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Fecha: 100-05-30-14-31-06 Dep. 2009 SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
TEL. 11 PATENTE VII Eje 375 BASE NACIONAL
400 400 000 PRESIDENTE Eje 45

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FORMULARIO UNICO DE OPOSICION 2000-12

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OPOSICION A:

- | | |
|---|---|
| ☒ Patente de Invención | ☐ Marca Colectiva |
| ☐ Patente de Modelo de Utilidad | ☐ Marca de Certificación |
| ☐ Diseño Industrial | ☐ Lema Comercial |
| ☐ Esquema de Trazado para Circuitos Integrados | |
| ☐ Marcas de Productos o Servicios | |

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SOLICITUD PUBLICADA

Número del expediente: 05.129.157
Solicitante: H. LUNDBECK A/S
Apoderado: EMILIO FERRERO
Título de la nueva creación o denominación del signo:
"GABOXADOL PARA EL TRATAMIENTO DE LA DEPRESIÓN Y OTROS TRASTORNOS AFECTIVOS"
Gaceta: 573 de 28-02-2007, Página 608- Número de Publicación 1138

3

OPOSICION PRESENTADA POR:

OPOSITOR	Nombre: Lafranco S.A. Dirección: Carrera 1 No. 46-84 Teléfono: (092) 449.30.51 Fax: Domicilio: Cali - Valle	IDENTIFICACION C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Número: 890 301 463 -8
REPRESENTANTE O APODERADO (74)	Nombre: José Luis Reyes Villamizar Dirección: Cra. 17 No. 88-23, Of. 205 Teléfono: 621.26.31 E-mail: info@reyes-abogados.com Fax: 621.26.42 Domicilio: Bogotá, D.C.	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Número: 79'152.473 de Usaquén TP 44655

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FUNDAMENTOS DE LA OPOSICION:

Causal: Incumplimiento de requisitos de patentabilidad (Título II, Capítulo I, Decisión 486 de 2000). Se violan los artículos 14, (las patentes de invención deben ser nuevas, tener nivel inventivo y ser susceptibles de aplicación industrial), 16 (una invención se considera nueva cuando no es obvia, ni se deriva de manera evidente del estado de la técnica), 18 (una invención tiene nivel inventivo si no es obvia para una persona versada en la materia) 20, (no son patentables los métodos terapéuticos o quirúrgicos) y 20d (los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales)

Justificación: VER ANEXO

5

Comprobante de pago No.

07- 43,502

(Oposición) Fecha

Mayo 20 de 2007

07- 43,394

(Prórroga) Fecha

Mayo 29 de 2007

86-488

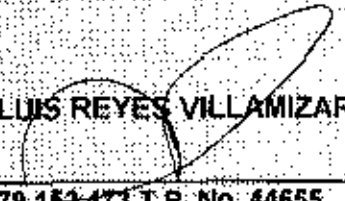
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Anexos:

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

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NOMBRE: JOSÉ LUIS REYES VILLAMIZAR

FIRMA: 
C.C.No. 79.152.473 T.P. No. 44655

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

REF: EXPEDIENTE 05-129-157

**TÍTULO SOLICITADO: "GABOXADOL PARA EL TRATAMIENTO DE LA
DEPRESIÓN Y OTROS TRASTORNOS AFECTIVOS"**

**PUBLICACIÓN: Gaceta 573 de 28-02-2007, número de publicación
1138**

SOLICITANTE: H. LUNDBECK A/S

**PRIORIDAD: DK PA 200300956 de 25-06-2003
DK PA 200400016 de 07-01-2004**

APODERADO: EMILIO FERRERO

TRÁMITE: PRESENTACIÓN DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **LABORATORIO FRANCO-COLOMBIANO LAFRANCOL S.A.**, en desarrollo de lo dispuesto por los artículos 42 y siguientes de la Decisión 486 de 2000 de la Comunidad Andina de Naciones, me permito solicitarle, muy respetuosamente, dar curso a la siguiente

I. PETICIÓN

Negar el beneficio patentario a la solicitud contenida en el expediente **05-129-157**, por no cumplir con los requisitos de patentabilidad a que se refieren los artículos 14, 16, 18 y 20 de la Decisión 486 de la Comunidad Andina de Naciones, con base

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en los fundamentos de hecho y de derecho que me permito exponer a continuación.

II. LEGÍTIMO INTERÉS

Asiste a **LAFRANCOL S.A.**, en su calidad de industria farmacéutica, legítimo interés para presentar esta oposición, pues la eventual concesión de la solicitud restringiría injustificadamente el empleo de ciertas sustancias, derivados y procesos que a nuestro juicio carecen de nivel inventivo, en detrimento de sus legítimos intereses comerciales. De igual manera mi cliente está interesado, por su misma condición de industria farmacéutica, en evitar la concesión de privilegios de patente que incumplan los requisitos materiales de patentabilidad establecidos en las normas vigentes, y que supongan un riesgo para la libre competencia.

III. FUNDAMENTOS DE LA OPOSICIÓN

3.1. Un método para el tratamiento de la depresión, que comprende administrar a un individuo que lo necesita, una cantidad farmacéuticamente aceptable de gaboxadol en forma de una sal de adición de ácido, o un zwitterión hidrato o zwitterión anhidrato, en forma de dosificación oral y que puede estar en combinación con un inhibidor de la reabsorción de serotonina (SRI) como citalopram, escitalopram, fluoxetina, sertralina, paroxetina, venlafaxina, duloxetina, dapoxetina, entre otros o sus sales, además de ser como un método terapéutico de prohibido patentamiento a la luz de las normas andinas, carece al menos de nivel inventivo, por obra del conocimiento previo de todos los constituyentes que se administran en dicho método.

En efecto, el solicitante en la memoria descriptiva de la solicitud colombiana en trámite, admite que el gaboxadol es conocido y que se describe en documentos como la EP 0000338 B1 y EP 0840601; por su parte los inhibidores de la reabsorción de serotonina SRI y algunas combinaciones que los contienen, también han sido revelados en documentos como la solicitud internacional WO 01/41766 A1 (14-07-2001), anteriores a la fecha de publicación de la solicitud colombiana en trámite.

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3.2. Por su parte, la patente europea EP 1 254 668 A2 publicada el 6 de noviembre de 2002 y titulada **"COMBINATION OF A SEROTONIN REUPTAKE INHIBITOR AND A GABA-A ALPHA 2/3 AGONIST FOR USE IN ANXIETY AND DEPRESSION"**, revela un método para tratar la depresión o la ansiedad en un mamífero, incluido el humano, caracterizado por la administración de un agonista GABA A alfa 2/3 con un SRI, en cantidades adecuadas que permiten tratar la ansiedad o la depresión con una eficacia aumentada.

Adicionalmente, en la página 3 de este documento se describe:

[0016] The compositions of the present invention are especially useful for the treatment of depression, especially refractory depression or anxiety where the use of an antidepressant or anxiolytic agent, respectively, is generally prescribed. By the use of a combination of a GABA-A alpha 2/3 agonist and an SRI antidepressant agent in accordance with the present invention, it is possible to treat depression, especially refractory depression, and/or anxiety in patients for whom conventional antidepressant or anxiolytic therapy might not be wholly successful or where a faster onset of action is needed.

Supone lo expuesto que la solicitud en trámite busca resolver el mismo problema técnico que ya había atendido la patente en cuestión- equivalente a la solicitud internacional WO 04/112786 A2-, al punto de describirse en la página 4 al final del párrafo lo siguiente:

In addition, gaboxadol may be used to augment and provide faster onset of the therapeutic effect of serotonin reuptake inhibitors, in particular citalopram and escitalopram.

It has now surprisingly been found that gaboxadol may be used to augment and provide faster onset of the therapeutic effect of serotonin reuptake inhibitors.

In one aspect, the invention relates to use of gaboxadol for the preparation of a pharmaceutical composition to be used in combination with a serotonin reuptake inhibitor or any other compound, which causes an elevation in the level of extracellular serotonin.

Es evidente, por lo expuesto, que tanto la anterioridad mencionada como la solicitud en trámite buscan proporcionar una formulación farmacéutica que comprenda un agonista de GABA-A alfa 2/3 y un inhibidor de la recaptación de serotonina (SRI), que permite un inicio más rápido del efecto terapéutico.

Para complementar lo anterior, es importante resaltar que la patente europea entre los compuestos referenciados como agonistas de GABA-A alfa 2/3 incluye a gaboxadol, ganaxolone, fengabine, entre otros y que son combinados con compuestos SRI que si bien es cierto no son los mismos de la solicitud colombiana en trámite, no lo es menos el hecho que en ambos documentos se hace referencia a la combinación de Gaboxadol y un SRI.

Es claro entonces, que la solicitud colombiana en trámite y en consecuencia la combinación allí revelada, carece por completo de nivel inventivo dadas las evidentes similitudes encontradas con la formulación propuesta en la EP 1 254 668 A2.

En lo que respecta a las dosis de gaboxadol reveladas en las reivindicaciones 4, 12, 26, 27, 42 y 43 de la solicitud colombiana en trámite y que corresponden a una cantidad que varía desde 2,5 hasta 20mg, tal como 5 hasta 15mg de gaboxadol por día; o que comprende gaboxadol en una cantidad que varía desde aproximadamente 0.1 hasta aproximadamente 2.5mg, carecen tanto de novedad como de nivel inventivo puesto que la solicitud europea tantas veces mencionada en su reivindicación 9 señala:

9. A pharmaceutical composition according to any one of claims 5-8 wherein the amount of the SRI antidepressant, or pharmaceutically acceptable salt thereof, in said composition is from about 0.5 mg to about 1500 mg and the amount of the GABA-A alpha 2/3 agonist or pharmaceutically acceptable salt thereof is from about 0.1 mg to about 500 mg.

3.3. En adición a lo descrito anteriormente, es importante resaltar lo revelado en la solicitud internacional WO 01/41768 A1 publicada el 14 de junio de 2001, de título: **"THE COMBINATION OF SEROTONIN REUPTAKE INHIBITOR AND IRINDALONE"**, pues en este documento también se busca obtener una combinación de un fármaco como irindalona con un inhibidor de la recaptación de la serotonina (SRI)) seleccionado de citalopram, escitalopram, fluoxetina, fluvoxamina, sertralina, paroxetina, venlafaxina, dapoxetina, nefazodona, entre otros, u otro compuesto, el cual provoca una elevación

en el nivel de serotonina extracelular, para el tratamiento de la depresión y otros desórdenes afectivos.

Nuevamente es importante resaltar que se está frente a la misma finalidad o solución que *propone* la solicitud colombiana en trámite –equivalente a la solicitud internacional WO 04/112786 A2-, pues ésta describe en la página 4, parte final del párrafo, lo siguiente:

In addition, gaboxadol may be used to augment and provide faster onset of the therapeutic effect of serotonin reuptake inhibitors, in particular citalopram and escitalopram.

It has now surprisingly been found that gaboxadol may be used to augment and provide faster onset of the therapeutic effect of serotonin reuptake inhibitors.

In one aspect, the invention relates to use of gaboxadol for the preparation of a pharmaceutical composition to be used in combination with a serotonin reuptake inhibitor or any other compound, which causes an elevation in the level of extracellular serotonin.

Es necesario concluir, entonces, que tanto la anterioridad explicada como en la solicitud en curso buscan proporcionar una formulación farmacéutica que comprenda un compuesto bien sea Gaboxadol o Irindalona **y un inhibidor de la recaptación de serotonina (SRI) que es capaz de elevar el nivel de serotonina extracelular.**

En consecuencia, la solicitud en trámite no está resolviendo un nuevo problema, pues se limita a realizar otra combinación predecible, que al igual que la de la revelada en la solicitud internacional mencionada, puede potenciar la acción de los fármacos.

3.4. La siguiente publicación científica también evidencia el uso de Gaboxadol o TPI (4,5,6,7-tetrahydroisoxazolo[5,4-c] pyridin-3-ol) y su posible uso con otros fármacos, los cuales pueden incrementar la actividad de las composiciones:

Pharmacodynamic effects and possible therapeutic uses of THIP, a specific GABA-agonist¹.

THIP (4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol) is a potent and **specific GABA** receptor **agonist** which does not influence the **GABA** uptake system or **GABA** metabolizing enzymes. The specificity for the **GABA** receptor is also demonstrated by lack of action on monoaminergic, cholinergic, histaminergic or opiate receptors. Since in recent years **GABA** receptor stimulants-among others **THIP**—have become available many have speculated as to what clinical indication **GABA**-ergic stimulation might be an important element. The first suggestion was that **GABA**-ergic drugs by an inhibitory effect on the dopamine neurons would improve the antischizophrenic effect of neuroleptics and improve tardive dyskinesia. Furthermore, studies on brains of deceased Parkinson and Huntington's chorea patients have demonstrated a low level of **GABA** and its synthesizing enzyme glutamic acid decarboxylase (GAD) in the basal ganglia. Also in epilepsy and diseases with dementia a deficit in the **GABA** system has been proposed. Therefore a **therapeutic** strategy for these diseases may be supplementary treatment with drugs which increase **GABA** receptor activity. Furthermore, recent results in humans have shown that **GABA** agonists perhaps also could be of benefit in mania and depressions. When considering the neurophysiological elements of nociception and muscle tone it is also reasonable to suggest that **GABA**-ergic stimulation may reduce pain perception and muscle tone.

