

FORMULARIO ÚNICO DE OPOSICIÓN

1

OPOSICIÓN A:

- ☒ 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

Número del expediente: 04-008776

Solicitante: J. LUNDBECK A/S

SOLICITUD

PUBLICADA

Apoderado: EMILIO FERRERO

Título de la nueva creación o denominación del signo: METODO PARA LA
PREPARACION DE ESCITALOPRAM

Gaceta: 555

3 OPOSICIÓN PRESENTADA POR:

SOLICITANTE

Nombre: GYNOPHARM

Dirección: CALLE 80 No. 78b-201

Nacionalidad o Domicilio: COLOMBIA

Lugar de Constitución: BARRANQUILLA

Teléfono: 371 99 00 Fax: 373 08 18

E-mail:

IDENTIFICACIÓN

C.C. ☐ NIT ☒

C.E. ☐ Otro ☐

Cual

Número 802.006.279-4

REPRESENTANTE
O APODERADO

Nombre: REINALDO PINILLA
MORENO

Dirección: TRANSVERSAL 13 A 119-95
OFICINA 104

Teléfono: 613 34 18 Fax: 24 47 87

E-mail: negocios@optimum-co.com

IDENTIFICACIÓN

C.C. ☒ NT ☐

C.E. ☐ Otro ☐

Cual

Número 80425609 TP 91563

4 FUNDAMENTOS DE LA OPOSICIÓN:

Art. 14, 16, 18, 20 y 30 de la Decisión 486 de la CAN

Causal: No cumple con los requisitos de patentabilidad.

Signo opositor:

Justificación:

La presente solicitud no cumple con los requisitos de patentabilidad dado que lo
revelado, ya se encontraba en el estado de la técnica o es posible derivarlo de la
misma tal y como se demostrará en el capítulo "Fundamento de Hechos".

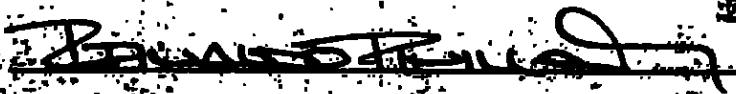
Comprobante de pago No. _____

Fecha _____

ANEXOS

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

NOMBRE: REINALDO PINILLA MORENO

FIRMA: 

C.C. 80425609

TP. 91563 CSJ

NOTARIA 39 DEL CIRCULO DE
BOGOTÁ, D.C.

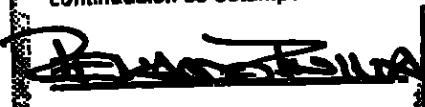
DILIGENCIA DE RECONOCIMIENTO

En el despacho de la Notaria Treinta y Nueve (E)
del círculo de Bogotá, D.C., el día

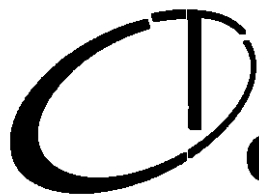
28 NOV 2005

Quien se identifica con la cédula de ciudadanía
No. 80425609 expedida en Bogotá

y dijo que reconoce el anterior
documento como cierto, y que la firma es de
su puño y letra. Igualmente reconoce como
suya la huella dactilar del índice derecho que a
continuación se estampa.


FRANCISCA ULLOA RIAÑO

NOTARIA 39(E)



Optimum

Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 04-008776

Asunto : Oposición a la solicitud de patente de Invención titulada "MÉTODO PARA LA PREPARACIÓN DE ESCITALOPRAM".

Solicitante : H. LUNDBECK A/S.

Opositora : GYNOPHARM S.A.

**Publicada en la Gaceta de la Propiedad Industrial :
N° 555 del 31 de Agosto de 2005**

Yo, **REINALDO PINILLA MORENO**, abogado con tarjeta profesional N° 91563 del consejo superior de la judicatura, en mi condición de apoderado de la sociedad **GYNOPHARM 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 **"MÉTODO PARA LA PREPARACIÓN DE ESCITALOPRAM"**, solicitada por **H. LUNDBECK A/S.**, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

**Calle 119 A N° 5399. Tel. (571) 6 13 34 18 - 6 13 33 74 - Fax. (571) 6 24 47 87
E-mail: negocios@optimum-co.com - www.optimum-co.com
Bogotá Colombia**

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 legítimo interés de nuestra representada debido a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida atentaría directamente a la comercialización que pretende mi representada, en materia de ESCITALOPRAM en particular. 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 4 de febrero de 2004, reivindicando prioridad bajo las solicitudes DK 2001 01101 del 2001-07-13; DK 2001 01851 del 2001-12-11; y, DK 2001 01852 del 2001-12-11 y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 555 del 31 de agosto de 2005, página 483, N° publicación 496, cuya publicación internacional corresponde a la WO03/006449 del 2003-01-23.

2.2. La solicitud colombiana 04-008776 objeto de la presente oposición, se refiere a un método novedoso para la manufactura de escitalopram. El método comprende la separación cromatográfica de los enantiómeros de citalopram o un intermediario en la producción de citalopram utilizando una fase inmóvil quiral como ser

Chiralpak™ AD o Chiralcel™ OD. También se proveen intermediarios quirales novedosos para la síntesis de Escitalopram preparados mediante dicho método.

2.3. En primera instancia, 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: Determination of citalopram enantiomers in human plasma by liquid chromatographic separation on a Chiral-AGP column, J Chromatogr B Biomed Appl, 1996 Oct 25; Abstract.
- D2: WO0143525, 2001-06-21

2.4. Ahora bien, el documento D1 que data de 1996, particularmente en el resumen se revela un método cromatográfico líquido para el análisis cuantitativo de S-Citalopram y R-Citalopram en el plasma humano previamente desarrollado y validado. Según dicho resumen, los enantiómeros del citalopram y el R-(+)-propranolol se han extraído del plasma alcalino con 2% n-butanol en n-hexano. Después del paso de la limpieza, la fase orgánica se evaporó y los residuos se disolvieron en 50 a 100 microlitros de 0.001M HCl. Por su parte, la separación se realizó en una columna Chiral-AGP™ con 3.0 mM de N-dodecyl-N,N-dimetilamonio-3-propanesulfonato y 10 mM de ácido hexanoico en fosfato de pH 6.5 como una fase móvil. El límite de detección fue estimado para estar en 1 ng/ml (aproximadamente igual a 3) para cada enantiómero que supervisa la absorción de



UV a 240 nm. En el rango estudiado, 2.31-191 ng/ml, las recuperaciones eran cuantitativas y los coeficientes de variaciones estaban entre 2.47% y 11.5%. Así las cosas, a los ojos de este documento D1, la presente solicitud objeto de oposición no cumple con el requisito de novedad dado que con anterioridad se demuestra la existencia de un método en el que la separación de enantiómeros se ha realizado por separación cromatográfica líquida que usa un quiral como fase estacionaria para la cromatografía.

2.5. Por otro lado, el documento D2 del mismo solicitante, ya revelaba con anterioridad dicho método, pues particularmente en la página 11, línea 19, afirmó que el S-citalopram puede ser preparado por separación de isómeros ópticamente activos mediante cromatografía. Ahora bien, debe ser claro y evidente que para cualquier persona versada en la materia, combinando lo referenciado en este documento D2 con lo indicado en documento D1, puede obtener el contenido la presente solicitud objeto de oposición, pues puede deducirse una separación cromatográfica de los enantiómeros de citalopram o un intermediario en la producción de citalopram utilizando una fase inmóvil quiral. Por lo tanto, el presente también carece de altura inventiva en relación con el documento D2.

2.6. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 04-008776 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.

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

2.7.1. **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, 13 de julio de 2001, ya era conocido, pues como se demostró, era parte del arte anterior con base en el documento D1, un método de separación cromatográfica de los enantiómeros de citalopram en la producción de citalopram utilizando una fase inmóvil quiral. sobre el cual busca protección en el capítulo reivindicatorio.

2.7.2. 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, 13 de julio de 2001, a partir de los documentos D1 y D2 en combinación, es posible deducir una separación cromatográfica de los enantiómeros de citalopram o un intermediario en la producción de citalopram utilizando una fase inmóvil quiral. según lo definido en las reivindicaciones de la presente solicitud.

2.8. 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.





2007

2.9. Por consiguiente, si se concede el registro solicitado se induciría al monopolio de un producto que no cumple con los requisitos primordiales exigidos por la mencionada Decisión 486.

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 **"MÉTODO PARA LA PREPARACIÓN DE ESCITALOPRAM"**, solicitada por **H. LUNDBECK A/S**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 555.

3. PRUEBAS

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

- D1: Determination of citalopram enantiomers in human plasma by liquid chromatographic separation on a Chiral-AGP column, J Chromatogr B Biomed Appl, 1996 Oct 25; Abstract.
- D2: WO0143525, 2001-06-21

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

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

- D1: Determination of citalopram enantiomers in human plasma by liquid chromatographic separation on a Chiral-AGP column, J Chromatogr B Biomed Appl, 1996 Oct 25; Abstract.
- D2: WO0143525, 2001-06-21

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 Transversal 13ª N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,


REINALDO PINILLA MORENO

C.C. 80'425.609 de Bogotá

T.P.A. 91563 del C.S. de la J.





Gynopharm

The primary support
for the woman's health specialist

PODER ESPECIAL

Yo, **LUIS PALACIOS ARAGON**, 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 **GYNOPHARM S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a **REINALDO PINILLA MORENO**, abogado titulado, identificado como aparece al pie de su firma, con tarjeta profesional No. 91563 expedida por el Consejo Superior de la Judicatura, poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 04-008776, de título: **"METODO PARA LA PREPARACIÓN DE ESCITALOPRAM"**, publicada en la gaceta No. 555 del 31 Agosto de 2005.

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 específicas 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 24 días del mes de noviembre de 2005.

GYNOPHARM S.A.
LUIS PALACIOS ARAGON
C.E. N° 319.788
Representante Legal

Acepto:

REINALDO PINILLA MORENO
C.C. 80'425.609 de Bogotá
T.P.A. 91563 del C.S. de la J.

ADY ISABEL NAMED SEGURA
NOTARIA SEGURA DEL CIRCULO DE BARRANQUILLA
CERTIFICA

Que la(s) firma(s) que aparece(n) en el documento que
entonces se remite(n) a la(s) de LUIS PALACIOS
ARAGON

Que aparecen en esta Notaría previa
conferencia de sus firmas.

