METHODS FOR IMPROVED STABILITY OF STEROID DERIVATIVES

FIELD OF THE INVENTION

[0001] The present invention relates generally to compositions comprising steroids and, in particular, to compositions with potent antiprogestational activity, minimal antiglucocorticoid activity and improved stability, comprising a 19-norprogesterone I derivative. The present invention also relates to methods using the compositions.

BACKGROUND OF THE INVENTION

[0002] There have been numerous attempts over the past few decades to prepare steroids with antihormonal activity. It has been generally recognized for some years, that antiprogestational steroids would find wide applicability in population control, while antiglucocorticoids would be extremely valuable in the treatment of, for example, Cushing's syndrome and other conditions characterized by excessive endogenous production of cortisone.

[0003] For purposes of contraception, it would be advantageous to have compounds which possess antiprogestational activity without (or with minimal) antiglucocorticoid activity. Although there have been a number of attempts to modify the mifepristone structure in order to obtain separation of the antiprogestational activity from the antiglucocorticoid activity, this goal has not yet been fully achieved. As such, there remains a need in the art for the development of new formulations comprising steroids which possess antiprogestational activity with minimal antiglucocorticoid activity.

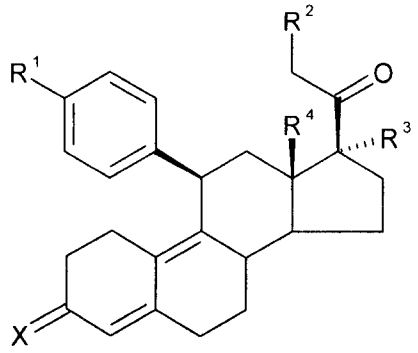
[0004] U.S. Patents 6,861,415 and 6,900,193, both incorporated herein by reference, disclose new compounds which possess antiprogestational activity with minimal antiglucorticoid activity. The compounds are steroid derivatives, and more

specifically they are structural modifications of 19-norprogesterone I, such as 17-α-substituted-11-β-substituted-4-aryl and 21-substituted 19-norpregnadienedione, and are poorly soluble in water. Therefore, a need remains in the art to develop formulations comprising the steroid derivatives with increased stability and improved bioavailability.

SUMMARY OF THE INVENTION

[0005] The present invention provides new formulations with potent antiprogestational activity, minimal antiglucocorticoid activity and improved stability.

[0006] More particularly, the present invention provides compositions comprising a pharmaceutically acceptable salt of a compound having the following general formula I:



[0007] Wherein: R^1 is a basic functional group upon which a salt may be prepared, preferably comprising a nitrogen, including, but not limited to, —$N(CH_3)_2$, —$NHCH_3$, —NC_4H_8, —NC_5H_{10}, —NC_4H_8O, —$O(CH_2)2N(CH_3)_2$, —$O(CH2)_2NC_4H_8$ and —$O(CH_2)_2NC_5H_{10}$; R^2 is a functional group including, but not limited to, hydrogen, halogen, alkyl, acyl, hydroxy, alkoxy (e.g., methoxy, ethoxy, vinyloxy, ethynyloxy, cyclopropyloxy, etc.), acyloxy (e.g., formyloxy, acetoxy, propionyloxy, heptanoyloxy, glycinate, etc.), alkylcarbonate, cypionyloxy, S-alkyl, —SCN, S-acyl

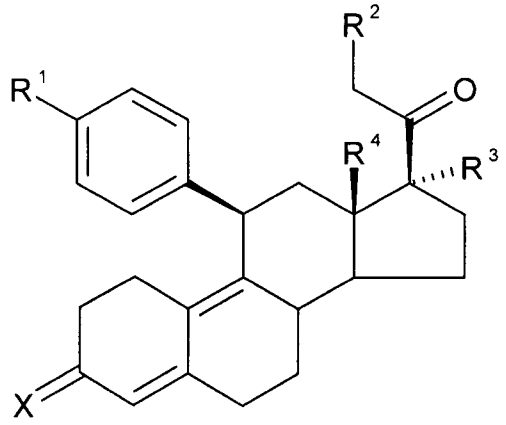
and —OC(O)R_6, wherein R6 is a functional group including, but not limited to, alkyl (e.g., methyl, ethyl, etc.), alkoxyalkyl (e.g., --CH_2OCH_3) and alkoxy (—OCH_3); R^3 is a functional group including, but not limited to, alkyl (e.g., methyl, methoxymethyl, etc.), hydroxy, alkoxy (e.g., methoxy, ethoxy, methoxyethoxy, vinyloxy, etc.), and acyloxy; R^4 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—OR^5, wherein R^5 is a member selected from the group consisting of hydrogen and alkyl and with the proviso that when R^1 is —$N(CH_3)_2$, R^2 is methoxy, R^3 is acetoxy, R^4 is methyl and X is =O, the salt is not an HCl or an HBr salt.