- 3.5. Por último, reitero que la solicitud colombiana en trámite pretende el patentamiento de un método terapéutico (reivindicaciones 1 a 8) y un uso (9 a 35):

En este punto es del caso recordar que, según el artículo 51 de la Decisión 486, el alcance de la protección conferida por la patente está determinado "por el tenor de las reivindicaciones". La clara e inequívoca redacción transcrita demuestra, sin más, que la protección solicitada en las reivindicaciones 1 a 8 versa única y exclusivamente en el método de tratamiento en cuestión, sin que sea dado realizar interpretaciones diversas sobre el alcance pretendido. Una simple lectura de dichas reivindicaciones

¹ Christensen AV; Svendsen O; Krogsgaard-Larsen P. Pharmacodynamic effects and possible therapeutic uses of TPI, a specific GABA-agonist. Pharmaceutisch Weekblad. Scientific Edition [Pharm Weekbl Sci] 1982 Oct 22; Vol.4 (5), pp 145-153.

demuestra que el objeto de la solicitud es un método terapéutico para el tratamiento humano o animal, excluido expresamente de la posibilidad de obtener patente según el artículo 20 (d) de la Decisión 486.

Lo expuesto supone que las reivindicaciones mencionadas son inaceptables a la luz del ordenamiento subregional andino, por la clara e inequívoca pretensión de obtener exclusiva sobre un método de tratamiento, cuyo patentamiento está expresamente prohibido por la norma citada.

También son inaceptables las reivindicaciones 9 a 35, dirigidas al "uso" de una composición, pues esta categoría no está incluida en el concepto de "Productos o Procedimientos" que establece el artículo 14 de la Decisión 486 de 2000. Lo anterior, además, en consonancia con la reiterada interpretación de la SIC sobre este punto.

En consecuencia, me permito reiterar que aún si los usos o métodos terapéuticos fueran permitidos en nuestro medio, éstos deberían cumplir necesariamente con los requisitos materiales de patentabilidad, novedad, nivel Inventivo y Aplicación Industrial.

Aunque a la ausencia de los dos primeros nos hemos referido ya, cabe desde ahora anotar que el último resulta de imposible cumplimiento, en tanto la *reproducción industrial* del uso separado, combinado o secuencial de medicamentos para tratar ciertas patologías es del resorte de la profesión médica y no de las actividades industriales.

De igual manera es importante resaltar en este punto de la solicitud que, si la novedad y el nivel inventivo están dados por la combinación de dos grupos de principios activos en una formulación farmacéutica, y a su administración como parte de un método terapéutico, no hace falta ser un experto en la materia para saber que el efecto sinérgico pretendido está dado por el efecto combinado de los principios activos, orientado al logro de un resultado mayor al que produciría la suma del efecto de cada uno de ellos individualmente considerado.

En farmacología y en la industria farmacéutica son muy comunes y conocidas las combinaciones de varios fármacos, y para ello existen múltiples ejemplos que no viene al caso mencionar, debido a su amplia divulgación y uso. La combinación de un compuesto como el descrito en la solicitud colombiana con otro tipo de agente como los mencionados en dichas reivindicaciones tiene la misma finalidad que en lo expuesto anteriormente, esto es, hacer que el efecto en el tratamiento de la depresión y la ansiedad, sea mayor que aquel que se obtendría mediante la administración individual de los componentes. Para el caso en cuestión no sólo son conocidos tales componentes, sino que es absolutamente predecible la posibilidad de su combinación y la obtención del efecto sinérgico pretendido.

El despacho debería considerar, además del conocimiento individual de los componentes de la combinación farmacéutica pretendida, la predecibilidad del pretendido efecto sinérgico entre ambas sustancias por obra de la compatibilidad y complementariedad de sus mecanismos de acción y del tratamiento de los síntomas o diversas manifestaciones para una patología determinada, razón por la cual la caracterización que nos ocupa carece de nivel inventivo.

Así las cosas, y con fundamento en los argumentos expuestos a lo largo del presente escrito, respetuosamente reitero la solicitud para que su despacho se abstenga de conceder el privilegio de patente solicitado, y ordene en consecuencia el archivo del expediente respectivo.

IV. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho el Capítulo 1, artículos 14, 16, 18 y 20-d (Requisitos de Patentabilidad) y el artículo 42 (Oposiciones) de la Decisión 486 de 2000.

V. SOLICITUD DE PLAZO EXTRA PARA SUSTENTAR LA OPOSICIÓN

En desarrollo de lo dispuesto por el artículo 42, inciso 2º de la Decisión 486, solicito comedidamente a su Despacho el plazo adicional de sesenta días para

sustentar la presente oposición. Para los anteriores efectos, me permito anexar la constancia de pago correspondiente.

VI. PRUEBAS

Ruego que se tengan como tales, sin perjuicio de que el Despacho considere oficiosamente, en particular de las allegadas por el suscrito a los expedientes mencionados en este escrito, las siguientes:

- 6.1. La patente europea EP 1 254 668 A2 publicada el 6 de noviembre de 2002 y titulada "COMBINATION OF A SEROTONIN REUPTAKE INHIBITOR AND A GABA-A ALPHA 2/3 AGONIST FOR USE IN ANXIETY AND DEPRESSION" pág 2, 3, 9 y capítulo reivindicatorio.
- 6.2. La solicitud internacional WO 01/41766 A1 publicada el 14 de junio de 2001, de título: "THE COMBINATION OF SEROTONIN REUPTAKE INHIBITOR AND IRINDALONE", pág 2-4, 8 y capítulo reivindicatorio.
- 6.3. Publicación Christensen AV; Svendsen O; Krogsgaard-Larsen P. Pharmacodynamic effects and possible therapeutic uses of THPI, a specific GABA-agonist. Pharmaceutisch Weekblad. Scientific Edition [Pharm Weekbl Sci] 1982 Oct 22; Vol.4 (5),Abstract.

VII. ANEXOS

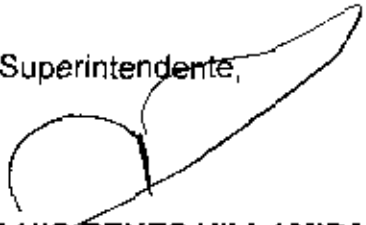
Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos

1. Certificado de existencia y representación legal de Lafranco! S.A.
2. Poder para actuar.
3. Constancia de pago de las tasas de tramitación de oposición.
4. Constancia de pago para sustentar la solicitud de prórroga a que se refiere el artículo 42, inciso 2º de la Decisión 486.
5. Copia para correr traslado al solicitante.
6. Los mencionados en el acápite de pruebas.

VIII. NOTIFICACIONES

El suscrito recibirá notificaciones en la secretaria de su Despacho o en mi oficina localizada en la Carrera 17 No. 88-23, Oficina 205, Fax (1) 621.25.42 de esta ciudad. Lafrancol S.A., las recibirá en sus oficinas localizadas en la Carrera 1 N° 46-84 de Cali.

Señor Superintendente,



JOSÉ LUIS REYES VILLAMIZAR

C.C. 79'152.473 de Usaquén

T.P.A. 44655 de C.S.J.

(19)



Europäisches Patentamt
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Office européen des brevets



(11)

EP 1 254 668 A2

(12)

EUROPEAN PATENT APPLICATION

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A61P 25/24

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Designated Extension States:
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(72) Inventor: **Howard, Harry Ralph, Jr.**,
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(30) Priority: **01.05.2001 US 287821 P**

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(71) Applicant: **Pfizer Products Inc.**
Groton, Connecticut 06340 (US)

(54) **Combination of a serotonin reuptake inhibitor and a GABA-A alpha 2/3 agonist for use in anxiety and depression**

(57) The present invention relates to a method of treating depression or anxiety in a mammal, including a human, by administering to the mammal a GABA-A alpha 2/3 agonist in combination with an SRI antidepressant agent with improvement in efficacy. It also relates

to pharmaceutical compositions containing a pharmaceutically acceptable carrier, a GABA-A alpha 2/3 agonist, and an SRI antidepressant agent.

EP 1 254 668 A2

DescriptionBackground Of The Invention

[0001] The present invention relates to a method of treating anxiety and depression with improved efficacy in a mammal, including a human, by administering to the mammal a GABA-A alpha 2/3 agonist in combination with a serotonin reuptake inhibitor (SRI). It also relates to pharmaceutical compositions containing a pharmaceutically acceptable carrier, a GABA-A alpha 2/3 agonist and a serotonin reuptake inhibitor (SRI).

[0002] Major depression is characterized by feelings of intense sadness and despair, mental slowing and loss of concentration, pessimistic worry, agitation, and self-deprecation. Physical changes also occur, especially in severe or "melancholic" depression. These include insomnia or hypersomnia, anorexia and weight loss (or sometimes overeating), decreased energy and libido, and disruption of normal circadian rhythms of activity, body temperature, and many endocrine functions.

[0003] Serotonin Selective Reuptake Inhibitors (SSRIs) currently provide efficacy in the treatment of major depressive disorder (MDD) and are generally perceived by psychiatrists and primary care physicians as effective, well-tolerated and easily administered. However, they are associated with undesirable features, such as high incidence of sexual dysfunction, delayed onset of action and a level of non-responsiveness estimated to be as high as 30% (see M. J. Gillin, *Journal of Clinical Psychiatry*, 1994, 55, 406-413 and R. T. Segraves, *Journal of Clinical Psychiatry*, 1992, 10 (2), 4-10). Preclinical and clinical evidence has indicated that the sexual dysfunction associated with SSRI therapy can be reduced through the use of serotonin reuptake inhibitors (SRI) and dopamine reuptake inhibitors (DRIs), such as bupropion (see A. K. Ashton, *Journal of Clinical Psychiatry*, 1998, 59(3), 112-115). Furthermore, the combination of SRI and DRI may hasten the onset of action as well as offering relief to refractory patients, possibly through a synergistic mechanism (see R. D. Marshall et al, *Journal of Psychopharmacology*, 1995, 9(3), 284-286) and prove beneficial in the treatment of substance abuse and attention deficit hyperactivity disorder (ADHD) according to Benickman et al, *Journal of the American Academy of Child and Adolescent Psychiatry*, 1995, 34(5), 649 and Shekim et al, *Journal of Nervous and Mental Disease*, 1989, 177(5), 296.

Summary Of The Invention

[0004] The present invention relates to a pharmaceutical composition for the treatment of depression and anxiety comprising: (a) a compound that exhibits activity as a Serotonin Reuptake Inhibitor, or a pharmaceutically acceptable salt thereof; (b) a GABA-A alpha 2/3 agonist or pharmaceutically acceptable salt thereof; and (c) a pharmaceutically acceptable carrier; wherein the active agents "a" and "b" above are present in amounts that render the composition effective in treating, respectively, anxiety or depression refractory to treatment with traditional antidepressant therapies alone.

[0005] This invention also relates to a method of treating depression or anxiety in a mammal, comprising administering to said mammal, respectively, an anxiolytic or antidepressant effective amount of a pharmaceutical composition comprising: (a) a Serotonin Reuptake Inhibitor (SRI) compound that exhibits activity as an antidepressant, or a pharmaceutically acceptable salt thereof; (b) a GABA-A alpha 2/3 agonist or pharmaceutically acceptable salt thereof; and (c) a pharmaceutically acceptable carrier; wherein the active agents "a" and "b" above are present in amounts that render the composition effective in treating, respectively, anxiety or depression with improvement in the efficacy achieved by either component individually.

[0006] This invention also relates to a method of treating anxiety or depression in a mammal, comprising administering to said mammal: (a) a Serotonin Reuptake Inhibitor (SRI) compound that exhibits activity as, respectively an antidepressant, or a pharmaceutically acceptable salt thereof; and (b) a GABA-A alpha 2/3 agonist or pharmaceutically acceptable salt thereof; wherein the active agents "a" and "b" above are present in amounts that render the combination of the two agents effective in treating, respectively, anxiety or depression with improvement in the efficacy achieved by either component individually in the treatment of anxiety, depression, especially refractory depression.

