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SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

REF: **EXPEDIENTE 04-016-758**

TÍTULO SOLICITADO: **"COMPOSICIÓN CRISTALINA QUE CONTIENE ESCITALOPRAM"**

PUBLICACIÓN: **Gaceta 556 de 30-09-2005, número de publicación 540, Página 454.**

PRIORIDAD: **DK PA200101164 (31/07/2001)**

SOLICITANTE: **H. LUNDBECK A/S**

APODERADO: **EMILIO FERRERO**

TRÁMITE: **SUSTENTACIÓN DE OPOSICIÓN**

JOSÉ LUIS REYES VILLAMIZAR, identificado como aparece al pie de mi firma, reconocido apoderado del opositor en el trámite de la referencia, estando dentro de los términos de la prórroga solicitada, por medio del presente escrito me permito ratificar y sustentar los argumentos del escrito de oposición, también radicado dentro del plazo de ley ante esa entidad.

I. RATIFICACIÓN

Reitero a su Despacho la solicitud de negar el beneficio patentario para la totalidad de las reivindicaciones contenidas en el expediente en referencia, por los argumentos que fueron expuestos en el escrito de oposición del 28 de diciembre de 2005. En efecto, es evidente que en el estado del arte ya se encontraban descritas composiciones cristalinas de Escitalopram, la sal de oxalato de Escitalopram, las partículas cristalinas de Oxalato de Escitalopram y la posibilidad de obtener formas farmacéuticas de mismo a través de compresión directa.

- En cuanto a la **SAL DE OXALATO DE ESCITALOPRAM** tenemos que: la patente americana US 4,650,884 en **17-03-1987**, en especial la reivindicación 3 muestra que no sólo se revela el compuesto 1-(3-dimethylaminopropyl) -1- (4´-fluorophenyl)-1, 3- dihydroisobenzofuran -5-Carbonitrile (ESCITALOPRAM), **sino sus sales ácidas de adición farmacéuticamente aceptables.** La generalidad de esta reivindicación permite concluir que la sal que ahora se pretende, en tanto es una sal ácida de adición farmacéuticamente aceptable- ya había sido revelada implícitamente en el documento reseñado, razón por la cual su conocimiento afectaría la **novedad** de la solicitud en curso.

  La patente US 4,943,590 (**24-07-1990**), por su parte, **revela sales farmacéuticamente aceptables de los enantiómeros de Citalopram** formadas con ácidos orgánicos o inorgánicos no tóxicos. Ejemplos de tales sales orgánicas son las formadas con ácido maléico, fumárico, benzóico, ascórbico, pamóico, succínico, **oxálico**, salicílico, propiónico, tartárico, cítrico, aspártico, entre otros.

  Como vemos, la posibilidad de formar la sal de Oxalato de Citalopram mediante la reacción de Citalopram con el ácido Oxálico está claramente expuesta en este documento, razón por la cual, la sal revelada en la solicitud colombiana en curso **carece por completo de Novedad**.

- En cuanto a **LAS PARTÍCULAS CRISTALINAS DE OXALATO DE ESCITALOPRAM** me permito demostrar que tales **partículas cristalinas** también pertenecen al estado del arte puesto que la anterioridad US 4,943,590 en el ejemplo 2 en donde se hace la resolución de la mezcla racémica de Citalopram, describe que:

  - La sal del ácido oxálico del isómero (+)-1-(3-(dimethylaminopropyl)-1-(4´-fluorophenyl) -1,3-dihydrobenzofuran-5-carbonitrile **CRISTALIZA** desde acetona, obteniéndose una sal con MP: 147°-148°C, [α]D= +12.31° (c=1, CH_3OH);
  - La sal del ácido oxálico del isómero (-)-1-(3-(dimethylaminopropyl)-1-(4´-fluorophenyl) -1,3-dihydrobenzofuran-5-carbonitrile **CRISTALIZA** desde acetona, obteniéndose una sal con MP: 147°-148°C, [α]D= +12.08° (c=1, CH_3OH).

- En cuanto a las partículas cristalinas de Escitalopram **PARA COMPRESIÓN DIRECTA,** tenemos que la patente US 4,943,590 tantas veces mencionada si bien es cierto no se refiere de manera textual a la forma de obtener tabletas de este principio activo mediante compresión directa, si se refiere a que es posible la preparación de tabletas donde el principio activo es principalmente mezclado con adyuvantes ordinarios de tabletas tales como almidón de maíz, almidón de papa, talco, Estearato de magnesio, gelatina, lactosa, gomas, entre otros. Como vemos, desde 1990 era posible la fabricación de tabletas donde el principio activo corresponde a (+) Citalopram en la forma de una sal ácida de adición (entre las que puede encontrarse Oxalato de Citalopram), al parecer viables y aptas para el consumo humano, como quiera que entre los objetivos de la anterioridad mencionada está en obtener un producto final sea cual fuere el proceso para llegar a el, que satisfaga al humano luego de la administración del mismo.

  Ahora bien, si estuviéramos frente a la supuesta novedad o nivel inventivo de someter a Citalopram o a una de sus sales a compresión directa para obtener una formulación adecuada, me permito citar que la publicación británica GB 2 357 762 A (04-07-2001) revela que: *"una formulación farmacéutica de la base libre de Citalopram o el Bromhidrato o Clorhidrato de dicha base, preferiblemente es para administración oral y puede ser preparada por compresión directa de Citalopram en mezcla con adyuvantes o diluentes convencionales"*, de tal manera que en el estado del arte ya se sugería que formulaciones de Citalopram pudieran ser preparadas por compresión directa por lo que puede pensarse que para esta fecha ya se había encontrado que "*este proceso es mucho más simple y económico que aquellos procesos que involucran granulación*", (tal como lo afirma el solicitante en la parte descriptiva de la solicitud colombiana), por lo que el problema técnico a resolver ya se había resuelto en julio 4 de 2001.

