OLARTERAISBECK

104

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA Y COMERCIO
Radicación : 03077389 [illegible] Folios: 4
Fecha (MM/DD): [illegible] 17:43:32
Tramite : 88: PET-PATENT 375 FREE [illegible] 325 [illegible]
Dependencia: [illegible] DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE CORRECCIONES Y MODIFICACIONES

SOLICITUD DE:

(1) [X] Corrección de Error Material. [ ] Modificación a una Solicitud.

(2) **SOLICITANTE (71)**

Nombre: ELI-LILLY AND COMPANY
Dirección: Indianapolis, Indiana 46285, Estados Unidos de América.
Nacionalidad o Domicilio: ESTADOUNIDENSE
Lugar de Constitución: ESTADOUNIDENSE
Teléfono: _____ **Fax:** _____
E-mail: _____

IDENTIFICACIÓN
C.C. [ ] NIT [ ]
C.E. [ ] Otro [ ]
Cual _____
Número _____

(3) **REPRESENTANTE APODERADO**

Nombre: CARLOS R. OLARTE
Dirección: World Trade Center Torre A Calle 100 No. 8A-37 Piso 10, Bogotá
Teléfono: 601-7700 **Fax:** 601-7799
E-mail: _____

IDENTIFICACIÓN
C.C. [x] NIT [ ]
C.E. [ ] Otro [ ]
Cual _____
Número 79.782.747Bta
TP 74.295

(4) **Número de expediente:** 03.077.389

(5) **Descripción de la corrección o modificación solicitada** Me permito **CORREGIR** un error de tipo material, con base en el Artículo 34 de la Decisión Andina 486: De forma involuntaria se presentó originalmente un Capítulo Reivindicatorio Modificado, por tanto, me permito presentar el capítulo original, el cual corresponde a las reivindicaciones presentadas en la Solicitud Internacional. Vale la pena aclarar al Despacho que no se añadió materia nueva.

(6) **Comprobante de pago No.** 31,163 **Fecha** Abril 29, 2005

(7) **Anexos**

[X] Comprobante de pago de la tasa.

[ ] Poderes, si fuere el caso.

[ ] Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

(8)

NOMBRE: CARLOS R. OLARTE **FIRMA:** _____

C.C. 79.782.747 Btá T.P. 74.295

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Radicación : 05027389 [illegible] Folios: 4
Fecha: [illegible]: 2005-04-29 17:43:20
Tramite : 011 PCT-PATENT 379 FASE NACI 329 COMPLEMEN
Dependencia: [illegible] DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : [illegible]039-2

RECIBO OFICIAL DE CAJA : [illegible] - [illegible],187
[illegible] : ABRIL [illegible] 2005

***** [illegible]

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. DOCT	FECHA PAGO	Vr. PAGO
[illegible] PAISBERG	CONSIGNACION	BANCO [illegible]	050-[illegible]-6	27058701	[illegible]2005	[illegible]
CLARTE [illegible]BERG	CONSIGNACION	BANCO POPULAR	[illegible]0113-6	[illegible]	28/04/2005	719,030.00

***** [illegible] E F [illegible]

CANT	CODIGO	CONCEPTO	TOTAL CONCEPTO
1	50005-[illegible]	[illegible] DE [illegible] Y [illegible] [illegible] Y LEMAS [illegible]	[illegible]1,000.00
		TOTAL : $	[illegible]

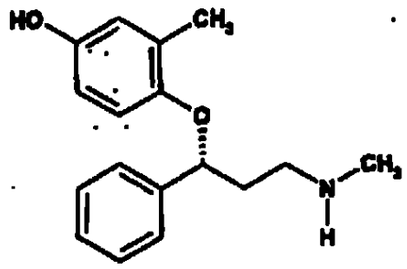
[illegible] [illegible] NOVENTA Y [illegible]

RESPONSABLE : ____________ . ____________ ________

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.____________ . ____________

CAPITULO REIVINDICATORIO

1. Un compuesto de Fórmula I:

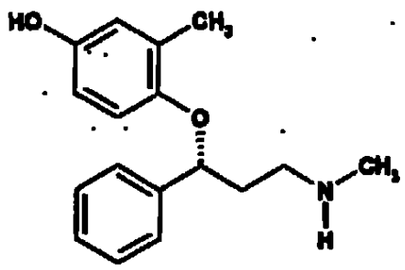


I

o una sal farmacéuticamente aceptable del mismo.

2. El compuesto clorhidrato de R-(-)-N-metil-3-((2-metil-4-hidroxifenil)oxi)-3-fenil-1-aminopropano.

3. Una formulación farmacéutica que comprende un compuesto de Fórmula I:



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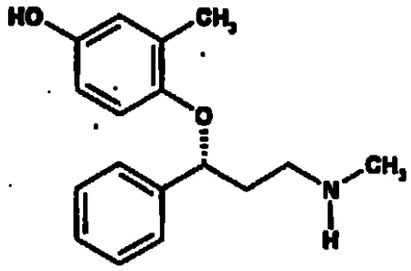
o una sal farmacéuticamente aceptable del mismo, en asociación con un vehículo, diluyente o excipiente farmacéuticamente aceptable.

4. Una formulación farmacéutica de la Reivindicación 3, en la que el compuesto de Fórmula I es el clorhidrato de R-(-)-N-metil-3-((2-metil-4-hidroxifenil)oxi)-3-fenil-1-aminopropano.

5. Un método para inhibir el aumento de norepinefrina y serotonina en mamíferos que comprende suministrar a un mamífero en necesidad de dicha inhibición de una cantidad farmacéuticamente efectiva del compuesto de Fórmula I:



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o una sal farmacéuticamente aceptable del mismo.

6. El método de la reivindicación 5 en donde el compuesto de Fórmula I se administra sistémicamente.

PC 10892

Industria y Comercio
SUPERINTENDENCIA

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 03- 77389

EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION – PCT, FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 546, DE FECHA 30 DE NOVIEMBRE DE 2004, EL TERMINO HABIL SEÑALADO POR LA LEY EXPIRA EL 24 DE FEBRERO DE 2005.

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI ___ _____ NO ___ X ____

Carrera 13 No. 27-00 Piso 5 y 10
Conmutador: 334 12 21-2-3-4
Fax: 281 51 25 e-mail: info@sic.gov.co
Santa Fe de Bogotá D.C. - Colombia

03 077 259

109 103
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United States Patent [19]

Molloy et al.

[11] **4,314,081**

[45] **Feb. 2, 1982**

[54] **ARLOXYPHENYLPROPYLAMINES**

[75] Inventors: **Bryan B. Molloy; Klaus K. Schmiegel, both of Indianapolis, Ind.**

[73] Assignee: **Eli Lilly and Company, Indianapolis, Ind.**

[21] Appl. No.: **432,379**

[22] Filed: **Jan. 10, 1974**

[51] Int. Cl.³ **C07C 93/06**

[52] U.S. Cl. **564/347; 260/301.18; 260/301.19; 424/313; 424/330; 564/103; 564/342; 564/343**

[58] Field of Search **260/570.6, 570.7, 501.18, 260/501.19; 424/330; 564/347**

[56] **References Cited**

U.S. PATENT DOCUMENTS

2,683,742	7/1954	Cusic	260/570.7 X
3,198,564	10/1963	Fleming et al.	260/559 B X
3,132,179	5/1964	Clarke	260/570.6
3,253,040	5/1966	Pater et al.	260/570.7 X

OTHER PUBLICATIONS

Yashiki et al., "Pharm. Soc. of Japan", vol 93, pp. 508–528 (1973).

Primary Examiner—Robert V. Hines
Attorney, Agent, or Firm—James L. Rowe; Arthur R. Whale

[57] **ABSTRACT**

3-Aryloxy-3-phenylpropylamines and acid additions salts thereof, useful as psychotropic agents, particularly as anti-depressants.

9 Claims, No Drawings

ARYLOXYPHENYLPROPYLAMINES

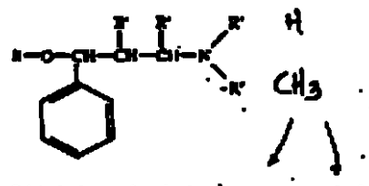
BACKGROUND OF THE INVENTION

Tertiary 3-phenoxy-2-phenylethylamines constitute the subject matter of U.S. Pat. No. 3,106,564. The compounds are said to be useful pharmacological agents exhibiting activity on the central nervous system including useful application as analeptic agents without significant effect on respiration. The compounds are also said to have a high order of activity as antihistaminic and anticholinergic agents. Several tertiary 3-phenoxy-3-phenylpropylamines and quaternary ammonium compounds are disclosed in *J. Pharmaceutical Society, Japan*, 93, 508–519, 1144–53, 1154–61 (1973). The compounds are said to be mydriatic agents.

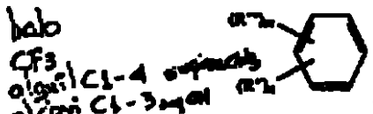
Secondary and primary 3-aryloxy-3-phenylpropylamines have not hitherto been known.

SUMMARY OF THE INVENTION

This invention provides 3-aryloxy-3-phenylpropylamines of the formula:



wherein each R' is independently hydrogen or methyl; wherein R is naphthyl or



wherein R'' and R''' are halo, trifluoromethyl, C_1–C_4 alkyl, C_1–C_3 alkoxy or C_3–C_4 alkenyl; and wherein n and m are 0, 1 or 2; and acid addition salts thereof formed with pharmaceutically-acceptable acids.

