

Señor

SUPERINTENDENTE DELEGADO PARA LA PROPIEDAD INDUSTRIAL
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Ref: P1.-PHARMACIA & UPJOHN COMPANY.-Expediente No.
00-049.691.-

1. Me refiero al asunto de la referencia.
2. Por medio del presente, atentamente me permito manifestar que hubo un **cambio** de apoderado para todos los asuntos de la Propiedad Industrial en Bogotá de la sociedad **PHARMACIA & UPJOHN COMPANY.**
3. En consecuencia, atentamente solicito a ese Despacho reconocirme personería en este asunto, de conformidad con la sustitución de poder adjunta, otorgada a favor de la SUSCRITA.
4. Por lo tanto, ruego a usted notificarme de las providencias expedidas dentro de este expediente y notificadas al anterior apoderado, que actualmente se encuentran pendientes de cumplimiento o de respuesta.
5. Solicito a ese Despacho proceder de conformidad.

Atentamente,


ALICIA LLOREDA RICAURTE

T.P. 53215

Código 231



301 308

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2005-09-15

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020

Bogotá, D.C., 07 de septiembre de 2005

Apoderado: Alicia Lloreda Ricaurte

Oficio;

8386

ASUNTO

Radicación: 00-49691

Trámite 002

Evento 001

Actuación 430

Folios

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

Documentos estudiados:

- ♦capítulo descriptivo, folios 5 a 42;
- ♦capítulo reivindicatorio, folios 62 y 63;
- ♦1° examen de forma, folios 51 y 52;
- ♦respuesta técnica al 1° examen de forma, folios 58 y 59;
- ♦solicitudes de las cuales se reivindica prioridad, folios 64 a 300; ✓
- ♦2° examen de forma, folio 301;
- ♦solicitud del examen de patentabilidad 303 a 305.

Objeto de la invención:

El título de la invención es "INHIBIDORES ALTAMENTE SELECTIVOS DE LA RECAPTACIÓN DE LA NOREPINEFRINA Y MÉTODOS DE USO DE LOS MISMOS".

El objeto de la presente solicitud se refiere a método terapéutico usando la roboxetina.

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la Decisión 486 de la Comunidad Andina establece que: "*Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento en todos los campos de la tecnología,*

siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial".

En cumplimiento del artículo 14 de la Decisión 486, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio. reivindicaciones 1 a 23, folios 75 a 79. Consultada la fuente de información con que cuenta este despacho se encontró los siguientes documentos:

Item	Documento	Fecha de publicación	Titulo
D1	GB2167407	29-may-1986	Enantiomers of phenoxy derivatives of benzyl morpholine and salts thereof
D2	GB2014981	05-sep-1979	Substituted propanolamine and morpholine derivatives
D3	WO9915163	01-abr-1999	Treatment of conduct disorders
D4	WO9915176	01-abr-1999	Treatment of oppositional defiant disorder
D5	WO9915177	01-abr-1999	Treatment of attention-deficit/hyperactivity disorder

Evaluación de la novedad:

El artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina dispone que: *“Una invención se considerará nueva cuando no está comprendida en el estado de la técnica”*.

En la solicitud en estudio describe un método de tratamiento con reboxetina, se reivindica una preparación de un medicamento a partir de una composición que comprende (S,S) reboxetina ópticamente pura o una sal farmacéuticamente pura.

-La anterioridad D1 describe composiciones la reboxetine todos los posibles enantiomeros que comprende la molecula, los métodos de obtener los enantioneros puros y composiciones farmacéuticas que la comprenden, al igual que sus efectos terapeuticos.

Tal como puede verse la reboxetina no es nueva, como es nuevo que se sepa que tiene enantiomeros y tampoco las composiciones que la comprenden, entonces son ya conocidas las formulaciones que comprenden reboxetina, por lo

tanto lo reclamado en la solicitud en estudio no es nuevo.

-D2 se enseña los métodos de obtención de la reboxetina al igual que sus enantiomeros y las composiciones que comprenden reboxetina, lo que demuestra en primer lugar que no es la primera vez que se sabe tiene enantiomeros, como tampoco es la primera vez que se prepara composiciones farmaceuticas con reboxetina, por lo tanto lo reclamado en la solicitud en estudio no es nuevo.

-D3 a D5 metodos terapeuticos donde se usan inhibidores altamente selectivos de la recapatación de la norepinefrina y el metodo terapeutico donde se usa composiciones farmaceuticas que comprenden reboxetina como ingrediente activo, tal como se muestra comprende el mismo procedimiento terapeutico, con la misma compsción que se reclama como nueva en la solicitud en estudio.

No	Documento:	Reivindicaciones afectadas:	Requisito afectado:
D1	GB2167407	1 a 2	Novedad
D2	GB2014981	1 a 2	Novedad
D3	WO9915163	1 a 2	Novedad
D4	WO9915176	1 a 2	Novedad
D5	WO9915177	1 a 2	Novedad

En cumplimiento del artículo 45 de la decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la circular única No. 10 de 2001.



ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha

~~15 SET 2012~~

CONCEPTO TÉCNICO No. 1388	EXAMINADOR TÉCNICO Código No. 202012
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305 312

(12) **UK Patent Application** (19) **GB** (11) **2 167 407 A**

(43) Application published 29 May 1986

(21) Application No **8429546**

(22) Date of filing **22 Nov 1984**

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(51) INT CL⁴

C07D 265/30 A61K 31/535

(52) Domestic classification

C2C 1562 215 220 226 22Y 246 255 25Y 29X 29Y 302
30Y 311 31Y 364 36Y 43X 624 634 662 694 699 774
777 778 802 80Y AA WH
U1S 2417 2418 C2C

(56) Documents cited

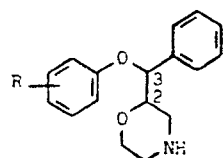
GB A 2014981
Eur J Med Chem-Chim Ther Vol 19 No 3 1984 pages
235-242

(58) Field of search

C2C

(54) **Enantiomers of phenoxy derivatives of benzyl morpholine and salts thereof**

(57) A 2R, 3R or 2S,3S enantiomer of a 2-(α -phenoxybenzyl)-morpholine derivative of formula (I):



(I)

wherein

R is a C₁-C₆ alkoxy group or a trihalomethyl group; and the pharmaceutically acceptable salts thereof are useful as an anti-depressant, in treating sleep disorders or as a minor tranquilizer.

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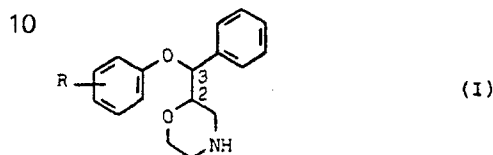
GB 2 167 407 A

SPECIFICATION

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Enantiomers of phenoxy derivatives of benzyl morpholine and salts thereof

- 5 The present invention relates to RR and SS enantiomers of phenoxy derivatives of benzyl morpholine and salts thereof, to a process for their preparation and to pharmaceutical compositions containing them. U.S. Patent No. 4,229,449 describes, among the others, 2-(α -phenoxy-benzyl)-morpholine derivatives of the following formula (I)



- 15 wherein R is a C_1 - C_6 alkoxy group or a trihalomethyl group, and their pharmaceutically acceptable salts. Due to the presence of the two chiral centres at the carbon atoms 2 and 3 in the above formula (I), for each compound of formula (I) two couples of enantiomers exist. These two
- 20 couples, which are in a diastereoisomeric relationship one to the other, are identified by the symbols ($\pm$) RS,RS and, respectively ($\pm$) RS,SR, in accordance with IUPAC, NOMENCLATURE OF ORGANIC CHEMISTRY, 1979 Edition, Section E, 489.

- In the formula (I) and in the other formulae of this specification the two chiral centres have been conventionally numbered 2 and 3 in order to be able to indicate unequivocally the absolute
- 25 configuration of each center, when available. Such a conventional numbering, however, is independent of the numbering required, e.g. by the IUPAC Nomenclature, for a correct naming of the involved compounds.

- While mention of specific diastereoisomers, i.e. couples of enantiomers, of the above formula (I) was given in U.S. Patent No. 4,229,449, no specific mention was therein made of the single
- 30 enantiomers deriving therefrom.

- The present invention provides a 2R, 3R or 2S, 3S enantiomer of a compound of formula (I) and the pharmaceutically acceptable salts thereof. An enantiomer of the invention will therefore be either a dextro (+) or a levo (-) enantiomer. Preferred compounds of the invention are those wherein R is methoxy, ethoxy or trifluoromethyl.

- 35 The present invention includes also the metabolites, the bioprecursors and, as already said, the pharmaceutically acceptable salts of the 2R, 3R or 2S, 3S enantiomers of formula (I), as well as the pharmaceutical compositions containing the said enantiomers or their salts. Examples of pharmaceutically acceptable salts of the enantiomers of the invention are both the salts with inorganic acids, for example hydrochloric acid, hydrobromic acid, sulphuric acid, and the salts
- 40 with organic acids including optically active acids, for example, citric acid, tartaric acid, methanesulphonic acid, fumaric acid, maleic acid and mandelic acid. Preferred salts are those with hydrochloric acid and methanesulphonic acid, the more preferred ones being those with methanesulphonic acid. Examples of specific preferred compounds of the invention are the following (+) and (-) enantiomers:

- 45 (+)-2-[α -(2-methoxy-phenoxy)-benzyl]-morpholine;
 (-)-2-[α -(2-methoxy-phenoxy)-benzyl]-morpholine;
 (+)-2-[α -(2-ethoxy-phenoxy)-benzyl]-morpholine;
 (-)-2-[α -(2-ethoxy-phenoxy)-benzyl]-morpholine;
 (+)-2-[α -(4-trifluoromethyl-phenoxy)-benzyl]-morpholine;
 50 (-)-2-[α -(4-trifluoromethyl-phenoxy)-benzyl]-morpholine,
 and their pharmaceutically acceptable salts, in particular the salts with hydrochloric acid or methanesulphonic acid.

