

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

202012
Bogotá, D.C., 28 de septiembre de 2010

Apoderado: James Ian Raisbeck

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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 Evento 001
 Actuación 430
 Oficio
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Patente de Invención ☒

Vía PCT fase nacional ☒ Cap.I ☒ Cap. II ☐

No. Sol. Internacional PCT/EP2005/055753

Fecha de Presentación Internal. 04/nov/2005

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

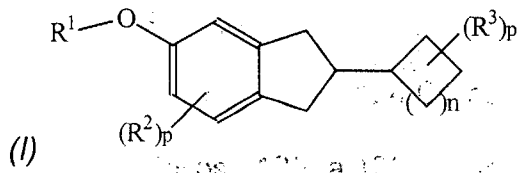
1. Documentos estudiados

- 1.1. Descripción: Folios: 59 a 124 Como se radicó inicialmente
- 1.2. Reivindicaciones: Folios: 125 a 129 Como se radicó inicialmente
 Folios: 150 a 154 Modificaciones
- 1.3. Prioridad: Folio 1: GB 0426828.0; 07/oct/2004
 GB 0519089.7; 19/sep/2005

2. Objeto de la invención

Título de la solicitud: DERIVADOS DE INDENILO Y USO DE LSO MISMO PARA EL TRATAMIENTO DE TRANSTORNOS NEUROLÓGICOS.

El objeto de la presente solicitud consiste en los derivados de 2-(azocicloalquil)-2,3-dihidro-1H-inden-5-oxi sustituido de fórmula Makush (I):



- Reivindicaciones 1- 9, 11,12: Compuestos de fórmula (I).
- Reivindicaciones 10,15: Composiciones que comprenden los compuestos de la fórmula (I).
- Reivindicación 13: el uso.
- Reivindicación 14: Método de tratamiento.

Se clasificó la invención de acuerdo con la Clasificación Internacional de Patentes (IPC): C07D213/82, C07D241/24, C07D213/64, C07D233/32, C07D213/74, C07D263/20, C07D213/80, A61K31/015, 31/395, A61P25/00

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D 486 de la C.A.N.)

-Las reivindicaciones 1,2,3 no son claras, ya que los sustituyentes no están definidos inequívocamente, solo se le han adjudicado denominaciones genéricas del tipo "-X-arilo, -X-heterociclilo, -Y-arilo, -X-aril-Y-heterociclilo, X-heteroaril-heteroarilo, X-heteroaril-Y-heterociclilo, -X-heterocicliil-Y-heroarilo, etc...arilsulfoniloxi arilsulfonilo, ariloxi, " y denominaciones similares no definen ni delimitan clara e inequívocamente el alcance de la invención, como tampoco encuentran un sustento técnico en la descripción para todas las estructuras que están involucradas dentro de esas denominaciones genéricas, menos encuentra sustento para todas las posibles permutaciones y sus combinaciones, por lo tanto resulta especulativa esa manera de redacción de las reivindicaciones, no son extrapolaciones estrechamente relacionadas con lo que se describió, las reivindicaciones deberán presentar una generalización razonable de los ejemplos dados en la parte descriptiva, El Art. 30 D486 de la C.A.N. dispone que las reivindicaciones deberán estar enteramente sustentadas en la memoria descriptiva. **Este es un requerimiento sustantivo y no simplemente una cuestión de consistencia puramente de enunciado.** Esto significa que debe existir una base técnica real en la memoria descriptiva, para el total del objeto de cada reivindicación y que el ámbito de las mismas no puede ser ampliado más allá de lo realmente justificado por el contenido de la memoria descriptiva.

- También debe corregir expresiones tales como por ejemplo "arilsulfonilalquil C₁C₆",
- Las reivindicaciones 10 y 15 son redundantes, ya que se reclama es el uso tácito de los compuestos en composiciones farmacéuticas, el hecho que en la reivindicación 15 le mezclen uso y método terapéutico, no hace diferente a la "composición".
- Las reivindicaciones 11 y 12, no son claras, ya que el encabezado es incongruente con el texto de la reivindicación, se encabezan como compuesto y el texto de la reivindicación es una mezcla de uso y método terapéutico, condiciones que no son elementos técnicos de compuesto, los compuestos se definen técnicamente por su

estructura química específica o mediante su nombre químico IUPAC.

Por lo tanto las reivindicaciones no cumplen con el requisito exigido en artículo 30 D 486 de la C.A.N.

4. Reivindicaciones relativas a un uso o a un uso distinto (artículos 14 y 21 D 486 de la C.A.N.)

-La reivindicación 13 reclama es uso de compuestos; el artículo 14 D 486 de la C.A.N. indica que los Países Miembros otorgarán patentes para las invenciones sean de productos o procedimientos en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial. En ningún caso se indica que se está protegiendo el uso.

Por demás, los usos o segundos usos no son patentables, de conformidad con la sentencia del TJAC 89-AI-2000, los usos en general no son patentables.

