REYES & REYES
A B O G A D O S



**SEÑOR**
**SUPERINTENDENTE DE INDUSTRIA Y COM**
**E. S. D.**

**REF:** **Expediente 08 095.718.**

**TÍTULO SOLICITADO:** **MÉTODO PARA LA ELABORACIÓN DE ESCITALOPRAM.**

**PUBLICACIÓN:** **GACETA No. 614 del 19/03/2010 N° de publicación: 12.**

**PRIORIDAD:** **DK PA200701314 de 11/09/2007.**

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

**APODERADO:** **EMILIO FERRERO.**

**TRÁMITE:** **SUSTENTACION DE OPOSICIÓN**

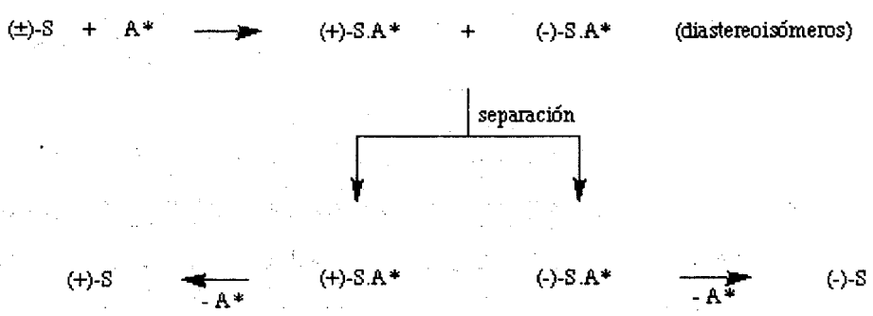
**JOSÉ LUIS REYES VILLAMIZAR**, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **LABORATORIO FRANCO-COLOMBIANO, LAFRANCOL S.A.,** dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2º de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar la oposición presentada oportunamente ante ese Despacho, en los siguientes términos:

## I. COMPLEMENTO DE INFORMACIÓN

Comedidamente me permito presentar los argumentos que demuestran que la solicitud de la referencia incumple los requisitos de patentabilidad establecidos por

los artículos 14, 16 y 18 de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario, veamos:

En primer lugar, y como cualquier persona medianamente versada en la materia debe reconocer, la resolución de mezclas racémicas se puede considerar como una estrategia clásica de obtención de productos enantioméricamente puros. El procedimiento consiste en la reacción de un compuesto quiral en su mezcla racémica con un agente de resolución homoquiral (ópticamente puro) para dar dos diastereoisómeros separables físicamente, que se tratan después de forma independiente liberando los dos enantiomeros iniciales.




Tan es así que hoy por hoy, dentro de la Química Orgánica sintética, una de las líneas de investigación que genera mayor número de publicaciones es la preparación de compuestos enantioméricamente puros. El interés por el tema ha llegado a ser tan pronunciado que se dedican a él periódicamente congresos o revistas específicas, como lo son "Asymmetry" o "Chirality"[1]. Este interés proviene, sin duda, del reconocimiento general de que los sistemas vivos, que a su vez están formados por componentes (los receptores a los que se unen los fármacos) que también son quirales.

También es importante resaltar el hecho que en el estado de la técnica se reconoce que un agente de resolución o un agente quiral de derivación (CDA por sus siglas en ingles) es un compuesto auxiliar quiralmente puro que puede convertir una mezcla de enantiómeros en diastereómeros. En el caso del ácido tartárico cabe resaltar además que Louis Pasteur fue el primero en llevar a cabo la resolución quiral cuando descubrió el concepto de la actividad óptica, fue el primero en separar cristales de los diastereómeros del acido tartárico en 1849. Es

[1] http://www.ch.ic.ac.uk/GIC/este/este1.html

así como un ejemplo clásico de resolución de este tipo puede ser el acido tartárico y su derivados, dado el hecho que nuevamente Luis Pasteur expuso el método para resolver el acido tartárico racémico mediante el uso de (+)-cinchotoxina en 1853[2].

Expuesto lo anterior, cualquier persona medianamente versada en la materia también debe reconocer que el proceso reivindicado en la solicitud colombiana en cuestión utiliza precisamente una de las formas más comunes de separación de enantiómeros, que es la conversión en diastereómeros. Es así como podemos constatar con anterioridad en el estado de la técnica, que por ejemplo es posible separar los dos enantiómeros de 1-feniletilamina mediante (L)-(+)-ácido tartárico como agente de resolución[3].

Siendo aun más específicos, el método que se utiliza en las reivindicaciones de la solicitud colombiana corresponde a lo que en el estado de la técnica se conoce como recristalización diastereomérica[4]. Esta estrategia de recristalización implica dos pasos. El primer paso consiste en convertir los enantiómeros en diastereómeros. El segundo paso, una vez que los diastereómeros se han formado, es separarlos mediante recristalización. Si observamos con detenimiento cada una de las reivindicaciones de la solicitud colombiana en trámite, podemos afirmar que el proceso que allí se describe concuerda en su esencia con un método convencional de recristalización diastereomérica.

Existen además documentos que permiten evidenciar con anterioridad el uso de derivados de acido tartárico en la resolución de diversos tipos de compuestos. Dichos documentos son WO9942460A1: PROCESS FOR THE PRODUCTION OF OPTICALLY ENRICHED (R)- OR (S)-ALBUTEROL (publicada el 26 de agosto de 1999), EP0365213A2: Method of resolving cis 3-amino-4-[2-(2-furyl)vinyl]-1-methoxy-carbonylmethyl-azetidin-2-one and di-p-toluoyl-tartaric acid salts thereof (publicada el 25 de abril de 1990) y US4798895: Process for preparing levomepromazine hydrogen maleate (publicada el 17 de enero de 1987).

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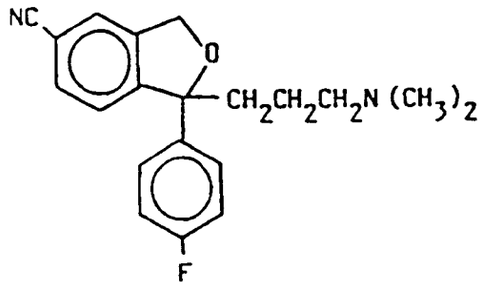
[2] http://en.wikipedia.org/wiki/Chiral_resolution
[3] Kazlauskas, R.J., Organic Syntheses, Coll. Vol. 9, p.77 (1998); Vol. 70, p.60 (1992).
[4] http://en.wikipedia.org/wiki/Diastereomeric_recrystallization

En especial la patente española ES 2068891 publicada el 20 de diciembre de 1989 y titulada "Nuevos enantiómeros y su aislamiento" revela:

La presente invención se refiere a los dos nuevos enantiómeros del medicamento antidepresivo 1 - (3 - dimetil - aminopropil) - 1 - (4' - fluorofenil) - 1,3 - dihidroisobenzofurano(5) - carbonitrilo (citalopram) de fórmula I siguiente:

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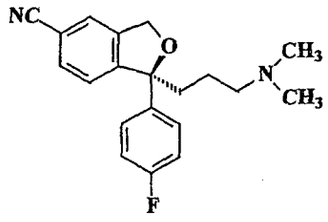
Según la invención, el compuesto II se hace reaccionar con:

a) Un derivado ácido enantioméricamente puro tal como cloruro de ácido, anhídrido o éster lábil como, por ejemplo, se ilustra en el esquema de reacción I mediante el cloruro de (+) - ó ( - ) - α - metoxi - α - trifluorometilfenilacetilo. La reacción se realiza preferentemente en un disolvente orgánico inerte como, por ejemplo, tolueno, diclorometano o tetrahidrofurano. Se añade una base (trietilamina, N,N - dimetilanilina, piridina o similares) para neutralizar el ácido clorhídrico liberado. Posteriormente se separan los diastereoisómeros mediante HPLC o cristalización fraccionada. Los diastereoisómeros así purificados se separan finalmente tratándolos con una base fuerte (por ejemplo, un alcóxido) en un disolvente orgánico inerte como, por ejemplo, tolueno, tetrahidrofurano, o dimetoxietano produciendo respectivamente los enantiómeros puros de citalopram. La reacción de cierre del anillo se realiza preferentemente a temperaturas relativamente bajas (desde - 20°C hasta temperatura ambiente).

Como se puede apreciar, en el estado de la técnica ya se encontraba descrito un proceso de recristalización diastereomérica para la preparación de Escitalopram, en donde se utilizan en esencia los mismos principios que en el proceso descrito en la solicitud colombiana en trámite, es decir, la preparación previa de diastereómeros con un agente de resolución (ácido ópticamente puro) y una posterior separación por cristalización en un sistema solvente.

De la misma manera la publicación internacional WO 2007/012954 publicada el 01 de febrero de 2007 y titulada "AN IMPROVED PROCESS FOR THE PREPARATION OF ESCITALOPRAM" revela:

The present invention relates to an industrially advantageous process for the preparation of pure Escitalopram, (*S*)-(+)-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile of Formula I, and its pharmaceutical acceptable salts.

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(...)

aqueous ammonia. The purified Diol thus obtained is treated with optically active acid, selected from dibenzoyltartaric acid, Di-*p*-toluoyltartaric acid, 10-camphorsulfonic acid and the like, in an organic solvent to resolve Diol enantiomers to obtain (*S*)-(-)-4-[4-(dimethylamino)-1-(4-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)benzonitrile. Preferably Di-*p*-toluoyl-D-tartaric acid is used to obtain (*S*)-Enantiomer of Diol (VII) having HPLC chiral purity of more than 99.5%.

(...)

DM water and concentrated at 50-55°C under reduced pressure. The obtained residue was dissolved in isopropyl alcohol (1125 ml) at 50-55°C. (+)-Di-*p*-toluoyl-*D*-tartaric acid (105 g, 0.27 mol) was added and slowly cooled to 25-30°C and stirred for 10 h. The crystals formed in the reaction mixture were filtered and washed with isopropyl alcohol (2x110 ml) to obtain ~ 180 g product (chiral purity: >96%).

Finalmente la publicación internacional WO 2006/106531 publicada el 12 de octubre de 2006 y titulada "PROCESS FOR THE PREPARATION OF ESCITALOPRAM OR ITS ACID ADDITION SALTS" revela:

The present invention relates an improved process for the preparation of Escitalopram, which is the S-enantiomer of well known antidepressant drug Citalopram, *i.e.* (S)-1-[3-(dimethylamino)propyl]-1-(4-flouorphenyl)-1,3-dihydro-5-isobenzofuran carbonitrile or a pharmaceutically acceptable salt thereof.

(...)

According to process of the present invention, racemic diol compound of formula III is treated with pure optically active acid in a mixture of solvents to get an enantiomerically pure diol of formula IIIA. The optically active acid used herein is selected from the group consisting of but not limited to tartaric acid, dibenzoyl tartaric acid, di-*p*-toluoyl tartaric acid, bis-napthyl phosphoric acid, and 10-camphor sulphonic acid preferably di-*p*-toluoyl tartatic acid. The reaction is carried out in a solvent selected from the group consisting of lower alcohol having 1 to 4 carbon atoms such as methanol, ethanol, isopropyl alcohol and butyl alcohol; acetonitrile; acetone or mixture thereof preferably in a mixture of methanol and isopropyl alcohol. The reaction is

(...)

**Process for the preparation of (-)-4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydoxy-1-butyl]-3-(hydroxymethyl)-benzonitrile hemi (+)-di-p-toloyltartaric acid salt.**

To a solution of 100 g of 4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydoxy-1-butyl]-3-(hydroxymethyl)-benzonitrile hydrobromide in 500 ml water 500 ml toluene was added. The pH of the solution was adjusted to 9.0 to 10.0 using 2M NaOH solution. The mixture was stirred for 30minutes and toluene layer was separated and dried. The organic layer was then removed under vacuum to get racemic diol base as oil. The oil was dissolved in a mixture of methanol (150mL) and ethanol (200mL) at 40-60°C followed by the addition of (+)-di-p-toloyl tartaric acid hydrate (50g) with vigorous stirring at 40-60°C. The mixture was cooled to 20-25°C and stirred for 6-10 hrs at the same temperature then cooled to 0-5°C. The solid formed was filtered off and dried.

Chiral purity: >99.0%

(...)

**Purification of (-)-4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydoxy-1-butyl]-3-(hydroxymethyl)-benzonitrile hemi (+)-di-p-toloyltartaric acid salt.**

(-)-4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydoxy-1-butyl]-3-(hydroxymethyl)-benzonitrile hemi (+)-di-p-toloyltartaric acid salt obtained as above (40g) was dissolved in a mixture of methanol (120mL) and ethanol (180mL) at 40-60°C. The mixture was cooled and the solid formed was filtered off and dried.

Chiral purity: > 99.8%

(...)

1. A process for the preparation of highly pure Escitalopram or its acid addition salts thereof, which comprises:

a) reacting racemic diol or its ester derivative (III) with an optically active acid and at least one solvent to get enantiomerically pure diastereomer (IIIA);

b) separating the enantiomerically pure diastereomer (IIIA) from its optically active acid salt by treating it with base and followed by stereo selective cyclization;

c) separating the Escitalopram base;

2. A process as claimed in claim 1, wherein said optically active acid is selected from the group consisting of tartaric acid, dibenzoyl tartaric acid, di-*p*-toluoyl tartaric acid, bis-napthyl phosphoric acid, and 10-camphor sulphonic acid.

3. A process as claimed in claims 1 or 2 wherein said solvent is selected from the group consisting of lower alcohol having 1 to 4 carbon atoms such as methanol, ethanol, isopropyl alcohol and butyl alcohol; acetonitrile; acetone or any mixture thereof.

Como se puede apreciar claramente en esta anterioridad, nuevamente se revela un proceso de recristalización diastereomérica para la resolución de Escitalopram, sino que además se hace mención del mismo derivado de ácido tartárico como agente de resolución que se emplea en el proceso de la solicitud colombiana en trámite. También se hace mención de algunas condiciones como el medio solvente y/o que la resolución no se realiza sobre la mezcla racémica de Citalopram directamente sino sobre un diol intermediario. Es evidente entonces que la información expuesta en estas dos últimas anterioridades resulta una clara evidencia de la carencia tanto de novedad como de nivel inventivo de proceso expuesto por la solicitud colombiana.

En conclusión la solicitud colombiana en trámite carece tanto de novedad como de nivel inventivo, en primer lugar porque busca reivindicar una estrategia técnica ampliamente descrita en el estado de la técnica, como lo es la recristalización diastereomérica, a través de agentes de resolución igualmente descritos y aplicados a la obtención de escitalopram y finalmente porque tanto las condiciones

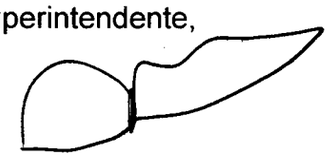
esenciales, intermediarios y reactivos de dicho proceso aparecen descritos para procesos esencialmente idénticos al que se busca reivindicar.

Por todo lo anterior, ruego se analicen los argumentos expuestos con el rigor y detenimiento habituales, y que en consecuencia el Despacho decrete, además de la negación de la solicitud en comento, el archivo del expediente que lo contiene.

