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(54) Titre : UTILISATION DE RIVASTIGMINE POUR LE TRAITEMENT DE TROUBLES OCULAIRES
(54) Title: RIVASTIGMINE FOR THE TREATMENT OF OCULAR DISORDERS

(57) **Abrégé/Abstract:**

The present invention is in particular related to the use of rivastigmine in the manufacture of a medicament for the treatment of ocular disorders selected from glaucoma, normal tension glaucoma and neurodegenerative disease conditions of the retina and the optic nerve.



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(54) Title: **RIVASTIGMINE FOR THE TREATMENT OF OCULAR DISORDERS**

(57) Abstract: The present invention is in particular related to the use of rivastigmine in the manufacture of a medicament for the treatment of ocular disorders selected from glaucoma, normal tension glaucoma and neurodegenerative disease conditions of the retina and the optic nerve.

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RIVASTIGMINE FOR THE TREATMENT OF OCULAR DISORDERS

This invention is in particular related to the use of rivastigmine in the manufacture of a medicament for the treatment of ocular disorders selected from glaucoma and neurodegenerative disease conditions of the retina and the optic nerve.

The term glaucoma includes symptoms of the eye which are especially to be attributed to increased intraocular pressure. Frequently, an obstruction to drainage of the aqueous humour leads to an increase in the intraocular pressure. Chronically raised intraocular pressure has a harmful effect on the optic nerve and the retina, which can terminally lead to blindness. Accordingly, for the treatment of glaucoma, active ingredients are used which are typically able to reduce the intraocular pressure (IOP). For example, increased IOP be treated with certain β -adrenoceptor blockers.

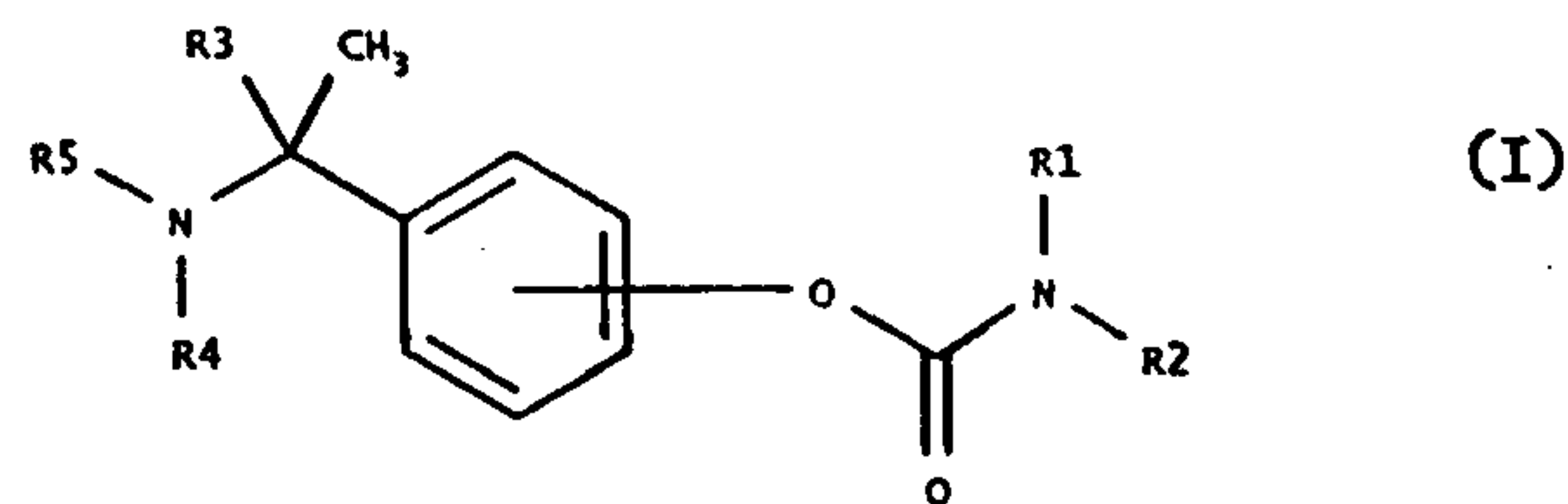
More recently, the phenomenon of so-called normal tension glaucoma ("low tension" or "normal tension glaucoma" is used synonymously) has now been clinically established in ophthalmology [J. Flammer, Fortschr. Ophthalmol. 87, 187(1990)]. Normal tension glaucoma is characterized by an intraocular pressure which is typically in the normal range, i.e. is not increased, but in which the optic disc (papilla nervi optici) is pathologically excavated and the field of vision is impaired. The pathogenetic factors are especially circulatory problems in the ocular blood vessels, which may be caused e.g. by atherosclerosis, hypotension, orthostasis, functional vasospasms and neurodegenerative factors.

