Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 05-067473- -00004-0000
Fecha: 2007-07-31 08:03:39 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 400 OPOSIOBSERVTER Folios: 92

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FORMULARIO ÚNICO DE OPOSICIÓN

① OPOSICIÓN A :

- [X] Patente de Invención.
- [ ] Patente de Modelo de Utilidad.
- [ ] Diseño Industrial.
- [ ] Esquema de Trazado para Circuitos Integrados.
- [ ] Marcas de Productos o Servicios.
- [ ] Marca Colectiva.
- [ ] Marca de Certificación.
- [ ] Lema Comercial.

② SOLICITUD PUBLICADA

Número del expediente: 05-067473
Solicitante: H. LUNDBECK A/S
Apoderado: EMILIO FERRERO
Título de la nueva creación o denominación del signo: "BROMHIDRATO DE ESCITALOPRAM Y UN METODO PARA SU PREPARACIÓN".
Gaceta: 575

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE

Nombre: PROCAPS S.A
Dirección: CALLE 80 No. 78B -201
Nacionalidad o Domicilio: COLOMBIA
Lugar de Constitución: BARRANQUILLA
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IDENTIFICACIÓN
C.C. [ ] NIT [X]
C.E. [ ] Otro [ ]
Cual
Número 890.106.527-5

REPRESENTANTE O APODERADO

Nombre: LAURA CATALINA SILVA BARRERA
Dirección: CARRERA 13 No. 119-95 OF 104
Teléfono: (571)2131213 Fax: (571)6121979
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IDENTIFICACIÓN
C.C. [ ] NIT [X]
C.E. [ ] Otro [ ]
Cual
Número 52.455.803 TP 147399

④ FUNDAMENTOS DE LA OPOSICIÓN:

Causal: Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN
No cumple con los requisitos de patentabilidad.

Signo opositor:

Justificación:
La presente solicitud no cumple con los requisitos de patentabilidad dado que lo reve-

⑤ Comprobante de pago No. _____ Fecha _____

⑥ ANEXOS

- [X] Comprobante de pago de la tasa.
- [X] Poderes, si fuere el caso.
- [X] Pruebas de los fundamentos de la oposición.
- [ ] Documentos que acrediten el legítimo interés, si fuere el caso.
- [X] Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑦

NOMBRE: LAURA CATALINA SILVA BARRERA

FIRMA: 

C.C. 52.455.803 TP. 147399

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

89 3

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia	: Expediente N° 05067473
Asunto	: Oposición a la solicitud de patente de Invención titulada "BROMHIDRATO DE ESCITALOPRAM Y UN MÉTODO PARA SU PREPARACIÓN".
Solicitante	: H. LUNDBECK A/S.
Opositora	: PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 575 del 30 de Abril de 2007

Yo, ***LAURA CATALINA SILVA BARRERA***, abogada con tarjeta profesional N° **147399** del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad ***PROCAPS S.A.*** conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la patente de Invención titulada ***"BROMHIDRATO DE ESCITALOPRAM Y UN MÉTODO PARA SU PREPARACIÓN"***, solicitada por ***H. LUNDBECK A/S***, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

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90 4

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legitimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular escitalopram. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 8 de julio de 2005, reivindicando prioridad bajo las solicitudes DK7PA/200202005 del 2002-12-23 y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial Nº 575 del 30 de Abril de 2007, página 516, Nº publicación 1425, cuya publicación internacional corresponde a la WO2004056791 del 08-07-2004.

2.2. La solicitud colombiana **05067473** objeto de la presente oposición, se refiere a escitalopram (S-citalopram) en la forma de su bromhidrato, en forma sólida, en forma cristalina. De igual forma este se refiere a una composición farmacéutica que contiene escitalopram bromhidrato conforme a cualquiera de las reivindicaciones 1 a 3 y portadores y diluyentes farmacéuticamente aceptables. Además se refiere al uso del mismo.

2.3.En primera instancia, se debe advertir que la reivindicación 5 se refieren al uso y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- "*Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)*", los usos no están contemplados como patentables. Solo serán patentables los productos o procedimientos.

2.4.Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente: "*Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial*". Así las cosas, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afectan la novedad y el nivel inventivo de la presente solicitud:

- D1: EP0347066. 20-12-1989.
- D2: WO0103694. 18-01-2001.
- D3: WO02087566. 7-11-2002.
- D4: EP1152000. 07-11-2001.

2.5.Ahora bien, el documento D1, define particularmente en la página 9, líneas 54 hasta la página 10 línea 4 menciona las sales de escitalopram como un potencial antidepresivo y de uso en el tratamiento de desordenes neuróticos. Este documento D1, define que aislando los enantiómeros de citalopram en forma de una sal de adición ácida, el ácido preferentemente es seleccionado para contener un anión como un no tóxico y farmacológicamente aceptable, al menos en dosis habituales terapéuticas. Las sales representativas que son incluidas en este grupo preferido son

92

los bromhidratos entre otros. Por lo tanto, a los ojos de este documento, el escitalopram (S-citalopram) en la forma de su bromhidrato, no es novedoso.

2.6. Por su parte el documento D2, se refiere al empleo del escitalopram (S-(+)-enantiómero de citalopram) o una sal farmacéuticamente aceptable para la preparación de un medicamento útil en el tratamiento de desórdenes neuróticos, incluyendo estados la ansiedad. Particularmente en la página 3 línea 27, revela que las sales del compuesto usado en esta invención son sales formadas con ácidos orgánicos e inorgánicos no tóxicos. El documento D3, relaciona el empleo de un enantiómerico puro de escitalopram de dosis bajas para el tratamiento de la depresión. El documento D4, revela la forma de síntesis del citalopram bromhidrato, particularmente en el ejemplo 1, página 7 parágrafo 51. De igual forma en el párrafo 2 de este documento D4, define el uso del citalopram bromhidrato como un antidepresivo. Por lo tanto, a partir de estos documentos D2 a D4 en combinación con el documento D1, es posible con anterioridad derivar de manera evidente y obvia la materia aquí reivindicada. Así las cosas a los ojos de estos documentos, la presente solicitud carece de altura o nivel inventivo.

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana **05067473** no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

2.8. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.8.1. **CARECE DE NOVEDAD**: Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *"Una invención se considerará nueva cuando no está*

comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.". A la fecha de prioridad, 23 de diciembre de 2002, ya era conocido tal y como lo revela el arte anterior con base en el documento D1, el escitalopram (S-citalopram) en la forma de su bromhidrato, sobre el cual busca protección en el capítulo reivindicatorio. Por lo tanto la presente solicitud no es novedosa.

2.8.2. CARENCIA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.".* A la fecha de prioridad, el 23 de diciembre de 2002, a partir de los documentos D1 a D4 en combinación, es posible deducir el escitalopram (S-citalopram) en la forma de su bromhidrato, según lo definido en las reivindicaciones de la presente solicitud. De esta forma, la presente solicitud tampoco comprende altura o nivel inventivo

2.9. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial.".* La solicitud pretendida no cumple con dos de los tres requisitos de patentabilidad.

2.10. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada ***"BROMHIDRATO DE ESCITALOPRAM Y UN MÉTODO PARA SU PREPARACIÓN"***, solicitada por ***H. LUNDBECK A/S,*** solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 575.

3. PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- D1: EP0347066. 20-12-1989.
- D2: WO0103694. 18-01-2001.
- D3: WO02087566. 7-11-2002.
- D4: EP1152000. 07-11-2001.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

4.1. Numeral 1 del artículo 586 del Código de Comercio.

4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.

4.3. En las demás normas concordantes.

5. ANEXOS

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Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de PROCAPS S.A.
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:

- D1: EP0347066. 20-12-1989.
- D2: WO0103694. 18-01-2001.
- D3: WO02087566. 7-11-2002.
- D4: EP1152000. 07-11-2001.

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 Nº 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,

Laura Catalina Silva B.

LAURA CATALINA SILVA BARRERA

C.C. 52'455.803 de Bogotá

T.P.A. 147399 del C.S. de la J.

ANEXO 1

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(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 347 066 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 89305532.7

(22) Date of filing: 01.06.89

(51) Int. Cl.4: C07D 307/87 , A61K 31/34 , //C07B57/00,C07C121/80, C07C143/68

(30) Priority: 14.06.88 GB 8814057

(43) Date of publication of application: 20.12.89 Bulletin 89/51

(84) Designated Contracting States: AT BE CH DE ES FR GB GR IT LI LU NL SE

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(54) New enantiomers and their isolation.

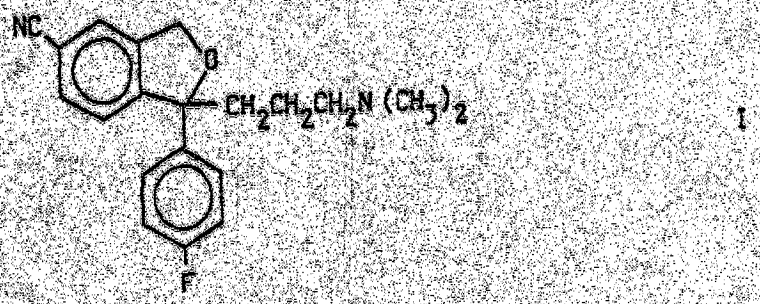
(57) The novel (+)-enantiomer of 1-(3-dimethylaminopropyl)-1-(4′-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile as well as acid addition salts thereof are described as valuable antidepressants, geriatrics or in the treatment of obesity and alcoholism.

Novel intermediates and a method for the preparation of the (+)-enentiomer as well as the racemic mixture are described.

EP 0 347 066 A1

NEW ENANTIOMERS AND THEIR ISOLATION

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



I

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

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

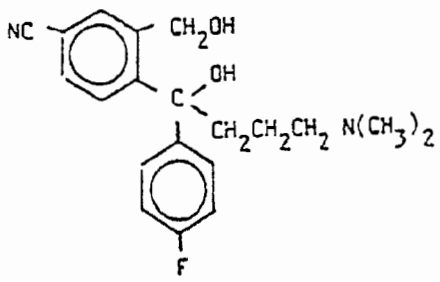
Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids. Of course, these salts may also be prepared by the conventional method of double decomposition of appropriate salts, which is well-known to the art.

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

The invention is also concerned with a method to resolve the racemate of I into the individual isomers.

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

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



II

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

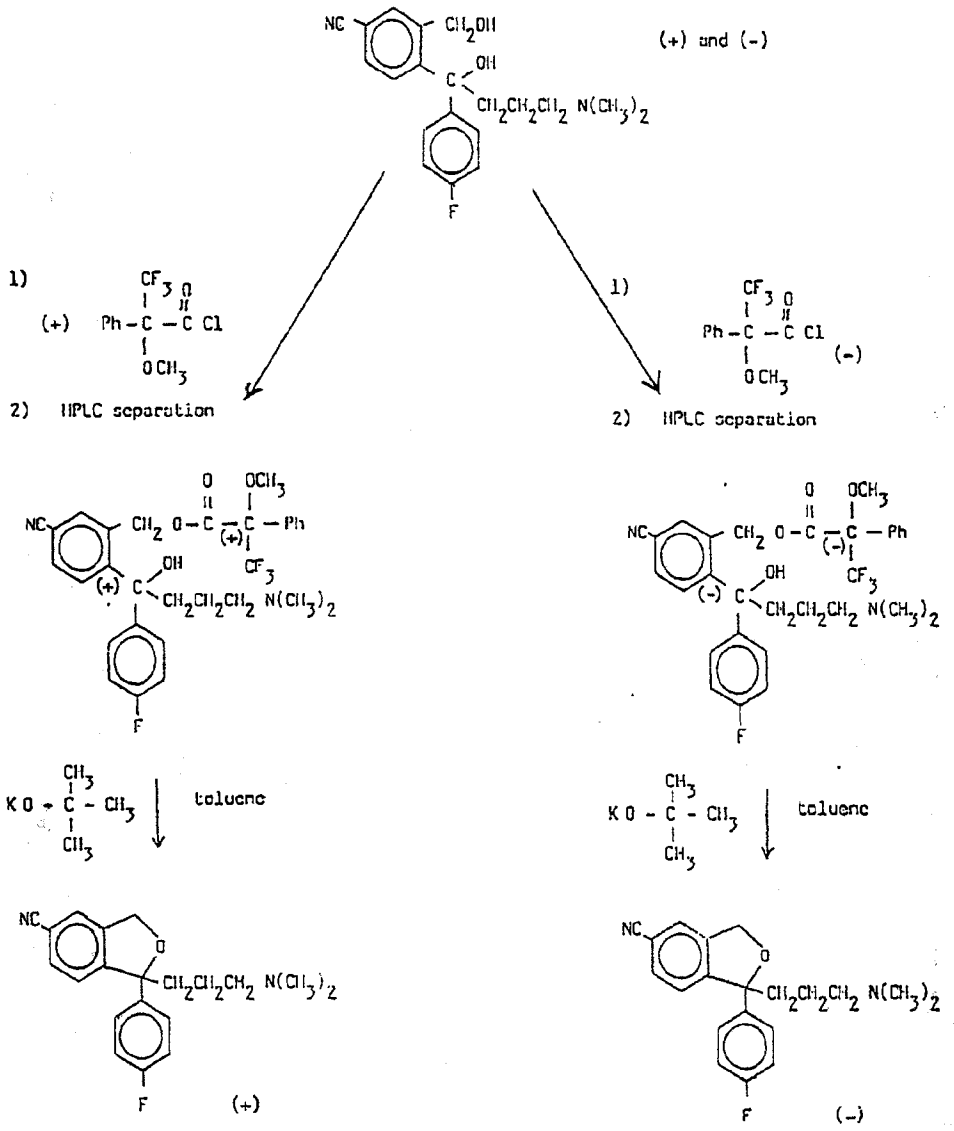
Furthermore, it was shown to our surprise that almost the entire 5-HT uptake inhibition resided in the (+)-citalopram enantiomer.

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

According to the invention, II is reacted with:

a) an enantiomerically pure acid derivative as an acid chloride, anhydride or labile ester as eg. examplified in reaction scheme I by (+)- or (-)-α-methoxy-α-trifluoromethylphenylacetyl chloride. The reaction is preferably performed in an inert organic solvent as eg. toluene, dichloromethane or tetrahydrofuran. A base (triethylamine, N,N-dimethylaniline, pyridin or the like) is added to neutralize liberated HCl. The diastereoisomers are subsequently separated by HPLC or fractional crystallization. The thus purified diastereoisomers are finally separately treated with strong base (eg. alkoxide) in an inert organic solvent as eg. toluene, tetrahydrofuran, or dimethoxyethane yielding the pure citalopram enantiomers respectively. The ringclosure reaction is preferably performed at relatively low temperatures (-20°C to room temperature).

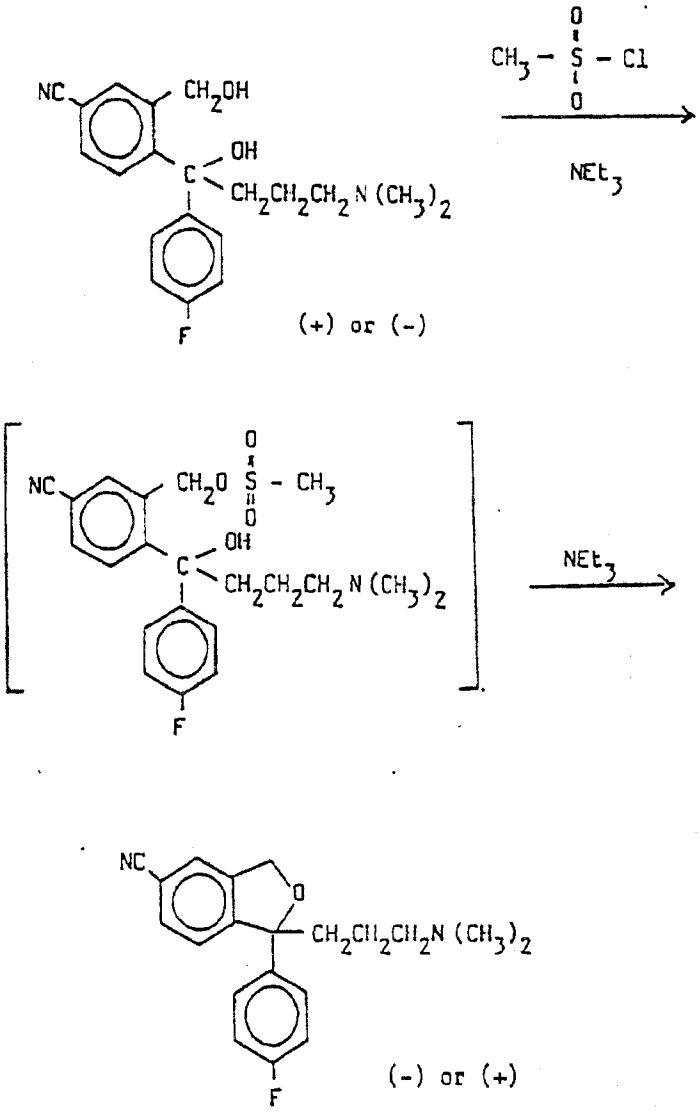
REACTION SCHEME I



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

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

REACTION SCHEME II



EXAMPLE 1

Resolution by method a)

To 11 g of (+)-1-methoxy-α-trifluoromethylacetic acid dissolved in 25 ml of chloroform were added 50 ml of thionylchloride and a few drops of dimethylformamide. The reaction mixture was refluxed for 2 hours. Excess of thionylchloride was evaporated with toluene leaving the (+)-α-methoxy-α-trifluoromethylacetyl chloride as a liquid. This liquid diluted with 50 ml of dichloromethane was added dropwise to an ice cooled solution of 17 gr of 4-(4-dimethylamino)-1-(4′-fluorophenyl)-1-hydroxybutyl)-3-(hydroxymethyl)-benzonitrile, II, and 8 ml of triethylamine in 150 ml of dichloromethane. The reaction mixture was further stirred for another hour at room temperature, subsequently washed with brine, dried ($MgSO_4$) and the solvent evaporated below 30°C in vacuo affording 29 gr of the ester as a diastereomeric mixture. By repeated

HPLC purification (eluted with ethyl acetate / tetrahydrofuran 9:1 containing 4% of triethylamine) and by collecting only the 5-10% initial substance in the main peak, 1.1 gr of enantiomerically pure compound was isolated.

The substance thus isolated was dissolved in dry toluene (50 ml) and added to a suspension of 0.3 gr of potassium t-butoxide in 20 ml of toluene at 0°C. The toluene solution was washed with water, dried ($MgSO_4$) and the solvent evaporated yielding 0.6 gr of (+)-1-(dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile as an oil. $[\alpha]_D$ = +11.81° (c = 1, CH_3OH) (determined with a substance containing 10% w/w of methanol). The optical purity was determined by ^1H NMR spectroscopy ($CDCl_3$ as solvent) (Bruker AC-250 MHz instrument) by addition of a 10:1 w/w surplus of the chiral reagent (-)-2,2,2-trifluoro-1-(9-anthryl)ethanol. Optical purity: 99.6%.

In a totally analogous way the (-)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile was synthesized. $[\alpha]_D$ = -12.34° (c = 1, CH_3OH) (determined with a substance containing 10% w/w of methanol). Optical purity: 99.8%.

