

Señor

SUPERINTENDENTE DELEGADO PARA LA PROPIEDAD INDUSTRIAL
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Ref: P1.-GRUNENTHAL GmbH.-Expediente No. 00-024.764.-

1. Me refiero al asunto de la referencia.
2. Por medio del presente, atentamente me permito manifestar que hubo un **cambio** de apoderado para todos los asuntos de la Propiedad Industrial en Bogotá de la sociedad **GRUNENTHAL GmbH**.
3. En consecuencia, atentamente solicito a ese Despacho reconocirme personería en este asunto, de conformidad con la sustitución de poder adjunta, otorgada a favor de la SUSCRITA.
4. Por lo tanto, ruego a usted notificarme de las providencias expedidas dentro de este expediente y notificadas al anterior apoderado, que actualmente se encuentran pendientes de cumplimiento o de respuesta.
5. Solicito a ese Despacho proceder de conformidad.

Atentamente,


ALICIA LLOREDA RICAURTE

T.P. 53215

Código 231

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Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. _____ S. _____ D. _____

Ref: P1.-GRUNENTHAL GmbH .-Expediente No.00-024.764.-

Yo, **JOSE ANTONIO LLOREDA**, mayor de edad y vecino de esta ciudad, abogado titulado e inscrito, identificado como aparece al pie de mi firma, actuando en mi carácter de Representante Legal en Bogotá para asuntos relacionados con la propiedad industrial de **GRUNENTHAL GmbH**, sociedad organizada y existente de conformidad con las leyes de Alemania, domiciliada en Aachen, Alemania, tal y como consta en este expediente, atentamente manifiesto a usted que **SUSTITUYO** el poder a mi conferido a la doctora **ALICIA LLOREDA RICAURTE**, abogada titulada e inscrita, identificada con la cédula de ciudadanía No. 39.690.713 de Usaquén, para que continúe representando a la mencionada sociedad en el expediente de la referencia.

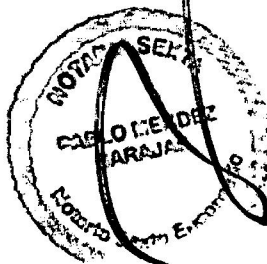
De conformidad con el artículo 66 del C.P.C., manifiesto bajo la gravedad de juramento que los demás apoderados citados en el documento otorgado a mi favor no desean ejercer el poder a ellos conferido.

El mencionado apoderado tendrá las mismas facultades a mi conferidas, en especial, renunciar, recibir, sustituir, desistir, presentar recursos, conciliar, transigir, y en fin, para todo lo que se encamine a la correcta defensa de los intereses de la sociedad en cuyo nombre hablo.

Atentamente,
25 AGO 2004
JOSE ANTONIO LLOREDA
T.P. 10784
Código 231

quien (as) exhibió(eron) la(s)
y declaró(aron) que es(son) la(s) original(es) y
que el (los) original(es) se encuentran en el poder
En constancia de lo anterior se firmó y se selló

JOSE ANTONIO LLOREDA
C.C. No. 17.159.681 de Bogotá



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165
2005-03-10
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**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

2020
Bogotá, D.C.,

Doctora
ALICIA LLOREDA RICAURTE
(Apoderado)

ASUNTO	Radicación	24764
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	12327
	Folios	013

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:

Documentos estudiados:

Los textos estudiados fueron la descripción (Folios: 5 a 8, 124 a 126, 12, 127 a 131, 18 a 20, 132, 22, 133, 24, 134 a 136, 28, 137 a 147) y las reivindicaciones 1 a 31 (Folios: 148 a 156).

La presente solicitud reivindica prioridad alemana N° DE19915602.6 de 07 de abril de 1999 y cumple con lo establecido en los artículos 9, 10 y 11 de la Decisión 486 de la Comisión de la Comunidad Andina.

Objeto de invención:

La presente solicitud se titula: "Derivados de 3-amino-3-arylpropano-1-ol, su preparación y uso".

El objeto de la presente solicitud se refiere a derivados de 3-amino-3-arylpropano-1-ol de la fórmula I (ver folio: 6).

Según la descripción, el tratamiento de estados algésicos crónicos o no crónicos tiene gran importancia en medicina porque el dolor es uno de los síntomas básicos en clínica. Actualmente existe universalmente la necesidad de una terapéutica antálgica adicional no exclusivamente opioide pero de buena eficacia. La necesidad urgente de un tratamiento de estados algésicos crónicos y no crónicos orientada al paciente y a determinada finalidad, entendiéndose bajo esto un tratamiento antálgico exitoso y satisfactorio para el paciente, está documentado en la gran cantidad de trabajos científicos que han aparecido últimamente en el campo de la analgesia aplicada o de la investigación fundamental de la nocicepción.

De acuerdo con la presente solicitud, la finalidad de ésta consiste en hallar una nueva clase estructural de sustancias de efecto analgésico adecuadas para la

terapéutica antálgica. Otra finalidad consiste en hallar sustancias que son adecuadas también para la utilización como anestésico local, y/o antiarrítmico, y/o antiemético, y/o nootrópico (neurotrópico), y/o para el tratamiento o terapéutica de enfermedades cardiovasculares, y/o incontinencia urinaria, y/o diarrea, y/o prurito, y/o dependencia de alcohol o drogas, y/o dependencia de fármacos, y/o inflamaciones.

Lo que se reivindica como novedoso es lo siguiente:

Derivados de 3-amino-3-arylpropan-1-ol de la fórmula general I (ver folio: 148) o sus diastereoisómeros o enantiómeros en forma de sus bases o sales con ácidos fisiológicamente tolerables.

El objeto de la solicitud definido anteriormente se clasificó en la IPC A61K 31/13, 31/75.

Determinación del estado de la técnica:

El artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "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.

Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40".

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 07/04/1999, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta.

Se hizo la búsqueda de documentos relevantes en el estado de la técnica, entendiendo como estado de la técnica la definición provista en el artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina y las excepciones fijadas en el artículo 17 de la misma.