It has now surprisingly been found that rivastigmine, its racemate, its analogs and/or its pharmaceutically acceptable salts are highly effective in the treatment of glaucoma and disorders of neurological pathogenesis (neurodegeneration), such as normal tension glaucoma.

Accordingly, a first aspect of the present invention is related to the use of a compound of formula (I),

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wherein

R₁ is hydrogen, lower alkyl, cyclohexyl, allyl or benzyl,

R₂ is hydrogen, methyl, ethyl or propyl or

R₁ and R₂ together with the nitrogen to which they are attached form a morpholino or piperidino radical,

R₃ is hydrogen or lower alkyl,

R₄ and R₅ are the same or different and each is a lower alkyl, and the dialkylaminoalkyl group is in the meta, ortho or para position,

in free base or pharmaceutically acceptable acid addition salt form,

in the preparation of a pharmaceutical composition for the treatment of an ocular disorder selected from the group consisting of glaucoma, normal tension glaucoma and neurodegenerative disease conditions of the retina and the optic nerve.

In accordance with another aspect of the invention, the compound described herein may be used in preparation of a pharmaceutical composition for lowering intraocular pressure in the eye of a subject in need thereof.

In a preferred embodiment the dialkylaminoalkyl group is in the meta position.

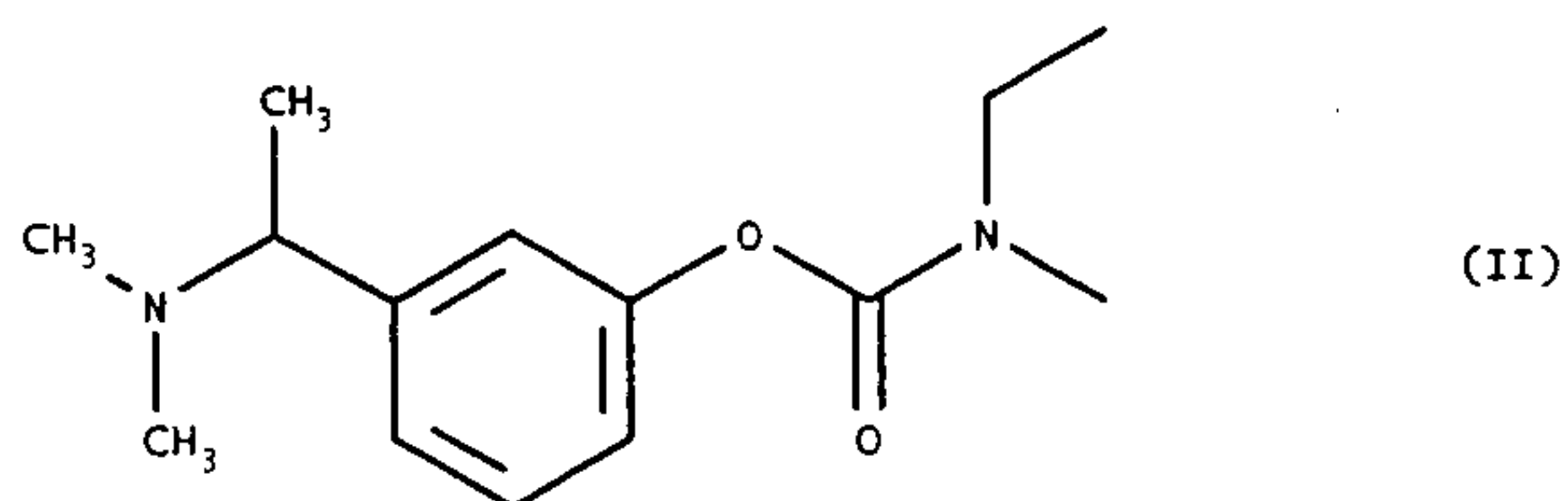
A more preferred compound in accordance to formula (I) is racemic N-ethyl-3-[(1-diethylamino)-ethyl]-N-methyl-phenyl-carbamate free base and / or acid addition salt.

An even more preferred compound in accordance to formula (I) is (S)-N-ethyl-3-[(1-diethylamino)-ethyl]-N-methyl-phenyl-carbamate free base and / or acid addition salt.

A preferred acid addition salt is derived from tartronic acid.