## II. ANEXOS

- Copia de todas las publicaciones mencionadas en el acápite de Complemento de Información.

Señor Superintendente,



**JOSE LUIS REYES VILLAMIZAR**
C.C. 79.152.473 de Usaquén
T.P. 44655 del C. S de la J.

9

# SINTESIS ASIMETRICA

## ALGUNOS MODELOS PARA LA PREDICCION DE CONFIGURACIONES DE ESTEREOCENTROS CREADOS EN PROCESOS ENANTIO O DIASTEREOSELECTIVOS.

Carmen López-Leonardo
Departamento de Química Orgánica
Facultad de Química, Universidad de Murcia
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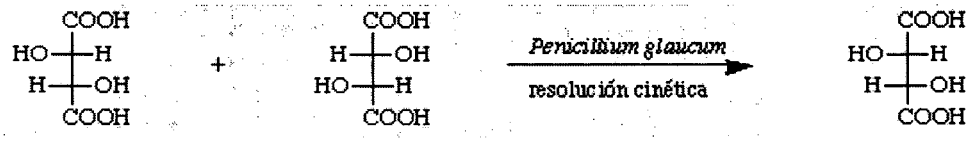
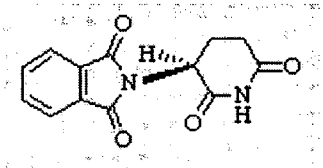
Hoy por hoy, dentro de la Química Orgánica sintética, una de las líneas de investigación que genera mayor número de publicaciones es la preparación de compuestos enantioméricamente puros. El interés por el tema ha llegado a ser tan pronunciado que se dedican a él periodicamente congresos o revistas específicas, con títulos encabezados por palabras como "Asymmetry" o "Chirality". Este interés proviene, sin duda, del reconocimiento general de que los sistemas vivos, que a su vez están formados por componentes quirales, interaccionan con dos enantiómeros de forma diferente, como resultado de relaciones diastereoisoméricas.

El ejemplo más antiguo de este campo de investigación data de 1858 cuando Pasteur realiza la resolución cinética del racemato del ácido tartárico, comprobando que si esta modificación se suministra como medio de cultivo al hongo *Penicillium glaucum* la fermentación cesa tan pronto como el enantiómero (R,R) se ha consumido. De esta forma el ácido (S,S)-(-)-tartárico pudo ser aislado del medio.




Sin embargo, la magnitud de esta diferenciación, por parte de los seres vivos hacia un determinado enantiómero, no era imaginable hace años hasta ver los efectos dramáticos producidos por la administración de algunos fármacos en su forma racémica. Un buen ejemplo de la marcada diferencia de la acción de las dos formas enantioméricas de un compuesto dado es la talidomida, que se utilizó como sedante en su forma racémica, comprobándose más tarde que el enantiomero (-) causa además deformaciones fetales importantes[1].

10



(-)-TALIDOMIDA

Este y otros ejemplos han forzado a la industria, ya no solo farmaceútica sino química en general, a focalizar más sus objetivos sintéticos; ya no basta obtener productos con una conectividad atómica concreta, además se necesitan con una estereoquímica dada. Para lograr este fin, es decir la obtención de productos en forma no racémica, se utilizan diferentes métodos que se pueden clasificar en tres grandes grupos:

- 1. Resolución de mezclas racémicas.
- 2. Interconversión de grupos funcionales presentes en moléculas ópticamente activas.
- 3. Síntesis asimétrica.

# Chiral resolution

From Wikipedia, the free encyclopedia

**Chiral resolution** in stereochemistry is a process for the separation of racemic compounds into their enantiomers.[1] It is an important tool in the production of optically active drugs. Other terms with the same meaning are **optical resolution** and **mechanical resolution**.

One disadvantage of chiral resolution of racemates compared to direct asymmetric synthesis of one of the enantiomers is that only 50% of a desired enantiomer is obtained. Several methods exist.

## Contents



## Resolution by crystallization

Typically 5-10% of all racemates are known to crystallize as mixtures of enantiopure crystals, so-called **conglomerates** [2]. Louis Pasteur was the first to conduct chiral resolution when he discovered the concept of optical activity in the first place by the manual separation of left-handed and right-handed tartaric acid crystals in 1849. Later in 1882 he went on to demonstrate that by seeding a supersaturated solution of sodium ammonium tartrate with a d-crystal on one side of the reactor and a l-crystal on the opposite side, crystals of opposite handedness will form on the opposite side of the reactor.

This type of resolution called **spontaneous resolution** has also been demonstrated with racemic methadone.[3] In a typical setup 50 grams dl-methadone is dissolved in petroleum ether and concentrated. Two millimeter-sized d- and l-crystals are added and after stirring for 125 hours at 40°C two large d- and l-crystals are recovered in 50% yield.

Another form of direct crystallization is preferential crystallization also called **resolution by entrainment** of one of the enantiomers. For example an added seed of (-)-hydrobenzoin to an ethanol solution of (±)-hydrobenzoin will have the (-)-enantiomer crystallizing out and after 15 cycles 97% optical purity can be obtained.

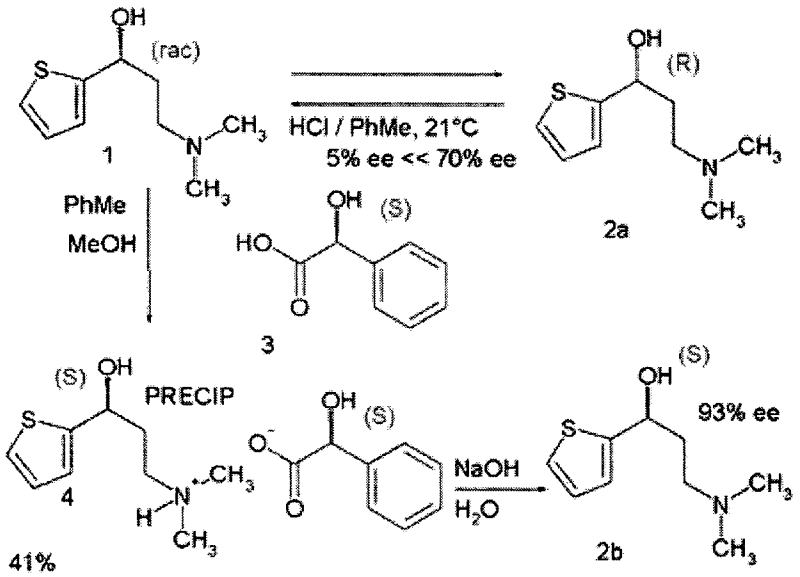
## Chiral resolving agents

Derivatization of racemic compounds is possible with optically pure reagents forming pairs of diastereomers which can be separated by conventional techniques in physical chemistry. Derivatization is possible by salt formation between an amine and a carboxylic acid. Simple deprotonation affords the pure

12

enantiomer. Examples of so-called chiral resolving agents are tartaric acid and brucine. The method was introduced (again) by Louis Pasteur in 1853 by resolving racemic tartaric acid with optically active (+)-cinchotoxine.

One modern-day method of chiral resolution is used in the organic synthesis of the drug Duloxetine:[4]




In one of its steps the racemic alcohol **1** is dissolved in a mixture of toluene and methanol to which solution is added optically active (S)-mandelic acid **3**. The alcohol (S)-enantiomer forms an insoluble diastereomeric salt with the mandelic acid and can be filtered from the solution. Simple deprotonation with sodium hydroxide liberates free (S)-alcohol. In the meanwhile the (R)-alcohol remains in solution unaffected and is recycled back to the racemic mixture by epimerization with hydrochloric acid in toluene. This process is known as **RRR synthesis** in which the R's stand for **Resolution-Racemization-Recycle**.

## Chiral column chromatography

- In chiral column chromatography the stationary phase is made chiral with similar resolving agents as described above.

## References

1. ^ William H. Porter (1991). "Resolution of chiral drugs" (http://www.iupac.org/publications/pac/1991/pdf/6308x1119.pdf) . *Pure Appl. Chem.* **63** (8): 1119–1122. doi:10.1351/pac199163081119 (http://dx.doi.org/10.1351%2Fpac199163081119) . http://www.iupac.org/publications/pac/1991/pdf/6308x1119.pdf.
2. ^ *Enantiomers, racemates, and resolutions* Jean Jacques, André Collet, Samuel H Wilen **1981** ISBN 0-471-08058-6
3. ^ Harold E. Zaugg (1955). "A Mechanical Resolution of dl-Methadone Base". *J. Am. Chem. Soc.* 77 (10): 2910. doi:10.1021/ja01615a084 (http://dx.doi.org/10.1021%2Fja01615a084) .
4. ^ Yoshito Fujima, Masaya Ikunaka, Toru Inoue, and Jun Matsumoto (2006). "Synthesis of (S)-3-(N-Methylamino)-1-(2-thienyl)propan-1-ol: Revisiting Eli Lilly's Resolution-Racemization-Recycle Synthesis of Duloxetine for Its Robust Processes". *Org. Process Res. Dev.* **10** (5): 905–913. doi:10.1021/op06011

13

(http://dx.doi.org/10.1021%2Fop06011) .

Retrieved from "http://en.wikipedia.org/wiki/Chiral_resolution"
Categories: Stereochemistry

14

# Diastereomeric recrystallization

From Wikipedia, the free encyclopedia

**Diastereomeric recrystallization** is a method of chiral resolution of enantiomers from a racemic mixture. It differs from asymmetric synthesis, which aims to produce a single enantiomer from the beginning, in that diastereomeric recrystallization separates two enantiomers that have already mixed into a single solution.

The strategy of diastereomeric recrystallization involves two steps. The first step is to convert the enantiomers into diastereomers by way of a chemical reaction. A mixture of enantiomers may contain two isomers of a molecule with one chiral center. After adding a second chiral center in a determined location, the two isomers are still different, but they are no longer mirror images of each other; rather, they become diastereomers. In a prototypical example, a mixture of R and S enantiomers with one chiral center would become a mixture of (R,S) and (S,S) diastereomers. (The R-S notation is explained here.)

The second step, once the diastereomers have formed, is to separate them using recrystallization. This is possible because enantiomers have shared physical properties such as melting point and boiling point, but diastereomers have different physical properties, so they can be separated like any two different molecules.

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(54) Title: PROCESS FOR THE PRODUCTION OF OPTICALLY ENRICHED (R)- OR (S)-ALBUTEROL

(57) Abstract

A process for the production of optically enriched (R)- or (S)-albuterol or (R)- or (S)-albuterol salts by the resolution of a novel ketal derivative 2-(N-t-butylamino)-1-(+2,2-dimethyl-1,2-benzodioxin-6-yl) ethanol, with a chiral tartaric acid derivative.

CLAIMS

1. A process for the preparation of 2-(N-t-butylamino)-1-(2,2-dimethyl-1,2-benzodioxin-6-yl) ethanol (2), which process includes the steps of:

   (1) suspending albuterol (1) or a salt thereof, in acetone;

   (2) adding to the mixture of step (1) a suitable acid with stirring to form the compound of the formula (2);

   (3) adding to the mixture of step (2) a suitable aqueous or non-aqueous basic solution; and

   (4) recovering the compound of the formula (2) from the mixture of step (3).

2. A process for the optical resolution of a mixture of enantiomers of 2-(N-t-butylamino)-1-(2,2-dimethyl-1,2-benzodioxin-6-yl) ethanol (2) into its (R)-isomer designated (R)-2 and its (S)-isomer designated (S)-2, which process includes the steps of:

   (i) reacting the mixture of enantiomers of the compound of the formula (2), dissolved in a suitable solvent, with an enantiopure tartaric acid derivative;

   (ii) precipitating selectively out of the solution of step (i) a compound of the formula:
   (R)-2:tartaric acid derivative salt
   or
   (S)-2:tartaric acid derivative salt;

   (iii) suspending the (R)-2:tartaric acid derivative salt or the (S)-2:tartaric acid derivative salt in a suitable organic solvent and stirring to improve optical purity, and then recovering the (R)-2:tartaric acid derivative salt or the (S)-2:tartaric acid derivative salt by filtration;

(iv) adding the (R)-2:tartaric acid derivative salt or the (S)-2:tartaric acid derivative salt from step (iii) to a mixture of an aqueous solution of a base and a suitable organic solvent; and

(v) recovering the compound (R)-2 or the compound (S)-2 from the organic phase of step (iv).

3. A process according to claim 2 wherein in step (i) the solvent is a lower alcohol

4. A process according to claim 2 or claim 3 wherein in step (i) the tartaric acid derivative is selected from the group consisting of (2S,3S)-(+)-di-O-benzoyl tartaric acid (3a), (2S,3S)-(+)-di-O-(p-toluoyl)-tartaric acid (4a), (2R,3R)-(-)-di-O-benzoyl tartaric acid (3b), and (2R,3R)-(-)-di-O-(p-toluoyl)-tartaric acid (4b).

5. A process for the hydrolysis of 2-(N-t-butylamino)-1-(2,2-dimethyl-1,2-benzodioxin-6-yl) ethanol (2) to give albuterol (1) either as the free base or as a salt, which process includes the steps of:

(a) dissolving the compound of the formula (2), either enantiomerically enriched or as the racemic mixture, in an excess of an acid, and water or any suitable organic solvent, to hydrolyse the compound of the formula (2); and

(b) recovering the compound of the formula (1) either as a salt of the acid used in step (a), or as the free base.

6. A process for resolving the enantiomers of albuterol (1) into the (R)-enantiomer designated (R)-1 and the (S)-enantiomer designated (S)-1, which process includes the steps of:

(i) suspending albuterol (1) or a salt thereof, in acetone;

(ii) adding to the mixture of step (i) a suitable acid with stirring to form 2-(N-t-butylamino)-1-(2,2-dimethyl-1,2-benzodioxin-6-yl) ethanol (2);

(iii) adding to the mixture of step (ii) a suitable aqueous or non-aqueous basic solution;

(iv) recovering the compound of the formula (2) as a mixture of enantiomers designated (R)-2 and (S)-2;

(v) reacting the mixture of enantiomers of the compound of the formula (2) from step (iv), dissolved in a suitable solvent, with an enantiopure tartaric acid derivative;

(vi) precipitating selectively out of the solution of step (v) a compound of the formula:

(R)-2:tartaric acid derivative salt or

(S)-2:tartaric acid derivative salt;

(vii) suspending the (R)-2:tartaric acid derivative salt or the (S)-2:tartaric acid derivative salt from step (vi) in a suitable organic solvent and stirring to improve optical purity, and then recovering the (R)-2:tartaric acid derivative salt or the (S)-2:tartaric acid derivative salt by filtration;

(viii) adding the (R)-2:tartaric acid derivative salt or the (S)-2:tartaric acid derivative salt from step (vii) to a mixture of an aqueous solution of a base and a suitable organic solvent;

(ix) recovering the compound (R)-2 or the compound (S)-2 from the organic phase of step (viii);

(x) dissolving the compound (R)-2 or the compound (S)-2 from step (ix) in an excess of an acid, and water or any other suitable organic solvent, to hydrolyse the compound (R)-2 or the compound (S)-2; and

(xi) recovering the compound (R)-1 or the compound (S)-1 either as a salt or as the free base.

