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Señora Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-023405- -00002-0000

Fecha 2008-02-20 17:04:07 Dep 2020 NUECREACIONE
Tra 11 PATENTILYII Eve 378 FASENACIONALI
Act 538 PLICION Folios 2

Trámite : 011

Evento : 378

Actuación : 538

Referencia : Expediente No. 07.023.405
Asunto : Solicitud de Patente para **ESTEROIDES 15B-SUSTITUIDOS QUE TIENEN ACTIVIDAD ESTROGENICA SELECTIVA**
Solicitante : **N.V. ORGANON**
Clase : A61K 031/056, A61P 005/000, C07J 001/000
Publicada en : La Gaceta No. **579** Del 31 de agosto de 2007
Fecha de Solicitud : 8 de marzo de 2007

1. Yo, Emilio FERRERO, identificado como aparece al pie de mi firma, actuando como apoderado en el asunto de la referencia, atentamente, solicito se efectúe el examen de patentabilidad de la solicitud en referencia presentada de acuerdo con el Capítulo I del PCT y según lo establecido en el artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina. Para tal efecto presento junto con este escrito el recibo por valor de \$420.000.00, que corresponde a la tasa fijada según lo dispuesto en la resolución No. 44372 de 26 de diciembre de 2007.

2. Ruego atentamente a la Señora Jefe se sirva ordenar que se anexe este recibo para que se efectúe dicho examen y se continúe con el trámite de la solicitud.

Señora Jefe,

EMILIO FERRERO

T.P.A. No. 31.929

COLO-00299-841-007-6
ASGVAHP\ID-119382\WPCL0299
No. M-2008-119382\ASG

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 9,453
FECHA : FEBRERO 4 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No 07-023405-00002-0000

Fecha 2008-02-04 09:09, 2020 NUL CREACIONE
PATENTABILIDAD DE INVEN. 378 FASE NACIONAL I
Act 358 RELECCION - Folio 2

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	2678327	04/02/2008	51,244,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	85 EXAMEN DE PATENTABILIDAD DE INVEN	420,000.00
		TOTAL :	\$ 420,000.00

SON: CUATROCIENTOS VEINTE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Colo 00299-841-007-6



US005686437A

United States Patent [19]
Labrie et al.

[11] **Patent Number:** **5,686,437**
[45] **Date of Patent:** **Nov. 11, 1997**

[54] **ESTROGEN NUCLEUS DERIVATIVES FOR USE IN THE INHIBITION OF SEX STEROID ACTIVITY**

5,204,337 4/1993 Labrie et al. 514/182
5,364,847 11/1994 Labrie et al. 514/182
5,372,996 12/1994 Labrie et al. 514/15

[75] **Inventors:** **Fernand Labrie; Yves Mérand**, both of Ste-Foy, Canada

FOREIGN PATENT DOCUMENTS

[73] **Assignee:** **Endorecherche Inc.**, Canada

703061 9/1964 Australia .
341263 2/1965 Australia .
5179264 5/1966 Australia .
5673265 7/1969 Australia .
0138504 4/1985 European Pat. Off. .
0280618 8/1988 European Pat. Off. .
0305242 3/1989 European Pat. Off. .
3242894 5/1984 Germany .

[21] **Appl. No.:** **475,710**

[22] **Filed:** **Jun. 7, 1995**

Related U.S. Application Data

[62] Division of Ser. No. 017,045, Feb. 12, 1993, Pat. No. 5,631,249, which is a division of Ser. No. 917,915, Jul. 21, 1992, Pat. No. 5,204,337, which is a continuation of Ser. No. 377,010, Jul. 7, 1989, abandoned, which is a continuation-in-part of Ser. No. 322,154, Mar. 10, 1989, abandoned, and a continuation-in-part of Ser. No. 265,716, Nov. 1, 1988, abandoned, and a continuation-in-part of Ser. No. 265,150, Oct. 31, 1988, abandoned.