5. Excepción a la patentabilidad (artículo 20 D486 literal d) de la C.A.N)

-La reivindicación 14 reclaman un método de tratamiento para el cuerpo humano o animal, por lo tanto está comprendida por lo depuesto en el artículo 20 D486 literal d), de la C.A.N

6. Determinación del Estado de la Técnica

Considerando la fecha de prioridad reclamada de la presente solicitud de patente 07/sep/2004, se realizó la búsqueda del estado de la técnica, en bases de datos donde ésta oficina tiene acceso libre, para búsquedas de documentos relacionados con la materia que se reclama como nueva e inventiva en la presente solicitud. Encontrándose los siguientes documentos relevantes:

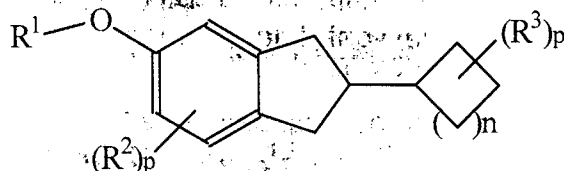
Nº	Documento	Título	Fecha de Publicación*
D1	GB1142724	Derivatives de 2-aminoindanes	12/feb/1969
D2	WO9504713	2-aminoindans as dopamine D3 ligands	16/feb/1995
D3	WO2004080968	6-substituted nicotinamide derivatives as opioids receptor antagonists	23/sep/2004

7. Análisis de patentabilidad (artículo 14 D486)

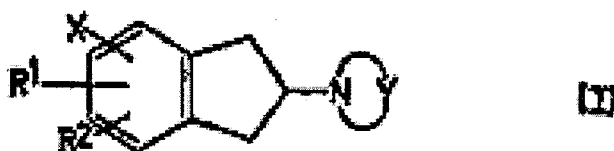
7.1. Novedad (artículo 16 D486 de la C.A.N.)

La presente Solicitud reclama los compuestos derivados de 2-(azocicloalquil)-2,3-

dihidro-1H-inden-5-oxi sustituido de fórmula general (I):

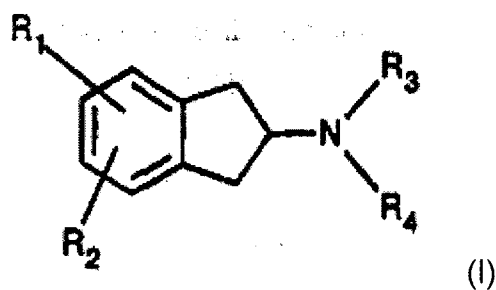


-D1 enseña compuestos de derivados de 2-aminoindanos sustituido de fórmula general (I):



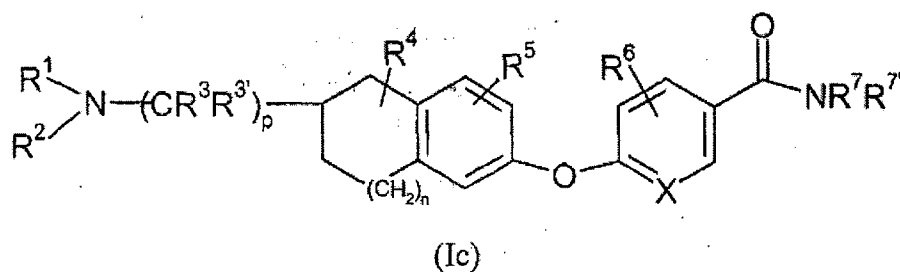
Véase, especialmente pags 1-2, los ejemplos 14, 15, 16, reivindicaciones 1, 9, 11, 12, 14, 15, 16, que es materia que se reclama en la presente solicitud

-D2 enseña compuestos de derivados de 2-aminoindanos sustituido de fórmula general (I):



Véase, especialmente pag 2 renglón 13- pag, 3 renglón 18, ejemplo 6 y reivindicaciones 1, 7, 8, 11 que es materia que se reclama en la presente solicitud como nueva e inventiva.

-D3 enseña compuestos de derivados de 2-aminoindanos sustituido de fórmula general (I):



Véase, especialmente compuestos de fórmula 1c, pag. 4 renglones 15-35, los ejemplos 140-142, pag 11 renglones 1-2, que es materia que se reclama en la presente solicitud como nueva e inventiva.

Tal como se puede ver la solicitud en estudio no cumple con lo exigido en el artículo 16 D486 de la C.A.N.

8. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

**Una solicitud que no posee novedad obviamente no ostenta nivel inventivo.*

Documento N°	Reivindicaciones Afectadas	Requisito que Afecta
D1	1-16	Novedad
D2	1-16	Novedad
D3	1-16	Novedad

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el artículo 8 de la resolución reglamentaria No. 00210 del 15 de enero de 2001, advirtiéndole que contra él no procede recurso alguno en la vía gubernativa.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 05 NOV. 2002

CONCEPTO TECNICO N° 3831	EXAMINADOR TECNICO Cód N°202012
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PATENT SPECIFICATION

NO DRAWINGS

1,142,724



Date of Application and filing Complete Specification: 13 May, 1966.