7. A process according to claim 6 for the recovery of the compound of the formula (R)-1.

8. A process according to claim 6 or claim 7 wherein in step (v) the enantiopure tartaric acid derivative is selected from the group consisting of (2S,3S)-(+)-di-O-benzoyl tartaric acid (3a), (2S,3S)-(+)-di-O-(p-toluoyl)-tartaric acid (4a), (2R,3R)-(-)-di-O-benzoyl tartaric acid (3b), and (2R,3R)-(-)-di-O-(p-toluoyl)-tartaric acid (4b).

9. A process for the racemisation of optically enriched albuterol (1) or a salt thereof or optically enriched 2-(N-t-butylamino)-1-(2,2-dimethyl-1,2-benzodioxin-6-yl) ethanol (2) or a salt thereof to give a mixture of enantiomers of the compound of the formula (1), which process includes the steps of:

(A) dissolving optically enriched compound of the formula (1) or a salt thereof, or optically enriched compound of the formula (2), in a solution of an excess of a suitable acid and a suitable solvent to produce racemised compound of the formula (1);

(B) adding to the solution of step (A) a suitable aqueous or non-aqueous base; and

(C) recovering a mixture of enantiomers of the compound of the formula (1) from the mixture of step (B).

10. A process according to claim 9 wherein in step (A) the solvent is selected from the group consisting of water, a lower alcohol, acetonitrile and tetrahydrofuran, or a mixture of water and a lower alcohol, acetonitrile or tetrahydrofuran.

**AMENDED CLAIMS**

[received by the International Bureau on 05 July 1999 (05.07.99);
original claims 1-10 replaced by amended claims 1-10 (4 pages)]

1. A process for the preparation of 2-(N-t-butylamino)-1-(2,2-dimethyl-1,3-benzodioxin-6-yl) ethanol (2), which process includes the steps of:

   (1) suspending albuterol (1) or a salt thereof, in acetone;

   (2) adding to the mixture of step (1) a suitable acid with stirring to form the compound of the formula (2);

   (3) adding to the mixture of step (2) a suitable aqueous or non-aqueous basic solution; and

   (4) recovering the compound of the formula (2) from the mixture of step (3).

2. A process for the optical resolution of a mixture of enantiomers of 2-(N-t-butylamino)-1-(2,2-dimethyl-1,3-benzodioxin-6-yl) ethanol (2) into its (R)-isomer designated (R)-2 and its (S)-isomer designated (S)-2, which process includes the steps of:

   (i) reacting the mixture of enantiomers of the compound of the formula (2), dissolved in a suitable solvent, with an enantiopure tartaric acid derivative;

   (ii) precipitating selectively out of the solution of step (i) a compound of the formula:
   (R)-2:tartaric acid derivative salt
   or
   (S)-2:tartaric acid derivative salt;

   (iii) suspending the (R)-2:tartaric acid derivative salt or the (S)-2:tartaric acid derivative salt in a suitable organic solvent and stirring to improve optical purity, and then recovering the (R)-2:tartaric acid derivative salt or the (S)-2:tartaric acid derivative salt by filtration;

(iv) adding the (R)-2:tartaric acid derivative salt or the (S)-2:tartaric acid derivative salt from step (iii) to a mixture of an aqueous solution of a base and a suitable organic solvent; and

(v) recovering the compound (R)-2 or the compound (S)-2 from the organic phase of step (iv).

3. A process according to claim 2 wherein in step (i) the solvent is a lower alcohol

4. A process according to claim 2 or claim 3 wherein in step (i) the tartaric acid derivative is selected from the group consisting of (2S,3S)-(+)-di-O-benzoyl tartaric acid (3a), (2S,3S)-(+)-di-O-(p-toluoyl)-tartaric acid (4a), (2R,3R)-(-)-di-O-benzoyl tartaric acid (3b), and (2R,3R)-(-)-di-O-(p-toluoyl)-tartaric acid (4b).

5. A process for the hydrolysis of 2-(N-t-butylamino)-1-(2,2-dimethyl-1,3-benzodioxin-6-yl) ethanol (2) to give albuterol (1) either as the free base or as a salt, which process includes the steps of:

(a) dissolving the compound of the formula (2), either enantiomerically enriched or as the racemic mixture, in an excess of an acid, and water or any suitable organic solvent, to hydrolyse the compound of the formula (2); and

(b) recovering the compound of the formula (1) either as a salt of the acid used in step (a), or as the free base.

6. A process for resolving the enantiomers of albuterol (1) into the (R)-enantiomer designated (R)-1 and the (S)-enantiomer designated (S)-1, which process includes the steps of:

(i) suspending albuterol (1) or a salt thereof, in acetone;

(ii) adding to the mixture of step (i) a suitable acid with stirring to form 2-(N-t-butylamino)-1-(2,2-dimethyl-1,3-benzodioxin-6-yl) ethanol (2);

(iii) adding to the mixture of step (ii) a suitable aqueous or non-aqueous basic solution;

(iv) recovering the compound of the formula (2) as a mixture of enantiomers designated (R)-2 and (S)-2;

(v) reacting the mixture of enantiomers of the compound of the formula (2) from step (iv), dissolved in a suitable solvent, with an enantiopure tartaric acid derivative;

(vi) precipitating selectively out of the solution of step (v) a compound of the formula:

(R)-2:tartaric acid derivative salt or

(S)-2:tartaric acid derivative salt;

(vii) suspending the (R)-2:tartaric acid derivative salt or the (S)-2:tartaric acid derivative salt from step (vi) in a suitable organic solvent and stirring to improve optical purity, and then recovering the (R)-2:tartaric acid derivative salt or the (S)-2:tartaric acid derivative salt by filtration;

(viii) adding the (R)-2:tartaric acid derivative salt or the (S)-2:tartaric acid derivative salt from step (vii) to a mixture of an aqueous solution of a base and a suitable organic solvent;

(ix) recovering the compound (R)-2 or the compound (S)-2 from the organic phase of step (viii);

(x) dissolving the compound (R)-2 or the compound (S)-2 from step (ix) in an excess of an acid, and water or any other suitable organic solvent, to hydrolyse the compound (R)-2 or the compound (S)-2; and

(xi) recovering the compound (R)-1 or the compound (S)-1 either as a salt or as the free base.

7. A process according to claim 6 for the recovery of the compound of the formula (R)-1.

8. A process according to claim 6 or claim 7 wherein in step (v) the enantiopure tartaric acid derivative is selected from the group consisting of (2S,3S)-(+)-di-O-benzoyl tartaric acid (3a), (2S,3S)-(+)-di-O-(p-toluoyl)-tartaric acid (4a), (2R,3R)-(-)-di-O-benzoyl tartaric acid (3b), and (2R,3R)-(-)-di-O-(p-toluoyl)-tartaric acid (4b).

9. A process for the racemisation of optically enriched albuterol (1) or a salt thereof or optically enriched 2-(N-t-butylamino)-1-(2,2-dimethyl-1,3-benzodioxin-6-yl) ethanol (2) or a salt thereof to give a mixture of enantiomers of the compound of the formula (1), which process includes the steps of:

(A) dissolving optically enriched compound of the formula (1) or a salt thereof, or optically enriched compound of the formula (2), in a solution of an excess of a suitable acid and a suitable solvent to produce racemised compound of the formula (1);

(B) adding to the solution of step (A) a suitable aqueous or non-aqueous base; and

(C) recovering a mixture of enantiomers of the compound of the formula (1) from the mixture of step (B).

10. A process according to claim 9 wherein in step (A) the solvent is selected from the group consisting of water, a lower alcohol, acetonitrile and tetrahydrofuran, or a mixture of water and a lower alcohol, acetonitrile or tetrahydrofuran.

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## (54) Method of resolving cis 3-amino-4-[2-(2-furyl)vinyl]-1-methoxy-carbonylmethyl-azetidin-2-one and di-p-toluoyl-tartaric acid salts thereof.

(57) Cis αα,ββ-3-amino-4-[2-(2-furyl)vinyl-1-yl]-1-methoxycarbonylmethyl-azetidin-2-one is resolved via optically active di-p-toluoyl tartaric acid.

EP 0 365 213 A2

isomer (II) in high enantiomeric excess.

As a further aspect of the present invention, there are provided the novel di-p-toluoyl-(D)tartaric acid salt of cis β,β-3-amino-4-[2-(2-furyl)vinyl]-1-yl-1-methoxycarbonylmethyl-azetidin-2-one and the di-p-toluoyl-(L)-tartaric acid salt of cis α,α-3-amino-4-[2-(2-furyl)vinyl]-1-yl-1-methoxycarbonylmethyl-azetidin-2-one.

The diastereomeric salt formed in the process is separated from the resolution mixture and the free amino azetidinone is recovered from the salt form by conventional methods. For example, the salt is treated in an aqueous medium with a base to form the free amine which can be extracted from the aqueous phase with a water immiscible solvent such as ethyl acetate. The process provides a high degree of separation of the two enantiomeric azetidinones as reflected by the observed enantiomeric excess (ee) of the product. While as a preferred aspect of the invention the β,β isomer (I) is crystallized out as its di-p-toluoyl-(D)-tartaric acid salt, it is appreciated by one skilled in the art that di-p-toluoyl-(L)-tartaric acid may be substituted, thereby selectively crystallizing the α,α isomer (II) away from the racemic mixture. Exhaustive crystallization of the α,α isomer (II) would thus leave mother liquors containing the β,β isomer (I) in high optical purity.

The following examples are set forth to further describe the invention but are in no way meant to be construed as limiting the scope thereof.

## Example 1

Di-p-toluoyl-(D)-tartaric acid salt of cis β,β-amino-4-[2-(2-furyl)vinyl]-1-methoxycarbonylmethyl-azetidin-2-one

A 1.0 g (4 mMol) sample of cis αα/ββ-4-[2-(2-furyl)vinyl]-1-yl-1-methoxycarbonylmethyl-azetidin-2]-one and 1.618 g (4 mMol) of di-p-toluoyl-(D)-tartaric acid were suspended in 8 ml of acetonitrile and heated to 50° C and allowed to stir overnight, gradually cooling to room temperature. The resulting solid was filtered and washed with acetonitrile to provide 370 mg of the title compound.

The mother liquors were diluted with 8 ml of acetonitrile and the mixture refrigerated for 5 hr. The resulting solid was filtered and washed with acetonitrile to provide an additional 262 mg of the title compound.

Yield (both crops ) = 632 mg (48.3% of one enantiomer); ee = 98.95%. The 3,5-dinitrobenzamide of the title compound was prepared by conventional techniques and used to determine optical purity utilizing both a YMC-AKO3S-5300A, 25 cm, 4.6 mm OD chiral HPLC column (YMC Corporation) and a Pirkle covalent D-napthylalanine chiral column (Regis).

## Example 2

Di-p-toluoyl(L)-tartaric acid salt of cis α,α-3-amino-4-[2-(2-furyl)vinyl]-1-methoxycarbonylmethyl-azetidin-2-one

The title compound was provided by following the general procedure of Example 1, while substituting di-p-toluoyl(L)tartaric acid for di-p-toluoyl-(D)tartaric acid.

Yield = 75 mg; optical rotation = +40.9° at a concentration of 5.8 mg/ml at 25° C.

## Claims

1. A method for resolving cis αα/ββ-3-amino-4-[2-(furyl)vinyl-1-yl]-1-methoxycarbonylmethyl-azetidin-2-one into its component enantiomers, which comprises the steps:

(a) contacting a polar organic solution of the cis αα/ββ racemate with at least about 0.5 mole-equivalents of an optically active di-p-toluoyl tartaric acid; and

(b) separating the insoluble salt formed thereby.

2. A process according to claim 1 wherein the polar organic solvent employed is acetonitrile or 1,2-

dichloroethane.

3. A process according to claim 2 wherein di-p-toluoyl-(D)-tartaric acid is employed as resolving agent.

4. A process according to claim 2 wherein di-p-toluoyl-(L)-tartaric acid is employed as resolving agent.

5. The di-p-toluoyl-(D)-tartaric acid salt of cis ββ-3-amino-4-[2-(furyl)vinyl-1-yl]-methoxycarbonylmethyl-azetidin-2-one.

6. The di-p-toluoyl(L)-tartaric acid salt of cis αα-3-amino-4-(furyl)vinyl-1-yl]-methoxycarbonylmethyl-azetidin-2-one.

Claims for the following Contracting State: ES

1. A method for resolving cis αα/ββ-3-amino-4-[2-(furyl)vinyl-1-yl]-1-methoxycarbonylmethyl-azetidin-2-one into its component enantiomers, which comprises the steps:

(a) contacting a polar organic solution of the cis αα/ββ racemate with at least about 0.5 mole-equivalents of an optically active di-p-toluoyl tartaric acid; and

(b) separating the insoluble salt formed thereby.

2. A process according to claim 1 wherein the polar organic solvent employed is acetonitrile or 1,2-dichloroethane.

3. A process according to claim 2 wherein di-p-toluoyl-(D)-tartaric acid is employed as resolving agent.

4. A process according to claim 2 wherein di-p-toluoyl-(L)-tartaric acid is employed as resolving agent.

# United States Patent [19]

**Berger**

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[54] **PROCESS FOR PREPARING LEVOMEPROMAZINE HYDROGEN MALEATE**


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[58] **Field of Search** ..... 544/41



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[57] **ABSTRACT**

Levomepromazine hydrogen maleate is prepared by resolving (±)-10-(3-dimethylamino-2-methylpropyl)-2-methoxyphenothiazine with (−)-di(p-toluoyl)-L-tartaric acid to produce the neutral salt of the dextrorotatory base and then adding maleic acid to the mother liquors to precipitate the levomepromazine hydrogen maleate.


**3 Claims, No Drawings**

# PROCESS FOR PREPARING LEVOMEPROMAZINE HYDROGEN MALEATE

The present invention relates to the preparation of levomepromazine hydrogen maleate from (±)-10-(3-dimethylamino-2-methylpropyl) -2-methoxyphenothiazine.

Levomepromazine or (−)-10-(3-dimethylamino-2-methylpropyl) -2-methoxyphenothiazine is a therapeutic agent which is especially useful as a tranquillizer, neuroleptic and analgesic.

It is known to prepare levomepromazine by resolution of (±)-10-(3-dimethylamino-2-methylpropyl)-2-methoxyphenothiazine with various resolving agents, e.g. tartaric acid (Hungarian Patent HU 32,813, Chem. Abstr. 102 203977 w; Hungarian Patent HU 157,158, Chem. Abstr. 72 132762 w) or dibenzoyl-D-tartaric acid (Hungarian Patent HU 152,208, Chem. Abstr. 63 13279 b), or with (−)-O-diacetyltartaramic acid (Polish Patent POL 66,636, Chem. Abstr. 80 3541 q). However, these processes do not always lead to satisfactory yields, or else they require the use of large amounts of resolving agent which may sometimes be obtainable only with difficulty.

