CONVENTION

AUSTRALIA

Patents Act 1990

NOTICE OF ENTITLEMENT 674130

We, **THE GOVERNMENT OF THE UNITED STATES OF AMERICA AS REPRESENTED BY THE SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES** of 200 Independence Avenue, Washington, D.C. 20201, United States of America state the following in connection with Australian Application No. 27544/92:

1. We are the nominated person.

2. The nominated person is the assignee of the actual inventors.

3. The nominated person is the assignee of the applicants of the basic applications listed in the declaration under Article 8 of the PCT.

4. The basic applications are the applications first made in a Convention country in respect of the invention.

Dated: 12 April 1994

By **PHILLIPS ORMONDE & FITZPATRICK**
Patent Attorneys for the Applicant
By:

David B Fitzpatrick
.....

To: The Commissioner of Patents

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Our Ref: 365025

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(54) Title
SUBSTITUTED PHENSERINES AND PHENYLCARBAMATES OF (-)-ESEROLINE, (-)-N1-NORESEROLINE, AND (-)-N1-BENZYLNORESEROLINE; AS SPECIFIC INHIBITORS OF ACETYLCHOLINESTERASE

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(56) Prior Art Documents
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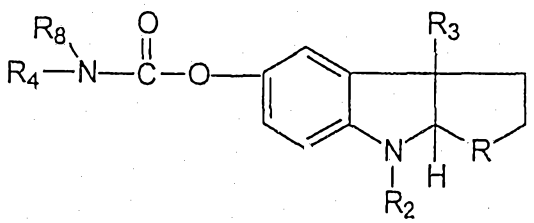
(57) Claim

1. A compound according to the Formula I

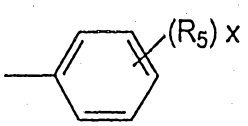
(I)



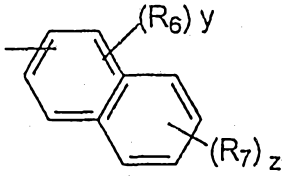
wherein R is -O- and

R_2 and R_3 are independently selected from H or -C_1- C_{10}-alkyl;

R_4 is



or



.../2

wherein

R_5 is a halogen

R_6 and R_7 are independently selected from H, halogen or -C_1-C_{10}-alkyl,

x is an integer from 1-5,

y is 0 or an integer from 1-3,

z is 0 or an integer from 1-4; and

R_8 is H or -C_1-C_{10}-alkyl;

including isomeric forms, and

pharmacologically acceptable salts.

12. A method for treating cholinergic disorders comprising administration of an effective amount of a compound according to any one of claims 1-10 to a mammal in need of such treatment.

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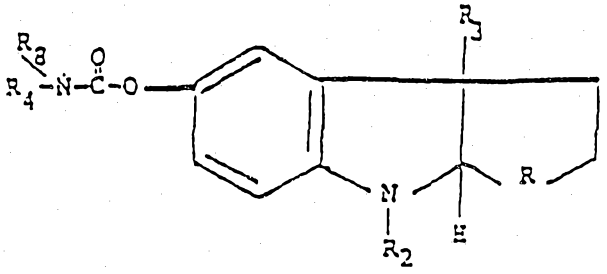

(I)

(57) Abstract

The present invention relates to substituted phenylcarbamate or naphthylcarbamate tricyclic compounds of formula (I), wherein R is -O- or NRi, which provide highly potent and selective cholinergic agonist and blocking activity and their use as pharmaceutical agents. The invention further relates to improvements in therapy relative to cholinergic diseases such as glaucoma, Myasthenia Gravis, Alzheimer's disease and to improvements in therapy and organophosphate poisoning. The invention further provides for a selective acetylcholinesterase and butyrylcholinesterase agents and a method for inhibiting these esterases.

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SUBSTITUTED PHENSERINES AND PHENYLCARBAMATES OF (-)-ESEROLINE, (-)-N1-NORESEROLINE, AND (-)-N1-BENZYLNORESEROLINE; AS SPECIFIC INHIBITORS OF ACETYLCHOLINESTERASE

Technical Field

The present invention relates to improvements in the treatment of diseases, and more particularly to compounds which exhibit selective inhibition of acetylcholinesterase and butyrylcholinesterase.

Background Art

Physostigmine, also called eserine, and particular derivatives of physostigmine are anti-cholinesterase inhibitors which are well known. Such well known compounds are also useful in the treatment of glaucoma, Myasthenia Gravis, Alzheimer's disease and as antidotes against poisoning with organophosphates.

Physostigmine was introduced into England in 1840 by Daniell (a British medical officer) in the form of the Calabar bean. The compound itself was first isolated by Jobst and Hesse in 1864. Physostigmine has been used as a treatment for glaucoma, and to reverse atropine-induced coma during the last century. Recent uses for this compound and its derivatives have been as effective antidotes to several drugs which possess central anti-cholinergic properties.

During the last two decades, studies related to the acetylcholine-receptor-ion-channel complex (AChR)

of the neuromuscular junction have provided significant increases in knowledge of the receptor function. This membrane receptor has been readily available for study since nicotinic AChRs occur at very high densities in Torpedo and Electrophorus electric organs. Further, the understanding of the morphology and function of this receptor has been increased significantly by specific chemical probes for the different active sites of the receptor.

Nearly 20 years ago a significant discovery was made which helped in the study of this AChR. Alpha-bungarotoxin (Alpha-PGT) was obtained from snake venoms which binds irreversibly and specifically to the acetylcholine (ACh) recognition site on the nicotinic AChR. Alpha-PGT was such a highly selective probe that researchers were able to isolate and purify the different sub-units which comprise the nicotinic AChR. The sub-units were functionally reconstituted into artificial lipid membranes and were ultimately cloned.

Further sites on the nicotinic AChR were soon made available by the discovery of another class of toxins. These toxins were called histrionicotoxins and were isolated from the skin secretion of frogs in the family Dendrobatidae. The new sites available because of the histrionicotoxins were discovered to be responsible for the allosteric alterations or non-competitive blockage of neuromuscular transmission. These sites are distinct from the against recognition site discovered through the alpha-PGT probe and are thought to be located on the ion channel component of the AChR.

Further, other drugs demonstrate the ability to modify non-competitively the activation of the AChR. Examples of such drugs are distinct and well known

pharmacological agents which act on the peripheral nervous system as well as in the central nervous system. In particular, tricyclic anti-depressants, phenothiazine antipsychotics, the hallucinogenic agent Phencyclidine (PCP), local anesthetics, antimuscarinics, anticholinesterase agents and similar compounds to mention but a few.

Further ways for studying AChR are available due to microscopic kinetic models and biochemical rapid mixing methods to study permeability changes initiated by the binding of agonist molecules and conformational transitions of nicotinic receptor molecules.

The agonist recognition site at the nicotinic ACh receptor has been reported as having strong stereo-specificity. This conclusion is based on the study of optical isomers of certain semi-rigid agonists, see for example Spivak et al., Mol. Pharmacol., Vol. 23, pages 337-343 (1983).

Conversely, the ion channel sites are apparently not stereospecific. This conclusion is based on the similar quantitative and qualitative actions of enantiomers of perhydrohistrionicotoxin at the nicotinic AChR, see for example Spivak et al, FEBS Lett. Vol. 163, pages 189-193 (1983).

It has been discovered that the natural isomer of physostigmine has blocking properties as well as agonist properties at the neuromuscular AChR. By contrast (+)-physostigmine shows only negligible inhibition of cholinesterase (ChE). See Brossi et al., FEBS Lett., Vol. 201, pages 190-192 (1986).

Even though (+)-physostigmine has only negligible ChE inhibitory activity it is every effective as a protective pretreatment drug against multiple lethal

doses of sarin, see Albuquerque et al, Fundam. Appl. Caltoxicol., Vol. 5, pages 182-203 (1985). The observed beneficial protection appears to be due to direct interactions of the carbamates with the postsynaptic nicotinic AChR. The protective effectiveness of the carbamates against organophosphates appears to be related to the direct ability of the carbamates to decrease the hyperactivation caused by accumulation of the neurotransmitter.

The above information, available due to the research in this field, is important in the evaluation of potential new pharmacological agents for treating cholinergic disorders, for example, Myasthenia Gravis and Alzheimer's disease. Potential agents can be evaluated for potency in vitro by testing the agents against electric eel acetylcholinesterase (AChE) and human plasma butyrylcholinesterase (BChE).

Of the two enzymes known to hydrolyze acetylcholine (ACh) in vivo, AChE, which is found in red blood cells, in the brain and in nerve tissues, seems to be more specific than BChE which is found in serum, pancreas and in the liver. It, however, has not previously been shown in the art that compounds which selectively inhibit one of the two enzymes more than the other would offer a medical advantage. The natural alkaloid (-)-physostigmine, its potential metabolite (-)-(N1)-norphysostigmine, and the natural alkaloid physovenine which are used as biological standards in this art area inhibit AChE and BChE in vitro similarly at similar concentrations.

Accordingly, there is need in the art for highly selective agents active against one of AChE and BChE and not very potent against the other which may lead to

better treatment of a particular cholinergic disorder and minimize negative side effects. Such compounds would be of great of medical importance in the treatment of cholinergic disorders.

Summary of the Invention

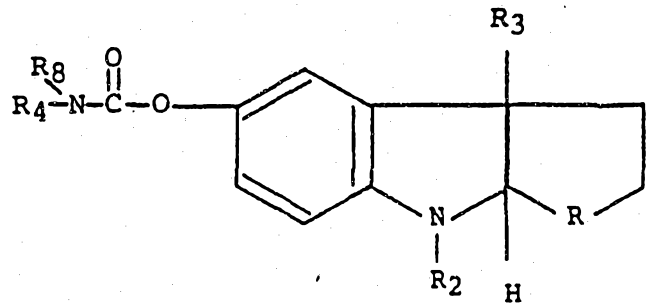
It is an object of the present invention to overcome the difficulties in the prior art as set forth in the background of the invention.

It is another object of the present invention to provide highly potent and selective cholinergic agonist and blocking compounds.

It is a further object of the present invention to provide improvements in therapy relative to cholinergic diseases such as glaucoma, Myasthenia Gravis, Alzheimer's disease, and organophosphate poisoning.

It is a still further object of the present invention to provide compounds with selective acetylcholinesterase and butyrylcholinesterase activity.

It is a yet further object of the present invention to provide compounds having the following formula:

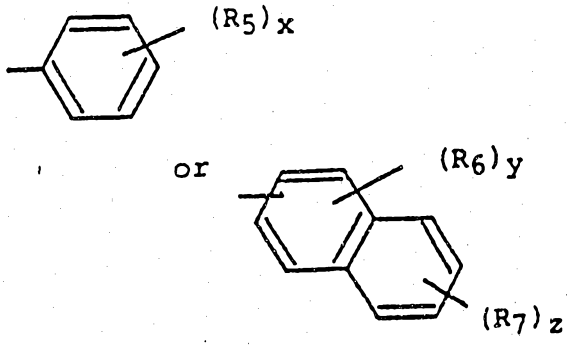


I

wherein and
~~wherein~~ R is -O- ~~or the group -N(-R1)- and~~
~~R1 is H or a -C1-C10-alkyl group;~~

R_2 and R_3 are independently selected from H or $-C_1-C_{10}$-alkyl;

R_4 is



wherein is a halogen
R_5, R_6 and R_7 are independently selected from H, halogen or $-C_1-C_{10}$-alkyl;

x is ~~0 or~~ an integer from 1-5,

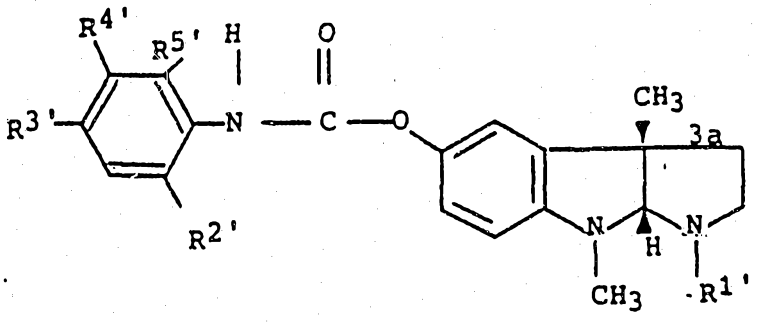
y is 0 or an integer from 1-3, and

z is 0 or an integer from 1-4; and

R_8 is H or C_1-C_{10}-alkyl;

including isomeric forms and pharmaceutically acceptable salts.

It is a still further object of the present invention to provide compounds having the following formula VIII :



VIII

wherein $R^{1'}$ is ~~H, a CH_3 group or~~ a benzyl group;

$R^{2'}$ is ~~H or~~ straight or branched chained C_1-C_{10} alkyl;

$R^{3'}$ is H or straight or branched chained C_1-C_{10} - alkyl;

and

$R^{4'}$ and $R^{5'}$ are independently hydrogen or $R^{4'}$ and $R^{5'}$ taken together along with the carbon atoms to which they are attached form a 6-membered aromatic hydrocarbon ring;

including isomeric forms and pharmaceutically acceptable salts.

Throughout the description and claims of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises", is not intended to exclude other additives, integers or process steps.

~~wherein $R^{1'}$ is H, a $-CH_3$ group or a benzyl group;~~
$R^{2'}$ is H or straight or branched chained C_1-C_{10} alkyl;
$R^{3'}$ is H or straight or branched chained C_1-C_{10}-alkyl;
and

$R^{4'}$ and $R^{5'}$ are independently hydrogen or $R^{4'}$ and $R^{5'}$ taken together along with the carbon atoms to which they are attached form a 6-membered aromatic hydrocarbon ring;

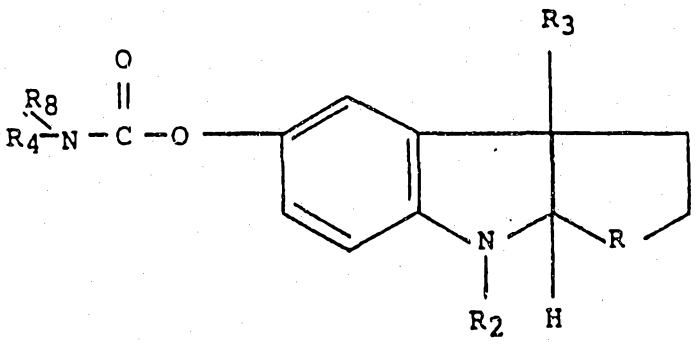
~~including isomeric forms and pharmaceutically acceptable salts.~~

Brief Description of the Figure

Figure 1 illustrates the time-dependent inhibiiton of plasma AChE in a rat host by physostigmine and its 2',4'-dimethylphenyl carbamate.

Description of Preferred Embodiments

In accordance with this invention there are disclosed compounds of the formula



I

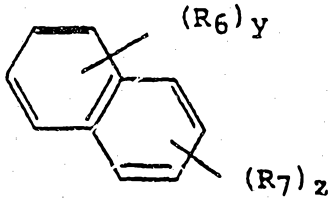
wherein R is -O- or the group $-N(-R_1)-$ and

R_1 is H or a $-C_1$-C_{10}-alkyl group:

wherein R is -O- and

R_4 is

or



wherein is a halogen

R_5, R_6 and R_7 are independently selected from H, halogen or $-C_1-C_{10}$-alkyl,

x is ~~0 or~~ an integer from 1-5,

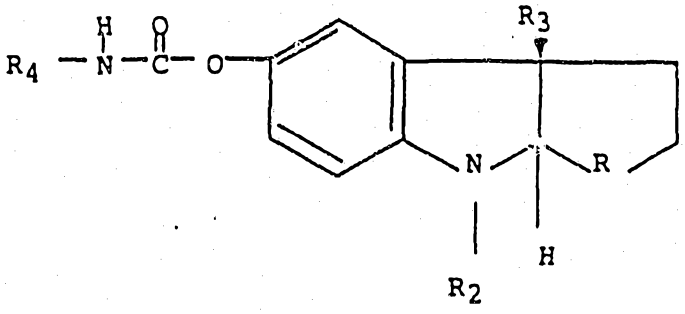
y is 0 or an integer from 1-3, and

z is 0 or an integer from 1-4, and

R_8 is H or $-C_1-C_{10}$-alkyl;

including isomeric forms and pharmaceutically acceptable salts.