- En cuanto a los **TAMAÑOS DE PARTÍCULAS** podemos decir que carecen de nivel inventivo, ya que si en gracia de discusión no estuviese descrito de manera textual en el arte anterior el tamaño de partícula revelado en la solicitud colombiana en trámite para la sustancia Oxalato de Escitalopram, me permito llamar la atención del Despacho a la muy conocida posibilidad de modificar la solubilidad, disolución y biodisponibilidad de principios activos manipulando el tamaño de partícula de los mismos (o su área o su distribución de tamaño), lo

que se ha convertido en una rutina requerida en lineamientos de la FDA cuando se está estudiando una nueva entidad química y que es crucial en el desarrollo galénico de formulaciones farmacéuticas.

- En cuanto al MÉTODO DE MANUFACTURA DE LAS PARTÍCULAS CRISTALINAS DE OXALATO DE ESCITALOPRAM, que comprende un enfriamiento gradual de la solución que contiene dicho principio activo en un sistema solvente adecuado (alcohol y opcionalmente agua, o preferiblemente etanol), carece de nivel inventivo puesto que, es ampliamente conocido que para efectuar la cristalización de un sólido hay que partir de una Solución Sobre-Saturada, la cual se puede obtener por enfriamiento de la solución o por la eliminación de una parte del Disolvente (por ejemplo: por evaporación) a fin de aumentar la concentración del soluto; la rapidez del enfriamiento juega un papel importante puesto que ella definirá el tamaño de los cristales resultantes, un enfriamiento rápido producirá cristales pequeños, mientras que un enfriamiento lento producirá cristales grandes; es por esto que el método de la solicitud colombiana hace un **enfriamiento gradual** (al menos una hora, más preferiblemente entre 4 y 24 horas y más preferiblemente 12 horas) de la solución que contiene Oxalato de Escitalopram donde se espera que se genere un cristal más grande que pueda tener mejores propiedades de flujo.

II. COMPLEMENTO DE INFORMACIÓN

Como adición a lo expuesto en el punto precedente y en el escrito inicial de oposición, ruego al Despacho se sirva tener en cuenta de igual manera lo consignado a continuación:

A. Según FDA, entre las patentes relacionadas con la aprobación en agosto 14 de 2002 del producto Lexapro® Escitalopram Oxalato (en tabletas de 5, 10 y 20mg), se encuentran las siguientes:

N°	Patent	Patent Expiration	Prioridad
1	RE34712	JUN 08,2009	GB 8814057 de 14-06-1988
2	6916941	JUL 25,2022	DK PA 2001 01164 de julio 31 de 2001

La patente US RE 34,712 es equivalente a la US 4,943,590, mencionada tantas veces en el numeral anterior y en el escrito de oposición del 28 de

diciembre de 2005, cuyo título "Pharmaceutically useful (+) 1,(3-dimethylaminopropyl) -1-(4'-fluorophenyl)-1,3- dihydroisobenzofuran—5-carbonitrile and non-toxic acid addition salts thereof" y publicada el 30 de agosto de 1994, revela los dos enantiómeros del fármaco antidepresivo de fórmula I (Citalopram), sus sales farmacéuticamente aceptables, métodos para resolver los intermediarios y su conversión estereoselectiva a sus enantiómeros correspondientes, enantiómero (+) de Citalopram, la sal del ácido pamóico y (-) de Citalopram. También se revelan composiciones farmacéuticas que comprenden un diluente o un adyuvante, el principio activo en cantidades entre 0.1 y 100mg por unidad de dosis, y el método de tratamiento para aliviar la depresión.

En la parte descriptiva se mencionan algunos ejemplos de formulaciones farmacéuticas como tabletas, jarabes, soluciones para inyección entre las que se encuentran:

(1) Tablets containing 5 milligrams of (+)-citalopram calculated as the free base:	
Compound 20	5 mg
Lactose	15 mg
Potato starch	27 mg
Saccharose	58 mg
Sorbitol	2 mg
Talcum	5 mg
Gelatine	2 mg
Povidone	1 mg
Magnesium stearate	0.5 mg
(2) Tablets containing 50 milligrams of (+)-citalopram calculated as the free base:	
(+)-citalopram	50 mg
Lactose	16 mg
Potato starch	45 mg
Saccharose	106 mg
Sorbitol	6 mg
Talcum	9 mg
Gelatine	4 mg
Povidone	3 mg
Magnesium stearate	0.6 mg
(3) Syrup containing per milliliter:	
(+)-citalopram	10 mg
Sorbitol	500 mg
Tragacanth	7 mg
Glycerol	50 mg
Methyl-paraben	1 mg
Propyl-paraben	0.1 mg
Ethanol	0.005 ml
Water ad	1 ml
(4) Solution for injection containing per milliliter:	
(+)-citalopram	50 mg
Acetic acid	17.9 mg
Sterile water ad	1 ml
(5) Solution for injection containing per milliliter:	
(+)-citalopram	10 mg
Sorbitol	42.9 mg
Acetic acid	0.63 mg
Sodium hydroxide	22 mg
Sterile water ad	1 ml

Es importante resaltar en este punto que la aprobación según la FDA para el producto Lexapro® cuyo principio activo es Oxalato de Escitalopram se basa en dos patentes, la US RE 34,712 que, como se mencionó antes es equivalente a la US 4,943,590 y la US 6916941 equivalente a la WO 03/11278 y a su vez equivalente a la solicitud colombiana en trámite.

Para el caso que nos ocupa me referiré a la US RE 34,712, ya que se basa en la generalidad de "LAS SALES ÁCIDAS DE ADICIÓN FARMACÉUTICAMENTE ACEPTABLES" formada con ácidos orgánicos o inorgánicos no tóxicos, en donde se ejemplifica que tales sales orgánicas son formadas con ácido maléico, fumárico, benzóico, ascórbico, pamóico, succínico, **oxálico**, salicílico, propiónico, tartárico, cítrico, aspártico, entre otros, lo que permite concluir una vez más que la sal que ahora se pretende, en tanto es una sal ácida de adición farmacéuticamente aceptable- ya había sido revelada por lo menos en la parte descriptiva del documento reseñado, razón por la cual su conocimiento afectaría la **novedad** de la solicitud en curso; además, es tenida en cuenta por la FDA como documento base para la aprobación ante esa Entidad del principio activo **OXALATO DE ESCITALOPRAM** y a su vez de las composiciones en forma de tabletas del mismo.