[0007] It will be appreciated that when using a combination method of the present invention, referred to immediately above, both the GABA-A alpha 2/3 agonist and the SRI antidepressant will be administered to a patient within a reasonable period of time. The compounds may be in the same pharmaceutically acceptable carrier and therefore administered simultaneously. They may be in separate pharmaceutical carriers such as conventional oral dosage forms that are taken simultaneously. The term combination, as used above, also refers to the case where the compounds are provided in separate dosage forms and are administered sequentially. Therefore, by way of example, the SRI antidepressant agent may be administered as a tablet and then, within a reasonable period of time, the GABA-A alpha 2/3 agonist may be administered either as an oral dosage form such as a tablet or a fast-dissolving oral dosage form. By a "fast dissolving oral formulation" is meant, an oral delivery form which when placed on the tongue of a patient, dissolves within about seconds.

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[0008] The compositions of the present invention that contain a GABA-A alpha 2/3 agonist and an SRI antidepressant are useful for the treatment of anxiety and depression, especially refractory depression. As used herein, the term "depression" includes depressive disorders, for example, single episodic or recurrent major depressive disorders, and dysthymic disorders, depressive neurosis, and neurotic depression: melancholic depression including anorexia, weight loss, insomnia and early morning waking, and psychomotor retardation; atypical depression (or reactive depression) including increased appetite, hypersomnia, psychomotor agitation or irritability, anxiety and phobias, seasonal affective disorder, or bipolar disorders or manic depression, for example, bipolar I disorder, bipolar II disorder, cyclothymic disorder and obsessive-compulsive disorder (OCD).

[0009] Other mood disorders encompassed within the term "depression" include dysthymic disorder with early or late onset and with or without atypical features; dementia of the Alzheimer's type, with early or late onset, with depressed mood; vascular dementia with depressed mood, disorders induced by alcohol, amphetamines, cocaine, hallucinogens, inhalants, opioids, phencyclidine, sedatives, hypnotics, anxiolytics and other substances; schizoaffective disorder of the depressed type; and adjustment disorder with depressed mood.

[0010] The compositions of the present invention that contain a GABA-A alpha 2/3 agonist and an SRI are useful for the quick-onset treatment of anxiety. As used herein, the term "anxiety" includes anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobias, for example, specific animal phobias, social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic stress disorder and acute stress disorder, and generalized anxiety disorders.

[0011] "Generalized anxiety" is typically defined as an extended period (e.g., at least six months) of excessive anxiety or worry with symptoms on most days of that period. The anxiety and worry is difficult to control and may be accompanied by restlessness, being easily fatigued, difficulty concentrating, irritability, muscle tension, and disturbed sleep.

[0012] "Panic disorder" is defined as the presence of recurrent panic attacks followed by at least one month of persistent concern about having another panic attack. A "panic attack" is a discrete period in which there is a sudden onset of intense apprehension, fearfulness or terror. During a panic attack, the individual may experience a variety of symptoms including palpitations, sweating, trembling, shortness of breath, chest pain, nausea and dizziness. Panic disorder may occur with or without agoraphobia.

[0013] "Phobias" includes agoraphobia, specific phobias and social phobias. "Agoraphobia" is characterized by an anxiety about being in places or situations from which escape might be difficult or embarrassing or in which help may not be available in the event of a panic attack. Agoraphobia may occur without history of a panic attack. A "specific phobia" is characterized by clinically significant anxiety provoked by feared object or situation. Specific phobias include the following subtypes: animal type, cued by animals or insects; natural environment type, cued by objects in the natural environment, for example storms, heights or water; blood-injection-injury type, cued by the sight of blood or an injury or by seeing or receiving an injection or other invasive medical procedure; situational type, cued by a specific situation such as public transportation, tunnels, bridges, elevators, flying, driving or enclosed spaces; and other type where fear is cued by other stimuli. Specific phobias may also be referred to as simple phobias. A "social phobia" is characterized by clinically significant anxiety provoked by exposure to certain types of social or performance circumstances. Social phobia may also be referred to as social anxiety disorder.

[0014] Other anxiety disorders encompassed within the term "anxiety" include anxiety disorders induced by alcohol, amphetamines, caffeine, cannabis, cocaine, hallucinogens, inhalants, phencyclidine, sedatives, hypnotics, anxiolytics and other substances, and adjustment disorders with anxiety or with mixed anxiety and depression.

[0015] Anxiety may be present with or without other disorders such as depression in mixed anxiety and depressive disorders. The compositions of the present invention are therefore useful in the quick-onset treatment of anxiety with or without accompanying depression.

[0016] The compositions of the present invention are especially useful for the treatment of depression, especially refractory depression or anxiety where the use of an antidepressant or anxiolytic agent, respectively, is generally prescribed. By the use of a combination of a GABA-A alpha 2/3 agonist and an SRI antidepressant agent in accordance with the present invention, it is possible to treat depression, especially refractory depression, and/or anxiety in patients for whom conventional antidepressant or anti-anxiety therapy might not be wholly successful or where a faster onset of action is needed.

[0017] The term "treatment", as used herein, refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such condition or disorder. The term "treatment" as used herein, refers to the act of treating, as "treating" is defined immediately above.

[0018] Examples of Serotonin Reuptake inhibitors (SRI) that may be used in the methods and pharmaceutical compositions of this invention are compounds of the formula

[2-(3,4-Dichlorophenoxy)-5-(5-methyl-[1,2,3]thiadiazol-4-yl)-benzyl]-methylamine;
 [2-(3,4-Dichlorophenoxy)-5-(2,4-dimethylthiazol-5-yl)-benzyl]-methylamine;
 [2-(3,4-Dichlorophenoxy)-5-(2,4-dimethylthiazol-5-yl)-benzyl]-methylamine;
 [2-(3,4-Dichlorophenoxy)-5-[1,2,4]triazol-1-ylbenzyl]-methylamine;
 [2-(3,4-Dichlorophenoxy)-5-(3-methyl-[1,2,4]triazol-1-yl)-benzyl]-methylamine;
 [2-(4-Chlorophenoxy)-5-(3,5-di(methyl-[1,2,4]triazol-1-yl)-benzyl)-methylamine;
 [2-(4-Chlorophenoxy)-5-tetrazol-1-ylbenzyl]-methylamine;
 [2-(4-Chlorophenoxy)-5-(5-methyltetrazol-1-yl)-benzyl]-dimethylamine;
 [2-(4-Chlorophenoxy)-5-[1,2,4]triazol-4-ylbenzyl]-dimethylamine;
 [2-(4-Chlorophenoxy)-5-(1-methyl-1H-tetrazol-5-yl)-benzyl]-dimethylamine; and
 {1-[2-(3,4-Dichlorophenoxy)-5-(1-methyl-1H-tetrazol-5-yl)-phenyl]-ethyl}-dimethylamine.

[0043] Suitable classes of a GABA-A alpha 2/3 agonist that may be used in the compositions and methods of this invention include the following compounds:

gaboxadol (4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol);
 ganaxolone (3 α -hydroxy-3 β -methyl-5 α -pregnan-20-one);
 tengabine (2-[(butylimino)-(2-chlorophenyl)methyl]-4-chlorophenol);
 2-(4-methoxyphenyl)-2,5,6,7,8,9-hexahydro-pyrazolo[4,3-c]cinnolin-3-one;
 7-cyclobutyl-6-(2-methyl-2H-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;
 (3-fluoro-4-methylphenyl)-N-[(1-[(2-methylphenyl)methyl]-benzimidazol-2-yl)methyl]-N-pentylcarboxamide; and
 3-(aminomethyl)-5-methylhexanoic acid.

Detailed Description Of The Invention

[0044] The following references refer to novel biaryl ether derivatives useful as monoamine reuptake inhibitors that exhibit activity as a Serotonin Reuptake Inhibitor and that can be used, in combination with a GABA-A alpha 2/3 agonist in the pharmaceutical compositions and methods of this invention, and to methods of preparing the same: PCT application No.: PCT/IB00/01373 Filed Sept 27, 2000 and PCT application No. PCT/IB00/00108 filed Feb 2, 2000. United States Patent No. 4,018,830, issued April 19, 1997, refers to phenylthioalkylamines and 2-phenylthiobenzylamines which are active as antiarrhythmics.

[0045] WO 97/17325, International Publication Date May 15, 1997, refers to derivatives of N,N-dimethyl-2-(arythio)benzylamine which selectively influence serotonin transport in the central nervous system and are useful as antidepressants.

[0046] United States Patent 5,190,965, issued March 2, 1993, and United States Patent 5,430,063, issued July 4, 1995, refer to phenoxyphenyl derivatives which have utility in the treatment of depression.

[0047] United States Patent 4,161,629, issued July 17, 1979, refers to pyrrolidine derivatives that possess anticholinergic and hypolipemic activity.

[0048] United States Provisional Application No. 60/121313, filed February 23, 1999, refers to biaryl ethers that have activity in inhibiting reuptake of both serotonin and dopamine. The foregoing patents and patent applications are incorporated herein by reference in their entirety.

[0049] The SRI antidepressants of the formula I can be prepared as described in the following patent application, which is referred to above and incorporated herein by reference in its entirety: PCT application NO. PCT/IB00/01373 filed September 27, 2000. SRI antidepressants of Formula II can be prepared as described in the following patent application, which is referred to above and incorporated herein by reference in its entirety: PCT application No. PCT/IB00/00108 filed February 2, 2000.

[0050] The GABA-A alpha 2/3 agonists that can be used, together with an SRI antidepressant agent in the pharmaceutical compositions and methods of this invention are those compounds and pharmaceutically acceptable salts described in the following references:

gaboxadol (4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol) claimed in JP-54 036290 issued (3-16-79) and US-4 278,676 issued (7-14-81);
 ganaxolone (3 α -hydroxy-3 β -methyl-5 α -pregnan-20-one) claimed in DE-2,162,555 issued (6-22-71) and US-4 962 429 issued (4-27-76);
 tengabine (2-[(butylimino)-(2-chlorophenyl)methyl]-4-chlorophenol) claimed in FR-2,475,543 issued (8-14-81) and US-4,410,536 issued (8-23-83);
 2-(4-methoxyphenyl)-2,5,6,7,8,9-hexahydro-pyrazolo[4,3-c]cinnolin-3-one claimed in WO-99/00391 published (1-7-99) and US-6,180,630 issued (4-12-00);

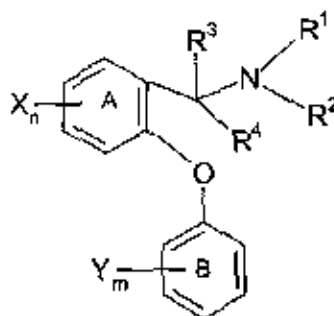
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[0077] When administered in combination, either as a single or as separate pharmaceutical composition(s), a GABA-A alpha 2/3 agonist and a SRI antidepressant agent, are presented in a ratio which is consistent with the manifestation of the desired effect. In particular, the ratio by weight of the GABA-A alpha 2/3 agonist and the SRI antidepressant agent will suitably be between 0.001 to 1 and 1000 to 1, and especially between 0.01 to 1 and 100 to 1.

[0078] As used herein the term "mammal" includes animals of economic importance such as bovine, ovine, and porcine animals, especially those that produce meat, as well as domestic animals (e.g. cats and dogs), sports animals (e.g. horses), zoo animals, and humans, the latter being preferred.

