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(54) Title: COMPOUNDS USEFUL FOR TREATING HYPERTRIGLYCERIDEMIA

(57) Abstract: The present invention is directed to a method for treating a patient having hypertriglyceridemia comprising administering thereto a compound of the formula: I

# COMPOUNDS USEFUL FOR TREATING HYPERTRIGLYCERIDEMIA

## CROSS REFERENCE TO RELATED APPLICATION

This application is claiming priority of U.S. Provisional Application No. 60/238,659 filed on October 6, 2000.

## FIELD OF THE INVENTION

The present invention relates to the use of derivatives of 5-androsten-17-one and 5-androstan-17-one for lowering triglycerides in patients who have hypertriglyceridemia, especially those having low levels of HDL cholesterol, and/or those who are obese.

## BACKGROUND OF THE INVENTION

Hyperlipidemia, a condition which is characterized by an abnormal increase in serum lipids, i.e., cholesterol, triglycerides and phospholipids, is a primary cause for cardiovascular disease (CVD) and other peripheral vascular diseases. Hyperlipidemics having high levels of LDL (Low Density Lypoprotein) and VLDL (Very Low Density Lipoprotein) cholesterol are at risk for CVD.

One form of hyperlipidemia is hypertriglyceridemia, a condition in which there is an excessive amount of triglycerides in the plasma. It is a common lipid abnormality afflicting about 20% of the middle-aged human population in the U.S. A patient suffering from hypertriglyceridemia is at risk for atherosclerosis and CHD. Moreover, hypertriglyceridemia in combination with low levels of plasma HDL cholesterol (high density lipoprotein cholesterol, sometimes designated as the good cholesterol) is associated with insulin resistance, and both independently are risk factors for coronary heart disease and other peripheral

vascular diseases. In fact, the major lipid abnormality in Type II diabetes is hypertriglyceridemia.

Insulin resistance is a disorder of glucose metabolism. Patients with insulin resistance have a diminished ability to properly utilize glucose. In insulin resistance, there is a diminished ability of insulin to exert its biological action. The body secretes abnormally high amounts of insulin to compensate for this defect, failing which, the plasma glucose concentration inevitably rises. Insulin resistance can cause or contribute to hypertension, obesity, atherosclerosis and a variety of other disorders. Eventually, it can progress to a point where a diabetic state is reached. Insulin resistant (or Type II) diabetes is a severe and potentially disabling disease, if not properly treated.

Insulin resistance and hypertriglyceridemia both have a contributory role in obesity, cardiovascular disease, atherosclerosis and Type II diabetes mellitus.

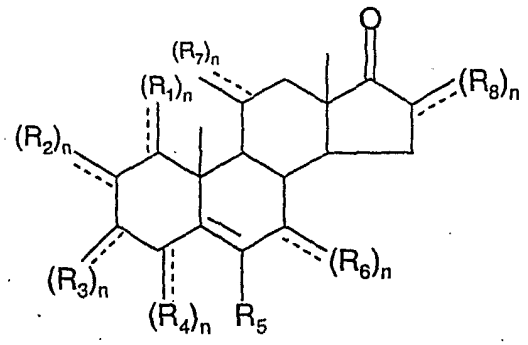
Thus, therapeutic agents which improve insulin resistance, lower plasma triglycerides, and increase HDL will have great significance in preventing cardiovascular morbidity and improving quality of life.

General measures such as weight reduction, exercise and avoidance of alcohol are initially used to control hypertriglyceridemia. If, however, triglyceride levels remain high, treatment with a fibric acid derivative, such as gemfibrozil or nicotinic acid, is frequently used. Gemfibrozil lowers triglycerides about 25-35%, and modestly raises HDL levels, but has no effect on insulin resistance. Nicotinic acid worsens insulin resistance. Moreover, nicotinic acid causes numerous side-effects, including intense flushing and associated pruritus, which limits its use.

Thus, the search continues for effective drugs which are capable of treating hypertriglyceridemia, raising HDL levels and treating insulin resistance. The

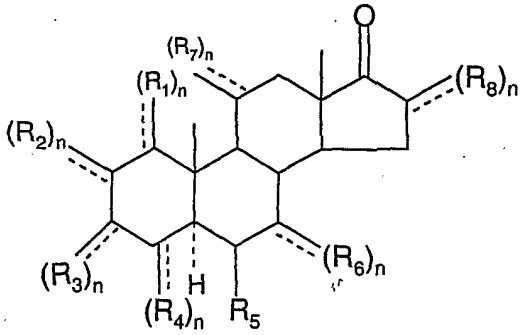
present inventor has found such drugs. The drugs are derivatives of 5-androsten-17-ones and 5α-androstan-17-ones.

U.S. Patent No. 5,804,576 and 5,714,481 describe 5-androsten-17-ones having the formula:




wherein $R_1$, $R_2$, $R_3$, $R_4$, $R_6$, $R_7$ and $R_8$ are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, halogen and hydroxyl; $R_5$ is hydrogen, alkyl, alkenyl, alkynyl or halogen, n is an integer from 1 to 2 inclusive with the proviso that when $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$ or $R_8$ is alkenyl or alkynyl, n is 1; and with the further provisos that at least one of $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$ or $R_8$ is other than hydrogen; that when $R_3$ is hydroxy, any one of the substituents $R_2$, $R_4$, $R_5$, $R_6$, $R_7$ or $R_8$ is other than hydrogen and $R_1$ is other than hydrogen or hydroxy; when $R_3$ is hydroxy, $R_1$ may only be alkyl when any one of $R_2$, $R_4$, $R_5$, $R_6$, $R_7$ or $R_8$ is other than hydrogen; when $R_3$ is hydroxy, $R_4$ may only be halogen or hydroxy when $R_1$, $R_2$, $R_5$, $R_6$, $R_7$ or $R_8$ is other than hydrogen; when $R_3$ is hydroxy, $R_6$ may only be hydroxy when $R_1$, $R_2$, $R_4$, $R_5$, $R_7$ or $R_8$ is other than hydrogen; when $R_3$ is hydroxy, $R_2$ may only be alkyl when one of $R_1$, $R_4$, $R_5$, $R_6$, $R_7$ or $R_8$ is other than hydrogen; when $R_3$ is hydroxy, $R_6$ can only be methyl when $R_1$, $R_2$, $R_4$, $R_7$ or $R_8$ is other than hydrogen and $R_5$ is other than hydrogen or methyl; when $R_3$ is hydroxy, $R_7$ may only be hydroxy when $R_1$, $R_2$, $R_4$, $R_5$, $R_6$ or $R_8$ is other than hydrogen; when $R_3$ is hydroxy, $R_8$ may only be methyl, ethyl, isopropyl, hydroxy or halogen when $R_1$, $R_2$, $R_4$, $R_5$,

$R_6$ or $R_7$ is other than hydrogen; when $R_3$ is hydroxy, $R_5$ may only be alkyl when $R_1$, $R_2$, $R_4$ or $R_7$ is other than hydrogen and $R_6$ or $R_8$ is other than hydrogen or methyl; when $R_3$ is fluorine, any one of the substituents $R_1$, $R_2$, $R_4$, $R_5$, $R_6$, $R_7$ or $R_8$ is other than hydrogen; when $R_3$ is iodine or chlorine, $R_5$ may only be methyl when $R_1$, $R_2$, $R_4$, $R_6$, $R_7$ or $R_8$ is other than hydrogen; and when $R_3$ is hydroxy, $R_4$ may only be hydroxy when $R_1$, $R_2$, $R_5$, $R_6$ or $R_8$ is other than hydrogen. They also disclose 16α-fluoro-5α-androstan-17-ones of the formula:

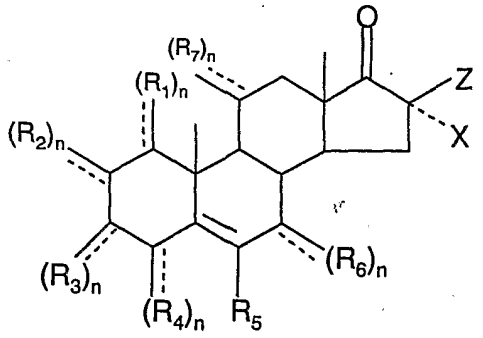



wherein $R_1$, $R_2$, $R_3$, $R_4$, $R_6$, $R_7$ or $R_8$ are selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, halogen and hydroxyl, $R_5$ is hydrogen, alkyl, alkenyl, hydroxy, alkynyl or halogen, n is an integer from 1 to 2 inclusive with the proviso that when $R_1$-$R_8$ are alkenyl or alkynyl, then n is 1 and with the further provisos that $R_3$ may be hydroxy or halogen only when any one of $R_1$, $R_2$, $R_4$, $R_5$, $R_6$, $R_7$ or $R_8$ is other than hydrogen; when $R_3$ is hydroxy, $R_1$ may be hydroxy or halogen only when any one of $R_2$, $R_4$, $R_5$, $R_6$, $R_7$ or $R_8$ is other than hydrogen; when $R_3$ is hydroxy, $R_2$ may be methyl or halogen only when any one of $R_4$, $R_5$, $R_6$, $R_7$ or $R_8$ is other than hydrogen; when $R_3$ is hydroxy, $R_4$ may be halogen, methyl or hydroxy only when any one of $R_1$, $R_2$, $R_3$, $R_5$, $R_6$, $R_7$ or $R_8$ is other than hydrogen; when $R_3$ is hydroxy, $R_5$ may be methyl, halogen or hydroxy only when $R_1$, $R_2$, $R_4$, $R_6$, $R_7$ or $R_8$ is other than hydrogen; when $R_3$ is hydroxy, $R_6$ may be hydroxy or methyl only when $R_1$, $R_2$, $R_4$, $R_5$, $R_7$ or $R_8$ is other than hydrogen;

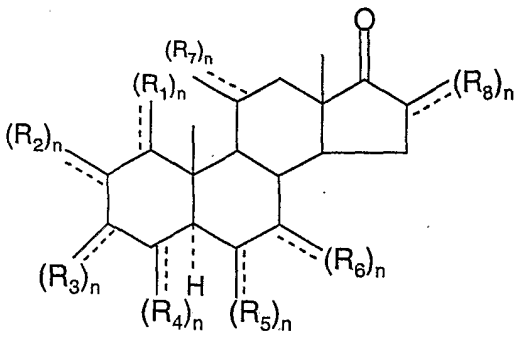
when $R_3$ is hydroxy, $R_7$ may be hydroxy only when $R_1$, $R_2$, $R_4$, $R_5$, $R_6$ or $R_8$ is other than hydrogen; when $R_3$ is hydroxy, $R_8$ may be methyl, hydroxy or halogen only when $R_1$, $R_2$, $R_4$, $R_5$, $R_6$ or $R_7$ is other than hydrogen; $R_7$ may be only hydroxy when anyone of $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$ and $R_8$ is other than hydrogen; and $R_8$ may be bromo only when $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$ or $R_7$ is other than hydrogen.

They describe that these compounds are useful for treating, inter alia, diabetes and hyperlipidemia.

U.S. Patent Nos. 5,744,462, 5,700,793, 5,696,106, 5,656,621, and 5,157,031 describe steroids of the formula:




and




wherein

$R_1$, $R_2$, $R_4$, $R_5$, $R_6$ and $R_7$ are each independently hydrogen or lower alkyl;

$R_3$ is hydrogen;

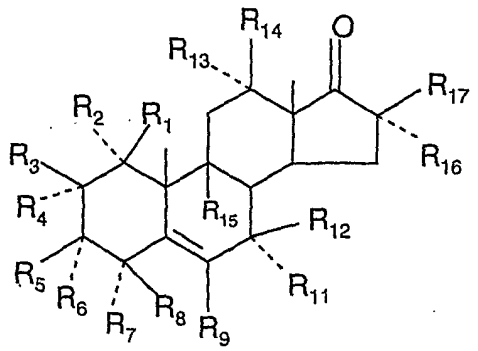
X is halogen, hydroxy, hydrogen, lower alkyl, or lower alkoxy;

Z is lower alkyl or hydrogen; and

n is 1 or 2, with the proviso that at least one of X and Z is other than hydrogen.

They teach that these compounds are useful for treating, inter alia, hyperlipidemia and diabetes.

U.S. Patent No. 5,001,119 disclose compounds of the formula:



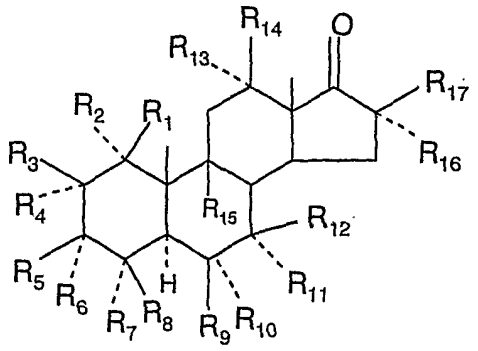

wherein

$R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$ and $R_{15}$ are independently hydrogen, lower alkyl, halogen, hydroxy or lower alkoxy;

$R_9$ is hydrogen, lower alkyl or halogen; and

$R_{16}$ and $R_{17}$ are independently hydrogen, amino, loweralkylamino, diloweralkylamino, aminoloweralkyl, loweralkyl aminolower alkyl, diloweralkylaminolower alkyl, loweralkoxyloweralkyl, lower alkoxy, hydroxy lower alkyl, monohaloloweralkyl, dihaloloweralkyl, trihaloloweralkyl, loweralkanoyl, formyl, lower carbalkoxy, or lower alkanoyloxy or $R_{16}$ and $R_{17}$ taken together with the carbons to which they are attached form a lower cycloalkyl or a cyclic ether containing one ring oxygen atom and up to 5 ring carbon atoms with theproviso that when $R_5$ is hydroxy and $R_1$, $R_2$, $R_3$, $R_4$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$ and $R_{15}$ are hydrogen, then $R_{16}$ is other than $CH_2N(CH_3)$ and with the further proviso that $R_{16}$ and $R_{17}$ are not hydrogen simultaneously.

