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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

SUPERINDUSTRIA Y COMERCIO
Radicacion : 00097926 00000003 Folios: 3
Fecha (AND): 2003-07-23 12:59:26
Tramite : 002 PATENTES D 1 REGISTRO/ 530 PETICION
Dependencia: ENEB DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Ref.: Expediente No. **00.097.926**

Solicitud de Patente de Invención Titulada:
"PROCEDIMIENTO PARA REDUCIR LA
MORBILIDAD Y EL RIESGO DE
MORTALIDAD".

Solicitante: **PFIZER PRODUCTS INC.**

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

ÁLVARO CORREA ORDOÑEZ, 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,

ÁLVARO CORREA ORDOÑEZ
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

Quién exhibió la C.C. No.

expedida en COLOMBIA T.º 1028

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

Memorial dirigido a interesado

Santafé de Bogotá D.C.

23 JUL 2013

Firma del Declarante

HUELLA

Autorizó la anterior Diligencia

NOTARIO ONCE DEL CIRCULO DE SANTAFÉ DE BOGOTÁ

DE COLOMBIA

NOTARIO ONCE DEL CIRCULO DE

SANTAFÉ DE BOGOTÁ, D.C.

MAVARRO DE BAUTISTA

NOTARIO ONCE

RAISBECK, LARA, RODRÍGUEZ & RUEDA
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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Ref.: Solicitud colombiana de patente No. **00.097.926**

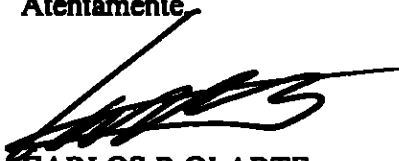
Solicitante: **PFIZER PRODUCTS INC.**
"PROCEDIMIENTO PARA REDUCIR LA
MORBILIDAD Y EL RIESGO DE MORTALIDAD".

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**

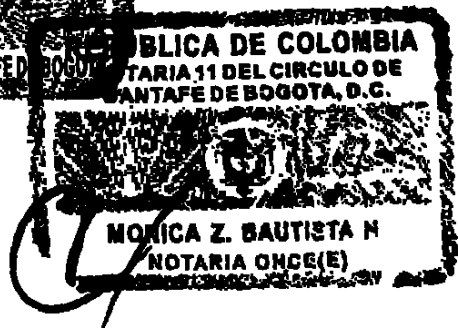
Ante el Notario Once del Circulo de Santafé de Bogotá compareció

Quién exhibió la C.C. No. _____
expedida en _____ T.P. MB
y declaró que la firma y huella que aparecen en
el presente memoria son suyas y que el conte-
nido del mismo es cierto.
Memoria dirigida a interesado

Santafé de Bogotá, D.C. 20 JUL 2013

Firma del Declarante _____
HUELLA _____
Autorizó la anterior Diligencia _____

NOTARIO ONCE DEL CIRCULO DE SANTAFÉ DE BOGOTÁ



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SUPERINDUSTRIA Y COMERCIO
Radicacion : 00097926 00000003 Folios: 3
Fecha (AMD): 2003-07-23 12:59:26
Tramite : 002 PATENTES D 1 REGISTRO/ 530 PETICION
Dependencia: 2928 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 43,901
FECHA : JUNIO 24 DE 2003

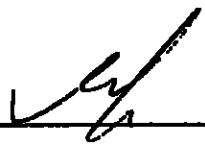
***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	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. 00-97926

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 calga 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** _____

United States Patent [19]

on et al.

[11] Patent Number: 5,552,412

[45] Date of Patent: Sep. 3, 1996

34
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- [54] **5-SUBSTITUED-6-CYCLIC-5,6,7,8-TETRAHYDRONAPHTHALEN-2-OL COMPOUNDS WHICH ARE USEFUL FOR TREATING OSTEOPOROSIS**
- [75] Inventors: Kimberly O. Cameron; Paul A. Danilva Jardine; Robert L. Romati, all of Groton, Conn.
- [73] Assignee: Pfizer Inc, New York, N.Y.
- [21] Appl. No.: 369,984
- [22] Filed: Jan. 9, 1995
- [51] Int. Cl.⁶ C07D 211/06; A61K 31/445; A61K 31/46; A61K 31/40
- [52] U.S. Cl. 514/317; 514/331; 514/428; 514/213; 540/582; 540/585; 546/192; 546/229; 546/233; 546/234; 546/236; 546/237; 548/566; 548/570; 548/571; 548/575
- [58] Field of Search 548/575, 566, 548/570, 571; 514/428, 317, 331, 213; 540/582, 585; 546/192, 229, 233, 234, 236, 237

