	3.5×10^{-5}	30
RA_{11} HCl		morpholino	H	$>2 \times 10^{-5}$	30
RA_4 HCl	CH_3	propyl	H	1.7×10^{-6}	60

Melting points of compounds (all in the hydrochloride form except for RA_{12} which is in the free base form as it precipitated from the reaction mixture before addition of hydrogen chloride) are in degrees Centigrade: RA_6 167–170; RA_{15} 141–143; RA_{14} 147–152; RA_{13} 146–148; RA_5 158–162; RA_{12} 75–77; RA_{10} 145; RA_7 135–136; RA_8 137–138; RA_{11} amorphous; RA_4 148–149.

Compound RA_{11} has an RF value of 0.59 in a system of 95 parts of ethyl acetate and 5 parts of 33% (w/w) dimethylamine in ethanol.

TABLE 2

Anticholinesterase activity of compounds in mouse brain compared to that of physostigmine

Compound	Relative potency to physostigmine after subcut. (s.c.) administration	Relative potency to physostigmine after oral administration	% cholinesterase inhibition 3 hours after s.c. administration
Physostigmine	100	100	0
Miotine	100	300	5
RA_6	11	19	35
RA_{15}	33	32	37
RA_{14}	15	22	35
RA_{13}	2	5	—
RA_5	36	29	30
RA_{12}	13	17	37
RA_{10}	81	92	7
RA_7	25	57	41
RA_8	2	5	32
RA_4	13	29	25

TABLE 3

Acute toxicity of carbamates in mice

Compound	LD_{50} µmoles/kg s.c.	Degree of* protection afforded by pretreatment with atropine	Therapeutic ratio LD_{50}/ED_{50} s.c.	LD_{50} oral / LD_{50} s.c.
Physostigmine	3.0	3.0	3.3	4.1
Miotine	4.5	2.4	4.9	1.2
RA_6	96	2.6	11.9	2.1

TABLE 3-continued

Compound	Acute toxicity of carbamates in mice: LD_{50} μmoles/kg s.c.	Degree of* protection afforded by pretreatment with atropine	Therapeutic ratio LD_{50}/ED_{50} s.c.	$\frac{LD_{50}\ oral}{LD_{50}\ s.c.}$
RA_{15}	31	4.1	11.1	4.5
RA_{14}	69	8.0	11.5	4.4
RA_{13}	65	4.5	1.6	1.1
RA_5	19	5.8	7.6	5.0
RA_{12}	42	3.8	5.8	3.6
RA_{10}	14	5.0	12.7	9.7
RA_7	46	10.4	12.4	1.2
RA_8	>568	—	>10.0	—
RA_4	72	4.9	10.0	1.7

*Ratio of LD_{50} after pretreatment with atropine sulphate 5 mg/kg to LD_{50} of drug alone.

The data in Tables 1 and 2 demonstrate that somewhat larger quantities are required of all the drugs of the RA series than of physostigmine to inhibit the enzyme acetylcholinesterase. However, a comparison of the data in Table 1 with that in Table 2, shows that compounds RA_5, RA_6, RA_{15}, RA_{14}, RA_{10}, RA_7 and RA_8 are all relatively more active in vivo compared to physostigmine than one would expect from the in vitro data. This greater in vivo potency is particularly marked when the drugs are administered orally. This relatively greater in vivo activity may be due to:

(a) greater chemical stability
(b) a slower metabolic degradation or/and excretion
(c) a higher lipid solubility, enabling a greater proportion of the drug to gain access to the enzyme in the central nervous system
(d) more efficient absorption from gastro-intestinal tract.

For the purposes of their therapeutic application it is of little importance if one needs to give the drug (to human subjects) at a dose of 1–2 mg (physostigmine) or 2–50 mg that may be required of the compounds of the RA series. What is important is the safety of the drugs and the presence and severity of side effects that may occur at therapeutic doses. A commonly-used measure of drug safety is the therapeutic index—or LD_{50}/ED_{50}

$$\frac{\text{Dose to kill 50\% of animals}}{\text{Dose to cause the desired therapeutic effect}}$$

It is assumed that the therapeutic effect of these anticholinesterase agents results from an elevation of brain cholinergic activity. This in turn, should be related to the degree of inhibition of acetylcholinesterase. For the purpose of the computation of the denominator of the therapeutic ratio, there is used the dose of drug that inhibits the activity of acetylcholinesterase by 50%. This is based on the observation by Thal et al. (Ann. Neurology 13: 491, 1983) that the maximum improvement in short term memory obtained in a series of patients with Alzheimer's disease was achieved with a dose of physostigmine which blocked the acetylcholinesterase in the cerebro-spinal fluid by 50%. The numerator is the dose found to kill 50% of the animals within 4 hours of a subcutaneous injection. The therapeutic ratios of compounds $RA^{4, 5, 6, 7, 8, 10, 14}$ and ^{15} are all significantly higher than of physostigmine (see Table 3). This indicates that all these compounds have a wider margin of safety than that of physostigmine. Moreover, these RA compounds do not produce any significant undesirable side effects such as defaecation, lachrymation, fasciculations or tremor at the doses which inhibit the brain enzyme by 50%, while the former 3 side effects are clearly evident when physostigmine is given at the appropriate dose (ED_{50}).