(Decreto 993 de 1991)
Barranquilla 25 de NOV de 2005

NOTARIA



***** 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
16*****

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

GYNOPHARM S.A.-----

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA,

C E R T I F I C A

Que por Escritura Pública No. 3.551 del 17 de Dic/bre de 1997, otorgada en la Notaria 3a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 18 de Dic/bre de 1997 bajo el No. 72.965 del libro respectivo, fue constituida la sociedad-----
anonima denominada GYNOPHARM S.A.-----

C E R T I F I C A

C E R T I F I C A

.463.982, actuando como Presidente y representante legal de la sociedad GYNOPHARM S.A., otorga Poder Especial, Amplio y Suficiente a KAREN JENNIFER FIGUEROA GARCIA C.C. No. 32.-732.070, para que en nombre y representación de la sociedad suscriba todas las declaraciones cambiarias a que esta obligada GYNOPHARM S.A., en el giro normal de sus negocios y operaciones sociales.---

C E R T I F I C A

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

Numero	aaaa/mm/dd	Notaria	No. Insc o Reg	aaaa/mm/dd
532	1999/03/25	Notaria 3a. de Barranquilla	80.373	1999/04/13

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:

GYNOPHARM S.A.-----

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 802.006.279-4.

MATRICULA MERCANTIL: 245.470.

C E R T I F I C A

Direccion para notificaciones judiciales:

CL 80 No 78 B -. 201.

De la ciudad de Barranquilla.

C E R T I F I C A

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



***** Pag. 2
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
16*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE
DOCUMENTOS.
GYNOPHARM S.A.-----

*****2.672.646.000 *****2.672.646 *****1.000
Pagado
*****2.672.646.000 *****2.672.646 *****1.000

C E R T I F I C A

ADMINISTRACION: Seran funciones de la junta directiva, entre otras:
Autorizar cualquier acto o contrato cuya cuantia sea superior al
equivalente en pesos Colombianos a cincuenta mil dolares de l s Es-
tados Unidos de America (US\$50.000.oo), liquidados a la tasa de cam-
bi representativa del mercado vigente el dia en que se surta la
aprobacion y para enajenar o gravar bienes inmuebles y demas activos
fij s de la sociedad, cualquiera que sea la cuantia de la transac-
ci n. Las demas que le sean propias y no esten atribuidas a otro or-
gano social y las que le correspondan en virtud de la ley. la socie-
dad tendra un Gerente General, quien ejercera la administraci n y
representacion legal de la sociedad y tendra las siguientes atribu-
ci nes, 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
l s presentes estatutos. Aprobar y celebrar en nombre de la sociedad
todo acto o contrato cuya cuantia sea igual o inferior al equivalen-
te en pesos Colombianos a cincuenta mil dolares de los Estados Uni-
d s de America (US\$50.000.oo), liquidados a la tasa de cambio repre-
sentativa del mercado vigente el dia en que se surta la aprobacion o
celebracion del acto. Para enajenar, a cualquier titulo, bienes in-
muebles de la sociedad o constituir gravámenes sobre los mismos, de-
bera obtener la aprobacion de la junta directiva, cualquiera que sea
la cuantia de la transaccion; o las demas funciones que le corres-
pondan como representante legal por disposicion de la ley, de estos
estatutos o de la junta directiva. El Gerente General tendra un su-
plente, designado por la junta directiva, quien lo reemplazara c n
identicas facultades en sus faltas temporales, absolutas o meramente
accidentales, sin que sea necesario para ello acreditar la ausencia
del principal.-----

C E R T I F I C A

Que por Escritura Pública No. 3.551 del 17 de Dic/bre de 1997,
torgada en la Notaria 3a. de Barranquilla
cuya parte pertinente se inscribió en esta Cámara de Comercio, el
18 de Dic/bre de 1997 bajo el No. 72.965 del libro respectivo, fueron
hechos los siguientes nombramientos:

CLASE: JUNTA DIRECTIVA

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



***** Pag. 3
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
16*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.
GYNOPHARM S.A.-----

Comercio el 9 de Marzo de 1.998 bajo los Numeros 1.348 y 1.349 de los libros respectivos, el señor MARIO LOMBANA GARZON C.C. No. 19.-358.058, quien actua en su condicion de Gerente General de la sociedad GYNOPHARM S.A., otorga Poder Especial a los señores WALTER TANAKA TATEKAWA C.C. No. 16.251.923, para que en nombre y representacion de GYNOPHARM S.A., suscriba todas las declaraciones tributarias, aduaneras y cambiarias a que este obligada la sociedad, así como para que responda todo tipo de requerimientos o solicitudes de informacion de las autoridades tributarias, aduaneras y cambiarias, en las ordenes distrital, departamental y nacional; y JOSEFINA DEL CARMEN MIELES BUELVAS C.C. No. 33.138.497, para que represente a GYNOPHARM S.A., ante todo tipo de autoridades administrativas y judiciales en asuntos de naturaleza aduanera, cambiaria, fiscal tales como contestar e interponer demandas y requerimientos, comparecer en juicio, pedir la practica de pruebas, recibir notificaciones, interponer recursos, ejercer la accion 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, la apoderada debera aportar la autorizacion escrita del representante legal de la sociedad. La apoderada podra presentar solicitudes de devolucion y/o compensacion de impuestos y rentas recibidos y pagos por devoluciones.-----

C E R T I F I C A

Que segun Documento Privado de fecha 10 de Octubre del 2.000, inscrito en esta Camara de Comercio el 12 de junio del 2.002, bajo el 2.164 del libro respectivo, consta que el señor JORGE CASTELLANOS MARTINEZ, identificado con C.C.No.19.460.089, actuando como representante legal de la sociedad GYNOPHARM S.A, otorga Poder Especial Amplio y Suficiente a KAREN FIGUEROA GARCIA, identificada con la cedula de ciudadanía No.32.732.070 de Barranquilla, mediante documento privado de octubre 10/2000, inscrito en la Camara de Comercio de Barranquilla bajo el No.1.872 del libro respectivo, para que en representacion de GYNOPHARM S.A, suscriba las declaraciones cambiarias a los que esta obligada GYNOPHARM S.A. en el giro ordinario de sus negocios y operaciones sociales.-----

C E R T I F I C A

.463.982, actuando como Presidente y representante legal de la sociedad GYNOPHARM S.A., otorga Poder Especial, Amplio y Suficiente a KAREN JENNIFER FIGUEROA GARCIA C.C. No. 32.-732.070, para que en nombre y representacion de la sociedad suscriba todas las declaraciones cambiarias a que esta obligada GYNOPHARM S.A., en el giro normal de sus

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



All Databases

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Protein

Genome

Structure

OMIM

PMC

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Review: 0

33

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New/Noteworthy

E-Utilities

☐ 1: J Chromatogr B Biomed Appl. 1996 Oct
25;685(2):299-305.

Related Articles, Compound via MeSH, Substance via

MeSH, Books, LinkOut

Determination of citalopram enantiomers in human plasma by liquid chromatographic separation on a Chiral-AGP column.**Haupt D.**

Uppsala University, Biomedical Centre, Sweden.

A liquid chromatographic method for the quantitative analysis of S-(+)- and R-(-)-citalopram in human plasma has been developed and validated. The enantiomers of citalopram and the internal standard, R-(+)-propranolol, were extracted from alkaline plasma with 2% n-butanol in n-hexane. After a clean-up step, the organic phase was evaporated and the residues dissolved in 50-100 microliters of 0.001 M HCl. The separation was performed on a Chiral-AGP column with 3.0 mM N-dodecyl-N,N-dimethylammonio-3-propanesulfonate and 10 mM hexanoic acid in phosphate buffer pH 6.5 as the mobile phase. The limit of detection was estimated to be 1 ng/ml (S/N approximately equal to 3) for each enantiomer monitoring UV absorption at 240 nm. In the range studied, 2.31-191 ng/ml, the recoveries were quantitative and the coefficients of variations were between 2.47% and 11.5%.

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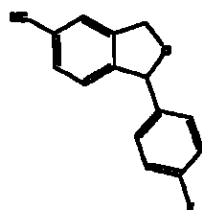
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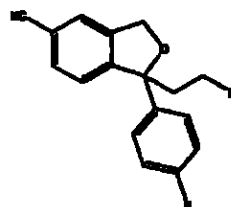
(54) Title: METHOD FOR THE PREPARATION OF CITALOPRAM



(I)



(II)



(III)

(57) Abstract: The present invention relates to a method for the preparation of citalopram comprising reaction a compound of formula (I) with a compound having formula (II) wherein X is a suitable leaving group and R is $-\text{CH}_2-\text{O}-\text{Pg}$, $-\text{CH}_2-\text{NPg}_1\text{Pg}_2$, $-\text{CO}-\text{N}(\text{CH}_3)_2$, $-\text{CH}(\text{OR}^1)(\text{OR}^2)$, $-\text{C}(\text{OR}^3)(\text{OR}^4)(\text{OR}^5)$, $-\text{COOR}^6$, $-\text{CH}_2-\text{CO}-\text{NH}_2$, $-\text{CH}=\text{CHR}^7$ and $-\text{CONHR}^8$ wherein Pg is a protection group for an alcohol group, Pg₁ and Pg₂ are protection groups for an amino group, R¹ and R² are independently selected from alkyl, allyl, alkynyl and optionally alkyl substituted aryl or aralkyl groups or R¹ and R² together form a chain of 2 to 4 carbon atoms, each of R³, R⁴, R⁵, R⁶ and R⁷ are independently selected from alkyl, allyl, alkynyl and optionally alkyl substituted aryl or aralkyl and R⁸ is hydrogen or methyl; to form a compound of formula (III) wherein R is as defined above; followed by conversion of the group R to form a dimethylaminomethyl group and isolation of citalopram base or a pharmaceutically acceptable salt thereof.

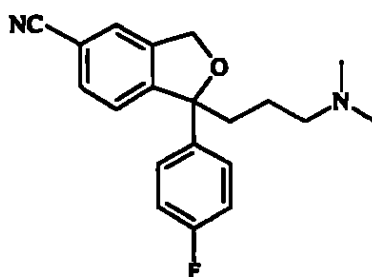
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Method for the Preparation of Citalopram

The present invention relates to a method for the preparation of the well-known antidepressant drug citalopram, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran-carbonitrile.

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:



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. Graven *Acta Psychiatr. Scand.* 1987, 75, 478-486. The compound has further been disclosed to show effects in the treatment of dementia and cerebrovascular disorders, EP-A-474580.

Citalopram was first disclosed in DE 2,657,013, corresponding to US 4,136,193. This patent publication describes the preparation of citalopram by one method and outlines a further method which may be used for preparing citalopram.

According to the process described, the corresponding 1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile is reacted with 3-(N,N-dimethylamino)propyl-chloride in the presence of methylsulfinylmethide as condensing agent. The starting material was prepared from the corresponding 5-bromo derivative by reaction with cuprous cyanide.

