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SOLICITUD

PATENTE DE INVENCION

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03-66215

21 EXPEDIENTE N°

54 TITULO "Uso de gestágenos para inhibir la maduración
acelerada del endometrio durante el tratamiento de la
infertilidad"

51 CLASIFICACIÓN INTERNACIONAL A61K 31/00

71 SOLICITANTE Schering Aktiengesellschaft

DOMICILIO Berlin, Alemania

74 APODERADO Gustavo Hellmann Restrepo

22 BOGOTÁ, D. C. 4 de agosto de 2003.

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FORMULARIO ÚNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

①

SOLICITUD DE:



Patente de Invención.



Patente de Modelo de Utilidad.



Capítulo I.



Capítulo II.

②

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C.E.



Otro



Cual

Número

③

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NIT



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Número **2.878.023** TP **5903**

④

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⑥

Título (54) **"USO DE GESTAGENOS PARA INHIBIR LA MADURACION ACELERADA DEL
ENDOMETRIO DURANTE EL TRATAMIENTO DE LA INFERTILIDAD",**

⑦

Clasificación Internacional (51) **A61K 31/00**

⑧

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NO ☐

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⑨

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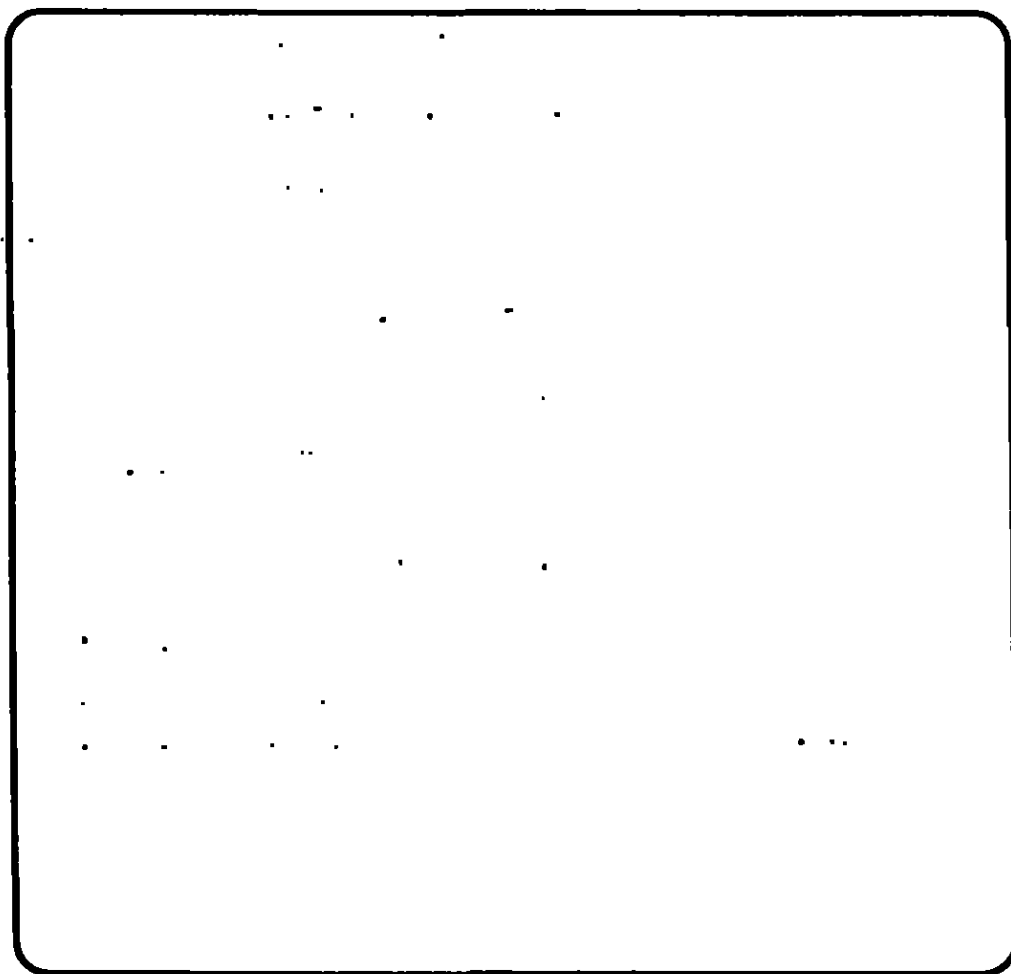
Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud.
- ☒ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. **Protocolizado bajo el No. 605.**
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- ☒ Traducción del examen preliminar internacional efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional.
- ☒ Otros Reporte búsqueda internacional.

11 FIGURA CARACTERÍSTICA:



12 Solicito la concesión de la patente,

NOMBRE: _____

FIRMA: _____

C.C. 2.878.023 Bogotá, D.C. 5903

Instrucciones para la presentación de los anexos, ver reverso de esta página.

**Continuación enumeración del nombre de los Inventores, con
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Otros anexos que se acompañan a la solicitud.

Notificación de recibo de inscripción de la solicitud (Formulario PCT/IB/301).

Petitorio de la solicitud (Formulario PCT/RO/101)

Copia carta de Schering AG a la Oficina Europea de Patentes informando su dirección.

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***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
GUSTAVO HOLLMAN	CONSIGNACION	BANCO POPULAR	050-00110-6	13226021	24/07/2003	5,873,000.00

***** C O N C E P T O *****

CANT. HISTORICO	CONCEPTO	TOTAL CONCEPTO
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(72) Inventors; and

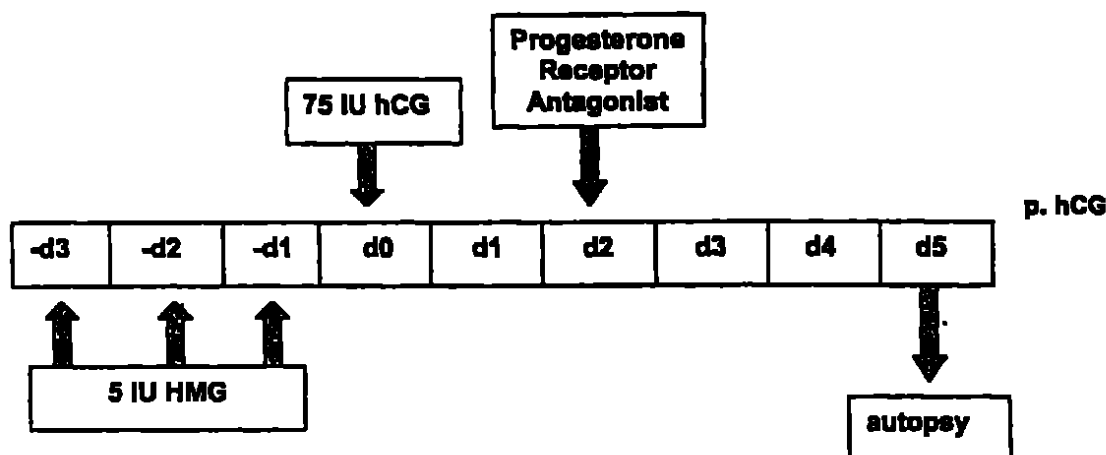
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(54) Title: THE USE OF ANTIGESTAGENS FOR INHIBITING ACCELERATED ENDOMETRIAL MATURATION DURING INFERTILITY TREATMENT

General study design in superovulated rabbits



(57) Abstract: 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 -fluoroalkylated progesterone receptor antagonist to the female mammal.

WO 02/067910 A2



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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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.

5

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.

15

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.

20

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),

25

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

- 3 -

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.

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;

5 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; implanting the embryo in the uterus or fallopian tubes of the mammal.

10 In another aspect, the invention relates to a method of inhibiting the occurrence of advanced endometrium maturation in a non-human female mammal undergoing fertility 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.

15 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 17α -fluoralkylated progesterone
20 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

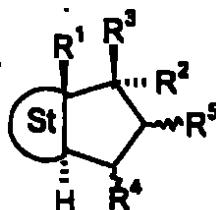
- 25 (a) administering gonadotropins for ovarian hyperstimulation to the mammal;
(b) removing eggs from the ovary of the stimulated animal;
(c) administering at least one 17α -fluoralkylated progesterone-receptor antagonist;
(d) fertilizing at least one of the removed eggs in vitro to obtain an embryo
30 (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).

5 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, 15 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

20 wherein

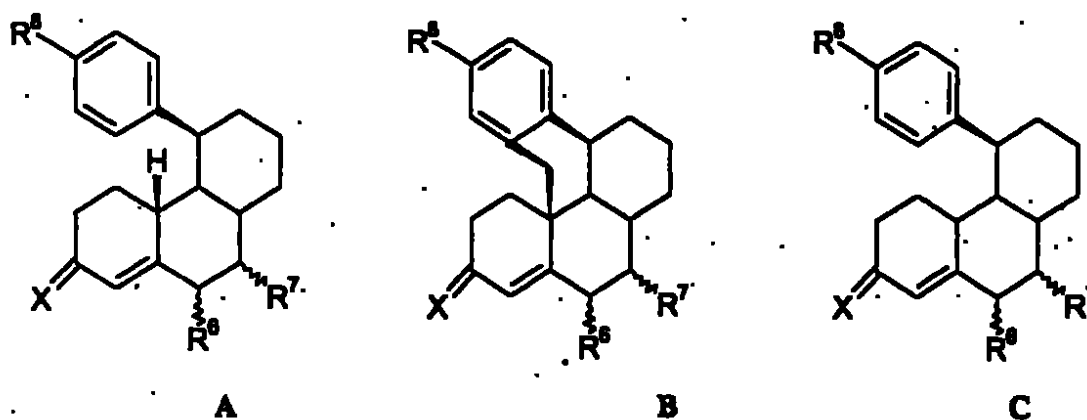
R^1 is methyl or ethyl,

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,

25 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,

5 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,

10 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,

15 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.

20 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.

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

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

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

4'-[17 β -hydroxy-3-oxo-17 α -(1,1,2,2,2-pentafluoroethyl)estr-4-en-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)estr-4-en-3-one;

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

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

20 4'-[17 β -hydroxy-3-oxo-17 α -(1,1,2,2,2-pentafluoroethyl)estra-4,15-dien-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-4,15-dien-3-one;

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

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

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

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

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;

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;

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

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 coatings, e.g., by microencapsulation, multiple coatings, etc. It is also possible to
30 freeze-dry the new compounds and use the lyophilizates obtained, for example, for the preparation of products for injection.

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.

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 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.

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.

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.

5 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

25 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.

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).

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.

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

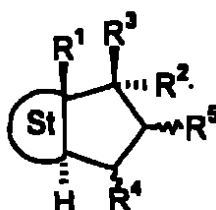
administering at least one 17 α -fluoralkylated progesterone receptor antagonist to the female subject during the post-ovulatory phase of the endometrial cycle.

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

R^1 is methyl or ethyl,

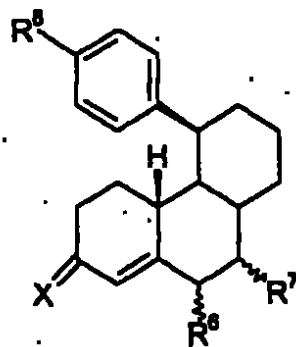
R^2 is $C_nF_mH_n$, wherein n is 1-6, preferably 2, 3, 4, 5 or 6, m > 1 and

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

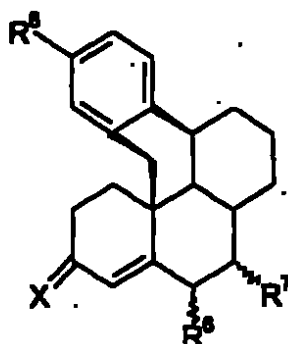
R^3 is a free, etherified or esterified hydroxy group,

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

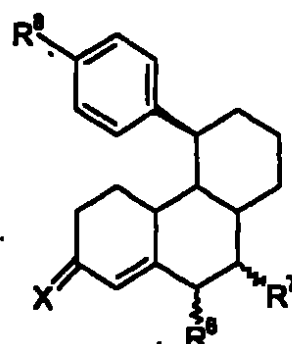
St is a steroidal ABC-ring system of partial formula A, B or C



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 $-NR^8R^9$ 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.

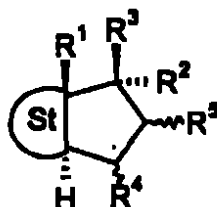
6. A method according to claim 4, wherein the 17α -fluoralkylated progesterone receptor antagonist is administered orally to the subject.

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.

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



I

wherein

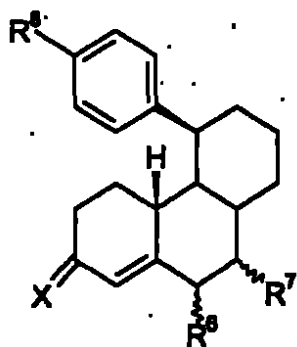
R^1 is methyl or ethyl,

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

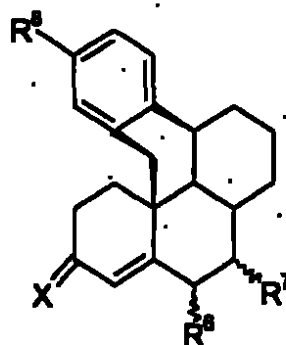
R^3 is a free, etherified or esterified hydroxy group,

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

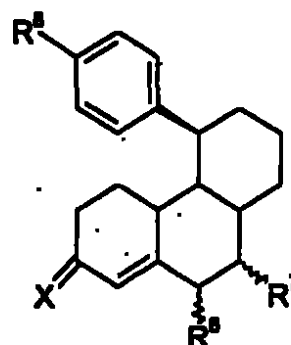
St is a steroidal ABC-ring system of partial formula A, B or C



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,

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,

- 22 -

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 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.

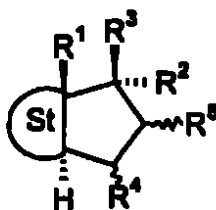
13. A method according to claim 12, wherein the 17 α -fluoralkylated progesterone receptor antagonist is administered to the mammal in a daily dosage amount of 0.01-1 mg/kg.

