



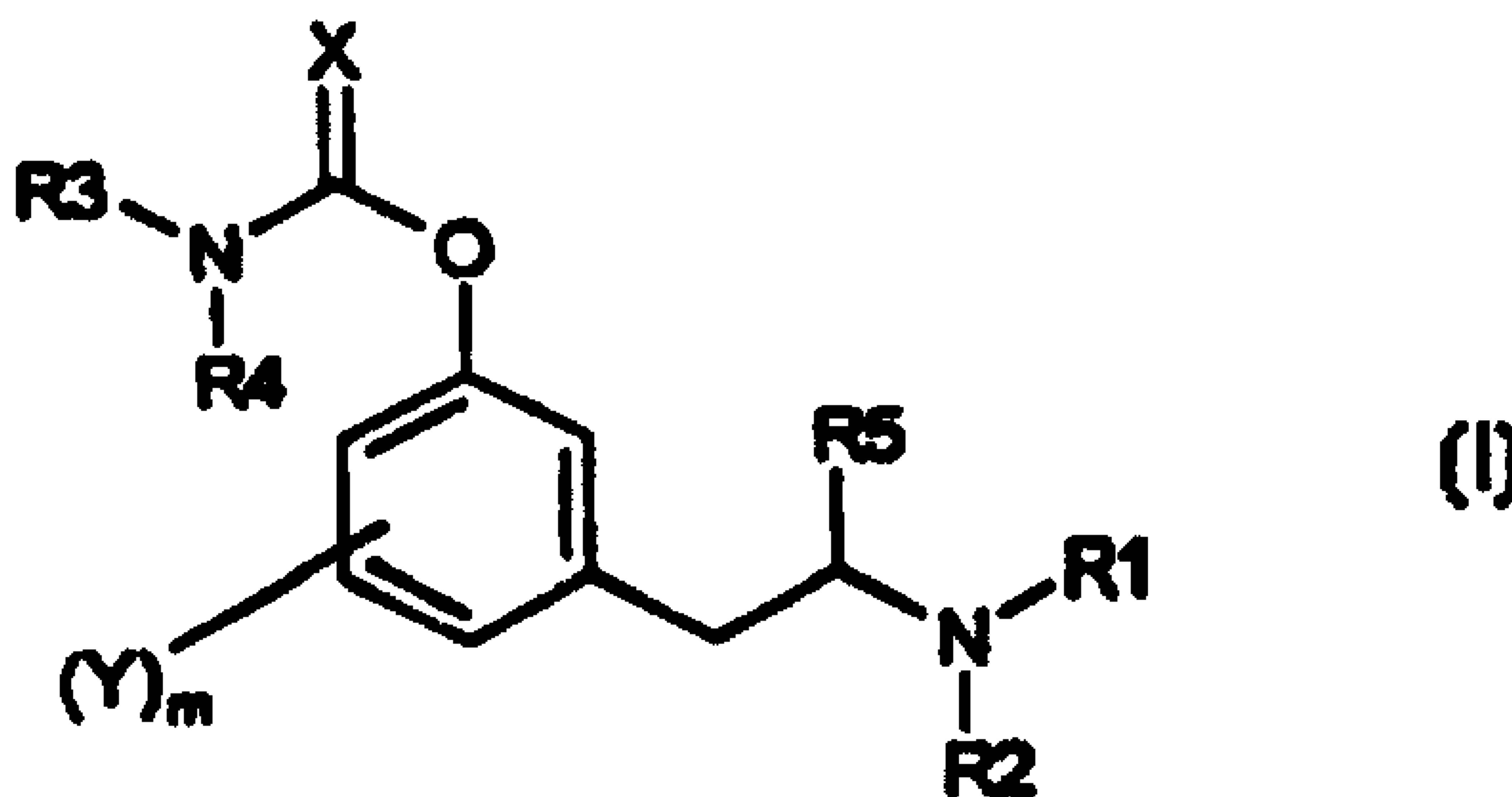
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(54) Titre : DERIVES DE PHENYLETHYLAMINE
(54) Title: PHENYLETHYLAMINE DERIVATIVES



(57) **Abrégé/Abstract:**

This invention is directed to compounds of formula (I) wherein m is from 0-4; X is O or S; Y is halogeno; R₁ is hydrogen or C₁₋₄ alkyl; R₂ is hydrogen, C₁₋₄ alkyl or optionally substituted propargyl; and R₃ and R₄ are each independently hydrogen, C₁₋₈ alkyl, C₆₋₁₂ aryl, C₆₋₁₂ cycloalkyl or C₆₋₁₂ aralkyl, R₅ is hydrogen or C₁₋₄ alkyl; and pharmaceutically acceptable salts thereof, provided that when X is O, R₂ is optionally substituted propargyl. This invention is also directed to the use of these compounds for treating depression, Attention Deficit Disorder (ADD), Attention Deficit and Hyperactivity Disorder (ADHD), Tourette's Syndrome, Alzheimer's Disease and other dementia's such as senile dementia, dementia of the Parkinson's type, vascular dementia and Lewy body dementia. This invention is further directed to a pharmaceutical composition comprising a therapeutically effective amount of the above-defined compounds and a pharmaceutically acceptable carrier.

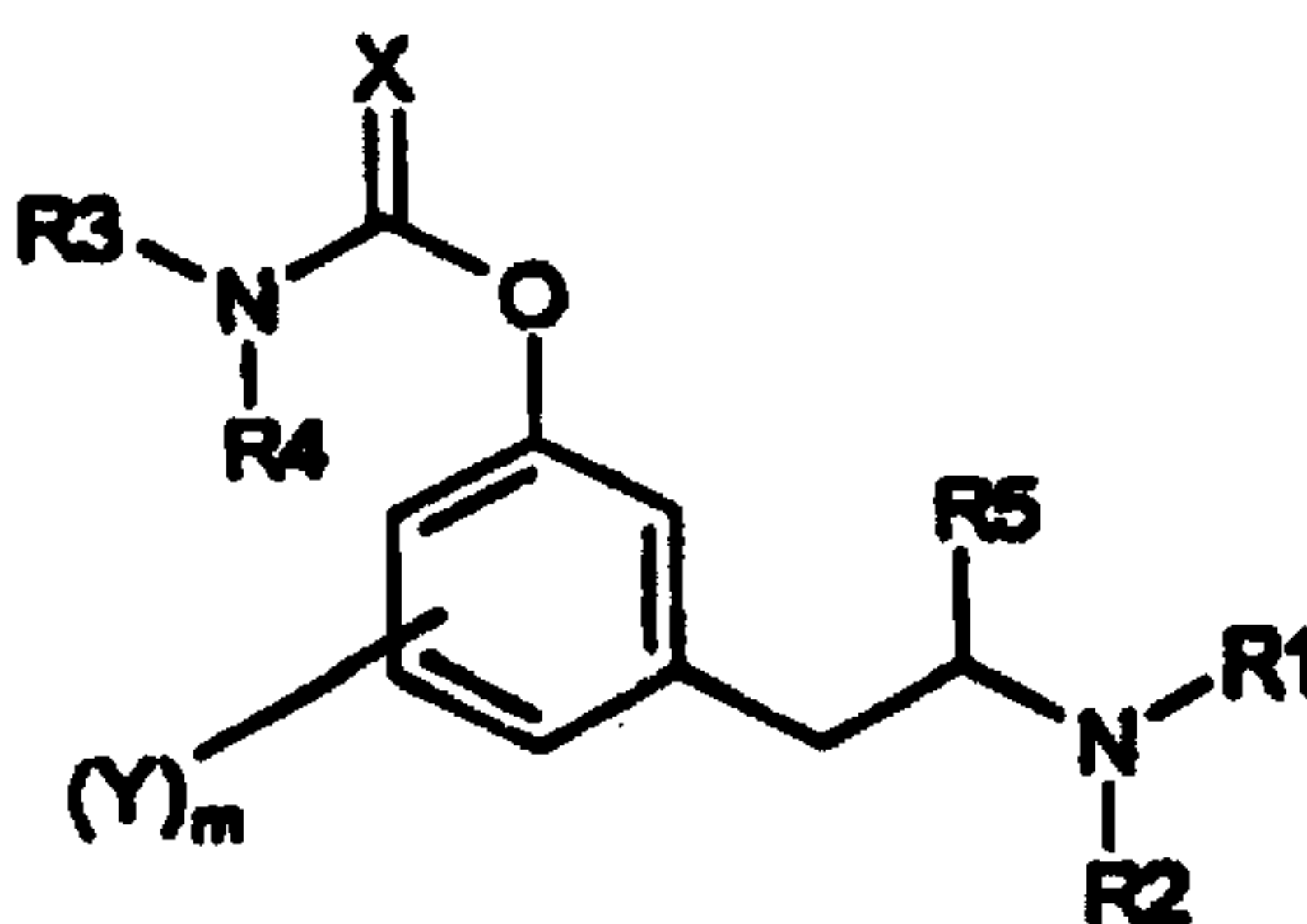
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(54) Title: PHENYLETHYLAMINE DERIVATIVES			
(57) Abstract			
This invention is directed to compounds of formula (I) wherein m is from 0-4; X is O or S; Y is halogeno; R₁ is hydrogen or C₁₋₄ alkyl; R₂ is hydrogen, C₁₋₄ alkyl or optionally substituted propargyl; and R₃ and R₄ are each independently hydrogen, C₁₋₈ alkyl, C₆₋₁₂ aryl, C₆₋₁₂ cycloalkyl or C₆₋₁₂ aralkyl, R₅ is hydrogen or C₁₋₄ alkyl; and pharmaceutically acceptable salts thereof, provided that when X is O, R₂ is optionally substituted propargyl. This invention is also directed to the use of these compounds for treating depression, Attention Deficit Disorder (ADD), Attention Deficit and Hyperactivity Disorder (ADHD), Tourette's Syndrome, Alzheimer's Disease and other dementia's such as senile dementia, dementia of the Parkinson's type, vascular dementia and Lewy body dementia. This invention is further directed to a pharmaceutical composition comprising a therapeutically effective amount of the above-defined compounds and a pharmaceutically acceptable carrier.		 (I)	

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PHENYLETHYLAMINE DERIVATIVES

Field of Invention

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The present invention relates to novel compounds, pharmaceutical compositions containing said compounds and their use in the treatment of various CNS disorders.

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Background to the Invention

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Dementia may take several forms including static dementia, Alzheimer's-type dementia, senile dementia, presenile dementia and progressive dementia. One of the common pathological features of several types of dementia is the lack of the neurotransmitter acetylcholine. This has led to the development of acetylcholine esterase inhibitors for use in the treatment of dementia's such as the compound tacrine.

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Recently, compounds that in addition to inhibiting acetylcholine esterase, have inhibitory activity against monoamine oxidase type A (MAO-A) have been developed. The perceived benefit of having the anti-MAO-A activity is stated to be an anti-depressant effect (European Patent Applications Publication Nos. 614,888 and 664,291). Fink et al., (Bioorg & Med Chem Letts (1996) 6 625-630) also disclose compounds having both acetylcholine esterase and monoamine oxidase inhibitory moieties.