B. Por su parte la solicitud internacional WO02/087566 titulada "THE USE OF ENANTIOMERIC PURE ESCITALOPRAM" revela el uso de Escitalopram que comprende menos del 3% p/p de R-citalopram en forma de **sal de oxalato cristalina**, para la preparación de una composición farmacéutica oral en forma de comprimido con una dosis unitaria que contiene 2.5mg a 20mg de Escitalopram, preferiblemente 5.0mg y que es útil en el tratamiento de pacientes con trastornos de depresión mayor. Aunque este documento fue publicado el 7 de noviembre de 2002, es decir, con posterioridad a la fecha de prioridad de la solicitud que nos ocupa, lo cierto es que el mismo fue presentado en mayo 1 de 2001, es decir, antes de la fecha de prioridad de la misma solicitud.

Como se observa, este documento ya se refería a la existencia de la SAL DE OXALATO DE ESCITALOPRAM CRISTALINA, composiciones y uso tal como la pretende reivindicar la solicitud colombiana CO 04-016-758; en consecuencia, el capítulo reivindicatorio y más específicamente las

reivindicaciones 1 y 2 de la misma, carece de novedad en virtud de la presencia de Escitalopram en forma cristalina y de la sal de Oxalato y de nivel inventivo ya que se conoce tanto la Sal cristalina de Oxalato de Escitalopram como que la determinación de los tamaños de partícula se ha convertido en una rutina requerida en lineamientos de la FDA cuando se está estudiando una nueva entidad química.

Por lo expuesto anteriormente reitero la petición de declarar fundada la presente oposición, de negar en consecuencia el privilegio solicitado, y de ordenar el archivo del expediente respectivo.

III. PRUEBAS

Ruego que se tengan como tales, sin perjuicio de que el Despacho considere oficiosamente, en particular de las allegadas por el suscrito a los expedientes mencionados en este escrito, las siguientes:

1. Patente Americana US RE 34,712 publicada el 30 de agosto de 1994.
2. Portada y páginas 8 y 9.de la Publicación Internacional WO 02/087566A1.

Señor Superintendente,

JOSÉ LUIS REYES VILLAMIZAR
C.C. 79.152.473 de Usaquén
T.P.A. 44.655 de C.S.J.

US00RE34712E

United States Patent [19]

Boegesoe et al.

[11] E Patent Number: Re. 34,712

[45] Reissued Date of Patent: Aug. 30, 1994

[54] **PHARMACEUTICALLY USEFUL (+)-1-(3-DIMETHYLAMINOPROPYL)-1-(4'-FLUOROPHENYL)-1,3-DIHYDROISO BENZOFURAN-5-CARBONITRILE AND NON-TOXIC ACID ADDITION SALTS THEREOF**

[75] Inventors: **Klaus P. Boegesoe, Hørnholm; Jens K. Perregaard, J gerspris, both of Denmark**

[73] Assignee: **H. Lundbeck A/S, Copenhagen-Valby, Denmark**

[21] Appl. No.: **122,809**

[22] Filed: **Sep. 14, 1993**

Related U.S. Patent Documents

Reissue of:

[64] Patent No.: 4,943,590
Issued: Jul. 24, 1990
Appl. No.: 363,589
Filed: Jun. 8, 1989

[30] **Foreign Application Priority Data**

Jun. 14, 1988 [GB] United Kingdom 8814057

[51] Int. Cl.[5] A61K 31/34; C07D 307/87; C07C 255/59

[52] U.S. Cl. 514/469; 549/467; 558/422

[58] Field of Search 549/467; 558/422; 514/469

[56] **References Cited**

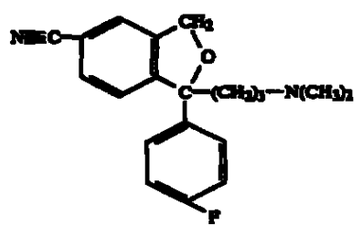
U.S. PATENT DOCUMENTS

4,136,193 1/1979 Boegesoe et al. 549/467
4,650,884 3/1987 Boegesoe 549/467

Primary Examiner—Bernard Dentz
Attorney, Agent, or Firm—Gordon W. Hueschen

[57] **ABSTRACT**

The two enantiomers of the anti-depressant drug of the formula I



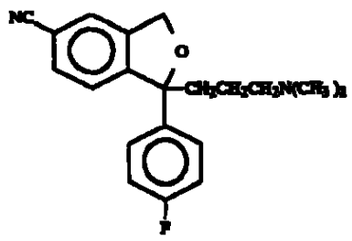
are disclosed. Methods for resolving intermediates and their [steroselective] *stereoselective* conversion to a corresponding [enatiomer] *enantiomer* of I are also disclosed.

12 Claims, No Drawings

PHARMACEUTICALLY USEFUL (+)-1-(3-DIMETHYLAMINOPROPYL)-1-(4'-FLUOROPHENYL)-1,3-DIHYDROISO BENZOFURAN-5-CARBONITRILE AND NON-TOXIC ACID ADDITION SALTS THEREOF

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

The present invention relates to the two novel enantiomers of the antidepressant drug 1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-[dihydroisobenzofuran] *dihydroisobenzofuran*-5-carbonitrile (citalopram) of the following formula I:



I

and to the use of these enantiomers as antidepressant compounds as well as the possible use as geriatrics or in the cure of obesity or alcoholism.

This invention also includes pharmaceutically acceptable salts of the enantiomers of compound I formed with non-toxic organic or inorganic acids. Such salts are easily prepared by methods known to the art. The base is reacted with either the calculated amount of organic or inorganic acid in an aqueous miscible solvent, such as acetone or ethanol, with isolation of the salt by concentration and cooling or an excess of the acid in aqueous immiscible solvent, such as ethyl ether, ethyl acetate or [dicloromethane] *dichloromethane*, with the desired salt separating directly. Exemplary of such organic]salt[*salts* are those with maleic, fumaric, benzoic, ascorbic, pamoic, succinic, oxalic, salicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-amino-benzoic, glutamic, benzene sulfonic and theophylline acetic acid, as well as the 8-halotheophyllines, for example 8-bromotheophylline.

Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids. Of course, these salts may also be prepared by the conventional method of double decomposition of appropriate salts, which is well-known to the art.

Furthermore it was found that non-hygroscopic acid addition salts might be obtained by [conventional] *conventional* freeze drying techniques from water solutions of appropriate salts of the above mentioned kinds.

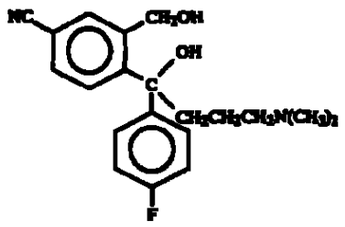
The invention is also concerned with a method to resolve the intermediate racemate and to produce the individual isomers of I therefrom.

BACKGROUND OF THE INVENTION

Citalopram, which has been disclosed in e.g. U.S. Pat. No. 4,136,193, has proven to be an efficient antidepressant compound in man (Ref.: A. Gravem et. al., Acta pysychiat. Scan., No. 75, p. 478–486 (1987). All work in the development of this compound has been made with the racemate. Citalopram has been shown pharmacologically to be a very selective inhibitor of 5-HT reuptake. Previous attempts to crystallize diastereomeric salts of citalopram enantiomers have failed.

SUMMARY OF THE INVENTION

Surprisingly, it has now proven possible to resolve the intermediate [4-(4-dimethylamino)-1-(4'-fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl)benzonitrile] *4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxy-1-butyl]-3-(hydroxymethyl)-benzonitrile*, II, into its enantiomers and finally in a stereoselective way to convert these enantiomers to the corresponding citalopram enantiomers. Likewise, monoesters of *II* formed by optically active carboxylic acids could be separated into the corresponding diastereomers and subsequently converted directly into citalopram enantiomers in a stereoselective ringclosure reaction. The intermediate diol, II, has been disclosed in e.g. U.S. Pat. No. 4,650,884 as a racemic mixture.



II

The enantiomers of the intermediate of formula II as well as monoesters fall likewise within the scope of the present invention.

Furthermore, it was shown to our surprise that almost the entire 5-HT uptake inhibition resided in the (+)-citalopram enantiomer.

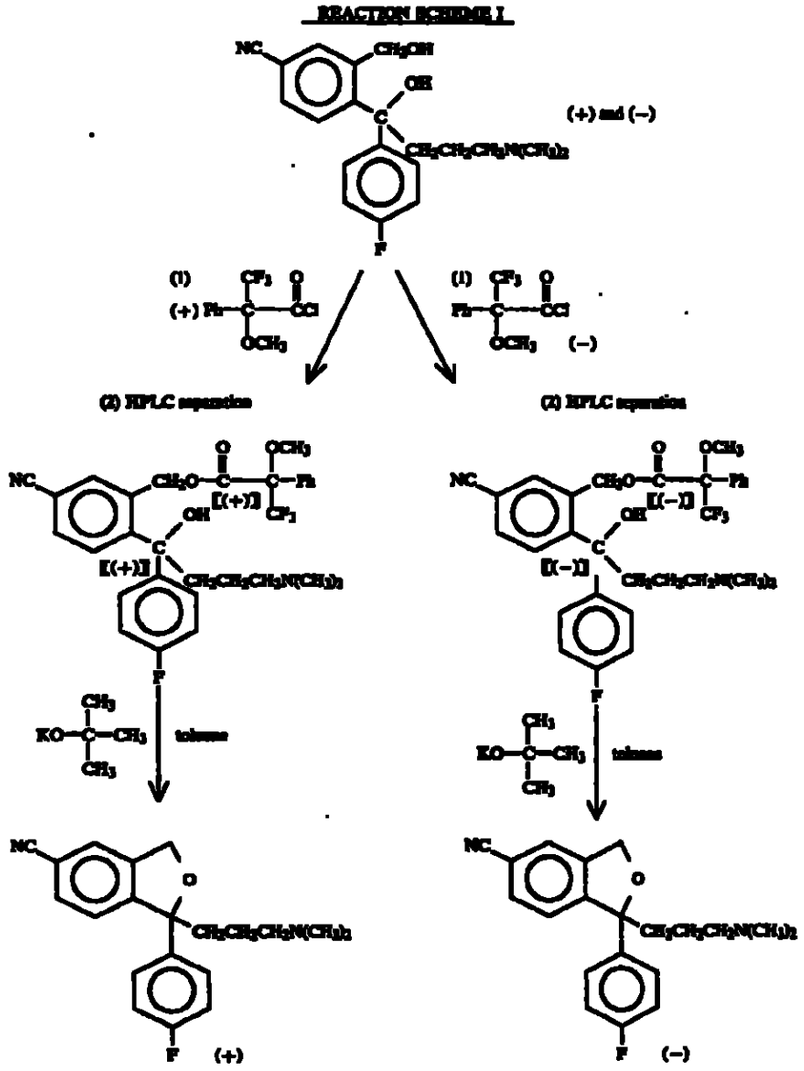
The present invention also includes a new method of synthesizing I from the diol compound II by esterification of the primary alcohol group into a labile ester, which in the presence of a base undergoes spontaneous ringclosure to citalopram or, if enantiomerically pure II is esterified, the corresponding citalopram enantiomer is produced with fully conservation of stereoconfiguration.

