

Copia Trazado Solicitante! 59
(No. es oposi! sino Comple/. de Informac.
(fuera de tiempo)

Doctor,

JAIRO RUBIO ESCOBAR

Superintendente de Industria y Comercio

E. S. D.

SUPERINDUSTRIA Y COMERCIO
Radicación: 00051031 00000004 Folios: 27
Fecha (AMT): 2004-10-12 17:02:12
Trámite: 002 PATENTES D 1 REGISTRO/ 329 COMPLETOS
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Referencia : Expediente N° 00-051031

Asunto : Remisión de información a la solicitud de patente de
Invención titulada "COMPOSICIONES DE
ESCITALOPRAM USADAS EN EL TRATAMIENTO DE
DESORDENES NEURÓTICOS".

Solicitante: H. LUNDBECK A/S.

Yo, Luis Fernando Rincón Cuellar, abogado con tarjeta profesional N° 113438 del consejo superior de la judicatura, en mi condición de apoderado 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 por orden expresa de mi representada, con el animo de colaborar con esa Entidad en la decisión que sobre la patentabilidad de la solicitud de la referencia se tomará, me permito solicitarle, muy respetuosamente, dar curso a la siguiente información relativa al arte anterior relevante para que sea tomado en cuenta en el estudio de patentabilidad de la solicitud de patente de Invención de la referencia.

1. PETICIÓN.

Ruego al Señor Superintendente, **NEGAR**, en los términos de artículo 48 de la Decisión 486 de 2000 de la CAN, la Solicitud de Patente de Invención denominada **"COMPOSICIONES DE ESCITALOPRAM USADAS EN EL TRATAMIENTO DE DESORDENES NEURÓTICOS"**, cuyo solicitante es **H. LUNDBECK A/S**, con base en los siguientes hechos y fundamentos de derecho, relacionados con el incumplimiento de los requisitos fundamentales exigidos para la concesión de Patentes de Invención, según la legislación vigente.

2. FUNDAMENTOS DE HECHOS

- 2.1. La solicitud objeto de la presente fue presentada el 7 de julio de 2000, reivindicando prioridad bajo la solicitud DK1999 del 8 de julio de 1999 y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 519, bajo NP 674., pág. 237.
- 2.2. La solicitud colombiana 00-051031 tiene como objeto el uso de escitalopram en el tratamiento de desordenes neuróticos que comprende menos de escitalopram o una sal farmacéuticamente aceptable del mismo en una cantidad desde 1 a 50 mg, preferiblemente 5 mg por día a 40 mg por día, más preferiblemente de 10 mg a 20 mg por día.
- 2.3. Lo primero que hay que decir es que esta solicitud de patente esta incurso en los impedimentos que consagra el artículo 21 de la Decisión 486 de la CAN, el cual indica: *"los productos o procedimientos ya patentados, comprendidos en el estado de la técnica de conformidad con el artículo 16 de la presente decisión, no serán objeto de nueva patente, por el simple hecho de atribuirse un uso distinto al originalmente comprendido por la patente inicial"*. Esto significa que en Colombia a la fecha no se conceden patente para los segundos usos. El escitalopram como tal es una

sustancia activa como droga antidepresiva tratada con anterioridad en el documento EP0347066 (D1) desde diciembre de 1989.

2.4. Por otra parte se está también tratando de reivindicar un método de tratamiento de desordenes neuróticos. La decisión 486 de la CAN establece claramente en su artículo número 20: *"No serán patentables: ...d) Los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o animales"*. Lo aquí reivindicado no es más que un plan de dosificación tal como un método de tratamiento. Claramente se deduce que el objeto de la presente solicitud no puede ser objeto de patente en Colombia.

2.5. El artículo 14 de la Decisión 486 de la CAN consagra en su artículo 14 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"*. A todas luces, un plan de dosificación no puede reproducirse a nivel industrial. La presente solicitud carece de aplicación Industrial ya que como se demostró en el apartado interior lo que se está reclamando es un método de tratamiento. Éstos no son aplicables industrialmente porque primero no se obtiene un resultado mediante el empleo de materias o fuerzas de la naturaleza; y segundo no es repetible ya que usados los medios previstos no se obtiene siempre el mismo resultado. Por lo tanto el objeto de la presente invención no cumple con el requisito de la aplicación industrial.

2.6. Ese mismo artículo 14 se refiere a que 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 (1989-12-09)
- D2 US5296507 (1994-03-22)

2.7. El documento D1 revela dos enantiomeros utilizados como droga antidepresiva tal como el escitalopram y al uso de estos enantiomeros como compuestos antidepresivos así como el posible uso como geriátricos o en la cura de obesidad o alcoholismo. En el documento D1 se revela una composición farmacéutica en forma de dosis con el compuesto activo de escitalopram. (Véase página 3 líneas 14 a 16 y reivindicación 5). Allí se revelan dosis desde 0,1 mg a 100 mg. Adicionalmente el documento relaciona el método de síntesis, según el ejemplo 3. De hecho, en el documento anterior se revelan varias presentaciones farmacéuticas para la administración del escitalopram. A todas luces, este documento anterior revela la misma materia reivindicada en la solicitud objeto de oposición con dosis de 10 a 50 mg. Por lo tanto, la presente solicitud, a la luz del documento D1, carece del requisito de NOVEDAD, dado que lo que pretende se encuentra publicado con 10 años antes de la radicación de la prioridad de la solicitud Colombiana.

2.8 El documento D2 revela un uso de escitalopram en tratamientos de demencia y desordenes cardiovasculares. Según lo expuesto en la columna 4, líneas 1 y 2 y líneas 42 a 45, se revela un plan de dosificación de 1 a 100 mg por día que puede incluir escitalopram. Este documento D2, en combinación con el documento D1, a todas luces, cualquier persona versada en la materia, puede deducir el plan de dosificación en 10 mg a 50 mg por día reivindicado en la presente solicitud. Por lo

tanto, la presente solicitud, a la luz del documento D1 en combinación con el documento D2, carece del requisito de ALTURA INVENTIVA, dado que lo que pretende es derivable del arte anterior.

2.9.1. **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, 8 de julio de 1999, ya era conocido, pues como se demostró, era parte del arte anterior la materia sobre la cual busca protección en el capítulo reivindicatorio con base en el documento D1.

2.9.2. **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, 8 de julio de 1999, el documento D1 en combinación con D2, es posible deducir el uso y las alternativas dosis de administración para tratamientos en desordenes neuróticos.

