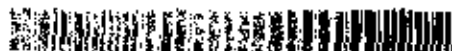


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Clarke, Modet & Cº

COLOMBIA

SECRETARÍA DE INDUSTRIA Y COMERCIO



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SECRETARÍA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES
BOGOTÁ, D.C. - COLOMBIA

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DIVISIÓN DE NUEVAS CREACIONES
E.S.D.

REF: EXPEDIENTE No. 0712095
SOLICITANTE: THE POPOLUTION COUNCIL, INC.
LABORATOIRE HRA PHARMA
PATENTE: COMPOSICIONES DE LIBERACIÓN SOSTENIDA QUE
CONTIENEN MODULARES DEL RECEPTOR DE
PROGESTERONA

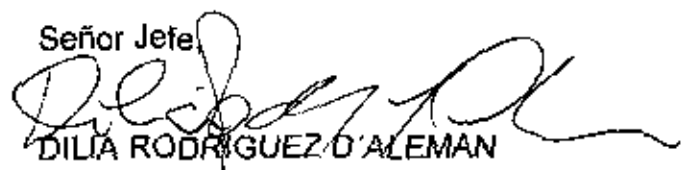
ASUNTO: SOLICITUD ESTUDIO DE FONDO

DILIA RODRÍGUEZ D'ALEMAN, en mi condición de apoderada de la Sociedad solicitante, por el presente escrito atentamente solicito a Usted que habiéndose surtido la publicación de la presente solicitud, en la Gaceta de la Propiedad Industrial No.587 de fecha 18 de enero de 2008 se proceda con el estudio de Fondo.

Para tal fin me permito anexar la tasa correspondiente.

Agradezco continuar con el presente trámite.

Señor Jefe


DILIA RODRÍGUEZ D'ALEMAN
C.C. 41.654.382 Bogotá

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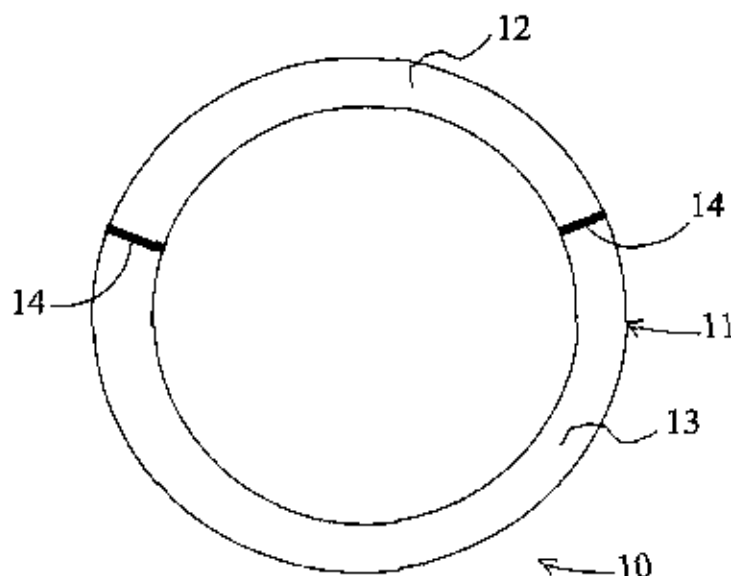
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- (71) Applicants (for all designated States except US): **THE GENERAL HOSPITAL CORPORATION** (US/US); Fruit Street, Boston, MA 02114 (US). **MASSACHUSETTS INSTITUTE OF TECHNOLOGY** (US/US); 5 Cambridge Center, NE25-230, Cambridge, MA 02142 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **RON, Eyal, S.** (US/US); 7 Coach Road, Lexington, MA 02420 (US).
- (74) Agent: **GYURE, Barbara, A.**; Palmer & Dodge LLP, 111 Huntington Avenue, Boston, MA 02199-7613 (US).
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[Continued on next page]

(54) Title: METHODS AND DEVICES FOR THE SUSTAINED RELEASE OF MULTIPLE DRUGS



(57) Abstract: The invention relates to an drug delivery device and a method for delivering multiple drugs over a prolonged period of time. The drug delivery device has two or more unitary segments comprising a drug-permeable polymeric substance, wherein at least one of the segments further comprises a pharmaceutically active agent. The invention also relates to a method for the treatment of a benign ovarian secretory disorder in a female mammal, a method of contraception, and a method of relieving the symptoms associated with menopausal, perimenopausal and post-menopausal periods in a woman.

WO 2004/096151 A2

WO 2004/096151

PCT/US2004/013172

METHODS AND DEVICES FOR THE SUSTAINED RELEASE OF MULTIPLE DRUGS

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 60/466,318, filed
5 on April 29, 2003, and U.S. Provisional Application No. 60/473,579, filed on May 27, 2003.
The entire teachings of the above applications are incorporated herein by reference.

FIELD OF THE INVENTION

The invention relates to drug delivery devices for the controlled release of multiple drugs
in a substantially constant ratio over a prolonged period of time. More specifically the invention
10 relates to intravaginal devices and methods for contraception, hormone replacement therapy, and
therapeutic methods for the treatment of reproductive conditions and disorders, such as benign
ovarian secretory disorders.