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

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:



I

wherein

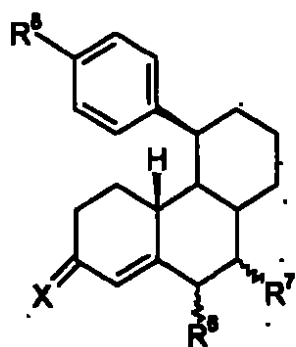
R¹ is methyl or ethyl,

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,

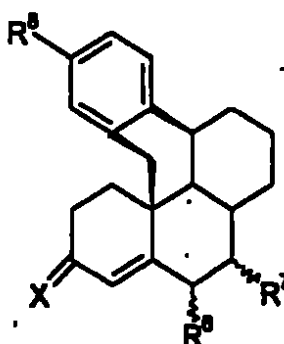
R³ is a free, etherified or esterified hydroxy group,

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

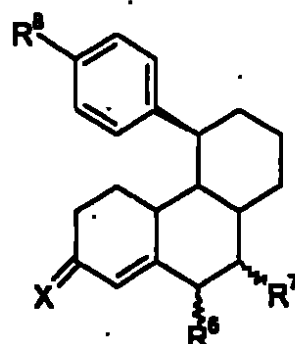
St is a steroidal ABC-ring system of partial formula A, B or C



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, $-OH$, $-NO_2$, $-N_3$, $-CN$, $-NR^{8a}R^{8b}$, $-NH-SO_2R^9$, $-CO_2R^9$, 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^{8a} and R^{8b} 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,

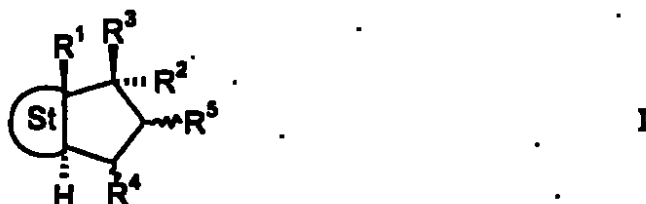
and for $-NR^{8a}R^{8b}$ radicals, as well as their physiologically compatible salts with acids and for $-CO_2R^9$ radicals with R^9 being hydrogen, as well as their physiologically compatible salts with bases.

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; transferring the embryo into 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:



wherein

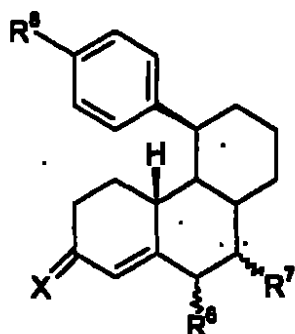
R¹ is methyl or ethyl,

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,

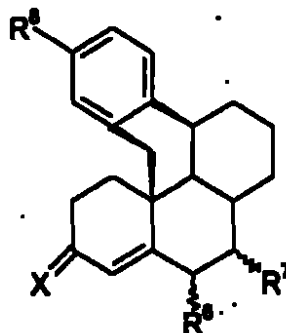
R³ is a free, etherified or esterified hydroxy group,

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

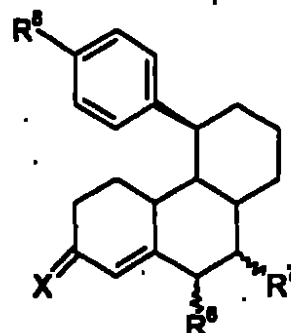
St is a steroidal ABC-ring system of partial formula A, B or C



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, $-OH$, $-NO_2$, $-N_3$, $-CN$, $-NR^{9a}R^{9b}$, $-NHSO_2R^9$, $-CO_2R^9$, 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,

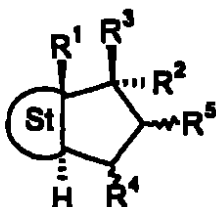
and for $-NR^{9a}R^{9b}$ radicals, as well as their physiologically compatible salts with acids and for $-CO_2R^9$ radicals with R^9 being hydrogen, as well as their physiologically compatible salts with bases.

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



I

- 27 -

wherein

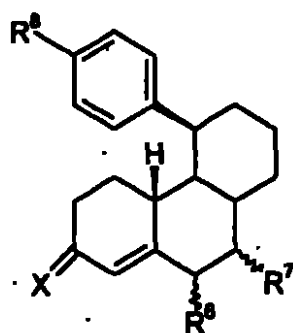
R^1 is methyl or ethyl,

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

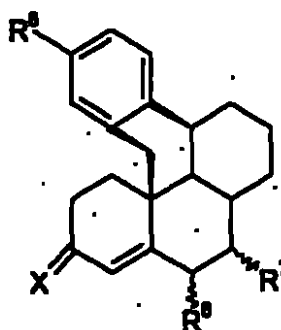
R^3 is a free, etherified or esterified hydroxy group,

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

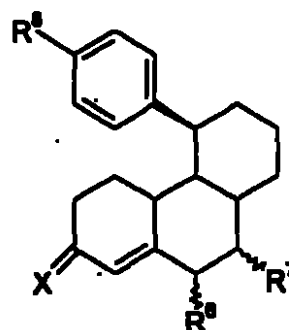
St is a steroidal ABC-ring system of partial formula A, B or C



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

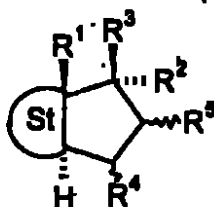
stimulating the ovaries of the subject by administering a follicle stimulating agent to the subject, wherein the agent comprises follicle stimulating hormone;

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



I

wherein

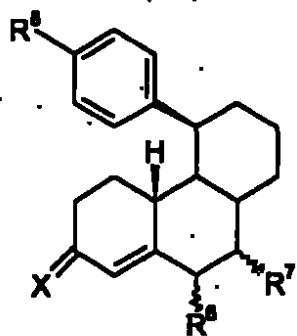
R^1 is methyl or ethyl,

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

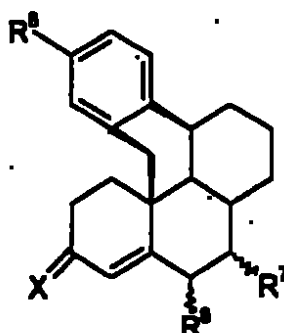
R^3 is a free, etherified or esterified hydroxy group,

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

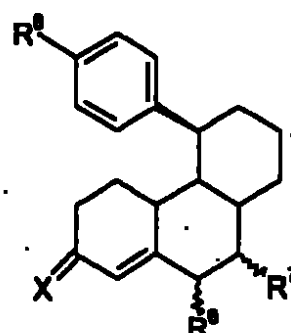
St is a steroidal ABC-ring system of partial formula A, B or C



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,

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,

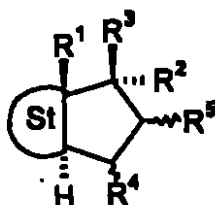
R^9 is hydrogen or C_1 - C_{10} alkyl,

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 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



I

wherein

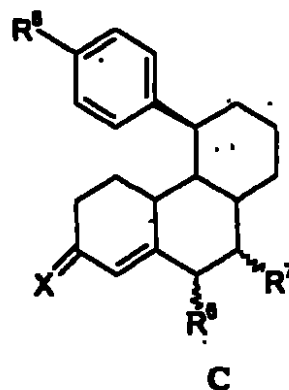
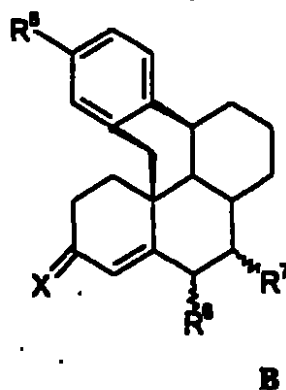
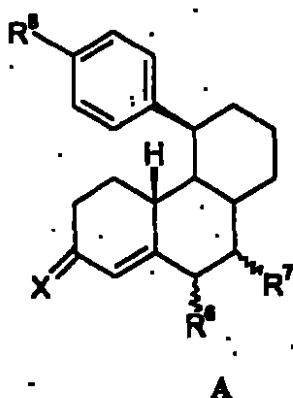
R^1 is methyl or ethyl,

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



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,

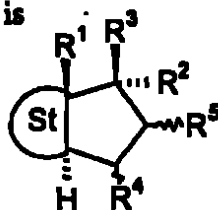
Y is hydrogen, halogen, $-OH$, $-NO_2$, $-N_3$, $-CN$, $-NR^{9a}R^{9b}$, $-NHSO_2R^9$, $-CO_2R^9$, C_1 - C_{10} alkyl, C_1 - C_{10} alkoxy, C_1 - C_{10} alkanoyloxy, benzoyloxy, C_1 - C_{10} alkanoyl, C_1 - C_{10} hydroxyalkyl or benzoyl,

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.

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



- 32 -

wherein

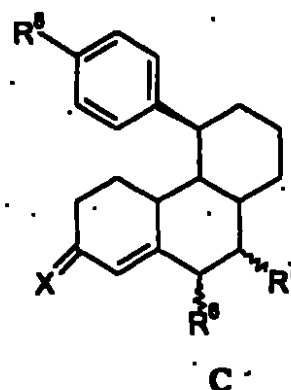
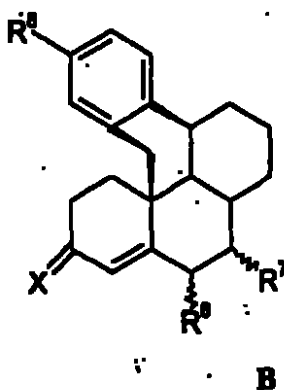
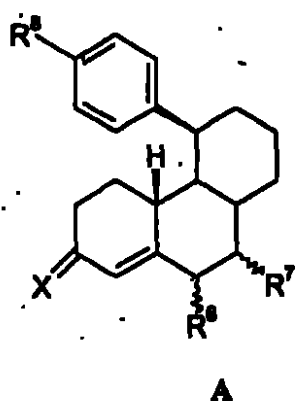
R^1 is methyl or ethyl,

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



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,

- 33 -

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 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.

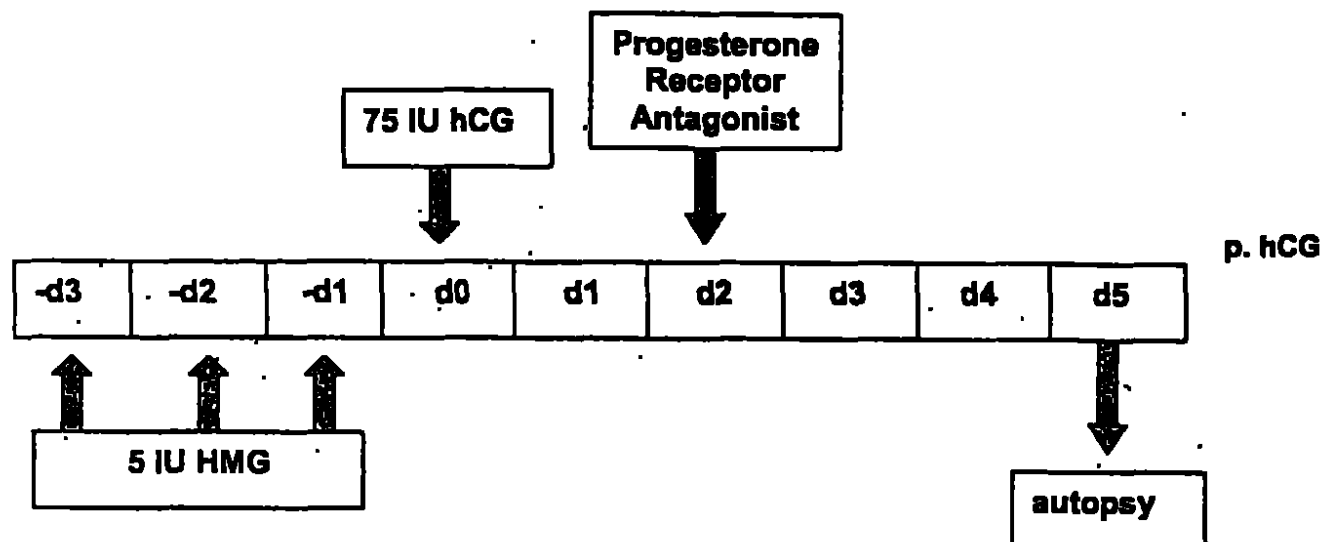
28. A method of inhibiting the occurrence of advanced endometrium maturation in a human female subject undergoing fertility enhancing treatment comprising

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.

Figure 1: General study design in superovulated rabbits



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(19) World Intellectual Property Organization
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(43) International Publication Date
6 September 2002 (06.09.2002) ✓

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(10) International Publication Number
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Patente
21. Feb. 2003
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(51) International Patent Classification: A61K 31/567.
31/57, A61P 15/08

(21) International Application Number: PCT/IB02/01764

(22) International Filing Date: 9 January 2002 (09.01.2002)

(25) Filing Language: English

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(30) Priority Data:
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(71) Applicant (for all designated States except US): SCHERING AKTIENGESELLSCHAFT [DE/DE]; Müllerstr. 178, 13353 Berlin (DE).

(72) Inventors: and

(75) Inventors/Applicants (for US only): HEGELE-HARTUNG, Christa [DE/DE]; Woellenbeck 101, 45470 Muchlheim a. d. Ruhr (DE). HESS-STUMPP, Holger [DE/DE]; Gabelweihstr. 19, 13505 Berlin (DE). BEIER, Henning, M. [DE/DE]; Rothendenstr. 19, 52076 Aachen (DE). KRUSCHE, Claudia [DE/DE]; Am Weissenberg 39, 52074 Aachen (DE).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GU, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BJ, BJ, CI, CG, CI, CM, GA, GN, OQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

(88) Date of publication of the international search report:
6 February 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: THE USE OF ANTIGESTAGENS FOR INHIBITING ACCELERATED ENDOMETRIAL MATURATION DURING INFERTILITY TREATMENT

(57) Abstract: 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.