[0008] The compositions may possess potent antiprogestational activity with minimal antiglucocorticoid activity in combination with improved stability. Therefore, the compositions may be suitable for long term use in the treatment of human endocrinological disorders or other conditions in steroid-sensitive tissues. Specific conditions for treatment include, but are not limited to, endometriosis, dysmenorrhea, uterine leiomyoma, uterine fibroid, meningioma and metastatic breast cancer. Other uses include, but are not limited to, contraception, including emergency post-coital contraception and inducement of cervical ripening.

[0009] Also provided is the use of any of the compositions of the present invention in the manufacture of a medicament for treatment of human endocrinological disorders or other conditions in steroid-sensitive tissues as described herein, including but not limited to, endometriosis, dysmenorrhea, uterine leiomyoma, uterine fibroid, meningioma and metastatic breast cancer.

DETAILED DESCRIPTION OF THE INVENTION

[0010] A composition is provided comprising a steroid derivative with the following general formula I:



[0011] In Formula I, R^1 is a basic functional group upon which a salt may be prepared, preferably comprising a nitrogen, including, but not limited to, —$N(CH_3)_2$, —$NHCH_3$, —NC_4H_8, —NC_5H_{10}, —NC_4H_8O, —$O(CH_2)2N(CH_3)_2$, —$O(CH2)_2NC_4H_8$ and —$O(CH_2)_2NC_5H_{10}$; R^2 is a functional group including, but not limited to, hydrogen, halogen, alkyl, acyl, hydroxy, alkoxy (e.g., methoxy, ethoxy, vinyloxy, ethynyloxy, cyclopropyloxy, etc.), acyloxy (e.g., formyloxy, acetoxy, propionyloxy, heptanoyloxy, glycinate, etc.), alkylcarbonate, cypionyloxy, S-alkyl, —SCN, S-acyl and —$OC(O)R^6$, wherein R^6 is a functional group including, but not limited to, alkyl (e.g., methyl, ethyl, etc.), alkoxyalkyl (e.g., —CH_2OCH_3) and alkoxy (—OCH_3); R^3 is a functional group including, but not limited to, alkyl, hydroxy, alkoxy and acyloxy; R^4 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—OR^5, wherein R^5 is a member selected from the group consisting of hydrogen and alkyl, with the proviso that when R^1 is —$N(CH_3)_2$, R^2 is methoxy, R^3 is acetoxy, R^4 is methyl and X is =O, the salt is not an HCl or an HBr salt.

[0012] Thus, compositions of the present invention comprise a compound of general formula I which is capable of forming a salt when the compound is reacted with a suitable acid. Preferably, a compound of general formula I comprises a basic functional group attached at the 4 position of the phenyl group located at the 11β position of the compound (i.e., the R^1 position); however, compounds of general formula I comprising a basic functional group attached at any position are within the scope of the invention so long as a salt of the compound may be prepared. In addition to the basic functional groups listed above, other suitable basic functional groups for R^1 upon which a salt may be prepared include, without limitation, methylamine, dimethylamine, ethylamine, diethylamine, ethylmethylamine, isopropylamine, diisopropylamine, n-butylamine, ethanolamine, diethanolamine, methylethanolamine, isopropanolamine, diisopropanolamine, ethyleneimine, ethylenediamine, pyridine and morpholine functional groups.

[0013] The term "alkyl" refers to a branched, unbranched, monovalent hydrocarbon radical having from 1-12 carbons. When the alkyl group has from 1-6 carbon atoms, it may be referred to as a "lower alkyl." Representative alkyl radicals include, for example, methyl, ethyl, n-propyl, i-propyl, 2-propenyl (or allyl), n-butyl, t-butyl, i-butyl (or 2-methylpropyl), etc. As used herein, the term alkyl encompasses "substituted alkyls." A substituted alkyl refers to alkyl further containing one or more functional groups such as lower alkyl, aryl, aralkyl, acyl, halogen (i.e., alkylhalos, e.g., CF_3), hydroxy (e.g., hydroxymethyl), amino, alkylamino, acylamino, acyloxy, alkoxy (e.g., methoxymethyl), mercapto and the like. These groups may be attached to any carbon atom of the lower alkyl moiety.

[0014] The term "alkoxy" may refer to a —OR group, where R is a lower alkyl, substituted lower alkyl, aryl, substituted aryl, aralkyl or substituted aralkyl. Suitable

alkoxy radicals include, for example, methoxy, ethoxy, phenoxy, t-butoxy (e.g., methoxyethoxy, methoxymethoxy, etc.), etc.

