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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. _____ S. _____

SUPERINDUSTRIA Y COMERCIO
Radicación: 00097925 00000003 Folios: 3
Fecha (MD): 2003-07-23 12:54:24
Trámite: 1 002 PATENTES 1 REGISTRO/ 338 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Ref.: Expediente No. 00.097.925

Solicitud de Patente de Invención Titulada:

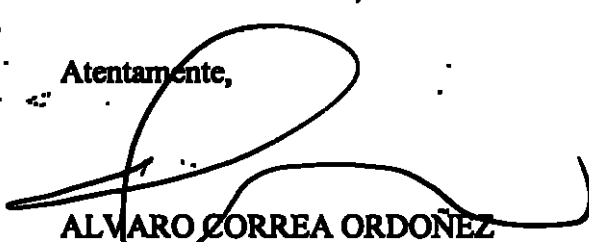
"COMPOSICIONES Y PROCEDIMIENTOS PARA
EL TRATAMIENTO DE AFECCIONES QUE
RESPONDEN A ESTROGENOS".

Solicitante: PFIZER PRODUCTS INC.

**SOLICITUD DE EXAMEN DE FONDO SEGÚN EL ARTICULO 44 DE LA
DECISIÓN 486, GACETA No. 527**

... ALVARO CORREA ORDÓÑEZ, mayor de edad y vecino de Bogotá, D.C.,
identificado según aparece al pie de mi firma, en mi condición de apoderado sustituto, de la
sociedad Pfizer Products Inc., respetuosamente me permito solicitar, dando cumplimiento a
lo establecido en el artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina
de Naciones, que se examine si la invención reúne los requisitos de patentabilidad previstos
en la misma. Adjunto recibo por el monto de \$ 335.000 pesos para cubrir la tasa
correspondiente, según la Resolución 41687 del año 2002.

Atentamente,


ALVARO CORREA ORDÓÑEZ
C.C. No. 79.143.366 de Usaquén
T.P. 20.281

Anexos: Sustitución de Poder
Recibo por \$ 335.000 pesos

**DILIGENCIA DE RECONOCIMIENTO
Y PRESENTACION PERSONAL**

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

Quien exhibió la C.C. No. 9945365

expedida en Uganda T.P. 028

y declaró que la firma o sello que aparecen en el presente memorial son suyos y que el contenido del mismo es cierto

Memorial dirigido a interesado

Santafé de Bogotá, D.C.

23 JUL 2005

Firma del declarante

HUELLA

Autorizó la anterior Diligencia

REPUBLICA DE COLOMBIA
NOTARIO ONCE DEL CIRCULO DE SANTAFÉ DE BOGOTÁ
CIRCULO DE SANTAFÉ DE BOGOTÁ, D.C.

J. MANABARRO DE BAUTISTA
NOTARIO ONCE

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RAISBECK, LARA, RODRÍGUEZ & RUEDA
MIEMBROS DE LA FIRMA
BAKER & MCKENZIE

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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Ref.: Solicitud colombiana de patente No. **00.097.925**

Solicitante: **PFIZER PRODUCTS INC.**

**"COMPOSICIONES Y PROCEDIMIENTOS PARA
EL TRATAMIENTO DE AFECCIONES QUE
RESPONDEN A ESTROGENOS".**

SUSTITUCIÓN DE PODER

CARLOS R. OLARTE, mayor y vecino de Bogotá. D.C., identificado como aparece al pie de mi firma, actuando en mi carácter de apoderado de la sociedad de la referencia, respetuosamente me permito manifestar que **SUSTITUYO** el poder a mi conferido por la mencionada sociedad en el doctor **ALVARO CORREA ORDÓÑEZ**, identificado con la Cédula de Ciudadanía número 79.143.366 de Usaquén y con la Tarjeta Profesional número 20.281, para que sea él quien en adelante, asuma el trámite de la presente solicitud.

El apoderado sustituto queda con las mismas facultades del principal.

Atentamente,



CARLOS R OLARTE
C.C. No. 79.782.747 de Bogotá
T. P. No. 74.295 del Consejo Superior de la Judicatura

**DILIGENCIA DE RECONOCIMIENTO
Y PRESENTACION PERSONAL**

Ante el Notario Once del Circuito de Santa Fe de Bogotá, compareció

Quién exhibió la C.C. No.

expedida en T.P.

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

Memorial dirigido a interesado

Santa Fe de Bogotá, D.C.

Firma del Declarante

HUELLA

Autorizó la anterior Diligencia

NOTARIO ONCE DEL CIRCULO DE SANTA FE DE BOGOTA

REPUBLICA DE COLOMBIA
NOTARIA 11 DEL CIRCULO DE
SANTA FE DE BOGOTA, D.C.

MONICA Z. BAUTISTA N
NOTARIA ONCE(E)

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SUPERINDUSTRIA Y COMERCIO
Radicacion : 00077925 00000003 Folios: 3
Fecha (HH): 2003-07-23 12:54:24
Tramite : 002 PATENTES 0 1 REGISTRO/ 530 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 43,892
FECHA : JUNIO 24 DE 2003

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
JULIAN ANDRES VARGAS	CONSIGNACION	BANCO POPULAR	050-00110-6	13228244	24/06/2003	18,050,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	85 EXAMEN DE PATENTABILIDAD DE INVEN	335,000.00
		TOTAL :	\$ 335,000.00

SON: TRESCIENTOS TREINTA Y CINCO MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 00-97925

**EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION
FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 527, DE
FECHA 30 DE ABRIL DE 2003, EL TERMINO HABIL SEÑALADO POR LA LEY
EXPIRA EL 29 DE JULIO DE 2003.**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X _____

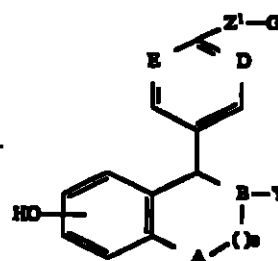
on et al.