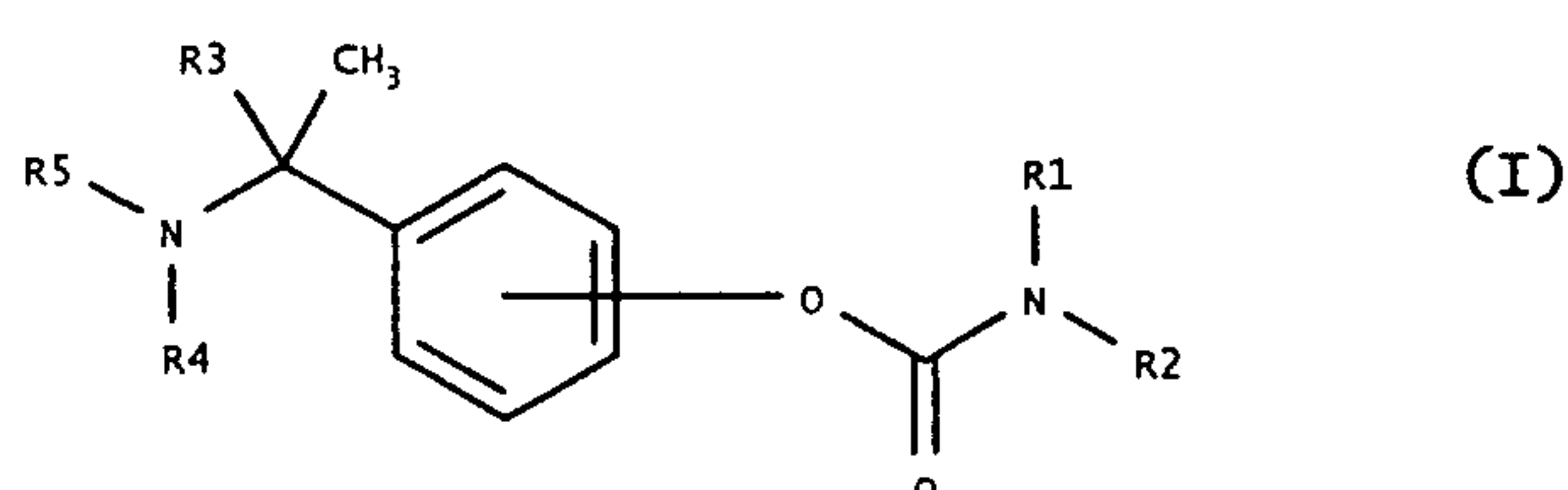
A highly preferred compound in accordance to formula (II) is (S)-N-ethyl-3-[(1-diethylamino)-ethyl]-N-methyl-phenyl-carbamate hydrogen tartrate (rivastigmine).

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This invention is preferably related to the treatment of normal tension glaucoma and neurodegenerative disease conditions of the retina and the optic nerve, and even more preferred to neurodegenerative disease conditions of the retina and the optic nerve.

A further aspect of the present invention is a method of treating an ocular disorder, which disorder is selected from the group consisting of glaucoma, normal tension glaucoma and neurodegenerative disease conditions of the retina and the optic nerve, which method comprises the repeated administration of a pharmaceutically effective amount of a compound of formula (I), to an individual in need of such treatment,



wherein

R1 is hydrogen, lower alkyl, cyclohexyl, allyl or benzyl,

R2 is hydrogen, methyl, ethyl or propyl or

R1 and R2 together with the nitrogen to which they are attached form a morpholino or piperidino radical,

R3 is hydrogen or lower alkyl,

R4 and R5 are the same or different and each is a lower alkyl, and the dialkylaminoalkyl group is in the meta, ortho or para position,

in free base or pharmaceutically acceptable acid addition salt form.

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A preferred mode of administering a compound of the present invention is the topical, and more preferably the topical ocular administration.

A preferred group of individuals are human beings.

The term repeated administration refers in particular a weekly and more preferably to a daily administration, wherein the active is administered in regular intervals from one to ten times, more preferably from one to six times, and even more preferably from one to three times.

For the purposes of the present invention, the term "lower" in connection with radicals and compounds, unless defined otherwise, denotes, in particular, radicals or compounds having up to 8 carbon atoms, preferably up to 4 carbon atoms.

Accordingly, lower alkyl has up to 8 carbon atoms, and can be straight-chain or branched, preferably up to 4 carbon atoms, and is, for example, methyl, ethyl, propyl, iso-propyl, butyl, sec-butyl, tert-butyl, pentyl, hexyl or isohexyl.

Alkyl has up to 18 carbon atoms and can be straight-chain or branched. Suitable examples are octadecyl, undecyl, octyl, hexyl, pentyl, butyl, propyl, ethyl, and the like.

MATERIALS AND METHODS

1. Animals

Male and female adult brown burgundy rabbits (2,6 - 4,4 kg) are used in this study. Animals are kept in individual cages under well-defined and standardized conditions (humidity and temperature controlled room, 13 h light / 11 h dark cycle) with standard dry food and water ad libitum. All animals are accustomed to the procedure of IOP measurement but only those animals that have stable records are included in the study. All experiments are conducted in accordance with the ARVO resolution for the use of animals in ophthalmic and vision research and are approved by the Federal and Local Ethical and Agricultural Committees.