Preferred are compounds according to Formula I having the Formula II:



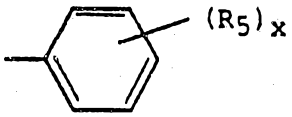
II

wherein R is -O- and ~~or the group -N(-R1)- and~~

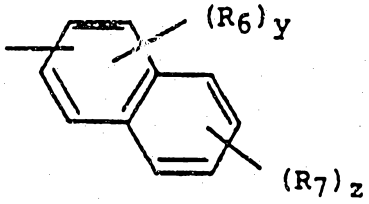
~~R1 is H or a -C1-C10 alkyl group;~~

R_2 and R_3 are independently selected from H, halogen or $-C_1-C_{10}$-alkyl; and

R_4 is



or



wherein

R_5, R_6, and R_7 are independently selected from H, ~~halogen~~ or $-C_1-C_{10}$-alkyl,

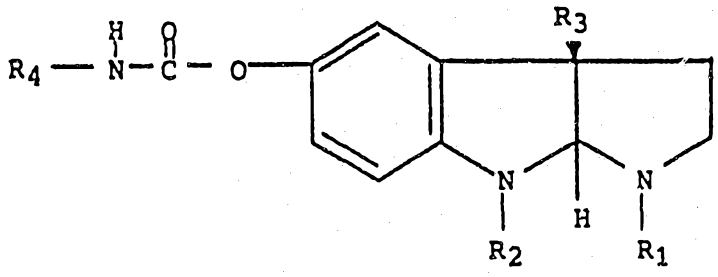
x is ~~0 or~~ an integer from 1-5,

y is 0 or an integer from 1-3, and

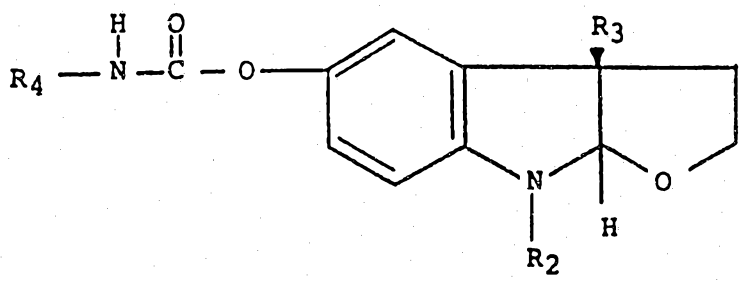
z is 0 or an integer from 1-4;

including isomeric forms and pharmaceutically acceptable salts.

Further preferred are compounds according to Formula II having the following Formula III and IV:

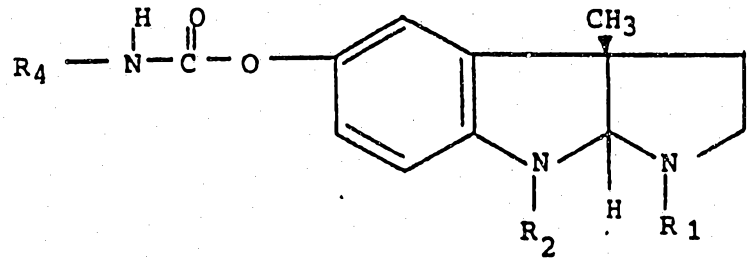


III

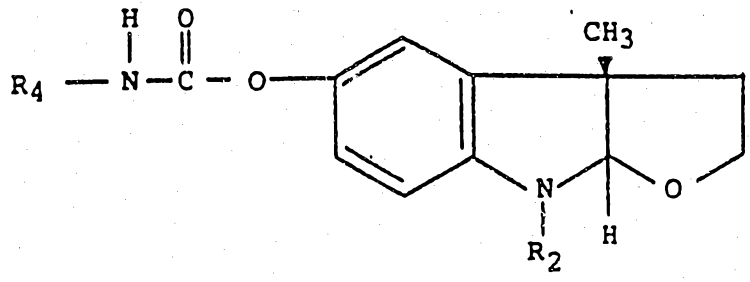


IV

Still further preferred are compounds according to Formulas III and IV having the following Formula V and VI:

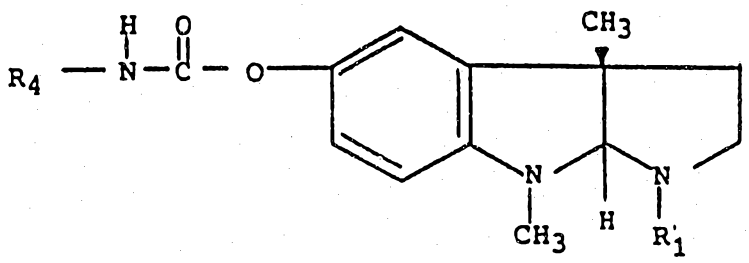


V



VI

Yet further preferred are compounds according to Formula V having the following Formula VII

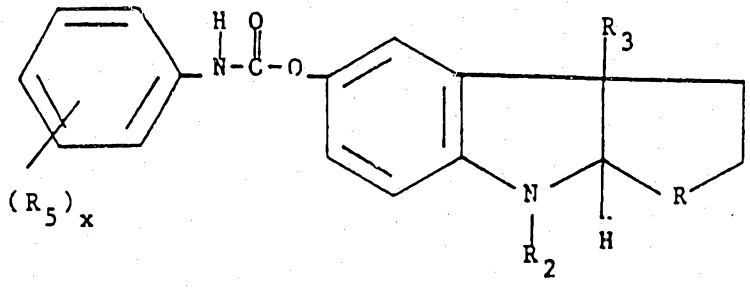


VII

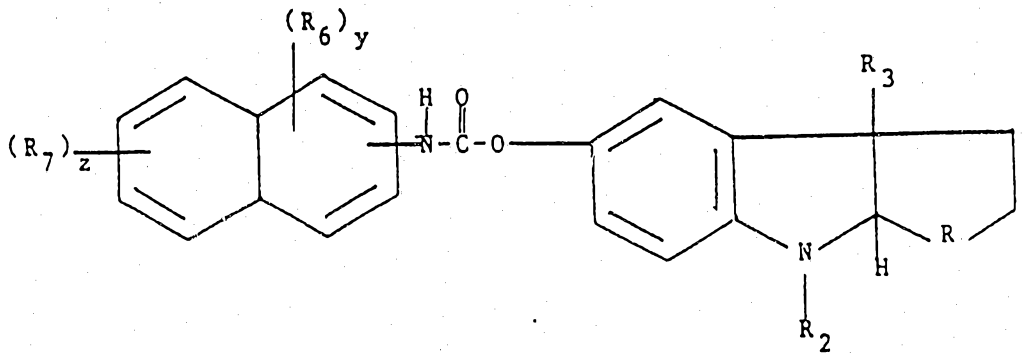
R_1-R_7 structures (where present) in the above Formulae III-VII are the same substituents defined above for Formula II.

Still further preferred are compounds of Formulae I-VII wherein x, y and z are 1 or 2. Even more preferred are compounds wherein x is 1 or 2 and R_5 is in the ortho and/or paraposition on the benzene ring. Particularly preferred R_5 groups are H, halogen and C_1-C_5 alkyl. Even more preferred R_5 groups are H, chloro, $-CH_3$, $-CH_2-CH_3$, $-CH_2-CH_2-CH_3$ and $-CH(-CH_3)_2$.

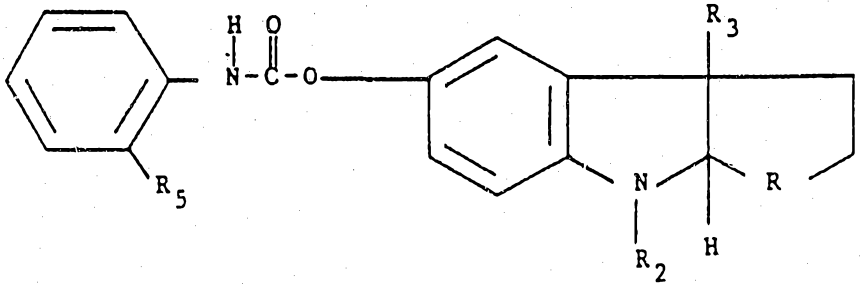
Preferred structures are set forth below wherein the main formula Roman numeral is further indicated with a lower case a, b, c or d in order to describe preferred groups for the R_4 substituent on each of the main formula which the Roman numerals alone represent, e.g., Ia-Id, IIa-IId, etc.:



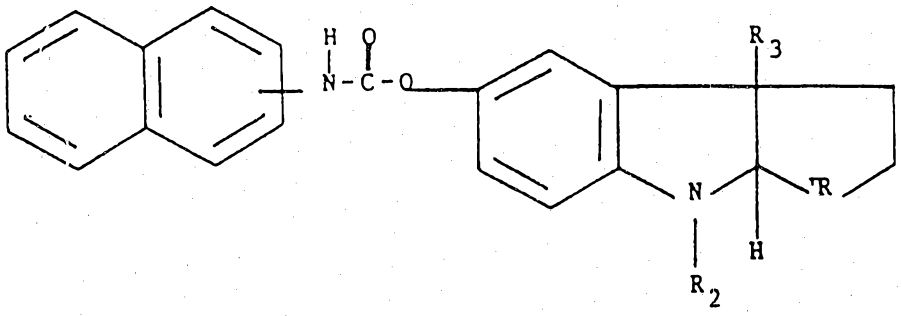
Ia



Ib



Ic



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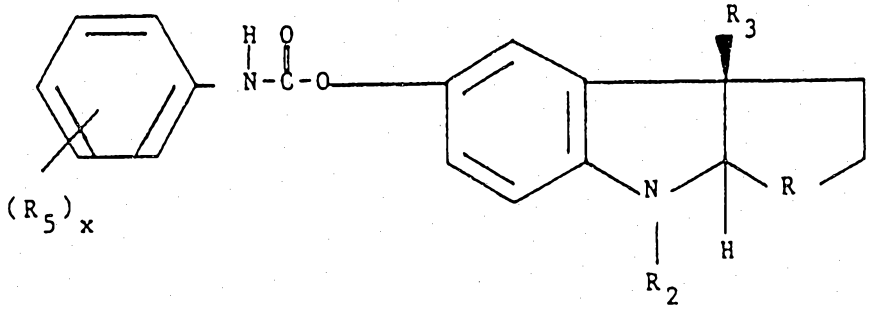
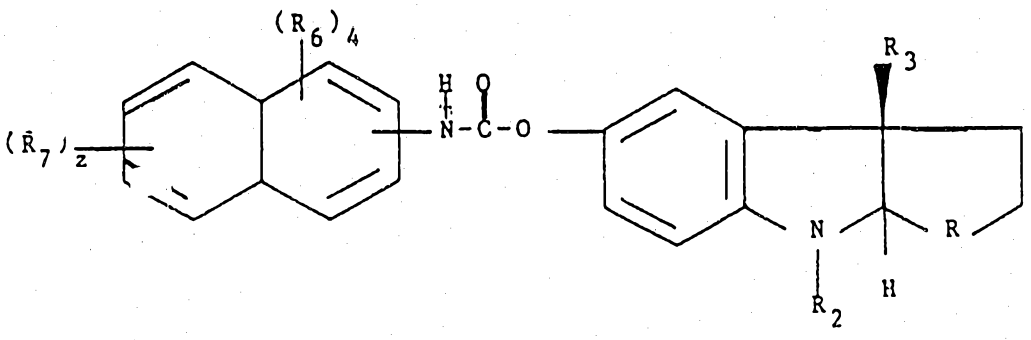
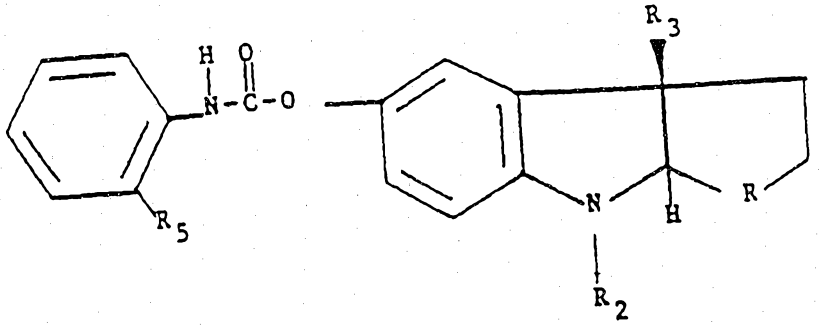