2.9.3. **CARENCIA DE APLICACIÓN INDUSTRIAL** La Decisión 486 de la CAN consagra en su artículo 14 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.* La presente solicitud carece de aplicación Industrial ya que

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

- D1 EP0347066 (1989-12-09)
- D2 US5296507 (1994-03-22)

4. FUNDAMENTO DE DERECHO

Fundamento esta remisión en las normas legales siguientes:

- 4.1. Numeral 1 del artículo 586 del Código de Comercio.
- 4.2. Artículo 48 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 EP0347066 (1989-12-09)
- D2 US5296507 (1994-03-22)

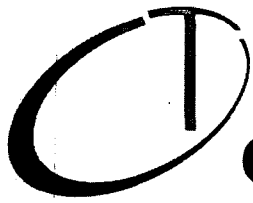
6. NOTIFICACIONES

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 de abogado situadas en la calle 119ª N° 53-99 de esta ciudad de Bogotá.

Señor Superintendente,

C.C. _____



Optimum

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Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

Doctor,

JAIRO RUBIO ESCOBAR

Superintendente de Industria y Comercio

E. S. D.

SUPERINDUSTRIA Y COMERCIO
Radicación : 00051031 00000004 Folios: 27
Fecha (AMD): 2004-10-12 17:02:12
Trámite : 000 PATENTES : 1 REGISTRO/ 329 COMPLETOS
Dependencia: 2220 DIVISION DE NUEVAS CREACIONES

Referencia : Expediente N° 00-051031

Asunto : Remisión de información a la solicitud de patente de
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Solicitante: H. LUNDBECK A/S.

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1. PETICIÓN.

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2. FUNDAMENTOS DE HECHOS

- 2.1. La solicitud objeto de la presente fue presentada el 7 de julio de 2000, reivindicando prioridad bajo la solicitud DK1999 del 8 de julio de 1999 y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 519, bajo NP 674., pág. 237.
- 2.2. La solicitud colombiana 00-051031 tiene como objeto el uso de escitalopram en el tratamiento de desordenes neuróticos que comprende menos de escitalopram o una sal farmacéuticamente aceptable del mismo en una cantidad desde 1 a 50 mg, preferiblemente 5 mg por día a 40 mg por día, más preferiblemente de 10 mg a 20 mg por día.
- 2.3. Lo primero que hay que decir es que esta solicitud de patente esta incurso en los impedimentos que consagra el artículo 21 de la Decisión 486 de la CAN, el cual indica: *"los productos o procedimientos ya patentados, comprendidos en el estado de la técnica de conformidad con el artículo 16 de la presente decisión, no serán objeto de nueva patente, por el simple hecho de atribuirse un uso distinto al originalmente comprendido por la patente inicial"*. Esto significa que en Colombia a la fecha no se conceden patente para los segundos usos. El escitalopram como tal es una

sustancia activa como droga antidepresiva tratada con anterioridad en el documento EP0347066 (D1) desde diciembre de 1989.

2.4. Por otra parte se está también tratando de reivindicar un método de tratamiento de desordenes neuróticos. La decisión 486 de la CAN establece claramente en su artículo número 20: *"No serán patentables: ...d) Los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o animales"*. Lo aquí reivindicado no es más que un plan de dosificación tal como un método de tratamiento. Claramente se deduce que el objeto de la presente solicitud no puede ser objeto de patente en Colombia.

2.5. El artículo 14 de la Decisión 486 de la CAN consagra en su artículo 14 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"*. A todas luces, un plan de dosificación no puede reproducirse a nivel industrial. La presente solicitud carece de aplicación Industrial ya que como se demostró en el apartado interior lo que se está reclamando es un método de tratamiento. Éstos no son aplicables industrialmente porque primero no se obtiene un resultado mediante el empleo de materias o fuerzas de la naturaleza; y segundo no es repetible ya que usados los medios previstos no se obtiene siempre el mismo resultado. Por lo tanto el objeto de la presente invención no cumple con el requisito de la aplicación industrial.

2.6. Ese mismo artículo 14 se refiere a que 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:

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2.8 El documento D2 revela un uso de escitalopram en tratamientos de demencia y desordenes cardiovasculares. Según lo expuesto en la columna 4, líneas 1 y 2 y líneas 42 a 45, se revela un plan de dosificación de 1 a 100 mg por día que puede incluir escitalopram. Este documento D2, en combinación con el documento D1, a todas luces, cualquier persona versada en la materia, puede deducir el plan de dosificación en 10 mg a 50 mg por día reivindicado en la presente solicitud. Por lo

tanto, la presente solicitud, a la luz del documento D1 en combinación con el documento D2, carece del requisito de ALTURA INVENTIVA, dado que lo que pretende es derivable del arte anterior.

2.9.1. **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, 8 de julio de 1999, ya era conocido, pues como se demostró, era parte del arte anterior la materia sobre la cual busca protección en el capítulo reivindicatorio con base en el documento D1.

2.9.2. **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, 8 de julio de 1999, el documento D1 en combinación con D2, es posible deducir el uso y las alternativas dosis de administración para tratamientos en desordenes neuróticos.

2.9.3. **CARENCIA DE APLICACIÓN INDUSTRIAL** La Decisión 486 de la CAN consagra en su artículo 14 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.* La presente solicitud carece de aplicación Industrial ya que



como se demostró lo que se está reclamando es un método de tratamiento tal como un plan matemático de dosificación. Éstos NO son aplicables industrialmente porque primero no se obtiene un resultado mediante el empleo de materias o fuerzas de la naturaleza; y segundo no es repetible ya que usando los medios previstos no se obtiene siempre el mismo resultado. Por lo tanto el objeto de la presente invención no cumple con el requisito de la aplicación industrial.

2.10. 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 los tres requisitos de patentabilidad.

2.11. 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.

2.12. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente remisión y negar el registro Patente de invención denominada **“COMPOSICIONES DE ESCITALOPRAM USADAS EN EL TRATAMIENTO DE DESORDENES NEURÓTICOS”**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 519 del 29 de agosto de 2002, en la página 237, bajo el NP 674.

3. PRUEBAS

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

- D1 EP0347066 (1989-12-09)
- D2 US5296507 (1994-03-22)

4. FUNDAMENTO DE DERECHO

Fundamento esta remisión en las normas legales siguientes:

- 4.1. Numeral 1 del artículo 586 del Código de Comercio.
- 4.2. Artículo 48 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.
- 4.3. En las demás normas concordantes.

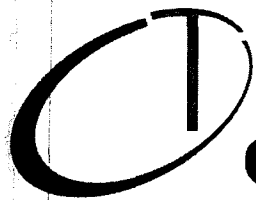
5. ANEXOS

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

- D1 EP0347066 (1989-12-09)
- D2 US5296507 (1994-03-22)

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



Optimum

74

Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas de
abogado situadas en la calle 119ª N° 53-99 de esta ciudad de Bogotá.