[0015] The term "acyloxy" may refer to an organic radical derived from an organic acid by the removal of a hydrogen. The organic radical can be further substituted with one or more functional groups such as alkyl, aryl, aralkyl, acyl, halogen, amino, thiol, hydroxy, alkoxy, etc. An example of such a substituted organic radical is glycinate (e.g., --$OC(O)CH_2NH_2$). Suitable acyloxy groups include, for example, acetoxy, i.e., CH3COO—, which may be derived from acetic acid, formyloxy, i.e., H(CO)O—, which may be derived from formic acid and cypionyloxy, which may be derived from 3-cyclopentylpropionic acid.

[0016] The term "halogen" may refer to fluorine, bromine, chlorine and iodine atoms. The term "hydroxyl" may refer to the group —OH. The term "acyl" may denote groups —C(O)R, where R is alkyl or substituted alkyl, aryl or substituted aryl as defined herein. The term "aryl" may refer to an aromatic substituent which may be a single ring or multiple rings which are fused together, linked covalently, or linked to a common group such as an ethylene or methylene moiety. The aromatic ring(s) may include phenyl, naphthyl, biphenyl, diphenylmethyl, 2,2-diphenyl-1-ethyl, and may contain a heteroatom, such as thienyl, pyridyl and quinoxalyl. The aryl group may also be substituted with halogen atoms, or other groups such as nitro, carboxyl, alkoxy, phenoxy, and the like. Additionally, the aryl group may be attached to other moieties at any position on the aryl radical which would otherwise be occupied by a hydrogen atom (such as 2-pyridyl, 3-pyridyl and 4-pyridyl).

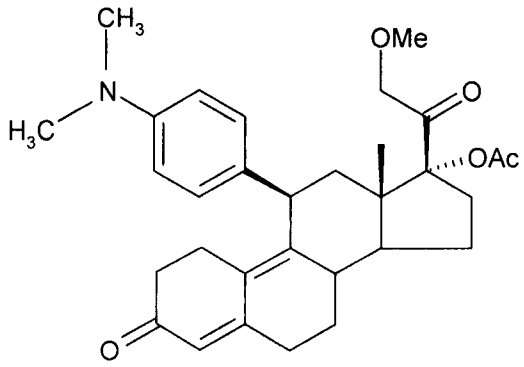
[0017] The term "alkyl carbonate" may refer to the group —OC(O)OR, where R is alkyl, substituted alkyl, aryl, or substituted aryl as defined herein.

[0018] The term "S-alkyl" may refer to the group —SR, where R is lower alkyl or substituted lower alkyl. The term "S-acyl" may refer to a thioester derived from the reaction of a thiol group with an acylating agent. Suitable S-acyls include, for example, S-acetyl, S-propionyl and S-pivaloyl. S-acyl may refer to such thioesters regardless of their method of preparation. The terms "N-oxime" and "N-alkyloxime" may refer to the group =N—OR^5, wherein R^5 is, for example, hydrogen (N-oxime) or alkyl (N-alkyloxime). The oximes can consist of the syn-isomer, the anti-isomer or a mixture of both the syn- and anti-isomers.

[0019] Representative compounds within Formula I, include those in which R^1 is --$N(CH_3)_2$; those in which R^2 is hydrogen, halogen or alkoxy; those in which R^3 is acyloxy; those in which R^4 is alkyl (e.g., methyl and ethyl); and those in which X is =O and =N—OR^5, wherein R^5 is hydrogen or alkyl. Additional compounds include those in which R^1 is --$N(CH_3)_2$; R^2 is halogen; R^3 is acyloxy; and R^4 is alkyl, such where R^2 is F, Br or Cl; and R^4 is methyl. Also included are compounds in which R^1 is —$N(CH_3)_2$; R^2 is alkyl; R^3 is acyloxy; R^4 is alkyl; and X is =O. Also included are compounds in which R^1 is --$N(CH_3)_2$; R^2 is alkoxy; R^3 is acyloxy; R^4 is alkyl; and X is =O. Additional compounds are those in which R^2 is methoxy or ethoxy; and R^3 is acetoxy or methoxy. Also included are compounds in which R^1 is —$N(CH_3)$; R^2 is hydroxy; R^3 is acyloxy; R^4 is alkyl; and X is =O. Also included are compounds in which R^1 is —$N(CH_3)_2$; R^2 and R^3 are both acyloxy; R^4 is alkyl; and X is =O. Additional compounds are those in which R^2 and R^3 are both acetoxy. Also included are compounds in which R^1 is —$N(CH_3)_2$; R^2 is S-acyl; R^3 is hydroxy or acyloxy; R^4 is alkyl; and X is =O. Also included are compounds in which R^1 is —$N(CH_3)_2$; R^2 is cypionyloxy; R^3 is acetoxy; R^4 is alkyl; and X is =O. Also included are compounds in which R^1 is —$N(CH_3)_2$; R^2 is methoxy; R^3 is acetoxy; R^4 is alkyl; and X is =O and