WO 02/067910 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 02/01764

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/567 A61K31/57 A61P15/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FUHRMANN U ET AL: "SYNTHESIS AND BIOLOGICAL ACTIVITY OF A NOVEL, HIGHLY POTENT PROGESTERONE RECEPTOR ANTAGONIST" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 43, no. 26, 2000, pages 5010-5016, XP001064233 ISSN: 0022-2623 the whole document — — — — — — / —	1-29

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *B* document member of the same patent family

Date of the actual completion of the international search

28 October 2002

Date of mailing of the international search report

13/11/2002

Name and mailing address of the ISA

European Patent Office, P.O. 5518 Patentlaan 2
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Tel. (+31-70) 340-2040, Tx. 31 651 apo nl,
Fax (+31-70) 340-2018

Authorized officer

Veronese, A

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 02/01764

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-20, 23-29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependant claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal

Application No

PCT/IB 02/01764

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9834947	A	13-08-1998	DE 19706061 A1 13-08-1998
			AT 216397 T 15-05-2002
			AU 742834 B2 10-01-2002
			AU 6100598 A 26-08-1998
			BG 103603 A 30-06-2000
			BR 9807667 A 15-02-2000
			CN 1324802 A 05-12-2001
			CN 1246865 T 08-03-2000
			DE 59803856 D1 23-05-2002
			DK 970103 T3 22-07-2002
			EE 9900339 A 15-02-2000
			WO 9834947 A1 13-08-1998
			EP 0970103 A1 12-01-2000
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			JP 2001510479 T 31-07-2001
			NO 993811 A 04-10-1999
			NZ 336989 A 27-04-2001
			PL 334878 A1 27-03-2000
			SK 103899 A3 16-05-2000
			TR 9901855 T2 21-04-2000
			US 6316432 B1 13-11-2001
			US 2002045774 A1 18-04-2002
			ZA 9800985 A 03-08-1999
WO 0039148	A	06-07-2000	DE 19860719 A1 29-06-2000
			AU 2285800 A 31-07-2000
			WO 0039148 A1 06-07-2000
			EP 1140972 A1 10-10-2001
			NO 20013168 A 22-06-2001

- (12) Publicación de la solicitud internacional bajo PCT
 (19) Organización mundial de propiedad intelectual
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 (43) Fecha de publicación internacional : 6 de septiembre de 2002
 (6.09.2002)
 (10) Número de publicación internacional: **WO 02/067910 A2**
-

- (51) Clasificación Internacional de patentes: **A61K 31/00**
 (21) Número de solicitud internacional: **PCT/IB02/01784**
 (22) Fecha de presentación internacional: 9 de enero de 2002
 (09.01.2002)
 (25) Idioma de la presentación: Inglés
 (26) Idioma de la publicación: Inglés
 (30) Antecedentes de prioridad:
 09/756,286 9 de enero de 2001 (9.1.2001) US
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 (71) Solicitante: (para todos los países designados excepto EEUU):
 SCHERING AKTIENGESELLSCHAFT [DE/DE], 13342 Berlin (DE).
 (72) Inventor y
 (75) Inventores en la solicitud (para EEUU solamente): **HEGELE-HARTUNG, Christa**
 [DE/DE]; Woellenbeck 101, 45470 Muelheim a.d.Ruhr (DE). **HESS-STUMPP, Holger**
 [DE/DE]; Gabelweihstr. 19, 13505 Berlin (DE). **BEIER; Henning, M. [DE/DE];**
 Rotbendenstr. 19, 52076 Aachen (DE). **KRUSCHE, Claudia [DE/DE];** Am
 Weissenberg 39, 52074 Aachen (DE).
 (81) Estados designados(nacionales): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR,
 BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD,
 GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
 LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD,
 SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
 (84) Estados designados(regionales): Patentes ARIPO (GH, GM, KE, LS, MW, MZ, SD,
 SL, SZ, TZ, UG, ZM, ZW), Patentes euroasiáticas (AM, AZ, BY, KG, KZ, MD, RU, TJ,
 TM), Patentes europeas (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU,
 MC, NL, PT, SE, TR), Patentes OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
 ML, MR, NE, SN, TD, TG).

Publicado:

- sin informe de búsqueda internacional y a ser publicado nuevamente al recibir dicho informe.

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- (54) Título: **Uso de gestágenos para inhibir la maduración acelerada del endometrio durante el tratamiento de la infertilidad**
 (57) Resumen:

**USO DE GESTÁGENOS PARA INHIBIR LA MADURACIÓN ACELERADA DEL
ENDOMETRIO DURANTE EL TRATAMIENTO DE LA INFERTILIDAD**

La presente solicitud es continuación parcial de la solicitud U.S. Acta Nro. 09/756.286 presentada el 9 de enero de 2001, que se incorpora íntegramente a la presente a modo de referencia.

ANTECEDENTES DE LA INVENCION

La presente invención se relaciona con el uso de anti-gestágenos para postergar la maduración pos-ovulatoria del endometrio durante el tratamiento de la infertilidad.

La estimulación ovárica con gonadotropinas se utiliza comúnmente en humanos en las tecnologías de reproducción asistida, incluyendo la fertilización *in vitro* y la terapia de transferencia embrionaria (IVF/ET). Sin embargo, luego de la hiperestimulación ovárica controlada, se adelanta la transformación pos-ovulatoria del endometrio (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). Por consiguiente, el desarrollo temporal del endometrio y del embrión, que normalmente están sincronizados con precisión, se ve perturbado, lo que da como resultado una baja tasa de implantación de blastocitos sanos.

RESUMEN DE LA INVENCION

La presente invención provee un método para mejorar la

fertilidad en los mamíferos mediante la administración de antagonistas 17α -fluoroalquilados del receptor de la progesterona, para inhibir la maduración endometrial adelantada durante el tratamiento de la infertilidad (es decir, la mejora de la fertilidad), incluyendo a todas las terapias de reproducción asistida.

Asimismo se contempla como parte de la presente invención que dicho método sea particularmente útil en un mamífero hembra que es sometido al tratamiento de fertilización. El tratamiento de fertilización, tal como se lo utiliza en la presente invención, se refiere a cualquier tratamiento que se provee a un mamífero hembra con el propósito de conseguir la preñez, independientemente de que se haya determinado que el mamífero es fértil, infértil o que presente impedimentos en su fertilidad. Los tratamientos de fertilización contemplados como parte de la presente invención comprenden, de manera no limitativa, la hiperestimulación ovárica (OH), la fertilización *in vitro* y la transferencia embrionaria (IVF/ET), así como OH en combinación con IVF/ET. En particular, se contempla un método para inhibir la maduración endometrial adelantada, la que generalmente ocurre junto con la hiperestimulación ovárica. Por ejemplo, la hiperestimulación ovárica se puede utilizar como una herramienta en el tratamiento de fertilización junto con, p.ej., el contacto sexual programado, la inseminación artificial,

la inseminación intrauterina, IVF/ET y la transferencia intrafalopiana de gametas (GIFT).

IVF/ET, como se utiliza en la presente invención, se refiere a cualquier técnica en la que se fertilizan oocitos in vitro y luego se los transfiere al tracto reproductivo de la hembra. Por ejemplo, la transferencia del embrión puede ocurrir por medio de la transferencia del embrión dentro del útero a través de la cervix, o mediante la transferencia del embrión dentro de las trompas de Falopio (transferencia intrafalopiana de cigotas (ZIFT)). La fertilización de oocitos in vitro se puede lograr, p.ej., incubando oocitos en presencia de esperma o mediante inyección de esperma intracitoplásmico (ICSI). La IVF/ET también puede lograrse utilizando huevos de donantes. Los tratamientos de la infertilidad pueden comprender los tratamientos tales como la inducción de estimulación ovárica seguida de la fertilización por coito normal.

La hiperestimulación ovárica, como se utiliza en la presente invención, se refiere al uso de un agente de estimulación folicular para estimular el desarrollo de los folículos. La hiperestimulación ovárica puede utilizarse en sujetos hembra que presentan una diversidad de anomalías ovulatorias, incluyendo sujetos que son anovulatorios, sujetos que tienen una ovulación impedida, reducida o irregular, y sujetos con patrones ovulatorios normales. Los agentes esti-

mulantes foliculares preferidos comprenden gonadotropinas, tales como por ejemplo hormona estimulante folicular (FSH), hormona luteinizante (LH), gonadotropinas menopáusicas humanas (hMG) y gonadotropina coriónica humana (hCG). Los nombres comerciales de las gonadotropinas disponibles para uso como agentes estimulantes de los folículos comprenden por ejemplo Perganol, Metrodin, Humegon, Fertinorm, Gonal F y Primogonil-1000, etc. Los agentes estimulantes foliculares, tales como se los utiliza en la presente invención, comprenden también agentes bloqueadores del estrógeno tales como por ejemplo citrato de clomifeno (disponible comercialmente como Clomid y Serofene). Las gonadotropinas que se pueden usar de acuerdo con la presente invención comprenden hormonas que son aisladas de materiales de origen naturales y hormonas que se obtienen por síntesis, inclusive hormonas producidas por medio de técnicas de ADN recombinante. Las gonadotropinas mutantes que retienen actividad como agentes estimulantes foliculares también son consideradas como parte de la presente invención.

La hiperestimulación ovárica puede lograrse utilizando más de un tipo de agente de estimulación folicular. Por ejemplo, un agente bloqueador del estrógeno tal como el clomifeno puede utilizarse en combinación con una gonadotropina. Se puede utilizar hiperestimulación ovárica para tratar una variedad de tipos de infertilidad, inclusive, aunque de

manera no limitativa, la infertilidad idiopática, la infertilidad anovulatoria, la infertilidad asociada con endometriosis, la infertilidad de factor tubárico y la infertilidad de factor masculino.

La hiperestimulación ovárica también puede lograrse junto con un antagonista de hormona liberadora de gonadotropina (GnRH), para anular la producción de hormona endógena del sujeto. Las GnRH que se pueden utilizar en conjunto con la presente invención comprenden, p.ej., Synarel o Lupron.

En una realización preferida, los métodos de la presente invención se emplean en conjunto con sujetos hembra humanos. Los métodos de la presente invención pueden asimismo emplearse con otros sujetos mamíferos hembra, incluyendo, de manera no limitativa, animales domésticos, animales de granja y animales de zoológico, en particular vacas, cerdos, caballos y ovejas. Cuando se utiliza en el tratamiento de fertilización de mamíferos no humanos, la administración de antigestágenos puede ayudar a lograr una mayor tasa de éxito en, por ejemplo, la fertilización *in vitro* y la transferencia embrionaria realizadas por razones económicas o de cría.

Los mamíferos no humanos producidos mediante los métodos revelados en la presente invención también se consideran como parte de la presente invención. Estos mamíferos no humanos comprenden, por ejemplo, mamíferos que han sido genéticamente modificados, inclusive, p.ej., mamíferos que han

sido genéticamente modificados utilizando técnicas de ADN recombinante.

En un aspecto, la presente invención se relaciona con un método para inhibir la ocurrencia del adelanto de la maduración del endometrio en un sujeto hembra humano que es sometido a un tratamiento de fertilización, método que comprende administrar al sujeto hembra por lo menos un antagonista del receptor de progesterona 17α -fluoroalquilado durante la fase pos-ovulatoria del ciclo endometrial.

En otro aspecto, la presente invención se relaciona con 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, en el que dicho agente comprende hormona estimulante; retirar los huevos del ovario del sujeto estimulado; administrar al sujeto por lo menos un antagonista del receptor de progesterona 17α -fluoroalquilado en la fase pos-ovulatoria del ciclo endometrial; fertilizar por lo menos un huevo *in vitro* para obtener un embrión; implantar el embrión en el útero o en las trompas de Falopio del mamífero.

En otro aspecto, la presente invención se relaciona con un método para inhibir la ocurrencia del adelanto de la maduración endometrial en un mamífero hembra no humano sujeto a un tratamiento de fertilización para obtener la preñez, que comprende administrar al mamífero por lo menos un anta-

gonista del receptor de progesterona 17 α -fluoroalquilado en la fase pos-ovulatoria del ciclo endometrial.

En otro aspecto, la presente invención se relaciona con un método para lograr la preñez en un mamífero no humano, que comprende estimular los ovarios del mamífero mediante la administración al mamífero 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 progesterona 17 α -fluoroalquilado en la fase pos-ovulatoria del ciclo endometrial, fertilizar por lo menos un huevo *in vitro* para obtener un embrión; implantar el embrión en el útero o en las trompas de Falopio del mamífero.

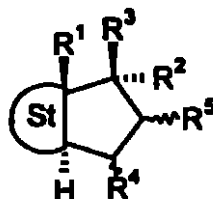
En otro aspecto, la presente invención se relaciona con un método para lograr la preñez en un mamífero hembra que comprende:

- (a) administrar gonadotropinas para la hiperestimulación ovárica del mamífero
- (b) retirar los huevos del ovario del mamífero estimulado
- (c) administrar por lo menos un antagonista del receptor de progesterona 17 α -fluoroalquilado
- (d) fertilizar *in vitro* por lo menos uno de los huevos retirados para obtener un embrión
- (e) introducir el embrión en el tracto reproductivo del mamífero.

Preferentemente, la gonadotropina administrada al mamífero para lograr la hiperestimulación ovárica comprende hormona estimulante folicular (FSH). Aún más preferentemente, la estimulación ovárica se logra mediante el uso de una primera gonadotropina que comprende FSH y el uso subsiguiente de una segunda gonadotropina que comprende gonadotropina coriónica, en particular gonadotropina coriónica humana (hCG). Preferentemente el embrión se introduce en el tracto reproductivo del mamífero mediante la introducción en el útero por vía cervical. También preferentemente se administra al mamífero hembra un agonista o antagonista de hormona liberadora de gonadotropina (GnRH, antes y durante la administración de las gonadotropinas.

Los compuestos útiles como antigestágenos según la presente invención comprenden todos los antagonistas del receptor de progesterona 17 α -fluoroalquilado que poseen una fuerte afinidad por el receptor de gestágeno (receptor de progesterona) y exhiben una mínima actividad de gestágeno propia. Por ejemplo, los compuestos esteroideos 17 α -fluoroalquilados que pueden utilizarse en conjunto con la presente invención se describen en la Solicitud de Patente de los EE.UU. No. de Acta 09/020.947, WO/98/34947, y Wang y Ruan, 1994, *Journal of Fluorine Chemistry* 69:1-3, todas las cuales se incorporan íntegramente a la presente a modo de referencia. Los antigestágenos útiles para la presente invención

comprenden, de manera no limitativa, p.ej. a los esteroides 17 α -fluoroalquilados de la fórmula I, principalmente de los documentos citados:



donde:

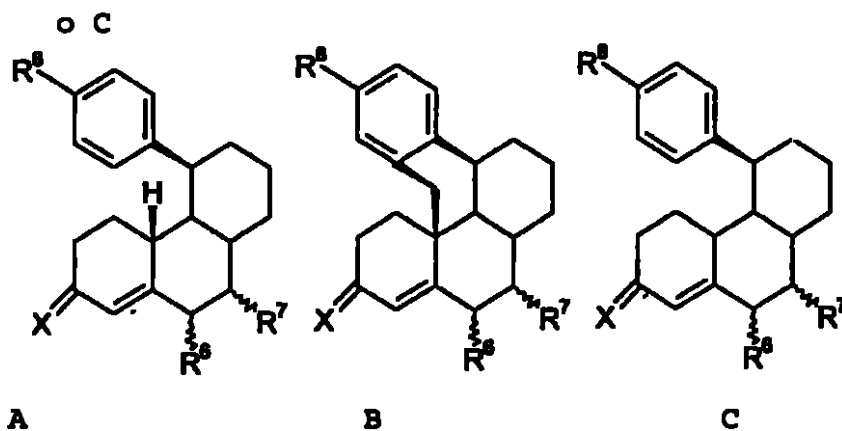
R¹ es metilo o etilo,

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,

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

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



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, 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.