The data in Table 3 show that atropine can afford considerably greater protection against the lethality of the derivatives $RA^{4, 5, 7, 10, 13}$ and ^{14}. This is particularly important in the treatment of drug overdose since the respiratory muscle paralysis which is not affected by atropine and which is the cause of death induced by excess drug administration in the presence of atropine cannot be satisfactorily reversed by specific antidotes.

The duration of significant brain enzyme inhibition (>30%) induced by physostigmine (ED_{50} dose) is less than 2 hours. Compounds $RA_{4, 5, 6, 7, 8, 12, 14, 15}$ all act for more than 3 hours at their respective ED_{50} doses and RA_6 and RA_7 still causes significant inhibition (36%) after 7 hours. Since none of these drugs caused noticeable side effects at the ED_{50} doses, an even longer duration of action may be achieved by giving between 50 and 100% larger doses. The longer duration of action is a distinct advantage, particularly if the drugs are to be administered chronically to subjects suffering from neurological and behavioural conditions associated with a deficit in cholinergic transmission in the central nervous system, e.g. Alzheimer's disease, tardive dyskinesias, Huntingdon's chorea, Down's syndrome and Friedrich's ataxia.

The better the absorption of the drug after oral administration the more closely the LD_{50} given by this route resembles that after subcutaneous injection. Table 3 shows that $RA_{6, 13, 7}$ and 4 are more efficiently absorbed from the gastro-intestinal tract than is physostigmine. The ED_{50} of RA_8 after oral administration is the same as that after S.C. injection, indicating a much better oral bioavailability than that of physostigmine. The higher oral bioavailability of these compounds may be a considerable advantage for their clinical use.

RA_{10}, RA_6, RA_{14} and RA_{15} produce significant antagonism of the respiratory depressant effects of morphine in rabbits for periods lasting between 3–5 hours depending on the drug and the dose administered. The analgesic activity of morphine is not reduced by the RA compounds. Muscle fasciculations are not evident at the doses of drugs administered. Physostigmine (0.1–0.2 mg/kg) antagonizes the respiratory depressant effect of morphine for 30–60 mins only and fasciculations are marked at the higher dose.

These findings show that the RA compounds may be given together with morphine to obtain adequate analgesia without significant degrees of respiratory depression.

The most preferred compounds of the RA series are RA_4, RA_5, RA_6, RA_{15}, RA_{14}, RA_7 and RA_8, all of which produce inhibition of brain acetylcholinesterase after parenteral administration of significantly longer duration than that induced by physostigmine or miotine. These compounds also have a greater safety margin (therapeutic ratio) than physostigmine. $RA_{4, 6, 7}$ and 8 also show better bioavailability after oral administration than physostigmine. In addition, the acute toxicity (lethality) induced by RA_7 can be decreased more than 10-fold and that of RA_{14} more than 8-fold by the antidote atropine, compared to only a 3-fold decrease for physostigmine and miotine.

The compounds of the invention are therefore useful for the treatment of senile dementia, Alzheimer's disease, Huntingdon's chorea, tardive dyskinesias, hyperkinesia, mania, acute confusion disorders, Down's syndrome and Friedrich's ataxia.

For these indications, the exact dosage will of course vary depending upon the compound employed, mode of administration and treatment desired. The compounds may be administered by any conventional route, nonoral or preferably orally.

In general, satisfactory results are obtained when administered at a daily dosage of from about 0.05 to 10 mg/kg animal body weight. For the larger mammals, an indicated total daily dosage is in the range from about 0.5 to about 25 mg of the compound, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing for example from about 0.1 to about 12 mg of the compound or in sustained release form.

The compounds may be administered in similar manner to known standards for use in these utilities. The suitable daily dosage for a particular compound will depend on a number of factors such as its relative potency of activity.

The compounds according to the invention may be administered in free base form or as a pharmaceutically acceptable acid addition salt. Such salts may be prepared in conventional manner and exhibit the same order of activity as the free forms.

It will be evident to those skilled in the art that the invention is not limited to the details of the foregoing illustrative embodiments and examples and that the present invention may be embodied in other specific forms without departing from the essential attributes thereof, and it is, therefore, desired that the present embodiments and examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing description, and all changes which come with the meaning and range of equivalency of the claims are, therefore, intended to be embraced therein.