Señor Superintendente,


C.C. 79532186 RST



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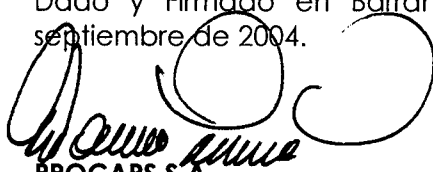
PODER ESPECIAL

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 **LUIS FERNANDO RINCON CUELLAR**, abogado titulado, identificado como aparece al pie de su firma, con tarjeta profesional No. 113438 expedida por el Consejo Superior de la Judicatura, poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 00-051031, de título: **"COMPOSICIONES DE ESCITALOPRAM USADAS EN EL TRATAMIENTO DE DESORDENES NEURÓTICOS"** publicada en la gaceta No. N° 519, del 29 Agosto de 2002, numero de publicación 519 cuyo solicitante es la sociedad **H. LUNDBECK A/S.**

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.

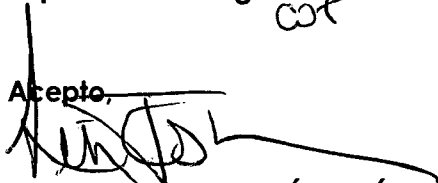
Dado y Firmado en Barranquilla (Colombia) a los 27 días del mes de septiembre de 2004.



PROCAPS S.A.

WALTER TANAKA TATEKAWA
C.C. N 16.251.923 de Palmira
Representante Legal

Acepto,



LUIS FERNANDO RINCÓN CUÉLLAR
C.C. No. 79.532.186
T.P. 113438

DILIGENCIA DE PRESENTACION PERSONAL

DECRETO 960 DE 1970 - ART. 68

MARIA DEL S. ROMAN DE ARTETA - NOTARIA SEGUNDA DE BARRANQUILLA

CERTIFICA

En B/quilla a los 09 días del mes de Sept de 2004 firmaron esta diligencia en su presencia: WALTER TONSA TEKANA

Portadores de las cédulas

16.951.923

Expedidas en

provincias

y que on el presente documento se ha comprobado que anteceden y son autorizados con sus firmas

Comparecientes

LA NOTARIA 2 del REPUBLICA DE COLOMBIA
NOTARIA SEGUNDA DEL CIRCULO
DE BARRANQUILLA

DILIGENCIA DE RECONOCIMIENTO Y PRESENTACION PERSONAL

Ante el Notario Once del Circulo de Santafé de Bogotá, compareció

Fernando RINCON

Quien exhibió la C.C. No. 7.953.276
expedida en 1977

y declaró que la firma y huella que aparecen en el presente memorial son suyas y que el contenido del mismo es cierto.

Memorial dirigido a 12 OCT 2004

Santafé de Bogotá, D.C.

[Firma]
Autorizó la anterior Diligencia

NOTARIO ONCE DEL CIRCULO DE SANTAFE DE BOGOTA

REPUBLICA DE COLOMBIA
NOTARIA 11 DEL CIRCULO DE
SANTAFE DE BOGOTA, D.C.
MONICA Z. BAUTISTA N
NOTARIA ONCE(E)

ANEXO 1

(9)



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

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

(22) Date of filing: 01.06.89

(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

(71) Applicant: H. LUNDBECK A/S
Ottlilavej 7-9
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(72) Inventor: Boegesoe, Klaus Peter
15, Moelleaaparken
DK-2800 Lyngby(DK)
Inventor: Perregaard, Jens
22, Thyrasvej
DK-3630 Jaegerspris(DK)

(74) Representative: Wilkinson, Stephen John et al
c/o Stevens, Hewlett & Perkins 5 Quality
Court Chancery Lane
London WC2A 1HZ(GB)

(54) New enantiomers and their isolation.

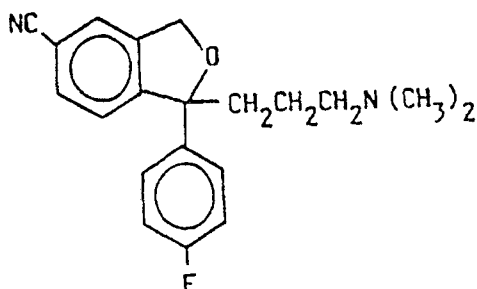
(57) The novel (+)-enantiomer of 1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile as well as acid addition salts thereof are described as valuable antidepressants, geriatrics or in the treatment of obesity and alcoholism.

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

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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-halothephyllines, for example 8-bromothephylline.

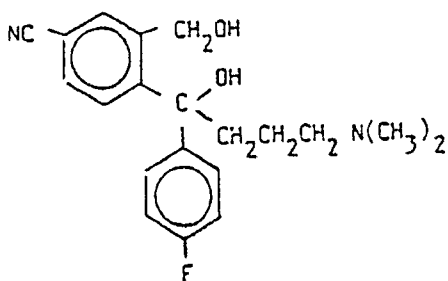
Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids. Of course, these salts may also be prepared by the conventional method of double decomposition of appropriate salts, which is well-known to the art.

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. exemplified 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