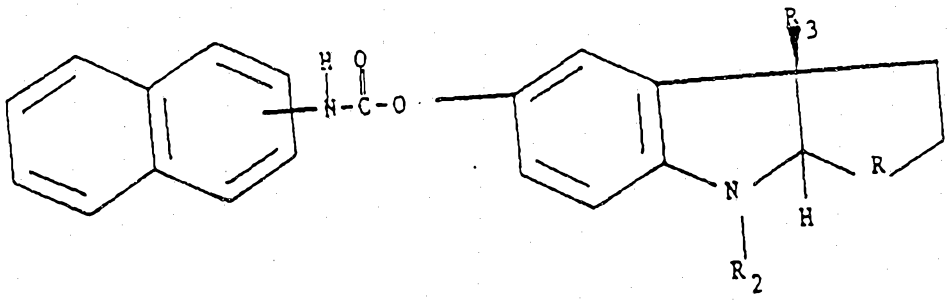
IIa



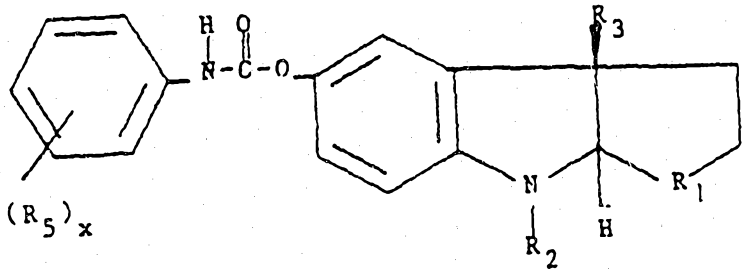
IIb



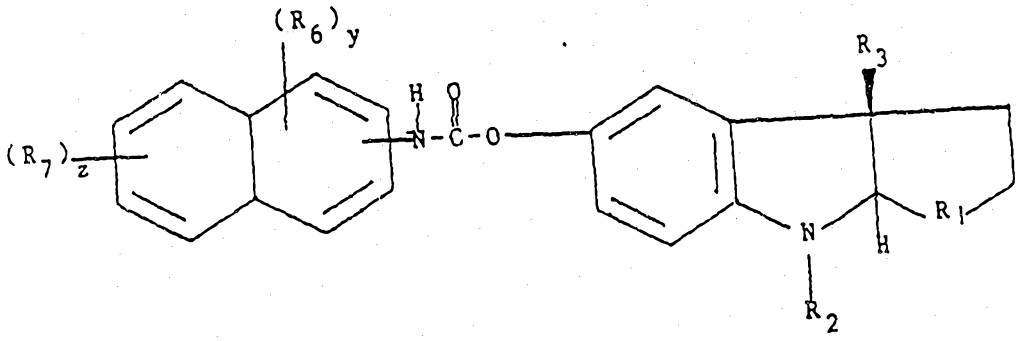
IIc



IId



IIIa



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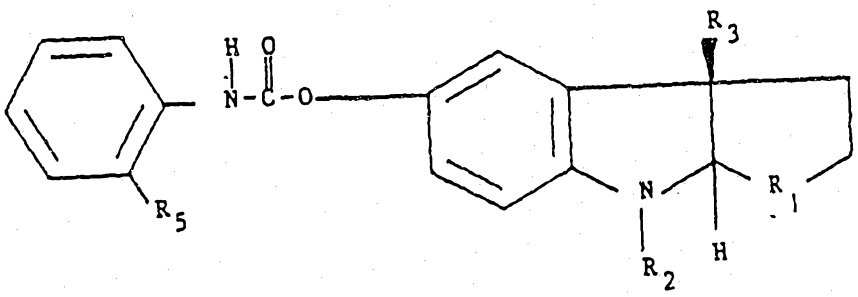
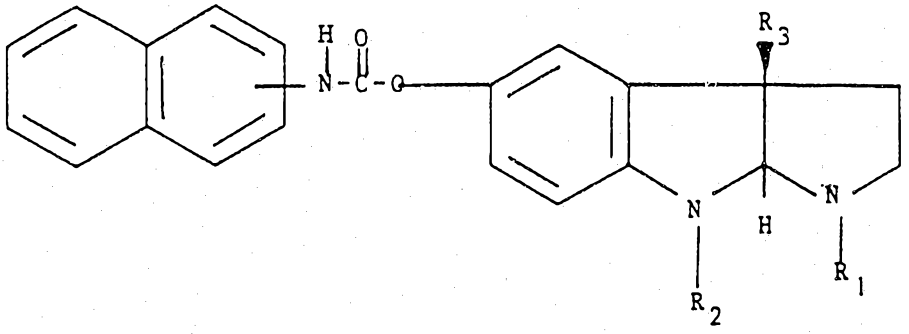
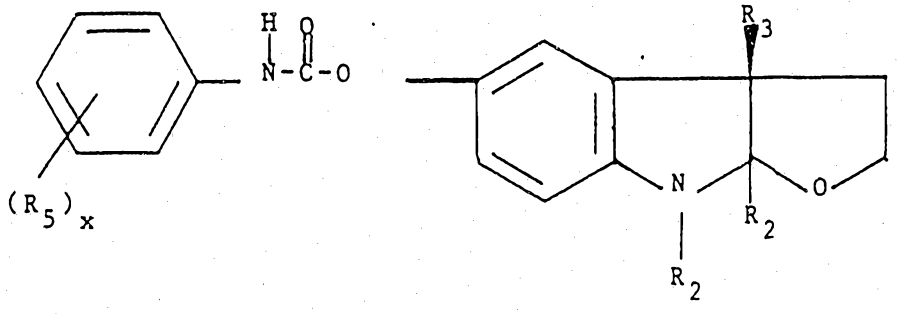