Primary Examiner—Ralph H. Dean

Attorney, Agent, or Firm—Ostrolenk, Faber, Gerb & Soffen, LLP

[51] **Int. Cl.⁶** **A61K 31/56; A61K 31/58**
[52] **U.S. Cl.** **514/172; 514/169; 514/177; 514/178; 514/182; 514/874**
[58] **Field of Search** **514/172, 178, 514/177, 169, 182, 874**

[57] **ABSTRACT**

Novel derivatives of estrogenic nuclei, contain a side-chain substitution of the formula $-R^1[B-R^2]_xL-G$ and may be used in pharmaceutical compositions as sex steroid activity inhibitors useful in the treatment of both androgen-related and estrogen-related diseases.

[56] **References Cited**

U.S. PATENT DOCUMENTS

2,875,199 2/1959 Cella .

6 Claims, 2 Drawing Sheets

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ESTROGEN NUCLEUS DERIVATIVES FOR USE IN THE INHIBITION OF SEX STEROID ACTIVITY

RELATED APPLICATIONS

This application is a division of application Ser. No. 08/017,045, filed Feb. 12, 1993, now U.S. Pat. No. 5,631,249, which is in turn a division of application Ser. No. 917,915 filed Jul. 21, 1992 now U.S. Pat. No. 5,204,337, which is in turn a continuation of application Ser. No. 07/377,010 filed Jul. 7, 1985, abandoned, which is in turn continuation-in-part of U.S. patent application Ser. No. 07/322,154 filed Mar. 10, 1989, now abandoned, and of U.S. application Ser. No. 07/265,716 filed Nov. 1, 1988, now abandoned, and of U.S. application Ser. No. 07/265,150 filed Oct. 31, 1988, now abandoned, the disclosures of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

This invention relates to novel inhibitors of sex steroid activity such as antiestrogen compounds having effective antagonistic capability while substantially lacking agonistic effects. More particularly, certain preferred embodiments of the invention relate to certain estradiol and non-steroidal diphenylethylene analogs which have high affinity for estrogen receptors but do not activate such receptors and/or which inhibit the production of sex steroids or their precursors.

During the treatment of certain sex steroid-dependent diseases, it is important to greatly reduce or, if possible, eliminate certain sex steroid-induced effects. For this purpose, it is desirable both to block receptor sites stimulated by sex steroids and also to reduce the amount of sex steroid available to act at these sites. For example, alternative or concurrent therapy to administration of antiestrogens could involve attempts to block the production of estrogens (e.g. by ovariectomy) such that less is available to activate receptor sites. However, prior art methods for blocking estrogen production insufficiently inhibit estrogen-induced functions. Moreover, it is possible that even in the total absence of sex steroids, unoccupied sex steroid receptors may be biologically active. Hence, antagonists of sex steroids may produce greater therapeutic results than therapy which only inhibits sex steroid production. Prior art antagonists, however, often have insufficient affinity for receptors, and some, although capable of binding the receptors, may themselves act as agonists and undesirably activate some receptors and induce the same effects as a sex steroid.

There is, therefore, a need in the art for antiestrogens which effectively block estrogen receptors with minimal or no agonistic effect. Numerous compounds have been tried in the art with mixed results. Known antiestrogens continue to exhibit undesirable agonistic activity. See, for instance, Wakeling and Bowler, "Steroidal Pure Antioestrogens", *J. Endocrinol.* (1987) 112, R7-R10. The net effectiveness of prior art compounds is determined by the balance between their agonistic and antagonistic activities. Certain steroidal derivatives similar to those disclosed in the foregoing article, and which are stated to have antioestrogenic effect, are set forth in Bowler et al., U.S. Pat. No. 4,659,516.

In U.S. Pat. No. 4,094,994, it is disclosed that the use of certain antiestrogens may inhibit certain human breast tumor cells.

H. Mooridsen et al., *Cancer Treatment Review* 5, 131-141, (1978), discloses that Tamoxiphen, an

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antiestrogen, is effective in remission of advanced breast cancer in about 30 percent of the women patients treated.