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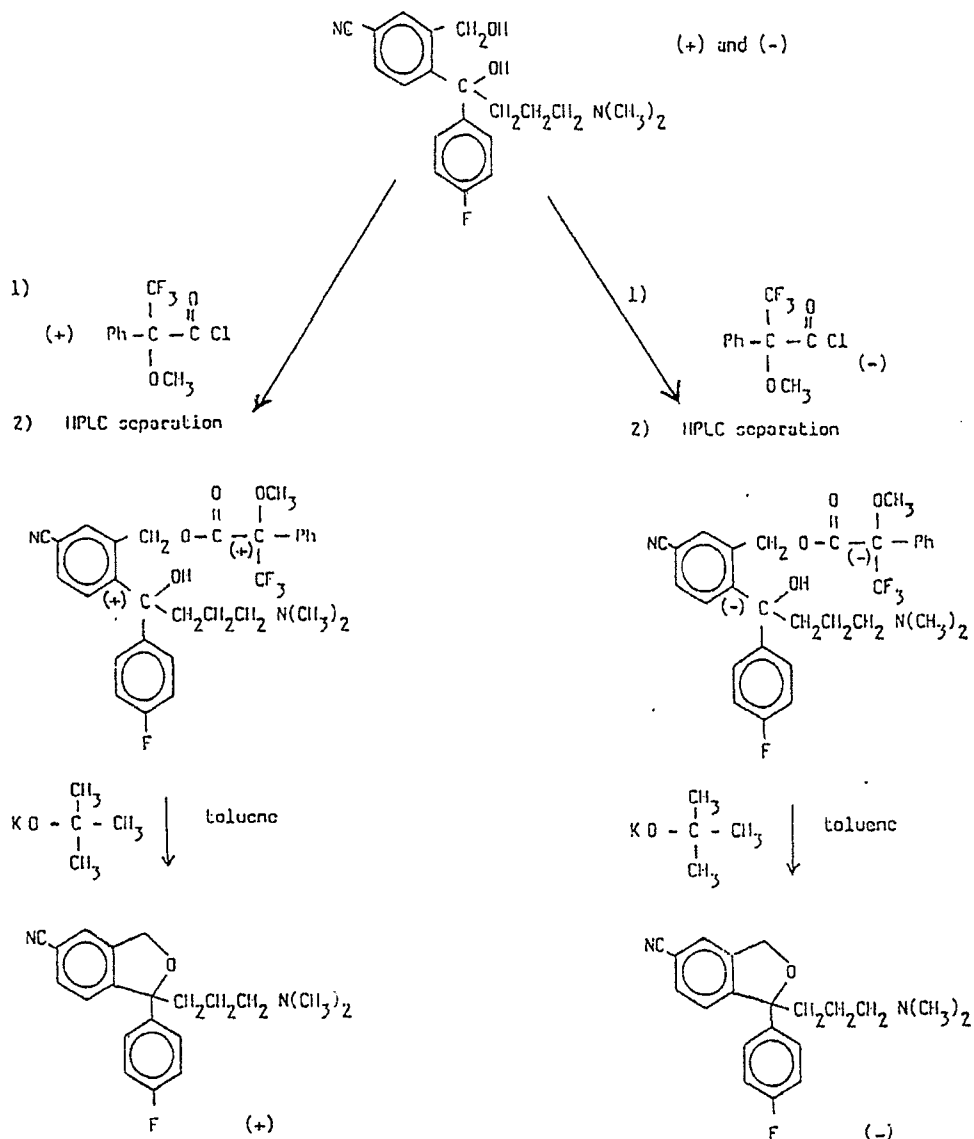
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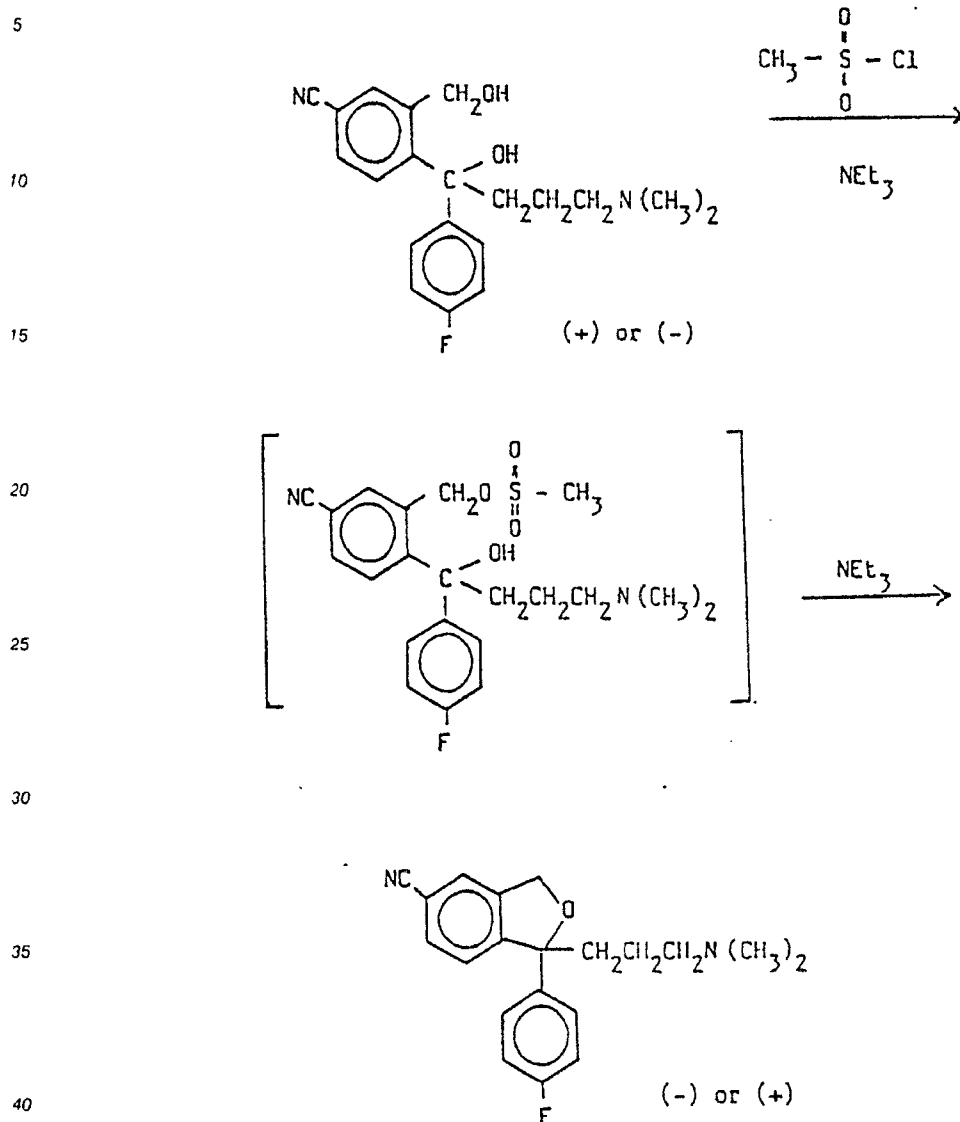
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b) the enantiomers of an optically active acid successively affording the pure diastereomeric salts. Optically antipodes of tartaric acid, di-benzoyltartaric acid, di-(p-toloyl) tartaric acid, bisnaphthylphosphoric acid, 10-camphorsulphonic acid and 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 exemplified in reaction scheme II:

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REACTION SCHEME IIEXAMPLE 1Resolution 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

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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 (MgSO₄) and the solvent evaporated yielding 0.6 gr of (+)-1-(dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile as an oil. $[\alpha]_D^{25} = +11.81^\circ$ (c = 1, CH₃OH) (determined with a substance containing 10% w/w of methanol). The optical purity was determined by ¹H NMR spectroscopy (CDCl₃ 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. $[\alpha]_D^{25} = -12.34^\circ$ (c = 1, CH₃OH) (determined with a substance containing 10% w/w of methanol). Optical purity: 99.9%.

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EXAMPLE 2Resolution by methods b) and c)

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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 (MgSO₄) 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, $[\alpha]_D^{25} = +10.0^\circ$ (c = 1, CH₃OH). 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 (MgSO₄) 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. $[\alpha]_D^{25} = +12.33^\circ$ (c = 1, CH₃OH).

The oxalic acid salt of the (+)-isomer crystallized from acetone. MP: 147-148°C, $[\alpha]_D^{25} = +12.31^\circ$ (c = 1, CH₃OH).

The pamoic acid salt of the (+)-isomer was prepared in the following manner: To 1.8 g of the base of the (+)-isomer was added 2 g of pamoic acid in 25 ml of MeOH. The mixture was refluxed for an hour and subsequently cooled to room temperature. The precipitate was filtered off yielding 3.0 g of the pamoic acid salt, MP: 264-266°C, $[\alpha]_D^{25} = +13.88^\circ$ (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 ($[\alpha]_D^{25} = -8.9^\circ$ (c = 1, CH₃OH)) which was converted to the corresponding diol base ($[\alpha]_D^{25} = +61.1^\circ$ (c = 1, CH₃OH)) and finally ringclosure reaction yielded 10 gr of (-)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile. $[\alpha]_D^{25} = -12.1^\circ$ (c = 1, CH₃OH).