EXAMPLE 2

Resolution by methods b) and c)

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

To an ice cooled solution of 14 gr of the (-)-isomer from above as a base in 300 ml of dry toluene were added 16 ml of triethylamine, and 3.6 ml of methansulfonyl chloride in 20 ml of dry toluene were added dropwise during 10 minutes. The reaction mixture was further stirred for 1/2 hour, washed with brine, dried ($MgSO_4$) and the solvent evaporated. The title compound was purified by column chromatography affording 8 g of (+)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile. $[\alpha]_D$ = +12.33° (c = 1, CH_3OH).

The oxalic acid salt of the (+)-isomer crystallized from acetone. MP: 147-148°C, $[\alpha]_D$ = +12.31° (c = 1, CH_3OH).

The pamoic acid salt of the (+)-isomer was prepared in the following manner: To 1.8 g of the base of the (+)-isomer was added 2 g of pamoic acid in 25 ml of MeOH. The mixture was refluxed for an hour and subsequently colled to room temperature. The precipitate was filtered off yielding 3.0 g of the pamoic acid salt, MP: 264-266°C, $[\alpha]_D$ = + 13.98°C (c = 1, dimethylformamide).

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

In a corresponding manner as above via the (+)-4-(4-dimethylamino)-1-(4'-fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl)benzonitrile, hemi (-)-di-(p-toloyl)tartaric acid salt ($[\alpha]_D$ = -8.9° (c = 1, CH_3OH)) which was converted to the corresponding diol base ($[\alpha]_D$ = +61.1° (c = 1, CH_3OH)) and finally ringclosure reaction yielded 10 gr of (-)-1-(d-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile. $[\alpha]_D$ = -12.1° (c = 1, CH_3OH).

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

EXAMPLE 3

Preparation of citalopram by method c)

To an ice cooled solution of 28 gr of racemic diol base, R, in 500 ml of dichloromethane were added 32 ml of triethylamine, and 7.5 ml of methansulfonyl chloride in 30 ml of dichloromethane were added dropwise during 9 hour. The reaction mixture was washed with 0.1 M NaOH solution twice, the organic phase separated, dried ($MgSO_4$) and the solvent evaporated, leaving 21.5 gr of the title (±)-citalopram as a crystalline base. The thus obtained material was dissolved in a mixture of 2-propanol and methanol (2:1) and an equivalent amount of gaseous HBr was introduced. The mixture was left overnight and the precipitated hydrobromide was filtered off. Yield: 26 gr with MP 184-186°C.

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

5-HTP-POTENTIATION

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

Procedure

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

The route of administration

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

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

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

Procedure

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

To 4000 µl of the synaptosomal suspension (5 mg original tissue) on ice are added 100 µl test substance in water. After preincubation at 37° for 5 min, 100 µl of ^{3}H-1-NA (final concentration 10 nM) are added and the samples are incubated for 10 min at 37°C. The incubation is terminated by filtering the samples under vacuum through Whatman GF/F filters with a wash of 5 ml buffer containing 10 µM of unlabelled 5-HT. The filters are placed in counting vials and 4 ml of appropriate scintillation fluid (e.g. Picofluor TM15) are added. After shaking for 1 h and storage 2 h in the dark the content of radioactivity is

determined by liquid scintillation counting. Uptake is obtained by subtracting the nonspecific binding and passive transport measured in the presence of 10 µM citalopram (Lu 10-171-B).

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

Table 1

PHARMACOLOGICAL TEST RESULTS		
Compound	5-HTP pot. ED_{50} µmol/kg	5-HT uptake inhibition IC_{50}(nM)
(+)-citalopram	2.0	1.1
(-)-citalopram	120	150
(±)-citalopram	3.3	1.8

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

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

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

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

1) Tablets containing 5 milligrams of (+)-citalopram calculated as the free base:	
Compound 20	6 mg
Lactose	18 mg
Potato starch	27 mg
Saccharose	58 mg
Sorbitol	3 mg
Talcum	5 mg
Gelatine	2 mg
Povidone	1 mg
Magnesium stearate	0.5 mg

2) Tablets containing 50 milligrams of (+)-citalopram calculated as the free base:	
(+)-citalopram	50 mg
Lactose	16 mg
Potato starch	45 mg
Saccharose	106 mg
Sorbitol	6 mg
Talcum	9 mg
Gelatine	4 mg
Povidone	3 mg
Magnesium stearate	0.6 mg

3) Syrup containing per milliliter:	
(+)-citalopram	10 mg
Sorbitol	500 mg
Tragacanth	7 mg
Glycerol	50 mg
Methyl-paraben	1 mg
Propyl-paraben	0.1 mg
Ethanol	0.005 ml
Water	ad 1 ml

4) Solution for injection containing per milliliter:	
(+)-citalopram	50 mg
Acetic acid	17.9 mg
Sterile water	ad 1 ml

5) Solution for injection containing per milliliter:	
(+)-citalopram	10 mg
Sorbitol	42.9 mg
Acetic acid	0.63 mg
Sodium hydroxide	22 mg
Sterile water	ad 1 ml

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

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

As previously stated, when isolating the enantiomers of citalopram in the form of an acid addition salt the acid is preferably selected so as to contain an anion which is a non-toxic and pharmacologically acceptable, at least in usual therapeutic doses. Representative salts which are included in this preferred group are the hydrochlorides, hydrobromides, sulphates, acetates , phosphates, nitrates, methanesulphonates, ethane-sulphonates, lactates, citrates, tartrates or bitartrates, pamoates and maleates of the

amines of Formula I. Other acids are likewise suitable and may be employed if desired. For example: fumaric, benzoic, ascorbic, succinic, salicyclic, bismethylenesalicylic, propionic, gluconic, malic, malonic, mandelic, cannamic, citraconic, stearic, palmitic, itaconic, glycolic, benzenesulphenic, and sulphamic acids may also be employed as acid addition saltforming acids.

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

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

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

Claims

-1- (+)-1-(3-Dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile and non-toxic acid addition salts thereof.

-2- The pamoic acid salt of (+)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile.

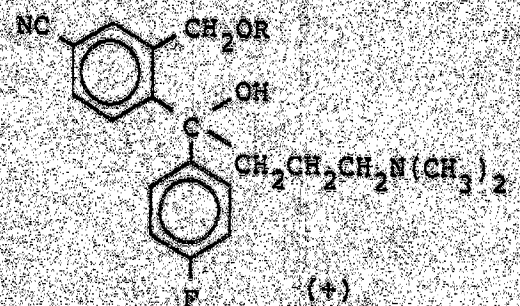
-3- A pharmaceutical composition in unit dosage form comprising as an active ingredient, a compound as defined in claim 1.

-4- A pharmaceutical composition in unit dosage form comprising, as an active ingredient, the compound of claim 2.

-5- A pharmaceutical composition in unit dosage form, according to claim 3 or 4, wherein the active ingredient is present in an amount from 0.1 to 100 milligram per unit dose.

-6- A method for the preparation of a compound as defined in claim 1, which comprises, converting (+)-4-(4-dimethylamino)-1-(4'-fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl)-benzonitrile or a monoester thereof in a stereoselective way to (+)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile which is isolated as such or as a non-toxic acid addition salt thereof.

-7-



II

(+)

wherein R is hydrogen of F, a labile ester group.

-8- A method for the preparation of 1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile in the form of a racemic mixture which comprises treating 4-(4-dimethylamino)-1-(4-fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl) benzonitrile, esterified at the primary alcohol group with an acid, forming a labile ester, with an agent causing ringclosure and isolating the compound formed as the free base or a pharmaceutically acceptable acid addition salt thereof.

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European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 89 30 5532

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	CHEMICAL ABSTRACTS, vol. 104, no. 19, 12th May 1986, page 43, abstract no. 161810v, Columbus, Ohio, US; M. HIBERT et al.: "Stereoselective blockade at the 5-HT autoreceptor and inhibition of radioligand binding to central 5-HT recognition sites by the optical isomers of methiothepin", & NEUROPHARMACOLOGY 1986, 25(1), 1-4	1-8	C 07 D 307/87 A 61 K 31/34 // C 07 B 57/00 C 07 C 121/80 C 07 C 143/68
D,A	EP-A-0 171 943 (H. LUNDBECK) * Whole document *	1-8	
D,A	US-A-4 136 193 (K.P. BOGESO) * Whole document *	1-8	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

C 07 D 307/00
C 07 C 121/00
C 07 C 143/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	30-08-1989	ALLARD M.S.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 January 2001 (18.01.2001)

PCT

(10) International Publication Number
WO 01/03694 A1

(51) International Patent Classification⁷: A61K 31/343, A61P 25/00, 25/22

(21) International Application Number: PCT/DK00/00377

(22) International Filing Date: 7 July 2000 (07.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PA 1999 00991 8 July 1999 (08.07.1999) DK

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: TREATMENT OF NEUROTIC DISORDERS

(57) Abstract: Use of the escitalopram (the S-(+)-enantiomer of citalopram) or a pharmaceutically acceptable salt thereof for the preparation of a medicament useful in the treatment of neurotic disorders is provided, including anxiety states, in particular generalised anxiety disorder and social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder and panic attacks.

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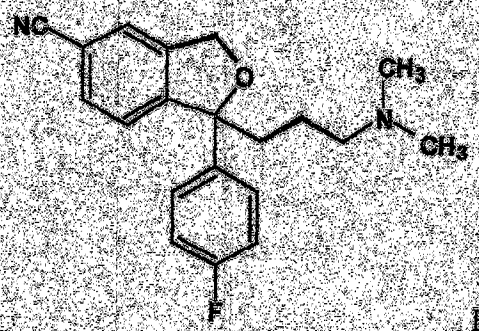
TREATMENT OF NEUROTIC DISORDERS

Field of invention

The present invention relates to the use of the compound escitalopram (INN-name), which is the S-enantiomer of the well-known antidepressant drug citalopram, i.e. (S)-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile, or a pharmaceutically acceptable salt thereof for the preparation of medicaments for the treatment of neurotic disorders, including anxiety states and panic attacks.

Background of the Invention

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



Formula I

It is a selective, centrally acting serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor, accordingly having antidepressant activities. The antidepressant activity of the compound has been reported in several publications, eg. J. Hyttel, *Prog. Neuro-Psychopharmacol. & Biol. Psychiat.*, **1982**, *6*, 277-295 and A. Gravem, *Acta Psychiatr. Scand.*, **1987**, *75*, 478-486, and it is now marketed for the treatment of depression and panic disorders. The compound has further been disclosed to show effects in the treatment of dementia and cerebrovascular disorders, EP-A 474580.

Escitolopram and a method for its preparation are disclosed in US Patent No 4,943,590. The stereo selectivity of citalopram, i.e. the 5-HT-reuptake inhibition in the S-enantiomer, and accordingly, the antidepressant effect of said enantiomer is also disclosed. S-citalopram is now in development as an antidepressant.

CONFIRMATION COPY

Studies have shown that patients suffering from neurotic disorders including anxiety disorders, especially generalised anxiety, and panic attacks, in particular in association with agoraphobia, have a quality of life impairment comparable with or greater than the disability found in patients with alcoholism, schizophrenia or personality disorders. Furthermore, current treatments are not always effective or cause unacceptable side effects.

Consequently, there is a need for alternative therapies useful in the treatment of neurotic disorders.

Escitalopram has now been found to show potent effects in models of neurotic disorders such as anxiolytic effect and prominent effect in the treatment of panic attacks and obsessive compulsive disorder.

Description of the Invention

According to the present invention, a novel use of escitalopram, namely for the preparation of a medicament useful in the treatment of neurotic disorders is provided.

Throughout this specification and claims the term neurotic disorders is used to designate a group of mental disorders, including anxiety states, in particular generalised anxiety disorder, and social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder and panic attacks.

The terms generalised anxiety disorder, social anxiety disorder, post traumatic stress disorder and obsessive compulsive disorder are as defined in DSM IV.

The phrase "panic attacks" contemplates treatment of any disease, which is associated with panic attacks including panic disorder, specific phobias, social phobia and agoraphobia in which panic attacks occur. These disorders are further defined in the DSM IV. A panic attack is a discrete period in which there is a sudden onset of intense apprehension, fearfulness or terror, often associated with feelings of impending doom. During the attack, symptoms such as palpitations, sweating, trembling, sensations of shortness of breath,

feeling of choking, chest pain or discomfort, nausea, feeling dizzy, feelings of unreality, fear of losing control or going crazy, fear of dying, paresthesias and chills or hot flushes are present.

Panic disorders are characterised by recurrent unexpected panic attacks about which there is a persistent concern. Agoraphobia is anxiety about, or avoidance of, places or situations from which escape might be difficult or in which help may not be available in the event of a panic attack. Specific phobia and social phobia (together formerly simple phobia) are characterised by marked and persistent fear that is excessive or unreasonable, cued by the presence or anticipation of a specific object or situation (flying, heights, animals, seeing blood etc.) or social performance situations.

The disorders in which panic attacks occur are differentiated from each other by the predictability of the occurrence of the attacks, for example, in panic disorder the attacks are unpredictable and not associated with any particular event, whereas in specific phobia the attacks are triggered by specific stimuli.

The phrase "treatment of panic disorder" means a reduction in the number or prevention of attacks and/or relief of the severity of the attacks. Similarly, the treatment of generalised anxiety disorder, social anxiety disorder, post traumatic stress disorder and obsessive compulsive disorder include the treatment or prevention of these diseases, or the relief of the symptoms thereof.

According to the invention, escitalopram may be used as the base of the compound or as a pharmaceutically acceptable acid addition salt thereof or as an anhydrate or hydrate of such salt. The salts of the compound used in the invention are salts formed with non-toxic organic or inorganic acids, in particular the oxalate.

Escitalopram has been found to show prominent effects different from the effects of the racemate in the "Inhibition of footshock-induced ultrasonic vocalisation in adult rats" - test, the "Mice Black and White Test" setup, and in the polydipsia test. These models are standard

animal models for anxiolytic effect and effect on panic attacks and for obsessive compulsive disorder, respectively.

According to the invention, escitalopram or a pharmaceutically acceptable salt thereof may be administered in any suitable way e.g. orally or parenterally, and it may be presented in any suitable form for such administration, e.g. in the form of tablets, capsules, powders, syrups or solutions or dispersions for injection. Preferably, and in accordance with the purpose of the present invention, the compound of the invention is administered in the form of a solid pharmaceutical entity, suitably as a tablet or a capsule or in the form of a suspension, solution or dispersion for injection.

Methods for the preparation of solid pharmaceutical preparations are well-known in the art. Tablets may thus be prepared by mixing the active ingredients with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a convenient tabletting machine. Examples of adjuvants or diluents comprise: corn starch, lactose, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvant or additive such as colourings, flavourings, preservatives, etc. may also be used provided that they are compatible with the active ingredients.

The compound of the invention is most conveniently administered orally in unit dosage forms such as tablets or capsules, containing the active ingredient in a dose from about 1.0 mg to 50 mg, preferably 5 mg/day to 40 mg/day, most preferably 10 mg/day to 20 mg/day.

The oxalate of escitalopram may be prepared as described in US Patent No 4,943,590 and the base and other pharmaceutically acceptable salts may be obtained therefrom by standard procedures.

Thus the acid addition salts used according to the invention may be obtained by treatment of escitalopram with the acid in an inert solvent followed by precipitation, isolation and optionally re-crystallisation by known methods and if desired micronisation of the crystalline product by wet or dry milling or another convenient process, or preparation of particles from a solvent-emulsification process.

Pharmacological Tests

Escitalopram was tested in well recognised and reliable test models of effects on neurotic disorders. Citalopram-racemate was included for comparison purposes.

The footshock- induced vocalisation test in adult rats.

The footshock- induced vocalisation test in adult rats (described in detail in Sánchez C., Effect of serotonergic drugs on footshock-induced ultrasonic vocalization in adult male rats. *Behav. Pharmacol.* **1993**; *4*:267-277) is a test for anxiolytic and anti-panic effects.

Experimental Procedure

Male rats (Wistar WU, Charles River, Germany), weighing 150-175 g at the beginning of the study were used.

Briefly, test cages (22 cm x 22 cm x 22 cm) made of grey Perspex and equipped with a metal grid floor were used. Footshocks were delivered from a two pole shocker and a microphone sensitive to ultrasounds in the range of 20-30 kHz was placed in the centre of the lid of the test cage. The ultrasounds were sent from the microphone to a preamplifier and converted from AC signals to DC signals in a signal rectifier. The accumulated time, in which the voltage of the rectified signal was larger than the voltage of a previously determined treshold level, was recorded.

Twenty-four hours before the first test session the animals were primed. A rat was placed in each test cage and received, immediately thereafter, four 1.0 mA inescapable footshocks each of a duration of 10 sec and with an intershock interval of 5 sec. The animals were left in the test cage for 6 min after the last shock. On test days, drug or saline was given 30 min before test. The rats received four 1.0 mA inescapable footshocks each of a duration of 10 sec. The intershock interval was 5 sec. Recording of ultrasonic vocalisation started 1 min after the last shock and lasted for 5 min. The total time spent on vocalisation was recorded. After a wash-out period of one week the rats were used in a new test session. The rats were used for a total of 7-8 weeks. At each test session, the animal groups were randomly allocated to treatment with saline or test drug. Each treatment group consisted of 8 animals.

one saline and 2-4 drug treated groups were included at each session. Each drug was tested at least in two separate experiments with overlapping doses.

Results

The experiments showed that the maximum effect was 60-70% inhibition for citalopram-racemate whereas escitalopram was able to inhibit vocalisation completely.

Black and White Box Test

This is a test for anxiolytic effects. The test model is further described in Sánchez, C. (1995) Pharmacol. Toxicol. 77, 71-78.

Test procedure

Male mice (Lundbeck strain, Charles River, Germany) weighing 30-35 g were housed in groups of 4 in macrolon cages type II under a reversed 12 h day /night cycle (lights off 7 p.m.). The mice were adapted to the reversed light/dark cycle for at least 3 weeks prior to testing. The room temperature (21 ± 2°C), relative humidity (55 ± 5%), and air exchange (16 times per h) were automatically controlled. The animals had free access to commercial food pellets and water.

The test box used was designed as described by Sánchez (1995) (*supra*). Briefly, the test box (45 cm x 27 cm x 27 cm) was open-topped and divided into two compartments (ratio 2:3) by a partition which was black on the side facing the black compartment and white on the side facing the white compartment. The smaller chamber was made of black perspex. The larger chamber was made of white perspex except for the lowest 7.5 cm. This part was made of transparent perspex (outer walls) and black perspex (partition). The white compartment was connected to the black compartment by a 7.5 cm x 7.5 cm opening in the partition. The floor of the white compartment was divided into 9 fields, and the floor of the black was divided into 6 fields. The white compartment was illuminated by means of a Schott KL 1500 electronic lamp emitting cold light corresponding to a light intensity of 560 Lux. The mouse test system was fully automated by 2 rows of 11 infrared light sources and photocells in the transverse direction and 1 row of 16 in the longitudinal direction (lower row). The lower row of photocells (2 cm above cage floor) detected horizontal locomotor activity (crossing, entries, and time in each compartment), whereas the upper row of photocells (5 cm above

cage floor) detected rearing activity. The accumulated data for 1 min intervals were recorded from 4 test boxed simultaneously and stored in a Paradox data base.

The test boxes were placed in a dark and quiet room. The mice were transported to the test room in a darkened container about 2 h before test. The test room was separated into two parts by a black curtain. The drug treatment took place in one part of the room using a minimum of red light. After dosing, the mice were placed individually in macrolon type II cages until test. The pretreatment time was 30 min. The test boxes were placed in the other part of the room. The test was started by placing the mouse in the centre of the brightly-lit white compartment facing the opening to the black compartment. The test duration was 5 min and the number of rears and line crossings between squares in both the black and the white compartment, number of entries into the black compartment and time spent in the white compartment were assessed.