The combined use of the antiestrogen Tamoxiphen and a luteinizing hormone-releasing hormone agonist, Buserelin, is also known for treatment of breast cancer. See, for instance, Klijn et al., *J. Steroid Biochem.* 420, No. 6b, 1381 (1984); The objective remission of such cancers, however, remains unacceptably low.

It has been found that certain 7 α -substituted derivatives of estradiol possess antiestrogenic activity (Bowler et al., 1985; Eur. Patent Application 0138504; Wakeling and Bowler, *J. Steroid Biochem.* 30: 141-147, 1988).

In U.S. Pat. No. 4,659,516, Bowler et al. report antiestrogenic activity for certain 7 α substituted derivatives of estradiol.

For a number of years, there has been research for compounds which can efficiently inhibit androgen and/or estrogen formation (e.g. enzyme inhibitors) or for compounds which may suppress androgen or estrogen action (steroid antagonists), without causing adverse effects to healthy tissues.

Recently, estradiol derivatives bearing a carboxyalkyl substituent at the 7 α -position maintained their affinity for the estrogen receptor when linked via their carboxy group to agarose or polyacrylamide resin for affinity chromatography purification of the estrogen receptor (Bucourt et al., *J. Biol. Chem.* 253: 8221, 1978).

Non steroidal compounds bearing a similar aliphatic side chain have also been found to possess antiestrogenic activity (U.S. Pat. No. 4,732,912).

Some steroid derivatives, such as especially 16-methylene estradiol and 16-methylene estrone, have been described as inhibitors of 17 β -hydroxysteroid dehydrogenase activity (Thomas et al., *J. Biol. Chem.* 258: 11500, 1983).

Prior art methods have not been completely effective in inhibiting sex steroid synthesis while avoiding undesirable side effects.

Certain nonsteroidal compounds which are stated to have antiandrogenic effect are described by Furr et al., *J. Endocr.* 113, R7-R9, 1987.

In U.S. Pat. No. 4,659,695 relates to a method of treatment of prostate cancer for susceptible male animals including humans whose testicular hormonal secretions are blocked by surgical or chemical means, e.g., by use of an LHRH agonist, e.g., [D-Trp⁶, des-Gly-NH₂¹⁰]LHRH ethylamide. The treatment includes administering an antiandrogen, e.g., flutamide in association with at least one inhibitor of sex steroid biosynthesis, e.g., aminoglutethimide and/or ketoconazole.

U.S. Pat. No. 4,472,382 relates to a method of treating prostate cancer using the combination of an antiandrogen and an LHRH agonist.

In U.S. Pat. No. 4,386,080 relates to new amide derivatives, and more particularly novel acylanilides, possess antiandrogenic properties.

In French, Patent 2528434 and in Jordan and Koch, "Regulation of Prolactin Synthesis in vitro by estrogenic and antiestrogenic derivatives of estradiol and Estrone", *Endocrinology* 124(4): 1717-1725 (1989), antiestrogenic effects are described for certain 11 β -long chain substituted estradiol derivatives.

In U.S. Pat. No. 3,995,060, U.S. Pat. No. 4,161,540 and U.S. Pat. No. 4,139,638, it is disclosed that certain 4'-substituted and 3', 4'-disubstituted anilides have antiandrogenic properties.

EP Pat. No. 138 504, EP Pat. No. 166 509, EP Pat. No. 124 369, EP Pat. No. 160 508, EP Pat. No. 163 416, U.S. Pat. No. 4,732,912, U.S. Pat. No. 4,760,061, U.S. Pat. No. 4,751,240, U.S. Pat. No. 4,659,516 and Wakeling A. E. and Bowler J., *J. Endocr.* 112, R7-R10, 1987, and *J. Steroid Biochem.* 30, 141-147, 1988 disclose that certain long chain substitutions onto an estrogenic nucleus may result in compositions exhibiting antiestrogenic activity.