[56] References Cited

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 Bencos, W. L., et al., J. Med. Chem. 10 139 (1967) "Synthetic Estrogens, Implantation Inhibitors, and Hypocholesterolemic Agents. I. Tetrahydronaphthalene Series".

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Jones, Robert C., Acta Endocrinologica (Copenh) 1987, 114:379-382 "The Effect of a Luteinizing Hormone-Releasing Hormone Antagonist on Experimental Endometriosis in the Rat".

Osteoporosis Conference, CRIP No. 1812/13 Apr. 16th/20th 1993, pp. 29-30.

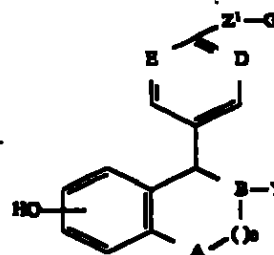
Jones, Charles D., et al., J. Med. Chem. (1984) 27, 1057-1066 "Antiestrogens. 2. Structure-Activity Studies in a Series of 3-Aryl-2-arylbenzo[b]thiophene Derivatives Leading to [6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]-phenyl]methanone Hydrochloride (LY156758), a Remarkably Effective Estrogen Antagonist with Only Minimal Intrinsic Estrogenicity".

Chemical Abstracts, vol. 65, No. 3, Abstract 5425b, Aug. 1, 1966.

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

[57] ABSTRACT

Compounds of this formula



253

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

11 Claims, No Drawings

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

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-tetrahydroquinoline.

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-dihydro-naphthalen-1-yl)phenoxy]ethyl]pyrrolidine and 1-[2-[4-(2-Bromo-6-methoxy-3,4-dihydro-naphthalen-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 C₅-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 comprises, 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, emulsions 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, sacrose 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 sticic 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 exercise the desired therapeutic 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.

hydrochloride corresponding to Example 1. [α_D -330.6 ($c=0.05, CH_2Cl_2$); mp 260°-263° C.

EXAMPLE 9

Cis-6-(4'-hydroxyphenyl)-5-[4-(2-piperidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol.

Following the procedures described for the preparation of Example 1, the title compound was obtained. 1H NMR ($CDCl_3$): δ 3.12 (m, 1H); 3.90 (m, 2H); 4.15 (d, 1H); 6.15-6.72 (m, 11H); FAB MS (M+1) 430.

EXAMPLE 10

1-(4'-Piperidinoethoxyphenyl)-2-(4'-hydroxyphenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride

Using the procedure of Example 3 described in step G, substituting N-2-chloroethylpiperidine hydrochloride for N-2-chloroethylpyrrolidine hydrochloride, the title compound was obtained. 1H NMR ($CDCl_3$): δ 2.65 (m, 2H); 2.75 (m, 2H); 3.45 (s, 1); 6.50-7.00 (m, 11H); FAB MS(M+1) 445.

EXAMPLE 11

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

The title compound was obtained using the procedure of Example 3 described in step A, substituting 4-fluoroaniline for 4-methoxyaniline. 1H NMR ($CDCl_3$): δ 2.12 (m, 2H); 3.65 (m, 2H); 4.45 (m, 2H); 6.10 (s, 1H); 7.5 (m, 2H); MS(M+1) 433.

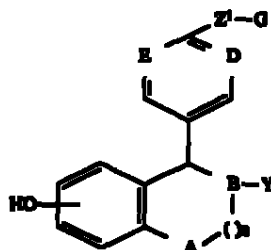
EXAMPLE 12

1-(4'-Pyrrolidinoethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride

The title compound was prepared using the procedure of Example 3 described in step A, substituting aniline for 4-methoxyaniline. 1H NMR ($CDCl_3$): δ 1.70 (m, 4H); 2.70 (m, 2H); 4.00 (m, 2H); 5.70 (s, 1H); 6.60-7.25 (m, 12H); FAB MS(M+1) 415.

