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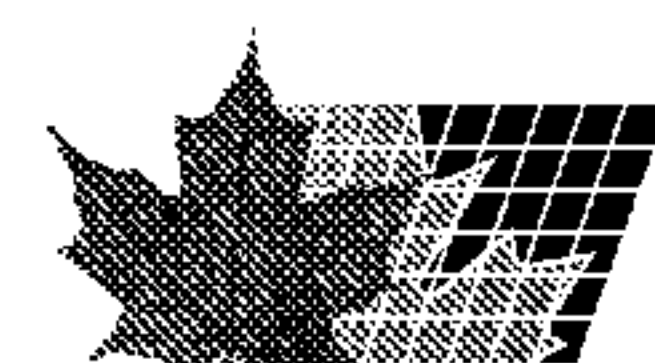
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(54) Titre : UTILISATION D'INHIBITEURS DE CHOLINESTERASE DANS LE TRAITEMENT DES TROUBLES
DEFICITAIRES DE L'ATTENTION
(54) Title: USE OF CHOLINESTERASE INHIBITORS FOR TREATING ATTENTION DEFICIT DISORDERS

(57) **Abrégé/Abstract:**

The invention provides the use of cholinesterase inhibitors, particularly acetylcholinesterase inhibitors such as galantamine, in the manufacture of a medicament for combatting attention deficit disorders.



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(21) International Application Number: PCT/GB98/02378 (22) International Filing Date: 7 August 1998 (07.08.98) (30) Priority Data: 9716879.3 8 August 1997 (08.08.97) GB (71) Applicant (for all designated States except US): SHIRE INTERNATIONAL LICENSING B.V. [NL/NL]; Frederiksplein 42, NL-1017 XN Amsterdam (NL). (71)(72) Applicant and Inventor: SNORRASON, Ernir [IS/IS]; Stigahlid 80, IS-105 Reykjavik (IS). (72) Inventor; and (75) Inventor/Applicant (for US only): MURRAY, James, Robert [GB/GB]; Lamb House, Ludwell, Shaftesbury, Dorset SP7 9ND (GB). (74) Agents: GRANT, Anne, Rosemary et al.; Frank B. Dehn & Co., 179 Queen Victoria Street, London EC4V 4EL (GB).	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: USE OF CHOLINESTERASE INHIBITORS FOR TREATING ATTENTION DEFICIT DISORDERS (57) Abstract The invention provides the use of cholinesterase inhibitors, particularly acetylcholinesterase inhibitors such as galantamine, in the manufacture of a medicament for combatting attention deficit disorders.		

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USE OF CHOLINESTERASE INHIBITORS FOR TREATING ATTENTION DEFICIT DISORDERS

5 The present invention relates to a method of
combatting attention deficit disorders (hereinafter
referred to as ADD). In particular, the invention
relates to the use of a pharmaceutically acceptable
cholinesterase inhibitor in the manufacture of a
10 medicament for use in combatting ADD.

 Attention deficit disorders affect children,
adolescents and adults affecting up to 10% of children
and at least 2% of adults. The childhood condition is
often known as attention-deficit hyperactivity disorder
15 (ADHD). Symptoms usually first manifest between the
ages of 2 - 5. These children have a short attention
span, motor hyperactivity, and are disorganised,
forgetful and impulsive. ADHD can have a serious effect
on the child's academic progress and performance and
20 causes stress to family and teachers and difficulties in
interacting with the child's peer group. The condition
can persist into adult life. In adults, the major
symptoms include distractibility, disorganisation and
accident proneness. The condition in adults and
25 children causes serious disruption to normal lifestyle
patterns, and creates great stresses to all aspects of
daily life, in the home, the workplace and in social
situations. ADD as used herein covers both the adult
and child forms of the condition, as well as
30 hyperkinetic disorders and disorders which include any
of the characterising criteria of the American
Psychiatric Association's DSM-IV Classification of the
disorders.

 Various therapies have been proposed but have not
35 proved satisfactory, due inter alia to lack of efficacy
and/or undesirable side effects. Stimulants such as
dexamphetamine, methylphenidate and pemoline have been

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used clinically in the management of ADD. Whilst they have been found to improve the primary manifestations such as motor activity, distractability and impulsivity in some sufferers, their side effects including anorexia, delayed onset of sleep, mood changes and exacerbation of pre-existing psychotic symptoms together with the possible potential for abuse, limits their utility. Other classes of drug such as tricyclic antidepressants have been suggested in the literature but are not generally regarded as being effective agents for the management of ADD. There is accordingly a need for a new therapeutic method for the management of ADD. The present invention provides such a method.

