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Solicitante: SCHERING AKTIENGESELLSCHAFT

Yo, GUSTAVO HOLLMANN RESTREPO, vecino de Bogotá D.C., portador de la tarjeta profesional No. 5903, obrando como apoderado en este negocio, digo a usted que acompaño al presente memorial, con carácter de anexión voluntaria, para que sean agregados al expediente de la referencia los siguientes documentos:

- Copia certificada de la solicitud de patente No. 09/756,286 presentada en estados Unidos el 9 de enero de 2001, con su correspondiente traducción al español de la carátula y Reivindicaciones.
- Copia certificada de la solicitud de patente No. 09/801,925 presentada en Estados Unidos el 9 de marzo de 2001, con su correspondiente traducción al español de la carátula y Reivindicaciones.

Señor Superintendente,


GUSTAVO HOLLMANN RESTREPO

C.C. No. 2.878.023 de Bogotá

T.P. No. 5903

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UNITED STATES DEPARTMENT OF COMMERCE

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February 01, 2002

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 09/756,286

FILING DATE: *January 09, 2001*

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS



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PATENT TRADEMARK OFFICE

Atty's Docket No. SCH-1754

Applicant(s) : Sybille BEIER et al.

For : THE USE OF ANTIGESTAGENS FOR INHIBITING ACCELERATED
ENDOMETRIAL MATURATION DURING INFERTILITY TREATMENT

The Honorable Commissioner
of Patents and Trademarks
Washington, D.C. 20231

SUBMISSION OF APPLICATION UNDER 37 C.F.R. §1.53(f)

Sir:

Herewith is the above-identified continuation-in-part application for Letters Patent including:

Applicant(s) Name(s) : Sybille BEIER
Holger HESS-STUMP

Assignee (by unrecorded assignment) :

Pages of Application: Specification - 17
Claims - 16
Abstract - 1
Sheets of Drawings - 1

NO DECLARATION IS ATTACHED.

☐ The benefit under 35 U.S.C. §119 is claimed of the filing date of :

Respectfully submitted,

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.

By:

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**THE USE OF ANTIGESTAGENS FOR INHIBITING ACCELERATED
ENDOMETRIAL MATURATION DURING INFERTILITY TREATMENT**

BACKGROUND OF THE INVENTION

This invention relates to the use of antigestagens for shifting post-ovulatory
endometrial maturation during infertility treatment.

Ovarian stimulation with gonadotropins is commonly used in humans in
assisted reproductive technologies, including in vitro fertilization and embryo
transfer therapy (IVF/ET). However, the post-ovulatory endometrial
transformation is advanced after controlled ovarian hyperstimulation (Garcia et al.,
1984, *Fertil. Steril.* 41:31-37; Paulson et al., 1997, *Fertil. Steril.* 76:321-325;
Kolb, 1997, *Fertil. Steril.* 67:625-630; Franchin et al., 1999, *Fertil. Steril.* 71:174-
181. As a consequence, the usual precisely synchronized temporal development of
the endometrium and the embryo is disrupted, resulting in low transplantation rates
for healthy zygotes.

SUMMARY OF THE INVENTION

This invention provides a method of enhancing fertility in mammals by the
administration of 17 α -fluoralkylated progesterone receptor antagonists to delay the
occurrence of endometrium maturation during infertility (i.e., fertility
enhancement) treatment including all assisted reproduction therapies.

It is also contemplated as part of this invention that such a method will be
particularly useful in a female mammal undergoing fertility treatment. Fertility
treatment, as used herein, refers to any treatment which is rendered to a female
mammal for the purposes of achieving a pregnancy, whether or not the mammal has
been determined to be fertile, infertile, or to have impaired fertility. Fertility
treatments contemplated as part of this invention include, but are not limited to
ovarian hyperstimulation (OH), in vitro fertilization and embryo transfer (IVF/ET),
and OH in combination with IVF/ET. Particularly, a method of delaying advanced
endometrial maturation which typically occurs in conjunction with ovarian
hyperstimulation is contemplated. For example, ovarian hyperstimulation may be

used as a tool in fertility treatment in conjunction with, for example, timed intercourse, artificial insemination, intrauterine insemination, IVF/ET, and gamete intra fallopian transfer (GIFT).

IVF/ET, as used herein, refers to any techniques wherein oocytes are fertilized in vitro and then transplanted into the female reproductive tract. For example, transplantation of the embryo may occur via transplantation of the embryo into the uterus through the cervix or via transplantation of the embryo into the fallopian tubes (zygote intra fallopian transfer (ZIFT)). Fertilization of oocytes in vitro may be accomplished, for example, by incubating oocytes in the presence of sperm or by intra cytoplasmic sperm injection. IVF/ET may also be accomplished using donor eggs. Infertility treatments also include treatments such as induction of ovarian stimulation followed by fertilization by normal coitus.

Ovarian hyperstimulation, as used herein, refers to the use of a follicle stimulating agent to stimulate follicle development. Ovarian hyperstimulation may be used in female subjects having a variety of ovulatory conditions, including subjects who are anovulatory, subjects who have impaired, reduced, or irregular ovulation, and subjects with normal ovulatory patterns. Preferred follicle stimulating agents, include gonadotropins, such as for example, follicle stimulating hormone (FSH), luteinizing hormone (LH), human menopausal gonadotropins (hMG), and human chorionic gonadotropin (hCG). Brand names of gonadotropins that are available for use as follicle stimulating agents, include for example, Perganol, Metrodin, Humegon, Fertinorm Gonal F, and Primogonyl-1000 etc. Follicle stimulating agents, as used herein, also include estrogen blocking agents such as, for example, clomiphene citrate (commercially available as Clomid and Serophene). Gonadotropins that may be used in accordance with this invention include hormones that are isolated from naturally occurring source materials and hormones that are produced synthetically, including hormones produced through recombinant DNA techniques. Mutant gonadotropins which retain activity as follicle stimulating agents are also contemplated as part of this invention.

Ovarian hyperstimulation may be accomplished using more than type of follicular stimulating agent. For example, an estrogen blocking agent such as

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clomiphene may be used in combination with a gonadotropin. Ovarian hyperstimulation may be used to treat a variety of types of infertility, including but not limited to, idiopathic infertility, anovulatory infertility, endometriosis associated infertility, tubal factor infertility and male factor infertility.

5 Ovarian hyperstimulation may also be accomplished in conjunction with a gonadotropin releasing hormone antagonist (GnRH) to turn off the subjects endogenous hormone production. GnRH's that may be used in conjunction with the invention include, for example, Synarel or Lupron.

10 In a preferred embodiment, the methods of this invention are employed in conjunction with human female subjects. The methods of this invention may also be employed with other mammalian female subjects, including but not limited to, household pets, farm animals and zoo animals, particularly including cows, pigs, horses, and sheep. When used in fertility treatment of non-human mammals, the administration of antigestagens can help to achieve a higher success rate in, for example, in vitro fertilization and embryo transfer undertaken for economic or breeding purposes.

15 Non-human mammals which are produced by the methods disclosed herein are also contemplated as part of the invention. These non-human mammals include, for example, mammals which have been genetically modified, including for example, mammals that have been genetically modified using recombinant DNA techniques.

20 In one aspect, the invention relates to a method of delaying the occurrence of endometrium maturation in a human female subject undergoing fertility treatment comprising administering at least one 17 α -fluoralkylated progesterone receptor antagonist to the female subject during the post-ovulatory phase of the endometrial cycle.

25 In another aspect, the invention relates to a method of achieving pregnancy in a human female subject comprising stimulating the ovaries of the subject by administering a follicle stimulating agent to the subject, wherein the agent comprises follicle stimulating hormone; removing eggs from the ovary of the stimulated subject; administering at least one

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17 α -fluoralkylated progesterone receptor antagonist to the subject in the post-ovulatory phase of the endometrial cycle; fertilizing at least one egg in vitro to obtain an embryo; implanting the embryo in the uterus or fallopian tubes of the mammal.

5 In another aspect, the invention relates to a method of delaying the occurrence of endometrium maturation in a non-human female mammal undergoing fertility treatment to achieve pregnancy comprising administering at least one 17 α -fluoralkylated progesterone receptor antagonist to the mammal during the post-ovulatory phase of the endometrial cycle.

10 In another aspect, the invention relates to a method of achieving pregnancy in a non-human mammal comprising stimulating the ovaries of the mammal by administering a follicle stimulating agent to the mammal, wherein the agent comprises follicle stimulating hormone; removing eggs from the ovary of the stimulated mammal; administering at least one 17 α -fluoralkylated progesterone receptor antagonist to the mammal in the post-ovulatory phase of the endometrial cycle; fertilizing at least one egg in vitro to obtain an embryo; implanting the embryo in the uterus or fallopian tubes of the mammal.

In a further aspect, the invention relates to a method of achieving pregnancy in a female mammal comprising

- 20 (a) administering gonadotropins for ovarian hyperstimulation to the mammal;
(b) removing eggs from the ovary of the stimulated animal;
(c) administering at least one 17 α -fluoralkylated progesterone receptor antagonist;
(d) fertilizing at least one of the removed eggs in vitro to obtain an embryo
25 (e) introducing the embryo into the reproductive tract of the mammal.

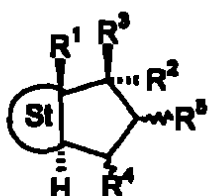
Preferably, the gonadotropin administered to the mammal to achieve ovarian hyperstimulation comprises follicle stimulating hormone (FSH). Even more preferably ovarian stimulation is achieved by the use of a first gonadotropin comprising FSH and the subsequent use of second gonadotropin comprising chorionic gonadotropin, particularly human chorionic gonadotropin (hCG).

30 Preferably the embryo is introduced into the reproductive tract of the mammal by

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introduction into the uterus via the cervix. Also preferably, a gonadotropin releasing hormone (GnRH) antagonist is administered to the female mammal prior to the administration of the gonadotropins.

Compounds useful as antigestagens according to the present invention include all 17 α -fluoroalkylated progesterone receptor antagonists which possess a strong affinity for the gestagen receptor (progesterone receptor) and show minimal gestagen activity of their own. For example, 17 α -fluoroalkylated steroidal compounds which may be employed in conjunction with the invention are described U.S. Patent Application Serial No. 09/020,947, WO/98/34947, Wang and Ruan, 1994, *Journal of Fluorine Chemistry* 69:1-3, all of which are hereby incorporated by reference in their entirety. Antigestagens useful for the present invention include but are not limited to, for example, 17 α -fluoroalkyl steroids of general formula I, primarily from the cited disclosures:



I

wherein

R¹ is methyl or ethyl,

R² is C_mF_nH_{2m+n}, wherein n is 1-6, preferably 2, 3, 4, 5 or 6, m > 1 and m+n = 2n+1,

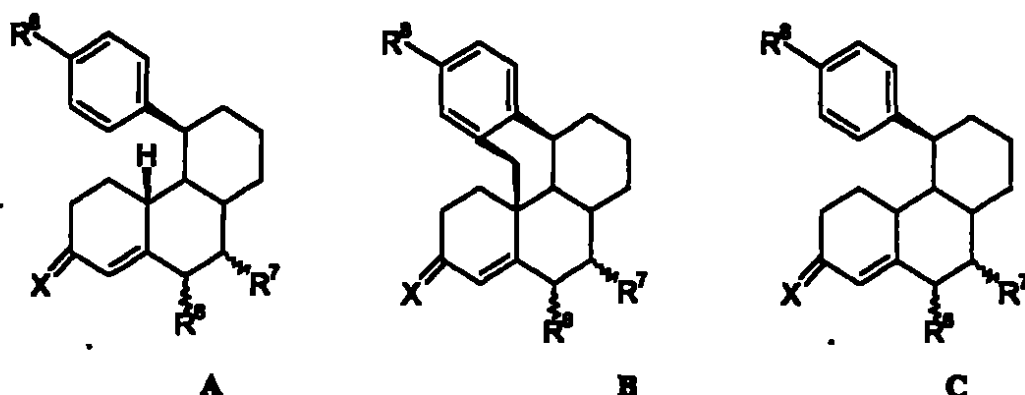
R³ is a free, etherified or esterified hydroxy group,

R⁴ and R⁵ each is a hydrogen, or together form an additional bond or a methylene group,

St is a steroidal ABC-ring system of partial formula A, B or C

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wherein

R^6 is hydrogen, a straight-chain C_1-C_4 alkyl group or branched C_3-C_4 alkyl group or halogen,

R^7 is hydrogen, a straight-chain C_1-C_4 alkyl group or a branched C_3-C_4 alkyl group, or

if St is a steroidal ABC-ring system A or B, in addition

R^6 and R^7 together can form an additional bond,

X is oxygen, hydroxyimino ($=N-OH$) or two hydrogen atoms,

R^8 is Y or aryl that is optionally substituted in several places with a group Y, other than H,

Y is hydrogen, halogen, $-OH$, $-NO_2$, $-N_3$, $-CN$, $-NR^{9a}R^{9b}$, $-NHSO_2R^9$, $-CO_2R^9$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_1-C_{10} alkanoyloxy, benzoyloxy, C_1-C_{10} alkanoyl, C_1-C_{10} hydroxyalkyl or benzoyl,

R^{9a} and R^{9b} are the same or different and each is hydrogen or C_1-C_{10} alkyl,

R^9 is hydrogen or C_1-C_{10} alkyl,

and for $-NR^{9a}R^{9b}$ radicals, as well as their physiologically compatible salts with acids and for $-CO_2R^9$ radicals with R^9 being hydrogen, as well as their physiologically compatible salts with bases.

The wavy lines mean that the substituent in question can be in α - or β -position.

Suitable alkyl groups within the scope of this formula include methyl, ethyl, or n- or iso-propyl, and n-, iso- or tert-butyl groups.

The other C_1 - C_{10} alkyl groups, Y, R^9 , R^{10} , R^{11} , include the higher homologs in addition, such as, for example, the pentyl, neo-pentyl, and hexyl to decyl groups.

C_1 - C_{10} alkyl groups are to be understood to encompass, however, carbocyclic or alkylcycloalkyl groups as well with up to 10 carbon atoms, for example cyclopropyl, cyclopentyl, cycloheptyl, methylcyclopropyl, methylcyclopentyl or methylcyclohexyl. A methyl or ethyl group is preferred for all cases above.

C_1 - C_{10} alkoxy groups are the radicals that are lengthened by one oxygen atom and derived from the alkyl groups that are mentioned above, thus, e.g., the methoxy, ethoxy, n- or iso-propoxy, n-, iso- or tert-butoxy radical, etc.

C_1 - C_{10} alkanoyl is defined as the acyl radicals of straight-chain and branched C_1 - C_{10} alkanecarboxylic acids, thus, for example, the formyl, acetyl, propionyl, butyryl or iso-butyryl radical, etc.

C_1 - C_{10} alkanoyloxy radicals are the radicals of the above alkanoyl radicals that are lengthened by one oxygen atom, thus, e.g., the acetyloxy, propionyloxy, and butyryloxy, etc.

If a halogen atom is mentioned as a substituent, this can be a fluorine, chlorine or bromine atom. Fluorine is preferred.

For radicals R^2 , perfluorinated side chains of length $n = 2-4$ are preferred and among the latter, in turn the pentafluoroethyl unit is especially preferred.

R^3 stands primarily for a free hydroxy group.

In the case of an etherified or esterified hydroxy group as a 17β -substituent, the latter is preferably etherified with a C_1 - C_{10} alkyl group or esterified with a C_1 - C_{10} alkanoyl group. For this alkyl or alkanoyl group, the same meanings as above apply. The etherification or esterification of the hydroxy group is carried out according to the methods that are familiar to one skilled in the art.

R^4 and R^5 preferably each are a hydrogen or together form an additional bond.

If R^6 is a group Y, this is preferably a C_1 - C_{10} alkanoyl or (1-hydroxy)- C_1 - C_{10} alkyl group; among these, acetyl and propionyl are especially preferred.

Preferred carbocyclic or heterocyclic aryl radicals are phenyl, 1- or 2-naphthalinyl, 2- or 3-furanyl, 2- or 3-benzofuranyl, 2- or 3-thienyl, 2-, 3- or 4-pyridinyl. Substituted aryl radicals R⁸, are primarily 4-cyanophenyl and 4-halophenyl, especially 4-fluorophenyl, can be cited.

5 Among all the radicals that are mentioned as preferred for R⁸, R⁹ in the meaning of Y and Y, in turn, equal to acetyl is especially to be preferred.

The compounds that are mentioned below are especially preferred according to the invention:

10 11β-(4-Acetylphenyl)-17β-hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)estr-4-en-3-one;

4'-[17β-hydroxy-3-oxo-17α-(1,1,2,2,2-pentafluoroethyl)estr-4-en-11β-yl][1,1'-biphenyl]-4-carbonitrile;

11β-(4'-fluoro[1,1'-biphenyl]-4-yl)-17β-hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)estr-4-en-3-one;

15 17β-hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)-11β-[4-(3-pyridinyl)phenyl]estr-4-en-3-one;

11β-(4-acetylphenyl)-17β-hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)estra-4,15-dien-3-one;

20 4'-[17β-hydroxy-3-oxo-17α-(1,1,2,2,2-pentafluoroethyl)estra-4,15-dien-11β-yl][1,1'-biphenyl]-4-carbonitrile;

11β-(4'-fluoro[1,1'-biphenyl]-4-yl)-17β-hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)estra-4,15-dien-3-one;

17β-hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)-11β-[4-(3-pyridinyl)phenyl]estr-4,15-dien-3-one;

25 11β-(4-acetylphenyl)-17β-hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)estra-4,9-dien-3-one;

4'-[17β-hydroxy-3-oxo-17α-(1,1,2,2,2-pentafluoroethyl)estra-4,9-dien-11β-yl][1,1'-biphenyl]-4-carbonitrile;

30 11β-(4'-fluoro[1,1'-biphenyl]-4-yl)-17β-hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)estra-4,9-dien-3-one;

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17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)-11 β -[4-(3-pyridinyl)phenyl]estra-4,9-dien-3-one;

11 β -(4-acetylphenyl)-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)estra-4,9,15-trien-3-one;

5 4'-[17 β -hydroxy-3-oxo-17 α -(1,1,2,2,2-pentafluoroethyl)estra-4,9,15-trien-11 β -yl][1,1'-biphenyl]-4-carbonitrile;

11 β -(4'-fluoro[1,1'-biphenyl]-4-yl)-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)estra-4,9,15-trien-3-one;

10 17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)-11 β -[4-(3-pyridinyl)phenyl]estra-4,9,15-trien-3-one;

6'-acetyl-9,11 α -dihydro-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)-4'H-naphth[3',2',1':10,9,11]estr-4-en-3-one;

4-[9,11 α -dihydro-17 β -hydroxy-3-oxo-17 α -(1,1,2,2,2-pentafluoroethyl)-4'H-naphth[3',2',1':10,9,11]estr-4-en-6'-yl]benzonitrile;

15 9,11 α -dihydro-6'-(4-fluorophenyl)-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)-4'H-naphth[3',2',1':10,9,11]estr-4-en-3-one;

9,11 α -dihydro-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)-6'-(3-pyridinyl)-4'H-naphth[3',2',1':10,9,11]estr-4-en-3-one;

20 6'-acetyl-9,11 α -dihydro-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)-4'H-naphth[3',2',1':10,9,11]estra-4,15-dien-3-one;

4-[9,11 α -dihydro-17 β -hydroxy-3-oxo-17 α -(1,1,2,2,2-pentafluoroethyl)-4'H-naphth[3',2',1':10,9,11]estra-4,15-dien-6'-yl]benzonitrile;

9,11 α -dihydro-6'-(4-fluorophenyl)-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)-4'H-naphth[3',2',1':10,9,11]estra-4,15-dien-3-one;

25 9,11 α -dihydro-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)-6'-(3-pyridinyl)-4'H-naphth[3',2',1':10,9,11]estra-4,15-dien-3-one;

17 β -hydroxy-11 β -(4-hydroxyphenyl)-17 α -(1,1,2,2,2-pentafluoroethyl)estra-4,9-dien-3-one;

30 17 β -hydroxy-11 β -(4-hydroxyphenyl)-17 α -(1,1,2,2,2-pentafluoroethyl)estr-4-en-3-one;

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9,11 α -dihydro-6',17 β -dihydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)-4'H-naphth[3',2',1':10,9,11]estr-4-en-3-one;

11 β -[4-(acetyloxy)phenyl]-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)estra-4,9-dien-3-one;

5 11 β -[4-(acetyloxy)phenyl]-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)estr-4-en-3-one

6'-acetyloxy-9,11 α -dihydro-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)-4'H-naphth[3',2',1':10,9,11]estr-4-en-3-one;

10 17 β -hydroxy-11 β -[4-(hydroxymethyl)phenyl]-17 α -(1,1,2,2,2-pentafluoroethyl)estra-4,9-dien-3-one;

17 β -hydroxy-11 β -[4-(hydroxymethyl)phenyl]-17 α -(1,1,2,2,2-pentafluoroethyl)estr-4-en-3-one;

9,11 α -dihydro-17 β -hydroxy-6'-hydroxymethyl-17 α -(1,1,2,2,2-pentafluoroethyl)-4'H-naphth[3',2',1':10,9,11]estr-4-en-3-one;

15 4-[17 β -hydroxy-3-oxo-17 α -(1,1,2,2,2-pentafluoroethyl)estra-4,9-dien-11 β -yl]benzaldehyde;

4-[17 β -hydroxy-3-oxo-17 α -(1,1,2,2,2-pentafluoroethyl)estr-4-en-11 β -yl]benzaldehyde;

20 9,11 α -dihydro-17 β -hydroxy-3-oxo-17 α -(1,1,2,2,2-pentafluoroethyl)-4'H-naphth[3',2',1':10,9,11]estr-4-en-6'-al;

4-[17 β -hydroxy-3-oxo-17 α -(1,1,2,2,2-pentafluoroethyl)estra-4,9-dien-11 β -yl]benzoic acid methyl ester;

4-[17 β -hydroxy-3-oxo-17 α -(1,1,2,2,2-pentafluoroethyl)estr-4-en-11 β -yl]benzoic acid methyl ester;

25 9,11 α -dihydro-17 β -hydroxy-3-oxo-17 α -(1,1,2,2,2-pentafluoroethyl)-4'H-naphth[3',2',1':10,9,11]estr-4-en-6'-carboxylic acid methyl ester;

17 β -hydroxy-11 β -[4-(1-hydroxyethyl)phenyl]-17 α -(1,1,2,2,2-pentafluoroethyl)estra-4,9-dien-3-one;

30 17 β -hydroxy-11 β -[4-(1-hydroxyethyl)phenyl]-17 α -(1,1,2,2,2-pentafluoroethyl)estr-4-en-3-one;

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9,11 α -dihydro-17 β -hydroxy-6'-(1-hydroxyethyl)-17 α -(1,1,2,2,2-pentafluoroethyl)-4'H-naphth[3',2',1':10,9,11]estr-4-en-3-one.

Preferred is 11 β -(4-acetylphenyl)-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)estra-4,9-dien-3-one (= Compound A).

5 The antigestagens can, for example, be applied locally, topically, enterally or parenterally.

For the preferred oral administration, particularly suitable are tablets, dragees, capsules, pills, suspensions or solutions which can be prepared in a conventional manner with additives and carriers used in pharmacy. For local or topical application, vaginal pessaries or percutaneous systems such as skin plasters can be used for
10 example. For parenteral application, particularly suitable are solutions, preferably oily or aqueous solutions, as well as suspensions or emulsions. Ampules are convenient unit dosages.

According to a preferred mode of operation, the 17 α - fluoralkylated
15 progesterone receptor antagonist is typically administered over a period of 1 to 6 days, preferably 1 to 4 days, and more preferably on day(s) 1-3 after ovulation and/or the removal of oocytes. Typically, the antigestagen is administered over a period of 1 to 6 days, preferably 1-4 days, and more preferably 1-3 days after ovulation induction with e.g. a chorionic gonadotropin.