Results

Escitalopram showed prominent effects in this model.

Schedule-Induced Polydipsia

Food deprived rats exposed to a procedure in which food is delivered intermittently will drink large amounts of water if given the opportunity to do so. This behavioural phenomenon is called schedule-induced polydipsia and can be considered as an excessive expression of a normal behaviour. Schedule-induced polydipsia is regarded as a model of obsessive-compulsive disorder (Woods et al. 1993).

Test Procedure:

Male wistar rats (Mollegård) housed in pairs and kept on a food-restricted diet (80% of normal body weight) for 2 weeks before the start of testing and throughout the duration of testing. To induce polydipsia rats were placed in test chambers where a pellet dispenser automatically dispensed one 60 mg food pellet every 60 seconds. Water was available at all times in the test chamber. Rats were tested 4-5 times per week, after 3-4 weeks training 70% of the rats were drinking >10ml per 30 min test session.

Once the rats had attained a steady drinking level compounds could be tested. Citalopram (40 mg/kg) or La 26-054 (20 mg/kg) were administered orally 60 min prior to testing and at

10:00 on the non-test days. The water intake was presented as a percentage of the pre-dosing (baseline) level.

Results:

Escitalopram produced a significant reduction in water intake, whereas citalopram was without effect.

All these studies show that escitalopram has potent anti neurotic diseases effects, in particular anxiolytic effects and effects on panic attacks and obsessive compulsive disorder.

Claims

1. Use of escitalopram or a pharmaceutically acceptable salt thereof for the preparation of a medicament useful in the treatment of neurotic disorders.

2. The use according to Claim **1**, **characterised in**, that the medicament is for administration as a unit dose.

3. The use according to Claim **1** or **2**, **characterised in**, that the unit dose is containing the active ingredient in an amount from 1.0 mg to 50 mg, preferably 5 mg/day to 40 mg/day, most preferably 10 mg/day to 20 mg/day.

4. Use of any of Claims **1** to **3**, **characterised in**, that the medicament is for the treatment of generalised anxiety disorder.

5. Use of any of Claims **1** to **3**, **characterised in**, that the medicament is for the treatment of social anxiety disorder.

6. Use of any of Claims **1** to **3**, **characterised in**, that the medicament is for the treatment of post traumatic stress disorder.

7. Use of any of Claims **1** to **3**, **characterised in**, that the medicament is for the treatment of obsessive compulsive disorder.

8. Use of any of Claims **1** to **3**, **characterised in**, that the medicament is for the treatment of panic attacks.

9. Use of any of Claim **8**, **characterised in**, that the medicament is for the treatment of panic disorder.

10. Use of any of Claim **8**, **characterised in**, that the medicament is for the treatment of specific phobias.

11. Use of any of Claim **8**, **characterised in**, that the medicament is for the treatment of social phobia.

12. Use of any of Claim **8**, **characterised in**, that the medicament is for the treatment of agoraphobia.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 00/00377

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/343, A61P 25/00, A61P 25/22
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, EPODOC, MEDLINE, CAPLUS, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Rev. Contemp. Pharmacother. Volume 10, 1999, A. F. Joubert et al., "Citalopram and Anxiety Disorders" page 79 - page 131 --	1-12
X	ACTA PSYCHIATRICA SCANDINAVICA, Volume 96, 1997, Koponen H. et al., "Citalopram an the treatment of obsessive-compulsive disorder: an open pilot study" page 343 - page 346 --	1-3,7
X	Journal of Serotonin Research, Volume 1, 1996, Dan J. Stein MB et al., "Use of serotonin selective reuptake inhibitor citalopram in obsessive-compulsive disorder" page 29 - page 33 --	1-3,7

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search	Date of mailing of the international search report
17 October 2000	25-10-2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Eva Johansson/GH Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 00/00377

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J Clin Psychiatry, Volume 59, No 10, October 1998, Ulla M. Lepola et al., "A Controlled, Prospedtive, 1-Year Trial of Citalopram in the Treatment of Panic Disorder" page 528 - page 534	1-3,8-12
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INTERNATIONAL SEARCH REPORT

Information on patent family members

03/10/00

International application No.
PCT/DK 00/00377

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INTERNATIONAL SEARCH REPORT

Information on patent family members

03/10/00

International application No.
PCT/DK 00/00377

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		SG 165594 G	12/05/95
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38
124

ANEXO 3

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 November 2002 (07.11.2002)

PCT

(10) International Publication Number
WO 02/087566 A1

(51) International Patent Classification⁷: A61K 31/343, A61P 25/00, 25/22, 25/24

(21) International Application Number: PCT/DK02/00281

(22) International Filing Date: 1 May 2002 (01.05.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PA 2001 00684 1 May 2001 (01.05.2001) DK

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(81) Designated States *(national)*: AE, AG, AL, AM, AT (utility model), AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, ES, FI (utility model), FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK (utility model), SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: THE USE OF ENANTIOMERIC PURE ESCITALOPRAM

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

WO 02/087566 A1

The use of enantiomeric pure escitalopram

The present invention relates to the use of enantiomeric pure escitalopram (INN-name) which is the S-enantiomer of the well-known antidepresssant drug citalopram, i.e. (S)-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile, or a pharmaceutically acceptable salt thereof for the preparation of medicaments, in particular medicaments for the treatment of major depression disorder.

Background of the Invention

Selective serotonin reuptake inhibitors (hereinafter called SSRIs) such as citalopram have become first-choice therapeutics in the treatment of depression, certain forms of anxiety and social phobias, because they are effective, well-tolerated and have a favourable safety profile compared to the classic tricyclic antidepressants.

However, clinical studies on depression and anxiety disorders indicate that non-response or resistance to SSRIs, i.e. where at least a 40-60% reduction in symptoms has not been achieved during the first 6 weeks of treatment, is substantial, namely up to 30%.

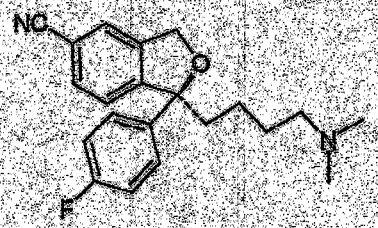
Moreover, there is the delay in therapeutic effect of SSRIs. Sometimes symptoms even worsen during the first weeks of treatment. Even in responders to SSRIs, several weeks of treatment are necessary to achieve a relief in symptoms.

In addition, sexual dysfunction is a side-effect common to all SSRIs.

Without addressing these problems, real progress in the pharmacotherapy of depression and anxiety disorders is not likely to happen.

Escitalopram is the S-enantiomer of the well-known antidepressant drug citalopram and has the following structure:

CONFIRMATION COPY



Formula I

Escitalopram and a method for its preparation are disclosed in US Patent No 4,943,590. The stereo selectivity of citalopram, i.e. the 5-HT-reuptake inhibition in the S-enantiomer, and accordingly, its potential antidepressant effect of said enantiomer is also disclosed. It appears that substantially all the 5-HT-reuptake inhibiting effect and accordingly the antidepressant effect is in the S-enantiomer. In view of the stereo-selectivity, escitalopram is expected to be two times as potent as the racemate in the treatment depression.

WO 103694 A1 relates to the use of escitalopram in the treatment of neurotic disorders, including anxiety states and panic attacks.

It has now, surprisingly, been found that the presence of R-citalopram has a negative impact on the effect of escitalopram and escitalopram has been found in pharmacological and clinical studies to be substantially more than two times as potent as the racemate. Furthermore, escitalopram has been found to show a faster onset of action in animal models and clinical studies than the racemate and other SSRIs and to give a more full response in various animal models. Finally, clinical studies have indicated that escitalopram may be an effective medicament in the treatment of depression in patients that do not respond to conventional SSRIs.

The mechanism behind the surprising negative impact of the R-enantiomer on the effect of the S-enantiomer is not known. One possible explanation could be that the R-enantiomer may have a negative influence on the transport of the S-enantiomer over the blood brain barrier. Alternatively, R-citalopram may convey local feed-back inhibition of 5-HT release or the R-enantiomer may modulate the effect of the S-enantiomer.

Description of the invention

Accordingly, the present invention thus relates to the use of escitalopram in low doses and/or comprising less than 3 % w/w of R-citalopram for the preparation of a pharmaceutical composition.

In a further aspect, the invention relates to a pharmaceutical composition characterised in that it comprises escitalopram with less than 3 % w/w of R-citalopram as an active ingredient.

In yet another aspect, the invention relates to the use of escitalopram for the treatment of major depression disorder characterised in that it is used in a daily dose of less than 10 mg of escitalopram.

As mentioned above, the present invention is based on the finding that R-citalopram has a negative impact on the effect on escitalopram. This may be shown in functional in-vivo pharmacological models and studies of 5-HT-reuptake effect and or in behaviour models, for example depression models.

Escitalopram has also been found to give a significant improvement compared to the double amount of citalopram-racemate and/or to give a more full response. So, it has been found in fixed dose studies that escitalopram in a dose of 10 mg has at least same effect as citalopram in a dose of 40 mg as determined by the MADRS rating scale and Clinical Global Impression (severity as well as improvement).

Escitalopram has also been found in animal models to give a faster response than citalopram-racemate. This has i.a. been found in the Chronic Mild Stress model (Willner P., Psychopharmachology 1997, 134, 319-329). This effect has been confirmed in an 8-week, double-blind, randomised, placebo-controlled, flexible-dose study that compared escitalopram and citalopram to placebo in primary care patients with major depression disorder. The patients received 10 mg escitalopram (155 patients), 20 mg citalopram (160 patients) and placebo (154 patients). Escitalopram showed effects after one week whereas citalopram did not show significant effect.

All these effects are very surprising in view of the prior art suggesting that the R-enantiomer does not influence the effect of the S-enantiomer and, accordingly that escitalopram should only be twice as potent as the racemate.

As a further advantage, the fact that escitalopram is effective in lower doses suggests that effective treatment with less side effects may be obtained, in particular, a reduced amount of serotonin reuptake inhibitor may reduce the risk of SSRI-induced sexual dysfunction and sleep disturbances.

Detailed description of the invention

The escitalopram is preferably used as an oxalate salt, preferably a crystalline oxalate salt.

Furthermore, in the escitalopram used, R-citalopram is preferably not present in an amount exceeding 2% w/w, most preferably 1% w/w. The percentage of R-citalopram is throughout the description given as w/w % compared to the amount of escitalopram present.

The pharmaceutical composition of the invention is preferably for the treatment of depression, in particular major depression disorder, neurotic disorders, acute stress disorder, eating disorders such as bulimia, anorexia and obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder or drug abuse.

Throughout this specification and claims the term "neurotic disorders" is used to designate a group of mental disorders, including anxiety states, in particular generalised anxiety disorder and social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder and panic attacks.

The terms "generalised anxiety disorder", "social anxiety disorder", "post traumatic stress disorder" and "obsessive compulsive disorder" are as defined in DSM IV.

The phrase "panic attacks" contemplates treatment of any disease, which is associated with panic attacks including panic disorder, specific phobias, social phobia and agoraphobia in which panic attacks occur. These disorders are further defined in the DSM IV.

The phrase "treatment of panic disorder" means a reduction in the number or prevention of attacks and/or relief of the severity of the attacks. Similarly, the treatment of generalised anxiety disorder, social anxiety disorder, post traumatic stress disorder and obsessive compulsive disorder include the treatment or prevention of these diseases, or the relief of the symptoms thereof.

Based on the pharmacological and clinical studies, preferred indications are major depression disorder and obsessive compulsive disorder.

Other preferred uses are treatment of neurotic disorders.

In particular, the composition may be useful for treatment of patients who have failed to respond to initial treatment with a conventional SSRI, in particular patients with major depression disorder who have failed to respond to initial treatment with a conventional SSRI. Such treatment resistant patients may in particular be defined a patients who do not achieve an alleviation in symptoms of 40-60% by treatment with citalopram or other marketed SSRIs. Further definitions are given in Kornstein SC and Schneider RK , Clinical features of treatment-resistant depression *J Clin Psychiatr* **2001**, *62*, Suppl 16, 18-25; Sackeim HA, The definition and meaning of treatment-resistant depression, *J. Clin Psychiatr* **2001**, *62* Suppl 16, 10-17; and Nierenber AA and DeCecco LM, Definitions of antidepressant treatment response, remission, non-response, partial response, and other relevant outcomes: A focus on treatment-resistant depression *J Clin Psychiatr* **2001**, *62* Suppl 16, 5-9.

The pharmaceutical composition according to the invention may comprise escitalopram in a unit dose preparation containing 2.5 to 20 mg escitalopram.

In view of the potent effect of the escitalopram used according to the invention, it may be effective in low doses, i.e. daily doses lower than 10 mg escitalopram, for example 7.5 mg

or lower, such as 7.5 or 5 mg pr day.

The pharmaceutical composition according to the invention is preferably an oral formulation, preferably a tablet.

Thus, tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a conventional tabletting machine. Examples of adjuvants or diluents comprise: corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvants or additives usually used for such purposes such as colourings, flavourings, preservatives etc. may be used provided that they are compatible with the active ingredients.

Solutions for injections may be prepared by dissolving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to desired volume, sterilisation of the solution and filling in suitable ampules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

Clinical Study

A total of 471 patients were randomised into the study. The *all-patient-treated set* comprised 469 patients and the *full-analysis set* comprised 468 patients. In the *full-analysis set* there were 155 patients in the escitalopram group, 159 patients in the citalopram group, and 154 patients in the placebo group.

There was an approximately 3 to 1 ratio of women to men in each treatment group, and almost all patients were Caucasian. The mean age was 43 years (SD 11). At baseline, the mean MADRS total score was approximately 29 for the treatment group, which signifies moderate to severely ill patients.

The efficacy analysis of the adjusted mean change in MADRS total score showed a significantly superior therapeutic effect for escitalopram *versus* placebo from Week 1 (p=0.023) to Week 4(p=0.002)) (observed cases). At Week 4, the adjusted mean change in

MADRS total score (last observation carried forward) for escitalopram *versus* placebo was 2.7 points >(p=0.002) compared to a statistically insignificant change of 1.5 points for citalopram *versus* placebo.

Escitalopram was significantly superior to placebo both on the CGI improvement and severity subscale from Week 1 (p<0.05)(observed cases) onwards, while citalopram was not statistically different from placebo during the 4-week period. At Week 4 (last observation carried forward), escitalopram was statistically significantly superior to placebo while there was no statistically significant difference between citalopram versus placebo.

CLAIMS

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

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

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

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

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

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

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

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

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

respond to initial treatment with a conventional SSRI.

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

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

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

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

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

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

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

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

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

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 02/00281

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/343, A61P 25/00, A61P 25/22, A61P 25/24
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, CHEM.ABS.DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0347066 A1 (H. LUNDBECK A/S), 20 December 1989 (20.12.89)	1-19
X	WO 0103694 A1 (H. LUNDBECK A/S), 18 January 2001 (18.01.01)	1-19

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 July 2002	22-07-2002
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50

136

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK02/00281

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 17-19
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK02/00281

Claims 17-19 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

06/07/02

International application No.
PCT/DK 02/00281

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139

ANEXO 4

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(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 152 000 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
07.11.2001 Bulletin 2001/45

(51) Int Cl.[7]: C07D 307/87

(21) Application number: 01108914.1

(22) Date of filing: 10.04.2001

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: 02.05.2000 JP 2000133995

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(54) Citalopram hydrobromide crystal and method for crystallization thereof

(57) According to the present invention, citalopram hydrobromide dissolved in a solvent containing at least one member selected from the group consisting of alcohol having 1 - 3 carbon atoms, water and acetone is crystallized or recrystallized while controlling the cooling rate, thereby to 1) provide an industrial method for crystallizing citalopram hydrobromide, which enables easy control of the crystal characteristics, such as particle size, particle size distribution and aspect ratio and the like of the crystal, and 2) provide citalopram hydrobromide crystal having crystal characteristics useful as a pharmaceutical bulk.

EP 1 152 000 A1

Description

TECHNICAL FIELD OF THE INVENTION

[0001] The present invention relates to a method for crystallizing citalopram hydrobromide useful as an antidepressant and citalopram hydrobromide having specific crystal properties.

BACKGROUND OF THE INVENTION

[0002] Citalopram hydrobromide is useful as an antidepressant. When it is used as a pharmaceutical bulk for the preparation of a pharmaceutical agent, particle size, particle size distribution and aspect ratio of the crystal are the important crystal characteristics. However, there is no teaching as to what crystal characteristics of citalopram hydrobromide are required as a beneficial pharmaceutical bulk, or a method for achieving such beneficial crystal characteristics.

[0003] According to US4650884, for example, a method for crystallizing citalopram hydrobromide comprises, crystallization in a single solvent of acetone, first recrystallization in a single solvent of water, second recrystallization in a mixed solvent of methanol and isopropyl alcohol, and third recrystallization in a mixed solvent of methanol, acetone and hexane. This method aims at purification of citalopram crystals but not at controlling particle size, particle size distribution or aspect ratio of crystals, not to mention a method for controlling these.

[0004] When citalopram hydrobromide is crystallized according to the method described in this publication, fine crystals having a particle size of less than 5 μm are formed in a large amount (41.9% of the total amount). When fine crystals are contained in a large amount, filtering performance after crystallization for medicament production is degraded. In addition, the fine particles scatter and the workers are exposed thereto during production of pharmaceutical preparations, which is an unpreferable aspect as a pharmaceutical bulk.

[0005] When citalopram hydrobromide is crystallized according to the method described in this publication, crystals having a smaller average aspect ratio of less than 2 are produced. Such crystals cause problems such as poor filtering performance after crystallization for the preparation of a pharmaceutical agent and poor fluidity when crystals are being taken out, which is not preferable as a pharmaceutical bulk.

[0006] It is therefore an object of the present invention to provide

(1) a method for industrially crystallizing citalopram hydrobromide, which method affords easy control of crystal characteristics, such as particle size, particle size distribution and aspect ratio of the crystals, and
(2) citalopram hydrobromide crystals having crystal characteristics useful as a pharmaceutical bulk.

SUMMARY OF THE INVENTION

[0007] Such object can be achieved by the present invention. According to the present invention, citalopram hydrobromide dissolved in a specific solvent is crystallized or recrystallized while controlling the cooling rate, thereby to control the particle size, particle size distribution and aspect ratio of citalopram hydrobromide crystals. It has been also found that citalopram hydrobromide crystals containing crystals having a particle size of less than of 5 μm in a proportion of 35% at most and citalopram hydrobromide crystals having an average aspect ratio of not less than 4.5 and not more than 6.0, which are obtained by this method, are advantageous as a pharmaceutical bulk.

[0008] Accordingly, the present invention provides the following.

(1) Citalopram hydrobromide crystals containing crystals having a particle size of less than 5 μm in a proportion of 35% at most.
(2) Citalopram hydrobromide crystals containing crystals having a particle size of less than 5 μm in a proportion of 35% at most, and containing crystals having a particle size of not less than 20 μm in a proportion of not less than 10%, or having an average aspect ratio of not less than 2.0 and not more than 9.0, or having an average aspect ratio of not less than 2.5 and less than 4.5, or having an average aspect ratio of not less than 4.5 and not more than 6.0.
(3) Citalopram hydrobromide crystals having an average aspect ratio of not less than 2.0 and not more than 9.0.
(4) Citalopram hydrobromide crystals having an average aspect ratio of not less than 2.5 and less than 4.5.
(5) Citalopram hydrobromide crystals having an average aspect ratio of not less than 4.5 and not more than 6.0.
(6) A method for crystallizing citalopram hydrobromide, which comprises the steps of

(A1) dissolving, by heating, citalopram hydrobromide in a solvent containing at least one member selected from the group consisting of alcohol having 1 to 3 carbon atoms, water and acetone and

(B1) cooling the resulting product to achieve crystallization, while controlling the cooling rate.