The oxalic acid salt of the (-)-isomer crystallized from acetone. MP: 147-148°C, $[\alpha]_D^{25} = -12.08^\circ$ (c = 1, CH₃OH).

55 EXAMPLE 3Preparation of citalopram by method c)

To an ice cooled solution of 28 gr of racemic diol base, II, in 500 ml of dichloromethane were added 32 ml of triethylamine, and 7.5 ml of 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 (MgSO₄) 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 administration of the test substance, the other groups are given 5-HTP (100 mg/kg) i.v. (injection time 5-10 sec.). After this 5-HTP dose normal, untreated mice remain unaffected, but if the animals have been pretreated with a substance, which inhibits the uptake of 5-HT or a 5-HT agonist, a 5-HTP syndrome will occur. The symptoms are the same as previously described: 1) excitation, 2) tremor, and 3) abduction of the hind limbs. The animals are observed for 15 minutes and each animal is given one point for each symptom present. Again the result is stated in fractions: 0/9, 1/9, ..., 9/9, where 0, 1, ..., 9 are the number of points per group after the dose in question. The ED₅₀ value is calculated by log-probit analysis.

INHIBITION OF ³H-SEROTONIN UPTAKE IN RAT BRAIN SYNAPTOSOMES

By this method the inhibition by drugs of the uptake of ³H-serotonin (³H-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 sacrificed 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 P₂ 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 ³H-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

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determined by liquid scintillation counting. Uptake is obtained by subtracting the nonspecific binding and passive transport measured in the presence of 10 μ M 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 μ M of citalopram.

Table 1

PHARMACOLOGICAL TEST RESULTS		
Compound	5-HTP pot. ED ₅₀ μ mol/kg	5-HT uptake inhibition IC ₅₀ (nM)
(+)-citalopram	2.0	1.1
(-)-citalopram	120	150
($\pm$)-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 administration 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	5 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

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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

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

5 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
10 manifestations of certain physiological-psychological abnormalities of animals, especially depressions by administering to a living animal body, including human beings, an adequate quantity of (+)-citalopram or a non-toxic acid addition salt thereof. An adequate quantity would be from about 0.001 mg to about 10 mg per kg of body weight in each unit dosage, and from about 0.003 milligrams to about 7 milligrams/kg of body weight per day.

15 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.

20 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-
25 5-carbonitrile.

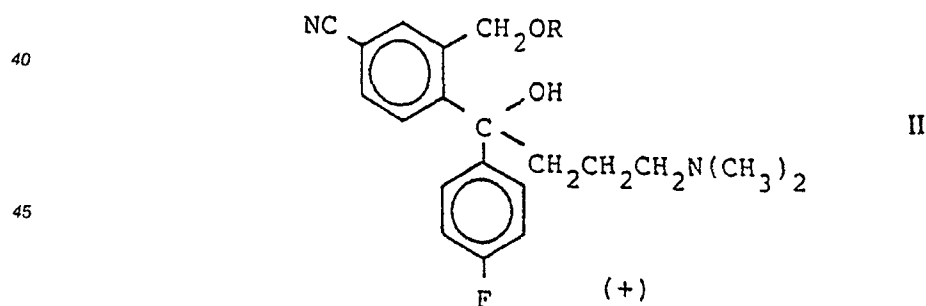
-3- A pharmaceutical composition in unit dosage form comprising as an active ingredient, a compound as defined in claim 1.

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

30 -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-
35 dihydroisobenzofuran-5-carbonitrile which is isolated as such or as a non-toxic acid addition salt thereof.

-7-



50 wherein R is hydrogen or 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
55 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.

ANEXO 2



US005296507A

United States Patent [19]

Tanaka et al.

[11] Patent Number: 5,296,507

[45] Date of Patent: Mar. 22, 1994

[54] TREATMENT OF CEREBROVASCULAR DISORDERS

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[21] Appl. No.: 1,571

[22] Filed: Jan. 6, 1993

Related U.S. Application Data

[63] Continuation of Ser. No. 742,907, Aug. 9, 1991, abandoned.

[30] Foreign Application Priority Data

Sep. 6, 1990 [DK] Denmark 2132/90

[51] Int. Cl.⁵ A61K 31/36

[52] U.S. Cl. 514/465

[58] Field of Search 514/465

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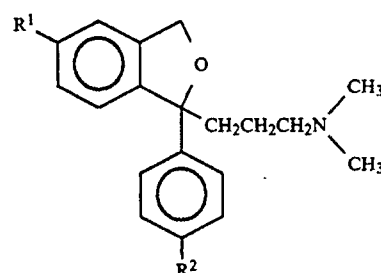
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Primary Examiner—S. J. Friedman

Attorney, Agent, or Firm—Gordon W. Hueschen

[57] ABSTRACT

A method for the treatment of dementia and cerebrovascular disorders and for inhibiting platelet aggregation in patients in need thereof comprising the step of administering a therapeutically effective amount of a 1-[3-(dimethylamino)propyl]-1-phenylphthalane of the general formula



Formula I

wherein R¹ and R² each are selected from the group consisting of halogen, trifluoromethyl, cyano and R—CO—, wherein R is an alkyl radical, or a pharmaceutically-acceptable acid addition salt thereof, is described.

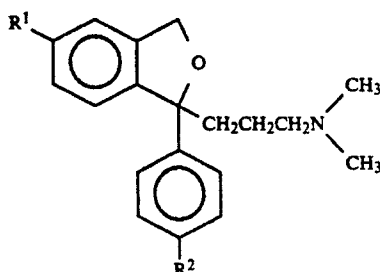
7 Claims, No Drawings

TREATMENT OF CERBROVASCULAR DISORDERS

This is a continuation of application Ser. No. 07/742,907, filed Aug. 9, 1991, now abandoned.

The present invention relates to the use of a class of 1-[3-(dimethylamino)propyl]-1-phenylphthalanes for the treatment of dementia and cerebrovascular disorders and for inhibiting platelet aggregation, and to the production of medicaments or pharmaceutical compositions containing the same for such purposes.

U.S. Pat. No. 4,136,193 relates to 1-[3-(dimethylamino)propyl]-1-phenylphthalanes having the general formula



Formula I

wherein R¹ and R² each are selected from the group consisting of halogen, trifluoromethyl, cyano and R—CO—, wherein R is an alkyl radical with 1 to 4 C-atoms inclusive, and acid addition salts thereof with pharmaceutically-acceptable acids.