It has now been found, and this forms the subject of the present invention, that levomepromazine hydrogen maleate can be obtained in good yield from (±)-10-(3-dimethylamino-2-methylpropyl)-2-methoxyphenothiazine (racemic base), by a process which comprises resolving (±)-10-(3-dimethylamino-2-methylpropyl)-2-methoxyphenothiazine with (−)-di(p-toluoyl)-L-tartaric acid to produce the neutral salt of (−)-di(p-toluoyl)tartaric acid and (+) -10-(3-dimethylamino-2-methylpropyl)-2-methoxyphenothiazine and mother liquors containing (−)-10-(3-dimethylamino-2-methylpropyl) -2-methoxy-phenothiazine, and then precipitating levomepromazine hydrogen maleate from the mother liquors by the action of maleic acid, and, optionally, isolating the unresolved racemic base and/or regenerating the (−)-di(p-toluoyl)-L-tartaric acid.

The process of the present invention for the resolution of (±)-10-(3-dimethylamino-2-methylpropyl)-2-methoxyphenothiazine may thus be performed in the following four stages:

(1) Crystallization of the neutral salt of di(p-toluoyl)-tartaric acid and the dextrorotatory base,

(2) crystallization of the acid maleate of the laevorotatory base (levomepromazine hydrogen maleate),

(3) isolation of the remaining racemic base, and

(4) recovery of the di(p-toluoyl)tartaric acid for the purpose of recycling. Stages 3 and 4 are optional but preferred for economy of operation.

In general, the neutral salt of di(p-toluoyl)tartaric acid with the dextrorotatory base may be obtained by gradually cooling a hot (approximately 60° C), stirred solution of a mixture of (±)-10-(3-dimethylamino-2-methylpropyl) -2-methoxyphenothiazine and (−)-di(p-toluoyl)-L-tartaric acid in an organic solvent such as ethanol, in which the neutral salt of the dextrorotatory base is only slightly soluble or insoluble at a temperature in the region of 20° C, down to a temperature in the region of 20° C, after seeding the crystallization with a few crystals of the neutral salt of (−)-di(p-toluoyl)tartaric acid with the dextrorotatory base. The crystallization of the neutral salt of (−)-di(p-toluoyl)tartaric acid with the dextrorotatory base is generally complete after about 4 hours. Preferably, 0.25 to 0.5 mole of (−)-di(p-toluoyl) -L-tartaric acid is used per mole of racemic base employed, optionally in the presence of formic acid.

The amount of solvent is that which is sufficient for dissolving the mixture of racemic base and resolving agent in the hot state.

In general, the levomepromazine hydrogen maleate may be obtained by adding, to the filtrate originating from the separation and the washing of the neutral salt of the dextrorotatory base, a sufficient amount of maleic acid dissolved in the same solvent. The levomepromazine hydrogen maleate which precipitates is separated by filtration.

According to a feature of the invention, the racemic base which has not been resolved can be recovered by concentration followed by alkalinization, e.g. with aqueous sodium carbonate solution, of the mother liquors of crystallization of the levomepromazine hydrogen maleate, followed by extraction with a suitable solvent.

In addition, the (−)-di(p-toluoyl)-L-tartaric acid used as a resolving agent, which is present in the neutral salt of the dextrorotatory base and in the alkaline washing liquors originating from the isolation of the unresolved racemic base, can be recovered and recycled.

For example, the dextrorotatory base may be displaced from its salt by the action of a base and the (−)-di(p-toluoyl)-L-tartaric acid is obtained after acidification of the basic solution thereof. It is generally possible to recover more than 80% of the (−)-di (p-toluoyl)-L-tartaric acid employed.

The process of the present invention makes it possible to prepare levomepromazine hydrogen maleate from the racemic base in yields which are generally greater than 85%, using only a relatively small amount of resolving agent.

The Examples which follow illustrate the invention.

## EAMPLE 1

(a) (±)-10-(3 Dimethylamino-2-methylpropyl)-2-methoxyphenothiazine (16.5 g; 0.05 mole), (-)-di(p-toluoyl)-L-tartaric acid monohydrate (10.15 g; 0.025 mole) and ethanol (75 cc) are introduced into a 250-cc three-necked round-bottomed flask equipped with a mechanical stirrer, a condenser and a nitrogen inlet. The stirred mixture is heated to 60° C. until a homogeneous solution is obtained. The mixture is cooled to 50° C. and crystallization is then seeded by adding a few crystals of the neutral salt of (−)-di(p-toluoyl)tartaric acid and the dextrorotatory base. While stirring is maintained, the mixture is kept for 1 hour at 50° C., cooled to 20° C. in the course of 2 hours, and maintained at 20° C. for 1 hour. The crystals obtained are separated by filtration, washed with ethanol (2×30 cc) and then dried. The neutral salt (12.99 g) of (−)-di(p-toluoyl)tartaric acid and dextrorotatory 10-(3-dimethylamino-2-methylpropyl) -2-methoxyphenothiazine is thereby obtained.

(b) A solution of maleic acid (2.94 g; 0.025 mole) in ethanol (11 cc) is added to the filtrate and to the washings of the crystals of the neutral salt obtained above. Crystals form spontaneously. The mixture is maintained for 2 hours with stirring at a temperature in the region of 20° C., and then for 18 hours at +4° C. After filtration, levomepromazine hydrogen maleate (9.76 g) is obtained in an 88% yield, its rotatory power being:

$[\alpha]_D^{20} = -7.7°$ C. (c=5, dimethylformamide)

The base liberated from an aliquot portion has a rotatory power of:

$[\alpha]_D^{20} = -15.15°$ (c=5, chloroform).

(c) The mother liquors of crystallization of the levomepromazine hydrogen maleate are concentrated to dryness under reduced pressure. The residue is taken up with methylene chloride (50 cc) and a solution of sodium carbonate (6 g) in water (60 cc) is then added. The mixture is stirred for 1 hour. The aqueous phase which is separated by decantation is washed with methylene chloride (10 cc). The organic phase is washed with water (50 cc) and then dried over sodium sulphate. After filtration and concentration under reduced pressure, (±)-10-(-3-di-methylamino-2-methylpropyl) -2-methoxyphenothiazine (1.64 g) is obtained.

(d) The neutral salt (12.99 g) of (−)-di(p-toluoyl)tartaric acid and dextrorotatory 10-(3-dimethylamino-2-methylpropyl) -2-methoxyphenothiazine is dissolved in methylene chloride (50 cc). Water (70 cc) is added and the pH adjusted to 11 by adding N sodium hydroxide solution (27.3 cc). The methylene chloride phase is separated by decantation and dried over sodium sulphate. After filtration and concentration under reduced pressure, (+)-10-(3-dimethylamino-2-methylpropyl)-2-methoxyphenothiazine (7.53 g) is obtained, its rotatory power being:

$[\alpha]_D^{20} = +15.8°$ (c=5, chloroform)

The aqueous phase (pH 11) and the washing liquors originating from the isolation of the racemic base are combined. Ethyl acetate (100 cc) is added and the pH adjusted to 2 by adding 2N hydrochloric acid (69.3 cc). The organic phase is separated by decantation and then dried over sodium sulphate. After filtration and concentration to dryness under reduced pressure, (-)-di(p-toluoyl)-L-tartaric acid (8.75 g; 86% yield) is obtained, its rotatory power being:

$[\alpha]_D^{20} = -122.8°$ (c=1, ethanol).

## EXAMPLE 2

(a) (±)-10-(3-Dimethylamino-2-methylpropyl)-2-methoxyphenothiazine (6.57 g; 0.02 mole), (−)-di(p-toluoyl)-L-tartaric acid monohydrate (2.09 g), 98% strength formic acid (0.38 cc), and ethanol (30 cc) are introduced into a 100-cc three-necked round-bottomed flask equipped with a mechanical stirrer, a condenser and a nitrogen inlet. The stirred mixture is heated to 60° C. until a homogeneous medium is obtained. The mixture is cooled to 50° C. and a few orystals of neutral salt of (−)-di(p-toluoyl)tartaric acid and dextrorotatory base are then added.

The temperature is kept for 1 hour at 50° C and the mixture is then cooled from 50° C. to 20° C. in the course of 2 hours. The mixture is maintained for 1 hour at 20° C. with stirring. The crystals obtained are separated by filtration, washed with ethanol (2×12 cc) and dried. The neutral salt (3.98 g) of (−)-di(p-toluoyl)tartaric acid and dextrorotatory 10-(3-dimethylamino-2-methylpropyl)-2-methoxyphenothiazine is thereby obtained, its rotatory power being:

$[\alpha]_D^{20} = +16.6°$ (c=5, chloroform).

(b) Maleic acid (1.16 g) is added to the filtrate and the washings of the crystals of the neutral salt obtained above. Crystals develop spontaneously at a temperature in the region of 20° C. The mixture is stirred for 2 hours at a temperature in the region of 20° C. and then for 18 hours at 4° C. After filtration, levomepromazine hydrogen maleate (3.52 g) is obtained.

The base liberated from an aliquot portion has a rotatory power of:

$[\alpha]_D^{20} = -13.7°$ (c=5, chloroform).

I claim:

1. A process for preparing levomepromazine hydrogen maleate from (±)-10-(3-dimethylamino-2-methylpropyl)-2-methoxyphenothiazine, which comprises resolving (±)-10-(3-dimethylamino-2-methylpropyl)-2-methoxyphenothiazine with (−)-di(p-toluoyl)-L-tartaric acid using 0.25 to 0.5 mole of (−)-di(p-toluoyl)-L-tartaric acid per mole of (±)-10-(3-dimethylamino-2-methylpropyl) -2-methoxy-phenothiazine to produce the neutral salt of (−)-di(p-toluoyl) tartaric acid and (±)-10-(3-dimethylamino-2-methylpropyl) -2-methoxyphenothiazine and mother liquors containing (−)-10-(3-dimethylamino-2-methylpropyl)-2-methoxyphenothiazine, and the precipitating levomepromazine hydrogen maleate from the mother liquors by the action of maleic acid, and, optionally, isolating the unresolved racemic base and/or regenerating the (−)-di(p-toluoyl)-L-tartaric acid.

2. Process according to claim 1, in which the said resolution is carried out in ethanol in sufficient amount to dissolve in the hot state the (±)-10-(3-dimethylamino -2-methylpropyl)-2-methoxyphenothiazine and (−)-di(p-toluoyl)-L-tartaric acid.

3. Process according to claim 5, in which one mole of maleic acid is used per mole of the racemic base resolved.

* * * * *

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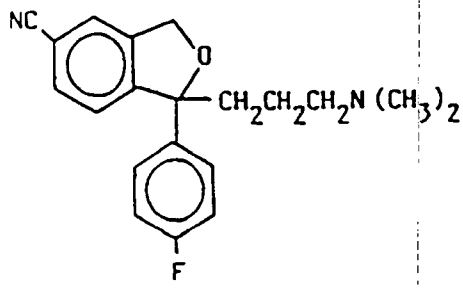
## DESCRIPCION

La presente invención se refiere a los dos nuevos enantiómeros del medicamento antidepresivo 1 - (3 - dimetil - aminopropil) - 1 - (4' - fluorofenil) - 1,3 - dihidroisobenzofurano(5) - carbonitrilo (citalopram) de fórmula I siguiente:




I

y al uso de estos enantiómeros como compuestos antidepresivos así como a su posible uso en geriatría o en la curación de la obesidad o del alcoholismo.

Esta invención incluye además las sales farmacéuticamente aceptables de los enantiómeros del compuesto I formadas con ácidos no tóxicos orgánicos o inorgánicos. Dichas sales se preparan fácilmente por métodos conocidos en la técnica. La base se hace reaccionar bien con la cantidad calculada de ácido orgánico o inorgánico en un disolvente miscible con el agua, tal como acetona o etanol, con aislamiento de la sal por concentración y enfriamiento o bien con un exceso del ácido en un disolvente inmiscible con el agua, tal como éter etílico, acetato de etilo o diclorometano, con separación directa de la sal deseada. Ejemplos típicos de dichas sales orgánicas son las formadas con los ácidos maleico, fumárico, benzoico, ascórbico, pamoico, succínico, oxálico, salicílico, metanosulfónico, etanodisulfónico, acético, propiónico, tartárico, cítrico, glucónico, láctico, málico, mandélico, cinámico, citracónico, aspártico, esteárico, palmítico, itacónico, glicólico, p - amino - benzoico, glutámico, benceno - - sulfónico y ácido teofilin - acético, así como las 8 - haloteofilinas, por ejemplo la 8 - bromoteofilina.

Ejemplos típicos de dichas sales inorgánicas son las formadas con los ácidos clorhídrico, bromhídrico, sulfúrico, sulfámico, fosfórico y nítrico.

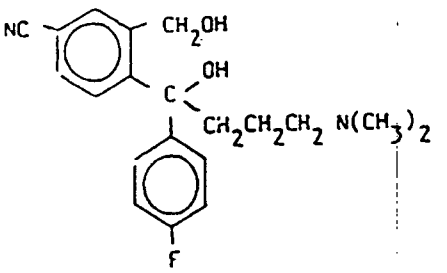
Por supuesto, estas sales se pueden preparar también por el método convencional de la doble descomposición de las sales apropiadas, que es bien conocido en la técnica.

Además, se ha encontrado que se pueden obtener sales no higroscópicas de adición de ácido mediante técnicas convencionales de liofilización a partir de soluciones acuosas de sales apropiadas de los tipos anteriormente mencionados.

La invención se refiere además de un método para resolver el racemato de I en los isómeros individuales.

El citalopram, que ha sido descrito, por ejemplo, en la patente de EE.UU. n° 4.136.193, ha demostrado ser un compuesto antidepresivo eficaz en el hombre (Referencia : A. Gravem et al., Acta psychiat. Scand., n° 75, páginas 478 - 486 (1987)). Todo el trabajo de desarrollo de este compuesto se ha realizado con el racemato. Se ha demostrado farmacológicamente que el citalopram es un inhibidor muy selectivo de la reabsorción del 5 - HT. Los intentos anteriores de cristalizar las sales diastereoisoméricas de los enantiómeros del citalopram habían fallado.

Sorprendentemente, se ha demostrado ahora que es posible resolver el producto intermedio 4 - [4 - (dimetilamino) - 1 - (4' - fluorofenil) - 1 - hidroxi - 1 - butil] - 3 - (hidroximetil)benzonitrilo, II, en sus enantiómeros y finalmente de una forma estereoselectiva convertir estos enantiómeros en los correspondientes enantiómeros del citalopram. Del mismo modo, los monoésteres de II formados con ácidos carboxílicos ópticamente activos pueden separarse en sus correspondientes diastereoisómeros y posteriormente convertirse directamente en los enantiómeros del citalopram mediante una reacción estereoselectiva de cierre de anillo. El producto intermedio diol, II, se describe, por ejemplo, en la patente de EE.UU. n° 4.650.884 como una mezcla racémica.



II

Los enantiómeros del producto intermedio de fórmula II así como los monoésteres entran igualmente dentro del alcance de la presente invención.

Además, se ha demostrado sorprendentemente que casi toda la inhibición de la absorción de 5 - HT residía en el enantiómero (+) - citalopram.