The compounds of the invention may be prepared by a process comprising:

- (a) reacting the ($\pm$)RS,RS racemic form of a compound of formula (I), as free base, with an
- 55 optically active acid, so obtaining a mixture of two diastereoisomeric salts;
- (b) separating the obtained salts by crystallization;
- (c) optionally liberating the dextro (+) or levo (-) enantiomeric base from the respective separated salt; and
- (d) optionally salifying the obtained dextro (+) or levo (-) enantiomeric base with a pharmaceuti-
- 60 cally acceptable salt.

- The reaction of the ($\pm$)RS,RS racemic form of a compound for formula (I) as free base with an optionally active acid may be carried out with any suitable optionally active acid which may be, for instance, L (+) mandelic acid, D (-) mandelic acid, 10 (+) camphorsulfonic acid, L (+) dibenzoyltartaric acid, L (-) pyrrolidon-carboxylic acid, L(+) tartaric acid or D (-) tartaric acid.

- 65 This salification reaction is preferably performed in an organic, preferably anhydrous, solvent.

which may be for instance, methanol, ethanol, dioxane or dimethylformamide.

If necessary, the precipitation of the obtained salt from the reaction solvent may be favoured by adding an anhydrous apolar solvent which may be, for example, diethylether, n-hexane or cyclohexane.

- 5 The separation of the desired salt from the diastereoisomeric mixture is preferably carried out by fractional crystallization from an appropriate solvent which may be, for example, methanol or ethanol. Preferably an anhydrous solvent is used.

- The optional liberation of the corresponding dextro (+) or levo (-) enantiomeric base from the separated salt may be carried out by treatment with a small excess of any suitable base. An inorganic base such as, for instance, an alkali metal or alkaline-earth metal hydroxide or carbonate or bicarbonate, is preferably used. Sodium or potassium carbonate or bicarbonate are particularly preferred bases.

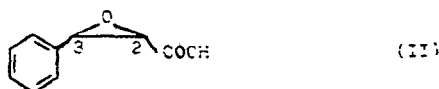
- The optional salification of an obtained dextro (+) or levo (-) enantiomeric base may be carried out by reaction with a stoichiometric amount or a small excess of the desired acid in an appropriate solvent. Thus, for example, the salt with hydrochloric acid may be obtained by treatment with anhydrous gaseous hydrochloric acid or an anhydrous alcoholic solution of hydrochloric acid in an anhydrous solvent such as, e.g., diethylether, toluene, ethanol, and isolating the hydrochloride by filtration or evaporation of the solvent. Analogously, the salt with methanesulphonic acid may be obtained, for example, by adding an ethanolic solution of methanesulphonic acid to the ethanolic mixture of the enantiomeric base.

The precipitation of the methanesulphonate salt may be, if necessary, favoured by the addition of an anhydrous apolar solvent which may be for example, diethylether, n-hexane or cyclohexane.

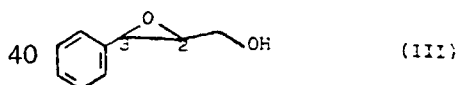
- All the reaction steps reported above from a) to d) may be carried out at a temperature varying from about 0°C to about 50°C, the room temperature being, in any case, the preferred one.

The preparation of the compounds of formula (I) as a mixture of diastereoisomers and as separated diastereoisomers is reported in U.S. patent No. 4,229,449. In an alternative approach, the compounds of the invention may be prepared by a process comprising:

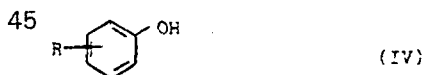
- 30 (a) reducing the (+) or (-) enantiomer of a glycidic acid of formula (II)



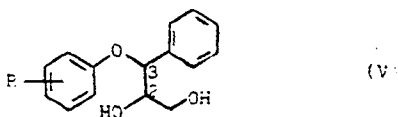
- 35 or a derivative thereof, so obtaining the (+) or (-) enantiomer of the cinnamyl alcohol-2,3-epoxide of formula (III)



- (b) reacting a (+) or (-) enantiomer of formula (III) with a phenol derivative of formula (IV)

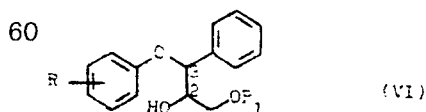


wherein R is as defined above, so obtaining a (+) or (-) enantiomer of formula (V)



wherein R is as defined above;

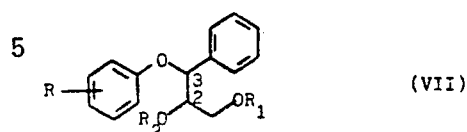
- (c) esterifying a (+) or (-) enantiomer of formula (V) with a carboxylic acid, or a reactive derivative thereof, so obtaining a (+) or (-) enantiomer of formula (VI)



- 65 wherein R is as defined above and R₁ is the residue of a carboxylic acid;

(d) esterifying a (+) or (-) enantiomer of formula (VI) with a sulphonic acid, or a reactive derivative thereof, so obtaining a (+) or (-) enantiomer of formula (VII)

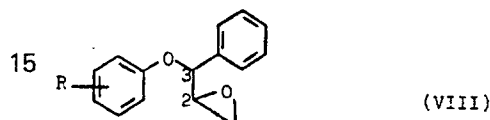
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- 10 wherein R and R₁ are as defined above and R₂ is the residue of a sulphonic acid;
(e) making an epoxide from a (+) or (-) enantiomer of formula (VII) so obtaining a (+) or (-) enantiomer of formula (VIII)

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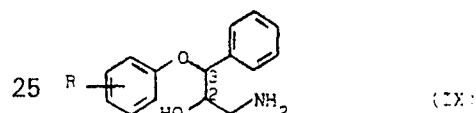


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wherein R is as defined above;

- 20 (f) reacting a (+) or (-) enantiomer of formula (VIII) with ammonia, so obtaining a (+) or (-) enantiomer of formula (IX)

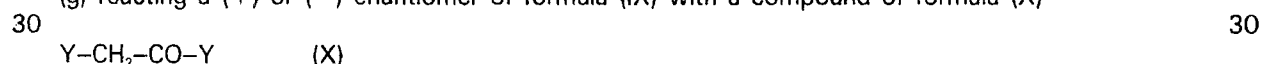
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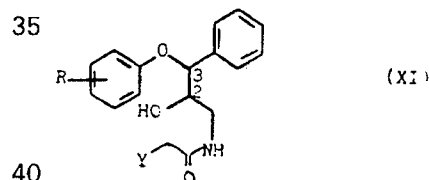
wherein R is as defined above;

- (g) reacting a (+) or (-) enantiomer of formula (IX) with a compound of formula (X)



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wherein Y is halogen, so obtaining a (+) or (-) enantiomer of formula (XI)



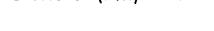
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40  (XI)

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wherein R and Y are as defined above;

- (h) cyclizing a (+) or (-) enantiomer of formula (XI) so obtaining a (+) or (-) enantiomer of formula (XII)

45  (XII)

45

50  (XII)

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wherein R is as defined above; and

- (i) reducing a (+) or (-) enantiomer of formula (XII) so obtaining a (+) or (-) enantiomer of formula (I) and, if desired, converting the obtained 2R,3R or 2S,3S enantiomer of formula (I) into a pharmaceutically acceptable salt thereof.

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A derivative of the glycidic acid of formula (II) may be, e.g., an anhydride, preferably a mixed anhydride. The carboxylic acid employed in the above esterification step (c) may be either aliphatic, e.g. a C₂-C₆ aliphatic carboxylic acid such as, for instance, acetic or propionic acid, or aromatic, e.g. benzoic or *p*-nitro-benzoic acid.

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The R₁ residue of a carboxylic acid in the above formulae (VI) and (VII) is, e.g., acetyl, propionyl, benzoyl or *p*-nitro-benzoyl.

The sulphonic acid employed in the esterification step (d) is, for example, methanesulphonic acid, ethanesulphonic acid, benzenesulphonic acid or *p*-toluenesulphonic acid. The R₂ residue of a sulphonic acid in the above formula (VII) is e.g. methanesulphonyl, ethanesulphonyl, benzenesul-

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phenyl or *p*-toluenesulphonyl, preferably methanesulphonyl. The halogen Y in the compounds of formula (X) and formula (XI) is, preferably, chlorine, bromine or iodine, most preferably chlorine.

The reduction step (a) may be carried out with BH_3 or a mixed hydride such as, e.g., NaBH_4 , followed known procedures, preferably operating under cooling, e.g. around 0°C , in a suitable anhydrous inert solvent which may be, for instance, absolute ethanol, diethyl ether or tetrahydrofuran.

The reaction of an enantiomer of formula (III) with a compound of formula (IV) is preferably carried out by heating, e.g. at a temperature between about 60°C and about 120°C , in the presence of a base such as, e.g., aqueous sodium or potassium hydroxide, preferably in absence of any other solvent.

The esterification of an enantiomer of formula (V) to give a compound of formula (VI) is preferably performed with a reactive derivative of a carboxylic acid, preferably a carboxylic acid halide, in particular chloride, operating under cooling, e.g. at about -10°C to 0°C , or at room temperature, in an anhydrous organic solvent, e.g. benzene or toluene, in the presence of a base which may be, for example, an organic base such as, e.g., triethylamine or pyridine: according to a preferred procedure, pyridine is used as solvent in absence of any other base.