For a number of years, there has been search for compounds which can efficiently inhibit androgen and/or estrogen formation without causing adverse effects to healthy tissues. More particularly, the inhibition of 17 β -hydroxysteroid dehydrogenase, which is involved in the biosynthesis of testosterone, androst-5-ene-3 β ,17 β -diol and estradiol, has been studied by some workers. Some affinity-label inhibitors for human placental estradiol 17 β -dehydrogenase have been described (C. C. Chin and J. C. Warren, *J. Biol. Chem.* 250, 7682-7686, 1975; Y. M. Bhatnagar et al., *J. Biol. Chem.* 253, 811-815, 1978; C. C. Chin et al., *J. Biol. Chem.* 255, 3660-3664, 1980; J. L. Thomas and R. C. Strickler, *J. Biol. Chem.* 258, 1587-1590, 1983).

B. Tobias et al., *J. Biol. Chem.* 257, 2783-2786, 1982 and R. J. Auchus and D. F. Covey, *Biochemistry* 25, 7295-7300, 1986 disclose, respectively, the use of 17 β -propynyl-substituted progestins and propynyl-substituted 3-hydroxy-14,15-secoestra-1,3,5(10)-trien-17-one as inhibitors of the 17 β -estradiol dehydrogenase.

Thomas J. L. et al., *J. Biol. Chem.* 258, 11500, 1983 have described that 16-methylene estradiol and 16-methylene estrone are inhibitors of 17 β -hydroxysteroid dehydrogenase activity.

OBJECTS OF THE INVENTION

It is an object of the present invention to provide methods of inhibiting sex steroid activity. Such methods may be useful in the treatment of sex steroid-related diseases.

It is another object of the invention to provide a steroidal pure antiestrogen for therapeutic use.

It is another object of the invention to provide compositions capable of inhibiting sex steroid synthesis, especially estrogen synthesis.

It is another object to provide an antiestrogen having good affinity for estrogen receptors, but substantially lacking undesirable agonistic activity regarding these receptors and substantially lacking hormonal activity.

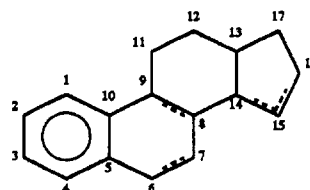
It is another object of the invention to provide a therapeutic antiestrogenic composition useful in the treatment of estrogen-related diseases. These diseases include, but are not limited to, breast cancer, uterine cancer, ovarian cancer, endometriosis, uterine fibroma, precocious puberty and benign prostatic hyperplasia.

It is another object of the invention to provide inhibitors of sex steroid production useful in the treatment of both estrogen- and androgen-related diseases. Androgen-related diseases include but are not limited to prostate cancer, ache vulgaris, hirsutism, precocious puberty, benign prostatic hyperplasia, seborrhea, androgenic alopecia and sexual deviants. Control of androgen activity may also be useful in male contraception.

SUMMARY OF THE INVENTION

The present invention provides a method of inhibiting sex steroid activity in a warm-blooded animal, including humans, comprising administering to said animal a therapeutically effective amount of a compound having as part of

its molecular structure an estrogenic nucleus of general structure I:



wherein the dotted lines represent optional pi bonds and wherein said compound includes as another part of its molecular structure a side chain substituents onto a ring carbon of said general structure I represented by the formula $-R^1[-B-R^2]_x-L-G$ wherein at least one of said side chains is substituted at a ring carbon selected from the group consisting of carbon 14, carbon 15, carbon 16 and carbon 17, wherein:

x is an integer from 0 to 6, wherein at least one of L and G is a polar moiety distanced from said ring carbon by at least three intervening atoms, and wherein:

R^1 and R^2 are independently either absent or selected from the group consisting of straight- or branched-chain alkylene, straight- or branched-chain alkynylene, straight- or branched-chain alkenylene, phenylene, and fluoro-substituted analogs of the foregoing;

B is either absent or selected from the group consisting of $-O-$, $-S-$, $-Se-$, $-SO-$, $-SO_2-$, $-NR^3-$, $-SiR^3_2-$, $-CR^3OR^3-$, $-NR^3CO-$, $-NR^3CS-$, $-CONR^3-$, $-CSNR^3-$, $-COO-$, $-COS-$, $-SCO-$, $-CSS-$, $-SCS-$, $-OCO-$ and phenylene (R^3 being hydrogen or lower alkyl);