No. 21399/66.

Application made in Germany (No. C 35833 IVd/12p) on 13 May, 1965.

Application made in Germany (No. C 37801 IVd/12p) on 30 Dec., 1965.

Complete Specification Published: 12 Feb., 1969.

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Index at acceptance:—C2 C(1E4K1, 1E4K4, 1E4K6, 3A13B3, 3A13C1C, 3A13C8C, 3A13C10F, 3A13C10H, 3A14A3D, 3A14A8D, B4A1, B4A2, B4A4, B4D, B4H, B4M)

Int. Cl.:—C 07 d 27/04, C 07 d 29/02, C 07 d 41/04, C 07 d 51/70, C 07 d 87/22

COMPLETE SPECIFICATION

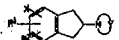
Derivatives of 2-Aminoindane

We, CHEMISCHE WERKE ALBERT, a German Body Corporate, of Wiesbaden-Biebrich, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to pharmaceutically useful derivatives of 2-aminoindane and to a process for preparing such compounds.

Derivatives of indane, especially also those which are substituted by amino groups, have been frequently described in the literature. Some derivatives of 2-aminoindane, alkoxylated in the nucleus, which furthermore may be alkylated on the nitrogen, have an analgesic effect. Other N-substituted derivatives of 2-aminoindane have a bronchodilatory effect.

The present invention provides hitherto unknown derivatives of indane in which a cyclic, basic group is attached to the indane group. The compounds of the invention have the formula



(where R¹ and R² which may be the same or different are hydrogen atoms, alkoxy groups with up to 3 carbon atoms or hydroxyl groups, X is a hydrogen or halogen atom and Y is a straight chain or branched alkylene group having from 4 to 7 carbon atoms) and their physiologically compatible inorganic or organic acid addition salts.

A methylene group or an alkylidene group in the group Y of the formula (I) may, if desired, be replaced by an oxygen atom, an imino group or an alkyl substituted imino group having up to 3 carbon atoms in the alkyl substituent. Such alkyl substituents may [Pr]

thus be ethyl, propyl or isopropyl, however, the preferred alkyl substituent is methyl.

Preferred compounds are those wherein R¹ and R² are methoxy groups and the group X, when representing a halogen atom, is preferably chlorine or bromine.

Physiologically compatible acid addition salts of the compounds of the formula (I) may, for example, be formed with inorganic acids, such as hydrogen halides, e.g. hydrobromic acid or hydrochloric acid, or sulfuric acid or phosphoric acid, or with organic acids, e.g. carboxylic acids having one or more carboxylic groups, which may also contain hydroxyl groups, such as acetic acid, propionic acid, malonic acid, maleic acid, succinic acid, adipic acid, lactic acid, malic acid, tartaric acid, citric acid or gluconic acid.

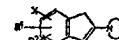
The compounds according to the invention are suitable for pharmaceutical purposes. Thus, 2 - piperidino - indane, 2 - pyrrolidino - indane, N - indenyl - (2) - piperazine and its N-alkyl derivatives show a broncholytic effect. The 2 - piperidino - indanes and the 2 - pyrrolidino - indanes have also, surprisingly, a stimulating action on the central nervous system resulting for example in increased motility, causes a reduction in narcosis times, especially in the case of narcosis produced with N - methyl - 5 - (Δ¹ - cyclohexenyl) - 5 - methyl - barbituric acid. They also cause a temporary elevation of the blood pressure of laboratory animals, e.g. cat or rat, whilst the hypertensive effect of adrenaline is partially checked. Moreover they have anorexiogenic effects. The following compounds according to the invention are suitable for use as analgesics: 2 - pyrrolidino - indane, 2 - piperidino - indane and its 4'-alkyl derivatives, its 5,6-dialkoxy or dihydroxy derivatives, 5-monohydroxy derivatives and N-indenyl - (2) - piperazine. Tussive irritations, especially that provoked by citric acid spray,

are inhibited by 2-pyrrolidinoindane and its 4'-alkyl derivatives, 2 - piperidino - indane and N-indenyl - (2) - piperazine. The perfusion of some organ regions, for instance musculature of the extremities of the rabbit or isolated ear of the rabbit, can be increased by pre-

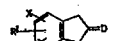
treating with 2 - piperidino - indane, its 3-alkyl derivatives, its 5-hydroxy or 5-alkoxy derivatives, 2 - pyrrolidino - indane, 2-hexamethylene - iminoindane and N - phenyl-N' - indenyl - (2) - piperazine. Accordingly, the invention also includes within its scope pharmaceutical compositions comprising one or more compounds of formula (I) or physiologically compatible acid addition salts thereof in association with pharmaceutical carriers or diluents e.g. aqueous solutions, tablets or pills with talcum, starch, silica, lactose, mannitol, hardened gelatin or other tableting excipients.