International patent application No. WO 98/019511 discloses a process for the manufacture of citalopram wherein a (4-(cyano, alkyloxycarbonyl or alkylaminocarbonyl)-2-hydroxymethylphenyl-(4-fluorophenyl)methanol compound is subjected to ring closure. The resulting 5-(alkyloxycarbonyl or alkylaminocarbonyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran is converted to the corres-

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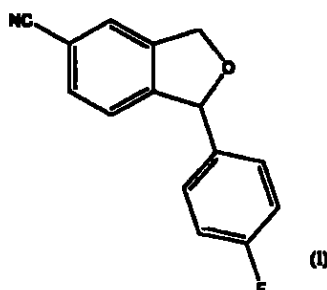
ponding 5-cyano derivative and the 5-cyano derivative is then alkylated with a (3-dimethylamino)propylhalogenide in order to obtain citalopram.

- 5 It has now, surprisingly, been found that citalopram may be manufactured by a novel favourable process where 5-cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran is alkylated with a compound which may be converted to a dimethylaminopropyl group.

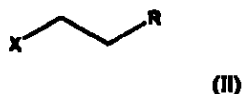
- 10 The alkylation process according to the invention is particularly advantageous because the formation of by-products by polymerisation of the alkylating agent is avoided whereby a reduction in the amount of alkylating reagent used is made possible. In addition, the process of the invention provides high yields.

Summary of the invention

- 15 The present invention relates to a method for the preparation of citalopram comprising reaction of a compound of formula (I)

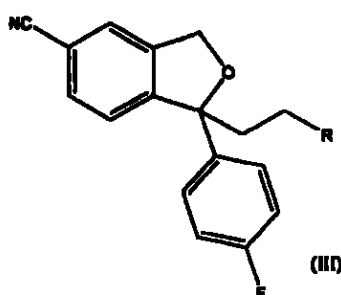


with a compound having the formula



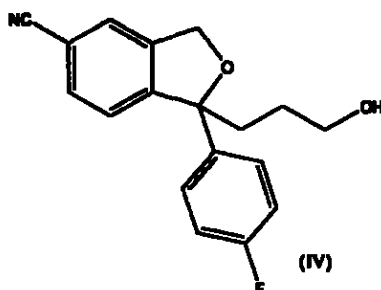
- 20 wherein X is a suitable leaving group and R is $-\text{CH}_2-\text{O}-\text{Pg}$, $-\text{CH}_2-\text{NPg}_1\text{Pg}_2$, $-\text{CH}_2-\text{NMePg}_1$, $-\text{CO}-\text{N}(\text{CH}_3)_2$, $-\text{CH}(\text{OR}^1)(\text{OR}^2)$, $-\text{C}(\text{OR}^3)(\text{OR}^4)(\text{OR}^5)$, $-\text{COOR}^3$, $-\text{CH}_2-\text{CO}-\text{NH}_2$, $-\text{CH}=\text{CHR}^7$ or $-\text{CO}-\text{NHR}^8$ wherein Pg is a protection group for an alcohol group, Pg_1 and Pg_2 are protection groups for an amino group, R^1 and R^2 are independently selected from alkyl, alkenyl, alkynyl and optionally alkyl substituted aryl or aralkyl groups or R^1 and R^2 together form a chain of 2 to 4 carbon atoms,
- 25 R^3 , R^4 , R^5 , R^6 and R^7 are independently selected from alkyl, alkenyl, alkynyl and optionally alkyl substituted aryl or aralkyl and R^8 is hydrogen or methyl;

to form a compound of the formula



wherein R is as defined above; followed by conversion of the group R to a dimethylaminomethyl group and isolation of citalopram in the form of the base or as a pharmaceutically acceptable salt thereof.

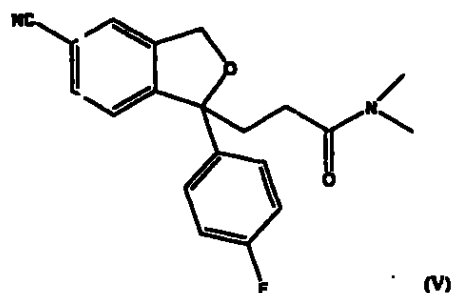
In a first embodiment of the invention, the compound of formula (I) is reacted with a compound of formula (II) wherein R is $-\text{CH}_2-\text{O}-\text{Pg}$, wherein Pg is a protection group for an alcohol group, followed by removal of the protection group to form the corresponding alcohol of the formula



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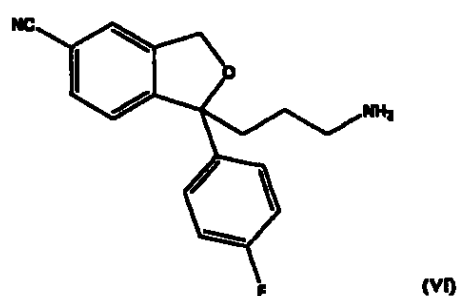
The alcohol group is then converted to a feasible leaving group such as halogen or $-\text{O}-\text{SO}_2-\text{R}^0$ wherein R^0 is alkyl, or optionally alkyl substituted aryl or aralkyl, and the resulting compound is then

- a) reacted with dimethylamin or a metal salt thereof to form citalopram,
 - 15 b) reacted with methylamin to form a compound of formula (XII) below followed by reductive amination to form citalopram, or
 - c) reacted with an azide followed by reduction to form the corresponding amino compound of formula (VI) below and thereafter methylation or reductive amination to form citalopram.
- 20 In a second embodiment, the compound of formula (I) is reacted with a compound of formula (II) wherein R is $-\text{CO}-\text{N}(\text{CH}_3)_2$, followed by reduction of the resulting compound of the formula



to form citalopram.

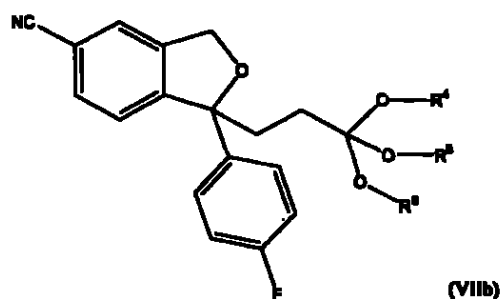
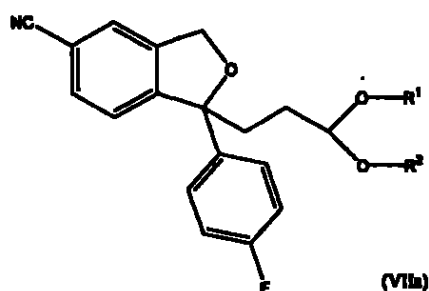
- In a third embodiment, the compound of formula (I) is reacted with a compound of formula (II) wherein R is $-\text{CH}_2-\text{N}(\text{Pg}_1)(\text{Pg}_2)$ where Pg_1 or Pg_2 are protection groups for an amino group and thereafter removal of the protection groups to form a compound of formula



followed by methylation of the free amino group or reductive amination to form citalopram.

10

In a fourth embodiment, citalopram may be prepared by reaction of a compound of formula (I) with a compound of formula (II) wherein R is $-\text{CH}(\text{OR}^1)(\text{OR}^2)$ or $-\text{C}(\text{OR}^4)(\text{OR}^5)(\text{OR}^6)$ where R^1 , R^2 , R^4 , R^5 and R^6 are as defined above to form a compound of the formula (VIIa) or (VIIb)

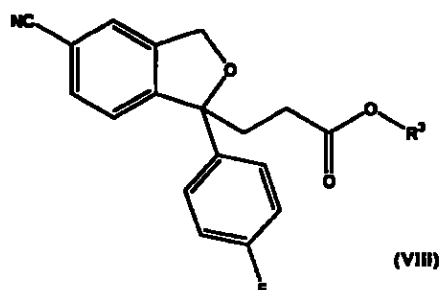


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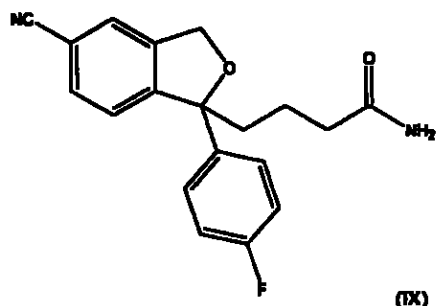
wherein R^1 , R^2 , R^4 , R^5 and R^6 are as defined above, followed by deprotection of the compound of formula (VIIa) or (VIIb) and consecutively reductive amination of the resulting aldehyde with dimethylamin to form citalopram.

- 5 In a fifth embodiment, citalopram may be prepared by reaction of a compound of formula (I) with a compound of formula (II) wherein R is $-\text{COOR}^3$ and R^3 is as defined above to form a compound of the formula

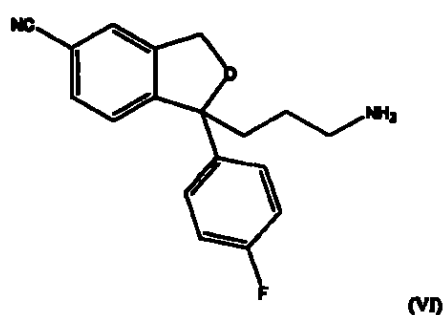


wherein R^3 is as defined above, which is then converted to an amide of formula (V) or an alcohol of formula (IV) which is converted to citalopram as described above.

- 10 In a sixth embodiment, the invention relates to a method for the preparation of citalopram wherein a compound of formula (I) is reacted with a compound of formula (II) wherein R is $-\text{CH}_2-\text{CONH}_2$ to form a compound of formula

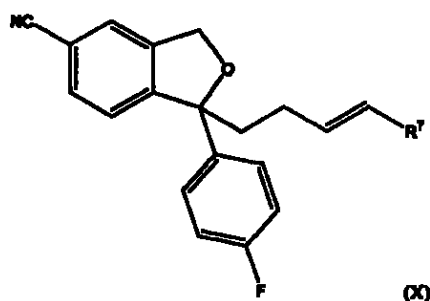


- 15 which is treated with hypohalide to form a compound of formula

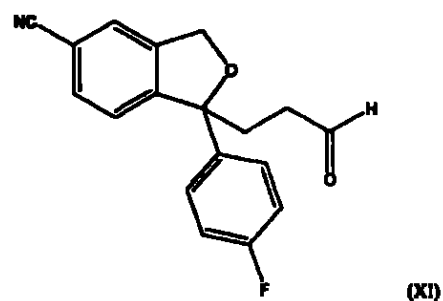


followed by methylation of the free amino group or reductive amination to form citalopram.