L is either a moiety which together with G, forms a heterocyclic ring having at least one nitrogen atom or is selected from the group consisting of lower alkyl, $-CONR^4-$, $-CSNR^4-$, $-NR^5CO-$, $-NR^5CS-$, $-NR^5CONR^4-$



$-SO_2NR^4-$, $-CSS-$, $-SOS-$, $-(NO)R^4-$, $-(PO)R^4-$, $-NR^5COO-$, $-NR^5SO_2-$, $-O-$, $-NR^4-$, $-S-$, $-SO-$ and $-SO_2-$ (R^4 and R^5 being independently selected from the group consisting of hydrogen and lower alkyl; and R^6 being selected from the group consisting of hydrogen, nitrile and nitro); and

G is either a moiety which together with L forms a heterocyclic ring having at least one nitrogen atom, or is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkynyl, (C_3-C_7) cycloalkyl, bromo(lower)alkyl, chloro(lower)alkyl, fluoro(lower)alkyl, iodo(lower)alkyl, cyano(lower)alkyl, carboxy(lower)alkyl, (lower)alkoxycarbonyl (lower)alkyl, (C_6-C_{10}) aryl, (C_7-C_{11}) arylalkyl, di(lower)alkylamino(lower)alkyl and fluoro-substituted analogs of the foregoing.

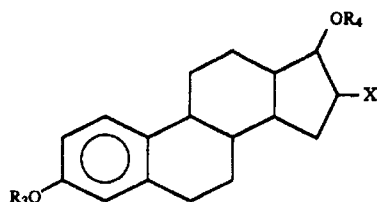
The invention further provides a method of inhibiting sex steroid activity in a warm-blooded animal, including humans, comprising administering a therapeutically effective amount of at least one compound having, as part of its molecular structure, a substituted or unsubstituted estrogenic nucleus of general structure I:

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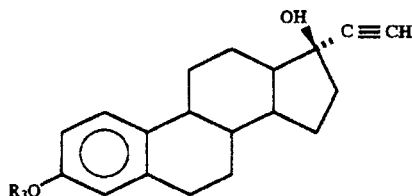
Preferred estrogenic nuclei suitable for use in accordance with the invention include but are not limited to estradiol and derivatives thereof. Other suitable estrogenic nuclei include but are not limited to those which (as reported in the references set forth below) effect more than the threshold increase in uterine weight of ovariectomized rats set forth above as defining an estrogenic nucleus (Simard et al., Mol. Endocrinol. 2:775-784 (1988)).

Some preferred estrogenic nuclei include but are not limited to:

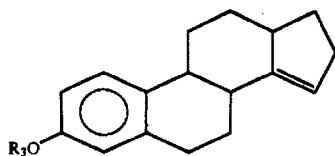
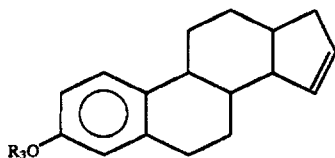


wherein x is a halogen, preferably chlorine or bromine;

wherein R₃ and R₄ are independently selected from the group consisting of hydrogen, lower alkyl, lower alkoxy carbonyl, (C₁-C₂₀), alkanoyl, (C₃-C₂₀) alkenoyl, (C₃-C₂₀) alkynoyl and (C₇-C₁₁) aroyl, alkylsilyl, 1-alkyloxy-alkyl and 1-alkyloxy cycloalkyl.

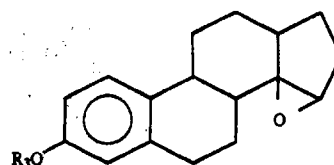


wherein R₃ is selected from the group consisting of hydrogen, lower alkyl, lower alkoxy carbonyl, (C₁-C₂₀), alkanoyl, (C₃-C₂₀) alkenoyl, (C₃-C₂₀) alkynoyl and (C₇-C₁₁) aroyl, alkylsilyl, 1-alkyloxy-alkyl and 1-alkyloxy cycloalkyl.