Thus we have surprisingly found that cholinesterase inhibitors such as galantamine can effectively combat ADD.

According to one aspect, the present invention provides a method of combatting ADD comprising administering to a subject a pharmaceutically acceptable cholinesterase inhibitor.

According to a related aspect, the invention provides the use of a pharmaceutically acceptable cholinesterase inhibitor in the manufacture of a medicament for combatting ADD.

As used herein the term 'combatting' includes both therapy and prophylaxis.

The invention encompasses the use of any cholinesterase inhibitor, provided of course that it is pharmaceutically acceptable.

Examples of cholinesterase inhibitors which may be used according to the invention include, but are not limited to, physostigmine, tacrine and tacrine analogues, fasciculin, metrifonate, heptyl-physostigmine, norpyridostigmine, norneostigmine, huperazine, donepezil and pro-drugs of any of these in which the inhibitor is modified in accordance with principles of pro-drug construction known in the art. Examples of such

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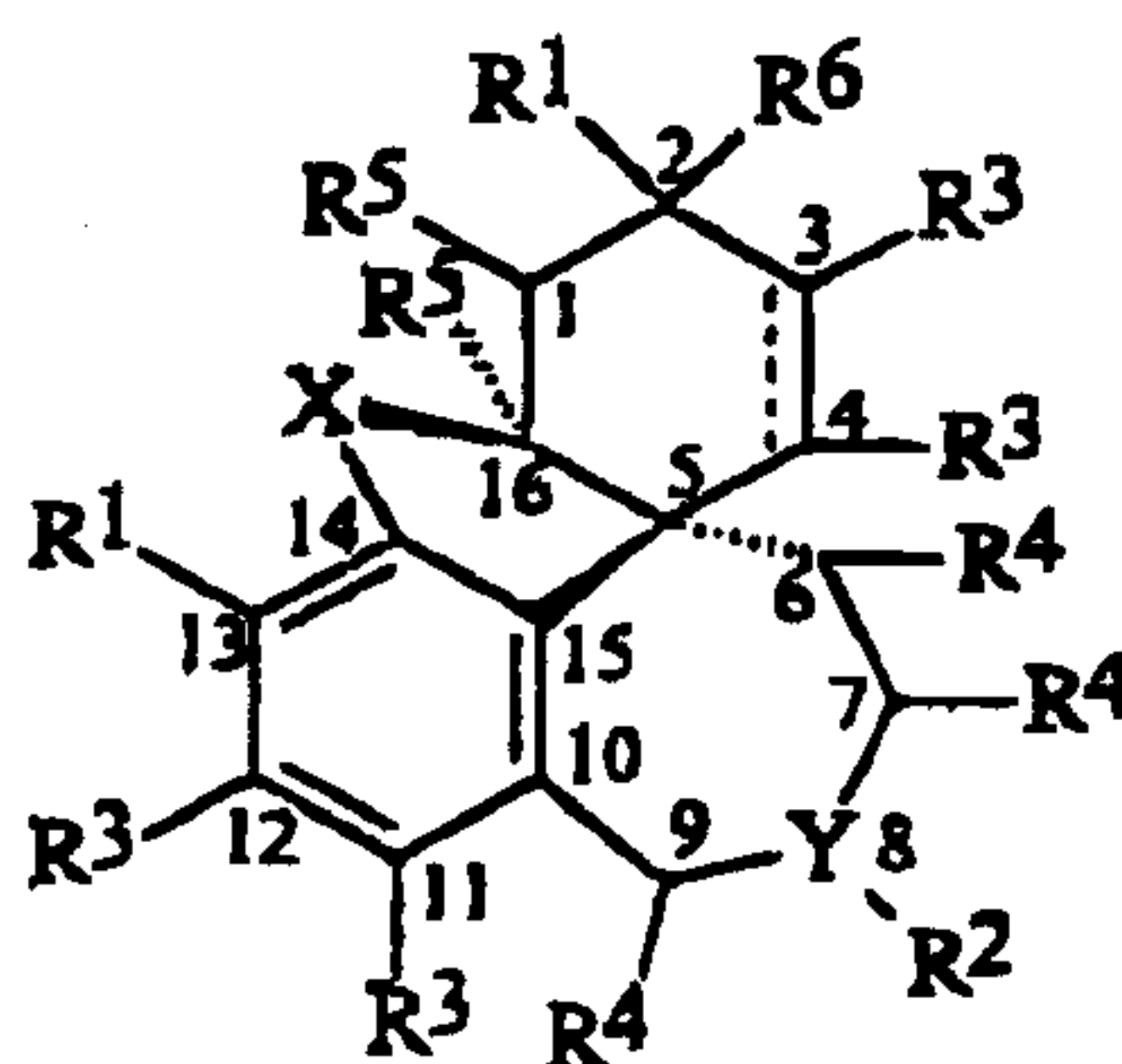
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modifications include the introduction of hydrophilic or lipophilic groups to enhance solubility, or penetration through cell membranes, respectively.