In the above formula when R is naphthyl, it can be either α-naphthyl or β-naphthyl. R'' and R''' when they are halo, C_1–C_4 alkyl, C_1–C_2 alkyloxy or C_3–C_4 alkenyl represent, illustratively, the following atoms or groups: fluoro, chloro, bromo, iodo, methyl, ethyl, isopropyl, n-propyl, n-butyl, isobutyl, sec.-butyl, t-butyl, methoxy, ethoxy, n-propoxy, isopropoxy, allyl, methallyl, crotyl and the like. R thus can represent o, m and p-trifluoromethylphenyl, o, m and p-chlorophenyl, o,m and p-bromophenyl, o,m and p-fluorophenyl, o,m and p-tolyl, xylyl including all position isomers, o,m and p-anisyl, o,m and p-allylphenyl, o,m and p-methylallylphenyl, o,m and p-phenetolyl(ethoxyphenyl), 2,4-dichlorophenyl, 3,5-difluorophenyl, 2-methoxy-4-chlorophenyl, 2-methyl-4-chlorophenyl, 2-ethyl-4-bromophenyl, 2,4,6-trimethylphenyl, 2-fluoro-4-trifluoromethylphenyl, 2,4,6-trichlorophenyl, 2,4,5-trichlorophenyl, and the like. Compounds illustrative of the scope of this invention include the following:

3-(p-isopropoxyphenoxy)-3-phenylpropylamine methanesulfonate

N,N-dimethyl 3-(3',4'-dimethoxyphenoxy)-3-phenylpropylamine p-hydroxybenzoate

N,N-dimethyl 3-(α-naphthoxy)-3-phenylpropylamine bromide

N,N-dimethyl 3-(β-naphthoxy)-3-phenyl-1-methylpropylamine iodide

3-(2'-methyl-4',5'-dichlorophenoxy)-3-phenylpropylamine nitrate

3-(p-t-butylphenoxy)-3-phenylpropylamine glutarate

N-methyl 3-(2'-chloro-p-tolyloxy)-3-phenyl-1-methylpropylamine lactate

3-(2',4'-dichlorophenoxy)-3-phenyl-2-methylpropylamine citrate

N,N-dimethyl 3-(m-anisyloxy)-3-phenyl-1-methylpropylamine malate

N-methyl 3-(p-tolyloxy)-3-phenylpropylamine sulfate

N,N-dimethyl 3-(2',4'-difluorophenoxy)-3-phenylpropylamine 2,4-dinitrobenzoate

3-(o-ethylphenoxy)-3-phenylpropylamine dihydrogen phosphate

N-methyl 3-(2'-chloro-4'-isopropylphenoxy)-3-phenyl-2-methylpropylamine malate

N,N-dimethyl 3-(2'-allyl-4'-fluorophenoxy)-3-phenyl-propylamine succinate

N,N-dimethyl 3-(o-isopropoxyphenoxy)-3-phenylpropylamine phenylacetate

N,N-dimethyl 3-(o-bromophenoxy)-3-phenylpropylamine β-phenylpropionate

N-methyl 3-(p-iodophenoxy)-3-phenyl-propylamine propiolate

N-methyl 3-(3-n-propylphenoxy)-3-phenyl-propylamine decanoate

Also included within the scope of this invention are the pharmaceutically-acceptable salts of the amine bases represented by the above formula formed with non-toxic acids. These acid addition salts include salts derived from inorganic acids such as: hydrochloric acid, nitric acid, phosphoric acid, sulfuric acid, hydrobromic acid, hydriodic acid, nitrous acid, phosphorous acid and the like, as well as salts of non-toxic organic acids including aliphatic mono and dicarboxylates, phenyl-substituted alkanoates, hydroxy alkanoates and alkanedioates, aromatic acids, aliphatic and aromatic sulfonic acids etc. Such pharmaceutically-acceptable salts thus include: sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, fluoride, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproic, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephthalate, benzenesulfonate, toluenesulfonate, chlorobenzenesulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β-hydroxybutyrate, glycollate, malate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like salts.

The compounds of this invention in the form of their free bases are high boiling oils, but white crystalline solids in the form of their acid addition salts. The compounds can be prepared in several ways. A particularly useful procedure for preparing compounds represented by the above formula (in which both R' groups attached to the nitrogen are methyl) involves the reduction of β-dimethylaminopropidiphenone produced by a Mannich reaction to yield N,N-dimethyl 3-phenyl-3-hydroxypropylamine. Replacement of the hydroxyl group

with a halogen, such as chlorine, yields the corresponding N,N-dimethyl 3-phenyl-3-chloropropylamine. Reaction of this chloro compound with a suitably substituted phenol, as for example o-methoxyphenol (guaiacol), produces a compound of this invention in which both R' groups are methyl. Treatment of the N,N-dimethyl compound with cyanogenbromide serves to replace one N-methyl group with a cyano group. Hydrolysis of the resulting compound with base yields a compound of this invention in which only one R' group on the nitrogen is methyl. For example, treatment of N,N-dimethyl 3-(o-anisyloxy)-3-phenylpropylamine with cyanogen bromide followed by alkaline hydrolysis of the N-cyano compound yields directly N-methyl 3-(o-anisyloxy)-3-phenylpropylamine [N-methyl 3-(o-methoxy phenoxy)-3-phenylpropylamine].

An alternate preparation of the compounds of this invention in which only one of the R' groups attached to the nitrogen is methyl is carried out as follows:

3-Chloropropylbenzene is reacted with a positive halogenating agent such N-bromosuccinimide to yield the corresponding 3-chloro-1-bromopropylbenzene. Selective replacement of the bromo atom with the sodium salt of a phenol, as for example, the sodium salt of o-methoxyphenol (guaicol) yields a 3-chloro-1-(1-methoxyphenoxy)-propylbenzene [also named as 3-chloro-1-(o-anisyloxy)propylbenzene]. Reaction of the 3-chloro derivative thus produced with methylamine yields the desired N-methyl 3-(o-anisyloxy)-3-phenylpropylamine.

Compounds in which both R' groups attached to the nitrogen in the above formula are hydrogen can be prepared from an intermediate produced in the previous preparation of the N-methyl compounds such as, for illustrative purposes, 3-chloro-1-(o-anisyloxy)-propylbenzene prepared by the reaction of 3-chloro-1-bromobenzene and sodium guaicol. This chloro compound is reacted with sodium azide to give the corresponding 3-azido-1-(o-anisyloxy)-propylbenzene. Reduction of the azide group with a metallo-organic reducing agent such as sodium borohydride yields the desired primary amine. Alternatively, the chloro compound can be reacted directly with a large excess of ammonia in a high pressure reactor to give the primary amine.

Compounds in which the R' group on the carbon atom alpha to the nitrogen is methyl can be prepared by reacting phenyl 2'-propenyl ketone with dimethylamine [See J. Am. Chem. Soc., 75, 4460 (1953)]. The resulting 3-dimethylaminobutyrophenone is reduced to yield the N,N-dimethyl 3-hydroxy-1-methyl-3-phenylpropylamine. Replacement of the hydroxyl with chlorine followed by reaction of the chloro-compound with the sodium salt of a suitably substituted phenol yields the N,N-dimethyl derivatives of this invention bearing an alpha methyl group on the propylamine backbone of the molecule. Production of the corresponding N-methyl derivative can be accomplished by the aforementioned reaction sequence utilizing cyanogen bromide. The N-methyl derivative can in turn be converted to the corresponding primary amine (in which both R' groups on the nitrogen are hydrogen) by oxidation in neutral permanganate according to the procedure of Booker and Pohland, Ser. No. 317,969, filed Dec. 24, 1972. Compounds in which the R' group attached to the β-carbon atom is methyl are prepared by a Mannich reaction involving propiophenone, formaldehyde and dimethylamine. The resulting ketone, a α-methyl-β-dimethylaminopropiophenone, is subjected to the same reduction procedure as before to yield a hydroxy compound. Replacement of the hydroxyl with chlorine followed by reaction of the chloro compound with the sodium salt of a phenol yields a dimethyl amine compound of this invention. Conversion of the dimethylamine to the corresponding monomethyl and primary amines is carried out as before.

Those compounds in which the R' group attached to either the α or β-carbon is methyl have two asymmetric carbon atoms, the carbon carrying the R' methyl and the γ-carbon carrying the phenoxy and phenyl groups. Thus, such compounds exist in four diastereomeric forms occurring as two racemic pairs, the less soluble pair being designated α-dl form and the more soluble the β-dl form. Each racemate can be resolved into its individual d and l isomers by methods well known in the art, particularly, by forming salts with optically active acids and separating the salts by crystallization.

This invention is further illustrated by the following specific examples:

EXAMPLE 1

Preparation of N-methyl 3-(p-trifluoromethylphenoxy)-3-phenylpropylamine and of N,N-dimethyl 3-(p-trifluoromethylphenoxy)-3-phenylpropylamine.

About 600 g. of β-dimethylaminopropiophenone hydrochlorides were converted to the corresponding free base by the action of 1.5 N aqueous sodium hydroxide. The liberated free base was taken up in ether, the ether layer separated and dried, and the ether removed therefrom in vacuo. The residual oil comprising β-dimethylaminopropiophenone was dissolved in two liters of tetrahydrofuran, and the resulting solution added in dropwise fashion with stirring to a solution of four moles of diborane in four liters of tetrahydrofuran. The reaction mixture was stirred overnight at room temperature. An additional mole of diborane in one liter of tetrahydrofuran was added, and the reaction mixture stirred again overnight at room temperature. Next, two liters of aqueous hydrochloric acid were added to decompose any excess diborane present. The tetrahydrofuran was removed by evaporation. The acidic solution was extracted twice with one liter portions of benzene, and the benzene extracts were discarded. The acidic solution was then made basic with an excess of 5 N aqueous sodium hydroxide. The basic solution was extracted three times with two liter portions of benzene. The benzene extracts were separated and combined, and the combined extracts washed with a saturated aqueous sodium chloride and then dried. Evaporation of the solvent in vacuo yields 442 g. of N,N-dimethyl 3-phenyl-3-hydroxypropylamine.

A solution containing 442 g. of N,N,-dimethyl 3-phenyl-3-hydroxypropylamine in 5 l. of chloroform was saturated with dry gaseous hydrogen chloride. 400 ml. of thionyl chloride were then added to the chloroform solution at a rate sufficient to maintain reflux. The solution was refluxed an additional 5 hours. Evaporation of the chloroform and other volatile constituents in vacuo yielded N,N-dimethyl 3-phenyl-3-chloropropylamine hydrochloride which was collected by filtration, and the filter cake washed twice with 1500 ml. portions of acetone. The washed crystals weighed about 500 g. and melted at 181°-3° C. with decomposition. An additional 30 g. of compound were obtained from the acetone wash by standard crystallization procedures. The structure of the above compound was verified by NMR and titration.

A solution of 50 g. p-trifluoromethylphenol, 12 g. of solid sodium hydroxide and 400 ml. of methanol was placed in a one liter round-bottom flask equipped with magnetic stirrer, condenser and drying tube. The reaction mixture was stirred until the sodium hydroxide had dissolved. Next, 29.8 g. of N,N-dimethyl 3-phenyl-3-chloropropylamine hydrochloride were added. The resulting reaction mixture was refluxed for about 5 days and then cooled. The methanol was then removed by evaporation, and the resulting residue taken up in a mixture of ether and 5 N aqueous sodium hydroxide. The ether layer was separated and washed twice with 5 N aqueous sodium hydroxide and three times with water. The ether layer was dried, and the ether removed by evaporation in vacuo to yield as a residue N,N-dimethyl 3-(p-trifluoromethylphenoxy)-3-phenylpropylamine.