BACKGROUND

The desirability of sustained release drug formulations has long been a goal in the
15 pharmaceutical industry. Sustained release systems solve many of the problems associated with
conventional drug delivery systems, e.g., pills. For example in conventional drug delivery
systems administration of the drug is given frequently and results in high variability in
circulating drug levels during the course of treatment. The concentration of the drug increases to
therapeutic concentrations after administration, but in some instances the concentration rises
20 above the minimal therapeutic level reaching the toxic threshold. After a relatively short period
of the drug concentration decreases via metabolism or excretion to levels that are no longer
therapeutic.

In order to achieve constant levels of drugs and avoid the inefficiencies of the drug
concentration peaks and valleys the drugs should be released from a delivery system at a rate
25 that does not change with time (so called zero- order release). Preferably, the initial dose of a
drug is the therapeutic dose, which is maintained by the delivery system. Examples of a current
sustained drug delivery system include the reservoir systems which consist of tubes, fibers,
laminates, or microspheres. In these systems, a drug reservoir is coated in a rate-controlling
membrane. Drug diffusion across the membrane is rate limiting and is constant (zero order) as

WO 2004/096151

PCT/US2004/013172

Additionally, constant and reliable delivery of drugs or combinations of drugs over long periods of time would be useful in a wide variety of applications, including treatment or prevention of AIDS/HIV, atherosclerosis, various cancers, cardiovascular diseases, hypertension, toxemia of pregnancy, seizures degenerative neurological disorders, diabetes, hematological disorders, addictions, and obesity and eating disorders, to name a few. Unfortunately, in addition to not always providing satisfactory release, release ratio or release term in some cases, all currently available intravaginal drug delivery devices suffer from being relatively complicated, making them expensive to manufacture. Thus, a need exists for an improved drug delivery device for the controlled release of multiple drugs, particularly a device which releases the drugs in a substantially constant ratio over a prolonged period of time, and which is easy and inexpensive to manufacture.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide a drug delivery device for the sustained release of multiple drugs over a prolonged period of time. Additionally, the present invention also provides for a less expensive and easier to produce device than currently available devices. It is also an object of the invention to provide a method of treating disease with the device, particularly benign ovarian secretory disorders. It is also an object of the invention to administer multiple drugs for use in contraception and hormone replacement therapy.

In a first aspect, the present invention relates to a drug delivery device comprising two or more unitary segments. Each segment comprises a drug-permeable polymeric substance, and at least one segment comprises a mixture of the drug-permeable polymeric substance and a drug. Two or more segments may each contain a drug, preferably a different drug in each segment. The drug-permeable polymeric substance may be a thermoplastic polymer, such as an ethylene-vinyl acetate copolymer. At least one end of a segment may be attached to the end of another unitary segment by a coupling means, such as an adhesive material or by annealing the ends of the segments to same or different thermoplastic polymers. The drug delivery device may be in the shape of a ring, a wafer, or a suppository, and may be suitable for use as a vaginal ring. The drug delivery device may have an overall diameter of from 40 mm to 80 mm, and a cross-sectional diameter of from 2 mm to 12 mm. The drug to be delivered may be a hormone replacement steroid or a contraceptive agent, for example an estrogenic compound, a progestational compound, and/or a gonadotropin releasing hormone or its peptide or non-peptide agonists or antagonist analogues. The drug may also be an interferon, anti-angiogenesis factors,

WO 2004/096151

PCT/US2004/013172

ethynodiol diacetate, medroxyprogesterone acetate, megestrol acetate, phytoprogestins, animal-derived progestins, and metabolic derivatives of animal-derived progestins. These compounds also include any steroidal or non-steroidal compounds that bind to the cytoplasmic or membrane bound progesterone and mimic any of the biologic effects of progesterone or
5 progestins.

As used herein, the terms "androgenic steroid" and "androgen" are used interchangeably to refer to a natural or synthetic agent that stimulates activity of the accessory male sex organs and/or muscle development and/or encourages development of male sex characteristics. Examples of suitable androgens include, without limitation, testosterone, methyltestosterone,
10 fluoxymesterone, testosterone cypionate, testosterone enanthate, testosterone propionate, oxymetholone, ethylestrenol, oxandrolone, nandrolone phenpropionate, nandrolone decanoate, testosterone buccilate, stanozolol, dromostanolone propionate, androstenedione, dehydroepiandrosterone, dehydroepiandrosterone sulfate (DHEAS), dihydrotestosterone, phytoandrogens, animal-derived androgens, and metabolic derivatives of animal-derived
15 androgens. This also included any steroidal or non-steroidal compounds that bind to either the cytoplasmic or membrane bound androgen receptor and produce biologic effects that mimic testosterone or other androgenic compounds.

A "selective estrogen receptor modulator" ("SERM") is a compound that is an estrogen analog and which exerts tissue-selective effects. Such compounds can function as
20 estrogen antagonists or partial agonists. Examples of suitable SERMs include tamoxifen, raloxifene, clomiphene, droloxifene, idoxifene, toremifene, tibolone, ICI 182,780, ICI 164,384, diethylstilbesterol, genistein, nafoxidine, moxestrol, 19-nor-progesterone derivatives, and 19-nor-testosterone derivatives.