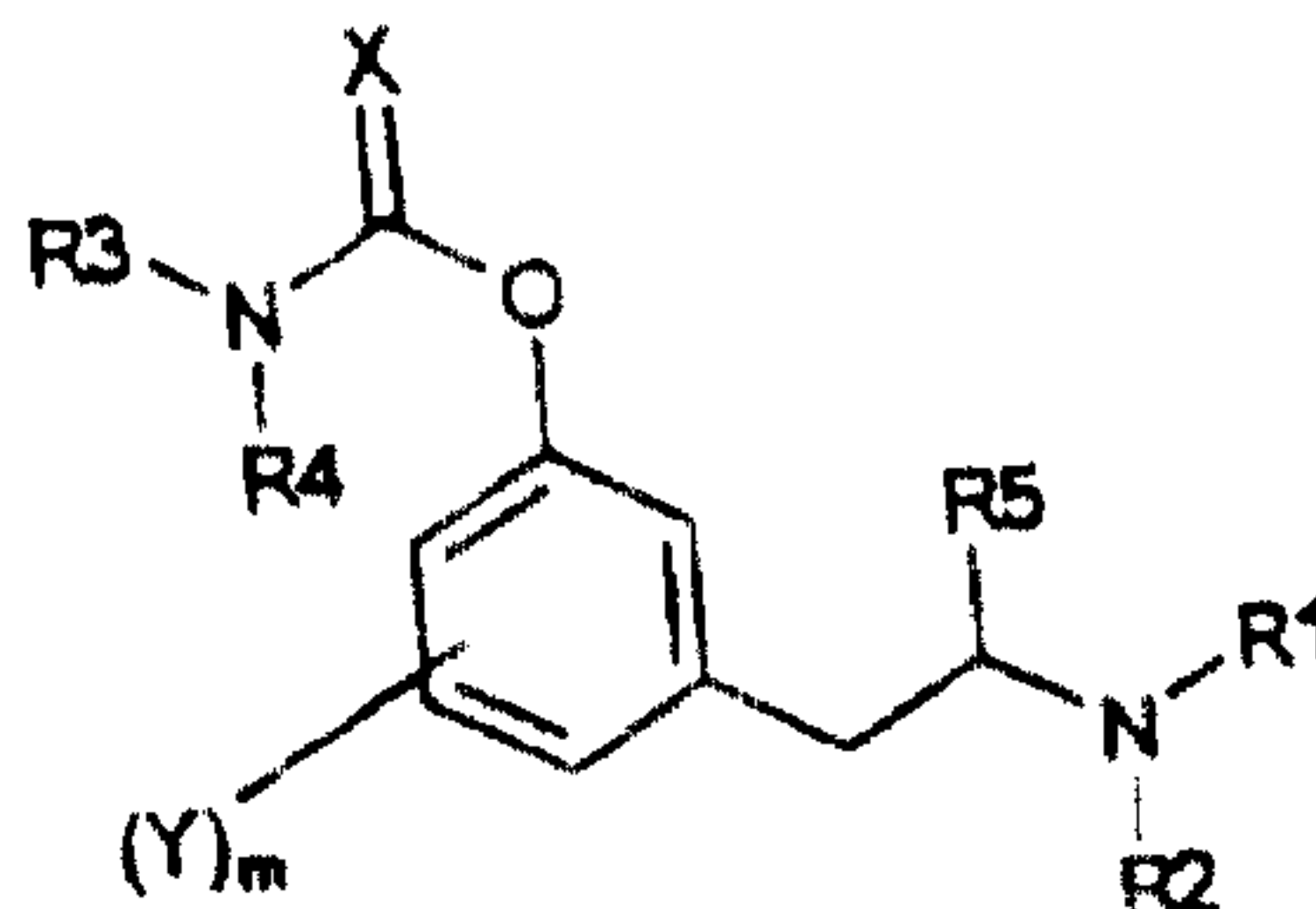
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International Patent Application Publication No. WO96/02524 relates to alkylamino substituted phenylcarbamate derivatives having acetylcholinesterase inhibitory activity and their use in the treatment of Alzheimer's Disease.

Summary of the Invention

The present invention relates to compounds of formula I having the following formula:



wherein m is from 0-4; X is O or S; Y is halogeno; R₁ is hydrogen or C₁₋₄ alkyl; R₂ is hydrogen, C₁₋₄ alkyl or optionally substituted propargyl; R₃ and R₄ are each independently hydrogen, C₁₋₈ alkyl, C₆₋₁₂ aryl, C₆₋₁₂ cycloalkyl or C₆₋₁₂ aralkyl; and R₅ is hydrogen or C₁₋₄ alkyl, with the proviso that when X is O, R₂ is optionally substituted propargyl.

As used hereinafter, references to the compounds of formula I include all compounds of formula I without the final proviso.

The invention relates to the compounds themselves, pharmaceutical compositions containing said compounds and their use in the treatment of depression, Attention Deficit Disorder (ADD), Attention Deficit and Hyperactivity Disorder (ADHD), Tourette's Syndrome, Alzheimer's Disease and other demetias such as senile dementia, dementia of the Parkinson's type, vascular dementia and Lewy body dementia.

A further aspect of the present invention relates to the use of the compounds of formula I wherein m is from 0-4; X is O or S; Y is halogeno; R₁ is hydrogen or C₁₋₄ alkyl; R₂ is hydrogen, C₁₋₄ alkyl or optionally substituted propargyl; R₃ and R₄ are each independently hydrogen, C₁₋₈ alkyl, C₆₋₁₂ aryl, C₆₋₁₂ cycloalkyl or C₆₋₁₂ aralkyl; and R₅ is hydrogen or C₁₋₄ alkyl, in the treatment of neurotrauma, memory disorder or depression.

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5 As used herein the term "neurotrauma" includes, but is not limited to, damage caused to the nervous system (both central and peripheral) by virtue of ischemic damage such as stroke, hypoxia or anoxia, neurodegenerative diseases, Parkinson's Disease, Alzheimer's Disease, Huntington's Disease, neurotoxic injury, head trauma injury, spinal trauma injury, peripheral neuropathy and any form of nerve damage.

The present invention relates to the racemic compounds themselves and optically active isomers thereof.

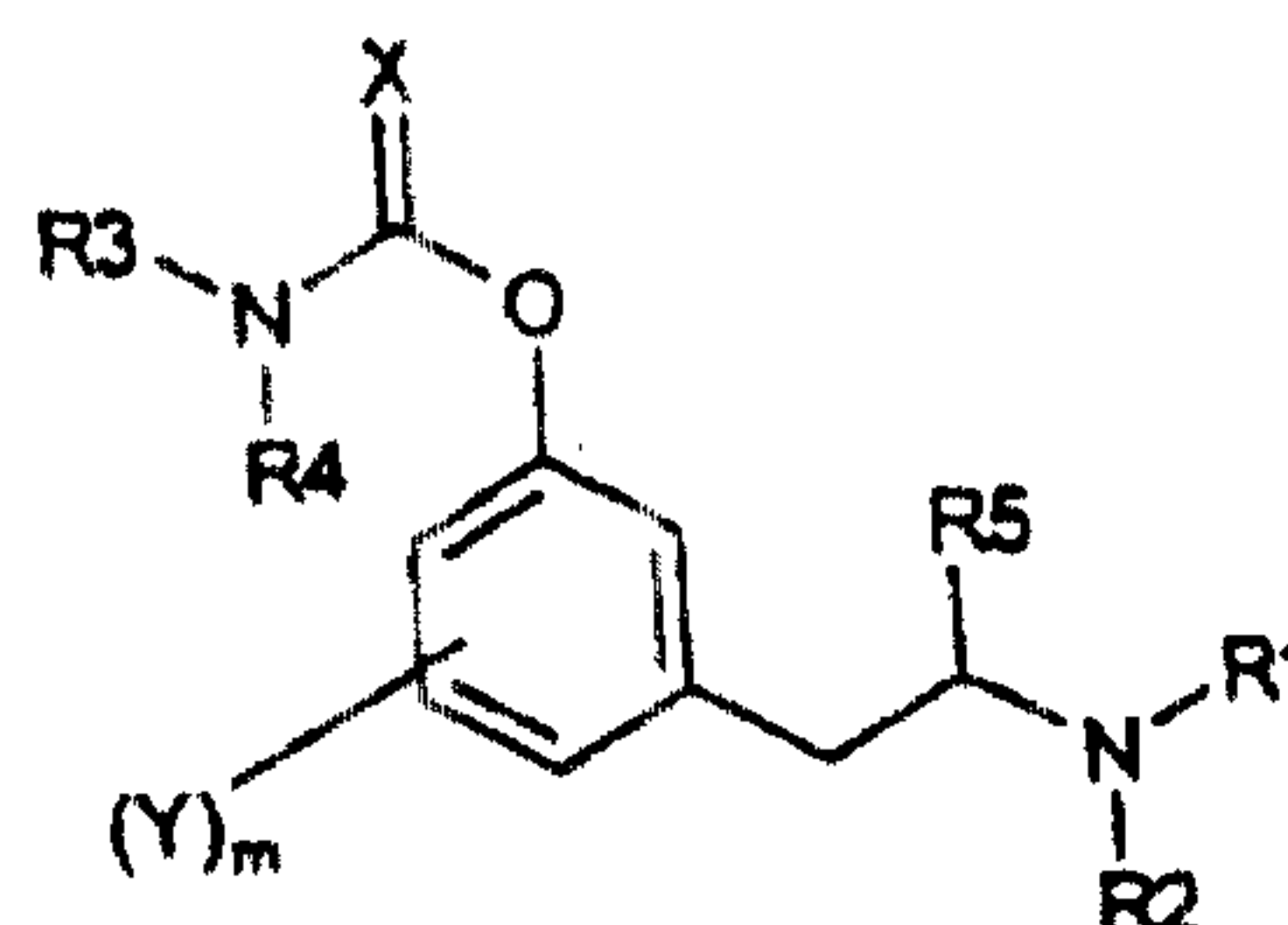
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Description of the Preferred Embodiments

The present invention is directed to compounds having the following formula:



wherein m is from 0-4;

X is O or S;

Y is halogeno;

R₁ is hydrogen or C₁₋₄ alkyl;

R₂ is hydrogen, C₁₋₄ alkyl or optionally substituted propargyl; and R₃ and R₄ are each independently hydrogen, C₁₋₂ alkyl, C₆₋₁₂ aryl, C₆₋₁₂ cycloalkyl or C₆₋₁₂ aralkyl, R₅ is hydrogen or C₁₋₄ alkyl; and pharmaceutically acceptable salts thereof, provided that when X is O, R₂ is optionally substituted propargyl.

In an embodiment of the present invention, X is O. In a further embodiment of the present invention, X is S.

In an embodiment of the present invention, the compound is selected from the group consisting of: (rac)-3-(N-methyl,N-propyl-carbamoyloxy)- α -methyl-N'-propargyl phenethylamine HCl; (rac)-3-(N,N-dimethyl-carbamoyloxy)- α -methyl-N'-methyl,N'-propargyl phenethylamine HCl; (rac)-3-(N-methyl,N-hexyl-carbamoyloxy)- α -methyl-N'-methyl, N'-propargyl phenethylamine mesylate; (rac)-3-(N-methyl,N-cyclohexyl-carbamoyloxy)- α -methyl-N'-methyl, N'-propargyl phenethylamine HCl; and (S)-3-(N-methyl, N-hexyl-carbamoyloxy)- α -methyl-N'-methyl,N'-propargyl phenethylamine ethanesulfonate.

A first object of the present invention relates to the compounds of formula I and their use in the treatment of

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Alzheimer's Disease and related dementias.

5 In an embodiment of the present invention R_1 is hydrogen, methyl or ethyl. When R_2 is propargyl then it may optionally be substituted. Such substitution is preferably on the methylene group (see R_6 in Scheme I) and is selected from the group consisting of C_{1-4} alkyl.

10 According to the present invention, "halogeno" is used to refer to fluoro, chloro, bromo or iodo.

In an embodiment of the present invention, when m is greater than 1, each Y may be the same or different.