According to the invention, II is reacted with:

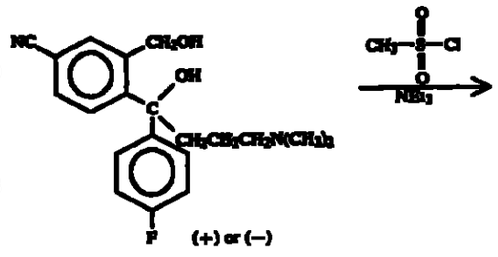
(a) an enantiomerically pure acid derivative as an acid chloride, anhydride or [llbile] *labile* ester as e.g. [exemplified] *exemplified* in reaction scheme 1 by (+)- or (−) -α-methoxy-α-trifluoromethylphenylacetyl chloride. The reaction is preferably performed in an inert organic solvent as e.g. toluene, dichloromethane or tetrahydrofuran. A base (triethylamine, N,N-dimethylaniline, pyridin or the like) is added to neutralise liberated HCl. The diastereoisomers are subsequently separated by HPLC or fractional crystallisation. The thus purified [diastereoisomers] *diastereoisomers* are [finnaly] *finally* separately treated with strong base (e.g. alkoxide) in an inert organic solvent as e.g. toluene, tetrahydrofuran, or dimethoxyethane yielding the pure citalopram enantiomers respectively. The ringclosure reaction is preferably performed at

relatively low temperatures (−20° C.) to room temperature).

REACTION SCHEME I



REACTION SCHEME II

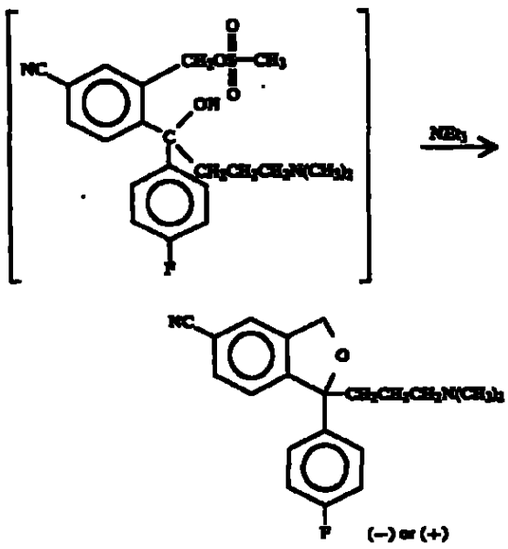


(b) the enantiomers of an optically active acid successively affording the pure diastereomeric salts. Optically antipodes of tartaric acid, di-benzoyltartaric acid, di-(p-[toloyl] *toluoyl*)tartaric acid, binaphthylphosphoric acid, 10-camphorsulphonic acid and the like are conveniently used.

(c) Stereoselective ringclosure of the pure enantiomers of II prepared as in (b) is performed via a labile ester as e.g. methanesulfonyl, p-toluenesulfonyl, 10-camphorsulfonyl, trifluoroacetyl or trifluoromethanesulfonyl with simultaneous addition of a base (triethylamine, dimethylaniline or pyridin) in an inert organic solvent at 0° C. The ringclosure reaction is [exemplified] *exemplified* in reaction scheme II:

-continued

REACTION SCHEME II



EXAMPLE 1

Resolution by method (a)

To 11 g of (+)-α-methoxy-α-trifluoromethylacetic acid dissolved in 25 ml of chloroform were added 50 ml of thionylchloride and a few drops of dimethylformamide. The reaction mixture was refluxed for 2 hours. Excess of thionylchloride was evaporated with toluene leaving the (+)-α-methoxy-α-trifluoromethylacetyl chloride as a liquid. This liquid diluted with 50 ml of dichloromethane was added dropwise to an ice cooled solution of 17 gr of [4-(4-dimethylamino-1-(4'-fluorophenyl)-1-hydroxybutyl)-3-(hydroxymethyl)-benzonitrile] *4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxy-1-butyl]-3-(hydroxymethyl)-benzonitrile*, II, and 8 ml of triethylamine in 150 ml of dichloromethane. The reaction mixture was further stirred for another hour at room temperature, subsequently washed with brine, dried ($MgSO_4$) and the solvent evaporated below 30° C. in vacuo affording 29 gr of the ester as a diastereomeric mixture. By repeated HPLC purification (eluted with ethyl acetate/tetrahydrofuran 9:1 containing 4% of triethylamine) and by collecting only the 5–10% initial substance in the main peak, 1.1 gr of enantiomerically pure compound was isolated.

The substance thus isolated was dissolved in dry toluene (50 ml) and added to a suspension of 0.3 gr of potassium t-butoxide in 20 ml of toluene at 0° C. The toluene solution was washed with water, dried ($MgSO_4$) and the solvent evaporated yielding 0.6 gr of (+)-1-(dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile as an oil. $[\alpha]_D$=+11.81° (c=1, CH_3OH) (determined with a substance containing 10% w/w of methanol). The optical purity was determined by ^1H NMR spectroscopy ($CDCL_3$ as solvent) (Bruker AC-250 MHz instrument) by addition of a 10:1 w/w surplus of the chiral reagent (−)-2,2,2-trifluoro-1-(9-anthryl)ethanol. Optical purity: 99.6%.

In a totally analogous way the (−)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile was synthesized. $[\alpha]_D$=−12.34° (c=1, CH_3OH) (determined with a substance containing 10% w/w of methanol). Optical purity: 99.0%.

EXAMPLE 2

Resolution by methods (b) and (c)

To a solution of 85 gr of [4-(4-dimethylamino)-1-4'-fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl)-benzonitrile] *4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxy-1-butyl]-3-(hydroxymethyl)-benzonitrile*, hydrobromide in 500 ml of water were added 200 ml of ice cooled 2M NaOH solution and 500 ml of ether. The mixture was stirred for ½ hour, the ether phase separated, dried ($MgSO_4$) and the ether evaporated. The remaining oil was dissolved in 400 ml of 2-propenol at 40° C., and 40 gr of (+)-di-p-[toloyltartaric] *toluoyltartaric* acid (as hydrate) were added under vigorous stirring. After a short while crystallization began. After 3 hours of stirring the precipitated salt was filtered off and dried yielding 29.2 gr (55.1%) of [(−)-4-(4-dimethylamino)-1-(4'fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl)benzonitrile] (−)-*4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxy-1-butyl]-3-(hydroxymethyl)benzonitrile*, hemi (+)-di-p-[toloyltartaric] *toluoyltartaric* acid salt. MP: 134°–135° C., $[\alpha]_D$=+10.0° (c=1, CH_3OH). The filtrate is used below.