Said compounds are described to be selective, centrally active serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors and accordingly to have antidepressant activities. One of the tests used to show such activities was inhibition of ¹⁴C-5-HT uptake in rabbit blood platelets in vitro. The compound of Formula I wherein R¹ is a cyano group and R² is a fluorine atom is the known antidepressant citalopram, the antidepressant activity of which has been reported in several publications, e.g. J. Hyttel, *Prog. Neuro-Psychopharmacol. & Biol. Psychiat.*, 1982, 6, 277-295 and A. Gravem, *Acta Psychiatr. Scand.*, 1987, 75, 478-486. A method for preparation of and intermediates for the preparation of citalopram are described in U.S. Pat. No. 4,650,884 and methods of preparing the individual enantiomers of citalopram are disclosed in U.S. Pat. No. 4,943,590.

Biochemical postmortem investigations of patients with Alzheimer's disease have shown hypofunction of the serotonin nervous system in the brain (D. M. Bowen et al., *J. Neurochem.*, 1983, 41, 266-272). It is also known that depression is one of the major symptoms in Alzheimer's disease, and citalopram has been reported to be effective against depression associated with Alzheimer's disease (C. G. Gottfries, *Psychopharmacology*, 1988, 96, 45 (Suppl.)). A study of a group of patients with moderate dementia of Alzheimer's type (AD/S-DAT) or multi-infarct dementia (MID) has shown significant improvements in emotional lability, motivation, confusion, fear-panic, irritation, reduced mood and restlessness, whereas citalopram did not appear to have effect on intellectual functions (Nyth, A. L. et al. "The effect of citalopram in dementia disorders", presentation at CINP, August 1988; subsequently reported in Nyth, A. L. and Gottfries, C. G., "The clinical efficacy of citalopram in treatment of emotional disturbances in dementia disorders. A nordic multicentre study." *Br. J.*

Psychiat., 1990, 157, 894-901). Later controlled studies showed that treatment with citalopram caused no significant improvement on emotional disturbances in patients with vascular dementia (VD, incl. MID) (Nyth, A. L. et al. "The efficacy of citalopram in treatment of emotional disturbances in dementia disorders", *ECNP Abstract* 1989, Sweden, 79).

It has also been described that certain 5-HT_{1A} agonists show effect in the treatment of *Apoplexia cerebri* (Danish Patent Application No 4616/89).

Cerebrovascular disorders, such as ischemia which are triggered by cerebral infarction, cerebral hemorrhage, cerebral arteriosclerosis, subarachnoid hemorrhage, cerebral thrombosis, cerebral embolism, and other diseases are of increasing importance among the population and there is a great demand for effective and safe drugs for the treatment of such disorders and the sequelae of such disorders. A particular problem is dementia not only caused by cerebrovascular disorders but also dementia of other genesis.

Surprisingly, it has now been found that the compounds of the above Formula I effect improvement of cerebrovascular disorders, in particular ischemia, and the brain damage and the impairment of memory functions in connection therewith, and that they show inhibiting action on platelet aggregation. Furthermore, the compounds of the general Formula I have been found to have an anti-amnesic effect and to improve cognitive function in elderly depressed patients having concomitant dementia, i.e. not only dementia of cerebrovascular origin, but also dementia as a result of chronic organic reactions, such as neurodegenerative disorders.

Accordingly, the present invention relates to the use of a compound of the above Formula I for the prevention or treatment of senile dementia and of cerebrovascular disorders and for the inhibition of platelet aggregation, and for the manufacture of medicaments or pharmaceutical compositions for such uses.

Senile dementia may be senile dementia of any genesis such as neurodegenerative, traumatic, cerebrovascular, anoxic, etc, i.e., dementia of Alzheimer's type, multi-infarct dementia or vascular dementia, etc.

Cerebrovascular disorders are brain damages caused by cerebral infarction, cerebral hemorrhage, cerebral arteriosclerosis, subarachnoid hemorrhage, cerebral thrombosis, cerebral embolism, or the like, e.g., ischemia, and the psychological and neurological sequelae of such damages.

The use of the optical isomers of the compounds of general Formula I and their mixtures, including racemic mixtures thereof, is embraced by the invention.

The compound of general Formula I may be used as the free base or as a pharmacologically-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, embonic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanedithionyl, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-amino-benzoic, glutamic, benzene sulfonic and theophylline acetic acids, 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.

An appropriate oral dose of the compound of general Formula I is 1-100 mg/day p.o.

Due to the inhibition of platelet aggregation the medicaments obtained and used in accordance with the invention are useful in the treatment and/or prevention of microcirculation disturbances in the brain resulting from the above cerebral conditions or from venous or arterial thrombosis, or elsewhere in the body resulting from venous or arterial thrombosis or related conditions.

In view of the beneficial effects on cognitive function and on brain damages and of the platelet aggregation inhibiting effects now found as well as of the known effects on 5-HT uptake, the medicaments obtained and used in accordance with the present invention are useful in the treatment of senile dementia and cerebrovascular disorders, and the sequelae of cerebrovascular disorders such as psychiatric symptoms, e.g., anxiety, depression, loss of memory, hypobulia, restlessness, dementia, hallucinations, delusions, disturbances of consciousness, hypochondriac tendency, insomnia, excitation, garrulity, hyperkinesia, deliriums, and disturbances of orientation, neurological symptoms, e.g., alalia, and hypodysphasia, and subjective symptoms, e.g., headache, dizziness, feeling of numbness, feeling of stiffness in the shoulder, feeling of exhaustion and heavy feeling in the head.

Additionally they have the further advantage of a very good safety profile.

A preferred compound of Formula I is citalopram.

The medicaments manufactured and used in accordance with the present invention are particularly useful in the treatment or prevention of ischemia in the brain and especially of dementia caused by ischemia.

Due to the pharmacological profile the medicaments manufactured and used in accordance with the present invention are especially useful in elderly patients.

Citalopram may be prepared by the methods disclosed in U.S. Pat. No. 4,650,884 and the other compounds used in accordance with the invention may be prepared analogously or by the methods of U.S. Pat. No. 4,136,193. The individual enantiomers of citalopram may be prepared as described in U.S. Pat. No. 4,943,590 and enantiomers of the other compounds of Formula I may be prepared by similar methods.

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.

The medicaments prepared and used in accordance with 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.

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.

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 the desired volume, sterilization 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.

The present compounds and their non-toxic acid addition salts may also be used in combination with other active ingredients, such as neuroleptics, thymoleptics, analgetics, etc.

TOXICITY STUDY

In toxicity studies male and female SD rats ranging in weight from 170 g to 200 g were used one day after fasting. Citalopram was dissolved in water and administered orally. Symptoms were observed for one week after citalopram administration. Even when citalopram was administered at a dose of 350 mg/kg no deaths were observed and accordingly it was obvious that citalopram has a very good safety profile.

PHARMACOLOGICAL TESTS

Ischemia-Induced Hippocampal Death in Gerbils

The overall objective of the study was to investigate the effects of citalopram on hippocampal lesions induced by ischemia in Mongolian gerbils.