A "selective androgen receptor modulator" ("SARM") is a compound that is an
25 androgen analog and which exerts tissue-selective effects. Such compounds can function as androgen antagonists or partial agonists. Examples of suitable SARMs include cyproterone acetate, hydroxyflutamide, bicalutamide, spironolactone, 4-(trifluoromethyl)-2(1H)-pyrrolidino[3,2-g]quinolinone derivatives, 1,2-dihydropyridono[5,6-g]quinoline derivatives, and piperidino[3,2-g]quinolinone derivatives.

30 A "selective progestin receptor modulator" ("SPRM") is a compound that is an progesterone analog and which exerts tissue-selective effects. Such compounds can function as

152

152

WO 2004/096151

PCT/US2004/013172

progesterone antagonists or partial agonists. Examples of suitable SPRMs include RU486, CDB2914, 19-nor-progesterone derivatives, 19-nor-testosterone derivatives, 6-aryl-1,2-dihydro-2,2,4-trimethylquinoline derivatives, 5-aryl-1,2-dihydro-5H-chromeno[3,4-f]quinoline derivatives, 5-alkyl 1,2-dihydrochromeno[3,4-f]quinoline derivatives, and 6-thiophenehydroquinoline derivatives.

Unless indicated otherwise, the hormonal steroids used in the methods of the present invention (e.g., estrogenic steroids, progestational steroids, and androgenic steroids) include the respective sex steroids (both natural and synthetic, including derivatives and analogues thereof), as well as their respective hormone receptor modulator compounds (e.g., SERMs, SPRMs, and SARMs). Hormonal steroids are well known in the art and are described, for example, in
10 *Remington's Pharmaceutical Sciences* (16th edition, 1980) at pages 925-939.

A "postmenopausal" woman is one who in the absence of hormone replacement therapy or other medication would experience at least 12 months of amenorrhea or levels of serum follicle-stimulating hormone greater than 30 mIU/mL.

15 A "perimenopausal" woman is one who in the absence of hormone replacement therapy or other medication would experience a change in her intermenstrual cycle interval and have associated symptoms of estrogen deficiency, such as vasomotor flushes, vaginal dryness, and worsening premenstrual syndrome. Also included are women who in the absence of hormone replacement therapy or other medication would experience less than 12 months of amenorrhea.

20 As used herein, the term "drug" means any physiologically or pharmacologically active substance that produces a local and/or systemic effect in a mammal, such as a human.

As used herein, "pharmacologically effective amount," "therapeutically effective amount" or simply "effective amount" refers to that amount of a drug effective to produce the intended pharmacological, therapeutic or preventive result. For example, if a given clinical
25 treatment is considered effective when there is at least a 25% reduction in a measurable parameter associated with a disease or disorder, a therapeutically effective amount of a drug for the treatment of that disease or disorder is the amount necessary to effect at least a 25% reduction in that parameter.

The term "controlled-release" is defined for purposes of the present invention as the
30 release of a drug at such a rate that blood (e.g., plasma) concentrations are maintained within the

WO 2004/096151

PCT/US2004/013172

administration of the delivery system is made via the vaginal route. Approximately 1-10% or greater of the LHRH composition is absorbed through the vaginal epithelium. Thus, the LHRH composition is administered via a vaginal delivery system using a matrix which permits transvaginal absorption. In this same first vaginal delivery system, an effective dosage of physiological amounts of an estrogenic steroid is also delivered. This delivery system allows complete suppression of gonadotropins, removal of reproductive function of the ovaries, total suppression of ovarian steroidogenesis, and yet still effects a physiological replacement of sufficient levels of estrogen to thwart the long term side effects of the estrogen deficiency that occurs during LHRH administration. This vaginal delivery device is preferably administered during the follicular phase of the menstrual cycle, beginning at the onset of menses.

The methods of the invention would also be useful to induce breeding. In seasonal breeding animals, such as sheep, sequential application of an induced follicular phase of variable length followed by an induced luteal phase would induce subsequent estrous. Such induced estrous provides a more timely and experimentally controllable breeding. The methods of the invention would also serve to induce breeding at a higher frequency, for example, to induce breeding more than once or twice a year.

V. Methods for Preventing Pregnancy in Mammals

In another embodiment, the invention relates to a method for preventing pregnancy in a mammal. The method comprises administering an effective amount of an LHRH composition (i.e., luteinizing hormone releasing hormone (LHRH), LHRH analogues, LHRH agonists and/or LHRH antagonists, and/or their non-peptide analogues capable of binding to the LHRH receptor) and an effective amount of an estrogenic steroid and/or a selective estrogen receptor modulator (SERM) during the follicular phase of the menstrual cycle, beginning at the onset of normal menses. Next, during the luteal phase of the menstrual cycle, the method comprises administering an effective amount of a LHRH composition, an effective amount of an estrogenic steroid and/or SERM, and an effective amount of a progestational steroid and/or a selective progestin receptor modulator (SPRM). Following the luteal phase, the LHRH composition and an effective amount of an estrogenic steroid and/or SERM are administered, at which time menstruation would typically occur. The continuous delivery of LHRH compositions in combination with sex steroid delivery for use as a contraceptive is described in detail in U.S. Pat. No. 4,762,717 (Crowley, Jr.), which is incorporated by reference in its entirety herein.