(7) A method for crystallizing citalopram hydrobromide, which comprises the steps of

(A2) dissolving, by heating, citalopram hydrobromide in a solvent containing at least one member selected from the group consisting of alcohol having 1 to 3 carbon atoms, water and acetone,
(B2) cooling the obtained solution to achieve crystallization,
(C2) dissolving a part of the obtained crystals by heating, and
(D2) recrystallizing the crystals while controlling the cooling rate.

[0009] A preferable mode of the above-mentioned (6) includes

(6-1) controlling the cooling rate within the temperature range of 0°C - 80°C,
(6-2) controlling the average cooling rate within the temperature range of 20°C - 40°C to not less than 30°C/hour and not more than 60°C/hour,
(6-3) controlling the average cooling rate within the temperature range of 20°C - 40°C to not less than 0.5°C/hour and less than 30°C/hour, and
(6-4) cooling the solution obtained in (A1) to a temperature range of not less than 30°C and less than 48°C and adding a seed crystal of citalopram hydrobromide to achieve crystallization.

[0010] A preferable mode of the above-mentioned (7) includes

(7-1) cooling to the temperature range of not less than 30°C and less than 48°C in (B2),
(7-2) after cooling to the temperature range of not less than 30°C and less than 48°C, adding a seed crystal of citalopram hydrobromide to achieve crystallization in (B2),
(7-3) heating to the temperature range of not less than 48°C and not more than 80°C to dissolve a part of the crystal in (C2),
(7-4) controlling the average cooling rate in the temperature range of from (heating temperature in (C2)) to (this heating temperature - 30°C) to not less than 30°C/hour and not more than 90°C/hour in (D2), and
(7-5) controlling the average cooling rate in the temperature range of from (heating temperature in (C2)) to (this heating temperature - 30°C) to not less than 1°C/hour and less than 30°C/hour in (D2).

BRIEF DESCRIPTION OF THE DRAWINGS

[0011]

Figure 1 shows ^{1}H-NMR of the compound obtained in Reference Example 1.
Figure 2 shows a powder X-ray crystal diffraction pattern of the compound obtained in Reference Example 1.
Figure 3 shows a powder X-ray crystal diffraction pattern of the compound obtained in Example 1.
Figure 4 shows a powder X-ray crystal diffraction pattern of the compound obtained in Example 4.
Figure 5 shows a powder X-ray crystal diffraction pattern of the compound obtained in Comparative Example 1.
Figure 6 shows a crystal particle size distribution of the compound obtained in Example 1.
Figure 7 shows a crystal particle size distribution of the compound obtained in Example 2.
Figure 8 shows a crystal particle size distribution of the compound obtained in Example 3.
Figure 9 shows a crystal particle size distribution of the compound obtained in Example 4.
Figure 10 shows a crystal particle size distribution of the compound obtained in Example 5.
Figure 11 shows a crystal particle size distribution of the compound obtained in Example 6.
Figure 12 shows a crystal particle size distribution of the compound obtained in Comparative Example 1.
Figure 13 shows a micrograph (400 magnifications) of the compound obtained in Example 1.
Figure 14 shows a micrograph (400 magnifications) of the compound obtained in Example 4.
Figure 15 shows a micrograph (400 magnifications) of the compound obtained in Example 6.
Figure 16 shows a micrograph (400 magnifications) of the compound obtained in Comparative Example 1.
Figure 17 shows a micrograph (400 magnifications) of a ruler graduated in 10 μm.

DETAILED DESCRIPTION OF THE INVENTION

[0012] The present invention is explained in detail in the following.

[0013] The average particle size in the present invention is an average diameter upon conversion of the volume of

the crystal particles into sphere.

[0014] The average aspect ratio in the present invention is an average value of the major axis/minor axis of crystal particles.

[0015] According to the present invention, crystal characteristics such as particle size, particle size distribution and aspect ratio of the crystals can be controlled easily. As the industrial method for crystallizing citalopram hydrobromide includes the following methods.

Method 1

[0016] A first method for crystallizing citalopram hydrobromide in the present invention includes

(A1) dissolving citalopram hydrobromide in a specific solvent, and
(B1) crystallization by cooling the resulting solution while controlling a cooling rate
(hereinafter this method is to be referred to as Method 1). The crystals obtained according to Method 1 generally show a smooth cone-shaped particle size distribution.

[0017] In the following, the steps (A1) and (B1) are explained in detail. In each step, it is preferable that the particles be stirred at 10 rpm - 250 rpm, particularly at 50 rpm - 220 rpm, so that the temperature of the system as a whole can be uniform and the crystals after stirring will not have a smaller aspect ratio.

[0018] According to Method 1, the cooling rate of the solution within the specific temperature range should be regulated to control the crystal characteristics. That is, the present inventors have found that the cooling rate of the solution within the temperature range of preferably 0°C - 80°C, particularly 20°C-40°C, in (B1) affects the crystal particle size of citalopram hydrobromide. For example, the crystals obtained when the average cooling rate of the solution within the temperature range of 20°C - 40°C is controlled to not less than 0.5°C/hour and less than 30°C/hour contain crystals having a particle size of less than 5 μm in a proportion of 35% at most, and have an average particle size of about 10 μm - 20 μm, and that the crystals obtained when it is controlled to not less than 30°C/hour and not more than 60°C/hour contain crystals having a particle size of less than 5 μm in a proportion of 35% at most, and have an average particle size of about 7 μm - 15 μm. Cooling within the above-mentioned temperature range is preferably conducted such that the cooling rate becomes almost constant.

[0019] A next important process for controlling the crystal characteristics is the addition of seed crystal in (B1) in the specific temperature range. Addition of a seed crystal for crystallization of a compound is a known preferable method for precipitating crystals, as demonstrated in US4650884 with regard to citalopram hydrobromide. In this publication, a seed crystal is added when the cooling temperature is 20°C. By reproductive crystallization according to this method by the present inventors, it was revealed that suitable growth of the precipitated crystals was not achieved, with a considerable amount of fine crystals having a particle size of less than 5 μm. When fine crystals are contained in a great amount, filterability after crystallization for the preparation of a pharmaceutical bulk becomes poor, and the fine particles scatter, to which particles the workers are exposed during production of pharmaceutical preparations.

[0020] The present inventors have also found that, in (B1), cooling to the temperature range of preferably not less than 30°C and less than 48°C, more preferably not less than 40°C and less than 48°C, followed by addition of a seed crystal to allow for crystallization, results in precipitation of crystals suitably grown. Thus, the particle size of the crystals can be controlled well, and generation of fine crystals having a particle size of less than 5 μm can be further inhibited by this method.

[0021] When the temperature, at which a seed crystal is added, is less than 30°C, crystallization occurs at once and fine crystals tend to increase. When it is not less than 48°C, the seed crystal tends to dissolve easily, and the effect of the addition of the seed crystal becomes low. The amount of the seed crystal added is not subject to any particular limitation, but it is preferably 0.0001 wt% - 1 wt%, more preferably 0.001 wt% - 0.01 wt%, relative to citalopram hydrobromide used for crystallization.

[0022] In (A1) in Method 1, citalopram hydrobromide is dissolved in a specific solvent preferably by heating to 50°C - 80°C, more preferably 55°C - 75°C.

[0023] The specific solvent used in Method 1 contains at least one member selected from the group consisting of alcohol having 1 to 3 carbon atoms (e.g., methanol, ethanol, isopropyl alcohol, 1-propanol), water and acetone, in a proportion of preferably not less than 70 wt%, more preferably not less than 80 wt%. The solvent that may be contained in addition to alcohol having 1 to 3 carbon atoms, water and acetone is not subject to any particular limitation, and may be any as long as it is miscible with these solvents and is not reactive with citalopram hydrobromide. Examples thereof include toluene, xylene, tetrahydrofuran, diisopropyl ether, 1,2-dimethoxyethane, diethylene glycol dimethyl ether and the like. These may be used alone or in a combination of 2 or more solvents, wherein the boiling point thereof is preferably higher than the above-mentioned heating temperature. More preferable examples of the above-mentioned specific solvent include those containing at least one member selected from the group consisting of methanol, ethanol,

isopropyl alcohol and 1-propanol in a proportion of not less than 80 wt%, particularly preferably those containing methanol and isopropyl alcohol in a proportion of not less than 90 wt%.

[0024] The amount of the above-mentioned specific solvent varies depending on the kind of each solvent used solely or in combination, the temperature at which citalopram hydrobromide is heated for dissolution and the like. However, it is generally preferably 2 L - 30 L, more preferably 4 L - 16 L, per 1 kg of citalopram hydrobromide. When a mixed solvent containing methanol and isopropyl alcohol is used, it is particularly preferable that the amounts thereof be 2 L - 5 L of methanol and 4 L - 8L of isopropyl alcohol, both per 1 kg of citalopram hydrobromide.

[0025] According to Method 1, after the completion of step 2, the crystallization of citalopram hydrobromide is preferably completed after aging at a temperature below the final cooling temperature (preferably -10°C to 30°C, more preferably 0°C to 20°C) for preferably 30 minutes - 48 hours, more preferably 2 hours - 24 hours, to achieve an improved yield.

[0026] By the foregoing steps, the characteristics of citalopram hydrobromide crystals can be controlled. For example, to shift the particle size distribution of the crystals toward that of the crystals having a greater particle size, the cooling rate may be slowed or a seed crystal may be added in (B1). To increase the aspect ratio, the cooling rate or the stirring speed may be slowed in (B1).

Method 2

[0027] The second method for crystallizing citalopram hydrobromide according to the present invention includes the steps of:

(A2) dissolving citalopram hydrobromide in a specific solvent by heating,
(B2) crystallizing citalopram hydrobromide by cooling the obtained solution,
(C2) heating the resulting crystals to dissolve a part of the obtained crystals, and
(D2) recrystallizing citalopram hydrobromide while controlling a cooling rate
(hereinafter this method is to be referred to as Method 2). The crystals obtained in Method 2 generally contain fine crystals in a smaller proportion than in Method 1. In Method 2, the steps of (A2) to (D2) can be performed in one pot. In each step, it is preferable that the particles be stirred at 10 rpm - 250 rpm, particularly at 50 rpm - 220 rpm, so that the temperature of the system as a whole will be uniform and the crystals after stirring will not have a smaller aspect ratio.

[0028] In Method 2, the control of the cooling rate of the solution within the specific temperature range in (D2) is particularly important for the control of the crystal characteristics. That is, the present inventors have found that the cooling rate of the solution particularly within the temperature range of from (heating temperature in (C2)) to (this heating temperature - 30°C) in (D2) in Method 2 affects the crystal particle size of the ultimate crystals. For example, the crystals obtained when the average cooling rate of the solution within this temperature range is controlled to not less than 30°C/hour and not more than 90°C/hour contain crystals having a particle size of less than 5 μm in a proportion of 35% at most, particularly not more than 25%, and have an average particle size of about 10 μm - 25 μm. The crystals obtained when it is controlled to not less than 1°C/hour and less than 30°C/hour contain crystals having a particle size of less than 5 μm in a proportion of 35% at most, particularly not more than 15%, and have an average particle size of about 15 μm - 30 μm. Cooling within the above-mentioned temperature range is preferably conducted such that the cooling rate becomes almost constant.

[0029] A next important process for controlling the crystal characteristics is the addition of a seed crystal within the specific temperature range in (B2) and dissolution by heating in (C2).

[0030] In (B2), the solution obtained in (A2) is cooled to the temperature range of preferably not less than 30°C and less than 48°C, particularly preferably not less than 40°C and less than 48°C. The present inventors have found that, in (B2), cooling to the temperature range of preferably not less than 30°C and less than 48°C, particularly preferably not less than 40°C and less than 48°C, which is followed by addition of a seed crystal to allow for crystallization results in the precipitation of crystals suitably grown. Thus, the particle size of the crystals can be controlled well, and generation of fine crystals having a particle size of less than 5 μm can be further inhibited.

[0031] When the temperature at which a seed crystal is added is less than 30°C, crystallization occurs at once and fine crystals tend to increase. When it is not less than 48°C, the seed crystal tends to dissolve easily, and the effect of the addition of the seed crystal becomes low. The amount of the seed crystal added is not subject to any particular limitation, but it is preferably 0.0001 wt% - 1 wt%, more preferably 0.001 wt% - 0.01 wt%, relative to citalopram hydrobromide used for crystallization.

[0032] In (C2), a part of the crystals obtained in (B2) is dissolved by heating, thereby preventing complete dissolution of the obtained crystals. This has a consequence that the finally obtained crystals have a greater average particle size. This is considered to be attributable to the fact that the crystals not dissolved by heating in (B2) become the seed

crystal in (D2). Therefore, combined with the addition of the seed crystal in (B2), crystals having a greater average particle size as compared to that obtained without such combination can be ultimately obtained. As used herein, the "part of the crystals obtained in (B2)" is not subject to any particular limitation, but it is preferably 10 wt% - 90 wt%, more preferably 20 wt% - 80 wt%, of the crystals obtained in (B2).

[0033] The temperature in (C2) is not subject to any particular limitation as long as it can dissolve only a part of the crystals obtained in (B2). Note that the crystals should not be dissolved completely in (B2). It is preferable that a part of the crystals be dissolved by heating to not less than 48°C and not more than 60°C, particularly not less than 48°C and not more than 55°C. When this temperature is less than 48°C, the crystals cannot be dissolved to the desired degree in this step, and when it exceeds 60°C, the crystals are dissolved to the degree beyond the intended degree in this step, both causing an increase in the content of the crystals having a particle size of less than 5 μm, as compared to (C2) performed in the above-mentioned temperature range.

[0034] In Method 2, the cooling rate controlled in (B2) also affects the particle size of the final crystals, as is the case with the aforementioned control of cooling rate in (D2), only to a smaller degree than in (D2). In (B2), the present inventors have found that the cooling rate within the temperature range of preferably 0°C - 80°C, particularly 20°C - 40°C, affects the crystal particle size of citalopram hydrobromide. The cooling in the above-mentioned temperature range is preferably performed such that the cooling rate becomes almost the same.

[0035] In (A2) in Method 2, citalopram hydrobromide is dissolved in a specific solvent preferably by heating to 50°C - 80°C, more preferably 55°C - 75°C.

[0036] The specific solvent used in Method 2 contains at least one member selected from the group consisting of alcohol having 1 to 3 carbon atoms (e.g., methanol, ethanol, isopropyl alcohol, 1-propanol), water and acetone, preferably in a proportion of not less than 70 wt%, more preferably not less than 80 wt%. The solvent that may be contained in addition to alcohol having 1 to 3 carbon atoms, water and acetone is not subject to any particular limitation, and may be any as long as it is miscible with these solvents and is not reactive with citalopram hydrobromide. Examples thereof include toluene, xylene, tetrahydrofuran, diisopropyl ether, 1,2-dimethoxyethane, diethylene glycol dimethyl ether and the like. These may be used alone or in a combination of 2 or more solvents, wherein the boiling point thereof is preferably higher than the above-mentioned heating temperature. More preferable examples of the above-mentioned specific solvent include those containing at least one member selected from the group consisting of methanol, ethanol, isopropyl alcohol and 1-propanol in a proportion of not less than 80 wt%. Those containing methanol and isopropyl alcohol in a proportion of not less than 90 wt% are particularly preferable.

[0037] The amount of the above-mentioned specific solvent varies depending on the kind of each solvent used solely or in combination, the temperature at which citalopram hydrobromide is heated for dissolution and the like. However, it is generally preferably 2 L - 30 L, more preferably 4 L - 16 L, per 1 kg of citalopram hydrobromide. When a mixed solvent containing methanol and isopropyl alcohol is used, it is particularly preferable that the amounts thereof be 2 L - 5 L of methanol and 4 L - 8L of isopropyl alcohol, both per 1 kg of citalopram hydrobromide.

[0038] In Method 2, (C2) and (D2) may be sequentially repeated after (D2). The crystallization of citalopram hydrobromide is preferably completed after aging at a temperature below the final cooling temperature (preferably -10°C to 30°C, more preferably 0°C to 20°C) for preferably 30 minutes - 48 hours, more preferably 2 hours - 24 hours, to achieve an improved yield.

[0039] By the foregoing steps, the characteristics of citalopram hydrobromide crystals can be controlled. For example, to shift the particle size distribution of the crystals toward that of the crystals having a greater particle size, the cooling rate may be slowed in (B2) and (D2), a seed crystal may be added in (B2), and the crystals may be heated for dissolution at a specific temperature in (C2). To increase the aspect ratio, the cooling rate or the stirring speed may be slowed in (B2) and (D2).

[0040] In Method 1 and Method 2, the obtained crystals are isolated and purified by conventional methods, such as washing with a suitable solvent after filtration.

[0041] The citalopram hydrobromide crystals wherein 35% at most, preferably not more than 30%, more preferably not more than 20%, thereof has a crystal particle size of less than 5 μm, and further the crystals wherein not less than 10%, more preferably not less than 20%, thereof preferably has a particle size of not less than 20 μm, can improve the filterability after crystallization for the production of pharmaceutical bulk and the like. In addition, they can improve the problems of scattering of fine particles and exposure of the workers to the fine particles during production of a pharmaceutical preparation, and the like. These crystals can be obtained by each method as follows.

[0042] In Method 1, the average cooling rate of the solution within the temperature range of from 20°C to 40°C in (B1) is controlled to not less than 0.5°C/hour and not more than 60°C/hour, preferably by adding a seed crystal at a temperature range of not less than 30°C and less than 48°C in (B1).

[0043] In Method 2, the cooling rate of the solution in the temperature range of from ((heating temperature in (C2)) to (this heating temperature - 30°C) in (D2) is controlled to not less than 1°C/hour and not more than 90°C/hour, or preferably a seed crystal is added at a temperature range of not less than 30°C and less than 48°C in (B2), or a part of the obtained crystals in (B2) is heated for dissolution in (C2).

[0044] The citalopram hydrobromide crystals having an average aspect ratio of generally not less than 2.0, preferably not less than 3, and more preferably not less than 4.5, and generally not more than 9.0, preferably not more than 7, and more preferably not more than 6.0, can improve the problems such as poor filtering performance after crystallization for the preparation of a pharmaceutical bulk and poor fluidity when crystals are being taken out, and can be advantageously used for the production of citalopram hydrobromide and the production of pharmaceutical products. From this viewpoint, the crystals having an average aspect ratio of not less than 4.5 and not more than 6.0 are particularly preferable. These crystals can be obtained by each method as follows.

[0045] In Method 1, the average cooling rate of the solution in the temperature range of 20°C - 40°C in (B1) is controlled to not less than 0.5°C/hour and not more than 60°C/hour, and preferably the stirring speed is set for 10 rpm - 250 rpm in (B1). In (B1), the speed at the tip of an agitation part is generally set to 0.1 m/s - 2.5 m/s, preferably 0.5 m/s - 2.0 m/s.