The esterification of an enantiomer of formula (VI) to give a compound of formula (VII) is preferably carried out with a reactive derivative of a sulfonic acid, preferably a sulfonic acid halide, in particular the chloride, e.g. methanesulfonyl chloride or *p*-toluenesulfonyl chloride, in the presence of an acid acceptor which may be, for instance, an organic base as triethylamine or pyridine.

The reaction is preferably performed under cooling, e.g. at -10° to 5°C , in a suitable anhydrous solvent such as, e.g., benzene, toluene, methylene chloride or pyridine: when pyridine is used as solvent, it also acts as a base. The transformation of a compound of formula (VII) into a compound of formula (VIII), is carried out by reaction with a suitable base, preferably an inorganic base such as, e.g., an alkali metal or alkaline-earth metal hydroxide, preferably sodium or potassium hydroxide. Preferably the reaction is carried out at room temperature in an aqueous organic solvent such as, e.g. dioxane or dimethylformamide.

The subsequent reaction of the epoxide of formula (VIII) with ammonia is preferably carried out at room temperature with 30–32% aqueous ammonia in a suitable solvent which may be, for instance, dimethylacetamide or an aliphatic alcohol, e.g. methanol or ethanol. The reaction between an obtained enantiomer of formula (IX) and a compound of formula (X) may be, e.g., performed in the presence of a base, e.g. an organic base such as, for instance, triethylamine, preferably operating under cooling, for example at -10°C to 0°C , in an anhydrous inert solvent, e.g. an halogenated hydrocarbon such as, e.g., methylene chloride.

The subsequent cyclization of an enantiomer of formula (XI) may be, e.g., performed by treatment with a base, for example with potassium tert.butoxide in tert.butyl alcohol at room temperature, according to known procedures.

The reduction of an obtained enantiomer of formula (XII) may be, e.g., carried out by treatment with BH_3 or a mixed hydride, for instance LiAlH_4 or NaBH_4 , in an anhydrous inert solvent such as, e.g., diethylether, tetrahydrofurane, dioxane or toluene, at temperatures varying from about 0°C to the reflux temperature; a particularly suitable reduction procedure involves the use of Red-Al (Vitrade[®]) as the reducing agent in anhydrous toluene at room temperature.

The optional salification of an obtained enantiomer of formula (I) may be carried out in any conventional way according to known salification procedures.

The glycidic acid enantiomers of formula (II), used as starting material in the alternative process approach described above, are either known compounds or compounds that can be prepared by known methods from known compounds: see, for instance, K. Harada, J. Org. Chem., 31, 1407, 1966.

The compounds of the invention are active on the central nervous system, in particular as antidepressant agents, as is shown, e.g., by their ability in raising the concentration of physiologically active monoamines, e.g. by blocking their uptake and/or by desensitizing α -2 presynaptic receptors. As is known, an important property of antidepressant agents is their ability of blocking neurotransmitter uptake at cerebral synapses (Iversen L.L., J.Pharm. Pharmacol., 17:42, 1965), and further important property may also be the ability of blocking or desensitizing α -2 adrenoceptors (Chapleo C.B., J. Med. Chem. 26:823, 1983).

The compounds of the invention were found to be able to increase the concentration of biogenic amines both *in vitro* (where activity was determined, e.g., with radioactively labelled compounds according to the experimental method described by Snyder S.H. in J. Pharmacol. Exp. Ther., 165:76, 1969) and *in vivo*, by a variety of methods.

The physiologically active monoamines whose concentration is raised by the compounds of this invention include serotonin, norepinephrine and dopamine. The antidepressant activity of the compounds of this invention is proved also by the fact that they are active in preventing reserpine-induced blepharospasm and hypothermia in mice.

The compounds of this invention may also find use, e.g., in treating disorders of sleep and as

minor tranquilizers.

The toxicity of the compounds of the invention is negligible, therefore they can be safely used in therapy.

The compounds of the present invention are preferably administered orally, although they can be administered also in other conventional ways, for example, by injection or by rectal way.

The dosage suitable for the oral administration to adult humans of the compounds of the invention, is preferably 0.5–10 mg pro dose 2–4 times a day. Pharmaceutical compositions according to the invention comprise a 2R,3R or 2S,3S enantiomer of a compound of formula (I) or a pharmaceutically acceptable salt thereof as active ingredient and a pharmaceutically acceptable carrier and/or diluent. The compositions may be prepared according to conventional methods with the usual ingredients. Thus, for oral administration, the pharmaceutical compositions containing the compounds of the invention are preferably tablets, pills or capsules which contain the active substance together with diluents, such as, for example, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose; lubricants, for instance, silica, talc, stearic acid, magnesium or calcium stearate and/or polyethylene glycols; or they may also contain binders, such as, for example, starches, gelatine, methylcellulose, gum arabic, tragacanth, polyvinylpyrrolidone; disintegrating agents, such as, for instance, starches, alginic acid, alginates; effervescent mixtures; dyestuffs; sweeteners; wetting agents, such as, for instance, lecithin, polysorbates, lauryl-sulphates; and in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tableting, sugar-coating, or film-coating processes.

Also the other pharmaceutical formulations containing the compounds of the invention may be prepared by known methods and they can be, for example, syrups or drops for the oral administration, sterile solutions for injection, or suppositories.

The following examples illustrate but do not in any way limit the present invention. Where unspecified, the $[\alpha]_D$ values are for 1% concentrations in 95% ethanol.

Example 1

To a solution of 2-[α -(2-ethoxy-phenoxy)-benzyl]-morpholine ($\pm$) RS,RS diastereoisomer (1.6 g) in anhydrous ethanol, methanesulphonic acid (0.33 ml) was added. By dilution with diethyl ether (200 ml) of a solid precipitated. This was collected by filtration to give 2-[α -(2-ethoxy-phenoxy)-benzyl]-morpholine methanesulphonate m.p. 146–147°C, U.V. (MeOH): λ_{max} = 275 nm; $E_{1cm}^{1\%}$ = 50, as the ($\pm$)RS,RS racemic form.

Example 2

An aqueous solution of ($\pm$) RS,RS 2-[α -(2-ethoxy-phenoxy)-benzyl]-morpholine methanesulphonate (m.p. 146–147°C; 40 g), made basic with potassium carbonate, was extracted twice with ethyl acetate. The organic solution was washed with water, dried on sodium sulphate and evaporated to dryness *under vacuo*. The free base (31 g) was dissolved in anhydrous ethanol (140 ml) and to the solution L(+) mandelic acid (15.06 g) dissolved in anhydrous ethanol (140 ml) was added. The precipitate was filtered to give 18.85 g of a solid having m.p. 134–151°C and $[\alpha]_D^{20}$ = (+) 48.01 (1% solution in 80% ethanol). After crystallization from anhydrous ethanol (200 ml), 16.86 g of a product (mandelate salt), melting at 151–153°C, were obtained; $[\alpha]_D^{20}$ = +49.09 (1% solution in 80% ethanol). This mandelate salt was dissolved in H₂O, the solution was basified with potassium carbonate and the base extracted with ethyl acetate. The organic solution was dried over sodium sulphate and evaporated to dryness *under vacuo*. The oily residue consisting of (+) 2S,3S-2-[α -(2-ethoxy-phenoxy)-benzyl]-morpholine (12.15 g) was taken up with ethanol and an ethanolic solution of methanesulphonic acid (3.72 g) was added. After dilution with diethyl ether a precipitate formed which was filtered to give (+) 2S,3S-2-[α -(2-ethoxy-phenoxy)-benzyl]-morpholine methanesulphonate (13.05 g); m.p. 100–102°C, $[\alpha]_D^{20}$ = +21.89° (1% solution in 95% ethanol).

Molar purity (D.S.C.) = 98%.

N.M.R. (CDCl₃) δ : 1.42 (t, 3H, CH₃-CH₂),

2.71 (s, 3H, CH₃SO₃),
2.84–3.50 (m, 4H, CH₂-N-CH₂),
3.85–4.40 (m, 3H, CH₂-O-CH),
4.05 (q, 2H, CH₂-O-Ar),
5.14 (d, 1H, O-CH-Ar),
6.64–6.92 (m, 4H, Ar<^o),
7.33 (m, 5H, Ar-CH),
9.20 (bs, 2H, N-H₂).

The same method was used to prepare, starting from D(–) mandelic acid, the levo isomers (–) 2R,3R-2-[α -(2-ethoxy-phenoxy)-benzyl]-morpholine and (–) 2R,3R-2-[α -(2-ethoxy-phenoxy)-

benzyl]-morpholine methanesulphonate, the latter having m.p. 100–102°C, $[\alpha]_D^{20} = -21.89^\circ$ (1% solution in 95% ethanol).

By proceeding analogously, the following enantiomers were prepared starting from the corresponding ($\pm$) RS,RS racemic forms:

- 5 (+) 2-[α -(2-methoxy-phenoxy)-benzyl]-morpholine; 5
(–) 2-[α -(2-methoxy-phenoxy)-benzyl]-morpholine;
(+) 2-[α -(4-trifluoromethyl-phenoxy)-benzyl]-morpholine;
(–) 2-[α -(4-trifluoromethyl-phenoxy)-benzyl]-morpholine;
(+) 2-[α -(2-methoxy-phenoxy)-benzyl]-morpholine methane-sulphonate;
10 (–) 2-[α -(2-methoxy-phenoxy)-benzyl]-morpholine methane-sulphonate; 10
(+) 2-[α -(4-trifluoromethyl-phenoxy)-benzyl]-morpholine methanesulphonate;
(–) 2-[α -(4-trifluoromethyl-phenoxy)-benzyl]-morpholine methanesulphonate.