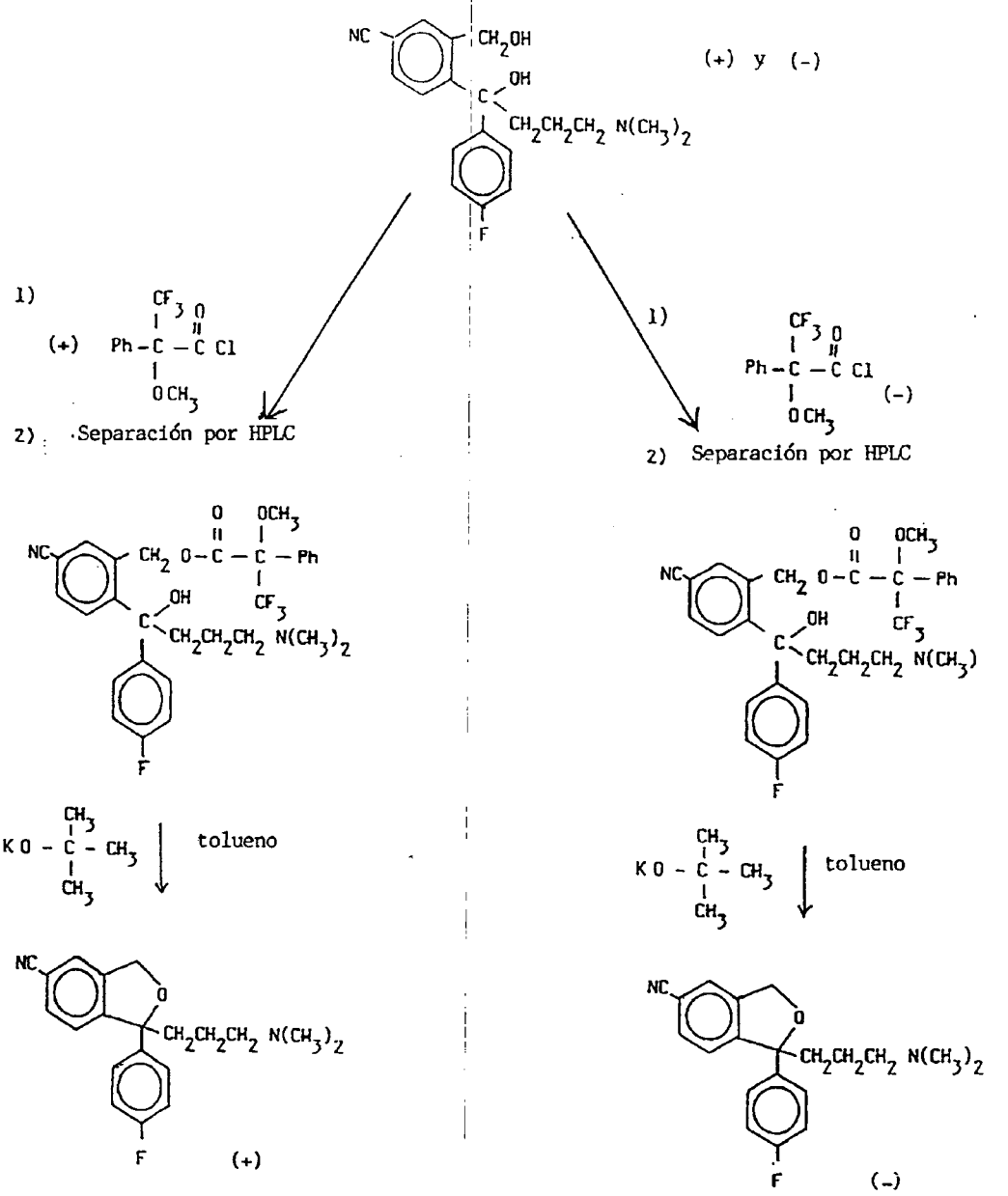
La presente invención incluye además un nuevo método de sintetizar el compuesto I a partir del compuesto diol II por esterificación del grupo alcohólico primario en un éster lábil, que en presencia de una base experimenta un cierre espontáneo del anillo hasta citalopram o, si se esterifica un compuesto II enantioméricamente puro, se produce el correspondiente enantiómero de citalopram con total conservación de la configuración.

Según la invención, el compuesto II se hace reaccionar con:

a) Un derivado ácido enantioméricamente puro tal como cloruro de ácido, anhídrido o éster lábil como, por ejemplo, se ilustra en el esquema de reacción I mediante el cloruro de (+) - ó ( - ) - $\alpha$ - metoxi - $\alpha$ - trifluorometilfenilacetilo. La reacción se realiza preferentemente en un disolvente orgánico inerte como, por ejemplo, tolueno, diclorometano o tetrahidrofurano. Se añade una base (trietilamina, N,N - dimetilanilina, piridina o similares) para neutralizar el ácido clorhídrico liberado. Posteriormente se separan los diastereoisómeros mediante HPLC o cristalización fraccionada. Los diastereoisómeros así purificados se separan finalmente tratándolos con una base fuerte (por ejemplo, un alcóxido) en un disolvente orgánico inerte como, por ejemplo, tolueno, tetrahidrofurano, o dimetoxietano produciendo respectivamente los enantiómeros puros de citalopram. La reacción de cierre del anillo se realiza preferentemente a temperaturas relativamente bajas (desde - 20°C hasta temperatura ambiente).

(Ver Esquema en la página siguiente.)

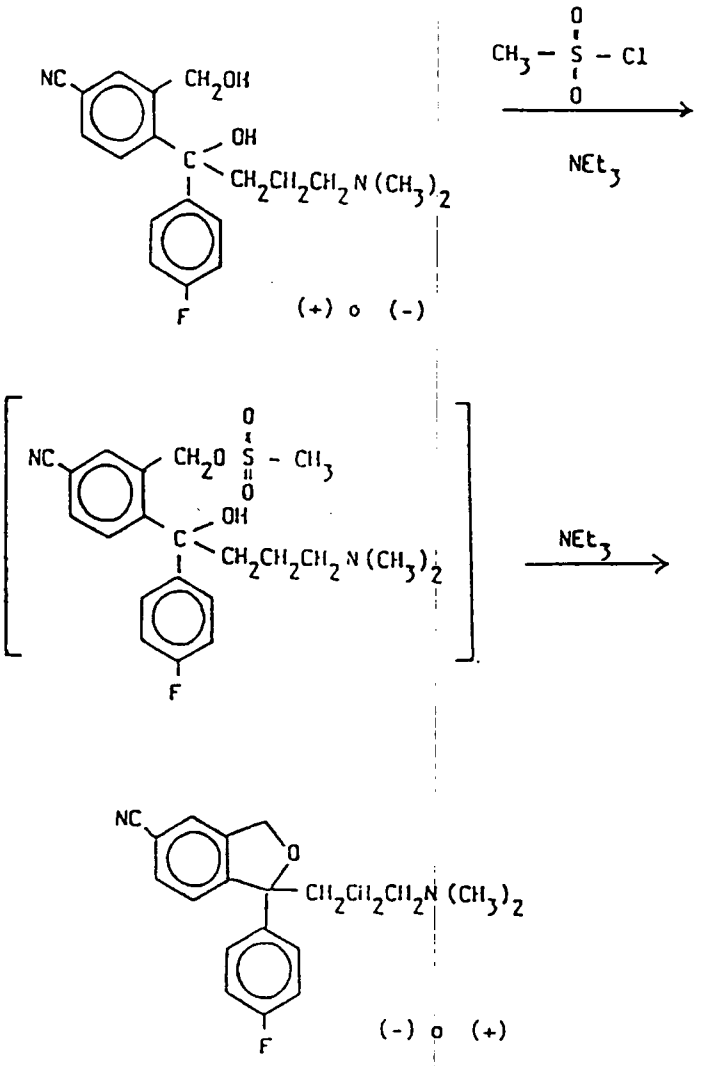
*Esquema de Reacción I*



b) Los enantiómeros de un ácido ópticamente activo, dando sucesivamente las sales diastereoisoméricas puras. Se emplean adecuadamente los antípodas ópticos del ácido tartárico, ácido di - benzoil-tartárico, ácido di - (p - toluil)tartárico, ácido bisnaftilfosfórico, ácido 10 - canforsulfónico y similares.

c) El cierre estereoselectivo del anillo de los enantiómeros puros de II preparados como en b) se realiza a través de un éster lábil como, por ejemplo, de metansulfonilo, p - toluenosulfonilo, 10 - canforsulfonilo, trifluoracetilo o trifluormetansulfonilo con adición simultánea de una base (trietilamina, dimetilanilina o piridina) en un disolvente orgánico inerte a 0°C. La reacción de cierre del anillo se ilustra con el ejemplo del esquema de reacción II:

*Esquema de Reacción II*



Ejemplo 1

*Resolución por el método a)*

A 11 g del ácido (+) - $\alpha$ - metoxi - $\alpha$ - trifluorometilacético disueltos en 25 ml de cloroformo se añadieron 50 ml de cloruro de tionilo y unas pocas gotas de dimetilformamida. La mezcla de reacción se sometió a reflujo durante 2 horas. El exceso de cloruro de tionilo se evaporó con tolueno, dejando el cloruro de (+) - $\alpha$ - metoxi - $\alpha$ - trifluormetilacetilo como un líquido. Este líquido se diluyó con 50 ml de diclorometano y se añadió gota a gota a una solución enfriada con hielo de 17 g de 4 - [4 - (dimetilamino) - 1 - (4' - fluorofenil) - 1 - hidroxi - 1 - butil] - 3 - (hidroximetil)benzonitrilo, II, y 8 ml de trietilamina en 150 ml de diclorometano. La mezcla de reacción se agitó adicionalmente durante otra hora a temperatura ambiente, se lavó posteriormente con salmuera, se secó (con $MgSO_4$) y el disolvente se evaporó al vacío por debajo de 30°C dando 20 g del éster como una mezcla diastereoisomérica. Purificando repetidamente por HPLC (elución con acetato de etilo/tetrahidrofurano 9:1 conteniendo un 4% de trietilamina) y recogiendo sólo 5 - 10% de la sustancia inicial en el pico principal, se aisló 1,1 g de compuesto enantioméricamente puro.

La sustancia así aislada se disolvió en tolueno seco (50 ml) y se añadió a una suspensión de 0,3 g de t - butóxido potásico en 20 ml de tolueno a 0°C. La solución de tolueno se lavó con agua, se secó (con $MgSO_4$) y se evaporó el disolvente rindiendo 0,6 g de *(+) - 1 - (dimetilaminopropil - 1 - (4' - fluorofenil) - 1,3 - dihidroisobenzofuran - 5 - carbonitrilo* en forma de aceite. $[\alpha]_D = +11,81°$ (c=1, $CH_3OH$) (determinado con una sustancia que contiene un 10% peso/peso de metanol). La pureza óptica se determinó por espectroscopía de RMN $^1H$ ($CDCl_3$ como disolvente) (instrumento Bruker AC - 250 MHz) añadiendo un exceso de 10:1 peso/peso del reactivo quiral ( - ) - 2,2,2 - trifluor - 1 - (9 - antril)etanol. Pureza óptica : 99,6%. De una forma totalmente análoga se sintetizó el *( - ) - 1 - (3 - dimetilaminopropil) - 1 - (4' - fluorofenil) - 1,3 - dihidroisobenzofuran - 5 - - carbonitrilo.* $[\alpha]_D = - 12,34°$ (c=1, $CH_3OH$) (determinado con una sustancia que contiene un 10% peso/peso de metanol). Pureza óptica : 99,9%.

Ejemplo 2

*Resolución por los métodos b) y c)*

A una solución de 85 g de hidrobromuro de 4 - [4 - (dimetilamino) - 1 - (4' - fluorofenil) - 1 - hidroxi - 1 - butil] - 3 - (hidroximetil)benzonitrilo en 500 ml de agua se añadieron 200 ml de solución 2M de NaOH enfriada con hielo y 500 ml de éter. La mezcla se agitó durante media hora, se separó la fase etérea, se secó (con $MgSO_4$) y se evaporó el éter. El aceite restante se disolvió en 400 ml de 2 - propanol a 40°C, y se añadieron con agitación vigorosa 40 g de ácido (+) - di - p - toluiltartárico (en forma de hidrato). Después de un corto período de tiempo empezó la cristalización. Después de 3 horas de agitación, se separó la sal precipitada por filtración y se secó rindiendo 29,2 g (55,1%) de la sal de *( - ) - 4 - [4 - (dimetilamino) - 1 - (4' - fluorofenil) - 1 - hidroxi - 1 - butil] - 3- (hidroximetil)benzonitrilo, hemi* y *ácido (+) - di - p - - toluiltartárico.* Punto de fusión : 134 - 135°C, $[\alpha]_D = +10,0°$ (c=1, $CH_3OH$). El filtrado se emplea más adelante.

A una solución enfriada con hielo de 14 g del isómero ( - ) obtenido antes como base en 300 ml de tolueno seco se añadieron 16 ml de trietilamina, y 3,6 ml de cloruro de metansulfonilo en 20 ml de tolueno seco se añadieron gota a gota durante 10 minutos. La mezcla de reacción se agitó adicionalmente durante media hora, se lavó con salmuera, se secó (con $MgSO_4$) y se evaporó el disolvente. El compuesto del título se purificó mediante cromatografía de columna dando 8 g de *(+) - 1 - (3 - dimetilaminopropil) - 1 - (4' - fluorofenil) - 1,3 - dihidroisobenzofuran - 5 - carbonitrilo.* $[\alpha]_D = +12,33°$ (c=1, $CH_3OH$).

La sal de ácido oxálico del isómero (+) se cristalizó desde acetona. Punto de fusión : 147 - 148°C, $[\alpha]_D = +12,31°$ (c=1, $CH_3OH$).

La sal de ácido pamoico del isómero (+) se preparó de la siguiente manera: A 1,8 g de la base del isómero (+) se añadieron 2 g de ácido pamoico en 25 ml de MeOH. La mezcla se sometió a reflujo durante 1 hora y posteriormente se enfrió a temperatura ambiente. El precipitado se separó por filtración rindiendo 3,0 g de la sal de ácido pamoico. Punto de fusión : 264 - 266°C, $[\alpha]_D = +13,88°$ (c=1, dimetilformamida).

Un compuesto de adición 2:1 del isómero (+) con ácido L(+) - tartárico se preparó de la siguiente manera: 4 g del isómero (+) - en forma de base se disolvieron en 100 ml de éter dietílico y se extrajeron con agitación en 100 ml de agua conteniendo 0,8 g de ácido L(+) - tartárico. Se separó la fase orgánica

y se desechó. La fase acuosa se liofilizó a vacío (0,1 mm de Hg) durante 18 horas dejando 3,8 g del compuesto del epígrafe como un polvo blanco. Este compuesto de adición fue estable y no higroscópico.

De una manera correspondiente a la anterior a través de la sal de (+) - 4 - [4 - (dimetilamino) - 1 - (4' - fluorofenil) - 1 - hidroxi - 1 - butil] - 3 - (hidroximetil)benzonitrilo, hemi - - ácido ( - ) - di - (p - toluil)tartárico $[\alpha]_D$ = - 8,9° (c=1, $CH_3OH$) que se convirtió en el correspondiente diol base $[\alpha]_D$ = +61,1° (c=1), $CH_3OH$) y finalmente la reacción de cierre del anillo rindió 10 g de *( - ) - 1 - (3 - dimetilaminopropil) - 1 - (4' - fluorofenil) - 1,3 - dihidroisobenzofuran - 5 - carbonitrilo.* $[\alpha]_D$ = - 12,1° (c=1, $CH_3OH$).