In a seventh embodiment, the invention relates to a method for the preparation of citalopram by
 5 reaction of a compound of formula (I) with a compound of formula (II) wherein R is $-\text{CH}=\text{CHR}^7$ to form a compound of formula



wherein R⁷ is as defined above, which is oxidised to form a compound of formula

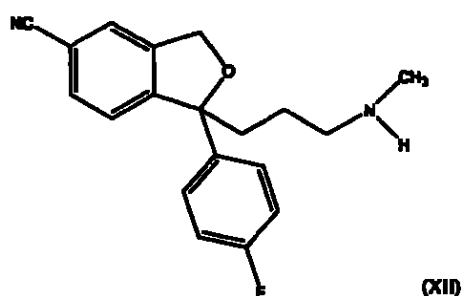


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followed by reductive amination with dimethylamin to form citalopram.

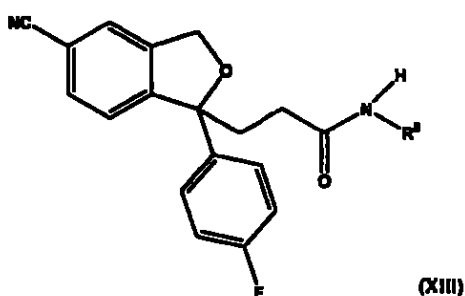
In a eight embodiment, the invention relates to a process for the preparation of citalopram wherein
 the compound of formula (I) is reacted with a compound of formula (II) wherein R is $-\text{CH}_2-\text{Me}(\text{Pg}_1)$
 15 followed by removal of the protection group to form a compound of formula

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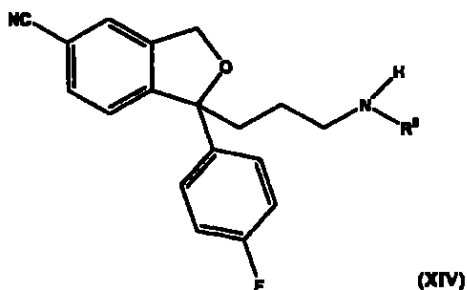


and thereafter methylation of the amino group or reductive amination to form citalopram.

- 5 In a final embodiment, the invention relates to a method for the preparation of citalopram wherein the compound of formula (I) is reacted with a compound of formula (II) wherein R is $-\text{CO}-\text{NHR}^8$ wherein R^8 is hydrogen or methyl, followed by reduction of the resulting compound of the formula



- 10 wherein R^8 is as defined above, to form a compound of formula



wherein R^8 is as defined above, followed by methylation or reductive amination to form citalopram.

- In another aspect, the present invention provides the novel intermediates of the general formula (III),
15 (IV), (VI), (XI) and (XII).

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In yet another aspect, the present invention relates to an antidepressant pharmaceutical composition comprising citalopram manufactured by the process of the invention.

The alkylation step where the compound of formula (I) is reacted with a compound of formula (II) is suitably carried out by treatment of the compound of formula (I) with a base such as for example LDA (lithiumdiisopropylamine), LiHMDS (hexamethyldisilazan lithium), NaH, NaHMDS (hexamethyldisilazan sodium) and metalalkoxides such as NaOMe, KOMe, LiOMe, NaO*tert*Bu, KO*tert*Bu and LiO*tert*Bu in an aprotic organic solvent such as THF (tetrahydrofuran), DMF (dimethylformamide), NMP (N-methylpyrrolidone), ethers such as diethylether or dioxalane, toluene, benzene, or alkanes and mixtures thereof. The anion formed is then reacted with a compound of formula (II) whereby a group of formula -CH₂-CH₂-R is introduced into position 1 of the isobenzofuranyl ring system.

Leaving groups X, may be a halogenide or a sulphonate of formula -O-SO₂-R⁰ wherein R⁰ is alkyl, or optionally alkyl substituted aryl or aralkyl. Suitably, R⁰ is methyl or p-methylphenyl.

The substituents R¹ and R² are preferably alkyl, or aralkyl or R¹ and R² together form a chain of 2 to 4 carbon atoms. Suitably, R¹ and R² are identical.

The substituents R³, R⁴, R⁵ and R⁶ are preferably alkyl, or aralkyl. Suitably, R⁴, R⁵ and R⁶ are identical.

R⁷ is preferably alkyl or aralkyl.

The alcohol protecting group Pg may be a trialkylsilyl group, a benzyl group or a tetrahydropyranyl group (THP).

According to the invention, the alcohol protecting group is removed to form the compound of formula (IV) using conventional methods for removal of the protection group in question.

Thus, where the protecting group is trialkylsilyl the protecting group may be removed by treatment with a base, an organic or mineral acid or a fluoride such as KF or trialkylaminofluoride.

Where Pg is benzyl, the protecting group may be removed by reduction using Pd/C or Pt/C as a catalyst.

Where Pg is a tetrahydropyranyl (THP) group, the protecting group may be removed by treatment with an organic or mineral acid, or resins carrying H⁺ groups such as Dowex H⁺ or Amberlyst.

5 The alcohol group in the compound of formula (IV) is converted to a feasible leaving group such as halogen, or a sulphonate of formula -O-SO₂-R⁰ wherein R⁰ is as defined above, by reaction with reagents such as thionylchloride, mesylchloride, tosylchloride, etc.

10 The resulting compound is then reacted with dimethylamin or a metal salt thereof, e.g. M⁺, N(CH₃)₂ wherein M⁺ is Li⁺ or Na⁺. The reaction is suitably carried out in an aprotic organic solvent such as THF (tetrahydrofuran), DMF (dimethylformamide), NMP (N-methyl pyrrolidon), ethers such as diethylether, or dioxalane, toluene, benzene, or alkanes and mixtures thereof. The compound of formula (IV) carrying a suitable leaving group may also be converted to citalopram by reaction with dimethylammonium chloride in presence of a base. Alternatively, the compound of formula (IV) carrying a suitable leaving group, such as a sulphonate of formula -O-SO₂-R⁰ wherein R⁰ is as defined above, may be reacted with an azide, such as sodium azide, followed by reduction using Pd/C as a catalyst to form a compound of formula (VI) and thereafter methylation or reductive amination to form Citalopram.

20 The compound of formula (IV) carrying a suitable leaving group, may also be converted to citalopram by reaction with methylamine to form a compound of formula (XII) above, followed by methylation or reductive amination to form Citalopram.

The reduction of the amide of formula (V) is conveniently carried out in toluene using Red-Al as a reducing agent.

25 Suitable groups Pg₁ and Pg₂ are aralkyl or -O-SO₂-R⁰ groups wherein R⁰ is as defined above, typically benzyl or tosyl, or Pg₁ and Pg₂ together with the N atom to which they are attached form an optionally substituted phthalimide group.

30 The protecting groups, Pg₁ and Pg₂ may be removed using conventional methods for removal of such protective groups. The phthalimide groups may thus be converted to an amino group by treatment with hydrazin or methylamine and ethanol.

Where the protecting group is an aralkyl group, such as benzyl, it may be removed by reduction, typically in presence of Pd/C or Pt/C as a catalyst.

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The sulphonate groups of formula -O-SO₂-R⁰ may be removed by treatment with Red-Al.

The free amino group in the compound of formula (VI) may be methylated with methylating agents such as MeI and Me₂SO₄, wherein Me is methyl. The methylation is carried out using conventional procedures for carrying out such reactions.

- 5 Alternatively, citalopram is formed by reductive amination. According to this procedure, the compound of formula (VI) is reacted with compounds such as formaldehyde, paraformaldehyde or trioxan in presence of a reducing agent such as NaBH₄ or NaBH₃CN. The reductive amination is carried out using conventional procedures for carrying out such reactions.
- 10 The compound of formula (VIIa) or (VIIb) may suitably be converted to the corresponding aldehyde by treatment with an organic or mineral acid or with resins carrying H⁺ groups such as Dowex H⁺ or Amberlyst.

- The resulting aldehyde may be converted to citalopram by reductive amination, i.e. by reaction with dimethylamine in the presence of a reducing agent such as NaBH₄ or NaBH₃CN. Dimethylamine may be added to the reaction in the form of the dimethylammonium chloride salt.
- 15

- The ester derivative of formula (VIII) may be converted to citalopram via the corresponding alcohol of formula (IV) by reduction of the ester using Red-Al as a reducing agent or via the corresponding amide of formula (V) by reaction of the ester with NH(Me)₂ or a metal salt thereof.
- 20

Suitable, the agent useful for conversion of a compound of formula (IX) to a compound of formula (VI) is NaOH/Br₂.

- Oxidation of the compound of formula (X) may be carried out by treatment of the compound with ozone in a polar solvent such as alcohol, water, acetic acid or esters thereof. Alternatively, the compound of formula (X) may be treated with oxidation agents such as NaIO₄, OsO₄/NaIO₄ and KMnO₄.
- 25

- The reductive amination of a compound of formula (XI) may suitably be carried out by reaction with dimethylamin in presence of a reducing agent such as NaBH₄ or NaBH₃CN. Dimethylamine may be added to the reaction in the form of dimethylammonium chloride.
- 30

- The amino group in the compounds of formula (XII) and (XIV) may be methylated with methylating agents such as MeI and Me₂SO₄, wherein Me is methyl. The methylation is carried out using conventional procedures for carrying out such reactions.
- 35

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Alternatively, the amino group in the compounds of formula (XII) and (XIV) may be methylated by reductive amination. According to this procedure, the compound of formula (XII) or (XIV) is reacted with compounds such as formaldehyde, paraformaldehyde or trioxan in presence of a reducing agent such as NaBH_4 or NaBH_3CN . The reductive amination is carried out using
5 conventional procedures for carrying out such reactions.

The reaction conditions, solvents, etc. used for the reactions described above are conventional conditions for such reactions and may easily be determined by a person skilled in the art.

10 The starting material of formula (I) may be prepared as described in US patent No. 4,136,193 or as described in WO 98/019511.

The compounds of formula (II) are commercially available or may be prepared from commercially available starting materials using conventional techniques.

15 Citalopram is on the market as an antidepressant drug in the form of the racemate. However, in the near future the active S-enantiomer of citalopram is also going to be introduced to the market.

S-citalopram may be prepared by separation of the optically active isomers by chromatography.

20 Throughout the specification and claims, the term alkyl refers to a branched or unbranched alkyl group having from one to six carbon atoms inclusive, such as methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl, 2,2-dimethyl-1-ethyl and 2-methyl-1-propyl.

25 Similarly, alkenyl and alkynyl, respectively, designate such groups having from two to six carbon atoms, including one double bond or triple bond respectively, such as ethenyl, propenyl, butenyl, ethynyl, propynyl and butynyl.

The term aryl refers to a mono- or bicyclic carbocyclic aromatic group, such as phenyl and naphthyl.
30 in particular phenyl.

The term aralkyl refers to aryl-alkyl, wherein aryl and alkyl is as defined above.

Optionally alkyl substituted aryl and aralkyl refers to aryl and aralkyl groups which may optionally
35 be substituted with one or more alkyl groups.