Preferred cholinesterase inhibitors for use according to the invention are acetylcholinesterase inhibitors, particularly those which are capable of crossing the blood brain barrier.

Particularly preferred cholinesterase inhibitors for use according to the invention include galantamine, epigalantamine and norgalantamine, and analogues, salts and derivatives of any of these. Galantamine was previously known as galanthamine. It is a tertiary alkaloid which can be extracted from various snowdrop bulbs e.g. the Caucasian snowdrop *galanthus woronowii* (Amaryllidaceae) and related species and daffodil bulbs or made by chemical synthesis. It has a high selectivity for acetylcholinesterase as opposed to butyrylcholinesterase. It is active substantially selectively at nicotinic receptor sites with substantially little effect on muscarinic receptor sites.

Particularly preferred cholinesterase inhibitors for use in the invention are galantamine and its derivatives of formula (I):



wherein the broken line represents an optionally present double bond between carbon atoms 3 and 4, each R_i is

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independently selected from hydrogen, hydroxyl, straight or branched chain alkyl, hydroxyalkyl, carboxyalkyl amino, alkylamino, acyl, lower alkanoyl, cyano, sulfhydryl, C₁₋₆alkoxy, alkylthio, aryloxy, arylthio, R₃-substituted aryloxy, R₃-substituted arylthio, aralkoxy, an optionally R₃-substituted aliphatic or aryl carbamyl group, aralkylthio, R₃-substituted aralkoxy, R₃-substituted aralkylthio, aryloxymethyl, R₃-substituted aryloxymethyl, alkanoyloxy, hydroxy-substituted alkanoyloxy, benzoyloxy, R₃-substituted benzoyloxy, aryloxy-carbonyl and R₃-substituted aryloxy-carbonyl,

R₂ is selected from hydrogen, straight or branched chain C₁₋₆alkyl, alkenyl or alkaryl group, optionally substituted by a halogen atom or a cycloalkyl, hydroxy, alkoxy, nitro, amino, aminoalkyl, acylamino, heteroaryl, heteroaryl-alkyl, aryl, arylalkyl, cyano, amyl, aroyl, cycloalkylmethyl, allyl, phenyl, R₃-substituted phenyl, alkylphenyl, R₃-substituted alkylphenyl, heterocyclyl selected from α - or β -furyl, α - or β -thienyl, thenyl, pyridyl, pyrazinyl, and pyrimidyl, alkyl-heterocyclyl or R'-substituted heterocyclyl, where R' is alkyl or alkoxy,

each R₃ is independently selected from hydrogen, hydroxyl, sulfhydryl, alkyl, hydroxyalkyl, aryl, aralkyl, alkoxy, mercaptoalkyl, aryloxy, thiaryloxy, alkaryloxy, mercaptoalkaryl, nitro, amino, N-alkylamino, N-arylamino, N-alkarylamino, fluoro, chloro, bromo, iodo, and trifluoromethyl,

each R₄ is independently selected from hydrogen, halo, trifluoromethyl or C₁₋₄-alkyl,

each R₅ is independently selected from hydrogen or hydroxymethyl,

R₆ is hydrogen or C₁₋₆alkyl, or when R₁ at carbon atom 2 is hydroxyl, R₆ may be a moiety of formula I wherein R₆ is hydrogen and R₁ is a linking bond; or