5,552,412

Sep. 3, 1996

- Primary Examiner—Zinna Northington Davis**
Attorney, Agent, or Firm—Peter C. Richardson; Gregg C. Benson; Mervin E. Brokke

Compounds of this formula



are useful for treating or preventing, obesity, breast cancer, osteoporosis, endometriosis, cardiovascular disease and prostatic disease.

11 Claims, No Drawings

Lednicher, Daniel, et al., *J. Med. Chem.* 10 78 (1967) "Mammalian Antifertility Agents. IV. Basic 3,4-Dihydronaphthalenes and 1,2,3,4-Tetrahydro-1-naphthols".
Beauchamp, W. L., et al., *J. Med. Chem.* 10 139 (1967) "Synthetic Estrogens, Implantation Inhibitors, and Hypocholesterolemic Agents. I. Tetrahydronaphthalene Series".

1-(4'-Pyrrolidinoethoxyphenyl)-2-(4'-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline;

Cis-6-(4-hydroxyphenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalen-2-ol; and
1-(4'-Pyrrolidinoethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline.

In another aspect this invention provides methods of treating or preventing a condition selected from breast cancer, osteoporosis, endometriosis and cardiovascular disease and hypercholesterolemia in male or female mammals and benign prostatic hypertrophy and prostatic carcinomas in male mammals which comprises administering to said mammal an amount of a compound of formula I and preferably a preferred compound of formula I compounds as described above which is effective in treating or preventing said condition.

In another aspect this invention provides a method of treating or preventing obesity in mammals which comprises administering to said mammal an amount of a compound of formula I and preferably a preferred compound of formula I as described above which is effective in treating or preventing obesity.

In yet another aspect this invention provides a pharmaceutical composition for treating or preventing breast cancer, osteoporosis, obesity, cardiovascular disease, hypercholesterolemia, endometriosis and prostatic disease comprising a compound of formula I and a pharmaceutically acceptable carrier.

In another aspect, this invention provides intermediate compounds useful in preparing compounds of Formula I. These are 1-[2-[4-(6-Methoxy-3,4-dihydronaphthalen-1-yl)phenoxy]ethyl]pyrrolidine and 1-[2-[4-(2-Bromo-6-methoxy-3,4-dihydronaphthalen-1-yl)phenoxy]ethyl]pyrrolidine.

DETAILED DESCRIPTION OF THE INVENTION

The terms C₁-C₃ chloroalkyl and C₁-C₃ fluoroalkyl include methyl, ethyl, propyl and isopropyl substituted to any desired degree with chlorine or fluorine atoms, from one atom to full substitution. The term C₃-C₇ cycloalkyl includes cyclopentyl, cyclohexyl and cycloheptyl.

Halo means chloro, bromo, iodo and fluoro. Aryl (Ar) includes phenyl and naphthyl optionally substituted with one to three substituents independently selected from R⁴ as defined above. DTT means dithiothreitol. DMSO means dimethyl sulfoxide. EDTA means ethylene diamine tetra acetic acid.

Estrogen agonists are herein defined as chemical compounds capable of binding to the estrogen receptor sites in mammalian tissue, and mimicking the actions of estrogen in one or more tissues.

Estrogen antagonists are herein defined as chemical compounds capable of binding to the estrogen receptor sites in mammalian tissue, and blocking the actions of estrogen in one or more tissues.

One of ordinary skill will recognize that certain substituents listed in this invention will be chemically incompatible with one another or with the heteroatoms in the compounds, and will avoid these incompatibilities in selecting compounds of this invention. Likewise certain functional groups may require protecting groups during synthetic procedures which the chemist of ordinary skill will recognize.

The chemist of ordinary skill will recognize that certain compounds of this invention will contain atoms which may

be in a particular optical or geometric configuration. All such isomers are included in this invention; exemplary levorotatory isomers in the cis configuration are preferred. Likewise, the chemist will recognize that various pharmaceutically acceptable esters and salts may be prepared from certain compounds of this invention. All of such esters and salts are included in this invention.

As used in this application, prostatic disease means benign prostatic hyperplasia or prostatic carcinoma.

The remedies for the prostatic diseases, breast cancer, obesity, cardiovascular disease, hypercholesterolemia and osteoporosis of this invention comprise, as active ingredient, a compound of formula I or a salt or ester thereof. The pharmaceutically acceptable salts of the compounds of formula I are salts of non-toxic type commonly used, such as salts with organic acids (e.g., formic, acetic, trifluoroacetic, citric, maleic, tartaric, methanesulfonic, benzenesulfonic or toluenesulfonic acids), inorganic acids (e.g., hydrochloric, hydrobromic, sulfuric or phosphoric acids), and amino acids (e.g., aspartic or glutamic acids). These salts may be prepared by the methods known to chemists of ordinary skill.

The remedies for prostatic diseases, breast cancer, obesity, cardiovascular disease, hypercholesterolemia and osteoporosis of this invention may be administered to animals including humans orally or parenterally in the conventional form of preparations, such as capsules, microcapsules, tablets, granules, powder, troches, pills, suppositories, injections, suspensions and syrups.