15 In a further embodiment of the present invention, at least one of R_3 and R_4 is methyl and the other is hydrogen, methyl, ethyl, propyl, hexyl or cyclohexyl. In an additional embodiment of the present invention, R_5 is hydrogen or methyl.

20 The subject invention further provides pharmaceutically acceptable salts of the compounds of formula I. Examples of pharmaceutically acceptable salts include, but are not limited to, esylate salts, mesylate salts, maleate salts, fumarate salts, tartrate salts, hydrochloride salts, hydrobromide salts, p-toluenesulfonate salts, benzoate salts, acetate salts, phosphate salts and sulfate salts.

30 The subject invention further provides a pharmaceutical composition which comprises a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. The "therapeutically effective amount" of a compound of formula I or a pharmaceutically acceptable salt thereof may be determined according to methods well known to those skilled in the art.

35 The compositions of the present invention may be prepared as medicaments to be administered orally, parenterally,

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rectally, or transdermally.

Suitable forms for oral administration include tablets, compressed or coated pills, dragees, sachets, hard or soft gelatin capsules, sublingual tablets, syrups and suspensions. In one embodiment, the pharmaceutically acceptable carrier is a solid and the pharmaceutical composition is a tablet.

The therapeutically effective amount may be an amount from about 0.5mg to about 2000 mg, preferably, from about 1mg to about 1000mg.

In an alternative embodiment, the pharmaceutically acceptable carrier is a liquid and the pharmaceutical composition is an injectable solution. The therapeutically effective amount may be an amount from about 0.5mg to about 2000mg, preferably from 1mg to about 1000mg. The volume administered may be an amount between 0.5 and 10ml.

In a further alternative embodiment, the carrier is a gel and the pharmaceutical composition is a suppository. For parenteral administration the invention provides ampoules or vials that include an aqueous or non-aqueous solution or emulsion. For rectal administration there are provided suppositories with hydrophilic or hydrophobic vehicles. For topical application as ointments and transdermal delivery there are provided suitable delivery systems as known in the art. For oral or suppository formulations, 0.5-2000 mg per unit dosage, and preferably 1-1000 mg per dosage unit is taken daily.

These compositions may be used alone to treat the above-listed disorders, or alternatively, as in the case of Alzheimer's Disease, for example, they may be used as an adjunct to the conventional treatments such as haloperidol, tacrine or deprenyl.

The invention will be better understood from the

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Experimental Details which follow. However, one skilled in the art will readily appreciate that the specific methods and results discussed are merely illustrative of the invention as described more fully in the claims which follow thereafter.

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Experimental Details

Introduction

Compounds of general formula I may be prepared (as shown in Scheme I) from the corresponding carbamoyl derivatives of phenethylamine IV by reacting the latter with propargyl compounds bearing an appropriate leaving group at the 3-position, e.g. a halide group, mesylate, tosylate, etc., under basic conditions provided by an inorganic base, e.g. K_2CO_3 , NaOH, or an organic base e.g. a tertiary amine, in a polar organic solvent, e.g. CH_3CN , DMF, etc., at 15-40°C, preferably at 20-25°C, for a period of time in the range of 5-24 hours, preferably 5-10 hours. The products, obtained after a suitable work-up and purification, are in the form of free bases. Preferably these are converted into their pharmaceutically acceptable salts.

Compounds of general formula IV may be prepared by Boc deprotection of compounds of general formula III. Preferably the deprotected compounds obtained are converted into their hydrochloride salts. Compounds of general formula III may be prepared by carbamylating a compound of general formula II in a conventional manner, e.g. by reacting the compound of formula II with an appropriate carbamoyl halogenide or an alkylisocyanate.

Compounds of general formula II may be prepared by Boc protection of the appropriate hydroxy phenethylamines, by methods known to those skilled in the art.

Compounds of general formula I, where R_1 is not H, may also be prepared (as shown in scheme II) by carbamylation of VII, by the same method described above for the carbamylation of II. Compounds of general formula VII may be prepared by propargylation of the 3-hydroxy phenethylamines of general formula VI, by methods analogous to those described for the propargylation of IV.

N,N dialkyl substituted compounds of formula I may be

prepared by the carbamylation of compounds of formula V or the N-alkylation of compounds of formula IV.

STARTING MATERIALS

3-Hydroxy-phenethylamine and its N-methyl analogue were obtained by demethylation of 3-methoxy phenethylamine and N-methyl-3-methoxy phenethylamine. The latter was prepared from 3-methoxy phenethylamine by reductive alkylation (ethyl formate, followed by lithium aluminium hydride).

N,N-Dimethyl-3-hydroxy phenethylamine was prepared by reductive amination (H_2 , Pd/C, Me_2NH) of (3-methoxyphenyl) acetonitrile¹, followed by O-demethylation.

3-Hydroxy-methyl phenethylamine was obtained by O-demethylation of the corresponding 3-methoxy analogue. The latter may be prepared by reductive amination ($NaCNBH_3$, NH_4OAc)² of 3-methoxyphenyl acetone³ or by reduction of 1-(3-methoxyphenyl)-2-nitro-1-propene (obtained by condensing 3-methoxy benzaldehyde with nitroethane)⁴. 3-Hydroxy-,N-dimethyl phenethylamine was prepared by O-demethylation of the corresponding 3-methoxy analogue. The latter was obtained by the reductive amination (methylamine, $NaCNBH_3$)² of 3-methoxyphenyl acetone³.

Alternatively, 3-hydroxy-(α ,N-dimethyl phenethylamine may be prepared by reductive methylation (N-formylation followed by reduction) of 3-hydroxy- α -methyl phenethylamine.

References:

1. JS Buck et al., *J. Amer. Chem. Soc.* (1938) 60: 1789
2. RF Borch et al., *J. Amer. Chem. Soc.* (1971) 93: 2897
3. *Org. Synth. Coll. Vol IV*, (1963) 573; and
4. A Carlsson, et al., *Acta. Pharm. Suecica*. (1970) 7: 293.

Preparation of Compounds of the Present Invention

A. Boc - protection and carbamylation

1. Boc protection

(3-hydroxy-N-Boc,N-methyl phenethylamine)

To a solution of 3-hydroxy N-methyl phenethylamine (8.33 g, 55.17 mmol) in dioxane (80 ml) and water (80 ml) was added NaHCO₃ (13.65 g) and di-t-butyl dicarbonate (13.65 g, 62.54 mmol). The reaction mixture was stirred at room temperature (RT) for 4 hrs and evaporated to dryness in-vacuo. The residue was taken up in a water:dioxane mixture (400 ml, 1:1), and the layers were separated. The aqueous layer was re-extracted with ether (2x75 ml) and the combined ether layer was dried (Na₂SO₄) and evaporated to dryness in-vacuo. The oily residue was purified by column chromatography (hexane:EtOAc 2:1) to give 10.2 g (74%) of the title compound as a viscous yellow oil.

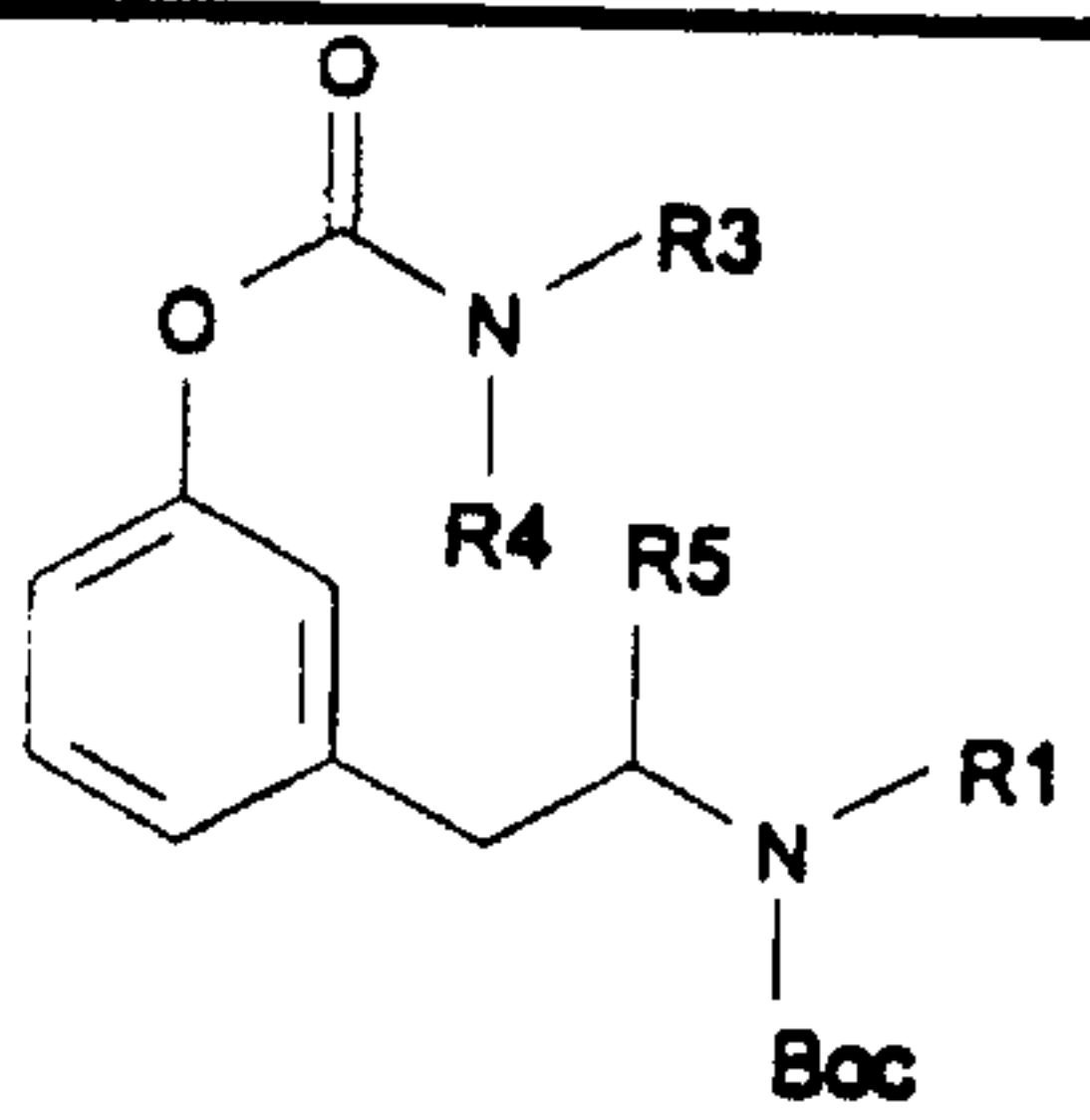
2. Carbamylation

3-(N-Me,N-nPr carbamyloxy) N-Boc,N-methyl phenethylamine

To an ice-cooled solution of 3-hydroxy-N-Boc,N-methyl phenethylamine (5.0 g, 19.9 mmol) in dry acetonitrile (65 ml) was added under nitrogen, N-methyl,N-n-propyl carbamoyl chloride (4.66 g, 34.43 mmol), followed by the portionwise addition of NaH (60% disp. in oil, 1.03 g, 25.87 mmol). The reaction mixture was stirred at RT under nitrogen for 6 hrs and evaporated to dryness in-vacuo. Water (200 ml) was added, the pH was adjusted to ~9 and the aqueous layer was extracted with ether (4x100 ml). The combined ether layer was washed with NaOH solution (pH 9.5), water (150 ml), dried (Na₂SO₄) and evaporated to dryness in-vacuo to give an oil which was purified by column chromatography (hexane:EtOAc 2:1), affording 6.0 g (86%) of the title compound as a yellow oil.