The compounds of the formula (I) may be prepared as follows:

1. Hydrogenating an indene-amine of the formula



in solution. The compound of the formula II can be prepared by reacting, in solution, cyclic ketone (indanone) of the formula

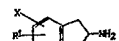


with a heterocyclic base of the formula



This method is illustrated by examples 1 and 3 to 7. In Example 2, the starting material of the formula II, N - indenyl - 2 - piperazine, is formed *in situ* when N - indenyl-2 - N' - benzylpiperazine is hydrogenated.

2. Reacting an amine of the formula



with a halogen compound of the formula



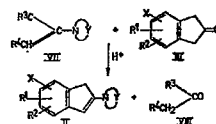
wherein Hal is a halogen atom, preferably chlorine and/or bromine. This reaction is illustrated by examples 8 to 11.

3. A compound of formula (I), in which X is a halogen atom, may also be prepared by halogenating in the aromatic nucleus, a compound of the formula (I), in which X is a hydrogen atom, preferably with elementary halogen, especially chlorine or bromine. This procedure is illustrated by example 12.

4. Although compounds of formula (I), in which R² and/or R² are hydroxyl groups, may be obtained by any one of the methods described above, they may with particular advantage be prepared by cleavage of the ether bond in compounds of formula (I) in which R¹ and/or R² are alkoxy groups, especially methoxy groups, for example, with hydriodic acid. This method is illustrated by examples 13 and 14.

The indene-amines of formula (II), which are used as starting materials in method 1, may be prepared by condensation of cyclic ketones of formula (III), e.g. indanone-2, with heterocyclic bases of the formula (IV), for example under atmospheric pressure and at a temperature of from ambient temperature to 120°C, especially 30 to 60°C, and in the presence of one or more solvents which are inert to the reactants, particularly alcohols e.g. lower aliphatic alcohols such as methanol, ethanol, iso-propanol, n-propanol, or one of the butanols. If the condensation product is to be isolated, the reaction mixture is preferably cooled to between -10 and +10°C.

The indene-amines of formula (II) may be prepared in good yields by reacting an enamine of formula (VII), shown below which may be obtained from aliphatic or alicyclic ketones of formula (VIII), shown below, or diketones (formula VIII, R⁴=carboxylic acyl as defined below) and heterocyclic amines of the formula (IV), with an indanone of the formula (III) in the presence of an acidic catalyst in a non-polar solvent at an elevated temperature between ambient temperature and the boiling point of the solution under the pressure applied, preferably under reflux. The reaction proceeds as follows:



and is illustrated by Examples 15 to 17.

In formulae VII and VIII R² is an alkyl group, generally one with up to 4 carbon atoms, and R⁴ is an alkyl or cycloalkyl group, or preferably an aromatic hydrocarbon group, or an aliphatic, cycloaliphatic or aromatic monocarboxylic acyl group. The expressions "aromatic hydrocarbon group" and "aromatic monocarboxylic acyl group" are used for at most dinuclear groups and include alkyl substituted aromatic groups such as those in

piperazine distilled at 188 to 193°C and 13 mm Hg. The di-hydrochloride, which melted with decomposition at 267 to 269°C was prepared from N - indanyl - 2 - piperazine and hydrochloric acid in conventional manner.

EXAMPLE 3

7.5 g of N - methyl - N' - indenyl - 2 - piperazine (m.p. 154 to 155°C, obtained by condensation of indanone-2 with N - methyl-piperazine) were dispersed homogeneously in 200 ml of isopropanol and hydrogenated in the presence of 0.5 g of an activated charcoal-palladium catalyst (Pd-content=10% by wt.) for 18 hours at ambient temperatures and atmospheric pressure. The catalyst was filtered off and the bulk of the alcohol removed by distillation. Ethereal hydrogen chloride was added to the remaining portion and the N-methyl - N' - indanyl - 2 - piperazine - di-hydrochloride, which precipitated, was filtered off with suction. The compound was recrystallized from isopropanol and had a melting point of 266 to 268° (with decomposition).

EXAMPLE 4

7.6 g of 2 - (4' - methylpiperidino) - indene (m.p. 125 to 126°C, obtained by condensation of indanone-2 with γ -pipercoline) were hydrogenated in 500 ml of isopropanol over 6 hours using 1 g of an activated charcoal-palladium catalyst (Pd-content=10%, by wt.) at 60°C and 60 atmospheres pressure. Catalyst was filtered off and ethereal hydrogen chloride was added to the filtrate to precipitate the hydrochloride of 2 - (4' - methylpiperidino) - indane. After recrystallization from isopropanol the acid addition compound melted at 259 to 260°C (with decomposition). The 2 - (4' - methylpiperidino) - indane melted at 64 to 65°C.