Claims

1. A combination comprising a compound that exhibits activity, respectively, as an SRI antidepressant, or a pharmaceutically acceptable salt thereof; and a GABA-A alpha 2/3 agonist or a pharmaceutically acceptable salt thereof.
2. A combination according to claim 1, wherein the SRI antidepressant agent, or pharmaceutically acceptable salt thereof, is selected from compounds of formula I, and their pharmaceutically acceptable salts:



wherein phenyl ring A and phenyl ring B can each, independently, be replaced by a naphthyl group, and wherein when phenyl ring A is replaced by a naphthyl group, the ethereal oxygen of structure I and the carbon to which R³, R⁴ and NR¹R² are attached, are attached to adjacent ring carbon atoms of the naphthyl group and neither of said adjacent ring carbon atoms is also adjacent to a fused ring carbon atom of said naphthyl group;

n and m are, selected, independently, from one, two and three;

R¹ and R² are selected, independently, from hydrogen, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, and (C₂-C₄)alkynyl, or R¹ and R², together with the nitrogen to which they are attached, form a four to eight membered saturated ring containing one or two heteroatoms, including the nitrogen to which R¹ and R² are attached, wherein the second heteroatom, when present, is selected from oxygen, nitrogen and sulfur, and wherein said ring may optionally be substituted at available binding sites with from one to three substituents selected, independently, from hydroxy and (C₁-C₆)alkyl;

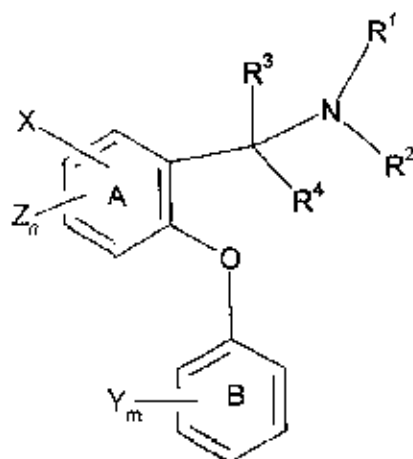
R³ and R⁴ are selected, independently, from hydrogen and (C₁-C₄) alkyl optionally substituted with from one to three fluorine atoms, or R³ and R⁴, together with the carbon to which they are attached, form a four to eight membered saturated carbocyclic ring, and wherein said ring may optionally be substituted at available binding sites with from one to three substituents selected, independently, from hydroxy and (C₁-C₆)alkyl;

or R³ and R⁴, together with the nitrogen to which R³ is attached and the carbon to which R⁴ is attached, form a four to eight membered saturated ring containing one or two heteroatoms, including the nitrogen to which R³ is attached, wherein the second heteroatom, when present, is selected from oxygen, nitrogen and sulfur, and wherein said ring may optionally be substituted at available binding sites with from one to three substituents selected, independently, from hydroxy and (C₁-C₆)alkyl;

each X and each Y is selected, independently, from hydrogen, halo (i.e., chloro, fluoro, bromo or iodo), (C₁-C₃)alkyl optionally substituted with from one to three fluorine atoms, (C₁-C₄)alkoxy optionally substituted with from one to three fluorine atoms, cyano, nitro, amino, (C₁-C₄)alkylamino, di-(C₁-C₄)alkylamino, NR⁵(C=O) (C₁-C₄)alkyl wherein R⁵ is hydrogen or (C₁-C₆)alkyl, and SO_p(C₁-C₆)alkyl wherein p is zero, one or two; and with the proviso that: (a) no more than one of NR¹R², CR³R⁴ and R²NCR³ can form a ring; and (b) at least one X must be other than hydrogen when (i) R³ and R⁴ are both hydrogen, (ii) R¹ and R² are selected, inde-

pendently, from hydrogen and (C₁-C₄)alkyl, and (iii) ring B is mono- or disubstituted with, respectively, one or two halo groups;
or a pharmaceutically acceptable salt thereof.

- d. A combination according to claim 1, wherein the SRI antidepressant agent, or pharmaceutically acceptable salt thereof, is selected from compounds of formula II, and their pharmaceutically acceptable salts:



wherein phenyl ring A and phenyl ring B can each, independently, be replaced by a naphthyl group, and wherein when phenyl ring A is replaced by a naphthyl group, the ethereal oxygen of formula II and the carbon to which R³, R⁴ and NR¹R² are attached are attached to adjacent ring carbon atoms of the naphthyl group and neither of said adjacent ring carbon atoms is also adjacent to a fused ring carbon atom of said naphthyl group;

n and m are, selected, independently, from one, two and three;

R¹ and R² are selected, independently, from hydrogen, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, and (C₂-C₄)alkynyl, or R¹ and R², together with the nitrogen to which they are attached, form a four to eight membered saturated ring containing one or two heteroatoms, including the nitrogen to which R¹ and R² are attached, wherein the second heteroatom, when present, is selected from oxygen, nitrogen and sulfur, and wherein said ring may optionally be substituted at available binding sites with from one to three substituents selected, independently, from hydroxy and (C₁-C₆)alkyl;

R³ and R⁴ are selected, independently, from hydrogen and (C₁-C₄)alkyl optionally substituted with from one to three fluorine atoms, or R³ and R⁴, together with the carbon to which they are attached, form a four to eight membered saturated carbocyclic ring, and wherein said ring may optionally be substituted at available binding sites with from one to three substituents selected, independently, from hydroxy and (C₁-C₆)alkyl;

or R³ and R⁴, together with the nitrogen to which R² is attached and the carbon to which R³ is attached, form a four to eight membered saturated ring containing one or two heteroatoms, including the nitrogen to which R² is attached, wherein the second heteroatom, when present, is selected from oxygen, nitrogen and sulfur, and wherein said ring may optionally be substituted at available binding sites with from one to three substituents selected, independently, from hydroxy and (C₁-C₆)alkyl;

each X is selected, independently, from phenyl, heteroaryl and heterocycle, and wherein each X may be further substituted by hydrogen, halo, (C₁-C₄)alkyl optionally substituted with from one to three fluorine atoms, (C₁-C₄)alkoxy optionally substituted with from one to three fluorine atoms, cyano, nitro, amino, hydroxy, carbonyl, (C₁-C₄)alkylamino, di-[(C₁-C₄)alkyl]amino, NR⁵(C=O)(C₁-C₄)alkyl, SO₂NR⁵R⁶ and SO₂(C₁-C₆)alkyl, wherein R⁵ and R⁶ are selected, independently, from hydrogen and (C₁-C₆)alkyl, and p is zero, one or two;

each Y_m is selected, independently, from hydrogen, halo, (C₁-C₄)alkyl optionally substituted with from one to three fluorine atoms, (C₁-C₄)alkoxy optionally substituted with from one to three fluorine atoms, cyano, nitro, amino, (C₁-C₄)alkylamino, di-[(C₁-C₄)alkyl]amino, NR⁵(C=O)(C₁-C₄)alkyl, SO₂NR⁵R⁶ and SO₂(C₁-C₆)alkyl, wherein R⁵ and R⁶ are selected, independently, from hydrogen and (C₁-C₆)alkyl, and p is zero, one or two; and each Z_n is selected, independently, from hydrogen, halo, (C₁-C₄)alkyl optionally substituted with from one to three fluorine atoms, (C₁-C₄)alkoxy;

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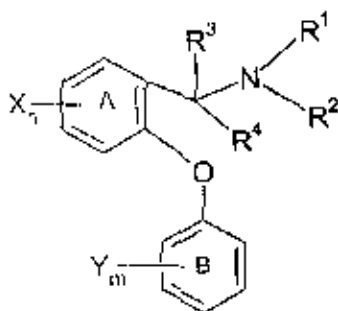
or a pharmaceutically acceptable salt thereof.

4. A composition according to any one of claims 1-3, wherein the GABA-A alpha 2/3 agonist, or a pharmaceutically acceptable thereof, is selected from:

gaboxadol (4,6,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol);
 ganaxolone (3 α -hydroxy-3 β -methyl-5 α -pregnan-20-one);
 fengatins (2-[(butylimino)-(2-chlorophenyl)methyl]-4-chlorophenol);
 2-(1-methoxyphenyl)-2,5,6,7,8,9-hexahydro-pyrazolo[4,3-c]cinnolin-3-one;
 7-cycloheptyl-6-(2-methyl-2H-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;
 (3-fluoro-4-methylphenyl)-N-({1-[(2-methylphenyl)methyl]-benzimidazol-2-yl}methyl)-N-pentylcarboxamide;
 and
 3-aminomethyl-5-methylhexanoic acid.

5. A pharmaceutical composition for the treatment of anxiety or depression in a mammal, comprising: (a) a compound that exhibits activity, respectively, as an SRI antidepressant, or a pharmaceutically acceptable salt thereof; (b) a GABA-A alpha 2/3 agonist or pharmaceutically acceptable salt thereof; and (c) a pharmaceutically acceptable carrier; wherein the above agents "a" and "b" above are present in amounts that render the composition effective in treating, respectively, anxiety or depression with increased efficacy.

6. A pharmaceutical composition according to claim 5, wherein the SRI antidepressant agent or pharmaceutically acceptable salt thereof is selected from compounds of the formula I, and their pharmaceutically acceptable salts:



wherein phenyl ring A and phenyl ring B can each, independently, be replaced by a naphthyl group, and wherein when phenyl ring A is replaced by a naphthyl group, the etheral oxygen of structure I and the carbon to which R³, R⁴ and R¹/R² are attached, are attached to adjacent ring carbon atoms of the naphthyl group and neither of said adjacent ring carbon atoms is also adjacent to a fused ring carbon atom of said naphthyl group;

n and m are selected, independently, from one, two and three;

R¹ and R² are selected, independently, from hydrogen (C₁-C₄)alkyl, (C₂-C₄)alkenyl, and (C₂-C₄)alkynyl, or R¹ and R², together with the nitrogen to which they are attached, form a four to eight membered saturated ring containing one or two heteroatoms, including the nitrogen to which R¹ and R² are attached, wherein the second heteroatom, when present, is selected from oxygen, nitrogen and sulfur, and wherein said ring may optionally be substituted at available binding sites with from one to three substituents selected, independently, from hydroxy and (C₁-C₆)alkyl;

R³ and R⁴ are selected, independently, from hydrogen and (C₁-C₄) alkyl optionally substituted with from one to three substituents, or R³ and R⁴, together with the carbon to which they are attached, form a four to eight membered saturated carbocyclic ring, and wherein said ring may optionally be substituted at available binding sites with from one to three substituents selected, independently, from hydroxy and (C₁-C₆)alkyl;

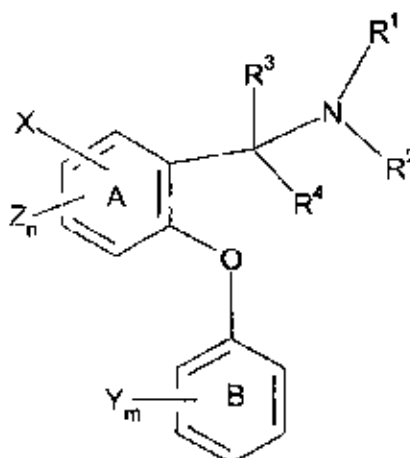
or R³ and R⁴, together with the nitrogen to which R² is attached and the carbon to which R³ is attached, form a four to eight membered saturated ring containing one or two heteroatoms, including the nitrogen to which R² is attached, wherein the second heteroatom, when present, is selected from oxygen, nitrogen and sulfur, and wherein said ring may optionally be substituted at available binding sites with from one to three substituents selected, independently, from hydroxy and (C₁-C₆)alkyl;

each X and each Y is selected, independently, from hydrogen, halo (i.e., chloro, fluoro, bromo or iodo), (C₁-C₄)

alkyl optionally substituted with from one to three fluorine atoms, (C₁-C₄)alkoxy optionally substituted with from one to three fluorine atoms, cyano, nitro, amino, (C₁-C₄)alkylamino, di-[(C₁-C₄)alkyl]amino, NR⁵(C=O)(C₁-C₆)alkyl wherein R⁵ is hydrogen or (C₁-C₆)alkyl, and SO_p(C₁-C₆)alkyl wherein p is zero, one or two; and with the proviso that (a) no more than one of NR¹R², CR³R⁴ and R²NCR³ can form a ring; and (b) at least one X must not other than hydrogen when (i) R³ and R⁴ are both hydrogen, (ii) R¹ and R² are selected, independently, from hydrogen and (C₁-C₄)alkyl, and (iii) ring B is mono- or disubstituted with, respectively, one or two halo groups.

or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition according to claim 5, wherein the SRI antidepressant agent or pharmaceutically acceptable salt thereof is selected from compounds of the formula II, as defined below, and their pharmaceutically acceptable salts:



wherein phenyl ring A and phenyl ring B can each, independently, be replaced by a naphthyl group, and wherein when phenyl ring A is replaced by a naphthyl group, the ethereal oxygen of formula II and the carbon to which R³, R⁴ and NR¹R² are attached, are attached to adjacent ring carbon atoms of the naphthyl group and neither of said adjacent ring carbon atoms is also adjacent to a fused ring carbon atom of said naphthyl group;

n and m are selected independently, from one, two and three;

R¹ and R² are selected, independently, from hydrogen, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, and (C₂-C₄)alkynyl, or R¹ and R², together with the nitrogen to which they are attached, form a four to eight membered saturated ring containing one or two heteroatoms, including the nitrogen to which R¹ and R² are attached, wherein the second heteroatom, when present, is selected from oxygen, nitrogen and sulfur, and wherein said ring may optionally be substituted at available binding sites with from one to three substituents selected, independently, from hydroxy and (C₁-C₆)alkyl;

R³ and R⁴ are selected, independently, from hydrogen and (C₁-C₄)alkyl optionally substituted with from one to three fluorine atoms, or R³ and R⁴, together with the carbon to which they are attached, form a four to eight membered saturated carbocyclic ring and wherein said ring may optionally be substituted at available binding sites with from one to three substituents selected, independently, from hydroxy and (C₁-C₆)alkyl;

or R³ and R⁴, together with the nitrogen to which R² is attached and the carbon to which R³ is attached, form a four to eight membered saturated ring containing one or two heteroatoms, including the nitrogen to which R² is attached, wherein the second heteroatom, when present, is selected from oxygen, nitrogen and sulfur, and wherein said ring may optionally be substituted at available binding sites with from one to three substituents selected, independently, from hydroxy and (C₁-C₆)alkyl;

each X is selected, independently, from phenyl, heteroaryl and heterocycle, and wherein each X may be further substituted by hydrogen, halo, (C₁-C₄)alkyl optionally substituted with from one to three fluorine atoms, (C₁-C₄)alkoxy, optionally substituted with from one to three fluorine atoms, cyano, nitro, amino, hydroxy, carbonyl, (C₁-C₄)alkylamino, di-[(C₁-C₄)alkyl]amino, NR⁵(C=O)(C₁-C₄)alkyl, SO₂NR⁵R⁶ and SO_p(C₁-C₆)alkyl, wherein R⁵ and R⁶ are selected, independently, from hydrogen and (C₁-C₆)alkyl, and p is zero, one or two;

each Y_m is selected, independently, from hydrogen, halo, (C₁-C₄)alkyl optionally substituted with from one to

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three fluorine atoms, (C₁-C₆)alkoxy optionally substituted with from one to three fluorine atoms, cyano, nitro, amino, (C₁-C₄)alkylamino, di-(C₁-C₄)alkylamino, NR⁵(C=O)(C₁-C₄)alkyl, SO₂NR⁵R⁶ and SO_p(C₁-C₆)alkyl, wherein R⁵ and R⁶ are selected, independently, from hydrogen and (C₁-C₆)alkyl, and p is zero, one or two; and each Z is selected independently from hydrogen, halo, (C₁-C₄)alkyl optionally substituted with from one to three fluorine atoms, (C₁-C₄)alkoxy or a pharmaceutically acceptable salt thereof.