20 Surprisingly, according the invention, it has been found that low doses of a 17 α -fluoralkylated progesterone receptor antagonists are effective in the methods disclosed herein. The 17 α -fluoralkylated progesterone receptor antagonists are preferably administered to a human female subject in a daily dosage amount of 0.1 - 2 mg/per subject, more preferably 0.1-1 mg/per subject, and most preferably 0.1-0.7
25 mg/per subject. For mammals in general, a daily dosage amount is typically 0.01-1 mg/kg, preferably 0.01-0.3 mg/kg, and more preferably 0.01-0.1 mg/kg. The daily dose of antigestagen can be administered as a single dose or as divided dosages throughout the day.

In a preferred embodiment according to the invention, the antigestagen is
30 administered on a single day to a human subject in an amount of 0.1 - 2 mg/per subject, more preferably 0.1-1 mg/per subject, and most preferably 0.1-0.7 mg/per

subject or to a mammal in an amount of 0.01-1 mg/kg, preferably 0.01-0.3 mg/kg, and more preferably 0.01-0.1 mg/kg. For example, on day 1, 2, 3, 4, 5 or 6 following ovulation, removal of oocytes, or administration of a chorionic gonadotropin, preferably day 1-3, and more preferably day 2.

5 For any particular 17 α -fluoralkylated progesterone receptor antagonist, the most appropriate dose can be determined, for example, by evaluation of the potency to induce premature menstruation in advanced luteal phase of the human cycle as described in e.g. Herrmann, W., et al, 1982, *Comptes Rendus* 294:933. The use of antigestagens for delaying endometrial maturation has been previously described,
10 for example, in U.S. Patent No. 4,764,513, EP 0219447B1, Hegele-Hartung et al., 1992, *Endocrinology* 131:2446-2460, all of which are incorporated herein by reference in their entirety.

The compounds of this invention can be employed in admixture with conventional excipients, i.e., pharmaceutically acceptable organic or inorganic carrier
15 substances suitable for, for example, parenteral, enthal (e.g., oral) or topical application which do not deleteriously react with the active compounds. Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions, alcohols, gum arabic, vegetable oils, benzyl alcohols, polyethylene glycols, gelatine, carbohydrates such as lactose, amylase or starch, magnesium stearate, talc,
20 silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxy methylcellulose, polyvinyl pyrrolidone, etc. The pharmaceutical preparations can be sterilized and if desired mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, flavoring and/or aromatic substances
25 and the like which do not deleteriously react with the active compounds. They can also be combined, where desired, with other active agents, e.g., vitamins.

Sustained or directed release compositions can be formulated, e.g., liposomes or those wherein the active compound is protected with differentially degradable
30 coatings, e.g., by microencapsulation, multiple coatings, etc. It is also possible to freeze-dry the new compounds and use the lyophilizates obtained, for example, for the preparation of products for injection.

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For topical application, there are employed as nonsprayable forms, viscous to semi-solid or solid forms comprising a carrier compatible with topical application and having a dynamic viscosity preferably greater than water. Suitable formulations include but are not limited to solutions, suspensions, emulsions, creams, ointments, powders, liniments, salves, aerosols, etc., which are, if desired, sterilized or mixed with auxiliary agents, e.g., preservatives, stabilizers, wetting agents, buffers or salts for influencing osmotic pressure, etc. For topical application, also suitable are sprayable aerosol preparations wherein the active ingredient, preferably in combination with a solid or liquid inert carrier material, is packaged in a squeeze bottle or in admixture with a pressurized volatile, normally gaseous propellant, e.g., a freon.

It will be appreciated that the actual preferred amounts of active compound in a specific case will vary according to the specific compound being utilized, the particular compositions formulated, the mode of application, and the particular situs and organism being treated. Dosages for a given host can be determined using conventional considerations, e.g., by customary comparison of the differential activities of the subject compounds of a known agent, e.g., by means of an appropriate, conventional pharmacological protocol.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a schematic illustration of the experiment described in Example 1. The day of administration of human chorionic gonadotropin (hCG) was designated as day 0 of pseudopregnancy (d0). As shown in the diagram, ovarian stimulation of the animals occurred on -d3, -d2 and -d1 of pseudopregnancy induction and the progesterone receptor antagonist was administered on d2 of pseudopregnancy.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

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In the foregoing and in the following examples, all temperatures are set forth uncorrected in degrees Celsius; and, unless otherwise indicated, all parts and percentages are by weight.

5 The entire disclosure of all applications, patents and publications, cited above or below, are hereby incorporated by reference.

EXAMPLES

Example 1: Improvement of endometrial receptivity with low doses of a 17 α -fluoralkylated progesterone receptor antagonist in the superovulated rabbit model.

10 The effects of a 17 α -fluoralkylated progesterone receptor antagonist on endometrial activity was evaluated in the superovulated pseudopregnant rabbit model. The pseudopregnancy of the rabbit has proven to be a model system for the human luteal phase (Beier and Kuhnel, 1973, *Hormone Res.* 4:1-27; Fischer et al., 1985, *Fertilitat* 1:101-109. In this species, ovarian stimulation induces an advancement of secretory transformation (Delbos-Winter et al., 1987, *Fertilitat* 3: 15 87-93) as well as an enhancement of gland formation.

A total of 25 sexually mature nulliparous New Zealand White rabbits with a body weight of 3.1 to 4.0 kg were used for the analysis. The animals were divided into two control groups (groups 1 and 2) and three treatment groups (groups 3-5), with five animals in each group.

20 Control group 1 received 75 international units (IU) of human chorionic gonadotropin (hCG) administered intravenously in order to induce pseudopregnancy. The day of hCG-injection was designated as day 0 of pseudopregnancy (d0 p.hCG).

25 Control group 2 and treatment groups 3, 4, and 5 were gonadotropin-stimulated with 5 IU of the human menopausal gonadotropin (HMG) Pergonal® (Serono Pharma, Unterschleißheim, Germany) for 3 days, by subcutaneous injection, in order to induce multiple follicular growth. Pseudopregnancy was induced by the administration of human chorionic gonadotropin (hCG) as described for control group 1 above.

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Treatment groups 3, 4 and 5 also received a single per oral application of a 17 α -fluoralkylated progesterone receptor antagonist (Compound A) two days after pseudopregnancy induction with the administration of human chorionic gonadotropin (d2 p.hCG). The detailed treatment schedule is shown in Figure 1.

Animals in all treatment groups were sacrificed on day 5 following pseudopregnancy induction (d5 p.hCG), and uteri were removed. Relative uterine wet weights were determined (in mg/100 g body weight) and a part of the uterus was snap frozen in liquid nitrogen for determination of uteroglobin expression by in situ hybridization. Uteroglobin expression is known as a highly sensitive parameter for determination of endometrial receptivity (Beier, H.N., 1968, *Biochem Biophys. Acta.* 160:289-291; Beier, H.N., 1982, in: Beier, H.N. and Karlson, P. (eds.), *Proteins and Steroids in Early Pregnancy*); and is a marker for secretory activity (Beier, 1976, *J. Reprod. Fertil. Suppl.* 25:53-69) and differentiation of the endometrial epithelium (Krusche & Beier, 1994, *Ann. Anat.* 176:23-31). In situ hybridization for detection of uteroglobin expression was conducted as previously described in Krusche & Beier, above. Another piece of the uterus was removed and processed for paraffin histology in order to determine the endometrial transformation status using the McPhail-Index (McPhail Mk, 1934, *J. Phys.* 83:145-156) The McPhail Index reflects different degrees of progestogenic (transforming) activity in the rabbit endometrium:

1. no transformation
2. low transformation
3. pronounced transformation
4. high transformation

The results are presented in Table 1 below.

Table 1

Effect of a single treatment of a 17 α -fluoralkylated progesterone receptor antagonist on uterus weight, endometrial transformation, and uteroglobin mRNA expression at five days after pseudopregnancy induction (d5 p.hCG) in the superovulated pseudopregnant rabbit.

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Group	Treatment Schedule			Measurement endpoints at d5 p. hCG		
	-d3, -d2, -d1 p.hCG	d0 p.hCG	d2 p.hCG			
	5 IU HMG	75 IU HCG	Progesterone receptor antagonist [mg/kg]	Uterine wet weight [mg/kg] [x ± SD]	Mc-Phail [x ± SD]	Uteroglobulin ISH [expression in luminal epithelial cells]
1	-	+	-	324 ± 99	3.2 ± 0.2	very high expression
2	+	+	0	448 ± 80	3.9 ± 0.1	very low expression
3	+	+	0.1	305 ± 48	3.0 ± 0.1	very high expression
4	+	+	1	227 ± 56	1.5 ± 0.3	very low expression
5	+	+	10	144 ± 30	1.1 ± 0.3	absent

As shown in the table, animals which were subject to ovarian hyperstimulation, but which were not treated with an antigestagen (Group 2), showed advanced endometrial maturation as demonstrated by nearly undetectable uteroglobulin expression, the weight of the uterus, and the relatively high Mc-Phail index score. However, animals which were subject to ovarian hyperstimulation and which were treated with an antigestagen, Groups 3-5, showed a delay in endometrial maturation, as demonstrated by the uterine wet weights and the Mc-Phail index scores. For animals which were treated with a low dose of progesterone receptor antagonist, 0.1 mg/kg (Group 3), endometrial maturation roughly corresponded with that of control animals which were not subject to ovarian hyperstimulation (Group 1). In contrast, higher doses of progesterone receptor antagonist, 1 mg/kg (group 4) and 10 mg/kg (group 5), apparently counteracted the advancement of endometrium maturation associated with ovarian hyperstimulation and also delayed the timing of maturation beyond that observed in animals which were not subject to hyperovarian stimulation (Group 1).

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

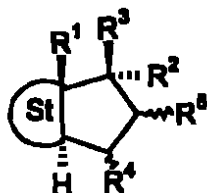
5 From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

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What is claimed is:

1. A method of delaying the occurrence of endometrium maturation in a human female subject undergoing fertility enhancing treatment comprising administering at least one 17 α -fluoralkylated progesterone receptor antagonist to the female subject during the post-ovulatory phase of the endometrial cycle.
2. A method according to claim 1, wherein the 17 α -fluoralkylated progesterone receptor antagonist is administered to the subject in a daily dosage amount of 0.1-2 mg per subject.
3. A method according to claim 2, wherein the fertility treatment comprises the administration to the subject of a follicle stimulating agent comprising follicle stimulating hormone.
4. A method according to claim 2, wherein the 17 α -fluoralkylated progesterone receptor antagonist is administered in an amount of 0.1-2 mg per subject on a single day during the post-ovulatory phase of the endometrial cycle.
5. A method according to claim 2, wherein the 17 α -fluoralkylated progesterone receptor antagonist is a compound of formula I:



I

wherein

R¹ is methyl or ethyl,

R² is C_nF_mH_o, wherein n is 1-6, preferably 2, 3, 4, 5 or 6, m > 1 and m+o = 2n+1,

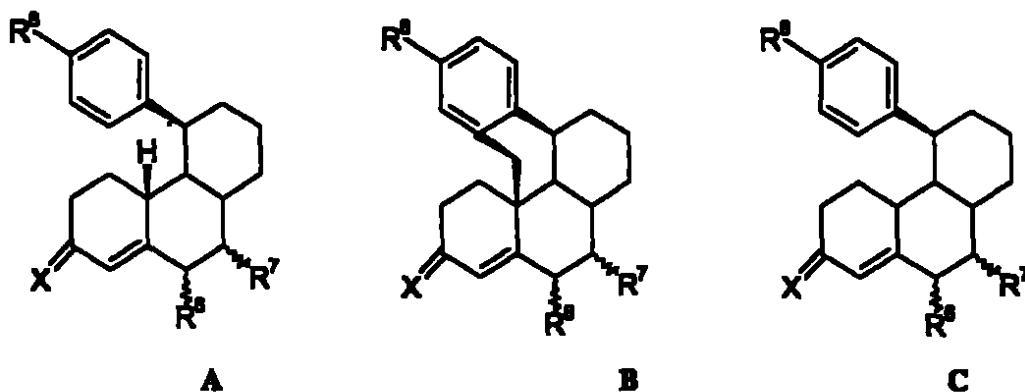
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R^3 is a free, etherified or esterified hydroxy group,

R^4 and R^5 each is a hydrogen, or together form an additional bond or a methylene group,

St is a steroidal ABC-ring system of partial formula A, B or C



wherein

R^6 is hydrogen, a straight-chain C_1-C_4 alkyl group or branched C_3-C_4 alkyl group or halogen,

R^7 is hydrogen, a straight-chain C_1-C_4 alkyl group or a branched C_3-C_4 alkyl group, or

if St is a steroidal ABC-ring system A or B, in addition

R^6 and R^7 together can form an additional bond,

X is oxygen, hydroxyimino ($=N-OH$) or two hydrogen atoms,

R^8 is Y or aryl that is optionally substituted in several places with a group Y, other than H,

Y is hydrogen, halogen, $-OH$, $-NO_2$, $-N_3$, $-CN$, $-NR^aR^b$, $-NHSO_2R^9$, $-CO_2R^9$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_1-C_{10} alkanoyloxy, benzoyloxy, C_1-C_{10} alkanoyl, C_1-C_{10} hydroxyalkyl or benzoyl,

R^a and R^b are the same or different and each is hydrogen or C_1-C_{10} alkyl,

R^9 is hydrogen or C_1-C_{10} alkyl,

and for $-NR^aR^b$ radicals, as well as their physiologically compatible salts with acids and for $-CO_2R^9$ radicals with R^9 being hydrogen, as well as their physiologically compatible salts with bases.

6. A method according to claim 4, wherein the 17 α -fluoralkylated progesterone receptor antagonist is administered orally to the subject.

7. A method of achieving pregnancy in a human female subject comprising stimulating the ovaries of the subject by administering a follicle stimulating agent to the subject, wherein the agent comprises follicle stimulating hormone; removing eggs from the ovary of the stimulated subject; administering at least one 17 α -fluoralkylated progesterone receptor antagonist to the subject in the post-ovulatory phase of the endometrial cycle; fertilizing at least one egg in vitro to obtain an embryo; implanting the embryo in the uterus or fallopian tubes of the mammal.

8. A method according to claim 7, wherein the 17 α -fluoralkylated progesterone receptor antagonist is administered to the subject in a daily dosage amount of 0.1-2 mg per subject

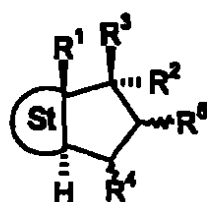
9. A method according to claim 8, wherein the 17 α -fluoralkylated progesterone receptor antagonist is administered in an amount of 0.1-2 mg per subject on a single day during the post-ovulatory phase of the endometrial cycle.

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10. A method according to claim 8, wherein the 17 α -fluoralkylated progesterone receptor antagonist is a compound of formula I:



I

wherein

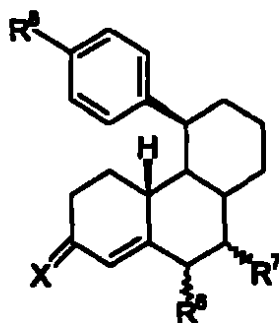
R¹ is methyl or ethyl,

R² is C_nF_mH_o, wherein n is 1-6, preferably 2, 3, 4, 5 or 6, m > 1 and m+o = 2n+1,

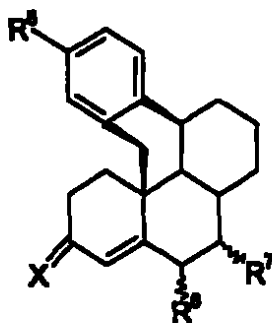
R³ is a free, etherified or esterified hydroxy group,

R⁴ and R⁵ each is a hydrogen, or together form an additional bond or a methylene group,

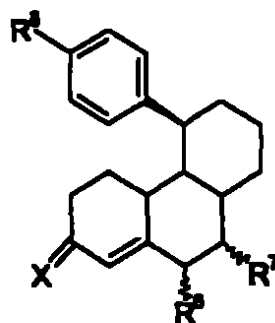
St is a steroidal ABC-ring system of partial formula A, B or C



A



B



C

wherein

R⁶ is hydrogen, a straight-chain C₁-C₄ alkyl group or branched C₃-C₄ alkyl group or halogen,

R⁷ is hydrogen, a straight-chain C₁-C₄ alkyl group or a branched C₃-C₄ alkyl group, or

if St is a steroidal ABC-ring system A or B, in addition

R⁶ and R⁷ together can form an additional bond,

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X is oxygen, hydroxyimino (=N-OH) or two hydrogen atoms,

R⁸ is Y or aryl that is optionally substituted in several places with a group Y, other than H,

Y is hydrogen, halogen, -OH, -NO₂, -N₃, -CN, -NR^{9a}R^{9b}, -NHSO₂R⁹, -CO₂R⁹, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkanoyloxy, benzoyloxy, C₁-C₁₀ alkanoyl, C₁-C₁₀ hydroxyalkyl or benzoyl,

R^{9a} and R^{9b} are the same or different and each is hydrogen or C₁-C₁₀ alkyl,

R⁹ is hydrogen or C₁-C₁₀ alkyl,

and for -NR^{9a}R^{9b} radicals, as well as their physiologically compatible salts with acids and for -CO₂R⁹ radicals with R⁹ being hydrogen, as well as their physiologically compatible salts with bases.

11. A method according to claim 9, wherein the 17 α -fluoralkylated progesterone receptor antagonist is administered orally to the subject.

12. A method of delaying the occurrence of endometrium maturation in a non-human female mammal undergoing fertility enhancement treatment to achieve pregnancy comprising

administering at least one 17 α -fluoralkylated progesterone receptor antagonist to the mammal during the post-ovulatory phase of the endometrial cycle.

13. A method according to claim 12, wherein the 17 α -fluoralkylated progesterone receptor antagonist is administered to the mammal in a daily dosage amount of 0.01-1 mg/kg.

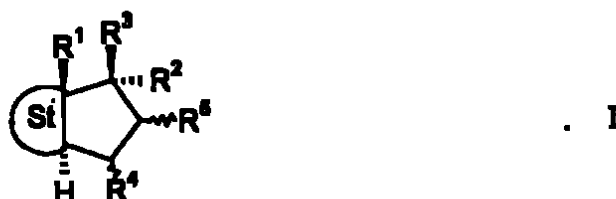
14. A method according to claim 13, wherein the fertility treatment comprises the administration to the mammal of a follicle stimulating agent comprising follicle stimulating hormone.

15. A method according to claim 13, wherein the 17 α -fluoralkylated progesterone receptor antagonist is administered to the mammal in an amount of

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0.1-1 mg/kg on a single day during the post-ovulatory phase of the endometrial cycle.

16. A method according to claim 13, wherein the 17 α -fluoralkylated progesterone receptor antagonist is a compound of formula I:



wherein

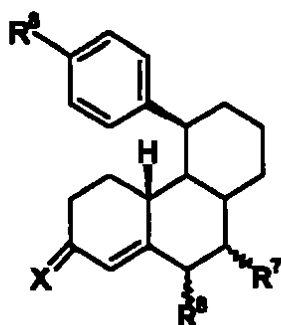
R¹ is methyl or ethyl,

R² is C_nF_mH_o, wherein n is 1-6, preferably 2, 3, 4, 5 or 6, m > 1 and m+o = 2n+1,

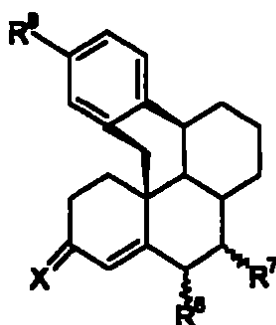
R³ is a free, etherified or esterified hydroxy group,

R⁴ and R⁵ each is a hydrogen, or together form an additional bond or a methylene group,

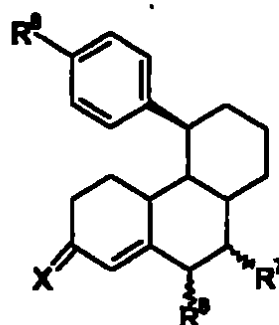
St is a steroidal ABC-ring system of partial formula A, B or C



A



B



C

wherein

R⁶ is hydrogen, a straight-chain C₁-C₄ alkyl group or branched C₃-C₄ alkyl group or halogen,

R^7 is hydrogen, a straight-chain C_1-C_4 alkyl group or a branched C_3-C_4 alkyl group, or

if St is a steroidal ABC-ring system A or B, in addition

R^6 and R^7 together can form an additional bond,

X is oxygen, hydroxyimino ($=N-OH$) or two hydrogen atoms,

R^8 is Y or aryl that is optionally substituted in several places with a group Y, other than H,

Y is hydrogen, halogen, $-OH$, $-NO_2$, $-N_3$, $-CN$, $-NR^{2a}R^{2b}$, $-NHSO_2R^9$, $-CO_2R^9$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_1-C_{10} alkanoyloxy, benzoyloxy, C_1-C_{10} alkanoyl, C_1-C_{10} hydroxyalkyl or benzoyl,

R^{2a} and R^{2b} are the same or different and each is hydrogen or C_1-C_{10} alkyl,

R^9 is hydrogen or C_1-C_{10} alkyl,

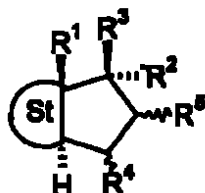
and for $-NR^{2a}R^{2b}$ radicals, as well as their physiologically compatible salts with acids and for $-CO_2R^9$ radicals with R^9 being hydrogen, as well as their physiologically compatible salts with bases.

17. A method of achieving pregnancy in a non-human mammal comprising stimulating the ovaries of the mammal by administering a follicle stimulating agent to the mammal, wherein the agent comprises follicle stimulating hormone; removing eggs from the ovary of the stimulated mammal; administering at least one 17α -fluoralkylated progesterone receptor antagonist to the mammal in the post-ovulatory phase of the endometrial cycle; fertilizing at least one egg in vitro to obtain an embryo; implanting the embryo in the uterus or fallopian tubes of the mammal.

18. A method according to claim 17, wherein the 17α -fluoralkylated progesterone receptor antagonist is administered to the mammal in a daily dosage amount of 0.01-1 mg/kg.

19. A method according to claim 18, wherein the 17 α -fluoralkylated progesterone receptor antagonist is administered to the mammal in an amount 0.1-1 mg/kg on a single day during the post-ovulatory phase of the endometrial cycle.

20. A method according to claim 18, wherein the 17 α -fluoralkylated progesterone receptor antagonist is a compound of formula I:



I

wherein

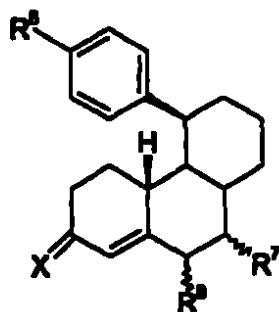
R¹ is methyl or ethyl,

R² is C_nF_mH_o, wherein n is 1-6, preferably 2, 3, 4, 5 or 6, m > 1 and m+o = 2n+1,

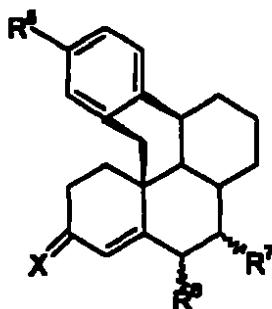
R³ is a free, etherified or esterified hydroxy group,

R⁴ and R⁵ each is a hydrogen, or together form an additional bond or a methylene group,

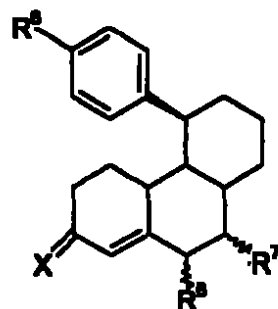
St is a steroidal ABC-ring system of partial formula A, B or C



A



B



C

wherein

R⁶ is hydrogen, a straight-chain C₁-C₄ alkyl group or branched C₃-C₄ alkyl group or halogen,

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R^7 is hydrogen, a straight-chain C_1-C_4 alkyl group or a branched C_3-C_4 alkyl group, or

if St is a steroidal ABC-ring system A or B, in addition

R^6 and R^7 together can form an additional bond,

X is oxygen, hydroxyimino ($=N-OH$) or two hydrogen atoms,

R^8 is Y or aryl that is optionally substituted in several places with a group Y, other than H,

Y is hydrogen, halogen, $-OH$, $-NO_2$, $-N_3$, $-CN$, $-NR^9R^{10}$, $-NHSO_2R^9$, $-CO_2R^9$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_1-C_{10} alkanoyloxy, benzoyloxy, C_1-C_{10} alkanoyl, C_1-C_{10} hydroxyalkyl or benzoyl,

R^9 and R^{10} are the same or different and each is hydrogen or C_1-C_{10} alkyl,

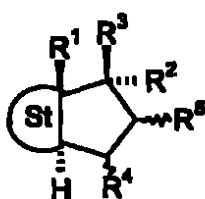
R^9 is hydrogen or C_1-C_{10} alkyl,

and for $-NR^9R^{10}$ radicals, as well as their physiologically compatible salts with acids and for $-CO_2R^9$ radicals with R^9 being hydrogen, as well as their physiologically compatible salts with bases.