154

WO 2004/096151

PCT/US2004/013172

dydrogesterone, ethynodiol diacetate, medroxyprogesterone acetate, megestrol acetate, phytoprogestins, and animal-derived progestins and metabolic derivatives thereof.

64. The method of claim 52, wherein said progestational steroid is selected from the group of selective progestin receptor modulators consisting of RU486, CDB2914, 19-nor-
5 progesterone derivatives, 19-nor-testosterone derivatives, 6-aryl-1,2-dihydro-2,2,4-trimethylquinoline derivatives, 5-aryl-1,2-dihydro-5H-chromeno[3,4-f]quinoline derivatives, 5-alkyl 1,2-dihydrochromeno[3,4-f]quinoline derivatives, and 6-thiophenehydroquinoline derivatives.
65. The method of claim 51, wherein the female mammal is a human female.
- 10 66. A method for increasing the breeding rate of a female mammal, wherein said female mammal is induced to breed by the method of claim 51.
67. A method for preventing pregnancy in a female mammal, comprising:
- 15 (a) providing a drug delivery device comprising a first segment comprising a drug-permeable polymeric substance and a luteinizing hormone releasing hormone (LHRH), a second segment comprising the drug-permeable polymeric substance and an estrogenic steroid, and a third segment comprising the drug-permeable polymeric substance and a progestational steroid; and
- 20 (b) inserting into the vagina of said mammal the drug delivery device of step (a) to release an effective amount of the LHRH, an effective amount of the estrogenic steroid, and an effective amount of the progestational steroid to said female mammal.
68. The method of claim 67, wherein the drug-permeable polymeric substance is a thermoplastic polymer.
69. The method of claim 68, wherein the thermoplastic polymer is an ethylene-vinyl acetate
25 copolymer.
70. The method of claim 67, wherein the drug delivery device is in the shape of a ring, a waffer, or a suppository.
71. The method of claim 67, wherein the drug delivery device is in the shape of a ring.

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(71) Applicant: THE POPULATION COUNCIL, INC. [US/US]; Dag Hammarskjöld Plaza, New York, NY 10017 (US).			
(72) Inventors: SALEH, Saleh, Ismail; Sayed Tawfig Building, El Mohafaza Street, in front of Villa George, Assuit (EG). NASH, Harold; 27 Kohring Circle, Harrington Park, NJ 07640 (US). BARDIN, C., Wayne; 910 Park Avenue, New York, NY 10021 (US). HARMON, Troy; 2207 Allebach Lane, Lansdale, PA 19446 (US).		Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	
(74) Agents: FOLEY, Shawn, P. et al.; Lerner, David, Littenberg, Krumholz & Mentlik, 600 South Avenue West, Westfield, NJ 07090 (US).			

(54) Title: INTRAVAGINAL RINGS WITH INSERTABLE DRUG-CONTAINING CORE

(57) Abstract

Disclosed is a vaginal ring containing a ring body made of a first polymeric material having at least one hollow internal channel defining an opening to the exterior of said body and which channel is adapted to receive a drug-containing core through said opening, and a core containing at least one intravaginally administrable drug dispersed in a second polymeric material disposed in the channel. The core is positioned in the vaginal ring body suitably prior to use in order to substantially avoid initial bursts of drug into the tissues of the subject and resultant side effects such as nausea and vomiting. Representative drugs include contraceptive agents and other steroidal substances for use in hormone replacement therapy. Also disclosed are methods for preparing the vaginal rings, kits for assembling the vaginal rings, and methods of using the vaginal rings to achieve intravaginal delivery of drugs to a female.

DESCRIPTIONINTRAVAGINAL RINGS WITH INSERTABLE DRUG-CONTAINING CORE
TECHNICAL FIELD

5 The present invention is directed to intravaginal drug delivery devices and methods for the intravaginal administration of drugs, and more particularly, the intravaginal administration of contraceptive agents and agents for hormone replacement therapy.

10 BACKGROUND ART

Vaginal rings are torous shaped devices designed to deliver a relatively constant dose of drug to the vagina usually over a period of weeks to months. Typically, they are made of a silicone elastomer and
15 contain a drug released by diffusion through the elastomer. The most common commercial applications have been to deliver low doses of steroids for post-menopausal vaginal conditions. They have also been under development for use in contraception and hormone
20 replacement therapy. Vaginal rings have also been used to administer spermicides, as well as a variety of locally or systemically active medicaments. Vaginal rings have provided several advantages in that their use is controlled by the female; they allow for a
25 better regulated dose of drug without attention by the user; and they avoid the destruction (by the intestine and by first pass through the liver) of an appreciable portion of the daily dosage of some steroids compared to their orally delivered counterparts.