It also discloses compounds of the formula:




wherein

$R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$ and $R_{15}$ are independently hydrogen, lower alkyl, halogen, hydroxy or lower alkoxy;

$R_9$ and $R_{10}$ are independently loweralkyl, hydrogen or halogen; and

$R_{16}$ and $R_{17}$ are independently amino, lower alkylamino, diloweralkyl amino, aminoloweralkyl, loweralkyl aminoloweralkyl, diloweralkylamino loweralkyl, lower alkoxy, hydroxyloweralkyl, monohaloloweralkyl, dihaloloweralkyl, trihaloloweralkyl, loweralkoxyloweralkyl, loweralkanoyl, formyl, lower carbalkoxy, hydrogen or lower alkanoyloxy; or

$R_{16}$ and $R_{17}$ taken together with the carbon to which they are attached form a lower cycloalkyl or a cyclic ether containing one ring oxygen atom and up to 5 ring carbon atoms, with the further proviso that $R_{16}$ and $R_{17}$ are not hydrogen simultaneously.

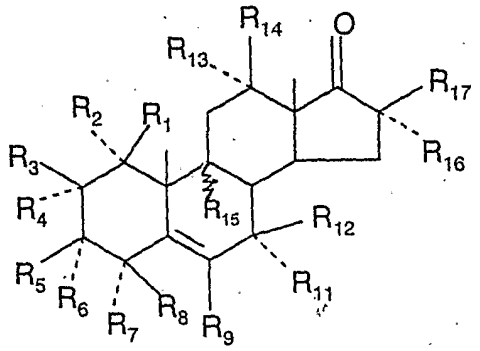
It discloses that these compounds are useful pharmaceuticals.

However, none of the aforementioned patents teach that the androstene and androstane derivatives described hereinbelow lower plasma triglyceride levels, especially in those patients who suffer from hypertriglyceridemia and who have low HDL levels. Moreover, none of the aforementioned patents teach that the androstene and androstane derivatives described

hereinbelow lower triglyceride levels of patients who suffer from hypertriglyceridemia and insulin resistance.

## SUMMARY OF THE INVENTION

Accordingly, the present invention is directed to the method of treating a patient suffering from hypertriglyceridemia comprising administering thereto a therapeutically (or antiglucoutoed) effective amount of a compound of the formula:



I

wherein

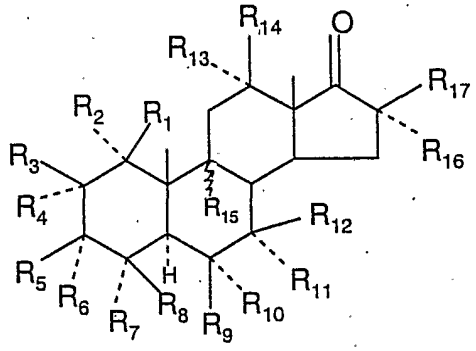
$R_1$, $R_2$, $R_3$, $R_4$, $R_7$, $R_8$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$ and $R_{15}$ are independently hydrogen, alkyl, halogen, hydroxy or alkoxy;

$R_5$ and $R_6$ are independently hydrogen, alkyl, alkoxy or halogen or hydroxy;

$R_9$ is hydrogen, alkyl, halogen or alkoxy;

$R_{16}$ and $R_{17}$ are independently hydrogen, alkyl, halogen, hydroxy, alkoxy, lower alkenyl, lower alkynyl, amino, lower alkylamino, diloweralkylamino, loweralkoxy lower alkyl, hydroxyloweralkyl, aminoloweralkyl, loweralkylaminoloweralkyl, diloweralkylamino lower alkyl, haloloweralkyl, dihaloloweralkyl or trihaloloweralkyl, with the proviso that only one of $R_{16}$ and $R_{17}$ may be alkenyl or alkynyl and with the further proviso that if $R_5$ or $R_6$ is hydroxy, then $R_{16}$ is other than hydrogen.

The present invention is also directed to a method for treating a patient having hypertriglyceridemia, comprising administering thereto a therapeutically (or antiglucoutoed) effective amount of a compound of the formula:




II

wherein

$R_1$, $R_2$, $R_3$, $R_4$, $R_7$, $R_8$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$ and $R_{15}$ are independently hydrogen, alkyl, halogen, hydroxy or alkoxy;

$R_5$ and $R_6$ are independently hydrogen, hydroxy alkyl, alkoxy or halogen;

$R_9$ is hydrogen, alkyl, halogen or alkoxy;

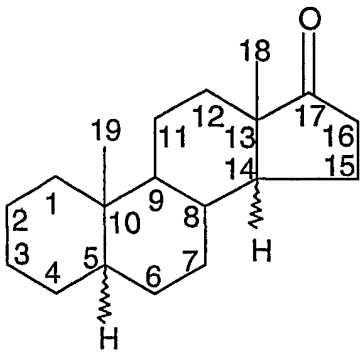
$R_{16}$ and $R_{17}$ are independently hydrogen, alkyl, halogen, hydroxy, alkoxy, lower alkenyl, lower alkynyl, amino, lower alkylamino, diloweralkylamino, loweralkoxy lower alkyl, hydroxyloweralkyl, aminoloweralkyl, loweralkylaminoloweralkyl, diloweralkylamino lower alkyl, haloloweralkyl, dihaloloweralkyl or trihaloloweralkyl, with the proviso that only one of $R_{16}$ and $R_{17}$ may be alkenyl or alkynyl.

The present invention is also directed to a method of treating a patient having hypertriglyceridemia, said method comprising administering thereto a therapeutically effective amount of a compound of Formula I or Formula II. It is also directed, in another embodiment to treating a patient having

hypertriglyceridemia and at least one of the following characteristics (a) insulin resistance; (b) obesity, especially with a BMI >30; (c) low HDL levels, said method comprising administering thereto a therapeutically effective amount of a compound of Formula I or II. The present invention is also directed to reducing the adverse effects of enhanced glucocouticoid activity in a mammal, including humans which comprise administering to said animal an anti-glucocorticoid effective amount of compounds of Formula I or II. The adverse effects may result from various factors, such as hypersecretion of glucocorticoids; the enzymatic action of 11ß-hydroxysteriod hydrogenase which converts cortisone to cortisol; the administration of glucocorticoids to the animal, and the like. These factors may result in enhanced glucocorticoid action which may manifest in certain diseases, symptoms, conditions or malady or side effects, resulting from the administration of glucocorticoids administration. Thus, the compounds of Formula I and II may be used to treat, ameliorate, prevent or retard the progression of an unwanted condition or symptom or malady in a patient relating to the enhanced antiglucocorticoids effect. Alternatively, if glucocortids are being administered to the patient e.g. for treatment, the compounds of Formula I or II may be coadministered in antiglucocorticoid effective amount to reduce, prevent the side effects associated with glucocorticoids treatment.

**DETAILED DESCRIPTION OF THE INVENTION**

The compounds utilized in the present invention are steroids. In accordance with I.U.P.A.C. nomenclature, the carbon atoms of the present invention are numbered as follows and the steroids have the designated I.U.P.A.C. stereochemistry:




The various substituents are designated as being in the α-position by means of a broken line (---) joining the substituent to the steroid nucleus. The substituents are designated as being in the β-position by means of a solid line (—) joining the substituent to the steroid nucleus. In those cases in which the substituents may be either in the α- or β-position, the substituents are indicated as being joined to the steroid nucleus by a broken line and solid line placed side by side.

As used herein, the term "alkyl", when used alone or in combination has 1-12 carbon atoms. The term "lower alkyl", refers to an alkyl group having one to six carbon atoms. The alkyl groups may be straight chain or branched. Examples include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, neopentyl, and hexyl. It is preferred that the alkyl group is lower alkyl. The preferred lower alkyl group contains 1-3 carbon atoms. The most preferred alkyl group is methyl.

The term "alkoxy" when used alone or in combination as used herein, refers to an alkoxy group having 1-12 carbon atoms. As used herein, the term "lower alkoxy", refers to an alkoxy group having 1-6 carbon atoms. It may be straight chain or branched. Examples include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentoxy and the like. It is preferred

that alkoxy is lower alkoxy. It is more preferred that alkoxy contains 1-3 carbon atoms. The most preferred alkoxy group is methoxy.

The halo atoms are preferably Br, I and especially Cl and most especially F.

The term "loweralkylamino", when used alone or in combination, refers to amino group bonded directly to the steroid nucleus and attached to the amino group is one alkyl group, i.e., $-NHR_{100}$ wherein the nitrogen atom is bonded to the steroid nucleus, and $R_{100}$ is lower alkyl, as defined herein. On the other hand, the term "lowerdialkylamino" refers to an amino group bonded directly to the steroid nucleus and attached to the amino group are two lower alkyl groups which may be the same or different, i.e., $N(R_{100})(R_{101})$, wherein $R_{100}$ and $R_{101}$ are lower alkyl, as defined herein.

The term "hydroxyloweralkyl", as used herein refers to a lower alkyl as defined herein, which is substituted by a hydroxy group. The hydroxy group may be substituted at any position on the alkyl chain.

The term "loweralkoxy loweralkyl" as used herein refers to a lower alkyl group as defined herein which is bonded to the steroid nucleus, which alkyl group is substituted at any position of the alkyl chain with a lower alkoxy group, as defined herein.

The term "amino lower alkyl" as used herein refers to a lower alkyl group, as defined herein, bonded to the steroid nucleus, which alkyl group is substituted by an amino group. The amino group may be substituted in any position of the alkyl chain.

The term "loweralkylaminoloweralkyl" as used herein, refers to a lower alkyl group, as defined herein, bonded to the steroid nucleus, and the lower alkyl group is substituted with a lower alkylamino group as defined herein, e.g., $NHR_{102}$, wherein $R_{102}$ is loweralkyl and wherein the nitrogen atom is bonded to the alkyl substituent which is bonded to the steroid nucleus. The lower

alkylamino group may be substituted on any position of the lower alkyl substituent.

The term "lowerdialkylamino loweralkyl," refers to a loweralkyl group, as defined herein which is substituted with a diloweralkyl amino group, e.g., -$NR_{102}R_{103}$ wherein $R_{102}$ and $R_{103}$ are independently lower alkyl and the nitrogen atom is bonded to the alkyl substituents which is bonded directly to the steroid nucleus. The diloweralkylamino group may be substituted on any position of the loweralkyl substituent.

The term "monohaloloweralkyl" refers to a loweralkyl group which is substituted by halo, as defined herein. The halo group may be substituted on any position of the lower alkyl substituent.

The term "dihaloloweralkyl" refers to a lower alkyl group which is substituted by two halo groups. It is preferred that the two halo groups are on the same carbon. It is also preferred that the two halo groups are the same. It is most preferred that the halo groups are chloro and especially fluoro. Examples include difluoromethyl, dichloromethyl, 2,2-difluoroethyl, and the like.

The term "trihaloloweralkyl" refers to a lower alkyl group which is substituted by three halo groups. It is preferred that the halo groups are the same. It is also preferred that the three halo groups are substituted on the same carbon. Examples include trifluoromethyl, tribromomethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2,2-trifluoroethyl and the like. The most preferred is trifluoromethyl.

The term "lower alkenyl" as used herein refers to an alkenyl group which contains two to six carbon atoms and at least one double bond. The alkenyl group may be straight chained or branched and may be in either the Z or E form. Examples include ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, isopropenyl, isobutenyl, 1-pentenyl, (Z)-2-pentenyl, (E)-2-pentenyl,

(Z)-4-methyl-2-pentenyl, (E)-4-methyl-2-pentenyl, pentadienyl, e.g., 1-3 or 2,4-pentadienyl, 1,3-butadienyl and the like. The preferred alkenyl group is ethenyl.

The term "lower alkynyl" refers to an alkynyl group containing 1-6 carbon atoms and at least one carbon-carbon triple bond. The alkynyl group may be straight chained or branched and may be either the E or Z form. Examples include 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl, 3-methyl-1-pentynyl, 3-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, and the like. The preferred alkynyl group is ethynyl.

Thus, in some embodiments, the formula I or formula II compound is a compound wherein $R_1$, $R_2$, $R_3$, $R_4$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$ and $R_{15}$ are independently -H, -OH, -F, -Cl, -Br, -I, $-OCH_3$, $-OC_2H_5$, $-OCH_2CH_2CH_3$, $-OCH(CH_3)_2$, $-OCH_2CH_2CH_2CH_3$, $-OCH_2CH(CH_3)_2$, $-OCH(CH_3)CH_2CH_3$, $-OC(CH_3)_3$, $-OC_5H_{11}$, $-OC_6H_{13}$, $-OC_7H_{15}$, $-OC_8H_{17}$, $-CH_3$, $-C_2H_5$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-C(CH_3)_3$, $-C_5H_{11}$, $-C_6H_{13}$, $-C_7H_{15}$ or $-C_8H_{17}$; $R_5$ and $R_6$ are defined as hereinabove for $R_1$ except neither $R_5$ or $R_6$ are OH, $R_{16}$ and $R_{17}$ are defined independently -H, -OH, $-NH_2$, -F, -Cl, -Br, -I, $-OCH_3$, $-OC_2H_5$, $-OCH_2$ $CH_2CH_3$, $-OCH(CH_3)_2$, $-OCH_2CH_2CH_2CH_3$, $-OCH_2CH(CH_3)_2$, $-OCH(CH_3)CH_2CH_3$, $-OC(CH_3)_3$, $-OC_5H_{11}$, $-OC_6H_{13}$, $-OC_7H_{15}$, $-OC_8H_{17}$, $-CH_3$, $-C_2H_5$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2$ $CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-C(CH_3)_3$, $-C_5H_{11}$, $-C_6H_{13}$, $-C_7H_{15}$, $-C_8H_{17}$, -COH, $-CHCH_2$, $-CHCHCH_3$, $-CHCHCH_2CH_3$, $-NHCH_3$, $-NHC_2H_5$, $-NHCH_2CH_2CH_3$, $-NHCH(CH_3)_2$, $-NHCH_2CH_2CH_2CH_3$, $-NHCH_2CH(CH_3)_2$, $-NHCH(CH_3)CH_2CH_3$, $-NHC(CH_3)_3$, $-NHC_5H_{11}$, $-NHC_6H_{13}$, $-NHC_7H_{15}$, $-NHC_8H_{17}$, $-CH_2OH$, $-C_2H_4OH$, $-C_3H_6OH$, $-C_4H_8OH$, $-C_5H_{10}OH$, $-C_6H_{12}OH$,

$-C_7H_{14}OH$, $-C_8H_{16}OH$, $-CH_2NH_2$, $-C_2H_4NH_2$, $-C_3H_6NH_2$, $-C_4H_8NH_2$, $-C_5H_{10}NH_2$, $-C_6H_{12}NH_2$, $-C_7H_{14}NH_2$, $-C_8H_{16}NH_2$, $-CH_2NH_2CH_3$, $-C_2H_4NH_2C_2H_5$, $-C_3H_6NH_2C_3H_7$, $-C_4H_8NH_2C_4H_9$, $-C_5H_{10}NHC_5H_{11}$, $-C_6H_{12}NHC_6H_{13}$, $-C_7H_{14}NH\ C_7H_{15}$, $-C_8H_{16}NHC_8H_{17}$, $-CH_2F$, $-C_2H_4F$, $-C_3H_6F$, $-C_4H_8F$, $-C_5H_{10}F$, $-C_6H_{12}F$, $-C_7H_{14}F$, $-C_8H_{16}F$, $-CH_2Cl$, $-C_2H_4Cl$, $-C_3H_6Cl$, $-C_4H_8Cl$, $-C_5H_{10}Cl$, $-C_6H_{12}Cl$, $-C_7H_{14}Cl$, $-C_8H_{16}Cl$, $-CH_2Br$, $-C_2H_4Br$, $-C_3H_6Br$, $-C_4H_8Br$, $-C_5H_{10}Br$, $-C_6H_{12}Br$, $-C_7H_{14}Br$, $-C_8H_{16}Br$, $-CH_2I$, $-C_2H_4I$, $-C_3H_6I$, $-C_4H_8I$, $-C_5H_{10}I$, $-C_6H_{12}I$, $-C_7H_{14}I$ or $-C_8H_{16}I$. In some of these embodiments 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 of the $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$ and $R_{15}$ variable groups are -H and the remaining variable groups are not -H.