21. A non-human mammal which results from a pregnancy achieved by a process according to claim 13.

22. A non-human mammal which results from a pregnancy achieved by a process according to claim 18.

23. A method of delaying the occurrence of endometrium maturation in a human female subject undergoing fertility enhancing treatment comprising administering at least one compound of formula I to the subject, wherein formula I is



I

wherein

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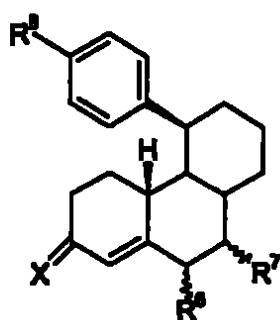
R^1 is methyl or ethyl,

R^2 is $C_nF_mH_o$, wherein n is 1-6, preferably 2, 3, 4, 5 or 6, $m > 1$ and $m+o = 2n+1$,

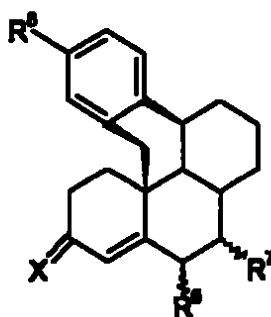
R^3 is a free, etherified or esterified hydroxy group,

R^4 and R^5 each is a hydrogen, or together form an additional bond or a methylene group,

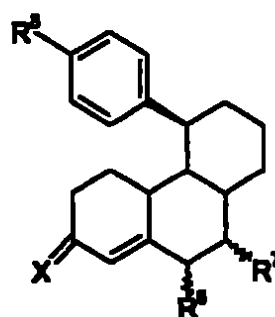
St is a steroidal ABC-ring system of partial formula A, B or C



A



B



C

wherein

R^6 is hydrogen, a straight-chain C_1-C_4 alkyl group or branched C_3-C_4 alkyl group or halogen,

R^7 is hydrogen, a straight-chain C_1-C_4 alkyl group or a branched C_3-C_4 alkyl group, or

if St is a steroidal ABC-ring system A or B, in addition

R^6 and R^7 together can form an additional bond,

X is oxygen, hydroxyimino ($=N-OH$) or two hydrogen atoms,

R^2 is Y or aryl that is optionally substituted in several places with a group Y, other than H,

Y is hydrogen, halogen, $-OH$, $-NO_2$, $-N_3$, $-CN$, $-NR^{2a}R^{2b}$, $-NHSO_2R^9$, $-CO_2R^9$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_1-C_{10} alkanoyloxy, benzoyloxy, C_1-C_{10} alkanoyl, C_1-C_{10} hydroxyalkyl or benzoyl,

R^{2a} and R^{2b} are the same or different and each is hydrogen or C_1-C_{10} alkyl,

R^9 is hydrogen or C_1-C_{10} alkyl,

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and for $-NR^8R^9$ radicals, as well as their physiologically compatible salts with acids and for $-CO_2R^9$ radicals with R^9 being hydrogen, as well as their physiologically compatible salts with bases.

24. A method of achieving pregnancy in a human female subject comprising

stimulating the ovaries of the subject by administering a follicle stimulating agent to the subject, wherein the agent comprises follicle stimulating hormone;

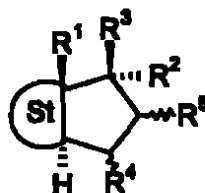
removing eggs from the ovary of the stimulated subject;

administering at least one compound of formula I to the subject in the post-ovulatory phase of the endometrial cycle;

fertilizing at least one egg in vitro to obtain an embryo;

implanting the embryo in the uterus or fallopian tubes of the mammal,

wherein formula I is



I

wherein

R^1 is methyl or ethyl,

R^2 is $C_nF_mH_n$, wherein n is 1-6, preferably 2, 3, 4, 5 or 6, $m > 1$ and $m + n = 2n + 1$,

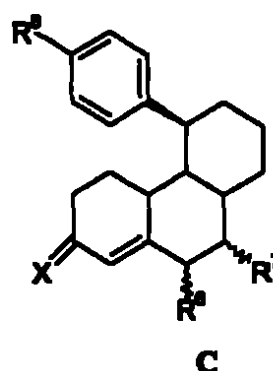
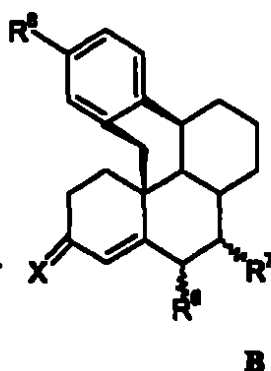
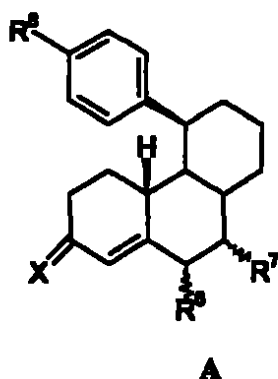
R^3 is a free, etherified or esterified hydroxy group,

R^4 and R^5 each is a hydrogen, or together form an additional bond or a methylene group,

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St is a steroidal ABC-ring system of partial formula A, B or C



wherein

R^6 is hydrogen, a straight-chain C_1-C_4 alkyl group or branched C_3-C_4 alkyl group or halogen,

R^7 is hydrogen, a straight-chain C_1-C_4 alkyl group or a branched C_3-C_4 alkyl group, or

if St is a steroidal ABC-ring system A or B, in addition

R^6 and R^7 together can form an additional bond,

X is oxygen, hydroxyimino ($=N-OH$) or two hydrogen atoms,

R^8 is Y or aryl that is optionally substituted in several places with a group Y, other than H,

Y is hydrogen, halogen, $-OH$, $-NO_2$, $-N_3$, $-CN$, $-NR^{9a}R^{9b}$, $-NHSO_2R^9$, $-CO_2R^9$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_1-C_{10} alkanoyloxy, benzoyloxy, C_1-C_{10} alkanoyl, C_1-C_{10} hydroxyalkyl or benzoyl,

R^{9a} and R^{9b} are the same or different and each is hydrogen or C_1-C_{10} alkyl,

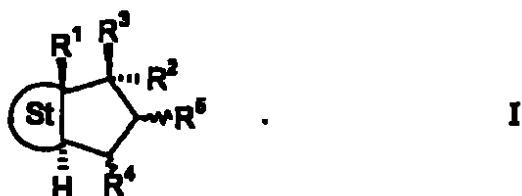
R^9 is hydrogen or C_1-C_{10} alkyl,

and for $-NR^{9a}R^{9b}$ radicals, as well as their physiologically compatible salts with acids and for $-CO_2R^9$ radicals with R^9 being hydrogen, as well as their physiologically compatible salts with bases.

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25. A method of delaying the occurrence of endometrium maturation in a non-human female mammal undergoing fertility enhancement treatment to achieve pregnancy comprising

administering at least one compound according to formula I to the mammal, wherein formula I is



wherein

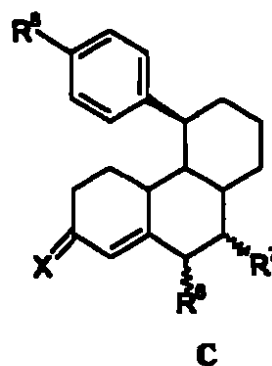
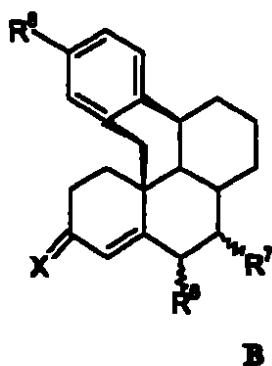
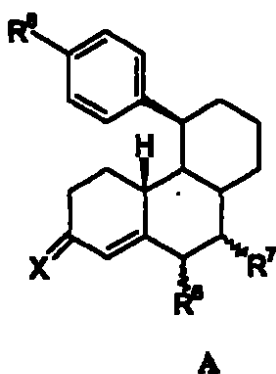
R^1 is methyl or ethyl,

R^2 is $C_nF_mH_o$, wherein n is 1-6, preferably 2, 3, 4, 5 or 6, $m > 1$ and $m+o = 2n+1$,

R^3 is a free, etherified or esterified hydroxy group,

R^4 and R^5 each is a hydrogen, or together form an additional bond or a methylene group,

St is a steroidal ABC-ring system of partial formula A, B or C



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wherein

R^6 is hydrogen, a straight-chain C_1-C_4 alkyl group or branched C_3-C_4 alkyl group or halogen,

R^7 is hydrogen, a straight-chain C_1-C_4 alkyl group or a branched C_3-C_4 alkyl group, or

if St is a steroidal ABC-ring system A or B, in addition

R^6 and R^7 together can form an additional bond,

X is oxygen, hydroxyimino ($=N-OH$) or two hydrogen atoms,

R^8 is Y or aryl that is optionally substituted in several places with a group Y, other than H,

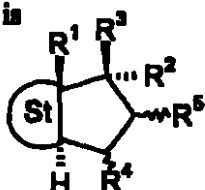
Y is hydrogen, halogen, $-OH$, $-NO_2$, $-N_3$, $-CN$, $-NR^{10}R^{11}$, $-NHSO_2R^9$, $-CO_2R^9$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_1-C_{10} alkanoyloxy, benzoyloxy, C_1-C_{10} alkanoyl, C_1-C_{10} hydroxyalkyl or benzoyl,

R^{10} and R^{11} are the same or different and each is hydrogen or C_1-C_{10} alkyl,

R^9 is hydrogen or C_1-C_{10} alkyl,

and for $-NR^{10}R^{11}$ radicals, as well as their physiologically compatible salts with acids and for $-CO_2R^9$ radicals with R^9 being hydrogen, as well as their physiologically compatible salts with bases.

26. A method of achieving pregnancy in a non-human mammal comprising stimulating the ovaries of the mammal by administering a follicle stimulating agent to the mammal, wherein the agent comprises follicle stimulating hormone; removing eggs from the ovary of the stimulated mammal; administering at least one compound of formula I to the mammal in the post-ovulatory phase of the endometrial cycle; fertilizing at least one egg in vitro to obtain an embryo; implanting the embryo in the uterus or fallopian tubes of the mammal, wherein formula I is



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wherein

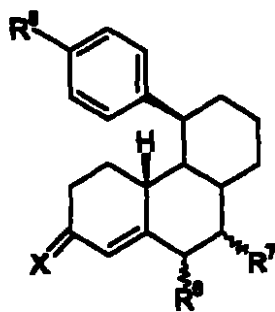
R^1 is methyl or ethyl,

R^2 is $C_nF_mH_o$, wherein n is 1-6, preferably 2, 3, 4, 5 or 6, $m > 1$ and $m+o = 2n+1$,

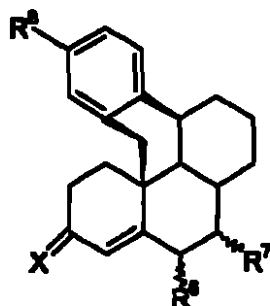
R^3 is a free, etherified or esterified hydroxy group,

R^4 and R^5 each is a hydrogen, or together form an additional bond or a methylene group,

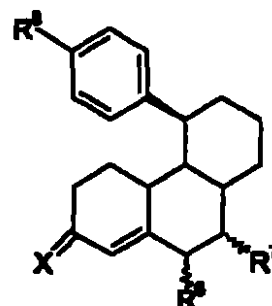
St is a steroidal ABC-ring system of partial formula A, B or C



A



B



C

wherein

R^6 is hydrogen, a straight-chain C_1 - C_4 alkyl group or branched C_3 - C_4 alkyl group or halogen,

R^7 is hydrogen, a straight-chain C_1 - C_4 alkyl group or a branched C_3 - C_4 alkyl group, or

if St is a steroidal ABC-ring system A or B, in addition

R^6 and R^7 together can form an additional bond,

X is oxygen, hydroxyimino ($=N-OH$) or two hydrogen atoms,

R^8 is Y or aryl that is optionally substituted in several places with a group Y, other than H,

Y is hydrogen, halogen, $-OH$, $-NO_2$, $-N_3$, $-CN$, $-NR^{9a}R^{9b}$, $-NHSO_2R^9$, $-CO_2R^9$, C_1 - C_{10} alkyl, C_1 - C_{10} alkoxy, C_1 - C_{10} alkanoyloxy, benzoyloxy, C_1 - C_{10} alkanoyl, C_1 - C_{10} hydroxyalkyl or benzoyl,

R^{9a} and R^{9b} are the same or different and each is hydrogen or C_1 - C_{10} alkyl,

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R^9 is hydrogen or C_1-C_{10} alkyl,

and for $-NR^9R^{9b}$ radicals, as well as their physiologically compatible salts with acids and for $-CO_2R^9$ radicals with R^9 being hydrogen, as well as their physiologically compatible salts with bases.

27. A method of modulating the occurrence of endometrium maturation in a human female subject undergoing fertility enhancing treatment comprising administering at least one 17 α -fluoralkylated progesterone receptor antagonist to the female subject during the post-ovulatory phase of the endometrial cycle.

28. A method of delaying the occurrence of endometrium maturation in a human female subject undergoing fertility enhancing treatment comprising administering at least one 17 α -fluoralkylated progesterone receptor antagonist to the female subject during the post-ovulatory phase of the endometrial cycle after said fertility enhancing treatment.

29. A method of delaying the occurrence of endometrium maturation in a non-human female mammal undergoing fertility enhancement treatment to achieve pregnancy comprising

administering at least one 17 α -fluoralkylated progesterone receptor antagonist to the mammal during the post-ovulatory phase of the endometrial cycle after said fertility enhancing treatment.

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ABSTRACT OF THE DISCLOSURE

A method of modulating the occurrence of endometrium maturation in a female mammal undergoing fertility treatment is disclosed. The method comprises the administration at least one 17 α -fluoralkylated progesterone receptor antagonist to the female mammal.

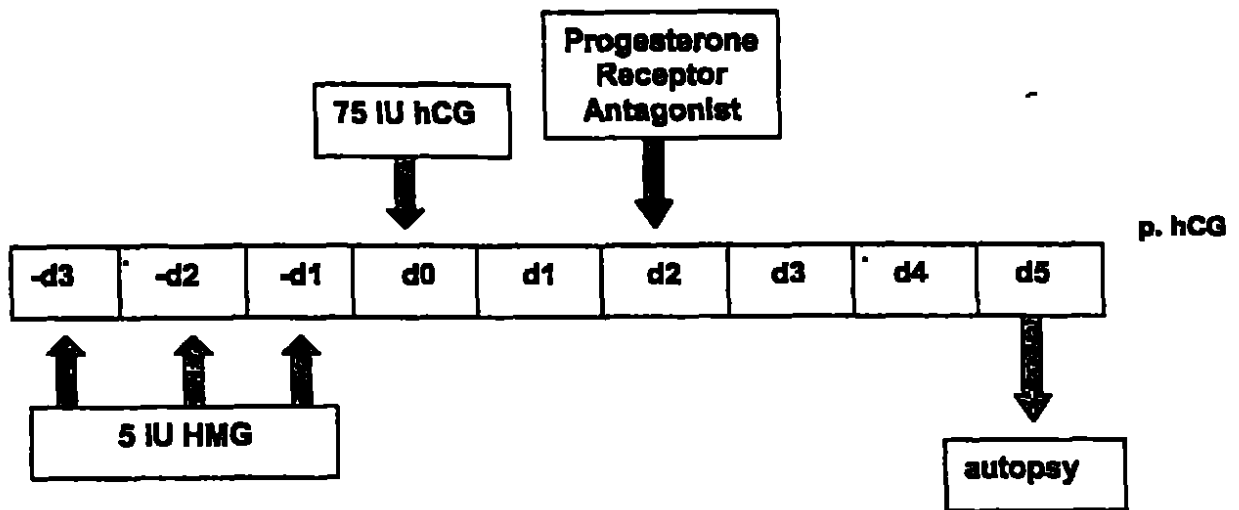
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Figure 1: General study design in superovulated rabbits



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LOS ESTADOS UNIDOS DE AMERICA

A TODOS CUANTOS LAS PRESENTES VIEREN:

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS
Oficina de Patentes y Marcas de los Estados Unidos

Febrero 01 del 2002

SE CERTIFICA QUE ADJUNTO SE ENCUENTRA UNA COPIA FIEL Y EXACTA DE LOS REGISTROS EXISTENTES EN LA OFICINA DE PATENTES Y MARCAS DE LOS ESTADOS UNIDOS RESPECTO A LOS DOCUMENTOS DE LA SOLICITUD DE PATENTE IDENTIFICADA ABAJO LA CUAL CUMPLIO LOS REQUISITOS PARA QUE SE LE OTORGARA UNA FECHA DE PRESENTACION DE CONFORMIDAD CON 35 USC 111.

NUMERO DE SOLICITUD: 09/756,286

FECHA DE PRESENTACION: Enero 09 del 2001

Por Autoridad del
COMISIONADO DE PATENTES Y MARCAS
E. BORNETT, Funcionario de Certificaciones
(Firma y Sello Oficial)

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REIVINDICACIONES

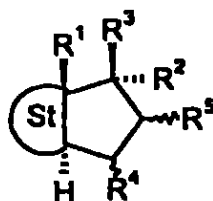
1. Un método para retardar la ocurrencia de la maduración endometrial en un sujeto hembra humano que está bajo tratamiento para mejorar la fertilidad, que comprende administrar por lo menos un antagonista del receptor de la progesterona 17 α -fluoroalquilado al sujeto hembra durante la fase pos-ovulatoria del ciclo endometrial.

2. Un método de acuerdo con la reivindicación 1, donde el receptor de progesterona 17 α -fluoroalquilado se administra al sujeto en una dosis diaria de 0,1-2 mg por sujeto.

3. Un método de acuerdo con la reivindicación 2, donde el tratamiento de fertilización comprende la administración al sujeto de un agente estimulante folicular que comprende hormona estimulante folicular.

4. Un método de acuerdo con la reivindicación 2, donde el antagonista del receptor de la progesterona 17 α -fluoroalquilado se administra en una cantidad de 0,1-2 mg por sujeto en un único día durante la fase pos-ovulatoria del ciclo endometrial.

5. Un método de acuerdo con la reivindicación 2, donde el antagonista del receptor de la progesterona 17 α -fluoroalquilado es un compuesto de la fórmula I:



donde:

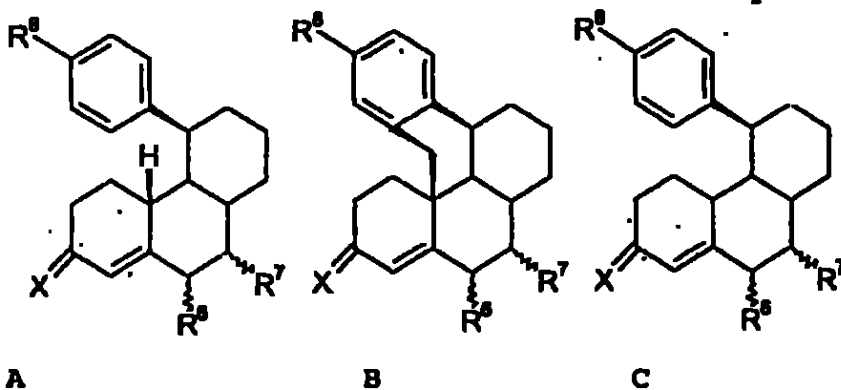
R^1 es metilo o etilo,

R^2 es $C_nF_mH_o$, donde n es 1-6, preferentemente 2, 3, 4, 5 o 6, $m > 1$ y $m+o = 2n+1$.

R_3 es un grupo hidroxilo libre, eterificado o esterificado,

cada uno de R^4 y R^5 es un hidrógeno, o juntos forman una ligadura adicional o un grupo metileno

St es un anillo esteroideal ABC de fórmula parcial A, B o C



donde:

R^6 es hidrógeno, un grupo C_1-C_4 alquilo de cadena lineal o C_3-C_4 alquilo de cadena ramificada o halógeno

R^7 es hidrógeno, un grupo C_1-C_4 alquilo de cadena lineal o C_3-C_4 alquilo de cadena ramificada, o

si St es un sistema de anillo ABC esteroideal, además

R⁶ y R⁷ juntos pueden formar una ligadura adicional,

X es oxígeno, hidroxiimino (=N-OH) o dos átomos de hidrógeno,

R⁸ es Y o arilo optativamente sustituido en múltiples sitios con un grupo Y distinto de H,

Y es hidrógeno, halógeno, -OH, -NO₂, -N₃, -CN, -NR^{9a}R^{9b}, -NHSO₂R⁹, CO₂R⁹, C₁-C₁₀ alquilo, C₁-C₁₀ alcoxi, C₁-C₁₀ alcanoiloxi, benzoiloxi, C₁-C₁₀ alcanoil, C₁-C₁₀ hidroxialquilo o benzoilo,

R^{9a} y R^{9b} son iguales o diferentes, y cada uno de ellos es hidrógeno o C₁-C₁₀ alquilo,

R⁹ es hidrógeno o C₁-C₁₀ alquilo,

y para los radicales-NR^{9a}R^{9b}, así como para sus sales compatibles desde el punto de vista fisiológico con ácidos y para los radicales-CO₂R⁹, donde R⁹ es hidrógeno, así como sus sales compatibles desde el punto de vista fisiológico con bases.

6. Un método de acuerdo con la reivindicación 4, donde el antagonista del receptor de la progesterona 17α-fluoroalquilado se administra al sujeto por vía oral.

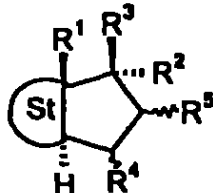
7. Un método para lograr la preñez en un sujeto hembra humano que comprende la estimulación de los ovarios del sujeto mediante la administración al sujeto de un agente estimulante folicular, donde el agente comprende hormona estimulante folicular; retirar los huevos del ovario del sujeto esti-

mulado; administrar al sujeto por lo menos un antagonista del receptor de la progesterona 17 α -fluoroalquilado en la fase pos-ovulatoria del ciclo endometrial; fertilizar por lo menos un huevo *in vitro* para obtener un embrión; y transferir el embrión al útero o a las trompas de Falopio del mamífero.

8. Un método de acuerdo con la reivindicación 7, donde el antagonista del receptor de la progesterona 17 α -fluoroalquilado se administra al sujeto en una dosis diaria de 0,1-10 mg por sujeto.

9. Un método de acuerdo con la reivindicación 8, donde el antagonista del receptor de la progesterona 17 α -fluoroalquilado se administra en una cantidad de 0,1-2 mg por sujeto en un día único durante la fase pos-ovulatoria del ciclo endometrial.