The remedies for prostatic diseases, breast cancer, obesity, cardiovascular disease, hypercholesterolemia and osteoporosis of this invention can be prepared by the methods commonly employed using conventional, organic or inorganic additives, such as an excipient (e.g., sucrose, starch, mannitol, sorbitol, lactose, glucose, cellulose, talc, calcium phosphate or calcium carbonate), a binder (e.g., cellulose, methylcellulose, hydroxymethylcellulose, polypropylpyrrolidone, polyvinylpyrrolidone, gelatin, gum arabic, polyethyleneglycol, sucrose or starch), a disintegrator (e.g., starch, carboxymethylcellulose, hydroxypropylstarch, low substituted hydroxypropylcellulose, sodium bicarbonate, calcium phosphate or calcium citrate), a lubricant (e.g., magnesium stearate, light anhydrous stearic acid, talc or sodium lauryl sulfate), a flavoring agent (e.g., citric acid, menthol, glycine or orange powder), a preservative (e.g., sodium benzoate, sodium bisulfite, methylparaben or propylparaben), a stabilizer (e.g., citric acid, sodium citrate or acetic acid), a suspending agent (e.g., methylcellulose, polyvinylpyrrolidone or aluminum stearate), a dispersing agent (e.g., hydroxypropylmethylcellulose), a diluent (e.g., water), and base wax (e.g., cocoa butter, white petrolatum or polyethylene glycol). The amount of the active ingredient in the medical composition may be at a level that will ensue the desired therapeutical effect; for example, about 0.1 mg to 50 mg in unit dosage for both oral and parenteral administration.

The active ingredient may be usually administered once to four times a day with a unit dosage of 0.1 mg to 50 mg in human patients, but the above dosage may be properly varied depending on the age, body weight and medical condition of the patient and the type of administration. A preferred dose is 0.25 mg to 25 mg in human patients. One dose per day is preferred.

Compounds of this invention are readily prepared by the reactions illustrated in the schemes below.

381
386

31

- (p) C₁-C₄ alkylamino;
 (q) C₁-C₄ dialkylamino;
 (r) -NHSO₂R;
 (s) -NO₂;
 (t) -aryl; or
 (u) -OH.

R² and R⁶ are independently C₁-C₈ alkyl or together form a C₅-C₁₀ carbocyclic ring;

R⁷ and R⁸ in ring form may optionally be substituted with up to three substituents independently selected from

C₁-C₈ alkyl, halogen, alkoxy, hydroxy and carboxy;

a ring formed by R⁷ and R⁸ may be optionally fused to a

phenyl ring;

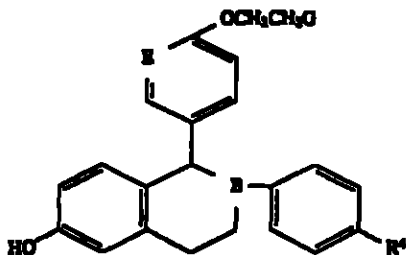
e is 1 or 2;

p is 0, 1, 2 or 3;

q is 0, 1, 2 or 3;

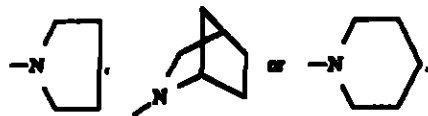
and optical and geometric isomers thereof; and nontoxic pharmacologically acceptable acid addition salts, N-oxides, esters, and quaternary ammonium salts thereof.

2. A compound of claim 1 which is of the formula:



32

3. A compound of claim 2 wherein G is



4. A compound of claim 3 wherein R⁴ is H, OH, F or Cl.

5. A compound of claim 4 wherein:

B and E are CH.

6. The compound of claim 1 which is

(-)-Cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol.

7. The compound of claim 1 which is

Cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol.

8. A pharmaceutical composition for treating or preventing osteoporosis comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

9. A method of treating or preventing osteoporosis in a mammal which comprises administering to a mammal in need of such treatment an effective amount of compound of claim 1.

10. The compound of claim 1 which is Cis-(6-(4-fluorophenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol.

11. The compound of claim 1 which is Cis-(6-(4'-hydroxyphenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol.

* * * * *

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**5-SUBSTITUTED-6-CYCLIC-5,6,7,8-
TETRAHYDRONAPHTHALEN-2-OL
COMPOUNDS WHICH ARE USEFUL FOR
TREATING OSTEOPOROSIS**

This invention relates to estrogen agonists and antagonists and their pharmaceutical uses.

BACKGROUND OF THE INVENTION

The value of naturally occurring estrogens and synthetic compositions demonstrating "estrogenic" activity has been in their medical and therapeutic uses. A traditional listing of the therapeutic applications for estrogens alone or in combination with other active agents includes: oral contraception; relief for the symptoms of menopause; prevention of threatened or habitual abortion; relief of dysmenorrhea; relief of dysfunctional uterine bleeding; an aid in ovarian development; treatment of acne; diminution of excessive growth of body hair in women (hirsutism); the prevention of cardiovascular disease; treatment of osteoporosis; treatment of prostatic carcinoma; and suppression of post-partum lactation [Goodman and Gilman, *The Pharmacological Basis Of Therapeutics* (Seventh Edition) Macmillan Publishing Company, 1985, pages 1421-1423]. Accordingly, there has been increasing interest in finding newly synthesized compositions and new uses for previously known compounds which are demonstrably estrogenic, this is, able to mimic the action of estrogen in estrogen responsive tissue.