We claim:

1. A compound of the formula:



wherein:

A is CH_2 ;

B, D and E are CH_2 ;

Y is

(a) phenyl, optionally substituted with 1-3 substituents independently selected from R^4 ;

- (b) naphthyl, optionally substituted with 1-3 substituents independently selected from R^4 ;
- (c) C_3 - C_8 cycloalkyl, optionally substituted with 1-2 substituents independently selected from R^4 ;
- (d) C_3 - C_8 cycloalkenyl, optionally substituted with 1-2 substituents independently selected from R^4 ;
- (e) a five membered heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NR²- and -S(O)_n-, optionally substituted with 1-3 substituents independently selected from R^4 ;
- (f) a six membered heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NR²- and -S(O)_n-, optionally substituted with 1-3 substituents independently selected from R^4 ; or
- (g) a bicyclic ring system consisting of a five or six membered heterocyclic ring fused to a phenyl ring, said heterocyclic ring containing up to two heteroatoms selected from the group consisting of -O-, -NR²-, NR²- and -S(O)_n-, optionally substituted with 1-3 substituents independently selected from R^4 .

Z' is

- (a) $-O(CH_2)_p CR^5R^6$;
- (b) $-O(CH_2)_p W(CH_2)_q$;
- (c) $-OCHR^1CHR^2$;

G is -NR⁷R⁸;

W is

- (a) $-CH_2-$;
- (b) $-CH=CH-$;
- (c) $-O-$;
- (d) -NR²-;
- (e) -S(O)_n-;



- (g) $-CR^2(OH)-$;
- (h) $-CONR^2-$;
- (i) $-NR^2CO-$;

(D)



or

- (k) $-C\equiv C-$;

R^2 and R^3 are independently

- (a) hydrogen; or
- (b) C_1 - C_4 alkyl;

R^4 is

- (a) hydrogen;
- (b) halogen;
- (c) C_1 - C_8 alkyl;
- (d) C_1 - C_8 alkoxy;
- (e) C_1 - C_8 acyloxy;
- (f) C_1 - C_8 alkylthio;
- (g) C_1 - C_8 alkylsulfinyl;
- (h) C_1 - C_8 alkylsulfonyl;
- (i) hydroxy (C_1 - C_8)alkyl;
- (j) aryl (C_1 - C_8)alkyl;
- (k) $-CO_2H$;
- (l) $-CN$;
- (m) $-CONHOR$;
- (n) $-SO_2NHR$;
- (o) $-NH_2$;

31

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

R⁵ and R⁶ are independently C₁-C₄ 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-C₄ alkyl, halogen, alkoxy, hydroxy and carboxy; a ring formed by R⁷ and R⁸ may be optionally fused to a phenyl ring;

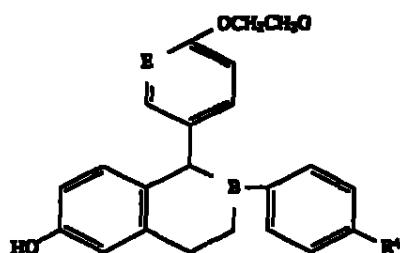
e is 1 or 2;

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:



f 259

32

3. A compound of claim 2 wherein G is

313
311

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

(-)-Cl₂-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol.

7. The compound of claim 1 which is

Cl₂-6-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 Cl₂-(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 Cl₂-(6-(4'-hydroxyphenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol.

* * * * *

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5-SUBSTITUED-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

314

312

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, 393, disclose that tamoxifen at 200 and 400 mg/kg/day reduces the weights of the testes and secondary sex organs in male rats.

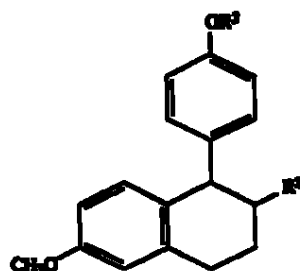
Recently it has been reported (Osteoporosis Conference Scrip No. 1812/13 Apr. 16/20, 1993, p. 29) that raloxifene, 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl] benzo[b] thiophene, mimics the favorable action of estrogen on bone and lipids but, unlike estrogen, has minimal uterine stimulatory 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-arylbenzothiophene and 2-phenyl-3-arylbenzothiophene-1-oxides which are useful as antifertility agents as well as suppressing the growth of mammary tumors.