Methods

Test compounds were administered intraperitoneally to Male Mongolian gerbils 30 min before carotid occlusion. Carotid occlusion time was 5 min. Seven days after recovery, the animals were killed, brains removed, sectioned and surviving neurons were counted along CA1 in the hippocampus.

Results

As is shown in Table 1, citalopram (20 mg/kg) had a weak but non-significant protective effect against neuronal lesions. The higher dose of this compound (40 mg/kg) showed a significant ($p < 0.05$) protective effect against neuronal lesions. Ketamine (100 mg/kg) showed significant ($p < 0.01$) protective effect.

TABLE 1

Drug	Dose (mg/kg i.p.)	Gerbils used	Effects on ischemia induced hippocampal neuronal damage in gerbils		
			Survival neurons/mm		
			mean	S.E.	p
Vehicle	—	10	12.8	2.6	
Citalopram	20	12	38.0	18.5	N.S.
Citalopram	40	11	95.8	27.9	<0.05
Ketamine	100	8	174.5	25.7	<0.01

Statistical analysis was carried out according to Dunnett's t-tests vs vehicle group.

Passive Avoidance in Ischemic Gerbils

The test employed was step-down passive avoidance in gerbils treated with test compounds prior to occlusion of carotid arteries followed by acquisition trial (training phase).

Methods

Test compounds were administered intraperitoneally to gerbils 30 min prior to carotid occlusion or ketamine was administered intraperitoneally 10 min prior to carotid occlusion. The gerbils were anesthetized with 2% halothane contained in a mixture of 70% nitrogen and

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30% oxygen. The right and left common carotid arteries were occluded for 5 min. The gerbils were trained for 5 min in a step-down type passive avoidance chamber (16×16×20 cm) two days after induced ischemia. Each gerbil was placed on a safety platform (6×16×20 cm) in the chamber and received a series of mild foot shocks (0.1 mA for 3 sec every 6 sec), when the gerbil stepped down to a floor made of metal rods. Gerbils were returned to the safety platform for testing 24 hrs later and their step-down latencies to the grid floor were recorded (max. 60 sec).

Results

Ischemia did not alter step-down latency measured during the training phase. Step-down latency during the training phase was not significantly modified in the gerbils treated with test compound.

Step-down latency in the testing phase was significantly decreased between ischemic control and sham operated gerbils. Citalopram (20 mg/kg) and ketamine (120 mg/kg) significantly increased the latency of ischemic gerbils. But the latency in indeloxazine (40 mg/kg) treated gerbils was not significantly different from that in ischemic control gerbils.

TABLE 2

Effect on passive avoidance in ischemic gerbils					
Drug	Dose (mg/kg i.p.)		Ischemic treatment	Step-down latency [log(sec)]	
	Number of gerbils			Mean	S.E.
Saline (sham)	—	15	—	1.471	0.075***
Saline (control)	—	20	+	0.953	0.116
Citalopram	20	7	+	1.386	0.083**
Indeloxazine	40	6	+	1.085	0.244
Ketamine	120	9	+	1.348	0.100*

*p < 0.05.

**p < 0.01.

***p < 0.001 (vs Saline control, by Student's t-test)

Brain Ischemia-Induced Death in Mice

Materials

Male ICR MICE (Charles River) weighing 30–40 g were used after they were fasted for 1 day.

Method

Test compounds were administered intraperitoneally to the mice 30 min prior to permanent ligation of bilateral common carotid arteries under conscious condition. Surviving mice were observed over 4 hrs.

Results

Citalopram (30 mg/kg) significantly prevented ischemia-induced death both 2 hrs and 4 hrs after bilateral carotid arterial ligation. Ifenprodil (30 mg/kg), however, did not significantly increase survival rate 4 hrs after ligation, although it showed significantly increased survival rate 2 hrs after the ligation.

TABLE 3

Effect on ischemia-induced death in bilateral carotid arterial ligation (BCAL) in mice				
Drug	Dose (mg/kg, p.o.)	Number of mice	Survival rate (%)	
			2 hr after BCAL	4 hr after BCAL
Saline	—	30	23	17
Citalopram	30	30	50*	43*
Saline	—	30	13	7
Ifenprodil	30	30	47**	20

*p < 0.05.

**p < 0.01 (Chi-square test vs each Saline)

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KCN-Induced Coma in Mice

Methods

Male mice (Crj:ICR) weighing 20–30 g were used. The mice were fasted for one day. The drugs, dissolved in saline, were injected intraperitoneally. 30 min after the injection, KCN, dissolved in saline, was injected intravenously at a dose of 1.3 mg/kg. The duration of disappearance of righting reflex was measured as coma time.

Results

Intraperitoneal injection of citalopram significantly reduced coma time at a dose of 10 mg/kg. Indeloxazine at a dose of 20 mg/kg also significantly reduced the coma time.

TABLE 4

Effects of intraperitoneal injection of citalopram on KCN-induced coma in mice				
Drug	Dose (mg/kg, i.p.)	Number of mice	Coma time (sec)	
			Mean	S.E.
Vehicle	—	16	55.9	8.8
Citalopram	1.25	15	38.5	4.2
Citalopram	2.5	15	33.2	10.0
Citalopram	5	16	35.0	8.2
Citalopram	10	16	27.4	6.9*
Indeloxazine	20	17	13.8	3.7**

*p < 0.05.

**p < 0.01, Significantly different from values of vehicle control (Dunnett's t-test).

Carbon Dioxide-Induced Amnesia in Rats (Passive Avoidance Test)

The test employed was a one-trial passive avoidance test in rats, using carbon dioxide asphyxiation to induce amnesia.

Methods

Female Sprague-Dawley (CD) rats (A. Tick & Son Ltd.) in the body weight range 160–180 g were used for the study.

The one-trial passive avoidance apparatus consisted of a 32×32×32 cm chamber with opaque walls and a metal grid floor. A 6 cm wide, 25 cm long runway protruded from the front wall of the chamber. The runway was illuminated while the chamber was dark. When placed on the runway, a rat could enter the chamber through a 6×6 cm opening. A scrambled foot-shock could be delivered through the metal grid floor of the chamber.

On the first day of the experiment, the rats received three pre-treatment training trials, during which each animal was placed on the end of the runway and the time taken to enter the chamber (the 'step-through' latency) was determined.

On the second day of the experiment, groups of 10 animals were treated p.o. with test compound dissolved in saline or with saline.

One hour after administration, an acquisition trial was performed. This was similar to a training trial, except that the rats received a footshock of 1.0 mA for 10 sec. commencing 10 sec after entering the chamber. Immediately after the application of the footshock the animals were subjected to amnesic treatment.

Amnesic treatment consisted of placing the rats in a box filled with carbon dioxide until respiratory arrest occurred; the rats were then revived by artificial respiration. 24 Hours after the acquisition trial, a single retrieval trial was given to each rat and the time taken to

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enter the chamber ('step-through' latency) was recorded for each animal.