Se encontró como anterioridades (documentos cuya fecha de publicación es anterior a la fecha de presentación de la primera solicitud de patente sobre la cual se reivindica prioridad o de la fecha de presentación de esta solicitud) que pueden afectar la patentabilidad del objeto de la presente solicitud:

Nº	Documento	Título	Fecha de Publicación
1	US 3937818	Benzylamine narcotic antagonists	10 de febrero de 1976
2	US 3975436	Benzylamine narcotic antagonists	17 de agosto de 1976

Evaluación de los requisitos de Patentabilidad:

El Artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina el cual establece: "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".

Se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación de Novedad:

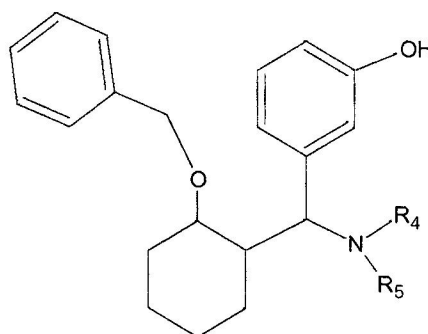
El artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "Una invención se considerará nueva cuando no está comprendida en el estado de la técnica". "El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.

Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40".

Esta se evaluó por comparación entre lo solicitado y los documentos encontrados en el estado de la técnica y que se relacionan con el objeto reivindicado y de acuerdo con la definición de novedad del Artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina.

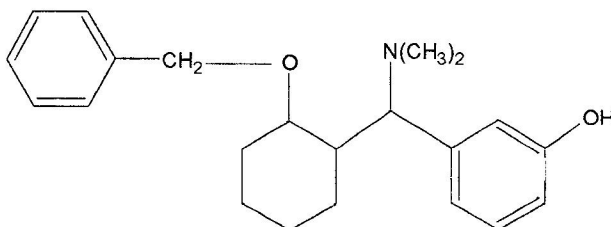
Comparando elemento por elemento el objeto de esta solicitud con lo mencionado en las anterioridades, tenemos que:

La Solicitud de Patente Colombiana No. 00024764 menciona derivados de 3-amino-3-arilpropan-1-ol de la fórmula general I:

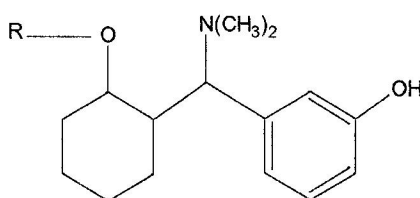


- R_4 y R_5 representan independientemente entre sí, C1-6-alquilo, C3-6 cicloalquilo, fenilo, bencilo, fenetilo, entre otros.

El documento **US 3937818** (folios: 170 a 173) menciona un compuesto de fórmula:



El documento **US 3975436** (folios: 174 a 177) menciona un compuesto de fórmula:



Donde R es etilo o bencilo.

Comparando las estructuras de los compuestos de las anterioridades encontradas con la estructura de compuestos de la presente solicitud, se encuentra que éstos últimos pueden ser idénticos a los de dichas anterioridades. Lo anterior puede evidenciarse cuando R_1 y R_2 en la presente solicitud, en conjunto, forman un ciclo de seis carbonos y tener como sustituyente un fenilo; cuando R_4 y R_5 cada uno es un metilo y cuando A representa un radical carbocíclico, que como puede verse en los ejemplos, puede ser insaturado, y estar sustituido por OH. Al hacer estos reemplazos se obtienen compuestos que se encuentran contemplados en las anterioridades citadas.

Como se observa, el objeto de esta solicitud puede ser idéntico a lo comprendido en el estado de la técnica, con lo cual se considera que podría no cumplir con el requisito de Novedad.

Evaluación de Nivel Inventivo:

El artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "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".

El Nivel Inventivo se evaluó por comparación entre lo solicitado y encontrado en el estado de la técnica y que se relaciona con el objeto reivindicado y de acuerdo con la definición de nivel inventivo del Artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina.

Las anterioridades encontradas mencionan compuestos que tienen actividad analgésica tal como los compuestos de la presente solicitud, y también están resolviendo el problema encontrado con el empleo de morfina. Así que la respuesta al problema técnico que se pretendía resolver, resulta obvia partiendo de las anterioridades citadas.

Como se observa, el objeto de esta solicitud podría resultar obvio para una persona del oficio normalmente versada en la materia y derivarse de manera evidente del estado de la técnica.

Evaluación de la Aplicación Industrial:

El artículo 19 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "Se considerará que una invención es susceptible de aplicación industrial, cuando su objeto pueda ser producido o utilizado en cualquier tipo de industria, entendiéndose por industria la referida a cualquier actividad productiva, incluidos los servicios".

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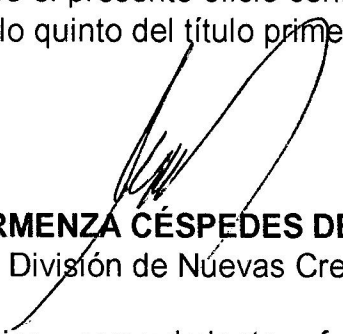
El objeto de la presente solicitud cumple con el requisito de Aplicación Industrial.

En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
1	US 3937818	1 a 31	Novedad y Nivel Inventivo
2	US 3975436	1 a 31	Novedad y Nivel Inventivo

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 la 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 numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL

Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 10 MAR. 2005

CONCEPTO TÉCNICO Nº: 309	EXAMINADOR TÉCNICO Código N°: 202005	EXAMINADOR JURÍDICO Código N°:
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United States Patent [19]

Fletcher et al.

[11] 3,937,818

[45] Feb. 10, 1976

[54] BENZYLAMINE NARCOTIC ANTAGONISTS

[75] Inventors: Horace Fletcher, Pottstown; Jerry L. Malis, Bluebell; John P. Yardley, King of Prussia, all of Pa.