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





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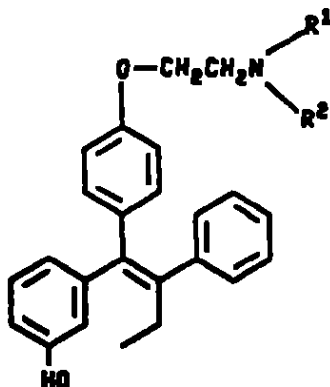
Remarks:

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

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(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:



(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;
for the manufacture of a medicament for increasing serum levels of testosterone.

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-gonadal axis, bone development, development of the prostate and metabolic function. In the hypothalamus, conversion of testosterone to estrogen results in negative feedback on gonadotrophin releasing hormone and subsequent gonadotrophin 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.

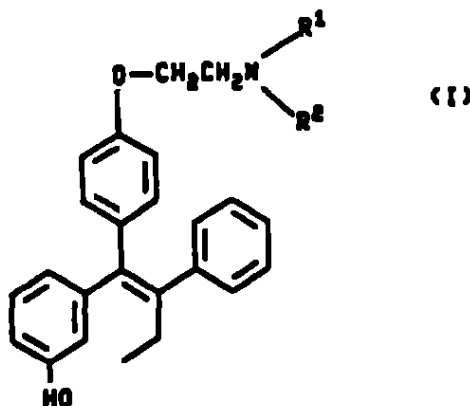
Males who received testosterone had a significant increase in bioavailable testosterone concentration, hematocrit, right hand muscle strength and osteocalcin concentration. They had a decrease in cholesterol (without a change in HDL-cholesterol) levels and decreased BUN/Creatinine ratios. Morley, et 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 normal and oligozoospermic men. (Lewis-Jones, et al., *androgens* 19 (1): 85-90 (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 and 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



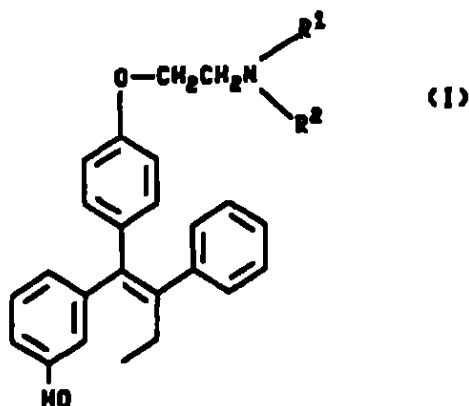
wherein

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.

317
315DETAILED 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

R^1 and R^2 may be the same or different provided that, when R^1 and R^2 are the same, each is a methyl or ethyl group, and, when R^1 and R^2 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 R^1 and R^2 each are methyl. This preferred compound is known as droloxifen 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, droloxifen 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, leonicotinate, nitrate, oxalate, phthalate, terephthalate, phosphate, mono-hydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, propiolate, 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

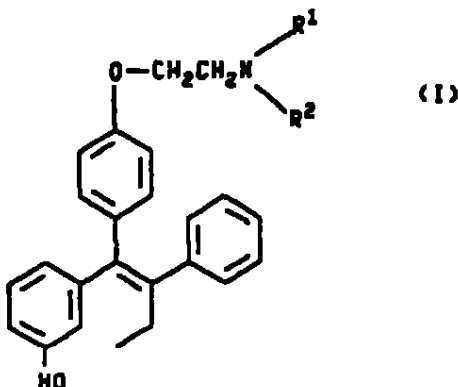
of beer.

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. 96th 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.