From the viewpoint of pharmacologists interested in developing new drugs useful for the treatment of human diseases and specific pathological conditions, it is most important to procure compounds with some demonstrable estrogen-like function but which are devoid of proliferative side-effects. Exemplifying this latter view, osteoporosis, a disease in which bone becomes increasingly more fragile, is greatly ameliorated by the use of fully active estrogens; however, due to the recognized increased risk of uterine cancer in patients chronically treated with active estrogens, it is not clinically advisable to treat osteoporosis in intact women with fully active estrogens for prolonged periods. Accordingly estrogen agonists are the primary interest and focus.

Osteoporosis is a systemic skeletal disease, characterized by low bone mass and deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. In the U.S., the condition affects more than 25 million people and causes more than 1.3 million fractures each year, including 500,000 spine, 250,000 hip and 240,000 wrist fractures annually. These cost the nation over \$10 billion. Hip fractures are the most serious, with 5%-20% of patients dying within one year, and over 50% of survivors being incapacitated.

The elderly are at greatest risk of osteoporosis, and the problem is therefore predicted to increase significantly with the aging of the population. Worldwide fracture incidence is forecast to increase three-fold over the next 60 years, and one study estimates that there will be 4.5 million hip fractures worldwide in 2050.

Women are at greater risk of osteoporosis than men. Women experience a sharp acceleration of bone loss during the five years following menopause. Other factors that increase the risk include smoking, alcohol abuse, a sedentary lifestyle and low calcium intake.

Estrogen is the agent of choice in preventing osteoporosis or post menopausal bone loss in women; it is the only

2

treatment which unequivocally reduces fractures. However, estrogen stimulates the uterus and is associated with an increased risk of endometrial cancer. Although the risk of endometrial cancer is thought to be reduced by a concurrent use of a progestogen, there is still concern about possible increased risk of breast cancer with the use of estrogen.

Black, et al. in EP 0605193A1 report that estrogen, particularly when taken orally, lowers plasma levels of LDL and raises those of the beneficial high density lipoproteins (HDL's). Long-term estrogen therapy, however, has been implicated in a variety of disorders, including an increase in the risk of uterine cancer and possibly breast cancer, causing many women to avoid this treatment. Recently suggested therapeutic regimens, which seek to lessen the cancer risk, such as administering combinations of progestogen and estrogen, cause the patient to experience unacceptable bleeding. Furthermore, combining progesterone with estrogen seems to blunt the serum cholesterol lowering effects of estrogen. The significant undesirable effects associated with estrogen therapy support the need to develop alternative therapies for hypercholesterolemia that have the desirable effect on serum LDL but do not cause undesirable effects.

There is a need for improved estrogen agonists which exert selective effects on different tissues in the body. Tamoxifen, 1-(4- β -dimethylaminoethoxyphenyl)-1,2-diphenyl-but-1-ene, is an antiestrogen which has a palliative effect on breast cancer, but is reported to have estrogenic activity in the uterus. Gill-Sharma, et al., *J. Reproduction and Fertility* (1993) 99, 395, disclose that tamoxifen at 200 and 400 mg/kg/day reduces the weights of the testes and secondary sex organs in male rats.

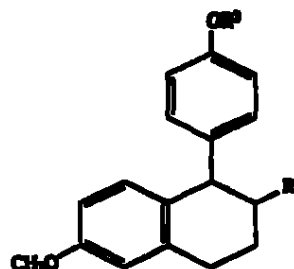
Recently it has been reported (Osteoporosis Conference Scrip No. 1812/13 Apr. 16/20, 1993, p. 29) that raloxifene, 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, mimics the favorable action of estrogen on bone and lipids but, unlike estrogen, has minimal uterine stimulatory effect. (*Breast Cancer Res. Treat.* 10(1), 1987 p 31-36 Jordan, V. C. et al.).

Neubauer, et al., *The Prostate* 2:3:245 (1993) teach that raloxifene treatment of male rats produced regression of the ventral prostate.

Raloxifene and related compounds are described as anti-estrogen and antiandrogenic materials which are effective in the treatment of certain mammary and prostate cancers. See U.S. Pat. No. 4,418,068 and Charles D. Jones, et al., *J. Med. Chem.* 1984, 27, 1057-1066.

Jones, et al in U.S. Pat. No. 4,133,814 describe derivatives of 2-phenyl-3-arylbenthiothiophene and 2-phenyl-3-arylbenthiothiophene-1-oxides which are useful as antiinflammatory agents as well as suppressing the growth of mammary tumors.

Lednicer, et al., *J. Med. Chem.*, 12, 881 (1969) describe estrogen antagonists of the structure





(11)

EP 0 793 961 A1

215
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(12)

EUROPEAN PATENT APPLICATION

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(30) Priority: 28.02.1996 US 21181

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New York, N.Y. 10017 (US)

Remarks:

Amended claims in accordance with Rule 86 (2)
EPC.

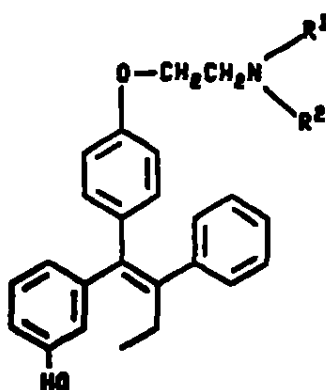
(72) Inventors:
• MacLean, David B.
Providence, Rhode Island 02908 (US)

(54) Use of droloxifene for the manufacture of a medicament for increasing serum levels of testosterone

(57) The use of a compound of the formula (I) or of a pharmaceutically acceptable salt thereof:

wherein:-

R¹ and R² may be the same or different provided that, when R¹ and R² are the same, each is a methyl or ethyl group, and, when R¹ and R² are different, one of them is a methyl or ethyl group and the other is hydrogen or a benzyl group;
for the manufacture of a medicament for increasing serum levels of testosterone.