La sal de ácido oxálico del isómero ( - ) se cristalizó en acetona. Punto de fusión : 147 - 148°C, $[\alpha]_D$ = - 12,08° (c=1, $CH_3OH$).

Ejemplo 3

*Preparación de citalopram por el método c)*

A una solución enfriada con hielo de 28 g del diol base racémico, II, en 500 ml de diclorometano, se añadieron 32 ml de trietilamina, y se añadieron gota a gota 7,5 g de cloruro de metansulfonilo en 30 ml de diclorometano durante media hora. La mezcla de reacción se lavó dos veces con una solución 0,1 M de NaOH, se separó la fase orgánica, se secó (con $MgSO_4$) y se evaporó el disolvente, dejando 21,5 g de *(+)* - citalopram del epígrafe como una base cristalina. El material así obtenido se disolvió en una mezcla (2:1) de 2 - propanol y metanol y se introdujo una cantidad equivalente de HBr gaseoso. Se dejó reposar la mezcla durante la noche y el hidrobromuro precipitado se separó por filtración.

Rendimiento : 26 g con un punto de fusión de 184 - 186°C.

Se ensayó la capacidad de los enantiómeros del ejemplo 1 para bloquear la reabsorción de 5 - HT mediante métodos de ensayo estándar y fiables. Los resultados se exponen en la Tabla 1 comparándolos con la mezcla racémica de citalopram.

*Potenciación de 5 - htp*

El ensayo evalúa la capacidad de la sustancia para potenciar el efecto del 5 - HTP, que resulta en el desarrollo del síndrome de 5 - HT (Christensen, Fjalland, Pedersen, Danneskiold - Sams⊘ Oe y Svendsen; European J. Pharmacol. 41, 153 - 162, 1977).

*Procedimiento*

Cada grupo de tratamiento consta de 3 ratones, y dos grupos son tratados con la dosis de ensayo más alta. Se incluyen un grupo testigo tratado solamente con 5 - HTP y un grupo tratado con 10 mg/kg de citalopram y con 5 - HTP se emplea como referencia de síndrome completo de 5 - HT.

*Ruta de administración*

30 minutos después de la administración de la sustancia de ensayo, se les da a los otros grupos 5 - HTP (100 mg/kg) por vía i.v. (tiempo de inyección : 5 - 10 segundos). Después de esta dosis normal de 5 - HTP, los ratones no tratados permanecen no afectados, pero si los animales han sido tratados previamente con una sustancia, que inhiba la absorción de 5 - HT o que sea un agonista de 5 - HT, se producirá un síndrome de 5 - HTP. Los síntomas son los mismos descritos anteriormente : 1) excitación, 2) temblor, y 3) abducción de los miembros traseros. Los animales se observaron durante 15 minutos y se dio a cada animal un punto por cada síntoma presente. De nuevo los resultados se expresan en fracciones: 0/9, 1/9, ..., 9/9, donde 0, 1 ..., 9 son el número de puntos por grupo después de la dosis en cuestión. El valor de la $DE_{50}$ se calculó por análisis de probabilidad logarítmica.

*Inhibición de la absorción de $^3h$ - serotonina en sinaptosomas de cerebro de ratas*

Mediante este método la inhibición por los fármacos de la absorción de $^3H$ - serotonina ($^3H$ - 5 - HT) (10 nM) en las sinaptosomas de cerebro de rata se determina in vitro. El método y los resultados aparecen en Hyttel, Psychopharmacology 1978, 60, 13 - 18; Hyttel, Prog. Neuro - Psychopharmacol. & Biol. Psychiat. 1982, 6, 277 - 295; Hyttel & Larsen, Acta pharmacol. tox. 1985, 56, suplemento 1, 146 - 153.

*Procedimiento*

Ratas machos (125 - 250 g) Wistar (Mol:Wist) se sacrificaron decapitándolas y se desangraron. Los tejidos del cerebro (menos el cerebelo) se homogeneizaron suavemente (homogeneizador de vidrio con teflón) en 40 volúmenes (peso/volumen) de una solución enfriada con hielo 0,32 M de sacarosa conteniendo 1 mM de nialamida. La fracción $P_2$ (fracción sinaptosómica) se obtuvo por centrifugación (600 g, 10 minutos y 25.000 g, 55 minutos, 4°C) y se suspendió en 800 volúmenes de un tampón de Krebs - Ringer - fosfato modificado, pH 7,4.

A 4000 $\mu$l de la suspensión sinaptosómica (5 mg de tejido original) sobre hielo se añadieron 100 $\mu$l de la sustancia de ensayo en agua. Después de una incubación previa a 37°C durante 5 minutos, se añadieron 100 $\mu$l de $^3$H - 1 - NA (concentración final 10 nM) y se incubaron las muestras durante 10 minutos a 37°C. La incubación se concluyó filtrando las muestras bajo vacío a través de filtros Whatman GF/F con un lavado con 5 ml de tampón conteniendo 10 $\mu$M de 5 - HT no marcado. Los filtros se colocaron en viales de recuento y se añadieron 4 ml de un líquido apropiado de centelleo (por ejemplo Picofluor $^{TM}$15). Después de agitar durante 1 hora y dejar reposar en la oscuridad durante 2 horas, se determinó el contenido en radiactividad por recuento de centelleo de líquidos. La absorción se obtiene restando lo enlazado no específicamente y el transporte pasivo medido en presencia de 10 $\mu$M de citalopram (Lu 10 - 171 - B).

Para determinar la inhibición de la absorción se emplearon cinco concentraciones de fármaco que cubren tres decenas.

Las cpm medidas se representaron frente a las concentraciones de fármaco en una gráfica semilogarítmica, y se dibujó la curva en S que mejor se adaptaba. El valor de $CI_{50}$ se determinó como la concentración, a la que la absorción es 50% de la absorción total en las muestras testigos menos lo enlazado no específicamente y la absorción en presencia de 10 $\mu$M de citalopram.

TABLA 1

*Resultados de los ensayos farmacológicos*

| Compuesto | Potenciación de 5 - HTP $DE_{50}$ $\mu$mol/kg | Inhibición de absorción de 5 - HT $CI_{50}$ (nM) |
|---|---|---|
| (+) - citalopram | 2,0 | 1,1 |
| ( - ) - citalopram | 120 | 150 |
| (±) - citalopram | 3,3 | 1,8 |

El (+) - 1 - (3 - dimetilaminopropil) - 1 - (4' - fluorofenil) - 1,3 - dihidroisobenzofurano - 5 - carbonitrilo((+) - citalopram) y sus sales de adición de ácidos no tóxicos pueden administrarse a animales, tales como perros, gatos, caballos y ovejas, (incluso a seres humanos), tanto oralmente como parenteralmente, y puede emplearse en forma de comprimidos, cápsulas, polvos, jarabes o en forma de soluciones estériles usuales para inyección.

Más cómodamente los compuestos de Fórmula 1 se administran oralmente en forma de dosis unitarias tales como comprimidos o cápsulas, conteniendo cada dosis unitaria la amina libre o una sal de adición de ácido no tóxico de uno de los citados compuestos en una cantidad desde unos 0,10 mg hasta alrededor de 100 mg, preferentemente, sin embargo, desde unos 5 mg hasta 50 mg, calculados en amina libre, variando la dosis total diaria generalmente en el intervalo desde alrededor de 1,0 hasta unos 500 mg. Las dosis exactas individuales así como las dosis diarias se determinarán en cada caso particular según los principios médicos establecidos bajo la dirección de un médico.

Al preparar comprimidos, el principio activo se mezcla, en la mayor parte de los casos, con los excipientes ordinarios de los comprimidos, tales como almidón de maíz, almidón de patata, talco, estearato de magnesio, gelatina, lactosa y gomas.

Ejemplos típicos de formulaciones que contienen como principio activo (+) - citalopram en forma de una sal de adición de ácido son los que siguen:

1) Comprimidos que contienen 5 mg de (+) - citalopram calculado en base libre:

| | |
|---|---|
| Compuesto 20 | 5 mg |
| Lactosa | 18 mg |
| Almidón de patata | 27 mg |
| Sacarosa | 58 mg |
| Sorbitol | 3 mg |
| Talco | 5 mg |
| Gelatina | 2 mg |
| Povidona | 1 mg |
| Estearato de magnesio | 0,5 mg |

2) Comprimidos que contienen 50 mg de (+) - citalopram alculado en base libre:

| | |
|---|---|
| (+) - citalopram | 50 mg |
| Lactosa | 16 mg |
| Almidón de patata | 45 mg |
| Sacarosa | 106 mg |
| Sorbitol | 6 mg |
| Talco | 9 mg |
| Gelatina | 4 mg |
| Povidona | 3 mg |
| Estearato de magnesio | 0,6 mg |

3) Jarabe que contiene por mililitro:

| | |
|---|---|
| (+) - citalopram | 10 mg |
| Sorbitol | 500 mg |
| Goma tragacanto | 7 mg |
| Glicerina | 50 mg |
| Metil - parabén | 1 mg |
| Propil - parabén | 0,1 mg |
| Etanol | 0,005 ml |
| Agua | hasta 1 ml |

4) Solución para inyección que contiene por mililitro:

| | |
|---|---|
| (+) - citalopram | 50 mg |
| Acido acético | 17,9 mg |
| Agua estéril | hasta 1 ml |

5) Solución para inyección que contiene por mililitro:

| | |
|---|---|
| (+) - citalopram | 10 mg |
| Sorbitol | 42,9 mg |
| Acido acético | 0,63 mg |
| Hidróxido sódico | 22 mg |
| Agua estéril | hasta 1 ml |

Se pueden emplear cualquiera de los demás excipientes de compresión farmacéutica siempre que éstos sean compatibles con el principio activo, y las composiciones adicionales y las formas de dosificación pueden ser similares a las actualmente utilizadas en los neurolépticos, analgésicos o antidepresivos.

También las combinaciones de (+) - citalopram así como de sus sales de ácidos no tóxicos con otros principios activos, especialmente con otros neurolépticos, timolépticos, tranquilizantes o analgésicos caen

dentro del alcance de la presente invención.

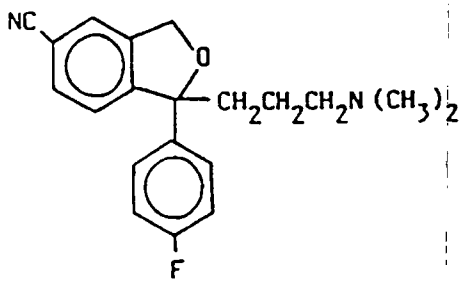
Como se ha expresado anteriormente, al aislar los enantiómeros de citalopram en forma de una sal de adición de ácido, los ácidos se seleccionan preferiblemente de modo que contengan un anión que no sea tóxico y sea farmacológicamente aceptable, como mínimo a dosis terapéuticas usuales. Como sales representativas que se incluyen en este grupo preferente están los hidrocloruros, hidrobromuros, sulfatos, acetatos, fosfatos, nitratos, metanosulfonatos, etano - sulfonatos, lactatos, citratos, tartratos o bitartratos, pamoatos y maleatos de las aminas de Fórmula I. Hay otros ácidos que son igualmente adecuados y que pueden emplearse si se desea. Por ejemplo : se pueden emplear además los ácidos fumárico, benzoico, ascórbico, succínico, salicílico, bismetilensalicílico, propiónico, glucónico, málico, malónico, mandélico, cinámico, citracónico, esteárico, palmítico, itacónico, glicólico, bencenosulfónico y sulfámico como ácidos formadores de sales de adición de ácido.

Cuando se desea aislar un compuesto de la invención en forma de base libre, esto se puede realizar según el procedimiento convencional de disolver en agua la sal aislada o sin aislar, tratarla con un material alcalino adecuado, extraer la base libre liberada con un disolvente orgánico adecuado, secar el extracto y evaporar a sequedad o someter a destilación fraccionada para realizar el aislamiento de la amina básica libre.

La invención comprende además un método para el alivio, paliación, mitigación o inhibición de las manifestaciones de ciertas anormalidades fisiológicas - psicológicas de los animales, especialmente depresiones mediante la administración al animal, incluyendo los seres humanos, de una cantidad adecuada de (+) - citalopram o de una de sus sales de adición de un ácido no tóxicas. Una cantidad adecuada sería desde alrededor de 0,001 mg hasta alrededor de 10 mg por kg de peso por unidad de dosis, y desde unos 0,003 miligramos hasta alrededor de 7 miligramos por kg de peso al día.

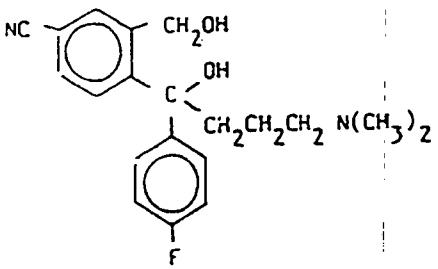
## REIVINDICACIONES

1. Un método para la preparación de (+) - 1 - (3 - dimetilaminopropil) - 1 - (4' - fluorofenil) - 1,3 - dihidroisobenzofuran - 5 - carbonitrilo que tenga la fórmula general




I

y de sus sales de adición de ácido no tóxicas que comprende convertir ( - ) - 4 - [4 - (dimetilamino) - 1 - (4' - fluorofenil) - 1 - hidroxi - 1 - butil] - 3 - (hidroximetil)benzonitrilo o un monoéster suyo que tiene la fórmula




II

donde R es H o un grupo éster lábil, de una forma estereoselectiva y, luego aislar el compuesto de Fórmula I como tal o como una de sus sales de adición de ácido no tóxicas.

2. Un método según la reivindicación 1, en el que el compuesto de Fórmula I se aísla como la sal de adición del ácido pamoico.

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(54) **Title:** AN IMPROVED PROCESS FOR THE PREPARATION OF ESCITALOPRAM

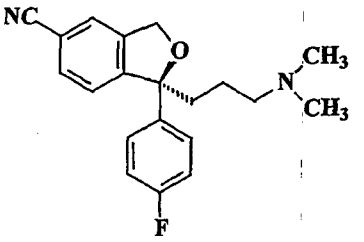
(57) **Abstract:** The present invention relates to an improved process for the preparation of Escitalopram of the Formula (I), which comprises, isolation of Diol compound as an oxalate salt, resolution of Diol compound and cyclization of resolved compound of Formula (VII). The present invention provides a process to obtain pure Diol compound by preparing its Oxalate salt, which is useful for resolution of enantiomers .

WO 2007/012954 A1

# AN IMPROVED PROCESS FOR THE PREPARATION OF ESCITALOPRAM

## FIELD OF THE INVENTION

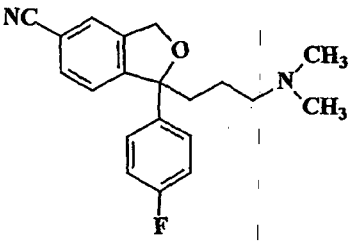
The present invention relates to an industrially advantageous process for the preparation of pure Escitalopram, (*S*)-(+)-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile of Formula I, and its pharmaceutical acceptable salts.