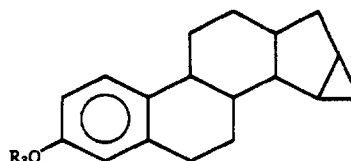


wherein R₃ is selected from the group consisting of hydrogen, lower alkyl, lower alkoxy carbonyl, (C₁-C₂₀), alkanoyl, (C₃-C₂₀) alkenoyl, (C₃-C₂₀) alkynoyl and (C₇-C₁₁) aroyl, alkylsilyl, 1-alkyloxy-alkyl and 1-alkyloxy cycloalkyl.

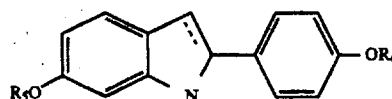
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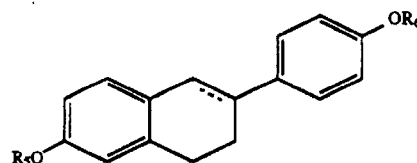
wherein R₃ is selected from the group consisting of hydrogen, lower alkyl, lower alkoxy carbonyl, (C₁-C₂₀), alkanoyl, (C₃-C₂₀) alkenoyl, (C₃-C₂₀) alkynoyl and (C₇-C₁₁) aroyl, alkylsilyl, 1-alkyloxy-alkyl and 1-alkyloxy cycloalkyl.



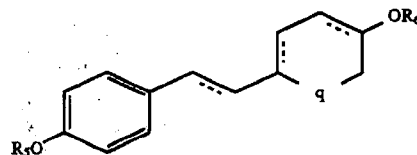
wherein R₃ is selected from the group consisting of hydrogens, lower alkyl, lower alkoxy carbonyl, (C₁-C₂₀), alkanoyl, (C₃-C₂₀) alkenoyl, (C₃-C₂₀) alkynoyl and (C₇-C₁₁) aroyl, alkylsilyl, 1-alkyloxy-alkyl and 1-alkyloxy cycloalkyl.



wherein the dotted lines are optional double bonds; wherein R₅ and R₆ are independently selected from the group consisting of hydrogen, lower alkyl, lower alkoxy carbonyl, (C₁-C₂₀), alkanoyl, (C₃-C₂₀) alkenoyl, (C₃-C₂₀) alkynoyl and (C₇-C₁₁) aroyl, alkylsilyl, 1-alkyloxy-alkyl and 1-alkyloxy cycloalkyl.



wherein the dotted lines are optional double bonds; wherein R₅ and R₆ are independently selected from the group consisting of hydrogens, lower alkyl, lower alkoxy carbonyl, (C₁-C₂₀), alkanoyl, (C₃-C₂₀) alkenoyl, (C₃-C₂₀) alkynoyl and (C₇-C₁₁) aroyl, alkylsilyl, 1-alkyloxy-alkyl and 1-alkyloxy cycloalkyl.



wherein q is absent, methylene or ethylene wherein R₅ and R₆ are independently selected from the group consisting of hydrogens, lower alkyl, lower alkoxy carbonyl, (C₁-C₂₀), alkanoyl, (C₃-C₂₀)



US006677329B1

(12) **United States Patent**
Loozen et al.

(10) **Patent No.:** US 6,677,329 B1
(45) **Date of Patent:** Jan. 13, 2004

(54) **NON-AROMATIC ESTROGENIC STEROIDS
WITH A HYDROCARBON SUBSTITUENT IN
POSITION 11**

(75) **Inventors:** Hubert Jan Jozef Loozen, Uden (NL);
Gerrit Herman Veeneman, Schaijk
(NL); Wilhelmus Gerardus Eduardus
Joseph Schoonen, Oss (NL)

(73) **Assignee:** Akzo Nobel N V., Arnhem (NL)

(*) **Notice:** Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 23 days.