R₁ at carbon atom 2 and R₆ may jointly form semicarbazone,

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X is oxygen or NR_3 ,

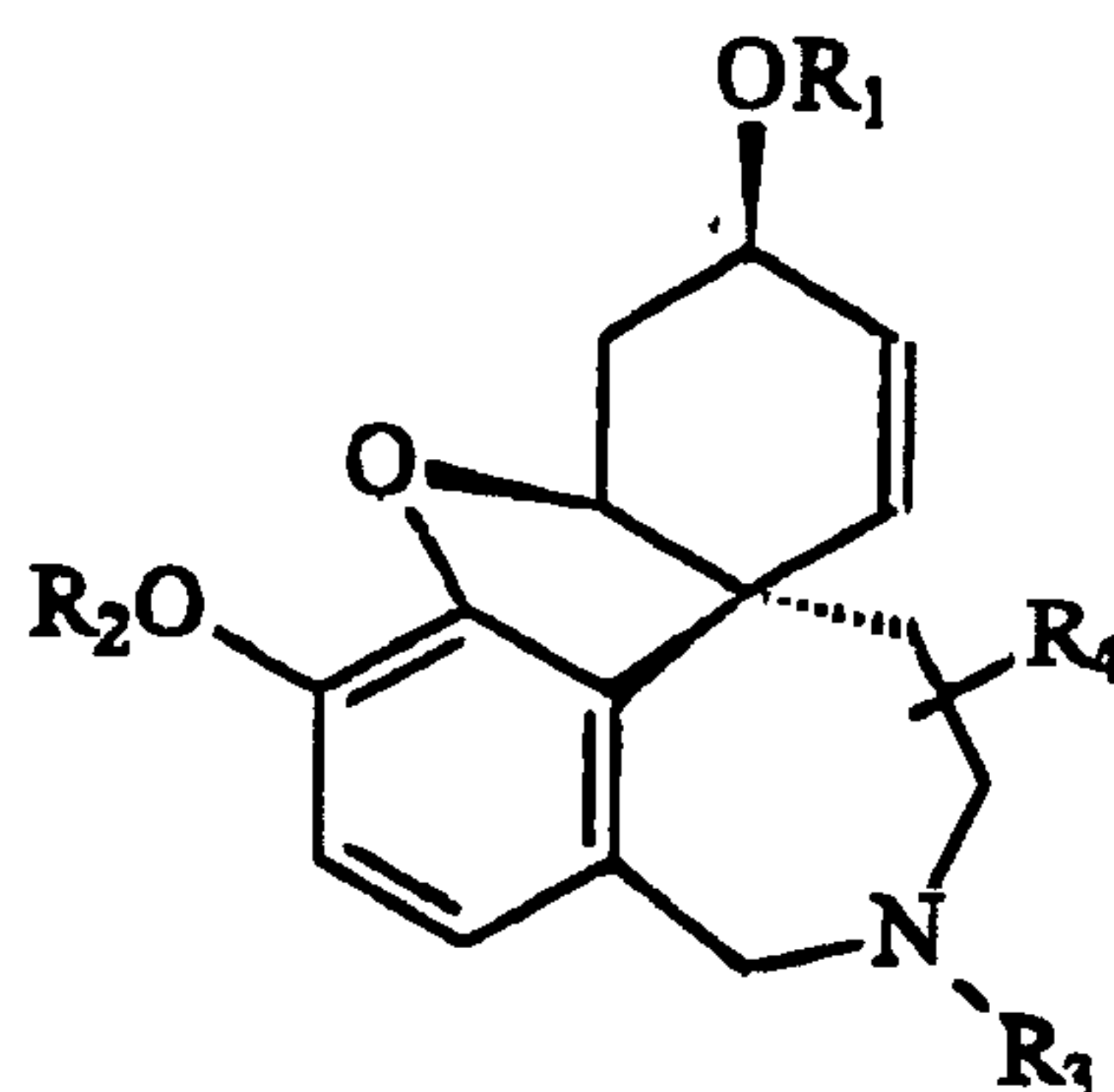
Y is nitrogen or phosphorus,

and methylenedioxy derivatives thereof and pharmaceutically acceptable acid addition salts thereof.

5 Of the compounds of formula I which may be used in the method of the invention, preferred compounds are those in which the alkyl moieties contain 1 to 8 carbon atoms, halogen atoms are preferably fluorine, bromine, chlorine, aryl moieties are preferably phenyl,

10 cycloalkyl groups are preferably 3- to 7-membered rings, especially cyclopropyl or cyclobutyl, acyl groups are preferably lower alkanoyl groups and heteroaryl moieties are preferably 5- to 8-membered rings, e.g., thienyl, furyl, pyridyl, pyrrolyl, or pyrizanyl.

15 Preferred compounds of formula I are the compounds of formula II



II

wherein R^1 and R^2 which may be the same or different each represents a hydrogen atom or an acyl group, such as a lower alkanoyl group, e.g. an acetyl group or a straight-chained or branched alkyl group, e.g. methyl, ethyl, propyl, or isopropyl;

30 R^3 is a straight or branched chain alkyl, alkenyl or alkaryl group which is optionally substituted by a halogen atom or a cycloalkyl, hydroxy, alkoxy, nitro, amino, aminoalkyl, acylamino, heteroaryl, heteroarylalkyl, aroyl, aroylalkyl or cyano group; and

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R' represents a hydrogen or a halogen atom attached to at least one of the ring carbons of the tetracyclic skeleton,

5 and pharmaceutically acceptable salts thereof, such as a hydrobromide, hydrochloride, methylsulphate or methiodide.