I

## BACKGROUND OF THE INVENTION

Escitalopram is the S-enantiomer of an antidepressant drug Citalopram of Formula II.



II

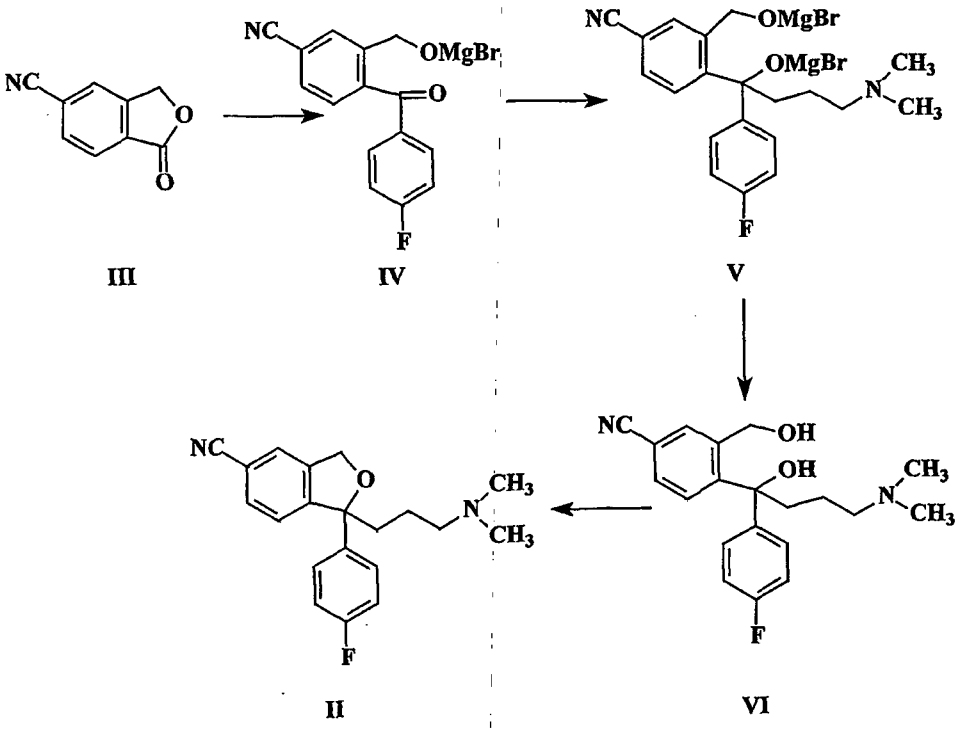
Citalopram is a well known antidepressant drug that has now been in the market for several years and is chemically known as 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile.

Citalopram is a selective centrally acting serotonin (5-HT) reuptake inhibitor. Citalopram was first disclosed in DE 2,657,013, corresponding to US 4,136,193.

The antidepressant activity of Citalopram has been reported in several publications, e.g. *J. Hyttel, Prog. Neuro-Psychophannacol & Biol. Psychiat., 1982, 6, 277-295 and A. Grravem, Acta Psychiatr. Scand., 1987, 75, 478-486.*

The process for the preparation of antidepressant Citalopram and its pharmaceutical properties were first disclosed in US 4,136,193. Citalopram was produced from the corresponding 5-bromo derivative by reaction with cuprous cyanide. Further, variants of this method are disclosed in PCT Publications, WO 00/13648 and WO 00/11926 wherein the exchange of 5-halogen or 5-$CF_3$-$(CF_2)_n$-$SO_2$-O- with cyano group is achieved with cyanide source such as KCN, NaCN or (R'$_4$ N)CN, where R'$_4$ indicates four groups which may be same or different and are selected from hydrogen and straight chain or branched $C_{1-6}$ alkane, in presence of palladium or nickel catalyst.

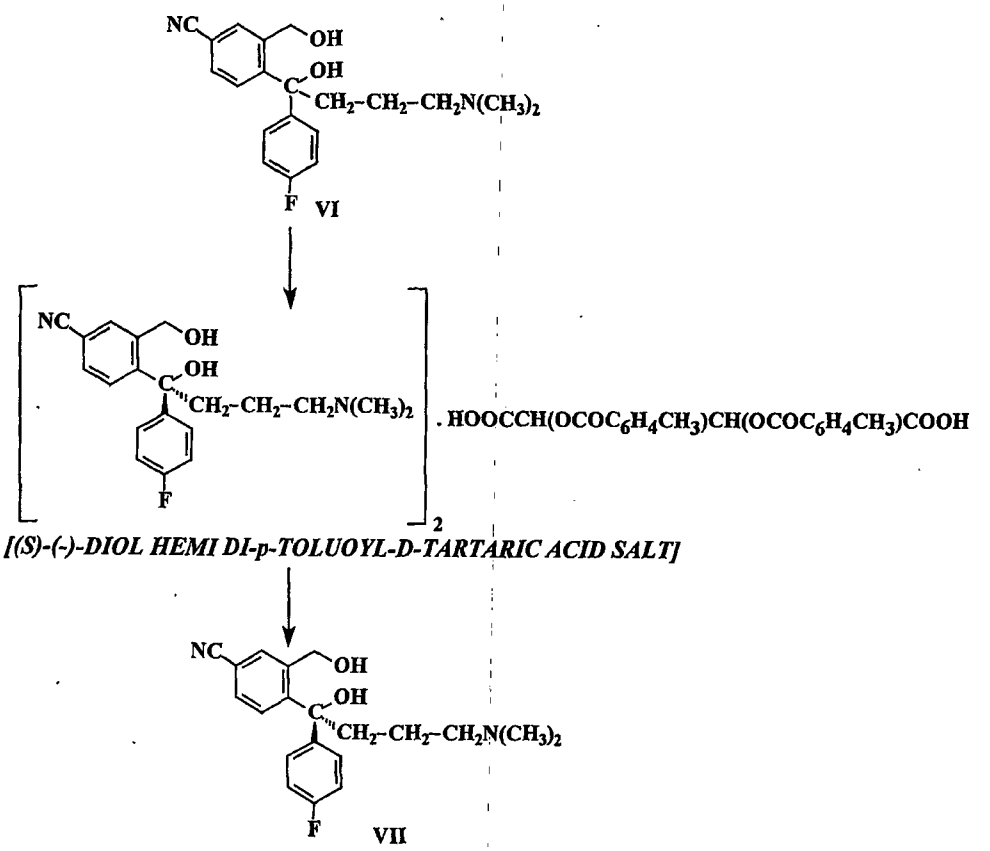
The diol, 4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile (VI), and its use as an intermediate in the preparation of Citalopram has been disclosed in US 4,650,884. In this reference, 5-cyanophthalide of Formula III is reacted successively with *p*-fluorophenylmagnesium bromide and 3-(N,N-dimethylamino)propylmagnesium chloride to get the compound of the Formula VI and its further conversion to Citalopram base is achieved by reaction with 70% sulfuric acid.




The S-enantiomer (Escitalopram) of the Formula I and the antidepressant effect of said enantiomer is disclosed in US 4,943,590, wherein use of Escitalopram for the treatment of neurotic disorders has been described. WO 02/087566 describes the use of Escitalopram for treating depressive patients who have failed to respond to conventional SSRIs.

Escitalopram has now been developed as an antidepressant and hence a need for a commercially feasible method to produce Escitalopram has emerged.

Process for the preparation of Escitalopram was first disclosed in US 4,943,590. According to this patent reference, attempts to resolve Citalopram enantiomers to produce Escitalopram were not successful. Therefore, resolution of enantiomers of the diol compound (VI) with optically active selective precipitant, Di-*p*-toluoyl-D-tartaric acid, has been carried out to obtain (*S*)-Enantiomer of Diol prior to ring closure in a stereospecific manner to obtain Escitalopram (I) as shown below:




The resolution of enantiomers requires high purity of Diol compound (VI) to selectively precipitate out (*S*)-Diol hemi Di-*p*-toluoyl-D-tartaric acid salt having substantially high chiral purity. The Diol compound (VI), obtained as described in US 4,650,884, is not sufficiently pure and extensive purification steps have been described in this reference, which involve repeated charcoal and silica gel treatment of the Diol compound. Further, purification of Diol compound has been carried out by preparing hydrobromide salt and subsequently by crystallization, first from water and thereafter from 2-propanol / ethanol.

The present invention provides a simple and economical process for the purification of Diol compound (VI), which can be used for commercial production of Escitalopram.

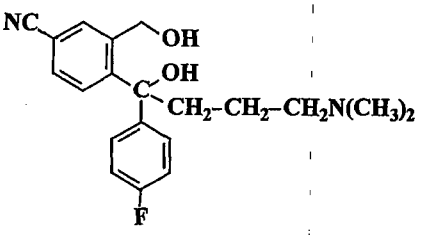
## OBJECTIVE OF THE INVENTION

The main objective of the invention is to provide an improved process for the preparation of highly pure Escitalopram in high yield.

## SUMMARY OF THE INVENTION

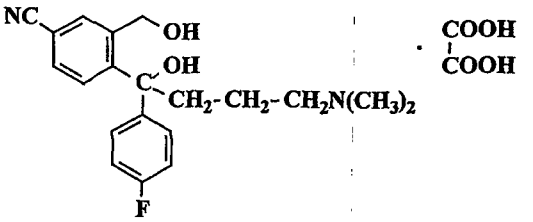
According to the present invention, a process is provided for the manufacture of highly pure (*S*)-(+)-1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-phthalanecarbonitrile of Formula I and its oxalate salt (Escitalopram oxalate), which comprises:

(i) reacting the Diol compound (VI),



VI

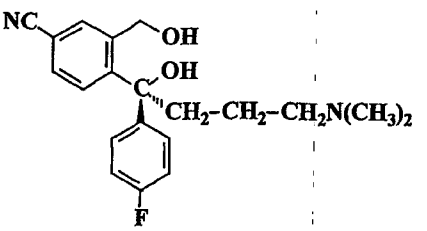
with oxalic acid in an organic solvent to get crystalline oxalate salt of (±)-4-[4-(dimethylamino)-1-(4-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl) benzonitrile [*(±)-Diol oxalate*] (VIa),



VIa

(ii) isolating the crystalline Citalopram diol oxalate (VIa) by filtration and neutralizing the oxalate salt to get pure diol compound (VI),

(iii) separating the enantiomers from the pure Diol compound (VI) with an optically active acid precipitant to obtain (*S*)-(-)-4-[4-(dimethylamino)-1-(4-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)benzonitrile (VII ),




VII

(iv) cyclizing the (*S*)-(-)-Diol (VII) in an organic solvent in the presence of sulfonyl halide and a base to produce Escitalopram (I).

## DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed towards the novel manufacturing process of Escitalopram of Formula I.

The Diol compound (VI), used as a starting material in the process of the present invention, is synthesized from 5-cyanophthalide by two successive Grignard reactions with 4-fluorophenylmagnesium bromide and 3-(*N,N*-dimethylamino)propylmagnesium chloride.

According to one embodiment of the present invention, oxalate salt of (±)-4-[4-(dimethylamino)-1-(4-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)benzonitrile [*(±)-Diol oxalate*] (VIa) is prepared by treating Diol compound (VI) with oxalic acid dihydrate in an alcohol solvent selected from methanol, ethanol, isopropanol, butanol, isobutanol etc., and preferably ethanol. The oxalate salt of Diol compound (VIa) is isolated by conventional methods with at least 99.5% HPLC purity and melting range 168-171°C.

In another embodiment of the present invention, (±)-Diol oxalate (VIa) is neutralized by treating with an organic or inorganic base, preferably inorganic base in an aqueous organic solvent, selected from ethyl acetate, toluene, methylene chloride, ethylene dichloride, cyclohexane, and preferably toluene. The inorganic base is selected from sodium hydroxide, potassium hydroxide and aqueous ammonia. The purified Diol thus obtained is treated with optically active acid, selected from dibenzoyltartaric acid, Di-*p*-toluoyltartaric acid, 10-camphorsulfonic acid and the like, in an organic solvent to resolve Diol enantiomers to obtain (*S*)-(-)-4-[4-(dimethylamino)-1-(4-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)benzonitrile. Preferably Di-*p*-toluoyl-D-tartaric acid is used to obtain (*S*)-Enantiomer of Diol (VII) having HPLC chiral purity of more than 99.5%.

The (*S*)-(-)-Diol (VII) is cyclized by using a sulfonyl halide, selected from alkylsulfonyl halide such as methanesulfonyl chloride, ethanesulfonyl chloride, *p*-toluenesulfonyl chloride etc., and preferably methanesulfonyl chloride, and in presence of a base selected from organic or inorganic base, preferably organic base selected from triethylamine, diethylamine, isopropylamine, diisopropylamine, *N,N*-diisopropylethylamine etc., and preferably triethylamine. The cyclized product thus obtained is dissolved in an organic solvent selected from acetone, acetonitrile, ethanol, methanol, isopropanol, tetrahydrofuran, toluene, cyclohexane, isopropyl ether etc., and preferably in acetone and is treated with oxalic acid dihydrate to obtain Escitalopram oxalate, which is isolated and dried by conventional methods.

This process of the present invention provides Escitalopram oxalate with HPLC purity more than 99.8%.

The details of the process of the invention are provided in the Examples given below which are provided by way of illustration only and therefore should not be construed to limit the scope of the invention

*EXAMPLE: 1*

**PREPARATION OF (±)-4-[4-DIMETHYLAMINO)-1-(4-FLUOROPHENYL)-1-HYDROXYBUTYL]-3-(HYDROXYMETHYL)-BENZONITRILE, OXALATE [(±)-DIOL OXALATE SALT]**

(±)-Diol compound (VI) (12 g, 0.035 mol) and oxalic acid dihydrate (4.64 g, 0.0368, 1.05 mol) were added to methanol (36 ml) and heated the contents to 55-60°C to obtain a clear solution. The obtained solution was cooled to 25-30°C and stirred for 3 h to complete the crystallization. Product was filtered and thereafter, dried at 50-60°C under reduced pressure to yield 11 g of diol oxalate salt (VIa) with HPLC purity 99.93 %.

*EXAMPLE 2*:

**PREPARATION OF (±)-4-[4-DIMETHYLAMINO)-1-(4-FLUOROPHENYL)-1-HYDROXYBUTYL]-3-(HYDROXYMETHYL)-BENZONITRILE, OXALATE [(±)-DIOL OXALATE SALT]**

(±)-Diol compound (VI) (360 g, 1.05 mol) was dissolved in ethanol (1400 ml) and heated to 50-55°C to obtain a clear solution. Oxalic acid dihydrate (164.40 g, 1.3 mol) was added slowly and cooled the obtained solution to 15-20°C and stirred for 4 hrs to complete the crystallization. Product formed was filtered and dried at 50-60°C under vacuum to yield 360 g of Diol oxalate salt (VIa), with HPLC purity of 99.95%. (Melting Range: 168-171°C)

$^1$H NMR (DMSO-$d_6$) δ ppm:

7.89-7.09 (m, 7H), 5.54 (d. 1H), 4.03 (d, 1H), 2.98-2.94 (m, 2H), 2.63 (s, 6H), 2.32-2.15 m, 2H), 1.6-1.3 (m, 2H)

IR (KBr, $cm^{-1}$):

3230, 3064, 2957, 2889, 2700, 2519, 2475, 2273, 2023, 1770, 1716, 651, 1602, 1560, 1544, 1505, 1487, 1441, 1412, 1397, 1363, 1299, 1241, 1215, 1190, 1157, 1106, 1088, 1041, 1024, 1006.