Halogen means chloro, bromo or iodo.

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Citalopram may be used as the free base, in particular the free base in crystalline form, or as a pharmaceutically acceptable acid addition salt thereof. As acid addition salts, such salts formed with organic or inorganic acids may be used. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, succinic, oxalic, dimethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzene sulfonic and theophylline acetic acids, as well as the 8-halothephyllines, for example 8-bromothephylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids.

10

The acid addition salts of the compounds may be prepared by methods known in the art. The base is reacted with either the calculated amount of acid in a water miscible solvent, such as acetone or ethanol, with subsequent isolation of the salt by concentration and cooling, or with an excess of the acid in a water immiscible solvent, such as ethylether, ethylacetate or dichloromethane, with the salt separating spontaneously.

15

The pharmaceutical compositions of the invention may be administered in any suitable way and in any suitable form, for example orally in the form of tablets, capsules, powders or syrups, or parenterally in the form of usual sterile solutions for injection.

20

The pharmaceutical formulations of the invention may be prepared by conventional methods in the art. For example, tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a conventional tableting machine. Examples of adjuvants or diluents comprise: Corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvant or additive, colourings, aroma, preservatives etc. may be used provided that they are compatible with the active ingredients.

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

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The invention is further illustrated by the following examples.

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129**Example 1**

A solution of 1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (4.8 g, 0.02 mol) in THF (50 mL) was added dropwise to a solution of LDA (Butyl lithium 1.6 M (15 mL), diisopropylamine 2.6 g) at -30 °C under an atmosphere of nitrogen. After stirring at -30 °C for 10 minutes a solution of the alkyl halide (0.02 mol) in THF (25 mL) was added dropwise and allowed to warm to room temperature and stirred for a further 60 minutes. The reaction was then quenched with ice, extracted with toluene (3 x 50 mL), washed with water (50 mL) and concentrated under reduced pressure. The residue was purified by chromatography on silica gel using mixtures of n-heptane/EtOAc as the eluent. The resulting anion is then reacted with a compound of formula (II).

Example 2

Preparation of 1-[(3-benzyloxy)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile:

A solution of 1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (2.2 g, 9.2 mmol) in THF (40 mL) was added to a solution of LDA (12 mmol) in THF (70 mL) at -78 °C under an atmosphere of nitrogen. After stirring at -78 °C for 30 min, a solution of benzyl-3-bromopropylether (2 mL, 12 mmol) in THF (10 mL) was added and the resulting mixture was allowed to warm to room temperature and stirred for 2 h. Then the mixture was poured into ice/H₂O (100 mL) and extracted with Et₂O (3 x 150 mL). The organic extracts were washed with H₂O (100 mL) and brine (100 mL), dried and evaporated. Silica gel chromatography (heptane, EtOAc 5:1) of the residue gave the product as an oil (2.0 g, 60%). ¹H NMR (DMSO-*d*₆) δ 1.35 (1H, m); 1.45 (1H, m); 2.23 (2H, m); 3.38 (2H, dd, *J* = 5.5 and 6.6 Hz); 4.38 (2H, s); 5.14 (1H, d, *J* = 13.7 Hz); 5.19 (1H, d, *J* = 13.7 Hz); 7.15 (2H, t, *J* = 8.8 Hz); 7.25 (3H, *J* = 7.27 Hz); 7.32 (2H, m); 7.58 (2H, dd, *J* = 5.6 and 8.8 Hz); 7.75 (3H, m).

Preparation of 1-(4-fluorophenyl)-1-[3-(tetrahydropyranyloxy)propyl]-1,3-dihydro-5-isobenzofurancarbonitrile:

The same procedure was used to give the title compound as an oil (2.0 g, 60%). ¹H NMR (DMSO-*d*₆) δ 1.40 (6H, m); 1.52 (1H, m); 1.65 (1H, m); 2.20 (2H, m); 3.30 (1H, m); 3.38 (1H, m); 3.55 (1H, m); 3.65 (1H, m); 4.45 (1H, dd); 5.15 (1H, d, *J* = 13.0 Hz); 5.19 (1H, d, *J* = 13.0 Hz); 7.15 (2H, t, *J* = 8.8 Hz); 7.58 (2H, dd, *J* = 5.7 and 9.0 Hz); 7.75 (1H, d, *J* = 8.0 Hz); 7.79 (2H, s + d, *J* = 8.0 Hz).

Example 3

Preparation of 1-(4-fluorophenyl)-1-(3-hydroxypropyl)-1,3-dihydro-5-isobenzofurancarbonitrile:

- 5 (i) A solution of 1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (13.4 g, 60 mmol) in THF (450 mL) was added to a solution of LDA (76 mmol) in THF (30 mL) at -78 °C under an atmosphere of nitrogen. After stirring at -78 °C for 30 min, a solution of (3-bromopropoxy)-*tert*-butyldimethylsilane (16.8 mL, 72 mmol) in THF (30 mL) was added and the resulting mixture was allowed to warm to room temperature and stirred for 2 h. Then the mixture was poured into ice/H₂O
- 10 (400 mL), and extracted with Et₂O (3 × 500 mL). The organic extracts were washed with H₂O (500 mL) and brine (500 mL), dried and evaporated. The residue was dissolved in methanol (400 mL) and was added 1 M HCl (200 mL). The resulting solution was stirred at room temperature for 1 h and evaporated. Silica gel chromatography (heptane, EtOAc 5:1) of the residue gave the title product as an oil (14.4 g, 81%). ¹H NMR (DMSO-*d*₆) δ 1.25 (2H, m); 2.18 (2H, t, *J* = 8.8 Hz); 3.31 (2H, q, *J* = 6.2 Hz); 4.34 (1H, t, *J* = 6.2 Hz); 5.12 (1H, d, *J* = 13.2 Hz); 5.17 (1H, d, *J* = 13.2 Hz); 7.15 (2H, t, *J* = 8.8 Hz); 7.58 (2H, dd, *J* = 6.0 and 8.8 Hz); 7.72 (1H, s); 7.78 (2H, br d, *J* = 6.0 Hz). ¹³C NMR (DMSO-*d*₆) δ 27.4; 37.3; 59.8; 71.0; 90.7; 110.5; 114.8; 115.2; 118.8; 123.2; 125.6; 126.9; 127.1; 132.0; 139.9; 140.6; 149.5; 160.9; 162.0.
- 20 (ii) To a solution of 1-[(3-benzyloxy)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (1.2 g, 3.1 mmol) and 1,4-cyclohexadiene (5.5 mL, 58.1 mmol) in ethanol (50 mL) was added Pd/C (4 g, 5%). The reaction mixture was refluxed under a nitrogen atmosphere for 2 days, then cooled to room temperature and filtered through Celite. The filtrate was evaporated and the residue was purified by silica gel chromatography to give the title product as an oil (0.75 g, 80%). ¹H NMR (CDCl₃) δ 1.5 (2H, m); 2.25 (2H, m); 3.5 (2H, t); 5.2 (2H, dd); 7.05 (2H, t, *J* = 10.0 Hz); 7.41 (3H, m); 7.49 (1H, br s); 7.56 (2H, *J* = 7.0 Hz).
- 30 (iii) To a solution of 1-(4-fluorophenyl)-1-[3-(tetrahydropyranyloxy)propyl]-1,3-dihydro-5-isobenzofurancarbonitrile (1.5 g, 4.1 mmol) in methanol was added catalytic amount of *p*-toluenesulfonic acid monohydrate (60 mg) and the resulting mixture was stirred at room temperature for 1 h and then evaporated. Silica gel chromatography (heptane, EtOAc 5:1) gave the title product (1.0 g, 91%). ¹H NMR (CDCl₃) was identical with that obtained from 1-[(3-benzyloxy)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile.

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1**Example 4**

Preparation of 1-(4-fluorophenyl)-1-[(3-*p*-toluenesulfonyloxy)propyl]-1,3-dihydro-5-isobenzofurancarbonitrile:

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To a solution of 1-(4-fluorophenyl)-1-(3-hydroxypropyl)-1,3-dihydro-5-isobenzofurancarbonitrile (2.5 g, 8.4 mmol) in toluene (50 mL) at 0-5 °C were added triethylamine (2.5 mL, 18.0 mmol) and a solution of *p*-toluenesulfonyl chloride (2.6 g, 13.6 mmol) in toluene (10 mL). The resulting mixture was stirred at room temperature for 3 days, then washed with H₂O and saturated aqueous NaHCO₃ solution. Evaporation of the organic extract followed by silica gel chromatography (heptane, EtOAc 4:1) of the residue gave the title product as an oil (1.6 g, 42%). ¹H NMR (CDCl₃) δ 1.6 (2H, m); 2.15 (2H, m); 2.45 (3H, s); 4.05 (2H, t, *J* = 8.0 Hz); 5.15 (2H, s); 7.05 (2H, t, *J* = 8.5 Hz); 7.30-7.42 (5H, m); 7.50 (1H, s); 7.6 (1H, d, *J* = 7.5 Hz); 7.75 (2H, d, *J* = 7.5 Hz).

15 **Example 5**

Preparation of 1-(4-fluorophenyl)-1-[(3-methanesulfonyloxy)propyl]-1,3-dihydro-5-isobenzofurancarbonitrile:

20 To a solution of 1-(4-fluorophenyl)-1-(3-hydroxypropyl)-1,3-dihydro-5-isobenzofurancarbonitrile (14.4 g, 50.0 mmol) in THF (500 mL) at 0-5 °C were added triethylamine (30 mL, 41.8 mmol) and a solution of methanesulfonyl chloride (11.6 mL, 150 mmol) in THF (20 mL). The resulting mixture was stirred at room temperature overnight, then added toluene (200 mL) and washed with H₂O and saturated aqueous NaHCO₃ solution. Evaporation of the organic phase
25 followed by silica gel chromatography (heptane, EtOAc 3:1) of the residue gave the title product as an oil (12.0 g, 64%). ¹H NMR (CDCl₃) δ 1.70 (2H, m); 2.25 (2H, m); 2.90 (3H, s); 4.22 (2H, t, *J* = 7.0 Hz); 5.14 (1H, d, *J* = 13.2 Hz); 5.14 (1H, d, *J* = 13.2 Hz); 7.01 (2H, t, *J* = 9.0 Hz); 7.41 (2H, d, *J* = 9.0 Hz); 7.45 (1H, d, *J* = 8.0 Hz); 7.52 (1H, s); 7.61 (1H, br d, *J* = 8.0 Hz).