The optical purity of the (+) 2S,3S- and (–) 2R,3R-2-[α -(2-ethoxy-phenoxy)-benzyl]-morpholine methanesulphonates obtained from the ($\pm$) RS,RS racemic form was determined as reported

15 below. 15

To a solution of (+) 2S,3S-2-[α -(2-ethoxy-phenoxy)-benzyl]-morpholine base (1 g) (obtained from the corresponding ($\pm$) RS,RS diastereoisomer) and Et_3N (0.90 ml) in anhydrous toluene (40 ml), L(–) menthoxy-acetyl-chloride (0.80 ml) in anhydrous toluene (10 ml) was added dropwise under vigorous stirring at 10°C temperature. After stirring 1 hour at room temperature, the

20 reaction was complete and the reaction mixture was washed with water, dried over sodium sulphate and evaporated to dryness *under vacuo*. 20

The same procedure was applied to the (–) 2R,3R-enantiomer obtained from ($\pm$) RS,RS 2-[α -(2-ethoxy-phenoxy)-benzyl]-morpholine.

Each of the two diastereoisomeric amides so obtained was analysed by HPLC technique/Parti-
25 sil * PXS 10/25; cyclohexane:ethylacetate 93:7 with 0.15% of isopropylamine] to give a Reten- 25
tion Time (R.T.) of 15.13 min. and, respectively, of 17.23 min.

The result was in both cases a relative purity $\geq 98.5\%$ from which an optical purity $\geq 97\%$ for both the (+) and (–) enantiomers may be inferred.

30 Example 3 30

A solution of 3.8 g (13.3 mmole) of (+) 2S,3R-phenyl-glycidic acid D(+)- α -methyl-phenethyl-amine salt was treated with 6.65 ml (13.3 mmole) of 2N HCl. The organic acid was extracted with diethylether and the solvent removed *in vacuo* after drying over Na_2SO_4 . The residue was dissolved in 70 ml of CH_2Cl_2 and 2 ml (14.3 mmole) of triethylamine were added. The solution

35 was cooled to 0°C and 1.36 ml (14.3 mmole) of ethyl-chlorocarbonate were added dropwise 35
under stirring during 1 hr. After 2hr the solution was slowly added under stirring to a suspension of 2.26 g (59.7 mmole) of sodium borohydride in 17 ml of absolute ethanol, at 0°C. After 0.5 hr the temperature was allowed to rise to room temperature and stirring was continued overnight.

The mixture was poured into water and the product extracted with CH_2Cl_2 . After separation on a flash chromatography column (CHCl_3 : CH_3OH 100:2 as eluant) 0.62 g (31%) of (+) 2R,3R-cinnamyl alcohol-2,3-epoxide were obtained as a colorless oil; $[\alpha]_D^{20} = +45.9^\circ$ (C 1.5, abs.ethanol). (Found: C, 71.68; H, 6.71. $\text{C}_9\text{H}_{10}\text{O}_2$ requires C, 71.97; H, 6.71%);

¹H-N.M.R. (CDCl_3) Δ : 3.24 (1H, ddd, $-\text{CH}-\text{CH}_2\text{OH}$),
45 3.76 (1H, dd, $\text{CH}_A\text{H}_B-\text{OH}$), 45
3.94 (1H, d, $\text{Ph}-\text{CH}$, $J=2.1$ Hz),
4.05 (1H, dd, $\text{CH}_A\text{H}_B-\text{OH}$),
7.35 (5H, s, Ph);

IR (CHCl_3) cm^{-1} : 3590–3450 (OH), 1600, 1490 (arom.C=C), 1220, 1060 (Alk-O-Alk, Alk-OH);

50 0.33 g (15.3%) of the starting (+)-(2S,3R) phenyl glycidic acid were recovered together with 50
0.92 g (36.5%) of its ethyl ester.

Example 4

To a solution of 1.77 g (44.3 mmole) of NaOH in 100 ml of water, 18.4 g (133 mmole) of 2-ethoxy-phenol were added. The mixture was stirred at 70° under nitrogen until the solid completely dissolved, and then 6.7 g (44.3 mmole) of (+) 2R,3R-cinnamyl alcohol-2,3-epoxide were added in 10 min. The solution was stirred at 70°C for 2.5 hr and then poured into 200 ml of 1N NaOH at 10–15°. After extraction with CH_2Cl_2 the organic solution was washed successively with 1N NaOH and brine. Elimination of the solvent gave 10.2 g of (+) 2R,3S-3-(2-ethoxy-phenoxy) 1,2-dihydroxy-3-phenylpropane, $[\alpha]_D^{20} = +7.8^\circ$; m.p. 87–89°; IR (KBr) cm^{-1} : 3440–3380 (OH), 1590, 1490 (arom.C=C), 1240 (Ar-O-Alk).

Example 5

To a solution of 10 g (34.6 mmole) of (+) 2R,3S-3-(2-ethoxy-phenoxy)-1,2-dihydroxy-3-phenylpropane in 100 ml of pyridine, 6.44 g (34.0 mmole) of 4-nitro-benzoyl-chloride in 100 ml

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of pyridine were added at -10° in 1.5 hr. After 0.5 hr the solution was poured into a mixture of 2 l of 2N HCl and 1300 g of ice and the oily precipitate was extracted with ethyl acetate. After an usual work-up the compound (+) 2R,3S-3-(2-ethoxy-phenoxy)-2-hydroxy-1-(4-nitro-benzoyloxy)-3-phenylpropane (8.2 g) was obtained as oil, $[\alpha]_D^{20} = +11.7^{\circ}$.

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Example 6

To a solution of 80 g (18.2 mmole) of (+) 2R,3S-3-(2-ethoxy-phenoxy)-2-hydroxy-1-(4-nitro-benzoyloxy)-3-phenylpropane and 3.86 ml (27.4 mmole) of triethylamine in 90 ml of CH_2Cl_2 , 1.54 ml (20.0 mmole) of $\text{CH}_3\text{SO}_2\text{Cl}$ were added dropwise at $0-5^{\circ}$ and the solution was kept for 0.5 hr at that temperature. After washing with 10% HCl and 5% NaHCO_3 solutions and water, the solution was dried over Na_2SO_4 and the solvent evaporated to dryness.

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After usual work-up the compound (+) 2R,3S-3-(2-ethoxyphenoxy)-2-mesyloxy-1-(4-nitrobenzoyloxy)-3-phenylpropane (7.5 g) was obtained as oil, $[\alpha]_D^{20} = +33.6^{\circ}$.

Example 7

A solution of 3.95 g (7.7 mmole) of (+) 2R,3S-3-(2-ethoxyphenoxy)-2-mesyloxy-1-(4-nitrobenzoyloxy)-3-phenylpropane in 40 ml of dioxane and 16 ml of 2N NaOH was stirred for 4 hr at room temperature. After diluting with 200 ml of water the solution was extracted with ethyl acetate and the organic phase washed with a 5% aqueous solution of NaHCO_3 then water. After evaporation of the solvent *in vacuo* the residual oily epoxide (–) 2S,3S-3-(2-ethoxy-phenoxy)-3-phenylpropane 1,2-epoxide weighed g. 2.05 (100%) and was used as such for the subsequent step, $[\alpha]_D^{20} = -3.1^{\circ}$.

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Example 8

A solution of 2.05 g (7.6 mmole) of (–) 2S,3S-3-(2-ethoxyphenoxy)-3-phenylpropane 1,2-epoxide in 50 ml of methanol and 30 ml of 32% NH_4OH was kept standing in a sealed flask for 6 hr. After evaporation of the solvent the residue was dissolved in ethyl acetate, and 0.52 ml (8 mmole) of $\text{CH}_3\text{SO}_3\text{H}$ in 10 ml of ethyl acetate were added to the solution. After 16 hr 2.13 g of a crystalline product (+) 2S,3S-1-amino-3-(2-ethoxy-phenoxy)-2-hydroxy-3-phenylpropane was collected, m.p. $97-99^{\circ}\text{C}$, $[\alpha]_D^{20} = +34.4$.

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Example 9

To a solution of 2.13 g (7.4 mmole) of the aminoalcohol (+) 2S,3S-1-amino-3-(2-ethoxy-phenoxy)-2-hydroxy-3-phenylpropane and 2.27 ml (16.2 mmole) of triethylamine in 70 ml of CH_2Cl_2 , kept at $-5-10^{\circ}$, 0.64 ml (8.0 mmole) of chloroacetylchloride dissolved in 20 ml of CH_2Cl_2 were added dropwise. After 0.5 hr the solution was washed with water, dried over NaSO_4 and evaporated to dryness. After usual work-up a residue of (+) 2S,3S-1-chloroacetyl-amino-3-(2-ethoxy-phenoxy)-2-hydroxy-3-phenylpropane (2.6 g) was obtained as oil, $[\alpha]_D^{20} = +18.6^{\circ}$.

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Example 10

To a solution of 2.0 g (18.0 mmole) of potassium *t*-butoxide in 15 ml of *tert*-butanol 3.3 g (9.0 mmole) of (+) 2S,3S-1-chloroacetyl-amino-3-(2-ethoxy-phenoxy)-2-hydroxy-3-phenylpropane in 40 ml of *tert*-butanol were added at room temperature in 2 hr. After a further hour, 8% HCl was added until pH 4–5 was reached and the solution was evaporated to dryness *in vacuo*. The residue was taken up with water, the solution was neutralized with solid NaHCO_3 and extracted with ethyl acetate. The organic phase was thoroughly washed with water, dried over Na_2SO_4 and the solvent distilled *in vacuo*. An oily residue was obtained of (–) 2S,3S-6-[α -(2-ethoxy-phenoxy)-benzyl]-morpholin-3-one (2.6 g), $[\alpha]_D^{20} = -21.2^{\circ}$.