The free base was converted to the corresponding oxalate salt by dissolving 32 g. of the amine in ethyl acetate to which was added a solution of 9 g. of oxalic acid also in ethyl acetate. N,N-dimethyl-3-p-trifluoromethylphenoxy-3-phenylpropylamine oxalate thus formed melted at 117°–119° C. with decomposition after recrystallization from ethyl acetate.

Analysis calc.: C, 58.11; H, 5.36; N, 3.39; F, 13.79; Found: C, 58.19; H, 5.49; N, 3.59; F, 13.85.

A solution containing 8.1 g. of cyanogen bromide in 300 ml. benzene and 50 ml. of toluene was placed in a one liter three-neck round-bottom flask equipped with thermometer, addition funnel, drying tube and inlet tube for nitrogen. The solution was cooled to about 5° C. with stirring, and nitrogen gas was bubbled thru the solution. Next, a solution of 32.146 g. of N,N-dimethyl 3-(p-trifluoromethylphenoxy)-3-phenylpropylamine dissolved in 40 ml. of benzene was added in dropwise fashion. The temperature of the reaction mixture was allowed to rise slowly to room temperature, at which temperature stirring was continued overnight while still maintaining a nitrogen atmosphere. 100 ml. of benzene were added. The reaction mixture was washed twice with water, once with 2 N aqueous sulfuric acid and then with water until neutral. The organic layer was dried, and the solvents removed therefrom by evaporation in vacuo to yield about 9.5 g. of an oil comprising N-methyl-N-cyano 3-(p-trifluoromethylphenoxy)-3-phenylpropylamine.

A solution of 100 g. potassium hydroxide, 85 ml. water, 400 ml. ethylene glycol and 9.50 g. of N-methyl-N-cyano 3-(p-trifluoromethylphenoxy)-3-phenylpropylamine was prepared in a one liter three-neck, round-bottom flask equipped with magnetic stirrer and condenser. The reaction mixture was heated to refluxing temperature (130° C.) for 20 hours, and was then cooled. 200 ml. of water were added. The reaction mixture was extracted with three 200 ml. portions of ether. The ether extracts were combined, and the combined extracts washed with water. The water wash was discarded. The ether solution was next contacted with 2 N aqueous hydrochloric acid. The acidic aqueous layer was separated. A second aqueous acidic extract with 2 N hydrochloric acid was made followed up three aqueous extracts and an extract with saturated aqueous sodium chloride. The aqueous layers were all combined and made basic with 5 N aqueous sodium hydroxide. N-methyl 3-(p-trifluoromethylphenoxy)-3-phenylpropylamine, formed in the above reaction, was insoluble in the basic solution and separated. The amine was extracted into ether. Two further ether extractions were carried out. The ether extracts were combined, and the combined extracts washed with saturated aqueous sodium chloride and then dried. Evaporation of the ether in vacuo yielded about 6.3 g. of N-methyl 3-(p-trifluoromethylphenoxy)-3-phenylpropylamine. The amine free base was converted to the corresponding oxalate salt by the method set forth above. N-methyl 3-(p-trifluoromethylphenoxy) -3-phenylpropylamine oxalate thus prepared melted at 179°–182° C. with decomposition after recrystallization from an ethyl acetate-methanol solvent mixture.

Analysis calc.: C, 57.14; H, 5.05; N, 3.51; F, 14.27; Found; C, 57.43; H, 5.30; N, 3.79; F, 14.24.

The amine free base was also converted to the maleate salt.

The following N,N-dimethyl or N-methyl 3-substituted phenoxy-3-phenylpropylamines were prepared by the above procedures.

N,N-dimethyl 3-(p-chlorophenoxy)-3-phenylpropylamine maleate which melted at 88°–90° C. after recrystallization from an ethyl acetate-cyclohexane solvent mixture.

Analysis calc.: C, 62.14; H, 5.96; N, 3.45; Cl, 8.73; Found; C, 61.94; H, 5.87; N, 3.66; Cl, 8.92.

N,N-dimethyl 3-(o-chlorophenoxy)-3-phenylpropylamine p-toluene-sulfonate which melted at 124°–6° C. after recrystallization from ethyl acetate.

Analysis calc.; C, 66.39; H, 5.70; N, 2.93; F, 11.50; S, 6.67; Found; C, 66.36; H, 5.52; N, 3.12; F, 11.80; S, 6.65.

N,N-dimethyl 3-(o-tolyloxy)-3-phenylpropylamine oxalate which melted at 160°–62° C. after recrystallization from a methanol-isopropanol solvent mixture.

Analysis calc.: C, 66.84; H, 7.01; N, 3.90. Found; C, 66.83; H, 7.02; N, 4.17.

N,N-dimethyl 3-(β-naphthyloxy)-3-phenylpropylamine oxalate; melting point=146°–7° C.

Analysis calc.: C, 69.86; H, 6.37; N, 3.54; Found: C, 69.80; H, 6.30; N, 3.74.

N-methyl 3-phenyl-3-(m-chlorophenoxy)propylamine oxalate; melting point=177°–9° C.

Analysis calc.; C, 59.10; H, 5.51; N, 3.83; Cl, 9.69; Found; C, 58.89; H, 5.45; N, 4.07; Cl, 9.24.

N,N-dimethyl 3-phenyl-3-(m-methoxyphenoxy)-propylamine oxalate; melting point=125°–8° C.

Analysis calc.: C, 63.99; H, 6.91; N, 3.73; Found: C, 63.95; H, 6.90; N, 3.59.

N,N-dimethyl 3-phenyl-3-(o-allylphenoxy)propylamine oxalate; melting point=159°–161° C.

Analysis calc.: C, 68.55; H, 7.06; N, 3.63; Found; C, 68.67; H, 7.15; N, 3.63.

N,N-dimethyl 3-phenyl-3-(p-chlorophenoxy)-propylamine oxalate; melting point=139°–141° C.

Analysis calc.: C, 60.08; N, 5.84; N, 3.69; Cl, 9.33; Found; C, 60.34; H, 5.99; N, 3.88; Cl, 9.61.

N,N-dimethyl 3-(p-methoxyphenoxy)-3-phenylpropylamine oxalate; m.p.=98°–103° C.

Analysis calc.: C, 65.82; H, 6.78; N, 3.49; Found; C, 65.83; H, 6.53; N, 3.63.

N,N-dimethyl 3-(p-methoxyphenoxy)-3-phenylpropylamine maleate; m.p.=101°–104° C.

Analysis calc.: C, 65.82; H, 6.78; N, 3.49; Found; C, 65.96; H, 6.50; N, 3.68.

N-methyl 3-(p-fluorophenoxy)-3-phenylpropylamine maleate; m.p.=112.5°–119° C.

Analysis calc.: C, 63.99; H, 5.91; N, 3.73; Found; C, 63.77; H, 6.19; N, 3.90.

N-methyl 3-(p-methoxyphenoxy)-3-phenylpropylamine maleate; m.p.=128.5°–135° C.

Analysis calc.: C, 65.10; H, 6.30; N, 3.62; Found: C, 64.94; H, 6.54; N, 3.67.

N,N-dimethyl 3-(o-bromophenoxy)-3-phenylpropylamine oxalate: melting point = 144°-6° C.

Analysis calc: C, 53.79 H, 5.23; N, 3.30; Br, 18.86; Found. C, 53.84; H, 5.52; N, 3.38; Br, 18.86.

N,N-dimethyl 3-(p-tolyloxy)-3-phenylpropylamine oxalate: melting point = 145°-147° C.

Analysis calc.; C, 66.84; H, 7.01; N, 3.90: Found; C, 66.61; H, 7.01; N, 4.06.

N-methyl 3-phenyl-3-(o-allylphenoxy)propylamine oxalate: melting point = 144°-147° C. (dec.).

Analysis calc.: C, 67.91; H, 6.78; N, 3.77; Found; C, 67.90; H, 6.85; N, 3.96.

N-methyl 3-phenyl-3-(p-tolyloxy)propylamine oxalate: melting point = 170°-173° C.

Analysis calc.: C, 66.07; H, 6.71, N, 4.06; Found; C, 65.93; H, 6.57; N, 3.87.

N,N-dimethyl 3-phenyl-3-(o-tolyloxy)propylamine oxalate: melting point = 134°-6° C.

Analysis calc.; C, 66.83; H, 7.01; N, 3.90; Found; C, 66.48; H, 7.32; N, 4.32.

N,N-dimethyl 3-phenyl-3-(m-trifluoromethylphenoxy)propylamine oxalate: melting point = 163°-5° C.

Analysis calc.; C, 58.11; H, 5.36; N, 3.39; F, 13.79; Found; C, 57.89; H, 5.26; N, 3.41, F, 13.69.

N,N-dimethyl 3-phenyl-3-(o-t-butylphenoxy)-propylamine oxalate: melting point = 146°-9° C. Analysis calc.; C, 68.88; H, 7.78; N, 3.49; Found; C, 68.56; H, 8.04; N, 3.69

N-methyl 3-phenyl-3-p-fluorophenoxy)propylamine oxalate: melting point = 159°-161° C. Analysis calc.; C, 61.88; H, 5.77; N, 4.01; F, 5.44; Found; C, 61.66; H, 5.90; N, 3.72. F, 5.70.

N-methyl 3-phenyl-3-(o-methoxyphenoxy)propylamine hydrochloride: melting point = 105°-8° C. (recrystallized from ethyl acetate); Analysis calc.; C, 66.33, H, 7.20, N, 4.55, Cl, 11.52; Found; C, 66.16; H, 7.36; N, 4.41; Cl, 11.48.

N-methyl 3-phenyl-3-(o-fluorophenoxy)propylamine oxalate, melting point = 148°-50° C.

Analysis calc.: C, 61.88; H, 5.77; N, 4.01; F, 5.44; Found; C, 61.83; H, 5.97; N, 4.14; F, 5.65.

N-methyl 3-phenyl-3-(m-methoxyphenoxy)propylamine oxalate; melting point = 140°-3° C.

Analysis calc.: C, 63.15; H, 6.42; N, 3.88; Found; C, 62.91; H, 6.40; N, 4.17.

N-methyl 3-phenyl-3-(o-tolyloxy)propylamine oxalate: melting point = 155°-7° C.

Analysis calc.: C, 66.07; H, 6.71; N, 4.06; Found; C, 65.81; H, 6.94; N, 4.36.

N,N-dimethyl 3-(o-ethylphenoxy)-3-phenylpropylamine oxalate melting point = 152°-4° C.

Analysis calc.: C, 67.54; H, 7.29, N, 3.75; Found; C, 67.33; H, 7.05, N, 3.98.

N,N-dimethyl 3-(o-isopropoxyphenoxy)-3-phenylpropylamine oxalate: melting point = 139°-142° C.