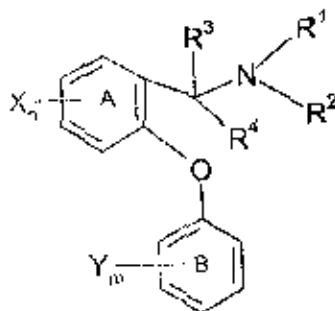
8. A pharmaceutical composition according to any one of claims 5-7 wherein a GABA-A alpha 2/3 agonist or a pharmaceutically acceptable salt thereof is selected from:

gaboxadol (4,5,6,7-tetrahydrosoxazolo[5,4-c]pyridin-3-ol);
 ganaxalone (3-oxo-4-oxo-5-oxo-6-methyl-5α-pregnan-20-one);
 4-chlorophenyl-((2-chlorophenyl)methyl)-4-chlorophenol;
 2-(6-chloro-2-methoxy-2,5,6,7,8,9-hexahydro-pyrazolo[4,3-c]cinnolin-3-one);
 1-(2-chlorophenyl)-2-methyl-2H-1,2,4-triazol-3-ylmethoxy-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;
 1-(2-chlorophenylphenyl)-N-((1-((2-methylphenyl)methyl)-benzimidazol-2-yl)methyl)-N-pentylcarboxamide;
 or
 2-(4-aminophenyl)-5-methylhexanoic acid.

9. A pharmaceutical composition according to any one of claims 5-8 wherein the amount of the SRI antidepressant or pharmaceutically acceptable salt thereof, in said composition is from about 0.5 mg to about 1500 mg and the amount of the GABA-A alpha 2/3 agonist or pharmaceutically acceptable salt thereof is from about 0.1 mg to about 500 mg.

10. Use of a combination that exhibits activity as an SRI antidepressant, or a pharmaceutically acceptable salt thereof; in combination with a GABA-A alpha 2/3 agonist or pharmaceutically acceptable salt thereof; in the preparation of a medicinal product for the treatment of anxiety or depression in a mammal, wherein the active agents are present in amounts that render the combination of the two agents effective in treating, respectively, anxiety or depression with increased efficacy.

11. The use according to claim 10, wherein the SRI antidepressant or pharmaceutically acceptable salt thereof is selected from compounds of the formula I,



wherein phenyl ring A and phenyl ring B can each, independently, be replaced by a naphthyl group, and wherein when phenyl ring A is replaced by a naphthyl group, the ethereal oxygen of structure I and the carbon to which R³, R⁴ and R² are attached are attached to adjacent ring carbon atoms of the naphthyl group and neither of said ring carbon atoms is also adjacent to a fused ring carbon atom of said naphthyl group;

wherein R³ and R⁴ are selected, independently, from one, two and three;
 wherein R¹ and R² are selected, independently, from hydrogen, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, and (C₂-C₄)alkynyl, or R¹ and R² together with the nitrogen to which they are attached, form a four to eight membered saturated ring containing one or two heteroatoms, including the nitrogen to which R¹ and R² are attached, wherein the second heteroatom, when present, is selected from oxygen, nitrogen and sulfur, and wherein said ring may optionally be substituted with from one to three substituents selected, independently, from hydroxy and (C₁-C₄)alkyl.

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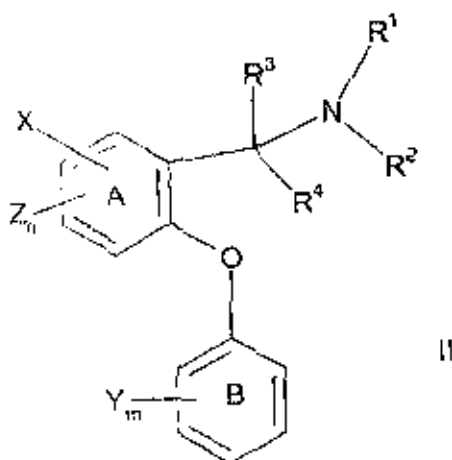
R¹ and R² are selected, independently, from hydrogen and (C₁-C₄) alkyl optionally substituted with from one to three fluoro atoms, or R³ and R⁴, together with the carbon to which they are attached, form a four to eight membered saturated carbocyclic ring, and wherein said ring may optionally be substituted at available binding sites with from one to three substituents selected, independently, from hydroxy and (C₁-C₆)alkyl;

or R³ and R⁴ together with the nitrogen to which R³ is attached and the carbon to which R⁴ is attached, form a four to eight membered saturated ring containing one or two heteroatoms, including the nitrogen to which R³ is attached, wherein the second heteroatom, when present, is selected from oxygen, nitrogen and sulfur, and wherein said ring may optionally be substituted at available binding sites with from one to three substituents selected, independently, from hydroxy and (C₁-C₆)alkyl;

where X and Z_m is selected, independently, from hydrogen, halo (i.e., chloro, fluoro, bromo or iodo), (C₁-C₄) alkyl optionally substituted with from one to three fluorine atoms, (C₁-C₄)alkoxy optionally substituted with from one to three fluoro atoms, cyano, nitro, amino, (C₁-C₄)alkylamino, di-[(C₁-C₄)alkyl]amino, NR⁵(C=O) (C₁-C₆)alkyl, wherein R⁵ is hydrogen or (C₁-C₆)alkyl, and SO_p(C₁-C₆)alkyl wherein p is zero, one or two; and with the proviso that (a) no more than one of NR¹R², CR³R⁴ and R²NCR³ can form a ring; and (b) at least one X must be other than hydrogen when (i) R³ and R⁴ are both hydrogen, (ii) R¹ and R² are selected, independently, from hydrogen and (C₁-C₄)alkyl, and (iii) ring B is mono- or disubstituted with, respectively, one or two halo groups;

or a pharmaceutically acceptable salt thereof.

12. The compound of claim 10, wherein the SR1 antidepressant or pharmaceutically acceptable salt thereof is selected from compounds of the formula II,



wherein phenyl, ring A and ring B can each, independently, be replaced by a naphthyl group, and wherein when phenyl, ring A or B is replaced by a naphthyl group, the etheral oxygen of structure I and the carbon to which R³, R⁴ and the nitrogen are attached, are attached to adjacent ring carbon atoms of the naphthyl group and neither of said adjacent ring carbon atoms is also adjacent to a fused ring carbon atom of said naphthyl group;

R³ and R⁴ are selected, independently, from one, two and three;

R¹ and R² are selected, independently, from hydrogen, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, and (C₂-C₄)alkynyl, or R¹ and R², together with the nitrogen to which they are attached, form a four to eight membered saturated ring containing one or two heteroatoms, including the nitrogen to which R¹ and R² are attached, wherein the second heteroatom, when present, is selected from oxygen, nitrogen and sulfur, and wherein said ring may optionally be substituted at available binding sites with from one to three substituents selected, independently, from hydroxy and (C₁-C₆)alkyl;

R³ and R⁴ are selected, independently, from hydrogen and (C₁-C₄) alkyl optionally substituted with from one to three fluoro atoms, or R³ and R⁴, together with the carbon to which they are attached, form a four to eight membered saturated carbocyclic ring, and wherein said ring may optionally be substituted at available binding sites with from one to three substituents selected, independently, from hydroxy and (C₁-C₆)alkyl;

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wherein R^2 and R^3 together, with the nitrogen to which R^2 is attached and the carbon to which R^3 is attached, form a five- or six-membered saturated ring containing one or two heteroatoms, including the nitrogen to which R^2 is attached; wherein the second heteroatom, when present, is selected from oxygen, nitrogen and sulfur, and wherein each R^2 and R^3 may optionally be substituted at available binding sites with from one to three substituents selected independently from hydroxy and (C_1-C_6) alkyl;

each R^1 is selected independently from phenyl, heteroaryl and heterocycle, and wherein each X may be further available to be hydrogen, halo, (C_1-C_2) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_4) alkoxy optionally substituted with from one to three fluorine atoms, cyano, nitro, amino, hydroxy, carbonyl, (C_1-C_6) alkylamino, $di[(C_1-C_4)alkyl]amino$, $NR^5(C=O)(C_1-C_4)alkyl$, $SO_2NR^5R^6$ and $SO_p(C_1-C_6)alkyl$, wherein R^5 and R^6 are selected independently from hydrogen and $(C_1-C_6)alkyl$, and p is zero, one or two;

each R^2 is selected independently from hydrogen, halo, $(C_1-C_4)alkyl$ optionally substituted with from one to three fluorine atoms, $(C_1-C_4)alkoxy$ optionally substituted with from one to three fluorine atoms, cyano, nitro, amino, $di[(C_1-C_4)alkyl]amino$, $NR^5(C=O)(C_1-C_4)alkyl$, $SO_2NR^5R^6$ and $SO_p(C_1-C_6)alkyl$, wherein R^5 and R^6 are selected independently from hydrogen and $(C_1-C_6)alkyl$, and p is zero, one or two; and each R^3 is selected independently from hydrogen, halo, $(C_1-C_4)alkyl$ optionally substituted with from one to three fluorine atoms, $(C_1-C_6)alkoxy$;

or a pharmaceutically acceptable salt thereof.

13. The use according to any one of claims 10-12, wherein the SRI antidepressant, or pharmaceutically acceptable salt thereof, and a GABA-A alpha 2/3 agonist or pharmaceutically acceptable salt thereof, are administered as part of the same composition.

14. The use according to any one of claims 10-13, wherein the GABA-A alpha 2/3 agonist, or pharmaceutically acceptable salt thereof, is administered in an amount from about 0.1 mg per day to about 500 mg per day, and the SRI antidepressant, or pharmaceutically acceptable salt thereof, is administered in an amount from about 10 mg per day to about 1800 mg per day.

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Striessnig et al. *J. Clin. Psychopharmacol.* **1987**, *7 suppl. 6*, 24S-35S). A key point in their hypothesis is that the effects of SSRIs on the release-controlling somatodendritic autoreceptors (5-HT_{1A}) limit the release of 5-HT in terminal areas and thus the effect of 5-HT on the reuptake in those regions. This is supported by microdialysis experiments in which the magnitude of the increase in extracellular 5-HT elicited by a single dose of an SSRI is antagonized by co-administration of a 5-HT_{1A} autoreceptor antagonist (Invernizzi et al. *Brain Res.* **1992**, *580*, p. 322-324 and Hjorth, S., *J. Neurochem.* **1993**, *60*, p. 776-779).

16. The effects of combined administration of a compound that inhibits serotonin reuptake and a 5-HT_{1A} receptor antagonist has been evaluated in several studies (Innis, R.B. et al. *Eur. J. Pharmacol.* **1987**, *141*, p. 1095-204 and Gartside, S.E., *Br. J. Pharmacol.* **1995**, *115*, p. 1569-1575, Hare, C. et al. *Trends in Pharmacol. Science* **1994**, *15*, 220). In these studies it was found that 5-HT_{1A} receptor antagonists would abolish the initial brake on 5-HT reuptake and thus induced by the serotonin reuptake inhibitors and thus produce an increase in the level of 5-HT transmission and a rapid onset of therapeutic action.

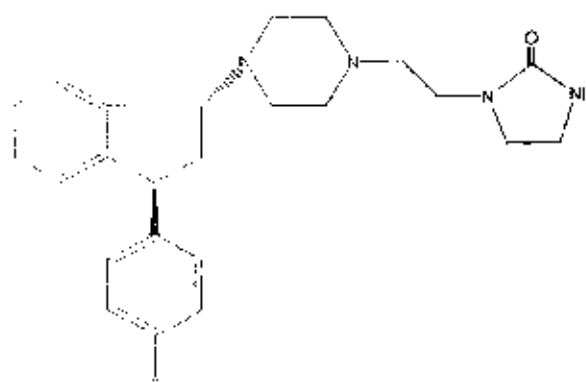
Several patent applications have been filed which cover the use of a combination of a 5-HT_{1A} antagonist and a serotonin reuptake inhibitor for the treatment of depression (see WO 96/03400, WO 97/28141 and EP-A2-714 663).