According to these methods the exemplary intermediates in Table 1 were prepared.

Table 1 N-Boc Protected carbamyloxy-phenylethylamines



R1	R3	R4	R5	yield (%)
H	Me	Me	H	85
H	Me	Pr	H	89
Me	Me	Me	H	86
H	Me	Et	H	83
Me	Me	Et	H	78
Me	Me	Pr	H	86
H	Me	Me	Me	80
H	Me	Et	Me	92
H	Me	Pr	Me	98

B. Boc - Deprotection and Salt Formation

3-(N-Me,N-nPr Carbamyloxy) N-methyl phenethylamine . HCl
(Compound 6)

3-(N-Me,N-nPr Carbamyloxy) N-Boc,N-methyl phenethylamine (6.0 g, 17.14 mmol) was dissolved in dioxane (60 ml) and 20% HCl/ether (60 ml) was added. The mixture was stirred at RT for 4 hrs and evaporated to dryness in-vacuo, and the residual oil was treated with ether (2x150 ml), to give, after stirring and ice-cooling, 4.6 g (93.5%) of the title compound as a white solid. In this manner the compounds shown in Table 2 were prepared, their analytical characteristics are given in Table 4.

Table 2 Carbamyloxy-phenylethylamines (HCl salts)

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Compound #	R1	R3	R4	R5	cryst/slurry solvent	mp (°C)	yield (%)
1	H	Me	Me	H	Et ₂ O	125-7	86
2	H	Me	Pr	H	Et ₂ O	83-5	85
3	Me	Me	Me	H	Et ₂ O	126-8	94
4	H	Me	Et	H	Et ₂ O	103-5	95
5	Me	Me	Et	H	Et ₂ O	-	68
6	Me	Me	Pr	H	Et ₂ O	86-8	93
7	H	Me	Me	Me	Et ₂ O	-	80
8	H	Me	Et	Me	Et ₂ O	-	81
9	H	Me	Pr	Me	Et ₂ O	-	78
10	Me,Me	Me	Me	H	iPrOH/Et ₂ O	127-9	49
23	H	H	Pr	H	Et ₂ O	205-7	
24	Me	Me	n-hexyl	Me	Et ₂ O	hygroscopic	89
25	Me	Me	cyclohexyl	Me	Et ₂ O	-	95

C. Propargylation and salt formation

3 - (N-Me, N-Et carbamyloxy) α -methyl, N-propargyl phenethylamine.HCl (Compound 17)

A solution of propargyl bromide (1.1 g, 9.1 mmol) in acetonitrile (8.5 ml) was added dropwise to a stirred mixture of 3 - (N-Me, N-Et carbamyloxy) α -methyl phenethylamine.HCl (2.4 g, 8.8 mmol) and potassium carbonate (2.8 g) in acetonitrile (25 ml), and the mixture was stirred

at RT for 7 hrs. The reaction mixture was filtered and the filtrate was removed under reduced pressure and the residue was purified by column chromatography (hexane:EtOAc 2:1) to give 1.76 g of the title compound as the free base (73%).

The free base was dissolved in dry ether (50 ml) and HCl/ether was added (to pH 1). The mixture was stirred for 4 hrs at RT, filtered and the solid was washed with cold ether, to give, after drying at 60°C in-vacuo, 1.5 g (4.82 mmol, 55%).

3-(N-Me,N-nPr carbamyloxy)N-methyl,N-propargyl phenethylamine.HCl
(Compound 18)

To a stirred mixture of 3-(N-Me,N-nPr carbamyloxy)N-methyl phenethylamine.HCl (4.02 g, 14.0 mmol) and potassium carbonate (3.87g, 28.0 mmol) in acetonitrile (150 ml), was added dropwise at RT a solution of propargyl bromide (1.67 g, 14.0 mmol) in acetonitrile (10 ml). The reaction mixture was stirred at RT for 21 hrs, filtered and the filtrate evaporated to dryness in-vacuo and the residual orange oil (4.1 g) was purified by column chromatography (EtOAc) to give 2.7 g of the free base.

The free base (1.35 g, 4.69 mmol) was dissolved in dry ether (70 ml) and HCl/ether (7 ml) was added dropwise. The mixture was stirred at RT for 1/2 hr and the supernatant was decanted off. The gummy residue was crystallized twice from iPrOH/ether to give 1.16 g (51.4%) of a white solid.

The methods were repeated and the following compounds of the present invention were prepared (Table 3), their analytical characteristics are given in Table 5.

D. Propargylation of 3-hydroxy phenethylamines

(S)-3-Hydroxy- α ,N-dimethyl-N-propargyl-phenethylamine
(Compound 42)

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To a solution of (S)-3-Hydroxy- α ,N-dimethyl phenethylamine.HCl (4.4g, 21.8mmol) in dimethylacetamide (200 ml) stirred at 25°C under a nitrogen atmosphere, was added K₂CO₃ (6.04g, 43.64 mmol), and the mixture was stirred for 10 minutes. Then a solution of propargyl bromide (2.34g, 19.64 mmol) in dimethylacetamide (10ml) was added over 2 minutes and the mixture was stirred at 25°C for 24 hours.

Water (250ml) was added and the mixture was stirred until all the solid material dissolved. The aqueous layer was extracted with toluene (10 x 75ml). The layers were separated and the combined toluene layer was washed with saturated brine (2 x 150ml) and dried (Na₂SO₄). Removal of solvent at reduced pressure gave an orange oil, which was purified by flash column chromatography using ethyl acetate as the eluent. This gave 3.60g (90.2%) of Compound 42 as an orange oil.

Using this procedure, the (R) isomer (Compound 41) was obtained in 80%.

E. Carbamylation and salt formation

(S)3-(N-methyl,N-ethyl-carbamyl-oxy)-(α ,N-dimethyl-N-propargyl-phenethylamine esylate (Compound 39)

To a solution of compound 42 (1.80 g, 8.87 mmol) in dry acetonitrile (100 ml) cooled in an ice bath, was added under nitrogen N-methyl-N-cyclohexylcarbonyl chloride (2.70 g, 15.39 mmol) followed by the portionwise addition of NaH (60% oil dispersion, 0.467 g, 11.69 mmol). The mixture was then stirred at RT under nitrogen for 18 hours. Solvent was removed at reduced pressure and water (100 ml) and ether (150 ml) were added. The mixture was stirred until all the material dissolved. The layers were separated and the aqueous layer was reextracted with ether (4 x 70ml). The combined ether layers were washed with KOH solution (pH 9.5), water and dried (Na₂SO₄).

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Removal of solvent at reduced pressure gave 3.87 g of an orange oil which was purified by flash column chromatography using the ethyl acetate as the eluent. This gave 2.57 g (84.5%) of the title compound (free base) as a yellow oil.

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The free base was dissolved in dry EtOAc (9 ml) and a solution of 95% ethanesulfonic acid (0.79 g, 6.81 mmol) in EtOAc (1.5 ml) was added. The solution was cooled to 5°C and stirred at this temperature. After about 15 minutes, a white solid precipitated and it was stirred at 5°C for 3 hours. The solid was filtered using a minimum amount of ice-cold ethyl acetate. This gave 2.3g (75%) of a white solid having a melting point of 118-120°C.

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The methods were repeated and the following compounds of the present invention were prepared (Table 3a), their analytical characteristics are given in Table 5.

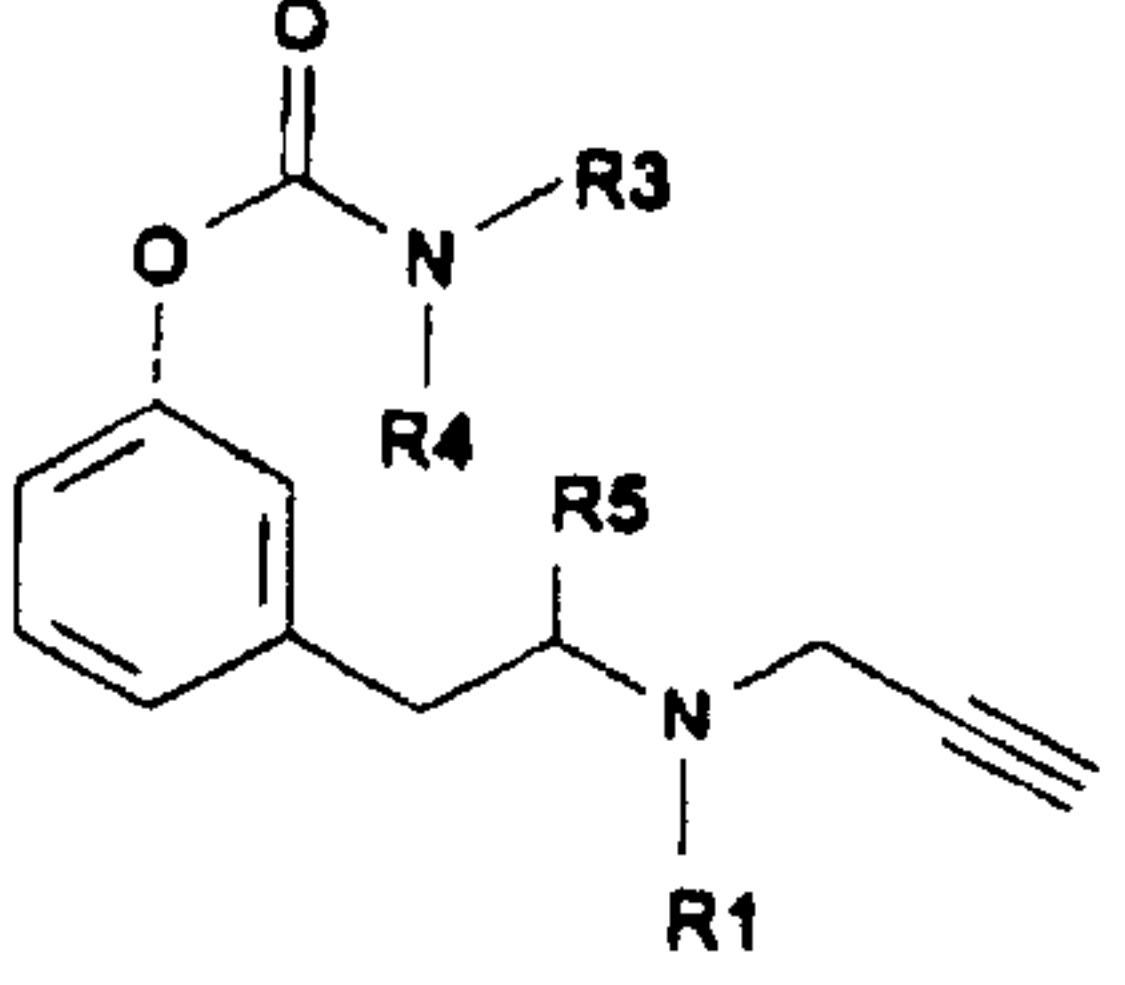
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Table 3 Carbamoyloxy-N-propargyl-phenylethylamines (HCl salts)