[73] Assignee: American Home Products Corporation, New York, N.Y.

[22] Filed: Mar. 27, 1974

[21] Appl. No.: 455,172

[52] U.S. Cl. 424/330; 260/570.5 CA; 424/260

[51] Int. Cl.² A61K 31/135

[58] Field of Search 424/330; 260/570.5 CA

[56] References Cited

UNITED STATES PATENTS

2,767,185 10/1956 Baltzly et al. 260/570.5

3,222,399 12/1965 Faust et al. 260/570.5 CA
3,397,272 8/1968 Doebl et al. 424/330
3,448,200 6/1969 Stoll et al. 424/330

Primary Examiner—Norman A. Drezin
Attorney, Agent, or Firm—Robert Wiser

[57]

ABSTRACT

A process for antagonizing the pharmacologic effects of a narcotic agent in warm-blooded animals, and compositions for effecting this process are disclosed.

8 Claims, No Drawings

BENZYLAMINE NARCOTIC ANTAGONISTS

BACKGROUND OF THE INVENTION

The problems associated with narcotic abuse and addiction and of the seemingly ubiquitous narcotics addict are very well known in today's society. Also well-known are the problems associated with curing an addict of his drug dependence. Because very often there is a psychological as well as a physiological dependence, the addict, once he has been withdrawn (cured) from his physiological drug dependence, will often return to narcotic usage for other, possibly psychological, reasons. Thus a long term treatment and rehabilitation program for the narcotics addict has been suggested as being necessary (p. 259, A. Goth, Medical Pharmacology, 2nd ed., C. V. Mosby, 1964). In addition, this long term program should allow the addict to otherwise function normally (i.e., attend school, maintain a job) during the ameliorative process. The drug, methadone, is today being utilized to aid in such long term treatment and rehabilitation programs.

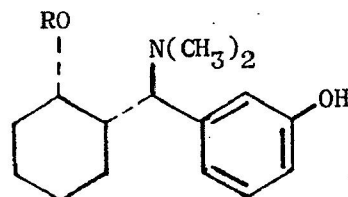
A major problem associated with long term methadone therapy is the fact that the drug itself is an addicting narcotic with euphoriant properties; thus one is not curing addiction but merely making it less objectionable.

It is well-known (see for example, pp. 274-278, The Pharmacological Basis of Therapeutics, L. S. Goodman, and A. Gillman, Third ed., 1966, MacMillan), that certain agents (called narcotic antagonists) are able to prevent or abolish some or all of the clinical effects of a dose of morphine or heroin in man and animals. Thus, for example, nalorphine prevents or abolishes, in appropriate species, narcotic induced euphoria, analgesia, drowsiness, respiratory depression and other well-known effects and side effects associated with narcotic usage. Several narcotic antagonists are in use clinically, for example, to treat narcotic-induced respiratory depression. It is also known that in patients who are physically dependent on narcotic usage small doses of a narcotic antagonist, such as nalorphine, will precipitate acute withdrawal symptoms qualitatively identical to those seen after abrupt withdrawal of the narcotic agent. Thus, administration of the antagonist may be used as a simple, albeit unpleasant, method to test for physical dependence of the suspected narcotics addict.

Many reports in the recent literature (see for example, Agonist and Antagonist Actions of Narcotic Analgesic Drugs, H. W. Kosterlitz, H. O. J. Collier, and J. E. Villarreal, editors, MacMillan, 1972, and references cited therein) propose the prophylactic use of a narcotic antagonist as an alternate medicinal approach to methadone therapy for the long term treatment and amelioration of narcotics addicts. Thus, it has been observed (M. Fink, A. M. Freedman, R. Resnick and A. Zaks in Agonist and Antagonist Actions of Narcotic Analgesic Drugs, H. W. Kosterlitz, H. O. J. Collier, and J. E. Villarreal, editors, MacMillan, 1972) that when most previously detoxified narcotics addicts, who are receiving prophylactic therapy with a narcotic antagonist, are challenged with a narcotic agent they do not experience any of the expected clinical effects of the narcotic and their use of narcotic agents, in most cases, is eventually reduced.

SUMMARY OF THE INVENTION

The invention sought to be patented in its process aspect resides in the concept of a process for antagonizing the effect of a narcotic agent in warm-blooded animals which comprises administering to a warm-blooded animal in need thereof a sufficient amount of a compound of the formula:



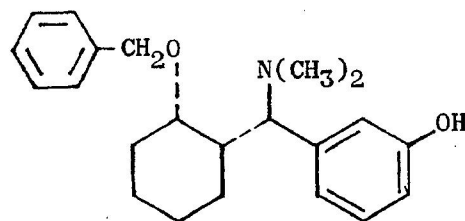
wherein R is ethyl or benzyl; and the pharmacologically acceptable acid addition salts thereof.

The invention sought to be patented in its first subgeneric process aspect resides in the concept of the process for antagonizing the effect of a narcotic agent in warm-blooded animals which comprises administering to a warm-blooded animal in need thereof a sufficient amount of the compound α -dimethylamino- α -(cis-2-ethoxy-cyclohexyl)-m-cresol.

The invention sought to be patented in its second subgeneric process aspect resides in the concept of the process for antagonizing the effect of a narcotic agent in warm-blooded animals which comprises administering to a warm-blooded animal in need thereof a sufficient amount of the compound α -dimethylamino- α -(cis-2-benzyloxycyclohexyl)-m-cresol.

The invention sought to be patented in its third subgeneric process aspect resides in the concept of the process for antagonizing the effect of a narcotic agent in warm-blooded animals which comprises administering to a warm-blooded animal in need thereof a sufficient amount of the compound (1)- α -dimethylamino-2-(cis-2-benzyloxycyclohexyl)-m-cresol.

The invention sought to be patented in a principal composition aspect resides in the concept of the compound having the formula:



substantially free of the trans epimer; and the pharmacologically acceptable acid addition salts thereof.