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Example 11

To a solution of 5.0 g (15.3 mmole) of (–) 2S,3S-6-[α -(2-ethoxy-phenoxy)-benzyl]-morpholin-3-one in 200 ml of anhydrous toluene, 12.7 ml (45.4 mmole) of 70% toluene solution of RED-AL (Vitride®), diluted with 40 ml of anhydrous toluene were added at room temperature in 15 min. After 4 hr the excess RED-AL was decomposed with 20 ml of 2N NaOH. The organic phase was separated, washed with water, dried, and evaporated to dryness. The residue was dissolved in ethyl acetate and 1.0 ml (15.4 mmole) of $\text{CH}_3\text{SO}_3\text{H}$ was added to the solution. After standing overnight at room temperature, the solid (+) 2S,3S-2-[α -(2-ethoxy-phenoxy)-benzyl]-morpholine methanesulphonate was collected by filtration; g 4.9 obtained, m.p. $100-102^{\circ}\text{C}$; IR (KBr) cm^{-1} : 3000–2400 (N-H_2), 1590–1495 (arom.C=C), 1250 (Ar-O-Alk), 1205 (Alk-O-Alk), 1190, 1040 (SO_3H); $[\alpha]_D^{20} = +21.81^{\circ}$.

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Example 12

The (+) 2S,3S-2-[α -(2-ethoxy-phenoxy)-benzyl]-morpholine (3.2 g) was dissolved in anhydrous ethanol (50 ml), then a slight excess of an ethanolic solution of hydrochloric acid was added. The solvent was evaporated to dryness under vacuum and diethyl ether was added to the oily

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residue. The solid obtained after grinding was filtered to give (+) 2S,3S-2-[α -(2-ethoxy-phenoxy)-benzyl]-morpholine.hydrochloride (3.3 g) m.p. 138–140°C.

By proceeding analogously, the following (+) and (–) enantiomer hydrochlorides were obtained:

- 5 (–) 2R,3R-2-[α -(2-ethoxy-phenoxy)-benzyl]-morpholine.hydrochloride, m.p. 138–140°C;
 (+) 2-[α -(2-methoxy-phenoxy)-benzyl]-morpholine.hydrochloride;
 (–) 2-[α -(2-methoxy-phenoxy)-benzyl]-morpholine.hydrochloride;
 (+) 2-[α -(4-trifluoromethyl-phenoxy)-benzyl]-morpholine.hydrochloride; and
 (–) 2-[α -(4-trifluoromethyl-phenoxy)-benzyl]-morpholine.hydrochloride.

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Example 13

Tablets were prepared, each weighing 200 mg and each containing 5 mg of active ingredient, in the manner described below:

15 Composition (for 10,000 tablets)

(+) 2S,3S-2-[α -(2-ethoxy-phenoxy)-benzyl]-morpholine
 methanesulphonate, the dextro (+) enantiomer
 deriving from the ($\pm$) RS,RS racemic form

Lactose

50 g

1.230 g

20 Corn starch

450 g

Talc (powdered)

50 g

Magnesium stearate

20 g.

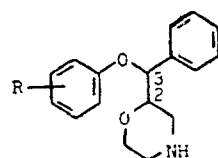
- 25 The (+) 2S,3S-2-[α -(2-ethoxy-phenoxy)-benzyl]-morpholine methanesulphonate, the lactose and half of the corn starch were mixed, sieved through a 0.55 mm mesh screen. 30 g of corn starch was dispersed in 300 ml of hot water. The mixture of the powders was granulated with the starch mucilage obtained. The granulate was dried and passed through a 1.4 mm mesh screen. The rest of the starch was added, as also the talc and the magnesium stearate. A careful blending was performed and the mass was compressed into tablets with 8 mm diameter punches.

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CLAIMS

1. A 2R,3R or 2S,3S enantiomer of a compound of formula (I):

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(I)

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wherein

R is a C₁–C₆ alkoxy group or a trihalomethyl group; and the pharmaceutically acceptable salts thereof.

- 45 2. A compound according to claim 1, wherein R is methoxy, ethoxy, or trifluoromethyl.

3. A compound according to claim 1 or 2, wherein the enantiomer is a dextro (+) enantiomer.

4. A compound according to claim 1 or 2, wherein the enantiomer is a levo (–) enantiomer.

5. A compound according to claim 3 selected from the group consisting of:

- 50 (+)2-[α -(2-methoxy-phenoxy)-benzyl]-morpholine;
 (+)2-[α -(2-ethoxy-phenoxy)-benzyl]-morpholine;
 (+)2-[α -(4-trifluoromethyl-phenoxy)-benzyl]-morpholine, and pharmaceutically acceptable salts thereof.

6. A compound according to claim 4 selected from the group consisting of:

- 55 (–)2-[α -(2-methoxy-phenoxy)-benzyl]-morpholine;
 (–)2-[α -(2-ethoxy-phenoxy)-benzyl]-morpholine;
 (–)2-[α -(4-trifluoromethyl-phenoxy)-benzyl]-morpholine, and pharmaceutically acceptable salts thereof.

7. A compound according to any one of the preceding claims which is a hydrochloride salt.

- 60 8. A compound according to any one of claims 1 to 6 which is a methanesulphonate salt.

9. A compound according to claim 5 which is (+)2-[α -(2-ethoxy-phenoxy)-benzyl]-morpholine or a pharmaceutically acceptable salt thereof.

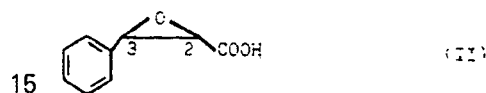
10. A compound according to claim 9 which is the hydrochloride salt.

11. A compound according to claim 9 which is the methanesulphonate salt.

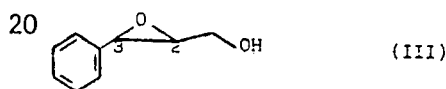
- 65 12. A process for the preparation of a compound according to any one of the preceding

claims, which process comprises:

- (a) reacting the ($\pm$)RS,RS racemic form of a compound of formula (I), as free base, with an optionally active acid so obtaining a mixture of two diastereoisomeric salts;
 - (b) separating the obtained salts by crystallization;
 - 5 (c) optionally liberating the dextro (+) or levo (-) enantiomeric base from the respective separated salt; and
 - (d) optionally salifying the obtained dextro (+) or levo (-) enantiomeric base with a pharmaceutically acceptable salt.
13. A process for the preparation of a compound according to any one of claims 1 to 11,
- 10 which process comprises:
- (a) reducing the (+) or (-) enantiomer of a glycidic acid of formula (II):



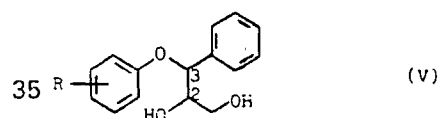
or a derivative thereof, so obtaining the (+) or (-) enantiomer of the cinnamyl alcohol-2,3-epoxide of formula (III)



- 25 (b) reacting a (+) or (-) enantiomer of formula (III) with a phenol derivative of formula (IV)

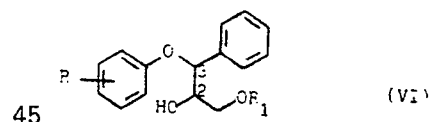


- 30 wherein R is as defined in claim 1, so obtaining a (+) or (-) enantiomer of formula (V)



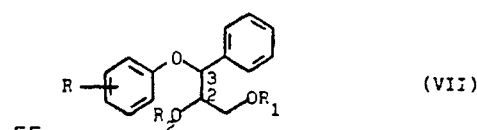
wherein R is as defined above;

- 40 (c) esterifying a (+) or (-) enantiomer of formula (V) with a carboxylic acid, or a reactive derivative thereof, so obtaining a (+) or (-) enantiomer of formula (VI)



wherein R is as defined above and R₁ is the residue of a carboxylic acid;

- 50 (d) esterifying a (+) or (-) enantiomer of formula (VI) with a sulphonic acid, or a reactive derivative thereof, so obtaining a (+) or (-) enantiomer of formula (VII)



wherein R and R₁ are as defined above and R₂ is the residue of a sulphonic acid;

- (e) making an epoxide from a (+) or (-) enantiomer of formula (VII) so obtaining a (+) or (-) enantiomer of formula (VIII)

pharmaceutically acceptable salts thus are the sulfate,
pyrosulfate, bisulfate, sulfite, bisulfite, phosphate,
monohydrogenphosphate, dihydrogenphosphate, metaphosphate,
pyrophosphate, chloride, bromide, iodide, acetate,
5 propionate, decanoate, caprylate, acrylate, formate,
isobutyrate, caproate, heptanoate, propiolate, oxalate,
malonate, succinate, suberate, sebacate, fumarate, maleate,
butyne-1,4-dioate, hexyne-1,6-dioate, benzoate,
chlorobenzoate, methylbenzoate, dinitrobenzoate,
10 hydroxybenzoate, methoxybenzoate, phthalate, sulfonate,
xylenesulfonate, phenylacetate, phenylpropionate,
phenylbutyrate, citrate, lactate, b-hydroxybutyrate,
glycollate, tartrate, methanesulfonate, propanesulfonate,
naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate
15 and the like. Preferred pharmaceutically acceptable salts
are those formed with hydrochloric acid.

Administration

The dosages of the drugs used in the present
20 invention must, in the final analysis, be set by the
physician in charge of the case, using knowledge of the
drugs, the properties of the drugs in combination as
determined in clinical trials, and the characteristics of
the patient, including diseases other than that for which
25 the physician is treating the patient. General outlines of
the dosages, and some preferred dosages, can and will be
provided here.