30 The use of a vaginal ring to deliver drugs requires a ring design that regulates the release rate so as to provide the user with the appropriate daily dose. Among the important factors governing release are the solubility of the drug in the ring elastomer,
35 the surface area of the drug reservoir, the distance the drug must diffuse through the ring body to reach its surface and the molecular weight of the drug. If very high release rates are desired, they can be



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

(10) Patent No.: **US 6,861,415 B2**
(45) Date of Patent: **Mar. 1, 2005**

(54) **21-SUBSTITUTED PROGESTERONE
DERIVATIVES AS NEW
ANTI-PROGESTATIONAL AGENTS**

(75) Inventors: **Hyun K. Kim, Bethesda, MD (US);
Richard P. Blye, Highland, MD (US);
Permaraju N. Rao, San Antonio, TX
(US); James W. Cessac, San Antonio,
TX (US); Carmle K. Acosta, San
Antonio, TX (US)**

(73) Assignee: **The United States of America as
represented by the Department of
Health and Human Services,
Washington, DC (US)**

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552, 553, 554, 555, 556, 595, 598, 602-608**

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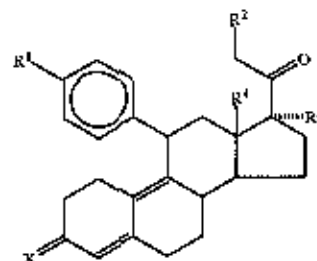
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Primary Examiner—Barbara P. Badio

(74) Attorney, Agent, or Firm—Townsend and Townsend
and Crew LLP

(57) **ABSTRACT**

A compound having the general formula:



in which: R¹ is a member selected from the group consisting of —OCH₃, —SCH₃, —N(CH₃)₂, —NHCH₃, —CHO, —COCH₃ and —CHOHCH₃; R² is a member selected from the group consisting of halogen, alkyl, acyl, hydroxy, alkoxy, acyloxy, alkyl carbonate, cyanoalkoxy, S-alkyl and S-acyl; R³ is a member selected from the group consisting of alkyl, hydroxy, alkoxy and acyloxy; R⁴ is a member selected from the group consisting of hydrogen and alkyl; and X is a member selected from the group consisting of =O and =N—OR⁵, wherein R⁵ is a member selected from the group consisting of hydrogen and alkyl.

In addition to providing the compounds of Formula I, the present invention provides methods wherein the compounds of Formula I are advantageously used, inter alia, to antagonize endogenous progesterone; to induce menses; to treat endometriosis; to treat dysmenorrhea; to treat endocrine hormone-dependent tumors; to treat uterine fibroids; to inhibit uterine endometrial proliferation; to induce labor; and for contraception.

36 Claims, 5 Drawing Sheets

US 6,861,415 B2

1

21-SUBSTITUTED PROGESTERONE DERIVATIVES AS NEW ANTIPIGESTATIONAL AGENTS

This application claims benefit of provisional application 60/016,628 filed May 1, 1996.

FIELD OF THE INVENTION

The present invention relates generally to the field of steroids and, in particular, to new 11 β -substituted-21-substituted-19-nor-progesterone analogs which possess potent antiprogestational activity with minimal antigluco-

BACKGROUND OF THE INVENTION

There have been numerous attempts over the past few decades to prepare steroids with antihormonal activity. These have been reasonably successful where anti-estrogens and anti-androgens are concerned. However, the discovery of effective antiprogestational and antigluco-

corticoid steroids has proved to be a formidable task for the steroid chemist. It has been generally recognized for some years, however, that antiprogestational steroids would find wide applicability in population control, while antigluco-

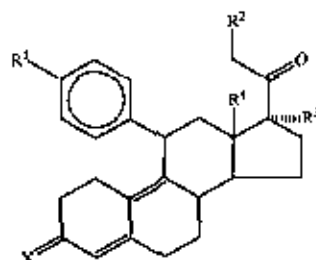
corticoids would be extremely valuable in the treatment of, for example, Cushing's syndrome and other conditions characterized by excessive endogenous production of cortisone. In the last decade, largely through the efforts of Teutsch, et al. of the Roussel-Uclaf group in France, a new series of 19-nortestosterone derivatives has been synthesized with strong affinity for the progesterone and glucocorticoid receptors and with marked antiprogestational and antigluco-

2

modify the mifepristone structure in order to obtain separation of the antiprogestational activity from the antigluco-

SUMMARY OF THE INVENTION

The present invention provides new steroids which possess potent antiprogestational activity with minimal antigluco-



wherein: R¹ is a functional group including, but not limited to, —OCH₃, —SCH₃, —N(CH₃)₂, —NHCH₃, —CHO, —COCH₃ and —CHOHCH₃; R² is a functional group including, but not limited to, halogen, alkyl, acyl, hydroxy, alkoxy, acyloxy (e.g., acetoxy, glycinate, etc.) alkyl carbonate, cyponyloxy, S-alkyl and S-acyl; R³ is a functional group including, but not limited to, alkyl (e.g., methyl, methoxymethyl, etc.), hydroxy, alkoxy (e.g., methoxy, ethoxy, methoxyethoxy, etc.), and acyloxy; R⁴ is a functional group including, but not limited to, hydrogen and alkyl; and X is a functional group including, but not limited to, —O and —N—OR⁵, wherein R⁵ is a member selected from the group consisting of hydrogen and alkyl.

In addition to providing compounds of Formula I, the present invention provides methods wherein the compounds of Formula I are advantageously used, inter alia, to antagonize endogenous progesterone; to induce menses; to treat endometriosis; to treat dysmenorrhea; to treat endocrine hormone-dependent tumors; to treat uterine fibroids; to inhibit uterine endometrial proliferation; to induce labor; and for contraception.