The tangible embodiments of the principal composition aspect of the invention possess the inherent general physical properties in the free base form of being colorless to yellow oils, or solids, substantially insoluble in water, and generally soluble in organic solvents such as ether, benzene, hexane, acetone and pyridine. In the form of their acid addition salts they are generally white or off-white crystalline solids, appreciably soluble in water. Examination of the compound reveals, upon infrared, ultraviolet, and nuclear magnetic resonance spectrographic analysis, spectral data supporting the molecular structure hereinbefore set forth. The

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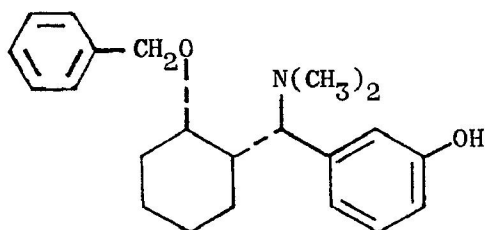
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aforementioned physical characteristics, taken together with the nature of the starting materials, the elemental analysis, and the products obtained therefrom, further confirm the molecular structure hereinbefore set forth.

The tangible embodiments of the principal composition aspect of the invention possess the inherent applied use characteristic of exerting narcotic antagonizing effects in warm-blooded animals as evidenced by pharmacological evaluation according to standard test procedures. In addition, the dose needed to produce these desirable narcotic antagonizing effects has been demonstrated to elicit, at most, only minimal analgesic effects when evaluated by standard pharmacological test procedures.

The invention sought to be patented in a second composition aspect resides in the concept of a composition suitable for administration to a warm-blooded animal comprising:

(a) the compound of the formula:



and the pharmacologically acceptable acid addition salts thereof;

and (b) a pharmacologically acceptable carrier.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

A convenient starting material for preparing the compositions of the instant invention is dl-cis-2-(α -dimethylamino-m-methoxymethoxybenzyl)cyclohexanol. This material may be prepared, for example, by condensing m-methoxymethoxybenzaldehyde and cyclohexanone under basic conditions to produce m-methoxymethoxybenzalcyclohexanone, which is reacted with dimethylamine producing dl-2-(α -dimethylamino-m-methoxymethoxybenzyl)cyclohexanone. Reduction of the ketone function produces a mixture of the cis and trans, dl-amino alcohols. The separation of the cis and trans isomers as well as the resolution of their respective racemic mixtures is within the skill of the art. This synthesis of starting material, as well as the isolation of the cis isomer, and the resolution of the dl racemic mixture, is fully described in the art, for example in Belgian Pat. No. 797,827. The remainder of the synthesis of the compositions of the invention will now be described using as an example, the specific product, 1- α -dimethylamino- α -(cis-2-benzyloxycyclohexyl)-m-cresol.

The secondary alcohol function of 1-cis-2-(α -dimethylamino-m-methoxymethoxybenzyl)cyclohexanol is first metalated, for example, by treatment with n-butyl lithium in tetrahydrofuran. The resulting lithium alcoholate is next alkylated with benzyl chloride and after acid hydrolysis of the methoxymethoxyl protecting group, the product, 1- α -dimethylamino- α -(cis-2-benzyloxycyclohexyl)-m-cresol is isolated and may be purified by standard procedures, for example, column chromatography and recrystallization. It will be obvi-

ous to those skilled in the art that treatment of the lithium alcoholate of 1-cis-2-(α -dimethylamino-m-methoxymethoxybenzyl)cyclohexanol with an ethylating agent such as triethyloxonium fluoroborate will enable one to prepare 1- α -dimethylamino- α -(cis-2-ethoxycyclohexyl)-m-cresol by a process analogous to that outlined above.

It will be obvious to those skilled in the art that the 1-cis isomer of the amino alcohol will yield 1-cis products and that utilization of d-cis or dl-cis amino alcohols will likewise yield d-cis or dl-cis products, and that the utilization of these additional isomers in the above described reactions is fully equivalent to and contemplated by the teachings herein.

In practicing the process aspect of the invention, the instant compositions can be administered in a variety of dosage forms, the oral route being used primarily for maintenance therapy while injectables tend to be more useful in acute emergency situations.

The daily dose requirements vary with the particular compositions being employed, the severity of the symptoms being presented, and the animal being treated.

The dosage also varies with the size of the animal. With large animals (about 70 kg. body weight), by the oral route, the dose is from about 5 milligrams to about 100 milligrams, and preferably from about 10 to about 50 milligrams, approximately every 4 hours, or as needed. By parenteral route, the ordinarily effective dose is from about 20 milligrams to about 50 milligrams, preferably about 25 milligrams per day.

For unit dosages the active ingredient can be compounded into any of the usual oral or parenteral dosage forms including tablets, capsules and liquid preparations such as elixirs and suspensions containing various coloring, flavoring, stabilizing and flavor masking substances. For compounding oral dosage forms the active ingredient can be diluted with various tableting materials such as starches of various types, calcium carbonate, lactose, sucrose and dicalcium phosphate to simplify the tableting and capsulating process. A minor proportion of magnesium stearate is useful as a lubricant. For compounding parenteral dosage forms the active ingredient can be suspended in various isotonic media such as glucose or saline solution or the active ingredient in the form of an acid addition salt may be dissolved in an isotonic medium and injected as a solution. In all cases, of course, the proportion of the active ingredient in said composition will be sufficient to impart narcotic antagonizing activity thereto. This will range upward from about 0.0001 percent by weight of active ingredient in said composition.

As has been previously stated, the dose necessary to evoke narcotic antagonism in warm-blooded animals has been observed to produce only minimal analgesic effects when tested in the same species of animal. This broad separation of narcotic antagonizing and analgesic effects is a desirable characteristic and is an additional benefit inuring to the practice of the instant invention. Thus, for example, a withdrawn narcotics addict receiving prophylactic therapy with a narcotic antagonist as taught by the instant invention would not be expected to experience any significant analgesia, ordinarily considered an undesirable unnecessary and unwanted side effect of narcotic antagonist maintenance therapy.