What is claimed is:

1. N-cyclohexyl-3-[1-(dimethylamino)ethyl]phenyl carbamate and pharmacologically acceptable salts thereof.

2. N-allyl-3-[1-(dimethylamino)ethyl]phenyl carbamate and pharmacologically acceptable salts thereof.

3. N-ethyl, N-methyl-3-[1-(dimethylamino)ethyl]phenyl carbamate and pharmacologically acceptable salts thereof.

4. A method of treating a subject suffering from senile dementia, Alzhemier's disease, Huntingdon's chorea, tardive dyskinesias,, hyperkinesia, mania, acute confusion disorders, Friedrich's ataxia and Down's syndrome, which comprises administering to such a subject a therapeutically effective amount of a compound selected from the group consisting of N-cyclohexyl-3-[1-(dimethylamino)ethyl]phenyl carbamate, N-allyl-3-[1-(dimethylamino)ethyl]phenyl carbamate, N-ethyl, N-methyl-3[1-(dimethylamino)ethyl]phenyl carbamate, and pharmacologically acceptable salts thereof.

* * * * *

Exhibit B

US005602176A

United States Patent [19]

Enz

[11] Patent Number: 5,602,176

[45] Date of Patent: Feb. 11, 1997

[54] **PHENYL CARBAMATE**

[75] Inventor: **Albert Enz**, Basel, Switzerland

[73] Assignee: **Sandoz Ltd.**, Basel, Switzerland

[21] Appl. No.: **466,502**

[22] Filed: **Jun. 6, 1995**

Related U.S. Application Data

[63] Continuation of Ser. No. 353,848, Dec. 24, 1994, abandoned, which is a continuation of Ser. No. 110,622, Aug. 23, 1993, abandoned, which is a continuation of Ser. No. 6,904, Jan. 21, 1993, abandoned, which is a continuation of Ser. No. 925,365, Aug. 4, 1992, abandoned, which is a continuation of Ser. No. 859,171, Mar. 27, 1992, abandoned, which is a continuation of Ser. No. 750,334, Aug. 27, 1991, abandoned, which is a continuation of Ser. No. 664,189, Mar. 4, 1991, abandoned, which is a continuation of Ser. No. 589,343, Sep. 27, 1990, abandoned, which is a continuation of Ser. No. 408,640, Sep. 18, 1989, abandoned, which is a continuation of Ser. No. 285,177, Dec. 15, 1988, abandoned, which is a continuation of Ser. No. 162,568, Mar. 1, 1988, abandoned.

[30] **Foreign Application Priority Data**

Mar. 4, 1987 [DE] Germany 37 06 914.4

[51] **Int. Cl.**[6] **A61K 31/27**

[52] **U.S. Cl.** **514/490**; 560/136

[58] **Field of Search** 560/136; 514/490

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,469,700 9/1984 Somers 424/265

FOREIGN PATENT DOCUMENTS

193926 9/1986 European Pat. Off. .

Primary Examiner—Michael L. Shippen

Attorney, Agent, or Firm—Robert S. Honor; Melvyn M. Kassenoff; Thomas O. McGovern

[57] **ABSTRACT**

The (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methyl-phenylncarbamate in free base or acid addition salt form is useful as pharmaceutical, particularly for systemic transdermal administration.

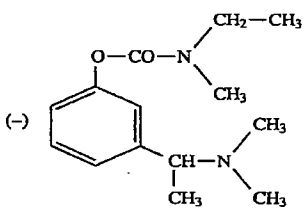
12 Claims, No Drawings

PHENYL CARBAMATE

This is a continuation of application Ser. No. 08/353,848 filed Dec.12, 1994, which in turn is a continuation of application Ser. No. 08/110,622, filed Aug. 23, 1993, which in turn is a continuation of application Ser. No. 08/006,904, filed Jan. 21, 1993, which in turn is a continuation of application Ser. No. 07/925,365, filed Aug. 4, 1992, which in turn is a continuation of application Ser. No. 07/859,171, filed Mar. 27,1992, which in turn is a continuation of application Ser. No. 07/750,334, filed Aug. 27,1991, which in turn is a continuation of application Ser. No. 07/664,189, filed Mar. 4, 1991 which in turn is a continuation of application Ser. No. 07/589,343, filed Sep. 27, 1990, which in turn is a continuation of application Ser. No. 07/408,640, filed Sep. 18, 1989, which in turn is a continuation of application Ser. No. 07/285,177, filed Dec. 15, 1988, which in turn is a continuation of application Ser. No. 07/162,568, filed Mar. 1, 1988, all now abandoned.

The present invention relates to a novel phenyl carbamate with anticholinesterase activity.

More particularly the invention relates to the (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methyl-phenyl-carbamate of formula I



I

in free base or acid addition salt form.

As can be seen from this formula, in free base form the sign of rotation of the compound of formula I is (–). However in acid addition salt form it may be (+) or (–). For instance the sign of rotation of the hydrogen tartrate is (+). The present invention covers the free base form as well as the acid addition salt forms, independently of their sign of rotation.

The racemic mixture (±)-N-ethyl-3-[(1-dimethylamino-)ethyl]-N-methyl-phenyl-carbamate in form of its hydrochloride is known from the European patent application 193,926 where it is identified as RA_7 HCl.