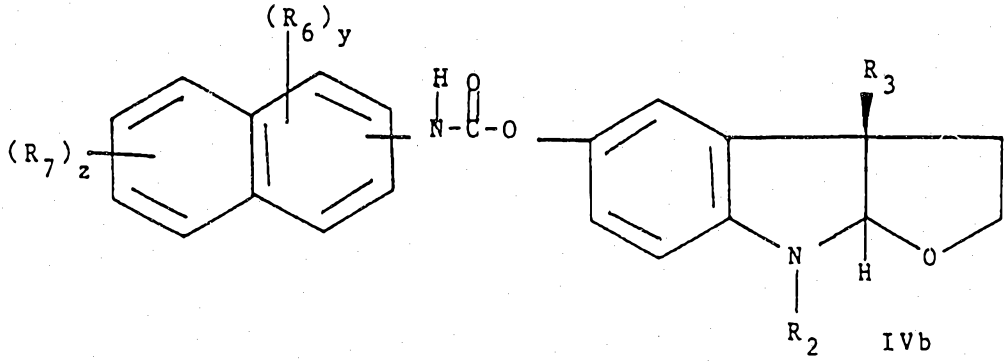
IIIc



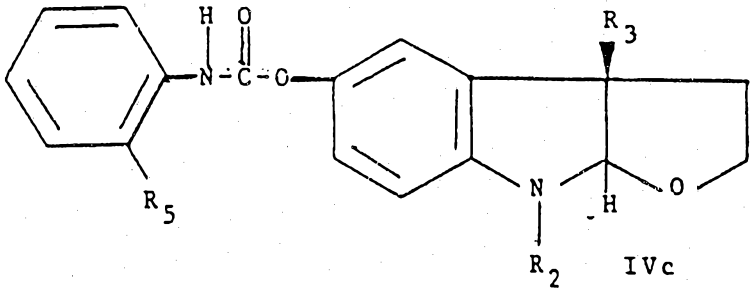
IIId



IVa

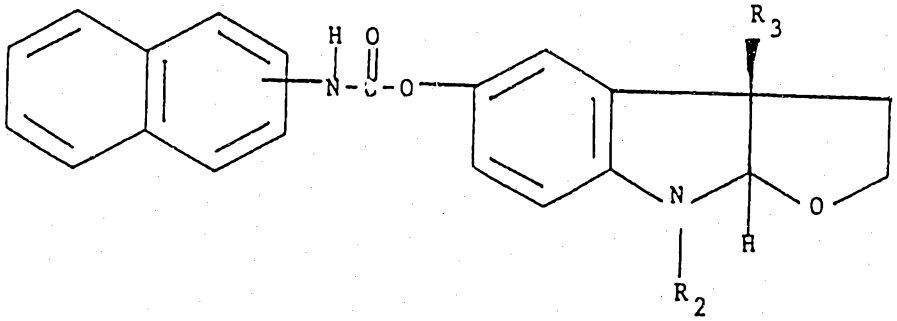


IVb

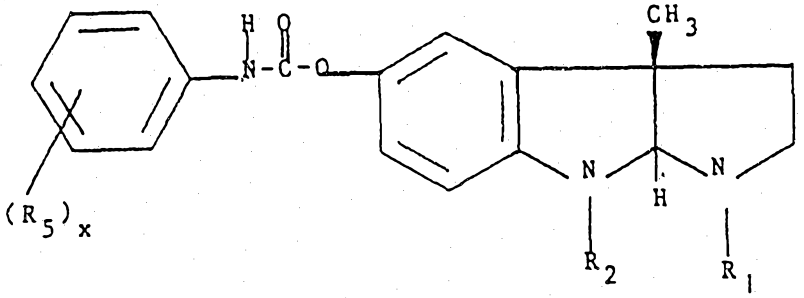


IVc

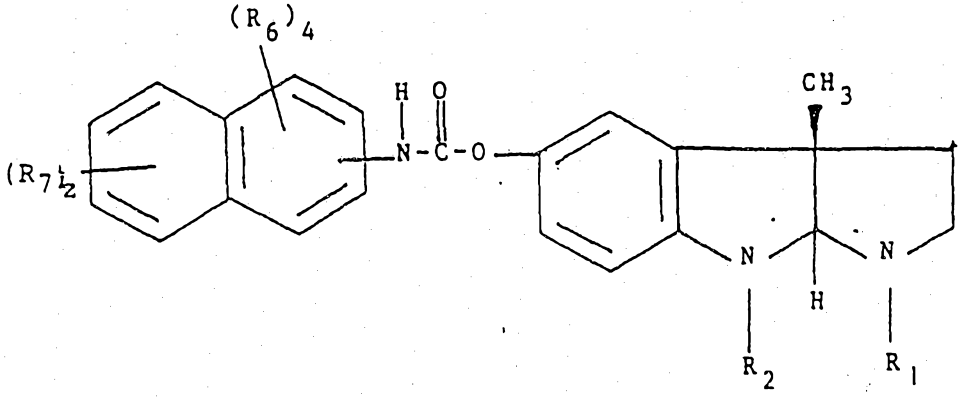
ar



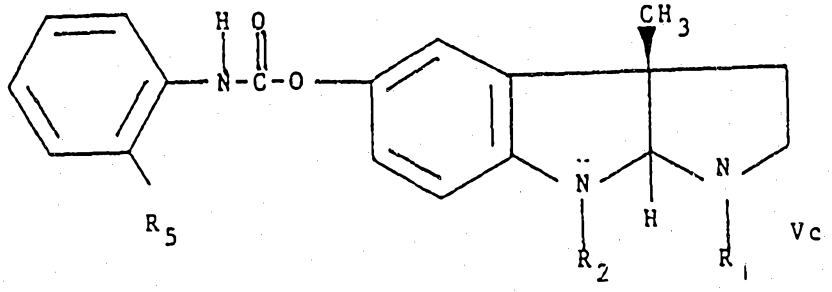
IVd



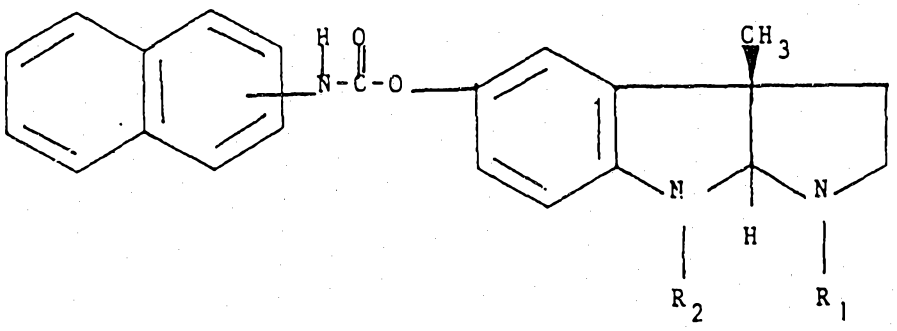
Va



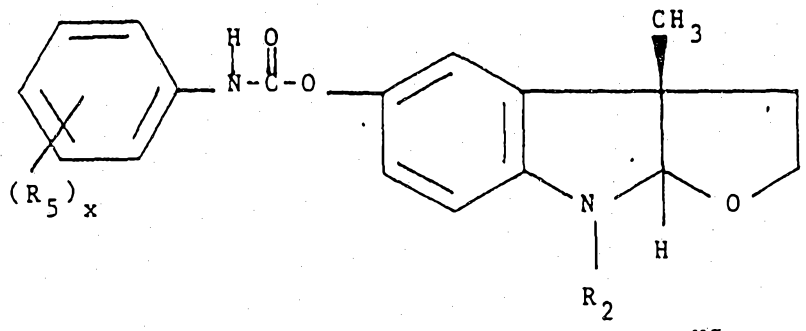
Vb



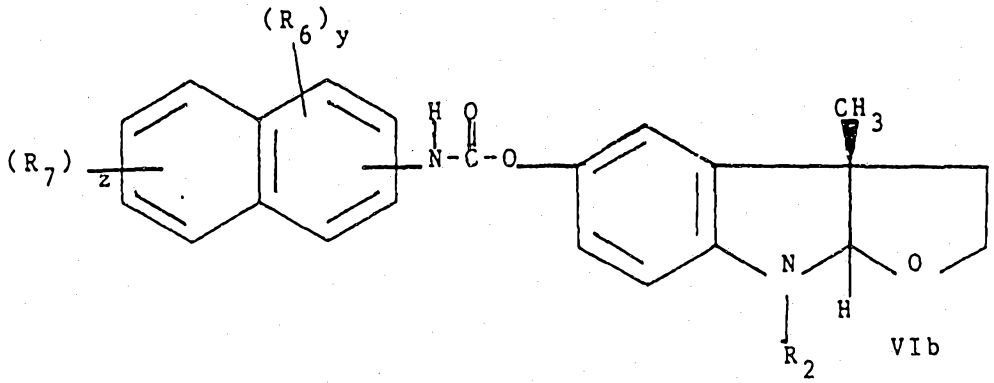
Vc



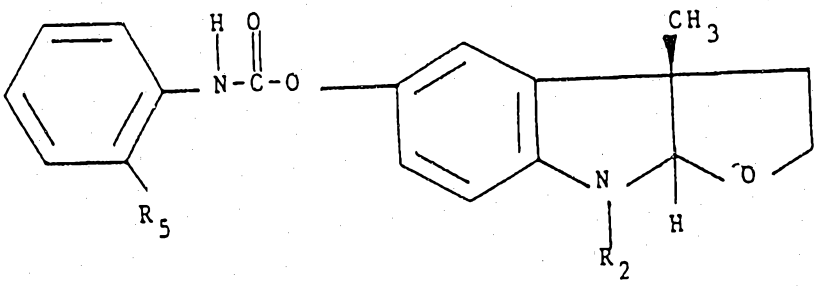
Vd



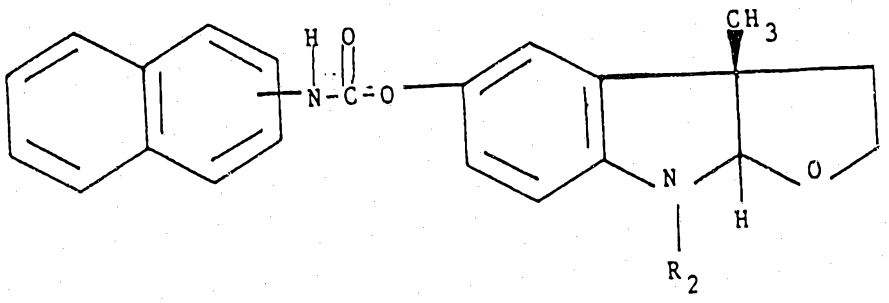
VIa



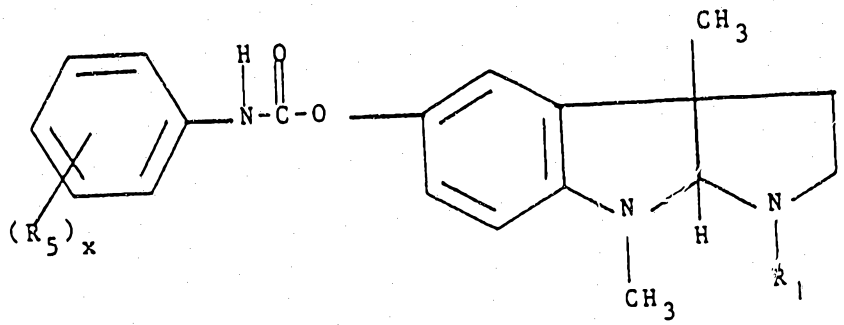
VIb



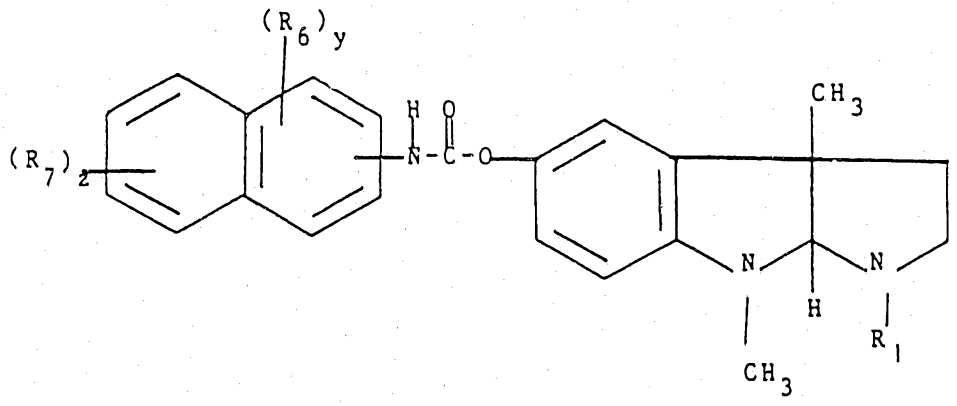
VIc



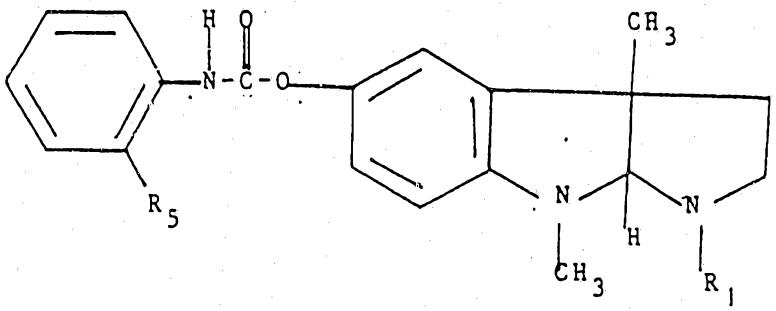
VId



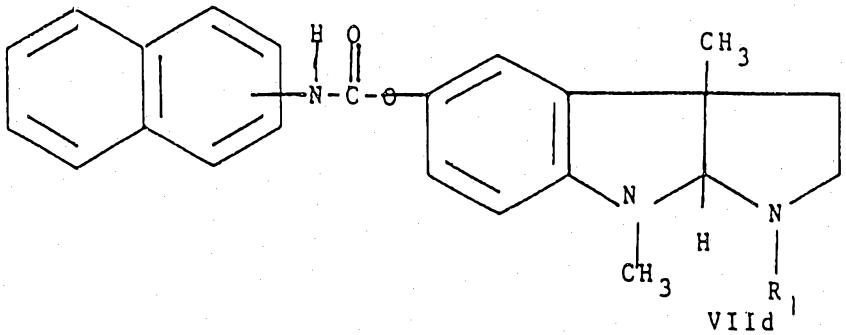
VIIa



VIIb

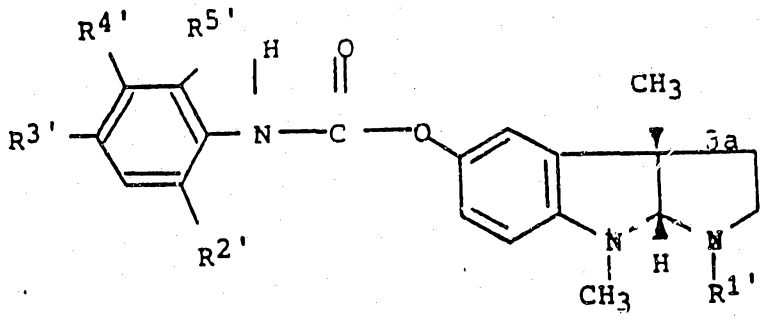


VIIc



VIId

Also, in accordance with this invention there are disclosed compounds of the formula VIII



wherein $R^{1'}$ is ~~H, a CH_3 group or~~ a benzyl group;

$R^{2'}$ is straight or branched chained C_1-C_{10}-alkyl;

$R^{3'}$ is H or straight or branched chained C_1-C_{10}-alkyl; and

$R^{4'}$ and $R^{5'}$ are independently hydrogen or R^4 and R^5 taken together along with the carbon atoms to which they are attached form a 6-membered aromatic carbocyclic ring;

including isomeric forms and pharmaceutically acceptable salts. Acceptable salts are salts such as tartrates, fumarates, phosphates, salicylates, and the like.

Preferred are compounds of Formula VIII, wherein $R^{4'}$ and $R^{5'}$ are both hydrogen.

Even more preferred are compounds wherein $R^{3'}$ is hydrogen and $R^{2'}$ is C_1-C_{10}-alkyl. Yet more preferred is where these two groups are independently $-CH_3$, $-CH_2-CH_3$, $-CH_2-CH_2-CH_3$ and $-CH(-CH_3)_2$.

The above Formula VIII compounds are eseroline and (1) N-noreseroline carbamates having high potency in the inhibition of acetylcholinesterase and butyryl-cholinesterase. Some of the carbamates were more specific for AChE, whereas others were more highly specific for BChE.

Also preferred are compounds according to the present invention in isomeric forms and pharmaceutically acceptable salts thereof. Pharmaceutically acceptable salts can be, for example, the alkali metal, alkali earth and ammonium salt. Further, pharmaceutically acceptable organic and inorganic acid addition salts may be used. Other examples of acceptable salts are tartrates, fumarates, phosphates, salicyclates, and the like.

The compounds according to Formula I have asymmetric carbon atoms and can exist as optical isomers. For the purpose of this invention, the racemic mixtures and dextro and laevo forms are included within the present invention. Hence, the particular dextro and laevo rotatory form or a particular isomer is sometimes indicated as a preferred optical isomer in particular formulae according to the invention.

Other cholinesterase inhibitors are known in the prior art. Physostigmine and physovenine are optically active alkaloids with a (3aS)-absolute configuration at the chiral carbon atom C(3a). Both of these compounds are potent inhibitors of cholinesterases in vitro and in vivo, blocking the conversion of acetylcholine into choline reversibly. Physostigmine has been found to have useful medical applications in disorders which result in a malfunction of this process.

Surprisingly, the carbamates according to the present invention have shown high potency. Thus, phenylcarbamate derivatives according to the present invention are longer lasting and appear to be less toxic than other carbamate analoges in this art.

Accordingly, the present compounds represent a significant advancement in the prior art.

Further, the above compounds according to the invention are useful as highly potent and selective cholinergic agonist and blocking pharmaceutical agents. Hence, the compounds of the present invention are useful in pharmaceutical compositions for systemic administration to human and animals in unit dosage forms, such as tablets, capsules, pills, powders, granules, suppositories, sterile parenteral solutions or suspensions, sterile non-parenteral solutions or suspensions, oral solutions or suspensions, oil and water or water in oil emulsions and the like, containing suitable quantities of the active ingredient. Topical application can be in the form of ointments, creams, lotions, jellies, sprays, douches, and the like. For oral administration either solid or fluid unit dosage forms can be prepared with the compounds of Formula I.

Compositions within the scope of the invention include compositions wherein the active ingredient is contained in an effective amount to achieve its intended purpose. The compounds can be administered in any pharmaceutically acceptable amount, for example, in amounts ranging from 0.001 gram to about 1 gram per kilogram of body weight. Based on the information which is presented herein, determination of effective amounts is well within the skill of the ordinary practitioner in the art. The compounds are generally useful in pharmaceutical compositions (wt%) of the active ingredient with a carrier or vehicle in the composition in about 0.1 to 99 wt% and preferably about 25-85 wt%.

Either fluid or solid unit dosage forms can be readily prepared for oral administration. For example, the compounds of Formula I can be admixed with conventional ingredients such as dicalcium phosphate, magnesium aluminum silicate, magnesium stearate, calcium sulfate, starch, talc, lactose, acacia, methyl cellulose and functionally similar materials as pharmaceutical excipients or carriers. The compounds according to the invention can also be administered as water soluble salts such as salicylates, oxalates, and such like. A sustained release formulation may optionally be used. Capsules may be formulated by mixing the compound with a pharmaceutical diluent which is inert and inserting this mixture into a hard gelatin capsule having the appropriate size. If soft capsules are desired a slurry of the compound with an acceptable vegetable, light petroleum or other inert oil can be encapsulated by making into a gelatin capsule.

Suspensions, syrups and elixirs may be used for oral administration of fluid unit dosage forms. A fluid preparation including oil may be used for oil soluble forms. A vegetable oil such as corn oil, peanut oil or safflower oil, for example, together with flavoring agents, sweeteners and any preservatives produces an acceptable fluid preparation. A surfactant may be added to water to form a syrup for fluid unit dosages. Hydro-alcoholic pharmaceutical preparations may be used having an acceptable sweetener, such as sugar, saccharin or a biological sweetener and a flavoring agent in the form of an elixir.

Pharmaceutical compositions for parenteral and suppository administration can also be obtained using techniques standard in the art.

A preferred use of the compounds according to the invention is as pharmaceutical agents suitable for oral administration. Another preferred use of the compounds is in transdermal parenteral cholinergic agonist and blocking pharmaceutical preparations, which are particularly useful in treating cholinergic disorders such as glaucoma, Myasthenia Gravis, Alzheimer's disease, and organophosphate poisoning. Accordingly, compositions suitable for administration to these areas are particularly included within the invention. The above parenteral solutions or suspensions may be administered transdermally and, if desired, a more concentrated slow release form may be administered. The above parenteral solutions or suspensions may be delivered with a skin patch. If desired these solutions or suspensions may be given by injection in an appropriate vehicle such as sesame oil.

Accordingly, incorporation of the active compounds and a slow release matrix may be implemented for administering transdermally. The compounds may be administered transdermally at about .01 to 99% of the composition and preferably about 25 to 85 wt% of the active ingredient in the vehicle or carrier.

Transdermal therapeutic systems are self-contained dosage forms that, when applied to intact skin, deliver drug(s) at a controlled rate to the systemic circulation. Advantages of using the transdermal routing include: enhanced therapeutic efficacy, reduction in the frequency of dosing, reduction of side effects due to optimization of blood-concentration vs.

time profile, increased patient compliance due to elimination of multiple dosing schedules, bypassing the hepatic "first pass" metabolism, avoiding gastro-intestinal incompatibilities and providing a predictable and extendable duration of activity. However, the main function of the skin is to act as a barrier to entering compounds. As a consequence, transdermal therapy has been preferred for a limited number of drugs that possess the desirable physiochemical properties for diffusion across the skin barrier. One effective method of overcoming the barrier function of the skin is to include a penetration enhancer in the formulation of the transdermal therapeutic system.

The penetration enhancer is a chemical compound that, when included in a formulation, temporarily increases the permeability of the skin to a drug line allowing more of the drug to be absorbed in a shorter period of time. Several different types of penetration enhancers have been reported such as dimethylsulfoxide, n-decylmethylsulfoxide, N,N-dimethylacetamide N,N-dimethylformamide, 1-dodecylazacycloheptane-2-one (Azone), propylene glycol, ethanol, pyrrolidones such as N-methyl-2-pyrrolidone (NMP) and surfactants.

The above compounds can be present in the reservoir alone or in combination with pharmaceutical carriers. The pharmaceutical carriers acceptable for the purposes of this invention are the art known carriers that do not adversely effect the drug, the host, or the material comprising the drug delivery device. Suitable pharmaceutical carriers include sterile water; saline; dextrose; dextrose in water or saline; condensation products of castor oil and

ethylene oxide combining about 30 to 35 moles of ethylene oxide per mole of castor oil; liquid acid; lower alkanols; oils such as corn oil; peanut oil; sesame oil and the like, with emulsifiers such as mono- or di-glyceride of a fatty acid; or a phosphatide, e.g., lecithin, and the like; glycols; polyalkylene glycols; aqueous media in the presence of a suspending agent, for example, sodium carboxymethyl cellulose; sodium alginate; poly(vinylpyrrolidone); and the like, alone, or with suitable dispensing agents such as lecithin; polyoxyethylene stearate; and the like. The carrier may also contain adjuvants such as preserving, stabilizing, wetting, emulsifying agents and the like together with the penetration enhancer and the compounds of this invention.

The effective dose for mammals may vary due to such factors as age, weight, activity level or condition of the subject being treated. Typically, an effective dosage of a compound according to the present invention is about 1 to 800 milligrams when administered by either oral or rectal dose from 1 to 3 times daily. This is about .002 to about 50 milligrams per kilogram of the subject's weight administered per day. Preferably about 10 to about 300 milligrams are administered orally or rectally 1 to 3 times a day for an adult human. The required dose is considerably less when administered parenterally, preferably about .01 to about 150 milligrams may be administered intramuscularly or transdermally, one or two times a day for an adult human.

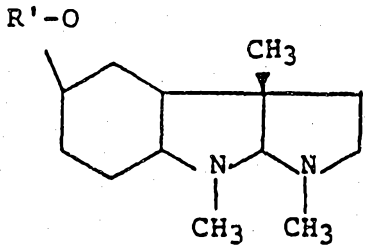
Compounds of the present invention may be administered topically at about .01 to about 99 wt% of the composition, and preferably about 25 to 85 wt%.

The present compounds are also useful in a method for treating cholinergic disorders such as glaucoma, Myasthenia Gravis, Alzheimer's disease, and as an antidote against poisoning with organo phosphates. The method according to the invention comprises some interesting effective amount of a compound according to the invention or an effective amount of a pharmaceutical composition according to the invention to a mammal in need of such treatment.

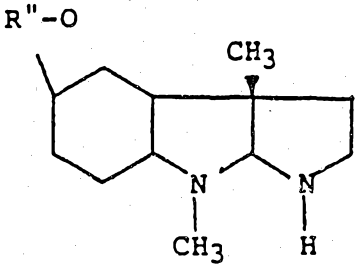
Surprisingly, the compounds according to the invention have shown selective cholinergic agonist and blocking activity. Of the two enzymes known to hydrolyze acetylcholine in vivo, acetylcholinesterase (AChE) which is found in red blood cells, in the brain, and in nerve tissues, seems to be more specific then butyrylcholinesterase (BChE) which is found in serum, pancreas and in the liver. It, however, was never shown that compounds which selectively inhibit one of the two enzymes more than the other, would offer a medical advantage.

The present invention relates to selective inhibition as follows. The natural alkaloid (-)-physostigmine, its potential metabolite (-)-(N1)-norphysostigmine and the natural alkaloid physovenine which were used as biological standards in the inhibited AChE and BChE in vitro similarly at similar concentrations.

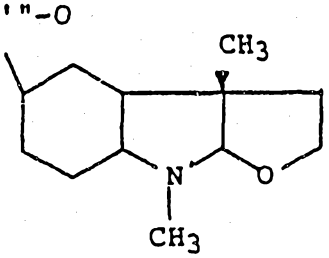
These biological standard compounds used for comparitive purposes and derivatives having protective groups have the following structures.



R' = CH_3-NH-C(=O)- 1
R' = $-CH_3$ 4



R" = -H 2
R" = $-CH_3$ 5



R'" = -H 3
R'" = $-CH_3$ 6

The above structures are also used as starting materials to produce compounds according to the present invention.

The phenylcarbamate of (-)-eseroline and referred to in the literature as phenserine, however, was determined by the present invention experimentation to inhibit AChE from human erythrocytes in vitro at a 50-times lower concentration than BChE from human plasma. Accordingly, further derivatives were made and tested.

It was discovered according to the present invention that substituting the phenyl group in para-position with a methyl group, a chlorine atom, or a methoxy group afforded derivatives which inhibited both enzymes at similar concentrations but such derivatives were considerably less potent than the biological standards described above. The phenylcarbamate of (-)-physovenol (22), also showed high preference for AChE (IC_{50} for AChE = 11, and for RChE = 700), whereas the cumylcarbamate (4'-isopropylphenylcarbamate) (24) showed a reverse enzyme specificity (AChE = 3800 and for BChE = 16.5).