10. Un método de acuerdo con la reivindicación 8, donde el antagonista del receptor de la progesterona 17 α -fluoroalquilado es un compuesto de la fórmula I:



donde:

R^1 es metilo o etilo,

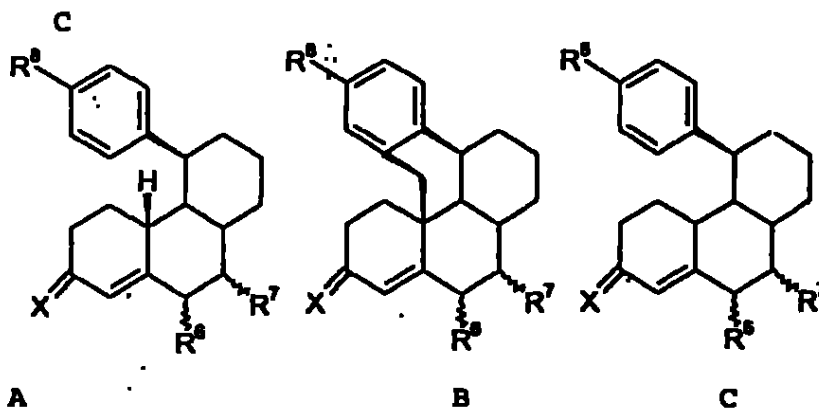
R^2 es $C_nF_mH_o$, donde n es 1-6, preferentemente 2, 3, 4, 5 o 6, $m > 1$ y $m+o = 2n+1$.

R_3 es un grupo hidróxilo libre, eterificado o esterifi-

cado,

R^4 y R^5 cada uno es un hidrógeno, o juntos forman una ligadura adicional o un grupo metileno

St es un anillo esteroidal ABC de fórmula parcial A, B o



donde:

R^6 es hidrógeno, un grupo C_1-C_4 alquilo de cadena lineal o C_3-C_4 alquilo de cadena ramificada o halógeno

R^7 es hidrógeno, un grupo C_1-C_4 alquilo de cadena lineal o C_3-C_4 alquilo de cadena ramificada, o

si St es un sistema de anillo ABC esteroidal, además

R^6 y R^7 juntos pueden formar una ligadura adicional,

X es oxígeno, hidroximinio ($=N-OH$) o dos átomos de hidrógeno,

R^8 es Y o arilo optativamente sustituido en múltiples sitios con un grupo Y distinto de H,

Y es hidrógeno, halógeno, $-OH$, $-NO_2$, $-N_3$, $-CN$, $-NR^{9a}R^{9b}$, $-NHSO_2R^9$, CO_2R^9 , C_1-C_{10} alquilo, C_1-C_{10} alcoxi, C_1-C_{10} alcanoiloxi, benzoiloxi, C_1-C_{10} álcanoilo, C_1-C_{10} hidro-

xialquilo o benzoilo,

R^{9a} y R^{9b} son iguales o diferentes, y cada uno de ellos es

hidrógeno o C_1-C_{10} alquilo,

R^9 es hidrógeno o C_1-C_{10} alquilo,

y para los radicales- $NR^{9a}R^{9b}$, así como para sus sales compatibles desde el punto de vista fisiológico con ácidos y para los radicales- CO_2R^9 , donde R^9 es hidrógeno, así como sus sales compatibles desde el punto de vista fisiológico con bases.

11. Un método de acuerdo con la reivindicación 9, donde el antagonista del receptor de la progesterona 17α -fluoroalquilado se administra al sujeto por vía oral.

12. Un método para retardar la ocurrencia de la maduración endometrial en un mamífero hembra no-humano que está siendo sometido a tratamiento para mejorar la fertilidad para alcanzar la preñez, que comprende administrar al mamífero por lo menos un antagonista del receptor de la progesterona 17α -fluoroalquilado durante la fase pos-ovulatoria del ciclo endometrial.

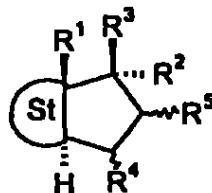
13. Un método de acuerdo con la reivindicación 12, donde el antagonista del receptor de la progesterona 17α -fluoroalquilado se administra al mamífero en una dosis diaria de 0,01-1 mg/kg.

14. Un método de acuerdo con la reivindicación 13, donde el tratamiento de fertilización comprende la administración al mamífero de un agente estimulante folicular que com-

prende hormona estimulante folicular.

15. Un método de acuerdo con la reivindicación 13, donde el antagonista del receptor de la progesterona 17 α -fluoroalquilado se administra al mamífero en una cantidad de 0,1-1 mg/kg en un día único durante la fase pos-ovulatoria del ciclo endometrial.

16. Un método de acuerdo con la reivindicación 13, donde el antagonista del receptor de la progesterona 17 α -fluoroalquilado es un compuesto de la fórmula I:



donde:

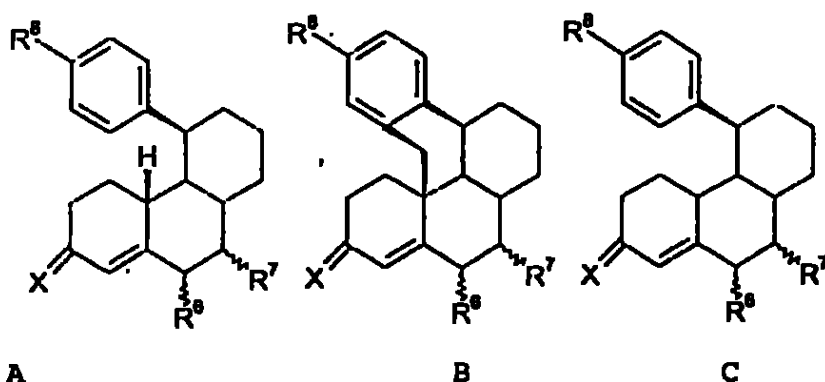
R¹ es metilo o etilo,

R² es C_nF_mH_o, donde n es 1-6, preferentemente 2, 3, 4, 5 o 6, m > 1 y m+o = 2n+1.

R₃ es un grupo hidroxilo libre, eterificado o esterificado,

R⁴ y R⁵ cada uno es un hidrógeno, o juntos forman una ligadura adicional o un grupo metileno

St es un anillo esteroidal ABC de fórmula parcial A, B o C



donde:

R^6 es hidrógeno, un grupo C_1-C_4 alquilo de cadena lineal o C_3-C_4 alquilo de cadena ramificada o halógeno

R^7 es hidrógeno, un grupo C_1-C_4 alquilo de cadena lineal o C_3-C_4 alquilo de cadena ramificada, o

si St es un sistema de anillo ABC esteroideal, además

R^6 y R^7 juntos pueden formar una ligadura adicional,

X es oxígeno, hidroximinio ($=N-OH$) o dos átomos de hidrógeno,

R^8 es Y o arilo optativamente sustituido en múltiples sitios con un grupo Y distinto de H,

Y es hidrógeno, halógeno, $-OH$, $-NO_2$, $-N_3$, $-CN$, $-NR^{9a}R^{9b}$, $-NHSO_2R^9$, CO_2R^9 , C_1-C_{10} alquilo, C_1-C_{10} alcoxi, C_1-C_{10} alcancilo, C_1-C_{10} hidroxicilo o benzoilo,

R^{9a} y R^{9b} son iguales o diferentes, y cada uno de ellos es hidrógeno o C_1-C_{10} alquilo,

R^9 es hidrógeno o C_1-C_{10} alquilo,

y para los radicales $-NR^{9a}R^{9b}$, así como para sus sales compa-

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tibles desde el punto de vista fisiológico con ácidos y para los radicales- CO_2R^3 , donde R^3 es hidrógeno, así como sus sales compatibles desde el punto de vista fisiológico con bases.

17. Un método para lograr la preñez en un mamífero no humano que comprende estimular los ovarios del mamífero mediante la administración al sujeto de un agente estimulante folicular, donde el agente comprende hormona estimulante folicular; retirar los huevos del ovario del mamífero estimulado; administrar al mamífero por lo menos un antagonista del receptor de la progesterona 17α -fluoroalquilado en la fase pos-ovulatoria del ciclo endometrial; fertilizar por lo menos un huevo in vitro para obtener un embrión; y transferir el embrión al útero o a las trompas de Falopio del mamífero.

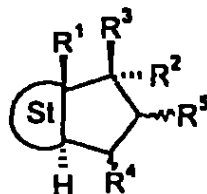
18. Un método de acuerdo con la reivindicación 17, donde el antagonista del receptor de la progesterona 17α -fluoroalquilado se administra al mamífero en una dosis diaria de 0,01-1 mg/kg.

19. Un método de acuerdo con la reivindicación 18, donde el antagonista del receptor de la progesterona 17α -fluoroalquilado se administra al mamífero en una cantidad de 0,1-1 mg/kg en un día único durante la fase pos-ovulatoria del ciclo endometrial.

20. Un método de acuerdo con la reivindicación 18, donde el antagonista del receptor de la progesterona 17α -

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fluoroalquilado es un compuesto de la fórmula I:



donde:

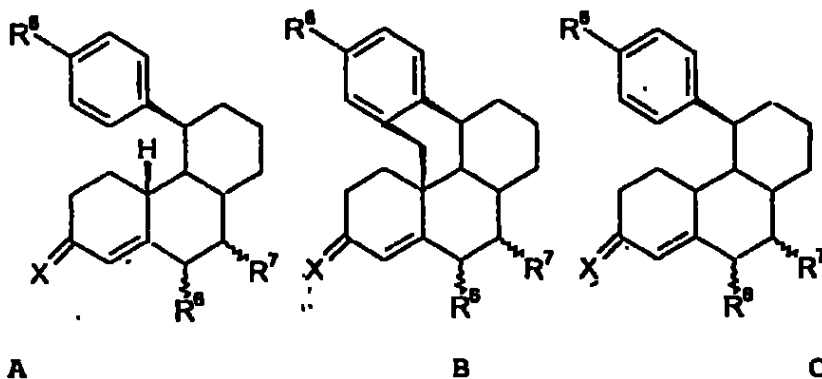
R^1 es metilo o etilo,

R^2 es $C_nF_mH_o$, donde n es 1-6, preferentemente 2, 3, 4, 5 ó 6, $m > 1$ y $m+o = 2n+1$.

R_3 es un grupo hidroxilo libre, eterificado o esterificado,

R^4 y R^5 cada uno es un hidrógeno, o juntos forman una ligadura adicional o un grupo metileno

St es un anillo esteroidal ABC de fórmula parcial A, B o C



donde:

R^6 es hidrógeno, un grupo C_1-C_4 alquilo de cadena lineal o C_3-C_4 alquilo de cadena ramificada o halógeno

R^7 es hidrógeno, un grupo C_1-C_4 alquilo de cadena lineal

o C₃-C₄ alquilo de cadena ramificada, o

si St es un sistema de anillo ABC esteroideal, además

R⁶ y R⁷ juntos pueden formar una ligadura adicional,

X es oxígeno, hidroxiiimino (=N-OH) o dos átomos de hidrógeno,

R⁸ es Y o arilo optativamente sustituido en múltiples sitios con un grupo Y distinto de H,

Y es hidrógeno, halógeno, -OH, -NO₂, -N₃, -CN, -NR^{9a}R^{9b}, -NHSO₂R⁹, CO₂R⁹, C₁-C₁₀ alquilo, C₁-C₁₀ alcoxi, C₁-C₁₀ alcanoiloxi, benzoiloxi, C₁-C₁₀ alcanoil, C₁-C₁₀ hidroalquilo o benzoilo,

R^{9a} y R^{9b} son iguales o diferentes, y cada uno de ellos es hidrógeno o C₁-C₁₀ alquilo,

R⁹ es hidrógeno o C₁-C₁₀ alquilo,

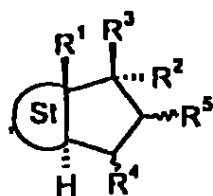
y para los radicales-NR^{9a}R^{9b}, así como para sus sales compatibles desde el punto de vista fisiológico con ácidos y para los radicales-CO₂R⁹, donde R⁹ es hidrógeno, así como sus sales compatibles desde el punto de vista fisiológico con bases.

21. Un mamífero no humano que resulta de la preñez obtenida mediante el proceso de acuerdo con la reivindicación 13.

22. Un mamífero no humano que resulta de la preñez obtenida mediante el proceso de acuerdo con la reivindicación 18.

23. Un método para retardar la ocurrencia de la maduración endometrial en un sujeto hembra humano que está sometido

a un tratamiento para mejorar la fertilidad, que comprende administrar al sujeto por lo menos un compuesto de la fórmula I, donde la fórmula I es



donde:

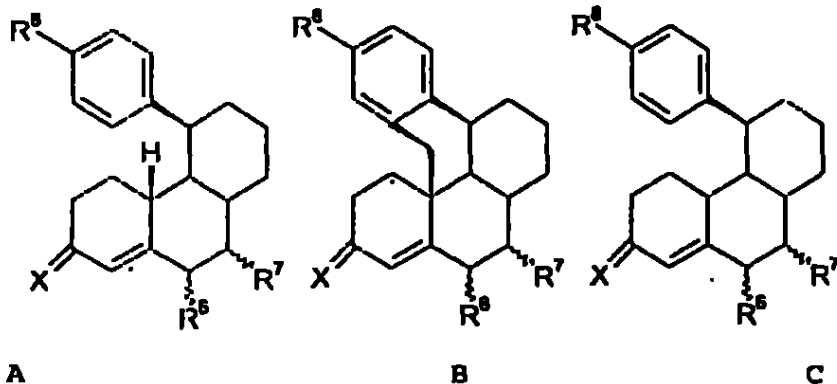
R^1 es metilo o etilo,

R^2 es $C_nF_mH_o$, donde n es 1-6, preferentemente 2, 3, 4, 5 o 6, $m > 1$ y $m+o = 2n+1$.

R_3 es un grupo hidroxilo libre, eterificado o esterificado,

R^4 y R^5 cada uno es un hidrógeno, o juntos forman una ligadura adicional o un grupo metileno

St es un anillo esteroidal ABC de fórmula parcial A,B o C



donde:

R^6 es hidrógeno, un grupo C_1-C_4 alquilo de cadena lineal

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o C₃-C₄ alquilo de cadena ramificada o halógeno
 R⁷ es hidrógeno, un grupo C₁-C₄ alquilo de cadena lineal
 o C₃-C₄ alquilo de cadena ramificada, o

si St es un sistema de anillo ABC esteroideal, además

R⁶ y R⁷ juntos pueden formar una ligadura adicional,

X es oxígeno, hidroximinio (=N-OH) o dos átomos de hidrógeno,

R⁸ es Y o arilo optativamente sustituido en múltiples sitios con un grupo Y distinto de H,

Y es hidrógeno, halógeno, -OH, -NO₂, -N₃, -CN, -NR^{9a}R^{9b}, -NHSO₂R⁹, CO₂R⁹, C₁-C₁₀ alquilo, C₁-C₁₀ alcoxi, C₁-C₁₀ alcanoiloxi, benzoiloxi, C₁-C₁₀ alcanoil, C₁-C₁₀ hidroxialquilo o benzoilo,

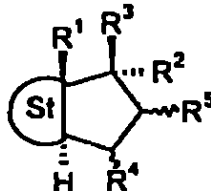
R^{9a} y R^{9b} son iguales o diferentes, y cada uno de ellos es hidrógeno o C₁-C₁₀ alquilo,

R⁹ es hidrógeno o C₁-C₁₀ alquilo,

y para los radicales-NR^{9a}R^{9b}, así como para sus sales compatibles desde el punto de vista fisiológico con ácidos y para los radicales-CO₂R⁹, donde R⁹ es hidrógeno, así como sus sales compatibles desde el punto de vista fisiológico con bases.

24. Un método para lograr la preñez en un sujeto hembra humano que comprende estimular los ovarios del sujeto mediante la administración al sujeto de un agente estimulante folicular, donde el agente comprende hormona estimulante folicular; retirar los huevos del ovario del sujeto estimula-

do; administrar al sujeto por lo menos un compuesto de la fórmula I en la fase pos-ovulatoria del ciclo endometrial; fertilizar por lo menos un huevo in vitro para obtener un embrión; y transferir el embrión al útero o a las trompas de Falopio del mamífero, tal que la fórmula I es:



donde:

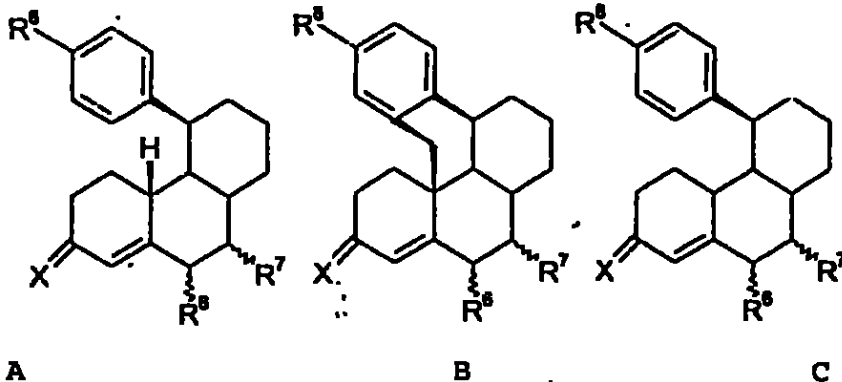
R^1 es metilo o etilo,

R^2 es $C_nF_mH_o$, donde n es 1-6, preferentemente 2, 3, 4, 5 o 6, $m > 1$ y $m+o = 2n+1$.

R_3 es un grupo hidroxilo libre, eterificado o esterificado,

R^4 y R^5 cada uno es un hidrógeno, o juntos forman una ligadura adicional o un grupo metileno

St es un anillo esteroidal ABC de fórmula parcial A, B o C



donde:

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R^6 es hidrógeno, un grupo C_1-C_4 alquilo de cadena lineal o C_3-C_4 alquilo de cadena ramificada o halógeno

R^7 es hidrógeno, un grupo C_1-C_4 alquilo de cadena lineal o C_3-C_4 alquilo de cadena ramificada, o

si St es un sistema de anillo ABC esteroideal, además

R^6 y R^7 juntos pueden formar una ligadura adicional,

X es oxígeno, hidroxiimino ($=N-OH$) o dos átomos de hidrógeno,

R^8 es Y o arilo optativamente sustituido en múltiples sitios con un grupo Y distinto de H,

Y es hidrógeno, halógeno, $-OH$, $-NO_2$, $-N_3$, $-CN$, $-NR^{9a}R^{9b}$, $-NHSO_2R^9$, CO_2R^9 , C_1-C_{10} alquilo, C_1-C_{10} alcoxi, C_1-C_{10} alcanoiloxi, benzoiloxi, C_1-C_{10} alcanoil, C_1-C_{10} hidroxialquilo o benzoilo,

R^{9a} y R^{9b} son iguales o diferentes, y cada uno de ellos es hidrógeno o C_1-C_{10} alquilo,

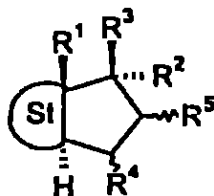
R^9 es hidrógeno o C_1-C_{10} alquilo,

y para los radicales $-NR^{9a}R^{9b}$, así como para sus sales compatibles desde el punto de vista fisiológico con ácidos y para los radicales $-CO_2R^9$, donde R^9 es hidrógeno, así como sus sales compatibles desde el punto de vista fisiológico con bases.

25. Un método para retardar la ocurrencia de la maduración endometrial en mamífero hembra no-humano que está sometido a un tratamiento para mejorar la fertilidad y lograr la preñez, que comprende administrar al mamífero por lo menos un

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compuesto de la fórmula I, donde la fórmula I es



donde:

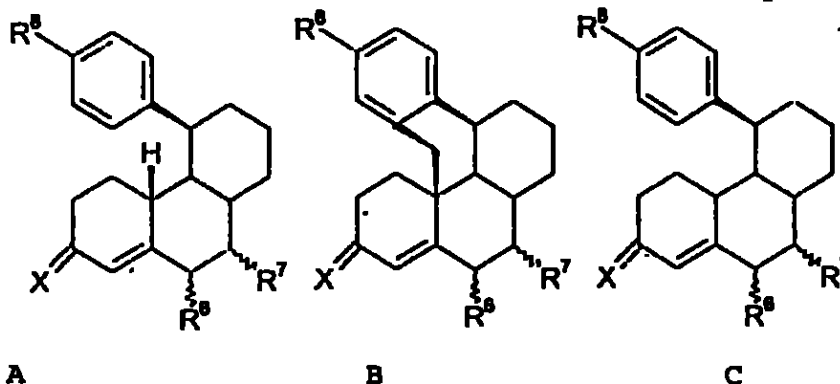
R^1 es metilo o etilo,

R^2 es $C_nF_mH_o$, donde n es 1-6, preferentemente 2, 3, 4, 5 o 6, $m > 1$ y $m+o = 2n+1$.

R_3 es un grupo hidroxilo libre, eterificado o esterificado,

R^4 y R^5 cada uno es un hidrógeno, o juntos forman una ligadura adicional o un grupo metileno

St es un anillo esteroidal ABC de fórmula parcial A, B o C



donde:

R^6 es hidrógeno, un grupo C_1-C_4 alquilo de cadena lineal o C_3-C_4 alquilo de cadena ramificada o halógeno

R^7 es hidrógeno, un grupo C_1-C_4 alquilo de cadena lineal

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o C₃-C₄ alquilo de cadena ramificada, o

si St es un sistema de anillo ABC esteroïdal, además

R⁶ y R⁷ juntos pueden formar una ligadura adicional,

X es oxígeno, hidroxiiimino (=N-OH) o dos átomos de hidrógeno,

R⁸ es Y o arilo optativamente sustituido en múltiples sitios con un grupo Y distinto de H,

Y es hidrógeno, halógeno, -OH, -NO₂, -N₃, -CN, -NR^{9a}R^{9b}, -NHSO₂R⁹, CO₂R⁹, C₁-C₁₀ alquilo, C₁-C₁₀ alcoxi, C₁-C₁₀ alcanoiloxi, benzoiloxi, C₁-C₁₀ alcanoil, C₁-C₁₀ hidroxialquilo o benzoilo,

R^{9a} y R^{9b} son iguales o diferentes, y cada uno de ellos es hidrógeno o C₁-C₁₀ alquilo,

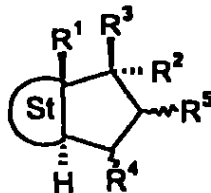
R⁹ es hidrógeno o C₁-C₁₀ alquilo,

y para los radicales-NR^{9a}R^{9b}, así como para sus sales compatibles desde el punto de vista fisiológico con ácidos y para los radicales-CO₂R⁹, donde R⁹ es hidrógeno, así como sus sales compatibles desde el punto de vista fisiológico con bases.

26. Un método para obtener la preñez en un mamífero no humano que comprende estimular los ovarios del mamífero mediante la administración al sujeto de un agente estimulante folicular, donde el agente comprende una hormona estimulante folicular; retirar huevos del ovario del mamífero estimulado; administrar al mamífero por lo menos un compuesto de la fórmula I durante la fase pos-ovulatoria del ciclo endome-

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trial; fertilizar por lo menos un huevo in vitro para obtener un embrión; transferir el embrión dentro del útero o las trompas de Falopio del mamífero, donde la fórmula I es:



donde:

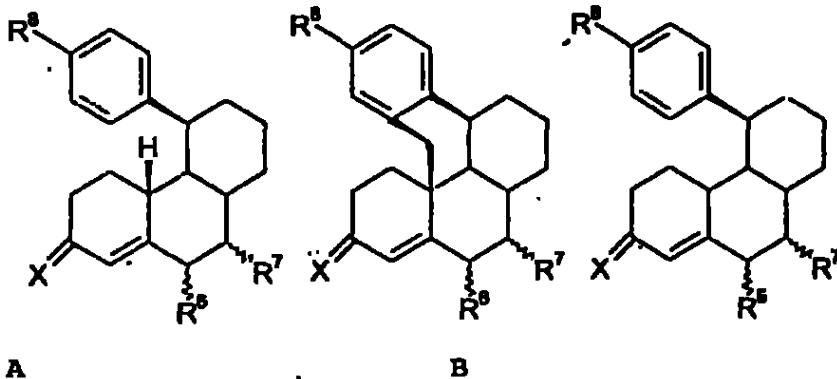
R^1 es metilo o etilo,

R^2 es $C_nF_mH_o$, donde n es 1-6, preferentemente 2, 3, 4, 5 o 6, $m > 1$ y $m+o = 2n+1$.

