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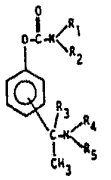
(56) Documents cited
EP A2 0193926

(58) Field of search
A5B
C2C
Selected US specifications from IPC sub-class
A61K

(54) Phenyl carbamates

(57) Compositions for systemic transdermal administration contain the compounds:

(-)  I'

where R_1 is –H, alkyl, cyclohexyl, allyl or benzyl
R_2 is –H, $-CH_3$, $-C_2H_5$ or $-C_3H_7$
or R_1 and R_2 together with –N for a morpholino or piperidino group
R_3 is –H or alkyl
R_4 and R_5 are alkyl, in their free base or acid addition salt form. The compositions particularly contain the novel compound (S)–N–ethyl–3–[1–dimethylamino)ethyl]–N–methyl–phenyl–carbamate and are used to treat Alzheimer's disease, mania etc.

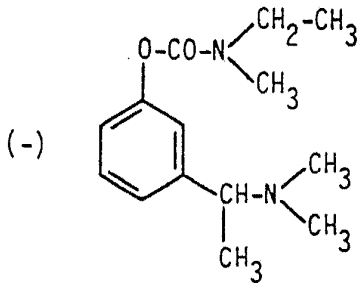
GB 2 203 040

CASE 100-7041

PHENYL CARBAMATE

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-O,O'-p-toluyl-tartaric 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.

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