Formula II includes galantamine itself.

10 Particularly preferred is galantamine itself, and salts thereof such as halides for example galantamine hydrobromide and the use of these compounds in the manufacture of a medicament for combatting ADD provides a further aspect of the invention.

15 Among these compounds are those described in EP-A-236684 and WO88/08708. Galantamine and its derivatives of formula I and II may be prepared by the methods described in these publications.

20 The cholinesterase inhibitors for use in the invention include compounds which are functionally similar to galantamine. These are defined herein as compounds which possess an at least 10-fold selectivity, preferably an at least 20-fold selectivity, more preferably an at least 40-fold selectivity, and most preferably an at least 50 fold selectivity, for acetylcholinesterase as opposed to butyryl-

25 cholinesterase, when measured by the in vitro method of Thomsen and Kewitz: Selective Inhibition of Human Acetylcholinesterase by Galantamine in vitro and in vivo, Life Sciences, Vol 46, pp. 1553-1558 (1990), and T. Thomsen, H. Kewitz and O. Pleul, J. Clin. Chem. Clin. Biochem. 26 469-475 (1988). The in vitro test described

30 by Thomsen and Kewitz in Life Sciences, Vol 46, pp 1553-1558 (1990) is the one referred to herein whenever numeric (10-fold, 20-fold, 40-fold) reference to selectivity for acetylcholinesterase as opposed to butyrylcholinesterase is made. According to Thomsen and

35 Kewitz, galantamine hydrobromide, when tested under the

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conditions described, shows a 50-fold selectivity; this selectivity value is taken as the "fix-point" whenever in vitro selectivities are discussed herein and could be used, for the purpose of determining the selectivities for other cholinesterase inhibitors, as a calibration value which is the one to establish with galantamine hydrobromide in any repetition of the experiment described by Thomsen and Kewitz. Thus, with reference to this determination method, a preferred acetylcholinesterase inhibitor is one which in the in vitro method described has an at least 10-fold selectivity for acetylcholinesterase as opposed to butyrylcholinesterase, such as an at least 20-fold selectivity for acetylcholinesterase as opposed to butyrylcholinesterase, e.g. an at least 40-fold selectivity for acetylcholinesterase as opposed to butyrylcholinesterase. A selectivity test is commercially available (from Sigma Diagnostics).

For use in the method of the invention the cholinesterase inhibitor such as galantamine and derivatives and salts thereof may be formulated according to conventional methods of pharmacy, together where appropriate with one or more pharmaceutically acceptable carriers, excipients or diluents such as, for example, are described in Remingtons Pharmaceutical Sciences. Such formulations may for example take the form of tablets, capsules, solutions, or lozenges, pessaries, creams, suppositories or transdermal formulations such as patches, creams, ointments or lotions, depending upon the administration route to be used, which may include enterally or parenterally, including orally or injection via the intravenous, intramuscular or subcutaneous routes, or intrathecally by means of an implanted device.

Oral and transdermal administration routes are preferred.

Precise dosage rates and regimes will depend upon

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the individual patient and may be determined by the medical practitioner based on individual circumstances. For oral administration doses may be within the range of 5-100 mg per day, such as 2 to 70 mg per day eg. 10 to 30 mg. For transdermal administration galanthamine may be delivered in equivalent daily doses. For parenteral administration, dosages may be in the range of 0.1 to 100 mg per day, such as 5 to 100 mg per day, e.g. 10 to 50 mg per day, including 5 to 30 mg per day; lower dosages are often preferred.

Galantamine and its acid addition salts form crystals. They are generally only sparingly soluble in water at room temperature; therefore, injectable compositions are normally in the form of an aqueous suspension. If necessary, pharmaceutically-acceptable suspension aids may be employed. Typically, such a suspension will be employed at a concentration of 0.1-50 mg/ml, such as 1-50 mg/ml, more commonly 5-40 mg/ml, for example, 5-30 mg/ml or 10-40 mg/ml, such as 10-30 mg/ml, especially 20-30 mg/ml of galantamine.

Cholinesterase inhibitors such as galantamine and salts thereof may be used as the sole drug in the management of ADD, or may be used together with other agents useful in managing ADD.

The invention will now be described with reference to the following non-limiting examples.