Where used in this specification and claims, the terminology "antagonizing the effect of a narcotic agent" means:

Results

Compound	ED ₅₀ (Mg/kg)
(dl)- α -dimethylamino- α -(cis-2-ethoxycyclohexyl)-m-cresol	2.0
(dl)- α -dimethylamino- α -(cis-2-benzyloxycyclohexyl)-m-cresol	0.95
(l)- α -dimethylamino- α -(cis-2-benzyloxycyclohexyl)-m-cresol	0.35
Nalorphine	1.0

approximately equal quantities of a less polar product with starting material. The residue (10.5 g.) after evaporation of the ether was subjected to descending dry-column chromatography on Woelm alumina. Elution with chloroform afforded 5.0 g. of oily 1-cis-benzyloxy- α -(m-methoxymethoxyphenyl)-N,N-dimethylcyclohexane methylamine $[\alpha]_D -118.9^\circ$ (c, 0.979 methanol). NMR (CDCl₃): δ 2.12 (6H singlet N(CH₃)₂—), 3.45 (3H singlet, CH₃O—CH₂—), 5.17 (2H singlet CH₂OCH₂O—), 7.39 (5H singlet, C₆H₅CH₂O). Further elution of the column with CHCl₃:MeOH (3:1) afforded 5 g. of starting material. The 1-cis-benzyloxy- α -(m-methoxymethoxyphenyl)-N,N-dimethylcyclohexane methylamine (4.5 g.) in tetrahydrofuran (50 ml.) was treated with 5 ml. of 4.6N HCl in isopropanol at room temperature during 60 hours. After evaporation of solvent the residue was triturated with ether and recrystallized from acetone to give 1- α -dimethylamino- α -(cis-2-benzyloxycyclohexyl)-m-cresol, hydrochloride, hemiacetone solvate, m.p. 175°–176°, $[\alpha]_D -83.15$ (c, 0.989 methanol) NMR: (DMSO) δ 2.08 (3H singlet 1/2 CH₃COCH₃). Found: C, 69.41; H, 8.43; N, 3.38; Cl, 9.21. C₂₂H₃₀NO₂Cl 1/2 CH₃COCH₃ requires: C, 69.68; H, 8.21; N, 3.46; Cl, 8.75 percent. dl-series

In a similar manner there was obtained dl- α -dimethylamino- α -(cis-2-benzyloxycyclohexyl)-m-cresol, hydrochloride m.p. 257°–258°. Found: C, 70.27; H, 8.18; N, 3.45; Cl, 9.64. C₂₂H₃₀NO₂Cl requires: C, 70.29; H, 8.04; N, 3.73; Cl, 9.43 percent.

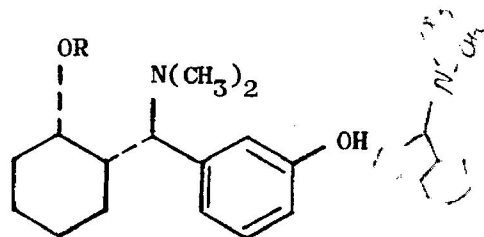
EXAMPLE 5

Antagonism of Morphine Induced Loss of Righting Reflex

Groups of three male Charles River rats (160 to 200 g.) were dosed subcutaneously with morphine base at 75 mg/kg. The degree of narcosis was measured at 15 and 30 minutes after injection. Criterion was loss of righting reflex. Antagonists were administered 40 minutes after the morphine. The degree of antagonism was measured at 20 minute intervals for 2 hours. Nalorphine at 2 mg/kg. served as a positive control while one group of morphinized rats in each determination received no antagonist and served as negative controls. Compounds were dissolved in water or suspended in Tween-80 and water and were administered intramuscularly. Each dose of the antagonist was tested in a minimum of three experiments. At least three doses of each antagonist was used to determine the ED₅₀. For each experiment the degree of reversal, by the antagonist, of the loss of righting reflex induced by morphine was calculated in the following manner. The total number of periods of loss of righting reflex in the experimental group was divided by the total number of periods of loss of righting reflex in the control group. This number was converted to percent and subtracted from 100 to give percent reversal of loss of righting reflex. The dose for which a 50 percent reversal of the loss of righting reflex was observed is the ED₅₀.

The subject matter which the applicants regard as their invention is particularly pointed out and distinctly claimed as follows:

1. A process for antagonizing the effect of a narcotic agent in warm-blooded animals which comprises administering to a warm-blooded animal in need thereof a sufficient amount of a compound of the formula:



wherein R is ethyl or benzyl; and the pharmacologically acceptable acid addition salts thereof.

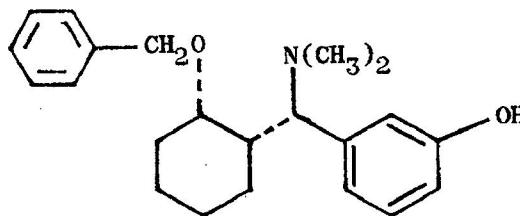
2. The process according to claim 1 wherein said compound is α -dimethylamino- α -(cis-2-ethoxycyclohexyl)-m-cresol.

3. The process according to claim 1 wherein said compound is α -dimethylamino- α -(cis-2-benzyloxycyclohexyl)-m-cresol.

4. The process according to claim 1 wherein said compound is (1)- α -dimethylamino- α -(cis-2-benzyloxycyclohexyl)-m-cresol.

5. A narcotic antagonist composition for administration to a warm-blooded animal comprising:

a. an amount, sufficient to elicit a narcotic antagonist response in a warm-blooded animal affected by a narcotic, of the compound of the formula:



and the pharmacologically acceptable acid addition salts thereof;

and b. a pharmaceutically acceptable carrier.

6. The composition according to claim 5 wherein said compound is substantially free from its d-enantiomeric isomer.

7. The composition of claim 5 in unit dose form.

8. The composition of claim 6 in unit dose form.

* * * * *

United States Patent [19]

Fletcher et al.