Analysis calc.; C, 68.20; H, 7.54; N, 3.61; Found, C, 68.50; H, 7.82, N, 3.85.

N-methyl 3-phenyl-(p-chlorophenoxy)propylamine oxalate: melting point = 163°-5° C.

Analysis calc.; C, 59.10; H, 5.31; N, 3.83; Cl, 9.69; Found; C, 59.11; H, 5.58; N, 4.07; Cl, 9.45.

N,N-dimethyl 3-(p-fluorophenoxy)-3-phenylpropylamine maleate: melting point = 103°-8° C.

Analysis calc.: C, 64.77; H, 6.21; N, 3.60; Found: C, 64.79; H, 6.50; N, 3.82.

N,N-dimethyl 3-(m-chlorophenoxy)-3-phenylpropylamine oxalate: melting point = 150°-2° C. (recrystallization from isopropanol)

Analysis calc.: C, 60.08; H, 5.87; N, 3.89; Cl, 9.33; Found: C, 59.90; H, 6.08; N, 3.42; Cl, 9.60.

N,N-dimethyl 3-(o-fluorophenoxy)-3-phenylpropylamine hydrochloride: melting point = 166°-8° C. (from acetonecyclohexane)

Analysis calc.: C, 65.91; H, 6.83; N, 4.52; Cl, 11.99; F, 6.13; Found: C, 65.78; H, 6.82; N, 4.78; Cl, 11.70; F, 5.99.

N-methyl 3-phenoxy-3-phenyl-2-methylpropylamine oxalate: melting point = 158°-160° C. (from isopropanol)

Analysis calc.: C, 66.07; H, 6.71; N, 4.06; Found: C, 66.12; H, 6.72; N, 4.26

N-methyl 3-phenoxy-3-phenyl-1-methylpropylamine oxalate: melting point = 80°-100° C. with decomposition (from ethyl acetate)

Analysis calc.: C, 66.07; H, 6.71; N, 4.06; Found: C, 65.85; H, 6.45, N, 4.20.

α-di-N,N-dimethyl-3-phenoxy-3-phenyl-1-methylpropylamine oxalate: melting point = 113°-16° C.

Analysis calc.: C, 66.84; H, 7.01; N, 3.90; Found: C, 67.03; H, 7.20; N, 4.13.

N,N-dimethyl 3-phenoxy-3-phenyl-2-methylpropylamine oxalate: melting point = 130°-4° C. Analysis calc.: C, 66.89; H, 7.01; N, 3.90; Found: C, 66.59; H, 7.08; N, 3.96.

N-methyl 3-(m-fluorophenoxy)-3-phenylpropylamine oxalate: melting point = 177°-9° C.

Analysis calc.: C, 61.87; H, 5.77; N, 4.01; F, 5.44; Found: C, 62.07, H, 6.02, N, 4.33, F, 5.23.

N,N-dimethyl 3-(o-ethoxyphenoxy)-3-phenylpropylamine oxalate: melting point = 101°-4° C.

Analysis calc.: C, 64.77: H, 6.99; N, 3.60; Found: C, 65.05; H, 7.00; N, 3.88.

N,N-dimethyl 3-(p-fluoro-o-tolyloxy)-3-phenylpropylamine oxalate: melting point = 149°-51° C.

Analysis calc.: C, 63.65; H, 6.41; N, 3.71; F, 5.03; Found: C, 63.82; H, 6.66; N, 3.95; F, 5.32.

N,N-dimethyl 3-(α-naphthyloxy)-3-phenylpropylamine maleate: melting point = 97°-99° C.

Analysis calc.: C, 70.48; H, 6.65; N, 3.42; Found: C, 69.80; H, 6.90; N, 3.74.

β-di-N,N-dimethyl-3-phenoxy-3-phenyl-1-methylpropylamine oxalate: melting point = 131°-33° C.

Analysis calc.: C, 66.89; H, 7.01; N, 3.90; Found: C, 66.64; H, 7.00; N, 3.77.

EXAMPLE 2

Preparation of N-methyl 3-(o-methoxyphenoxy)-3-phenylpropylamine hydrochloride.

A reaction mixture consisting of 1000 g. of 3-chloropropylbenzene, 1500 g. of N-bromosuccinimide, 5 g. of benzoyl peroxide and 6 l. of carbon tetrachloride were placed in a 12 l. 3-neck, round-bottom flask equipped with stirrer and condenser. The reaction mixture was stirred and heated until an exothermic reaction began. The heat source was then removed, and the refluxing of reaction mixture controlled by external cooling. After the reaction had been completed as noted by the disappearance of the N-bromosuccinimide, the reaction mixture was cooled and crystalline succinimide collected by filtration. The succinimide filter cake was washed with carbon tetrachloride. The combined filtrate and wash was concentrated in vacuo. The residue comprising 3-chloro-1-bromopropylbenzene obtained in the

above reaction was shown by a NMR to be the desired material and was used without further purification. The yield was essentially quantitative.

Next, a solution of sodium guaiacol (o-methoxyphenol) was prepared by dissolving 156 g. of sodium hydroxide and 485.6 g. of guaiacol in 2.5 L of ethanol. The ethanol was removed by evaporation in vacuo, benzene added, and the benzene also removed by evaporation in vacuo. This process was repeated several times in order to dry completely the sodium guaiacol. The sodium guaiacol obtained by the above procedure was dissolved in approximately 3 L of dimethylsulfoxide. The solution was cooled to about 20° C. 3-chloro-1-bromopropylbenzene was added thereto in dropwise fashion over a period of ½ hour while the reaction temperature was maintained at about 25° C. The reaction mixture was allowed to stir at room temperature overnight and was then poured onto ice. The resulting aqueous layer was extracted with four 2 L. portions of hexane. The hexane extracts were washed with water and dried. Removal of the hexane in vacuo yielded as a residue 3-chloro-1-(o-methoxyphenoxy)propylbenzene prepared by the above procedure. The compound was distilled in vacuo. 3-Chloro-1-(o-methoxyphenoxy)propylbenzene thus purified distilled in the range of 135°–145° C. (0.03 torr). The structure of the compound was verified by NMR.

A reaction mixture consisting of 200 ml. of methylamine, 225 ml. of methanol and 75 g. of 3-chloro-1-(o-methoxyphenoxy)propylbenzene was heated in an autoclave for 12 hours at 140° C. The reaction mixture was cooled, and the solvent was removed by evaporation. The semisolid residue was mixed with concentrated aqueous sodium hydroxide. The resulting mixture was extracted several times with ether. N-methyl 3-(o-methoxyphenoxy)-3-phenylpropylamine, formed in the above reaction, was insoluble in the alkaline solution and was extracted therefrom with ether. The ether extracts were combined, and the combined extracts washed with water and dried. The ether was removed therefrom in vacuo leaving the amine as a dark colored residue. The residue was dissolved in ether and 1 equivalent of oxalic acid in methanol added slowly. N-methyl 3-(o-methoxyphenoxy)-3-phenylpropylamine oxalate formed an insoluble precipitate which was collected by filtration, and the filter cake washed with ether and dried. N-methyl 3-(o-methoxyphenoxy)-3-phenylpropylamine oxalate melted at 150°–152° C. The NMR spectrum of the compound was consistent with the expected structure.

N-methyl 3-(o-methoxyphenoxy)-3-phenylpropylamine oxalate was dissolved in a minimum quantity of water with heating, and concentrated aqueous sodium hydroxide added. After cooling, the alkaline solution was extracted several times with ether. The combined ether extracts were washed with water and dried, and the ether removed therefrom in vacuo. N-methyl 3(o-methoxyphenoxy)-3-phenylpropylamine free base thus isolated was dissolved in ether, and the ether solution saturated with dry gaseous hydrogen chloride. N-methyl 3(o-methoxyphenoxy)-3-phenylpropylamine hydrochloride thus formed was recrystallized from ethyl acetate containing a small amount of methanol. N-methyl 3-(o-methoxyphenoxy)-3-phenyl-propylamine hydrochloride thus prepared and purified melted at 129°–131° C.

EXAMPLE 3

Preparation of 3-(o-methoxyphenoxy)-3-phenylpropylamine.

A solution of 2.6 g. of sodium azide in 10 ml. of water was placed in a 100 ml. three-neck, round-bottom flask equipped with stirrer, condenser and thermometer. A second solution containing 2.76 g. of 3-chloro-1-(o-methoxyphenoxy)propylbenzene (as provided by the procedure of Example 2) in 30 ml. of dimethylformamide was added to the sodium azide solution, and the resulting mixture heated at 95° C. overnight. The reaction mixture was cooled, diluted with water and extracted three times with ether. The ether extracts were combined, the combined extracts were washed five times with water followed by a saturated aqueous sodium chloride wash, and were then dried. Evaporation of the ether in vacuo yielded a colorless liquid comprising 3-azido-1-(o-methoxyphenoxy)propylbenzene. Forty-one grams of this latter compound were dissolved in 350 ml. of isopropanol. The resulting solution was placed in a 1 L. round-bottom flask equipped with magnetic stirrer condenser and drying tube. Fifteen and two-tenths grams of 96% sodium borohydride in the solid form were added to the azide solution. The resulting mixture was heating to refluxing temperature overnight and then cooled. The alcohol was evaporated therefrom in vacuo. After 1.5 L of water were added, and the resulting aqueous mixture acidified cautiously with 2 N aqueous hydrochloric acid. 3-(o-methoxyphenoxy)-3-phenylpropylamine produced in the above reaction was soluble in the aqueous acidic layer as the hydrochloride salt. The acidic aqueous layer was extracted three times with ether, and the ether extracts saved to recover unreacted starting material. The acidic layer was then made basic with 5 N aqueous sodium hydroxide. The primary amine, being insoluble in base, separated and was extracted into ether. The ether layer was separated, and the aqueous alkaline layer extracted twice more with ether. The ether extracts were combined, and the combined layers washed with a saturated aqueous sodium chloride solution. Evaporation of the ether in vacuo yielded about 17 g. of 3-(o-methoxyphenoxy)-3-phenylpropylamine which was converted to the oxalate salt by the procedure of Example 1: 3-(o-methoxyphenoxy)-3-phenylpropylamine oxalate thus prepared melted at 118°–121° C. after recrystallization from an ethyl acetate-cyclohexane solvent mixture. The oxalate salt was converted to the hydrochloride salt by forming the free base in ether solution and then saturating the ether solution with gaseous hydrogen chloride. The hydrochloride salt melted at 77°–8° C.

Analysis calc.: C, 65.91; H, 6.86; N, 4.77; Cl, 12.07; Found: C, 65.13; H, 7.12; N, 4.61; Cl, 12.21.