[0046] In Method 2, the cooling rate of the solution within the temperature range of from (heating temperature in (C2)) to (this heating temperature - 30°C) is controlled to not less than 1°C/hour and not more than 90°C/hour in (D2), and preferably the stirring speed is set for 10 rpm - 250 rpm in (B2) and (D2). In (B2) and (D2), the speed at the tip of an agitation part is generally set to 0.1 m/s - 2.5 m/s, preferably 0.5 m/s - 2.0 m/s.

[0047] By setting the speed at the tip of an agitation part to generally from not less than 2.5 m/s to less than 5.0 m/s, preferably from not less than 3.0 m/s to not more than 4.0 m/s, in (B1) in Method 1 and (B2) and (D2) in Method 2, crystals having an average aspect ratio of not less than 2.5 and less than 4.5 can be obtained. The crystals having an average aspect ratio of not less than 2.5 and less than 4.5 are preferable because they can be used as they are as a pharmaceutical preparation.

[0048] The citalopram hydrobromide to be used may be any that can be obtained by any method. It is preferably purified by active charcoal and the like before being subjected to the crystallization according to the present invention. The citalopram hydrobromide can be obtained, for example, according to the disclosure in, for example, US4650884.

[0049] The present invention is explained in more detail in the following by referring to Examples that do not limit the present invention in any way.

[0050] The powder X-ray crystal diffraction and average particle size were measured in the following Reference Example, Examples and Comparative Example, according to the following methods.

Powder X-ray crystal diffraction:	Rigaku Corporation MiniFlex Irradiated X-ray CuKα
Average particle size:	SHIMADZU CORPORATION SALD1100 (medium : diisopropyl ether)

Reference Example 1

[0051] Citalopram base (167 g) was dissolved in acetone (837 ml). Thereto was blown in a hydrobromic acid gas at 15°C - 40°C to make the pH of the solution 3. When about 1/2 of the hydrobromic acid gas was blown in, crystals began to precipitate. The reaction mixture was stirred at 25°C - 35°C for 1 hour, and at 0°C - 5°C for 1 hour. The resulting crystals were filtered, washed with cold acetone (167 ml) and dried in vacuo at 50°C - 70°C (5 Torr - 30 Torr) for 3 hours to give citalopram hydrobromide crystals (162 g). The crystals had an HPLC purity of 97.3% (254 nm).

melting point 180.3°C
^{1}H-NMR (DMSO-d_6, 400 MHz): shown in Figure 1.
Powder X-ray crystal diffraction pattern: shown in Figure 2.

Example 1

[0052] Citalopram hydrobromide (5.0 g) was synthesized according to Reference Example 1 and dissolved in methanol (15 ml) at 60°C. Thereto was added active charcoal (0.5 g) and the mixture was stirred for 15 minutes. The active charcoal was filtered off and isopropyl alcohol (25 ml) was added. The mixture was heated to 58°C to dissolve the crystals. When the mixture was cooled to 43°C while stirring at 200 rpm (propeller diameter: 0.05 m, speed at the tip of propeller: 0.05 × (200/6) × 3.14= ca. 0.5 m/s), the seed crystal (about 0.1 mg) of citalopram hydrobromide was added. The mixture was cooled to 40°C over 15 minutes and then cooled from 40°C to 20°C over 5 hours while stirring at 200 rpm to make the cooling rate almost the same (average cooling rate: 4°C/hour). The cooled suspension was stirred at 20°C for 18 hours (retention time at 20°C) at 200 rpm and the resulting crystals were filtrated. The crystals were dried at 50°C (0.67 kPa - 1.33 kPa) for 3 hours in vacuo while stirring them at 30 rpm, and stood for drying at

70°C (0.4 kPa - 0.8 kPa) for 15 hours.

[0053] The obtained citalopram hydrobromide crystals weighed 4.2 g, and the crystals had a melting point of 184.4°C and an HPLC purity of 99.9% (254 nm).

powder X-ray crystal diffraction pattern: shown in Figure 3
crystal particle size distribution

less than 5 μm 17.1%,
not less than 5 μm and less than 10 μm 22.2%,
not less than 10 μm and less than 20 μm 29.1%,
not less than 20 μm and less than 40 μm 27.0%,
not less than 40 μm 4.6% (shown in Figure 6)

average particle size 12.9 μm
micrograph (400 magnifications): shown in Figure 13
average aspect ratio: 4.8

Examples 2 - 3

[0054] The procedure followed Example 1 except that the cooling time of from 40°C to 20°C and the retention time at 20°C were changed to those shown in Table 1.

Table 1

Ex.	Cooling time of from 40°C to 20°C (cooling rate in parenthesis)	Retention time at 20°C	Crystal particle size distribution (D)	Average particle size (μm)
2	30 min (40°C/hour)	19 hr 30 min	D<5 μm 31.4% 5 μm≦D<10 μm 30.3% 10 μm≦D<20 μm 25.7% 20 μm≦D<40 μm 12.2% D≧40 μm 0.3% (shown in Figure 7)	7.8
3	1 hr (20°C/hour)	19 hr	D<5 μm 19.6% 5 μm≦D<10 μm 26.0% 10 μm≦D<20 μm 31.0% 20 μm≦D<40 μm 21.6% D≧40 μm 1.6% (shown in Figure 8)	11.0

Example 4

[0055] Citalopram hydrobromide (5.0 g) was synthesized according to Reference Example 1 and dissolved in methanol (15 ml) at 50°C. Thereto was added active charcoal (0.5 g) and the mixture was stirred for 15 minutes. The active charcoal was filtered off and isopropyl alcohol (25 ml) was added. The mixture was heated to 58°C to dissolve the crystals. When the mixture was cooled to 43°C while stirring at 200 rpm (propeller diameter: 0.05 m), the seed crystal (0.1 mg) of citalopram hydrobromide was added. The mixture was cooled to 41°C over 15 minutes and heated to 50°C

over 5 minutes, and then stirred at the same temperature for 30 minutes to allow dissolution of a part of the crystals (about half). Then, the mixture was cooled from 50°C to 20°C over 2.5 hours to make the cooling rate almost the same (average cooling rate: 12°C/hour). The cooled suspension was stirred at 20°C for 17.5 hours at 200 rpm and the precipitated crystals were filtrated. The crystals were dried at 50°C (0.67 kPa - 1.33 kPa) for 3 hours in vacuo with stirring at 30 rpm, and stood for drying at 70°C (0.4 kPa - 0.8 kPa) for 15 hours.

[0056] The obtained citalopram hydrobromide crystals weighed 4.1 g and the crystals had an HPLC purity of 99.9% (254 nm) and a melting point of 184.7°C.

powder X-ray crystal diffraction pattern: shown in Figure 4.
crystal particle size distribution

less than 5 μm 9.6%,
not less than 5 μm and less than 10 μm 12.3%,
not less than 10 μm and less than 20 μm 20.9%,
not less than 20 μm and less than 40 μm 31.7%,
not less than 40 μm 25.5% (shown in Figure 9)

average particle size 23.8 μm
micrograph (400 magnifications): shown in Figure 14
average aspect ratio: 5.4

Example 5

[0057] The procedure followed Example 4 except that the cooling time of from 50°C to 20°C and the retention time at 20°C were changed to those shown in Table 2.

Table 2

Ex.	Cooling time of from 50°C to (cooling rate in parenthesis)	Retention time at 20°C	Crystal particle size distribution (D)	Average particle size (μm)
5	30 min (60°C/hr)	19 hr 30 min	D<5 μm 15.6% 5 μm≦D<10 μm 19.3% 10 μm≦D<20 μm 26.9% 20 μm≦D<40 μm 31.0% D≧40 μm 7.2% (shown in Figure 10)	15.1

Example 6

[0058] Citalopram hydrobromide (16.2 kg) was synthesized according to Reference Example 1 and dissolved in methanol (37.4 kg) at 45°C - 50°C. Thereto was added active charcoal (1.8 kg) and the mixture was stirred for 55 minutes. The active charcoal was filtered off and washed with warm methanol (7.2 kg). The washings and the filtrate were combined and heated to about 60°C. Isopropyl alcohol (71.9 kg) heated to 40°C - 50°C was added, and upon confirmation of dissolution at 52°C, the mixture was cooled with stirring at 169 rpm (diameter of impeller of agitator (Pfaudler type): 0.45 m, speed at the tip of impeller of agitator: ca. 4.0 m/s). When the mixture was cooled to 44°C, the seed crystal (about 400 mg) of citalopram hydrobromide was added. Stirring at 40°C - 43°C for 30 minutes enabled confirmation of the precipitation of the crystals at 41.5°C.

[0059] The mixture was cooled from 40°C to 20°C over 4 hours (average cooling rate: 5°C/hour), and further cooled to 10°C over 3 hours. The suspension was stirred at 5°C - 10°C at 80 rpm for 13 hours and the crystals were filtrated. A mixture of isopropyl alcohol (9.6 kg) and methanol (4.8 kg) was cooled to 0°C - 10°C. The crystals were washed with this mixture. The wet crystals (19.8 kg) were dried under reduced pressure (10 kPa - 1.33 kPa), at 30°C - 50°C for 10 hours, at 45°C - 55°C for 5 hours, and at 70°C - 75°C for 8 hours, with stirring at 30 rpm.

[0060] The obtained citalopram hydrobromide crystals weighed 15.0 kg (recrystallization yield : 82%) and the crystals had an HPLC purity of 99.75% (220 nm) and a melting point of 185.0°C.

crystal particle size distribution

less than 5 μm 12.6%,
not less than 5 μm and less than 10 μm 20.2%,
not less than 10 μm and less than 20 μm 35.5%,
not less than 20 μm and less than 40 μm 29.3%,
not less than 40 μm 2.4% (shown in Figure 11)

average particle size: 14.6 μm
micrograph (400 magnifications): shown in Figure 15
average aspect ratio: 3.0
bulk density: 0.2 g/ml
tap density 0.42 g/ml

Comparative Example 1

[0061] Citalopram hydrobromide (5.0 g) was synthesized according to Reference Example 1 and dissolved in methanol (15 ml) at 50°C. Thereto was added active charcoal (0.5 g) and the mixture was stirred for 15 minutes. The active charcoal was filtered off and isopropyl alcohol (25 ml) was added. The mixture was heated to 68°C to dissolve the crystals. The mixture was cooled to 40°C over 5 min and then cooled from 40°C to 20°C over 5 min with stirring at 200 rpm. When the mixture was cooled to 20°C, the seed crystal (0.1 mg) was added. The mixture was stirred at the same temperature for 20 hours and the crystals were filtrated. The crystals were dried at 50°C (0.67 kPa - 1.33 kPa) for 8 hours in vacuo with stirring at 30 rpm, and stood for drying at 70°C (0.4 kPa - 0.8 kPa) for 15 hours.

[0062] The obtained citalopram hydrobromide crystals weighed 4.3 g and the crystals had an HPLC purity of 99.9% (254 nm) and a melting point of 184.2°C.

powder X-ray crystal diffraction pattern: shown in Figure 5
crystal particle size distribution

less than 5 μm 41.9%,
not less than 5 μm and less than 10 μm 30.2%,
not less than 10 μm and less than 20 μm 23.9%,
not less than 20 μm and less than 40 μm 4.0%,
not less than 40 μm 0% (shown in Figure 12)

average particle size: 8.3 μm
micrograph (400 magnifications): shown in Figure 16

[0063] According to the method of the present invention, the crystal characteristics of citalopram hydrobromide, such as particle size, particle size distribution, aspect ratio and the like, can be controlled easily and industrially. In addition, citalopram hydrobromide crystals having crystal characteristics useful as a pharmaceutical bulk can be provided.

Claims

1. Citalopram hydrobromide crystals containing crystals having a particle size of less than 5 μm in a proportion of 35% at most.

2. The citalopram hydrobromide crystals of claim 1, which comprise crystals having a particle size of not less than 20 μm in a proportion of not less than 10%.

3. The citalopram hydrobromide crystals of claim 1, which have an average aspect ratio of not less than 2.0 and not more than 9.0.

4. The citalopram hydrobromide crystals of claim 1, which have an average aspect ratio of not less than 2.5 and less than 4.5.

5. The citalopram hydrobromide crystals of claim 1, which have an average aspect ratio of not less than 4.5 and not

more than 6.0.

6. Citalopram hydrobromide crystals having an average aspect ratio of not less than 2.0 and not more then 9.0.

7. Citalopram hydrobromide crystals having an average aspect ratio of not less than 2.5 and less than 4.5.

8. Citalopram hydrobromide crystals having an average aspect ratio of not less than 4.5 and not more than 6.0.

9. A method for crystallizing citalopram hydrobromide, which comprises the steps of

(A1) dissolving, by heating, citalopram hydrobromide in a solvent comprising at least one member selected from the group consisting of alcohol having 1 to 3 carbon atoms, water and acetone and
(B1) cooling the resulting product to allow for crystallization while controlling a cooling rate.

10. The method of claim 9, which comprises controlling the cooling rate of the solution in a temperature range of from 0°C to 80°C.

11. The method of claim 9, which comprises controlling an average cooling rate of the solution in the temperature range of from 20°C to 40°C to not less than 30°C/hour and not more than 60°C/hour.

12. The method of claim 9, which comprises controlling an average cooling rate of the solution in a temperature range of from 20°C to 40°C to not less than 0.5°C/hour and less than 30°C/hour.

13. The method of claim 9, which comprises, after cooling to a temperature range of from not less than 30°C to less than 48°C, adding a seed crystal of citalopram hydrobromide for crystallization.

14. A method for crystallizing citalopram hydrobromide, which comprises the steps of

(A2) dissolving, by heating, citalopram hydrobromide in a solvent comprising at least one member selected from the group consisting of alcohol having 1 to 3 carbon atoms, water and acetone,
(B2) cooling the obtained solution to achieve crystallization,
(C2) dissolving a part of the obtained crystals by heating, and
(D2) recrystallizing while controlling a cooling rate.

15. The method according to claim 14, which comprises cooling to a temperature range of from not less than 30°C to less than 48°C in (B2).

16. The method according to claim 14, which comprises, after cooling to a temperature range of from not less than 30°C to less than 48°C, adding a seed crystal of citalopram hydrobromide for crystallization in (B2).

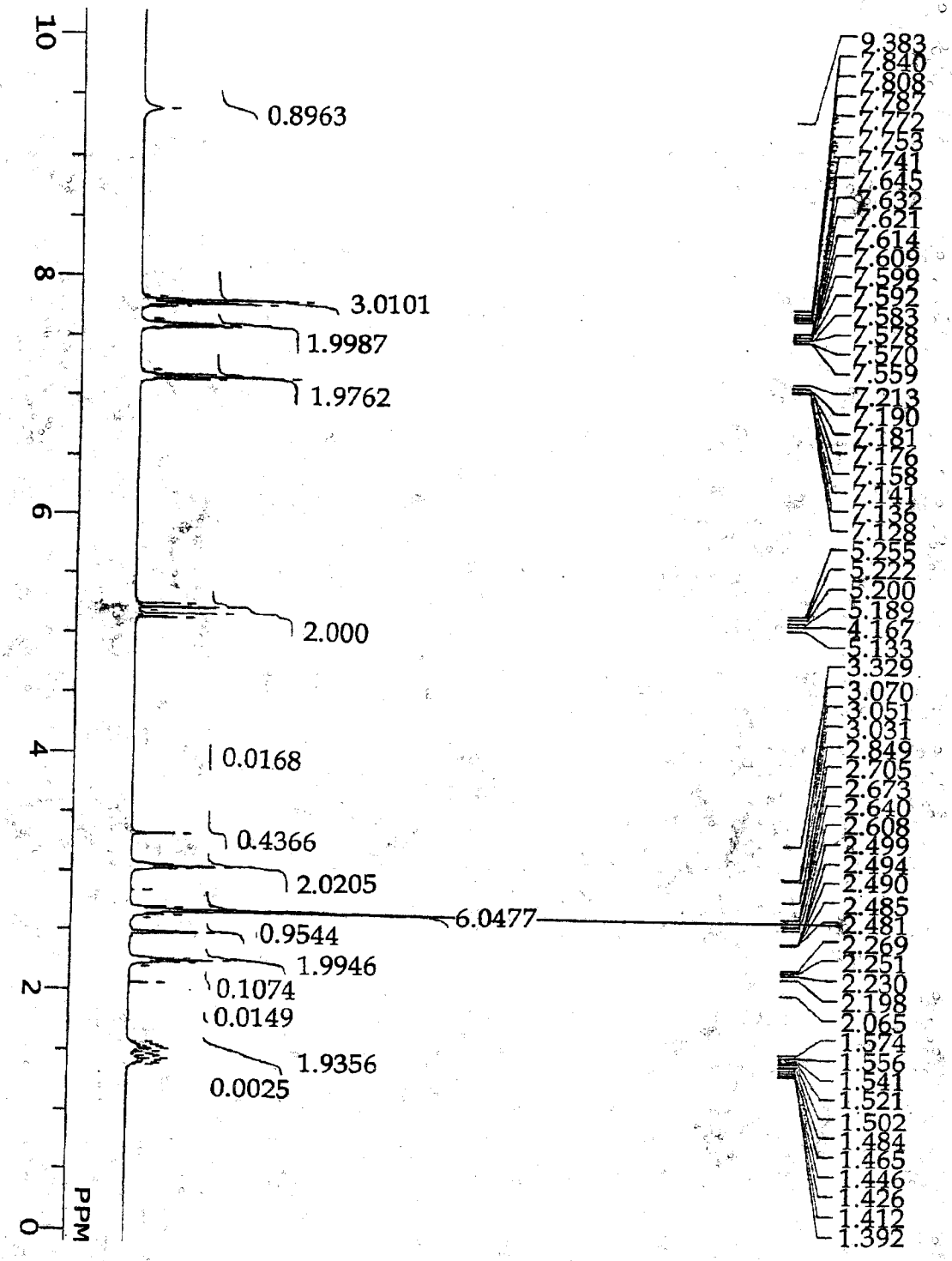
17. The method according to claim 14, which comprises dissolving a part of the crystals by heating to not less than 48°C and not more than 60°C in (C2).

18. The method according to claim 14, which comprises controlling the average cooling rate of the solution in the temperature range of from (heating temperature in (C2)) to (said heating temperature - 30°C) to not less than 30°C/hour and not more than 90°C/hour in (D2).

19. The method according to claim 14, which comprises controlling the average cooling rate of the solution in the temperature range of from (heating temperature in (C2)) to (said heating temperature - 30°C) to not less than 1°C/hour and less than 30°C/hour in (D2).