(21) **Appl. No.:** 10/070,262

(22) **PCT Filed:** Aug. 28, 2000

(86) **PCT No.:** PCT/EP00/08406

§ 371 (c)(1),

(2), (4) **Date:** May 29, 2002

(87) **PCT Pub. No.:** WO01/18027

PCT Pub. Date: Mar. 15, 2001

(30) **Foreign Application Priority Data**

Sep. 6, 1999 (EP) 99202900

(51) **Int. Cl.⁷** A61K 31/56; C07J 1/00

(52) **U.S. Cl.** 514/182; 552/642; 552/644;
552/645; 552/649

(58) **Field of Search** 514/182; 552/642,
552/644, 645, 649

(56) **References Cited**

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vol. 15(2) pp. 281-288, 1990.*

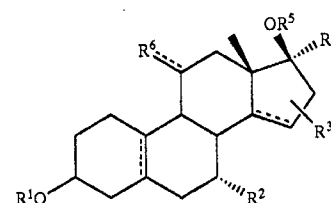
* cited by examiner

Primary Examiner—Barbara P. Badio

(74) *Attorney, Agent, or Firm*—Mark W. Milstead

(57) **ABSTRACT**

Disclosed are novel, selective estrogens type having a ste-
roid skeleton with a non-aromatic A-ring and a free or
capped hydroxyl group at carbon atom No. 3. The estrogens
satisfy general formula (I), in which R¹ is H, (C₁-C₃)alkyl
or (C₂-C₃)acyl; R² is H, α-(C₁-C₄)alkyl, α-(C₂-C₄)alkenyl
or α-(C₂-C₄)alkynyl; R³ is H or (C₁-C₄)alkyl, (C₂-C₄)
alkenyl or (C₂-C₄)alkynyl, each at location 15 or 16 of the
steroid skeleton; R⁴ is H or (C₁-C₃)alkyl, (C₂-C₃)alkenyl or
(C₂-C₃)alkynyl, each optionally substituted with halogen;
preferred is ethynyl; R⁵ is H, (C₁-C₃)alkyl or (C₂-C₃)acyl;
R⁶ is (C₁-C₅)alkyl, (C₂-C₅)alkenyl, (C₂-C₅)alkynyl or
(C₁-C₅)alkylidene, each optionally substituted.



(I)

9 Claims, No Drawings

US 6,677,329 B1

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NON-AROMATIC ESTROGENIC STEROIDS WITH A HYDROCARBON SUBSTITUENT IN POSITION 11

This application is a 371 of PCT/EP00/08406 filed Aug. 28, 2000.

FIELD OF THE INVENTION

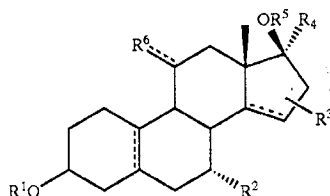
The invention is in the field of estrogenic compounds with a steroid skeleton having a non-aromatic A-ring and a free or capped hydroxyl group at carbon atom No. 3. Estrogenic compounds have a generally recognised utility in contraception and in the treatment of estrogen-deficiency related disorders, such as menopausal complaints, and osteoporosis.

BACKGROUND OF THE INVENTION

Many estrogenic compounds are known. For example, an instructive publication on estrogenic compounds with a non-aromatic A-ring and a free or capped hydroxyl group at carbon atom 3 is U.S. Pat. No. 3,413,287. Other documents describing estrogenic or hormonal effects of non-aromatic steroids with 3-hydroxyl substitution and a 4-5 double bond are WO 94 18224, U.S. Pat. No. 3,465,010, FR 2099385, U.S. Pat. No. 3,652,606 and EP 145 493. A document in which non-aromatic steroids with 3-keto substitution and a 5-10 double bond are disclosed is Baran et al (U.S. Pat. No. 3,377,366. Such compounds are described in general terms as agents with, among other, estrogenic or anti-estrogenic effects. Recently, in the field of drugs for estrogen receptors (ER) attention is focussed on the discovery of two distinct types of estrogen receptors, denoted ER α and ER β (Mosselman et al., *FEBS Letters* 392 (1996) 49-53 as well as EP-A-0 798 378). Since these receptors have a different distribution in human tissue, the finding of compounds which possess a selective affinity for either of the two is an important technical progress, making it possible to provide a more selective treatment of estrogen-deficiency related disorders, with a lower burden of estrogen-related side-effects.