[11] 3,975,436

[45] Aug. 17, 1976

[54] BENZYLAMINE NARCOTIC ANTAGONISTS

[75] Inventors: Horace Fletcher, Pottstown; Jerry L. Malis, Bluebell; John P. Yardley, King of Prussia, all of Pa.

[73] Assignee: American Home Products Corporation, New York, N.Y.

[22] Filed: Oct. 30, 1975

[21] Appl. No.: 627,485

Related U.S. Application Data

[62] Division of Ser. No. 455,172, March 27, 1974, Pat. No. 3,937,818.

[52] U.S. Cl. 260/570.5 R; 260/501.17; 260/600 R; 424/316; 424/330

[51] Int. Cl.² C07C 87/28

[58] Field of Search 260/570.5 R, 570.8 R, 260/501.17

[56] References Cited

UNITED STATES PATENTS

2,133,779 10/1938 Clifford 260/570.6 X

Primary Examiner—Robert V. Hines

Attorney, Agent, or Firm—Robert Wisner

[57] ABSTRACT

A process for antagonizing the pharmacologic effects of a narcotic agent in warm-blooded animals, and compositions for effecting this process are disclosed.

2 Claims, No Drawings

BENZYLAMINE NARCOTIC ANTAGONISTS

This is a division of application Ser. No. 455,172, filed Mar. 27, 1974, now U.S. Pat. No. 3,937,818.

BACKGROUND OF THE INVENTION

The problems associated with narcotic abuse and addiction and of the seemingly ubiquitous narcotics addict are very well known in today's society. Also well-known are the problems associated with curing an addict of his drug dependence. Because very often there is a psychological as well as a physiological dependence, the addict, once he has been withdrawn (cured) from his physiological drug dependence will often return to narcotic usage for other, possibly psychological, reasons. Thus a long term treatment and rehabilitation program for the narcotics addict has been suggested as being necessary (p. 259. A. Goth. Medical Pharmacology, 2nd. ed., C. V. Mosby, 1964). In addition, this long term program should allow the addict to otherwise function normally (i.e. attend school, maintain a job) during the ameliorative process. The drug, methadone, is today being utilized to aid in such long term treatment and rehabilitation programs.

A major problem associated with long term methadone therapy is the fact that the drug itself is an addicting narcotic with euphoriant properties; thus one is not curing addiction but merely making it less objectionable.

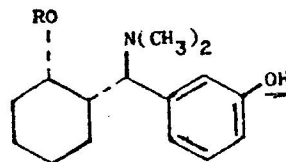
It is well-known (see for example, pp. 274-278, The Pharmacological Basis of Therapeutics, L. S. Goodman, and A. Gillman, Third ed., 1966, MacMillan), that certain agents (called narcotic antagonists) are able to prevent or abolish some or all of the clinical effects of a dose of morphine or heroin in man and animals. Thus, for example, nalorphine prevents or abolishes, in appropriate species, narcotic induced euphoria, analgesia, drowsiness, respiratory depression and other well-known effects and side effects associated with narcotic usage. Several narcotic antagonists are in use clinically, for example, to treat narcotic-induced respiratory depression. It is also known that in patients who are physically dependent on narcotic usage small doses of a narcotic antagonist, such as nalorphine, will precipitate acute withdrawal symptoms qualitatively identical to those seen after abrupt withdrawal of the narcotic agent. Thus, administration of the antagonist may be used as a simple, albeit unpleasant, method to test for physical dependence of the suspected narcotics addict.

Many reports in the recent literature (see for example, Agonist and Antagonist Actions of Narcotic Analgesic Drugs, H. W. Kosterlitz, H. O. J. Collier, and J. E. Fillarreal, editors, MacMillan, 1972, and references cited therein) propose the prophylactic use of a narcotic antagonist as an alternate medicinal approach to methadone therapy for the long term treatment and amelioration of narcotics addicts. Thus, it has been observed (M. Fink, A. M. Freedman, P. Resnick and A. Zaks in Agonist and Antagonist Actions of Narcotic Analgesic Drugs, H. W. Kosterlitz, H. O. J. Collier, and J. E. Villarreal, editors, MacMillan, 1972) that when most previously detoxified narcotics addicts, who are receiving prophylactic therapy with a narcotic antagonist, are challenged with a narcotic agent they do not experience any of the expected clinical effects of the

narcotic and their use of narcotic agents, in most cases, is eventually reduced.

SUMMARY OF THE INVENTION

The invention sought to be patented in its process aspect resides in the concept of a process for antagonizing the effect of a narcotic agent in warm-blooded animals which comprises administering to a warm-blooded animal in need thereof a sufficient amount of a compound of the formula:



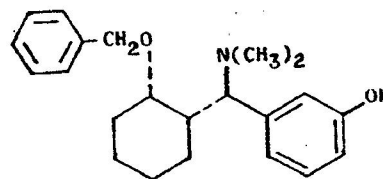
wherein R is ethyl or benzyl; and the pharmacologically acceptable acid addition salts thereof.

The invention sought to be patented in its first subgeneric process aspect resides in the concept of the process for antagonizing the effect of a narcotic agent in warm-blooded animals which comprises administering to a warm-blooded animal in need thereof a sufficient amount of the compound α -dimethylamino- α -(cis-2-ethoxy-cyclohexyl)-m-cresol.

The invention sought to be patented in its second subgeneric process aspect resides in the concept of the process for antagonizing the effect of a narcotic agent in warm-blooded animals which comprises administering to a warm-blooded animal in need thereof a sufficient amount of the compound α -dimethylamino- α -(cis-2-benzyloxycyclohexyl)-m-cresol.

The invention sought to be patented in its third subgeneric process aspect resides in the concept of the process for antagonizing the effect of a narcotic agent in warm-blooded animals which comprises administering to a warm-blooded animal in need thereof a sufficient amount of the compound (1)- α -dimethylamino-2-(cis-2-benzyloxycyclohexyl)-m-cresol.