PCT

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(51) International Patent Classification 6: C07D 295/08, A61K 31/40	A1	(11) International Publication Number: WO 97/16434 (43) International Publication Date: 9 May 1997 (09.05.97)
(21) International Application Number: PCT/IB96/01049 (22) International Filing Date: 4 October 1996 (04.10.96) (30) Priority Data: 60/006,125 2 November 1995 (02.11.95) US (71) Applicant (for all designated States except US): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US). (72) Inventors; and (73) Inventors/Applicants (for US only): CHIU, Charles, K. [GB/US]; 12 Devon Drive, Pawcatuck, CT 06379 (US). MELTZ, Morgan [GB/US]; 115 Roxbury Road, Niantic, CT 06357 (US). (74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).		(51) Designated States: AU, BG, BR, BY, CA, CN, CZ, HU, IL, IS, JP, KR, KZ, LK, LV, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.
(54) Title: (-) CIS-6(S)-PHENYL-5(R)-[4-(2-PYRROLIDIN-1-YLETHOXY)PHENYL]-5,6,7,8-TETRAHYDRONAPHTHALEN-2-OL D-TARTRATE (57) Abstract An advantageous process for the preparation of (-) cis-6(S)-phenyl-5(R)-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol D-tartrate.		

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**(-) CIS-6(S)-PHENYL-5(R)-[4-(2-PYRROLIDIN-1-YL ETHOXY)
PHENYL]-5,6,7,8-TETRAHYDRONAPHTHALEN-2-OL D-TARTRATE**

BACKGROUND OF THE INVENTION

The present invention relates to (-) cis-6(S)-phenyl-5(R)-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol D-tartrate which is useful as an estrogen agonist, and to a process for its preparation.

The preparation of (-) cis-6(S)-phenyl-5(R)-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol, as its free base and R-binap salt is described in commonly owned United States patent application serial no. 08/369,954, the text of which is hereby incorporated by reference.

SUMMARY OF THE INVENTION

This invention is directed toward (-) cis-6(S)-phenyl-5(R)-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol D-tartrate.

In another aspect, this invention is directed toward a method of preparation of (-)cis-6(S)-phenyl-5(R)-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol D-tartrate which comprises:

- 1) dissolving racemic or partially optically enriched cis-6(S)-phenyl-5(R)-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol in boiling aqueous ethanol to form a solution;
- 2) adding an equal molar amount of D-tartaric acid dissolved in aqueous ethanol to said solution to form a second solution;
- 3) cooling said second solution; and
- 4) collecting the product formed in step 3.

In another aspect, this invention provides a pharmaceutical composition comprising (-)cis-6(S)-phenyl-5(R)-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol D-tartrate and a pharmaceutically acceptable carrier.

In yet another aspect, this invention provides methods for treating or preventing diseases or conditions which are susceptible to treatment or prevention by estrogen agonists which comprises administering to a mammal in need of such treatment or prevention an effective amount of (-)cis-6(S)-phenyl-5(R)-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol D-tartrate.

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optically active compounds. Resolution of this racemate has been previously accomplished by crystallization of the salt with R-(-)-1, 1' binaphthyl-2,2'-diyl hydrogen phosphate (R-binap) as described in commonly owned U.S. application serial no. 08/369,954. Since R-binap is not a suitable salt for pharmaceutical use,
5 the R-binap product must be further converted to the free base and finally to a pharmaceutically acceptable salt.

D-tartaric acid has been found to form a 1:1 salt with racemic or partially optically enriched cis-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol in aqueous ethanol.

10 Upon cooling, the desired (-) isomer separates as a solid and is easily collected, thus providing a pharmaceutically acceptable salt of the (-) cis isomer in high yield and purity in a single reaction step. Aqueous ethanol is the preferred solvent for this procedure; 95% aqueous ethanol is the preferred mixture.

This invention is readily carried out by dissolving racemic or partially
15 optically enriched cis-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol with an equal molar amount of D-tartaric acid in boiling aqueous ethanol; 95% ethanol is preferred. The amount of solvent must be adequate to effect complete solution of the salt. This has been found to be about 10 to 15mL per gram of racemic compound.

20 Upon cooling to room temperature, the desired (-) cis isomer separates as a solid. This product has an optical purity of about 95%. Washing with 95% ethanol under reflux produces a product with greater than 99% optical purity.