20. Another approach to increase terminal 5-HT would be through blockade of the 5-HT_{1B} autoreceptors. Microdialysis experiments in rats have indeed shown that increase of extracellular 5-HT by citalopram is potentiated by GMC 2-29, an experimental 5-HT_{1B} antagonist (see *ibid.*).
21. Several patent applications covering the combination of an SSRI and a 5-HT_{1B} antagonist have also been filed (WO 97/28141, WO 96/03400, EP-A 701819 and WO 97/28141).

It has also been found that mirdalone having the general formula

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or pharmaceutically acceptable salts thereof may be used to augment and provide faster onset of the therapeutic effect of serotonin reuptake inhibitors.

5. Indication

The present invention thus provides:

1. The present invention relates to the use of irindalone or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition to be used in combination with a serotonin reuptake inhibitor or any other compound, which causes an elevation in the level of extracellular serotonin.

2. The present invention relates to the use of irindalone or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition useful for the treatment of depression, providing faster onset of the therapeutic effect of a serotonin reuptake inhibitor or any other compound, which causes an elevation in the level of extracellular serotonin.

3. The present invention relates to the use as above, of irindalone, or a pharmaceutically acceptable salt thereof, for the treatment of depression, anxiety disorders, affective disorders, eating disorders such as bulimia, anorexia and binge eating, dyslexia, premenstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder and drug abuse, in particular depression.

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a) the serotonin reuptake inhibitor or any other compound, which causes an elevation in the level of extracellular serotonin.

- 15 The anxiety disorders mentioned above include general anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post trauma stress disorder or social phobia disorder.

- As used herein, the term augmenting covers improving the therapeutic effect and/or
20 augmenting the therapeutic effect of an SRI or a compound which causes an elevation in the level of extracellular 5-HT.

- Furthermore, the invention relates to the use of irindalone or a
pharmaceutically acceptable salt thereof and a compound, which is a serotonin reuptake
inhibitor or a compound, which causes an elevation in the level of extracellular
25 serotonin, for the preparation of a pharmaceutical composition or kit for the treatment of
the anxiety disorders responsive to the therapeutic effect of a serotonin reuptake inhibitor,
or a compound, which causes an elevation in the level of extracellular serotonin,

- the anxiety disorders responsive to a serotonin reuptake inhibitor include depression, anxiety
30 disorders, phobic or obsessive disorders, eating disorders such as bulimia, anorexia and
vomiting, premenstrual syndrome, cognitive disorders, impulse control
disorders, attention deficit hyperactivity disorder and drug abuse, in particular depression.

- The term anxiety disorders is as defined above.

- 25 The term combination in the present invention relates to the use of irindalone or a
pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical
composition, in which is adapted for simultaneous administration of the active
ingredient and at least one other such pharmaceutical compositions may contain the active
30 ingredients within the same unit dosage form, e.g. in the same tablet or capsule. Such
pharmaceutical compositions may contain the active ingredients as a homogenous mixture or in
physically distinct parts of the unit dosage form.

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113**Claims:**

1. The use of irindalone or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition to be used in combination with a serotonin reuptake inhibitor or any other compound, which causes an elevation in the level of extracellular serotonin.
2. The use of irindalone or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition useful for augmenting and/or providing faster onset of the therapeutic effect of a serotonin reuptake inhibitor or any other compound, which causes an elevation in the level of extracellular serotonin.
3. The use according to claims 1 or 2 wherein the serotonin reuptake inhibitor or the compound, which causes an elevation in the level of extracellular serotonin, is used in the treatment of depression, anxiety disorders and other affective disorders, eating disorders such as bulimia, anorexia and obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder and drug abuse.
4. The use according to claim 3 wherein the serotonin reuptake inhibitor or the compound, which causes an elevation in the level of extracellular serotonin, is used in the treatment of anxiety disorders including general anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post trauma stress disorder or social anxiety disorder.
5. The use according to claim 3 wherein the serotonin reuptake inhibitor or the compound, which causes an elevation in the level of extracellular serotonin, is used in the treatment of depression.
6. The use according to claims 1 to 5 wherein the tartrate salt of irindalone is used.
7. The use according to claims 1 to 6 wherein the serotonin reuptake inhibitor is

selected from citalopram, escitalopram, fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, dapoxetine, nefazodone, imipramin, femoxetine and clomipramine or a pharmaceutically acceptable salt of any of these compounds.

- 5 8. The use according to claim 7 wherein the serotonin reuptake inhibitor is a *selective serotonin reuptake inhibitor*.
9. The use according to claim 8 wherein the serotonin reuptake inhibitor is selected from citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline and paroxetine or a
10 pharmaceutically acceptable salt of any of these compounds.
10. The use of irindalone or a pharmaceutically acceptable salt thereof and a compound, which is a serotonin reuptake inhibitor, or any other compound which causes an elevation in the level of extracellular serotonin, for the preparation of a
15 pharmaceutical composition or kit for the treatment of diseases or disorders responsive to the therapeutic effect of a serotonin reuptake inhibitor or any other compound causing an elevation in the level of extracellular serotonin.
11. The use according to claim 10 for the preparation of a pharmaceutical
20 composition or kit useful for the treatment of depression, anxiety disorders and other affective disorders, eating disorders such as bulimia, anorexia and obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder and drug abuse.
- 25 12. The use according to claim 11 for the preparation of a pharmaceutical composition or kit useful for the treatment of anxiety disorders, including general anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post trauma stress disorder or social anxiety disorder.
- 30 13. The use according to claim 11 for the preparation of a pharmaceutical composition for the treatment of depression.

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14. The use according to claims 10 to 13 wherein irindalone is used in the form of a tartrate salt.

15. The use according to claims 10 to 14 wherein the serotonin uptake inhibitor is selected from citalopram, escitalopram, fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, dapoxetine, nefazodone, imipramin, femoxetine and clomipramine or a pharmaceutically acceptable salt of any of these compounds.

16. The use according to claim 15 wherein the serotonin reuptake inhibitor used is a selective serotonin reuptake inhibitor.

17. The use according to claim 16 wherein the selective serotonin reuptake inhibitor is citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline and paroxetine or a pharmaceutically acceptable salt of any of these compounds.

18. The use according to claims 10-17 wherein the pharmaceutical composition prepared is adapted for simultaneous administration of the active ingredients.

19. The use according to claim 18 wherein the active ingredients are contained in the same unit dosage form.

20. The use according to claims 10-17 wherein the pharmaceutical composition prepared is adapted for sequential administration of the active ingredients.

21. The use according to claim 20 wherein the active ingredients are contained in discrete unit dosage forms.

22. A pharmaceutical composition or kit comprising irindalone or a pharmaceutically acceptable salt thereof and a compound, which is a serotonin reuptake inhibitor, or any other compound which causes an elevation in the level of extracellular serotonin, and optionally pharmaceutically acceptable carriers or diluents.

23. A pharmaceutical composition or kit according to claim 22 containing irindalone in the form of the tartrate salt thereof.

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24. The pharmaceutical composition or kit according to claims 22 to 23 characterised in that the serotonin uptake inhibitor is selected from citalopram, escitalopram, fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, dapoxetine, nefazodone, imipramin, fenoxetone and clomipramine or a pharmaceutically acceptable salt of any of these compounds.

25. The pharmaceutical composition or kit according to claim 24 wherein the serotonin reuptake inhibitor is a selective serotonin reuptake inhibitor.

26. The pharmaceutical composition or kit according to claim 25 wherein the selective serotonin reuptake inhibitor is citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline and paroxetine or a pharmaceutically acceptable salt of any of these compounds.

27. The pharmaceutical composition according to claims 22 to 26 which is adapted for simultaneous administration of the active ingredients.

28. The pharmaceutical composition according to claim 27 wherein the active ingredients are contained in the same unit dosage form.

29. The pharmaceutical composition or kit according to claims 22 to 26 which is adapted for sequential administration of the active ingredients.

30. The pharmaceutical composition according to claim 29 wherein the active ingredients are contained in discrete dosage forms.

31. A method for the treatment of diseases or disorders responsive to a serotonin reuptake inhibitor or any other compound which causes an elevation in the level of extracellular serotonin, comprising administering irindalone or a pharmaceutically acceptable salt thereof and a serotonin reuptake inhibitor, or a compound which causes an elevation in the level extracellular serotonin, to an individual in need thereof.

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32. A method for augmenting and/or providing faster onset of the therapeutic effect of a serotonin reuptake inhibitor, or any other compound which causes an elevation in the level of extracellular serotonin, comprising administering irindalone or a pharmaceutically acceptable salt thereof to an individual to be treated with or undergoing
5 treatment with the serotonin reuptake inhibitor, or any other compound which causes an elevation in the level of extracellular serotonin.

33. A method according to claims 31 to 32 wherein the individual suffers from depression, anxiety disorders and other affective disorders, eating disorders such as
10 bulimia, anorexia and obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder and drug abuse.

34. The method according to claim 33 wherein the individual suffers from anxiety
15 disorder, including general anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post trauma stress disorder or social anxiety disorder.

35. The method according to claim 33 wherein the individual suffers from depression.

20 36. The method according to claims 31 to 32 wherein irindalone is used in the form of the tartrate salt.

37. The method according to claims 31 to 32 wherein the serotonin uptake inhibitor is selected from citalopram, escitalopram, fluoxetine, sertraline, paroxetine, fluvoxamine,
25 venlafaxine, dapoxetine, nefazodone, imipramin, femoxetine and clomipramine or a pharmaceutically acceptable salt of any of these compounds.

38. The method according to claim 37 wherein the serotonin reuptake inhibitor is a selective serotonin reuptake inhibitor.

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39. The pharmaceutical composition according to claim 38 wherein the selective serotonin reuptake inhibitor is citalopram, escitalopram, fluoxetine, fluvoxamine,

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sertraline and paroxetine or a pharmaceutically acceptable salt of any of these compounds.

40. The method according to claims 31-39 wherein the active ingredients are
5 administered simultaneously.

41. The method according to claim 40 wherein the active ingredients are administered
in the same unit dosage form.

10 42. The method according to claims 31-39 wherein the active ingredients are
administered sequentially.

43. The method according to claim 42 wherein the active ingredients are contained in
two discrete unit dosage forms.

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119[Atrás](#)

1 página o páginas que se imprimirán.

Registro: 1

Título: Pharmacodynamic effects and possible therapeutic uses of THIP, a specific GABA-agonist.

Autor(es): Christensen AV; Svendsen O; Krogsgaard-Larsen P

Fuente: Pharmaceutisch Weekblad. Scientific Edition [Pharm Weekbl Sci] 1982 Oct 22; Vol. 4 (5), pp. 145-53.

Tipo de publicación: Journal Article; Review

Idioma: English

Journal Information: Country of Publication: NETHERLANDS NLM ID: 7907992 Publication Model: Print Cited Medium: Print ISSN: 0167-6555 (Print) Subsets: MEDLINE

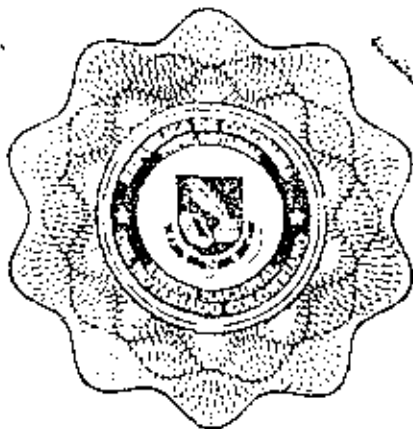
Términos MeSH: Isoxazoles/*pharmacology
Oxazoles/*pharmacology
gamma-Aminobutyric Acid/*physiology
Analgesics; Animals; Brain/physiology; Humans; Isoxazoles/therapeutic use; Methylphenidate/pharmacology; Neurons/physiology; Stereotyped Behavior/drug effects; Synaptic Transmission/drug effects

Resumen: THIP (4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol) is a potent and specific GABA receptor agonist which does not influence the GABA uptake system or GABA metabolizing enzymes. The specificity for the GABA receptor is also demonstrated by lack of action on monoaminergic, cholinergic, histaminergic or opiate receptors. Since in recent years GABA receptor stimulants-among others THIP--have become available many have speculated as to what clinical indication GABA-ergic stimulation might be an important element. The first suggestion was that GABA-ergic drugs by an inhibitory effect on the dopamine neurons would improve the antischizophrenic effect of neuroleptics and improve tardive dyskinesia. Furthermore, studies on brains of deceased Parkinson and Huntington's chorea patients have demonstrated a low level of GABA and its synthesizing enzyme glutamic acid decarboxylase (GAD) in the basal ganglia. Also in epilepsy and diseases with dementia a deficit in the GABA system has been proposed. Therefore a therapeutic strategy for these diseases may be supplementary treatment with drugs which increase GABA receptor activity. Furthermore, recent results in humans have shown that GABA agonists perhaps also could be of benefit in mania and depressions. When considering the neurophysiological elements of nociception and muscle tone it is also reasonable to suggest that GABA-ergic stimulation may reduce pain perception and muscle tone.