Following the above procedure, 3-(p-trifluoromethylphenoxy)-3-phenylpropylamine oxalate was prepared: melting point = 162°–164° C. The oxalate salt was converted to the hydrochloride salt by forming the free base, extracting the free base into ether and then saturating an ether solution of the free base with gaseous hydrogen chloride. The hydrochloride salt melted at 130°–132° C.

Analysis calc.: C, 57.93; H, 5.17; N, 4.22; Cl, 10.69; F, 17.18; Found: C, 57.66; H, 5.08; N, 4.09; Cl, 11.15; F, 16.66.

EXAMPLE 4

Preparation of 3-phenoxy-3-phenylpropylamine.

Eight grams of 3-phenoxy-3-phenylpropylchloride provided by the procedure of Example 2 were heated with 150 ml. of liquid ammonia in a high pressure reactor at 100° C. for 20 hours. The volatile constituents of the reaction mixture were evaporated, and the residue, comprising 3-phenoxy-3-phenylpropylamine formed in the above reaction, was dissolved in ethanol and the volatile constituents again removed by evaporation. The resulting residue was dissolved in a mixture of ether and 5 N aqueous sodium hydroxide. The ether layer was separated, and the alkaline aqueous layer extracted three more times with ether. The ether extracts were combined, and the combined extracts washed with water. The ether layer was next extracted twice with 2 N aqueous hydrochloric acid, the primary amine passing into the acidic layer. The acidic extracts were combined and made basic by the addition of an excess of 5 N aqueous sodium hydroxide. The primary amine, being insoluble in the basic solution, separated and was extracted into ether. The ether extract was separated, and the basic solution extracted twice more with ether. The ether extracts were combined, the combined extracts washed with saturated aqueous sodium chloride and then dried. Evaporation of the ether in vacuo yielded 3-phenoxy-3-phenylpropylamine as an oil. The oxalate salt of the primary amine was prepared by the procedure of Example 1 and melted at 170°–173° C.

Analysis calc.: C, 64.34; H, 6.04; N, 4.41; Found: C, 64.49; H, 5.80; N, 4.67.

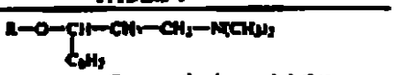
EXAMPLE 5

Preparation of Salts

Salts of the free bases of this invention, other than the hydrochloride, maleate and oxalate salts whose preparation is illustrated in Examples 1–4, are prepared by dissolving the free base in ether and adding an equivalent of a suitable non-toxic acid, also in ether. The salts thus formed, as for example the acetate and benzoate salts, are insoluble in ether and can be isolated by filtration. Alternatively, the amine base can be dissolved in ethanol and an equivalent of the acid added as an ethanolic solution. In this instance, since the salts thus formed are soluble in the reaction mixture, they are isolated by evaporation of the solvent in vacuo. Salts which can be formed by the above procedure include the sulfate, hydrobromide, phosphate, hydrogen phosphate, dihydrogen phosphate, acetate, methanesulfonate, succinate, tartrate, citrate, benzoate, and p-toluene sulfonate salts.

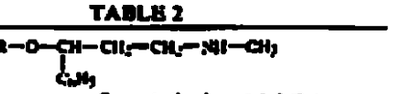
As indications of their psychotropic activity, the compounds of this invention have been found to block the uptake of various physiologically active monoamines. This blockade is shown both in vitro with radioactive labelled compounds to determine the amount of monoamine uptake by synaptosomes from rat brain, and in vivo by a variety of methods. Among the physiologically active monoamines whose uptake is blocked by the compounds of this invention are included serotonin, norepinephrine and dopamine (3,4-dihydroxyphenylethylamine). While all of the compounds of this invention block the uptake of monoamines, certain of them possess a unique selectivity in that they block the uptake of one of the monoamines to a far greater extent than they do the uptake of the other two. Tables 1 and 2 which follow set forth the results of some of the in vitro determinations of the blockage of monoamine uptake by the compounds of this invention. In the tables, column 1 gives the R substituent on the 3-phenylpropylamine and columns 2–4, the concentration in micrograms per ml. that blocks the uptake of a particular amine by 50 percent for the amines—norepinephrine, serotonin, and dopamine. At the head of each column is given the concentration of the particular monoamine used in the experiment.

TABLE 1



R	Concentration in mcg./ml. Can block 50% of amine uptake: Norepinephrine 0.04 μM	Serotonin 0.1 μM	Dopamine 0.2 μM
m-Nitrophenyl	.15	.03	.4
phenyl	1	6	.3
α-naphthyl	3	.01	2.5
p-chlorophenyl	.3	.01	1.3
m-methoxyphenyl	.2	.08	.4
m-trifluoromethyl phenyl	2	.12	>100
o-bromophenyl	—	.1	5
m-chlorophenyl	.03	.13	2
p-trifluoromethylphenyl	70	.16	>100
o-chlorophenyl	.43	.2	.2
o-tolyl	.15	2	0.2
m-tolyl	13	.7	>0
p-tolyl	.015	.4	>100
o-ethylphenyl	>100	2.3	>100
o-isopropyl-phenyl	1.5	>100	>100
o-t-butylphenyl	1.5	60	>100
o-ethylphenyl	1	.2	50
m-trifluoromethylphenyl	70	.14	>100
o-anisyl	.3	2.6	20
p-anisyl	7	1	3.6
o-phenetyl	3	6	>100
o-fluorophenyl	.07	.3	.15
p-fluorophenyl	>100	1	.45
β-naphthyl	>100	1	>100
4-Chloro-o-tolyl	2.5	.8	60
2,4-difluorophenyl	.2	.3	10

TABLE 2



R	Concentration in mcg./ml. that blocks 50% of amine uptake: Norepinephrine 0.04 μM	Serotonin 0.1 μM	Dopamine 0.2 μM
p-trifluoromethylphenyl	20	10	>100
m-chlorophenyl	.07	.15	.50
phenyl	.12	.25	1
o-tolyl	20	.25	4
p-tolyl	1.2	.25	45
o-ethylphenyl	.5	1	>100
o-trifluoromethylphenyl	6.0	2.5	>100
o-anisyl	.06	.3	.6
m-anisyl	.13	4.0	.05
p-anisyl	.16	12	—
o-fluorophenyl	.3	2.5	50
m-fluorophenyl	.06	.3	1
p-fluorophenyl	2	1	.25
p-chlorophenyl	.4	.3	>100
2,4-difluorophenyl	>100	4.5	>100

One demonstration of the in vivo effect of the compounds of this invention in blocking serotonin uptake was made indirectly by the following experiment, based on a previous experiment of Meek et al. *Biochem. Pharmacol.*, 20, 707 (1971) who found that inhibitors of serotonin uptake prevent the depletion of brain serotonin caused by the injection of 4-chloromethamphetamine. In our procedure, an amount of 4-chloroamphetamine known to deplete the brain serotonin level about 30 percent was injected into rats. Following this injection, the protecting drug was injected at a dose of 15 mg./kg. of rat-weight intraperitoneally and determinations of brain serotonin levels were carried out 4 hours later. In Table 3 which follows, column 1 gives the name of the drug employed, and column 2, the brain serotonin levels in mcg./g. of brain tissue. Chlorimipramine and N-desmethylimipramine were employed as controls since Meek et al. (loc. cit.) had previously shown that these drugs were capable of preventing the depletion of brain serotonin by 4-chloromethamphetamine.

TABLE 3

Name of drug	Brain serotonin level in mcg./g.
none	0.13 ± .02
N-methyl 3-(p-trifluoromethylphenoxy)-3-phenylpropylamine oxalate	0.39 ± .02
chlorimipramine	0.43 ± .03
desmethylimipramine	0.44 ± .02
mice control	0.70 ± .03

As can be seen from Table 3, N-methyl 3-(p-trifluoromethylphenoxy)-3-phenylpropylamine as the oxalate salt prevented the depletion of serotonin caused by the injection of 4-chloroamphetamine; and brain levels of serotonin were indistinguishable from those of the control rats to whom no drugs were given. The corresponding tertiary and primary amine derivatives, N,N-dimethyl 3-(p-trifluoromethylphenoxy)-3-phenylpropylamine oxalate and 3-(p-trifluoromethylphenoxy)-3-phenylpropylamine oxalate gave similar results. The secondary amine also prevented the depletion of serotonin in the brain occasioned by the administration of α-ethyl-4-methyl-m-tyramine but not the depletion of norepinephrine.

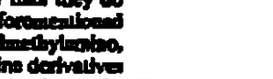
The tricyclic antidepressant drugs presently being marketed inhibit the uptake of monoamines by brain neurons, most of them being more effective in inhibiting the uptake of norepinephrine. Many of the compounds of this invention behave similarly in that they block norepinephrine uptake more effectively than they do serotonin uptake. Exceptions are the aforementioned p-trifluoromethyl derivatives, the dimethylamino, monomethylamino and unsubstituted amine derivatives being far more effective in inhibiting serotonin uptake than in inhibiting norepinephrine uptake. Thus, although the compounds of this invention clearly have potential as anti-depressant compounds, it is apparent that N-methyl 3-(p-trifluoromethylphenyloxy)-3-phenylpropylamine and its tertiary and primary amine analogs will have a different type of anti-depressant action from the presently marketed drugs. The compounds may also find use in the treatment of schizophrenia according to the hypothesis of Wyatt et al. *Science*, 177, 1124 (1972) who were able to produce mild to moderate improvement in 6 or 7 chronic undifferentiated schizophrenic patients by the oral administration of 1-5-hydroxytryptophane, a serotonin precursor.

In addition to their usefulness as psychotropic agents, the above compounds may also find use in treating disorders of sleep, sexual performance, appetite, muscular function, and pituitary function. All of these physiologic functions have been shown to be subject to influence by brain serotoninergic neural systems.

In another aspect of their action as psychotropic drugs, specifically as antidepressants, the compounds of this invention show activity in antagonizing hypothermia induced by the injection of apomorphine and also in antagonizing the central effects of tremorine and oxotremorine, including hypothermia. In addition, the compounds are effective in reversing reserpine hypothermia, but are less effective in preventing reserpine hypothermia. In this regard, the monomethylamines of this invention above are in general more active in antagonizing or reversing hypothermia than are their dimethylamino analogs.