2. Drugs

Compounds in accordance to formula (I) indicated above and in particular (S)-N-ethyl-3-[(1-diethylamino)-ethyl]-N-methyl-phenyl-carbamate.

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Topical anaesthesia of the cornea is induced with Novocaine 0,2 % (Inselspital Pharmacy) eye drops.

Solutions of a test drug are freshly prepared before each experiment by dissolution in sterile balanced salt solution (BSS) (Alcon Pharmaceuticals Ltd, Forth Worth, Texas, USA) at the required concentrations under sterile conditions. One 50- μ L drop of the test solution is applied topically to the right eye whereas the contralateral eye receives the carrier BSS only.

3. IOP Measurements

IOP is measured with a TonoPen XL (Mentor, Norvel, MA), the device being calibrated daily according to the manufacturer's instructions. The first measurement result with a coefficient of variation displayed $<5\%$ is noted. Less than 5% of the measurements are repeated until the coefficient of variation displayed is $<5\%$. Corneas are anaesthetized by topical application of a 50- μ L drop of 0,2 % Novocaine prior to each IOP measurement.

Measurements are always initiated at the same time (8 a.m.), a sufficient recovery period of at least 7 days is provided for the animals between the experiments. Control readings are taken 10 minutes before instillation of the test drug to the right eye and of the vehicle to the left one. IOP is recorded at 1-hour intervals for the ensuing 8 hours. Baseline measurements are likewise performed hourly in all animals prior to treatment, for monitoring of diurnal rhythms. (9)

4. Pupil Diameter

Pupil diameter is measured horizontally in both eyes using a pupil gauge closely applied to the cornea under diffuse illumination conditions.

5. Slit-Lamp Examination

Slit-lamp biomicroscopy is performed by a trained ophthalmologist before drug administration and 4 and 8 hours thereafter. Eyes are controlled for conjunctival redness

and discharge, for integrity of the corneal epithelium and for the absence or presence of flare (protein in the anterior chamber being an indication of blood aqueous barrier breakdown).

6. Statistical Analysis

Data are analyzed according to the Mann-Whitney U- test. IOP values recorded before and after application of Rivastigmine or the drug vehicle are compared in the same eye, differences with a first order error of $P < 0.05$ being considered as statistically significant.

RESULTS

Rivastigmine lowers the IOP significantly in the treated eye. Maximal mean decreases in IOP are time-staggered according to the concentration of the drug solution used, occurring 1, 3 and 5 hours after application of 5% (3.5 ± 1.2 mm Hg), 2% (2.2 ± 0.8 mm Hg) and 1% rivastigmine (2.6 ± 1.2 mm Hg), respectively. After administration of the 1% rivastigmine solution the longest significant IOP-lowering effect is observed during 5 hours in the treated eyes. (table 1A) In untreated eyes, maximal mean decreases in IOP are likewise time-staggered, occurring 1, 3 and 4 hours after application of 5%, 2% and 1% rivastigmine, respectively, to the contralateral ones. However, only the effect induced by 5% rivastigmine is significant (table 1B). Overall in the treated and nontreated eyes the maximal IOP decrease occurs 1 hour after administration of the 5% drug solution.

An insignificant miotic pupil reaction is observed in some drug-treated eyes. No signs of rivastigmine-related local toxicity are manifested.

Table 1A

Right eye data (treated)

Time (hrs)	0	1	2	3	4	5	6	7	8
IOP (mm) Control	12.1	13.8	14.0	12.3	12.3	13.0	12.9	11.5	13.0
1% Rivastigmine	12.3	12.0	11.2	10.8	10.5	10.1	11.1	11.5	11.6
2% Rivastigmine	11.5	11.5	11.0	9.2	10.8	11.5	11.1	10.8	12.0
5% Rivastigmine	13.7	10.0	11.1	10.8	10.5	12.9	12.5	14.0	11.8

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Table 1B

Left eye data (untreated)

Time (hrs)	0	1	2	3	4	5	6	7	8
IOP (mm) Control	12.2	13.4	13.2	12.0	12.8	13.9	13.5	12.1	14.0
1% Rivastigmine	12.0	11.6	11.2	11.1	10.2	11.0	10.7	11.1	11.4
2% Rivastigmine	11.2	11.9	11.2	10.2	12.3	11.5	11.2	11.0	13.0
5% Rivastigmine	13.4	10.7	11.5	11.3	11.9	13.2	12.5	13.3	13.0