Número de referencias: 63

CAS Registry Number: 0 (Analgesics)
0 (Isoxazoles)
0 (Oxazoles)
113-45-1 (Methylphenidate)
56-12-2 (*gamma-Aminobutyric Acid*)
64603-91-4 (4,5,6,7-tetrahydroisoxazolo(5,4-c)pyridin-3-ol)

Fecha(s) de la entrada: Date Created: 19830119 Date Completed: 19830119 Latest Revision: 20041117



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AA 8567146

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REPUBLICA DE COLOMBIA

NOTARIA 33 DE BOGOTA D.C.

ESCRITURA PUBLICA NUMERO: 1 6 5 8

- - MIL SEISCIENTOS CINCUENTA Y OCHO - -

FECHA DE OTORGAMIENTO: CUATRO (4) DE

JULIO

DEL AÑO DOS MIL DOS (2002).

ACTO:

1.- PODER ESPECIAL.

OTORGADO POR: LAFRANCOL S.A., con Nit. No. 890.301.463-E

a favor de: JOSE LUIS REYES VILLAMIZAR, con C.C.No. 79.152.473 de Usaquén - Bogotá.

DIANA BEATRIZ LOPEZ

NOTARIA TREINTA Y TRES (33) DE BOGOTA D.C.

EN LA CIUDAD DE BOGOTA, DISTRITO CAPITAL,
DEPARTAMENTO DE CUNDINAMARCA, REPUBLICA DE COLOMBIA,
ANTE MI, DIANA BEATRIZ LOPEZ,

NOTARIA TREINTA Y TRES (33)

DE ESTE CIRCULO SE OTORGA LA ESCRITURA PUBLICA QUE
SE CONSIGNA EN LOS SIGUIENTES TERMINOS:-----COMPARECIO: JUAN MARIA RENDON, mayor de edad,
vecino de Bogotá, D.C, identificado con la cédula de
ciudadanía número 17.125.100

Expedida en Bogotá

Y manifestó:-----

PRIMERO: Que obra en su carácter de Representante
Legal de en nombre y representación de LAFRANCOL
S.A, sociedad comercial organizada y existente
conforme a las leyes colombianas, con domicilio
sede principal en Cali - Valle, constituida mediante
escritura pública número

De la Notaría

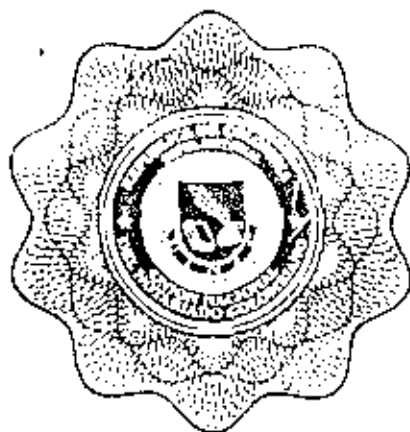
De fecha

Reformada en distintas oportunidades, según consta en el certificado expedido por la Cámara de Comercio de Cali - Valle.-----

SEGUNDO: Que en tal carácter, por este público instrumento, concede PODER ESPECIAL, PERO AMPLIO Y SUFICIENTE a JOSE LUIS REYES VILLAMIZAR, mayor de edad, vecino de Bogotá, D.C, identificado con la cédula de ciudadanía número 79.152.473 de Usaquén, abogado en ejercicio, portador de la T.P.No. 446 55 del C.S. de la J., domiciliado en Bogotá, D.C, República de Colombia, con dirección en la carrera 17 No. 88-23, Oficina 205, de la misma ciudad, como su representante con poder especial, amplio y suficiente, para obtener la protección los derechos de propiedad industrial y de libre competencia de Lafrancol S.A., a cuyo efecto lo autorizo, par que nos represente ante cualesquiera entidad o persona, ejerza o no jurisdicción, especialmente ante las el orden administrativo, contencioso, administrativo y judicial, en todo lo concerniente a los siguientes asuntos:-----

a.- Obtención, formulación de oberservaciones y oposición a patentes de invención, modelos y dibujos industriales y el registro de licencias de uso de esos derechos.-----

b.- Las acciones de oposición, cancelación, nulidad, medidas cautelares, concesión de licencias y en general los procesos civiles, penales, administrativos o contencioso- administrativos relacionados con estos derechos u otros de diferente naturaleza, acciones y procesos que



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AA 8567152

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promueva Lafrancol S.A., o se
promuevan contra esta y.-----

c.- Para que en todos los asuntos
arriba determinados, tanto en
los términos señalados por los
artículos 42 y complementarios

de la decisión 486 de la Comunidad Andina como del
artículo 70 del C.P.C. pueda sustituir este
mandato, transigir, conciliar, admitir los hechos del
proceso, desistir, cancelar, recibir, renunciar y
ratificar los actos de agentes oficiosos y ceder a
título gratuito y/o oneroso, licenciar, inscribir
contratos de cesión y de licencia, inscripción de
prendas, levantamiento de prendas, inscribir
derechos de retención y en general todos los asuntos
que se deban tramitar ante la Superintendencia de
Industria y Comercio.-----

Manifestamos que de la veracidad de las
declaraciones del contenido y autenticidad de los
documentos anexos en éste instrumento público sólo
respondemos los comparecientes.-

HASTA AQUI LA MINUTA PRESENTADA

OTORGAMIENTO Y AUTORIZACION: Leído el presente
instrumento Público por los comparecientes y
advertidos de la formalidad de su contenido, dentro
del término legal, lo hallaron conforme con sus
intenciones y lo aprobaron en todas sus partes y
firmaron junto con la Suscrita Notaria quien da fe y
lo autoriza. -----

Se utilizaron las hojas de papel Notarial Números
AA 8567146, 8567152.



DERECHOS NOTARIALES: \$ 49.600.00

RESOLUCION No. 4188 del 28 de Diciembre del 2001

JUAN MARIA RENDON

C.C. No. 14.125.100 de Bogotá

LAFRANCOL S.A.

Nit. No. 890.301.463-8

TEL: 622-04-66.

ACEPTO :

Como Notario Ventisiete del Circuito de Bogotá, hago constar que esta copia coincide con original que se ha presentado Bogotá D.C. - Colombia.

20 DIC 2005

GUSTAVO SAMPER RODRIGUEZ
NOTARIO VENTISIEVE

JOSE LUIS REYES VILLAMIZAR

C.C. No. 79.152.473

TEL: 621-2631

DIANA BEATRIZ LOPEZ

NOTARIA 33 DE BOGOTA D.C.

n.c.a.

Es segunda COPIA (FOTOCOPIA)

tomada de su original que se expide conforme al

Artículo 79 del Decreto 960 de 1970 en 06

hojas útiles con destino a Jose Luis Reyes

Villamizar

Sancti Spiritus

1999: Dec. 1772/79

05 JUL 2002

Qui Amun





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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070529

Hora Certificado : 123616

Operacion: 02NA80529024

PAGINA No. 1

null

CERTIFICA:

NOMBRE: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.
DOMICILIO: CALI VALLE
DIRECCION COMERCIAL : ---K 1 46 84
DIRECCION NOTIFICACION JUDICIAL: ---K 1 46 84
CIUDAD: CALI
MATRICULA MERCANTIL NRO. 5233-4 FECHA MATRICULA : 02 DE OCTOBER DE 1958
DIRECCION ELECTRONICA : esperanzacortes@lafrancol.net
AFILIADO

CERTIFICA:

NIT : 890301463-6

CERTIFICA:

QUE POR ESCRITURA NRO. 1434 DEL 29 DE SEPTIEMBRE DE 1958 NOTARIA CUARTA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 02 DE OCTOBER DE 1958 BAJO EL NRO. 18319 DEL LIBRO IX , SE CONSTITUYO LA SOCIEDAD DENOMINADA LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.

CERTIFICA:

REFORMAS

DOCUMENTO	FECHA.DOC	ORIGEN	FECHA.INS	NRO.
INS LIBRO				
E.P. 1104 19467	30/06/1959	NOTARIA CUARTA DE CALI	07/07/1959	
E.P. 2309 20089	26/12/1959	NOTARIA CUARTA DE CALI	29/12/1959	
E.P. 1725 24528	24/07/1962	NOTARIA CUARTA DE CALI	26/07/1962	
E.P. 1824	31/07/1963	NOTARIA CUARTA DE CALI	14/08/1963	

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070529

Hora Certificado : 123616

Operacion: 02NA80529024

PAGINA No. 2

26360					
E.P. 2422	25/10/1963	NOTARIA CUARTA DE CALI	28/10/1963		
26717					
E.P. 1720	16/09/1964	NOTARIA CUARTA DE CALI	22/09/1964		
28406					
E.P. 101	31/01/1966	NOTARIA CUARTA DE CALI	01/02/1966		
31039					
E.P. 552	21/03/1968	NOTARIA CUARTA DE CALI	01/04/1968		
35711					
E.P. 4964	12/12/1972	NOTARIA CUARTA DE CALI	16/01/1973		
2975 IX					
E.P. 1956	30/05/1973	NOTARIA CUARTA DE CALI	13/06/1973		
4337 IX					
E.P. 4964	12/12/1972	NOTARIA CUARTA DE CALI	28/11/1973		
5994 IX					
E.P. 5579	12/11/1973	NOTARIA CUARTA DE CALI	28/11/1973		
5995 IX					
E.P. 4406	30/09/1974	NOTARIA CUARTA DE CALI	28/11/1974		
10887 IX					
E.P. 192	03/02/1978	NOTARIA CUARTA DE CALI	14/02/1978		
25355 IX					
E.P. 3479	07/09/1979	NOTARIA CUARTA DE CALI	19/09/1979		
34204 IX					
E.P. 4274	12/12/1984	NOTARIA NOVENA DE CALI	19/12/1984		
73088 IX					
E.P. 1155	21/05/1985	NOTARIA SEPTIMA DE CALI	03/06/1985		
76917 IX					
E.P. 1553	20/06/1986	NOTARIA SEPTIMA DE CALI	08/07/1986		
86997 IX					
E.P. 1458	09/06/1987	NOTARIA SEPTIMA DE CALI	24/12/1987		
3508 IX					
E.P. 7222	14/12/1988	NOTARIA TERCERA DE CALI	19/12/1988		
13847 IX					
E.P. 4530	04/09/1989	NOTARIA TERCERA DE CALI	07/09/1989		
21508 IX					
E.P. 3865	02/08/1990	NOTARIA TERCERA DE CALI	13/08/1990		
31708 IX					
E.P. 8305	13/12/1995	NOTARIA TERCERA DE CALI	23/01/1996		
557 IX					
E.P. 4559	16/11/1999	NOTARIA TERCERA DE CALI	26/11/1999		
7911 IX					
E.P. 6.004	02/12/2004	NOTARIA TERCERA DE CALI	14/12/2004		
13371 IX					
E.P. 6241	27/12/2006	NOTARIA TERCERA DE CALI	19/01/2007		

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070529

Hora Certificado : 123616

Operacion: 02NA80529024

PAGINA No. 3

625 IX

CERTIFICA:

VIGENCIA: 29 DE SEPTEMBER DEL AÑO 2057

CERTIFICA:

OBJETO SOCIAL. SE OCUPA EN: A) FABRICACION, DISTRIBUCION Y VENTA EN EL TERRITORIO DE LA REPUBLICA DE COLOMBIA O EN EL EXTRANJERO DE CUALESQUIERA TIPOS DE VACUNAS, PRODUCTOS QUIMICOS, FARMACEUTICOS ALIMENTICIOS FUNCIONALES, COSMETICOS Y FISIOLOGICOS, REACTIVOS, ANTIBIOTICOS PARA USO HUMANO Y VETERINARIO, PRODUCTOS DIETETICOS, COLORANTES DE PERFUMERIA Y AFINES. B) LA REPRESENTACION DE CASAS FABRICANTES NACIONALES O EXTRANJERAS DE ESTOS MISMOS PRODUCTOS. C) FABRICACION, IMPORTACION, DISTRIBUCION Y VENTA DE CUALESQUIERA TIPOS DE PRODUCTOS VETERINARIOS. D) LA REALIZACION DE TODOS LOS ACTOS, CONTRATOS, CONVENIOS, DIRECTAMENTE RELACIONADOS CON LOS FINES ANTES INDICADOS. EN DESARROLLO DE SU OBJETO SOCIAL PODRA LA SOCIEDAD ADQUIRIR Y VENDER BIENES RAICES Y MUEBLES, DARLOS Y TOMARLOS EN ARRENDAMIENTO, GARANTIZAR CON HIPOTECA SOBRE LOS BIENES RAICES O CON PRENDA SOBRE LOS BIENES MUEBLES, OBLIGACIONES A CARGO DE LA SOCIEDAD; DAR Y RECIBIR A MUTUO COMERCIAL DINERO Y CELEBRAR LOS CONTRATOS COMERCIALES DE CAMBIO EN TODAS SUS MANIFESTACIONES, FUNDAR EMPRESAS QUE TENGAN LA MISMA FINALIDAD SOCIAL O ASOCIARSE CON ELLAS.