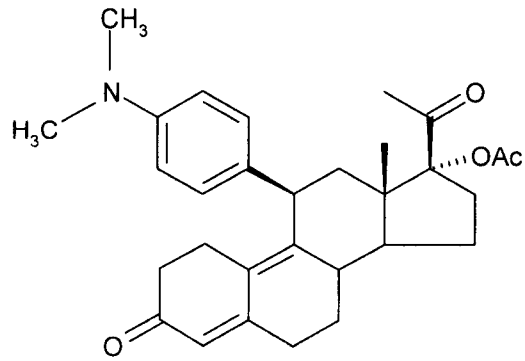
=N—OR^5, wherein R^5 is, for example, hydrogen or alkyl (e.g., methyl, ethyl, etc.). Also included are compounds in which R^1 is —N(CH$_3$)$_2$; R^2 and R^3 are both acetoxy; R^4 is alkyl; and X is =O and =N—OR^5, wherein R^5 is, for example, hydrogen or alkyl (e.g., methyl, ethyl, etc.).

[0020] Exemplar compounds include, but are not limited to, 17α-acetoxy-11β-[4-(N,N-dimethylamino)phenyl]-21-methoxy-19-norpregna-4,9(10)-diene-3,20-dione (CDB-4124) with the following structural formula:



with the proviso that salts of CDB-4124 are not HCl or HBr acid salts.

[0021] Another exemplar compound is 17α-acetoxy-11β-[4-(N,N-dimethylamino)phenyl]-19-norpregna-4,9-diene-3,20-dione (CDB-2914) with the following structural formula:



[0022] Other exemplar compounds include, but are not limited to, 17α-acetoxy-21-chloro-11β-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione; 17α-acetoxy-21-bromoro-11β-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-

diene-3,20-dione; 17-,21-diacetoxy-11β-(4-N,N-dimethylaminophenyl) 19-norpregna-4,9-diene-3,20-dione; 17α-hydroxy-21-acetylthio-11β-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione; 17α-acetoxy-21-acetylthio-11β-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione; 17α-acetoxy-21-ethoxy-11β-(4N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione; 17α-acetoxy-21-methyl-11β-(4-N,N-dimethylamino-phenyl)-19-norpregna-4,9-diene-3,20-dione; 17α-acetoxy-21-methoxy-11β-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione; 17α-acetoxy-21-ethoxy-11β-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione; 17α-acetoxy-21-(3′-cyclopentylpropionyloxy) 11β-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione; 17α-acetoxy-21-hydroxy-11β-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione; 17α,21-diacetoxy-11β-(4-N,N-dimethylaminophenyl) 9-norpregna-4,9-diene-3,20-dione 3-oxime; 17α-acetoxy-21-methoxy-11β-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,2-dione 3-oxime; 17α-acetoxy-11β-[4-(N-methylamino)phenyl]-19-norpregna-4,9-diene-3,20-dione; and 17α,21-diacetoxy-11β-[4-(N-methylamino)phenyl]-19-norpregna-4,9-diene-3,20-dione.

[0023] Also included are those compounds in which R^1 is —$N(CH_3)_2$, —NC_4H_8, --NC_4H_{10}, —NC_4H_8O, —$O(CH_2)_2N(CH_3)_2$, —$O(CH_2)_2NC_4H_8$, --$O(CH_2)_2NC_3H_{10}$, and —$O(CH_2)_2NC_5H_{10}$; those in which R^2 is hydrogen, alkyloxy, alkoxy, —SAc, —SCN, —$OC(O)CH_2N(CH_3)_2$, and —$OC(O)R^6$, wherein R^6 is a functional group including, but not limited to, alkyls (e.g., —CH_2CH_3), alkoxy esters (e.g., —CH_2OMe) and alkoxys (e.g., —OCH_3); those in which R^3 is alkyl, alkoxy, acyloxy and hydroxy; those in which R^4 is alkyl (e.g., methyl and ethyl); and those is which X is =O or =N—OR^5, wherein R^5 is hydrogen or alkyl. Also preferred are compounds in which R^1 is —$N(CH_3)_2$; R^2 is hydrogen; R^3 is methoxymethyl; R^4 is methyl; and X is =O.