(I)

EP 0 793 961 A1

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Description

BACKGROUND OF THE INVENTION

In males, small amounts of estrogen are produced by aromatization of testosterone both in the testes and peripheral tissues. Although present in only small amounts, generally less than one-fourth to one-tenth that in premenopausal women, estrogen may play a role in the regulation of the male hypothalamic pituitary gonadaxis, bone development, development of the prostate and metabolic function. In the hypothalamus, conversion of testosterone to estrogen results in negative feedback on gonadotropin releasing hormone and subsequent gonadotropin release. Estrogens thus normally reduce circulating testosterone and anti-estrogens result in corresponding increases. As men age, the proportion of fat to lean tissue gradually increases. Aromatization of testosterone in fat may lead to gradually increased estrogen to testosterone ratios and negative feedback that reduces total testosterone levels.

Hypogonadism is recognized as a common occurrence in older males. A number of studies have suggested that hypogonadism may result in some of the observed decrements in muscle and skeletal mass associated with advancing age. Recent studies have suggested that androgen therapy produces a small but significant improvement in muscle strength in eugonadal males. Testosterone deficiency has been associated with hip fracture, and bone mass has been correlated with testosterone levels in older persons.

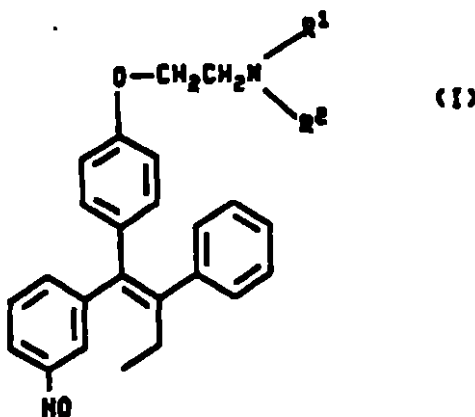
Males who received testosterone had a significant increase in bioavailable testosterone concentration, hematocrit, right hand muscle strength and osteocalcin concentration. They had a decrease in cholesterol (without a change in HDL-cholesterol) levels and decreased BUN/Creatinine ratios. Morley, et al. *JAGS* 41:149-152 (1993).

The estrogen antagonist tamoxifen has been used in males to treat advanced breast cancer. Treatment with tamoxifen has been shown to increase serum levels of testosterone in both mammal and oligozoospermic men. (Lewie-Jones, et al., *andrologia* 19 (1): 88-90 (1987)). In addition, the anti-estrogen clomiphene is used to treat decreased libido, hypogonadotropic hypogonadism and associated infertility. A potential role for anti-estrogens in the older male has not been systematically evaluated.

Droloxifene (Formula I, below, R¹, R² = methyl) is a new tissue-specific estrogen agonist/antagonist that is being developed for the treatment of advanced breast cancer and osteoporosis. Although droloxifene has been studied in a few men with advanced colon or pancreatic cancer, its endocrine effects in the normal male have not been studied. Droloxifene is chemically related to tamoxifen, but in preclinical studies in rats is devoid of tamoxifen's hepatocarcinogenicity. In humans, droloxifene has a superior pharmacokinetic profile with fewer, inactive, metabolites a shorter half life of 24 hours (vs. tamoxifen's 1 to 2 weeks and multiple metabolites).

SUMMARY OF THE INVENTION

The present invention relates to methods for increasing serum levels of testosterone comprising administering to a mammal in need of such treatment an effective amount of a compound of formula I



wherein

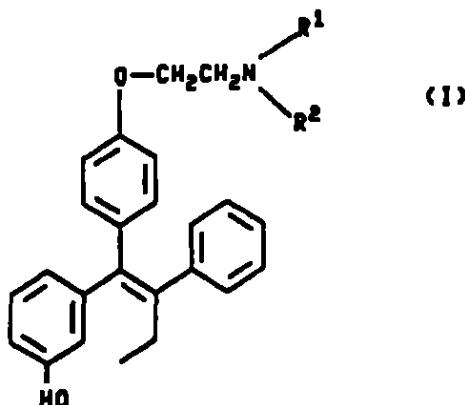
R¹ and R² may be the same or different provided that, when R¹ and R² are the same, each is a methyl or ethyl group, and, when R¹ and R² are different, one of them is a methyl or ethyl group and the other is hydrogen or a benzyl group; or a pharmaceutically acceptable salt thereof. A preferred compound of formula I is that in which R¹ and R² are methyl. A preferred salt is the citrate salt.

387 392

DETAILED DESCRIPTION OF THE INVENTION

The present invention concerns methods for increasing serum levels of testosterone in a mammal. The present methods include both medical therapeutic and/or prophylactic treatment, as appropriate. Low testosterone levels, especially in the elderly, may lead to frailty, impotence and lowered libido.

The methods of this invention are practiced by administering to an individual in need of treatment an effective amount of a compound formula I



wherein

R¹ and R² may be the same or different provided that, when R¹ and R² are the same, each is a methyl or ethyl group, and, when R¹ and R² are different, one of them is a methyl or ethyl group and the other is hydrogen or a benzyl group; or a pharmaceutically acceptable salt thereof.