Tomoxetine: from about 5 mg/day to about 100
mg/day; preferably in the range from about 5 to about 70
30 mg/day; more preferably from about 10 to about 60 mg/day;
and still more preferably from about 10 to about 50 mg/day;

Compounds of formula I: from about 0.01 mg/kg to
about 20 mg/kg; preferred daily doses will be from about

0.05 mg/kg to 10 mg/kg; ideally from about 0.1 mg/kg to about 5 mg/kg;

Reboxetine: from about 1 to about 30 mg, once to four times/day; preferred, from about 5 to about 30 mg once/day;

Duloxetine: from about 1 to about 30 mg once/day; preferred, from about 5 to about 20 mg once/day;

Venlafaxine: from about 10 to about 150 mg once-thrice/day; preferred, from about 25 to about 125 mg thrice/day; and

Milnacipran: from about 10 to about 100 mg once-twice/day; preferred, from about 25 to about 50 mg twice/day.

All of the compounds concerned are orally available and are normally administered orally, and so oral administration is preferred. However, oral administration is not the only route or even the only preferred route. For example, transdermal administration may be very desirable for patients who are forgetful or petulant about taking oral medicine. The drugs may also be administered by the percutaneous, intravenous, intramuscular, intranasal or intrarectal route, in particular circumstances. The route of administration may be varied in any way, limited by the physical properties of the drugs and the convenience of the patient and the caregiver.

The best description of conduct disorder is the diagnostic criteria published by the American Psychiatric Association in the DSM-III-R (Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised (1987)), as follows.

Diagnostic criteria for Conduct Disorder

A. A disturbance of conduct lasting at least six months, during which at least three of the following have been present:

- 5 (1) has stolen without confrontation of a
victim on more than one occasion
(including forgery)
- (2) has run away from home at least twice
while living in parental or parental
surrogate home (or once without
returning)
- 10 (3) often lies (other than to avoid physical
or sexual abuse)
- (4) has deliberately engaged in fire-setting
- (5) is often truant from school (for older
person, absent from work)
- (6) has broken into someone else's house,
building, or car
- 15 (7) has deliberately destroyed others'
property (other than fire-setting)
- (8) has been physically cruel to animals
- (9) has forced someone into sexual activity
with him or her
- 20 (10) has used a weapon in more than one fight
- (11) often initiates physical fights
- (12) has stolen with confrontation of a
victim (e.g., mugging, purse-snatching,
extortion, armed robbery)
- 25 (13) has been physically cruel to people
- B. If 18 or older, does not meet criteria for
Antisocial Personality Disorder.

30 Conduct disorder has been classified into three
diagnostic categories. The method of the present invention
is useful for the treatment of patients within any of these
diagnostic categories. The DSM-III-R diagnostic code and a
description of each of these subtypes are described in the
following paragraphs.

312.20 Group Type

5 The essential feature is the predominance of the conduct problems occurring mainly as a group activity with peers. Aggressive physical behavior may or may not be present.

312.00 Solitary Aggressive Type

10 The essential feature is the predominance of aggressive physical behavior, usually toward both adults and peers, initiated by the person (not as a group activity).

312.90 Undifferentiated Type

15 This is a subtype for children or adolescents with Conduct Disorder with a mixture of clinical features that cannot be classified as either Solitary Aggressive Type or Group Type.

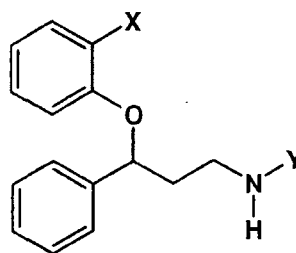
20 Patients suffering from Conduct Disorder also commonly suffer concomitantly from Attention-deficit Hyperactivity Disorder, Bipolar Disorder, and Specific Developmental Disorders. The patient will benefit from the use of norepinephrine reuptake inhibitors in the amelioration of the symptoms of Conduct Disorder regardless of co-morbid conditions. Furthermore, a patient suffering from Conduct Disorder and Attention-deficit Hyperactivity Disorder will receive benefit in the amelioration of symptoms of both conditions through the method of the present invention.

30 The method of the present invention is effective in the treatment of patients who are children, adolescents or adults, and there is no significant difference in the symptoms or the details of the manner of treatment among patients of different ages. In general terms, however, for purposes of the present invention, a child is considered to

We claim:

1. A method of treating conduct disorder comprising administration to a patient in need of such treatment an effective amount of a norepinephrine reuptake inhibitor.

2. A method of Claim 1 wherein the norepinephrine reuptake inhibitor is selected from the group consisting of tomoxetine, reboxetine, duloxetine, venlafaxine, milnacipran, and a compound of formula I:



I

wherein X is C₁-C₄ alkylthio, and Y is C₁-C₂ alkyl or a pharmaceutically acceptable salt thereof.

3. A method of Claim 2 wherein the norepinephrine reuptake inhibitor is tomoxetine, reboxetine, or a compound of formula I.

4. A method of Claim 3 wherein the norepinephrine reuptake inhibitor is tomoxetine.

5. A method of Claim 3 wherein the norepinephrine reuptake inhibitor is reboxetine.

6. A method of Claim 3 wherein the norepinephrine reuptake inhibitor is (R)-N-methyl-3-(2-methylthiophenoxy)-3-phenylpropylamine.

7. A method of any of claims 1-6 wherein the group type of conduct disorder is treated.

8. A method of any of claims 1-6 wherein the solitary aggressive type of conduct disorder is treated.

9. A method of any of claims 1-6 wherein the undifferentiated type of conduct disorder is treated.



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/535, 31/135	A1	(11) International Publication Number: WO 99/15176 (43) International Publication Date: 1 April 1999 (01.04.99)
(21) International Application Number: PCT/US98/18114 (22) International Filing Date: 1 September 1998 (01.09.98) (30) Priority Data: 60/059,629 23 September 1997 (23.09.97) US (71) Applicant (for all designated States except US): ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): HEILIGENSTEIN, John, Harrison [US/US]; 1202 West 56th Street, Indianapolis, IN 46228 (US). (74) Agents: TITUS, Robert, D. et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).		(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, 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, RO, RU, SD, 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), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: TREATMENT OF OPPOSITIONAL DEFIANT DISORDER (57) Abstract Norepinephrine reuptake inhibitors are used to treat oppositional defiant disorder. D 4		

TREATMENT OF OPPOSITIONAL DEFIANT DISORDER 336

The invention belongs to the fields of pharmaceutical chemistry and psychiatric medicine, and provides a method of treatment of the psychiatric disorder known as oppositional defiant disorder.

Children and adolescents suffering from oppositional defiant disorder exhibit a pattern of hostile, defiant, and negative behavior more often than is commonly observed in other individuals of the same mental age. They are argumentative with adults, are often angry and resentful, frequently lose their temper, swear, defy rules and requests from adults, and deliberately engage in annoying behavior. They also tend to not see themselves as a problem, but rather justify their behavior as a response to unreasonable circumstances.

Oppositional defiant disorder (ODD) is many times treated with the same therapies employed for the treatment of Attention-deficit Hyperactivity Disorder (ADHD), e.g., methylphenidate (RitalinTM), which exhibits noradrenergic and dopaminergic effects. Gross has demonstrated that certain ODD symptoms may be ameliorated by augmentation of standard ADHD therapies with buspirone in certain patients (Gross, J. *Am. Acad. Child Adolesc. Psychiatry*, 34(10), 1260 (1995)).

Many patients are refractory to these treatments, or discontinue treatment due to intolerable side effects. Furthermore, due to the high potential for substance abuse in oppositional defiant disorder patients, the use of stimulants such as methylphenidate is problematic.

The need for a safe and effective treatment for oppositional defiant disorder, without the disadvantages of current therapies, continues to be a concern of the psychiatric community.

The present invention provides a method of treating oppositional defiant disorder comprising the administration to a patient in need of such treatment of an effective amount of a norepinephrine reuptake inhibitor.

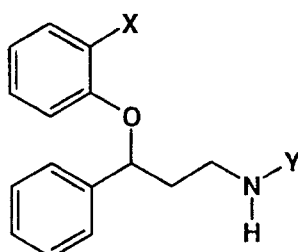
5 Many compounds, including those discussed at length below, are norepinephrine reuptake inhibitors, and no doubt many more will be identified in the future. In the practice of the present invention, it is intended to include reuptake inhibitors which show 50% effective concentrations
10 of about 1000 nM or less, in the protocol described by Wong *et al.*, *Drug Development Research*, 6, 397 (1985). The norepinephrine reuptake inhibitors useful for the method of the present invention are characterized in being selective for the inhibition of neurotransmitter reuptake relative to
15 their ability to act as direct agonists or antagonists at other receptors. Norepinephrine reuptake inhibitors useful for the method of the present invention include, but are not limited to:

Tomoxetine, (R)-(-)-N-methyl-3-(2-methylphenoxy)-
20 3-phenylpropylamine, is usually administered as the hydrochloride salt. Tomoxetine was first disclosed in U.S. Patent #4,314,081. The word "tomoxetine" will be used here to refer to any acid addition salt or the free base of the molecule. See, for example, Gehlert, *et al.*, *Neuroscience*
25 *Letters*, 157, 203-206 (1993), for a discussion of tomoxetine's activity as a norepinephrine reuptake inhibitor;

The compounds of formula I:

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wherein X is C₁-C₄ alkylthio, and Y is C₁-C₂ alkyl or a pharmaceutically acceptable salt thereof. The compounds of formula I were described in U.S. Patent 5,281,624, of Gehlert, Robertson, and Wong, and in Gehlert, et al., *Life Sciences*, 55(22), 1915-1920, (1995). The compounds are there taught to be inhibitors of norepinephrine reuptake in the brain. It is also explained that the compounds exist as stereoisomers, and that they accordingly include not only the racemates, but also the isolated individual isomers as well as mixtures of the individual isomers. For example, the compounds of formula I include the following exemplary species:

N-ethyl-3-phenyl-3-(2-methylthiophenoxy)propylamine benzoate;

(R)-N-methyl-3-phenyl-3-(2-propylthiophenoxy)propylamine hydrochloride;

(S)-N-ethyl-3-phenyl-3-(2-butylthiophenoxy)propylamine;

N-methyl-3-phenyl-3-(2-ethylthiophenoxy)propylamine malonate;

(S)-N-methyl-3-phenyl-3-(2-tert-butylthiophenoxy)propylamine naphthalene-2-sulfonate;

(R)-N-methyl-3-(2-methylthiophenoxy)-3-phenylpropylamine;

Reboxetine (EdronaxTM), 2-[α -(2-ethoxy)phenoxybenzyl]morpholine, is usually administered as the racemate. It was first taught by U.S. Patent 4,229,449, which describes its utility for the treatment of depression.