According to this disclosure the racemate in free base form is obtained by amidation of α-m-hydroxyphenylethyldimethylamine with a corresponding carbamoyl halogenide. The resulting compound and its pharmacologically acceptable acid addition salts, which can be prepared from the free base in known manner, are disclosed as acetylcholinesterase inhibitors in the central nervous system.

It has now surprisingly been found that the (–)-enantiomer of formula I and its pharmacologically acceptable acid addition salts, hereinafter referred to as compounds according to the invention, exhibit a particularly marked and selective inhibition of the acetylcholinesterase.

These findings are unexpected, particularly since it is not believed that the dialkylaminoalkyl side chain, which contains the optically active centre, is mainly responsible for the acetylcholinesterase inhibiting activity of the phenyl carbamates.

The compounds according to the invention have never been specifically disclosed in the literature. The free base may be prepared from the racemate by separation of the enantiomers in accordance with known methods, e.g. using di-0,0'-p-toluyl-taratric acid. The acid addition salts may be

prepared from the free base in known manner. These include e.g. the hydrogen tartrate.

The compounds according to the invention exhibit pharmacological activity as indicated in standard tests and are therefore useful as pharmaceuticals. They reach the central nervous system rapidly after s.c., i.p. or p.o. administration in rats. They exert a brain region-selective inhibition of acetylcholinesterase activity, hippocampal and cortical enzyme being more inhibited than acetylcholinesterase originating from striatum and pons/medulla. Furthermore they have a long duration of action.

The following results, for example, illustrate the pharmacological profile of the compounds according to the invention as compared to the corresponding isomers and racemates. Compound A is the compound of formula I in form of its hydrogen tartrate. Compound B is the optical isomer of said salt. C designates the racemic mixture of the compound of formula I and its optical isomer, in form of the hydrochloride.

In Vitro Assays

Electrically evoked ^{3}H-acetylcholine release from rat hippocampal slices

Electrically evoked ^{3}H-acetylcholine (^{3}H-ACh) release from rat hippocampal slices is a functional in vitro model to investigate presynaptic muscarinic autoreceptor agonists and antagonists. This model can also be used as an indirect method to evaluate drugs which inhibit acetylcholinesterase (AChE). Inhibition of AChE activity leads to the accumulation of endogenous ACh which then interacts with presynaptic muscarinic autoreceptors and inhibits further release of ^{3}H-ACh.

Rat hippocampal slices (Wistar strain, 180–200 g) are prepared by chopping into cross sections whole hippocampal slices at a distance of 0.3 mm with a McIlwain tissue chopper. Hippocampal slices obtained from 3 rats are incubated for 30 min. at 23° C. in 6 ml Krebs-Ringer containing 0.1 uCi ^{3}H-choline and transferred into the superfusion chamber and superfused with Kreb's medium containing 10 μM hemicholinium-3 at a rate of 1.2 ml/min. at 30° C. Collection of 5 min. fractions of the superfusate begins after 60 min. of superfusion. Two periods of electrical stimulation (2 Hz rectangular pulses 2 msec, 10 mA, 2 min.) are applied after 70 min. (S_1) and after 125 min. (S_2) of superfusion. Test substances are added 30 min. before S_2 and are present in the superfusion medium until 145 min. of superfusion. At the end of the experiments the slices are solubilized in conc. formic acid and tritium content is determined in the superfusate and the solubilized slices. Tritium outflow is expressed as the fractional rate of tritium outflow per min. Electrically evoked tritium outflow is calculated by subtraction of the extrapolated basal tritium outflow from the total tritium outflow during the two min. of electrical stimulation and the following 13 min. and is expressed as percent of the tritium content at the beginning of the sample collection. Drug effects on stimulation evoked tritium outflow are expressed as the ratios S_2/S_1. All experiments are run in dublicates using a programmable 12 channel superfusion system. For the calculation a computer program is used.

In this test compound A inhibits electrically evoked ^{3}H-ACh release from hippocampal slices by approximately 40% (100 μM) while racemate C (100 μM) inhibits by approximately 25%. The inhibitory effects of compound A and racemate C can be antagonized by atropine. These results are compatible with an AChE-inhibiting activity. Compound B is inactive in this model.

Acetylcholinesterase inhibition in different rat brain regions

AChE preparations of different rat brain regions (Cortex, hippocampus and striatum) are used in this test and the IC_{50} (inhibitory concentrations in μM) are determined. The enzyme preparations are preincubated with the inhibitor 15 minutes before the determination.

The AChE activity is measured according to the method described by Ellman (Arch. Biochem. Biophys. 82, 70, 1959). Rat brain tissue is homogenized in cold phosphate buffer pH 7.3 (0.25 mM) containing 0.1% of Triton X-100. After centrifugation aliquots of the clear supernatant is used as enzyme source. The enzyme is preincubated with different concentrations of the inhibitor. After different times, substrate (acetylthiocholinjodide 0.5 mM) is added and the remaining activity determined.