The compound of this invention is a valuable estrogen agonist and is useful for oral contraception; relief for the symptoms of menopause; prevention of
25 threatened or habitual abortion; relief of dysmenorrhea; relief of dysfunctional uterine bleeding; relief of endometriosis; an aid in ovarian development; treatment of acne; diminution of excessive growth of body hair in women (hirsutism); the prevention and treatment of cardiovascular disease; prevention and treatment of atherosclerosis; prevention and treatment of osteoporosis; treatment of benign
30 prostatic hyperplasia and prostatic carcinoma obesity; and suppression of post-partum lactation. This compound also has a beneficial effect on plasma lipid levels and as such are useful in treating and preventing hypercholesterolemia.

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-12-

CLAIMS

1. A method of preparation for the compound (-) cis-8(S)-phenyl-5(R)-[4-(2-pyrrolidin-1-yl ethoxy) phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol D-tartrate which comprises:
- 5 a) dissolving racemic or partially optically enriched cis-8-phenyl-5-[4-(2-pyrrolidin-1-yl ethoxy) phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol in boiling aqueous ethanol to form a solution;
- b) adding an equal molar amount of D-tartaric acid dissolved in aqueous ethanol to said solution to form a second solution;
- 10 c) cooling said second solution; and
- d) collecting the product formed in step 3.
2. A method of treating osteoporosis in a mammal which comprises administering to a mammal in need of such treatment an effective amount of the compound of claim 1.
- 15 3. A method of treating cardiovascular disease or hyperlipidemia in a mammal which comprises administering to a mammal in need of such treatment an effective amount of the compound of claim 1.
4. A method of treating prostatic disease in a mammal which comprises administering to a mammal in need of such treatment an effective amount of the compound of claim 1.
- 20 5. A method of lowering serum cholesterol levels in a mammal which comprises administering to a mammal in need of such treatment an effective amount of the compound of formula I.
6. A method of treating obesity in a mammal which comprises administering to a mammal in need of such treatment an effective amount of the compound of claim 1.
- 25 7. A method of treating breast cancer in a mammal which comprises administering to a mammal in need of such treatment an effective amount of the compound of claim 1.
- 30 8. A method of treating endometriosis in a mammal which comprises administering to a mammal in need of such treatment an effective amount of the compound of claim 1.

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SUPERINTENDENCIA DE INDUSTRIA Y C MERCIO100

DIVISION DE NUEVAS CREACIONES

2020
Bogotá, D.C., Agosto 18 de 2006

Abogado
ALVARO CORREA ORDÓÑEZ

ASUNTO	Radicación No.	00 097 926
	Trámite	002
	Evento	001
	Actuación	430
	Oficio No.	9776
	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: "Procedimiento para reducir la Morbilidad y el riesgo de Mortalidad".

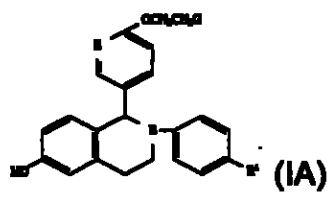
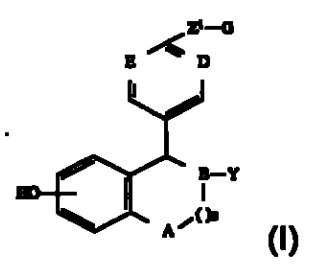
1. Documentos estudiados

Para el presente estudio se tuvieron en cuenta el capítulo descriptivo comprendido en los folios 184 - 262 y el capítulo reivindicatorio de los folios 263 - 288 de la solicitud.

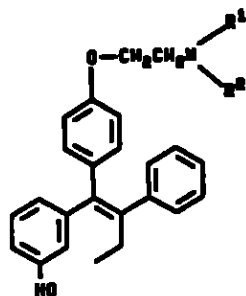
2. Objeto de la Invención

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

Las reivindicaciones 1 - 13 y 25 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 14 - 24 se refieren a un estuche que comprende una composición farmacéutica e instrucciones para utilizarla.

El problema planteado en esta solicitud es la necesidad de tratar de reducir la morbilidad y el riesgo de mortalidad producidas por enfermedad cardiovascular, cáncer de mama, osteoporosis.

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 60 175 663 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 - 13 y 25 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 - 13 y 25 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 - 13 y 25, 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 14 - 24 se refieren a un estuche que comprende una composición farmacéutica e instrucciones para utilizarla.