It is preferred that $R_1$, $R_2$, $R_3$, $R_4$, $R_7$, $R_8$, $R_9$, $R_{13}$, $R_{14}$ and $R_{15}$ are independently hydrogen, halogen, (especially chloro and more especially fluoro), hydroxy, alkyl containing 1-3 carbon atoms or alkoxy containing 1-3 carbon atoms, especially methoxy. It is most preferred that $R_1$, $R_2$, $R_3$, $R_4$, $R_7$, $R_8$, $R_{13}$, $R_{14}$ and $R_{15}$ are hydrogen, hydroxy, methyl, and halo (especially chloro and more especially fluoro) or methoxy. It is most preferred that $R_1$, $R_2$, $R_3$, $R_4$, $R_7$, $R_8$, $R_9$, $R_{13}$, $R_{14}$, $R_{15}$ are hydrogen.

It is preferred that $R_{11}$ and $R_{12}$ are independently hydrogen, halogen (especially chloro and more especially fluoro), hydroxy, alkyl containing 1-3 carbon atoms (especially methyl) or alkoxy containing 1-3 carbon atoms, especially methoxy. It is most preferred that one of $R_{11}$ and $R_{12}$ is hydrogen and the other is as defined hereinabove. It is most preferred that one of $R_{11}$ and $R_{12}$ is hydrogen and the other is hydrogen, or hydroxy or methoxy or fluoro or chloro or methyl.

When the compound utilized is an androstene, it is preferred that $R_9$ is hydrogen, alkyl containing 1-3

carbon atoms or alkoxy containing 1-3 carbon atoms or halo, especially fluoro or chloro. It is most preferred that $R_9$ is hydrogen, alkyl containing 1-3 carbon atoms or halo. It is even more preferred that $R_9$ is hydrogen.

When the compound utilized is an androstane, both $R_9$ and $R_{10}$ are present on the ring. It is preferred that $R_9$ and $R_{10}$ are independently hydrogen, alkyl containing 1-3 carbon atoms, especially methyl, alkoxy containing 1-3 carbon atoms, especially methyl, halo, especially fluoro or chloro or hydroxy. It is most preferred that one of $R_9$ and $R_{10}$ is hydrogen and the other is as defined hereinabove.

In the preferred embodiment, the carbon atoms to which $R_1$, $R_2$, $R_3$, $R_4$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$ or $R_{15}$ are either unsubstituted or monosubstituted. In other words, in the preferred embodiment, at least one of $R_1$ and $R_2$ is hydrogen, and at least one of $R_3$ and $R_4$ is hydrogen, and at least one of $R_7$ and $R_8$ is hydrogen, and at least one of $R_{11}$ and $R_{12}$ is hydrogen and at least one of $R_{13}$ and $R_{14}$ is hydrogen. When the compound utilized is in androstene, $R_9$ can have any of the values indicated hereinabove; however, when the compound utilized is an androstene, in the preferred embodiment, at least one of $R_9$ and $R_{10}$ is hydrogen.

In the most preferred embodiment, either all of $R_1$, $R_2$, $R_3$, $R_4$, $R_7$, $R_8$, $R_9$, $R_{10}$ (when present), $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$ or $R_{15}$ are all hydrogen, or one of $R_1$, $R_2$, $R_3$, $R_4$, $R_7$, $R_8$, $R_9$, $R_{10}$ (when present), $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, is a non-hydrogen substituent and the rest are hydrogen. In the latter case, it is preferred that only one of $R_9$, $R_{10}$, $R_{11}$ or $R_{12}$ is substituted, as defined herein, and $R_1$, $R_2$, $R_3$, $R_4$, $R_7$, $R_8$, $R_{13}$, $R_{14}$ and $R_{15}$ are hydrogen.

It is preferred that $R_5$ and $R_6$ in both Formula I and II are other than hydroxy. It is preferred that $R_5$ and $R_6$ are independently hydrogen, lower alkyl, especially alkyl containing 1-3 carbon atoms, or halo, especially chloro or fluoro. In the most preferred

embodiment, $R_5$ and $R_6$ are independently lower alkyl, especially alkyl containing 1-3 carbon atoms or hydrogen. It is even more preferred that $R_5$ and $R_6$ are independently hydrogen or methyl. In the most preferred embodiment, $R_6$ is hydrogen and $R_5$ is hydrogen, alkyl containing 1-3 carbon atoms, especially methyl or halo, especially fluoro or chloro. It is even more preferred that $R_6$ is hydrogen and $R_5$ is hydrogen or alkyl containing 1-3 carbon atoms, especially methyl. It is most preferred that both $R_5$ and $R_6$ are hydrogen.

In the definitions hereinabove, $R_{16}$ and $R_{17}$ can have any of the aforementioned values. However, the present inventor has found that when $R_{16}$ is either an alkenyl or alkynyl, $R_{17}$ cannot also be an alkenyl or alkynyl and vice versa. In other words, only one of $R_{16}$ and $R_{17}$ can contain an alkenyl or alkynyl group, if present.

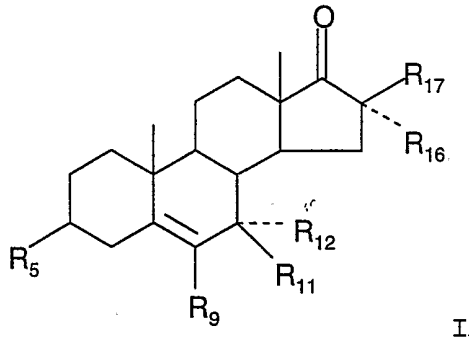
It is preferred that $R_{16}$ and $R_{17}$ are independently hydrogen, lower alkyl, lower alkoxy, or hydroxy or halo, especially chloro and most especially fluoro. In a more preferred embodiment, $R_{16}$ and $R_{17}$ are independently hydrogen, alkyl containing 1-3 carbon atoms, alkoxy containing 1-3 carbon atoms, hydroxy or halo, especially chloro and most especially fluoro. It is even more preferred that $R_{16}$ and $R_{17}$ are independently hydrogen or halo, especially chloro or fluoro.

It is especially preferred that at least one of $R_{16}$ and $R_{17}$ is other than hydrogen. It is most preferred that $R_{17}$ is hydrogen and $R_{16}$ is other than hydrogen. In the more especially preferred embodiment, $R_{17}$ is hydrogen and $R_{16}$ is halo, especially chloro and most especially fluoro, lower alkyl, especially alkyl containing 1-3 carbon atoms, hydroxy, lower alkoxy, especially alkoxy containing 1-3 carbon atoms, or hydroxy. In the even more preferred embodiment, $R_{17}$ is hydrogen and $R_{16}$ is halo, especially chloro and most especially fluoro, methyl, methoxy or hydroxy.

It is most especially preferred that $R_{17}$ is hydrogen and $R_{16}$ is halo, especially chloro or fluoro. It is most especially preferred that $R_{17}$ is hydrogen and $R_{16}$ is fluoro.

Moreover, in the compounds of Formula I and II it is preferred that the hydrogen atom in the 8 position is ß. it is also preferred that the hydrogen atom in the 14 position is alpha. Thus the substituent on the C-9($R_{15}$) may be α or ß configuration. It is indicated herein by a wavy line. It is preferred that the $R_{15}$ substituent is alpha.

Preferred compounds of the Formula I have the formula:




IA

wherein

$R_5$ is hydrogen or lower alkyl;

$R_9$ is hydrogen or halo or lower alkyl;

$R_{11}$ and $R_{12}$ are independently hydrogen, lower alkyl, hydroxy, lower alkoxy, or halo;

$R_{17}$ is hydrogen, lower alkyl or halo, especially fluoro; and

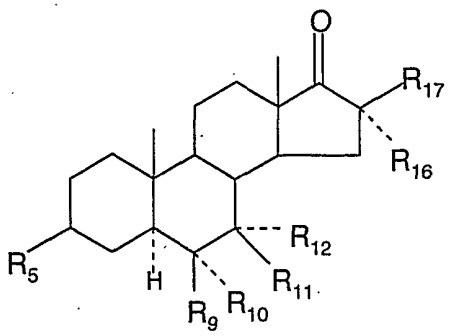
$R_{16}$ is hydroxy, lower alkyl, lower alkoxy or halo, especially chloro and most especially fluoro.

In this embodiment, it is preferred that $R_5$ is hydrogen or methyl and especially hydrogen. It is also preferred that $R_9$ is hydrogen. The preferred embodiments of $R_{11}$ and $R_{12}$ are hydrogen, methyl, hydroxy or methoxy or halo, especially chloro and most especially fluoro.

It is preferred that $R_{16}$ is halo, especially chloro and most especially fluoro.

The preferred values of $R_{17}$ is hydrogen, methyl or halo, especially fluoro. It is more preferred that $R_{17}$ is fluoro and most especially hydrogen.

Preferred compounds of Formula II have the formula:




IIA

wherein

$R_5$ is hydrogen or lower alkyl;

$R_9$ is hydrogen or halo or lower alkyl;

$R_{11}$ and $R_{12}$ are independently hydrogen, lower alkyl, hydroxy, lower alkoxy, or halo; and

$R_{17}$ is hydrogen, lower alkyl or halo, especially fluoro; and

$R_{16}$ is hydroxy, lower alkyl, lower alkoxy or halo, especially chloro and most especially fluoro.

In this embodiment, it is preferred that $R_3$ is hydrogen or methyl and especially hydrogen.

It is preferred that $R_9$ and $R_{10}$ are independently hydrogen, methoxy, methyl or halogen, especially chloro and most especially fluoro. It is most preferred, however, that $R_9$ and $R_{10}$ are hydrogen.

The preferred embodiments of $R_{11}$ and $R_{12}$ are hydrogen, methyl, hydroxy, methoxy or halo, especially chloro and most especially fluoro.

It is preferred that $R_{16}$ is halo, especially chloro and most especially fluoro.

The preferred values of $R_{17}$ is hydrogen, methyl or halo, especially fluoro. It is especially preferred that $R_{16}$ is fluoro and most especially hydrogen.

It is to be understood that in the formulae depicted hereinabove, the various combinations and permutations of the various definitions of $R_1$-$R_{17}$ are contemplated to be within the scope of the compounds utilized in the present invention.

Preferred compounds for use in the present invention include:

1α-methyl-5-androsten-17-one,

2α,6,16α-trimethyl-5-androsten-17-one,

16α-ethynyl-6-chloro-5-androsten-17-one,

3β-methyl-5-androsten-17-one,

3β-ethyl-5-androsten-17-one,

3β-butyl-5-androsten-17-one,

6,16α-dimethyl-5-androsten-17-one,

2α,7β-dimethyl-5-androsten-17-one,

1α-chloro-3β-methyl-5-androsten-17-one,

4α-methyl-5-androsten-17-one,

3β-methyl-7β-chloro-5-androsten-17-one,

3β-methyl-16α-ethyl-5-androsten-17-one,

3β-methyl-16α-ethynyl-5-androsten-17-one,

3β,16α, 16β-trimethyl-5-androsten-17-one,

3β-methyl, 16α, 16β-difluoro-5-androsten-17-one,

2α,3β-dimethyl-5-androsten-17-one,

3β,4α, 7β-trimethyl-5-androsten-17-one,

2α,3β, 6-trimethyl-5-androsten-17-one,

3β,4α, 7β-trimethyl-5-androsten-17-one,

6-methyl-5-androsten-17-one,

7β-methyl-5-androsten-17-one,

16α-fluoro-3β-methyl-5-androsten-17-one,
16α-methoxy-5-androsten-17-one,
11α-methyl-5-androsten-17-one,
16α-methyl-5-androsten-17-one,
3β,16β-dimethyl-5-androsten-17-one,
16α-hydroxy-3β-methyl-5-androsten-17-one,
16β-fluoro-5-androsten-17-one,
3β-hydroxy-16α-fluoro-5-androsten-17-one,
16α-fluoro-3β-methyl-5-androsten-17-one,
16α-fluoro-3β, 16β-dimethyl-5-androsten-17-one,
16α-fluoro-16β-methyl-5-androsten-17-one,
3β-methyl-5α-androstan-17-one,
3β-methyl-7α-chloro-5α-androstan-17-one,
3β-methyl-16α-ethyl-5α-androstan-17-one,
3β-methyl-16α-ethynyl-5α-androstan-17-one,
2α,3β-dimethyl-5α-androstan-17-one,
3β,4α-dimethyl-5α-androstan-17-one;
1α-methyl-5α-androstan-17-one,
3β,16α-dimethyl-5α-androstan-17-one,
16α-hydroxy-3β-methyl-5α-androstan-17-one,
16α-fluoro-3β-methyl-5α-androstan-17-one,
16α-hydroxy-3β-methyl-5α-androstan-17-one,
16α-fluoro-3β-methyl-5α-androstan-17-one,
16α-fluoro-3β,16β-dimethyl-5α-androstan-17-one,
16α-fluoro-3β,16β-dimethyl-5α-androstan-17-one,
3β,16α,16β-trimethyl-5α-androstan-17-one,
3β-methyl-16α,16β-difluoro-5α-androstan-17-one,
16α-hydroxy-5-androsten-17-one,
16α-fluoro-5-androsten-17-one,
16α-fluoro-16β-methyl-5-androsten-17-one,

16α-methyl-5-androsten-17-one,

16β-methyl-5-androsten-17-one,

16α-hydroxy-5α-androstan-17-one,

16α-fluoro-5α-androstan-17-one,

3β-hydroxy-16α-fluoro-5α-androstane-17-one

16α-fluoro-16β-methyl-5α-androstan-17-one,

16α-methyl-5α-androstan-17-one,

16α-fluoro-7α-hydroxy-5-androsten-17-one,

16α-fluoro-7α-hydroxy-5α-androstan-17-one,

16α-fluoro-7β-hydroxy-5-androsten-17-one,

16α-fluoro-7β-hydroxy-5α-androstan-17-one,

16α-methoxy-5α-androstan-17-one,

3β-methyl-16α-fluoro-7-hydroxy-5-androsten-17-one, and

3β-methyl-16α-fluoro-7-hydroxy-5α-androstan-17-one.