The above tables 1A and 1B exhibit baseline measurements (positive SD) and mean IOP measurements recorded after topical application of a single 50- μ L drop of 1% (n=8) (negative SD), 2% (n=4) and 5% (n=6) rivastigmine to the right eyes (A), and of a similar volume of the drug vehicle to the left ones (B), of normotensive adult rabbits. In the drug-treated group, maximal effects occur after 1 hour (5% rivastigmine), 3 hours (2% rivastigmine) and 5 hours (1% rivastigmine). In the untreated eyes, maximal IOP-reductions occur 1,3 and 4 hours after administration of 5%, 2% and 1% rivastigmine, respectively, to the partner ones. (**P<0.05)

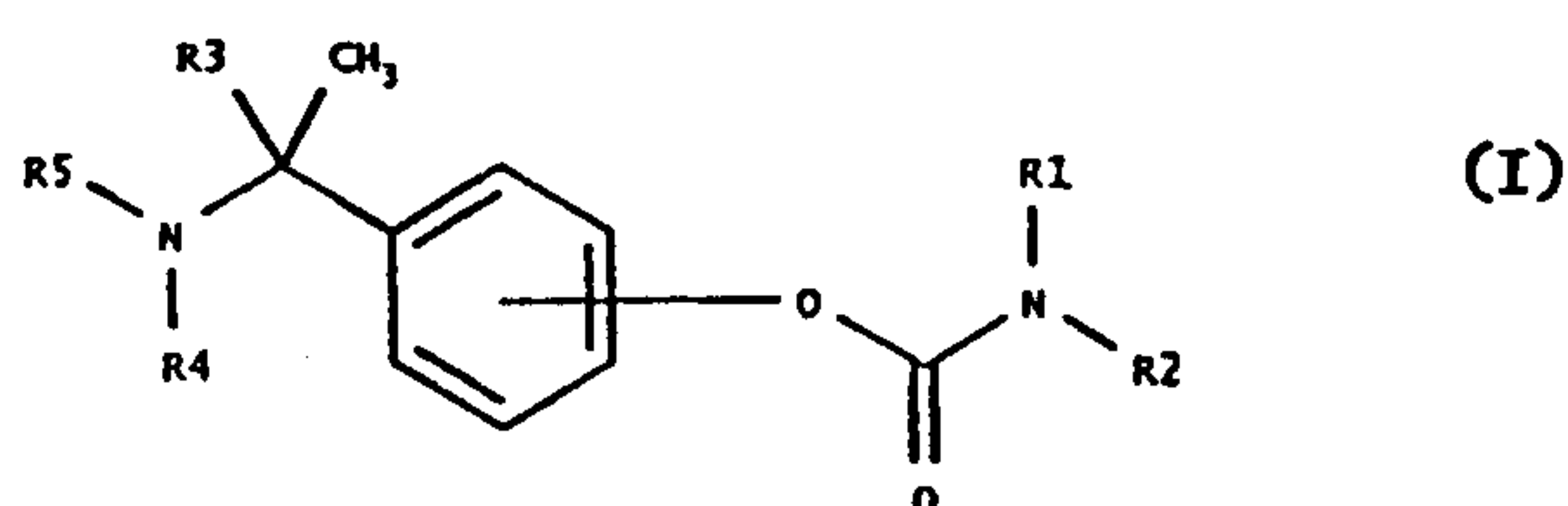
The neuroprotective effect of rivastigmine - after topical application - in addition to its well-tolerated ocular hypotensive effect makes it a compound of choice for the treatment of normotensive glaucoma.

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CLAIMS:

1. Use of a compound of formula (I),



wherein

R₁ is hydrogen, lower alkyl, cyclohexyl, allyl or benzyl,

R₂ is hydrogen, methyl, ethyl or propyl or

R₁ and R₂ together with the nitrogen to which they are attached form a morpholino or piperidino radical,

R₃ is hydrogen or lower alkyl,

R₄ and R₅ are the same or different and each is a lower alkyl, and the dialkylaminoalkyl group is in the meta, ortho or para position,

in free base or pharmaceutically acceptable acid addition salt form,

in preparation of a pharmaceutical composition for treatment of an ocular disorder selected from the group consisting of glaucoma, and neurodegenerative disease conditions of the retina and the optic nerve by lowering intra ocular pressure in the eye in a patient in need thereof.

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2. The use of claim 1, wherein said dialkylaminoalkyl group is in the meta position.

3. The use of claim 1, wherein said compound in accordance to formula (I) is racemic N-ethyl-3-
5 [(1-diethylamino)-ethyl]-N-methyl-phenyl-carbamate in the free base or in the acid addition salt form.