30 **Example 6**

Preparation of 1-[3-(*N,N*-dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile, (Citalopram, Oxalate):

35 To a solution of 1-(4-fluorophenyl)-1-[(3-*p*-toluenesulfonyloxy)propyl]-1,3-dihydro-5-isobenzofurancarbonitrile:

furancarbonitrile (0.20 g, 0.4 mmol) in DMF (10 mL) was added triethylamine (1.4 mL, 7.0 mmol) and dimethylammonium chloride (0.41 g, 5.0 mmol). The reaction mixture was stirred at 70 °C overnight, then cooled to room temperature, poured into ice/H₂O and extracted with Et₂O (3 × 30 mL). The organic extracts were washed with H₂O and brine, and evaporated. The residue was
5 purified by silica gel chromatography (heptane, EtOAc, triethylamine 1:3:4%) and crystallised from acetone as the oxalate salt (0.12 g, 70%). DSC (open chamber), $T_{\text{onset}} = 158.96$, $T_{\text{peak}} = 162.14$. ¹H NMR (DMSO-*d*₆) δ 1.42 (1H, m); 1.51 (1H, m); 2.22 (2H, t, *J* = 8.0 Hz); 2.62 (6H, s); 2.95 (2H, t, *J* = 8.0 Hz); 5.15 (1H, d, *J* = 14.0 Hz); 5.23 (1H, d, *J* = 14.0 Hz); 7.18 (2H, t, *J* = 9.0 Hz); 7.59 (2H, dd, *J* = 5.0 and 8.0 Hz); 7.74 (1H, d, *J* = 7.5 Hz); 7.79 (1H, d, *J* = 7.0 Hz); 7.80 (1H, br s). ¹³C NMR
10 (DMSO- *d*₆) δ 19.3; 37.0; 42.3; 56.7; 71.2; 90.3; 110.7; 115.2; 115.3; 118.8; 123.2; 125.8; 127.0; 132.1; 139.9; 140.0; 148.161.4; 164.3. Anal. (C₂₀H₂₁N₂O, C₂H₂O₄) calcd. C: 63.76; H: 5.59; N: 6.76. Found C: 63.50; H: 5.78; N: 6.63.

Example 7

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Preparation of 1-[3-(*N,N*-dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile, (Citalopram, Oxalate):

Dimethylamine (18 mL, 100 mmol, 33% in ethanol) was added to a solution of 1-(4-fluorophenyl)-
20 1-[(3-methanesulfonyloxy)propyl]-1,3-dihydro-5-isobenzofurancarbonitrile (1.0 g, 2.7 mmol) in ethanol (10 mL) and THF (20 mL). The resulting mixture was stirred at room temperature for 1 h and at 60 °C for 3 h. After cooling, the reaction mixture was evaporated. 1 M NaOH (70 mL) was added to the residue and extracted with Et₂O (100 mL). The organic extract was washed with brine, dried and evaporated. The residue was filtered through silica gel (EtOAc, heptane, triethylamine
25 75:25:1) and crystallised from acetone as the oxalate salt (0.72 g, 65%). DSC (open chamber), $T_{\text{onset}} = 158.56$, $T_{\text{peak}} = 161.59$. The NMR-spectra were identical with those obtained from citalopram. oxalate prepared in example 6. Anal. (C₂₀H₂₁N₂O, C₂H₂O₄) calcd. C: 63.76; H: 5.59; N: 6.76. Found C: 63.57; H: 5.51; N: 6.77.

30 Example 8

Preparation of 1-(4-fluorophenyl)-1-[3-(phthalimidopropyl)]-1,3-dihydro-5-isobenzofurancarbonitrile:

35 A solution of 1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (4.4 g, 20 mmol) in THF (40 mL) was added to a solution of LDA (24 mmol) in THF (70 mL) at -78 °C under an atmosphere

of nitrogen. After stirring at -78°C for 30 min, a solution of 2-(3-bromopropyl)phthalimide (6.4 g, 24 mmol) in THF (20 mL) was added and the resulting mixture was allowed to warm to room temperature and stirred for 5 h. Then the mixture was poured into ice/ H_2O (200 mL), and extracted with Et_2O (3×250 mL). The organic extracts were washed with H_2O (100 mL) and brine (100 mL),
5 dried and evaporated. Silica gel chromatography (heptane, EtOAc 5:1) of the residue gave the product as a yellow powder (3.0 g, 36%). A sample was recrystallised from ethanol. ^1H NMR (CDCl_3) δ 1.69 (1H, m); 1.74 (1H, m); 1.93 (1H, m); 3.08 (1H, dt, $J = 4.7$ and 12.2 Hz); 3.85 (1H, ddd, $J = 1.4$ and 7.1 and 11.8 Hz); 4.08 (1H, ddd, $J = 4.2$ and 10.8 and 17.9 Hz); 5.09 (1H, d, $J = 13.1$ Hz); 5.20 (1H, d, $J = 13.1$); 6.60 (1H, d, $J = 7.5$ Hz); 7.06 (2H, t, $J = 9.4$ Hz); 7.28 (1H, t, $J = 7.5$ Hz); 7.42 (1H, t, $J = 7.5$ Hz); 7.43 (1H, s); 7.58 (1H, d, $J = 8.0$ Hz); 7.77 (1H, d, $J = 7.5$ Hz);
10 7.80 (1H, t, $J = 5.2$ Hz); 7.95 (1H, d, $J = 8.0$ Hz). ^{13}C NMR (CDCl_3) δ 23.4; 31.8; 59.3; 72.6; 92.3; 112.6; 114.7; 118.2; 122.9; 123.7; 124.8; 125.2; 129.0; 131.1; 131.6; 132.9; 135.8; 140.9; 144.1; 145.6; 161.6; 163.6; 170.9. Anal. ($\text{C}_{26}\text{H}_{19}\text{FN}_2\text{O}_3$, $\frac{1}{2} \text{C}_2\text{H}_5\text{OH}$) calcd. C: 72.15; H: 4.93; N: 6.23. Found C: 72.66; H: 5.14; N: 6.09.

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Example 9**Preparation of 1-(3-Azidopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile:**

20 Sodium azide (5.5 g, 80.5 mmol) was added to a solution of 1-(4-fluorophenyl)-1-[(3-methanesulfonyloxy)propyl]-1,3-dihydro-5-isobenzofurancarbonitrile (4.0 g, 10.6 mmol) in DMF (100 mL). The resulting mixture was stirred at 40°C for 3 h, and then refluxed for 2 h. After cooling the reaction mixture was poured into H_2O and extracted with Et_2O (4×200 mL). The organic extracts were washed with H_2O and brine, dried and evaporated to give the crude product as a brown oil (1.3 g,
25 45%). ^1H NMR ($\text{DMSO}-d_6$) δ 1.40 (2H, m); 2.22 (2H, m); 3.30 (2H, t, $J = 6.6$ Hz); 5.10 (1H, d, $J = 13.7$ Hz); 5.21 (1H, d, $J = 13.7$ Hz); 7.18 (2H, t, $J = 8.5$ Hz); 7.59 (2H, dd, $J = 5.2$ and 8.5 Hz); 7.78 (3H, s + d, $J = 8.1$ Hz).

Preparation of 1-(3-Aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile:

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A mixture of 1-(3-azidopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (1.3 g, 4.4 mmol) and palladium on carbon (0.6 g, 5%) in ethanol (50 mL) was hydrogenated for 2 h. The mixture was filtered through Celite and evaporated to give the crude product as a brown oil (0.8 g, 66%). ^1H NMR ($\text{DMSO}-d_6$) δ 1.11 (1H, m); 1.22 (1H, m); 2.12 (2H, m); 2.48 (2H, t, $J = 7.1$ Hz);
35 5.15 (1H, d, $J = 13.7$ Hz); 5.19 (1H, d, $J = 13.7$ Hz); 7.15 (2H, t, $J = 8.9$ Hz); 7.58 (2H, dd, $J = 5.2$ and 8.5 Hz); 7.72 (1H, d, $J = 8.4$ Hz); 7.78 (2H, s + d, $J = 8.1$ Hz).

Preparation of 1-[3-(*N,N*-Dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran-carbonitrile, (Citalopram, Oxalate):

Sodium cyanoborohydride (0.34 g, 5.4 mmol) was added to a mixture of 1-(3-Aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (0.80 g, 2.7 mmol) and formaldehyde (0.44 mL, 5.4 mmol, 37% in H₂O) in methanol (10 mL). The resulting mixture was stirred at room temperature for 3 h, then was added more sodium cyanoborohydride (0.17 g, 2.7 mmol) and formaldehyde (0.22 mL, 2.7 mmol). After stirring at room temperature for 1 h, the mixture was quenched with H₂O and extracted with Et₂O. The organic extracts were dried and evaporated. Silica gel chromatography (EtOAc, heptane, triethylamine 75:25:1) of the residue gave the crude product, which was isolated as the oxalate salt from acetone (0.31 g, 0.8 mmol, 30 %). The NMR-spectra were identical with those obtained from citalopram oxalate prepared in example 6. Anal. (C₂₀H₂₁N₂O, C₂H₂O₄, ½ H₂O) calcd. C: 63.06; H: 5.67; N: 6.69. Found C: 63.28; H: 5.64; N: 6.67.

Example 10

Preparation of 1-(4-fluorophenyl)-1-[3-(*N*-methylamino)propyl]-1,3-dihydro-5-isobenzofurancarbonitrile, Oxalate Salt:

The compound was prepared from methylamine (60 mL, 120 mmol, 2 M solution in THF) using the method described in example 7. Yield: 760 mg, 36%. ¹H NMR (DMSO- *d*₆) δ 1.40 (1H, m); 1.41 (1H, m); 2.25 (2H, t); 2.47 (3H, s); 2.83 (2H, t, *J* = 8.0 Hz); 5.15 (1H, d, *J* = 13.2 Hz); 5.21 (1H, d, *J* = 13.2 Hz); 7.18 (2H, t, *J* = 9.0 Hz); 7.59 (2H, dd, *J* = 5.6 and 7.5 Hz); 7.73 (1H, d, *J* = 8.1 Hz); 7.81 (3H, d + s, *J* = 8.1 Hz).

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Preparation 1-[3-(*N,N*-Dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile, (Citalopram, Oxalate):

A solution of 1-[3-(*N*-methyl-ammonium)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran-carbonitrile (0.70 g, 2.24 mmol) and formaldehyde (0.5 mL, 6.7 mmol, 37% aqueous solution) in 98% formic acid (5 mL) was refluxed for 4 h. After cooling, 4 M HCl (2 mL) was added and the resulting mixture was evaporated. 1 M NaOH (50 mL) was added to the residue and extracted with Et₂O (3 × 100 mL). The organic extract was washed with brine, dried and evaporated. The oxalate salt was isolated from acetone (0.22 g, 30%). DSC (open chamber), T_{onset} = 157.73, T_{peak} = 160.80.