To an ice cooled solution of 14 gr of the (−)-isomer from above as a base in 300 ml of dry toluene were added 16 ml of triethylamine, and 3.6 ml of methanesulfonyl chloride in 20 ml of dry toluene were added dropwise during 10 minutes. The reaction mixture was further stirred for ½ hour, washed with brine, dried ($MgSO_4$) and the solvent evaporated. The title compound was purified by column chromatography affording 8 g of (+)-1-(3-dimethylaminopropyl)-1-(4'-[fluorophenyl] *fluorophenyl*-1,3-dihydroisobenzofuran-5-carbonitrile. $[\alpha]_D$=+12.33° (c=1, CH_3OH). The oxalic acid salt of the (+)-isomer crystallized from acetone. MP: 147°–148° C., $[\alpha]_D$=+12.31° (c=1, CH_3OH).

The pamoic acid salt of the (+)-isomer was prepared in the following manner: To 1.8 g of the base of the (+)-isomer was added 2 g of pamoic acid in 25 ml of MeOH. The mixture was refluxed for an hour and subsequently cooled to room temperature. The precipitate was filtered off yielding 3.0 g of the pamoic acid salt. MP: 264°–266° C., $[\alpha]_D$=+13.88° C. (c=1, dimethylformamide).

A 2:1 addition compound of the (+)-isomer with L(+)-tartaric acid was prepared in the following manner: 4 g of the (+)-isomer as base were dissolved in 100 ml of diethyl ether and extracted into 100 ml of water containing 0.8 g of L(+)-tartaric acid by stirring. The organic phase was separated and discarded. The water-phase was freeze-dried in vacuo (<0.1 mm Hg) for 18 hours leaving 3.8 g of a white powder of the title compound. This addition compound was stable and not hygroscopic.

In a corresponding manner as above via the [(+)-4-(4-dimethylamino)-1-(4'-fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl)benzonitrile] (+)-*4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxy-1-butyl]-3-(hydroxymethyl)-benzonitrile*, hemi (−)-di-(p-toloyl)-tartaric acid salt ($[\alpha]_D$=−8.9° (c=1, CH_3OH)) which was converted to the corresponding diol base ($[\alpha]_D$=+61.1° (c=1, CH_3OH)) and finally ringclosure

reaction yielded 10 gr of (−)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile. $[\alpha]_D = -12.1°$ (c=1, CH_3OH).

The oxalic acid salt of the (−)-isomer crystallized from acetone, MP: 147°–148° C., $[\alpha]_D = -12.08°$ (c=1, CH_3OH).

EXAMPLE 3

Preparation of citalopram by method (c)

To an ice cooled solution of 28 gr of racemic diol base, II, in 500 ml of dichloromethane were added 32 ml of triethylamine, and 7.5 ml of methanesulfonyl chloride in 30 ml of dichloromethane were added dropwise during a half hour. The reaction mixture was washed with 0.1M NaOH solution twice, the organic phase separated, dried ($MgSO_4$) and the solvent evaporated, leaving 21.5 gr of the title (±)-citalopram as a crystalline base. The thus obtained material was dissolved in a mixture of 2-propanol and methanol (2:1) and an equivalent amount of gaseous HBr was introduced. The mixture was left overnight and the precipitated hydrobromide was filtered off. Yield: 26 gr with MP 184°–186° C.

The enantiomers from Example 1 were tested for their ability to block 5-HT reuptake in standard and reliable test method. Results are shown in Table I in comparison with the racemic mixture of citalopram.

5-HTP-POTENTIATION

The test evaluates the ability of the substance to potentiate the effect of 5-HTP, which results in development of 5-HT syndrome (Christensen, Fjalland, Pedersen, Dunnekloid-Samsoe and Svendsen; European J. Pharmacol. 41, 153–162, 1977).

Procedure

Each treatment group consists of 3 mice, and two groups are treated with the highest test dose. A control group only treated with 5-HTP is included and a group treated with citalopram 10 mg/kg and 5-HTP is used as reference for full 5-HT syndrome.

The Route of Administration

30 minutes after the administration of the test substance, the other groups are given 5-HTP (100 mg/kg) i.v. (injection time 5–10 sec.). After this 5-HTP dose normal, untreated mice remain unaffected, but if the animals have been pretreated with a substance, which inhibits the uptake of 5-HT or a 5-HT agonist, a 5-HTP syndrome will occur. The symptoms are the same as previously described: (1) excitation, (2) tremor, and (3) abduction of the hind limbs. The animals are observed for 15 minutes and each animal is given one point for each symptom present. Again the result is stated in fractions: 0/9, 1/9, . . . 9/9, where 0, 1, . . . , 9 are the number of points per group after the dose in question. The ED_{50} value is calculated by log-probit analysis.

INHIBITION OF ^{3}H-SEROTONIN UPTAKE IN RAT BRAIN SYNAPTOSOMES

By this method the inhibition by drugs of the uptake of [$_3$H-serotonin] *^{3}H-serotonin* (^{3}H-5-HT)(10 nM) in rat brain synaptosomes is determined in vitro. Method and results in Hyttel, Psychopharmacology 1978, 60, 13–18; Hyttel, Prog. Neuro-Psychopharmacol. & Biol. [Psychiat.] *Psychiat.* 1982, 6,277–295; Hyttel & Larsen, Acta pharmacol. tox. 1985, 56, suppl. 1, 146–153. [Procedure p]

Procedure

Male Wistar (Mol: Wist) rats (125–250 g) are sacrified by decapitation and [exsanguinated] *exsanguinated*. Brain tissue (minus cerebellum) is gently homogenized (glass teflon homogeniser) in 40 vol (w/v) of ice cold 0.32M of sucrose containing 1 mM of nialamide. The P_2 fraction (synaptosomal fraction) is obtained by centrifugation (600 g. 10 min and 25000 g. 55 min, 4° C.) and suspended in 800 volumes of a modified Krebs-Ringer-phosphate buffer, pH 7.4.