BRIEF SUMMARY OF THE INVENTION

This invention provides estrogens satisfying the general formula



in which

- R¹ is H, (C₁-C₃)alkyl or (C₂-C₃)acyl;
- R² is H, α -(C₁-C₄)alkyl, α -(C₂-C₄)alkenyl or α -(C₂-C₄)alkynyl;
- R³ is H or (C₁-C₄)alkyl, (C₂-C₄)alkenyl or (C₂-C₄)alkynyl, each at location 15 or 16 of the steroid skeleton;
- R⁴ is H or (C₁-C₅)alkyl, (C₂-C₅)alkenyl or (C₂-C₅)alkynyl, each optionally substituted with halogen; preferred is ethynyl;
- R⁵ is H, (C₁-C₃)alkyl or (C₂-C₃)acyl;
- R⁶ is (C₁-C₅)alkyl, (C₂-C₅)alkenyl, (C₂-C₅)alkynyl or (C₁-C₅)alkylidene, each optionally substituted with

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halogen or (C₁-C₃)alkyloxy; allyl is preferred; preferred halogens in R⁶ are fluorine and chlorine.

Dotted bonds represent optional double bonds. When R⁶ is alkylidene, the dotted line to R⁶ represents the additional bond present in an alkylidene moiety, and when R⁶ is alkyl or alkenyl, the bond from atom 11 to R⁶ is a single bond.

It has been found that these non-aromatic estradiol derivatives with a substituent at the 11 position of the steroid skeleton possess selective affinity for the ER α -receptor.

The compounds according to the present invention are suitable as improved estrogens, in the sense that they can be used in estrogen-related disorders, such as menopausal complaints and osteoporosis. Utility they also find in contraception, and they further may be suitable in the treatment or prevention of Alzheimer's disease, breast tumor, benign prostate hypertrophy, and cardiovascular disorders. The compounds of the invention are particularly suitable in the treatment and prevention of estrogen-deficiency related disorders under diminished estrogen-related side-effects.

DETAILED DESCRIPTION OF THE INVENTION

In this description terms have the following meaning:

(C₁-C₅)alkyl is a branched, unbranched or cyclized alkyl group having 1-5 carbon atoms, for example methyl, ethyl, isopropyl, 2-methylcyclopropyl, butyl, sec-butyl, tert-butyl etc.;

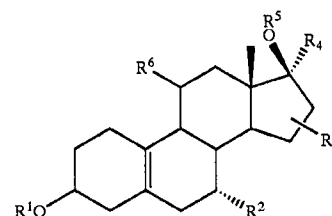
(C₂-C₅)alkenyl is a branched, unbranched or cyclized alkenyl group having 2 to 5 carbon atoms, such as ethenyl, 2-butenyl, etc.

(C₂-C₅)alkynyl is a branched or unbranched alkynyl group having 2-5 carbon atoms, such as ethynyl and propynyl.

(C₂-C₃)acyl is a group having 2-3 carbon atoms and derived from an alkylcarboxylic acid, the alkyl moiety having the meaning as defined previously.

(C₁-C₅)alkylidene is a branched, unbranched or cyclized alkylidene group having 1-5 carbon atoms, such as methylene and ethylene.

Within the general formula given above, the compounds of the invention preferably are those satisfying the general formula II,



formula II

in which

- R¹ is H, (C₁-C₃)alkyl, (C₂-C₃)acyl;
- R² is H, α -(C₁-C₄)alkyl, α -(C₂-C₄)alkenyl, α -(C₂-C₄)alkynyl;
- R³ is H or (C₁-C₄)alkyl at location 16 of the steroid skeleton;
- R⁴ is ethynyl
- R⁵ is H or (C₁-C₃)alkyl, (C₂-C₃)acyl;
- R⁶ is (C₁-C₅)alkyl, (C₂-C₅)alkenyl, (C₂-C₅)alkynyl; each can be substituted with chlorine or fluorine. When