*EXAMPLE: 3*

**PREPARATION OF (±)-4-[4-DIMETHYLAMINO)-1-(4-FLUOROPHENYL)-1-HYDROXYBUTYL]-3-(HYDROXYMETHYL)-BENZONITRILE, OXALATE [(±)-DIOL OXALATE SALT]**

(±)-Diol compound (VI) (7 g, 0.0205 mol) and oxalic acid dihydrate (2.83 g, 0.0225 ml) were added to isopropyl alcohol (77 ml) and heated the contents to 75-80°C to obtain a clear solution. The obtained solution was cooled to 10-15°C and stirred for 2 h to complete the crystallization. The product was filtered, and thereafter dried at 50-60°C under reduced pressure for 6 h to give 8.6 g of diol oxalate salt (VIa), with HPLC purity of 99.94%.

*EXAMPLE: 4*

(±)-Diol compound (VI) (7 g, 0.0205 mol) and oxalic acid dihydrate (2.96 g, 0.0235 mol) were added to n-butanol (77 ml) and the contents were heated to 80-85°C to obtain a clear solution. Obtained solution was cooled slowly to 15-20°C and stirred for 3 h to complete the crystallization. The product formed was filtered and washed with n-butanol (2 x 7 ml). Thereafter, product was dried at 50-60°C under reduced pressure to give 8.5 g of diol oxalate salt (VIa), with HPLC purity of 99.93%.

*EXAMPLE: 5*

**PREPARATION OF ESCITALOPRAM OXALATE**

**STEP-1:**

**PREPARATION OF (*S*)-(-)-4-[4-(DIMETHYLAMINO)-1-(4-FLUOROPHENYL)-1- HYDROXYBUTYL]-3-(HYDROXYMETHYL)-BENZONITRILE, HEMI (+)-DI-P-TOLUOYL-D-TARTARIC ACID SALT [(*S*)-(-)-DIOL DPTTA SALT]**

(±)-Diol oxalate (VIa) (225 g, 0.52 mol) was suspended in a mixture of DM water (2250 ml) and toluene (2250 ml) at 30-35°c and pH was raised to 9.8 using aqueous ammonia solution. The organic layer was separated, was washed with DM water and concentrated at 50-55°C under reduced pressure. The obtained residue was dissolved in isopropyl alcohol (1125 ml) at 50-55°C. (+)-Di-*p*-toluoyl-*D*-tartaric acid (105 g, 0.27 mol) was added and slowly cooled to 25-30°C and stirred for 10 h. The crystals formed in the reaction mixture were filtered and washed with isopropyl alcohol (2x110 ml) to obtain ~ 180 g product (chiral purity: >96%).

The above salt was suspended in isopropyl alcohol (1500 ml) and heated to 80°C to obtain a clear solution. The resulting solution was cooled to 20-25°C and stirred for 1 hr. The solids were filtered and washed with isopropyl alcohol (2 x 50 ml) and thereafter dried to yield 102 g of the above salt. Chiral purity (by HPLC): 99.94%; $[\alpha]_D$: +8.0 (c=1, in methanol, on anhydrous basis).

**STEP-2:**

**PREPARATION OF ESCITALOPRAM OXALATE**

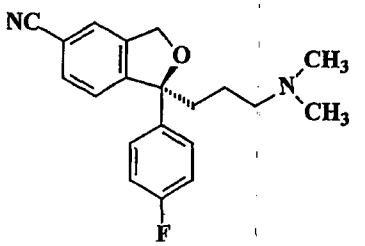
(*S*)-(-)- Diol DPTTA salt (80 g, 0.075 mol) was suspended in a mixture of DM water (800 ml) and methylene chloride (800 ml) at 20-25°C. The pH of the resulting solution was adjusted to 10.1 using aqueous sodium hydroxide solution at 20-25°C. Organic layer was separated and washed with DM water (1x300 ml). Thereafter, the organic layer was partially concentrated at atmospheric pressure at 35-39°C and the resulting concentrated mass was cooled to -5°C to -10°C.

Triethylamine (42.30 g, 0.41 mol) was added under nitrogen atmosphere, followed by addition of methanesulfonyl chloride (18 g, 0.16 mol) slowly at -5°C to -10°C over a period of 3 h and progress of the reaction was monitored by qualitative HPLC analysis. After completion of the cyclization, the reaction mass was washed with 0.5% w/w aqueous sodium hydroxide solution followed by DM water at 0-10°C. Methylene chloride was distilled from reaction mass at 20-30°C in vacuum to get Escitalopram base. Chiral purity: 99.12%; Chromatographic purity (by HPLC): 98.42%.

The oxalate salt of the above base was obtained by treating it with oxalic acid dihydrate in acetone. Chiral purity: 99.01%; Chromatographic purity: 99.85%; $[\alpha]_D$: +13.4 (c=1, in methanol, on anhydrous basis).

## WE CLAIM

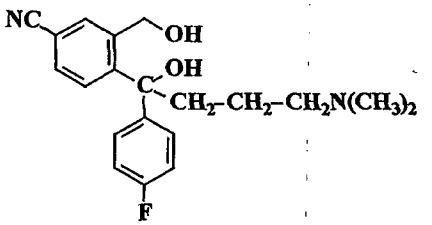
1. A process for the preparation of Escitalopram of Formula I,



I

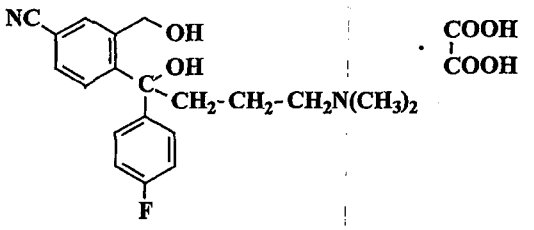
which comprises,

(i) reacting the diol compound (VI),



VI

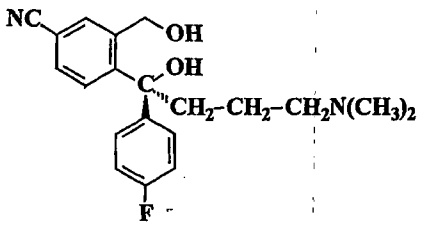
with oxalic acid in an organic solvent to get crystalline oxalate salt of (±)-4-[4-(dimethylamino)-1-(4-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile [*(±)-Diol oxalate*] (VIa),



VIa

(ii) isolating the crystalline Diol oxalate (VIa) by filtration and neutralizing the oxalate salt to get pure diol compound (VI),

(iii) separating the enantiomers from the pure Diol compound (VI) with an optically active acid precipitant to obtain (*S*)-(-)-4-[4-(dimethylamino)-1-(4-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)benzonitrile (VII ),



VII

(iv) cyclizing the (*S*)-(-)-Diol (VII) in an organic solvent in the presence of sulfonyl halide and a base to produce Escitalopram (I).

2. The process as claimed in claim 1, wherein the organic solvent used in step-(i) is selected from methanol, ethanol, isopropanol, *n*-butanol, isobutanol.

3. The process as claimed in claim 1, wherein the neutralization in step-(ii) is carried out using inorganic base, selected from aqueous ammonia, aqueous sodium hydroxide or aqueous potassium hydroxide.

4. The process as claimed in claim-1, wherein the optically active precipitant is Di-*p*-toluoyl-D-tartaric acid

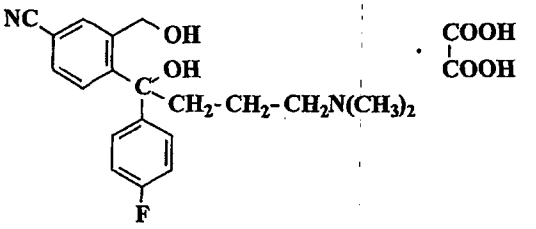
5. The process as claimed in claim 1, wherein the solvent is used for cyclization is selected from methylene chloride, toluene, cyclohexane, tetrahydrofuran, acetonitrile.

6. The process as claimed in claim 1, wherein the sulfonyl halide used for cyclization step is methanesulfonyl chloride.

7. The process as claimed in claim 1, wherein the base used in cyclization step is an organic or an inorganic base and preferably an organic base.

8. The process as claimed in claim 7, the organic base is triethylamine.

9. Crystalline oxalate salt of (±)-4-[4- (dimethylamino)-1-(4-fluorophenyl)-1-hydroxy-1-butyl]-3-(hydroxymethyl)benzonitrile [(±)-Diol oxalate] of Formula VIa,




VIa

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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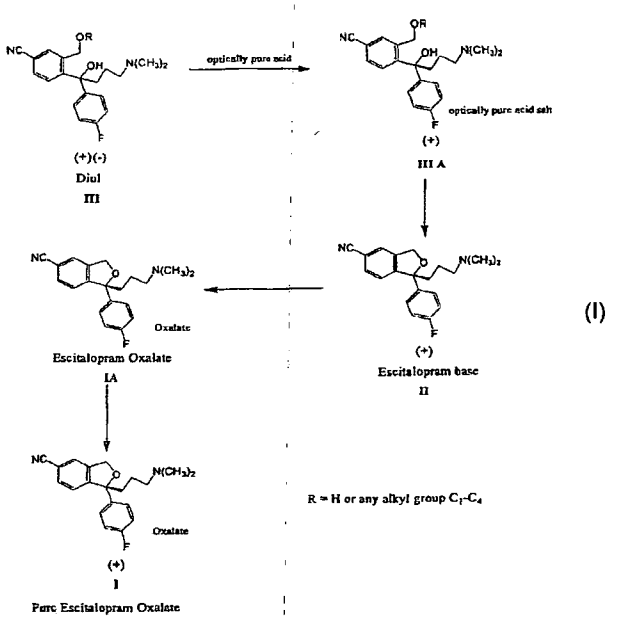
**Declaration under Rule 4.17:**

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

*[Continued on next page]*

(54) Title: PROCESS FOR THE PREPARATION OF ESCITALOPRAM OR ITS ACID ADDITION SALTS




(I)

(57) Abstract: The present invention relates to Formula (I), a process for the preparation of highly pure Escitalopram or its acid addition salts which comprises: a) reacting racemic diol or its ester derivative (III) with an optically active acid and at least one solvent to get enantiomerically pure diastereomer (IIIA); b) separating the enantiomerically pure diastereomer (IIIA) from its optically active acid salt by treating it with base and followed by stereo selective cyclization; c) separating the Escitalopram base.

WO 2006/106531 A1

# PROCESS FOR THE PREPARATION OF ESCITALOPRAM OR ITS ACID ADDITION SALTS

## Field of Invention

The present invention relates an improved process for the preparation of Escitalopram, which is the S-enantiomer of well known antidepressant drug Citalopram, *i.e.* (S)-1-[3-(dimethylamino)propyl]-1-(4-flouorphenyl)-1,3-dihydro-5-isobenzofuran carbonitrile or a pharmaceutically acceptable salt thereof.

## Background of Invention

Citalopram is a well-known antidepressant drug that has now been in the market for some years and has the following structure shown in figure 1:

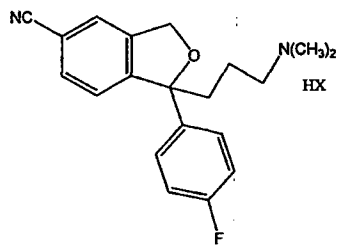



Figure1

It is a selective centrally acting serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor, accordingly having antidepressant activities.

Citalopram was first disclosed in DE 2,657,013, corresponding to US 4,136,193. This patent publication outlines a process for preparation of Citalopram from the corresponding 5-bromo derivatives by reaction with cuprous cyanide in a suitable solvent. US'193 describes the C-alkylation reaction of 5-cyanophthalane with 3-N,N'-dimethylaminopropyl chloride using sodium hydride as a base in dimethyl sulphoxide (DMSO) medium. 13 volumes of DMSO is used in this reaction with respect to 5-cyanophthalane. After the completion of the reaction Citalopram base is isolated as oil, which is purified by high vacuum distillation (0.03mm at 175-180°C) and then converted into acid addition salts by conventional methods. A main drawback of this process is the need to purify the oily Citalopram base using high vacuum distillation (0.03mm) at 175-180°C. Achieving such a high vacuum at plant level is difficult and apart from these constraints, the process has another drawback in that Citalopram base having a cyano group at the 5$^{th}$ position of the bicyclic ring system may decompose during high vacuum distillation at high temperature to form

We Claim:

1. A process for the preparation of highly pure Escitalopram or its acid addition salts thereof, which comprises:

a) reacting racemic diol or its ester derivative (III) with an optically active acid and at least one solvent to get enantiomerically pure diastereomer (IIIA);

b) separating the enantiomerically pure diastereomer (IIIA) from its optically active acid salt by treating it with base and followed by stereo selective cyclization;

c) separating the Escitalopram base;

2. A process as claimed in claim 1, wherein said optically active acid is selected from the group consisting of tartaric acid, dibenzoyl tartaric acid, di-*p*-toluoyl tartaric acid, bis-napthyl phosphoric acid, and 10-camphor sulphonic acid.

3. A process as claimed in claims 1 or 2 wherein said solvent is selected from the group consisting of lower alcohol having 1 to 4 carbon atoms such as methanol, ethanol, isopropyl alcohol and butyl alcohol; acetonitrile; acetone or any mixture thereof.

4. A process as claimed in any preceding claim wherein said base is selected from the group consisting of triethyl amine, alkali metal carbonates, bicarbonates and their hydroxides and liquid ammonia.

5. A process as claimed in any preceding claim wherein said stereo selective cyclization is carried out by reacting with methane sulphonyl chloride or p-toluene sulphonyl chloride in presence of a base.

6. A process as claimed in claim 5 wherein said base is triethyl amine.

7. A process as claimed in any preceding claim wherein said enantiomerically pure diastereomer (IIIA) is optionally purified in a solvent or a mixture of solvents.

8. A process as claimed in claim 7 wherein said solvent is selected from the group consisting of methanol, ethanol, isopropyl alcohol, ethyl acetate and acetone or mixture thereof.

9. A process as claimed in any preceding claim wherein said Escitalopram or its acid addition salt is purified using a mixture of solvents.

10. A process as claimed in claim 9 wherein said mixture of solvents contains at least isopropyl alcohol and one or more of methanol, ethanol, ethyl acetate, acetone or mixtures thereof.

11. A process as claimed in any preceding claim wherein said highly pure Escitalopram is optionally converted into its acid addition salt.

12. Pure Escitalopram or its acid addition salts with chiral purity of 99.5% or greater and HPLC purity of 99.5% or greater.

13. Escitalopram base with a chiral purity of 99.5% or greater and HPLC purity of 99% or greater.

14. A compound of formula IIIA, according to claim 1 having a chiral purity of 99% or greater.