The results are given in the following table 1:

TABLE 1

IC_{50}	Cortex	Hippocampus	Striatum
Compound A	2.8	3.7	3.0
Compound B	16.1	14.5	13.8
Racemate C	3.2	3.9	3.2

As can be seen from this table the AChE inhibition with compound A is slightly superior than that with racemate C, whereas compound B is significantly less active.

Acetylcholinesterase inhibition ex vivo in different rat brain regions

30 minutes after administration of different doses of compound A, the AChE activity in different rat brain regions is measured ex vivo. The method is as disclosed above. The IC_{50} values found are 7 μmol/kg p.o. in striatum, 4 μmol/kg p.o. in hippocampus and 2 μmol/kg p.o. in cortex. The IC_{50} obtained after administration of the racemate C are for all examined regions about 2–3 times higher. Six hours after administration of compound A (10 μmol/kg p.o.) the AChE in striatum is still inhibited by 16%, whereas at the same time the activities in cortex and hippocampus are inhibited by 39% and 44% respectively.

In Vivo Assays

Influence on dopamine metabolism

Male OFA rats (150–200 g) were used both for acute and subchronic experiments. The animals are maintained under 12 hour periods of light and dark. The animals are sacrificed always between 11.00 and 13.00 h. The brains are excised immediately, dissected on ice according to the method of GLOWINSKI and IVERSEN, J. Neurochem. 13, 655 (1966), frozen on dry ice and the tissue samples stored at −80° C. until analysis.

Dopamine and its metabolites DOPAC (3,4-dihydroxyphenylacetic acid) and HVA (homovanillic acid) are determined in brain tissue extracts which are obtained by homogenisation of the stored brain tissue samples in 0.1N HCl containing 0.05 mM ascorbic acid and subsequent centrifugation. Striatal and cortical tissues are used.

The determination of the metabolites is performed using either the gas chromatography/mass fragmentography (GCMS) technique as described by KAROUM et al., J. Neurochem. 25, 653 (1975) and CATABENI et al., Science 178, 166 (1972) or the fluorometric method as described by WALDMEIER and MAITRE, Analyt. Biochem. 51, 474 (1973). For the GCMS method, tissue extracts are prepared by adding known amounts of deuterated monoamines and their respective metabolites as internal standards.

Dopamine metabolism in striatum is increased following the administration of compounds A and B and racemate C (This property is a consequence of the acetylcholine accumulation provoked by said compounds). However compound A is more active than compound B and racemate C in enhancing the striatal dopamine metabolite concentration.

Muscarinic and nicotinic effects on brain glucose utilisation

Changes in the functional activity of the CNS are associated with altered deoxyglucose (DOG) utilisation in the brain which can be visualised simultaneously in several brain regions using the autoradiographic method of Sokoloff et al., J. Neurochem. 28, 897 (1977). The administration of cholinergic drugs either direct (muscarinic agonists) or indirect (accumulation of acetylcholine) induces in this model a characteristic "fingerprint" pattern by modifying the regional glucose metabolism.

Male Wistar rats (150–200 g) are used. Drugs are administered at various doses and by different routes (i.v., p.o., i.p.) to animals. [14C]-2-deoxyglucose (125 μC/kg) is injected 45 min. before the animals are sacrificed. The brains are immediately excised, frozen at −80° C. and subsequently cut in slices with a thickness of 20 μm. The optical densities of the radiographic images are measured according to a modification of Sokoloff et al.

After p.o. application of compounds A and B (7.5 μmol/kg) significant changes in DOG utilisation in various rat brain regions are observed. The effect of compound A is more potent than that of compound B during the initial 30 minutes. The most marked changes are found in the visual regions and the anteroventral thalamus and also in the lateral habenula mucleus.

Acetylcholine levels in different rat brain regions

The effects of compounds A and B and racemate C as AChE inhibitors in vivo is determined by measuring the levels of ACh in different regions of rat brain at various times after drug administration.

OFA rats (200–230 g) are used. The animals are killed by microwave irradiation focused on the head (6 kW operating power 2450 Mhz exposure 1.7 sec., Pueschner Mikrowellen-Energietechnik, Bremen). The brains are removed dissected according to Glowinski and Iversen (1966) and stored at −70° C. until analysis. The brain parts are homogenized in 0.1M perchloric acid containing internal deuterated standards of ACh-d_4 and Ch(choline)-d_4. After centrifugation, endogenous ACh and Ch together with their deuterated variants are extracted with dipicrylamine (2,2',4,4',6,6'-hexanitrodiphenylamine) in dichlormethane as ion pairs. The Ch moities are derivatized with propionyl chloride and the resulting mixture of ACh and propyl choline derivatives are demethylated with sodiumbenzenethiolate and analyzed by mass-fragmentography according to Jenden et al. Anal. Biochem., 55, 438–448, (1973).