The invention sought to be patented in a principal composition aspect resides in the concept of the compound having the formula:



substantially free of the trans epimer; and the pharmacologically acceptable acid addition salts thereof.

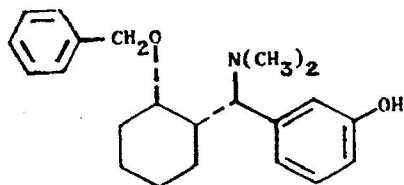
The tangible embodiments of the principal composition aspect of the invention possess the inherent general physical properties in the free base form of being colorless to yellow oils, or solids, substantially insoluble in water, and generally soluble in organic solvents such as ether, benzene, hexane, acetone and pyridine. In the form of their acid addition salts they are generally white or off-white crystalline solids, appreciably soluble in water. Examination of the compound reveals, upon infrared, ultraviolet, and nuclear magnetic resonance spectrographic analysis, spectral data supporting the molecular structure hereinbefore set forth. The

aforementioned physical characteristics, taken together with the nature of the starting materials, the elemental analysis, and the products obtained therefrom, further confirm the molecular structure hereinbefore set forth.

The tangible embodiments of the principal composition aspect of the invention possess the inherent applied use characteristic of exerting narcotic antagonizing effects in warm-blooded animals as evidenced by pharmacological evaluation according to standard test procedures. In addition, the dose needed to produce these desirable narcotic antagonizing effects has been demonstrated to elicit, at most, only minimal analgesic effects when evaluated by standard pharmacological test procedures.

The invention sought to be patented in a second composition aspect resides in the concept of a composition suitable for administration to a warm-blooded animal comprising:

a. the compound of the formula:



and the pharmacologically acceptable acid addition salts thereof;

and b. a pharmacologically acceptable carrier.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

A convenient starting material for preparing the compositions of the instant invention is dl-cis-2-(α -dimethylamino-m-methoxymethoxybenzyl)cyclohexanol. This material may be prepared, for example, by condensing m-methoxymethoxybenzaldehyde and cyclohexanone under basic conditions to produce m-methoxymethoxybenzalcyclohexanone, which is reacted with dimethylamine producing dl-2-(α -dimethylamino-m-methoxymethoxybenzyl)cyclohexanone. Reduction of the ketone function produces a mixture of the cis and trans, dl-amino alcohols. The separation of the cis and trans isomers as well as the resolution of their respective racemic mixtures is within the skill of the art. This synthesis of starting material, as well as the isolation of the cis isomer, and the resolution of the dl racemic mixture, is fully described in the art, for example in Belgian Pat. No. 797,827. The remainder of the synthesis of the compositions of the invention will now be described using as an example, the specific product, 1- α -dimethylamino- α -(cis-2-benzyloxycyclohexyl)-m-cresol.

The secondary alcohol function of 1-cis-2-(α -dimethylamino-m-methoxymethoxybenzyl)cyclohexanol is first metalated, for example, by treatment with n-butyl lithium in tetrahydrofuran. The resulting lithium alcoholate is next alkylated with benzyl chloride and after acid hydrolysis of the methoxymethoxyl protecting group, the product, 1- α -dimethylamino- α -(cis-2-benzyloxycyclohexyl)-m-cresol is isolated and may be purified by standard procedures, for example, column chromatography and recrystallization. It will be obvious to those skilled in the art that treatment of the lithium alcoholate of 1-cis-2-(α -dimethylamino-m-

methoxymethoxybenzyl) cyclohexanol with an ethylating agent such as triethyloxonium fluoroborate will enable one to prepare 1- α -dimethylamino- α -(cis-2-ethoxycyclohexyl)-m-cresol by a process analogous to that outlined above.

It will be obvious to those skilled in the art that the 1-cis isomer of the amino alcohol will yield 1-cis products and that utilization of d-cis or dl-cis amino alcohols will likewise yield d-cis or dl-cis products, and that the utilization of these additional isomers in the above described reactions is fully equivalent to and contemplated by the teachings herein.

In practicing the process aspect of the invention, the instant compositions can be administered in a variety of dosage forms, the oral route being used primarily for maintenance therapy while injectables tend to be more useful in acute emergency situations.

The daily dose requirements vary with the particular compositions being employed, the severity of the symptoms being presented, and the animal being treated.

The dosage also varies with the size of the animal. With large animals (about 70 kg. body weight), by the oral route, the dose is from about 5 milligrams to about 100 milligrams, and preferably from about 10 to 50 milligrams, approximately every 4 hours, or as needed. By parenteral route, the ordinarily effective dose is from about 20 milligrams to about 50 milligrams, preferably about 25 milligrams per day.

For unit dosages, the active ingredient can be compounded into any of the usual oral or parenteral dosage forms including tablets, capsules and liquid preparations such as elixirs and suspensions containing various coloring, flavoring, stabilizing and flavor masking substances. For compounding oral dosage forms the active ingredient can be diluted with various tableting materials such as starches of various types, calcium carbonate, lactose, sucrose and dicalcium phosphate to simplify the tableting and capsulating process. A minor proportion of magnesium stearate is useful as a lubricant. For compounding parenteral dosage forms the active ingredient can be suspended in various isotonic media such as glucose or saline solution or the active ingredient in the form of an acid addition salt may be dissolved in an isotonic medium and injected as a solution. In all cases, of course, the proportion of the active ingredient in said composition will be sufficient to impart narcotic antagonizing activity thereto. This will range upward from about 0.0001 percent by weight of active ingredient in said composition.

As has been previously stated, the dose necessary to evoke narcotic antagonism in warm-blooded animals has been observed to produce only minimal analgesic effects when tested in the same species of animal. This broad separation of narcotic antagonizing and analgesic effects is a desirable characteristic and is an additional benefit inuring to the practice of the instant invention. Thus, for example, a withdrawn narcotics addict receiving prophylactic therapy with a narcotic antagonist as taught by the instant invention would not be expected to experience any significant analgesia, ordinarily considered an undesirable unnecessary and unwanted side effect of narcotic antagonist maintenance therapy.