Also included are compounds in which R^1 is —$N(CH_3)_2$; R^2 is hydrogen; R^3 is —$OC(O)H$, —$OC(O)CH_2CH_3$ or —$OC(O)C_6H_{13}$; R^4 is methyl; and X is =O. Also included are compounds in which R^1 is —NC_4Hs, —NC_5H_{10}, or —NC_4H_8O; R^2 is hydrogen; R^3 is acetoxy; R^4 is methyl; and X is =O. Also included are compounds in which R^1 is —$N(CH_3)_2$ or —NC_5H_{10}; R^2 is hydrogen; R^3 is methoxy; R^4 is methyl; and X is =O. Also included are compounds in which R^1 is --NC_5H_{10}; R^2 and R^3 are both acetoxy; R^4 is methyl; and X is =O. Also included are compounds in which R^1 is —NC_5H_{10} or --$O(CH_2)_2N(CH_3)_2$; R^2 is methoxy; R^3 is acetoxy; R^4 is methyl; and X is =O. Also included are compounds in which R^1 is —$N(CH_3)_2$; R^2 is —$OC(O)CH_2CH_3$, --$OC(O)OCH_3$, —$OC(O)OCH_2OCH_3$, —$OCH{=}CH_2$, —$OC(O)CH_2N(CH_3)_2$ or —SCN; R^3 is acetoxy; R^4 is methyl; and X is =O. Also included are compounds in which R^1 is --$N(CH_3)_2$; R^2 is —$OC(O)H$; R^3 is —$OC(O)H$; R^4 is methyl; and X is =O. Also included are compounds in which R^1 is —$N(CH_3)_2$; R^2 is —$OC(O)H$; R^3 is hydroxy; R^4 is methyl; and X is =O. Also included are compounds in which R^1 is —NC_5H_{10}; R^2 is hydrogen; R^3 is acetoxy; R^4 is methyl; and X is =N—OR^5, wherein R^5 is hydrogen. Also included are compounds in which R^1 is —$N(CH_3)_2$ or —NC_5H_{10}; R^2 is hydrogen or methoxy; R^3 is methoxy or ethoxy; R^4 is methyl; and X is =N—OR^5, wherein R^5 is hydrogen.

[0024] Exemplar compounds also include, but are not limited to, 17α-acetoxy-11β-[4-(N,N-dimethylamino)phenyl]-21-methoxy-19-norpregna-4,9(10)-diene-3,20-dione; 17α-formyloxy-11β-[4-(N,N-diethylamino)phenyl]-19-norpregna-4,9-diene-3,20-dione; 17α-propionoxy-11β-[4-(N,N-dimethylamino)phenyl]-19-norpregna-4,9-diene-3,20-dione; 17α-heptanoyloxy-11β-[4-(N,N-dimethylamino)phenyl]-19-norpregna-4,9-diene-3,20-dione; 17α-methoxymethyl-11β-[4-N,N-dimethylamino)phenyl]-19-norpregna-4,9-diene-3,20-dione; 17α-acetoxy-11β-(4-N-pyrrolidinophenyl)-19-

norpregna-4,9-diene-3,20-dione; 17α-acetoxy-11β-(4-N-piperidinophenyl)-19-norpregna-4,9-diene-3,20-dione; 17α-acetoxy-11β-(4-N-morpholinophenyl)-19-norpregna-4,9-diene-3,20-dione; 17α-methoxy-11β-[4-(N,N-dimethylamino)phenyl]-19-norpregna-4,9-diene-3,20-dione; 17α-methoxy-11β-(4-N-piperidinophenyl)-19-norpregna-4,9-diene-3,20-dione; 17α,21-diacetoxy-11β-(4-N-piperidinophenyl)-19-norpregna-4,9-diene-3,20-dione; 17α,21-dimethoxy-11β-[4-(N,N-dimethylamino)phenyl]-19-norpregna-4,9-diene-3,20-dione; 17α,21-dimethoxy-11β-(4-N-pyrrolidinophenyl)-19-norpregna-4,9-diene-3,20-dione; 17α,21-dimethoxy-11β-(4-N-piperidinophenyl) 19-norpregna-4,9-diene-3,20-dione; 17α-acetoxy-11β-{4-[2′-(N,N-dimethylamino)ethoxy]phenyl}-21-methoxy-19-norpregna-4,9-diene-3,20-dione; 17α,21-diformyloxy-11β-[4-(N,N-dimethylamino)phenyl]-19-norpregna-4,9-diene-3,20-dione; 17α-acetoxy-11β-[4-(N,N-dimethylamino)phenyl]-21-propionyloxy-19-norpregna-4,9-diene-3,20-dione; 17α-acetoxy-11β-[4-(N,N-dimethylamino)phenyl]-21-(2′-methoxyacetyl)oxy-19-norpregna-4,9-diene-3,20-dione; 17α-acetoxy-21-hydroxy-11β-[4-(N,N-dimethylamino)phenyl]-19-norpregna-4,9-diene-3,20-dione-21-methyl carbonate; 17α-acetoxy-11β-[4-(N,N-dimethylamino)phenyl]-21-(1′-ethenyloxy)-19-norpregna-4,9-diene-3,20-dione; 17α-acetoxy-11β-[4-(N,N-dimethylamino)phenyl]-21-(2′-N,N-dimethylamino)acetoxy-19-norpregna-4,9-diene-3,20-dione; 17α-acetoxy-11β-[4-(N,N-dimethylamino)phenyl]-21-thiocyanato-19-norpregna-4,9-diene-3,20-dione; 17α-acetoxy-11β-(4-N-piperidinophenyl)-19-norpregna-4,9-diene-3,20-dione 3-oxime; 17α-methoxy-11β-[4-(N,N-dimethylamino)phenyl]-19-norpregna-4,9-diene-3,20-dione 3-oxime; 17α-methoxy-11β-(4-N-piperidinophenyl)-19-norpregna-4,9-diene-3,20-dione 3-oxime; and 17α,21-dimethoxy-11β-[4-(N,N-dimethylamino)phenyl]-19-norpregna-4,9-diene-3,20-dione 3-oxime.