A single application of 25 μmol/kg p.o. increases ACh concentrations in striatum, cortex and hippocampus. The maximal effect is achieved about 30 min. after oral application and declines during the next 3–4 hours. In cortex and hippocampus the ACh levels are still significantly higher at 4 hours compared to controls. The effects are dose dependent. The influence of compound B is significantly weaker than that induced by racemate C, and the influence of racemate C is significantly weaker than that induced by compound A.

Furthermore the compounds according to the invention are indicated to be well tolerated and orally active, and they have a long duration of action, e.g. in the above and other standard tests.

The compounds according to the invention are therefore useful for the treatment of senile dementia, Alzheimer's

disease, Huntington's chorea, tardive dyskinesias, hyperkinesia, mania, acute confusion disorders, Down's syndrome and Friedrich's ataxia.

For these indications, the appropriate dosage will, of course, vary depending upon, for example, the compound according to the invention employed, the host, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in animals are indicated to be obtained at daily dosages from about 0.01 to about 10 mg/kg, e.g. about 0.1 to about 5 mg/kg animal body weight. In larger mammals, for example humans, an indicated daily dosage is in the range from about 0.1 to about 25 mg, e.g. about 0.1 to about 5 mg of a compound according to the invention, conveniently administered, for example, in divided doses up to four times a day.

The compounds according to the invention may be administered by any conventional route, in particular enterally, preferably orally, e.g. in the form of tablets or capsules, or parenterally, e.g. in the form of injectable solutions or suspensions.

The above mentioned compound A is the preferred compound for the above mentioned indications. The preferred indication is senile dementia.

The present invention also provides pharmaceutical compositions comprising a compound according to the invention in association with at least one pharmaceutical carrier or diluent. Such compositions may be manufactured in conventional manner. Unit dosage forms contain, for example, from about 0.025 to about 12.5 mg of a compound according to the invention. Conveniently an acid addition salt form is used. The preferred salt form is compound A, especially for orally administrable forms, e.g. from the point of view of stability.

In the following example, the temperatures are uncorrected and are in degrees centigrade.

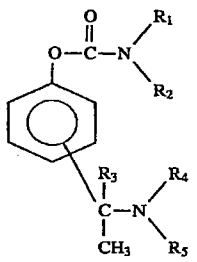
EXAMPLE 1

(S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methyl-phenyl-carbamate

130 g of (±)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methyl-phenylcarbamate and 210 g of (+)-di-0,0'-p-toluoyl tartaric acid monohydrate are dissolved while heating in 1.3 liter of methanol/water (2:1). The salt precipitated after cooling is filtered and recrystallised 3 times from methanol/water (2:1). The (S)-enantiomer is released by partitioning between 1N NaOH and ether. $[\alpha]D_D^{20}=-32.1°$ (c=5 in ethanol).

The hydrogen tartrate of the title compound (from ethanol) melts at 123°–125°. $[\alpha]_D^{20}=+4.7°$ (c=5 in ethanol).

The present invention furthermore provides the systemic transdermal application of the phenyl carbamates of formula I',



I'

wherein

R_1 is hydrogen, lower alkyl, cyclohexyl, allyl or benzyl,

R_2 is hydrogen, methyl, ethyl or propyl, or

R_1 and R_2 together with the nitrogen to which they are attached form a morpholino or piperidino radical,

R_3 is hydrogen or lower alkyl,

R_4 and R_5 are the same or different and each is a lower alkyl, and the dialkylaminoalkyl group is in the meta, ortho or para position,

in free base or pharmaceutically acceptable acid addition salt form.

The compounds of formula I' and their pharmaceutically acceptable acid addition salts as well as their preparation and their use as acetylcholinesterase inhibitors are known from the above mentioned European patent application 193,926.

The compounds of formula I' include for example the above defined compound A and racemate C.

It has now surprisingly been found that the compounds of formula I' in free base or pharmaceutically acceptable acid addition salt form, hereinafter referred to as compounds for administration according to the invention, exhibit unexpectedly good skin penetration when administered percutaneously.

The penetration through the skin of the compounds for administration according to the invention may be observed in standard in vitro or in vivo tests.

One in vitro test is the well known diffusion test which may be effected according to the principles set out in GB 2098865 A and by T. J. Franz in J. Invest. Dermatol. (1975) 64, 194–195. Solutions containing the active agent in unlabelled or radioactively labelled form are applied to one side of isolated pieces of intact human skin or hairless rat skin about 2 cm^2 in area. The other side of the skin is in contact with physiological saline. The amount of active agent in the saline is measured in conventional manner, e.g. by HPLC or spectrophotometric techniques, or by determining the radioactivity.

In this test using rat skin the following penetration rates, for example, have been found:

Above defined compound A: 23.6±14.9%

Compound of formula I in free base form: 28.0±8.2%

Moreover it has been found that transdermal administration of the compounds for administration according to the invention induces a long-lasting and constant inhibition of acetylcholinesterase activity as indicated in standard tests, with a slow onset of action, which is particularly advantageous with respect to the tolerability of these compounds.