EXAMPLE 5

8.4 g of 2 - (3' - methylpiperidino) - indene (m.p. 81 to 83°C, obtained by condensation of indanone-2 with β -pipercoline) were dissolved in 500 ml of isopropanol and hydrogenated over 6 hours using 1 g. of an activated charcoal-palladium catalyst (Pd-content=10%, by wt.) at 90°C and 80 atmospheres pressure. The catalyst was filtered off and isopropanol removed by distillation. The residue was dissolved in ether and the solution extracted with 2N hydrochloric acid. To purify the product the hydrochloric acid solution was made strongly alkaline by the addition of a 50% by wt. potassium hydroxide solution and the base obtained was extracted with ether. By addition of ethereal hydrogen chloride the hydrochloride of 2 - (3' - methylpiperidino) - indane was precipitated. After recrystallization from isopropanol the product melted at 240—242°C (with decomposition).

EXAMPLE 6

8 g of 2 - hexamethylenecimino - indene (m.p. 106.5 to 107.5°C (with decomposition)) obtained by condensing indanone-2 with hexamethylenecimino and recrystallizing the product from isopropanol) were hydrogenated in 500 ml of isopropanol with 1 g of an activated charcoal-palladium catalyst (Pd-content=10% by wt.) at 60°C and 70 atmospheres pressure for 6 hours. Catalyst was filtered off and 350 ml of isopropanol were removed by distillation. The residue was treated with ethereal hydrogen chloride and the precipitated hydrochloride of hexamethylenecimino-indane was filtered off with suction and recrystallized from isopropanol with addition of activated charcoal. The product obtained was shown to be uniform by thin-layer-chromatography and melted at 232°C (with decomposition).

EXAMPLE 7

9 g of 2 - pyrrolidino - indene were dissolved in 500 ml of isopropanol and hydrogenated with 5 g of Raney-nickel as catalyst at 85 atmospheres pressure and 70°C for 6½ hours. The catalyst was filtered off and the filtrate mixed with the theoretical amount of ethereal hydrogen chloride and highly concentrated. The precipitated compound was filtered off by suction and dried. After recrystallization from isopropanol the 2-pyrrolidino-indane hydrochloride melted at 191 to 193°C.

EXAMPLE 8

7.9 g of 2 - amino - γ -indane, 4.6 g of pentamethylenedibromide and 0.1 g of pulverized potassium iodide were stirred in 25 ml of dry benzene for 2 hours at ambient temperature, advantageously in an atmosphere of nitrogen. The reaction mixture was then refluxed for 12 hours, using a water bath, and after cooling was mixed with 100 ml of dry ether. The hydrobromide of 2-amino-indane was filtered off. From the filtrate, the hydrochloride of 2 - piperidino - indane was precipitated by the addition of ethereal hydrogen chloride. After recrystallization from isopropanol the product which was shown to be uniform by thin - layer - chromatography, melted at 252 to 253°C (with decomposition). The free base melted at 66 to 68°C. The same compound could also be prepared from 2 - piperidino - indene according to the method of Example 4.

EXAMPLE 9

11.5 g of 5,6 - dimethoxy - 2 - amino-indane, 4.6 g of pentamethylenedibromide and 0.1 g of pulverized potassium iodide were stirred in 110 ml of dried benzene for 2 hours in an atmosphere of nitrogen and refluxed with stirring for 20 hours. The benzene was distilled off and the residue suspended

in ether and filtered by suction. The ethereal solution thus obtained was extracted four times with 2N hydrochloric acid, the extract made alkaline with a 30% by wt. sodium hydroxide solution and the free base was extracted with ether. The 2 - piperidino - 5,6-dimethoxyindane was purified by chromatography on a silica gel column. The hydrochloride of this compound was prepared by reaction with ethereal hydrogen chloride. Melting point 242 to 243°C (with decomposition).

EXAMPLE 10

4.8 g of 2 - amino - indane, 2.9 g of hexamethylenedibromide and 0.1 g of pulverized potassium iodide were stirred in 25 ml of dried benzene for 2 hours under nitrogen, then refluxed for 15 hours. The bulk of the benzene was distilled off and the residue treated with dry ether. The residue was filtered and ethereal hydrogen chloride was added to the filtrate. The 2 - hexamethylenecimino - indane hydrochloride was purified by dissolving in water, filtering and rendering the filtrate alkaline with a 50% by wt. potassium hydroxide solution. The free base was taken up in ether and precipitated with ethereal hydrogen chloride. The compound was identical with that prepared according to Example 6.