Compounds of formula I are known in the art and essentially are prepared via the methods described in U.S. Pat. No. 5,047,431, which is hereby incorporated herein by reference.

A preferred formula I compound is that in which R¹ and R² each are methyl. This preferred compound is known as droloxifene which previously has been described as an antiestrogenic agent and is useful for the treatment of hormone dependent mammary tumors (U.S. Pat. No. 5,047,431), and for the relief of bone diseases caused by the deficiency of estrogen or the like (U.S. Pat. No. 5,254,594). Furthermore, droloxifene is known to have less uterotrophic effect than other antiestrogenic compounds such as tamoxifen.

Although the free-base form of formula I compounds can be used in the methods of the present invention, it is preferred to prepare and use a pharmaceutically acceptable salt form. Thus, the compounds used in the methods of this invention form pharmaceutically acceptable acid and base addition salts with a wide variety of inorganic and, preferably, organic acids and include the physiologically acceptable salts which are often used in pharmaceutical chemistry. Such salts are also part of this invention. Typical inorganic acids used to form such salts include hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, hypophosphoric, and the like. Salts derived from organic acids, such as aliphatic mono and dicarboxylic acids, phenyl substituted alkanic acids, hydroxyalkanoic and hydroxyalkandioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, may also be used. Such pharmaceutically acceptable salts thus include acetate, phenylacetate, trifluoroacetate, acrylate, ascorbate, benzoate, chlorobenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, methylbenzoate, o-acetoxybenzoate, naphthalene-2-benzoate, bromide, isobutyrate, phenylbutyrate, β-hydroxybutyrate, butyne-1,4-dioate, hexyne-1,4-dioate, caprate, caprylate, chloride, cinnamate, citrate, formate, fumarate, glycolate, heptanoate, hippurate, lactate, malate, maleate, hydroxymaleate, malonate, mandelate, mesylate, nicotinate, isonicotinate, nitrate, oxalate, phthalate, terephthalate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, propionate, propionate, phenylpropionate, salicylate, sebacate, succinate, suberate, sulfate, bisulfate, pyrosulfate, sulfite, bisulfite, sulfonate, benzenesulfonate, p-bromophenylsulfonate, chlorobenzenesulfonate, ethanesulfonate, 2-hydroxyethanesulfonate, methanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, p-toluenesulfonate, xylenesulfonate, tartrate, and the like. A preferred salt is the citrate salt.

The pharmaceutically acceptable acid addition salts are typically formed by reacting a compound of formula I with an equimolar or excess amount of acid. The reactants are generally combined in a mutual solvent such as diethyl ether or benzene. The salt normally precipitates out of solution within about one hour to 10 days and can be isolated by filtration or the solvent can be stripped off by conventional means.

The pharmaceutically acceptable salts of formula I compounds generally have enhanced solubility characteristics compared to the compound from which they are derived, and thus are often more amenable to formulation as liquids

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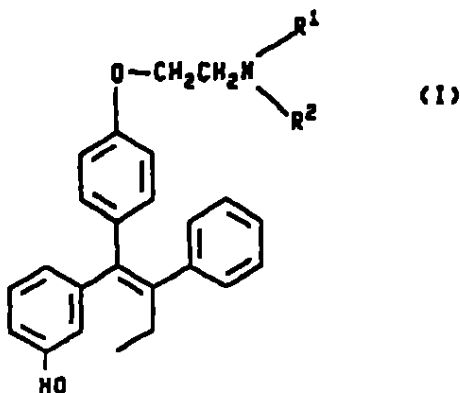
of beer.

4. Clinically significant abnormalities on screening electrocardiogram.

The study is of parallel design and placebo controlled comparing two doses of a compound of formula I at 10 and 40 mg/day vs. placebo for 14 weeks. Subjects are randomized to compound or placebo. Testosterone levels are measured every two weeks with the RIA, Coat-a-Count Kit available from Diagnostic Products Co. 5700 W. 98th Street, Los Angeles, CA 90045. A statistically significant increase in testosterone levels over the placebo indicates that a compound of formula I is effective in increasing serum testosterone.

Claims

1. The use of a compound of the formula (I) or of a pharmacologically acceptable salt thereof:



wherein

R¹ and R² may be the same or different provided that, when R¹ and R² are the same, each is a methyl or ethyl group, and, when R¹ and R² are different, one of them is a methyl or ethyl group and the other is hydrogen or a benzyl group; for the manufacture of a medicament for increasing serum levels of testosterone.

2. A use according to claim 1 wherein the compound of formula I is a compound wherein R¹ and R² each are methyl, or a pharmaceutically acceptable salt thereof.
3. A use according to claim 1 or 2 wherein said salt thereof is the citrate salt.

394
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO 100
DIVISION DE NUEVAS CREACIONES

2020
Bogotá, D.C., Agosto 22 de 2006

Abogado
ALVARO CORREA ORDÓÑEZ

ASUNTO	Radicación No.	00 097 925
	Trámite	002
	Evento	001
	Actuación	430
	Oficio No.	00009775
	Folios	0

Como resultado del examen de patentabilidad de la solicitud de patente de invención, realizado según lo establece el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se notifica el siguiente concepto técnico:

Título de la solicitud: "Composiciones y Procedimientos para el Tratamiento de Afecciones que responden a Estrógenos".