[0025] The stability of a compound having general formula I may be significantly increased when the compound is in the form of a salt. A composition is provided comprising a pharmaceutically acceptable salt of a compound of formula I and optionally a pharmaceutically acceptable carrier.

[0026] In practice, the use of the salt form inherently amounts to use of the free base form. Accordingly, acids which are suitable to prepare the salts include preferably those which produce, when combined with the free base, pharmaceutically acceptable salts, that is, salts whose anions are non-toxic to the patient in pharmaceutical doses of the salts, so that the beneficial pharmaceutical effects of these compounds in the free base are not vitiated by side effects ascribable to the anions. The compounds of general formula I may be regenerated from the salts by the application or adaptation of known methods. For example, the compounds can be regenerated from their acid addition salts by treatment with an alkali, e.g., sodium bicarbonate solution.

[0027] The salts can be prepared in situ during the final isolation and purification of a compound of general formula I or by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Representative salts include the hydrobromide, halide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, tosylate, citrate, maleate, fumarate, succinate, tartrate, napthylate, mesylate, glucoheptonate, lactiobionate, laurylsulphonate salts and the like (See, for example, S. M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 66:1-19, 1977, the contents of which are hereby incorporated herein by reference). For example, the salts may be prepared either by dissolving the free base in aqueous or aqueous-alcohol solution or other suitable solvents containing the appropriate acid and isolating the salt by evaporating

the solution, or by reacting the free base and acid in an organic solvent, in which case the salt separates directly or can be obtained by concentration of the solution.

[0028] The term "pharmaceutically acceptable salt" refers to a relatively non-toxic, inorganic or organic acid addition salt of a compound of general formula I.

[0029] Compositions are provided comprising a pharmaceutically acceptable salt of a compound of general formula I. It is expected that salts of a compound of general formula I will have increased stability relative to an equivalent amount of the free base form of the compound under equivalent conditions. Thus, it is expected that compositions of the instant invention will have increased resistance to chemical modification. The stability of a pharmaceutically acceptable salt of a compound of general formula I may be enhanced by at least 1, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100, 150, 200, 300, 400, 500, 600, 700, 800, 900, or 1000 percent or more relative to an equivalent amount of the free base form of the same compound under equivalent conditions.

[0030] A typical parameter of stability is shelf life, which is defined as the time period during which a drug product is expected to remain within the approved shelf life specification. Accelerated testing may be performed for a 6-month period at 40 degrees C and 75% relative humidity. Under these conditions, a change in drug concentration of about 5% from the initial assay values is considered significant. It is expected that compositions comprising pharmaceutically acceptable salts of compounds of general formula I will exhibit an increased shelf life relative to equivalent compositions comprising the free base form of the same compounds under equivalent conditions.

[0031] Stability, as used herein, refers to the ability to detect the active ingredient (i.e., a compound of general formula I), in a composition, typically by HPLC, after

storage interval under predetermined conditions of temperature and humidity. Although HPLC is preferred, any method for detecting the active ingredient capable of identifying chemical modification and/or change in concentration of the active ingredient may be used.

[0032] Also provided is a method for increasing the stability of a compound of general formula I by reacting the compound with a suitable acid to form a pharmaceutically acceptable salt.

[0033] The compositions may possess potent antiprogestational activity and minimal antiglucocorticoid activity, combined with improved stability, which may render these compositions suitable for oral administration.

[0034] The compositions can be 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 meningioma; to treat uterine leiomyonas, to treat uterine fibroids; to inhibit uterine endometrial proliferation; to induce labor; to induce cervical ripening, for hormone therapy; and for contraception.

[0035] The compositions having antiprogestational activity may also be characterized by antagonizing the effects of progesterone. As such, the compositions may be of particular value in the control of hormonal irregularities in the menstrual cycle, for controlling endometriosis and dysmenorrhea, and for inducing menses. In addition, the compositions can be used as a method of providing hormone therapy either alone or in combination with estrogenic substances in postmenopausal women, or in women whose ovarian hormone production is otherwise compromised.