The NMR-spectra were identical with those obtained from citalopram oxalate prepared in example

6. Anal. ($C_{20}H_{21}N_2O$, $C_2H_2O_4$, $\frac{1}{4} H_2O$) calcd. C: 63.06; H: 5.67; N: 6.69. Found C: 63.24; H: 5.65; N: 6.62.

Example 11

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Preparation of 1-[3-([1,3]dioxolan-2-yl)ethyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile:

A solution of 1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (4.46 g, 18.7 mmol) in THF (40 mL) was added to a solution of LDA (24 mmol) in THF (100 mL) at -78°C under an atmosphere of nitrogen. After stirring at -78°C for 30 min, a solution of 2-2-(2-bromoethyl)-[1,3]-dioxolane (2.8 mL, 24 mmol) in THF (20 mL) was added and the resulting mixture was allowed to warm to room temperature and stirred for 2 h. Then the mixture was poured into ice/ H_2O (100 mL), and extracted with Et_2O (3×300 mL). The organic extracts were washed with H_2O (100 mL) and brine (100 mL), dried and evaporated. Silica gel chromatography (heptane, EtOAc 5:1) of the residue gave the product as an oil (5.5 g, 86%). 1H NMR ($CDCl_3$) δ 1.52 (1H, m); 1.70 (1H, m); 2.28 (2H, m); 3.81 (2H, m); 3.89 (2H, m); 4.85 (1H, t, $J = 4.0$ Hz); 5.14 (1H, d, $J = 13.2$ Hz); 5.19 (1H, d, $J = 13.2$ Hz); 7.04 (2H, t, $J = 8.5$ Hz); 7.41 (3H, m); 7.49 (1H, s); 7.58 (1H, d, $J = 8.0$ Hz). ^{13}C NMR ($CDCl_3$) δ 27.8; 34.4; 64.2; 70.6; 90.1; 103.2; 111.2; 114.5; 114.8; 117.9; 122.2; 124.5; 126.1; 126.2; 131.2; 138.7; 139.7; 148.5; 159.0.

Preparation of 1-(4-fluorophenyl)-1-(3-formylethyl)-1,3-dihydro-5-isobenzofurancarbonitrile:

A solution of 1-[3-([1,3]dioxolan-2-yl)ethyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (5.30 g, 16 mmol) in 30 % aqueous acetic acid (200 mL) was refluxed for 5 h. The reaction mixture was cooled and extracted with CH_2Cl_2 (3×400 mL). The organic extracts were dried and evaporated to give the crude product (5.0 g, contained about 8.0 mmol of the product as judged by NMR and HPLC, 50%), which was used in the next step without further purification. 1H NMR ($CDCl_3$) δ 1.49 (1H, m); 1.61 (1H, m); 2.38 (1H, m); 2.51 (1H, m); 5.15 (2H, br s); 7.01 (2H, t, $J = 8.0$ Hz); 7.41 (3H, dd + s, $J = 5.6$ and 8.0 Hz); 7.51 (2H, d, $J = 8.0$ Hz); 7.61 (2H, d, $J = 8.0$ Hz).

Preparation of 1-[3-(*N,N*-dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile, (Citalopram, Oxalate):

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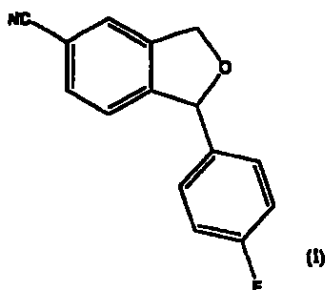
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Sodium cyanoborohydride (0.76 g, 14.4 mmol) was added to a mixture of crude 1-(3-formylethyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (5.0 g, contained about 8.0 mmol of the compound as judged by NMR and HPLC) and dimethylammonium chloride (1.17 g, 14.4 mmol) in methanol (50 mL) at 0-5 °C. The resulting mixture was stirred at room temperature overnight, then
5 added toluene (100 mL) and EtOAc (100 mL) and washed with H₂O (100 mL). The aqueous phase was extracted with Et₂O (2 × 100 mL). The combined organic extracts were dried and evaporated. Silica gel chromatography (heptane, EtOAc, triethylamine 25:25:1) of the residue gave the title compound, which was isolated from acetone as the oxalate salt (2.7 g, 82%). DSC (open chamber), T_{onset} = 159.55, T_{peak} = 163.54. The NMR-spectra were identical with those obtained from citalopram
10 oxalate prepared in example 6. Anal. (C₂₀H₂₁N₂O, C₂H₂O₄) calcd. C: 63.76; H: 5.59; N: 6.76. Found C: 63.65; H: 5.69; N: 6.80.

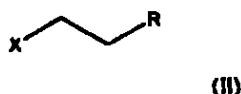
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CLAIMS

1. A method for the preparation of citalopram comprising reaction a compound of formula (I)

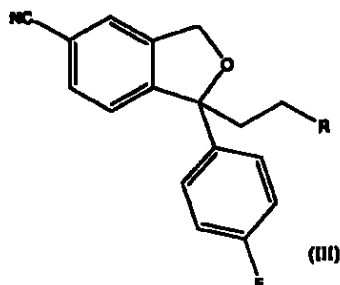


with a compound having the formula



- wherein X is a suitable leaving group and R is $-\text{CH}_2-\text{O}-\text{Pg}$, $-\text{CH}_2-\text{NPg}_1\text{Pg}_2$, $-\text{CH}_2-\text{NMePg}_1$, $-\text{CO}-\text{N}(\text{CH}_3)_2$, $-\text{CH}(\text{OR}^1)(\text{OR}^2)$, $-\text{C}(\text{OR}^4)(\text{OR}^5)(\text{OR}^6)$, $-\text{COOR}^3$, $-\text{CH}_2-\text{CO}-\text{NH}_2$, $-\text{CH}=\text{CHR}^7$ or $-\text{CO}-\text{NHR}^8$, wherein Pg is a protection group for an alcohol group, Pg_1 and Pg_2 are protection groups for an amino group, R^1 and R^2 are independently selected from alkyl, alkenyl, alkynyl and optionally alkyl substituted aryl or aralkyl groups or R^1 and R^2 together form a chain of 2 to 4 carbon atoms, each of R^3 , R^4 , R^5 , R^6 and R^7 are independently selected from alkyl, alkenyl, alkynyl and optionally alkyl substituted aryl or aralkyl and R^8 is hydrogen or methyl;

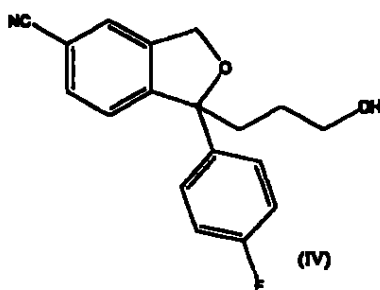
to form a compound of the formula



- wherein R is as defined above; followed by conversion of the group R to form a dimethylaminomethyl group and isolation of citalopram base or a pharmaceutically acceptable salt thereof.

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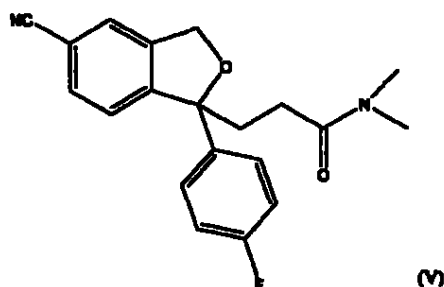
2. The method according to claim 1 wherein the compound of formula (I) is reacted with a compound of formula (II) wherein R is $-\text{CH}_2-\text{O}-\text{Pg}$ followed by removal of the protection group to form the corresponding alcohol of the formula



- 5 and thereafter conversion of the alcohol group to a feasible leaving group and reaction of the resulting compound
- a) with dimethylamin or a metal salt thereof to form citalopram,
 - b) with methylamin followed by reductive amination to form citalopram, or
 - c) with an azide followed by reduction to form the corresponding amino compound and thereafter
- 10 methylation or reductive amination to form citalopram.

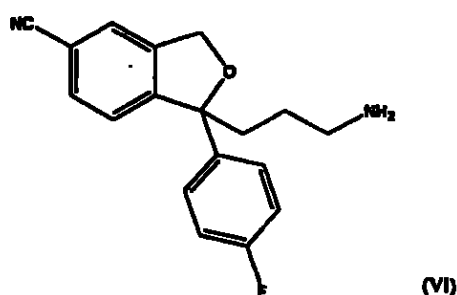
3. The method according to claim 1 wherein the compound of formula (I) is reacted with a compound of formula (II) wherein R is $-\text{CO}-\text{N}(\text{CH}_3)_2$, followed by reduction of the resulting compound of the formula

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to form citalopram.

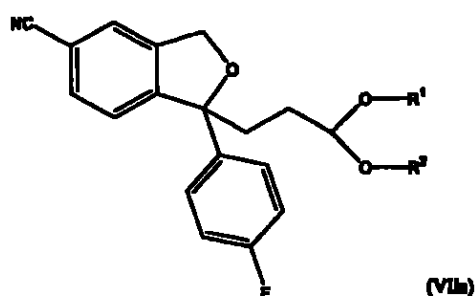
4. The method according to claim 1 wherein the compound of formula (I) is reacted with a
- 20 compound of formula (II) wherein R is $-\text{CH}_2-\text{N}(\text{Pg1})(\text{Pg2})$ followed by removal of the protection groups to form a compound of formula

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130

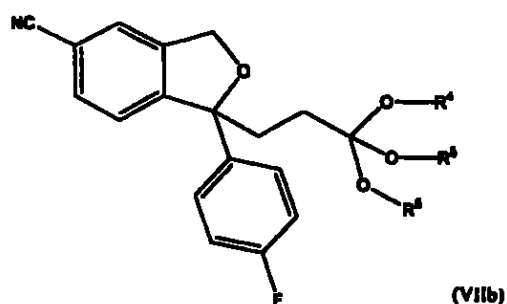
(VI)

and thereafter reductive amination or methylation of the free amino group to form citalopram.