							
Compound #	R1	R3	R4	R5	cryst/slurry solvent	mp (°C)	yield (%)
11	H	Me	Me	H	iPrOH/Et ₂ O	138-9	47
12	Me	Me	Me	H	iPrOH/Et ₂ O	150-2	54
13	H	Me	Et	H	iPrOH/Et ₂ O	113-15	36
14	H	Me	Pr	H	iPrOH/Et ₂ O	108-10	20
15	Me	Me	Et	H	iPrOH/Et ₂ O	152-4	41
16	H	Me	Me	Me	Et ₂ O	166-70	34
17	H	Me	Et	Me	Et ₂ O	119-121	60
18	Me	Me	Pr	H	iPrOH/Et ₂ O	114-6	51
19	H	Me	Pr	Me	Et ₂ O	170-2	31
20	Me	Me	Me	Me	iPrOH/Et ₂ O	158-160	78
21	Me	Me	Et	Me	iPrOH/Et ₂ O	144-6	59
22	Me	Me	Pr	Me	iPrOH/Et ₂ O	ND	60
26	H	H	Pr	H	iPrOH/Et ₂ O	209-11	20
27*	Me	Me	n-hexyl	Me	Et ₂ O	95-7	13
28	Me	Me	cyclohexyl	Me	Et ₂ O	105-7	35
29**	H	Me	Me	H	iPrOH/Et ₂ O	151-3	88
30**	H	Me	Et	H	iPrOH/Et ₂ O	135-7	89
36	H	Me	cyclohexyl	Me	Et ₂ O	100-2	54

* mesylate salt

** substituted propargyl derivative, R6 in Scheme I is Me.

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Table 3a

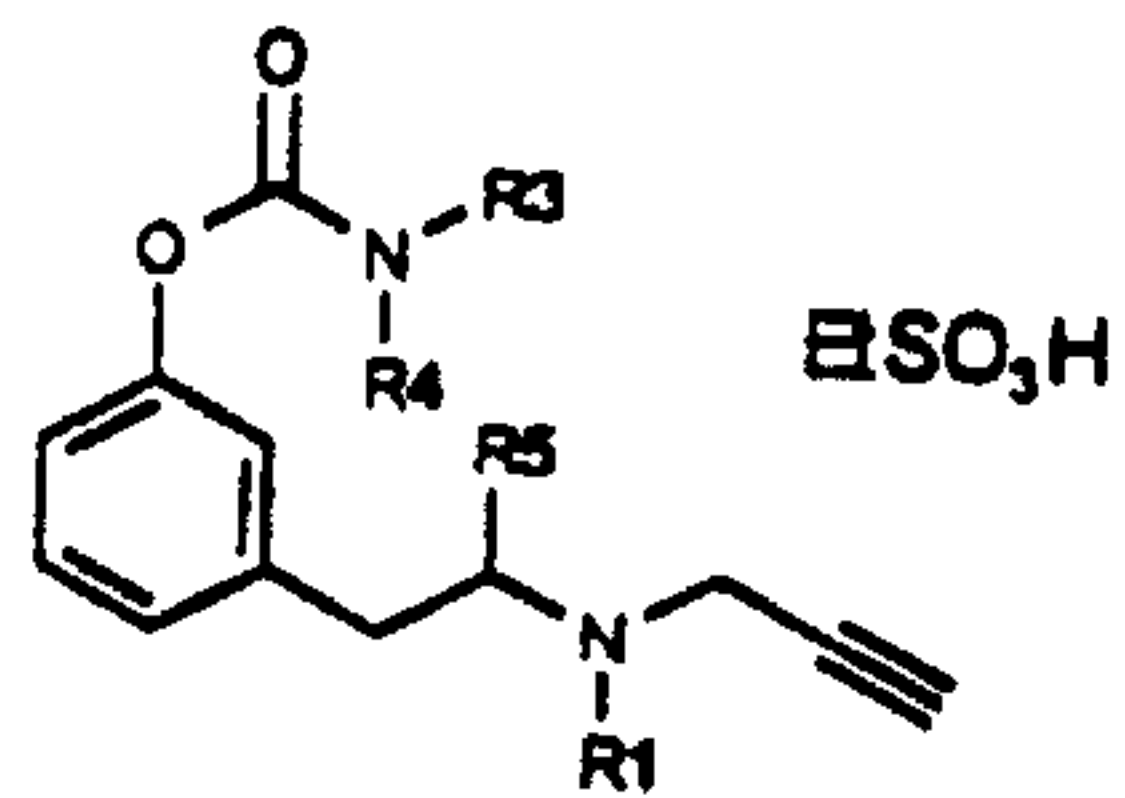
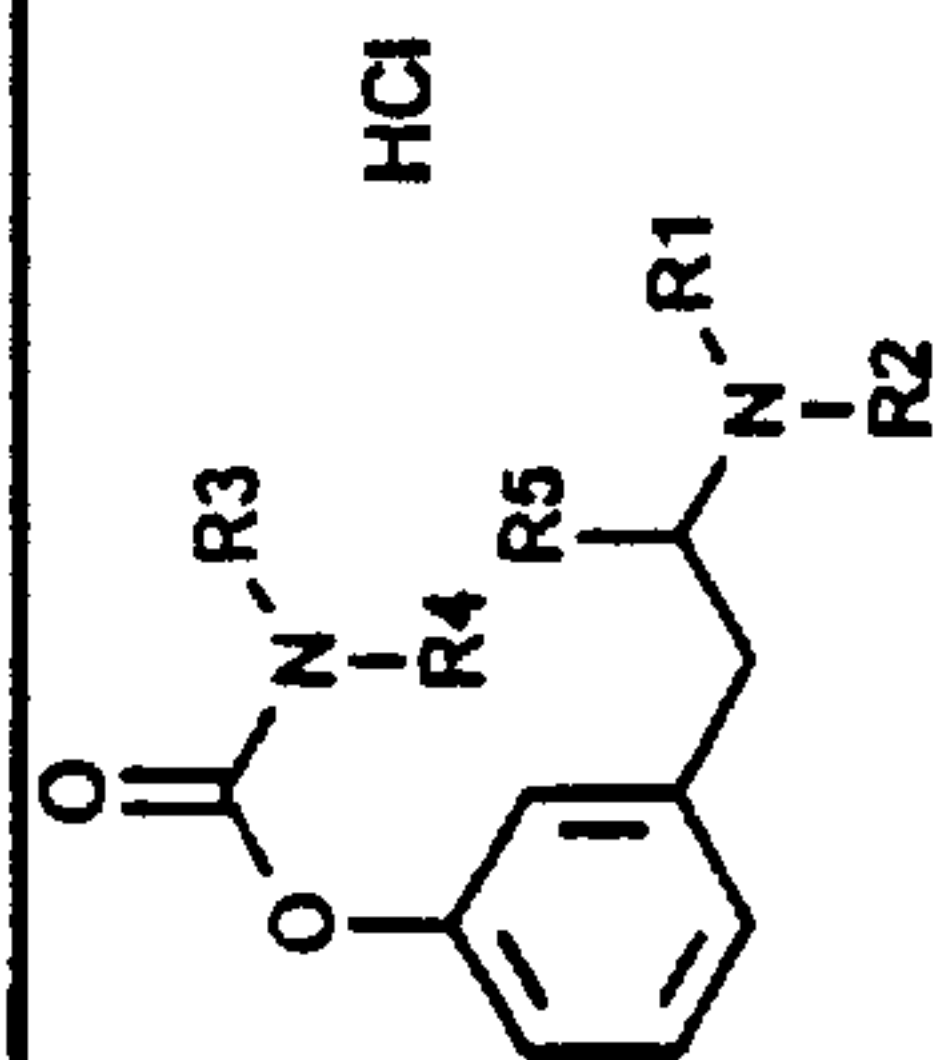
						
#	stereo.	R3	R4	cryst/slurry solvent	mp(C)	yield (%)
35	rac	Me	Pr	EtOAc	121-3	81
37	R	Me	n-hexyl	"	92-4	59
38	S	Me	n-hexyl	"	94-6	40
39	S	Me	cyclohexyl	"	118-20	63
40	R	Me	cyclohexyl	"	117-9	70

Table 4. Analytical Characteristics Relating To Compounds Of Table 2

				NMR ¹					IR	MS (MH ⁺)	elem. anal. (C,H,N)		
				#									R3, R4
					aryl	ethyl	R5	R1, R2					
	1	7.47,7.27, 7.09	3.30, 3.02			3.13,2.98							
	2							3095,2975 1724,1703 1461,1401	237	calc.: 5728,7.70,1027 found: 56.99,7.88,10.23			
	3	7.47,7.27 7.10	3.36, 3.07		2.73	3.16,3.0		2941,2775 2454,1734 1384,1237		calc.: 55.74,7.35,10.83 found: 55.47,7.41,10.85			
	4	7.46,7.27 7.08	3.30 3.05			3.54,3.39 3.13,3.0 1.27,1.19							
	6	7.33,7.12 7.02	3.35, 2.98		2.54	3.24,3.12 3.02,2.90 1.60,0.91 0.87			251	calc.: 58.63,8.08,9.77 found: 58.54,8.04,9.65			

¹ D₂O, unless specified otherwise

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Table 4 cont.

10	7.42, 7.24 7.16	3.42 3.08		2.89	3.10, 2.96	3533, 3443 2937, 2666 1711, 1485 1394, 1243	237	calc.: 57.24, 7.76, 10.27 found: 57.61, 7.66, 10.27
23	7.47, 7.27, 7.12	3.33, 3.06			3.20, 1.59, 0.97		223	calc.: 55.70, 7.40, 10.83 found: 55.63, 8.02, 11.01

Table 5. Analytical Characteristics of Compounds of Table 3

		#	NMR ²							IR	MS (MH ⁺)	elem. anal. (C,H,N)
			aryl	ethyl	R5	R1	proparg.	R3, R4				
		11	7.48,7.27 7.11	3.50, 3.11			3.96,3.02	3.16,3.01	3230,2934 2782,1713 1393,1275	247	calc.: 59.46,6.77,9.91 found: 59.26,6.84,9.90	
		12	7.43,7.24 7.06	3.55 3.11		2.96	4.08,3.11	3.10,2.98	3197,2935 2616,1730 1388,1242	261	: 60.70,7.13,9.44 found: 60.50,7.04,9.32	
		13	7.43,7.22 7.07	3.43 3.05			3.90,2.96	3.50,3.34 3.09,2.95 1.23,1.15	3228,2934 2781,1707 1395,1248	261	calc.: 60.70,7.08,9.44 found: 60.51,7.13,9.39	
		14	7.45,7.25 7.08	3.47 3.07			3.82,2.98	3.47,3.31 3.11,2.96 1.67,0.98 0.95		275	calc.: 61.83,7.40,9.01 found: 61.70,7.29,9.24	
		15	7.45,7.27 7.10	3.57 3.15		3.0	4.10,3.15	3.55,3.37 3.12,2.97 1.25,1.17	3299,2905 1725,1485 1396	275	calc.: 61.83,7.46,9.01 found: 61.05,7.40,8.88	

² D₂O, unless specified otherwise

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16	7.57,7.35 7.24	3.50 3.36 3.10	1.47		4.21,3.45	3.18,3.31	3262,2935 1699,1394 1241,1171	261	calc.: 60.70,7.08,9.44 found: 60.57,7.10,9.28
17	7.45,7.23 7.10,7.08	3.75 3.52 3.38	1.30		3.96,2.97	3.12,3.11 2.97,2.95 1.25,1.17	3420,1709 1402,1242 1171	275	calc.: 61.83,7.40,9.01 found: 61.58,7.36,8.98
18	7.46,7.26, 7.08	3.56 3.14		3.0	4.10,3.11	3.46,3.32 3.11,2.98 1.66,0.96 0.92	3446,3203 2940,2622 1722,1468 1402,1232	289	calc.: 62.85,7.76,8.63 found: 62.67,7.69,8.59
19	7.47,7.26 7.10	3.80 3.48 3.33	1.33		4.0,3.02	3.15,3.14 3.0,2.95 1.7,0.97 0.92	3448,2937 1733,1403 1232,1165	289	calc.: 62.86,7.70,8.63 found: 63.0,7.87,8.62
20	7.50,7.29 7.15	4.02 3.25 2.97	1.33	2.99	4.15,3.18	3.18,3.02	3413,3182 2928,2491 2120,1724 1392,1172	275	calc.: 61.83,7.46,9.02 found: 61.58,7.48,8.85
21	7.48,7.29 7.14	3.98 3.23 2.97	1.32	2.95	4.12,3.15	3.55,3.40 3.16,3.02 1.29,1.22		289	calc.: 62.85,7.76,8.68 found: 62.84,7.93,8.83
22	7.49,7.28 7.13	4.01 3.23 2.97	1.32	2.96	4.12,3.18	3.50,3.35 3.16,3.02 1.70,0.99 0.93		303	calc.: 63.81,7.97,8.27 found: 62.23,8.01,7.85