151

Fig.1


10
8
6
4
2
0
PPM
0.8963
3.0101
1.9987
1.9762
2.000
0.0168
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1.9356
0.0025
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7.128
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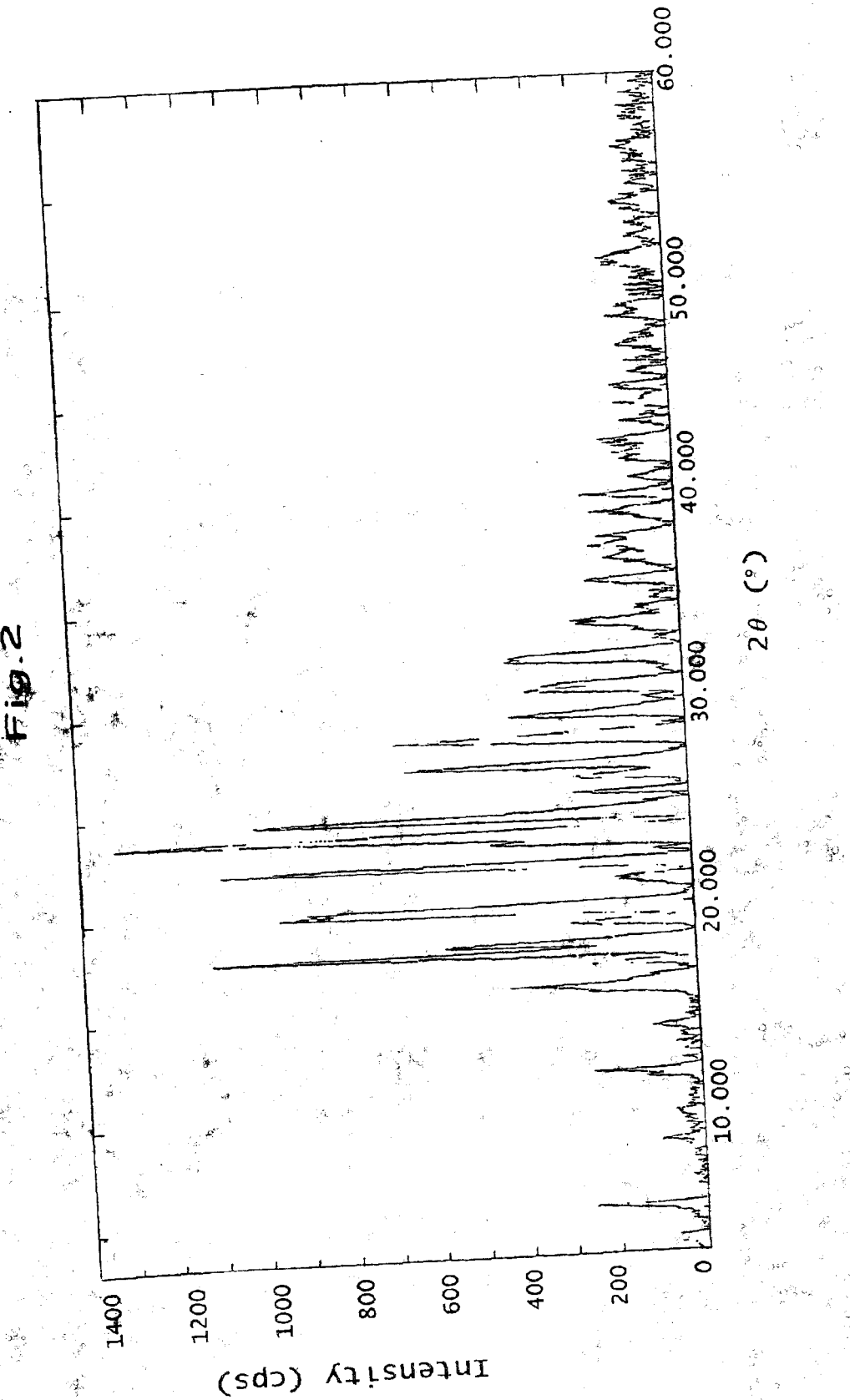

Intensity (cps)
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800
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20.000
30.000
40.000
50.000
60.000
2θ (°)

Fig.2

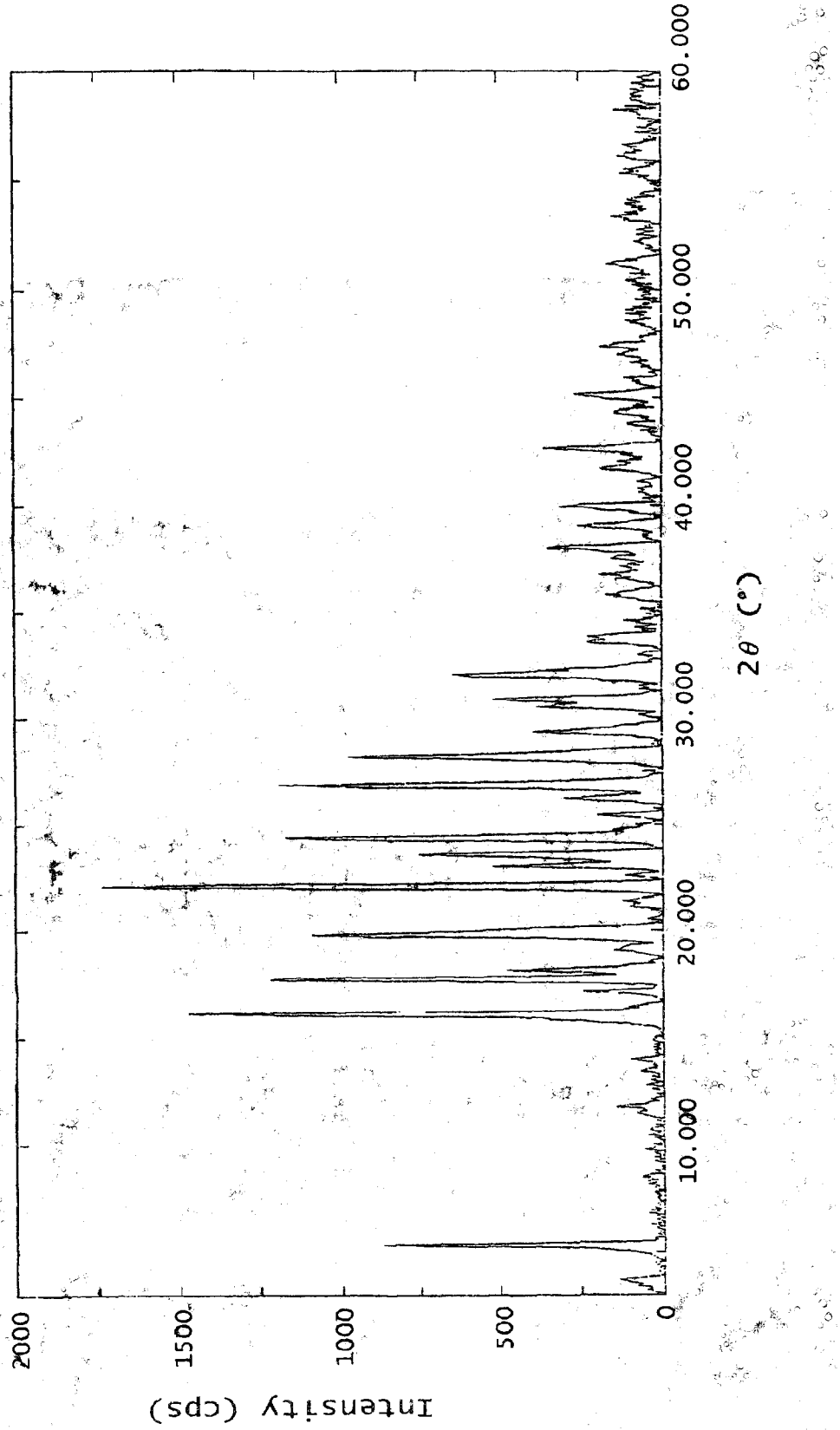

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2θ (°)

Fig.3

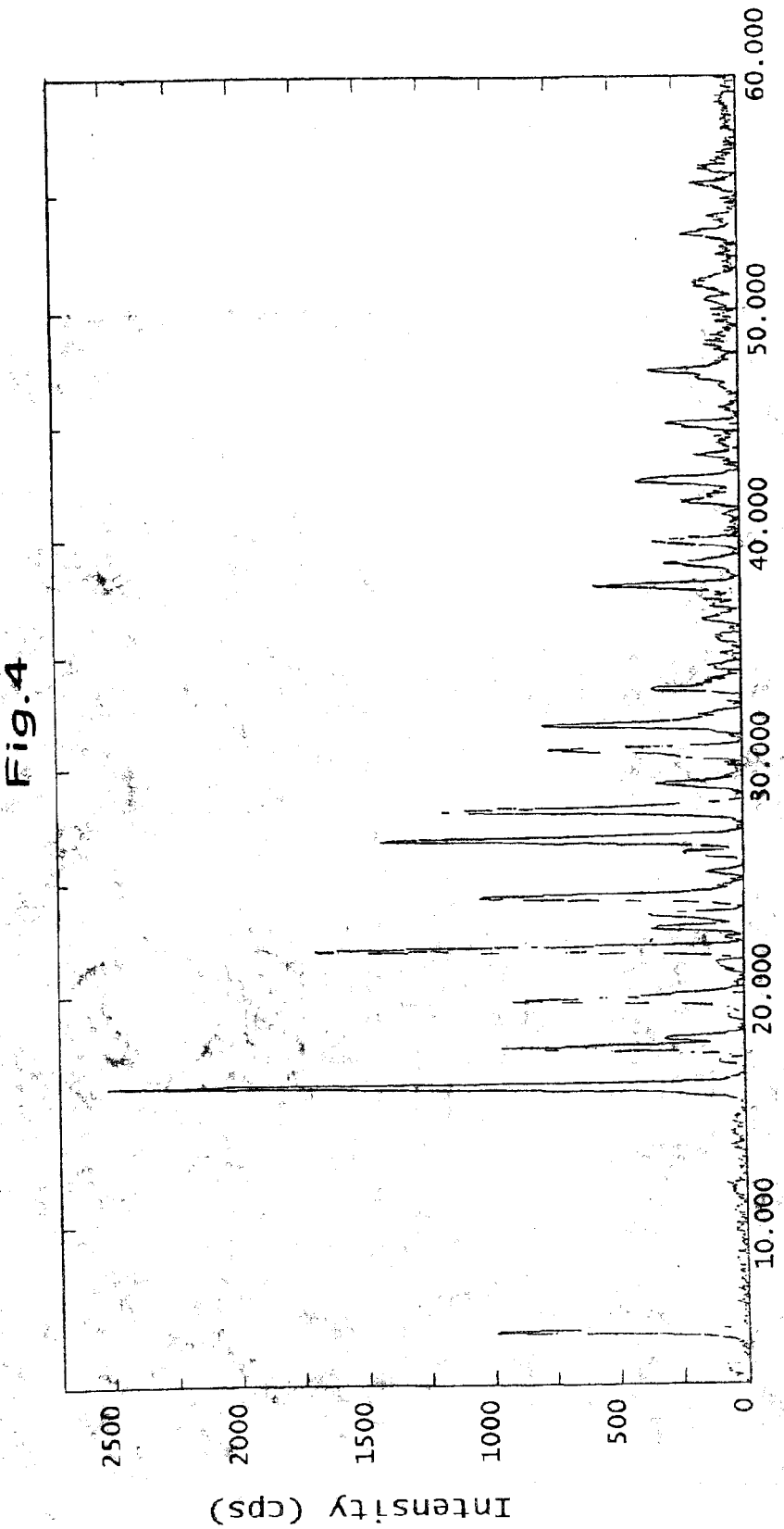

Intensity (cps)
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20.000
30.000
40.000
50.000
60.000
2θ (°)

Fig.4

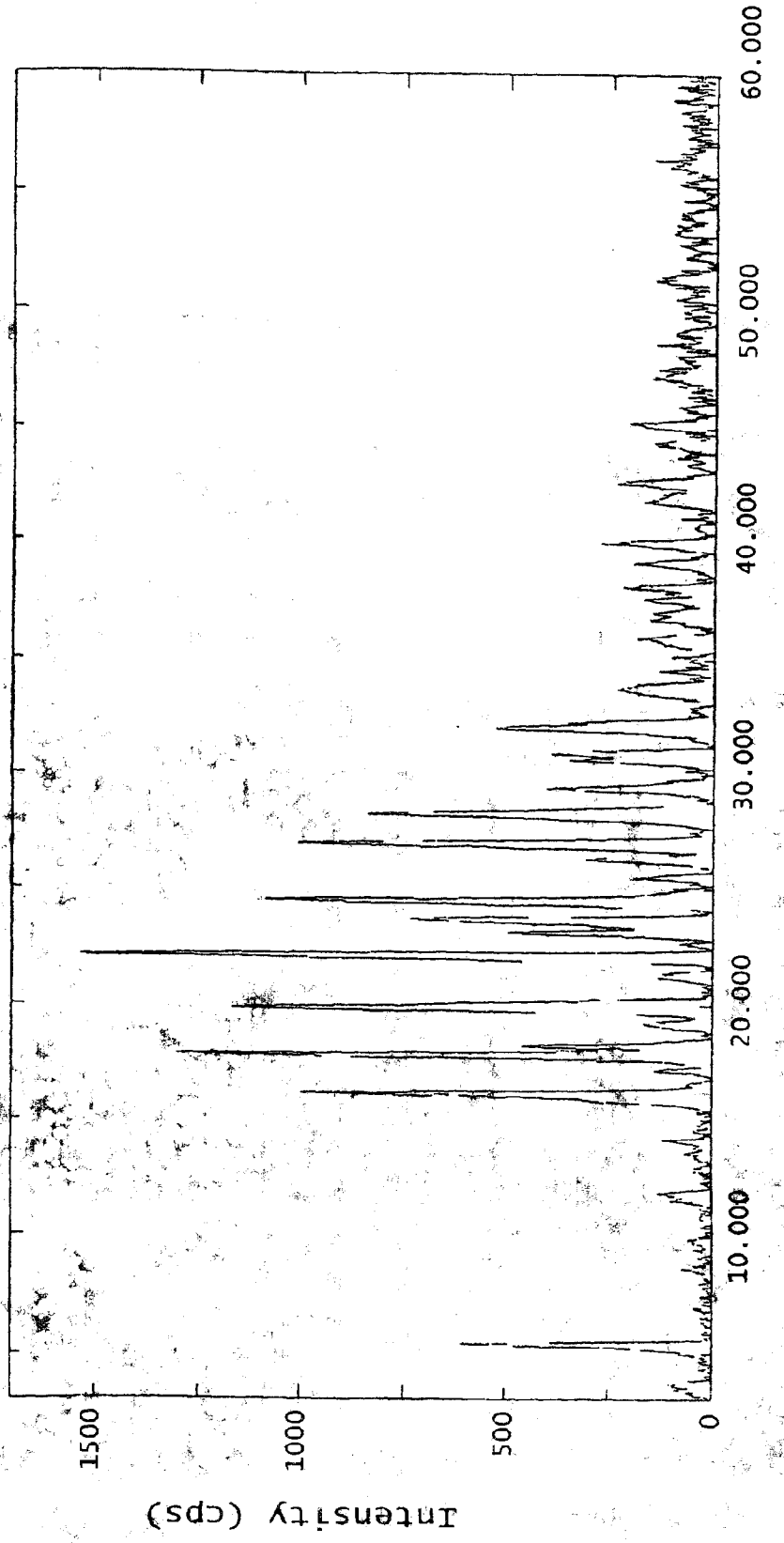

Intensity (cps)
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50.000
60.000
2θ (°)