Las líneas onduladas significan que el sustituyente en cuestión puede estar en posición α-o β-.

Los grupos alquilo dentro del alcance de esta fórmula comprenden grupos metilo, etilo o n-o iso-propilo y n-, iso- o tert-butilo.

Los otros grupos C_1 - C_{10} alquilo, Y, R^9 , R^{9a} , R^{9b} , comprenden los homólogos superiores además de, por ejemplo, grupos pentilo, neo-pentilo, y hexilo a decilo.

Se entiende, sin embargo, que los grupos C_1 - C_{10} alquilo comprenden grupos carbocíclicos o alquilocicloalquilo, así como grupos con hasta 10 átomos de carbono, por ejemplo ciclopropilo, ciclopentilo, cicloheptilo, metilciclopropilo, metilciclopentilo o metilciclohexilo. Un grupo metilo o etilo es preferido para todos los casos precedentes.

Los grupos C_1 - C_{10} alcoxi son los radicales que se prolongan en un átomo de oxígeno y son derivados de los grupos alquilo mencionados precedentemente, p.ej., los radicales metoxi, etoxi, n-o iso-propoxi, n-, iso-o tert-butoxi, etc.

Los C_1 - C_{10} alcanoilos son definidos como los radicales acilo de los ácidos C_1 - C_{10} alcanocarboxílicos de cadena lineal o ramificada, como, por ejemplo, los radicales formilo, acetilo, propionilo, butirilo o iso-butirilo, etc.

Los radicales C_1 - C_{10} alcanoiloxi son los radicales de los radicales alcanoilos precedentes que son prolongados por un átomo de oxígeno, como por ejemplo los radicales acetiloxi, propioniloxi, y butiriloxi, etc.

En caso de que un átomo de halógeno sea mencionado como sustituyente, el mismo puede ser un átomo de flúor, cloro o bromo. Se prefiere el flúor.

Para los radicales R^2 , se prefieren las cadenas latera-

les perfluoradas de longitud $n = 2-4$, y entre estas últimas, la unidad pentafluoroetilo es especialmente preferida.

En el caso de un grupo hidroxilo eterificado o esterificado como sustituyente como un 17β , este último es preferentemente eterificado con un grupo C_1-C_{10} alquilo o esterificado con un grupo C_1-C_{10} alcanilo. Para este grupo alquilo o alcanilo se aplican los mismos significados que precedentemente. La eterificación o esterificación del grupo hidroxilo se lleva a cabo de acuerdo con los métodos que son familiares para los expertos en el arte.

R^4 y R^5 son preferentemente cada uno de ellos un átomo de hidrógeno o juntos forman una ligadura adicional.

Si R^6 es un grupo Y, éste es preferentemente un grupo C_1-C_{10} alcanilo o un grupo(1-hidroxil)- C_1-C_{10} alquilo; entre éstos, se prefiere especialmente a acetilo y propionilo.

Los radicales arilo carbocíclicos o heterocíclicos son fenilo, 1-o 2-naftalinilo, 2-o 3-furanilo, 2-o 3-benzofuranilo, 2-o 3-tienilo, 2-, 3-o 4-piridinilo. Entre los radicales arilo sustituidos R^8 , se pueden citar principalmente 4-cianofenilo y 4-halofenilo, especialmente 4-fluorofenilo.

Entre todos los radicales que se mencionan como preferidos para R^8 , R^8 con el significado de Y, e Y, se prefiere especialmente acetilo.

Los compuestos que se mencionan a continuación son especialmente preferidos para la presente invención:

11 β -(4-Acetilfenil)-17 β -hidroxi-17 α -(1,1,2,2,2-pentafluoroetil)estr-4-en-3-ona;

4'-[17 β -hidroxi-3-oxo-17 α -(1,1,2,2,2-pentafluoroetil)estr-4-en-11 β -il][1,1'-bifenil]-4-carbonitrilo;

11 β -(3-(4'-fluoro[1,1'-bifenil]-4-il)-17 β -hidroxi-17 α -(1,1,2,2,2-pentafluoroetil)estr-4-en-3-ona;

17 β -hidroxi-17 α -(1,1,2,2,2-pentafluoroetil)-11b-[4-(3-piridinil)fenil]estr-4-en-3-ona;

11 β -(4-acetilfenil)-17 β -hidroxi-17 α -(1,1,2,2,2-pentafluoroetil)estra-4,15-dien-3-ona;

4'-[17 β -hidroxi-3-oxo-17 α -(1,1,2,2,2-pentafluoroetil)estra-4,15-dien-11 β -il][1,11-bifenil]-4-carbonitrilo;

11 β -(4'-fluoro[1,1'-bifenil]-4-il)-17 β -hidroxi-17 α -(1,1,2,2,2-pentafluoroetil)estra-4,15-dien-3-ona;

17 β -hidroxi-17 α -(1,1,2,2,2-pentafluoroetil)-11 β -[4-(3-piridinil)fenil]estr-4,15-dien-3-ona;

11 β -(4-acetilfenil)-17 β -hidroxi-17 α -(1,1,2,2,2-pentafluoroetil)estra-4,9-dien-3-ona;

4'-[17 β -hidroxi-3-oxo-17 α -(1,1,2,2,2-pentafluoroetil)estra-4,9-dien-11 β -il][1,1'-bifenil]-4-carbonitrilo;

11 β -(4'-fluoro[1,1'-bifenil]-4-il)-17 β -hidroxi-17 α -(1,1,2,2,2-pentafluoroetil)estra-4,9-dien-3-ona;

17 β -hidroxi-17 α -(1,1,2,2,2-pentafluoroetil)-11 β -[4-(3-piridinil)fenil]estra-4,9-dien-3-ona;

11 β -(4-acetilfenil)-17 β -hidroxi-17 α -(1,1,2,2,2-penta-

fluoroetil) estra-4,9,15-trien-3-ona;

4' - [17 β -hidroxi-3-oxo-17 α - (1,1,2,2,2-pentafluoroetil) estra-4,9,15-trien-11 β -il] [1,1'-bifenil] -4-carbonitrilo;

11 β - (4'-fluoro [1,1'-bifenil] -4-il) -17 β -hidroxi-17 α - (1,1,2,2,2-pentafluoroetil)) estra-4,9,15-trien-3-ona;

17 β -hidroxi-17 α (1,1,2,2,2-pentafluoroetil) -11 β - [4- (3-piridinil) fenil] estra-4,9,15-trien-3-ona;

6'-acetil-9,11 α -dihidro-17 β -hidroxi-17 α - (1,1,2,2,2-pentafluoroetil) -4'H-naft [3',2',1':10,9,11] estr-4-en-3-ona;

4- [9,11 α -dihidro-17 β -hidroxi-3-oxo-17 α - (1,1,2,2,2-pentafluoroetil) -4'H-naft [3',2',1':10,9,11] estr-4-en-6'-il] benzonitrilo;

9,11 α -dihidro-6' - (4-fluorofenil) -17 β -hidroxi-17 α - (1,1,2,2,2-pentafluoroetil) -4'H-naft [3',2',1':10,9,11] estr-4-en-3-ona;

9,11 α -dihidro-17 β -hidroxi-17 α - (1,1,2,2,2-pentafluoroetil) -6' - (3-piridinil) -4'H-naft [3',2',1':10,9,11] estr-4-en-3-ona;

6'-acetil-9,11 α -dihidro-17 β -hidroxi-17 α - (1,1,2,2,2-pentafluoroetil) -4'H-naft [3',2',1':10,9,11] estra-4,15-dien-3-ona;

4- [9,11 α -dihidro-17 β -hidroxi-3-oxo-17 α - (1,1,2,2,2-pentafluorbetil) -4'H-naft [3',2',1':10,9,11] estra-4,15-dien-6'-il] benzonitrilo;

9,11 α -dihidro-6'-(4-fluorofenil)-17 β -hidroxi-17 α -(1,1,2,2,2-pentafluoroetil)-4'H-naft[3',2',1':10,9,11]estra-4,15-dien-3-ona;

9,11 α -dihidro-17 β -hidroxi-17 α -(1,1,2,2,2-pentafluoroetil)-6'-(3-piridinil)-4'H-naft[3',2',1':10,9,11]estra-4,15-dien-3-ona;

17 β -hidroxi-11 β -(4-hidroxifenil)-17 α -(1,1,2,2,2,-pentafluoroetil)estra-4.9-dien-3-ona;

17 β -hidroxi-11 β -(4-hidroxifenil)-17 α -(1,1,2,2,2,-pentafluoroetil)estr-4-en-3-ona;

9,11 α -dihidro-6',17 β -dihidroxi-17 β -(1,1,2,2,2-pentafluoroetil)-4'H-naft[3',2',1':10,9,11]estr-4-en-3-ona;

11 β -[4-(acetiloxi)fenil]-17 β -hidroxi-17 α -(1,1,2,2,2-pentafluoroetil)estra-4,9-dien-3-ona;

11 β -[4-(acetiloxi)fenil]-17 β -hidroxi-17 α -(1,1,2,2,2-pentafluoroetil)estr-4-en-3-ona;

6'-acetiloxi-9,11 α -dihidro-17 β -hidroxi-17 α -(1,1,2,2,2-pentafluoroetil)-4'H-naft[3',2',1':10,9,11]estr-4-en-3-ona;

17 β -hidroxi-11 β -[4-(hidroximetil)fenil]-17 α -(1,1,2,2,2-pentafluoroetil)estra-4,9-dien-3-ona;

17 β -hidroxi-11 β -[4-(hidroximetil)fenil]-17 α -(1,1,2,2,2-pentafluoroetil)estr-4-en-3-ona;

9,11 α -dihidro-17 β -hidroxi-6'-hidroximetil-17 α -(1,1,2,2,2-pentafluoroetil)-4'H-naft[3',2',1':10,9,11]estr-4-en-3-ona;

4-[17 β -hidroxi-3-oxo-17 α -(1,1,2,2,2-pentafluoroetil)estra-4,9-dien-11 β -il]benzaldehido;

4-[17 β -hidroxi-3-oxo-17 α -(1,1,2,2,2-pentafluoroetil)estr-4-en-11 β -il]benzaldehido;

9,11 α -dihidro-17 β -hidroxi-3-oxo-17 α -(1,1,2,2,2-pentafluoroetil)-4'H-naft[3',2',1':10,9,11]estr-4-en-6'-al;

metiléster del ácido 4-[17 β -hidroxi-3-oxo-17 α -(1,1,2,2,2-pentafluoroetil)estra-4,9-dien-11 β -il]benzoico;

metiléster del ácido 4-[17 β -hidroxi-3-oxo-17 α -(1,1,2,2,2-pentafluoroetil)estr-4-en-11 β -il]benzoico;

metiléster del ácido 9,11 α -dihidro-17 β -hidroxi-3-oxo-17 α -(1,1,2,2,2-pentafluoroetil)-4'H-naft[3',2',1.:10,9,11]estr-4-en-6'-carboxílico;

17 β -hidroxi-11 β -[4-(1-hidroxietil)fenil]-17 α -(1,1,2,2,2-pentafluoroetil)estra-4,9-dien-3-ona;

17 β -hidroxi-11 β -[4-(1-hidroxietil)fenil]-17 α -(1,1,2,2,2-pentafluoroetil)estr-4-en-3-ona;

9,11 α -dihidro-17 β -hidroxi-6'-(1-hidroxietil)-17 α -(1,1,2,2,2-pentafluoroetil)-4'H-naft[3',2',1':10,9,11]estr-4-en-3-ona.

Se prefiere 11 β -(4-acetilfenil)-17 β -hidroxi-17 α -(1,1,2,2,2-pentafluoroetil)estra-4,9-dien-3-ona (= Compuesto A).

Los antigestágenos pueden aplicarse, por ejemplo, localmente, por vía tópica, enteral o parenteral.

Para la administración oral preferida, son particular-

mente adecuadas las tabletas,grageas,cápsulas,píldoras, suspensiones o soluciones que se pueden preparar de manera convencional con aditivos y vehículos utilizados en farmacia. Para aplicación local o tópica,se pueden utilizar tabletas vaginales o sistemas percutáneos tales como apósitos para la piel,p.ej. Para aplicación parenteral son particularmente apropiadas las soluciones,preferentemente las soluciones acuosas u oleosas,así como las suspensiones o emulsiones. Las ampollas constituyen unidades de dosificación convenientes.

De acuerdo con un modo de operación preferido, el antagonista del receptor de progesterona 17α -fluoroalquilado, se administra en general a lo largo de un período de 4 a 6 días, y más preferentemente durante los días 1-3 después de la ovulación y/o del retiro de los oocitos. En general, el antigestágeno se administra a lo largo de un período de 1 a 6 días, preferentemente 1-4 días, y más preferentemente 1-3 días después de la inducción de la ovulación con, por ejemplo, gonadotropina coriónica.

Sorprendentemente se ha encontrado, de acuerdo con la presente invención, que dosis reducidas de antagonistas del receptor de progesterona 17α -fluoroalquilado son eficaces para los métodos que se describen en la presente invención. Los antagonistas del receptor de progesterona 17α -fluoroalquilado se administran preferentemente a un sujeto humano en una dosis diaria de hasta 10 mg por sujeto,

preferentemente entre 0,1 y 2 mg por sujeto, más preferentemente entre 0,1 y 1 mg por sujeto, y de la forma más preferente, entre 0,1 y 0,7 mg por sujeto. Para mamíferos en general, la dosis diaria es en general de entre 0,01 y 1 mg/kg, preferentemente entre 0,01 y 0,3 mg/kg, y más preferentemente entre 0,01 y 0,1 mg/kg. La dosis diaria de anti-gestágeno se puede administrar como una dosis única o en dosis divididas a lo largo del día.

En una realización preferida de acuerdo con la presente invención, el antigestágeno se administra en un día único a un sujeto humano en una cantidad de entre 0,1 y 2 mg por sujeto, más preferentemente entre 0,1 y 1 mg por sujeto, y más preferentemente aún entre 0,1 y 0,7 mg por sujeto; o a un mamífero en una cantidad de entre 0,01 y 1 mg/kg, más preferentemente entre 0,01 y 0,3 mg/kg, y más preferentemente aún entre 0,01 y 0,1 mg/kg. Por ejemplo, en los días 1, 2, 3, 4, 5 ó 6 luego de la ovulación, remoción de los oocitos, o administración de una gonadotropina coriónica, preferentemente días 1-3, y más preferentemente día 2.