R_3 es un grupo hidroxilo libre, eterificado o esterificado,

R^4 y R^5 cada uno es un hidrógeno, o juntos forman una ligadura adicional o un grupo metileno

St es un anillo esteroidal ABC de fórmula parcial A, B o C



donde:

R^6 es hidrógeno, un grupo C_1-C_4 alquilo de cadena lineal o C_3-C_4 alquilo de cadena ramificada o halógeno

ST
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R^7 es hidrógeno, un grupo C_1-C_4 alquilo de cadena lineal o C_3-C_4 alquilo de cadena ramificada, o

si St es un sistema de anillo ABC esteroideal, además

R^6 y R^7 juntos pueden formar una ligadura adicional,

X es oxígeno, hidroxilimino ($=N-OH$) o dos átomos de hidrógeno,

R^8 es Y o arilo optativamente sustituido en múltiples sitios con un grupo Y distinto de H,

Y es hidrógeno, halógeno, $-OH$, $-NO_2$, $-N_3$, $-CN$, $-NR^{9a}R^{9b}$, $-NHSO_2R^9$, CO_2R^9 , C_1-C_{10} alquilo, C_1-C_{10} alcoxi, C_1-C_{10} alcanciloxi, benzoiloxi, C_1-C_{10} alcancililo, C_1-C_{10} hidroxialquilo o benzoilo,

R^{9a} y R^{9b} son iguales o diferentes, y cada uno de ellos es hidrógeno o C_1-C_{10} alquilo,

R^9 es hidrógeno o C_1-C_{10} alquilo,

y para los radicales $-NR^{9a}R^{9b}$, así como para sus sales compatibles desde el punto de vista fisiológico con ácidos y para los radicales $-CO_2R^9$, donde R^9 es hidrógeno, así como sus sales compatibles desde el punto de vista fisiológico con bases.

27. Un método para modular la ocurrencia de la maduración endometrial en un sujeto hembra humano que está sometido a tratamiento para mejorar la fertilidad, que comprende administrar al menos un antagonista del receptor de progesterona 17α -fluoroalquilado al sujeto hembra durante la fase pos-ovulatoria del ciclo endometrial.

28. Un método para retardar la ocurrencia de maduración endometrial en un sujeto hembra humano que está bajo tratamiento para mejorar la fertilidad, que comprende administrar al sujeto hembra al menos un antagonista del receptor de progesterona 17α -fluoroalquilado durante la fase pos-ovulatoria del ciclo endometrial después del mencionado tratamiento para mejorar la fertilidad.

29. Un método para retardar la ocurrencia de maduración endometrial en un sujeto hembra humano que está bajo tratamiento para mejorar la fertilidad y lograr la preñez, que comprende administrar al sujeto hembra al menos un antagonista del receptor de progesterona 17α -fluoroalquilado durante la fase pos-ovulatoria del ciclo endometrial después del mencionado tratamiento para mejorar la fertilidad.

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THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

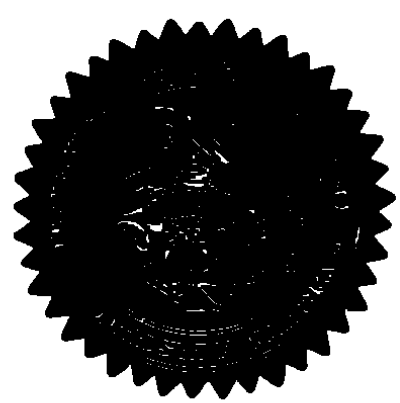
United States Patent and Trademark Office

February 01, 2002

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 09/801,925

FILING DATE: March 09, 2001



**By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS**

T. Lawrence

**T. LAWRENCE
Certifying Officer**

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Atty's Docket No. SCH-1754-P1

Applicant(s) : Sybille BEIER et al.

For : THE USE OF ANTIGESTAGENS FOR INHIBITING ACCELERATED
ENDOMETRIAL MATURATION DURING INFERTILITY TREATMENT

The Honorable Commissioner
of Patents and Trademarks
Washington, D.C. 20231

SUBMISSION OF APPLICATION UNDER 37 C.F.R. §1.53(f)

Sir:

Herewith is the above-identified continuation-in-part application for Letters Patent including:

Applicant(s) Name(s) : Sybille BEIER
Holger HESS-STUMP

Assignee (by unrecorded assignment) :

Pages of Application: Specification - 17
Claims - 16
Abstract - 1
Sheets of Drawings - 1

NO DECLARATION IS ATTACHED.

☐ The benefit under 35 U.S.C. §119 is claimed of the filing date of :

Respectfully submitted,

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.

By: Anthony J. Zelano (Reg. No. 27,969)
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Filed: March 9, 2001

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**THE USE OF ANTIGESTAGENS FOR INHIBITING ACCELERATED
ENDOMETRIAL MATURATION DURING INFERTILITY TREATMENT**

This application is a continuation in part of U.S. Serial No. 09/756,286 filed January 9, 2001, which is incorporated by reference herein in its entirety.

BACKGROUND OF THE INVENTION

This invention relates to the use of antigestagens for shifting post-ovulatory endometrial maturation during infertility treatment.

Ovarian stimulation with gonadotropins is commonly used in humans in assisted reproductive technologies, including in vitro fertilization and embryo transfer therapy (IVF/ET). However, the post-ovulatory endometrial transformation is advanced after controlled ovarian hyperstimulation (Garcia et al., 1984, *Fertil. Steril.* 41:31-37; Paulson et al., 1997, *Fertil. Steril.* 76:321-325; Kolb, 1997, *Fertil. Steril.* 67:625-630; Franchin et al., 1999, *Fertil. Steril.* 71:174-181.) As a consequence, the usual precisely synchronized temporal development of the endometrium and the embryo is disrupted, resulting in low implantation rates for healthy blastocysts.

SUMMARY OF THE INVENTION

This invention provides a method of enhancing fertility in mammals by the administration of 17 α -fluoralkylated progesterone receptor antagonists to inhibit the advancement of endometrium maturation during infertility (i.e., fertility enhancement) treatment including all assisted reproduction therapies.

It is also contemplated as part of this invention that such a method will be particularly useful in a female mammal undergoing fertility treatment. Fertility treatment, as used herein, refers to any treatment which is rendered to a female mammal for the purposes of achieving a pregnancy, whether or not the mammal has been determined to be fertile, infertile, or to have impaired fertility. Fertility treatments contemplated as part of this invention include, but are not limited to ovarian hyperstimulation (OH), in vitro fertilization and embryo transfer (IVF/ET),

100A

and OH in combination with IVF/ET. Particularly, a method of inhibiting advanced endometrial maturation, which typically occurs in conjunction with ovarian hyperstimulation, is contemplated. For example, ovarian hyperstimulation may be used as a tool in fertility treatment in conjunction with, for example, timed intercourse, artificial insemination, intrauterine insemination, IVF/ET, and gamete intra fallopian transfer (GIFT).

IVF/ET, as used herein, refers to any techniques wherein oocytes are fertilized in vitro and then transferred into the female reproductive tract. For example, transfer of the embryo may occur via transfer of the embryo into the uterus through the cervix or via transfer of the embryo into the fallopian tubes (zygote intra fallopian transfer (ZIFT)). Fertilization of oocytes in vitro may be accomplished, for example, by incubating oocytes in the presence of sperm or by intra cytoplasmic sperm injection (ICSI). IVF/ET may also be accomplished using donor eggs. Infertility treatments also include treatments such as induction of ovarian stimulation followed by fertilization by normal coitus.

Ovarian hyperstimulation, as used herein, refers to the use of a follicle stimulating agent to stimulate follicle development. Ovarian hyperstimulation may be used in female subjects having a variety of ovulatory conditions, including subjects who are anovulatory, subjects who have impaired, reduced, or irregular ovulation, and subjects with normal ovulatory patterns. Preferred follicle stimulating agents, include gonadotropins, such as for example, follicle stimulating hormone (FSH), luteinizing hormone (LH), human menopausal gonadotropins (hMG), and human chorionic gonadotropin (hCG). Brand names of gonadotropins that are available for use as follicle stimulating agents, include for example, Perganol, Metrodin, Humegon, Fertinorm, Gonal F, and Primogonyl-1000 etc. Follicle stimulating agents, as used herein, also include estrogen blocking agents such as, for example, clomiphene citrate (commercially available as Clomid and Serophene). Gonadotropins that may be used in accordance with this invention include hormones that are isolated from naturally occurring source materials and hormones that are produced synthetically, including hormones produced through

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recombinant DNA techniques. Mutant gonadotropins which retain activity as follicle stimulating agents are also contemplated as part of this invention.

Ovarian hyperstimulation may be accomplished using more than type of follicular stimulating agent. For example, an estrogen blocking agent such as clomiphene may be used in combination with a gonadotropin. Ovarian hyperstimulation may be used to treat a variety of types of infertility, including but not limited to, idiopathic infertility, anovulatory infertility, endometriosis associated infertility, tubal factor infertility and male factor infertility.

Ovarian hyperstimulation may also be accomplished in conjunction with a gonadotropin releasing hormone antagonist (GnRH) to turn off the subjects endogenous hormone production. GnRH's that may be used in conjunction with the invention include, for example, Synarel or Lupron.

In a preferred embodiment, the methods of this invention are employed in conjunction with human female subjects. The methods of this invention may also be employed with other mammalian female subjects, including but not limited to, household pets, farm animals and zoo animals, particularly including cows, pigs, horses, and sheep. When used in fertility treatment of non-human mammals, the administration of antigestagens can help to achieve a higher success rate in, for example, in vitro fertilization and embryo transfer undertaken for economic or breeding purposes.

Non-human mammals which are produced by the methods disclosed herein are also contemplated as part of the invention. These non-human mammals include, for example, mammals which have been genetically modified, including for example, mammals that have been genetically modified using recombinant DNA techniques.

In one aspect, the invention relates to a method of inhibiting the occurrence of advanced endometrium maturation in a human female subject undergoing fertility treatment comprising administering at least one 17 α -fluoralkylated progesterone receptor antagonist to the female subject during the post-ovulatory phase of the endometrial cycle.

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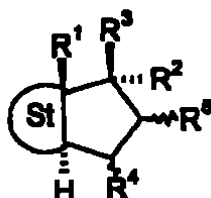
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hyperstimulation comprises follicle stimulating hormone (FSH). Even more preferably ovarian stimulation is achieved by the use of a first gonadotropin comprising FSH and the subsequent use of second gonadotropin comprising chorionic gonadotropin, particularly human chorionic gonadotropin (hCG).

Preferably the embryo is introduced into the reproductive tract of the mammal by introduction into the uterus via the cervix. Also preferably, a gonadotropin releasing hormone (GnRH) agonist or antagonist is administered to the female mammal prior and during the administration of the gonadotropins.

Compounds useful as antigestagens according to the present invention include all 17 α -fluoralkylated progesterone receptor antagonists which possess a strong affinity for the gestagen receptor (progesterone receptor) and show minimal gestagen activity of their own. For example, 17 α -fluoralkylated steroidal compounds which may be employed in conjunction with the invention are described U.S. Patent Application Serial No. 09/020,947, WO/98/34947, Wang and Ruan, 1994, *Journal of Fluorine Chemistry* 69:1-3, all of which are hereby incorporated by reference in their entirety. Antigestagens useful for the present invention include but are not limited to, for example, 17 α -fluoroalkyl steroids of general formula I, primarily from the cited disclosures:



I

wherein

R¹ is methyl or ethyl,

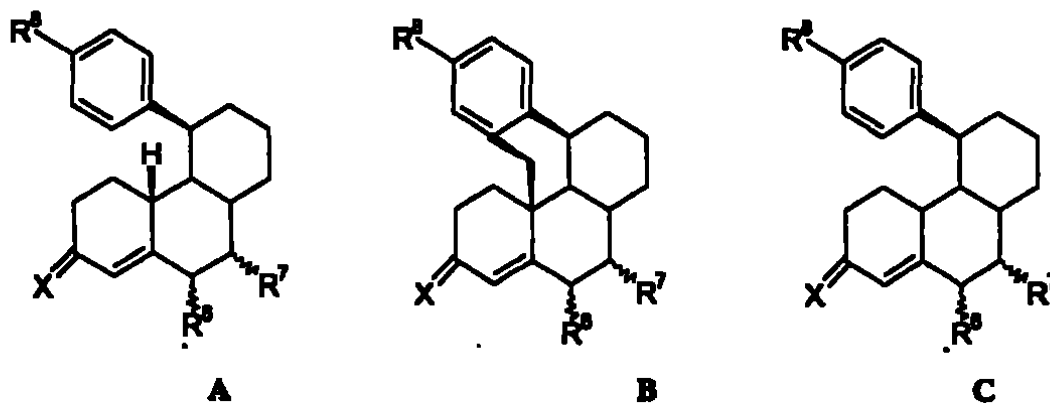
R² is C_nF_mH_o, wherein n is 1-6, preferably 2, 3, 4, 5 or 6, m > 1 and m+o = 2n+1,

R³ is a free, etherified or esterified hydroxy group,

R⁴ and R⁵ each is a hydrogen, or together form an additional bond or a methylene group,

St is a steroidal ABC-ring system of partial formula A, B or C

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wherein

R^6 is hydrogen, a straight-chain C_1-C_4 alkyl group or branched C_3-C_4 alkyl group or halogen,

R^7 is hydrogen, a straight-chain C_1-C_4 alkyl group or a branched C_3-C_4 alkyl group, or

if St is a steroidal ABC-ring system A or B, in addition

R^6 and R^7 together can form an additional bond,

X is oxygen, hydroxyimino ($=N-OH$) or two hydrogen atoms,

R^8 is Y or aryl that is optionally substituted in several places with a group Y, other than H,

Y is hydrogen, halogen, $-OH$, $-NO_2$, $-N_3$, $-CN$, $-NR^9R^{10}$, $-NHSO_2R^9$, $-CO_2R^9$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_1-C_{10} alkanoyloxy, benzoyloxy, C_1-C_{10} alkanoyl, C_1-C_{10} hydroxyalkyl or benzoyl,

R^9 and R^{10} are the same or different and each is hydrogen or C_1-C_{10} alkyl,

R^9 is hydrogen or C_1-C_{10} alkyl,

and for $-NR^9R^{10}$ radicals, as well as their physiologically compatible salts with acids and for $-CO_2R^9$ radicals with R^9 being hydrogen, as well as their physiologically compatible salts with bases.

The wavy lines mean that the substituent in question can be in α - or β -position.

Suitable alkyl groups within the scope of this formula include methyl, ethyl, or n- or iso-propyl, and n-, iso- or tert-butyl groups.

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The other C_1 - C_{10} alkyl groups, Y, R^9 , R^{10} , R^{11} , include the higher homologs in addition, such as, for example, the pentyl, neo-pentyl, and hexyl to decyl groups.

C_1 - C_{10} alkyl groups are to be understood to encompass, however, carbocyclic or alkylcycloalkyl groups as well with up to 10 carbon atoms, for example cyclopropyl, cyclopentyl, cycloheptyl, methylcyclopropyl, methylcyclopentyl or methylcyclohexyl. A methyl or ethyl group is preferred for all cases above.

C_1 - C_{10} alkoxy groups are the radicals that are lengthened by one oxygen atom and derived from the alkyl groups that are mentioned above, thus, e.g., the methoxy, ethoxy, n- or iso-propoxy, n-, iso- or tert-butoxy radical, etc.

C_1 - C_{10} alkanoyl is defined as the acyl radicals of straight-chain and branched C_1 - C_{10} alkanecarboxylic acids, thus, for example, the formyl, acetyl, propionyl, butyryl or iso-butyryl radical, etc.

C_1 - C_{10} alkanoyloxy radicals are the radicals of the above alkanoyl radicals that are lengthened by one oxygen atom, thus, e.g., the acetyloxy, propionyloxy, and butyryloxy, etc.

If a halogen atom is mentioned as a substituent, this can be a fluorine, chlorine or bromine atom. Fluorine is preferred.

For radicals R^2 , perfluorinated side chains of length $n = 2-4$ are preferred and among the latter, in turn the pentafluoroethyl unit is especially preferred.

R^3 stands primarily for a free hydroxy group.

In the case of an etherified or esterified hydroxy group as a 17β -substituent, the latter is preferably etherified with a C_1 - C_{10} alkyl group or esterified with a C_1 - C_{10} alkanoyl group. For this alkyl or alkanoyl group, the same meanings as above apply. The etherification or esterification of the hydroxy group is carried out according to the methods that are familiar to one skilled in the art.

R^4 and R^5 preferably each are a hydrogen or together form an additional bond.

If R^6 is a group Y, this is preferably a C_1 - C_{10} alkanoyl or (1-hydroxy)- C_1 - C_{10} alkyl group; among these, acetyl and propionyl are especially preferred.

Preferred carbocyclic or heterocyclic aryl radicals are phenyl, 1- or 2-naphthalinyl, 2- or 3-furanyl, 2- or 3-benzofuranyl, 2- or 3-thienyl, 2-, 3- or 4-pyridinyl. Substituted aryl radicals R^a, are primarily 4-cyanophenyl and 4-halophenyl, especially 4-fluorophenyl, can be cited.

Among all the radicals that are mentioned as preferred for R^a, R^b in the meaning of Y and Y, in turn, equal to acetyl is especially to be preferred.

The compounds that are mentioned below are especially preferred according to the invention:

11β-(4-Acetylphenyl)-17β-hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)estr-4-en-3-one;

4'-[17β-hydroxy-3-oxo-17α-(1,1,2,2,2-pentafluoroethyl)estr-4-en-11β-yl][1,1'-biphenyl]-4-carbonitrile;

11β-(4'-fluoro[1,1'-biphenyl]-4-yl)-17β-hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)estr-4-en-3-one;

17β-hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)-11β-[4-(3-pyridinyl)phenyl]estr-4-en-3-one;

11β-(4-acetylphenyl)-17β-hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)estra-4,15-dien-3-one;

4'-[17β-hydroxy-3-oxo-17α-(1,1,2,2,2-pentafluoroethyl)estra-4,15-dien-11β-yl][1,1'-biphenyl]-4-carbonitrile;

11β-(4'-fluoro[1,1'-biphenyl]-4-yl)-17β-hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)estra-4,15-dien-3-one;

17β-hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)-11β-[4-(3-pyridinyl)phenyl]estr-4,15-dien-3-one;

11β-(4-acetylphenyl)-17β-hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)estra-4,9-dien-3-one;

4'-[17β-hydroxy-3-oxo-17α-(1,1,2,2,2-pentafluoroethyl)estra-4,9-dien-11β-yl][1,1'-biphenyl]-4-carbonitrile;

11β-(4'-fluoro[1,1'-biphenyl]-4-yl)-17β-hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)estra-4,9-dien-3-one;

17 β -hydroxy-11 β -(4-hydroxyphenyl)-17 α -(1,1,2,2,2-pentafluoroethyl)estr-4-
30 en-3-one;

9,11 α -dihydro-6',17 β -dihydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)-4'H-naphth[3',2',1':10,9,11]estr-4-en-3-one;

11 β -[4-(acetyloxy)phenyl]-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)estra-4,9-dien-3-one;

5 11 β -[4-(acetyloxy)phenyl]-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)estr-4-en-3-one

6'-acetyloxy-9,11 α -dihydro-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)-4'H-naphth[3',2',1':10,9,11]estr-4-en-3-one;

10 17 β -hydroxy-11 β -[4-(hydroxymethyl)phenyl]-17 α -(1,1,2,2,2-pentafluoroethyl)estra-4,9-dien-3-one;

17 β -hydroxy-11 β -[4-(hydroxymethyl)phenyl]-17 α -(1,1,2,2,2-pentafluoroethyl)estr-4-en-3-one;

9,11 α -dihydro-17 β -hydroxy-6'-hydroxymethyl-17 α -(1,1,2,2,2-pentafluoroethyl)-4'H-naphth[3',2',1':10,9,11]estr-4-en-3-one;

15 4-[17 β -hydroxy-3-oxo-17 α -(1,1,2,2,2-pentafluoroethyl)estra-4,9-dien-11 β -yl]benzaldehyde;

4-[17 β -hydroxy-3-oxo-17 α -(1,1,2,2,2-pentafluoroethyl)estr-4-en-11 β -yl]benzaldehyde;

20 9,11 α -dihydro-17 β -hydroxy-3-oxo-17 α -(1,1,2,2,2-pentafluoroethyl)-4'H-naphth[3',2',1':10,9,11]estr-4-en-6'-al;

4-[17 β -hydroxy-3-oxo-17 α -(1,1,2,2,2-pentafluoroethyl)estra-4,9-dien-11 β -yl]benzoic acid methyl ester;

4-[17 β -hydroxy-3-oxo-17 α -(1,1,2,2,2-pentafluoroethyl)estr-4-en-11 β -yl]benzoic acid methyl ester;

25 9,11 α -dihydro-17 β -hydroxy-3-oxo-17 α -(1,1,2,2,2-pentafluoroethyl)-4'H-naphth[3',2',1':10,9,11]estr-4-en-6'-carboxylic acid methyl ester;

17 β -hydroxy-11 β -[4-(1-hydroxyethyl)phenyl]-17 α -(1,1,2,2,2-pentafluoroethyl)estra-4,9-dien-3-one;

30 17 β -hydroxy-11 β -[4-(1-hydroxyethyl)phenyl]-17 α -(1,1,2,2,2-pentafluoroethyl)estr-4-en-3-one;

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9,11 α -dihydro-17 β -hydroxy-6'-(1-hydroxyethyl)-17 α -(1,1,2,2,2-pentafluoroethyl)-4'H-naphth[3',2',1':10,9,11]estr-4-en-3-one.

Preferred is 11 β -(4-acetylphenyl)-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)estra-4,9-dien-3-one (= Compound A).

5 The antigestagens can, for example, be applied locally, topically, enterally or parenterally.

For the preferred oral administration, particularly suitable are tablets, dragees, capsules, pills, suspensions or solutions which can be prepared in a conventional manner with additives and carriers used in pharmacy. For local or topical application,
10 vaginal pessaries or percutaneous systems such as skin plasters can be used for example. For parenteral application, particularly suitable are solutions, preferably oily or aqueous solutions, as well as suspensions or emulsions. Ampules are convenient unit dosages.

According to a preferred mode of operation, the 17 α -fluoralkylated
15 progesterone receptor antagonist is typically administered over a period of 1 to 6 days, preferably 1 to 4 days, and more preferably on day(s) 1-3 after ovulation and/or the removal of oocytes. Typically, the antigestagen is administered over a period of 1 to 6 days, preferably 1-4 days, and more preferably 1-3 days after ovulation induction with e.g. a chorionic gonadotropin.

20 Surprisingly, according the invention, it has been found that low doses of a 17 α -fluoralkylated progesterone receptor antagonists are effective in the methods disclosed herein. The 17 α -fluoralkylated progesterone receptor antagonists are preferably administered to a human female subject in a daily dosage amount of up to 10 mg per subject, preferably 0.1 - 2 mg per subject, more preferably 0.1-1 mg per
25 subject, and most preferably 0.1-0.7 mg per subject. For mammals in general, a daily dosage amount is typically 0.01-1 mg/kg, preferably 0.01-0.3 mg/kg, and more preferably 0.01-0.1 mg/kg. The daily dose of antigestagen can be administered as a single dose or as divided dosages throughout the day.

In a preferred embodiment according to the invention, the antigestagen is
30 administered on a single day to a human subject in an amount of 0.1 - 2 mg/per subject, more preferably 0.1-1 mg/per subject, and most preferably 0.1-0.7 mg/per

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subject or to a mammal in an amount of 0.01-1 mg/kg, preferably 0.01-0.3 mg/kg, and more preferably 0.01-0.1 mg/kg. For example, on day 1, 2, 3, 4, 5 or 6 following ovulation, removal of oocytes, or administration of a chorionic gonadotropin, preferably day 1-3, and more preferably day 2.

5 For any particular 17 α -fluoralkylated progesterone receptor antagonist, the most appropriate dose can be determined, for example, by evaluation of the potency to induce premature menstruation in advanced luteal phase of the human cycle as described in e.g. Herrmann, W., et al, 1982, *Comptes Rendus* 294:933. The use of antigestagens for delaying endometrial maturation has been previously described,
10 for example, in U.S. Patent No. 4,764,513, EP 0219447B1, Hegele-Hartung et al., 1992, *Endocrinology* 131:2446-2460, all of which are incorporated herein by reference in their entirety.