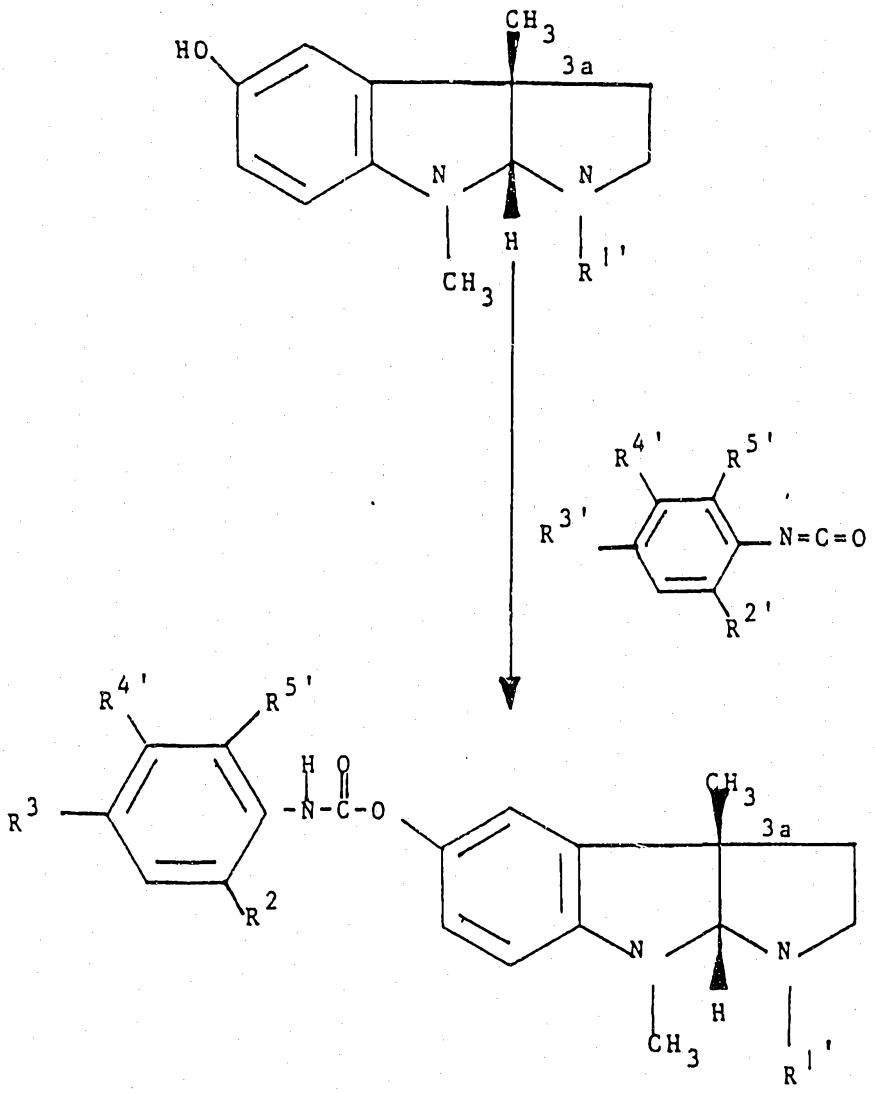
These above discoveries clearly indicated that selective inhibition of either AChE or BChE could be achieved by replacing the hydrogens on the phenyl group in phenylcarbamates with various substituents and inserting these modified phenylcarbamates on the basic core structure present in the three alkaloids that are the biological standards described above. The increased possibility of designing specifically acting inhibitors of AChE or BChE prompted an extension of these investigations and the results are the subject of the present invention.

The phenylcarbamates listed below in Table 1 and Table 2 were prepared from (-)-eseroline (4), (-)-N1)-benzylnoreseroline (5) as the N-protected equivalent of (2), and from (-)-physovenol (6) which all have the natural (3aS)-absolute configuration (these numbers for the starting materials correspond to the numbers on the comparative structures and protected derivatives, whose structures are listed just previously in the above specification).

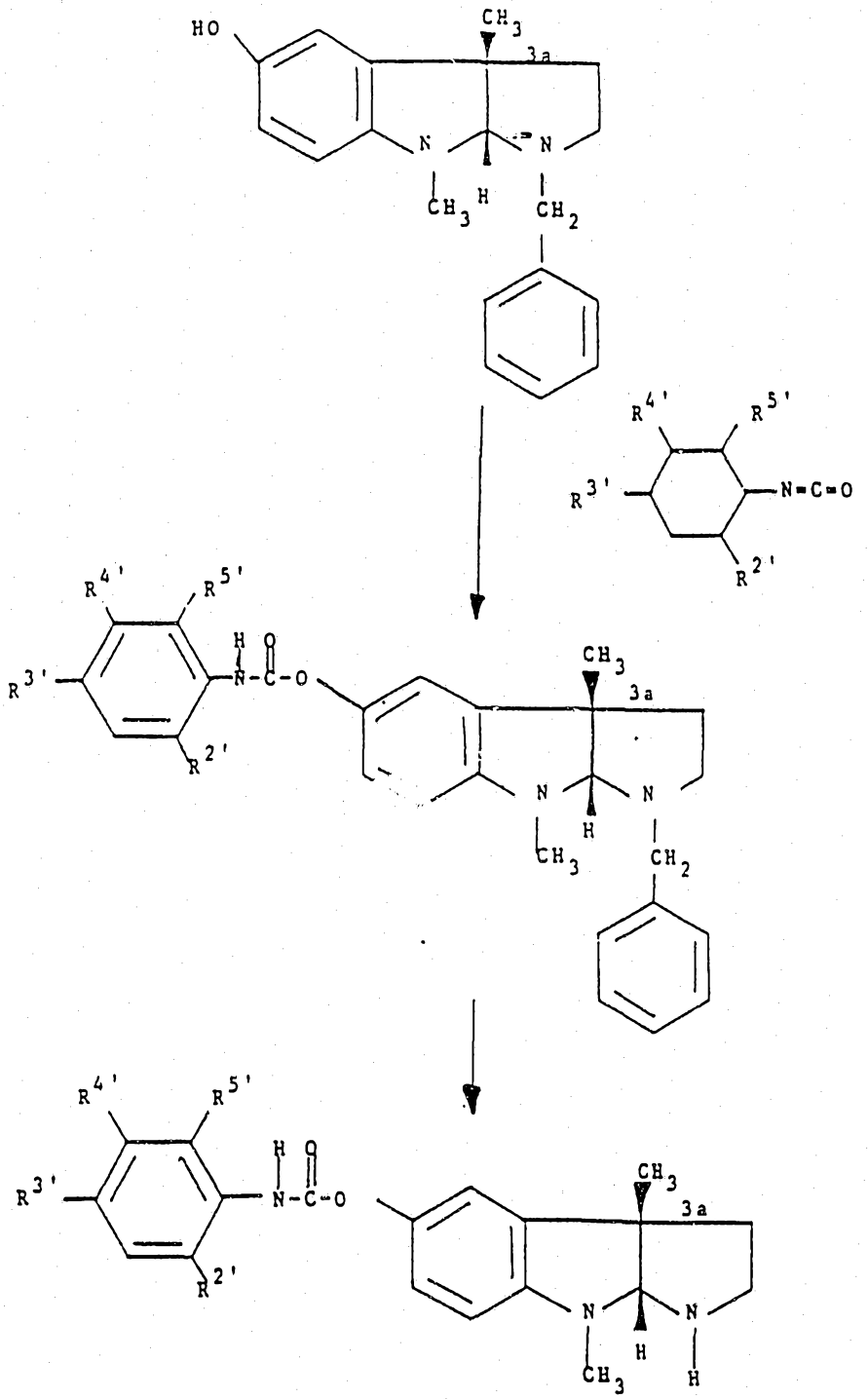
Reaction of phenols having the natural (3aS)-absolute configuration, i.e., (-)-eseroline, (-)-(N1)-noreseroline, or (-)-(N1)-benzylnoreseroline with commercially available isocyanates in dry ether and in the presence of a catalytic amount of sodium, afforded the desired carbamates. See Reaction Scheme 1, below. They were separated from "dimers", which invariably formed, by chromatography, and removed as the faster running materials. The structures of the carbamates which often were amorphous were secured by MS and ^{1}H-NMR spectra, and they were characterized by TLC-analysis and by optical rotation. Details of the preparation of the carbamates according to the present invention are given in the experimental section. Conversion of the (N1)-protected carbamates into compounds of the (N1)-series was accomplished by catalytic hydrogenation over $Pd(OH)_2$ catalyst as shown in Scheme 2 and described below.

The resulting phenylcarbamates are listed below in Tables 1-3, following the illustration of reaction Schemes 1 and 2. The phenyl carbamates of Formula VIII, which all have the natural (3aS)-absolute configuration, are listed below in Table 3.

SCHEME I

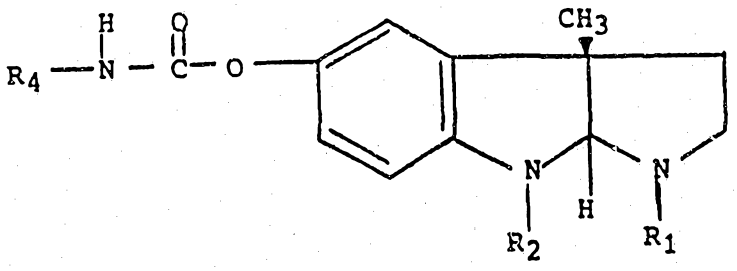


SCHEME I



~~Compounds according to the present invention~~, i.e., Compounds 7-24, are listed in Table 1 and Table 2, below.

Table 1



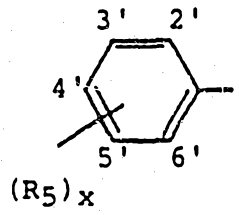
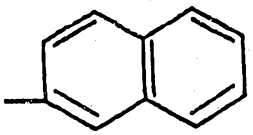
	R_4	x	R_1	R_2	R5
7		1	$-CH_3$	$-CH_3$	2'-CH_3
8	"	2	$-CH_3$	$-CH_3$	2', 4'-CH_3
9	"	1	$-CH_3$	$-CH_3$	4'-$CH(CH_3)_2$
10	"	1	$-CH_3$	$-CH_3$	4'-CH_3
11	"	2	$-CH_3$	$-CH_3$	2', 6'-CH_2-CH_3
12	"	1	$-CH_3$	$-CH_3$	2'-CH_2-CH_3
13	"	1	$-CH_3$	$-CH_3$	2'-$CH(-CH_3)_2$
14	"	1	$-CH_3$	$-CH_3$	H
15	"	3	$-CH_3$	$-CH_3$	2', 4', 6'-CH_3
16		-	$-CH_3$	$-CH_3$	-

Table 1 (Continued)

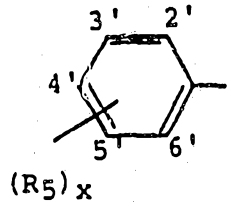
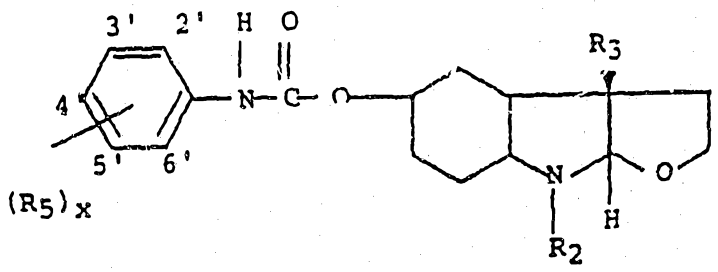
	R_4	x	R_1	R_2	R5
17		1	$-CH_3$	$-CH_3$	2'-Cl
18	"	2	$-CH_3$	$-CH_3$	2', 6'-Cl
19	"	1	-H	$-CH_3$	2'-CH_3
20	"	2	-H	$-CH_3$	2', 4'-CH_3
21	"	1	-H	$-CH_3$	4'-$CH(-CH_3)_2$

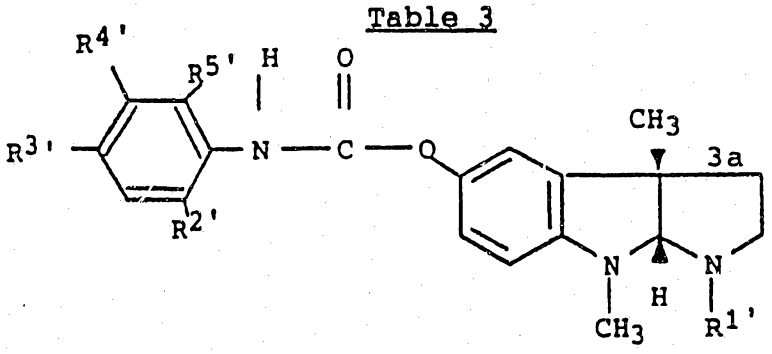
Table 2

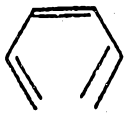


22	-O-	1	$-CH_3$	$-CH_3$	H
23	"	1	$-CH_3$	$-CH_3$	2'-CH_3
24	"	1	$-CH_3$	$-CH_3$	4'-$CH(-CH_3)_2$

~~Compounds according to the present invention~~, ~~i.e.~~, Compounds 25-38 and comparative compounds A', B', and C' are listed in Table 3, below.

Table 3



	$R^{4'}$, $R^{5'}$	$R^{1'}$	$R^{2'}$	$R^{3'}$
25.	-H,-H	$-CH_3$	$-CH_3$	-H
26.	-H,-H	$-CH_3$	$-CH_3$	$-CH_3$
27.	-H,-H	$-CH_3$	-H	$-CH(-CH_3)_2$
28.	-H,-H	$-CH_3$	$-CH_2-CH_3$	-H
29.	-H,-H	$-CH_3$	$-CH(CH_3)_2$	-H
30.		$-CH_3$	-H	-H
31.	-H,-H	$-CH_2-Ph$	$-CH_3$	-H
32.	-H,-H	$-CH_2-Ph$	$-CH_3$	$-CH_3$
33.	-H,-H	$-CH_2-Ph$	-H	$-CH(CH_3)_2$
34.	-H,-H	$-CH_2-Ph$	-H	-H
35.	-H,-H	-H	$-CH_3$	-H
36.	-H,-H	-H	$-CH_3$	$-CH_3$
37.	-H,-H	-H	-H	$-CH(CH_3)_2$
38.	-H,-H	-H	-H	-H
A'.	-H,-H	$-CH_3$	-H	$-CH_3$
B'.	-H,$-CH_2CH_3$	$-CH_3$	$-CH_2CH_3$	-H
C'.	-H,$-CH_3$	$-CH_3$	$-CH_3$	$-CH_3$

Experimental

Melting points (uncorrected): Fisher-Johns apparatus; optical rotations ($[\alpha]_D$, $CHCl_3$: Perkin-Elmer-241 MC automatic polarimeter, IR spectra (cm^{-1}, $CHCl_3$): Beckman-IR-4230 instrument, BIO-RAD FTS-45 instrument; ^1H NMR (in $CDCl_3$ with Me_4Si as internal reference, δ ppm, J Hz): Varian XL-300 MHz, Gemini 300 MHz spectrometer, MS (m/z) for chemical ionization (CI): Finnigan-1015D mass spectrometer, for electron impact (EI): V.G. Micromass 7070 mass spectrometer, for HR MS (FAB): JEOL JMS-SX 102 magnetic sector mass spectrometer thin layer chromatography (silica gel GHLF), 250 μm): Analtech Inc.; column chromatography (silica gel GHLF, 250 μm); Merck 60 (230-400 mesh); the solvent systems used for TLC analysis were the following: CH_2Cl_2/5% MeOH; CH_2Cl_2/10% MeOH; the solvent systems used for column chromatography: CH_2Cl_2/5% MeOH(A); CH_2Cl_2/10% MeOH(B).