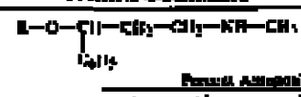
The apomorphine hypothermia antagonism test is carried out as follows: mice are injected with a dose of apomorphine known to reduce body temperature approximately 4° C. The compound under test is injected ½ hour before the injection of the apomorphine and the temperatures measured ½ hour after injection. The degree of antagonism is expressed as a percent reduction (as compared with controls) of the temperature decrease produced by the injection of the apomorphine. The reserpine hypothermia reversal test is carried out as follows: groups of mice are injected with reserpine and 16.5 hours later are injected intraperitoneally with graded doses of the drug, a different dose level being given to each group of mice. Temperatures are measured at 1 hour after injection of the drug under test and again the effectiveness of the drug is expressed as a percentage decrease in the hypothermia induced by the injection of reserpine as compared with the control group. In the tables which follow, Table 4 gives the results in the apomorphine antagonism and reserpine reversal hypothermia tests for the secondary amines of this invention. In the table, the first column gives the substituent attached to the oxygen atom at the 3 position of the propylamine chain; columns 2 to 4 the percent antagonism against apomorphine hypothermia at dose levels of 9.3, 1 and 3 mg./kg. and columns 5–7 the percent reversal of reserpine hypothermia at the same dose levels. Table 5 gives similar information for the dimethylamino compounds of this invention.

TABLE 4



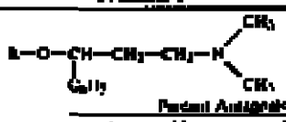
	Percent Antagonism					
	Apomorphine Test-30 min			Reserpine Test-60 min		
	Dosage in mg./kg.					
R	.3	1	3	.3	1	3
phenyl	16	36	66	7	27	36
o-tolyl	20	37	92	14	11	34
o-ethylphenyl	19	29	138	—	11	20
o-trifluoromethylphenyl	—	13	38	—	9	5
p-trifluoromethylphenyl	—	11	25	—	—	10
p-tolyl	—	—	33	—	—	17
3,4-difluorophenyl	20	33	64	13	17	27
o-tolyl	47	101	121	17	46	38
m-tolyl	15	15	71	8	14	21
p-tolyl	0	31	41	11	23	38
o-fluorophenyl	13	37	87	10	8	34
m-fluorophenyl	21	53	84	13	13	19
p-fluorophenyl	7	15	66	7	16	22
m-chlorophenyl	11	31	134	—	13	28

TABLE 4-continued



	Percent Antagonism					
	Apomorphine Pre-30 min.			Reserpine Pre-60 min.		
	Dosage in mg./kg.					
R	.5	1	2	.5	1	3
p-chlorophenyl	42	59	92	—	5	91

TABLE 5



	Percent Antagonism							
	Apomorphine Pre-30 min.				Reserpine Pre-60 min.			
	Dosage in mg./kg.							
R	.5	1	3	10	.5	1	3	10
phenyl			7	54			20	79
methyl			18	96			25	71
o-ethylphenyl			20	74		17	17	35
o-isopropylphenyl	7	17	39	86	18	31	31	15
o-allylphenyl			12	67				27
o-trifluoromethylphenyl		21	51	88				81
p-trifluoromethylphenyl				36				30
2,6-difluorophenyl		36	35	48	23	11	12	30
α-naphthyl		11	30	84		17	16	48
β-naphthyl		— 12	— 7	— 5		— 1	0	3
7-indolyl				23				67
o-phenetyl			13	36			16	40
o-fluorophenyl		— 10	11	11		— 1	26	41
o-furanmethyl			24	41			10	25
p-fluorophenyl		26	62	116	16	20	21	49
o-aminophenyl		— 10	— 11	57		3	4	23
o-methylphenyl		11	13	16		9	10	21
p-chlorophenyl		7	43	85		5	11	29
o-benzylphenyl		75	40	47			18	20
o-naphthyl		— 17	— 10	— 7		13	4	13

Reversal of reserpine hypothermia and antagonism of apomorphine hypothermia are pharmacologic tests in which a number of marketed antidepressants drugs in particular, imipramine, amitriptyline, nortriptyline and desmethylimipramine, are active. One of the compounds of this invention, N-methyl-3-(o-methoxyphenoxy)-3-phenylpropylamine has been found to be an apomorphine and reserpine hypothermia antagonist or reversant having an activity of the same order of magnitude as the aforementioned marketed antidepressant drugs. This compound, when its effect is measured 60 minutes after injection of the apomorphine, at a 10 mg./kg. dose gives 100 percent reduction of hypothermia, as do imipramine and amitriptyline. Similarly the same drug is extremely effective in reversing the effects of reserpine hypothermia and comparus favorable in this regard with the same four marketed antidepressant compounds, giving a similar degree of reversal of hypothermia measured at 60 and 120 minutes.

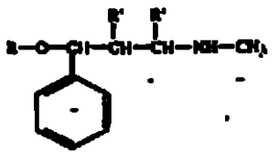
In manifesting their psychotropic action, the compounds of this invention alter the behavior of animals trained in a variety of operant behavior schedules. Again, the activity of compounds of this invention in this type of test parallels that of known antidepressant drugs, particularly desmethylimipramine. For example, N-methyl 3-(o-methoxyphenoxy)-3-phenylpropylamine increased response rates of pigeons in a fixed-ratio, fixed interval schedule and there was a persistence of this effect lasting for more than 24 hours. A similar effect was obtained with desmethylimipramine although it is possible that the persistence encountered was the result of training under the influence of the drug. In Sidman avoidance, using squirrel monkeys, the response of the monkeys increased at a dose level of 3 mg./kg. with N-methyl 3-(o-methoxyphenoxy)-3-phenylpropylamine. Similarly, in monkeys on a multiple fixed-ratio fixed-interval schedule, responses were reduced at dose levels of 2.5 or 5 mg./kg. of the drug. With pigeons trained under an adjusting ratio schedule, the drugs of this invention affect behavior in the same way as does the marketed antidepressant, desmethylimipramine (DMI). In this test, drugs with this type of activity do not markedly affect the response rate but pausing is decreased, as reflected in an increased response per reinforcement. N-methyl 3-(o-methoxyphenoxy)-3-phenylpropylamine, however, gave a significant percent increase in the ratio of responses to reinforcements at dose levels one-fourth of that required by DMI to produce a similar increase. The above results are consistent with antidepressant action.

Finally, the compounds of this invention do not have significant antiserotonin, antihistaminic and anticholinergic effects when tested in isolated muscle strips using routine laboratory procedures. Again, there was a difference between N-methyl 3-(o-methoxyphenoxy)-3-phenylpropylamine as compared with desmethylimipramine, which latter compound was 150 times more potent as an antihistaminic and anticholinergic agent and three times more potent as an antiserotonin agent. In anesthetized cats, intravenous injection of amitriptyline and other marketed tricyclic antidepressants causes a widening of the QRS complex of the electrocardiogram, indicating a delay in intraventricular conduction. 3-(o-Methoxyphenoxy)-3-phenyl propylamine affects the electrocardiogram similarly, but at far higher dose than are found with the aforementioned marketed antidepressants.

In testing humans suffering from various psychoses having a depressive component, the compounds of this invention can be given orally or parenterally. In either instance, it is preferred to use an acid addition salt of the compound formed with a pharmaceutically-acceptable non-toxic acid. For purposes of oral administration, the salt can be mixed with standard pharmaceutical excipients and placed in telescoping gelatin capsules. Similarly, the compound can be mixed with starch, binders, etc. and formulated into tablets, which tablets may be scored for ease of divided dosage administration. For parenteral administration, a water soluble salt of the compound of this invention, which salt is pharmaceutically-acceptable, is dissolved in an isotonic solution and administered intramuscularly, intravenously or subcutaneously. For chronic administration, the oral pharmaceutical forms are naturally preferred. The dose level should vary from 1 to 50 mg./dose given from 1 to 4 times a day with a total daily dosage of 1 to 200 mg./day/human.

We claim:

1. A compound of the formula



wherein each R' is independently H or Cl; and R is m- or p-chlorophenyl, o-, m-, or p-methoxyphenyl, phenyl, o- or m-fluorophenyl, o- or p-tolyl, 2,4-difluorophenyl or p-trifluoromethylphenyl and acid addition salts formed with pharmaceutically-acceptable acids.

2. A compound according to claim 1, said compound being N-methyl 3-(o-tolyloxy)-3-phenylpropylamine and pharmaceutically-acceptable acid addition salts thereof.

3. A compound according to claim 2, said compound being N-methyl 3-(o-tolyloxy)-3-phenylpropylamine hydrochloride.

4. A compound according to claim 1, said compound being N-methyl 3-(p-trifluoromethylphenoxy)-3-phenylpropylamine, and pharmaceutically-acceptable acid addition salts thereof formed with non-toxic acids.

5. A compound according to claim 4, said compound being N-methyl 3-(p-trifluoromethylphenoxy)-3-phenylpropylamine hydrochloride.

6. A compound according to claim 1, said compound being N-methyl 3-(o-methoxyphenoxy)-3-phenylpropylamine, and pharmaceutically-acceptable acid addition salts thereof formed with non-toxic acids.

7. A compound according to claim 1, said compound being N-methyl 3-(o-methoxyphenoxy)-3-phenylpropylamine hydrochloride.

8. A compound according to claim 1, said compound being N-methyl 3-(2,4-difluorophenoxy)-3-phenylpropylamine.

9. A compound according to claim 8, said compound being N-methyl 3-(m-fluorophenoxy)-3-phenylpropylamine oxalate.

* * * * *

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(73) Titular/es: ELI LILLY AND COMPANY
Lilly Corporate Center
Indianapolis, Indiana 46285, US

(72) Inventor/es: Heiligenstein, John Harrison y
Tollefson, Gary Dennis

(74) Agente: Carpintero López, Francisco

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DESCRIPCION

Uso de tomoxetina para el tratamiento de la hiperactividad inducida por trastornos de la atención.

La invención pertenece a los campos de la química farmacéutica y medicina psiquiátrica, y proporciona el uso de tomoxetina para la fabricación de un medicamento para el tratamiento del trastorno psiquiátrico conocido como hiperactividad inducida por trastornos de la atención.

Antecedentes de la invención

Durante algunas décadas se ha reconocido que un número significativo de niños son persistentemente hiperactivos y que tienen un alcance de su atención tan corto como para incapacitarles en la escuela y en muchas relaciones interpersonales. Estos niños, en otros tiempos, habrían sido calificados indudablemente como incorregibles y se les habría castigado o incluso confinado en una institución. No obstante, hace algún tiempo se descubrió que estos niños no pueden controlar su hiperactividad y su falta de atención, y los profesionales médicos comenzaron a intentar ayudarlos. Durante algún tiempo se ha utilizado metilfenidato (Ritalin™) para tratar a estos niños que, a menudo, mejoran significativamente en su funcionalidad y en su capacidad para conciliar con otras personas en el colegio y en casa. No obstante, el fármaco tiene las desventajas de requerir varias administración al día y de producir un efecto rebote a medida que se va desvaneciendo el efecto de cada dosis. Además, el fármaco provoca somnolencia y falta de apetito en algunos pacientes. Metilfenidato tiene actividad noradrenérgica y dopaminérgica.