4. The use of claim 1, wherein said compound in accordance to formula (I) is (S)-N-ethyl-3-
[(1-diethylamino)-ethyl]-N-methyl-phenyl-carbamate in the
10 free base or in the acid addition salt form.

5. The use of any one of claims 1 to 4, wherein said acid addition salt is derived from tartaric acid.

6. The use of claim 1, wherein said compound in accordance to formula (I) is (S)-N-ethyl-3-
15 [(1-diethylamino)-ethyl]-N-methyl-phenyl-carbamate hydrogen tartrate.

7. The use of any one of claims 1 to 6, wherein the ocular disorder is glaucoma.

8. The use of any one of claims 1 to 6, wherein the
20 ocular disorder is a neurodegenerative disease condition of the retina or the optic nerve.

9. The use of claim 8, wherein the neurodegenerative disease condition of the retina or the optic nerve is normal tension glaucoma.

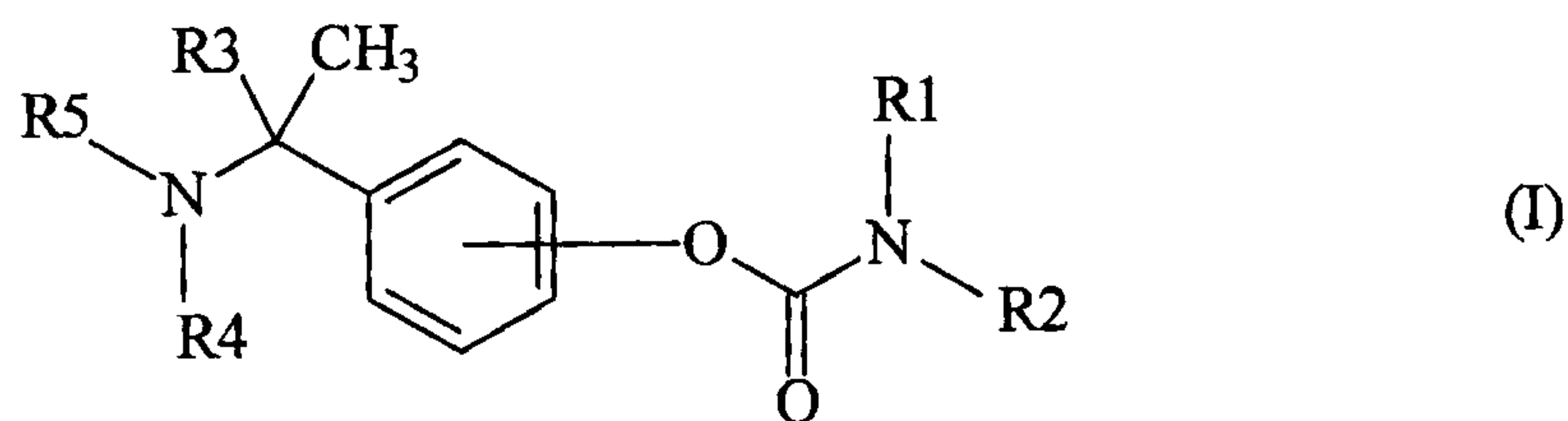
25 10. The use of any one of claims 1 to 9, wherein the compound is for topical ocular administration.

11. The use of any one of claims 1 to 10, wherein the ocular disorder is in a human being.

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12. Use of a compound of formula (I),



5

wherein

R1 is hydrogen, lower alkyl, cyclohexyl, allyl or benzyl,

R2 is hydrogen, methyl, ethyl or propyl or

10 R1 and R2 together with the nitrogen to which they are attached form a morpholino or piperidino radical,

R3 is hydrogen or lower alkyl,

R4 and R5 are the same or different and each is a lower alkyl, and the dialkylaminoalkyl group is in the meta,
15 ortho or para position,

in free base or pharmaceutically acceptable acid addition salt form,

for treatment of an ocular disorder selected from the group consisting of glaucoma and neurodegenerative
20 disease conditions of the retina and the optic nerve by lowering intra ocular pressure in the eye of a patient in need thereof.

13. The use of claim 12, wherein said dialkylaminoalkyl group is in the meta position.

25 14. The use of claim 12, wherein said compound in accordance to formula (I) is racemic N-ethyl-3-

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[(1-diethylamino)-ethyl]-N-methyl-phenyl-carbamate in the free base or in the acid addition salt form.

15. The use of claim 12, wherein said compound in accordance to formula (I) is (S)-N-ethyl-3-

5 [(1-diethylamino)-ethyl]-N-methyl-phenyl-carbamate in the free base or in the acid addition salt form.

16. The use of any one of claims 12 to 15, wherein said acid addition salt is derived from tartaric acid.

17. The use of claim 12, wherein said compound in
10 accordance to formula (I) is (S)-N-ethyl-3-
[(1-diethylamino)-ethyl]-N-methyl-phenyl-carbamate hydrogen tartrate.