Reboxetine is a selective norepinephrine reuptake inhibitor. The term "reboxetine" will be used here to refer to any acid addition salt or the free base of the molecule existing as the racemate or either enantiomer;

5 Duloxetine, N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine, is usually administered as the hydrochloride salt and as the (+) enantiomer. It was first taught by U.S. Patent 4,956,388, which shows its high potency. The word "duloxetine" will be used here to refer
10 to any acid addition salt or the free base of the molecule;

Venlafaxine is known in the literature, and its method of synthesis and its activity as an inhibitor of serotonin and norepinephrine uptake are taught by U.S. Patent 4,761,501. Venlafaxine is identified as compound A
15 in that patent; and

Milnacipran (N,N-diethyl-2-aminomethyl-1-phenylcyclopropanecarboxamide) is taught by U.S. Patent 4,478,836, which prepared milnacipran as its Example 4. The patent describes its compounds as antidepressants. Moret et
20 al., *Neuropharmacology* 24, 1211-19 (1985), describe its pharmacological activities as an inhibitor of serotonin and norepinephrine reuptake.

All of the U.S. patents which have been mentioned above in connection with compounds used in the present
25 invention are incorporated herein by reference.

A preferred duloxetine enteric formulation is a pellet formulation comprising a) a core consisting of duloxetine and a pharmaceutically acceptable excipient; b) an optional separating layer; c) an enteric layer comprising
30 hydroxypropylmethylcellulose acetate succinate (HPMCAS) and a pharmaceutically acceptable excipient; d) an optional finishing layer. The following example demonstrates the preparation of a preferred such formulation.

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chlorobenzoate, methylbenzoate, dinitrobenzoate,
hydroxybenzoate, methoxybenzoate, phthalate, sulfonate,
xylenesulfonate, phenylacetate, phenylpropionate,
phenylbutyrate, citrate, lactate, b-hydroxybutyrate,
5 glycollate, tartrate, methanesulfonate, propanesulfonate,
naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate
and the like. Preferred pharmaceutically acceptable salts
are those formed with hydrochloric acid.

10 Administration

The dosages of the drugs used in the present
invention must, in the final analysis, be set by the
physician in charge of the case, using knowledge of the
drugs, the properties of the drugs in combination as
15 determined in clinical trials, and the characteristics of
the patient, including diseases other than that for which
the physician is treating the patient. General outlines of
the dosages, and some preferred dosages, can and will be
provided here.

20 Tomoxetine: from about 5 mg/day to about 100
mg/day; preferably in the range from about 5 to about 70
mg/day; more preferably from about 10 to about 60 mg/day; and
still more preferably from about 10 to about 50 mg/day;

Compounds of formula I: from about 0.01 mg/kg to
25 about 20 mg/kg; preferred daily doses will be from about
0.05 mg/kg to 10 mg/kg; ideally from about 0.1 mg/kg to
about 5 mg/kg;

Reboxetine: from about 1 to about 30 mg, once to
four times/day; preferred, from about 5 to about 30 mg
30 once/day;

Duloxetine: from about 1 to about 30 mg once/day;
preferred, from about 5 to about 20 mg once/day;

Venlafaxine: from about 10 to about 150 mg once-thrice/day; preferred, from about 25 to about 125 mg thrice/day; and

5 Milnacipran: from about 10 to about 100 mg once-twice/day; preferred, from about 25 to about 50 mg twice/day.

10 All of the compounds concerned are orally available and are normally administered orally, and so oral administration is preferred. However, oral administration is not the only route or even the only preferred route. For example, transdermal administration may be very desirable for patients who are forgetful or petulant about taking oral medicine. The drugs may also be administered by the percutaneous, intravenous, intramuscular, intranasal or
15 intrarectal route, in particular circumstances. The route of administration may be varied in any way, limited by the physical properties of the drugs and the convenience of the patient and the caregiver.

20 The best description of oppositional defiant disorder is the diagnostic criteria published by the American Psychiatric Association in the DSM-III-R (Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised (1987)), as follows.

25 **Diagnostic criteria for Oppositional Defiant Disorder**

A. A disturbance of at least six months, during which at least five of the following are present:

- 30 (1) often loses temper
(2) often argues with adults
(3) often actively defies or refuses adult requests or rules, e.g., refuses to do chores at home

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(4) often deliberately does things that annoy other people, e.g., grabs other children's hats

(5) often blames others for his or her own mistake

(6) is often touchy or easily annoyed by others

(7) is often angry and resentful

(8) is often spiteful or vindictive

(9) often swears or uses obscene language

B. Does not meet the criteria for Conduct Disorder, and does not occur exclusively during the course of a psychotic disorder, Dysthymia, or a Major Depressive, Hypomanic, or Manic Episode.

Patients suffering from Oppositional Defiant Disorder also commonly suffer concomitantly from Attention-deficit Hyperactivity Disorder. The patient will benefit from the use of norepinephrine reuptake inhibitors in the amelioration of the symptoms of Oppositional Defiant Disorder regardless of this or other co-morbid conditions. Furthermore, a patient suffering from Oppositional Defiant Disorder and Attention-deficit Hyperactivity Disorder will receive benefit in the amelioration of symptoms of both conditions through the method of the present invention.

The method of the present invention is effective in the treatment of patients who are children or adolescents, and there is no significant difference in the symptoms or the details of the manner of treatment among patients of different ages. In general terms, however, for purposes of the present invention, a child is considered to be a patient below the age of puberty, and an adolescent is

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considered to be a patient from the age of puberty up to about 18 years of age.

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Inhibition or norepinephrine reuptake

5 The ability of compounds to inhibit the reuptake of norepinephrine may be measured by the general procedure of Wong, *et al.*, *supra*.

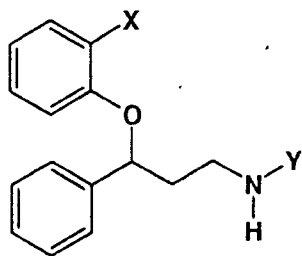
10 Male Sprague-Dawley rats weighing 150-250 gm are decapitated and brains are immediately removed. Cerebral cortices are homogenized in 9 volumes of a medium containing 0.32 M sucrose and 10 mM glucose. Crude synaptosomal preparations are isolated after differential centrifugation at 1000 x g for 10 minutes and 17,000 x g for 28 minutes. The final pellets are suspended in the same medium and kept
15 in ice until use within the same day.

 Synaptosomal uptake of ³H-norepinephrine is determined as follows. Cortical synaptosomes (equivalent to 1 mg of protein) are incubated at 37°C for 5 minutes in 1 mL Krebs-bicarbonate medium containing also 10 mM glucose, 0.1 mM iproniazide, 1 mM ascorbic acid, 0.17 mM EDTA and 50 nM ³H-norepinephrine. The reaction mixture is immediately diluted with 2 mL of ice-chilled Krebs-bicarbonate buffer and filtered under vacuum with a cell harvester (Brandel, Gaithersburg, MD). Filters are rinsed twice with
25 approximately 5 mL of ice-chilled 0.9% saline and the uptake of ³H-norepinephrine assessed by liquid scintillation counting. Accumulation of ³H-norepinephrine at 4°C is considered to be background and is subtracted from all measurements. The concentration of the test compound
30 required to inhibit 50% of the ³H-norepinephrine accumulation (IC₅₀ values) are determined by linear regression analysis.

We claim:

1. A method of treating oppositional defiant disorder comprising administration to a patient in need of such treatment an effective amount of a norepinephrine reuptake inhibitor.

2. A method of Claim 1 wherein the norepinephrine reuptake inhibitor is selected from the group consisting of tomoxetine, reboxetine, duloxetine, venlafaxine, milnacipran, and a compound of formula I:



I

wherein X is C₁-C₄ alkylthio, and Y is C₁-C₂ alkyl or a pharmaceutically acceptable salt thereof.

3. A method of Claim 2 wherein the norepinephrine reuptake inhibitor is tomoxetine, reboxetine, or a compound of formula I.

4. A method of Claim 3 wherein the norepinephrine reuptake inhibitor is tomoxetine.

5. A method of Claim 3 wherein the norepinephrine reuptake inhibitor is tomoxetine hydrochloride.

6. A method of Claim 3 wherein the norepinephrine reuptake inhibitor is reboxetine.

7. A method of Claim 3 wherein the norepinephrine reuptake inhibitor is (R)-N-methyl-3-(2-methylthiophenoxy)-3-phenylpropylamine.



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/535	A1	(11) International Publication Number: WO 99/15177 (43) International Publication Date: 1 April 1999 (01.04.99)
(21) International Application Number: PCT/US98/18139 (22) International Filing Date: 1 September 1998 (01.09.98) (30) Priority Data: 60/059,626 23 September 1997 (23.09.97) US (71) Applicant (for all designated States except US): ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): HEILIGENSTEIN, John, Harrison [US/US]; 1202 West 56th Street, Indianapolis, IN 46228 (US). (74) Agents: TITUS, Robert, D. et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US)		(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, 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, RO, RU, SD, 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), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report.