Fig.5

Fig.6

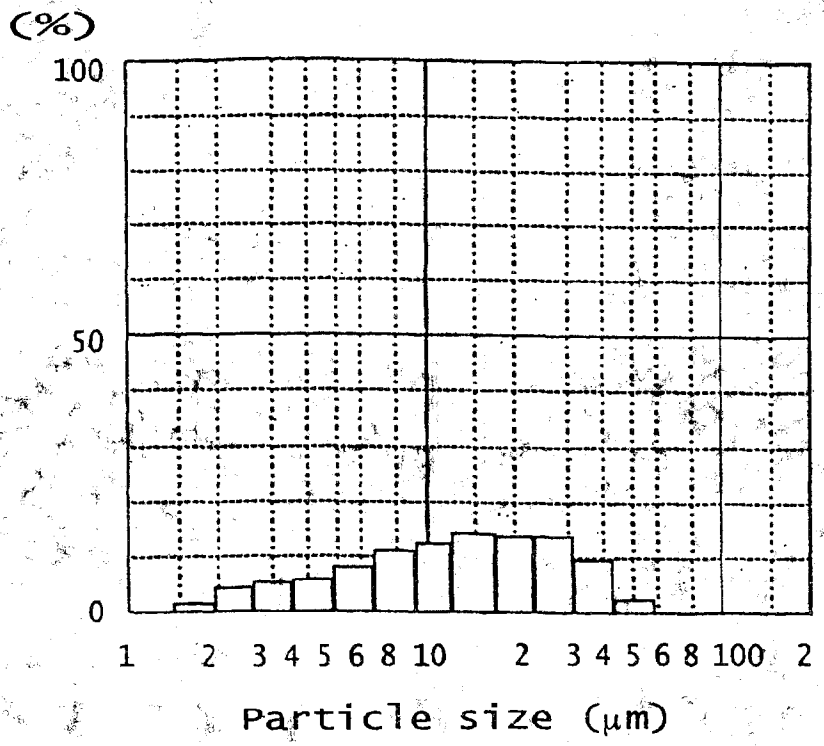


Fig.7

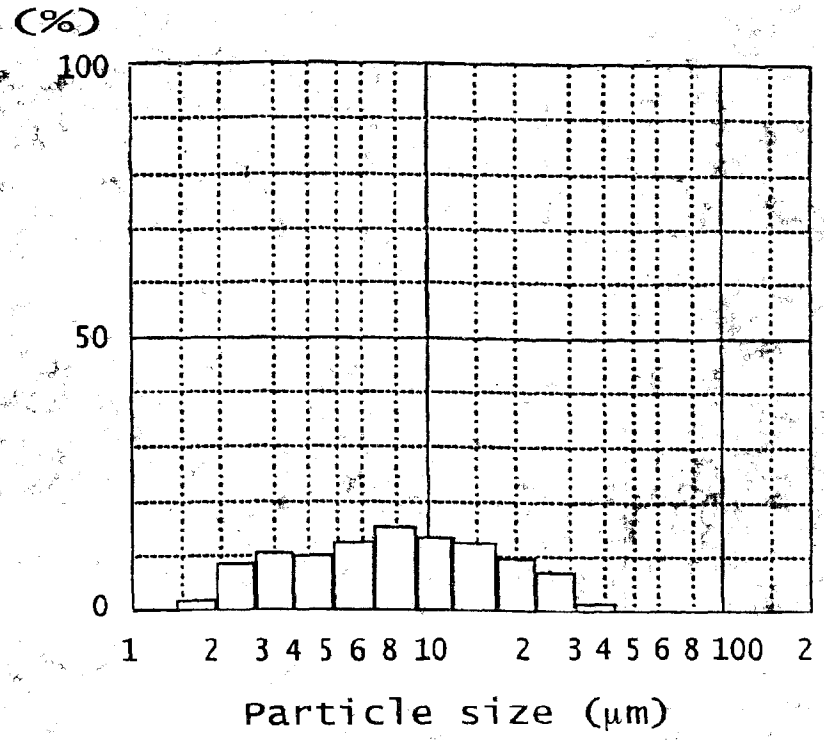


Fig.8

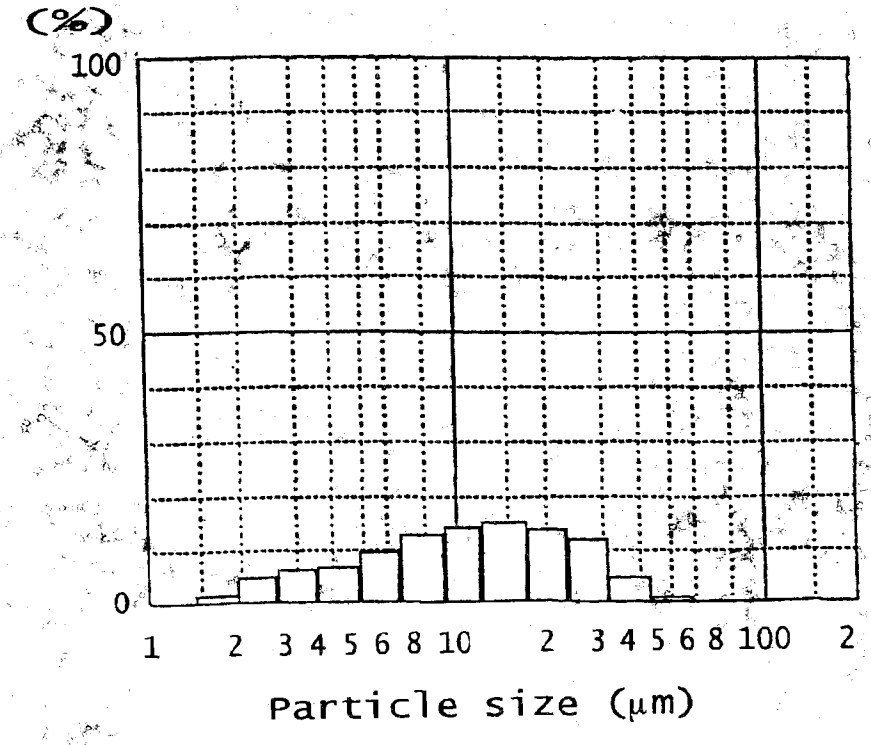


Fig.9

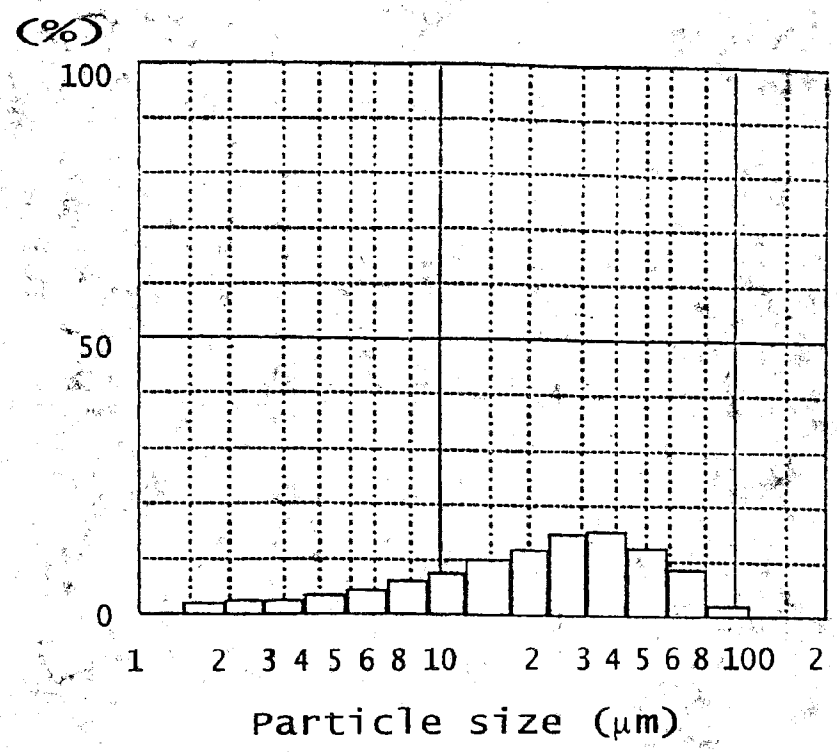


Fig.10

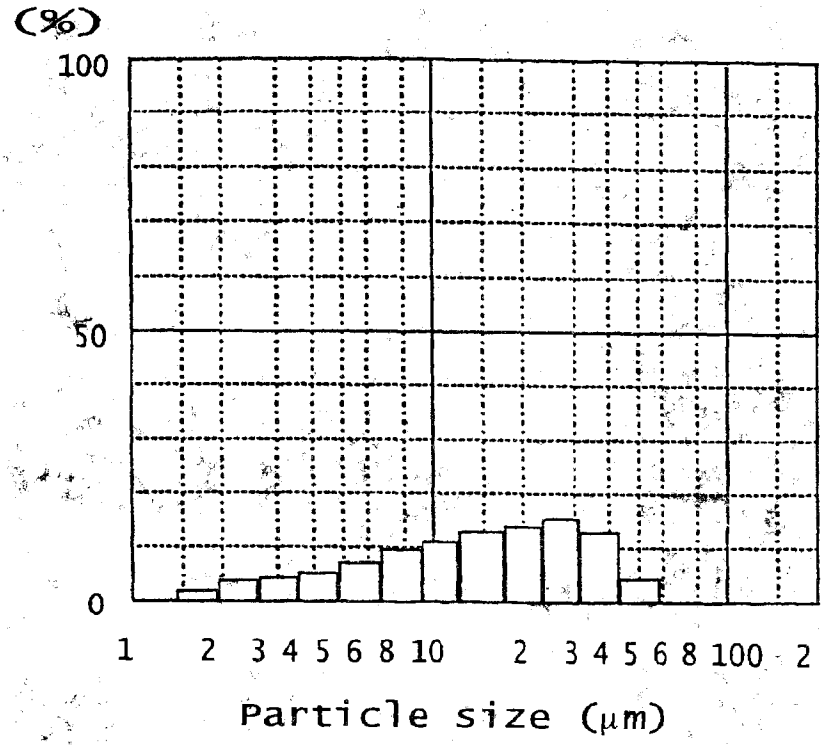


Fig.11

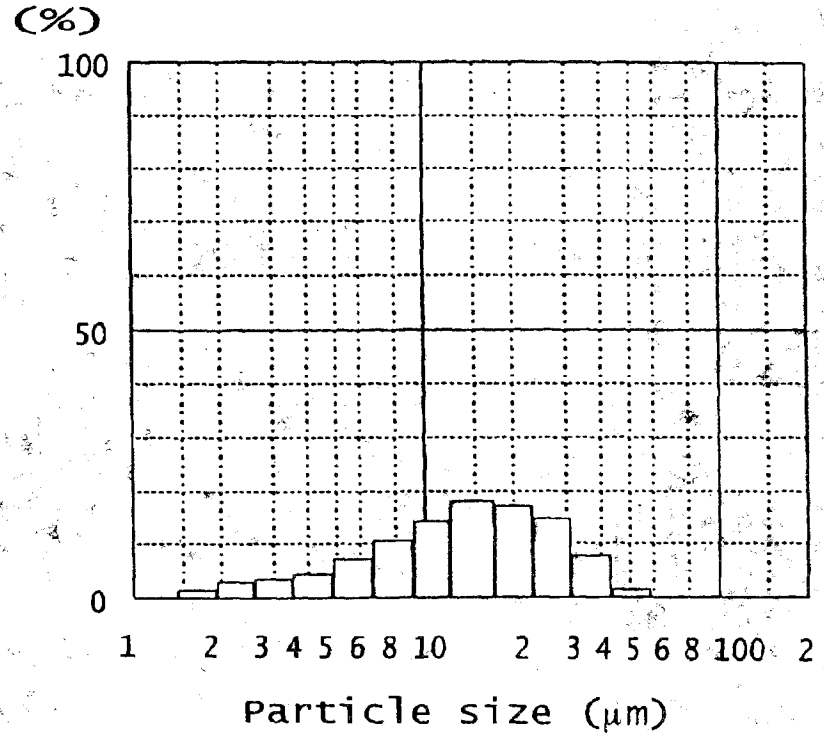


Fig.12

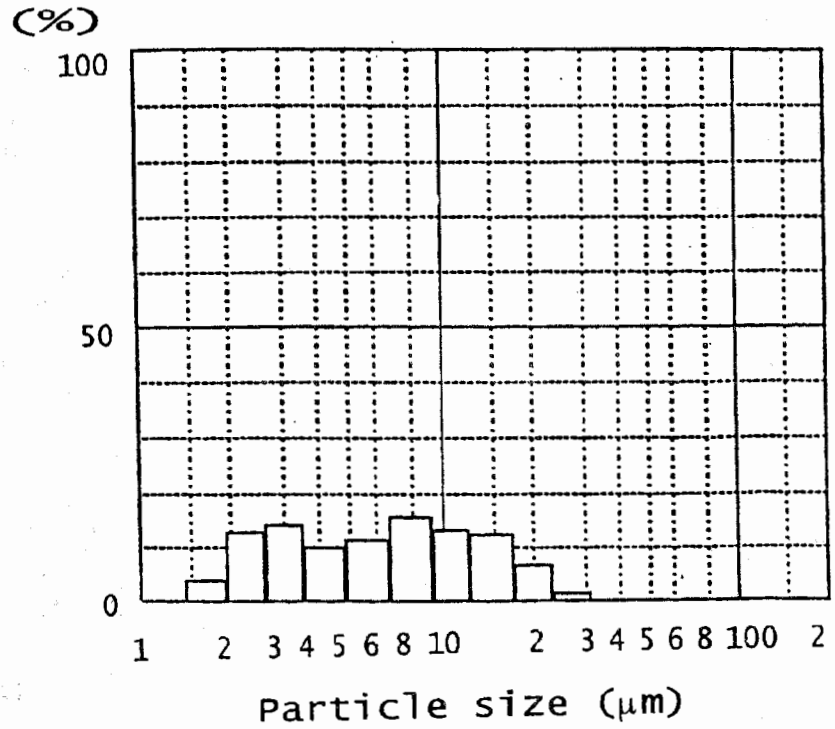


Fig.13

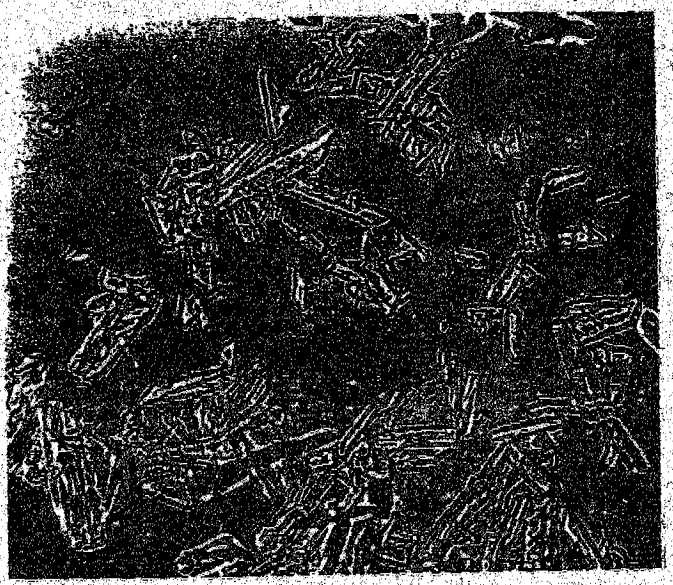


Fig.14



Fig.15



166 80

Fig.16

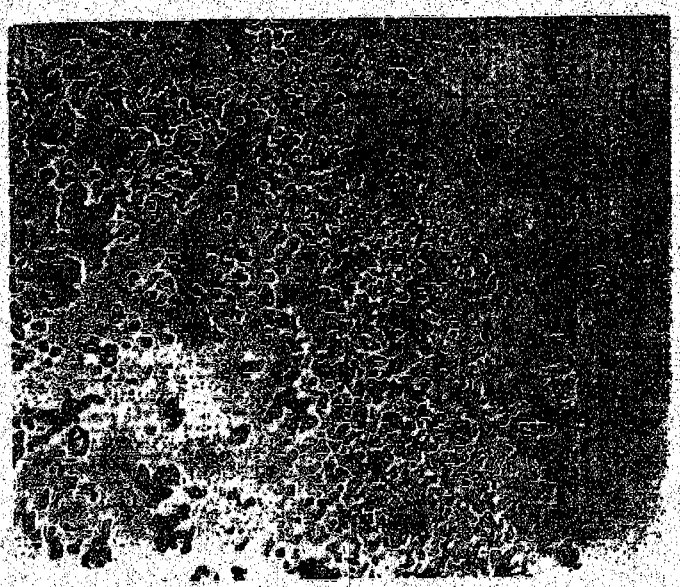
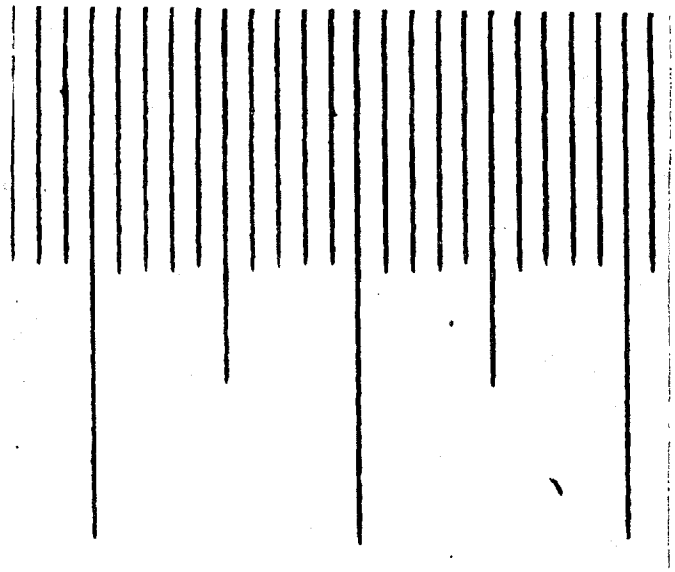


Fig.17



European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 01 10 8914

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Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
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TECHNICAL FIELDS SEARCHED (Int.Cl.7)
C07D

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	19 July 2001	Kyriakakou, G

CATEGORY OF CITED DOCUMENTS
X : particularly relevant if taken alone
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A : technological background
O : non written disclosure
P : intermediate document

T : theory or principle underlying the invention
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ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 01 10 8914

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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19-07-2001

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EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 01 10 8914

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

19-07-2001

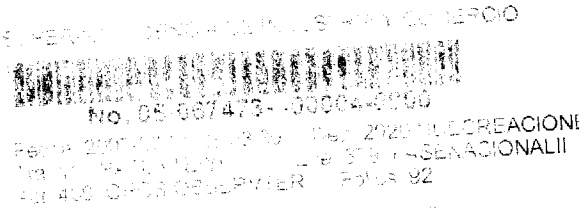
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EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

99
171

85



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 51,775
FECHA : JUNIO 27 DE 2007

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LAB. PROCAPS	CONSIGNACION	BANCO POPULAR	050-00110-6	50770484	26/06/2007	1,280,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04 PRESENTACION DE OBSERVACIONES	12 MARCAS Y LEMAS COMERCIALES	256,000.00
		TOTAL : $	256,000.00

SON: DOSCIENTOS CINCUENTA Y SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

160
172.

PROCAPS

PODER ESPECIAL

Yo, **WALTER TANAKA TATEKAWA,** mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **PROCAPS S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **LAURA CATALINA SILVA BARRERA,** abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 147399, poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 05067473, titulada **"BROMHIDRATO DE ESCITALOPRAM Y UN MÉTODO PARA SU PREPARACIÓN"** de **H. LUNDBERG,** publicada en la gaceta No. 575 del 30 de Abril de 2007.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar administrativa y judicialmente todo lo que fuere resuelto en el expediente a que se hace expresa referencia en el presente poder, con todas las facultades generales y especificas que fuera requerido para ella.

De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

Dado y Firmado en Barranquilla (Colombia) a los 16 días del mes de Julio de 2007.

PROCAPS S.A.
WALTER TANAKA TATEKAWA
C.C. Nº 16.251.923
Representante Legal

Acepto:

LAURA CATALINA SILVA BARRERA
C.C. 52'455.803 de Bogotá
T.P.A. 147399 del C.S. de la J.

ADY ISABEL NAMEN SEGURA
NOTARIA SEGUNDA DEL CIRCULO DE BARRANQUILLA

CERTIFICA

Que la(s) firma(s) que aparece(n) en el documento que antecede se asemeja(n) a la(s) de Walter Acosta Tobasco

Que aparece(n) registrada(s) en esta Notaría previa confrontación de la(s) misma(s).

(Decreto 960 / 70)

Barranquilla 19 de Julio de 2007

NOTARIA

REPUBLICA DE COLOMBIA
NOTARIA SEGUNDA
23.
MARTA L. ROJAS ZAMBRANO
Notaria Encargada
CIRCULO DE BARRANQUILLA

AUTENTICACIÓN DE FIRMA
MEDIANTE COMPARECENCIA PERSONAL
(Art. 84 C.P.C. mod. Decr. 2282 de 1989, art. 1 mod. 38)

Ante el Notario Cuarenta y Uno (41) del círculo de esta ciudad compareció personalmente: Silva Barrera Laura

identificado con C.C. 52.452.803 expedida en: Bta y tarjeta profesional de abogado(a) No. 114.345 del Consejo Superior de la Judicatura, con documento de: SLC

y declaro que la firma puesta en este escrito es suya.

Firma del declarante

En Bogotá D.C. a 25 JUL. 2007

AUTORIZÓ ESTA DILIGENCIA EL SUSCRITO NOTARIO

REPUBLICA DE COLOMBIA
Círculo de Santafé de Bogotá, D.C.
NOTARIA 44
Carrera 12 Nº 93-26
AGUSTIN MORALES RIVEIRA
SECAU

03-1[illegible]7678 024802 PROCAPS S.A.
Barranquilla, 17 de Julio de 2007 Hr:09:52:49

No. 11263222

CAMARA DE COMERCIO DE BARRANQUILLA

********** Pag. 1
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
10**********

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.
PROCAPS S.A.----------
NIT: 890.106.527-5.

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA,

C E R T I F I C A

Que por Escritura Pública No. 1,190 del 22 de Julio de 1976, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 28 de Julio de 1976 bajo el No. 6,070 del libro respectivo, fue constituida la sociedad----------
limitada denominada "PRODUCTORA DE CAPSULAS DE GELATINAS LIMITADA "PROCAPS LIMITADA".----------

C E R T I F I C A

Que por Escritura Pública No. 1,307 del 28 de Junio de 1979, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Julio de 1979 bajo el No. 10,039 del libro respectivo, la sociedad antes mencionada----------
se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A.".----------

C E R T I F I C A

Que por Escritura Pública No. 3,810 del 31 de Dic/bre de 1980, otorgada en la Notaria Primera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 30 de Enero de 1981 bajo el No. 12,705 del libro respectivo, la sociedad antes mencionada----------
se transformo en sociedad de responsabilidad limitada bajo al razon social de "PRODUCTORA DE CAPSULAS DE GELATINA LIMITADA "PROCAPS LI - MITADA".----------

C E R T I F I C A

Que por Escritura Pública No. 3,755 del 10 de Nov/bre de 1983, otorgada en la Notaria Unica de Soledad, inscrito(as) en esta Cámara de Comercio, el 22 de Nov/bre de 1983 bajo el No. 17,922 del libro respectivo, la sociedad antes mencionada----------
se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A. "PROCAPS S.A.".----------

C E R T I F I C A

Que por Escritura Pública No. 3,615 del 06 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 20 de Dic/bre de 1996 bajo el No. 67,218 del libro respectivo, la sociedad antes mencionada----------

********** C O N T I N U A **********

FESA S.A. NIT. 890.321.151-0 FORMAS EFICIENTES 19422

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCI[illegible] DE DOCUMENTOS.