EXAMPLE 11

9.5 g of 2 - amino - 5 - methoxyindane were dissolved in 80 ml of dried benzene and 0.1 g of pulverized potassium iodide were added. Under an atmosphere of nitrogen a solution of 4.6 g of pentamethylenedibromide in 30 ml of anhydrous benzene was added dropwise to the stirred mixture, which was then refluxed for 20 hours. The bulk of the benzene was distilled off and the residue treated with dried ether. Unreacted 2 - amino-5 - methoxyindane hydrobromide which precipitated was filtered off with suction and the 2 - piperidino - 5 - methoxy - indane contained in the filtrate was purified by chromatography on a silica gel column. By reaction with ethereal hydrochloric acid the hydrochloride of 2 - piperidino - 5 - methoxyindane was prepared. The compound was recrystallized from isopropanol and melted at 198 to 199°C.

EXAMPLE 12

1.5 g of 2 - piperidino - 5,6 - dimethoxyindane hydrochloride were dissolved in 60 ml of glacial acetic acid. 1.7 g of bromine in 8 ml of glacial acetic acid were added dropwise to the vigorously stirred solution. The mixture was stirred for a further 3 hours, then kept in a cold place overnight. The precipitated crystals were filtered off with suction, dried, then suspended in water. The mixture was rendered alkaline by the addition

of 30% by wt. sodium hydroxide solution and extracted with ether. The ethereal solution was dried, and the hydrochloride of 2 - piperidino - 4 - bromo - 5,6 - dimethoxyindane was precipitated with ethereal hydrochloric acid. After recrystallization from isopropanol with addition of activated charcoal the compound melted at 230—231°C (with decomposition).

EXAMPLE 13

25 ml of hydriodic acid (density 1.7 g/cc.) were poured over 2.25 g of 2 - piperidino-5,6 - dimethoxyindane hydrochloride and the mixture heated in a stream of nitrogen for 1 hour at 140—170°C on an oil bath. Methyl iodide distilled off and, after cooling crystals which precipitated were filtered off with suction and boiled with concentrated hydrochloric acid to remove iodine. The 2 - piperidino - 5,6 - dihydroxyindane hydrochloride could be recrystallized from concentrated hydrochloric acid. The substance melted at 276—279°C (with decomposition). With ferric chloride the compound gave a green colour which quickly became yellow.

EXAMPLE 14

50 ml of hydriodic acid (density 1.7 g/cc) were poured over 1.5 g of 2 - piperidino-5 - methoxyindane hydrochloride and the mixture heated in a stream of nitrogen for 30 minutes at 140 to 160°C. After cooling, the precipitated crystals were filtered off by suction and boiled with concentrated hydrochloric acid. The 2 - piperidino - 5 - hydroxyindane hydrochloride was recrystallized from water in the presence of activated charcoal and melted at 210 to 213°C (with decomposition).

EXAMPLE 15

(A) A mixture of 7.5 g of 1 - (4' - methylpiperazino) - cyclohexene, 5.5 g of indanone-2, 50 ml of petroleum ether, and 5 drops of glacial acetic acid was refluxed for 2 hours. After cooling the reaction product was filtered off with suction and washed with petroleum ether. The yield was 8 g of 2 - (4' - methylpiperazino) - indene melting at 155 to 157°C (90% of theory).

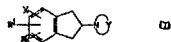
(B) A mixture of 8 g of 2 - (4' - methylpiperazino) - indene, 300 ml of isopropanol and 6 g of Raney-nickel, suspended in methanol, was hydrogenated in an autoclave, equipped with a stirrer, under a pressure of 60 atmospheres at 80°C for 6 hours. After filtering off the catalyst with suction and neutralizing with dilute hydrochloric acid, the reaction mixture was evaporated to dryness *in vacuo* and the residue was recrystallized from isopropanol. 10 g of 2 - (4' - methylpiperazino) - indane dihydrochloride, which melted at 266—268°C, were obtained, corresponding to 92% of the theoretical amount.

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counter. The number of counts within 2 hours was related to the values of the control group, tested at the same time.

WHAT WE CLAIM IS:—

- 5 1. Compounds of the formula:



(where R¹ and R² which may be the same or different are hydrogen atoms, alkoxy groups with up to 3 carbon atoms or hydroxyl groups, X is a hydrogen or halogen atom and Y is a straight chain or branched alkylene group having from 4 to 7 carbon atoms) and their physiologically compatible inorganic or organic acid addition salts.

- 15 2. Compounds as claimed in claim 1 wherein a methylene group or an alkylidene group in the group Y is replaced by an oxygen atom, an imino group or an alkyl-substituted imino group having up to 3 carbon atoms in the alkyl substituent.

- 20 3. Compounds as claimed in claim 2 wherein said alkyl substituent is a methyl group.

- 25 4. Compounds as claimed in any of the preceding claims wherein R¹ and R² are methoxy groups.

5. Compounds as claimed in any of the preceding claims wherein X is a chlorine or bromine atom.

- 30 6. 2 - Morpholino - indane.
7. N - Indanyl - 2 - piperazine.
8. N - Methyl - N' - indanyl - 2 - piperazine.

- 35 9. 2 - (4' - Methylpiperidino) - indane.
10. 2 - (3' - Methylpiperidino) - indane.
11. 2 - Hexamethylenecumino - indane.
12. 2 - Pyrrolidino - indane.
13. 2 - Piperidino - indane.