(54) Title: TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

(57) Abstract

Reboxetine is used to treat attention-deficit/hyperactivity disorder.

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TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

The invention belongs to the fields of pharmaceutical chemistry and psychiatric medicine, and provides a method of treatment of the psychiatric disorder known as attention-deficit/hyperactivity disorder.

For some decades it has been recognized that a significant number of children are persistently hyperactive and have an attention span so short as to be disabling in school and in many personal relationships. Such children in earlier times would no doubt have been dismissed as incorrigible and punished or even confined in an institution. More recently, however, it was realized that these children cannot control their hyperactivity and inattention, and the medical professions began to try to help them. Methylphenidate (Ritalin™) has been used for some time to treat such children and it often significantly improves their ability to function and coexist with other people at school and at home. However, the drug has the disadvantages of requiring several doses per day, and producing a rebound effect as the effect of each dose fades away. Further, the drug causes sleeplessness and lack of appetite in some patients. Methylphenidate has both noradrenergic and dopaminergic activities.

Imipramine, desipramine, nortriptyline, amitriptyline and clomipramine are also used in some cases of attention-deficit/hyperactivity disorder (ADHD). Those tricyclic drugs, however, have a number of physiological mechanisms and, as a class, tend to produce a number of side effects and require careful supervision and dose titration.

In the last decade, psychiatrists have realized that ADHD is not only a disorder of childhood, but often continues in the adult. It is obvious that hyperactivity and short attention span cause grave disruption in an adult's life, but it is only recently that such patients have been able to obtain any treatment.

The need for a safe and convenient treatment for ADHD, applicable to both children and adults and without the disadvantages possessed by methylphenidate continues to be a concern of the psychiatric profession.

5 The present invention provides a method of treating attention-deficit/hyperactivity disorder comprising the administration to a patient in need of such treatment of an effective amount of reboxetine.

10 Reboxetine, 2-[α -(2-ethoxy)phenoxybenzyl]morpholine, is usually administered as the racemate. It was first taught by U.S. Patent 4,229,449, which describes its utility for the treatment of depression. Reboxetine is a selective norepinephrine reuptake inhibitor. The term "reboxetine" will be used here to refer to any acid addition salt or the
15 free base of the molecule existing as the racemate or either enantiomer.

Reboxetine is a safe drug, and its use in ADHD, in both adults and children, is a superior treatment for that disorder because of its improved safety. The compound is
20 particularly selective, having few if any physiological effects besides those on norepinephrine processing, and therefore is free of side effects and unwanted activities. Further, it is effective at relatively low doses, as discussed below, and may safely and effectively be
25 administered once per day. Thus, difficulties created by the multiple dosing of patients, who are children and disorganized adults, are completely avoided.

The effective dose of reboxetine for ADHD is in the range from about 1 mg/day to about 100 mg/day. The
30 preferred adult dose is in the range from about 5 to about 80 mg/day, and a more highly preferred adult dose is from about 10 to about 60 mg/day. The children's dose of course is smaller, in the range from about 1 to about 70 mg/day, more preferably from about 5 to about 60 mg/day and still
35 more preferably from about 5 to about 50 mg/day. The optimum dose for each patient, as always, must be set by the physician in charge of the case, taking into account the

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patient's size, other medications which the patient requires, severity of the disorder and all of the other circumstances of the patient.

5 Since reboxetine is readily orally absorbed and requires only once/day administration, there is little or no reason to administer it in any other way than orally. It may be formulated in the usual oral pharmaceutical forms, such as tablets, capsules, suspensions, and the like. The usual methods of pharmaceutical scientists are applicable.

10 It may usefully be administered, if there is any reason to do so in a particular circumstance, in other pharmaceutical forms, such as injectable solutions, depot injections, suppositories and the like, which are well known to and understood by pharmaceutical scientists. It will

15 substantially always be preferred, however, to administer reboxetine as a tablet or capsule and such pharmaceutical forms are recommended.

The ADHD patient is rather readily recognized, and most people have been in contact with children, if not

20 adults, who exhibit some or all of the symptoms of the disorder. The best description of the disorder is the diagnostic criteria for ADHD, published by the American Psychiatric Association in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Version (1994), as

25 follows.

**Diagnostic criteria for Attention-Deficit/
Hyperactivity Disorder**

A. Either (1) or (2):

- (1) six (or more) of the following symptoms
of **inattention** have persisted for at
least 6 months to a degree that is
maladaptive and inconsistent with
developmental level:

Inattention

- (a) often fails to give close attention
to details or makes careless
mistakes in schoolwork, work, or
other activities
- (b) often has difficulty sustaining
attention in tasks or play
activities
- (c) often does not seem to listen when
spoken to directly
- (d) often does not follow through on
instructions and fails to finish
schoolwork, chores, or duties in
the workplace (not due to
oppositional behavior or failure to
understand instructions)
- (e) often has difficulty organizing
tasks and activities
- (f) often avoids, dislikes, or is
reluctant to engage in tasks that
require sustained mental effort
(such as schoolwork or homework)
- (g) often loses things necessary for
tasks or activities (e.g., toys,
school assignments, pencils, books,
or tools)
- (h) is often easily distracted by
extraneous stimuli

(i) is often forgetful in daily activities

(2) six (or more) of the following symptoms of **hyperactivity-impulsivity** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Hyperactivity

(a) often fidgets with hands or feet or squirms in seat

(b) often leaves seat in classroom or in other situations in which remaining seated is expected

(c) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)

(d) often has difficulty playing or engaging in leisure activities quietly

(e) is often "on the go" or often acts as if "driven by a motor"

(f) often talks excessively

Impulsivity

(g) often blurts out answers before questions have been completed

(h) often has difficulty awaiting turn

(i) often interrupts or intrudes on others (e.g., butts into conversations or games)

B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.

- C. Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home).
- D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.
- E. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).

It will be seen that ADHD is a disorder made up of two components, the attention deficit component and the hyperactivity component, which are to a degree independent. Treatment with reboxetine is effective in patients who are primarily suffering from either component or from the combined disorder.

While ADHD is still primarily regarded as a disorder of children, it is now understood that many ADHD patients, as many as 50%, continue to suffer from the disorder as they grow through adolescence into adulthood. Biederman and associates have extensively studied the adult ADHD patient, and have found numerous cases. See, for example, Biederman, et al., Am. J. Psychiatry 150, 1792-98 (1993). They found that cases of adult ADHD were frequently found among the parents and adult siblings of childhood ADHD patients. Thus, it appears that the disease is not only carried forward into adulthood, but is inheritable.

The Biederman, et al. article cited immediately above, as well as another article by the same authors, Am. J. Psychiatry 148, 564-77 (1991), reports studies of ADHD patients who also have one or more other psychiatric disorders. The authors indicate that such psychiatric comorbidity is quite common among ADHD patients and, naturally, cloud the diagnosis and treatment of such

patients. Reboxetine is effective in the treatment of ADHD, even though the situation of the treated patient may be complicated by co-morbidity with one or more additional disorders.

5 The mere listing of the above diagnostic criteria indicates the seriousness of ADHD and the damage which it does to the patient. A person having a moderately severe case of ADHD is substantially entirely unable to concentrate and hence unable to do meaningful work or study; is a
10 continuing distraction and nuisance to those around her or him, because of the uselessly impulsive activity which the disorder causes; and consumes his or her family in cleaning up and repairing the damage and disruption which he or she causes. Such a patient of school age may substantially
15 damage the teacher's ability to accomplish the class' goals, because the ADHD child will continually disrupt the class, distract the other children and consume the teacher's effort. Thus, it is readily apparent that an improved treatment of ADHD is needed, and that the present invention
20 is accordingly important to many people.

 The method of the present invention is effective in the treatment of patients who are children, adolescents or adults, and there is no significant difference in the symptoms or the details of the manner of treatment among
25 patients of different ages. In general terms, however, for purposes of the present invention, a child is considered to be a patient below the age of puberty, an adolescent is considered to be a patient from the age of puberty up to about 18 years of age, and an adult is considered to be a
30 patient of 18 years or older.

We claim:

1. A method of treating attention-deficit/hyperactivity disorder comprising administering to a patient in need of such treatment an effective amount of reboxetine.

5 2. A method of Claim 1 wherein the predominantly inattentive type of attention-deficit/hyperactivity disorder is treated.

10 3. A method of Claim 1 wherein the predominantly hyperactive-impulsive type of attention-deficit/hyperactive disorder is treated.

4. A method of Claim 1 wherein the combined type of attention-deficit/hyperactivity disorder is treated.

5. A method of Claim 1 wherein the patient is an adult.

15 6. A method of Claim 5 wherein the predominantly inattentive type of attention-deficit/hyperactivity disorder is treated.

20 7. A method of Claim 5 wherein the predominantly hyperactive-impulsive type of attention-deficit/hyperactive disorder is treated.

8. A method of Claim 5 wherein the combined type of attention-deficit/hyperactivity disorder is treated.

9. A method of Claim 1 wherein the patient is an adolescent.

25 10. A method of Claim 9 wherein the predominantly inattentive type of attention-deficit/hyperactivity disorder is treated.

30 11. A method of Claim 9 wherein the predominantly hyperactive-impulsive type of attention-deficit/hyperactive disorder is treated.

12. A method of Claim 9 wherein the combined type of attention-deficit/hyperactivity disorder is treated.

13. A method of Claim 1 wherein the patient is a child.

35 14. A method of Claim 13 wherein the predominantly inattentive type of attention-deficit/hyperactivity disorder is treated.

15. A method of Claim 13 wherein the predominantly hyperactive-impulsive type of attention-deficit/hyperactive disorder is treated.

5 16. A method of Claim 13 wherein the combined type of attention-deficit/hyperactivity disorder is treated.