The compounds of the present invention can be prepared by art recognized techniques from known compounds or readily preparable intermediates. Exemplary procedures are described in U.S. Patent Nos. 5,804,576, 5,744,462, 5,714,481, 5,700,793, 5,696,106, 5,656,621, 5,157,031 and 5,001,119, the contents of all of which are incorporated by reference. If substituents on the steroidal ring are themselves reactive under the reaction conditions, then these substituents can themselves be protected utilizing protecting groups according to chemical techniques known in the art. A variety of protecting groups known in the art may be employed. Examples of many of these possible groups can be found in "Protective Groups in Organic Synthesis," by J. W. Green, John Wiley and Sons, 1981.

If more than one substituent is to be added to the steroidal ring, the substituents can be added in any

order except that it is preferred that the halogens are added last.

Finally, it should be noted that the procedures described in the aforementioned patents are applicable to all of the steroids contemplated to be utilized in the present invention, regardless of whether a double bond is present at the 5,6 position of the steroidal ring. Moreover, the steroids of Formula II can be prepared from the corresponding steroids of Formula I by techniques known to one skilled in the art, e.g., by catalytic hydrogenation using, e.g., $H_2$/Pd, $H_2$/Pt or $H_2$/Ni.

The compounds utilized in the present method are used in therapeutically effective amounts.

The physician will determine the dosage of the present therapeutic agents which will be most suitable and it will vary with the form of administration and the particular compound chosen, and furthermore, it will vary depending upon various factors, including but not limited to the patient under treatment and the age of the patient, the severity of the condition being treated and the like. He will generally wish to initiate treatment with small dosages substantially less than the optimum dose of the compound and increase the dosage by small increments until the optimum effect under the circumstances is reached. It will generally be found that when the composition is administered orally, larger quantities of the active agent will be required to produce the same effect as a smaller quantity given parenterally. The compounds are useful in the same manner as comparable therapeutic agents and the dosage level is of the same order of magnitude as is generally employed with these other therapeutic agents. When given parenterally, the compounds are administered generally in dosages of, for example, about 0.1 to about 100 mg/kg/day, also depending upon the host and the severity of the condition being treated and the compound utilized.

In a preferred embodiment, the compounds

utilized are orally administered in amounts ranging from about 4 mg to about 35 mg per kilogram of body weight per day, depending upon the particular mammalian host and more preferably from about 6 to about 28 mg/kg body weight per day. This dosage regimen may be adjusted by the physician to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

The compounds of Formulae I or II may be administered in a convenient manner, such as by oral, intravenous, intramuscular or subcutaneous routes.

The compounds of Formula I or II may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsules, or it may be compressed into tablets, or it may be incorporated directly into the food of the diet. For oral therapeutic administration, the compounds of Formula I or II may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 1% of active compound of Formula I or II. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 5 to about 80% of the weight of the unit. The amount of the compound of Formula I or II used in such therapeutical compositions is such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention contain between about 200 mg and about 4000 mg of active compound of Formula I or II.

The tablets, troches, pills, capsules and the like may also contain the following: A binder such as gum tragacanth, acacia, corn starch or gelatin; excipients

such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin may be added or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier.

Various other materials may be present as coatings or otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and formulations. For example, sustained release dosage forms are contemplated wherein the active ingredient is bound to an ion exchange resin which, optionally, can be coated with a diffusion barrier coating to modify the release properties of the resin or wherein the active ingredient, i.e., a compound of Formula I or II, is associated with a sustained release polymer known in the art, such as hydroxypropylmethylcellulose and the like.

The active compound may also be administered parenterally or intraperitoneally. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, e.g., PEG 100, PEG 200, PEG 300, PEG 400, and the like, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a

preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form is usually sterile and must be fluid to the extent that syringability exists. It must be stable under the conditions of manufacture and storage and usually must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and one or more liquid polyethylene glycol, e.g. as disclosed herein and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredient into a sterile vehicle which contains the basic dispersion medium and the required other

ingredients from those enumerated above. In the case of sterile powders, the above solutions are vacuum dried or freeze-dried, as necessary.

The compounds of Formula I or Formula II can also be applied topically, as e.g., through a patch using techniques known to one of ordinary skill in the art.

The active ingredients, that is compounds of Formula I and/or II can be administered buccally by preparing a suitable formulation of the compounds of the present invention and utilizing procedures well known to those skilled in the art. These formulations are prepared with suitable non-toxic pharmaceutically acceptable ingredients. These ingredients are known to those skilled in the preparation of buccal dosage forms. Some of these ingredients can be found in Remington's Pharmaceutical Sciences, 17$^{th}$ edition, 1985, a standard reference in the field. The choice of suitable carriers is highly dependent upon the exact nature of the buccal dosage form desired, e.g., tablets, lozenges, gels, patches and the like. All of these buccal dosage forms are contemplated to be within the scope of the present invention and they are formulated in a conventional manner. Preferably, an effective amount of active ingredient in the buccal form ranges from about 0.15 mg/Kg to 1.5 mg/Kg.

As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents for pharmaceutical active substances well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, their use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for

the subjects to be treated; each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier.

The principal active ingredient is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier in dosage unit form as hereinbefore described. A unit dosage, for example, contains the principal active compound in amounts ranging from about 10 mg e.g. in humans, or as low as 1 mg (for small animals) to about 2000 mg. If placed in solution, the concentration of the compounds of Formula I or Formula II preferably ranges from about 10 mg/mL to about 250 mg/mL. In the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients. In the case of buccal administration, the compounds of Formula I or II are preferably in the buccal unit dosage form present in an amount ranging from about 10 to about 50 mg.

As used herein the term "patient" or "subject" refers to a warm blooded animal, and preferably mammals, such as, for example, cats, dogs, horses, cows, pigs, mice, rats and primates, including humans. The preferred patient is humans.

The compounds described hereinabove are useful in the treatment of patients having hypertriglyceridemia. It is most effective when the triglyceride concentration in the plasma is greater than about 200 mg/dl, as described hereinbelow.

The term "treat" when referring to patients having hypertriglyceridemia refers to reducing the plasma triglycerides of the patient in a detectable amount. Such reduction may be, e.g. a reduction of about 10%, 20%, 30% or 40% in a patient's plasma triglyceride level When referring to other diseases, it refers to the

management and care of a mammalian subject, preferably human, for the purpose of combating the disease, condition or disorder, and includes the administration of a compound of the present invention to prevent or delay the onset of the symptoms or complications, alleviating the symptoms or complications or eliminating the disease, condition or disorder.

The preferred patient population to be treated by the method of the present invention includes diabetic patients having type II diabetes mellitus and hyperlipidemia and/or hyperlipidemics who are non-diabetic but have insulin-resistance.

The compounds utilized herein lower the triglyceride concentration in the patient, suffering from hypertriglyceridemia. The compounds described herein are effective in treating patients having a concentration of free plasma triglycerides of greater than about 200 mg/dl and preferably greater than or equal to about 300 mg/dl and especially greater than or equal to about 500 mg/dl.

They are especially effective in treating patients having hypertriglyceridemia, which also have a low HDL level in the plasma. As used herein, low "HDL levels" refer to the concentration of HDL cholesterol in the plasma of less than about 40 mg/dl for men and less than about 45 mg/dl for women. It is even more effective in treating men having an HDL level less than 35 mg/dl and women having HDL levels less than about 40 mg/dl.

The compounds of Formula I and II herein are especially effective in reducing the triglyceride concentration in patients having hypertriglyceridemia who are also obese patients. The term "obese" and "obesity" refers to a patient, e.g., humans, having a body mass index (BMI) greater than 30 $kg/m^2$ BMI, by definition, equals weight (kg)/height$^2$ ($m^2$). Often times, an obese patient also has low levels of HDL, as defined herein and/or is insulin resistant.

In addition, the compounds of Formula I and II herein are also effective in reducing the triglyceride concentration in patients who are and insulin resistant.

The term "insulin resistance" can be defined generally as a disorder generally a disorder of glucose metabolism. More specifically, insulin resistance can be defined as the diminished ability of insulin to exert its biological action across a broad range of concentrations producing less than expected biologic effect. (see, e.g., Reaven, G.M., J. Basic & Clin. Phys. & Pharm. (1998) 9: 387-406 and Flier, J. Ann Rev. Med. (1983) 34:145-60). Insulin resistant persons have a diminished ability to properly metabolize glucose and respond poorly, if at all, to insulin therapy. Manifestations of insulin resistance include insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in liner. Insulin resistance can cause or contribute to polycystic ovarian syndrome, Impaired Glucose Tolerance (IGT), gestational diabetes, hypertension, obesity, atherosclerosis and a variety of other disorders. Eventually, the insulin resistant individuals can progress to a point where a diabetic state is reached. The association of insulin resistance with glucose intolerance, an increase in plasma triglyceride and a decrease in high-density lipoprotein cholesterol concentrations, high blood pressure, hyperuricemia, smaller denser low-density lipoprotein particles, and higher circulating levels of plaminogen activator inhibitor-1), has been referred to as "Syndrome X" (see, e.g., Reaven, G.M., Physiol. Rev. (1995) 75: 473-486).

The compounds of Formula I and II are useful in modulating insulin resistance in a patient, e.g., mammal, the method comprising administering to the patient a therapeutically effective amount of the compound of Formula I or Formula II. Insulin resistance, may be a

marker for generalized lipodystrophies. Thus, the compounds of the present invention are useful in treating lipodystrophies. Lypodystrophies have been known for over a century and are characterized by selective loss of body fat that can vary from small indentation or depressed areas in patients with localized lipodystrophies to near complete absence of adipose tissue in generalized lipodystrophies. More particularly, the compounds of Formula I and II are useful in treating generalized lipodystrophies.

The amounts of compounds of Formula I and II used in the treatment are therapeutically effective amounts, as described hereinabove. In treating this malady, the compounds of Formula I and II can be administered to the patient using any of the modes of administration described herein.

Thus, the steroids of the Formula I and II are useful for treating and lowering the triglyceride levels in patients having hypertriglyceridemia and more preferably having, in addition at least one of the following characteristics:

(a) obese, especially those having a BMI >30;

(b) low HDL; and

(c) insulin-resistant.

By administering a therapeutically effective amount of the compounds described hereinabove to such patients, the compounds of the present invention reduces the plasma triglycerides, as shown hereinbelow.

The compounds of Formula I and II described herein are each effective in treating hypertriglyceridemic patients.

In addition the compounds of Formula I and II are each effective in treating hypertriglyceridemic patients having at least one of the following traits: low HDL, or insulin resistance or patients which are obese, those having a BMI greater than 30. The compounds used in the present invention are useful for treating

hypertriglyceridemics which exhibit none or one, two or three of these traits.

Moreover, the compounds of Formula I and II are each useful for the treatment of Syndrome-X, also known as the insulin resistance syndrome. It includes hyperlipidemia, hyperinsulinemia, obesity, insulin resistance, insulin resistance leading to type-2 diabetes and diabetic complications thereof, i.e., diseases in which insulin resistance is the pathophysiological mechanism.

Moreover, the compounds of Formula I and II are useful for treating hypertriglyceridemia, hypertension and coronary artery disease.

The compounds of Formula I and II are also useful in treating familial combined hyperlipidemia. Familial combined hyperlipidemia is a common disorder in which affected individuals have either hypercholesterolemia, hypercholesterolemia with hypertriglyceridemia or hypertriglyceridemia. These individuals are prone to premature atherosclerosis and coronary heart disease.

Patients with hypertriglyceridemia insulin resistance low HDL and/or obesity having BMI's greater than 30 are prone to suffering from atherosclerosis and coronary heart disease and/or stroke. Thus, the present invention is directed to a method of treating or preventing atherosclerosis or stroke resulting from hypertriglyceridemia by administering to said mammalian species in need of treatment a therapeutically effective amount of compound I or II.

The compounds of the present invention have beneficial effects on the risk factors for the development of cardiovascular disease, type-2-diabetes, vascular disease and stroke. It is believed, without wishing to be bound, that elevated levels in the plasma of acute phase proteins and inflammatory cytokines, such

as C-reactive proteins, interleukin-6, Pa AI-1, or TNFα and the like are sensitive markers for systemic inflammation and for the development of cardiovascular disease, type-2-diabetes, vascular disease and stroke. Without wishing to be bound, it is believed that elevated amounts (relative to normal) are markers and/or present during the development of these diseases. By elevated amounts, it is meant that their concentrations in the plasma are greater than normal levels. For example, elevated levels of C-reactive proteins are present in the plasma in concentrations greater than 1.15 mg/l for both men and women. These amounts can be measured and determined using standard techniques known to one skilled in the art. Without wishing to be bound, it is believed that compounds of Formula I and II depress plasma levels of these, one or more of cytokines and acute phase proteins, such as C-reactive proteins, and the like, especially if given in effective doses, as defined herein. Thus, the treatment utilizing compounds of Formula I and II reduce the development or severity of cardiovascular disease and stroke.