The compounds of this invention can be employed in admixture with conventional excipients, i.e., pharmaceutically acceptable organic or inorganic carrier
15 substances suitable for, for example, parenteral, enthal (e.g., oral) or topical application which do not deleteriously react with the active compounds. Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions, alcohols, gum arabic, vegetable oils, benzyl alcohols, polyethylene glycols, gelatine, carbohydrates such as lactose, amylase or starch, magnesium stearate, talc,
20 silicic acid, viscous paraffin, perfume-oil, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxy methylcellulose, polyvinyl pyrrolidone, etc. The pharmaceutical preparations can be sterilized and if desired mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, flavoring and/or aromatic substances
25 and the like which do not deleteriously react with the active compounds. They can also be combined, where desired, with other active agents, e.g., vitamins.

Sustained or directed release compositions can be formulated, e.g., liposomes or those wherein the active compound is protected with differentially degradable
30 coatings, e.g., by microencapsulation, multiple coatings, etc. It is also possible to freeze-dry the new compounds and use the lyophilizates obtained, for example, for the preparation of products for injection.

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For topical application, there are employed as nonsprayable forms, viscous to semi-solid or solid forms comprising a carrier compatible with topical application and having a dynamic viscosity preferably greater than water. Suitable formulations include but are not limited to solutions, suspensions, emulsions, creams, ointments, powders, liniments, salves, aerosols, etc., which are, if desired, sterilized or mixed with auxiliary agents, e.g., preservatives, stabilizers, wetting agents, buffers or salts for influencing osmotic pressure, etc. For topical application, also suitable are sprayable aerosol preparations wherein the active ingredient, preferably in combination with a solid or liquid inert carrier material, is packaged in a squeeze bottle or in admixture with a pressurized volatile, normally gaseous propellant, e.g., a freon.

It will be appreciated that the actual preferred amounts of active compound in a specific case will vary according to the specific compound being utilized, the particular compositions formulated, the mode of application, and the particular situs and organism being treated. Dosages for a given host can be determined using conventional considerations, e.g., by customary comparison of the differential activities of the subject compounds of a known agent, e.g., by means of an appropriate, conventional pharmacological protocol.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a schematic illustration of the experiment described in Example 1. The day of administration of human chorionic gonadotropin (hCG) was designated as day 0 of pseudopregnancy (d0). As shown in the diagram, ovarian stimulation of the animals occurred on -d3, -d2 and -d1 of pseudopregnancy induction and the progesterone receptor antagonist was administered on d2 of pseudopregnancy.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

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In the foregoing and in the following examples, all temperatures are set forth uncorrected in degrees Celsius; and, unless otherwise indicated, all parts and percentages are by weight.

The entire disclosure of all applications, patents and publications, cited above or below, are hereby incorporated by reference.

EXAMPLES

Example 1: Improvement of endometrial receptivity with low doses of a 17 α -fluoralkylated progesterone receptor antagonist in the superovulated rabbit model.

The effects of a 17 α -fluoralkylated progesterone receptor antagonist on endometrial activity was evaluated in the superovulated pseudopregnant rabbit model. The pseudopregnancy of the rabbit has proven to be a model system for the human luteal phase (Beier and Kuhnel, 1973, *Hormone Res.* 4:1-27; Fischer et al., 1985, *Fertilitat* 1:101-109. In this species, ovarian stimulation induces an advancement of secretory transformation (Delbos-Winter et al., 1987, *Fertilitat* 3: 87-93) as well as an enhancement of gland formation.

A total of 25 sexually mature multiparous New Zealand White rabbits with a body weight of 3.1 to 4.0 kg were used for the analysis. The animals were divided into two control groups (groups 1 and 2) and three treatment groups (groups 3-5), with five animals in each group.

Control group 1 received 75 international units (IU) of human chorionic gonadotropin (hCG) administered intravenously in order to induce pseudopregnancy. The day of hCG-injection was designated as day 0 of pseudopregnancy (d0 p.hCG).

Control group 2 and treatment groups 3, 4, and 5 were gonadotropin-stimulated with 5 IU of the human menopausal gonadotropin (HMG) Pergonal[®] (Serono Pharma, Unterschleißheim, Germany) for 3 days, by subcutaneous injection, in order to induce multiple follicular growth. Pseudopregnancy was induced by the administration of human chorionic gonadotropin (hCG) as described for control group 1 above.

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Treatment groups 3, 4 and 5 also received a single per oral application of a 17 α -fluoralkylated progesterone receptor antagonist (Compound A) two days after pseudopregnancy induction with the administration of human chorionic gonadotropin (d2 p.hCG). The detailed treatment schedule is shown in Figure 1.

Animals in all treatment groups were sacrificed on day 5 following pseudopregnancy induction (d5 p.hCG), and uteri were removed. Relative uterine wet weights were determined (in mg/100 g body weight) and a part of the uterus was snap frozen in liquid nitrogen for determination of uteroglobin expression by in situ hybridization. Uteroglobin expression is known as a highly sensitive parameter for determination of endometrial receptivity (Beier, H.M., 1968, *Biochem Biophys. Acta.* 160:289-291; Beier, H.M., 1982, in: Beier, H.M. and Karlson, P. (eds.), *Proteins and Steroids in Early Pregnancy*), and is a marker for secretory activity (Beier, 1976, *J. Reprod. Fertil. Suppl.* 25:53-69) and differentiation of the endometrial epithelium (Krusche & Beier, 1994, *Ann. Anat.* 176:23-31). In situ hybridization for detection of uteroglobin expression was conducted as previously described in Krusche & Beier, above. Another piece of the uterus was removed and processed for paraffin histology in order to determine the endometrial transformation status using the McPhail-Index (McPhail Mk, 1934, *J. Phys.* 83:145-156) The McPhail Index reflects different degrees of progestogenic (transforming) activity in the rabbit endometrium:

1. no transformation
2. low transformation
3. pronounced transformation
4. high transformation

The results are presented in Table 1 below.

Table 1

Effect of a single treatment of a 17 α -fluoralkylated progesterone receptor antagonist on uterus weight, endometrial transformation, and uteroglobin mRNA expression at five days after pseudopregnancy induction (d5 p.hCG) in the superovulated pseudopregnant rabbit.

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Group	Treatment Schedule			Measurement endpoints at d5 p. hCG		
	-d3, -d2, -d1 p.hCG	d0 p.hCG	d2 p.hCG			
	5 IU HMG	75 IU HCG	Progesterone receptor antagonist [mg/kg]	Uterine wet weight [mg/kg] [x ± SD]	Mc-Phail [x ± SD]	Uteroglobin ISH [expression in luminal epithelial cells]
1	-	+	-	324 ± 99	3.2 ± 0.2	very high expression
2	+	+	0	448 ± 80	3.9 ± 0.1	very low expression
3	+	+	0.1	305 ± 48	3.0 ± 0.1	very high expression
4	+	+	1	227 ± 56	1.5 ± 0.3	very low expression
5	+	+	10	144 ± 30	1.1 ± 0.3	absent

As shown in the table, animals which were subject to ovarian hyperstimulation, but which were not treated with an antigestagen (Group 2), showed advanced endometrial maturation as demonstrated by nearly undetectable uteroglobin expression in endometrial luminal epithelial cells, the weight of the uterus, and the relatively high Mc-Phail index score. However, animals which were subject to ovarian hyperstimulation and which were treated with an antigestagen, Groups 3-5, showed a delay in endometrial maturation, as demonstrated by the uterine wet weights and the Mc-Phail index scores. For animals which were treated with a low dose of progesterone receptor antagonist, 0.1 mg/kg (Group 3), endometrial maturation roughly corresponded with that of control animals which were not subject to ovarian hyperstimulation (Group 1). In contrast, higher doses of progesterone receptor antagonist, 1 mg/kg (group 4) and 10 mg/kg (group 5), apparently counteracted the advancement of endometrium maturation associated with ovarian hyperstimulation and also delayed the timing of maturation beyond that observed in animals which were not subject to hyperovarian stimulation (Group 1).

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The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

- 5 From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

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What is claimed is:

1. A method of inhibiting the occurrence of advanced endometrium maturation in a human female subject undergoing fertility enhancing treatment comprising

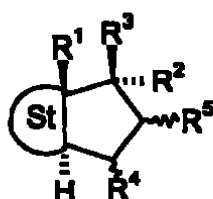
administering at least one 17 α -fluoralkylated progesterone receptor antagonist to the female subject during the post-ovulatory phase of the endometrial cycle.

2. A method according to claim 1, wherein the 17 α -fluoralkylated progesterone receptor antagonist is administered to the subject in a daily dosage amount of 0.1-2 mg per subject.

3. A method according to claim 2, wherein the fertility treatment comprises the administration to the subject of a follicle stimulating agent comprising follicle stimulating hormone.

4. A method according to claim 2, wherein the 17 α -fluoralkylated progesterone receptor antagonist is administered in an amount of 0.1-2 mg per subject on a single day during the post-ovulatory phase of the endometrial cycle.

5. A method according to claim 2, wherein the 17 α -fluoralkylated progesterone receptor antagonist is a compound of formula I:



I

wherein

R¹ is methyl or ethyl,

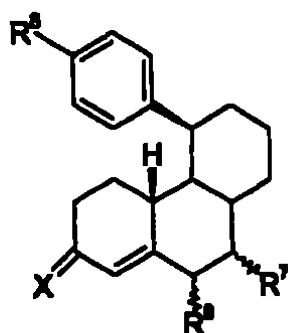
R² is C_nF_mH_{n-m}, wherein n is 1-6, preferably 2, 3, 4, 5 or 6, m > 1 and

$$m+o = 2n+1,$$

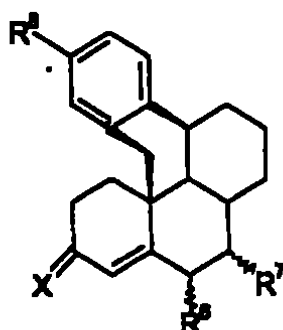
R^3 is a free, etherified or esterified hydroxy group,

R^4 and R^5 each is a hydrogen, or together form an additional bond or a methylene group,

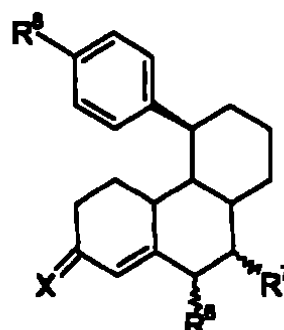
St is a steroidal ABC-ring system of partial formula A, B or C



A



B



C

wherein

R^6 is hydrogen, a straight-chain C_1-C_4 alkyl group or branched C_3-C_4 alkyl group or halogen,

R^7 is hydrogen, a straight-chain C_1-C_4 alkyl group or a branched C_3-C_4 alkyl group, or

if St is a steroidal ABC-ring system A or B, in addition

R^6 and R^7 together can form an additional bond,

X is oxygen, hydroxyimino ($=N-OH$) or two hydrogen atoms,

R^8 is Y or aryl that is optionally substituted in several places with a group Y, other than H,

Y is hydrogen, halogen, $-OH$, $-NO_2$, $-N_3$, $-CN$, $-NR^{9a}R^{9b}$, $-NHSO_2R^9$, $-CO_2R^9$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_1-C_{10} alkanoyloxy, benzoyloxy, C_1-C_{10} alkanoyl, C_1-C_{10} hydroxyalkyl or benzoyl,

R^{9a} and R^{9b} are the same or different and each is hydrogen or C_1-C_{10} alkyl,

R^9 is hydrogen or C_1-C_{10} alkyl,

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and for $-NR^aR^b$ radicals, as well as their physiologically compatible salts with acids and for $-CO_2R^c$ radicals with R^c being hydrogen, as well as their physiologically compatible salts with bases.

6. A method according to claim 4, wherein the 17α -fluoralkylated progesterone receptor antagonist is administered orally to the subject.

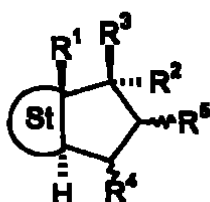
7. A method of achieving pregnancy in a human female subject comprising stimulating the ovaries of the subject by administering a follicle stimulating agent to the subject, wherein the agent comprises follicle stimulating hormone; removing eggs from the ovary of the stimulated subject; administering at least one 17α -fluoralkylated progesterone receptor antagonist to the subject in the post-ovulatory phase of the endometrial cycle; fertilizing at least one egg in vitro to obtain an embryo; transferring the embryo into the uterus or fallopian tubes of the mammal.

8. A method according to claim 7, wherein the 17α -fluoralkylated progesterone receptor antagonist is administered to the subject in a daily dosage amount of 0.1-10 mg per subject

9. A method according to claim 8, wherein the 17α -fluoralkylated progesterone receptor antagonist is administered in an amount of 0.1-2 mg per subject on a single day during the post-ovulatory phase of the endometrial cycle.

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10. A method according to claim 8, wherein the 17 α -fluoroalkylated progesterone receptor antagonist is a compound of formula I:



I

wherein

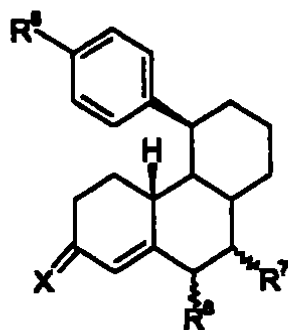
R¹ is methyl or ethyl,

R² is C_nF_mH_o, wherein n is 1-6, preferably 2, 3, 4, 5 or 6, m > 1 and m+o = 2n+1,

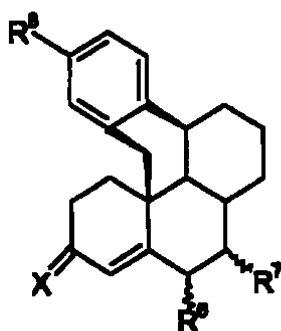
R³ is a free, etherified or esterified hydroxy group,

R⁴ and R⁵ each is a hydrogen, or together form an additional bond or a methylene group,

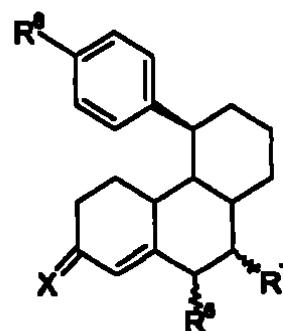
St is a steroidal ABC-ring system of partial formula A, B or C



A



B



C

wherein

R⁶ is hydrogen, a straight-chain C₁-C₄ alkyl group or branched C₃-C₄ alkyl group or halogen,

R⁷ is hydrogen, a straight-chain C₁-C₄ alkyl group or a branched C₃-C₄ alkyl group, or

if St is a steroidal ABC-ring system A or B, in addition

R⁶ and R⁷ together can form an additional bond,

R⁹ is Y or aryl that is optionally substituted in several places with a group Y, other than H.

R^a and R^b are the same or different and each is hydrogen or C₁-C₁₀ alkyl,

and for $\text{-NR}^a\text{R}^b$ radicals, as well as their physiologically compatible salts

with acids and for $-\text{CO}_2\text{R}^9$ radicals with R^9 being hydrogen, as well as their physiologically compatible salts with bases.

11. A method according to claim 9, wherein the 17 α -fluoralkylated progesterone receptor antagonist is administered orally to the subject.

12. A method of inhibiting the occurrence of advanced endometrium maturation in a non-human female mammal undergoing fertility enhancement treatment to achieve pregnancy comprising

administering at least one 17 α -fluoralkylated progesterone receptor antagonist to the mammal during the post-ovulatory phase of the endometrial cycle.

13. A method according to claim 12, wherein the 17 α -fluoralkylated progesterone receptor antagonist is administered to the mammal in a daily dosage amount of 0.01-1 mg/kg.

14. A method according to claim 13, wherein the fertility treatment comprises the administration to the mammal of a follicle stimulating agent comprising follicle stimulating hormone.

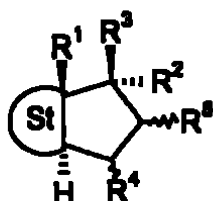
15. A method according to claim 13, wherein the 17 α -fluoralkylated progesterone receptor antagonist is administered to the mammal in an amount of

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0.1-1 mg/kg on a single day during the post-ovulatory phase of the endometrial cycle.

16. A method according to claim 13, wherein the 17α -fluoralkylated progesterone receptor antagonist is a compound of formula I:



I

wherein

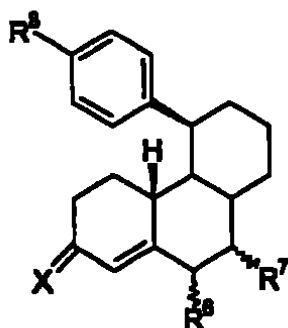
R^1 is methyl or ethyl,

R^2 is $C_nF_mH_o$, wherein n is 1-6, preferably 2, 3, 4, 5 or 6, $m > 1$ and $m+o = 2n+1$,

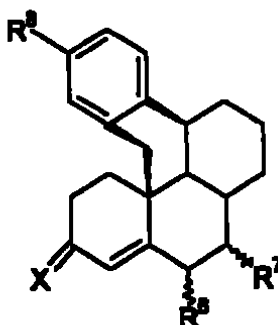
R^3 is a free, etherified or esterified hydroxy group,

R^4 and R^5 each is a hydrogen, or together form an additional bond or a methylene group,

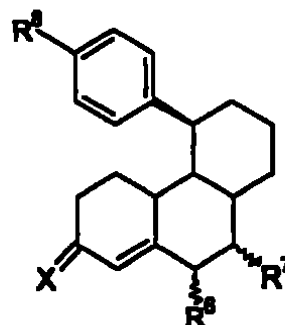
St is a steroidal ABC-ring system of partial formula A, B or C



A



B



C

wherein

R^6 is hydrogen, a straight-chain C_1 - C_4 alkyl group or branched C_3 - C_4 alkyl group or halogen,

R⁷ is hydrogen, a straight-chain C₁-C₄ alkyl group or a branched C₃-C₄ alkyl group, or

if St is a steroidal ABC-ring system A or B, in addition

R⁶ and **R⁷** together can form an additional bond,

X is oxygen, hydroxyimino (=N-OH) or two hydrogen atoms,

R⁸ is Y or aryl that is optionally substituted in several places with a group Y, other than H,

Y is hydrogen, halogen, -OH, -NO₂, -N₃, -CN, -NR^aR^b, -NHSO₂R⁹, -CO₂R⁹, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkanoyloxy, benzoyloxy, C₁-C₁₀ alkanoyl, C₁-C₁₀ hydroxyalkyl or benzoyl,

R^a and **R^b** are the same or different and each is hydrogen or C₁-C₁₀ alkyl,

R⁹ is hydrogen or C₁-C₁₀ alkyl,

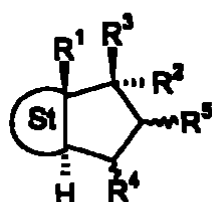
and for -NR^aR^b radicals, as well as their physiologically compatible salts with acids and for -CO₂R⁹ radicals with R⁹ being hydrogen, as well as their physiologically compatible salts with bases.

17. A method of achieving pregnancy in a non-human mammal comprising stimulating the ovaries of the mammal by administering a follicle stimulating agent to the mammal, wherein the agent comprises follicle stimulating hormone; removing eggs from the ovary of the stimulated mammal; administering at least one 17 α -fluoralkylated progesterone receptor antagonist to the mammal in the post-ovulatory phase of the endometrial cycle; fertilizing at least one egg in vitro to obtain an embryo; transferring the embryo into the uterus or fallopian tubes of the mammal.

18. A method according to claim 17, wherein the 17 α -fluoralkylated progesterone receptor antagonist is administered to the mammal in a daily dosage amount of 0.01-1 mg/kg.

19. A method according to claim 18, wherein the 17 α -fluoralkylated progesterone receptor antagonist is administered to the mammal in an amount 0.1-1 mg/kg on a single day during the post-ovulatory phase of the endometrial cycle.

20. A method according to claim 18, wherein the 17 α -fluoralkylated progesterone receptor antagonist is a compound of formula I:



I

wherein

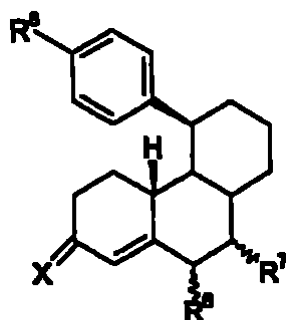
R¹ is methyl or ethyl,

R² is C_nF_mH_o, wherein n is 1-6, preferably 2, 3, 4, 5 or 6, m > 1 and m+o = 2n+1,

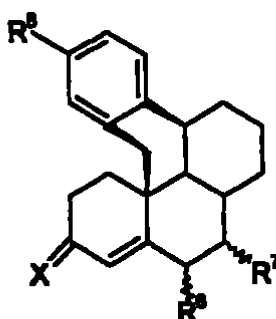
R³ is a free, etherified or esterified hydroxy group,

R⁴ and R⁵ each is a hydrogen, or together form an additional bond or a methylene group,

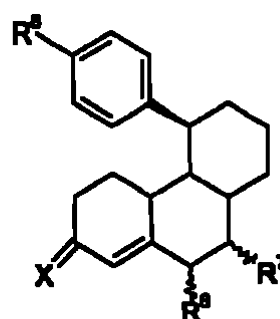
St is a steroidal ABC-ring system of partial formula A, B or C



A



B



C

wherein

R⁶ is hydrogen, a straight-chain C₁-C₄ alkyl group or branched C₃-C₄ alkyl group or halogen,

התאחדות המורים

R³ is Y or aryl that is optionally substituted in several places with a group Y, other than H,

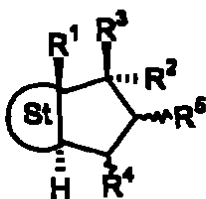
R⁹ is hydrogen or C₁-C₁₀ alkyl,

21. A non-human mammal which results from a pregnancy achieved by a process according to claim 13.

22. A non-human mammal which results from a pregnancy achieved by a process according to claim 18.

23. A method of inhibiting the occurrence of advanced endometrium maturation in a human female subject undergoing fertility enhancing treatment comprising

administering at least one compound of formula I to the subject, wherein
formula I is



1

wherein

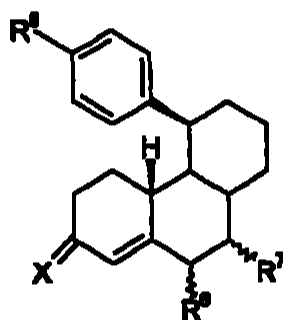
R^1 is methyl or ethyl,

R^2 is $C_nF_mH_o$, wherein n is 1-6, preferably 2, 3, 4, 5 or 6, $m > 1$ and $m+o = 2n+1$,

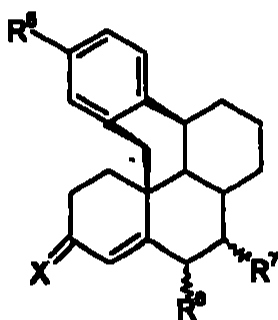
R^3 is a free, etherified or esterified hydroxy group,

R^4 and R^5 each is a hydrogen, or together form an additional bond or a methylene group,

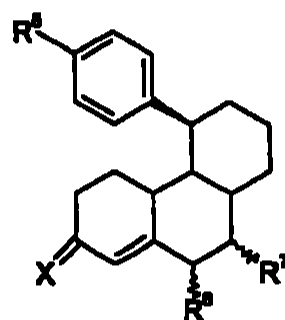
St is a steroidal ABC-ring system of partial formula A, B or C



A



B



C

wherein

R^6 is hydrogen, a straight-chain C_1-C_4 alkyl group or branched C_3-C_4 alkyl group or halogen,

R^7 is hydrogen, a straight-chain C_1-C_4 alkyl group or a branched C_3-C_4 alkyl group, or

if St is a steroidal ABC-ring system A or B, in addition

R^6 and R^7 together can form an additional bond,

X is oxygen, hydroxyimino ($=N-OH$) or two hydrogen atoms,

R^8 is Y or aryl that is optionally substituted in several places with a group Y, other than H,

Y is hydrogen, halogen, $-OH$, $-NO_2$, $-N_3$, $-CN$, $-NR^{9a}R^{9b}$, $-NHSO_2R^9$, $-CO_2R^9$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_1-C_{10} alkanoyloxy, benzoyloxy, C_1-C_{10} alkanoyl, C_1-C_{10} hydroxyalkyl or benzoyl,

R^{9a} and R^{9b} are the same or different and each is hydrogen or C_1-C_{10} alkyl,

R^9 is hydrogen or C_1-C_{10} alkyl,

and for $-NR^9R^{10}$ radicals, as well as their physiologically compatible salts with acids and for $-CO_2R^9$ radicals with R^9 being hydrogen, as well as their physiologically compatible salts with bases.