[0036] Moreover, the compositions can be used for control of fertility during the whole of the reproductive cycle. For long-term contraception, the compositions can

be administered either continuously or periodically depending on the dose. In addition, the compositions may be of particular value as post-coital contraceptives, for rendering the uterus inimical to implantation, and as "once a month" contraceptive agents.

[0037] A further important utility for the compositions lies in their ability to slow down growth of hormone-dependent tumors and/or tumors present in hormone-responsive tissues. Such tumors include, but are not limited to, kidney, breast, endometrial, ovarian, and prostate tumors, e.g., cancers, which may be characterized by possessing progesterone receptors. In addition, such tumors include meningiomas. Other utilities of the compositions include the treatment of fibrocystic disease of the breast and uterine.

[0038] The compositions 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.

[0039] The amount of active ingredient that can be combined with an optimal 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 may comprise between 0.1 milligram and 1 gram of the active ingredient or between 0.001 and 0.5 grams. However, 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.

[0040] The compositions can be administered by a variety of methods. For example, the compositions can be administered via the oral route in a form of 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.

[0041] The compositions can be also administered as an implant including SILASTIC and biodegradable implants or via intramuscular and intravenous injections.

[0042] The 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 alginic 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.

[0043] 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, calcium 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.

[0044] Aqueous suspensions may 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 (erg., 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 monooleate). 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.

[0045] 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.

[0046] Dispersible powders and granules 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.

[0047] The pharmaceutical composition 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 monooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion can also contain sweetening and flavoring agents.

[0048] 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.

[0049] The pharmaceutical composition can be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated 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 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.

[0050] The compound 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.

[0051] They can also be administered by in intranasal, intraocular, intravaginal, and intrarectal routes including suppositories, insufflation, powders and aerosol formulations.

[0052] Compounds administered by the topical route can be administered as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols.

[0053] The invention will be described in greater detail by way of the following specific, but not limiting, example.

Example 1. Formulations of the Instant Invention Can Be Prepared As Tablets.

[0054] To obtain tablets for practicing the instant invention, the following ingredients can be pressed together in a tablet press:

10.0 mg	of a pharmaceutically acceptable salt of CDB-4124
140.5 mg	of lactose
69.5 mg	of corn starch
2.5 mg	of poly-N-vinylpyrrolidone
2.0 mg	of aerosil
0.5 mg	of magnesium stearate

[0055] To obtain oily preparations for practicing the instant invention, the following ingredients can be mixed together and loaded into ampoules:

100.0 mg	of a pharmaceutically acceptable salt of CDB-4124

343.3 mg of castor oil

608.6 mg of benzyl benzoate

Example 2. Formation of the perchloric, methanesulfonic and phosphoric acid salts of CDB-4124

[0056] CDB-4124 was dissolved in one-part acetone and five-parts ethyl acetate and the resulting solution was split into five fractions. To each fraction, either citric acid, mandelic acid, perchloric acid, methanesulfonic acid or phosphoric acid was added in sufficient molar quantity to create the corresponding acid salt of CDB-4124. The reaction mixtures were stirred for about 2 hours at about 20 C followed by 2 hours below 0 C. The resulting solids were then filtered and washed with cold ethyl acetate and dried.

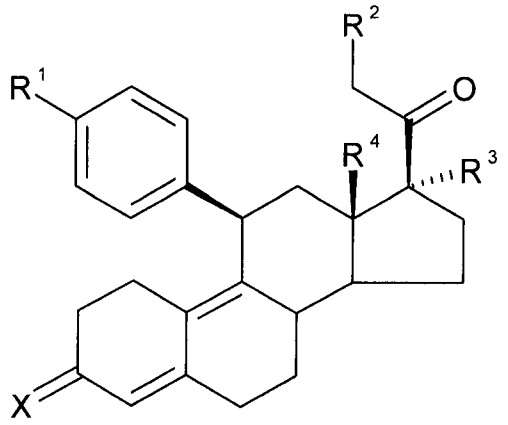
[0057] The citric and mandelic acid salts were not formed under these conditions. The perchloric, methanesulfonic and phosphoric acid steroid salts were all prepared in good recovery yields (~90%). It was immediately determined that these acid steroid salts were hygroscopic and required handling in a glove bag with a nitrogen atmosphere. Recrystallizations using various solvent systems (e.g. ethanol/ethyl ether) were attempted with no success. It was believed that the starting steroid used (90% peak area purity) was not high enough in purity and perhaps was contributing to the difficulty in recrystallization of the acid salts.

[0058] Accordingly, a higher purity yield of CDB-4124 was used for the formation of the methanesulfonic acid salt, by the procedure described above. The methanesulfonic acid salt was successfully recrystallized using an acetone/water solvent system.