Another preferred embodiment of the present invention is to use the compounds of Formula I or II to lower the abnormal levels of C-reactive protein IL-6, Pa AI-1, or TNFα in patients having high levels of C-reactive proteins.

Without wishing to be bound, it is believed that the compounds of Formula I and II of the present invention behave by two possible mechanisms.

It has been found that hypercortisolism, an exceedingly high concentration of hydrocortisone, a glucocorticoid found in humans, directly contributes to the phenotype and metabolic abnormalities of the metabolic syndrome (Syndrome X), including obesity, insulin resistance, and hypertriglyceridemia. (See, Peeke, et al., Annals. NY Acad. Sci., 771, 665-676

(1995). The steroids of Formula I and II have an antiglucortoicd effect. Thus, it is believed, without wishing to be bound, that the compounds of the present invention reduce the hypercortisolism.

Without wishing to be bound, it is also believed that a state of chronic subclinical inflammation also directly contributes to the phenotypic and metabolic abnormalities of Syndrome X. In addition, it is believed that proinflammatory cytokines may act directly to induce insulin resistance and hypertriglyceridemia or act indirectly through the stimulation of cortisol production. The steroids of Formula I and II are anti-inflammatory agents, and this contributes to the selective triglyceride lowering effect in obese patients.

The compounds of Formula I and II are also used to reduce the enhance glucocorticoid activity or actions in an animal, e.g. mammal.

Enhanced glucocorticoid action has been implicated as a cause for or as being associated with a number of ailments affecting animals, including mammals, especially man. For example, individuals may be immunosuppressed as a consequence of endogenous elevations in adrenal glucocorticoid (GCS) levels. These elevated levels can result from a variety of causes, including, but not limited to, stress and trauma (including, for example, post surgical trauma, and burn trauma), as a secondary consequence to any clinical condition which causes an elevated production of interleukin-1 (IL-1) or therapeutic treatment for a variety of clinical conditions. These elevated GCS levels can result in an imbalance in the production of essential interleukins. As a consequence thereof, the animals exhibit a depressed capacity to produce species of lymphokines which are essential to the development of protective forms of immunity. Plasma glucocorticoid steroid levels can also be elevated exogenously as a

consequence of therapeutic treatment for a variety of clinical conditions. In addition to the above, it is well known that certain essential functions to the immune system decline with age, a situation which correlates with elevations in adrenal output of glucocorticoid steroid and abatement in production of other types of adrenal steroid hormones.

Excess glucocorticoid actions is widely believed to be associated with mood changes, depression, vertigo, memory loss or impairment, disorientation, and the like.

Elevated glucocorticoid action are also linked with hippocampal pathology in aging rodents. Basal plasma corticosterone levels in aged rats have been found to correlate with hippocampal atrophy and spatial learning deficits. It has also been found that cumulative exposure to constant high levels of glucocorticoids disrupts electrophysiological function, leading to atrophy and ultimately the death of hippocampal neurons. It is widely believed that elevated glucocorticoid levels directly contribute to the development of cognitive impairments. Hippocampulatrophy has been reported in patients with Cushing's syndrome as a result of the hypersecretion of glucocorticoids.

Thus, the compounds of Formula I and Formula II have an anti-glucocorticoid effect. They are useful in treating, ameliorating, preventing or retarding the progression of the unwanted condition or symptom or malady in a patient relating to an enhanced glucocorticoid effect, said method comprising administering to said patient an anti-glucocrtiocoid effected amount of a compound Formula I or II.

An enhanced glucocorticoid activity, as defined herein, refers to an enhanced glucocorticoid effect relative to normal which is attributable or results from various factors, such as hypersecretion of the glucocorticoid, enhanced activity of 11-beta-

hydroxysteriod dehydrogenase, which is an enzyme which converts cortisone to cortisol the administration a glucocorticoid to patient, an enhanced concentration of glucocorticoid in the plasma relative to normal and the like. For example, the normal concentration of cortisol in the plasma in humans is about 7-20 ug/dL in the morning and about 3-13 ug/dL in the afternoon.

The compounds of the present invention are also useful in retarding immunosescence. Glucocorticoids, e.g., cortisol, are known to suppress the immune system and destroy lymphocytes in animals. As shown herein, the size of the thymus and the spleen are reduced in the presence of glucocorticoids, such as dexamethasone. The thymus and to some extent the spleen have a role in establishing the immunological capacity of the body. The thymus secretes hormones which are responsible for the production of cells with the capability of making antibodies and rejecting foreign bodies from the body. Moreover, both organs can produce lymphocytes and produce antibodies, which protect the body against invading microbes or foreign tissue. When the size of the thymus and spleen are reduced, their capacity to produce lymphocytes is also reduced, and the immune system is suppressed. Thus, as shown hereinabove, the compounds of the present protect against the atrophy of the spleen and thymus.

As one ages, the size of the spleen and the thymus also decreases. Further, as one ages, the cortisol levels also increase. Since glucocorticoids reduce the size of these two organs as one ages, the administration of compounds of Formula I and II retards the reduction of the size of these organs. Thus, the administration of the compounds of Formula I and II in antiglucocorticoid effective amounts retards the suppression of the immune system through the aging process.

It is also known that cortisol and other glucocorticoids damage and/or cause the atrophy of the hypothalmus, and more specifically causes hippocampalatrophy. (See, Lupien, et al., Nature Neuroscience, 1998, Vol. 1, 69-73). It is believed that mental disorders and spatial performance are associated with hippocampal function. Sustained glucocorticoid exposure damages the hippocampus in humans. Elevated glucocorticoid levels have been linked to the damage of the hippocampus and the impairment of learning and memory. As indicated hereinabove, as one ages, the amount of cortisol in the body increases. This memory loss as one ages is believed to be attributable to the increase in the cortisol concentration in the body. Thus, the administration of compounds I and II in antiglucocorticoid effective amounts retards the loss of memory.

The compounds utilized in the present method are used in therapeutically effective amounts, i.e., in antiglucocorticoid effective amounts. These amounts are sufficient to detectably treat, ameliorate, prevent or detectably retard the progression of an unwanted condition or symptom associated with an excess concentration of glucocorticoids.

The compounds of Formula I and II in therapeutically effective amounts are useful to inhibit unwanted biological or cellular responses to glucocorticoid steroids, e.g., (1) glucocorticoid-induced immune suppression, (2) glucocorticoid-induced bone loss, or (3) modulation of glucocorticoid-induced gene transcription or expression, e.g., increased or decreased expression. The present invention includes administration of a therapeutically effective amount of the compound of Formula I or II to a subject having or being susceptible to developing a glucocorticoid-associated symptom or condition, wherein the condition or symptom is prevented, detectably ameliorated or its onset

of progression is detectably delayed or slowed. Thus, the compounds of Formula I and II can be used to prevent or ameliorate, e.g., immune suppression, decreased immune cell proliferation or adverse neurological effects (e.g., mood changes, depression, memory loss or impairment, disorientation, headache, vertigo and the like) of glucocorticoid steroids.

An excess or unwanted level of glucocorticoid steroids ("GCS") in a subject such as a mammal or a human can arise from natural causes, such as infections, cancer or injury, or such levels can arise from the use of GCS to treat various disease conditions or symptoms. Other causes of increased values of cortisol include: adrenal hyperplasia, adrenal adenoma, adrenal carcinoma, pituitary tumor, ectopic ACTH syndrome, pregnancy, prior exercise, prior tobacco smoking, emotional or physical stress, exogenous estrogens, chronic renal failure, hyperthyroidism, exogenous cortisone or hydrocortisone and the like.

The GCS that are associated with such conditions or symptoms can be natural or synthetic. GCS levels that are associated with or that cause an unwanted condition or symptom can arise from a natural disease or from the administration of a natural or synthetic glucocorticoid steroid to a subject such as a mammal, e.g., human.

Thus, compounds of Formula I and II can be used diseases that are associated therewith for example. Moreovere, corticosteroids are used to treat the following disorders: Achilles tendon disorders, Addison's disease, ankylosing spondylitis, asthma, athletic injury, atopic dermatitis, bacterial meningitis, carcinoid tumor, chickenpox, chronic lymphocytic leukemia, congenital adrenal hyperplasia, COPD, Crohn's disease, croup, cystic fibrosis, discoid lupus erythematosus, focal segmental glomerulosclerosis, gout, hay fever, Henoch-Schonlein

purpura, hypercalcemia, idiopathic hypereosinophilic syndrome, idiopathic thrombocytopenic purpura, infectious mononucleosis lichen planus, minimal change disease, multiple myeloma, multiple schlerosis, neutropenia, nummular dermatitis, pemphigus, polyarteritis nodosa, polymyositis, psoriasis, rapidly progressive glomerulonephritis, recurrent aphthous stomatitis, respiratory failure, rheumatoid arthritis, sarcoidosis, spinal cord injury, systemic lupus erythematosus, tendenitis, toxic epodermal necrolysis, transplantation, tuberculosis, typhoid fever, ulcerative colitis and furthermore, Cortisol is used to treat the following disorders: Addison's disease, Cushing's disease, ectopic ACTH syndrome, hyponatremia, liver disease, pediatric cardiopulmonary resuscitation. The compounds of Formula I or II thus can limit the unwanted side effects of GCS, without eliminating all of their beneficial, e.g., anti-inflammatory, effects. Thus, in some embodiments, a therapeutic treatment using a compound of Formula I and II is coadministered with one or more GCS. The GCS are used in a number of clinical situations, e.g., in chemotherapy, to decrease the intensity or frequency of flares or episodes of inflammation or autoimmune reactions in conditions such as rheumatoid arthritis, osteoarthritis, ulcerative colitis, bronchial asthma, psoriasis or systemic lupus erythematosus. Other side effects include but are not limited to, asceptic necrosis host defense alterations opportunistic infections and the like.

The compounds of Formula I and II reduce the side effects associated with the glucocorticois treatment of these indications such as endocrine disorders, including adrenal cortical insufficiency, congenital adrenal hyperplasia, nonsuppurative thyroiditis, hypercalcemia associated with cancer, rheumatic disorders, including

psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, bursitis, acute nonspecific tenosynovitis, acute gouty arthritis, post-traumatic opsteoarthritis, synovitis of osteoarthritis, epicondylitis, collagen diseases, including systemic lupus erythematosus, acute rheyumatic carditis, dermatologic diseases, including pemphigus, bullous dermatitis herpetiformis, severe erythema multiforme, exfoliative dermatitis, mycoses fungoides, severe psoriasis, severe seborrheic dermatitis, allergic states, including allergic rhinitis, bronchial asthma, contact dermatitis, atopic dermatitis, serum sickness, drug hypersensitivity reactions, ophthalmic diseases, including allergic conjunctivitis, keratitis, allergic corneal marginal ulcers, herpes zoster ophthalmicus, iritis and iridocyclitis, chorioretinitis, anterior segment inflammation, diffuse posterior uveitis and chorioditis, optic neuritis, sympathetic ophthalmia, respiratory diseases, including symptomatic sarcoidosis, Loeffler's syndrome, Berylliosis, pulmonary tuberculosis, aspiration pneumonitis, hematologic disorders, including idopathic and secondary thrombocytopenic purpura , acquired hemolytic anemia, erythroblastopenia, congenital hypoplastic anemia, neoplastic diseases, inlcuding leukemias and lymphomas, edematous states, gastrointestinal diseases, including ulcerative colitis, regional enteritis, cerebral edema, including brain tumor, craniotomy, head injury, aging, and the like.

Adverse reactions that would be ameliorated by compounds of Formula I or II either through direct action or through allowing a lower dose of glucocorticoid to be used, for example: include but are not limited to fluid and electrolyte disturbances, including sodium retention, fliuid retention, congestive heart failure, potassium

loss, hypokalemic alkalosis, hypertension, muskuloskeletal, inlcuding muscle weakness, steroid myopathy, loss of muscle mass, osteoporaosis, vertebral compression fractures, asceptic necrosis, pthologic fracture of long bones, tendon rupture, gastrointestinal, including peptic ulcer, perforation of small and/or large bowel, pancreatitis, abdominal distention, ulcerative esophagitis,dermatologic, including impaired wound healing, thin fragile skin, petechiae & ecchymoses, erythema, increased sweating, suppressed reactions to skin tests, allergic dermatitis, urticaria, angioneurotic edema,neurologic, including convulsions, intracranial pressure, vertigo, headache, psychic disturbances, endocrine, including menstrual irregularities, cushingoid state, suppression of growth n chilkdren, adrenocortical and or pituitary unresponsivenesss, decreased carbohydrate tolerance, manifestations of latent diabetes mellitus, increased requirements for insulin or oral hypoglycemic agents in diabetics, hirsutism, ophthalmic, including posterior subcapsular cataracts, increased intraocular pressure, glaucoma, exophthalmus, metabolic, including negative nitrogen balance, cadiovascular, including myocardial rupture, other, including hypersensitivity, thromboembolism, weight gain, increased appetite, nausea, malaise, hiccups, nightmares, hallucinations, immune deficiencies, and the like.

The compounds of Formula I and II are useful to counteract the adverse effects or toxicities of glucocorticoids without negating all of the desired therapeutic capacity of the glucocorticoids. This allows the continued use, or a modified dosage of the glucocorticoid, e.g., an increased dosage, without an intensification of the side effects or toxicities or a decreased glucocorticoid dosage. The side-effects or toxicities that can be treated, prevented, ameliorated or

reduced include one or more of the following: bone loss, reduced bone growth, enhanced bone resorption, osteoporosis, immunosuppression, increased susceptibility to infection, mood or personality changes, depression, headache, vertigo, high blood pressure or hypertension, muscle weakness, fatigue, nausea, malaise, peptic ulcers, pancreatitis, thin or fragile skin, growth suppression in children or preadult subjects, thromboembolism, cataracts, and edema.

The following non-limiting examples further illustrate the present invention.

**EXAMPLE 1**

Twelve patients were treated with 16α-fluoro-5-androstene-17-one.