Para cualquier antagonista del receptor de progesterona 17 α -fluoroalquilado en particular, se puede determinar la dosis más apropiada, por ejemplo, por evaluación de la potencia para inducir la menstruación prematura en la fase luteal avanzada del ciclo humano, como se describe en, p. ej., Herrmann, W. et al., 1982, *Comptes Rendues* 294:933. La utili-

zación de antigestágenos para demorar la maduración endometrial ha sido descrita con anterioridad en, p.ej., la Paente de los EE.UU. N° 4.764.513, EP 0219447B1, Hegele-Hartung et al., 1992, Endocrinology 131:2446-2460, todas las cuales se incorporan íntegramente a la presente a modo de referencia.

Los compuestos de la presente invención se pueden utilizar mezclados con excipientes convencionales, es decir, sustancias portadoras orgánicas o inorgánicas aceptables para uso farmacéutico, adecuadas para, p.ej., aplicación parenteral, enteral (p.ej., oral) o tópica, que no reaccionan de manera adversa con los compuestos activos. Los vehículos aceptables para uso farmacéutico comprenden, de manera no limitativa, agua, soluciones salinas, alcoholes, goma arábiga, aceites vegetales, alcoholes bencílicos, polietilenglicoles, gelatina, carbohidratos tales como lactosa, amilasa o almidón, estearato de magnesio, talco, ácido silícico, parafina viscosa, aceite perfumado, monoglicéridos y diglicéridos de ácidos grasos, ésteres de ácidos grasos de pentaeritrol, hidroximetilcelulosa, polivinilpirrolidona, etc. Las preparaciones farmacéuticas se pueden esterilizar y, si se desea, se pueden mezclar con agentes auxiliares tales como p.ej. lubricantes, conservantes, estabilizantes, agentes humectantes, emulsificantes, sales para influir sobre la presión osmótica, tampones, sustancias colorantes, saborizantes y/o aromáticas, y similares que no reaccionan de manera adversa con

los compuestos activos. Los mismos pueden combinarse, cuando se desee, con otros agentes activos, como p. ej. vitaminas.

Es posible formular composiciones de liberación sostenida o dirigida, p.ej. liposomas, o aquellos en los que el compuesto activo es protegido mediante recubrimientos degradables en forma diferencial, p.ej. por microencapsulado, recubrimientos múltiples, etc. También es posible secar por congelamiento los compuestos novedosos y utilizar los liofilizados obtenidos para, p.ej., la preparación de productos para inyección.

Para la aplicación tópica, se emplean como formas no rociables, formas viscosas a semisólidas o sólidas que comprenden un vehículo compatible con la aplicación tópica y que tiene una viscosidad dinámica preferentemente mayor que la del agua. Las formulaciones adecuadas comprenden, de manera no limitativa, soluciones, suspensiones, emulsiones, cremas, ungüentos, polvos, linimentos, pomadas, aerosoles, etc., los cuales, si se desea, pueden esterilizarse, o mezclarse con agentes auxiliares, p.ej., conservantes, estabilizantes, agentes humectantes, tampones o sales para influir sobre la presión osmótica, etc. Para la aplicación tópica también son adecuadas las preparaciones en aerosol rociables en las que el ingrediente activo es envasado en una botella flexible o en una mezcla con un propelente normalmente gaseoso, por ejemplo un freón, preferentemente en combinación con un ma-

terial portador inerte sólido o líquido.

Se apreciará que las cantidades preferidas reales del compuesto activo en cada caso específico variarán según el compuesto específico que se utilice, las composiciones particulares formuladas, el modo de aplicación y el sitio y organismo particular bajo tratamiento. Las dosis para un paciente específico se pueden determinar en base a consideraciones convencionales, por ejemplo por comparación acostumbrada de las actividades diferenciales de los compuestos en cuestión de un agente conocido, por ejemplo por medio de un protocolo farmacológico convencional apropiado.

BREVE DESCRIPCIÓN DE LAS FIGURAS

La Figura 1 es una ilustración esquemática del experimento descrito en el Ejemplo 1. El día de administración de la gonadotropina coriónica humana (hCG) fue designado como día 0 de la pseudopreñez (d0). Como se muestra en el diagrama, la estimulación ovárica de los animales ocurrió en -d3, -d2 y -d1 de la inducción de la pseudopreñez, y el antagonista del receptor de la progesterona se administró en d2 de la pseudopreñez.

Sin elaboración ulterior, se entiende que una persona experimentada en el arte, utilizando la descripción precedente, puede utilizar la presente invención en toda su amplitud. Las siguientes realizaciones específicas preferidas deben considerarse por lo tanto como meramente ilustrativas y no

limitativas en ninguna forma del resto de lo que se revela.

En lo que sigue y en los ejemplos a continuación, todas las temperaturas se expresan no corregidas en grados Celsius y, a menos que se indique lo contrario, todas las proporciones y porcentajes se expresan en peso.

La totalidad de lo revelado acerca de las aplicaciones, patentes y publicaciones citadas precedentemente o a continuación, se incorporan a la presente a modo de referencia.

EJEMPLOS

Ejemplo 1: Mejora de la receptividad endometrial con bajas dosis de antagonista del receptor de la progesterona 17 α -fluoroalquilado en el modelo de conejo superovulado.

Se evaluaron los efectos de un antagonista del receptor de la progesterona 17 α -fluoroalquilado en el modelo de conejo pseudopreñado superovulado. Se ha demostrado que la pseudopreñez del conejo es un sistema modelo para la fase luteal humana. (Beiser y Kuhnel, 1973, *Hormone Res.* 4:1-27; Fischer et al., 1985, *Fertilitat* 1:101-109. En estas especies, la estimulación ovárica induce un avance de la transformación secretora (Delbos-Winter et al., 1987, *Fertilitat* 3:87-93) así como una mejora de la formación glandular.

Se utilizaron para el análisis un total de 25 conejos blancos de Nueva Zelanda nulíparos sexualmente maduros con un peso corporal de 3,1 a 4,0 kg. Los animales se dividieron en dos grupos de control (grupos 1 y 2) y tres grupos de

tratamiento (grupos 3-5), con cinco animales en cada grupo.

El grupo de control 1 recibió 75 unidades internacionales (IU) de gonadotropina coriónica humana (hCG) administrada en forma intravenosa con el objeto de inducir la pseudopreñez. El día de la inyección de hCG se designó como día 0 de la pseudopreñez (d0 p.hCG).

El grupo de control 2 y los grupos de tratamiento 3,4 y 5 fueron estimulados con gonadotropina con 5 IU de gonadotropina menopáusica humana (HMG) Pergonal® (Serono Pharma, Unterschleißheim, Alemania) durante tres días, mediante inyección subcutánea, para inducir el crecimiento folicular múltiple. La pseudopreñez se indujo mediante la administración de gonadotropina coriónica humana (hCG) como se describió precedentemente para el grupo de control 1.

Los grupos de tratamiento 3,4 y 5 también recibieron una aplicación única por vía oral de un antagonista del receptor de la progesterona 17 α -fluoroalquilado (Compuesto A) dos días después de la inducción de la pseudopreñez con la administración de gonadotropina coriónica humana (d2 p.hCG). El programa detallado del tratamiento se muestra en la Fig. I.

Los animales de todos los grupos de tratamiento se sacrificaron en día 5 a continuación de la inducción de la pseudopreñez (d5 p.hCG), y se retiraron los úteros. Se determinaron los pesos uterinos relativos en húmedo (en mg/100

g de peso corporal) y una parte del útero se congeló en forma instantánea en nitrógeno líquido para la determinación de la expresión de la uteroglobina mediante hibridización *in situ*. Se sabe que la expresión de la uteroglobina es un parámetro altamente sensible para la determinación de la receptividad endometrial (Beier, H.M., 1968. *Biochem Biophys. Acta*. 160:289-291; Beier H.M., 1982, in: Beier, H.M. y Karlson, P. (eds), *Proteins and Steroids in Early Pregnancy*), y es un marcador para la actividad secretora (Beier, 1976, *J. Reprod. Fertil. Suppl.* 25:53-69) y la diferenciación del epitelio endometrial (Krusche & Beier, 1994, *Ann. Anat.* 176:23-31). La hibridización *in situ* para la detección de la expresión de la uteroglobina se llevó a cabo como se describió precedentemente en Krusche & Beier. Otra parte del útero se retiró y se procesó para realizar la histología en parafina para determinar el estado de la transformación endometrial utilizando el Índice McPhail (McPhail Mk, 1934, *J. Phys.* 83:145-156). El Índice McPhail refleja diferentes grados de actividad progestogénica (transformadora) en el endometrio del conejo.:

1. sin transformación
2. baja transformación
3. transformación pronunciada
4. alta transformación

Los resultados se presentan en la Tabla I más adelante.

Tabla I

Efecto del tratamiento único de un antagonista del receptor de la progesterona 17 α -fluoroalquilado en el peso del útero, la transformación endometrial y la expresión del ARNm de la uteroglobina cinco días después de la inducción de la pseudopreñez (d5 p.hCG) en el conejo pseudopreñado superovulado.

Grupo	Programa de Tratamiento			Puntos finales de medición a d5 p.hCG		
	-d3, -d2, -d1 p.hCG	D0 P.Hcg	D2 p.hCG			
	5 IU HMG	75 IU HCG	Antagonista de receptor de progesterona [mg/kg]	Peso uterino húmedo [mg/kg]	McPhail [x $\pm$ SD]	Uteroglobina ISH (expresión en células epiteliales luminales)
1	-	+	-	324 $\pm$ 99	3,2 $\pm$ 0,2	Expresión muy alta
2	+	+	0	448 $\pm$ 80	3,9 $\pm$ 0,1	Expresión muy baja
3	+	+	0,1	305 $\pm$ 48	3,0 $\pm$ 0,1	Expresión muy alta
4	+	+	1	227 $\pm$ 56	1,5 $\pm$ 0,3	Expresión muy baja
5	+	+	10	144 $\pm$ 30	1,1 $\pm$ 0,3	Ausente

Como se muestra en la Tabla, los animales que fueron sometidos a hiperestimulación ovárica, pero que no fueron tratados con un antigestágeno (Grupo 2) exhibieron maduración endometrial adelantada como quedó demostrado por la expresión de la uteroglobina prácticamente indetectable en las células epiteliales luminales endometriales, el peso del

útero y el valor del índice de McPhail relativamente alto. Sin embargo, los animales que fueron sometidos a la hiperestimulación ovárica y que fueron tratados con un antigestágeno, Grupos 3-5, exhibieron un retardo en la maduración endometrial, como quedó evidenciado por los pesos uterinos húmedos y los valores del índice de McPhail. Para los animales que fueron tratados con una baja dosis de antagonista de receptor de progesterona, 0,1 mg/kg (grupo 3), la maduración endometrial correspondió en términos generales con la de los animales de control que no fueron sometidos a hiperestimulación ovárica (Grupo 1). En contraste, las dosis más altas de antagonista de receptor de la progesterona, 1 mg/kg (grupo 4) y 10 mg/kg (grupo 5), en apariencia contrarrestaron el avance de la maduración endometrial asociada con la hiperestimulación ovárica, y también retardaron el avance de la maduración más allá de la que se observó en los animales que no fueron sometidos a la hiperestimulación ovárica (Grupo 1).

Los ejemplos precedentes pueden repetirse con éxito similar sustituyendo los reactivos descritos en forma genérica o específica, y/o las condiciones de operación de la presente invención, por aquellas utilizadas en los ejemplos precedentes.

A partir de la descripción que se da a continuación, una persona experimentada en el arte está en condiciones de determinar fácilmente las características esenciales de la

presente invención, y puede efectuar diversos cambios y modificaciones de la invención para adaptarla a diversos usos y condiciones, sin apartarse del espíritu y el alcance de la misma.

REIVINDICACIONES

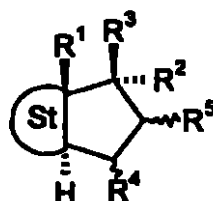
1. Un método para inhibir la ocurrencia de la maduración endometrial adelantada en un sujeto hembra humano que está bajo tratamiento para mejorar la fertilidad, que comprende administrar por lo menos un antagonista del receptor de la progesterona 17 α -fluoroalquilado al sujeto hembra durante la fase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

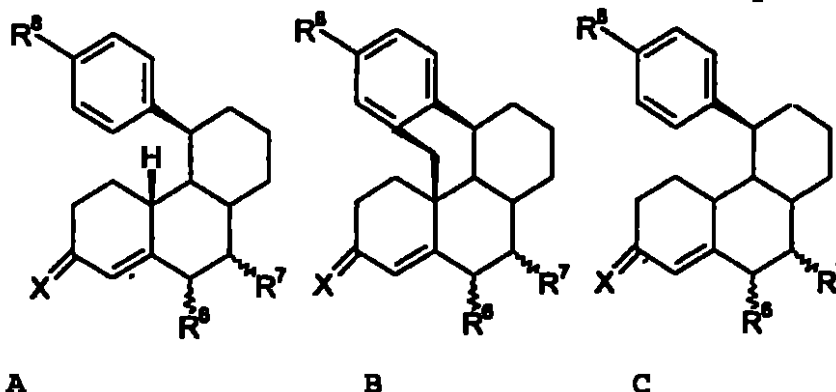
R^1 es metilo o etilo,

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 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

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, $-OH$, $-NO_2$, $-N_3$, $-CN$, $-NR^{9a}R^{9b}$, $-NH-SO_2R^9$, 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.

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.

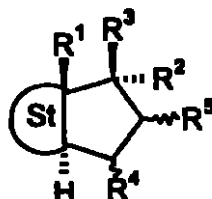
7. Un método para lograr la preñez en un sujeto hembra humano que comprende la estimulación de los ovarios del sujeto mediante la administración al sujeto de un agente estimulante folicular, donde el agente comprende hormona estimulante folicular; retirar los huevos del ovario del sujeto esti-

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:

R¹ es metilo o etilo,

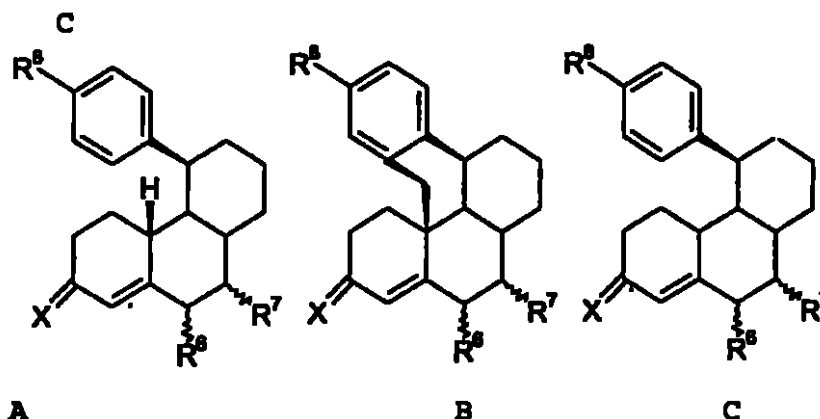
R² es C_nF_mH_o, donde n es 1-6, preferentemente 2, 3, 4, 5 o 6, m > 1 y m+o = 2n+1.