Where used in this specification and claims, the terminology "antagonizing the effect of a narcotic agent" means:

1. the reversal of the clinical manifestations of a narcotic overdose, such as respiratory depression; and

126
173

clohexane methylamine $[\alpha]_D -118.9^\circ$ (c, 0.979 methanol). NMR (CDCl_3): δ 2.12 (6H singlet $\text{N}(\text{CH}_3)_2$ —), 3.45 (3H singlet, $\text{CH}_3\text{O}-\text{CH}_2$ —), 5.17 (2H singlet CH_3OCH_2 —), 7.39 (5H singlet, $\text{C}_6\text{H}_5\text{CH}_2\text{O}$). Further elution of the column with $\text{CHCl}_3:\text{MeOH}$ (3:1) afforded 5 g. of starting material. The 1-cis-benzyloxy- α -(m-methoxymethoxyphenyl)-N,N-dimethylcyclohexane methylamine (4.5 g.) in tetrahydrofuran (50 ml.) was treated with 5 ml. of 4.6N HCl in isopropanol at room temperature during 60 hours. After evaporation of solvent the residue was triturated with ether and recrystallized from acetone to give 1- α -dimethylamino- α -(cis-2-benzyloxycyclohexyl)-m-cresol, hydrochloride, hemiacetone solvate, m.p. $175^\circ-176^\circ$, $[\alpha]_D -83.15^\circ$ (c, 0.989 methanol) NMR: (DMSO) δ 2.08 (3H singlet $\frac{1}{2} \text{CH}_3\text{COCH}_3$). Found: C, 69.41; H, 8.43; N, 3.38; Cl, 9.21. $\text{C}_{22}\text{H}_{30}\text{NO}_2\text{Cl} \cdot \frac{1}{2} \text{CH}_3\text{COCH}_3$ requires: C, 69.68; H, 8.21; H, 3.46; Cl, N, 8.75%. dl-series

In a similar manner there was obtained dl- α -dimethylamino- α -(cis-2-benzyloxycyclohexyl)-m-cresol, hydrochloride m.p. $257^\circ-258^\circ$. Found: C, 70.27; H, 8.18; N, 3.45; Cl, 9.64. $\text{C}_{22}\text{H}_{30}\text{NO}_2\text{Cl}$ requires: C, 70.29; H, 8.04; N, 3.73; Cl, 9.43%.

EXAMPLE 5

Antagonism of Morphine Induced Loss of Righting Reflex

Groups of three male Charles River rats (160 to 200 g.) were dosed subcutaneously with morphine base at 75 mg/kg. The degree of narcosis was measured at 15 and 30 minutes after injection. Criterion was loss of righting reflex. Antagonists were administered 40 minutes after the morphine. The degree of antagonism was measured at 20 minute intervals for 2 hours. Nalorphine at 2 mg/kg. served as a positive control while one group of morphinized rats in each determination received no antagonist and served as negative controls. Compounds were dissolved in water or suspended in Tween-80 and water and were administered intramuscularly. Each dose of the antagonist was tested in a

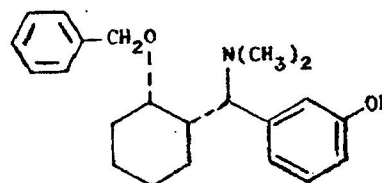
minimum of three experiments. At least three doses of each antagonist was used to determine the ED_{50} . For each experiment the degree of reversal, by the antagonist, of the loss of righting reflex induced by morphine was calculated in the following manner. The total number of periods of loss of righting reflex in the experimental group was divided by the total number of periods of loss of righting reflex in the control group. This number was converted to percent and subtracted from 100 to give percent reversal of loss of righting reflex. The dose for which a 50% reversal of the loss of righting reflex was observed is the ED_{50} .

Results

Compound	ED_{50} (Mg/kg)
(dl)- α -dimethylamino- α -(cis-2-ethoxycyclohexyl)-m-cresol	2.0
(dl)- α -dimethylamino- α -(cis-2-benzyloxycyclohexyl)-m-cresol	0.95
(l)- α -dimethylamino- α -(cis-2-benzyloxycyclohexyl)-m-cresol	0.35
Nalorphine	1.0

The subject matter which the applicants regard as their invention is particularly pointed out and distinctly claimed as follows:

1. The compound having the formula:



substantially free of the trans epimer; and the pharmacologically acceptable acid addition salts thereof.

2. The compound according to claim 1 substantially free from its d-enantiomer; and the pharmacologically acceptable acid addition salts thereof.

* * * * *

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RADICACIÓN: 0-24764

EDICTO No. 8209

LA SECRETARÍA GENERAL ADHOC
HACE SABER:

Que esta Superintendencia profirió Resolución No. 14559 de 24-JUN-2005. Que el contenido de la parte resolutive es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud correspondiente a "DERIVADOS DE 3-AMINO-3-ARILPROPANO-1-OL-, SU PREPARACION Y USO".

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución a la doctora Alicia Lloreda Ricaurte, o a quien haga sus veces, en su calidad de apoderada de Grunenthal GmbH., entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

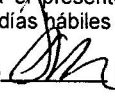
NOTIFÍQUESE Y CUMPLASE

Dada en Bogotá, D.C., a los 24 JUN. 2005

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,


JAIRO RUBIO ESCOBAR

Para notificar a los interesados, se fija el presente EDICTO en lugar visible al público en la SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, por el término de (10) diez días hábiles contados a partir de las 8:30 a.m. de hoy.

Secretaría General Ad-Hoc 12-JUL-2005  Este edicto se desfija hoy 26-JUL-2005 a las cinco (5:00 p.m.) 
Secretaría General Ad-Hoc
EDICTO No. 8209