Since excessive alcohol consumption or increased caloric intake elevates serum triglycerides, for one week, prior to the start of the study, the subjects were not allowed to ingest excessive amounts of coffee, tea or alcohol or to follow a diet which deviated notably from the normal diet. The amounts did not exceed 0.5 L of beer or 0.25L of wine per day or drinking up to 4 cups of xanthine containing beverages per day was allowed. Smoking and intake of xanthine-containing beverages or food (coffee, tea, cola, chocolate) and alcohol within 24 hours, before and during the stay in the clinical research facilities were not allowed.

The human patients received 1600 mg of 16α-fluoro-5-androstene-17-one daily. Controls were set up so that they received 1600 mg of placebo. The triglyceride concentration in the plasma were measured pretreatment and at the end of the study.

There was a significant triglyceride-lowering effect caused by the drug in the 14-day, multiple dose, study.

In 12 patients (excluding 2 placebos) receiving 1600 mg of 16α-fluoro-5-androsten-17-one daily, 4 patients, 3 males and one female, had pretreatment triglyceride levels>200 mg/dL. In this group of 4 patients there was a highly significant reduction in triglyceride values, whereas there was no apparent effect in the 8 patients with non-elevated triglycerides. The decline in one female patient was additionally quite striking. The data in the one female, 3 males, and the combined data are shown below.

**Elevated Triglyceride Group**

| | |
|---|---|
| **Female (1)** | **Conc. (mg/dL)** |
| Pretreatment | 540 ± 42 (n=2) |
| Treatment | 118 ± 19 (n=3) |
| | p ~ 0.001 |
| **Male (3)** | 333 ± 75 (n=6) |
| Pretreatment | 168 ± 61 (n=8) |
| Treatment | p ~ 0.001 |
| **Female and Male (4)** | 385 ± 116 (n=8) |
| Pretreatment | 154 ± 57 (n=11) |
| Treatment | p ~ 0.0001 |

**Normal Triglyceride Group**

| | |
|---|---|
| Pretreatment | 106 ± 34 (n=16) |
| Treatment | 128 ± 77 (n=23) |

In addition, the fasting plasma glucose (FPG) levels were also measured in the patients before and after treatment. The results are as follows. In the study, 3 of the 4 patients with elevated triglycerides had pre-treatment FPG levels> 6.1 mM. The American Diabetes Association (ADA) has recently classified individuals with FPG of 6.1 - 6.9 mM as having impaired fasting glucose (IFG). Such individuals have 40% probability of developing ADA criteria for diabetes within 5 years.

**FPG LEVELS OF INDIVIDUALS WITH IFG**

| Pretreatment | Treatment |
|---|---|

| | |
|---|---|
| 6.28 ± 0.33 (6) | 5.63 ± 0.45 (8) (p < 0.02) |

There was a significant lowering of FPG levels during treatment using 16α-fluoro-5-androsten-17-one. These data suggest that at least part of the triglyceride-lowering effect of the compounds described herein is attributable to improvement in insulin sensitivity.

**EXAMPLE 2**

Five hypertriglyceridemic patients had high baseline HDL levels (>50 mg/dL, 64.2 ± 8.5, n=10, mean ± S.D.) and four hypertriglyceridemic patients had low HDL levels 40.4 ± 4.1, n=8). They were treated as before, as described in Example 1, except they received 1200 mg of 16α-fluoro-5-androsten-17-one daily. Controls were set up so that they received 1200 mg of placebo. The triglyceride concentration in the plasma were measured pretreatment and at the end of the study. The results are as follows.

In those patients with high HDL levels, the triglycerides fell from 330 ± 163 (n=10) to 214 ± 56.1 (n=5). However, in 4 patients with low HDL levels (40.0 ± 4.1), treatment with 1200 mg of 16α-fluoro-5-androsten-17-one daily for 3 to 12 weeks lowered triglyceride levels from 245 ± 55.1 (n=8) to 139 ± 10.6 (n=4), p<0.01. Thus, these experiments show that this compound is effective in lowering plasma triglycerides in patients with high triglycerides and low HDL.

It is to be noted that the lipid profile of high triglyceride (>200 mg/dL) and low HDL (<40 mg/dL if male and <45 mg/dL if female) is associated with a high cardiovascular disease mortality. This was demonstrated in a study in the Lipid Research Clinic Study on 1405 middle aged women. See Bass, et al. Arch. Int. Med., 153:2209, 1993. In the Copenhagen Male Study in 2910

middle-aged men, individuals in the highest third of triglyceride level (avg:248 mg/dL) and lowest third of HDL (avg:39 mg/dL) experienced an increased incidence of ischemic heart disease that was at least as great as individuals with isolated high LDL (highest one-fifth of LDL level) (See, Teppesen, et al., Atherioscler. Throm. Vasc. Biol., 17:1114 (1997). The high-to-low HDL lipid profile is the characteristic of dyslipidemia associated with insulin resistance.

**EXAMPLE 3**

The following example, tested the effects of buccal administration of 16α-fluoro-5-andorsten-17-one (hereinafter "drug").

Eight week old male BKS.Cg-m$^{+}$/$_{+}$ Lepr$^{db}$ mice were obtained from Jackson Laboratories. The mice were initially housed five per cage on Alphacel bedding with ad libitum access to Purina 5015 chow and acidified water. The mice wee housed in the Central Animal Facility (6$^{th}$ Floor, Pharmacy building) with twelve hours of alternating light and darkness.

Five days later, the chow was removed from the mice at approximately 3:30p.m. This was done so that a fasting plasma glucose level could be obtained on the next day. The next day, a pretreatment plasma glucose determination was made. The mice were lightly anesthetized with Isoflurane and were bled form the orbital sinus (~400μL of blood was taken). The blood was obtained between 10:00 a.m. and noon. Blood was kept on ice until analysis. After the blood for the glucose measurement was taken out, the remaining blood was centrifuged at 3000 xg for 15 minutes. The plasma was removed and frozen for use in determining plasma triglyceride levels.

**A. Fasting Plasma Glucose ands Triglyceride Determination:**

Plasma glucose levels were assayed by a Sigma kit 510. Briefly, 0.2mL of blood was added to 1.8mL of distilled water. The contents of the test tube were mixed and 1.0 mL of 0.3N barium hydroxide solution was added and the tube contents were mixed by swirling. One mL of 5% zinc sulfate solution was added to the test tube and mixed by shaking. The test tubes were centrifuged at 3000xg for 20 minutes. One-half mL of the clear supernatant was transferred to a clean test tube and 5 mL of Combined Enzyme-Color Reagent solution was added and mixed well. Blanks were made using 0.2 mL of distilled water instead of blood and standards containing 100, 200, and 300 mg/dL of glucose were also simultaneously assayed. The tubes were incubated at room temperature for 45 minutes and were read at 450 nm in a Beckman DU 640 spectrophotometer. All readings were completed within a 30 minute period after the end of the incubation period.

Plasma triglyceride levels were determined with a Sigma kit (334-UV). The determination is based on the enzymatic hydrolysis of triglycerides to glycerol and free fatty acids by lipase. Glycerol is subsequently phosphorylated by ATP to produce glycerol-1-phosphate and ADP. ATP is regenerated by a pyruvate kinase-catalyzed reaction between ADP lactate with simultaneous oxidation of equimolar amounts of NADH in the presence of lactate dehydrogenase. NADH absorbs at 340 nm, thus the decrease in absorbance, measured at this wavelength, is directly proportional to the triglyceride concentration in this sample.

Triglyceride Reagent A (containing ATP, lactate dehydrogenase, lipase, NADH, phosphoenol pyruvate, pyruvate kinase) and Triglyceride Reagent B were reconstituted with 10 mL and 2 mL of distilled water

respectively. The Sample Reagent was prepared by adding 0.25 mL of Triglyceride Reagent B to 10 mL to Triglyceride Reagent A. Blank, standard (50, 100 and 200 mg/dL) and sample tubes were prepared. One mL of Sample Reagent was added to all tubes. To the Blank tube, 20 µL of distilled water was added. For each Sample tube, 20 µL of plasma was added to the tube. All tubes were incubated at room temperature for 10 minutes. The tubes were read against a Reference containing distilled water. Triglyceride concentration in the samples were calculated by subtracting the absorbance of the Sample form the absorbance of the Blank and using the following formula:

Serum triglyceride concentration = $\Delta A$

**B. Treatment of mice:**

One week after obtaining the mice, the mice were distributed into either groups of 6 mice (Control, buccal and 5 mg/kg drug buccal), or 7 mice (10 mg/kg drug buccal). The mice were weighed.

The buccally administered groups were treated with a suspension of drug 16α-5-androsten-17-one obtained form Eminent Services Corp. The mice were lightly anesthetized with isoflurane and then injected i.m. with 0.05 mL of a solution of ketamine (50 mg/kg), xylazine (10mg.kg) and atropine (0.1 mg/kg) injected near tail). Approximately 10 minutes post injection, while the animals were anesthetized, the mice were placed on their backs and were treated with one-half of the dose of drug necessary in each buccal area. The mice remained anesthetized and on their backs for approximately 30 minutes post-treatment. The 5 mg/kg drug group was treated with 2.04 µL of suspension (1.02 µL per buccal area) and the 10mg/kg drug group was treated with 4.2 µL(2.1 µL per buccal area) while the Control Buccal group received 4.2 µL (2.1 µL per buccal area) for the duration

of the experiment. The cages of the mice were placed on heating pads on a low temperature to prevent loss of animals due to hypothermia during anesthesia. The cages were kept on the heating pads for 30 minutes after all the mice in the cage were awake.

During the second week of the experiment, the mice in the tem mg/kg buccal group were coming out of the anesthesia quicker than the 5mg/kg group and Control groups (20 minutes versus 30 minutes).

The results are tabulated hereinbelow.

**Pre-treatment)**

| | **Control, buccal** | **5 mg/kg buccal drug** | **10 mg/kg buccal drug** |
|---|---|---|---|
| | **Plasma triglycerides mg/dl** | **Plasma triglycerides mg/dl** | **Plasma triglycerides mg/dl** |
| Mice 1 | 123.8 | 110.7 | 93.7 |
| Mice 2 | 161.1 | 153.8 | 102.1 |
| Mice 3 | 126.1 | 105.9 | 162.1 |
| Mice 4 | 115.6 | 116.8 | 97.1 |
| Mice 5 | 159.4 | 222.8 | 102.1 |
| Mice 6 | 117.8 | 120.6 | 89.4 |
| Mice 7 | | | 184.4 |
| | 134.0 ± 20.7 | 138.4 ± 44.6 | 118.7 ± 38.1 |

**(AFTER 6 DAYS OF TREATMENT)**

| | **Control, buccal** | **5 mg/kg buccal** | **10 mg/kg buccal** |
|---|---|---|---|
| | **Plasma triglycerides mg/dl** | **Plasma triglycerides mg/dl** | **Plasma triglycerides mg/dl** |
| Mice 1 | 126.4 | 77.2 | 108.7 |
| Mice 2 | 156.8 | 106.0 | 83.5 |
| Mice 3 | 165.0 | 87.3 | 96.8 |
| Mice 4 | 156.2 | 414.0 | 61.2 |
| Mice 5 | 179.8 | 146.6 | 104.6 |
| Mice 6 | 157.8 | 105.4 | 64.3 |
| Mice 7 | | | 156.7 |

| | | | |
|---|---|---|---|
| | 157.0 ± 17.4 | 110.6 ± 28.0 p<0.01 vs. control buccal | 96.5 ± 32.4 p<0.01 vs. Control buccal |

**(AFTER 13 DAYS OF TREATMENT)**

| | Control, buccal | 5 mg/kg buccal | 10 mg/kg buccal |
|---|---|---|---|
| | **Plasma triglycerides mg/dl** | **Plasma triglycerides mg/dl** | **Plasma triglycerides mg/dl** |
| Mice 1 | 132.3 | 97.8 | 102.0 |
| Mice 2 | 172.0 | 89.3 | 83.5 |
| Mice 3 | 154.6 | 65.3 | 93.6 |
| Mice 4 | 199.9 | 79.1 | 133.5 |
| Mice 5 | 193.0 | 78.3 | 118.1 |
| Mice 6 | 151.7 | | 97.8 |
| Mice 7 | | | 99.2 |
| | 167.3 ± 26.0 | 82.0 ± 12.3 p<0.0005 vs. Control buccal | 104.0 ± 16.6 P<0.001 vs. Control buccal |

The data herein clearly show that buccally administered 16α-fluoro-5-andrsten-17-one, even at concentrations as low as 5 mg/kg and 10 mg/kg significantly lower the triglyceride levels in mice.

**EXAMPLE 4**

Patients used in the following study had an average baseline triglyceride level >200 mg/dl in a two week screening test. However, there was one patient included in the study which had a BMI of 42.9 and a borderline high triglyceride level (176 ± 21.2). Before the test was commenced, the triglyceride levels of each of the patients were measured. The patents were then

treated for 3 to 12 weeks with a daily dose of 1200 mg 16α-fluoro-5-androstene-17-one of in capsule form (2 x 200 mg drug/capsule at each meal). At the end of the study, the triglyceride levels in the plasma for each patient was measured. The results were divided into two groups, patients with BMI >30 (obese patients) and patients with BMI <30 (non-obese patients). The BMI of the obese patients were (mean ± S.D) 36.6 ± 4.0, while the BMI for the non-obese patients was 27.1 ± 1.5.

Using the pretreatment values as the triglyceride value prior to the test, and the last triglyceride measurement as the treatment value, the data are as follows:

| | | Triglyceride Concentration (mg/Kg) |
|---|---|---|
| Obese | 5 patients | 231 ± 57.1(10) to 135 ± 12(5) p< 0.005 |
| Non-obese | 5 patients | 330 ± 163(10) to 248 ± 90(5) n.s. |

As shown by the data, treatment with 16α-fluoro-5-androsten-17-one significantly reduced plasma triglyceride levels in obese patients. The average triglyceride concentration in the obese patients before the test began was 231 mg/kg ± 57.1 and at the end of the test, the average dropped to 135 mg/kg ± 12. This effect is more pronounced in the obese group then in the non-obese group. This is particularly interesting since it is well established that obesity is a major risk factor for coronary heart disease in men and women. (See, Curb, J.D., Marcus, Am. J. Clin. Nutr., 53:1612S 1991; Rexrode, K.M., et al. JAMA 280:1843 (1948).