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26	7.49,7.28 7.13	3.50 3.11				3.96,3.02	3.21,1.61 0.98	261		
27	7.42,7.26 7.02	3.92 3.43 3.33	1.31	2.95		4.11,3.16	3.21,3.06 2.95,1.62 1.28,0.88		calc.: 56.48,8.57,6.27 found: 55.85,7.94,5.71	
28	7.50,7.29 7.12	4.05 3.27 3.23	1.33	3.0		4.15,3.17	3.0,2.0-1.0		calc.: 66.57,8.19,7.39 found: 66.10,8.28,7.10	
29*	7.47,7.27 7.10	3.57 3.43 3.09				4.25,3.10 1.58	3.15,3.0	261	calc.: 60.70,7.13,9.44 found: 60.76,7.31,9.13	
30*	7.49,7.29 7.12	3.58 3.43 3.14				4.27,3.13 1.60	3.58,3.43 3.12,3.0 1.27,1.21	275	calc.: 61.83,7.46,9.02 found: 61.62,7.42,8.98	
35	7.49,7.30, 7.13	4.05 3.50 3.35	1.33	3.0		4.15,3.15	3.16,3.0, 1.69,0.96	303	calc.: 58.22,7.82,6.79 found: 57.92,7.83,6.79	
36	7.47,7.27, 7.11	4.10 3.88 3.16 2.98	1.34			4.00,3.03	3.80,3.00, 1.85,1.65, 1.35,1.18		calc.: 66.02,7.70,7.70 found: 65.81,7.42,7.98	
38	7.47,7.28, 7.11	4.01 3.52 3.38	1.32	2.98		4.14,3.13	3.23,3.17, 2.99,1.68, 1.36,0.90	345	calc.: 60.17,8.45,6.10 found: 60.17,8.41,6.20	

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39	7.49,7.28, 7.12	4.05 3.25 2.98	1.32	2.98	4.15,3.17	3.90,2.97, 1.85,1.65 1.35,1.16			calc.: 61.03,8.02,6.19 found:60.78,8.13,5.93
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* substituted propargyl derivative, R6 in Scheme I is Me.

5 BIOLOGICAL EXAMPLES

Example 1

Acetylcholinesterase Inhibition in Mice

10 1.1 In vitro measurement of Acetylcholinesterase (AChE) Inhibition

Human erythrocyte acetylcholinesterase (type XIII, Sigma Israel), was prepared in a stock solution of 1U/ml, containing Triton® (1%) and bovine serum albumin (0.05%) in phosphate buffer (pH 8). The enzyme
15 (0.05U) was incubated with 3-5 different concentrations of test compound (in triplicate) for periods of from 15 to 60 minutes at 37°C. The substrate acetylthiocholine (0.075M) and 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB, 0.01M) were then added and the rate of hydrolysis of the substrate which yields a yellow product monitored
20 spectrophotomerically at 412nm (Eliman, et al., *Biochem Pharmacol.* (1961) 7: 88-95). The percentage inhibition of AChE by each concentration of drug is calculated by comparison with that of enzyme in the absence of drug. The concentration of each drug that inhibits AChE by 50% (IC₅₀) at the time of peak activity was calculated and is
25 given in Table 6 below.

1.2 Ex vivo measurement of Acetylcholinesterase (AChE) Inhibition

Test drugs or saline were administered sub-cutaneously to male mice
30 (Sabra strain, 28-35g). At least 4-5 mice were used per dose and a minimum of 3 doses per drug were tested.

The mice were sacrificed 15, 30, 60, 70, 90, 120 or 180 minutes after drug administration, the brains rapidly removed (minus cerebellum), weighed and homogenized in 0.1M phosphate buffer pH 8.0, containing
35 Triton® (1mg/100g tissue) and centrifuged to remove cell debris. Aliquots (25 µl) of the supernatant were then incubated with acetylthiocholine and DTNB. AChE activity measured as described above. The % inhibition of whole brain AChE by each dose of drug was

calculated by comparison with enzyme activity from 3 saline treated control mice run at the same time. The dose of each drug that inhibits AChE by 50% at the peak of activity (ED_{50}) was calculated and is given in Table 6.

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1.3 Acute Toxicity in Mice

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Drugs were administered sub-cutaneously in at least 3 doses, to a minimum of 10 mice per dose. The dose that was lethal to 50% of the mice (LD_{50}) within 6 hours after administration was calculated for each drug and is given in Table 6. Therapeutic Ratio was calculated as LD_{50} divided by ED_{50} (acetylcholine esterase ex vivo).

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Example 2

2.1 Inhibition of MAO activity in vitro

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The MAO enzyme source was a homogenate of rat brain in 0.3M sucrose, which was centrifuged at 600G for 15 minutes. The supernatant was diluted appropriately in 0.05M phosphate buffer, and pre-incubated with serial dilutions of test compounds for 20 minutes at 37°C. ^{14}C -Labeled substrates (2-phenylethylamine, hereinafter PEA; 5-hydroxytryptamine, hereinafter 5-HT) were then added, and the incubation continued for a further 20 minutes (PEA), or 30-45 minutes (5-HT). Substrate concentrations used were 50 μ M (PEA) and 1mM (5-HT). In the case of PEA, enzyme concentration was chosen so that not more than 10% of the substrate was metabolized during the course of the reaction. The deaminated products were extracted into toluene-ethyl acetate (1:1, v/v) containing 0.6% (w/v) 2,5-diphenyloxazole prior to determination by liquid scintillation counting. Radioactivity in the eluate indicates the production of neutral and acidic metabolites formed as a result of MAO activity. Activity of MAO in the sample was expressed as a percentage of control activity in the absence of inhibitors after subtraction of appropriate blank values. The activity determined using PEA as substrate is referred

to as MAO-B, and that determined using 5-HT as MAO-A.

Concentrations of inhibitor producing 50% inhibition of substrate metabolism (IC_{50}) were calculated from the inhibition curves, and are shown in Table 6.

2.2 Inhibition of MAO activity ex vivo

Male Sabra mice, weighing 45-50g were injected with test compound solutions (prepared in 0.9% saline). Each dose was administered to two or three mice. The mice were sacrificed two hours after drug administration or at a time corresponding to the peak AChE inhibition time (see Table 6). The brain and liver were rapidly dissected and stored in appropriate vials on ice. The tissues were weighed, diluted to 1/20 in sucrose 0.3M and stored at -20°C before performance of the MAO assay described above. The results given in Table 6 relate to measurements made on brain tissue only.

2.3 Inhibition of MAO activity following sub-acute administration to rats

Experiments were done with Spague Dawley male rats. Procedures were repeated as described in Examples 2.1 and 2.2, but drug administration was continued daily for 14 days. At the end of this period animals were sacrificed and MAO levels determined in the brain, liver and intestines. Compound 17 was administered sub-cutaneously or per os at a dose of 20mg/kg. The results are shown in Table 6a.

Table 6.

	AChE Inhibition		Time		MAO-B Inhibition		MAO-A Inhibition		Acute Toxicity	
	In vitro	Ex vivo	to peak activity	to return to 50% of peak	In vitro	Ex vivo	In vitro	Ex vivo		
	IC50 μ M	ED50 μ moles/kg (AC)	t (min)	t (min)	IC50 μ M	ED50 μ moles/kg	IC50 μ M	ED50 μ moles/kg	LD50 μ moles/kg	Therapeutic Ratio (LD/AC)
11	0.82	3.2	15	70	25	>>30	2.5	40	44.2	13.8
12	0.88	2.8	15-30	120	2.5	21	0.38	4	46	11.5
13	30.0	53.8	30-90	120	8.3	50	3.3	75	458	8.5
14	12.5	100	30		0.3	0.6	1.8	4.5		
15	67.2	145	30		1	35	1	35	1250	8.6
16	0.37	2.3	15	70	6	>20	7	>20	42	18.3
17	36.0	64	30-60	120	2	40	12	>40	600	9.4
19	20.0	170	30-60		0.17	1.5	14.6	>70	1300	7.6
1	0.31	NT			>1000		100			
4	48.4	NT			>1000		200			
2	8.2	NT			>1000		500			
3	0.31	39.2	10	30	>1000		50		57.7	1.5
5	20.8	NT			>1000	>>160	25	>>160		
10	0.2	2.0	15-30		>1000		51		16	8
31					500		500			
32					100	200	67	>>200		
33					5	>10	1.8	>10		
20	1.7	15			0.4	7	0.12	6	170	11.3
21	230				0.2		0.12			
27	3.1	>50			1.5	3.4	20	>430	>1000	
29	0.15	2.5				>>12.5		>>12.5		
30	14	45				>>270		>>270		
28	11.5	21	60		0.24	1.75	1.7	109	2000	>47
34					>1000		500			
35	50	>200								
36	3.4	>50								
38	3.1	>50								

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Table 6a. Effect of compound 17 on MAO activity
following sub-acute chronic treatment

Organ	Administration	%MAO-A inhibition	% MAO-B inhibition
Brain	sc	76	87
	po	59	72
Intestine	sc	10	33
	po	25	40
Liver	sc	33	51
	po	59	74

Example 3

Effect of drug treatment following closed head injury (CHI) in mice

The procedure for closed head injury followed was as described for rats in Shohami et al. (J. Neurotrauma (1993) 10(2) 109-119) with changes as described.

Animals: Male Sabra mice (Hebrew University strain) weighing 34-40g were used. They were housed in groups of 10 per cage, in a 12hr:12hr light:dark cycle. Food and water were provided ad libitum .

Trauma was induced under ether anesthesia. A longitudinal incision was performed in the skin covering the skull and the skin retracted to expose the skull. The head was fixed manually at the lower plane of the impact apparatus. A weight of 333g was delivered by an electric device from a height of 3cm to the left hemisphere, 1-2mm lateral to the midline in the midcoronal plane. Test compounds were injected sub-cutaneously at a dosage corresponding to the

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ED₅₀ for acetylcholinesterase inhibition, once 15 min. after CHI.

3.1 Assessment of Motor Function.

Motor function and reflexes were evaluated in the injured mice at different times after closed head injury (CHI) using a neurological severity score (NSS) as shown in Table 7 below, which is modified from that described for rats (Shohami et al. supra.). One point was awarded for the lack of a tested reflex or for the inability to perform the tasks outline in the Table. The maximal score that can be reached at 1 hour post-CHI is 25 points and 21 at later times. The difference in NSS at 1hr and at any other time reflects the recovery, and is referred to as NSS. An NSS score of 15-19 at 1hr denotes severe injury, 11-14 moderate injury and less than 10 mild injury. The NSS recorded after treatment with test compound or control is shown in Table 8.