(-)-2'-Methylphenylcarbamoyleseroline (7):

(-)-Eseroline (4) 0 (0.12 g, 0.55 mmol) was dissolved in anhydrous Et_2O (10 mL) and a small piece of Na metal was added. After stirring for about 2 min at room temperature under nitrogen, 2-methylphenylisocyanate (0.09 g, 0.70 mmol) was added dropwise. After complete addition the solvent was evaporated immediately. The residue was flash chromatographed on a silica gel column (system B) to give (7) as a foam (0.88g, 46%); $[\alpha]_D$-69.6° (c=0.5, $CHCl_3$), CI MS (m/z): 352 (M^++1); EI MS (m/z): 351 (M^+), HR MS (FAB) calcd for (M^++1) $C_{21}H_{26}N_3O_2$ 352.2025, found 352.2020, IR; 3410, 2930, 1745; ^1H NMR 1.46 (s, 3H,

C10-CH_3), 1.90-2.12 (m 2H, c3-H), 2.32 (s, 3H, Me-Ph), 2.55 (s, 3H, N1-CH_3, 2.58-2.70 (m, 2H, C2-H_2), 2.91 (s, 3H, N*-CH_3), 4.18 (s, 1H, C9-H), 6.33 (d, J = 8.4, 1H, C7-H), 6.63 (br s, 1H, N-H), 6.85-6.95 (m, 2H, C4-H, C6-H), 7.05 (t, J = 1H, C5'-H), 7.15-7.23 (m, CH, CH3'-H, C6'-H), 7.85 (br s, 1H, C4'-H).

All other carbamates: (-)-2'-4'-dimethylphenylcarbamoyleseroline (8), (-)-4'-isopropylcarbamoyleseroline (9), (-)-4'-methylphenylcarbamoyleseroline (10), (-)-2',6'-diethylphenylcarbamoyleseroline (11), (-)-2'-ethylphenylcarbamoyleseroline (12), (-)-2'-isopropylphenylcarbamoyleseroline (13), (-)-phenylcarbamoyleseroline (14), (-)-(-)-2',4',6'-trimethylphenylcarbamoyleseroline (15), naphthylcarbamoyleseroline (16), (-)-2'-chlorophenylcarbamoyleseroline (17) and (-)-2',6'-dichlorophenylcarbamoyleseroline (18) were similarly prepared from (-)-eseroline (4) with the corresponding isocyanates and showed similar IR and NMR spectra to (7). The important data for these compounds is shown in Table 4 below.

The carbamates: (-)-2'methylphenylcarbamoyl-N1-noreseroline (19), (-)-2',4'-dimethylphenylcarbamoyl-N1-noreseroline (20) and (-)-4'-isopropylphenyl-carbamoyl-N1-noreseroline (21) were similarly prepared from (-)-(N1)-benzylnoreseroline (5) instead of (4) by reacting (5) with the corresponding isocyanates. The benzyl protecting group was then removed to yield the noreseroline compound from the benzylnoreseroline compound. The important data for these compounds is shown in Table 4 below.

The following example shows the removal of a benzyl protecting group from (-)-2'-Methylphenylcarbamoyl-(N1)-benzylinoreseroline to yield compound (19).

(-)-2'Methylphenylcarbamoyl-N1-Noreseroline (19):

(-)-2'-Methylphenylcarbamoyl-(N1)-benzylinoreseroline (0.09g, 0.21 mmol) was dissolved in MeOH (10 mL), and palladium hydroxide on carbon (7 mg) was added. After hydrogenation under atmospheric pressure for 5 h, the palladium catalyst was filtered through Celite and the solvent was evaporated in vacuo. The residue was chromatographed by preparative TLC (silica gel plate 2000 μm, CH_2Cl_2/10% MeOH) to give compound (19) as a foam (0.04g, 56%): $[\alpha]_D$-62.4° (c = 0.5, $CHCl_3$), CI MS (m/z):338 (M^++1); EI MS (m/z): 337 (M^+), HR MS (EI) (M^+) calcd, for $C_{20}H_{23}N_3O_2$ 337.1790, found 337.1776 ^{1}H NMR: 1.42 (s,3H, C10-CH_3), 1.70-1.80 (m, 1H, C3-H), 1.95-2.08 (m, 1H, C2-H), 2.29 (s, 3H, C2'-CH_3), 2.70-2.80 (m, 1H, C2-H), 2.81 (s, 1H, N8-CH_3), 3.01-3.10 (ddd, J = 2.5, 2.5, 2.5, 1H, C2-H), 4.51 (s, 1H, C9-H), 6.25 (d, J = 9.0, 1H, C7-H), 6.63 (br s, 1H, N-H), 6.83-6.86 (m, 2H, C4-H, C6-H), 7.02 (t, J - 7.5, 1H, C5'-H), 7.15-7.22 (m, 2H, C3'-H, C6'-H), 7.85 (br s, 1H, C4'-H).

Compounds (20) and (21) showed similar IR and NMR spectra to compound (19), see Table III below.

(-)-5-O-(2'-Methylphenylcarbamoyl)physovenol (23):

(-)-Physovenol (6) (0.042 g. 0.20 mmol) was dissolved in anhydrous Et_2O (8 mL) and a small piece of Na metal was added. After stirring for about 2 min at room temperature under nitrogen, 2-methylphenylisocyanate (0.032 g, 0.24 mmol) was added dropwise. After complete addition the reaction mixture was

stirred at room temperature for an additional 1 h and then refluxed for 1.5 h. The solvent was evaporated and the residue was flash chromatographed on a silica gel column (system B) to give (23) as a foam (not TLC pure). This material was further purified by preparative HPLC on an Axiom silica column (5μ, 10 x 250 mm) using 1.5% MeOH in CH_2Cl_2 at a flow rate of 5 mL/min. The product thus obtained (.03 g, 43%) as a foam was TLC pure: $[\alpha]_D$-31.0° (c=1.0 $CHCl_3$), CI MS (m/z): 339 (M^++1); EI MS (m/z): 338 (M^+); IR: 3400, 2950, 1740; ^1H NMR; 1.46 (s, 3H, C10-CH_3), 1.95-2.20 (m, 2H, C3-H), 2.32 (s, 3H, C2'-CH_3), 2.91 (s, 3H, N8-CH_3), 3.40-3.55 (ddd, J = 5.3; 8.6; 11.0, 1H, C2-H), 3.98 (dt, J = 1.4; 8.6 H, C2-H), 5.10 (s, 1H, C9-H), 6.31 (d, J = 9.0, 1H, C7-H), 6.55 (br s, 1H, N-H), 6.85 (m, 2H, C4-H, C6H), 7.05 (t, J = 7.4 1H, C5'-H), 7.13 (m, 2H, C3'-H, C6'-H), 7.86 (br s, 1H, C4'-H).

Compounds (22) and (24) were produced similarly to compound (23) by substituting phenylisocyanate and 4-isopropylphenylisocyanate, respectively, for the 2-methylisocyanate in the above procedure. Compounds (22) and (24) showed similar IR and NMR spectra to compound (23).

Table 4 below lists the important physical data for compounds according to the invention. The compound numbers in Table 4 correspond to the compound numbers in Table 1 and Table 2.

TABLE 4

	$[\alpha]_D$ (°f) (c=1, $CHCl_3$)	mp(°C)	CIMS (m/z) m±+1)	HRMS m/z) calcd	(FAB) (M^+=1) (+)mmz	^1H NMR
8	-79.6	foam	366			2.28 (s,3H, C2-CH_3)
9						2.29 (s,3H, C4' -CH-(CH_3)
10	-74.2	143-145	392	$C_{21}H_{26}N_3O_2$		231 (s,3H,C4' -CH_3)
11	-36.1	oil	394	C_{24}-$H_{32}N_3O_2$ 394,2495(+0.3)		1.24 (d,J= 7.4, 6H,2-CH_2-CH_3) 2.68 (m,6H)
12	-62.8	foam	366	$C_{22}H_{18}N_3O_2$		1.26 (d, J=7.5, 3H, CH_2-CH_3), 2.55-2.78 (M,4H, C2-H -CH_2-CH_3)

TABLE 4 Cont.

14	-74.2	142-143	338		7.01 (d J = 7.4, 1H,C4'-H), 7.22 (d,J = 7.4, 2H, C3' -H,C5' -H), 734 (d,J = 7.4, 2H,C2'-H,(6'-H)
15	-55.8	foam	380		228 (3s, CH, C2', C4', C6-CH_3
16	-62.0	foam	388	$C_{28}C_{26}N_3O_2$ 3882025(-1.6)	7.51 (m, 3H), 7.69 (d,J = 8.1, 1H), 7.89 (d,J = 7.5, 1H), 7.96 (d,J = 7.9,2H)
17	-67.2	oil	372		7.02 (dJ=7.8, C4' -H)
18	-66.2	oil	406		7.19 (dJ=7.8, C4' -H), 7.39 (d,J = 7.8, C3', C5' -H)
19	-60.7 C=0.6	126-127	324(M^+)		
(24)	-54.6	167-169	397		1.24 (d,J=7.0, 2.90 (m superimposed with N-CH_3, 4H,CH-iPr)

EXAMPLE 25: (-)-2'-Methylphenylcarbamoyleseroline

(-)-Eseroline 0 (0.12 g, 0.55 mmol) was dissolved in anhydrous Et_2O (10 mL) and a small piece of Na metal was added. After stirring for about 2 min at room temperature under nitrogen, 2'-methylphenylisocyanate (0.09 g, 0.70 mmol) was added dropwise. After complete addition the solvent was evaporated immediately. The residue was flash chromatographed on a silica gel column (system B) to give (-)-2'-methylphenylcarbamoyl-eseroline as a foam (0.88g, 46%); $[\alpha]_D$-69.6° (c=0.5, $CHCl_3$), CI MS (m/z): 352 (M^++1); EI MS (m/z): 351 (M^+), HR MS (FAB) calcd for (M^++1) $C_{21}H_{26}N_3O_2$ 352.2025, found 352.2020, IR; 3410, 2930, 1745; ^1H NMR 1.46 (s, 3H, C10-CH_3), 1.90-2.12 (m 2H, c3-H), 2.32 (s, 3H, Me-Ph), 2.55 (s, 3H, N1-CH_3, 2.58-2.70 (m, 2H, C2-H_2), 2.91 (s, 3H, N*-CH_3), 4.18 (s, 1H, C9-H), 6.33 (d, J = 8.4, 1H, C7-H), 6.63 (br s, 1H, N-H), 6.85-6.95 (m, 2H, C4-H, C6-H), 7.05 (t, J = 1H, C5'-H), 7.15-7.23 (m, CH, CH3'-H, C6'-H), 7.85 (br s, 1H, C4'-H).

All other carbamates: (-)-2'-4'-dimethylphenyl-carbamoyleseroline, 4'-isopropylcarbamoyleseroline, (-)-2'-ethylphenylcarbamoyleseroline, (-)-2'iso-propylphenylcarbamoyleseroline, naphthylcarbamoyl-eseroline, were similarly prepared from (-)-eseroline with the corresponding isocyanates. The important physical data for these compounds are shown below.

EXAMPLE 26

(-)-2'-4'-Dimethylphenyl-carbamoyleseroline

The important data is as follows: a foam, $[\alpha]_D$-79.6° (c=1, $CHCl_3$), CI MS (m/z): 366; ^1H NMR 2.28 (s, 3H, C2'-CH_3), 2.29 (s, 3H, C4'-CH_3).

EXAMPLE 27

(-)-4'-Isopropylphenylcarbamoyleseroline

The important data is as follows: m.p. (^{o}C) 152-153 $[\alpha]_D$ -67.8° (c=1, $CHCl_3$) CI MS (m/z) 380 (M^+= 1); HR MS (FAB): calcd for (M^++1) $C_{23}H_{30}N_3O_2$, 380.2338; ^{1}H-NMR: 1.23 (d, J=6.8, 6H, $CH(CH_3)_2$.

EXAMPLE 28

(-)-2'-Ethylphenylcarbamoyleseroline

The important data is as follows: a foam, $[a]_D$ -62.8° (c=1, $CHCl_3$) CI MS (m/z) 366 (M^+= 1); HR MS (FAB): calcd for (M^++1) $C_{22}H_{28}N_3O_2$, 366.2182; ^{1}H-NMR: 1.26(t, J=7.5, 3H, $-CH_2-CH_3$), 2.55-2.78 (m, 4H, C2-H, $-CH_2-CH_3$).

EXAMPLE 29

(-)-2'-Isopropylphenylcarbamoyleseroline

The important data is as follows: a foam, $[a]_D$ -58.8° (c=1, $CHCl_3$) CI MS (m/z) 380 (M^+= 1); HR MS (FAB): calcd for (M^++1) $C_{23}H_{29}N_3O_2$, 379.2259; ^{1}H-NMR: 1.30(d, J=6.8, 6H, $-CH-(CH_3)_2$).

EXAMPLE 30

(-)-1-Naphthylcarbamoyleseroline

The important data is as follows: a foam, $[\alpha]_D$ -62.0° (c=1, $CHCl_3$) CI MS (m/z) 388 (M^+= 1); HR MS (FAB): calcd for (M^++1) $C_{24}H_{26}N_3O_2$, 388.2025; ^{1}H-NMR: 7.51(m,3H), 7.69 (d, J=8.1, 1H), 7.89 (d, J=7.5, 1H), 7.96 (d, J=7.9, 2H).

The related carbamates: (-)-2'methylphenylcarbamoyl-N1-noreseroline, (-)-2',4'-dimethylphenylcarbamoyl-N1-noreseroline, and (-)-4'-isopropylphenylcarbamoyl-N1-noreseroline and

phenylcarbamoyl-N1-noreseroline and (-)-phenyl-carbamoyl-N1-noreseroline were similarly prepared from (-)-(N1)-benzylnoreseroline instead of eseroline by reacting (-)-(N1)-benzylnoreseroline with the corresponding isocyanates. The benzyl protecting group was then removed to yield the noreseroline compound from the benzylnoreseroline compound.

The following example shows the removal of a benzyl protecting group from (-)-2'-methylphenyl-carbamoyl-(N1)-benzylinoreseroline to yield compound (-)-2'-methylphenylcarbamoyl-(N1)-noreseroline.

EXAMPLE 31

(-)-2'-Methylphenylcarbamoyl-N1-benzylnoreseroline

(N^1)-Benzylnoreseroline (2.0 g) was dissolved in anhydrous Et_2O (10 ml), and a small piece of Na added. After stirring for 2 minutes at room temperature under nitrogen, 2-methylphenyl isocyanate was added (0.04 g). After stirring for 15 minutes the solvent was evaporated and the residue was chromatographed to give the carbamate as a foam: $[\alpha]_D$ -62.0° (c=0.5, $CHCl_3$); CI MS (m/z) 428 (M^+ + 1).

EXAMPLES 32-34

The carbamates of Examples 32-34 belonging to the (-)-N^1-benzylnoreseroline series have been prepared from (-)-N^1-benzylnoreseroline and isocyanates as described in Example 31. The important physical data is as follows.

EXAMPLE 32

(-)-2'-4'-Dimethylphenylcarbamoyl-(N1)-benzyl-noreseroline

The important data is as follows: a foam, $[\alpha]_D$ -58.4° (c=0.5 $CHCl_3$), CI MS (m/z): 442; ^1H NMR 2.28 (2s, 6H), 3.91 (dd, 2H).

EXAMPLE 33

(-)-4'-Isopropylphenylcarbamoyl-(N1)-benzyl-noreseroline

The important data is as follows: a foam, $[\alpha]_D$ -44.8° (c=0.5, $CHCl_3$) CI MS (m/z) 456 (M^++1); ^1H-NMR: 1.24 (d, J=7.0, 6H), 3.94 (dd, 2H).