Other features, objects and advantages of the invention and its preferred embodiments will become apparent from the detailed description which follows.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. 1 (1A, 1B and 1C) through 3 illustrate the synthetic schemes used to prepare the compounds of Formula I.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

In one aspect, the present invention provides compounds having the general formula:

erone and/or glucocorticoid receptors using the assays described in the examples. Moreover, a given compound can readily be screened for its ability to inhibit malignant tumor cell growth or to abolish tumorigenicity of malignant cells in vitro or in vivo. For instance, tumor cell lines can be exposed to varying concentrations of a compound of interest, and the viability of the cells can be measured at set time points using, for example, the alamar Blue® assay (commercially available from BioSource, International of Camarillo, Calif.). Other assays known to and used by those of skill in the art can be employed to identify compounds useful in the methods of the present invention.

The compounds according to the present invention can be administered to any warm-blooded mammal such as humans, domestic pets, and farm animals. Domestic pets include dogs, cats, etc. Farm animals include cows, horses, pigs, sheep, goats, etc.

The amount of active ingredient that can be combined with a carrier material to produce a single dosage form will vary depending upon the disease treated, the mammalian species, and the particular mode of administration. For example, a unit dose of the steroid can preferably contain between 0.1 milligram and 1 gram of the active ingredient. A more preferred unit dose is between 0.001 and 0.5 grams. It will be understood, however, that the specific dose level for any particular patient will depend on a variety of factors including the activity of the specific compound employed; the age, body weight, general health, sex and diet of the individual being treated; the time and route of administration; the rate of excretion; other drugs which have previously been administered; and the severity of the particular disease undergoing therapy, as is well understood by those of skill in the area.

The compounds of the present invention can be administered by a variety of methods. Thus, those products of the invention that are active by the oral route can be administered in solutions, suspensions, emulsions, tablets, including sublingual and intrabuccal tablets, soft gelatin capsules, including solutions used in soft gelatin capsules, aqueous or oil suspensions, emulsions, pills, lozenges, troches, tablets, syrups or elixirs and the like. Products of the invention active on parenteral administration can be administered by depot injection, implants including Silastic™ and biodegradable implants, intramuscular and intravenous injections.

Compositions can be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions can contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents. Tablets containing the active ingredient in admixture with nontoxic pharmaceutically acceptable excipients which are suitable for manufacture of tablets are acceptable. These excipients can be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate, granulating and disintegrating agents, such as maize starch, or alginate acid; binding agents, such as starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid and talc. Tablets can be uncoated or, alternatively, they can be coated by known methods to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay such as glyceryl monostearate or glyceryl distearate alone or with a wax can be employed.

Formulations for oral use can also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example calcium carbonate, cal-

cium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions of the invention contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethylene oxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol (e.g., polyoxyethylene sorbitol mono-oleate), or a condensation product of ethylene oxide with a partial ester derived from fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan mono-oleate). The aqueous suspension can also contain one or more preservatives such as ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose, aspartame or saccharin. Ophthalmic formulations, as is known in the art, will be adjusted for osmolality.

Oil suspensions can be formulated by suspending the active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oil suspensions can contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents can be added to provide a palatable oral preparation. These compositions can be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules of the invention suitable for preparation of an aqueous suspension by the addition of water can be formulated from the active ingredients in admixture with a dispersing, suspending and/or wetting agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, can also be present.

The pharmaceutical compositions of the invention can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan mono-oleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan mono-oleate. The emulsion can also contain sweetening and flavoring agents.

Syrups and elixirs can be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations can also contain a demulcent, a preservative, a flavoring or a coloring agent.

The pharmaceutical compositions of the invention can be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation can also be a sterile injectable

solution or suspension in a nontoxic parenterally-acceptable diluent or solvent, such as a solution of 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water and Ringer's solution, an isotonic sodium chloride. In addition, sterile fixed oils can conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can likewise be used in the preparation of injectables.

The compounds of this invention can also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperatures and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

They can also be administered by in intranasal, intracocular, intravaginal, and intrarectal routes including suppositories, insufflation, powders and aerosol formulations.

Products of the invention which are preferably administered by the topical route can be administered as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols.

The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are intended neither to limit or define the invention in any manner.

EXAMPLES

A. Preparation of the Compounds of Formula I

Example I

This example illustrates the preparation and properties of 17 α -acetoxy-21-fluoro-11 β -(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione(13) via the Silicon Nucleophilic Annulation Process (SNAP) of 5.

Step 1. 3,3-Ethylenedioxy-17 β -cyano-17 α -trimethylsilyloxyestra-5(10),9(11)-diene (2):

Under nitrogen, a solution of the cyanohydrin ketal (1, 15 g, 43.9 mmol) in pyridine (85 mL) was treated with chlorotrimethylsilane (28 mL-27.11 g, 221 mmol) and the mixture was stirred at room temperature for 5 hours. The reaction was monitored by Thin Layer Chromatography (TLC) in 2% acetone in CH_2Cl_2 . The reaction mixture was poured into a 50:50 mixture of ice/saturated sodium bicarbonate solution (1L), stirred until the ice was melted, and extracted with hexanes (3x). The organic extracts were washed with water (2x), brine (1x), combined, dried over Na_2SO_4 , and concentrated in vacuo. The remaining pyridine was azeotropically removed in vacuo with heptane to give 18 g of the crude product as a foam. Crystallization from ether/hexanes gave 16.35 g of the pure silyl ether (2) as a white solid in 90% yield; mp=100-102° C. FTIR (KBr, diffuse reflectance) ν_{max} 2880, 2232 and 1254 cm^{-1} . NMR (CDCl_3) δ 0.11 (s, 9H, OSiMe_3), 0.73 (s, 3H, 18- CH_3), 3.83 (s, 4H, $-\text{OCH}_2\text{CH}_2\text{O}-$) and 5.49 (br s, 1H, 11 α -H).