En algunos casos de hiperactividad inducida por trastornos de la atención (ADHD) se han utilizado imipramina, desipramina, nortriptilina, amitriptilina y clomipramina. No obstante, estos fármacos tricíclicos tienen varios mecanismos fisiológicos y, como clase, tienden a producir varios efectos secundarios y requieren una cuidadosa supervisión y calibración de la dosis.

En la última década, los psiquiatras se han dado cuenta de que la ADHD no es sólo un trastorno de la infancia, sino que, a menudo, continúa en la edad adulta. Es evidente que la hiperactividad y el alcance corto de su atención provocan un trastorno grave en la vida del adulto, pero sólo hasta recientemente han podido estos pacientes disponer de un tratamiento.

La necesidad de disponer de un tratamiento seguro y cómodo para la ADHD que sea aplicable tanto a los niños como a los adultos, y que no tenga las desventajas que posee el metilfenidato sigue preocupando a los psiquiatras.

El documento WO 96/0756 se refiere a los clorhidrato-5-(2-naftaleniloxi)pirrolo <3,4c> pirroles como inhibidores selectivos de la recaptación de la serotonina. El documento WO 96/12486 se refiere al uso de duloxetina en el tratamiento de varios trastornos, incluido el trastorno obsesivo-compulsivo, el trastorno de pánico, la ADHD y la drogodependencia.

La invención también proporciona el uso de tomoxetina para la fabricación de un medicamento para el tratamiento de la hiperactividad inducida por trastornos de la atención; y el uso de tomoxetina para el tratamiento de la hiperactividad inducida por trastornos de la atención.

La tomoxetina es un fármaco bien conocido cuyo nombre químico es (R)-(-)N-metil-3-(2-metilfenoxi)-3-fenilpropilamina. Se usa habitualmente en forma racémica, y ella actúa de forma en el cerebro. Véase, por ejemplo, en Gehlert y cols, Neuroscience Letters 157, 203-206, 1993, un artículo sobre el mecanismo de la actividad de tomoxetina como un inhibidor de la recaptación de norepinefrina. La tomoxetina es bastante activa en esa función, y además carece sustancialmente de otras actividades del sistema nervioso central en las concentraciones o dosis en las que inhibe eficazmente la recaptación de norepinefrina. Por lo tanto, está esencialmente libre de efectos secundarios y se considera correctamente como un fármaco selectivo.

La tomoxetina es un fármaco notablemente seguro y su uso en la ADHD, tanto en adultos como en niños, es un tratamiento superior para este trastorno por su seguridad mejorada. Además, tomoxetina es eficaz en dosis relativamente bajas, como se comentará más adelante, y puede administrarse una vez al día de forma segura y eficaz. Por lo tanto, se evitan completamente las dificultades creadas por la administración múltiple a los pacientes, en particular en los niños y en los adultos desorganizados.

La dosis eficaz de tomoxetina en la ADHD oscila entre 5 mg/día y 100 mg/día. La dosis preferida en el adulto se encuentra en un intervalo entre 10 y 80 mg/día, y la dosis más preferida en los adultos se sitúa entre los 20 y los 60 mg/día. La dosis en los niños es menor, en un intervalo entre 5 y 70 mg/día, más preferiblemente entre 10 y 60 mg/día, y aún más preferiblemente entre 10 y 50 mg/día. Es el médico responsable del caso quien debe establecer la dosis óptima en cada paciente, como siempre, teniendo en cuenta el peso del paciente, otras medicaciones que pudiera necesitar, la importancia del trastorno y todas las demás circunstancias que rodean su caso.

Como la tomoxetina se absorbe fácilmente por vía oral y requiere una administración sólo una vez al día, hay pocas razones, o ninguna, para administrarla por otra vía que no sea la oral. Puede producirse en forma de un cristal transparente y estable y, por tanto, se formula fácilmente en las formas farmacéuticas orales habituales, como comprimidos, cápsulas, suspensiones, etc. No pueden aplicar los métodos habituales que utilizan los científicos farmacéuticos. Puede administrarse de forma segura, si hay alguna razón para hacerlo así en circunstancias particulares, en otras formas farmacéuticas como soluciones inyectables, inyecciones depot, supositorios, etc., que son formas que los científicos farmacéuticos conocen y entienden bien. No obstante, siempre se preferirá, sustancialmente, administrar tomoxetina como comprimido o cápsula y se recomienda el empleo de estas formas farmacéuticas.

El paciente con ADHD dista mucho de reconocerse fácilmente y la mayoría de la gente ha estado en contacto con niños, y con adultos, que muestran algunos o todos los síntomas

de este trastorno. La mejor descripción del trastorno es la que utiliza los criterios diagnósticos de ADHD publicados por la *Asociación Americana de Psiquiatría* en la cuarta versión del Manual Diagnóstico y Estadístico de Trastornos Mentales (1994), y es la siguiente:

Criterios diagnósticos de la hiperactividad inducida por trastornos de la atención

A. (1) o (2):

(1) Seis (o más) de los siguientes síntomas de desatención han persistido por lo menos durante 6 meses con una intensidad que es desadaptativa e incoherente en relación con el nivel de desarrollo:

Desatención

(a) a menudo no presta atención suficiente a los detalles o incurre en errores por descuido en las tareas escolares, en el trabajo o en otras actividades.

(b) a menudo tiene dificultades para mantener la atención en tareas o en actividades lúdicas.

(c) a menudo parece no escuchar cuando se le habla directamente

(d) a menudo no sigue instrucciones y no finaliza tareas escolares, encargos u obligaciones en el centro de trabajo (*no se debe a un comportamiento negativista o a la incapacidad para comprender instrucciones*).

(e) a menudo tiene dificultades para organizar tareas y actividades

(f) a menudo evita, le disgusta o es renuente en cuanto a dedicarse a tareas que requieren un esfuerzo mental sostenido (como trabajos escolares o domésticos)

(g) a menudo extravía objetos necesarios para tareas o actividades (p. ej., juguetes, ejercicios escolares, lápices, libros o herramientas).

(h) a menudo se distrae fácilmente por estímulos irrelevantes

(i) a menudo es descuidado en las actividades diarias

(2) Seis (o más) de los siguientes síntomas de hiperactividad-impulsividad han persistido por lo menos durante 6 meses con una intensidad que es *desadaptativa* e *incoherente* en relación con el nivel de desarrollo:

Hiperactividad

(a) a menudo mueve en exceso manos y pies o se remueve en su asiento

(b) a menudo abandona su asiento en la clase o en otras situaciones en que se espera que permanezca sentado

(c) a menudo corre o salta excesivamente en situaciones en que es inapropiado hacerlo (en adolescentes o adultos, puede limitarse a sentimientos subjetivos de inquietud)

(d) a menudo tiene dificultades para jugar o dedicarse tranquilamente a actividades de ocio

(e) a menudo "está en marcha" o suele actuar como si "tuviera dentro un motor"

(f) a menudo habla en exceso

Impulsividad

(g) a menudo precipita las respuestas antes de haber sido completadas las preguntas

(h) a menudo tiene dificultades para guardar turno

(i) a menudo interrumpe o se inmiscuye en las actividades de otros (p. ej., se entromete en conversaciones o juegos).

B. Algunos síntomas de hiperactividad-impulsividad o desatención que causaban alteraciones estaban presentes antes de los 7 años de edad

C. Algunas alteraciones provocadas por los síntomas se presentan en dos o más ambientes (p. ej., en la escuela [o en el trabajo] y en la casa)

D. Deben existir pruebas claras de un deterioro clínicamente significativo de la actividad social, académica o laboral.

E. Los síntomas no aparecen exclusivamente en el transcurso de un trastorno generalizado del desarrollo, esquizofrenia u otro trastorno psicótico, y no se explican mejor por la presencia de otro trastorno mental (p. ej., trastorno del estado de ánimo, trastorno de ansiedad, trastorno disociativo o un trastorno de la personalidad).

Se verá que la ADHD es un trastorno constituido por dos componentes, el componente del déficit de atención y el componente de hiperactividad, que son independientes en cierto modo. El tratamiento con tomoxetina es eficaz en pacientes que tienen principalmente uno de estos componentes o que tienen el trastorno combinado.

Si bien la ADHD se considera principalmente un trastorno *de la infancia*, se sabe ahora que hay muchos pacientes con ADHD, hasta el 50 %, que continúan sufriendo el trastorno cuando crecen en su adolescencia hasta la edad adulta. Biederman y asociados han estudiado extensamente el paciente adulto con ADHD y han encontrado numerosos casos. Véase, por ejemplo, Biederman y cols, Am J Psychiatry 150, 1792-1798, 1993. Estos autores encontraron que los casos de ADHD del adulto eran frecuentes entre los padres y familiares adultos de los pacientes infantiles con ADHD. Por lo tanto, parece que la enfermedad no sólo se traslada hasta la edad adulta, sino que es hereditaria.

El artículo de Biederman y cols citado en el párrafo anterior, así como otro artículo de los mismos autores publicado en Am J Psychiatry 148:564-577, 1991, describen estudios de pacientes con ADHD que también tienen uno o más trastornos psiquiátricos de otro tipo. Los autores indican que esta morbilidad psiquiátrica asociada es bastante frecuente entre los pacientes con ADHD y, naturalmente, ocurren el diagnóstico y tratamiento de los mismos. La tomoxetina es eficaz en el tratamiento de la ADHD, incluso aunque la situación del paciente tratado pueda complicarse por la morbilidad asociada con uno o más trastornos adicionales.

La mera enumeración de los criterios diagnósticos citados anteriormente indica la gravedad de la ADHD y el daño que provoca al paciente. Una persona que tenga un caso moderadamente grave de ADHD es, esencialmente, totalmente incapaz de concentrarse y, por tanto, incapaz de hacer un trabajo o un estudio significativo; es una distracción y un fastidio para todos los que le rodean, por la actividad impulsiva y sin utilidad que causa el trastorno; y agota a su familia al tener que limpiar y reparar el daño y los trastornos que provoca. Un paciente de este tipo en edad escolar puede entorpecer sustancialmente la capacidad del profesor para alcanzar los objetivos de la clase, porque el niño con ADHD interrumpirá continuamente en

clase, distraerá a los demás niños y agotará al profesor. Por tanto, es claramente evidente que se necesita un tratamiento mejorado de la ADHD y que la presente invención es, en consecuencia, importante para mucha gente.