- 40 14. 2 - Piperidino - 5,6 - dimethoxy-indane.

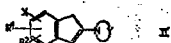
15. 2 - Piperidino - 5 - methoxyindane.
16. 2 - Piperidino - 4 - bromo - 5,6-dimethoxyindane.

- 45 17. 2 - Piperidino - 5,6 - dihydroxy-indane.

18. 2 - Piperidino - 5 - hydroxyindane.
19. 2 - (4' - Methylpiperazine) - indane.

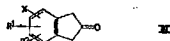
20. Compounds as claimed in any of the preceding claims in the form of their hydrobromic, hydrochloric sulphuric phosphoric, acetic, propionic, malonic, maleic, succinic, adipic, lactic, malic, tartaric, citric or gluconic acid addition salts.

- 50 21. A process for the preparation of compounds as claimed in any of claims 1—19 wherein an indene-amine of the formula



(where R¹, R², X and Y have the meanings assigned in claim 1) is hydrogenated in solution.

22. A process as claimed in claim 21 wherein said indene-amine is prepared by reacting an indanone of the formula



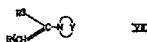
(where R¹, R² and X have the meanings assigned in claim 1) with a heterocyclic base of the formula



(where Y has the meaning assigned in claim 1).

23. A process as claimed in either claim 21 or claim 22 wherein the hydrogenation is carried out in solution in a lower aliphatic alcohol.

24. A process as claimed in claim 21 wherein said indene-amine is prepared by reacting an enamine of the formula



where Y has the meaning assigned in claim 1, R³ is an alkyl group and R⁴ is an alkyl, cycloalkyl or aromatic hydrocarbon (as defined herein) group or an aliphatic, cycloaliphatic or aromatic monocarboxylic acyl (as defined herein) group, or R³ and R⁴ together form part of an alicyclic ring) with an indanone of the formula III in a nonpolar solvent in the presence of an acidic catalyst at a temperature elevated to between ambient temperature and the boiling point of the solution under the pressure applied.

25. A process as claimed in claim 24, wherein R³ has up to four carbon atoms and R⁴ is an alkyl or cycloalkyl group with up to 6 carbon atoms, an aromatic hydrocarbon group, an aliphatic or cycloaliphatic monocarboxylic acyl group with up to 6 carbon atoms, an aromatic monocarboxylic acyl group, any alkyl substituents in the aromatic groups containing together up to 4 carbon atoms or R³ and R⁴ are linked to form part of an aliphatic ring with 5 or 6 C-atoms.

26. A process as claimed in any of claims 21 to 25 wherein the hydrogenation is carried out at a pressure of from atmospheric pressure to 120 atmospheres and at temperatures of from ambient temperature to the boiling point of the solution under the pressure used.

27. A process as claimed in any of claims 21 to 26, wherein the hydrogenation is carried out in the presence of a noble metal of group VIII of the periodic table of elements

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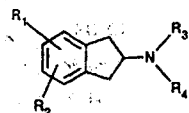
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification: C07C 211/42, 233/43, C07D 207/32, A61K 31/135, 31/165, 31/40, 31/435, C07C 309/66, A61K 31/18, C07C 309/73, 229/50, 217/74, 237/48, 311/08, 311/21, C07D 295/08, C07C 225/20, 223/04		(11) International Publication Number: WO 95/04713
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(30) Priority Data: 08/103,270 6 August 1993 (06.08.93) US		
(60) Parent Application or Grant (63) Related by Continuation US 08/103,270 (CON) Filed on 6 August 1993 (06.08.93)		(74) Agent: CORNEGLIO, Donald, L.; Corporate Intellectual Property Law, The Upjohn Company, 301 Henrietta Street, Kalamazoo, MI 49001 (US).
(71) Applicant (for all designated States except US): THE UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US).		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD).
(72) Inventors; and (75) Inventors/Applicants (for US only): HAADSMAN- SVENSSON, Susanne, R. [US/US]; 4318 Squire Heath Lane, Portage, MI 49002 (US). ANDERSSON, Bengt, R. [SE/SE]; Lungmansgatan 31E/5, S-413 11 Goteborg (SE). SONESSON, Clas, A. [SE/SE]; Sveagatan 16, S-413 14		Published With international search report.
(54) Title: 2-AMINOINDANS AS SELECTIVE DOPAMINE D3 LIGANDS		
(57) Abstract		
Compounds and their pharmaceutically acceptable salts suitable for treating central nervous system disorders associated with the dopamine D3 receptor activity of formula (I), wherein R₁ and R₂ are independently chosen from hydrogen, C₁-C₈ alkyl, OCH₃, OH, OSO₂CF₃, OSO₂CH₃, SOR₅, CO₂R₅, CONH₂, CONR₅R₆, COR₅, CF₃, CN, SR₅, SO₂NH₂, SO₂NR₅R₆, SO₂R₅, -OCO-C₁-C₆ alkyl, -NCO-C₁-C₆ alkyl, -CH₂O-C₁-C₆ alkyl, -CH₂OH, -CO-Aryl, -NHSO₂-Aryl, -NHSO₂-C₁-C₆ alkyl, phthalimide, thiophenyl, pyrrol, pyrrolinyl, oxazol, halogen (Br, Cl, F, I), R₆ or R₁ and R₂ together form -O(CH₂)_mO- (where m is 1-2) or -CH₂(CH₂)_pCH₂- (where p is 1-4); (except that only one of R₁ and R₂ can be hydrogen, OCH₃ or OH in any such compound); R₃ and R₄ are independently chosen from C₂-C₄ alkenyl, C₃-C₈ alkynyl, C₃-C₈ cycloalkyl, -(CH₂)_p-thienyl (where p is 1-4), hydrogen (except that only one of R₃ and R₄ can be hydrogen in any such compound) or C₁-C₈ alkyl (except where R₁ or R₂ are hydrogen, OCH₃ or OH); R₅ is hydrogen, C₁-C₈ alkyl, C₂-C₄ alkenyl, C₃-C₈ cycloalkyl; and R₆ is C₁-C₈ alkyl, C₂-C₄ alkenyl, C₂-C₈ alkynyl, C₃-C₈ cycloalkyl, or Aryl.		