PROCAPS S.A.----------
NIT: 890.106.527-5.

cambio de razon social, por la denominacion LABORATORIOS PROCAPS S.A
.----------

C E R T I F I C A

Que por Escritura Pública No. 3,775 del 18 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Enero de 1997 bajo el No. 67,704 del libro respectivo, la sociedad antes mencionada----------
cambio de razon social, por la denominacion PROCAPS S.A. ----------

C E R T I F I C A

Que dicha sociedad ha sido reformada por las siguientes escrituras y/o documentos privados:

Numero	aaaa/mm/dd	Notaria	No. Insc o Reg	aaaa/mm/dd
39	1979/01/18	Notaria 3a. de Barranquilla.	9,452	1979/01/24
992	1981/04/30	Notaria 1a. de Barranquilla.	13,112	1981/05/06
1,464	1982/08/27	Notaria Unica de Soledad	15,533	1982/09/08
2,744	1983/08/18	Notaria Unica de Soledad	17,416	1983/08/26
3,826	1984/07/16	Notaria Unica de Soledad	19,554	1984/07/27
3,835	1985/08/26	Notaria Unica de Soledad	22,230	1985/09/04
2,260	1986/09/10	Notaria Unica de Soledad.	24,995	1986/09/15
1,849	1989/07/11	Notaria 2a. de Barranquilla.	33,909	1989/07/13
444	1990/02/21	Notaria 2a. de Barranquilla.	36,101	1990/03/16
3,090	1991/12/17	Notaria 2a. de Barranquilla	43,993	1992/01/28
269	1993/02/01	Notaria 2a. de Barranquilla	48,428	1993/02/16
2,342	1993/07/28	Notaria 2a. de Barranquilla	50,582	1993/08/10
3,652	1993/11/09	Notaria 2a. de Barranquilla	51,798	1993/11/22
3,615	1996/12/06	Notaria 2a. de Barranquilla	67,218	1996/12/20
89	1997/01/16	Notaria 2a. de Barranquilla	67,704	1997/01/23
2,070	1997/07/17	Notaria 2a. de Barranquilla	70,627	1997/07/31
2,281	1997/08/04	Notaria 2a. de Barranquilla	70,813	1997/08/14
765	1999/04/22	Notaria 3a. de Barranquilla	80,628	1999/04/23
459	2001/02/21	Notaria 2a. de Barranquilla	91,502	2001/02/23
2,608	2001/10/05	Notaria 2a. de Barranquilla	95,771	2001/11/08
1,730	2004/07/29	Notaria 2. de Barranquilla	112,999	2004/08/26
416	2005/03/03	Notaria 2. de Barranquilla	116,364	2005/03/10
1,613	2005/07/28	Notaria 2. de Barranquilla	119,322	2005/08/18

C E R T I F I C A

Que de acuerdo con la(s) escritura(s) arriba citada(s), la sociedad se rige por las siguientes disposiciones:
DENOMINACION O RAZON SOCIAL:
PROCAPS S.A.----------
SIGLA: PROCAPS.
DOMICILIO PRINCIPAL: Barranquilla.
NIT No: 890.106.527-5.
MATRICULA MERCANTIL: 24,802.

C E R T I F I C A

********** C O N T I N U A **********

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.
PROCAPS S.A.----------
NIT: 890.106.527-5.

Direccion para notificaciones judiciales:
CL 80 No 78 B - 201.
De la ciudad de Barranquilla.

C E R T I F I C A

DURACION: El término de duración de la sociedad se fijó hasta el 18 de Agosto de 2073.

C E R T I F I C A

OBJETO SOCIAL: El objeto principal de la sociedad sera: a)-La fabricacion de capsulas y otros productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas y cosmeticas, para uso y consumo humano y veterinario; b)-La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas y cosmeticas para uso y consumo humano, animal y vegetal; c)-La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas,alimenticias y cosmeticas, asi como la comercializacion interna y externa de los productos terminados, d) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos medicos,quirurgicos,odontologicos,y hospitalarios para la salud humana y animal. e)La compra,venta,exportacion y disdistribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. f) Actuar como representante o agente de personas naturales y juridicas, nacionacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualquiera de las actividades descritas en los literales a), b), c). d) y e) antes descritos; g) Prestar los servicios de asesoria y consultoria en las areas administrativas, de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion, exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de PROCAPS S.A., asi como los de publicidad y promocion de productos quimicos, cosmeticos y farmaceuticos para uso humano, animal o industrial; h)-Adquirir, operar, administrar y explotar, a cualquier titulo, empresa o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista, socio o fundador de empresas que tengan igual o similar objeto, com-

********** C O N T I N U A **********

FENOA S.A. NIT. 890.321.161-0 FORMAS EFICIENTES 9602

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCI[illegible] DE DOCUMENTOS.

PROCAPS S.A.----------

NIT: 890.106.527-5.

prar, vender, importar y exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades; tomar dinero en prestamo, financiar y garantizar las operaciones comerciales que celebre con terceros relativas a su objeto; celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operaciones; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables; comprar, vender y constituir gravamenes sobre bienes muebles e inmuebles; designar representantes o apoderados en el pais y en el exterior y, en general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor proteccion de sus intereses corporativos o la de sus socios. La sociedad podra garantizar el cumplimiento de obligaciones adquiridas por terceros o por sus socios, para lo cual podra inclusive constituir gravamenes reales sobre sus bienes de cualquier naturaleza.----------

C E R T I F I C A

CAPITAL	Nro Acciones	Valor Acción
Autorizado		
$**********2,000,000,000	**********2,000,000	**********1,000
Suscrito		
$**********1,224,500,000	**********1,224,500	**********1,000
Pagado		
$**********1,224,500,000	**********1,224,500	**********1,000

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad corresponderá a la Asamblea General de Accionistas, a la Junta Directiva, al Presidente, al Vicepresidente y a un Gerente General. Corresponde a la Junta Directiva las siguientes funciones y atribuciones entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion. Cuando se trate de operaciones en virtud de las cuales la sociedad garantice obligaciones de terceros o de los socios, se requerira que la operacion sea aprobada con el voto de por lo menos 2/3 partes de los integrantes de la Junta Directiva. La sociedad tendra un Presidente, quien ejercera la representacion legal de la sociedad y tendra las siguientes atribuciones entre otras: Ejecutar las decisiones de la Asamblea General de Accionistas y de la Junta Directiva. Ejercer la Representacion Legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, disistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la socieda todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a doscientos cincuenta mil dolares de los

********** C O N T I N U A **********

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.
PROCAPS S.A.----------
NIT: 890.106.527-5.

Estados Unidos de America (US$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion o celebracion del acto. Las demas funciones que le correspondan como Representante Legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Presidente tendra un suplente, designado por la Junta Directiva, quien reemplazara al Presidente en sus faltas temporales, absolutas o meramente accidentales, con entidades facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un Vicepresidente designado por la Junta Directiva, quien tambien ejercera la representacion legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el Presidente. El vicepresidente tendra las siguentes facultades entre otras. Ejecutar dentro de su competencia las decisiones de la Asamblea General de Accionistas, de la Junta Directiva y del Presidente. Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a ciento cincuenta mil dolares de los Estados Unidos de America (US$150.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza muebles, acciones, cuotas o partes de interes inversiones y todo tipo de derechos de la sociedad, o de constituir gravamenes sobre cualquiera de los anteriores, facultades que radican exclusiva y privativamente en cabeza del Presidente. Las demas funciones que le corresponda como Representante legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Vicepresidente tendra (1) suplente, designado por la Junra Directiva, quien lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con identicas facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un (1) Gerente General, con su respectivo Suplente, designados por la Junta Directiva. El Suplente reemplazara al Gerente General, en sus faltas temporales, absolutas o meramente accidentales, quien junto con el gerente general, llevaran la representacion legal de la sociedad, con identicas facultades, pudiendolas ejercer conjunta o separadamente con el Presidente y Vicepresidente, con identicas facultades que el Gerente General y sin que sea necesario para ello acreditar

FISCA S.A. NIT. 890.321.151-0 FORMAS CONTINUAS 1942

la ausencia del titular. El Gerente General tendra las siguientes facultades entre otras: Ejercer la representacion legal de la sociedad, en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos Colombianos a Cincuenta Mil dolares de los Estados Unidos de America (US$50.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar a cualquier titulo bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza mueble, acciones, cuotas o partes de interes, inversiones y todo tipo de derechos de la sociedad o de constituir gravamenes sobre cualquiera de las anteriores facultades que radican exclusiva y privativamente en cabeza del Presidente.

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:
PROCAPS S.A.
cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, y según Acta No. 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:
PROCAPS S.A.
cuya parte pertinente se inscribió en esta Cámara de Comercio, el 29 de Mayo de 2000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE: JUNTA DIRECTIVA

Principales	
1. Minski Gontovnik Ruben	CC.********7,463,982
2. Minski Gontovnik Meyer	CC.********7,461,324
3. Minski Gontovnik Jose	CC.********8,671,834
Suplentes	
1. Minski Zilberblum Elliot	CC.******72,219,541
2. Minski Deitel Daniel	.****************
3. Minski Sharon	PA.*990,212,082,805

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Presidente.	
Minski Gontovnik Ruben	CC.********7,463,982

********** C O N T I N U A **********

No. 11263225

CAMARA DE COMERCIO DE BARRANQUILLA

C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
10**********

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.
PROCAPS S.A.----------
NIT: 890.106.527-5.

Suplente del Presidente
Minski Minski Abraham CC.*********802,575
Vicepresidente
Minski Gontovnik Meyer CC.*******7,461,324
Suplente del vicepresidente
Minski Gontovnik Jose CC.*******8,671,834

C E R T I F I C A

Que según Acta No. 11 del 01 de Febrero de 2001 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 12 de Febrero de 2001 bajo el No. 91,273 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre Identificación
Gerente General.
Uribe Ochoa Guillermo Luis CC.******70,073,754

C E R T I F I C A

Que según Acta No. 406 del 02 de Sep/bre de 2004 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 09 de Sep/bre de 2004 bajo el No. 113,263 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre Identificación
Suplente del Gerente.
Tanaka Walter CC.******16,251,923

C E R T I F I C A

Que según Acta No. 124 del 29 de Marzo de 1999 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 04 de Agosto de 1999 bajo el No. 82,226 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre Identificación
Revisor Fiscal Ppal.
Vargas Pertuz Ana Isabel CC.******32,696,645

C E R T I F I C A

Que según Acta No. 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio,

********** C O N T I N U A **********

Cámara de Comercio de Barranquilla - NIT. 890.102.321-0 - Todos los derechos reservados - 2006

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS

PROCAPS S.A.----------

NIT: 890.106.527-5.

el 29 de Mayo de 2000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Revisor Fiscal.	
Lozada Villareal Milena	CC.******32,748,111

C E R T I F I C A

Que por escritura publica No. 2.608 del 5 de Octubre del 2.001,otorgada en la Notaria 2a. de Barranquilla, inscrita en esta Camara de Comercio el 8 de Noviembre del 2.001, bajo los Nos. 95.771, 2.056, 2.057, 2.058, 2.059, 2.060, 2.061, 2.062 y 2.064 del libro respectivo, se reforma totalmente el articulo 65, contenido en la escritura publica No. 3.705 de Noviembre 6 de 1.998, de la Notaria Segunda del Circuito de Barranquilla, y se constituyen los siguientes Apoderados Generales, quienes tendran las funciones que a continuacion se indican en razon de su cargo en la sociedad: 1.-Se confiere Poder Especial, Amplio y Suficiente a los senores: WALTER TANAKA TATEKAWA, C.C. No. 16.251.923; WILIIAM ALBERTO BARROS CERRA, C.C. No. 8.715.941, para que cada uno en forma independiente en nombre y representacion de PROCAPS S.A., suscriba todas las declaraciones tributarias, aduaneras y cambiarias a que este obligada la sociedad, asi como para que responda todo tipo de requerimiento o solicitudes de informacion de las autoridades tributarias, aduaneras o cambiarias,en los ordenes Distrital, Departamental y Nacional. 2.-Se confiere Poder Especial,amplio y suficiente,a los siguientes senores que conforman el Grupo A y el Grupo B para que conjuntamente suscriban contratos de suministros de mercancias y servicios con entidades oficiales, hasta por la suma de US$800.000.oo (OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA), liquidados a la tasa representativa del mercado vigente en el dia que se realice la respectiva transaccion. GUPO A: CLAUDIA TANGARIFE CASTILLO C.C. No. 41.660.293. BRUPO B: WALTER TANAKA TATEKAWA C.C. No. 16.251.923, CARMEN ALICIA FLOREZ C.C. No. 22.434.044, CARMEN ALICIA HERRERA DIAZGRANADOS C.C. No. 22.377.540. Para el ejercicio de estas facultades se requerira por lo menos la firma de uno (1) de los apoderados especiales del Grupo A y uno de los apoderados especiales del Grupo B; 3.-Se otorga Poder General, Amplio y Suficiente a la Doctora JOSEFINA MIELES BUELVAS C.C. No. 33.138.497, a la Doctora MARCELA CARVAJALINO PAGANO C.C. No. 22.579.748, y al Doctor DANIEL MORENO VILLALBA, C.C. No. 19.113.210; para que cada uno representen a PROCAPS S.A., ante todo tipo de autoridades administrativas y judiciales, en asuntos de naturaleza cambiaria y fiscal, tales como: Contestar e interponer demandas y requerimientos, comparecer en juicios,pedir la practica de pruebas,recibir notificaciones,interponer recursos y ejercer acciones contencioso administrativas y de tutela,transigir,conciliar,recibir en nombre de la sociedad desistir, sustituir y reasumir este mandato. Para la celebracion de cualquier acuerdo conciliatorio o transaccional, judicial o extrajudicial, cualquiera que sea su cuantia,los Apoderados deberan aportar la autorizacion escrita del Representante Legal de la sociedad. Los Apoderados podran presentar solicitudes de devolucion y/o compensacion de impuestos y recibir los pagos por devoluciones de

********** C O N T I N U A **********

03-12007678 024802 PROCAPS S.A.
Barranquilla, 17 de Julio de 2007 Hr:09:52:49

No. 11263226

CAMARA DE COMERCIO DE BARRANQUILLA

********** Pag. 5
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
10**********

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.
PROCAPS S.A.----------
NIT: 890.106.527-5.

impuestos, firmar, notificarse y realizar todo acto necesario para cumplir con el mandato encomendado.----------

C E R T I F I C A

Que segun documento privado de fecha 7 de junio de 2000, inscrito en esta Camara de Comercio el 8 de junio de 2000, bajo el No.1.786 del libro respectivo, consta que RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982 de Barranquilla, actuando como Presidente y Representante Legal de la sociedad PROCAPS S.A, confiere poder especial, amplio y suficiente a KAREN FIGUEROA GARCIA, C.C.No.32.732.070 de Barranquilla, para que en su nombre y representacion de la sociedad suscriba todas declaraciones cambiarias a que este obligada PROCAPS S.A, en el giro normal de sus negocios y operaciones sociales.--

C E R T I F I C A

Que segun Documento Privado del 13 de diciembre del 2.002, inscrito en esta Camara de Comercio el 15 de enero del 2.003 bajo el No.2.290 del libro respectivo, el senor RUBEN MINSKI GONTOVNIK, C.C.No.7.463.982, en calidad de REPRESENTANTE LEGAL, y en condicion de PRESIDENTE de PROCAPS S.A., mediante el presente documento otorgo PODER ESPECIAL al Sr. MARLON TATIS PAREDES, C.C.No.72.176.874, para que en representacion de PROCAPS S.A., suscriba declaraciones, reportes y cualquier tipo de documentos relacionados con tramites o registros de Comercio Exterior ante el Ministerio de Comercio Exterior y/o cualquier entidad del Estado que haga sus veces. En consecuencia, el Sr. MARLON TATIS PAREDES, podra suscribir en representacion de PROCAPS S.A. declaraciones, reportes y cualquier tipo de documentos relacionados con tramites o registros de Comercio Exterior ante el Ministerio de Comercio Exterior y/o cualquier entidad del Estado que haga sus veces.----------

C E R T I F I C A

Que segun documento privado del 10 de noviembre del 2004, inscrito en esta Camara de Comercio el 1 de diciembre del 2.004, bajo el No. 2.753 del libro respectivo consta que RUBEN MINSNSKI GONTOVNIK, C.C. 7.463.982 de Barranquilla, actuando como Presidente y Representante Legal de la sociedad PROCAPS S.A, confiere poder especial, amplio y suficiente a ANTONIO VARELA DIAZ, C.C.No.72.004.669 de Barranquilla, para que en nombre y representacion de la sociedad firme las declaraciones cambiarias a que este obligada PROCAPS S.A., a suscribrir en el giro normal de sus negocios y operaciones sociales. Por lo anterior, el senor ANTONIO VARELA DIAZ, queda facultado

********** C O N T I N U A **********

PEGA S.A. NIT. 890.921.151-0 FORMAS CONTINUAS 2002

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.----------
NIT: 890.106.527-5.

para firmar las declaraciones comabiarias y demas documentos relacionados con las declaraciones, notificaciones, aportar y solicitar las pruebas que sean necesarias, desistir en general a realizar todo acto necesario de tal forma que pueda cumplir con el mandato dado.-

C E R T I F I C A

Que segun documento privado del 22 de Febrero de 2005, inscrito en esta Camara de Comercio el 28 de Marzo de 2.005, bajo el No. 2.820 del libro respectivo, consta que WALTER TANAKA TATEKAWA C.C. 16.251-923 de Palmira, quien actua como representante legal de la sociedad PROCAPS S.A, otorga Poder Especial, Amplio y Suficiente al senor MARLON TATIS PAREDES C.C. No. 72.176.874, para que en representacion de PROCAPS S.A., suscriba declaraciones aduaneras, reportes y cualquier tipo de documentos relacionados con los tramites o registros de comercio exterior ante la direccion de impuestos y aduanas nacionales y/o cualquier entidad que haga sus veces, y para que responda todo tipo de requerimientos y/o solicitudes de informacion de las autoridades aduaneras en los ordenes distrital, departamental y nacional.----------

C E R T I F I C A

Que por Escritura Pública No. 2,011 del 10 de Octubre de 2006, otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Dic/bre de 2006 bajo el No. 3,183 del libro respectivo,----------
Consta que RUBEN MINSKI GONTOVNIK CC.No.7.463.928, quien manifesto que en su condicion de Presidente y Representante Legal de la ------ sociedad PROCAPS S.A.,confiere poder especial amplio y suficiente a los siguientes senores que conforman el Grupo A y el Grupo B, para que conjuntamente suscriban contratos de suministro de mercancias y servicios con entidades oficiales, hasta por la suma de ochocientos mil dolares de los Estados Unidos de America (US$800.000.00), ---- liquidados a la tasa representativa del mercado vigente en el dia que se realice la respectiva transaccion. Grupo A: IVAN VILLAREAL CAMACHO CC.No.91.201.749. FERNANDO RINCON RIVERA CC.No.79.484.187. CLAUDIA TANGARIFE CASTILLO CC.No.41.660.293.Grupo B. WALTER TANAKA TATEKAWA CC.No.16.251.923. CARMEN ALICIA FLOREZ DE LA ROTA ---------- CC.No 22.434.044. RICARDO DORADO HURTADO CC.No.79.715.772.----------

C E R T I F I C A

Que en esta Cámara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disolución, liquidación o nombramientos de representantes legales de la expresada sociedad.

C E R T I F I C A

Que su última Renovación fue el: 20 de Marzo de 2007.

La información sobre embargos de establecimiento se suministra en Certificados de Matrícula, la de contratos sujetos a registro, en

********** C O N T I N U A **********