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Table 7 Neurological Severity Score for Mice After Closed Head Injury

Parameter	Points at 1 hour	Points at any other time
Inability to exit from a circle (30cm diameter) when left in its center		
for 30min	1	
for 60 min	1	
for >60 min	1	1
Loss of righting reflex		
for 10 second	1	
for 20 seconds	1	
for >30 seconds	1	1
Hemiplegia - inability of mouse to resist forced changes in position	1	1
Flexion of hind limb when lifted by tail	1	1
Inability to walk straight when placed on the floor	1	1
Reflexes		
Pinna reflex	1	1
Corneal reflex	1	1
Startle reflex	1	1
Clinical grade		
Loss of seeking behaviour	1	1
Prostration	1	1
Loss of reflexes		
Left forelimb	1	1
Right forelimb	1	1
Left hindlimb	1	1
Right hindlimb	1	1
Functional test		
Failure in beam balancing task (0.5cm wide)	1	1
for 20 seconds	1	1
for 40 seconds	1	1
for > 60 seconds		
Failure in round stick balancing task (0.5cm in diameter)		
for 10 seconds	1	1
Failure in beam walking task		
3cm wide	1	1
2cm wide	1	1
1cm wide	1	1
Maximum Points	25	21

ResultsAssessment of Motor Function.

Table 8 Change in Neurological Severity Score after Closed Head Injury in Mice

Drug/dose	N	Δ NSS, 24 hr post-CHI	Δ NSS, 7 days post-CHI	Δ NSS, 14 days post-CHI
Saline, 1ml/kg	51	4.75 ± 0.17	5.83 ± 0.36	5.96 ± 0.4
17	12	$5.58 \pm 0.38^*$	$6.92 \pm 0.36^*$	$7.83 \pm 0.53^*$

* significantly different from saline control ($p < 0.05$)

3.2 Assessment of Reference Memory

Morris Water Maze Test: the water maze consists of a circular aluminium pool, 1m in diameter and 60cm in depth, filled with water to a depth of 17.5cm. The hidden goal platform is a glass vessel (15cm diameter x 16.5cm height) placed upside down at a fixed location in the pool, 1cm below the surface of the water. The water temperature is maintained at 24°C and the pool is always placed in the same position in the room to provide the same extra-maze cues. Prior to CHI (as described in Example 3 above), mice were given 3 trials per day for 5 consecutive days to establish a baseline performance - measured as the latency to find the platform from the same start location. Commencing 24hr after CHI, mice were retested daily for 2 weeks in 3 trials per day.

Figure 1 shows the reduction in latency for mice treated with compound 17 compared to saline treated controls after CHI. It appears that immediately post-CHI mice forget the location of the goal. Memory is enhanced following treatment with test compounds, as compared to saline treated

mice. In Figure 1 the arrow shows the time of CHI.

Example 5:

Effect On Mice Having Experienced A Hypobaric Hypoxic Episode

The hypobaric hypoxic model is a well accepted model for assessing the activity of compounds believed to possess neuroprotective activity. The model is based on that described in Nakanishi, M. et al. *Life Sci.* (1973) 13: 467; Oshiro, et al., *J. Med. Chem.* (1991) 34: 2004-2013; and US Patent 4,788,130.

A 12 liter desiccator (desiccator A) and a 2.5 liter desiccator (desiccator B) were separately connected to a vacuum pump. Desiccator B was disconnected and allowed to equilibrate with room air whilst desiccator A was evacuated to a pressure of 100mmHg. Four male ICR albino mice (22-28g) were placed in desiccator B. Desiccator B was then closed to room air and connected to desiccator A. The pressure inside desiccator B was monitored using a mercury manometer and at the point the pressure in desiccator B reached 200mmHg (usually within 14 seconds), the two desiccators were disconnected from the vacuum pump and the pump switched off. The survival time from the moment of induction of hypoxia to the time of cessation of respiration was recorded for each mouse for a maximum of 15 minutes after which time room air was reintroduced to desiccator B. Survivors were monitored for signs of lethargy or vitality.

Effect of drug treatment was assessed as the percent of the survival time of the drug treated group with respect to the saline injected or vehicle injected control group. Control groups were run twice, before and after each experimental group and consisted of 8 mice in groups of 4 mice to ensure a constant residual volume of oxygen in all tests. The effect of each dose of test drug was determined in duplicate i.e. two groups of 4 mice. The range of survival times of control mice was from 108-180 seconds.

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Positive reference drugs were sodium pentobarbital at a dose of 40 mg/kg, and diazepam 10 mg/kg given 0.5h prior to hypoxia, physostigmine 0.2 and 0.4 mg/kg and neostigmine 0.2 mg/kg given sc 30 min before hypoxia. Methyl atropine 1 mg/kg was given sc. 10 min. before physostigmine.

Test drugs were dissolved in 0.9% saline, and injected sc. in the nip of the neck at a dose in accordance with body weight, 60-90 min. before hypoxia. The volume of injection was 0.2-0.3 mL per mouse (10 mL/kg). The initial dose was about one third of the reported LD₅₀ for acetylcholine esterase inhibition. If no protection could be obtained, the dose was further increased to the nearest non-toxic dose. In case of protection, the dose was further reduced in an attempt to locate the "protective" dose range.

Per cent survival times as compared to saline treated control is shown in Table 9.

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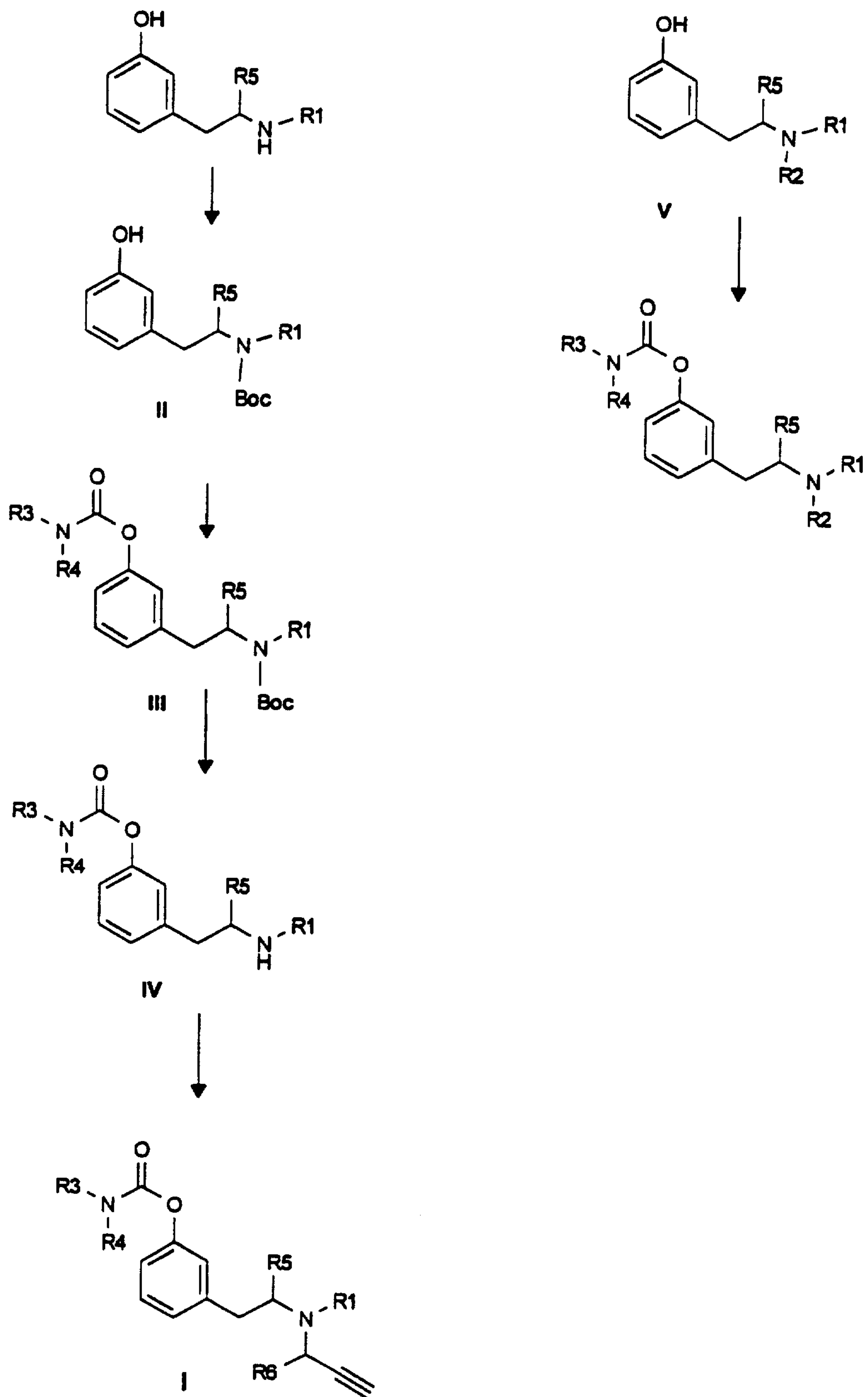
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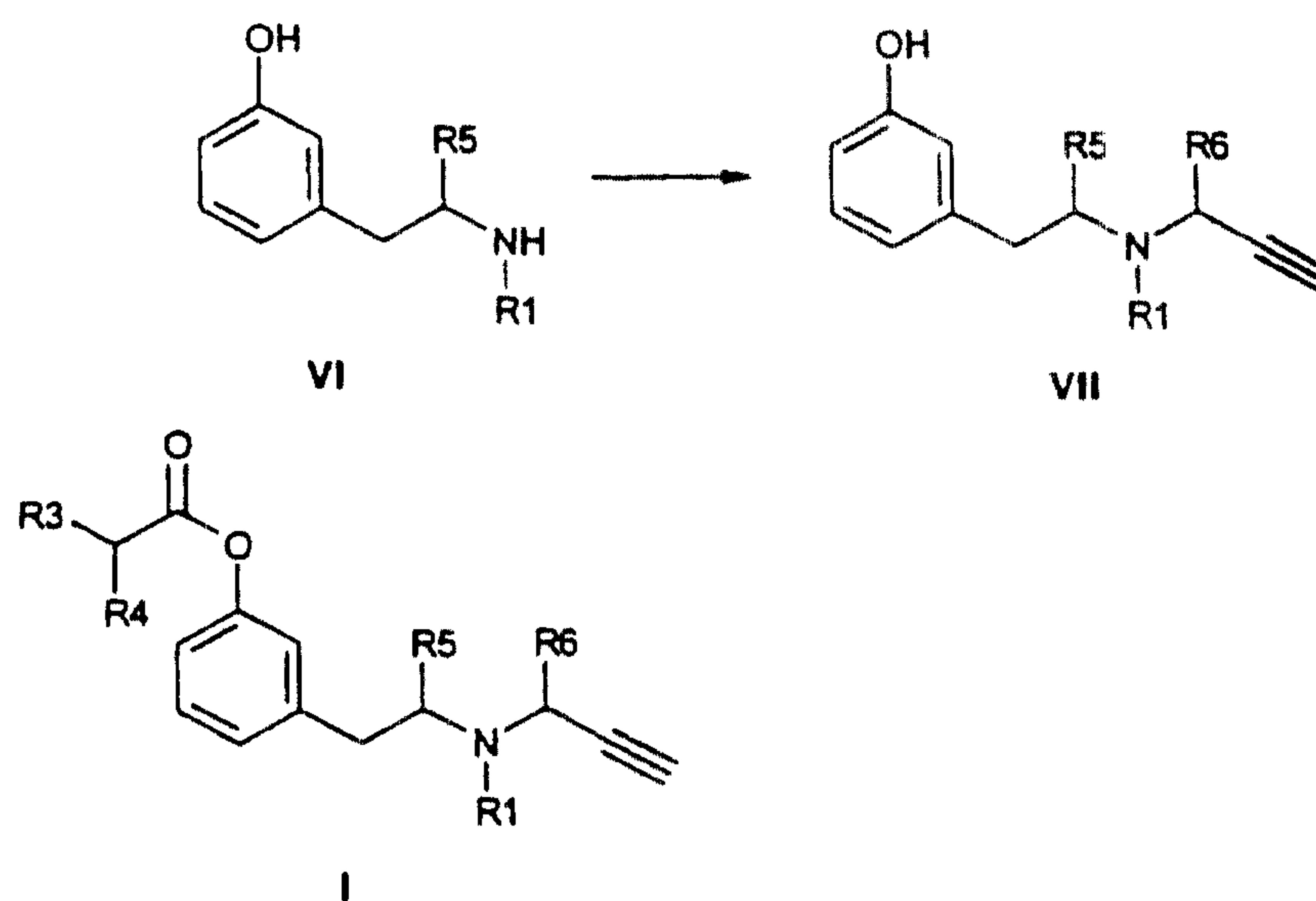
Table 9. Survival Time of Mice Having Experienced a Hypobaric Episode