18. The use of any one of claims 12 to 17, wherein the ocular disorder is glaucoma.

15 19. The use of any one of claims 12 to 17, wherein the ocular disorder is a neurodegenerative disease condition of the retina or the optic nerve.

20. The use of claim 19, wherein the neurodegenerative disease condition of the retina or the optic nerve is normal
20 tension glaucoma.

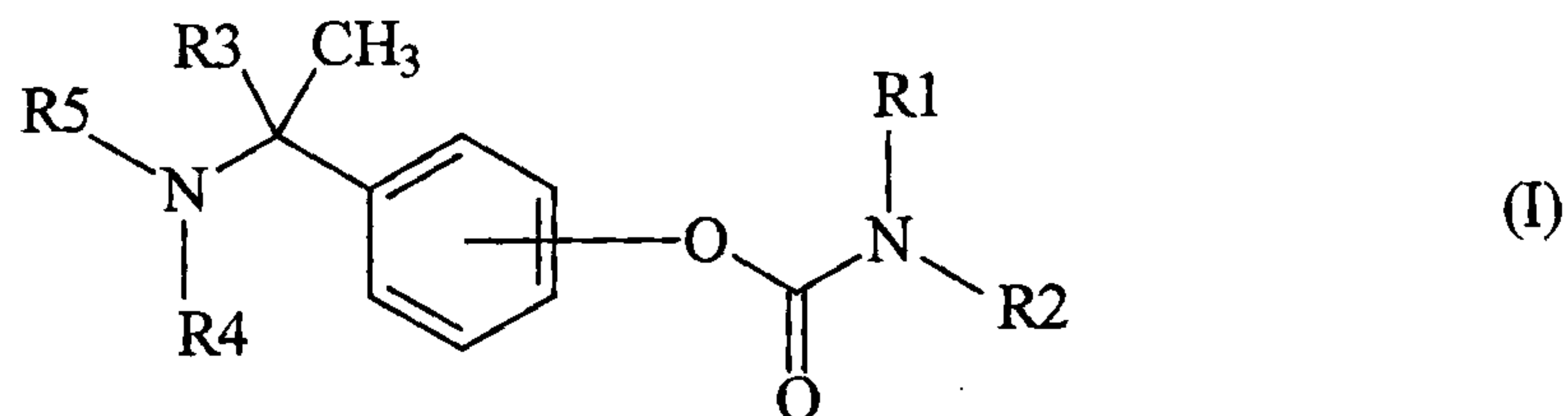
21. The use of any one of claims 12 to 20, wherein the compound is for topical ocular administration.

22. The use of any one of claims 12 to 21, wherein the ocular disorder is in a human being.

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23. A compound of formula (I),



5 wherein

R1 is hydrogen, lower alkyl, cyclohexyl, allyl or benzyl,

R2 is hydrogen, methyl, ethyl or propyl or

10 R1 and R2 together with the nitrogen to which they are attached form a morpholino or piperidino radical,

R3 is hydrogen or lower alkyl,

R4 and R5 are the same or different and each is a lower alkyl, and the dialkylaminoalkyl group is in the meta, ortho or para position,

15 in free base or pharmaceutically acceptable acid addition salt form,

for treatment of an ocular disorder selected from the group consisting of glaucoma and neurodegenerative disease conditions of the retina and the optic nerve by
20 lowering intra ocular pressure in the eye of a patient in need thereof.

24. The compound of claim 23, wherein said dialkylaminoalkyl group is in the meta position.

25. The compound of claim 23, wherein said compound in accordance to formula (I) is racemic N-ethyl-3-

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[(1-diethylamino)-ethyl]-N-methyl-phenyl-carbamate in the free base or in the acid addition salt form.

26. The compound of claim 23, wherein said compound in accordance to formula (I) is (S)-N-ethyl-3-

5 [(1-diethylamino)-ethyl]-N-methyl-phenyl-carbamate in the free base or in the acid addition salt form.

27. The compound of any one of claims 23 to 26, wherein said acid addition salt is derived from tartaric acid.

10 28. The compound of claim 23, wherein said compound in accordance to formula (I) is (S)-N-ethyl-3-[(1-diethylamino)-ethyl]-N-methyl-phenyl-carbamate hydrogen tartrate.

29. The compound of any one of claims 23 to 28,
15 wherein the ocular disorder is glaucoma.

30. The compound of any one of claims 23 to 28, wherein the ocular disorder is a neurodegenerative disease condition of the retina or the optic nerve.

31. The compound of claim 30, wherein the
20 neurodegenerative disease condition of the retina or the optic nerve is normal tension glaucoma.