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Example 1Formulation of tablets containing galantamine5 Composition of 1 tablet containing 1 mg galantamine

	Galantamine hydrobromide	0.001 g
	Calcium phosphate	0.032 g
	Lactose	0.005 g
10	Wheat Starch	0.0056 g
	Microcrystalline Cellulose	0.015 g
	Talc	0.0007 g
	Magnesium Stearate	0.0007 g

15 Composition of 1 tablet containing 5 mg galantamine

	Galantamine hydrobromide	0.005 g
	Calcium phosphate	0.024 g
	Lactose	0.004 g
20	Wheat Starch	0.004 g
	Microcrystalline Cellulose	0.04 g
	Talc	0.002 g
	Magnesium Stearate	0.001 g

25 Composition of 1 tablet containing 10 mg galantamine

	Galantamine hydrobromide	0.010 g
	Lactose	0.040 g
	Wheat Starch	0.0234 g
30	Microcrystalline Cellulose	0.0374 g
	Talc	0.0036 g
	Magnesium Stearate	0.0012 g
	Gelatin	0.0044 g

35 Preparation

All the tablets are prepared according to routine
tableting procedures.

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Example 2Treatment of patients suffering from ADD

5 Three patients aged 9 to 11 years diagnosed as
having ADD were treated with 5 mg of galantamine given 3
times per day for a total of 14 days. After this period
of time, the patients showed marked improvement of
symptoms, particularly as regards attention and
restlessness, as judged on an ecological behavioural
scale (translated: Barkley, RA et al, Assessing
10 situational variation in children's problem behaviours:
The Home and School Situations Questionnaires, in RJ
Prinz (Ed), Advances in Behavioural Assessment of
Children and Families, vol 3, pp 157-176, Greenwich, CT,
JAI Press, Inc).

15 A further cohort of two 5 year old patients with
ADD have been treated and again symptoms have generally
improved, especially attention, as measured by ANT
(Amsterdam Neuropsychological Tests), which are standard
tests that measure reaction times for different tasks.

20 The protocol in this case is first a baseline
testing before medication and retesting after 2 days on
medication and then after a week repeated testing.
Ecological scales were also used before and are now
being evaluated after one week after two weeks etc. for
25 a treatment of one month duration. The following table
shows a selection of results obtained for these two
children before and after treatment with galantamine.

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		Before:				After:			
		mean	Sd	miss ¹	Fa ²	mean	Sd	miss	Fa
Patient A									
5	Baseline:	685	766			727	470		
	GoNoGo	705	158	1	1	655	173	1	2
	Sustained Att.	1302	565	14	13	1222	472	4	6
	Focused Att.	1214	404			1352	434	0	
Patient B									
10	Baseline:	1051	899			780	418		
	GoNoGo	804	162	2	9	766	172	3	3
	Sustained Att.	1444	721	31	29	1152	600	20	50
	Focused Att.	2444	1367	1		1166	270	3	