EXAMPLE 34

(-)-Phenylcarbamoyl-(N1)-benzylnoreseroline

The important data is as follows: m.p. (°C) 158-159, $[\alpha]_D$ -56.4° (c=0.5, $CHCl_3$) CI MS (m/z) 414 (M^++1); ^1H-NMR: 3.92 (dd, 2H).

EXAMPLE 35

(-)-2'-Methylphenylcarbamoyl-N1-noreseroline

(-)-2'-Methylphenylcarbamoyl-N1-benzylnor-eseroline (0.09g, 0.21 mmol) from Example 31 was dissolved in MeOH (10 mL), and palladium hydroxide on carbon (7 mg) was added. After hydrogenation under atmospheric pressure for 5 h, the palladium catalyst was filtered through Celite and the solvent was evaporated in vacuo. The residue was chromato-graphed by preparative TLC (silica gel plate 2000 μm, CH_2Cl_2/10% MeOH) to give (-)-2'-methyl-phenylcarbamoyl-N1-noreseroline as a foam (0.04g, 56%): $[\alpha]_D$-62.4° (c = 0.5, $CHCl_3$), CI MS (m/z):338 (M^++1); EI MS (m/z): 337 (M^+), HR MS (EI) (M^+) calcd, for $C_{20}H_{23}N_3O_2$ 337.1790, found 337.1776 ^1H NMR: 1.42

$C_{20}H_{23}N_3O_2$ 337.1790, found 337.1776 ^1H NMR: 1.12 (s,3H, C10-CH_3), 1.70-1.80 (m, 1H, C3-H), 1.95-2.08 (m, 1H, C2-H), 2.29 (s, 3H, C2'-CH_3), 2.70-2.80 (m, 1H, C2-H), 2.81 (s, 1H, N8-CH_3), 3.01-3.10 (ddd, J = 2.5, 2.5, 2.5, 1H, C2-H), 4.51 (s, 1H, C9-H), 6.25 (d, J = 9.0, 1H, C7-H), 6.63 (br s, 1H, N-H), 6.83-6.86 (m, 2H, C4-H, C6-H), 7.02 (t, J - 7.5, 1H, C5'-H), 7.15-7.22 (m, 2H, C3'-H, C6'-H), 7.85 (br s, 1H, C4'-H).

EXAMPLES 36-38

The carbamates of Examples 36-38, belonging to the (-)-N^1-noreseroline series, were prepared from Examples 32-34, belonging to the (-)-N^1-benzylnoreseroline series, by catalytic debenzylation as described in Example 35. The important physical data is as follows.

EXAMPLE 36

(-)-2'-4'-Dimethylphenylcarbamoyl-(N1)-noreseroline

The important data is as follows: a foam, $[a]_D$ -55.4° (c=0.5 $CHCl_3$), CI MS (m/z): 352; ^1H NMR 2.45 (2s, 6H).

EXAMPLE 37

(-)-4'-Isopropylphenylcarbamoyl-(N1)-noreseroline

The important data is as follows: m.p. (^oC) 82-84, $[\alpha]_D$ -43.5° (c=0.5, $CHCl_3$) CI MS (m/z) 366 (M^++1); ^1H-NMR: 1.23 (d, J=7.0, 6H).

EXAMPLE 38

(-)-Phenylcarbamoyl-(N1)-noreseroline

The important data is as follows: m.p. (^oC) 129-131, $[\alpha]_D$ -50.4° (c=0.5, $CHCl_3$) CI MS (m/z) 324 (M^++1); ^1H-NMR: 7.25-7.52 (m, 5H).

The following inactive compounds were provided using the above method.

EXAMPLE A'

(-)-4'-methylphenylcarbamoyleseroline

The important data is as follows: m.p. (^{o}C) 143-145 $[\alpha]_D$ -74.2° (c=1, $CHCl_3$) CI MS (m/z) 352 (M^+= 1); HR MS (FAB): calcd for (M^++1) $C_{21}H_{26}N_3O_2$, 352.2025 ^{1}H-NMR:2.31 (s,3H, C4'-CH_3).

EXAMPLE B'

(-)-2',6'-diethylphenylcarbamoyleseroline

The important data is as follows: an oil, $[\alpha]_D$ -36.1° (c=1, $CHCl_3$) CI MS (m/z) 394 (M^+= 1); HR MS (FAB): calcd for (M^++1) $C_{24}H_{32}N_3O_2$, 394.2495; ^{1}H-NMR: 1.24 (t, J=7.4, 6H, 2-CH_2-CH_3), 2.68 (m, 6H, C2-H, 2-CH_2CH_3).

EXAMPLE C'

(-)-2',4',6'-trimethylphenylcarbamoyleseroline

The important data is as follows: a foam, $[\alpha]_D$ -55.8° (c=1, $CHCl_3$) CI MS (m/z) 380 (M^+= 1); ^{1}H-NMR: 2.28(3s, 9H, C2', C4', C6'-CH_3).

The comparative (-)-phenylcarbamoyleseroline compound ((-)-phenserine) was provided as follows.

EXAMPLE D': (-)-Phenylcarbamoyleseroline:

(-)-Eseroline 0 (0.12 g, 0.55 mmol) was dissolved in anhydrous Et_2O (10 mL) and a small piece of Na metal was added. After stirring for about 2 min at room temperature under nitrogen, phenylisocyanate (0.09 g, 0.70 mmol) was added dropwise. After complete addition the solvent was evaporated immediately. The

addition the solvent was evaporated immediately. The residue was flash chromatographed on a silica gel column (system B) to give (-)-phenylcarbamoyleseroline mp(^{o}C) 142-143 (0.88g, 46%); $[\alpha]_D$-74.2° (c=1, $CHCl_3$), CI MS (m/z): 338; ^{1}H NMR 7.01 (t, J=7.4, 1H, C4'-H), 7.22 (t, J7.4, 2H, C3'-H, C5'-H), 7.34 (d, J=7.4, 2H, C2'-H, C6'-H). The common name for this compound is (-)-phenserine.

The compound numbers in Tables 3 and 5 correspond to one another and to the above Examples. Comparative Example D' is (-)-Phenserine.

Table 5 below lists the important physical data for compounds according to the invention, which correspond to the compound numbers in Table 3.

Table 5

IC_{50} Values of Phenylcarbamates of (-)-Eseroline, (-)-Physovenol, and (-)-N^1-[illegible]eroline vs. Human Erythrocyte AChE and Human Plasma BChE

No.		IC_{50} [nmol] AChE		IC_{50} [nmol] BChE	
Biological standards					
A	physostigmine	27.9 ±	2.4	16.0 ±	2.9
B	N'norphysostigmine	21.0 ±	1.0	2.0 ±	1.0
C	physovenine	27.1 ±	0.8	3.7 ±	1.4
D'	phenserine	24.0 ±	6.0	1300 ±	85.0
Examples					
Ex. 25		10.3 ±	1.6	1948.5 ±	245.5
Ex. 26		13.6 ±	1.0	1817.0 ±	558.5
Ex. 27		758.2 ±	21.2	51.3 ±	0.9
Ex. 28		9.7 ±	0.7	2916.0 ±	537.0
Ex. 29		15.5 ±	1.3	647.8 ±	46.2
Ex. 30		16.1 ±	1.0	1832.0 ±	35.5
Ex. 31		not tested			
Ex. 32		not tested			
Ex. 33		> 10,000		45.3 ±	4.6
Ex. 34		not tested			
Ex. 35		17.0 ±	0.2	2165.0 ±	85.0
Ex. 36		17.3 ±	1.2	1139.0 ±	26.0
Ex. 37		322.4 ±	3.7	8.3 ±	1.0
Ex. 38		13.8 ±	0.7	612.0 ±	0.4
Inactive Compounds					
Ex. A'		139.2 ±	3.7	251.1 ±	8.6
Ex. B'		1493.7 ±	49.8	1073.5 ±	48.0
Ex. C'		1291.9 ±	73.8	1817.0 ±	885.0

In vitro assay of human anti-AChE and -BChE activity, IC_{50}

A classical enzyme inhibition assay was undertaken to quantitate the activity of the derivatives against AChE and BChE. Anti-cholinesterase activity was determined against human erythrocyte AChE and plasma BChE in 0.1 M Na_3PO_4 buffer (pH 8.0) using the spectrophotometric method of Ellman et al. (Biochem. Pharmacol. 7:88, 1961). Freshly collected plasma was diluted 1.125 with 0.1 M Na_3PO_4 (pH 7.4) and lysed erythrocytes similarly diluted to 1:200. Acetyl-B-methylthiocholine (0.5 mM) and s-butyrylthiocholine (0.5 mM) were used as specific substrates for AChE and BChE, respectively, 25 µl of substrate and 25 µl of enzyme in a total volume of 0.75 ml.

Physostigmine derivatives, diluted in half log-intervals to a concentration range of between $1x10^{-5}$M and $3x10^{-10}$M, were preincubated with enzyme (30 min at 21°C) prior to addition of substrates. Following incubation (30 min at 37°C), production of a yellow thionitrobenzoate anion was measured with a spectrophotometer set to 412 nm wavelength. Nonspecific substrate hydrolysis was determined under conditions of complete enzyme inhibition (by addition of physostigmine $1x10^{-5}$M), and the associated change in absorbance subtracted from that observed with the test compounds. Finally, the activity of each compound was assessed alongside that of physostigmine, as an external standard, whose activity has been previously reported (Atack et al., J. Pharm. Expl. Ther. 249:294, 1989).

The AChE and BChE activity of each compound was expressed as an IC_{50}, which is defined as the concentration in nmol required to inhibit 50% of enzyme activity (calculated as described by Atack et al., J. Pharm. Expl. Ther. 249:294, 1989)).

In vivo duration of activity studies

Catheters, filled with heparinized saline, were tied into the right femoral vein and artery of anesthetized male rats, which then were restrained in a plaster cast and allowed to recover from anesthesia in a temperature-controlled enclosure. Plasma samples were withdrawn to quantitrate untreated levels of AChE activity. At 90 min. after surgery, hexamethonium bromide (5 mg/kg, i.p.) was administered, followed by atropine methylbromide (4 mg/kg, s.c.) 10 min. later. These quaternary nicotinic and muscarinic antagonists, do not enter brain and inhibit peripheral cholinergic overdrive associated with cholinesterase inhibition, which may be deleterious to the animal. Two hours after surgery, either (i) physostigmine, (ii) physostigmine derivatives, or (III) THA was administered i.v. Plasma samples were removed at intervals between 2 min. and 8 hr., immediately frozen to -70°C and then assayed for cholinesterase inhibition. AChE inhibition was measured as described above, with necessary modifications required for quantitation from rat plasma.

All drugs were formulated in a manner consistent with i.v. administration. Specifically, drugs were dissolved in Tween 80/EtOH (3:1, V:V), approximately 100 µl, and then were diluted in excess of 1:9 (V:V) with isotonic saline. The use of Tween 80/EtOH did not

affect either AChE or BChE inhibitory activity of compounds in in vitro studies (Yu et al., Helv. Chim. Acta 74, pages 761-766, (1991)). Doses were determined in prior studies involving the measurement of rectal temperature and tremor; two centrally-mediated actions of cholinesterase inhibitiors and cholinergic agonists.

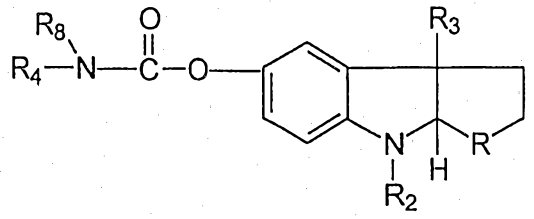
Figure 1 demonstrates the in vivo inhibition of the enzyme acetylcholinesterase (AChE) by physostigmine and its 2',4'-dimethylphenyl carbamate derivative, i.e., the time-dependent activity of these cholinesterase inhibitors in rats. As predicted from the in vitro IC_{50} studies, physostigmine and the substituted phenyl carbamates to which this patent relates (which are represented in this case by 2',4'-dimethylphenyl physostigmine) possess excellent in vivo cholinesterase inhibitory properties. However, the duration of enzyme inhibition is short following an intravenous bolus of physostigmine. Whereas as peak inhibition of 46% occurred within 2 minutes of administration, this rapidly declined to 25% by 15 minutes and was negligible at one hour. An equal dose of the 2'4'-methylphenyl carbamate resulted in immediate 60% AChE inhibiiton at 2 minutes. This was maintained at a steady level for 2 hours and then slowly declined to 36% inhibition at 8 hours. The high activity, specificity and persistence of 2',4'-dimethylphenyl physostigmine, which is achieved without side-effects or toxicity, is surprising and supports the contention that these compounds represent a class of potent, new and selective cholinesterase inhibitors.

The foregoing description of the specific embodiments will so fully reveal the general nature of the invention that others can, by applying current knowledge, readily modify and/or adapt for various applications such specific embodiments without departing from the generic concept and therefore such adaptations are intended to be comprehended within the meaning and range of equivalents of the disclosed embodiments. It is to be understood that the phraseology or terminology employed herein is for the purpose of description only and not of limitation.

The claims defining the invention are as follows:

1. A compound according to the Formula I

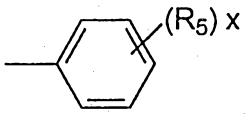
(I)



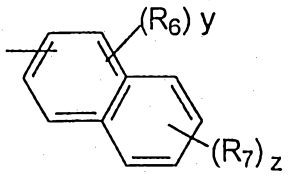
wherein R is -0- and

R_2 and R_3 are independently selected from H or -C_1- C_{10}-alkyl;

R_4 is



or



wherein

R_5 is a halogen

R_6 and R_7 are independently selected from H, halogen or -C_1-C_{10}-alkyl,

x is an integer from 1-5,

y is 0 or an integer from 1-3,

z is 0 or an integer from 1-4; and

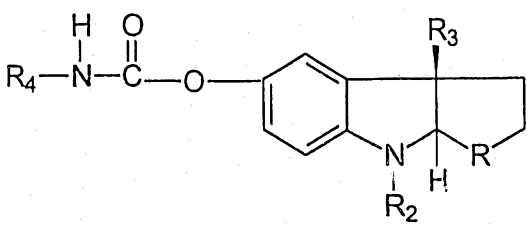
R_8 is H or -C_1-C_{10}-alkyl;

including isomeric forms, and

pharmacologically acceptable salts.

2. A compound according to claim 1, Formula I and having the Formula II

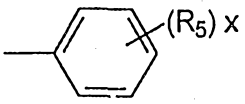
(II)



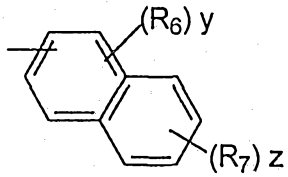
wherein R is -0- and

R_2 and R_3 are independently selected from H, halogen or -C_1-C_{10}-alkyl; and

R_4 is



or



wherein

R_5 is a halogen

R_6 and R_7 are independently selected from H or -C_1-C_{10}-alkyl,

x is an integer from 1-5,

y is 0 or an integer from 1-3, and

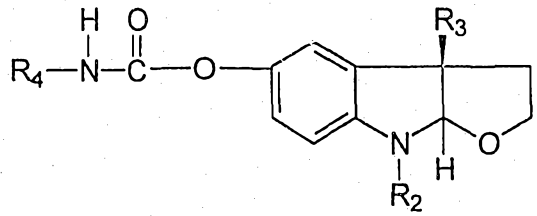
z is 0 or an integer from 1-4;

including isomeric forms, and

pharmacologically acceptable salts.