24. A method of achieving pregnancy in a human female subject comprising

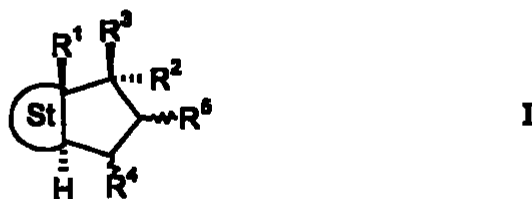
stimulating the ovaries of the subject by administering a follicle stimulating agent to the subject, wherein the agent comprises follicle stimulating hormone;

removing eggs from the ovary of the stimulated subject;

administering at least one compound of formula I to the subject in the post-ovulatory phase of the endometrial cycle;

fertilizing at least one egg in vitro to obtain an embryo;

transferring the embryo into the uterus or fallopian tubes of the mammal, wherein formula I is



wherein

R^1 is methyl or ethyl,

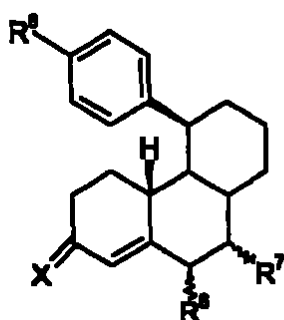
R^2 is $C_nF_mH_o$, wherein n is 1-6, preferably 2, 3, 4, 5 or 6, $m > 1$ and $m+o = 2n+1$,

R^3 is a free, etherified or esterified hydroxy group,

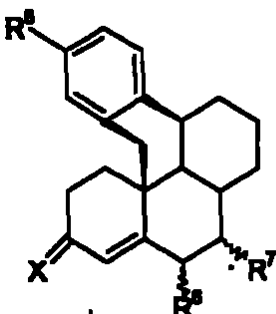
R^4 and R^5 each is a hydrogen, or together form an additional bond or a methylene group,

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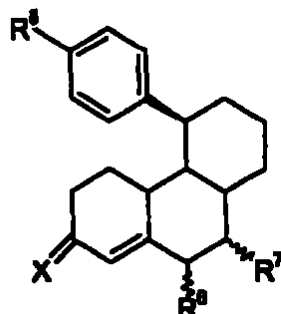
St is a steroidal ABC-ring system of partial formula A, B or C



A



B



C

wherein

R^6 is hydrogen, a straight-chain C_1-C_4 alkyl group or branched C_3-C_4 alkyl group or halogen,

R^7 is hydrogen, a straight-chain C_1-C_4 alkyl group or a branched C_3-C_4 alkyl group, or

if St is a steroidal ABC-ring system A or B, in addition

R^6 and R^7 together can form an additional bond,

X is oxygen, hydroxyimino ($=N-OH$) or two hydrogen atoms,

R^8 is Y or aryl that is optionally substituted in several places with a group Y, other than H,

Y is hydrogen, halogen, $-OH$, $-NO_2$, $-N_3$, $-CN$, $-NR^{2a}R^{2b}$, $-NHSO_2R^9$, $-CO_2R^9$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_1-C_{10} alkanoyloxy, benzoyloxy, C_1-C_{10} alkanoyl, C_1-C_{10} hydroxyalkyl or benzoyl,

R^{2a} and R^{2b} are the same or different and each is hydrogen or C_1-C_{10} alkyl,

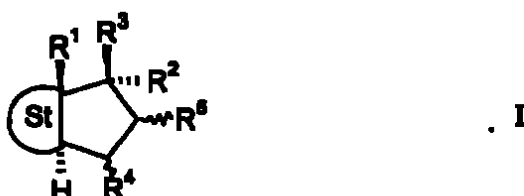
R^9 is hydrogen or C_1-C_{10} alkyl,

and for $-NR^{2a}R^{2b}$ radicals, as well as their physiologically compatible salts with acids and for $-CO_2R^9$ radicals with R^9 being hydrogen, as well as their physiologically compatible salts with bases.

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25. A method of inhibiting the occurrence of advanced endometrium maturation in a non-human female mammal undergoing fertility enhancement treatment to achieve pregnancy comprising

administering at least one compound according to formula I to the mammal, wherein formula I is



wherein

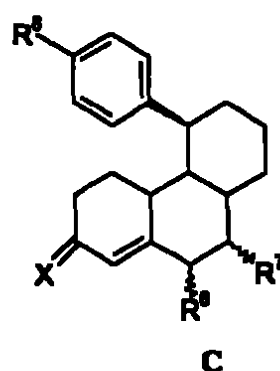
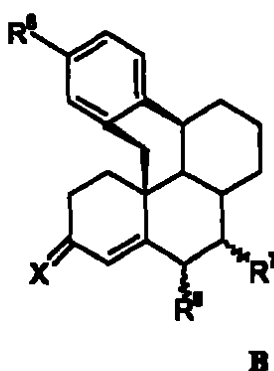
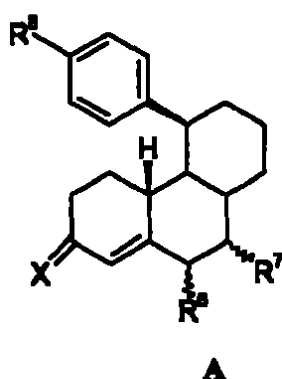
R^1 is methyl or ethyl,

R^2 is $C_nF_mH_o$, wherein n is 1-6, preferably 2, 3, 4, 5 or 6, $m > 1$ and $m+o = 2n+1$,

R^3 is a free, etherified or esterified hydroxy group,

R^4 and R^5 each is a hydrogen, or together form an additional bond or a methylene group,

St is a steroidal ABC-ring system of partial formula A, B or C



00000195-020001

R' is hydrogen, a straight-chain C₁-C₄ alkyl group or a branched C₁-C₄

if St is a steroidal ABC-ring system A or B, in addition

X is oxygen, hydroxyimino (=N-OH) or two hydrogen atoms,

Y is hydrogen, halogen, -OH, -NO₂, -N₃, -CN, -NR^aR^b, -NHSO₂R⁹, -

CO₂R⁹, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkanoyloxy, benzoyloxy, C₁-C₁₀

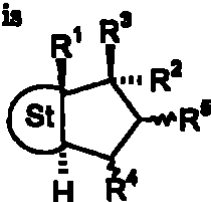
alkanoyl, C₁-C₁₀ hydroxyalkyl or benzoyl,

R^a and R^b are the same or different and each is hydrogen or C₁-C₁₀ alkyl,

R⁹ is hydrogen or C₁-C₁₀ alkyl,

and for $-NR^aR^b$ radicals, as well as their physiologically compatible salts with acids and for $-CO_2R^c$ radicals with R^c being hydrogen, as well as their physiologically compatible salts with bases.

26. A method of achieving pregnancy in a non-human mammal comprising stimulating the ovaries of the mammal by administering a follicle stimulating agent to the mammal, wherein the agent comprises follicle stimulating hormone; removing eggs from the ovary of the stimulated mammal; administering at least one compound of formula I to the mammal in the post-ovulatory phase of the endometrial cycle; fertilizing at least one egg in vitro to obtain an embryo; transferring the embryo into the uterus or fallopian tubes of the mammal, wherein formula I is



I

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210

wherein

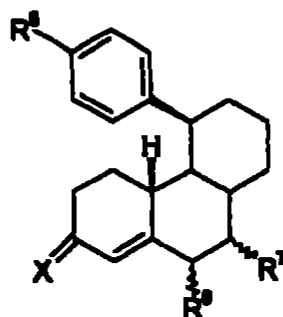
R^1 is methyl or ethyl,

R^2 is $C_nF_mH_o$, wherein n is 1-6, preferably 2, 3, 4, 5 or 6, $m > 1$ and $m+o = 2n+1$,

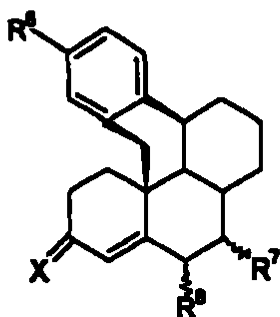
R^3 is a free, etherified or esterified hydroxy group,

R^4 and R^5 each is a hydrogen, or together form an additional bond or a methylene group,

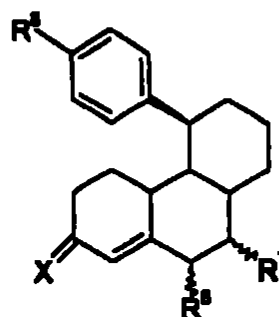
St is a steroidal ABC-ring system of partial formula A, B or C



A



B



C

wherein

R^6 is hydrogen, a straight-chain C_1-C_4 alkyl group or branched C_3-C_4 alkyl group or halogen,

R^7 is hydrogen, a straight-chain C_1-C_4 alkyl group or a branched C_3-C_4 alkyl group, or

if St is a steroidal ABC-ring system A or B, in addition

R^6 and R^7 together can form an additional bond,

X is oxygen, hydroxyimino ($=N-OH$) or two hydrogen atoms,

R^8 is Y or aryl that is optionally substituted in several places with a group Y, other than H,

Y is hydrogen, halogen, $-OH$, $-NO_2$, $-N_3$, $-CN$, $-NR^{9a}R^{9b}$, $-NHSO_2R^9$, $-CO_2R^9$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_1-C_{10} alkanoyloxy, benzoyloxy, C_1-C_{10} alkanoyl, C_1-C_{10} hydroxyalkyl or benzoyl,

R^{9a} and R^{9b} are the same or different and each is hydrogen or C_1-C_{10} alkyl,

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R^9 is hydrogen or C_1-C_{10} alkyl,
and for $-NR^{9a}R^{9b}$ radicals, as well as their physiologically compatible salts
with acids and for $-CO_2R^9$ radicals with R^9 being hydrogen, as well as their
physiologically compatible salts with bases.

27. A method of inhibiting the occurrence of advanced endometrium
maturation in a human female subject undergoing fertility enhancing treatment
comprising

administering at least one 17α -fluoralkylated progesterone receptor
antagonist to the female subject during the post-ovulatory phase of the endometrial
cycle.

28. A method of inhibiting the occurrence of advanced endometrium
maturation in a human female subject undergoing fertility enhancing treatment
comprising

administering at least one 17α -fluoralkylated progesterone receptor
antagonist to the female subject during the post-ovulatory phase of the endometrial
cycle after said fertility enhancing treatment.

29. A method of inhibiting the occurrence of advanced endometrium
maturation in a non-human female mammal undergoing fertility enhancement
treatment to achieve pregnancy comprising

administering at least one 17α -fluoralkylated progesterone receptor
antagonist to the mammal during the post-ovulatory phase of the endometrial cycle
after said fertility enhancing treatment.

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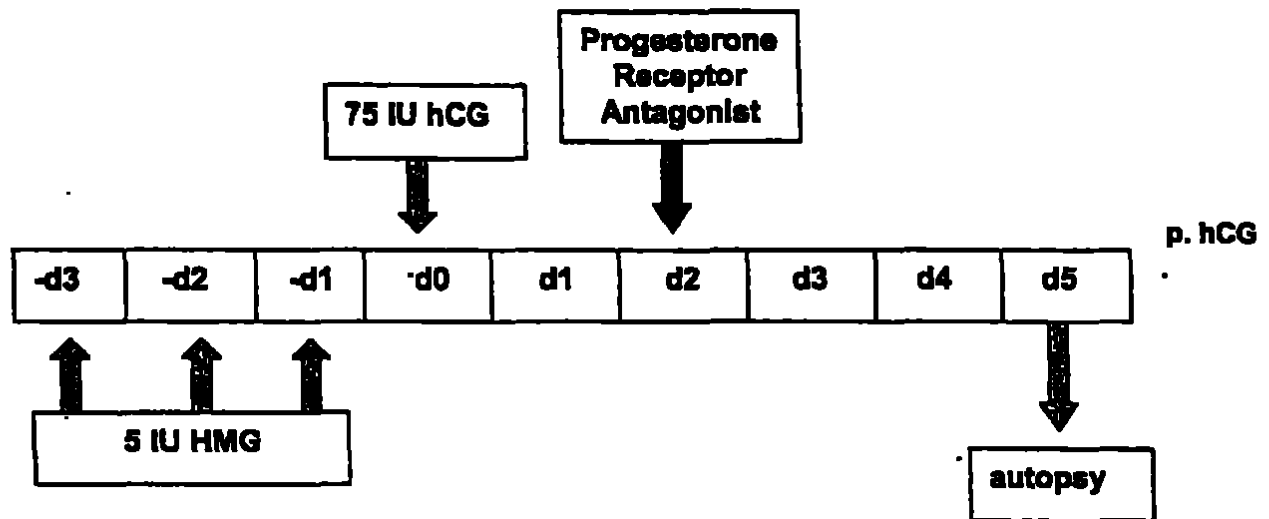
ABSTRACT OF THE DISCLOSURE

A method of inhibiting the occurrence of advanced endometrium maturation in a female mammal undergoing fertility treatment is disclosed. The method comprises the administration at least one 17 α -fluoralkylated progesterone receptor antagonist to the female mammal.

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106020-52610880

Figure 1: General study design in superovulated rabbits



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LOS ESTADOS UNIDOS DE AMERICA

A TODOS CUANTOS LAS PRESENTES VIEREN:

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS
Oficina de Patentes y Marcas de los Estados Unidos

Febrero 01 del 2002

SE CERTIFICA QUE ADJUNTO SE ENCUENTRA UNA COPIA FIEL Y EXACTA DE LOS REGISTROS EXISTENTES EN LA OFICINA DE PATENTES Y MARCAS DE LOS ESTADOS UNIDOS RESPECTO A LOS DOCUMENTOS DE LA SOLICITUD DE PATENTE IDENTIFICADA ABAJO LA CUAL CUMPLIO LOS REQUISITOS PARA QUE SE LE OTORGARA UNA FECHA DE PRESENTACION DE CONFORMIDAD CON 35 USC 111.

NUMERO DE SOLICITUD: 09/801,925

FECHA DE PRESENTACION: Marzo 09 del 2001

Por Autoridad del
COMISIONADO DE PATENTES Y MARCAS
T. LAWRENCE, Funcionario de Certificaciones
(Firma y Sello Oficial)

REIVINDICACIONES

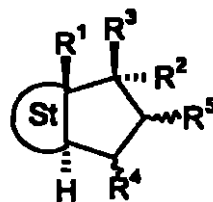
1. Un método para inhibir la ocurrencia de la maduración endometrial adelantada en un sujeto hembra humano que está bajo tratamiento para mejorar la fertilidad, que comprende administrar por lo menos un antagonista del receptor de la progesterona 17α -fluoroalquilado al sujeto hembra durante la fase pos-ovulatoria del ciclo endometrial.

2. Un método de acuerdo con la reivindicación 1, donde el receptor de progesterona 17α -fluoroalquilado se administra al sujeto en una dosis diaria de 0,1-2 mg por sujeto.

3. Un método de acuerdo con la reivindicación 2, donde el tratamiento de fertilización comprende la administración al sujeto de un agente estimulante folicular que comprende hormona estimulante folicular.

4. Un método de acuerdo con la reivindicación 2, donde el antagonista del receptor de la progesterona 17α -fluoroalquilado se administra en una cantidad de 0,1-2 mg por sujeto en un único día durante la fase pos-ovulatoria del ciclo endometrial.

5. Un método de acuerdo con la reivindicación 2, donde el antagonista del receptor de la progesterona 17α -fluoroalquilado es un compuesto de la fórmula I:



donde:

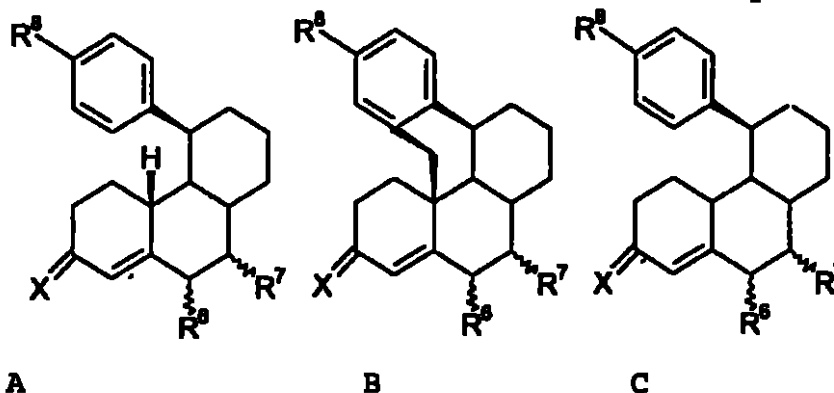
R^1 es metilo o etilo,

R^2 es $C_nF_mH_o$, donde n es 1-6, preferentemente 2, 3, 4, 5 o 6, $m > 1$ y $m+o = 2n+1$.

R_3 es un grupo hidroxilo libre, eterificado o esterificado,

cada uno de R^4 y R^5 es un hidrógeno, o juntos forman una ligadura adicional o un grupo metileno

St es un anillo esteroidal ABC de fórmula parcial A, B o C



donde:

R^6 es hidrógeno, un grupo C_1-C_4 alquilo de cadena lineal o C_3-C_4 alquilo de cadena ramificada o halógeno

R^7 es hidrógeno, un grupo C_1-C_4 alquilo de cadena lineal o C_3-C_4 alquilo de cadena ramificada, o

si St es un sistema de anillo ABC esteroidal, además

R⁶ y R⁷ juntos pueden formar una ligadura adicional,
X es oxígeno, hidroximinio (=N-OH) o dos átomos de hidrógeno,

R⁸ es Y o arilo optativamente sustituido en múltiples sitios con un grupo Y distinto de H,

Y es hidrógeno, halógeno, -OH, -NO₂, -N₃, -CN, -NR^{9a}R^{9b}, -NH₂SO₂R⁹, CO₂R⁹, C₁-C₁₀ alquilo, C₁-C₁₀ alcoxi, C₁-C₁₀ alcanoiloxi, benzoiloxi, C₁-C₁₀ alcanoil, C₁-C₁₀ hidroxialquilo o benzoilo,

R^{9a} y R^{9b} son iguales o diferentes, y cada uno de ellos es hidrógeno o C₁-C₁₀ alquilo,

R⁹ es hidrógeno o C₁-C₁₀ alquilo,

y para los radicales-NR^{9a}R^{9b}, así como para sus sales compatibles desde el punto de vista fisiológico con ácidos y para los radicales-CO₂R⁹, donde R⁹ es hidrógeno, así como sus sales compatibles desde el punto de vista fisiológico con bases.

6.Un método de acuerdo con la reivindicación 4, donde el antagonista del receptor de la progesterona 17 α -fluoroalquilado se administra al sujeto por vía oral.

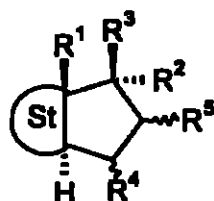
7.Un método para lograr la preñez en un sujeto hembra humano que comprende la estimulación de los ovarios del sujeto mediante la administración al sujeto de un agente estimulante folicular, donde el agente comprende hormona estimulante folicular; retirar los huevos del ovario del sujeto esti-

mulado; administrar al sujeto por lo menos un antagonista del receptor de la progesterona 17 α -fluoroalquilado en la fase pos-ovulatoria del ciclo endometrial; fertilizar por lo menos un huevo *in vitro* para obtener un embrión; y transferir el embrión al útero o a las trompas de Falopio del mamífero.

8.Un método de acuerdo con la reivindicación 7, donde el antagonista del receptor de la progesterona 17 α -fluoroalquilado se administra al sujeto en una dosis diaria de 0,1-10 mg por sujeto.

9.Un método de acuerdo con la reivindicación 8, donde el antagonista del receptor de la progesterona 17 α -fluoroalquilado se administra en una cantidad de 0,1-2 mg por sujeto en un día único durante la fase pos-ovulatoria del ciclo endometrial.

10.Un método de acuerdo con la reivindicación 8, donde el antagonista del receptor de la progesterona 17 α -fluoroalquilado es un compuesto de la fórmula I:



donde:

R¹ es metilo o etilo,

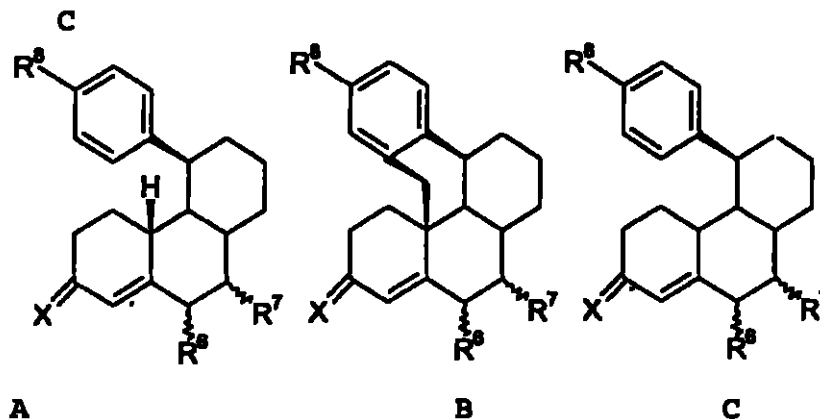
R² es C_nF_mH_o, donde n es 1-6, preferentemente 2, 3, 4, 5 o 6, m > 1 y m+o = 2n+1.

R₃ es un grupo hidroxilo libre, eterificado o esterifi-

cado,

R^4 y R^5 cada uno es un hidrógeno, o juntos forman una ligadura adicional o un grupo metileno

St es un anillo esteroidal ABC de fórmula parcial A, B o



donde:

R^6 es hidrógeno, un grupo C_1-C_4 alquilo de cadena lineal o C_3-C_4 alquilo de cadena ramificada o halógeno

R^7 es hidrógeno, un grupo C_1-C_4 alquilo de cadena lineal o C_3-C_4 alquilo de cadena ramificada, o

si St es un sistema de anillo ABC esteroidal, además

R^6 y R^7 juntos pueden formar una ligadura adicional,

X es oxígeno, hidroximinio ($=N-OH$) o dos átomos de hidrógeno,

R^8 es Y o arilo optativamente sustituido en múltiples sitios con un grupo Y distinto de H,

Y es hidrógeno, halógeno, $-OH$, $-NO_2$, $-N_3$, $-CN$, $-NR^{9a}R^{9b}$, $-NHSO_2R^9$, CO_2R^9 , C_1-C_{10} alquilo, C_1-C_{10} alcoxi, C_1-C_{10} alcanoiloxi, benzoiloxi, C_1-C_{10} alcanoil, C_1-C_{10} hidro-

xialquilo o benzoilo,

R^{9a} y R^{9b} son iguales o diferentes, y cada uno de ellos es hidrógeno o C_1-C_{10} alquilo,

R^9 es hidrógeno o C_1-C_{10} alquilo,

y para los radicales- $NR^{9a}R^{9b}$, así como para sus sales compatibles desde el punto de vista fisiológico con ácidos y para los radicales- CO_2R^9 , donde R^9 es hidrógeno, así como sus sales compatibles desde el punto de vista fisiológico con bases.

11. Un método de acuerdo con la reivindicación 9, donde el antagonista del receptor de la progesterona 17α -fluoroalquilado se administra al sujeto por vía oral.