15

¹ Missed task² Failed attempt

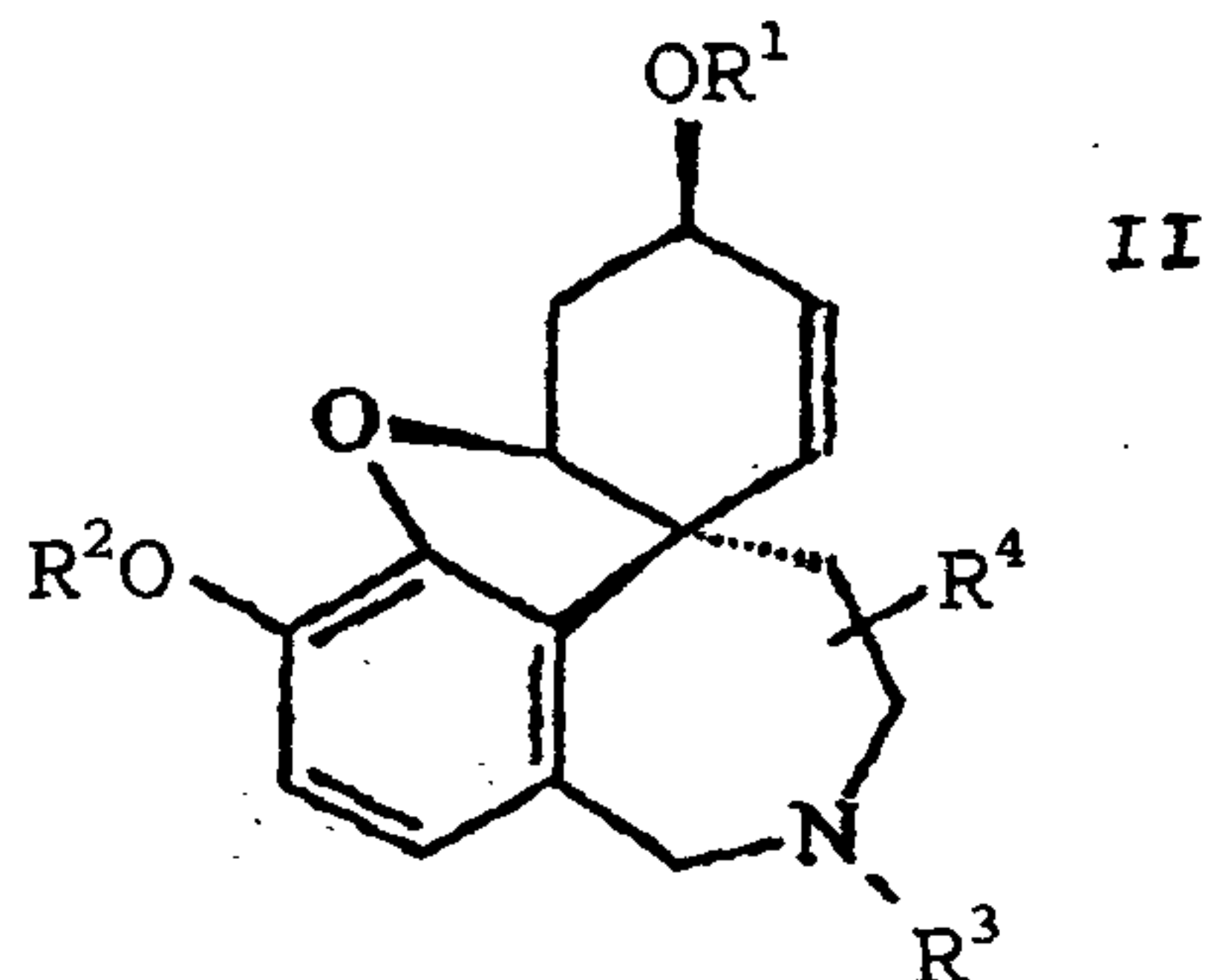
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This data was normalized and submitted to error analysis that showed an improvement in attention (reduction in time (msec) to complete certain tasks and with fewer errors) over 2.5 standard deviations after medication with galantamine hydrobromide 2.5 mg 3 times a day.

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The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. The use of galantamine or a derivative thereof of formula II:



wherein R^1 and R^2 which may be the same or different each represents a hydrogen atom, an acyl group or a straight-chained or branched alkyl group;

R^3 is a straight or branched chain alkyl, alkenyl or alkaryl group which is optionally substituted by a halogen atom or a cycloalkyl, hydroxy, alkoxy, nitro, amino, aminoalkyl, acylamino, heteroaryl, heteroarylalkyl, aroyl, aroylalkyl or cyano group; and