**EXAMPLE 5**

Female CD-1 mice were obtained from Charles River Laboratories, Kingston, NY at 43-45 days of age. The mice were housed five per cage in plastic shoebox cages on corn cob bedding in the Fels Animal Facility at 72° ± 2°F with 50% ± 5% humidity and twelve hours of alternate light and darkness. The mice had ad libitum access to Purina chain 5015 and acidified water for pretreatment.

Six days later, the mice were weighed, earmarked and redistributed into six groups for treatment: 1) a control group, 2) a group treated with dexamethasone ("DEX"), a glucocorticoid which induces thymic and splenic atrophy, 3) a group treated with 200 mg/kg 16α-fluoro-5-androsten-17-one (hereinafter "drug"), 4) a group treated with 400 mg/kg of, 5) a group treated with dexamethasone and 200 mg/kg drug and 6) a group treated with dexamethasone and 400 mg/kg drug. The treatment in the groups were as follows and were conducted simultaneously.

The control group was intubated with 0.2 mL of sesame oil for three days. On the third day after commencement of the intubation, the mice were injected subcutaneously with 0.05 mL of absolute ethanol one hour after the last treatment with sesame oil.

The second group was intubated with 0.2 mL of sesame oil for three days. On the third day after the commencement of the intubation, the mice were injected subcutaneously with 1.6 mg of dexamethasone dissolved in 0.05 mL of absolute ethanol approximately one hour after the last treatment with sesame oil.

The third and fourth groups were intubated with 200 mg/Kg and 400 mg/Kg drug, respectively, suspended in 0.2 mL of sesame oil for three days. After commencement of the intubation, the mice were injected subcutaneously with 0.05 mL of absolute ethanol approximately one hour after the last treatment with sesame oil.

The fifth and sixth groups were intubated with 200 mg/kg and 400 mg/kg, respectively, of drug, suspended in 0.2 mL of sesame oil for three days. On the third day after commencement of the intubation, the mice were injected subcutaneously with 1.6 mg of dexamethasome dissolved in 0.05 mL of absolute ethanol approximately one hour after the last treatment with sesame oil.

All of the mice were sacrificed by an overdose of $CO_2$ approximately 24 hours after the injection of ethanol (first, third and fourth groups) or approximately 24 hours after injection with dexamethasone (second, fifth and sixth groups). The mice were weighed and the thymus was excised, cleaned of adventia, rinsed in phosphate-buffered saline (P.B.S.), blotted and weighed. The spleen was also excised, cleaned, rinsed, blotted and weighed.

The results are tabulated hereinbelow:

**Table 1**

| **Treatment** | **Body Weight (gm)** | **Thymus Wt. (mg)** | **Spleen Wt. (mg)** | **No.** |
|---|---|---|---|---|
| Control | 24.0 ± 1.0 | 67.6 ± 8.1 | 100.6 ± 13.8 | 10 |
| DEX | 23.4 ± 1.1 | 36.8 ± 7.1 | 45.2 ± 7.5 | 10 |
| 200 mg/kg drug | 23.7 ± 0.9 | 65.0 ± 5.8 | 103.5 ± 9.2 | 10 |
| 400 mg/kg drug | 24.7 ± 1.9 | 74.3 ± 7.1 | 129.4 ± 17.9 | 10 |
| 200 mg/kg drug + DEX | 23.6 ± 1.3 | 39.5 ± 9.1 | 55.9 ± 19.7 | 9 |
| 400 mg/kg drug + DEX | 23.7 ± 1.1 | 53.6 ± 5.7* | 69.0 ± 5.8* | 10 |

* Significantly greater than DEX group, $p<0.001$.

As shown in Table 1, treatment with 16α-fluoro-5-androstene-17-one at 400 mg/kg significantly reduced dexamethasone-induced thymic and splenic atrophy. The data clearly show that 16α-fluoro-5-androsten-17-one produces an anti-glucocorticoid effect.

In addition, the data show that the drug prevents the dexamethasone, a glucocorticoid, from reducing the size of the spleen and the thymus.

**EXAMPLE 6**

In this experiment the capacity of a compound of Formula I and II to alter the production of IL-2 and IL-4 following in vitro lymphocyte treatment or exposure is evaluated. The effect of these compounds on the production of IL-2 over a wide dose range, is examined.

Spleen cells are obtained from normal BALB/c mice and prepared as a single cell suspension at a concentration of about $10^7$ cells/ml in RPMI 1640 supplemented with 2 mM L-glutamine, $5x10^{-5}$ mercaptoethanol, 20 ug/ml gentamycin-sulfate, and 1% Nutridona-NS (Boehringer-Mannheim). Individual aliquots of cells are then pulsed for 30 minutes at 37°C with selected concentrations of Compounds of Formula I or II. After pulsing, the cells are washed several times in balanced salt solution, resuspended in fresh medium, and then dispensed into 24-well culture plates with a stimulatory concentration of anti-CD3 (Leo et al. Proc. Natl. Acad. Sci. U.S.A., 84:1374 (1987)). After a 24-hour incubation period, culture supernatants are harvested for assessment of IL-2 and IL-4 activity using, e.g., the method of Mossman (J. Immunol. Meth. 65:55 (1983)). 100% control titers of IL-2 and IL-4 from normal stimulated splenocytes are obtained, exemplary values may be about 640 and 160 units/ml, respectively. This same experiment is optionally repeated to assay for α-IFN production. A dose response curve similar to that for IL-2 or IL-4 is obtained for α-IFN.

**EXAMPLE 7**

In this series of experiments, the capacity of the compounds of Formula I and/or II to facilitate a reversal of glucocorticoid-induced suppression of IL-2

production by either normal murine lymphocytes, or cloned T cell lines with similarities to either Th1-type or Th2-type helper T cells is evaluated.

For splenocytes, the effects of corticosterone ($10^{-7}$M) are generally a reduction in the capacity of cells to produce IL-2 subsequent to activation with anti-CD3. The treatment of compounds of Formula I and/or II, such as 16α-5-androsten-17-one alone on IL-2 production is examined. Lymphocytes exposed to corticosterone and compounds of Formula I and/or II followed by their activation in vitro, are examined for levels of IL-2 and IL-4 expression.

OVA/2 (an ovalbumin (OVA)-specific cloned T cell line with characteristics similar to Th2-type cells), and OVA/3 (a cloned T cell line with characteristics similar to Th1-type cells), are exposed in vitro to the effects of the compounds of Formula I and/or II and/or GCSs prior to their culture with antigen and syngeneic antigen-presenting cells. Treatment of OVA/3 with a compound of Formula I and II, such as 16α-fluro-5-androsten-17-one, is examined for effects on of this cell line to produce IL-2. Exposure to DEX generally results in an IL-4 dominant phenotype, similar to what is observed with Th2-type clones. Treatment of OVA/3 with DEX followed by a demonstration of compounds of Formula I and II, such as 16α-fluro-5-androsten-17-one, is examined for elevation in IL-2 production with limited enhancement of IL-4. Exposure of the OVA/2 T cell clone to a compound of Formula I or II is used to examine a shift in the pattern of TCGF production from a Th2-like to a Th1-like phenotype (IL-2 dominant). DEX treatment alone generally augments IL-4 production following activation in vitro with OVA. Treatment of OVA/2 with both DEX and a compound of Formula I or II are used to determine the effect thereof to modulate IL-2 and IL-4.

Single cell suspensions of normal murine spleen

cells are prepared in Nutridoma-supplemented complete RPMI at $10^{-7}$ cells/ml. They are then pulsed with $10^{-7}$M Corticosterone and/or $10^{-8}$M of the compounds of Formula I or II. After several washes, the cells are stimulated with anti-CD3. IL-2 production in normal splenocytes in the presence and absence of the compounds of Formula I and/or II is determined. OVA-specific T cell clones are derived from nylon-wool enriched splenic T cells from OVA-immunized (C3H X C57/B6) F. mice, using the method of Berzofsky (J. Immunol. 35:2628 (1985)). OVA/3 and OVA/2 cell lines were derived from different clonings, each having distinct patterns of lymphokine production. Culture conditions and assay procedures for IL-2 and IL-4 are essentially as in Example 5 above.

**EXAMPLE 8**

Anti-glucocorticoid activity vis-a-vis dexamethasone. Study in vitro Incorporation of uridine in rat thymocytes.

Glucocorticoids generally cause an inhibition of the incorporation of nucleosides in lymphoid tissue and the measurement of the incorporation of radio-active uridine in the thymocytes in the presence of a compound of Formula I and/or II allows its anti-glucocorticoid activity to be evaluated.

The thymus of a suprarenalectomized rat weighing 160 to 180 g is removed, shredded and homogenized slowly using a teflon-flask homogenizer in Hanks solution. The cellular suspension is filtered on gauze, then centrifuged at 800 x 10g. A new centrifugation is carried out at 800 x 10g and the deposit is suspended in a nutritive medium (M.E.M. Gibco). The cellular concentration is adjusted to approximately $20x10^6$ cells per ml and aliquots of 250 ml are incubated under carbogen for 3 hours at 37°C with $5x10^{-8}$ M of dexamethasone in the absence and presence of

increasing concentrations of compounds of Formula I or II, e.g., 16α-fluoro-5-androsten-17-one (e.g., about $10^{-8}$ to $10.^{-5}$ M). 0.1 μCi of tritiated uridine is added to each incubate and the incubation is continued for one hour. The incubates are cooled and 1 ml of a cold solution of trichloroacetic acid (TCA) at 5% weight/volume is added. The precipitates are collected on Whatman GF/C filters and are washed with 4 X with 2 ml of 5% iced TCA. The radioactivity retained on the filters (representing the tritiated uridine incorporated in the thymocytes) is measured using a liquid scintillation spectrometer. The measurements are used to determine the anti-glucocorticoid activity of the tested compounds.

**EXAMPLE 9**

A series of tests is run in triplicate using BALB/c mouse spleen cells to demonstrate the effect of a compound of Formula I or II and hydrocortisone ("Hycort") on cellular proliferation in the absence of a mitogen. Cultures of spleen cells are prepared essentially using the procedure outlined above and steroids of the Formula I and/or II are added at, e.g., 0.1, 0.5, 1, 5 μM. Suitable controls are used. Twenty four hours after setup, about 50 mu Ci [$^3$H]-thymidine is added to each cell. Four to six hours later, the cells are harvested and counted on a scintillation counter.

**EXAMPLE 10**

Another series of cultures is run using a COMPOUND OF Formula I or II and/or hydrocortisone with cell cultures to which concanavalin A is added in a manner similar to those of Example 8. Preliminary tests on cultures to which concanavalin A is added at concentrations of 10.0, 5.0, 2.5 and 1.0 mu-g/ml. All tests on the effects of a compound of Formula I or II on

cultures stimulated with concanavalin A are performed with concanavalin A at, e.g., about 2.5 mu-g/ml. A mitogen such as ConA generally increases cell proliferation and the GCS can decrease proliferation. Partial or complete reversal of the inhibitor effects of hydrocortisone indicate an anti-glucorticoid effect.

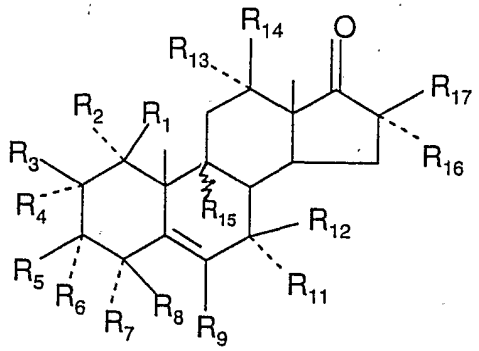
**EXAMPLE 11**

Exemplary compounds of Formula I or II are tested to determine whether their effect on the level of the cytokine IL-3 expression by cells in tissue culture and for their capacity to reverse the effects of a GCS in IL-3 expression. The cultures are prepared in accordance with the general method set out above. After 30 hours the level of IL-3 in the supernatants of the cultures was measured using the IL-3 ELISA kit manufactured by EndoGen Inc., Boston, Mass. A GCS such as hydrocortisone generally suppresses the production of IL-3 and the exemplary compound of Formula I or II are examined for their capacity to modify this effect. The IL-3 expressed by cells in culture may be recovered from the media containing IL-3 by known methods such as single or sequential reverse-phase HPLC steps on a preparative HPLC column. (See Urdal, et al., J. Chromatog. 296:171 (1984) and U.S. Pat. No. 5,128,450).

The above preferred embodiments and examples are given to illustrate the scope and spirit of the present invention. The embodiments and examples described herein will make apparent to those skilled in the art other embodiments and examples. These other embodiments and examples are within the contemplation of the present invention. Therefore, the present invention should be limited only by the appended claims.

**WHAT IS CLAIMED IS:**

1. A method for treating a patient having hypertriglyceridemia comprising administering thereto a therapeutically effective amount of a compound of the formula:




wherein0

$R_1$, $R_2$, $R_3$, $R_4$, $R_7$, $R_8$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$ and $R_{15}$ are independently hydrogen, alkyl, halogen, hydroxy or alkoxy;

$R_5$ and $R_6$ are independently hydrogen, alkyl, halogen or alkoxy;

$R_9$ is hydrogen, alkyl, halogen or alkoxy;

$R_{16}$ and $R_{17}$ are independently hydrogen, alkyl, halogen, hydroxy, alkoxy, loweralkenyl, loweralkynyl, amino, lower alkylamino, diloweralkylamino, lower alkoxy lower alkyl, hydroxy lower alkyl, amino lower alkyl, loweralkylamino lower alkyl, diloweralkylamino lower alkyl, haloloweralkyl, dihaloloweralkyl or trihaloloweralkyl, with the proviso that only one of $R_{16}$ or $R_{17}$ may be alkenyl or alkynyl.

2. The method according to Claim 1 wherein $R_{16}$ and $R_{17}$ are independently hydrogen, lower alkyl, hydroxy, loweralkoxy or halogen.

3. The method according to Claim 2 wherein $R_{17}$ is hydrogen and $R_{16}$ is lower alkyl, hydroxy, lower alkoxy or halogen.