Step 2. 3,3-Ethylenedioxy-5 α ,10 α -epoxy-17 β -cyano-17 α -trimethylsilyloxyestra-9(11)-ene (3):

Hydrogen peroxide (30%, 6 mL, 58.6 mmol) was added to a vigorously stirred mixture of hexafluoroacetone trihydrate (11.8 g, 53.6 mmol) and Na_2HPO_4 (6.8 g, 47.9 mmol) in CH_2Cl_2 (150 mL) cooled to 0° C. in an ice bath. After stirring at 0° C. for 30 minutes, a solution of the silyl ether (2, 16 g, 38.7 mmol) in CH_2Cl_2 (10 mL), pre-cooled to 0°

C. was added. The mixture was then stirred at 0° C. for 8 hr. At that time TLC in 5% acetone/ CH_2Cl_2 indicated incomplete reaction and the mixture was then stirred overnight at 4° C. The reaction mixture was diluted with CH_2Cl_2 (200 mL) and washed with 10% sodium sulfite solution (2x), saturated sodium bicarbonate solution (1x) and brine (1x). The organic layers were combined, dried over Na_2SO_4 , filtered and concentrated in vacuo to give 16.8 g of the crude epoxide mixture which consists of a 70:30 mixture of the 5 α ,10 α -epoxide and 5 β ,10 β -epoxide. Crystallization of the crude mixture from ether/hexanes afforded 8.5 g of the pure 5 α ,10 α -epoxide (3) as a white solid in 51% yield; mp=164-165° C. FTIR (KBr, diffuse reflectance) ν_{max} 2940, 2872, 2228 and 1252 cm^{-1} . NMR (CDCl_3) δ 0.23 (s, 9H, OSiMe_3), 0.91 (s, 3H, 18- CH_3), 3.91 (s, 4H, $\text{OCH}_2\text{CH}_2\text{O}$) and 6.12 (br s, 1H, 11 α -H).

Step 3. 3,3-Ethylenedioxy-5 α -hydroxy-11 β -4-N,N-dimethylaminophenyl-17 β -cyano-17 α -trimethylsilyloxyestra-9(10)-ene (4):

Magnesium (2.6 g, 107 mmol) was added to a 1.0 L, 3-neck flask equipped with a magnetic stir bar, addition funnel and a condenser. A crystal of iodine was added followed by dry THF (100 mL) and a few drops of 1,2-dibromoethane. The mixture was stirred under nitrogen and heated in a warm water bath until evidence of reaction was observed. A solution of 4-bromo-N,N-dimethylaniline (19.6 g, 98 mmol) in dry THF (100 mL) was then added dropwise over a period of 20 min. and the mixture stirred for an additional 1.5 hours. Solid copper (I) chloride (1 g, 10.1 mmol) was added followed 30 minutes later by a solution of the 5 α ,10 α -epoxide (3, 8.4 g, 19.55 mmol) in dry THF (10 mL). The mixture was stirred at room temperature for 1 hr., then quenched by the addition of saturated NH_4Cl solution (100 mL). With vigorous stirring, air was drawn through the reaction mixture for 30 minutes. The mixture was diluted with ether (250 mL) and the layers allowed to separate. The THF/ether solution was washed with 10% NH_4Cl solution (3x), 2 N NH_4OH solution (3x) and brine (1x). The organic layers were combined, dried over Na_2SO_4 , filtered and concentrated in vacuo to give the crude product. Crystallization of the crude product from ether gave 8.6 g of the pure product 4 as a white solid in 80% yield; mp=222-224° C. dec. FTIR KBr, diffuse reflectance) ν_{max} 3221, 2951, 2232, 1613, 1517 and 1253 cm^{-1} . NMR (CDCl_3) δ 0.20 (s, 9H, OSiMe_3), 0.5 (s, 3H, 18- CH_3), 2.83 (s, 6H NMe_2), 3.9 (m, 4H, $\text{OCH}_2\text{CH}_2\text{O}$), 4.3 (m, 1H, 11 α -H), 6.63 (d, J=9 Hz, 2H, 3' and 5' aromatic CH) and 7.03 (d, J=9 Hz, 2', and 6' aromatic CH).