- 5 5. The method according to claim 1 wherein a compound of formula (I) is reacted with a compound of formula (II) wherein R is $-\text{CH}(\text{OR}^1)(\text{OR}^2)$ or $-\text{C}(\text{OR}^4)(\text{OR}^5)(\text{OR}^6)$ to form a compound of the formula (VIIa) or (VIIb)



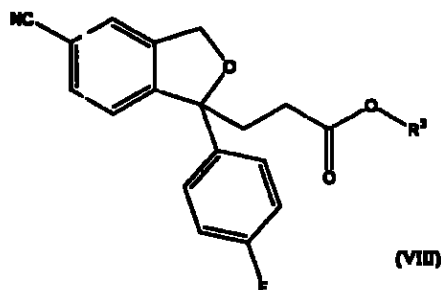
(VIIa)



(VIIb)

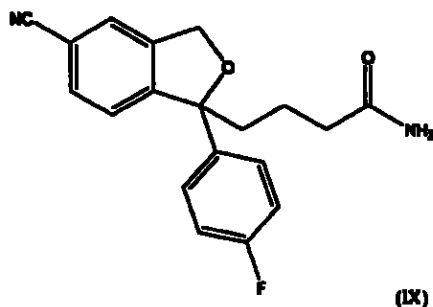
- wherein R^1 , R^2 , R^4 , R^5 and R^6 are as defined above, followed by deprotection of the compound of
 10 formula (VIIa) or (VIIb) and consecutive reductive amination of the resulting aldehyde to form citalopram.

6. The method according to claim 1 wherein a compound of formula (I) is reacted with a compound of formula (II) wherein R is $-\text{COOR}^3$ to form a compound of the formula

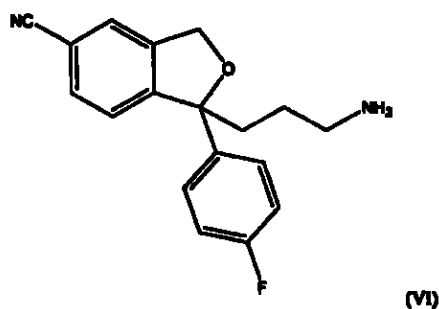
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131

which is converted to an amide of formula (V) followed by reduction to form citalopram, or the compound of formula (VIII) is reduced to form the corresponding alcohol of formula (IV) followed by conversion of the alcohol group to feasible leaving group and consecutively reaction

- 5 a) with dimethylamin or a metal salt thereof to form citalopram,
 - b) with methylamin followed by reductive amination to form citalopram, or
 - c) with an azide followed by reduction to form the corresponding amino compound and thereafter methylation or reductive amination to form citalopram.
- 10 7. The method according to claim 1 wherein a compound of formula (I) is reacted with a compound of formula (II) wherein R is $-\text{CH}_2-\text{CONH}_2$ to form a compound of formula



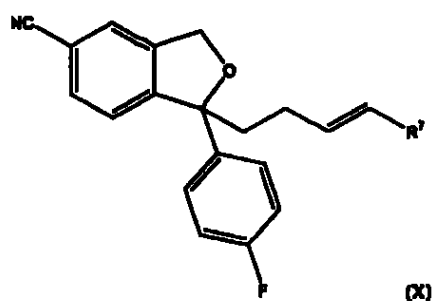
which is treated with hypohalide to form a compound of formula



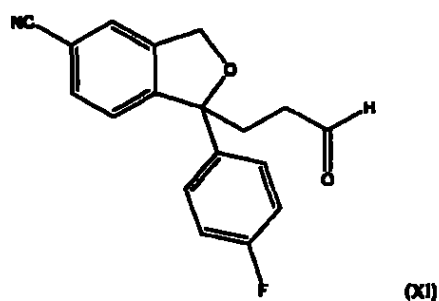
followed by methylation of the free amino group or reductive amination to form citalopram.

8. The method according to claim 1 wherein a compound of formula (I) is reacted with a compound of formula (II) wherein R is $-\text{CH}=\text{CHR}^7$ to form a compound of formula

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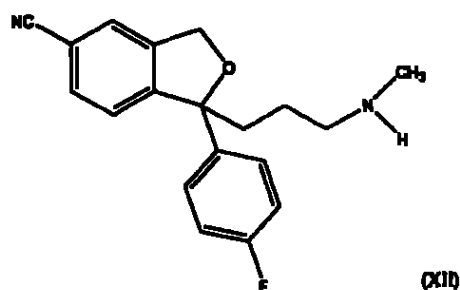


wherein R^7 is as defined above, which is oxidised to form a compound of formula



10 followed by reductive amination to form citalopram.

9. The method according to claim 1 wherein the compound of formula (I) is reacted with a compound of formula (II) wherein R is $-\text{CH}_2-\text{Mc}(\text{Pg}_1)$ followed by removal of the protection group to form a compound of formula

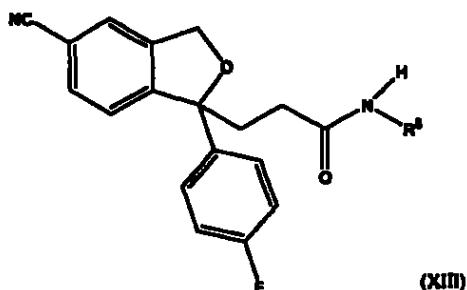


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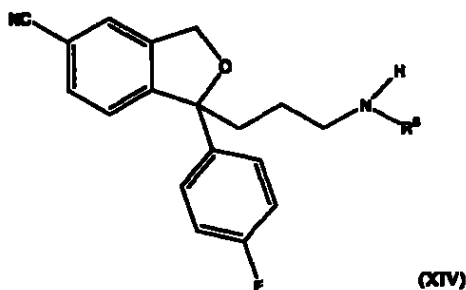
4A
133

and thereafter methylation of the amino group or reductive amination to form citalopram.

10. The method according to claim 1 wherein the compound of formula (I) is reacted with a compound of formula (II) wherein R is $-\text{CO}-\text{NHR}^a$ wherein R^a is hydrogen or methyl, followed by
5 reduction of the resulting compound of the formula



wherein R^a is as defined above, to form a compound of formula



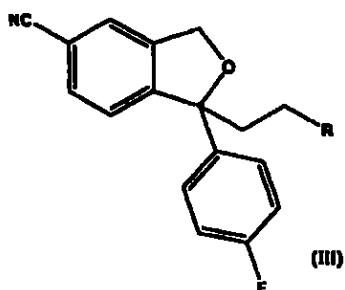
- 10 wherein R^a is as defined above, followed by methylation or reductive amination to form citalopram.

11. The method according to claim 1 wherein the reaction of the compound of formula (I) with a compound of formula (II) is carried out in presence of a base selected from LDA (lithiumdiisopropylamine), LiHMDS (hexamethyldisilazan lithium), NaH, NaHMDS
15 (hexamethyldisilazan sodium) and metalalkoxides such as NaOMe, KOMe, LiOMe, NaO*tert*Bu, KO*tert*Bu and LiO*tert*Bu.

12. An antidepressant pharmaceutical composition comprising citalopram manufactured by the process of any of claims 1 to 11.

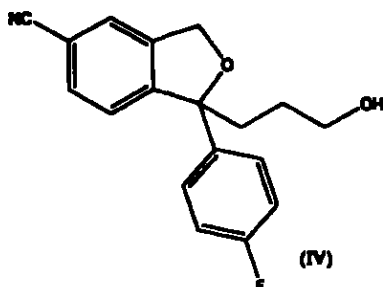
20

13. An intermediate having the general formula



- wherein R is $-\text{CH}_2-\text{O}-\text{Pg}$, $-\text{CH}_2-\text{NPg}_1\text{Pg}_2$, $-\text{CH}_2-\text{NMePg}_1$, $-\text{CO}-\text{N}(\text{CH}_3)_2$, $-\text{CH}(\text{OR}^1)(\text{OR}^2)$, $-\text{C}(\text{OR}^4)(\text{OR}^5)(\text{OR}^6)$, $-\text{COOR}^3$, $-\text{CH}_2-\text{CO}-\text{NH}_2$, $-\text{CH}=\text{CHR}^7$ or $-\text{CO}-\text{NHR}^8$, wherein Pg is a protection group for an alcohol group, Pg_1 and Pg_2 are protection groups for an amino group, R^1 and R^2 are independently selected from alkyl, alkenyl, alkynyl and optionally alkyl substituted aryl or aralkyl groups or R^1 and R^2 together form a chain of 2 to 4 carbon atoms, each of R^3 , R^4 , R^5 , R^6 and R^7 are independently selected from alkyl, alkenyl, alkynyl and optionally alkyl substituted aryl or aralkyl and R^8 is hydrogen or methyl, and acid addition salts thereof.

- 10 14. An intermediate having the formula

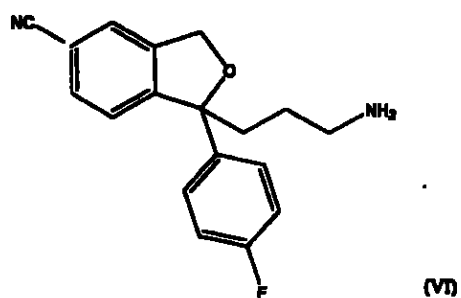


and acid addition salts thereof.

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15. An intermediate having the formula

28

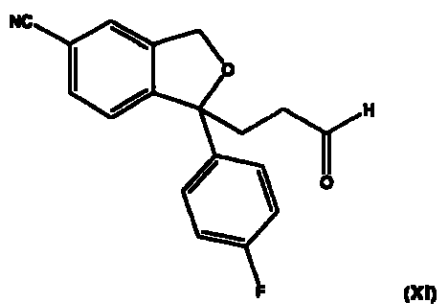


(v)

and acid addition salts thereof.

16. An intermediate having the formula

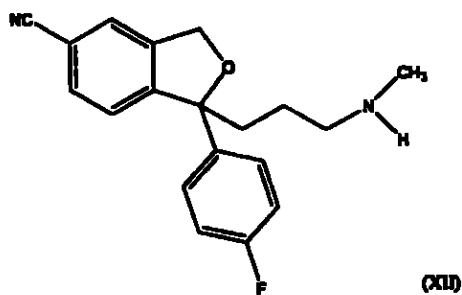
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(xi)

and acid addition salts thereof.

10 17. An intermediate having the formula



(xii)

and acid addition salts thereof.

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA
COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER
SUSTITUIDA POR NINGUN RECIBO.

136

SUPERINDUSTRIA Y COMERCIO
Radicacion : 84000776 00000004 Folios: 44
Fecha (AMB): 2005-11-28 15:51:16
Tramite : 011 PCT-PATENT 379 FASE NACI 400 OPOSICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 05 - 90,940
FECHA : NOVIEMBRE 28 DE 2005

***** CONSIGNACION *****

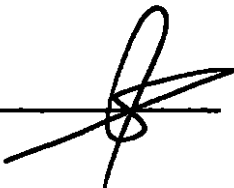
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BYNOPHARM S.A.	CONSIGNACION	BANCO POPULAR	050-00110-6	43554250	03/11/2005	235,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	5005-01-04	PRESENTACION DE OBSERVACIONES	
12		MARCAS Y LEHAS COMERCIALES	235,000.00
		TOTAL :	\$ 235,000.00

SON: DUSCIENTOS TREINTA Y CINCO MIL PESOS

RESPONSABLE : _____



RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____