For example the acetylcholinesterase inhibition in different rat brain regions ex vivo has been measured after transdermal administration of the compounds for administration according to the invention, and compared to the inhibition obtained after administration via different routes.

The compounds are dissolved in or diluted with n-heptane to a concentration of 1 or 3 mg/20 µl. Male rats (OFA strain, ca. 250 g) are shaved in the neck region and the solution is applied with a micropipette on the skin. The application place is immediately covered using a thin plastic film and a plaster. The animal has no access to the plaster. Various times after the administration the animals are killed by decapitation and the remaining AChE activity is measured.

Transdermal administration of the above defined compound A, for example, induces a long-lasting, dose-dependent inhibition of AChE activity. In contrast to the rapid onset of the effect after either oral or subcutaneous application (max. 15 and 30 min. respectively), the AChE inhibition occurs slowly after this application route (max.>2

hours) without affecting the brain region selective AChE inhibition.

The results are shown in the following table 2. Twenty four hours after transdermal application, the AChE activity is still inhibited in central and peripheral regions. After the same time, orally applied compound A has no effect on the enzyme, whereas after the s.c. application only the enzyme in the heart is significantly inhibited.

TABLE 2

Time after Treatment	n	AChE activity in % of controls ± SD Cortex	Hippocampus	Striatum	Pons/Medulla	Heart	Blood
Transdermal 30 μmol/kg							
0.5 hours	6	86.1 ± 5.6	86.7 ± 5.9	89.7 ± 8.4	91.5 ± 3.8	109.0 ± 9.3	71.3 ± 12.3
6 hours	6	42.4 ± 11.7	45.7 ± 15.0	65.9 ± 15.5	53.6 ± 13.3	52.0 ± 13.1	41.9 ± 13.1
24 hours	6	73.8 ± 5.7	80.4 ± 8.8	81.0 ± 8.2	85.3 ± 4.2	63.9 ± 12.5	78.1 ± 17.8
Oral 10 μmol/kg							
0.5 hours	6	21.0 ± 3.5	19.7 ± 3.8	32.9 ± 10.7	26.6 ± 4.0	71.2 ± 11.2	34.0 ± 2.0
6 hours	6	65.3 ± 21.3	62.0 ± 15.4	87.5 ± 8.8	80.3 ± 9.2	101.0 ± 7.0	77.2 ± 14.7
24 hours	6	99.2 ± 8.9	97.2 ± 7.1	96.7 ± 3.3	104.1 ± 6.8	94.2 ± 9.2	97.2 ± 13.8
Subcutaneous 8 μmol/kg							
0.5 hours	6	16.8 ± 2.0	18.3 ± 3.1	28.2 ± 12.2	20.9 ± 2.9	33.3 ± 5.6	17.4 ± 4.1
6 hours	6	85.1 ± 1.6	81.4 ± 7.6	82.9 ± 2.8	87.1 ± 4.1	51.0 ± 17.9	79.5 ± 8.2
24 hours	6	93.8 ± 5.9	99.9 ± 9.9	91.0 ± 2.3	98.7 ± 6.0	65.7 ± 21.2	105.7 ± 16.8

Control values (pmole/mg × min. ± SD n = 15):
Cortex: 3.67 ± 0.30
Hippocampus: 4.42 ± 0.30
Striatum: 33.8 ± 3.08
Pons/Medulla: 7.98 ± 0.36
Heart: 2.27 ± 0.39
Blood: 311.4 ± 44.2

Thus in another aspect the present invention provides a pharmaceutical composition for systemic transdermal administration incorporating as an active agent a compound of formula I' in free base or pharmaceutically acceptable acid addition salt form.

In a further aspect the present invention provides a method of systemically administering an active agent of formula I' in free base or pharmaceutically acceptable acid addition salt form which comprises administering the active agent to the skin.

The active agents may be administered in any conventional liquid or solid transdermal pharmaceutical composition, e.g. as described in Remington's Pharmaceutical Sciences 16th Edition Mack; Sucker, Fuchs and Spieser, Pharmazeutische Technologie 1st Edition, Springer and in GB 2098865 A or DOS 3212053 the contents of which are incorporated herein by reference.

Conveniently the composition is in the form of a viscous liquid, ointment or solid reservoir or matrix. For example the active agent is dispersed throughout a solid reservoir or matrix made of a gel or a solid polymer, e.g. a hydrophilic polymer as described in European Patent Application No. 155,229.

The active agent may be incorporated in a plaster.

The compositions for transdermal administration may contain from about 1 to about 20% by weight of active agent of formula I' in free base or pharmaceutically acceptable acid addition salt form.