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, 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} alcanoiilo, benzoilo, C_1-C_{10} alcanoiilo, 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 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.

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 madura-
ción 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.

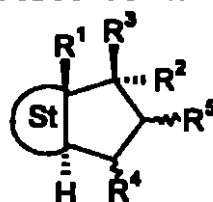
13. Un método de acuerdo con la reivindicación 12, don-
de el antagonista del receptor de la progesterona 17α -
fluoroalquilado se administra al mamífero en una dosis dia-
ria de 0,01-1 mg/kg.

14. Un método de acuerdo con la reivindicación 13, don-
de el tratamiento de fertilización comprende la administra-
ción 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:

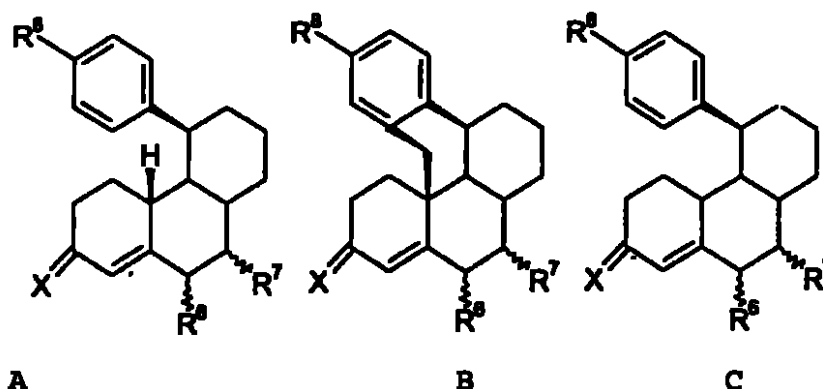
R¹ es metilo o etilo,

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} alcanciloxi, benzoiloxi, C_1-C_{10} alcancilo, 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^3 , donde R^3 es hidrógeno, así como sus sales compatibles desde el punto de vista fisiológico con bases.

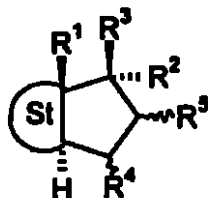
17. Un método para lograr la preñez en un mamífero no humano que comprende estimular los ovarios del mamífero mediante la administración al sujeto de un agente estimulante folicular, donde el agente comprende hormona estimulante folicular; retirar los huevos del ovario del mamífero estimulado; administrar 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 -

fluoroalquilado es un compuesto de la fórmula I:



donde:

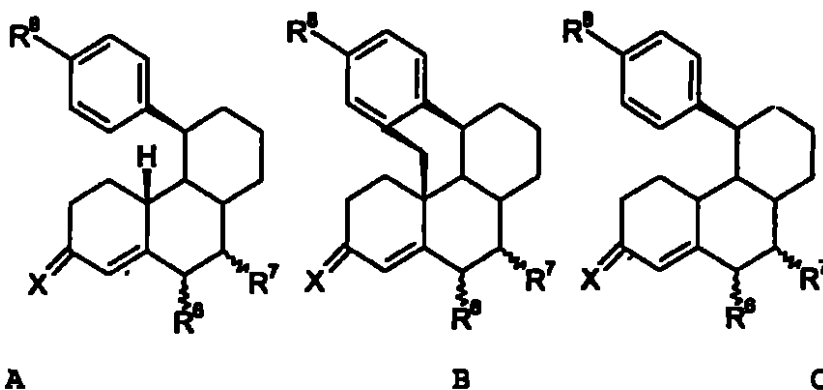
R^1 es metilo o etilo,

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,

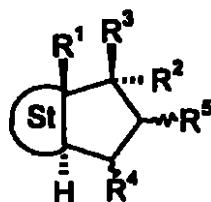
y para los radicales-NR^{9a}R^{9b}, así como para sus sales compatibles desde el punto de vista fisiológico con ácidos y para los radicales-CO₂R⁹, donde R⁹ es hidrógeno, así como sus sales compatibles desde el punto de vista fisiológico con bases.

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:

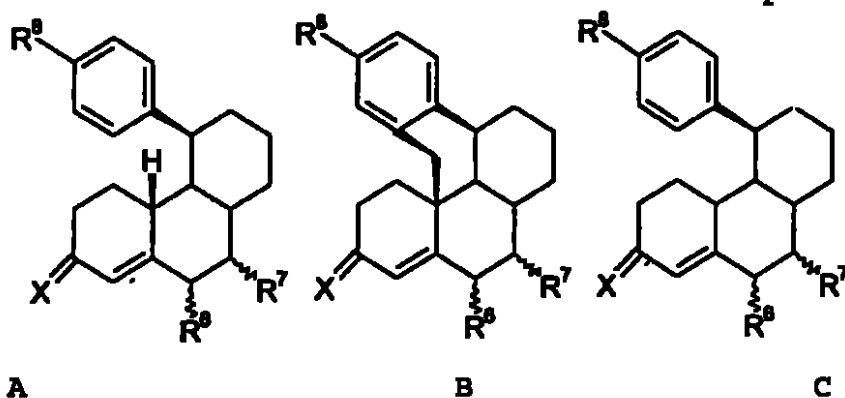
R^1 es metilo o etilo,

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 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, 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,

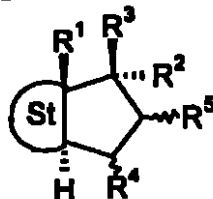
R^{9a} y R^{9b} son iguales o diferentes, y cada uno de ellos es hidrógeno o C₁-C₁₀ alquilo,

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.

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:

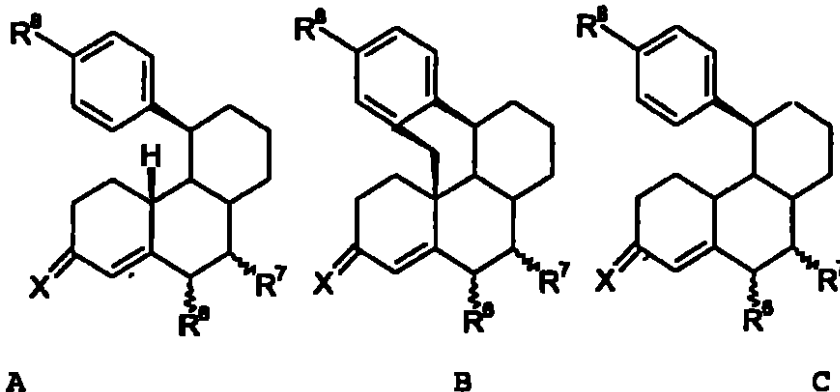
R^1 es metilo o etilo,

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

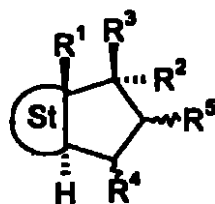


donde:

- 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, 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} alcanoiloxi, benzoiloxi, C_1-C_{10} alcanoilo, 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 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:

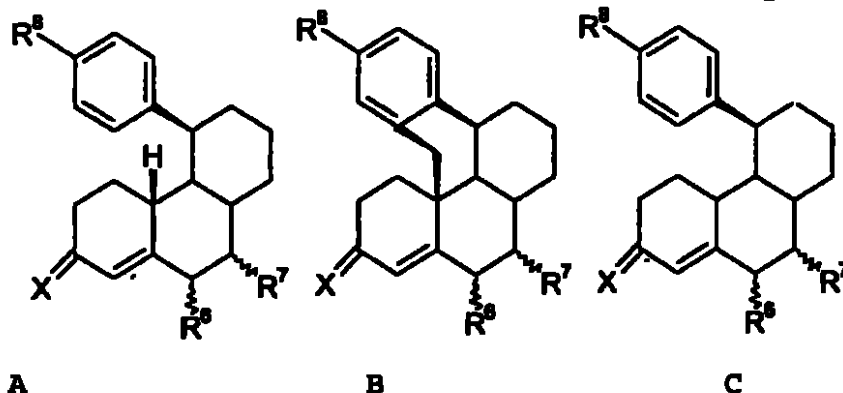
R^1 es metilo o etilo,

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,

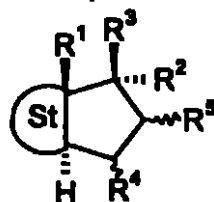
R^{9a} y R^{9b} son iguales o diferentes, y cada uno de ellos es hidrógeno o C₁-C₁₀ alquilo,

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:

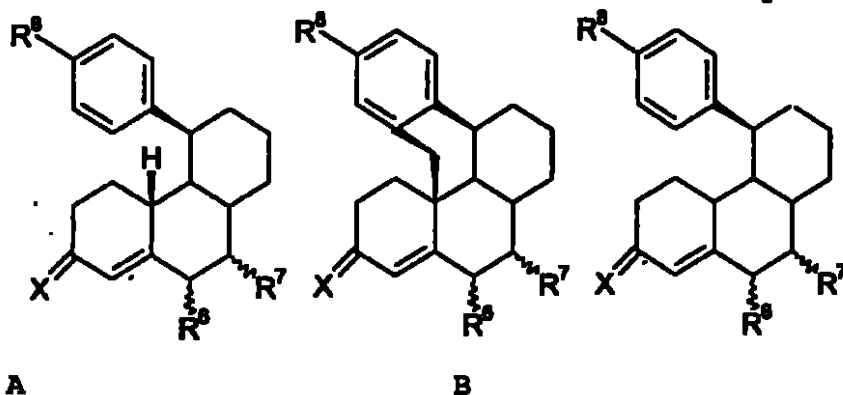
R^1 es metilo o etilo,

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

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} 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.

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 posovulatoria del ciclo endometrial.

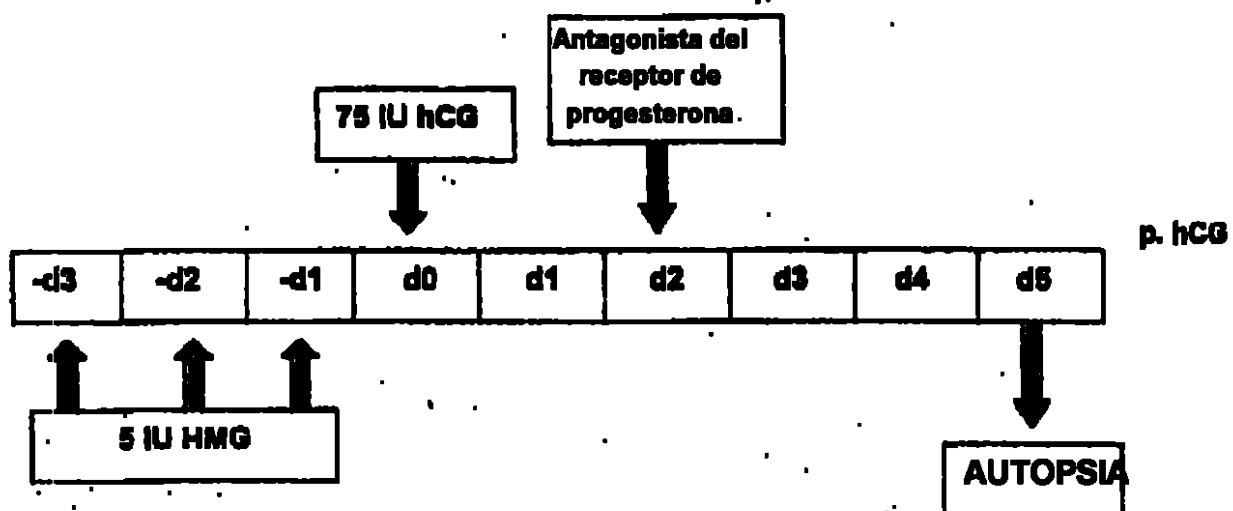
28. Un método para inhibir la ocurrencia de maduración endometrial adelantada en un sujeto hembra humano en tratamiento para mejorar la fertilidad, que comprende administrar al menos un antagonista del receptor de progesterona 17α -fluoroalquilado al sujeto hembra durante la fase pos-ovulatoria del ciclo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

29. Un método para inhibir la ocurrencia de maduración endometrial adelantada en un sujeto hembra no humano en tratamiento para mejorar la fertilidad y lograr la preñez, que comprende administrar al menos un antagonista del receptor de progesterona 17α -fluoroalquilado al sujeto hembra durante la fase pos-ovulatoria del ciclo endometrial después de dicho tratamiento para mejorar la fertilidad.

RESUMEN

Un método para inhibir la ocurrencia de la maduración endometrial adelantada en un mamífero hembra que está sometido a un tratamiento de fertilización. El método comprende la administración al mamífero hembra de por lo menos un antagonista del receptor de progesterona 17α -fluoroalquilado.

Figura 1: Diseño de estudio general en conejos sobreovulados



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

(Rationalised Report according to the Notice of the President of the EPO published in the OJ11/2001)

Applicant's or agent's file reference 51845AWOM1XX00+P	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IP/EA/416)	
International application No. PCT/IB 02/ 01764	International filing date (day/month/year) 09/01/2002	Priority date (day/month/year) 09/01/2001
International Patent Classification (IPC) or national classification and IPC A61K31/567		
Applicant SCHERING AKTIENGESELLSCHAFT et al.		

- This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 2 sheets, including this cover sheet.
☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
These annexes consists of a total of _____ sheets.

- This report contains indications relating to the following items:
 - ☒ Basis of the report
 - ☐ Priority
 - ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - ☐ Lack of unity of invention
 - ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement
 - ☐ Certain documents cited
 - ☐ Certain defects in the international application
 - ☐ Certain observations on the international application

Date of submission of the demand 08/08/2002	Date of completion of this report 15/01/2003
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 eptou d Fax: (+49-89) 2399-4465	Authorized officer SEEGERT K Tel. (+49-89) 2399 2828



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**International application No.PCT/ IB 02/ 01764

I. Basis of the report

The basis of this international preliminary examination is the application as originally filed.

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(e) PCT); see also international search report).

V. Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability

To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:

In light of the documents cited in the international search report, it is considered that the invention as defined in the independent claims, which have been the subject of an international search report, meets the criteria mentioned in Article 33(1) PCT, i.e. appears to be novel, to involve an inventive step and to be industrially applicable.