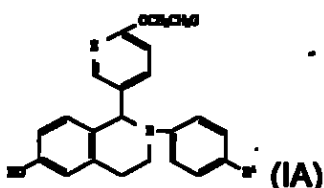
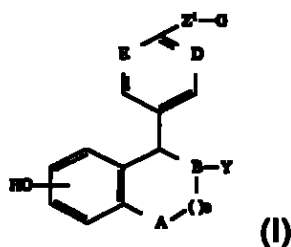
1. Documentos estudiados

Para el presente estudio se tuvieron en cuenta el capítulo descriptivo comprendido en los folios 229 - 327 y el capítulo reivindicatorio de los folios 328 - 361 de la solicitud.

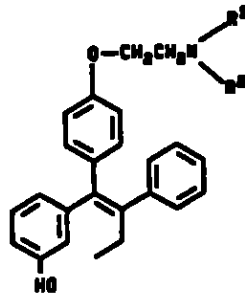
2. Objeto de la invención

El objeto de la presente solicitud de patente de invención consiste en:

Las reivindicaciones 1 - 17 y 31 se refieren a un procedimiento de tratamiento que consiste en administrar un compuesto de fórmulas (I), (IA), (II):



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(II)

Las reivindicaciones 18 - 28 se refieren a un estuche que comprende una composición farmacéutica e instrucciones para utilizarla.

Las reivindicaciones 29 - 30 se refieren a una formulación que contiene un compuesto de fórmula (I)

El problema planteado en esta solicitud es la necesidad de tratar artritis reumatoide, cáncer de colon, heridas de tejidos, arrugas de la piel, cataratas.

Para resolver este problema técnico la solicitud en estudio proporciona un procedimiento de tratamiento que consiste en administrar agonista/antagonista de estrógenos, de fórmulas (I), (IA), (II).

El objeto de la invención definido anteriormente se clasificó de acuerdo con la IPC: A 61 K 31/138 // 31/435 // 45/00 // 45/06.

A 61 P 5/30 // 5/32 // 15/10 // 15/12.

También se reivindica prioridad de la Solicitud de Patente de los Estados Unidos US 60 175 752 de enero 12 de 2000, con respecto a la cual la fecha de presentación de la actual solicitud cumple el plazo máximo permitido.

3. Excepciones a la Patentabilidad

El artículo 20 de la Decisión 486 establece: *"No serán patentables: d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales"*

Las reivindicaciones 1 - 17 y 31 se refieren a un procedimiento de tratamiento que consiste en administrar un agonista/antagonista de estrógenos, de fórmulas (I), (IA), (II).

Se observa que el procedimiento de tratamiento de las reivindicaciones 1 - 17 y 31 que comprende administrar un agonista/antagonista de estrógenos, no es patentable de acuerdo con la norma citada, que especifica que *los métodos terapéuticos para el tratamiento humano o animal* no son patentables.

En conclusión, el procedimiento de tratamiento de las reivindicaciones 1 - 17 y 31, que comprende administrar una composición, no es patentable de acuerdo con el Art 20, literal d), de la decisión 486.

4. Unidad de invención

El artículo 25 de la Decisión 486 establece: *"La solicitud de patente sólo podrá comprender una invención o un grupo de invenciones relacionadas entre sí, de manera que conformen un único concepto inventivo"*.

En una solicitud de patente se puede reivindicar:

- a) una sola invención; o
- b) un grupo de invenciones relacionadas entre sí por un único concepto inventivo.

Cuando se trate del caso b), se debe considerar que el concepto inventivo único que relaciona las invenciones debe ser técnico, cumplir por sí mismo con los requisitos de novedad y nivel inventivo, y ser común a todas las reivindicaciones.

Las reivindicaciones 18 - 28 se refieren a un estuche que comprende una composición farmacéutica e instrucciones para utilizarla.

Se observa que las reivindicaciones 18 - 28 que se refieren a un estuche que comprende una composición farmacéutica e instrucciones para utilizarla, no mantienen el principio de la unidad de invención porque la composición no pertenece al mismo campo técnico que las instrucciones para utilizarla.

Dichas instrucciones para utilizarla pueden ser protegidas mediante el Registro de Derechos de Autor.

Debe hacerse la corrección respectiva.

5. Determinación del Estado de la Técnica

El artículo 16 de la decisión 486 de la comisión de la Comunidad Andina que establece que *"El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida."*

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

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es enero 12 de 2000, se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontraron los siguientes documentos que anticipan los compuestos mencionados en esta solicitud:

No.	Documento	Título	Fecha de Publicación
D1	US 5 552 412	5-substitued-6-cyclic-5,6,7,8-tetrahydronaphthalen2-ol compounds which are useful for treating osteoporosis	Sep 3, 1996
D2	EP 0 793 961	Use of droloxifene for the manufacture of a medicament for increasing serum levels of testosterone	Sep 10, 1997

6. Evaluación de los requisitos de Patentabilidad

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El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece que *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*.