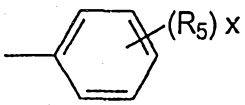
3. A compound according to claim 1 having the formula IV wherein

(IV)

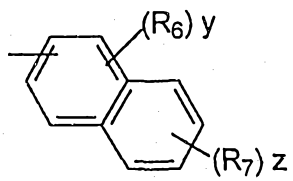


R_2 and R_3 are independently selected from H or -C_1-C_{10}-alkyl; and

R_4 is



or



wherein

R_5 is a halogen,

R_6 and R_7 are independently selected from H, halogen or -C_1-C_{10}-alkyl,

x is an integer from 1-5,

y is 0 or an integer from 1-3, and

z is 0 or an integer from 1-4;

including isomeric forms, and

pharmacologically acceptable salts.

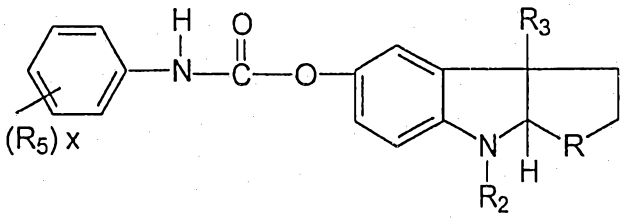
4. A compound according to any one of claims 1-3 wherein R_2 and R_3 are independently selected from -C_2-C_{10}-alkyl.

5. A compound according to claim 3, wherein R_3 is a methyl group.

6. A compound according to claim 3, wherein R_2 and R_3 both represent a methyl group.

7. A compound according to claim 1, having the formula Ia

(Ia)



wherein

R is -0- and

R_2 and R_3 are independently selected from H or -C_1-C_{10}-alkyl; and

R_5 is a halogen and x is an integer from 1-5 including isomeric forms, and

pharmacologically acceptable salts.

8. A compound according to claim 6, where x is 1 or 2 and R_5 is in the ortho and/or para position.

9. A compound according to claim 6, wherein R_5 is CHLORO and x is an integer from 1-5.

10. A compound according to any one of claims 7-9 wherein R_2 and R_3 are independently selected from -C_2-C_{10}-alkyl.

11. A pharmaceutical composition comprising the pharmaceutically effective amount of a compound according to any one of claims 1-10 and a carrier.

12. A method for treating cholinergic disorders comprising administration of an effective amount of a compound according to any one of claims 1-10 to a mammal in need of such treatment.

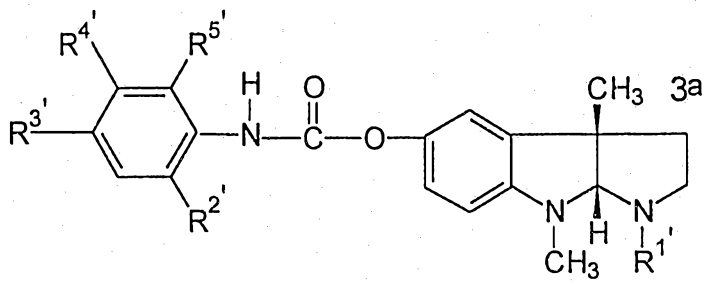
13. A method according to claim 12, wherein the cholinergic disorder is selected from the group consisting of glaucoma, Myasthenia Gravis, Alzheimer's disease.

14. A method for inhibiting acetylcholinesterase activity comprising administering an effective amount of a compound according to any one of claims 1-10 to a mammal in need thereof.

15. A method for inhibiting butyrylcholinesterase activity in a mammal comprising administering an effective amount of a compound according to any one of claims 1-10.

16. A method for treating organophosphate poisoning in a mammal comprising administering an effective amount of a compound according to any one of claims 1-10.

17. A compound according to the formula



wherein $R^{1'}$ is a benzyl group;

$R^{2'}$ is straight or branched chained C_1-C_{10} alkyl;

$R^{3'}$ is H or a straight or branched C_1-C_{10} alkyl; and

$R^{4'}$ and $R^{5'}$ are independently hydrogen or $R^{4'}$ and $R^{5'}$ taken together along with the carbon atoms to which they are attached form a 6-membered aromatic carbocyclic ring;

and pharmaceutically acceptable salts.

18. A compound selected from the group consisting of

(-) -2' -methylphenylcarbamoyleseroline,

(-) -2' -4' -dimethylphenylcarbamoyleseroline,

(-) -4' -isopropylcarbamoyleseroline,

(-) -2' -ethylphenylcarbamoyleseroline,

(-) -2' -isopropylphenylcarbamoyleseroline,

(-) -naphthylcarbamoyleseroline,

(-) -2' -methylphenylcarbamoyl-N1-noreseroline,

(-) -2', 4' -dimethylphenylcarbamoyl-N1-noreseroline,

(-) -4' -isopropylphenylcarbamoyl-N1-noreseroline,

(-) -phenylcarbamoyl-N1-noreseroline,

(-) -2' -methylphenylcarbamoyl-N1-benzyl-noreseroline,

(-) -2', 4' -dimethylphenylcarbamoyl-N1-benzyl-noreseroline,

(-) -4' -isopropylphenylcarbamoyl-N1-benzyl-noreseroline,

and (-) -phenylcarbamoyl-N1-benzyl-noreseroline.

19. A compound for the selective inhibition of acetylcholinesterase selected from the group consisting of:

(-) -2' -methylphenylcarbamoyleseroline,

(-) -2' -methylphenylcarbamoyl-N1-noreseroline,

(-) -phenylcarbamoyl-N1-noreseroline,

and pharmaceutically acceptable salts thereof.

20. A compound according to claim 17, wherein $R^{1'}$ is a benzyl group.

21. A compound according to claim 15, wherein

$R^{1'}$ is a benzyl group;

$R^{2'}$ is straight or branched chained C_2-C_{10}-alkyl;

$R^{3'}$ is H or straight or branched chained C_2-C_{10}-alkyl; and

$R^{4'}$ and $R^{5'}$ are independently hydrogen or $R^{4'}$ and $R^{5'}$ taken together along with the carbon atoms to which they are attached form a 6-membered aromatic carbocyclic ring;

and pharmaceutically acceptable salts.

22. A pharmaceutical composition comprising a pharmaceutically effect amount of a compound according to claim 17 and a carrier.

23. A pharmaceutical composition comprising a pharmaceutically effect amount of a compound according to claim 18 and a carrier.

24. A pharmaceutical composition comprising a pharmaceutically effective amount of at least one compound according to claim 19 and a pharmaceutically acceptable carrier.

25. The compound according to claim 18, wherein the compound is selected from the group consisting of:

(-) -2' -methylphenylcarbamoyleseroline,

(-) -2', 4' -dimethylphenylcarbamoyleseroline,

(-) -2' -ethylphenylcarbamoyleseroline,

(-) -2' -isopropylphenylcarbamoyleseroline,

(-) -2' -methylphenylcarbamoyl-N1-noreseroline,

(-) -2', 4' -dimethylphenylcarbamoyl-N1-noreseroline,

(-) -4' -isopropylphenylcarbamoyl-N1-noreseroline,

(-) -phenylcarbamoyl-N1-noreseroline,

and pharmaceutically acceptable salts thereof.

26. A compound for inhibiting acetylcholinesterase activity, said compound being selected from the group consisting of:

(-) -2' -methylphenylcarbamoyleseroline,

(-) -2', 4' -dimethylphenylcarbamoyleseroline,

(-) -2' -ethylphenylcarbamoyleseroline,

(-) - 2' -isopropylphenylcarbamoyleseroline,

(-) -2' -methyllphenylcarbamoyl-N1-noreseroline,

(-) -2', 4' -dimethylphenylcarbamoyl-N1-noreseroline,

(-) -phenylcarbamoyl-N1-noreseroline,

and pharmaceutically acceptable salts thereof.

27. A pharmaceutical composition comprising a pharmaceutically effective amount of at least one compound according to claim 26 and a pharmaceutically acceptable carrier.

28. A method for inhibiting acetylcholinesterase activity comprising administering an effective amount of at least one compound according to claim 26 to a mammal in need thereof.

29. The method according to claim 28, wherein said at least one compound is administered transdermally.

30. A compound for inhibiting butyrylcholinesterase activity, said compound being selected from the group consisting of:

(-) -4' -isopropylphenylcarbamoyleseroline,

(-) -4' -isopropylphenylcarbamoyl-N1-benzyl-noreseroline,

(-) -4' -isopropylphenylcarbamoyl-N1-noreseroline and pharmaceutically acceptable salts thereof.

31. A pharmaceutical composition comprising a pharmaceutically effective amount of at least one compound according to claim 30 and a pharmaceutically acceptable carrier.

32. A method for inhibiting butyrylcholinesterase activity comprising administering an effective amount of at least one compound according to claim 31 to a mammal in need thereof.

33. The method according to claim 32, wherein said at least one compound is administered transdermally.

34. A method for treating cholinergic disorders comprising administration of an effective amount of at least one compound according to claim 25 to a mammal in need of such treatment.

35. A method according to claim 34, wherein the cholinergic disorder is selected from the group consisting of glaucoma, Myasthenia Gravis and Alzheimer's disease.

36. A method for treating organophosphate poisoning in a mammal comprising administering an effective amount of at least one compound according to claim 25.

37. The compound according to claim 18, wherein said compound is (-) -2' -methylphenylcarbamoyleseroline and pharmaceutically acceptable salts thereof.

38. The compound according to claim 18, wherein said compound is (-) -2', 4' -dimethylphenylcarbamoyleseroline and pharmaceutically acceptable salts thereof.

39. The compound according to claim 18, wherein said compound is (-) -4' -isopropylphenylcarbamoyleseroline and pharmaceutically acceptable salts thereof.

40. The compound according to claim 18, wherein said compound is (-) -2' -ethylphenylcarbamoyleseroline and pharmaceutically acceptable salts thereof.

41. The compound according to claim 18, wherein said compound is (-) -2' - isopropylphenylcarbamoyleseroline and pharmaceutically acceptable salts thereof.

42. The compound according to claim 18, wherein said compound is (-) -4' -isopropylphenylcarbamoyl-N1-benzyl-noreseroline and pharmaceutically acceptable salts thereof.

43. The compound according to claim 18, wherein said compound is

(-) -2' -methylphenylcarbamoyl-N1-noreseroline and pharmaceutically acceptable salts thereof.

44. The compound according to claim 18, wherein said compound is

(-) -2', 4' -dimethylphenylcarbamoyl-N1-noreseroline and pharmaceutically acceptable salts thereof.

45. The compound according to claim 18, wherein said compound is

(-) -4' -isopropylphenylcarbamoyl-N1-noreseroline and pharmaceutically acceptable salts thereof.

46. The compound according to claim 18, wherein said compound is

(-) -phenylcarbamoyl-N1-noreseroline and pharmaceutically acceptable salts thereof.

47. A compound according to claim 1 substantially as hereinbefore described with reference to any one of the examples.

DATED: 6 August, 1996

PHILLIPS ORMONDE & FITZPATRICK

Attorneys for:

THE GOVERNMENT OF THE UNITED STATES OF AMERICA AS REPRESENTED BY THE SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES

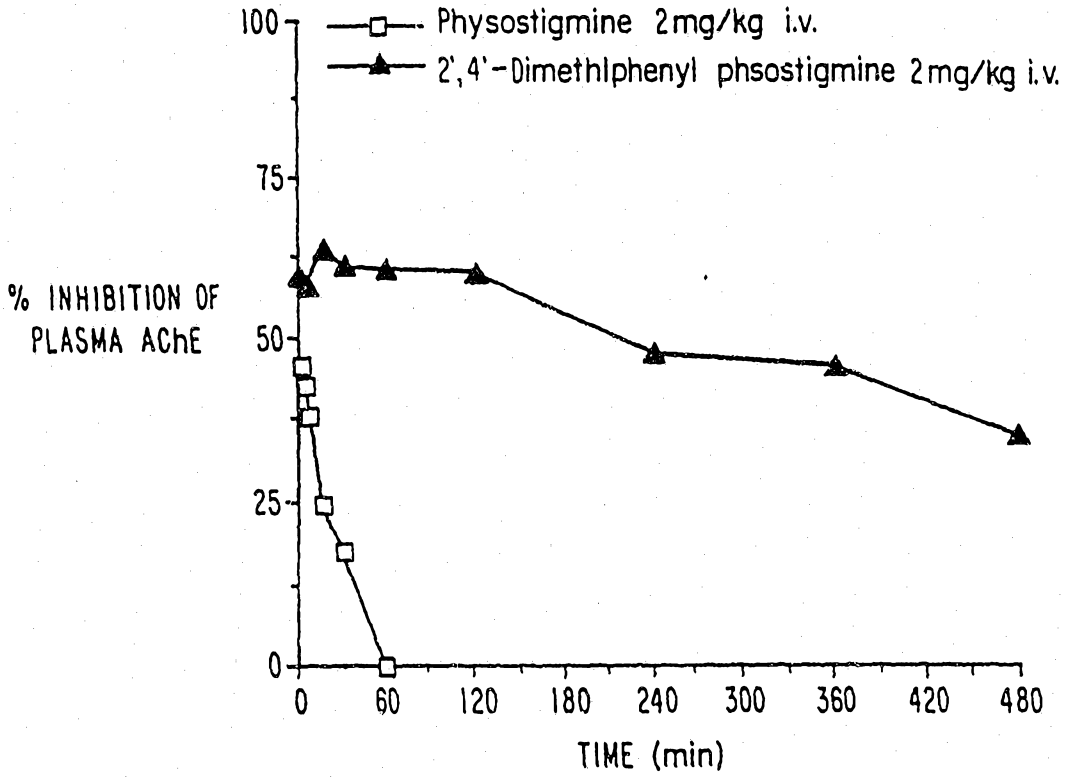

Physostigmine 2mg/kg i.v.
2',4'-Dimethlphenyl phsostigmine 2mg/kg i.v.
% INHIBITION OF PLASMA AChE
100
75
50
25
0
0
60
120
180
240
300
360
420
480
TIME (min)

Figure 1

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/08228

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D487/04; C07D491/048; A61K31/40; //(C07D487/04, 209:00,209:00)(C07D491/048,307:00,209:00)

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	HELVETICA CHIMICA ACTA vol. 74, no. 4, 19 June 1991, BASEL CH pages 761 - 766 Q.-S. YU ET AL. 'Physovenines: Efficient synthesis of (-)- and (+)-physovenine and synthesis of carbamate analogues of (-)-physovenine. Anticholinesterase activity and analgesic properties of optically active physovenines' see page 761, abstract; page 762, compounds 9a,10a; page 763, Table 1	1,10,12, 13
X	EP,A,0 154 864 (CONSIGLIO NAZIONALE DELLE RICERCHE) 18 September 1985 see page 2, line 1 - line 12; claims 1,5; example 4	15,23,24

-/--

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
02 DECEMBER 1992	28. 01. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	VOYIAZOGLOU D.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	EP,A,0 253 372 (HOECHST-ROUSSEL) 20 January 1988 see claims 1,12; example 26	15,23,24

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9208228 SA 65478

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 02/12/92

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0154864	18-09-85	EP-A- 0354594	14-02-90
		JP-B- 3054952	21-08-91
		JP-A- 60208982	21-10-85
		US-A- 4831155	16-05-89
EP-A-0253372	20-01-88	US-A- 4791107	13-12-88
		AU-B- 612583	18-07-91
		AU-A- 7566887	21-01-88
		JP-A- 63023881	01-02-88

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