El método de la presente invención es eficaz para el tratamiento de pacientes en edad infantil, adolescentes o adultos, y no hay una diferencia significativa en los síntomas o en los detalles de la forma de tratamiento entre los pacientes de las distintas edades. En términos generales, Sin embargo, y para los fines de la presente invención, se considera niño a aquel paciente que se encuentra por debajo de la edad de la pubertad, *adolescente* es aquel paciente que se encuentra entre la edad de la pubertad hasta los 18 años de edad, y un *adulto* es el paciente que tiene 18 años de edad o más.

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REIVINDICACIONES

1. Uso de tomoxetina para la fabricación de un medicamento para el tratamiento de la hiperactividad inducida por trastornos de la atención.

2. Uso de acuerdo con la reivindicación 1 en el que el paciente es un adulto.

3. Uso de acuerdo con la reivindicación 1 en el que el paciente es un adolescente.

4. Uso de acuerdo con la reivindicación 1 en el que el paciente es un niño.

5. Uso de acuerdo con cualquiera de las reivindicaciones 1-4 en el que se trata el tipo predominantemente de falta de la hiperactividad inducida por trastornos de la atención.

6. Uso de acuerdo con cualquiera de las reivindicaciones 1-4 en el que se trata el tipo predominantemente hiperactivo-impulsivo de la hiperactividad inducida por trastornos de la atención.

7. Uso de acuerdo con cualquiera de las reivindicaciones 1-4 en el que se trata el tipo combinado de la hiperactividad inducida por trastornos de la atención.

NOTA INFORMATIVA: Conforme a la reserva del art. 167.2 del Convenio de Patentes Europeo (CPE) y a la Disposición Transitoria del RD 2424/1991, de 10 de octubre, relativo a la aplicación del Convenio de Patente Europea, las patentes europeas que designen a España y solicitadas antes del 7-10-1992, no producirán ningún efecto en España en la medida en que confieran protección a productos químicos y farmacéuticos como tales.

Esta información no prejuzga que la patente esté o no incluida en la mencionada reserva.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCI

DIVISION DE NUEVAS CREACIONES

2020
Bogotá, D.C., Junio 6 de 2007

Abogado
CARLOS R. OLARTE

ASUNTO	Radicación No.	03 077389
	Trámite	002
	Evento	001
	Actuación	430
	Oficio No.	[illegible]7339
	Folios	0

Solicitante: Eli Lilly and Company

Título de la solicitud: Inhibidor de la captación de monoamina

Como resultado del examen de fondo, realizado conforme a lo establecido por el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se notifica el siguiente concepto técnico:

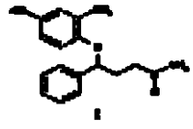
Documentos estudiados

Para el presente estudio se tuvieron en cuenta el capítulo descriptivo comprendido en los folios 38 – 61 y el nuevo capítulo reivindicatorio de los folios 106 – 107 de la solicitud.

Objeto de la invención

El objeto de la presente solicitud de patente de invención consiste en:

Reivindicación 1: Compuesto de fórmula I:



Reivindicación 2: Clorhidrato de R-(-)-N-metil-3-((2-metil-4-hidroxifenil)oxi)-3-fenil-1-aminopropano

Reivindicaciones 3–4: Formulaciones farmacéuticas que los contienen

Reivindicaciones 5–6: Método de Tratamiento

El problema planteado en esta solicitud es la necesidad de una composición para tratar trastornos asociados a la disminución de transmisión de norepinefrina y serotonina tales como depresión, dolor migrañoso, bulimia, alcoholismo, tabaquismo, pánico, ansiedad, pérdida de memoria, demencia senil.

Para resolver este problema técnico la solicitud n estudio proporciona una composición que contiene un compuesto de fórmula I.

El objeto de la invención definido anteriormente se clasificó de acuerdo con la IPC: A6K 31/138, A61P 25/00, C07C 217/48

También se reivindica prioridad de la Solicitud de Patente de los Estados Unidos US 60 273 730 de Marzo 8 de 2001, con respecto a la cual la fecha de presentación de la actual solicitud cumple el plazo máximo permitido.

Título

El título debe mencionar también el tipo de compuestos químicos objeto de la solicitud.

Excepciones a la Patentabilidad

El artículo 20 de la Decisión 486 establece: "*No serán patentables: d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales*"

El Método de tratamiento de las reivindicaciones 5–6 que consiste en administrar un compuesto a un paciente, no es patentable de acuerdo con el Art 20, literal d), de la decisión 486.

Con respecto a los Art. 28 y 30 de la D 486

El artículo 30 de la Decisión 486 establece: "*Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción.*

Las reivindicaciones podrán ser independientes o dependientes. Una reivindicación será independiente cuando defina la materia que se desea proteger sin referencia a otra reivindicación anterior. Una reivindicación será dependiente cuando defina la materia que se desea proteger refiriéndose a una reivindicación anterior. Una reivindicación que se refiera a dos o más reivindicaciones anteriores se considerará una reivindicación dependiente múltiple".

La Reivindicación 1 debe contener el nombre químico del compuesto reivindicado. La Reivindicación 2 debe contener la estructura química del compuesto reivindicado; no tiene razón para ser una reivindicación independiente; por lo cual se solicita hacerla dependiente de la Reivindicación 1.

Determinación del Estado de la Técnica

El artículo 16 de la decisión 486 de la comisión de la Comunidad Andina que establece que "*El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.*

Solo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40".

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es marzo 8 de 2001, se consultaron las bases

de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

No.	Documento	Titulo	Fecha de Publicación
D1	US 4 314 081	Ariloxifenilpropilaminas	Feb 02 de 1982
D2	ES 2 181 846	Uso de Tomoxetina para el tratamiento de la hiperactividad inducida por trastornos de la atención	Jul 17 de 1996

Evaluación de los requisitos de Patentabilidad

El artículo 14 de la Decisión 486 de la Comisión 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 el cumplimiento de 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.

Evaluación del Nivel Inventivo

El artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina establece que *Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.*

El Estado de la Técnica más cercano es de D2, porque divulga R-(-)-N-metil-3-((2-metilfenil)oxi)-3-fenil-1-aminopropano que sirve para el mismo propósito: inhibidor de la recaptación de norepinefrina (ver D2, columna 2, renglones 4-20) para tratamiento de trastornos psiquiátricos, que la invención reivindicada.
La única diferencia con D2 es que el compuesto de esta solicitud tiene un sustituyente hidroxi (-OH) adicional en el grupo fenoxi. Pero este no parece conceder un efecto técnico inesperado porque el compuesto reivindicado, por su actividad como inhibidor de la recaptación de norepinefrina, sigue siendo activo para el tratamiento de trastornos psiquiátricos; por lo cual se considera que es un compuesto alternativo al compuesto previamente conocido.
El Problema Técnico Objetivo fundamental de la invención Reivindicada que es: "cómo modificar el compuesto R-(-)-N-metil-3-((2-metilfenil)oxi)-3-fenil-1-aminopropano de D2 para lograr el compuesto R-(-)-N-metil-3-((2-metil-4-hidroxifenil)oxi)-3-fenil-1-aminopropano, para tratar trastornos asociados a la disminución de transmisión de norepinefrina y serotonina tales como depresión, dolor migrañoso, bulimia, alcoholismo, tabaquismo, pánico, ansiedad, pérdida de memoria, demencia senil"; sería solucionado fácilmente por el Experto en la Materia con base en el compuesto divulgado en D2. Porque el grupo –OH que modifica el compuesto divulgado en D2 se obtiene "in vivo" como producto del metabolismo del compuesto de D2, lo cual pertenece a los conocimientos generales comunes del experto en la Materia. Y además D1; con la mención de que los sustituyentes del grupo fenoxi pueden ser metil (-CH3) y metoxi (-OCH3) (ver D1, columna 1, renglones 45-52) en los compuestos que tienen acción sicotrópica antidepresiva debida a su actividad como inhibidores de la recaptación de norepinefrina y serotonina en las neuronas cerebrales (Ver D1, columna 13, renglones 45-50); sugiere al Experto en la Materia el compuesto reivindicado que tiene como sustituyentes del grupo fenoxi: metil (-CH3) e

hidroxi (-OH); de manera que este lo lograría fácil y obviamente sin necesidad de emplear Habilidad Inventiva.

Por lo cual el compuesto de la Reivindicación 1 y su sal clorhidrato de la Reivindicación 2 no tienen Nivel Inventivo.

Las Reivindicaciones 3–4 que se refieren a Formulaciones farmacéuticas, no tienen Nivel Inventivo porque el compuesto que las Caracteriza no es Inventivo.

Conclusión

En conclusión, los requisitos de patentabilidad de la presente solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US 4 314 081	1 – 4	Nivel Inventivo
D2	ES 2 181 845	1 – 4	Nivel inventivo

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.

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

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

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

15 JUL 2008.

CONCEPTO TÉCNICO No. 774	EXAMINADOR TÉCNICO Código 202007

ITV

EXAMEN TÉCNICO DE FONDO			
Nº Solicitud	03 077389	Fecha de presentación	05-09-2003
Nº Prioridad	US 60 273 730	Fecha de Prioridad	06-03-2001

Palabras clave	3-ariloxi-3-sustituidos- 1-aminopropanos

CLASIFICACIONES INTERNACIONALES DE BÚSQUEDA
A6K 31/138, A61P 25/00, C07C 217/48

DOCUMENTOS CORRESPONDIENTES EN OTROS PAÍSES	
Patente Original	WO02070457 (A1)
Otros	WO02070457 (A1) EP1379492 (A1) EP1379492 (A1) OA12494 (A) LU91038 (A1) GB2389851 (A) ES2201942 (A1) EP1379492 (A0) EE200300419 (A) CN1494526 (A) CH695982 (A5) CA2440161 (A1) SE526596 (C2) SE0302361 (L) LV13119 (B) LT5143 (B) CN1229331C (C)

BASES DE DATOS CONSULTADAS			
OEPM	Epoline	Espacenet	Oficina US

INFORMES DE EXÁMENES EN OTRAS OFICINAS		
Documento	Fecha	Rels. Afectadas
WO 02 070457	Sept 12 de 2002	1 – 6

ANTERIORIDADES ENCONTRADAS		
Documento de Patentes	Rels. Afectadas	Relevancia
US 4 314 081	1 – 4	Nivel Inventivo
ES 2 161 845	1 – 4	Nivel Inventivo
LITERATURA NO PATENTES		
Documento no Patentes	Rels. Afectadas	Relevancia

Observaciones

Fecha Informe	Junio 7 de 2007