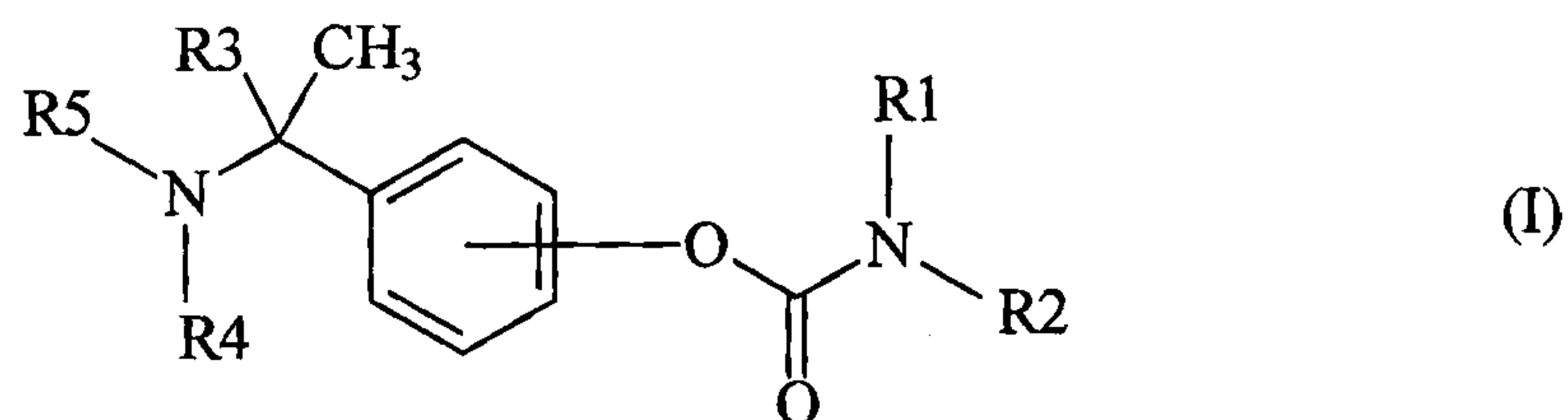
32. The compound of any one of claims 23 to 31, wherein the compound is for topical ocular administration.

33. The compound of any one of claims 23 to 32,
25 wherein the ocular disorder is in a human being.

34. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound of formula (I),

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5 wherein

R1 is hydrogen, lower alkyl, cyclohexyl, allyl or benzyl,

R2 is hydrogen, methyl, ethyl or propyl or

10 R1 and R2 together with the nitrogen to which they are attached form a morpholino or piperidino radical,

R3 is hydrogen or lower alkyl,

R4 and R5 are the same or different and each is a lower alkyl, and the dialkylaminoalkyl group is in the meta, ortho or para position,

15 in free base or pharmaceutically acceptable acid addition salt form,

for treatment of an ocular disorder selected from the group consisting of glaucoma and neurodegenerative disease conditions of the retina and the optic nerve by
20 lowering intra ocular pressure in the eye of a patient in need thereof.

35. The pharmaceutical composition of claim 34, wherein said dialkylaminoalkyl group is in the meta position.

25 36. The pharmaceutical composition of claim 34, wherein said compound in accordance to formula (I) is

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racemic N-ethyl-3-[(1-diethylamino)-ethyl]-N-methyl-phenyl-carbamate in the free base or in the acid addition salt form.

37. The pharmaceutical composition of claim 34,
5 wherein said compound in accordance to formula (I) is (S)-N-ethyl-3-[(1-diethylamino)-ethyl]-N-methyl-phenyl-carbamate in the free base or in the acid addition salt form.

38. The pharmaceutical composition of any one of
claims 34 to 37, wherein said acid addition salt is derived
10 from tartaric acid.

39. The pharmaceutical composition of claim 34,
wherein said compound in accordance to formula (I) is (S)-N-ethyl-3-[(1-diethylamino)-ethyl]-N-methyl-phenyl-carbamate hydrogen tartrate.

15 40. The pharmaceutical composition of any one of
claims 34 to 39, wherein the ocular disorder is glaucoma.

41. The pharmaceutical composition of any one of
claims 34 to 39, wherein the ocular disorder is the
neurodegenerative disease condition of the retina or the
20 optic nerve.

42. The pharmaceutical composition of claim 41,
wherein the neurodegenerative disease condition of the
retina or the optic nerve is normal tension glaucoma.

43. The pharmaceutical composition of any one of
25 claims 34 to 42, wherein the compound is for topical ocular
administration.

44. The pharmaceutical composition of any one of
claims 34 to 43, wherein the ocular disorder is in a human
being.