12. Un método para inhibir la ocurrencia de la maduración endometrial adelantada en un mamífero hembra no humano que se encuentra bajo tratamiento para mejorar la fertilidad para lograr la preñez, que comprende administrar al mamífero por lo menos un antagonista del receptor de la progesterona 17α -fluoroalquilado durante la fase pos-ovulatoria del ciclo endometrial.

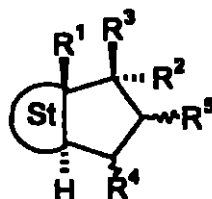
13. Un método de acuerdo con la reivindicación 12, donde el antagonista del receptor de la progesterona 17α -fluoroalquilado se administra al mamífero en una dosis diaria de 0,01-1 mg/kg.

14. Un método de acuerdo con la reivindicación 13, donde el tratamiento de fertilización comprende la administración al mamífero de un agente estimulante folicular que com-

prende hormona estimulante folicular.

15.Un método de acuerdo con la reivindicación 13, donde el antagonista del receptor de la progesterona 17 α -fluoroalquilado se administra al mamífero en una cantidad de 0,1-1 mg/kg en un día único durante la fase pos-ovulatoria del ciclo endometrial.

16.Un método de acuerdo con la reivindicación 13, donde el antagonista del receptor de la progesterona 17 α -fluoroalquilado es un compuesto de la fórmula I:



donde:

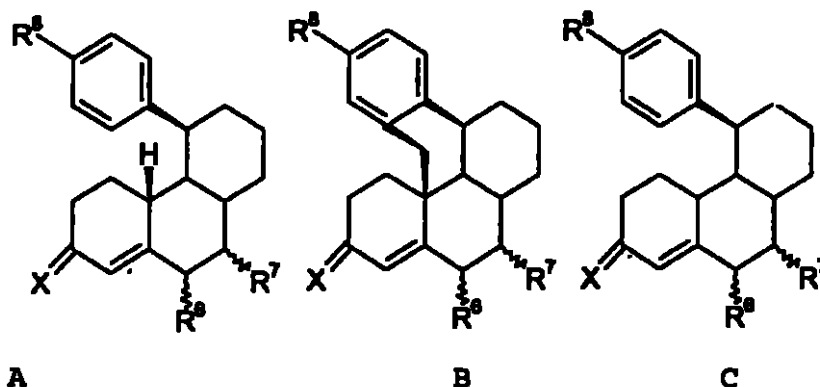
R¹ es metilo o etilo,

R² es C_nF_mH_o, donde n es 1-6, preferentemente 2, 3, 4, 5 o 6, m > 1 y m+o = 2n+1.

R₃ es un grupo hidroxilo libre, eterificado o esterificado,

R⁴ y R⁵ cada uno es un hidrógeno, o juntos forman una ligadura adicional o un grupo metileno

St es un anillo esteroidal ABC de fórmula parcial A, B o C



donde:

R^6 es hidrógeno, un grupo C_1-C_4 alquilo de cadena lineal o C_3-C_4 alquilo de cadena ramificada o halógeno

R^7 es hidrógeno, un grupo C_1-C_4 alquilo de cadena lineal o C_3-C_4 alquilo de cadena ramificada, o

si St es un sistema de anillo ABC esteroideal, además

R^6 y R^7 juntos pueden formar una ligadura adicional,

X es oxígeno, hidroximiino ($=N-OH$) o dos átomos de hidrógeno,

R^8 es Y o arilo optativamente sustituido en múltiples sitios con un grupo Y distinto de H,

Y es hidrógeno, halógeno, $-OH$, $-NO_2$, $-N_3$, $-CN$, $-NR^{9a}R^{9b}$, $-NHSO_2R^9$, CO_2R^9 , C_1-C_{10} alquilo, C_1-C_{10} alcoxi, C_1-C_{10} alcanoiloxi, benzoiloxi, C_1-C_{10} alcanoil, C_1-C_{10} hidroxialquilo o benzoilo,

R^{9a} y R^{9b} son iguales o diferentes, y cada uno de ellos es hidrógeno o C_1-C_{10} alquilo,

R^9 es hidrógeno o C_1-C_{10} alquilo,

y para los radicales $-NR^{9a}R^{9b}$, así como para sus sales compa-

tibles desde el punto de vista fisiológico con ácidos y para los radicales- CO_2R^9 , donde R^9 es hidrógeno, así como sus sales compatibles desde el punto de vista fisiológico con bases.

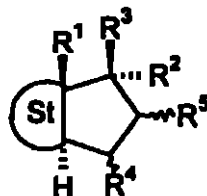
17. Un método para lograr la preñez en un mamífero no humano que comprende estimular los ovarios del mamífero mediante la administración al sujeto de un agente estimulante folicular, donde el agente comprende hormona estimulante folicular; retirar los huevos del ovario del mamífero estimulado; administrar al mamífero por lo menos un antagonista del receptor de la progesterona 17α -fluoroalquilado en la fase pos-ovulatoria del ciclo endometrial; fertilizar por lo menos un huevo in vitro para obtener un embrión; y transferir el embrión al útero o a las trompas de Falopio del mamífero.

18. Un método de acuerdo con la reivindicación 17, donde el antagonista del receptor de la progesterona 17α -fluoroalquilado se administra al mamífero en una dosis diaria de 0,01-1 mg/kg.

19. Un método de acuerdo con la reivindicación 18, donde el antagonista del receptor de la progesterona 17α -fluoroalquilado se administra al mamífero en una cantidad de 0,1-1 mg/kg en un día único durante la fase pos-ovulatoria del ciclo endometrial.

20. Un método de acuerdo con la reivindicación 18, donde el antagonista del receptor de la progesterona 17α -

fluoroalquilado es un compuesto de la fórmula I:



donde:

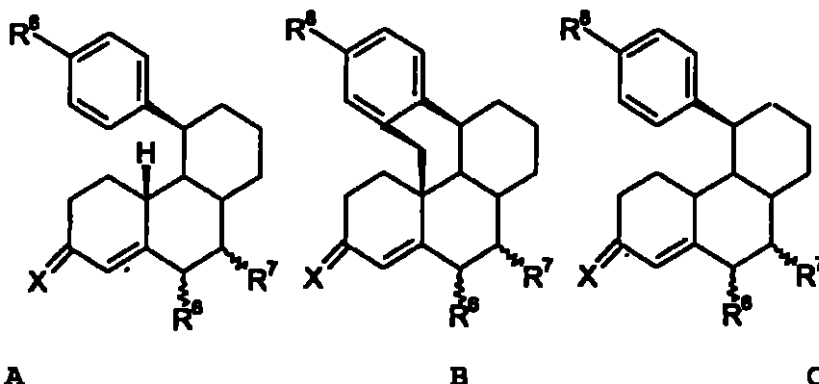
R^1 es metilo o etilo,

R^2 es $C_nF_mH_o$, donde n es 1-6, preferentemente 2, 3, 4, 5 ó 6, $m > 1$ y $m+o = 2n+1$.

R_3 es un grupo hidroxilo libre, eterificado o esterificado,

R^4 y R^5 cada uno es un hidrógeno, o juntos forman una ligadura adicional o un grupo metileno

St es un anillo esteroidal ABC de fórmula parcial A, B o C



donde:

R^6 es hidrógeno, un grupo C_1-C_4 alquilo de cadena lineal o C_3-C_4 alquilo de cadena ramificada o halógeno

R^7 es hidrógeno, un grupo C_1-C_4 alquilo de cadena lineal

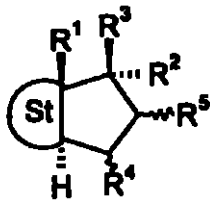
o C₃-C₄ alquilo de cadena ramificada, o
 si St es un sistema de anillo ABC esteroideal, además
 R⁶ y R⁷ juntos pueden formar una ligadura adicional,
 X es oxígeno, hidroximinio (=N-OH) o dos átomos de hidrógeno,
 R⁸ es Y o arilo optativamente sustituido en múltiples sitios con un grupo Y distinto de H,
 Y es hidrógeno, halógeno, -OH, -NO₂, -N₃, -CN, -NR^{9a}R^{9b}, -NHSO₂R⁹, CO₂R⁹, C₁-C₁₀ alquilo, C₁-C₁₀ alcoxi, C₁-C₁₀ alcanoiloxi, benzoiloxi, C₁-C₁₀ alcanoil, C₁-C₁₀ hidroxialquilo o benzoilo,
 R^{9a} y R^{9b} son iguales o diferentes, y cada uno de ellos es hidrógeno o C₁-C₁₀ alquilo,
 R⁹ es hidrógeno o C₁-C₁₀ alquilo,
 y para los radicales-NR^{9a}R^{9b}, así como para sus sales compatibles desde el punto de vista fisiológico con ácidos y para los radicales-CO₂R⁹, donde R⁹ es hidrógeno, así como sus sales compatibles desde el punto de vista fisiológico con bases.

21. Un mamífero no humano que resulta de la preñez obtenida mediante el proceso de acuerdo con la reivindicación 13.

22. Un mamífero no humano que resulta de la preñez obtenida mediante el proceso de acuerdo con la reivindicación 18.

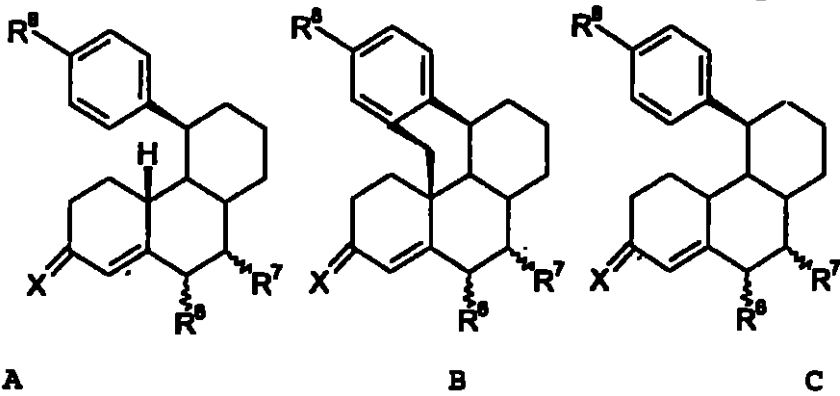
23. Un método para inhibir la ocurrencia de la madura-

ción endometrial adelantada en un sujeto hembra humano que está sometido a un tratamiento de mejora de fertilidad, que comprende administrar al sujeto por lo menos un compuesto de la fórmula I, donde la fórmula I es



donde:

- R¹ es metilo o etilo,
- R² es C_nF_mH_o, donde n es 1-6, preferentemente 2, 3, 4, 5 o 6, m > 1 y m+o = 2n+1.
- R₃ es un grupo hidroxilo libre, eterificado o esterificado,
- R⁴ y R⁵ cada uno es un hidrógeno, o juntos forman una ligadura adicional o un grupo metileno
- St es un anillo esteroidal ABC de fórmula parcial A,B o C



donde:

- R⁶ es hidrógeno, un grupo C₁-C₄ alquilo de cadena lineal

o C₃-C₄ alquilo de cadena ramificada o halógeno

R⁷ es hidrógeno, un grupo C₁-C₄ alquilo de cadena lineal o C₃-C₄ alquilo de cadena ramificada, o

si St es un sistema de anillo ABC esteroideal, además

R⁶ y R⁷ juntos pueden formar una ligadura adicional,

X es oxígeno, hidroxiimino (=N-OH) o dos átomos de hidrógeno,

R⁸ es Y o arilo optativamente sustituido en múltiples sitios con un grupo Y distinto de H,

Y es hidrógeno, halógeno, -OH, -NO₂, -N₃, -CN, -NR^{9a}R^{9b}, -NHSO₂R⁹, CO₂R⁹, C₁-C₁₀ alquilo, C₁-C₁₀ alcoxi, C₁-C₁₀ alcanoiloxi, benzoiloxi, C₁-C₁₀ alcanoil, C₁-C₁₀ hidroxialquilo o benzoilo,

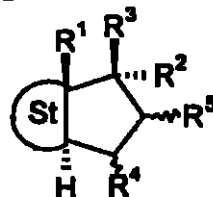
R^{9a} y R^{9b} son iguales o diferentes, y cada uno de ellos es hidrógeno o C₁-C₁₀ alquilo,

R⁹ es hidrógeno o C₁-C₁₀ alquilo,

y para los radicales-NR^{9a}R^{9b}, así como para sus sales compatibles desde el punto de vista fisiológico con ácidos y para los radicales-CO₂R⁹, donde R⁹ es hidrógeno, así como sus sales compatibles desde el punto de vista fisiológico con bases.

24. Un método para lograr la preñez en un sujeto hembra humano que comprende estimular los ovarios del sujeto mediante la administración al sujeto de un agente estimulante folicular, donde el agente comprende hormona estimulante folicular; retirar los huevos del ovario del sujeto estimula-

do; administrar al sujeto por lo menos un compuesto de la fórmula I en la fase pos-ovulatoria del ciclo endometrial; fertilizar por lo menos un huevo in vitro para obtener un embrión: y transferir el embrión al útero o a las trompas de Falopio del mamífero, tal que la fórmula I es:



donde:

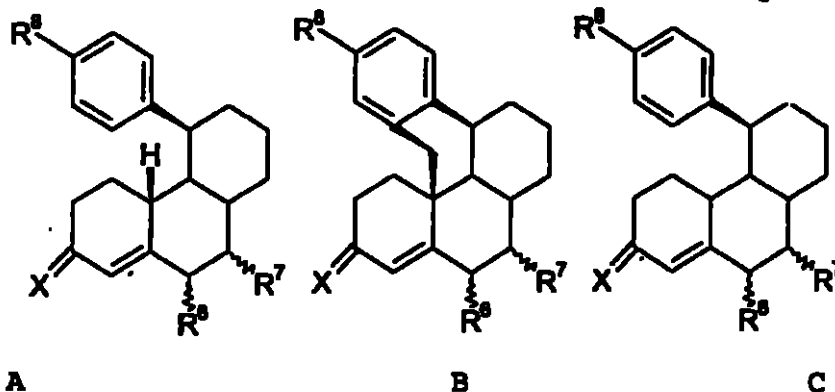
R^1 es metilo o etilo,

R^2 es $C_nF_mH_o$, donde n es 1-6, preferentemente 2, 3, 4, 5 o 6, $m > 1$ y $m+o = 2n+1$.

R_3 es un grupo hidroxilo libre, eterificado o esterificado,

R^4 y R^5 cada uno es un hidrógeno, o juntos forman una ligadura adicional o un grupo metileno

St es un anillo esteroidal ABC de fórmula parcial A, B o C



donde:

R⁶ es hidrógeno, un grupo C₁-C₄ alquilo de cadena lineal o C₃-C₄ alquilo de cadena ramificada o halógeno

R⁷ es hidrógeno, un grupo C₁-C₄ alquilo de cadena lineal o C₃-C₄ alquilo de cadena ramificada, o

si St es un sistema de anillo ABC esteroidal, además

R⁶ y R⁷ juntos pueden formar una ligadura adicional,

X es oxígeno, hidroximinio (=N-OH) o dos átomos de hidrógeno,

R⁸ es Y o arilo optativamente sustituido en múltiples sitios con un grupo Y distinto de H,

Y es hidrógeno, halógeno, -OH, -NO₂, -N₃, -CN, -NR^{9a}R^{9b}, -NHSO₂R⁹, CO₂R⁹, C₁-C₁₀ alquilo, C₁-C₁₀ alcoxi, C₁-C₁₀ alcanoiloxi, benzoiloxi, C₁-C₁₀ alcanilo, C₁-C₁₀ hidroxialquilo o benzoilo,

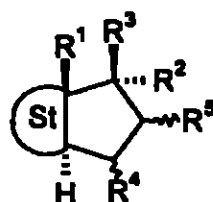
R^{9a} y R^{9b} son iguales o diferentes, y cada uno de ellos es hidrógeno o C₁-C₁₀ alquilo,

R⁹ es hidrógeno o C₁-C₁₀ alquilo,

y para los radicales-NR^{9a}R^{9b}, así como para sus sales compatibles desde el punto de vista fisiológico con ácidos y para los radicales-CO₂R⁹, donde R⁹ es hidrógeno, así como sus sales compatibles desde el punto de vista fisiológico con bases.

25. Un método para inhibir la ocurrencia de la maduración endometrial adelantada en un mamífero hembra no humano que está sometido a un tratamiento para mejorar la fertilidad y lograr la preñez, que comprende administrar al mamífe-

ro por lo menos un compuesto de la fórmula I, donde la fórmula I es:



donde:

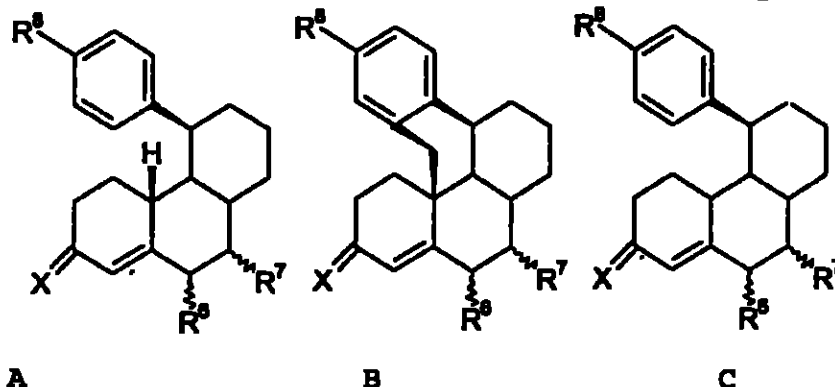
R^1 es metilo o etilo,

R^2 es $C_nF_mH_o$, donde n es 1-6, preferentemente 2, 3, 4, 5 o 6, $m > 1$ y $m+o = 2n+1$.

R_3 es un grupo hidroxilo libre, eterificado o esterificado,

R^4 y R^5 cada uno es un hidrógeno, o juntos forman una ligadura adicional o un grupo metileno

St es un anillo esteroidal ABC de fórmula parcial A,B o C



donde:

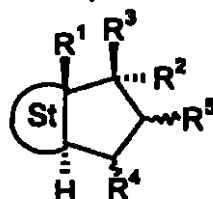
R^6 es hidrógeno, un grupo C_1-C_4 alquilo de cadena lineal o C_3-C_4 alquilo de cadena ramificada o halógeno

R^7 es hidrógeno, un grupo C_1-C_4 alquilo de cadena lineal

o C₃-C₄ alquilo de cadena ramificada, o
 si St es un sistema de anillo ABC esteroideal, además
 R⁶ y R⁷ juntos pueden formar una ligadura adicional,
 X es oxígeno, hidroxilimino (=N-OH) o dos átomos de hidrógeno,
 R⁸ es Y o arilo optativamente sustituido en múltiples sitios con un grupo Y distinto de H,
 Y es hidrógeno, halógeno, -OH, -NO₂, -N₃, -CN, -NR^{9a}R^{9b}, -NHSO₂R⁹, CO₂R⁹, C₁-C₁₀ alquilo, C₁-C₁₀ alcoxi, C₁-C₁₀ alcanoiloxi, benzoiloxi, C₁-C₁₀ alcanoil, C₁-C₁₀ hidroxialquilo o benzoilo,
 R^{9a} y R^{9b} son iguales o diferentes, y cada uno de ellos es hidrógeno o C₁-C₁₀ alquilo,
 R⁹ es hidrógeno o C₁-C₁₀ alquilo,
 y para los radicales-NR^{9a}R^{9b}, así como para sus sales compatibles desde el punto de vista fisiológico con ácidos y para los radicales-CO₂R⁹, donde R⁹ es hidrógeno, así como sus sales compatibles desde el punto de vista fisiológico con bases.

26. Un método para obtener la preñez en un mamífero no humano que comprende estimular los ovarios del mamífero mediante la administración al sujeto de un agente estimulante folicular, donde el agente comprende una hormona estimulante folicular; retirar huevos del ovario del mamífero estimulado; administrar al mamífero por lo menos un compuesto de la fórmula I durante la fase pos-ovulatoria del ciclo endome-

trial; fertilizar por lo menos un huevo in vitro para obtener un embrión; transferir el embrión dentro del útero o las trompas de Falopio del mamífero, donde la fórmula I es:



donde:

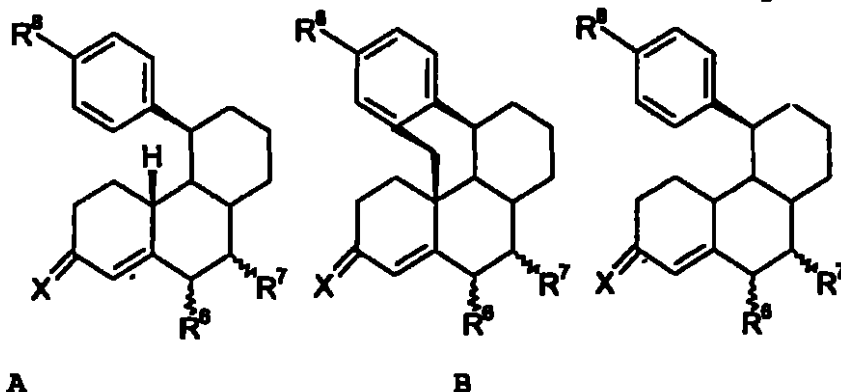
R^1 es metilo o etilo,

R^2 es $C_nF_mH_o$, donde n es 1-6, preferentemente 2, 3, 4, 5 o 6, $m > 1$ y $m+o = 2n+1$.

R_3 es un grupo hidroxilo libre, eterificado o esterificado,

R^4 y R^5 cada uno es un hidrógeno, o juntos forman una ligadura adicional o un grupo metileno

St es un anillo esteroidal ABC de fórmula parcial A, B o C



donde:

R^6 es hidrógeno, un grupo C_1-C_4 alquilo de cadena lineal o C_3-C_4 alquilo de cadena ramificada o halógeno

R⁷ es hidrógeno, un grupo C₁-C₄ alquilo de cadena lineal o C₃-C₄ alquilo de cadena ramificada, o

si St es un sistema de anillo ABC esteroidal, además

R⁶ y R⁷ juntos pueden formar una ligadura adicional,

X es oxígeno, hidroxiimino (=N-OH) o dos átomos de hidrógeno,

R⁸ es Y o arilo optativamente sustituido en múltiples sitios con un grupo Y distinto de H,

Y es hidrógeno, halógeno, -OH, -NO₂, -N₃, -CN, -NR^{9a}R^{9b}, -NH₂SO₂R⁹, CO₂R⁹, C₁-C₁₀ alquilo, C₁-C₁₀ alcoxi, C₁-C₁₀ alcanoiloxi, benzoiloxi, C₁-C₁₀ alcanoil, C₁-C₁₀ hidroxi alquilo o benzoilo,

R^{9a} y R^{9b} son iguales o diferentes, y cada uno de ellos es hidrógeno o C₁-C₁₀ alquilo,

R⁹ es hidrógeno o C₁-C₁₀ alquilo,

y para los radicales-NR^{9a}R^{9b}, así como para sus sales compatibles desde el punto de vista fisiológico con ácidos y para los radicales-CO₂R⁹, donde R⁹ es hidrógeno, así como sus sales compatibles desde el punto de vista fisiológico con bases.

27. Un método para inhibir la ocurrencia de maduración endometrial adelantada en un sujeto hembra humano en tratamiento para mejorar la fertilidad, que comprende administrar al menos un antagonista del receptor de progesterona 17α-fluoroalquilado al sujeto hembra durante la fase pos-ovulatoria del ciclo endometrial.

28. Un método para retardar la ocurrencia de maduración endometrial en un sujeto hembra humano que está bajo tratamiento para mejorar la fertilidad, que comprende administrar al sujeto hembra al menos un antagonista del receptor de progesterona 17α -fluoroalquilado durante la fase pos-ovulatoria del ciclo endometrial después del mencionado tratamiento para mejorar la fertilidad.

29. Un método para retardar la ocurrencia de maduración endometrial en un sujeto hembra humano que está bajo tratamiento para mejorar la fertilidad y lograr la preñez, que comprende administrar al sujeto hembra al menos un antagonista del receptor de progesterona 17α -fluoroalquilado durante la fase pos-ovulatoria del ciclo endometrial después del mencionado tratamiento para mejorar la fertilidad.