The pharmaceutical compositions for transdermal administration may be used for the same indications as for oral or intravenous administration. The amount of pharmaceutically active agent to be administered will individually depend on the drug release characteristics of the pharmaceutical compositions, the drug penetration rate observed in in vitro and in vivo tests, the potency of active agent, the size of the skin contact area, the part of the body to which the unit is stuck, and the duration of action required. The amount of active agent and area of the pharmaceutical composition etc. may be determined by routine bioavailability tests comparing the blood levels of active agents after administration of the active agent in a pharmaceutical composition according to the invention to intact skin and blood levels of active agent observed after oral or intravenous administration of a therapeutically effective dose of the pharmacologically active agent.

Given the daily dose of a drug for oral administration, the choice of a suitable quantity of drug to be incorporated in a transdermal composition according to the invention will depend upon the pharmacokinetic properties of the active agent, including the first pass effect; the amount of drug which can be absorbed through the skin from the matrix in question for a given area of application and in a given time; and the time for which the composition is to be applied. Thus, a drug with a high first pass effect may require a relatively low quantity in the transdermal composition when compared with the oral daily dose, since the first pass effect will be avoided. On the other hand, generally a maximum of only approximately 50% of the drug in the matrix is released through the skin in a 3 day period.

The pharmaceutical compositions of the invention in general have for example an effective contact area of drug reservoir on the skin of from about 1 to about 50 square centimeters, preferably about 2 to 20 square centimeters, and are intended to be applied for from 1–7 days, preferably 1–3 days.

Compound A may for example be administered at a dose of 10 mg in a patch of ca. 10 cm^2, once every three days.

The following example illustrates the invention.

EXAMPLE 2

Preparation of a Transdermal Composition Containing a Hydrophilic Polymer

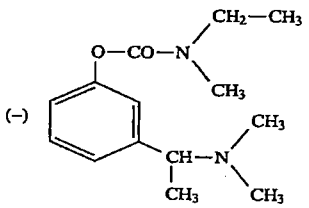
Composition	
Compound of formula I', e.g. compound A	20%
Hydrophilic polymer, e.g. Eudragit E 100*	30%
Non swellable acrylate polymer, e.g. Durotack 280–2416**	44%
Plasticizer, e.g. Brij 97***	6%

*Registered Trade Mark, available from Röhm, Darmstadt, W. Germany
**Registered Trade Mark, available from Delft National Chemie Zutphen, Netherlands
***Registered Trade Mark, available from Atlas Chemie, W. Germany

The components are added to acetone or ethanol or another appropriate volatile organic solvent and mixed to give a viscous mass. The mass is spread on top of an aluminised polyester foil (thickness 23 microns) using a conventional apparatus, to produce a film of thickness 0.2 mm when wet. The film is allowed to dry at room temperature over 4 to 6 hours. The aluminium foil is then cut up into patches about 10 sq cm in area.

What we claim is:

1. The (S)-[N-ethyl-3-[(1-dimethylamino)ethyl]-N-methyl-phenyl-carbamate] enantiomer of formula I substantially free of its (R) isomer



I

in free base or acid addition form.

2. The compound of claim **1** which is the hydrogen tartrate salt of (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methyl-phenylcarbamate.

3. A pharmaceutical composition which comprises a compound of claim **1** in free base or pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.

4. A method of treating senile dementia, which comprises administering a therapeutically effective amount of a compound of claim **1** in free base or pharmacologically acceptable acid addition salt form to a subject in need of such treatment.

5. A method of treating Alzheimer's disease, which comprises administering a therapeutically effective amount of a compound of claim **1** in free base or pharmacologically acceptable acid addition salt form to a subject in need of such treatment.

6. A method of treating Huntington's chorea, tardive dyskinesias, hyperkinesia, mania, acute confusion disorders, Down's syndrome or Friedrich's ataxia, which comprises administering a therapeutically effective amount of a compound of claim **1** in free base or pharmacologically acceptable acid addition salt form to a subject in need of such treatment.

7. A method of systemically administering a compound of claim **1** in free base or pharmaceutically acceptable acid addition salt form, which comprises administering the active agent transdermally through the skin.

8. A systemic transdermal pharmaceutical composition according to claim **3** comprising a therapeutically effective amount of (S)-N-ethyl-3-[(1-dimethyl-amino)ethyl]-N-methyl-phenyl-carbamate in free base or pharmaceutically acceptable acid addition salt form, and a pharmaceutically acceptable carrier therefor suitable for systemic transdermal administration.

9. A systemic transdermal pharmaceutical composition according to claim **3** comprising a therapeutically effective amount of the hydrogen tartrate salt of (S)-N-ethyl-3-[(1-dimethyl-amino)ethyl]-N-methyl-phenyl-carbamate, and a pharmaceutically acceptable carrier therefor suitable for systemic transdermal administration.

10. A systemic transdermal pharmaceutical composition according to claim **8** in which the (S)-N-ethyl-3-[(1-dimethyl-amino)ethyl]-N-methyl-phenyl-carbamate is in free base form.

11. A systemic transdermal pharmaceutical composition according to claim **8** in which the pharmaceutically acceptable carrier is a transdermal patch.

12. A method according to claim **7** in which the compound is in free base form.

* * * * *