To 4000 µl of the synaptosomal suspension (5 mg original tissue) on ice are added 100 µl test substance in water. After preincubation at 37° C. for 5 min, 100 µl of ^{3}H-1-NA (final [concentration] *concentration* 10 nM) are added and the samples are incubated for 10 min at 37° C. The incubation is terminated by filtering the samples under vacuum through [Whatman] *Whatman* GF/F filters with a wash of 5 ml buffer containing 10 µM of unlabeled 5-HT. The filters are placed in counting vials and 4 ml of appropriate scintillation fluid (e.g. Picofluor ®15) are added. After shaking for 1 h and storage 2 h in the dark the content of radioactivity is determined by liquid scintillation counting. Uptake is obtained by subtracting the nonspecific binding and passive transport measured in the presence of 10 µM citalopram (Lu 10-171-B).

For determination of the inhibition of uptake five concentrations of drugs covering 3 decades are used. The measured cpm are plotted against drug concentration on semilogarithmic paper, and the best fitting s-shaped curve is drawn. The IC_{50}-value is determined as the concentration, at which the uptake is 50% of the total uptake in control samples minus the nonspecific binding and uptake in the presence of 10 µM of citalopram.

TABLE 1

PHARMACOLOGICAL TEST RESULTS

Compound	5-HTP pot. ED_{50} µmol/kg	5-HT uptake inhibition IC_{50} (nM)
(+)-citalopram	2.0	1.1
(−)-citalopram	120	150
(±)-citalopram	3.0	1.8

(+)-1-(3-Dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile ((+)-citalopram) and the non-toxic acid addition salts thereof may be administered to animals such as dogs, cats, horses, sheeps or the like, including human beings, both orally and parenterally, and may be used for example in the form of tablets, [capsules] *capsules*, powders, syrups or in the form of the usual [steriel] *sterile* solutions for injection. [Results upon administration to human being have been very gratifying.]

Most conveniently the compounds of Formula I are administered orally in unit dosage form such as tablets or capsules, each dosage unit containing the free amine or a non-toxic acid addition salt of one of the said compounds in [a] *an* amount of from about 0.10 to about 100 mg, most preferably, however, from about b 5 to 50 mg, calculated as the free amine, the total daily dosage usually ranging from about 1.0 to about 500 mg. The exact individual dosages as well as daily dosages in a particular case will, of course, be determined according to established medical principles under the direction of a physician.

When preparing tablets, the [active] *active* ingredient is for the most part mixed with ordinary tablet adjuvants such as corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, or the like.

Typical examples of formulas for [composition] *compositions* containing (+)-citalopram in the form of an acid addition salt as the active ingredient, are as follows:

(1) Tablets containing 5 milligrams of (+)-citalopram calculated in the free base:	
Compound 20	5 mg
Lactose	18 mg
Potato starch	27 mg
Saccharose	58 mg
Sorbitol	3 mg
Talcum	3 mg
Gelatine	3 mg
Povidone	1 mg
Magnesium stearate	0.5 mg
(2) Tablets containing 30 milligrams of (+)-citalopram calculated as the free base:	
(+)-citalopram	30 mg
Lactose	16 mg
Potato starch	45 mg
Saccharose	106 mg
Sorbitol	6 mg
Talcum	9 mg
Gelatine	4 mg
Povidone	3 mg
Magnesium stearate	0.6 mg
(3) Syrup containing per milliliter:	
(+)-citalopram	10 mg
Sorbitol	500 mg
Tragacanth	7 mg
Glycerol	50 mg
Methyl-paraben	1 mg
Propyl-paraben	0.1 mg
Ethanol	0.005 ml
Water ad	1 ml
(4) Solution for injection containing per milliliter:	
(+)-citalopram	50 mg
Acetic acid	17.9 mg
Sterile water ad	1 ml
(5) Solution for injection containing per milliliter:	
(+)-citalopram	10 mg
Sorbitol	42.9 mg
Acetic acid	0.63 mg
Sodium hydroxide	22 mg
Sterile water ad	1 ml

Any other pharmaceutical tableting adjuvants may be used provided that they are compatible with the active ingredient, and additional compositions and dosage forms may be similar to those presently used for neuroleptics, analgesics or antidepressants.

Also combinations of (+)-citalopram as well as its non-toxic acid salts with other active ingredients, especially other neuroleptics, thymoleptics, tranquilizers, analgetics or the like, fall within the scope of the present invention.

As previously stated, when isolating the enantiomers of citalopram in the form of an acid addition salt the acid is preferably selected so as to contain an anion which is non-toxic and pharmacologically acceptable, at least in usual therapeutic doses. Representative salts which are included in this preferred group are the hydrochlorides, hydrobromides, sulphates, acetates, phosphates, nitrates, methanesulphonates, ethane-sulphonates, lactates, citrates, tartrates or bitartrates, pamoates and maleates of the amines of Formula I. Other acids are likewise suitable and may be employed if desired. For example: fumaric, benzoic, ascorbic, succinic, salicylic, bimethylenesalicylic, propionic, gluconic, malic, malonic, mandelic, [cinnamic] *cinnamic*, citraconic, stearic, palmitic, itaconic, glycolic, benzenesulphonic, and sulphamic acids may [be] also be employed as acid addition salt-forming acids.

When it is desired to isolate a compound of the invention in the form of the free base, this may be done according to conventional procedure as by dissolving the isolated or unisolated salt in water, treating with a suitable alkaline material, extracting the liberated free base with a suitable organic [solvent] *solvent*, drying the extract and evaporating to dryness or fractionally distilling to effect isolation of the free basic amine.

The invention also comprises a method for the alleviation, palliation, mitigation or inhibition of the manifestations of certain physiological-psychological [abnormalities] *abnormalities* of animals, especially depressions, by administering to a living animal body, including human beings, an adequate quantity of (+)-citalopram or a non-toxic acid addition salt thereof. An adequate quantity would be from about 0.001 mg to about 10 mg per kg of body weight in each unit dosage, and from about 0.003 milligrams to about 7 milligrams/kg of body weight per day.