Compound	Dose mg/kg	Time of dose (min before hypoxia)	Protection (% of control)	p
Control (saline)			100	
Nembutal	40	30	253±200	<0.005
Diazepam	10	30	316±78	<0.003
Neostigmine	0.2	30	141±32	<0.01
Physostigmine	0.2	30	453±222	<0.001
	0.4	30	552±210	<0.001
Physostigmine and Atropine methyl nitrate	0.4	30	296±193	<0.05
	1.0	40		
11	6.2	60	331±168	
	4.1	60	416±211	
	4.1	30	501±201	
	2	60	128±40	
	2	30	302±212	
12	7	60	217±120	<0.02
	4.5	60	97±36	NS
17	94	60	281±158	<0.001
	62	60	419±122	<0.001
	31	60	149±44	<0.05
16	15	60	toxic	
	6.2	60	324±155	<0.001
	4.1	60	335±202	<0.01
19	75	60	773±228	p<0.001
	50	60	309±253	p<0.05
	25	60	169±50	p<0.01

SCHEME I

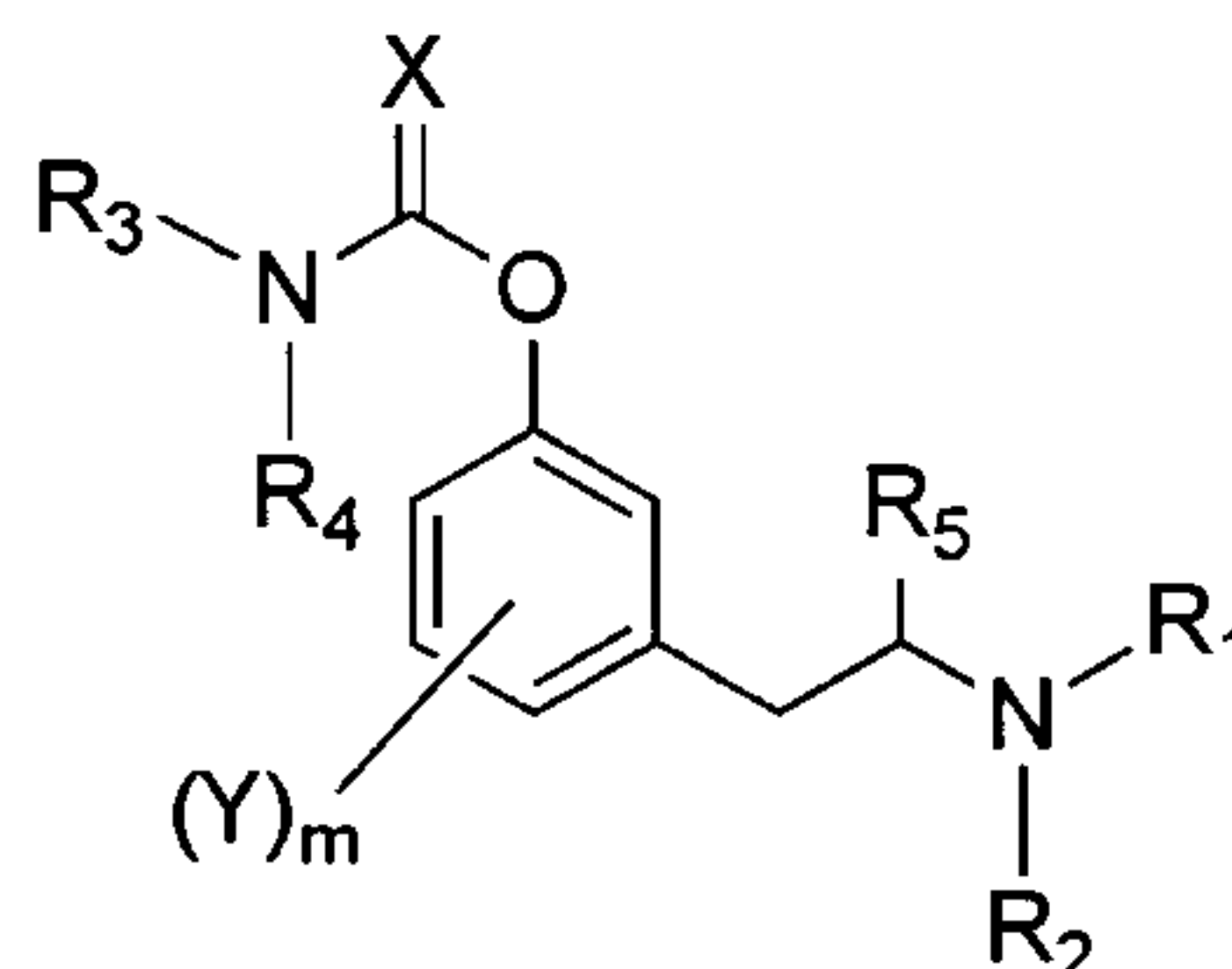


SCHEME II



5 What is claimed is:

1 A compound having the formula:



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wherein m is from 0-4;

X is O or S;

Y is halogeno;

15 R₁ is hydrogen or C₁₋₄ alkyl;

R₂ is hydrogen, C₁₋₄ alkyl or propargyl optionally substituted by C₁₋₄ alkyl; and

R₃ and R₄ are each independently hydrogen, C₁₋₈ alkyl, C₆₋₁₂ aryl, C₆₋₁₂ cycloalkyl or C₆₋₁₂ aralkyl, R₅ is hydrogen or C₁₋₄ alkyl; and

20 pharmaceutically acceptable salts thereof,

provided that when X is O, R₂ is propargyl optionally substituted by C₁₋₄ alkyl.

2. A compound according to claim 1 wherein X is O.

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3. A compound according to claim 1 wherein X is S.

5 4. A compound according to claim 1, wherein the compound is
selected from the group consisting of: (rac)-3-(N-methyl,
N-propyl-carbamyloxy)- α -methyl-N'-propargyl phenethylamine HCl;
(rac)-3-(N,N-dimethyl-carbamyloxy)- α -methyl-N-methyl,N'-
propargyl phenethylamine HCl; (rac)-3-(N-methyl,N-hexyl-
10 carbamyloxy)- α -methyl-N'-methyl, N'-propargyl phenethylamine
mesylate; (rac)-3-(N-methyl, N-cyclohexyl-carbamyloxy)- α -methyl-
N'-methyl, N'-propargyl phenethylamine HCl; and (S)-3-(N-methyl,
N-hexyl-carbamyloxy)- α -methyl-N'-methyl, N'-propargyl
phenethylamine ethanesulfonate.

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5. A compound according to claim 1, wherein at least one of R₃
and R₄ is methyl and the other is hydrogen, methyl, ethyl,
propyl, hexyl or cyclohexyl.

20 6. A compound according to claim 2, wherein at least one of R₃
and R₄ is methyl and the other is hydrogen, methyl, ethyl,
propyl, hexyl or cyclohexyl.

7. A compound according to claim 1, wherein said compound is
25 an optically active enantiomer.

8. A compound according to claim 2, wherein said compound is
an optically active enantiomer.

30 9. A compound according to claim 3, wherein said compound is
an optically active enantiomer.

- 5 10. A compound according to claim 4, wherein said compound is an optically active enantiomer.
11. A compound according to claim 1, wherein R_2 is propargyl optionally substituted by C_{1-4} alkyl.
- 10 12. A compound according to claim 2, wherein R_2 is propargyl optionally substituted by C_{1-4} alkyl.
13. A compound according to claim 3, wherein R_2 is propargyl
- 15 optionally substituted by C_{1-4} alkyl.
14. A compound according to claim 5 or 6, wherein R_2 is propargyl optionally substituted by C_{1-4} alkyl.
- 20 15. A compound according to claim 1, wherein
- m is 0;
- X is 0;
- R_1 is methyl;
- R_2 is propargyl;
- 25 R_3 is methyl;
- R_4 is ethyl; and
- R_5 is methyl.
16. A pharmaceutical composition comprising the compound of
- 30 claim 1 and a pharmaceutically acceptable carrier.

- 5 17. A pharmaceutical composition comprising the compound of
claim 2 and a pharmaceutically acceptable carrier.
18. A pharmaceutical composition comprising the compound of
claim 3 and a pharmaceutically acceptable carrier.
- 10 19. A pharmaceutical composition comprising the compound of
claim 4 and a pharmaceutically acceptable carrier.
20. A pharmaceutical composition comprising a therapeutically
15 effective amount of the compound of any one of claims 1 to 15
for use in the treatment of neurotrauma, ADD, ADHD,
Tourette's Syndrome, memory disorder or depression and a
pharmaceutically acceptable carrier.
- 20 21. The pharmaceutical composition of claim 20, wherein the
neurotrauma comprises central nervous system damage and/or
peripheral nervous system damage.
22. The pharmaceutical composition of claim 21, wherein the
25 central nervous system damage and/or peripheral nervous system
damage is ischemic damage resulting from stroke, hypoxia or
anoxia, neurodegenerative diseases, Parkinson's Disease,
Alzheimer's Disease, Huntington's Disease, neurotoxic injury,
head trauma injury, spinal trauma injury, or peripheral
30 neuropathy.

- 5 23. A pharmaceutical composition comprising a therapeutically effective amount of the compound of any one of claims 1 to 15 for use in the treatment of Alzheimer's disease or dementias and a pharmaceutically acceptable carrier.
- 10 24. The pharmaceutical composition of claim 23, wherein the dementia is static dementia, Alzheimer's-type dementia, senile dementia, presenile dementia, progressive dementia, vascular dementia or Lewy body dementia.
- 15 25. Use of the compound of any one of claims 1 to 15 for the preparation of a medicament for the treatment of neurotrauma, ADD, ADHD, Tourette's Syndrome, memory disorder, or depression.
- 20 26. The use of claim 25, wherein the neurotrauma comprises central nervous system damage and/or peripheral nervous system damage.
- 25 27. The use of claim 26, wherein the central nervous system damage and/or peripheral nervous system damage is ischemic damage resulting from stroke, hypoxia or anoxia, neurodegenerative diseases, Parkinson's Disease, Alzheimer's Disease, Huntington's Disease, neurotoxic injury, head trauma injury, spinal trauma injury, or peripheral neuropathy.
- 30 28. Use of the compound of any one of claims 1 to 15 for the preparation of a medicament for the treatment of Alzheimer's disease or dementias.

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29. The use of claim 28, wherein the dementia is static dementia, Alzheimer's-type dementia, senile dementia, presenile dementia, progressive dementia, vascular dementia or Lewy body dementia.

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