Tratado de Cooperación en Materia de Patentes

Informe de Examen Preliminar Internacional

(Artículo 36 y Regla 70 PCT)

(Informe racionalizado de acuerdo con el aviso del

**Presidente de la Oficina Europea de Patentes publicado en la
OJ11/2001)**

Referencia del solicitante o agente: 51845AWOM1XX00+P

**Actuación subsiguiente: véase la Comunicación con respecto
al envío del informe de examen preliminar internacional
(formulario PCT/IPEA/416)**

Número de acta internacional: PCT/IB02/01764

Fecha de presentación internacional (día/mes/año) 09/01/2002

Fecha de Prioridd (día/mes/año) 09/01/2001

**Clasificación internacional de Patentes (IPK) o
clasificación nacional e IPC A61K31/567**

Solicitante: SCHERING AKTIENGESELLSCHAFT y otros

**1. El informe de examen preliminar internacional fue
preparado por la repartición a quien fue encomendado el
examen preliminar internacional y le es enviada al
solicitante de acuerdo con el artículo 36.**

2. Este informe comprende en total 2 hojas incluida ésta.

**(x) Además se agregan adjuntos al informe, se trata de hojas
con descripciones, reivindicaciones y/o dibujos que fueron**

modificados y sirven como base a este informe, y/u hojas con rectificaciones llevadas a cabo ante esta reparatición (véase Regla 70.16 y Párrafo 607 de las Disposiciones Administrativas del PCT)

Estos adjuntos comprenden en total hojas.

3. Este informe contiene datos y las correspondientes hojas con respecto a los siguientes puntos:

- | | | |
|------|---|--|
| I | X | Base del informe |
| II | | Prioridad |
| III | X | No preparación de una evaluación con respecto a novedad, altura inventiva y aplicación industrial |
| IV | | escasa unidad inventiva |
| V | X | Determinación fundada de acuerdo con el artículo 35(2) con respecto a la novedad, altura inventiva y aplicación industrial; documentación y aclaraciones para respaldar esta determinación |
| VI | | Determinados antecedentes mencionados |
| VII | | Determinadas carencias de la solicitud internacional |
| VIII | | Determinadas observaciones con respecto a la solicitud internacional. |

Fecha de presentación de la petición: 08/08/2002

Fecha de terminación de este informe: 15/01/2003

Nombre y dirección postal de la repartición a quien fue
encomendado el examen preliminar internacional
Oficina Europea de Patentes - Munich - Alemania

Informe de Examen Preliminar Internacional

Solicitud internacional No. PCT/IB02/01764

I. Base del informe

Este examen preliminar internacional se ha efectuado sobre la solicitud tal como fuera presentada originalmente.

III. No determinación de una opinión con respecto a la novedad, la altura inventiva y la aplicación industrial.

La cuestión de si la invención reivindicada aparenta ser nueva, tener altura inventiva o ser industrialmente aplicable no ha evaluada en el examen preliminar internacional con respecto a las reivindicaciones que no han sido objeto de la búsqueda (Artículo 17(2)(a) o (3) y Regla 66.1(2) PCT), véase también el informe de búsqueda internacional.

V. Declaración razonada bajo Artículo 66.2(a)(ii) con respecto a novedad, altura inventiva y aplicación industrial Hasta el alcance en el que ha sido realizado el examen preliminar internacional (véase el ítem III más arriba), se puntualiza lo siguiente:

A la luz de los documentos citados en el informe de búsqueda internacional, se considera que el invento tal como está

definido en las reivindicaciones independientes que han sido objeto de un informe de búsqueda internacional, está de acuerdo con los criterios mencionados en el Artículo 33(1) PCT, es decir que aparenta ser nueva, tener altura inventiva y ser aplicable industrialmente.

PATENT COOPERATION TREATY

PCT

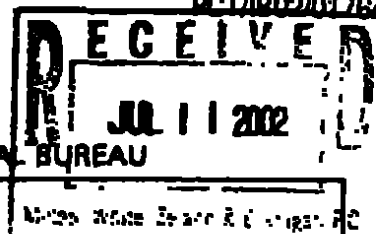
NOTIFICATION OF RECEIPT OF
RECORD COPY

(PCT Rule 24.2(a))

From the INTERNATIONAL BUREAU

To:

ZELANO, Anthony, J.
Millen, White, Zelano & Branigan,
P.C.
Arlington Courthouse Plaza 1
2200 Clarendon Boulevard
Suite 1400
Arlington, VA 22201
ETATS-UNIS D'AMERIQUE



Date of mailing (day/month/year) 18 June 2002 (18.06.02)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference SCH 1754 WO	International application No. PCT/IB02/01764

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

SCHERING AKTIENGESELLSCHAFT (for all designated States except US)
HEGELE-HARTUNG, Christa et al (for US)

International filing date : 09 January 2002 (09.01.02)
Priority date(s) claimed : 09 January 2001 (09.01.01)
09 March 2001 (09.03.01)

Date of receipt of the record copy
by the International Bureau : 28 May 2002 (28.05.02)

List of designated Offices :

AP : GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW
EA : AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
EP : AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR
OA : BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
National : AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ,
EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,
LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR,
TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.36

Authorized officer:

Ki-Nam HA

Telephone No. (41-22) 338.83.38

Form PCT/IB/301 (April 2002)

004825738

1/22/02
1/22/02

PCT REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

International Application No. PCT/IB 02/01764
International Filing Date 09 JANUARY 2002 (09.01.02)
INTERNATIONAL BUREAU OF WIPO Name of receiving Office PCT International Application
Applicant's or agent's file reference SCH 1754 WO (if desired) (12 characters maximum)

Box No. I TITLE OF INVENTION

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

Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

SCHERING AKTIENGESellschaft
-13342, Berlin
DE

☐ This person is also inventor

Telephone No. _____

Facsimile No. _____

Teleprinter No. _____

N/A

State (that is, country) of nationality: **DE**

State (that is, country) of residence: **DE**

This person is applicant for the purposes of: ☐ all designated States
☐ the United States of America only

☒ all designated States except the United States of America
☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

HEGELE-HARTUNG, Christa
Wockenbeck 101
D-45470, Muelheim a.d. Ruhr
DE

This person is:
☐ applicant only

☒ applicant and inventor

☐ inventor only (if this check-box is marked, do not fill in below.)

State (that is, country) of nationality: **DE**

State (that is, country) of residence: **DE**

This person is applicant for the purposes of: ☐ all designated States
☒ the United States of America only

☐ all designated States except the United States of America
☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet

Box No. IV AGENT OR COMMON REPRESENTATIVE: OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as ☒ agent ☐ common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

ZELANO, Anthony J.
MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
Arlington Courthouse Plaza I
2200 Clarendon Boulevard, Suite 1400
Arlington, Virginia 22201
US

Telephone No. _____

(703) 243-6333

Facsimile No. _____

(703) 243-6410

Teleprinter No. _____

N/A

☒ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTORS	
If none of the following sub-boxes is used, this sheet should not be included in the request.	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) HESS-STUMPP, Holger Gabelweihstr. 19 D-13505, Berlin DE	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (if this check-box is marked, do not fill in below.)
State (that is, country) of nationality: DE	State (that is, country) of residence: DE
This person is applicant ☐ all designated States ☐ all designated States except the United States of America for the purposes of: ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) BEIER, Henning M. Sendenstr. 19 D-52076, Aachen DE	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (if this check-box is marked, do not fill in below.)
State (that is, country) of nationality: DE	State (that is, country) of residence: DE
This person is applicant ☐ all designated States ☐ all designated States except the United States of America for the purposes of: ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) KRUSCHE, Claudia Am Weissenberg 39 D-52074, Aachen DE	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (if this check-box is marked, do not fill in below.)
State (that is, country) of nationality: DE	State (that is, country) of residence: DE
This person is applicant ☐ all designated States ☐ all designated States except the United States of America for the purposes of: ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only (if this check-box is marked, do not fill in below.)
State (that is, country) of nationality:	State (that is, country) of residence:
This person is applicant ☐ all designated States ☐ all designated States except the United States of America for the purposes of: ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.	

Box No. V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes as many as may be marked)

- Regional Patent**
- [X] **AF** ARIPO Patent: GH Ghana, CM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- [X] **EA** Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- [X] **EP** European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- [X] **OA** OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Cote d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line) SG

National Patent (if other kind of protection or treatment desired, specify on dotted line)

- | | |
|--|---|
| [X] AE United Arab Emirates | [X] KZ Kazakhstan |
| [X] AG Antigua and Barbuda | [X] LC Saint Lucia |
| [X] AL Albania | [X] LK Sri Lanka |
| [X] AM Armenia | [X] LR Liberia |
| [X] AT Austria | [X] LS Lesotho |
| [X] AU Australia | [X] LT Lithuania |
| [X] AZ Azerbaijan | [X] LU Luxembourg |
| [X] BA Bosnia and Herzegovina | [X] LV Latvia |
| [X] BB Barbados | [X] MA Morocco |
| [X] BG Bulgaria | [X] MD Republic of Moldova |
| [X] BR Brazil | [X] MC Madagascar |
| [X] BY Belarus | [X] MK The former Yugoslav Republic of Macedonia |
| [X] BZ Belize | [X] MN Mongolia |
| [X] CA Canada | [X] MW Malawi |
| [X] CH and LI Switzerland and Liechtenstein | [X] MX Mexico |
| [X] CN China | [X] MZ Mozambique |
| [X] CO Colombia | [X] NO Norway |
| [X] CR Costa Rica | [X] NZ New Zealand |
| [X] CU Cuba | [X] PH Philippines |
| [X] CZ Czech Republic | [X] PL Poland |
| [X] DE Germany | [X] PT Portugal |
| [X] DK Denmark | [X] RO Romania |
| [X] DM Dominica | [X] RU Russian Federation |
| [X] DZ Algeria | [X] SD Sudan |
| [X] EC Ecuador | [X] SE Sweden |
| [X] EE Estonia | [X] SG Singapore |
| [X] ES Spain | [X] SI Slovenia |
| [X] FI Finland | [X] SK Slovakia |
| [X] GB United Kingdom | [X] SL Sierra Leone |
| [X] GD Grenada | [X] TJ Tajikistan |
| [X] GE Georgia | [X] TM Turkmenistan |
| [X] GH Ghana | [X] TR Turkey |
| [X] GM Gambia | [X] TT Trinidad and Tobago |
| [X] HR Croatia | [X] TZ United Republic of Tanzania |
| [X] HU Hungary | [X] UA Ukraine |
| [X] ID Indonesia | [X] UG Uganda |
| [X] IL Israel | [X] US United States of America |
| [X] IN India | [X] UZ Uzbekistan |
| [X] IS Iceland | [X] VN Viet Nam |
| [X] JP Japan | [X] YU Yugoslavia |
| [X] KE Kenya | [X] ZA South Africa |
| [X] KG Kyrgyzstan | [X] ZW Zimbabwe |
| [X] KP Democratic Peoples Republic of Korea | |
| [X] KR Republic of Korea | |

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet

[X] Any countries available at time of filing but not included on this form

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

Sheet No. 4

Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request*

- 1 If in any of the Boxes, the space is insufficient to furnish all the information in each case, write "Continuation of Box No. ..." (indicate the number of the Box) and furnish the information in the same manner as required according to the caption of the Box in which the space was insufficient, as particular:
- (a) If more than two persons are involved in applications under invention and no "continuation sheet" is available; in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's (name, firm or, country of residence if no firm of residence is indicated below).
- (b) If in Box No. II or in any of the sub-boxes of Box No. III, the indication "the Signs indicated on the Supplemental Box" is checked; in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, near to (near) each name, the Sign(s) (number, where applicable, AIPO, Eureka, European or OAPI priority) for the purposes of which the named person is applicant.
- (c) If in Box No. II or in any of the sub-boxes of Box No. III, the country of the inventor/applicant is not indicated for the purposes of all designated States or for the purposes of the United States of America; in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, near to (near) each name, the Sign(s) (number, where applicable, AIPO, Eureka, European or OAPI priority) for the purposes of which the named person is inventor.
- (d) If in addition to the sign(s) indicated in Box No. IV, there are further signs; in such case, write "Continuation of Box No. IV" and indicate for each further sign the same type of information as required in Box No. IV.
- (e) If in Box No. V, the name of an Sign (or OAPI) is accompanied by the indication "parent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "sub-division" or "sub-division-in-part" in such case, write "Continuation of Box No. V" and the name of each Sign involves (for OAPI), and after the name of each such Sign (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application.
- (f) If in Box No. VI, there are more than three earlier applications whose priority is claimed; in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.
- (g) If in Box No. VI, the earlier application is an AIPO application; in such case, write "Continuation of Box No. VI", specify the number of the case corresponding to the earlier application and indicate in bold one country party to the Paris Convention for the Protection of Industrial Property for which this earlier application was filed.
- 2 If with regard to the preliminary designation statement contained in Box No. V, the applicant wishes to exclude any Sign(s) from the scope of that statement in such case, write "Designation(s) excluded from preliminary designation statement" and indicate the name or two-letter code of each Sign so excluded.
- 3 If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-patentable disclosures or exceptions to laws of novelty; in such case write "Indicate character(s) non-patentable disclosures or exceptions to laws of novelty" and furnish the necessary details.

Continuation of Box No. IV:

AXELROD, Nancy J.
BRANIGAN, Alan E. J.
BRANIGAN, Jennifer J.
HEANEY, Brian P.
LEBOVITZ, Richard M.
MILLEN, I. William
MOSES, John R.
RULAND, James R.
SHUBIN, Harry B.
SOPP, John A.
THOMAS, John H.
TRAVERSO, Richard J.
WHITE, John L.
ZELANO, Anthony J.
MCCARTHY, Robert E.
BROWN, Jonathan G.

All members of the firm of MILLEN, WHITE, ZELANO & BRANIGAN, P.C. at the address, telephone and facsimile numbers as indicated in Box No. IV

Sheet No 5

Box No. VI PRIORITY CLAIM

[] Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application: regional Office	international application: receiving Office
item (1) 09 JANUARY 2001	09/756,286	US		
item (2) 09 MARCH 2001	09/801,925	US		
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s) 1 and 2.

* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(a)(i)). See Supplemental Box.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two more International Searching Authorities are competent to carry out the international search indicate the Authority chosen, the two-letter code may be used):
ISA US EP

Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority).

Date (day/month/year) Number Country (or regional Office)

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application consists the following number of sheets:

request	5 sheets
description (including sequence listing part)	17 sheets
claims	16 sheets
abstract	1 sheet
drawings	1 sheet
sequence listing part of description	_____ sheets
Total number of sheets	40 sheets

This international application is accompanied by the item(s) marked below.