CERTIFICA:

ORGANOS DE DIRECCION Y ADMINISTRACION: 1) ASAMBLEA GENERAL DE ACCIONISTAS; 2) JUNTA DIRECTIVA; 3) GERENCIA GENERAL. TAMBIEN TENDRA UN REVISOR FISCAL.

ADMINISTRACION: LA ADMINISTRACION INMEDIATA DE LA SOCIEDAD, SU REPRESENTACION LEGAL Y LA GESTION DE LOS NEGOCIOS SOCIALES ESTARAN A CARGO DE UN GERENTE, DESIGNADO POR LA ASAMBLEA GENERAL DE ACCIONISTAS, PARA PERIODOS DE DE DOS (2) AÑOS REELEGIBLE INDEFINIDAMENTE Y REMOVIBLE LIBREMENTE POR ELLA EN CUALQUIER TIEMPO.

PARAGRAFO PRIMERO. SUPLENTE: EL GERENTE Y REPRESENTANTE LEGAL TENDRA LOS SIGUIENTES SUPLENTE: PRIMERO, SEGUNDO Y TERCERO QUE LO REEMPLAZARAN EN LOS CASOS DE AUSENCIAS ACCIDENTAL, TEMPORAL Y ABSOLUTA CON LAS LIMITACIONES QUE MAS ADELANTE SE ESTABLECEN.

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070529

Hora Certificado : 123616

Operacion: 02NA80529024

PAGINA No. 4

PARAGRAFO SEGUNDO. EL TERCER SUPLENTE DEL GERENTE GENERAL Y REPRESENTANTE LEGAL ESTARA LIMITADO EN SUS FUNCIONES A: COMPROMETER LOS NEGOCIOS SOCIALES EN CUANTIA NO SUPERIOR A CUATRO MIL DOSCIENTOS SALARIOS MINIMOS MENSUALES LEGALES VIGENTES (4.200 SMLV); CELEBRAR CONTRATOS COMERCIALES DE COMPRAVENTA EN GENERAL YA SEA CON LA NACION (MINISTERIOS Y DEPARTAMENTOS ADMINISTRATIVOS), ENTIDADES DESCENTRALIZADAS (ESTABLECIMIENTOS PUBLICOS, EMPRESAS INDUSTRIALES Y COMERCIALES DEL ESTADO, SOCIEDADES DE ECONOMIA MIXTA), EMPRESAS SOCIALES CIVILES Y COMERCIALES, CUALQUIERA QUE SEA SU NATURALEZA CON FACULTADES PARA EXIGIR O SUSCRIBIR LOS DOCUMENTOS Y GARANTIAS NECESARIOS HASTA LA CUANTIA ANTES MENCIONADA.

FUNCIONES DEL GERENTE: A) ... B) EJECUTAR Y HACER CUMPLIR LOS ACUERDOS Y DECISIONES DE LA ASAMBLEA GENERAL DE ACCIONISTAS Y DE LA JUNTA DIRECTIVA Y HACER USO DE LA RAZON SOCIAL. C) REPRESENTAR LEGALMENTE A LA SOCIEDAD CONFORME A LA LEY ANTE TODAS LAS AUTORIDADES CIVILES, JUDICIALES, MILITARES, SANITARIAS, DE POLICIA, ADUANALES, POSTALES, ETC. G) LLEVAR A CABO LA GESTION COMERCIAL Y FINANCIERA. H) TENDRA LA PLENA RESPONSABILIDAD DE LA ACCION ADMINISTRATIVA, LA COORDINACION Y LA SUPERVISION GENERAL DE LA SOCIEDAD, LAS CUALES CUMPLIRA CON ARREGLO A LAS NORMAS DE LOS ESTATUTOS.

EN EL EJERCICIO DE SUS FUNCIONES, EL GERENTE PUEDE: 1.- COMPARECER EN LOS JUICIOS, TRANSIGIR Y COMPROMETER LOS NEGOCIOS SOCIALES DE CUALQUIERA NATURALEZA QUE FUEREN, INTERPONER TODO GENERO DE RECURSOS Y CONSTITUIR APODERADOS QUE LO REPRESENTEN JUDICIAL O EXTRAJUDICIALMENTE. 2.- ENAJENAR A CUALQUIER TITULO Y COMPRAR BIENES MUEBLES, CELEBRAR CONTRATOS COMERCIALES DE COMPRA Y VENTA EN GENERAL YA SEA CON LA NACION (MINISTERIOS Y DEPARTAMENTOS ADMINISTRATIVOS), ENTIDADES DESCENTRALIZADAS (ESTABLECIMIENTOS PUBLICOS), EMPRESAS INDUSTRIALES Y COMERCIALES DEL ESTADO, SOCIEDADES DE ECONOMIA MIXTA), EMPRESAS O SOCIEDADES CIVILES Y COMERCIALES CUALQUIERA QUE SEA SU NATURALEZA Y SU CUANTIA, CON AMPLIAS FACULTADES QUE EXIGIR O SUSCRIBIR LOS DOCUMENTOS, Y GARANTIAS NECESARIAS. CONTRATAR PRESTAMOS CUALQUIERA QUE SEA SU CUANTIA, CELEBRAR EL CONTRATO COMERCIAL DE MUTUO EN TODAS SUS MANIFESTACIONES Y SUSCRIBIR LOS DOCUMENTOS Y COMPROMISOS RESPECTIVOS. HACER DEPOSITOS EN BANCOS Y AGENCIAS BANCARIAS, FIRMAR CHEQUES, LETRAS, PAGARES, GIROS, LIBRANZAS Y CUALQUIER OTRO DOCUMENTO, ASI COMO NEGOCIAR ESTOS INSTRUMENTOS, TENERLOS, COBRARLOS, PAGARLOS, DESCARGARLOS, ETC.

CERTIFICA:

DOCUMENTO: ACTA No. 99 DEL 14 DE MARCH DE 2002

ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS

INSCRIPCION: 09 DE SEPTEMBER DE 2002 No. 14675 DEL LIBRO IX

FUE(ON) NOMBRADO(S):

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070529

Hora Certificado : 123616

Operacion: 02NA80529024

PAGINA No. 5

VICEPRESIDENTE

ROBERTO S. VENTURA PAULY

C.C.16697614

GERENTE GENERAL Y REPRESENTANTE LEGAL

JUAN MARIA RENDON GUTIERREZ

C.C.17123100

PRIMER SUPLENTE DEL GERENTE

ESTHER ISABEL VENTURA DE RENDON

C.C.38979831

SEGUNDO SUPLENTE DEL GERENTE

ROBERTO M. VENTURA CRISPINO

C.C.9086003

PRESIDENTE

ESTHER ISABEL VENTURA DE RENDON

C.C.38979831

CERTIFICA:

DOCUMENTO: ACTA No. 105 DEL 09 DE NOVEMBER DE 2004

ORIGEN: ASAMBLEA DE ACCIONISTAS

INSCRIPCION: 17 DE FEBRUARY DE 2005 No. 2032 DEL LIBRO IX

FUE(ON) NOMBRADO(S):

TERCER SUPLENTE DEL GERENTE

JUAN PABLO REYES VILLAMIZAR

C.C.80419709

CERTIFICA:

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070529 Hora Certificado : 123616

Operacion: 02NA80529024 PAGINA No. 6

DOCUMENTO: ACTA No. 99 DEL 14 DE MARCH DE 2002
ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS
INSCRIPCION: 09 DE SEPTEMBER DE 2002 No. 14675 DEL LIBRO IX

DOCUMENTO: ACTA No. 105 DEL 09 DE NOVEMBER DE 2004
ORIGEN: ASAMBLEA DE ACCIONISTAS
INSCRIPCION: 17 DE FEBRUARY DE 2005 No. 2031 DEL LIBRO IX

FUE(SON)_NOMBRADO(S)

JUNTA DIRECTIVA

PRINCIPALES

PRIMER RENGLON
ESTHER ISABEL VENTURA DE RENDON
C.C.38979831

SEGUNDO RENGLON
ROSA VICTORIA VENTURA DE VISBAL
C.C.38992048

TERCER RENGLON
JUAN PABLO REYES VILLAMIZAR
C.C.80419709

SUPLENTES

PRIMER RENGLON
JUAN MARIA RENDON GUTIERREZ
C.C.17125100

SEGUNDO RENGLON
ROBERTO M. VENTURA CRISPINO
C.C.9086003

TERCER RENGLON
ROBERTO S. VENTURA PAULY
C.C.16697614

CERTIFICA:

*** CONTINUA ***



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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070529

Hora Certificado : 123616

Operacion: 02NA80529024

PAGINA No. 7

DOCUMENTO: ACTA No. 99 DEL 14 DE MARCH DE 2002

ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS

INSCRIPCION: 09 DE SEPTEMBER DE 2002 No. 14675 DEL LIBRO IX

FUE(RON) NOMBRADO(S):

REVISOR FISCAL

ALFREDO LOPEZ & CIA. LTDA

NIT.800026893-5

CERTIFICA:

DOCUMENTO: DOCUMENTO PRIVADO DEL 20 DE OCTOBER DE 2006

ORIGEN: ALFREDO LOPEZ & CIA LTDA

INSCRIPCION: 07 DE NOVEMBER DE 2006 No. 12672 DEL LIBRO IX

FUE(RON) NOMBRADO(S):

REVISOR FISCAL PRINCIPAL

ALFREDO LOPEZ CAMPO

C.C.8241912

REVISOR FISCAL SUPLENTE

GEOVANA GONZALEZ GALINDO

C.C.66959852

CERTIFICA:

CAPITAL AUTORIZADO: \$7,500,000,000

NUMERO DE ACCIONES: 750,000,000

VALOR NOMINAL: \$10

CAPITAL SUSCRITO: \$6,000,000,000

NUMERO DE ACCIONES: 600,000,000

VALOR NOMINAL: \$10

CAPITAL PAGADO: \$6,000,000,000

NUMERO DE ACCIONES: 600,000,000

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070529 Hora Certificado : 123616

Operacion: 02NAB0529024 PAGINA No. 8

VALOR NOMINAL: \$10

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.5234- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO
LAFRANCOL
UBICADO EN: ---K 1 46 84 DE CALI
RENOVO : POR EL AÑO 2007

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.369809- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO
LAFRANCOL S A
UBICADO EN: --K 1 46A 70 DE CALI
FECHA MATRICULA : 29 DE ABRIL DE 1994
RENOVO : POR EL AÑO 2007

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.369810- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO
LAFRANCOL S A
UBICADO EN: ---K 1A 46 A 32 DE CALI
FECHA MATRICULA : 29 DE ABRIL DE 1994
RENOVO : POR EL AÑO 2007

CERTIFICA:

QUE LA SOCIEDAD EFECTUO LA RENOVACION DE SU MATRICULA MERCANTIL EL 29 DE
MARCH DE 2007 .

CERTIFICA:

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070529

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Operacion: 02NAB0529024

PAGINA No. 9

QUE NO FIGURAN OTRAS INSCRIPCIONES QUE MODIFIQUEN TOTAL O PARCIALMENTE EL PRESENTE CERTIFICADO.

LOS ACTOS Y DOCUMENTOS REGISTRADOS QUEDAN EN FIRME CINCO (5) DIAS HABILES DESPUES DE LA FECHA DE SU INSCRIPCION, SIEMPRE Y CUANDO DENTRO DE DICHO TERMINO NO SEAN OBJETO DE RECURSOS EN LA VIA GUBERNATIVA.

DE CONFORMIDAD CON EL DECRETO 2150 DE 1.995 Y LA AUTORIZACION IMPARTIDA POR LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO LA FIRMA MECANICA QUE APARECE A CONTINUACION TIENE PLENA VALIDEZ PARA TODOS LOS EFECTOS LEGALES.

DADO EN CALI A LOS 29 DIAS DEL MES DE MAY

DEL AÑO 2007 HORA: 12:28:45



45x31
129



RECIBO DE PAGO
NIT: 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 42.794
FECHA : MAYO 29 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	54661354	28/05/2007	216,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-08	PRORROGA DE TERMINOS	72,000.00
TOTAL :			72,000.00

SON: SETENTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____