(I)

Ma, S. et al., J. Pharmacol. Exp. Ther., 256, 751 (1991) describes dopaminergic structure activity relationships of 2-aminoindans with mainly di-substitution in the 4,5 positions.

Nichols, D.E. et al., J. Med. Chem., 33, 703 (1990) describes nonneurotoxic tetralin and indan analogues of 3,4 (methylenedioxy)amphetamine.

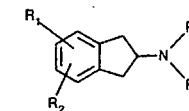
5 PCT Patent Publication No. WO90/07490 describes 2-aminotetralins and 2-aminoindans with aromatic substitution with an OCH₃ or OH in conjunction with a Br group.

European Patent 88302599.1 filed March 24, 1988 discloses antiarrhythmic aminoindanes having a bicyclic structure and methyl group on the amine not disclosed in the subject invention.

10 US 4,132,737 discloses trifluoromethyl substituted 1-aminoindanes whereas the subject invention is 2-aminoindanes.

SUMMARY OF THE INVENTION

In one aspect the subject invention is directed toward compounds and pharmaceutically acceptable salts of Formula I:



15 20 wherein R₁ and R₂ are independently chosen from hydrogen, C₁-C₈ alkyl, OCH₃, OH, OSO₂CF₃, OSO₂CH₃, SOR₅, CO₂R₅, CONH₂, CONR₅R₆, COR₅, CF₃, CN, SR₅, SO₂NH₂, SO₂NR₅R₆, SO₂R₅, -OCO-C₁-C₆ alkyl, -NCO-C₁-C₆ alkyl, -CH₂O-C₁-C₆ alkyl, -CH₂OH, -CO-Aryl, -NHSO₂-Aryl, -NHSO₂-C₁-C₆ alkyl, phthalimide, thiophenyl, pyrrol, pyrrolinyl, oxazol, halogen (Br, Cl, F, I), R₆ or R₁ and R₂ together form -O(CH₂)_mO- (where m is 1-2) or -CH₂(CH₂)_pCH₂- (where p is 1-4); (except that only one of R₁ and R₂ can be hydrogen, OCH₃ or OH in any such compound);

25 30 R₃ and R₄ are independently chosen from C₂-C₄ alkenyl, C₃-C₈ alkynyl, C₃-C₈ cycloalkyl, -(CH₂)_p-thienyl (where p is 1-4), hydrogen (except that only one of R₃ and R₄ can be hydrogen in any such compound) or C₁-C₈ alkyl (except where R₁ or R₂ are hydrogen, OCH₃ or OH);

R₅ is hydrogen, C₁-C₈ alkyl, C₂-C₄ alkenyl, C₃-C₈ cycloalkyl; and

R₆ is C₁-C₈ alkyl, C₂-C₄ alkenyl, C₂-C₈ alkynyl, C₃-C₈ cycloalkyl, or Aryl.

In another aspect the subject invention is directed toward compounds and
35 pharmaceutically acceptable salts of Formula I, above,
wherein R₁ and R₂ are independently chosen from hydrogen, OCH₃, OH, OSO₂CF₃,

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
FERRERO EMILIO
Apoderado(a) y/o Representante de
W.R. GRACE & CO. -CONN.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-056337- -00001-0000

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	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	

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Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486. Cuando se trate de documentos otorgados en el extranjero, deben legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.


CLARA C. DE JAIMES
Jefe de la división de Nuevas Creaciones (E)

El anterior requerimiento fue notificado por fijación en lista de fecha 6 JUL. 2007
adpa11