- ☒ fee calculation sheet (duplicate)
- ☐ separate signed power of attorney
- ☐ copy of general power of attorney, reference number, if any:
- ☐ statement explaining lack of signature
- ☐ priority document(s) identified in Box No. VI as item(s)
- ☐ translation of international application into (language):
- ☐ separate indications concerning deposited microorganism or other biological material
- ☐ nucleotide and/or amino acid sequence listing in computer readable form
- ☒ other (specify): Transmittal

Figure of the drawings which should accompany the abstract Fig. 1

Language of filing of the international application: ENGLISH

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Place an own signature, indicating the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Anthony J. Zelano
Agent for the Applicant(s)

SCHERING AKTIENGESELLSCHAFT
i.V. Dr. Brösamle i.A. Durst

For receiving Office use only

1. Date of actual receipt of the purported international application:	JC07 Rec'd PCT/FTO 09 JAN 2002	2 Drawings.
3. Corrected date of actual receipt due to later but merely received papers or drawings completing the purported international application:		[] received:
4. Date of timely receipt of the required corrections under PCT Article 17(2).		[] not received:
5 International Searching Authority (if two or more are competent) ISA/	6 [] Transmittal of search copy delayed until search fee is paid	

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

Supplemental Box

If the Supplemental Box is not used, this sheet should not be included in the request.

1. If, in any of the Boxes, except Boxes Nos. VIII(i) to (v) for which a special continuation box is provided, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:
 - (i) If more than two persons are to be indicated as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;
 - (ii) If, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;
 - (iii) If, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;
 - (iv) If, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;
 - (v) If, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;
 - (vi) If, in Box No. VI, there are more than five earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.
2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.

Christa Hegele-Hartung
HEGELE-HARTUNG, Christa

Holger Hess-Stumpp
HESS-STUMPP, Holger

Henning M. Beier
BEIER, Henning M.

Claudia Krusche
KRUSCHE, Claudia

For receiving Office use only

PCT
REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

International Application No.
International Filing Date
Name of receiving Office and "PCT International Application"
Applicant's or agent's file reference : SCH 1754 WO (if desired) (12 characters maximum)

Box No. I TITLE OF INVENTION THE USE OF ANTIGESTAGENS FOR INHIBITING ACCELERATED ENDOMETRIAL MATURATION DURING INFERTILITY TREATMENT	
Box No. II APPLICANT	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) SCHERING AKTIENGESELLSCHAFT D-13342, Berlin DE	☐ This person is also inventor. Telephone No. _____ Facsimile No. _____ Teleprinter No. _____ N/A
State (that is, country) of nationality: DE	State (that is, country) of residence: DE
This person is applicant ☐ all designated States ☒ all designated States except the United States of America for the purposes of: ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) HEGELE-HARTUNG, Christa Woolenbeck 101 D-45470, Muelheim a.d. Ruhr DE	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)
State (that is, country) of nationality: DE	State (that is, country) of residence: DE
This person is applicant ☐ all designated States ☐ all designated States except the United States of America for the purposes of: ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.	
Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE	
The person identified below is hereby/has been appointed to act on behalf ☒ agent ☐ common representative of the applicant(s) before the competent International Authorities as:	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) ZELANO, Anthony J. MILLEN, WHITE, ZELANO & BRANIGAN, P.C. Arlington Courthouse Plaza 1 2200 Clarendon Boulevard, Suite 1400 Arlington, Virginia 22201 US	Telephone No. (703) 243-6333 Facsimile No. (703) 243-6410 Teleprinter No. N/A
☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.	

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

HESS-STUMPP, Holger

Gabelwehstr. 19

D-13505, Berlin

DE

This person is:

☐ applicant only☒ applicant and inventor☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality: DE

State (that is, country) of residence: DE

This person is applicant ☐ all designated States☐ all designated States except the United States of Americafor the purposes of: ☒ the United States of America only☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

BEIER, Henning M.

Lottbendenstr. 19

D-52076, Aachen

DE

This person is:

☐ applicant only☒ applicant and inventor☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality: DE

State (that is, country) of residence: DE

This person is applicant ☐ all designated States☐ all designated States except the United States of Americafor the purposes of: ☒ the United States of America only☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

KRUSCHE, Claudia

Am Weisenberg 39

D-52074, Aachen

DE

This person is:

☐ applicant only☒ applicant and inventor☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality: DE

State (that is, country) of residence: DE

This person is applicant ☐ all designated States☐ all designated States except the United States of Americafor the purposes of: ☒ the United States of America only☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

☐ applicant only☐ applicant and inventor☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant ☐ all designated States☐ all designated States except the United States of Americafor the purposes of: ☐ the United States of America only☐ the States indicated in the Supplemental Box☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a)(mark the applicable check-boxes at least one must be marked):

Regional Patent

- [X] AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- [X] EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- [X] EP European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- [X] OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line)

- | | |
|--|--|
| [X] AE United Arab Emirates | [X] KZ Kazakhstan |
| [X] AG Antigua and Barbuda | [X] LC Saint Lucia |
| [X] AL Albania | [X] LK Sri Lanka |
| [X] AM Armenia | [X] LR Liberia |
| [X] AT Austria | [X] LS Lesotho |
| [X] AU Australia | [X] LT Lithuania |
| [X] AZ Azerbaijan | [X] LU Luxembourg |
| [X] BA Bosnia and Herzegovina | [X] LV Latvia |
| [X] BB Barbados | [X] MA Morocco |
| [X] BG Bulgaria | [X] MD Republic of Moldova |
| [X] BR Brazil | [X] MG Madagascar |
| [X] BY Belarus | [X] MK The former Yugoslav Republic of Macedonia |
| [X] BZ Belize | [X] MN Mongolia |
| [X] CA Canada | [X] MW Malawi |
| [X] CH and LI Switzerland and Liechtenstein | [X] MX Mexico |
| [X] CN China | [X] MZ Mozambique |
| [X] CO Colombia | [X] NO Norway |
| [X] CR Costa Rica | [X] NZ New Zealand |
| [X] CU Cuba | [X] PH Philippines |
| [X] CZ Czech Republic | [X] PL Poland |
| [X] DE Germany | [X] PT Portugal |
| [X] DK Denmark | [X] RO Romania |
| [X] DM Dominica | [X] RU Russian Federation |
| [X] DZ Algeria | [X] SD Sudan |
| [X] EC Ecuador | [X] SE Sweden |
| [X] EE Estonia | [X] SG Singapore |
| [X] ES Spain | [X] SI Slovenia |
| [X] FI Finland | [X] SK Slovakia |
| [X] GB United Kingdom | [X] SL Sierra Leone |
| [X] GD Grenada | [X] TJ Tajikistan |
| [X] GE Georgia | [X] TM Turkmenistan |
| [X] GH Ghana | [X] TR Turkey |
| [X] GM Gambia | [X] TT Trinidad and Tobago |
| [X] HR Croatia | [X] TZ United Republic of Tanzania |
| [X] HU Hungary | [X] UA Ukraine |
| [X] ID Indonesia | [X] UG Uganda |
| [X] IL Israel | [X] US United States of America |
| [X] IN India | [X] UZ Uzbekistan |
| [X] IS Iceland | [X] VN Viet Nam |
| [X] JP Japan | [X] YU Yugoslavia |
| [X] KE Kenya | [X] ZA South Africa |
| [X] KG Kyrgyzstan | [X] ZW Zimbabwe |
| [X] KP Democratic People's Republic of Korea | Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet: |
| [X] KR Republic of Korea | [X] Any countries available at time of filing but not included on this form |

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 18 month time limit.)

Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

1. If, in any of the Boxes, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No. ..." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:
 - (i) If more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;
 - (ii) If, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;
 - (iii) If, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor-applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;
 - (iv) If, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;
 - (v) If, in Box No. V, the name of one State (or OAPI) is accompanied by the indication "parent of addition," or "verifications of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;
 - (vi) If, in Box No. VI, there are more than three earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;
 - (vii) If, in Box No. VI, the earlier application is an ARIPO application: in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed.
2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.
3. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty: in such case write "Statement concerning non-prejudicial disclosures or exceptions to lack of novelty" and furnish that statement below.

Continuation of Box No. IV:

AXELROD, Nancy J.
 BRANIGAN, Alan E. J.
 BRANIGAN, Jennifer J.
 HEANEY, Brian P.
 LEBOVITZ, Richard M.
 MILLEN, I. William
 MOSES, John R.
 RULAND, James E.
 SHUBIN, Harry B.
 SOPP, John A.
 THOMAS, John H.
 TRAVERSO, Richard J.
 WHITE, John L.
 ZELANO, Anthony J.
 MCCARTHY, Robert E.
 BROWN, Jonathan G.

All members of the firm of MILLEN, WHITE, ZELANO & BRANIGAN, P.C. at the address, telephone and facsimile numbers as indicated in Box No. IV.

Box No. VI PRIORITY CLAIM		☐ Further priority claims are indicated in the Supplemental Box.		
		Where earlier application is:		
Filing date of earlier application (day/month/year)	Number of earlier application	national application: country	regional application:* regional Office	international application: receiving Office
item (1) 09 JANUARY 2001	09/756,286	US		
item (2) 09 MARCH 2001	09/801,925	US		
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present International application is the receiving Office) identified above as item(s): 1 and 2

* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10b)(ii). See Supplemental Box.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):
ISA/US

Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):
Date (day/month/year) Number Country (or regional Office)

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following number of sheets:

request	:	5 sheets
description (excluding sequence listing part)	:	17 sheets
claims	:	16 sheets
abstract	:	1 sheet
drawings	:	1 sheets
sequence listing part of description	:	_____ sheets
Total number of sheets	:	40 sheets

This international application is accompanied by the item(s) marked below:

1. ☒ fee calculation sheet (duplicate)
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☒ other (specify): Transmittal

Figure of the drawings which should accompany the abstract: Fig. 1

Language of filing of the international application: ENGLISH

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Anthony J. Zelano #32,004

Anthony J. Zelano (Reg. No. 27,969)
Agent for the Applicant(s)

For receiving Office use only

1. Date of actual receipt of the purported international application:		2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:		
4. Date of timely receipt of the required corrections under PCT Article 11(2):		
5. International Searching Authority (if two or more are competent): <u>ISA/</u>	6. ☐ Transmittal of search copy delayed until search fee is paid	

For International Bureau use only

Date of receipt of the international application: 10

Fax (1 Page)



Schering AG
Corporate Patents

EUROPÄISCHES PATENTAMT

ERHARDTSTRASSE 27
D-80298 MÜNCHEN

Your Ref.

Your letter dated

Our Ref. (please indicate when replying)

Telephone: +49-30-466-11532

Date

Dr.Brösamle/Du

+49-30-4 66-11 11

Telefax: +49-30-466-12058

2002-09-13

International Application PCT/IB02/01764

Applicant: SCHERING AKTIENGESELLSCHAFT

Our Ref.: 51845AWOM1XX00+P

COMMUNICATION IN CASE FOR WHICH NO OTHER FORM IS APPLICABLE
dated 16.08.2002

SCHERING AKTIENGESELLSCHAFT is the applicant of the above-mentioned international patent application.

SCHERING AKTIENGESELLSCHAFT is based in D-13353 Berlin, Müllerstr. 178, Germany.

The address for correspondence is SCHERING AKTIENGESELLSCHAFT, Corporate Patents, D-13342 Berlin, Germany.

SCHERING AKTIENGESELLSCHAFT

i.V.

i.A.


Dr. Kostrucha
Corporate Patents


Durst
Corporate Patents

Postal address: Schering AG, D-13342 Berlin, Germany • For visitors: Berlin-Wedding, Müllerstrasse 178 • Cable: Scheringchemie Berlin • Internet: <http://www.schering.de>

Executive board: Hubertus Erlen (Chairman), Klaus Pohl (Vice-Chairman), Ulrich Kösten, Lutz Lingrau, Jörg Spiekardt (Deputy), Günter Stock - Chairman of the supervisory board.
Giuseppe Vita • Registered seat: Berlin • Trade register: AG Charlottenburg 93 HRB 283 • Commerzbank AG, Berlin, Account No. 108700800, Bank prefix No. 100 400 00 • BfF-Bank AG, Berlin, Account No. 70045224, Bank prefix No. 100 202 00 • Deutsche Bank AG, Berlin, Account No. 2415008, Bank prefix No. 100 700 00

03 66215

| MANTENIMIENTO DE PROTOCOLOS

|Numero : 605

|Fecha : 15/01/1974

|Conferido: SCHERINGAKTIENGESSELLSCHAFT

|

|Pais : DE ALEMANIA

|Ciudad : 355 BERGKAMEN

|Represent: S Sustituir: S Desistir: S

|No. Radicacion : Clase: Seev: Seac:

|

leucia	Codigo	Ctr	Nombre
8	231	A	LLOREDA CAMACHO JOSE
9	267	B	HOLLMANN RESTREPO GUSTAVO
10	2006		ESGUERRA CAMARGO LUIS
	Encontrados (1/1) registro(s)		

|

| There are no more rows in the direction you are going

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION ☒ MODELO DE UTILIDAD	()	()
- Indicación de que se solicita la concesión de una patente.	()	()
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	()
- Descripción de la invención.	()	()
- Dibujos de ser estos pertinentes.	()	()
- Comprobante de Pago de las tasas establecidas.	()	()

COMPLETA () **INCOMPLETA** ()

DISEÑO INDUSTRIAL ()

- Indicación de que se solicita el registro de Diseño Industrial	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	()	()
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	()	()
- Comprobante de pago de las tasas establecidas	()	()

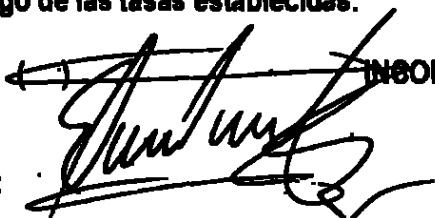
COMPLETA () **INCOMPLETA** ()

ESQUEMA DE TRAZADO ()

- Indicación de que solicita el registro de un Esquema de trazado.	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	()	()
- Representación gráfica del esquema de trazado	()	()
- Comprobante de pago de las tasas establecidas.	()	()

COMPLETA ☒ **INCOMPLETA** ()

Firma Responsable:



SUPERINDUSTRIA Y COMERCIO

Radicación: 03066215 0000000

Folios: 114

Fecha (AÑO): 2003-08-04 16:15:20

Fecha:

Trámite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES



416
117

2020
Bogotá, D.C.,

Doctor:
Gustavo Hollmann Restrepo
Apoderado
SCHERING AKTIENGESELLSCHAFT.

Oficio N°

09114

ASUNTO:	Radicación N°	03-66215
	Solicitud internacional	PCT/IB2002/01764
	Fecha Inicio fase nacional	09/08/2003
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

- ☐ La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 28-k) Decisión 486).

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


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

El anterior requerimiento fue notificado por fijación en lista de fecha,

24 OCT. 2003