It is to be understood that the invention is not limited to the exact details of operation or exact [compound] *compounds* or compositions shown and described, as obvious modifications and equivalents will be apparent to one skilled in the art.

We claim:

1. A compound selected from substantially pure (+)-1-(3-Dimethylaminopropyl)-1-(4'- fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile and non-toxic acid addition salts thereof.

2. A compound of claim 1 being *the* pamoic acid salt of substantially pure (+)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile.

3. A pharmaceutical composition in unit dosage form comprising a pharmaceutically acceptable diluent or adjuvant and, as an active ingredient, a compound as defined in claim 1.

4. A pharmaceutical composition in unit dosage form comprising a pharmaceutically acceptable diluent or adjuvant and, as an active ingredient, the compound of claim 2.

5. A pharmaceutical composition in unit dosage form, according to claim 3, wherein the active ingredient is present in an amount from 0.1 to 100 milligram per unit dose.

6. A pharmaceutical composition in unit dosage form, according to claim 4, wherein the active ingredient is present in an amount from 0.1 to 100 milligram per unit dose.

7. A method for the alleviation of depression in a living animal body subject thereto which comprises the step of administering to the living animal body an amount of a compound of claim 1 which is effective for said purpose.

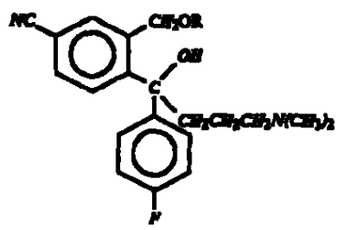
8. A method for the alleviation of depression in a living animal body subject thereto which comprises the step of administering to the living animal body an amount of a compound of claim 2 which is effective for said purpose.

9. Method of claim [10] 7 wherein the compound is administered in the form of a pharmaceutical composition thereof.

10. Method of claim 8 wherein the compound is administered in the form of a pharmaceutical composition thereof.

11. A method for the preparation of a compound as defined in claim 1, which comprises, converting substantially, pure [(+)-4-(4-dimethylamino)-1-(4'-fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl)-benzonitrile] *(−)-4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxy-1-butyl]-3-(hydroxymethyl)-benzonitrile* or a [monoester] *monoester* thereof in a stereoselective way to substantially pure (+)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile which is isolated as such or as a non-toxic acid addition salt thereof.

12. A compound of the formula *(3I)-Enantiomer of the compound 4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxy-1-butyl]-3-(hydroxymethyl)-benzonitrile or an ester of said (−)enantiomer, which has the formula*



wherein R is hydrogen or represents a group completing a labile ester.

* * * * *

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(54) Title: THE USE OF ENANTIOMERIC PURE ESCITALOPRAM

(57) Abstract: The present invention relates to the use of enantiomeric pure escitalopram and/or of low dose medicaments thereof for the improved treatment of depression, in particular major depression disorder, neurotic disorders, acute stress disorder, eating disorders such as bulimia, anorexia and obesity, phobias, dysthymia, pre-menstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder or drug abuse. The medicaments may also be used in the treatment of major depression disorder in "treatment resitant" patients.

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CLAIMS

1. Use of escitalopram comprising less than 3% w/w of R-citalopram for the preparation of a pharmaceutical composition.

2. The use according to claim 1, characterised in that escitalopram is used as an oxalate salt, preferably a crystalline oxalate salt.

3. The use according to claim 1 or 2, characterised in that escitalopram comprising not more than 2% w/w R-citalopram is used.

4. The use according to claim 3, characterised in that escitalopram comprising not more than 1% w/w.

5. The use according to any of Claims 1 – 4, characterised in that the pharmaceutical composition is for treatment of depression, in particular major depression disorder, neurotic disorders, acute stress disorder, eating disorders such as bulimia, anorexia and obesity, phobias, dysthymia, pre-menstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder or drug abuse.

6. The use according to Claim 5, characterised in that the pharmaceutical composition is for treatment of major depression disorder.

7. The use according to Claim 5, characterised in that the medicament is for treatment of a neurotic disorder.

8. The use according to any of Claims 5 to 7, characterised in that the pharmaceutical composition is for treatment of patients who have failed to respond to initial treatment with a conventional SSRI.

9. The use according to Claims 8, characterised in that the pharmaceutical composition is for treatment of patients with major depression disorder who have failed to

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respond to initial treatment with a conventional SSRI.

10. Pharmaceutical composition, characterised in that it comprises escitalopram with less than 3% w/w of R-citalopram as an active ingredient.

11. Pharmaceutical composition of claim 10, characterised in that it comprises escitalopram with not more than 2% w/w of R-citalopram as an active ingredient.

12. Pharmaceutical composition according to claim 11, characterised in that it comprises escitalopram with not more than 1% w/w.

13. Pharmaceutical composition according to any of claims 10 to 12, characterised in that it is a unit dose preparation containing 2.5 to 20 mg escitalopram.

14. Pharmaceutical composition according to claim 13, characterised in that it is a unit dose preparation containing not more than 10 mg escitalopram.

15. Pharmaceutical composition according to claim 14, characterised in that it is a unit dose preparation containing not more than 7.5 mg escitalopram, preferably 5.0 mg.

16. Pharmaceutical composition according to any of claims 10 to 15, characterised in that it is a oral formulation, preferably a tablet.

17. Use of escitalopram for the treatment of major depression disorder characterised in that it is used in a daily dose of less than 10 mg of escitalopram.

18. Use of escitalopram for the treatment of major depression disorder characterised in that it is used in a daily dose of 7.5 mg or less of escitalopram.

19. Use of escitalopram for the treatment of major depression disorder characterised in that it is used in a daily dose of 5.0 mg of escitalopram.

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2020
Bogotá, D.C.,

Doctor:
Emilio Ferrero
Apoderado

Oficio Nº: 6339

ASUNTO:

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Trámite	011
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Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor José Luis Reyes Villamizar, en su calidad de apoderado de Tecnoquímicas S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

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 CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

09 JUN 2006

El anterior requerimiento fue notificado por fijación en lista de fecha_____.

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