4. The method according to Claim 2 wherein $R_{16}$ and $R_{17}$ are independently hydrogen, fluoro or chloro.

5. The method according to Claim 2 wherein $R_{16}$ is fluoro and $R_{17}$ is hydrogen.

6. The method according to Claim 1 wherein $R_5$ and $R_6$ are hydrogen.

7. The method according to Claim 2 wherein $R_5$ and $R_6$ are hydrogen.

8. The method according to Claim 3 wherein $R_5$ and $R_6$ are hydrogen.

9. The method according to Claim 8 wherein $R_{16}$ is fluoro.

10. The method according to Claim 1 wherein $R_1$, $R_2$, $R_3$, $R_4$, $R_7$, $R_8$, $R_{13}$, $R_{14}$ and $R_{15}$ are hydrogen, $R_9$ is hydrogen, lower alkyl, or halogen and $R_{11}$ and $R_{12}$ are independently hydrogen, hydroxy, lower alkoxy, halogen or lower alkyl and $R_{16}$ and $R_{17}$ are independently hydrogen, halogen, lower alkyl, lower alkoxy or hydroxy and $R_5$ and $R_6$ are independently hydrogen or lower alkyl.

11. The method according to Claim 10 wherein $R_{16}$ is fluoro, chloro, methyl, methoxy, $R_{17}$ is hydrogen, $R_9$ is hydrogen, methyl or fluoro or chloro and $R_{11}$ and $R_{12}$ are independently hydrogen, hydroxy, methoxy or methyl, fluoro or chloro.

12. The method according to Claim 11 wherein $R_{16}$ is fluoro.

13. The method according to Claim 10 wherein one of $R_9$, $R_{11}$ and $R_{12}$ is other than hydrogen.

14. The method according to Claim 10 wherein $R_5$ and $R_6$ are hydrogen.

15. The method according to Claim 14 wherein $R_{17}$ is hydrogen or halogen; $R_{11}$ and $R_{12}$ are independently hydrogen, hydroxy, lower alkyl, $R_9$ is hydrogen.

16. The method according to Claim 14 wherein $R_{17}$ is hydrogen; $R_9$ is hydrogen; $R_{11}$ and $R_{12}$ are independently hydrogen or hydroxy and $R_{16}$ is fluoro, chloro or methyl.

17. The method according to Claim 10 wherein $R_{16}$ is chloro or fluoro.

18. The method according to Claim 1 wherein the compound is 16α-fluoro-5-androsten-17-one.

19. The method according to Claim 1 or 10 wherein the patient has in addition at least one of the following characteristics:

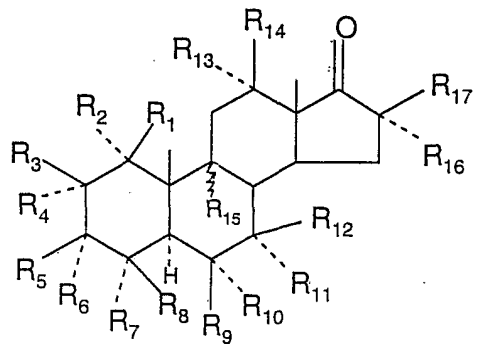
(a) is insulin resistant

(b) is obese

(c) has a HDL level less than about 40 mg/dl if male and less than about 45 mg/dl if female.

20. The method according to Claim 19 wherein the patient has a BMI greater than about 30 $Kg/m^2$.

21. A method for treating a patient having hypertriglyceridemia comprising administering thereto a therapeutically effective amount of a compound of the formula:




wherein

$R_1$, $R_2$, $R_3$, $R_4$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$ and $R_{15}$ are independently hydrogen, alkyl, halogen, hydroxy or alkoxy;

$R_5$ and $R_6$ are independently hydrogen, hydroxy, alkyl, halogen or alkoxy;

$R_{16}$ and $R_{17}$ are independently hydrogen, alkyl, halogen, hydroxy, alkoxy, loweralkenyl, loweralkynyl, amino, lower alkylamino, diloweralkylamino, lower alkoxy lower alkyl, hydroxy lower alkyl, amino lower alkyl,

loweralkylamino lower alkyl, diloweralkylamino lower alkyl, haloloweralkyl, dihaloloweralkyl or trihaloloweralkyl, with the proviso that only one of $R_{16}$ or $R_{17}$ may be alkenyl or alkynyl.

22. The method according to Claim 21 wherein $R_5$ or $R_6$ is other than hydroxy.

23. The method according to Claim 21 wherein $R_{16}$ and $R_{17}$ are independently hydrogen, lower alkyl, hydroxy, loweralkoxy or halogen.

24. The method according to Claim 23 wherein $R_{17}$ is hydrogen and $R_{16}$ is lower alkyl, hydroxy, lower alkoxy or halogen.

25. The method according to Claim 23 wherein $R_{16}$ and $R_{17}$ are independently hydrogen, fluoro or chloro.

26. The method according to Claim 25 wherein $R_{16}$ is fluoro and $R_{17}$ is hydrogen.

27. The method according to Claim 21 wherein $R_5$ and $R_6$ are hydrogen.

28. The method according to Claim 23 wherein $R_5$ and $R_6$ are hydrogen.

29. The method according to Claim 24 wherein $R_5$ and $R_6$ are hydrogen.

30. The method according to Claim 29 wherein $R_{16}$ is fluoro.

31. The method according to Claim 21 wherein $R_1$, $R_2$, $R_3$, $R_4$, $R_7$, $R_8$, $R_{13}$, $R_{14}$ and $R_{15}$ are hydrogen, $R_9$ is hydrogen, lower alkyl, or halogen and $R_{11}$ and $R_{12}$ are independently hydrogen, hydroxy, lower alkoxy, halogen or lower alkyl, $R_{16}$ and $R_{17}$ are independently hydrogen, halogen, lower alkyl, lower alkoxy or hydroxy and $R_5$ and $R_6$ are independently hydrogen or lower alkyl.

32. The method according to Claim 31 wherein $R_{16}$ is fluoro or chloro, methyl, methoxy, $R_{17}$ is hydrogen, $R_9$ is hydrogen, methyl or fluoro or chloro and $R_{11}$ and $R_{12}$ are independently hydrogen, hydroxy, methoxy or methyl, fluoro or chloro, and $R_5$ and $R_6$ are hydrogen.

33. The method according to Claim 31 wherein $R_{16}$ is fluoro.

34. The method according to Claim 21 wherein one of $R_9$, $R_{11}$ and $R_{12}$ is other than hydrogen, $R_{17}$ is hydrogen and $R_{16}$ is chloro or fluoro.

35. The method according to Claim 21 wherein $R_5$ and $R_6$ are hydrogen.

36. The method according to Claim 35 wherein $R_{17}$ is hydrogen or fluoro; $R_{11}$ and $R_{12}$ are independently hydrogen, hydroxy, lower alkyl or halogen; $R_9$ is hydrogen, and $R_{16}$ is fluoro or chloro.

37. The method according to Claim 35 wherein $R_{17}$ is hydrogen; $R_9$ is hydrogen and $R_{11}$ and $R_{12}$ are independently hydrogen or hydroxy and $R_{16}$ is fluoro, chloro or methyl.

38. The method according to Claim 37 wherein $R_{16}$ is chloro or fluoro.

39. The method according to Claim 21 wherein the compound is 16α-fluoro-5α-androstan-17-one.

40. The method according to Claim 1 or 21 wherein the patient additionally has at least one of the following characteristics:

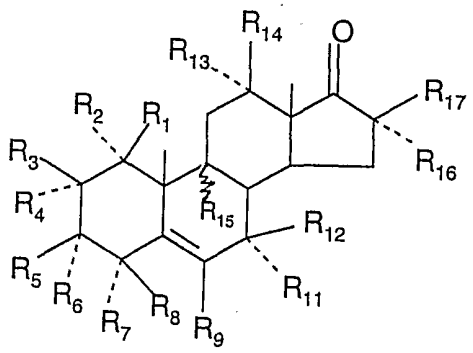
(a) is insulin resistant

(b) is obese

(c) has a HDL level less than about 40 mg/dl if male and less than about 45 mg/dl if female.

41. The method according to Claim 40 wherein the patient has a BMI greater than about 30 $Kg/m^2$.

42. A method of treating a patient having atherosclerosis relating to hypertriglyceridemia comprising administering thereto a therapeutically effective amount of a compound of the formula:



wherein

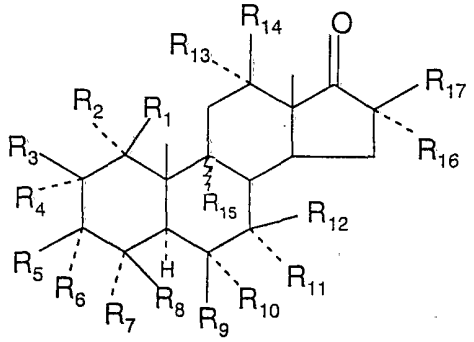
$R_1$, $R_2$, $R_3$, $R_4$, $R_7$, $R_8$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$ and $R_{15}$ are independently hydrogen, alkyl, halogen, hydroxy or alkoxy;

$R_5$ and $R_6$ are independently hydrogen, alkyl, halogen or alkoxy;

$R_9$ is hydrogen, alkyl, halogen or alkoxy;

$R_{16}$ and $R_{17}$ are independently hydrogen, alkyl, halogen, hydroxy, alkoxy, loweralkenyl, loweralkynyl, amino, lower alkylamino, diloweralkylamino, lower alkoxy lower alkyl, hydroxy lower alkyl, amino lower alkyl, loweralkylamino lower alkyl, diloweralkylamino lower alkyl, haloloweralkyl, dihaloloweralkyl or trihaloloweralkyl, with the proviso that only one of $R_{16}$ or $R_{17}$ may be alkenyl or alkynyl.

43. A method of treating a patient having a atherosclerosis relating to hypertriglyceridemia comprising administering thereto a therapeutically effective amount of a compound of the formula:



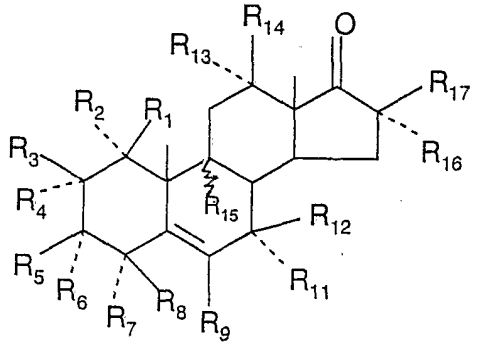
wherein

$R_1$, $R_2$, $R_3$, $R_4$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$ and $R_{15}$ are independently hydrogen, alkyl, halogen, hydroxy or alkoxy;

$R_5$ and $R_6$ are independently hydrogen, alkyl, halogen or alkoxy;

$R_{16}$ and $R_{17}$ are independently hydrogen, alkyl, halogen, hydroxy, alkoxy, loweralkenyl, loweralkynyl, amino, lower alkylamino, diloweralkylamino, lower alkoxy lower alkyl, hydroxy lower alkyl, amino lower alkyl, loweralkylamino lower alkyl, diloweralkylamino lower alkyl, haloloweralkyl, dihaloloweralkyl or trihaloloweralkyl, with the proviso that only one of $R_{16}$ or $R_{17}$ may be alkenyl or alkynyl and with the further proviso that when $R_5$ or $R_6$ are hydroxy, then $R_{16}$ is other than hydrogen.

44. A method of treating Syndrome X which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound of the Formula:




wherein

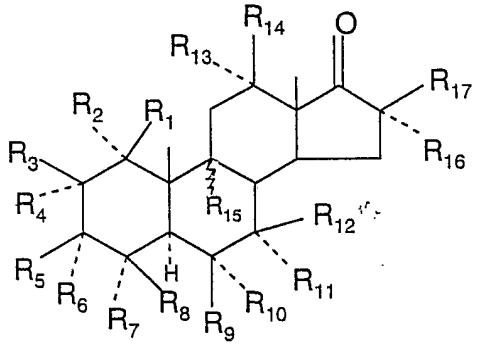
$R_1$, $R_2$, $R_3$, $R_4$, $R_7$, $R_8$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$ and $R_{15}$ are independently hydrogen, alkyl, halogen, hydroxy or alkoxy;

$R_5$ and $R_6$ are independently hydrogen, hydroxy alkyl, halogen or alkoxy;

$R_9$ is hydrogen, alkyl, halogen or alkoxy;

$R_{16}$ and $R_{17}$ are independently hydrogen, alkyl, halogen, hydroxy, alkoxy, loweralkenyl, loweralkynyl, amino, lower alkylamino, diloweralkylamino, lower alkoxy lower alkyl, hydroxy lower alkyl, amino lower alkyl, loweralkylamino lower alkyl, diloweralkylamino lower alkyl, haloloweralkyl, dihaloloweralkyl or trihaloloweralkyl, with the proviso that only one of $R_{16}$ or $R_{17}$ may be alkenyl or alkynyl.

45. A method of treating Syndrome X which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound of the formula:




wherein

$R_1$, $R_2$, $R_3$, $R_4$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$ and $R_{15}$ are independently hydrogen, alkyl, halogen, hydroxy or alkoxy;

$R_5$ and $R_6$ are independently hydrogen, hydroxy, halogen or alkoxy;

$R_{16}$ and $R_{17}$ are independently hydrogen, alkyl, halogen, hydroxy, alkoxy, loweralkenyl, loweralkynyl, amino, lower alkylamino, diloweralkylamino, lower alkoxy lower alkyl, hydroxy lower alkyl, amino lower alkyl, loweralkylamino lower alkyl, diloweralkylamino lower alkyl, haloloweralkyl, dihaloloweralkyl or trihaloloweralkyl, with the proviso that only one of $R_{16}$ or $R_{17}$ may be alkenyl or alkynyl.

46. The method according to any one of Claims 1, 42 or 44 wherein the compound is 16α-fluoro-5-androsten-17-one, 7α-hydroxy-16α-fluoro-5-androsten-17-one or 7β-hydroxy-16α-fluoro-5-androsten-17-one.

47. The method according to any one of Claims 21, 43 or 45 wherein the compound is 16α-fluoro-5α-androstan-17-one, 7α-hydroxy-16α-fluoro-5α-androstan-17-one or 16α-fluoro-7β-hydroxy-5α-androstan-17-one.

48. The method according to any one of Claims 1, 21, 42, 43, 44 or 45 wherein the compound is administered buccally.

49. The method according to Claim 46, where the compound is administered buccally.

50. The method according to Claim 47 wherein the compound is administered buccally.