CLAIMS:

What is claimed is:

1. A composition comprising a pharmaceutically acceptable salt of a compound having the general formula:



wherein:

R^1 is a basic functional group selected from the group consisting of —$N(CH_3)_2$, —$NHCH_3$, —NC_4H_8, --NC_5H_{10}, and —NC_4H_8O;

R^2 is a member selected from the group consisting of hydrogen, halogen, alkyl, acyl, hydroxy, alkoxy, acyloxy, alkylcarbonate, cypionyloxy, S-alkyl, —SCN, S-acyl, and —$OC(O)R^6$, wherein R^6 is a member selected from the group consisting of alkyl, alkoxy ester and alkoxy;

R^3 is a member selected from the group consisting of alkyl-alkoxy, alkoxy and acyloxy;

R^4 is a member selected from the group consisting of hydrogen and alkyl;

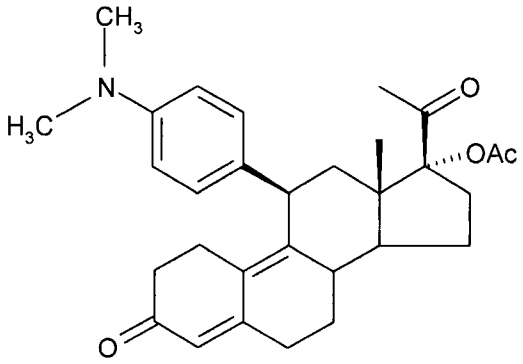
X is a member selected from the group consisting of =O and =N—OR^5, wherein R^5 is a member selected from the group consisting of hydrogen and alkyl;

wherein said pharmaceutically acceptable salt has increased stability compared to an equivalent amount of the free base of said compound; and with the proviso that when R^1 is —$N(CH_3)_2$, R^2 is methoxy, R^3 is acetoxy, R^4 is methyl and X is =O, the salt is not an HCl or an HBr salt.

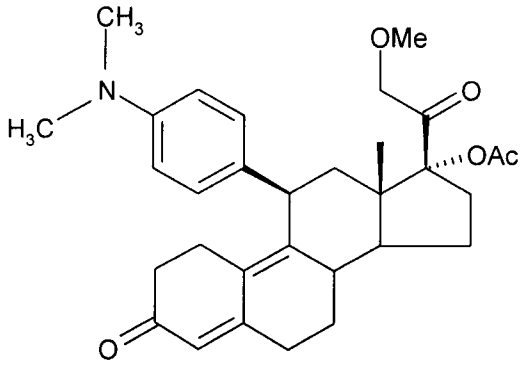
2. The composition of claim 1, wherein said compound is 17α-acetoxy-11β-[4-(N,N-dimethylamino)phenyl]-19-norpregna-4,9(10)-diene-3,20-dione.

3. The composition of claim 1, wherein said compound is 17α-acetoxy-11β-[4-(N,N-dimethylamino)phenyl]-21-methoxy-19-norpregna-4,9-diene-3,20-dione.

4. The composition of claim 1 wherein the compound has the structural formula:



5. The composition of claim 1 wherein the compound has the structural formula:



6. The composition of claim 5, wherein the salt is the perchloric, methanesulfonic or phosphoric acid salt of said compound.

7. The composition of claim 5, wherein the salt is the methanesulfonic salt.

8. A method of producing an antiprogestational effect in a patient, said method comprising administering to said patient an effective amount of the composition of claim 1 or claim 6.

9. A method of inducing menses in a patient, said method comprising administering to said patient an effective amount of the composition of claim 1 or claim 6.

10. A method of treating endometriosis, said method comprising administering to said patient an effective amount of the composition of claim 1 or claim 6.
11. A method of treating dysmenorrhea, said method comprising administering to said patient an effective amount of the composition of claim 1 or claim 6.
12. A method of treating endocrine hormone-dependent tumors, said method comprising administering to said patient an effective amount of the composition of claim 1 or claim 6.
13. A method of treating meningiomas, said method comprising administering to said patient an effective amount of the composition of claim 1 or claim 6.
14. A method of treating uterine fibroids in a patient, said method comprising administering to said patient an effective amount of the composition of claim 1 or claim 6.
15. A method of inhibiting uterine endometrial proliferation in a patient, said method comprising administering to said patient an effective amount of the composition of claim 1 or claim 6.
16. A method of inducing labor, said method comprising administering to a patient an effective amount of the composition of claim 1 or claim 6.
17. A method of contraception, said method comprising administering to a patient an effective amount of the composition of claim 1 or claim 6.
18. A method of post-coital contraception, said method comprising administering to a patient an effective amount of the composition of claim 1 or claim 6.