Se observa que las reivindicaciones 14 - 24 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-tetrahydronaphthalen-2-ol compounds which are useful for treating osteoporosis	Sep 3, 1996
D2	EP 0 793 981	Use of droloxifene for the manufacture of a medicament for increasing serum levels of testosterone	Sep 10, 1997
D3	WO 97 16434	(-) CIS-6(S)-PHENYL-5(R)[4-(2-PYRROLIDIN-1-YLETHOXY)PHENYL]-5,6,7,8-TETRAHYDRONAPHTHALEN-2-OL D-TARTRATE	May 9, 1997

6. Evaluación de los requisitos de Patentabilidad

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"*.

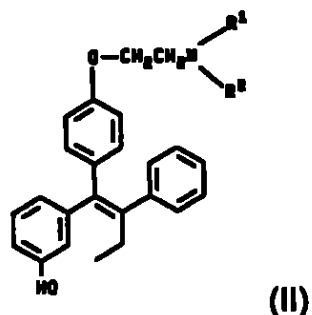
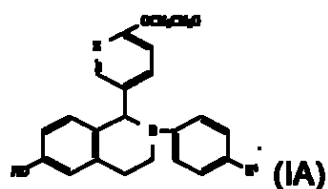
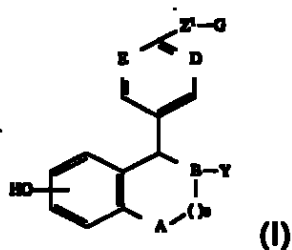
En cumplimiento del artículo 14 de la Decisión 486, se procedió a evaluar el cumplimiento de los requisitos de novedad, nivel inventivo y aplicación industrial, con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

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 esté 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."*

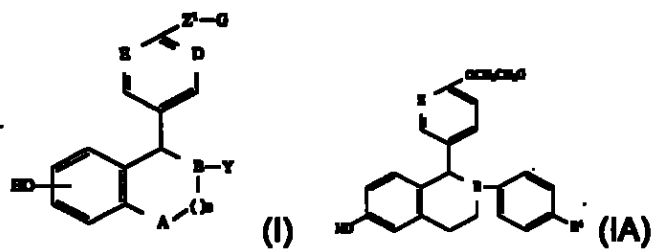
Solo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de 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):

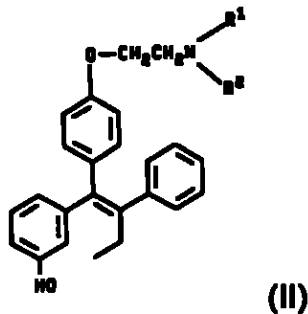


Se observa que los agonistas/antagonistas de estrógenos mencionados en esta solicitud eran conocidos, así:

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



D2 enseña compuestos de fórmula (II).



D3 enseña (ver folio 322) (-) cis-6(S)-fenil-5(R)[4-(2-pirrolidin-1-il etoxi)fenil]-5,6,7,8-tetrahidronaftalen-2-ol D-tartrato. Menciona el procedimiento de tratamiento de enfermedad cardiovascular, cáncer de mama, osteoporosis que consiste en administrar este compuesto.

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

Ni lo es el procedimiento de tratamiento de enfermedad cardiovascular, cáncer de mama, osteoporosis que consiste en administrar este compuesto.

7. 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 – 25	Novedad
D2	EP 0 793 961	1 – 25	Novedad
D3	WO 97 16434	1 – 25	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.

328
326

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 AGO. 2006

CONCEPTO TÉCNICO No. 1339	EXAMINADOR TÉCNICO Código 202007
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

327

RADICACIÓN: 0-97828

EDICTO No. 605

**LA SECRETARÍA GENERAL AD-HOC
HACE SABER:**

Que esta Superintendencia profirió Resolución No. 34977 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 "PROCEDIMIENTO PARA REDUCIR LA MORBILIDAD Y EL RIESGO DE MORTALIDAD".

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,


JAIRO RUBIO ESCOBAR

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

Secretaría General Ad-Hoc 10-ENE-2007
Secretaría General Ad-Hoc
EDICTO No. 605

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