Step 4. 11 β -(4-N,N-Dimethylaminophenyl)-17 β -cyano-17 α -hydroxyestra-4,9-dien-3-one (5):

A solution of the Grignard adduct (4, 8.5 g, 15.4 mmol) was dissolved in THF (50 mL) and the system was flushed with nitrogen. Glacial acetic acid (150 mL) and water (50 mL) were added and the mixture was heated at 50° C. for 4 hrs. The volatile substances were removed in vacuo under a stream of nitrogen and the residual acid neutralized with NH_4OH . The mixture was extracted with CH_2Cl_2 (3x). The organic fractions were washed with water (2x), brine (1x), combined, dried over Na_2SO_4 , filtered and concentrated in vacuo. Crystallization of the residue from ether gave 3.1 g of cyanohydrin (5) as a pale yellow solid. Chromatography of the mother liquors eluting with 50% EtOAc in hexanes followed by crystallization gave 1.8 g of an additional product. Total yield of the cyanohydrin 5, was 4.9 g in 76.2% yield, m.p.=152-154° C. FTIR (KBr, diffuse reflectance) ν_{max} 3384, 2950, 2231, 1646, 1606 and 1520 cm^{-1} . NMR (CDCl_3) δ 0.67 (s, 3H, 18- CH_3), 2.97 (s, 6H NMe_2), 4.38 (br

161

161

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES**

2020
Bogotá, D.C.,

Abogado: DILIA MARIA RODRIGUEZ D'ALEMAN

ASUNTO: Radicación No. 07-012095
Trámite 002
Evento 001
Actuación 430
Oficio 161
Folios 161

Como resultado del Examen de Fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

Documentos estudiados:

Descripción: Folios 34 a 64 como se radicó inicialmente.
Reivindicaciones: Folios 65 a 68 como se radicó inicialmente.
Dibujos: Folios 70 a 73 como se radicó inicialmente.

Prioridad: US 200460586783 (20040709)

Objeto de la Invención

Titulo de la invención:

Composiciones de liberación sostenida que contienen moduladores del receptor de progesterona.

Problema Técnico Planteado:

Necesidad de una composición de liberación sostenida de moléculas anticonceptivas,

Solución:

Composición de liberación sostenida en forma de anillo vaginal en la cual esta contenida una cantidad efectiva de del modulador del receptor de progesterona como molécula anticonceptiva.

IPC: A61K31/56 - A61F6/14 - A61P15/16

Excepciones a la Patentabilidad (Art 20 D 486 literales (a) – (d))

Teniendo en cuenta el artículo 20 D486 en el cual se señalan que los métodos terapéuticos o quirúrgicos no son patentables, la solicitud en su reivindicación 16

Análisis de la Solicitud de Patente

Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la fecha de prioridad (solicitud prioritaria 2004-07-09 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

ITEM	DOCUMENTO	TÍTULO	FECHA DE PRIORIDAD
D1	WO04096151	<i>Methods and devices for the sustained release of multiple drugs</i>	2003-04-29
D2	WO9804220	<i>Intravaginal rings with insertable drug containing core</i>	1996-07-31
D3	US6861415	<i>21-substituted progesterone derivatives as new antiprogestational agents</i>	2002-02-28

Análisis de Patentabilidad (Art 14 D486)

Novedad (Art 16 D486)

Respecto a la solicitud en estudio:

La reivindicación 1 dice: "Una composición de **anillo vaginal** caracterizada porque comprende un **polímero sintético** que tiene contenido en el mismo una cantidad **anticonceptivamente** efectiva de un **modulador del receptor de progesterona (PRM)**".

Respecto al estado de la técnica D1 describe un dispositivo intravaginal tipo anillo, con uno o mas segmentos de características poliméricas y permeables a fármacos que contienen una cantidad farmacológicamente activa de sustancias tales como moduladores de receptores de progesterona (PRM), moduladores de receptores de andrógenos (ARM), moduladores de receptores de estrógenos (ERM), entre otros y se utilizan como método anticonceptivo.

Las características esenciales de la composición de la reivindicación 1 habian sido divulgadas previamente en D1, es decir : un **dispositivo intravaginal tipo anillo** (página 1 línea 9 y 10), con uno o mas segmentos de características poliméricas (**polímero sintético**) y permeables a fármacos (pagina 5 líneas 19 a 21). Estos segmentos tienen contenidos una cantidad farmacológicamente activa (página 37 líneas 25 a 27) de sustancias tales como **moduladores de receptores de progesterona (PRM)**, (pagina 17 línea 30 y 31, página 18 línea 1 y 2) ; y se utilizan como método **anticonceptivo** (Pagina 37 línea 18 a 31). Por lo cual la reivindicación no es nueva.

La reivindicación 12 dice: El anillo vaginal de conformidad con la reivindicación 1, caracterizado porque el PRM comprende 17^a-acetoxi-11B-(4-N,N-dimetilaaminofenil)-19-norpregna-4,9-dieno-3,20-diona (CDB-2914), o un

163

Teniendo en cuenta la anterioridad D1 la cual describe las características esenciales del objeto de esta solicitud, el objeto reivindicado bajo la reivindicación 1 y sus reivindicaciones dependientes **NO ES NUEVO**

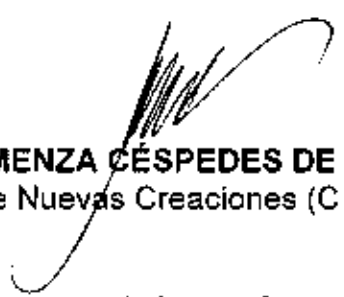
Conclusión

Los requisitos de Patentabilidad de la presente Solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO04096151	1-15	NOVEDAD

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

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


ALIX CARMENZA CÉSPEDES DE VERGEL
Directora de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha
22 ALC. 2010

CONCEPTO TECNICO NUMERO: 2188	EXAMINADOR TÉCNICO Código:202093
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