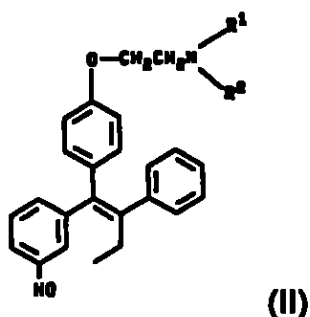
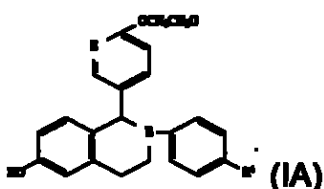
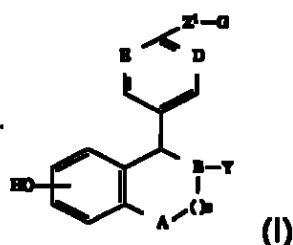
En cumplimiento del artículo 14 de la Decisión 486, se procedió a evaluar el cumplimiento de los requisitos de novedad, nivel inventivo y aplicación industrial, con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación de la Novedad

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

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

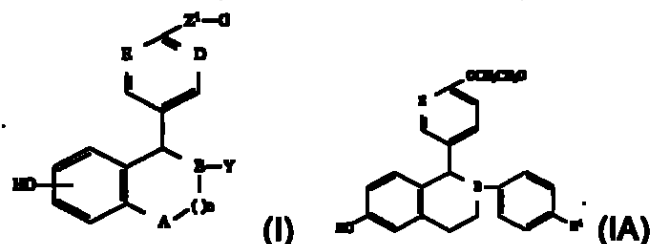
Esta solicitud menciona agonistas/antagonistas de estrógenos, de fórmulas (I), (IA), (II):



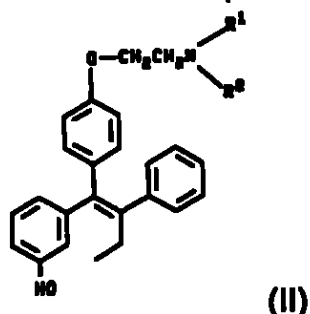
Se observa que los agonistas/antagonistas de estrógenos mencionados en esta

solicitud eran conocidos, así:

D1 enseña compuestos de fórmulas (I) y (IA):



D2 enseña compuestos de fórmula (II).

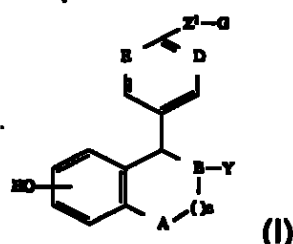


Se observa que los agonistas/antagonistas de estrógenos mencionados en esta solicitud no son nuevos.

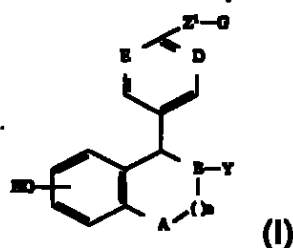
Evaluación del Nivel Inventivo

El artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina establece que *Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.*

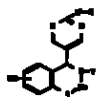
Las reivindicaciones 29 – 30 se refieren a una formulación que contiene un compuesto de fórmula (I):



D1 enseña compuestos de fórmula (I):



Se observa que:

- (a) debido a que el compuesto de fórmula (I):  era conocido en la anterioridad D1, una persona de habilidades ordinarias en el arte adaptará fácilmente el compuesto como principio activo de una composición farmacéutica;
- (b) las reivindicaciones de esta solicitud no mencionan una característica que

conceda un efecto diferente o especial al compuesto de fórmula (I):



, ni a las composiciones preparadas con él, que pueda considerarse como un aporte a la técnica, así que son obvios para una persona versada en la materia;

- (c) el problema planteado en esta solicitud que era la necesidad de tratar artritis reumatoide, cáncer de colon, heridas de tejidos, arrugas de la piel, cataratas se resuelve proporcionando un procedimiento de tratamiento que consiste en administrar agonista/antagonista de estrógenos, de fórmulas (I), (IA), (II), es decir de la misma manera como se resolvía en las anterioridades;
- (d) el resultado obtenido: es decir las composiciones farmacéuticas que contienen el compuesto de fórmula (I) no es inesperado;
- (e) no parece haberse superado un prejuicio técnico anterior, con las composiciones farmacéuticas que contienen el compuesto de fórmula (I) propuestas

de manera que el objeto reivindicado no tiene nivel inventivo.

6. Conclusión

En conclusión, los requisitos de patentabilidad de la presente solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US 5 552 412	1 - 17 y 31 29 - 30	Novedad Nivel inventivo
D2	EP 0 793 961	1 - 17 y 31	Novedad

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

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

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista, de fecha 31/10/2006

CONCEPTO TÉCNICO No. 1352	EXAMINADOR TÉCNICO Código 202007
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395

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RADICACIÓN: 0-87925

EDICTO No. 606

LA SECRETARÍA GENERAL AD-HOC
HACE SABER:

Que esta Superintendencia proferió Resolución No. 34978 de 20-DIC-2006. Que el contenido de la parte resolutive es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

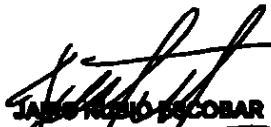
ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud correspondiente a "COMPOSICIONES Y PROCEDIMIENTOS PARA EL TRATAMIENTO DE AFECCIONES QUE RESPONDEN A ESTROGENOS".

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución al doctor Álvaro Correa Ordoñez, o a quien haga sus veces, en su calidad de apoderado de Pfizer Products Inc., entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE

Dada en Bogotá, D.C., a los 20 DIC. 2006

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,


JAIR RUBIO ESCOBAR

Para notificar a los interesados, se fija el presente EDICTO en lugar visible al público en la SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, por el término de (10) diez días hábiles contados a partir de las 8:00 a.m. de hoy.

Secretaría General Ad-Hoc 10-ENE-2007
Secretaría General Ad-Hoc
EDICTO No. 606

Este edicto se desfija hoy 23-ENE-2007 a las 4:30 p.m.