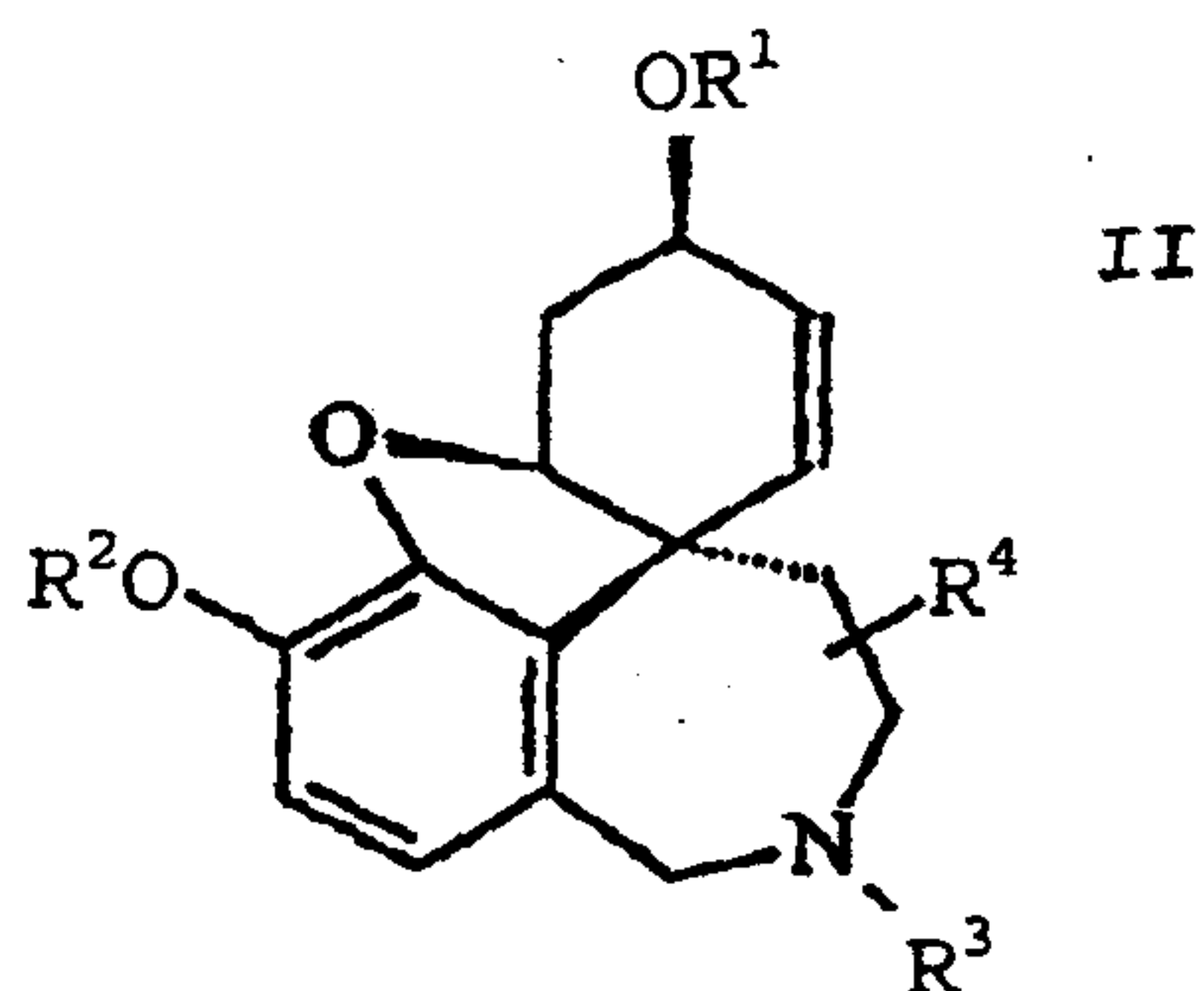
R^4 represents a hydrogen or a halogen atom attached to at least one of the ring carbons of the tetracyclic skeleton;

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for combatting an attention deficit disorder.

2. The use according to claim 1, wherein the acyl group is an acetyl group.
3. The use according to claim 1, wherein R^1 and R^2 each comprise methyl, ethyl, propyl or isopropyl.

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4. The use of galantamine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for combatting an attention deficit disorder.
5. The use according to any one of claims 1 to 4, wherein the pharmaceutically acceptable salt comprises a hydrobromide, a hydrochloride, a methylsulphate or a methiodide.
6. The use according to any one of claims 1 to 5, wherein the disorder is attention deficit hyperactivity disorder.
7. The use according to any one of claims 1 to 5, wherein the disorder is a hyperkinetic disorder.
8. A pharmaceutical composition for combatting attention deficit disorders, the pharmaceutical composition comprising galantamine or a derivative thereof of formula II:



wherein R^1 and R^2 which may be the same or different each represents a hydrogen atom, an acyl group or a straight-chained or branched alkyl group;

R^3 is a straight or branched chain alkyl, alkenyl or alkaryl group which is optionally substituted by a halogen atom or a cycloalkyl, hydroxy, alkoxy, nitro, amino, aminoalkyl,

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acylamino, heteroaryl, heteroarylalkyl, aroyl, aroylalkyl or cyano group; and

R⁴ represents a hydrogen or a halogen atom attached to at least one of the ring carbons of the tetracyclic skeleton;

or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.

9. The pharmaceutical composition according to claim 8, wherein the acyl group is an acetyl group.

10. The pharmaceutical composition according to claim 8, wherein R¹ and R² each comprise methyl, ethyl, propyl or isopropyl.

11. A pharmaceutical composition for combatting attention deficit disorders, the pharmaceutical composition comprising galantamine, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.

12. The pharmaceutical composition according to any one of claims 8 to 11, wherein the pharmaceutically acceptable salt comprises a hydrobromide, a hydrochloride, a methylsulphate or a methiodide.

13. The pharmaceutical composition according to any one of claims 8 to 12, wherein the disorder is attention deficit hyperactivity disorder.

14. The pharmaceutical composition according to any one of claims 8 to 12, wherein the disorder is a hyperkinetic disorder.