If a rat did not enter the chamber within 180 seconds it was taken from the runway.

Results

There were no significant differences between the time of entry ('step-through' latency) of rats dosed with either vehicle, citalopram or piracetam, thus indicating that at oral doses of 40 or 1000 mg/kg, these compounds did not induce marked muscle incoordination of CNS effects of sufficient magnitude to modify entry times. The amnesic effect of carbon dioxide has been clearly demonstrated in this study. In those rats receiving foot-shock, but no drug treatment, treatment with carbon dioxide asphyxiation caused a decrease in 'step-through' latency.

Oral administration of citalopram at all doses tested caused dose-related increases in the group mean 'step-through' times, which in most cases were statistically significant when compared to the saline-treated control group using Student's t-test. At the 2 highest doses tested (i.e., 20 and 40 mg/kg), a marked and highly significant increase in time was observed.

As expected, piracetam treatment gave statistically significantly longer 'step-through' latencies.

TABLE 5

Effects of oral administration of citalopram on carbon dioxide-induced amnesia in rats.				
Drug	Dose (mg/kg; p.o.)	CO ₂ Treatment	Number of animals	Latency (sec)
Saline	—	—	10	119.6***
Saline	—	+	10	0.8
Citalopram	5	+	10	31.2
Citalopram	10	+	10	77.2**
Citalopram	20	+	10	114.3***
Piracetam	300	+	10	108.8***

**p < 0.01.

***p < 0.001, significantly different from values of relevant control group (Students t-test).

In Vitro Platelet Aggregation

Methods

The test was performed with fresh human platelets. The drugs were diluted in physiological saline to give a solution at a concentration ten times that of the final concentration. The drug was added to the platelets and incubated at 37° C. for 15 min. and then platelet aggregation was induced by the addition of collagen (10 microgram/ml).

Results

Citalopram at a final concentration of 100 microgram/ml inhibited the aggregation of human platelet induced by collagen by 58%. The same concentration of indeloxazine revealed weaker inhibitory effect (8%) than citalopram did on the aggregation by collagen.

Ex Vivo Platelet Aggregation

Effect on collagen-induced platelet aggregation using blood of rats administered orally with citalopram was investigated.

Materials

Male Wistar rats (Charles River) in the body weight range 350–400 g were used.

Methods

One hour after oral dosing the rats were lightly anesthetized with ether and blood was collected by cardiac puncture. Nine ml of the blood was mixed with 1 ml of 3.8% sodium citrate and platelet rich plasma (300000 platelets/cmm) was prepared. At the end of the incubation

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period at 37° C. for 2 min. effects of addition of 10 microgram/ml collagen on platelet aggregation were determined.

Results

A moderate inhibition of collagen-induced aggregation was noted following citalopram at 30 mg/kg (60.4%). At doses of 10 mg/kg only slight inhibition of collagen-induced aggregation was noticed (16.7%).

TABLE 6

Effect on platelet aggregation ex vivo in rats.					
Drug	Dose (mg/kg, p.o.)	Number of rats	Mean (%)	S.D. (%)	[% Change from control]
Vehicle	—	12	54.6	27.3	[—]
Citalopram	10	8	45.5	16.0	[−16.7]
Citalopram	30	8	21.6	21.6**	[−60.4]

S.D.: Standard deviation.

Statistical significance using analysis of variance of treatment groups as compared to vehicle treated groups.

**P < 0.01.

It appears from the foregoing Ischemia Induced Hippocampal Death Test that the compound according to the invention tested shows improving effect on neuronal lesion. The Passive Avoidance Test is Ischemic gerbils indicates improving effect on memory following ischemic attack, the Brain Ischemia-Induced Death Test in mice indicate effect on survival rate following ischemic attack, the KCN-induced Coma test in mice indicates improving effect following anoxia, and the Carbondioxide-Induced Amnesia Test in rats show positive effect on amnesia.

The results of the in vitro and the in vivo Platelet Aggregation Tests show inhibiting effects on platelet aggregation.

Clinical Test

In a group of depressed patients having concomitant dementia, it was observed that cognitive functions improved after treatment with compounds of the general Formula I but not after treatment with placebo. Accordingly, compounds of general Formula I clinically have memory improving effect in patients having dementia which may not only be of cerebrovascular origin but also may result from chronic organic reactions such as neurodegenerative disorders. This is in contradiction to the earlier study of Nyth et al. mentioned above (Nyth, A. L. et al. "The effect of citalopram in dementia disorders", presentation at CINP, August 1988).

FORMULATION EXAMPLES

The following examples show typical formulations of the medicaments manufactured in accordance with the invention.

1) Tablets containing 0.5 milligram of citalopram calculated as the free base:

Citalopram	100 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 1 milligram of citalopram calculated as the free base:

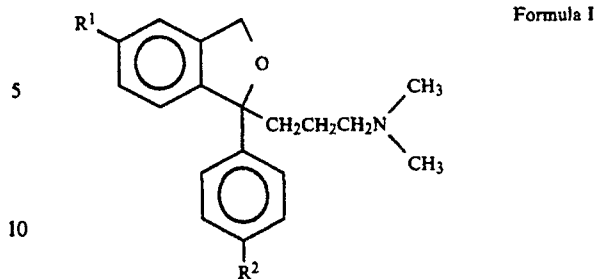
Citalopram	50 mg
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Lactose	16 mg
Potato starch	45 mg
Saccharose	106 mg
Sorbitol	6 mg
Talcum	9 mg
Gelatine	4 mg
Povidone	3 mg
Magnesium stearate	0.6 mg
3) Syrup containing per milliliter:	
Citalopram	5.0 mg
Sorbitol	500 mg
Tragacanth	7 mg
Glycerol	50 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

We claim:

1. A method for the treatment of dementia cognitive disorders, or amnesia associated with and cerebrovascular disorders in a patient in need thereof comprising the step of administering an amount of a 1-[3-(dimethylamino)propyl]-1-phenylphthalane of the formula



wherein R¹ and R² each are selected from the group consisting of halogen, trifluoromethyl, cyano and R—CO—, wherein R is an alkyl radical with 1 to 4 C-atoms inclusive a, or a pharmaceutically-acceptable acid addition salt thereof which is effective for such purpose to the said patient.

2. A method according to claim 1 wherein the cerebrovascular disorder is caused by cerebral infarction, cerebral hemorrhage, cerebral arteriosclerosis, sub-arachnoid hemorrhage, cerebral thrombosis, or cerebral embolism.

3. A method according to claim 2 wherein the disorder is ischemia.

4. A method according to claim 2 wherein the disorder is amnesia associated with ischemia.

5. A method according to claim 2 wherein the disorder is Vascular or Multiinfarct dementia.

6. A method according to claim 1 wherein the disorder is dementia of the Alzheimer's type.

7. A method according to claim 1 wherein the compound of Formula I is citalopram or a pharmaceutically-acceptable acid addition salt thereof.

* * * * *