EUROPEAN PATENT SPECIFICATION

(54) USE OF THIAZOLIDINEDIONE DERIVATIVES AND RELATED ANTIHYPERGLYCEMIC AGENTS IN THE TREATMENT OF DISEASE STATES AT RISK FOR PROGRESSING TO NONINSULIN-DEPENDENT DIABETES MELLITUS

Verwendung von Thiazolidinedionderivaten und Verwandten antihyperglykämischen Mitteln zur Behandlung von Erkrankungen mit dem Risiko zur Entwicklung von insulinabhängigen Diabetes Mellitus

UTILISATION DE DERIVES DE THIAZOLIDINEDIONE ET D’AGENTS ANTI-HYPERGLYCEMIANTS APPARENTES POUR LE TRAITEMENT DES ÉTATS PATHOLOGIQUES RISQUANT D’ÉVOLUER EN DIABETE SUCRE NON INSULINODEPENDANT

(56) References cited:

- DIABETES CARE, vol.15, no.8, 1992 pages 1075 - 1078 C.A. HOFMAN ET AL. 'NEW ORAL THIAZOLIDINEDIONE ANTI DIABETIC AGENTS ACT AS INSULIN SENSITIZERS'
- CHEMICAL ABSTRACTS, vol.119, no.1, 5 July 1993, Columbus, Ohio, US; abstract no. 97, 'CS-045, AN AMELIORATOR FOR INSULIN RESISTANCE' & DIABETES FRONT., vol.3, no.6, 1992 pages 570 - 574 KANAZAWA ET AL.
- ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, vol.687, May 1993 pages 60 - 64 A. DUNAIF 'INSULIN RESISTANCE IN POLYCYSTIC OVARIAN SYNDROME'
- DIABETOLOGIA, vol.34, 1991 page A198 S. ROBINSON ET AL. 'INSULIN RESISTANCE IS AN EARLY FEATURE OF GESTATIONAL DIABETES'

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The present invention pertains to the use of a number of compounds which can be used to treat certain disease states in order to prevent or delay the onset of noninsulin-dependent diabetes mellitus (NIDDM). More specifically, the present invention involves in one embodiment the use of certain known thiazolidinedione derivatives and related antihyperglycemic agents for the manufacture of pharmaceutical compositions for treating polycystic ovary syndrome which is at increased risk in the development of NIDDM, thus preventing or delaying the onset of NIDDM or complications resulting therefrom.

BACKGROUND OF THE INVENTION

Diabetes is one of the most prevalent chronic disorders worldwide with significant personal and financial costs for patients and their families, as well as for society. Different types of diabetes exist with distinct etiologies and pathogeneses. For example, diabetes mellitus is a disorder of carbohydrate metabolism, characterized by hyperglycemia and glycosuria and resulting from inadequate production or utilization of insulin.

NIDDM, or otherwise referred to as Type II diabetes, is the form of diabetes mellitus which occurs predominantly in adults in whom adequate production of insulin is available for use, yet a defect exists in insulin-mediated utilization and metabolism of glucose in peripheral tissues. Overt NIDDM is characterized by three major metabolic abnormalities: resistance to insulin-mediated glucose disposal, impairment of nutrient-stimulated insulin secretion, and overproduction of glucose by the liver. It has been shown that for some people with diabetes a genetic predisposition results in a mutation in the gene(s) coding for insulin and/or the insulin receptor and/or insulin-mediated signal transduction factor(s), thereby resulting in ineffective insulin and/or insulin-mediated effects thus impairing the utilization or metabolism of glucose.

Reports indicate that insulin secretion is often enhanced early-on, presumably as compensation for the insulin resistance. People who actually develop NIDDM appear to do so because their B-cells eventually fail to maintain sufficient insulin secretion to compensate for the insulin resistance. Mechanisms responsible for the B-cell failure have not been identified, but may be related to the chronic demands placed on the B-cells by peripheral insulin resistance and/or to the effects of hyperglycemia to impair B-cell function. The B-cell failure could also occur as an independent, inherent defect in “pre-diabetic” individuals.

NIDDM often develops from certain at risk populations, one such population is individuals with polycystic ovary syndrome (PCOS). PCOS is the most common endocrine disorder in women of reproductive age. This syndrome is characterized by hyperandrogenism and disordered gonadotropin secretion producing oligo- or anovulation. Recent prevalence estimates suggest that 5-10% of women between 18-44 years of age (about 5 million women, according to the 1990 census) have the full-blown syndrome of hyperandrogenism, chronic anovulation, and polycystic ovaries. Despite more than 50 years since its original description, the etiology of the syndrome remains unclear. The biochemical profile, ovarian morphology, and clinical features are non-specific; hence, the diagnosis remains one of exclusion of disorders, such as androgen-secreting tumors, Cushing's Syndrome, and late-onset congenital adrenal hyperplasia.

PCOS is associated with profound insulin resistance resulting in substantial hyperinsulinemia. As a result of their insulin resistance, PCOS women are at increased risk to develop NIDDM. Hirsutism, acne, and alopecia, which are commonly found in PCOS women, are clinical manifestations of hyperandrogenism. Menstrual disturbances and infertility are the result of ovulatory dysfunction related to the disordered gonadotropin secretion. Androgen excess, probably by eventual conversion of androgens to estrogen, also plays an important role in disrupting gonadotropin release in PCOS.

There are two leading hypotheses for the association between PCOS and insulin resistance: 1) androgens produce insulin resistance or 2) hyperinsulinemia produces hyperandrogenism. In support of the first hypothesis, synthetic androgen administration can increase insulin levels in women. However, in PCOS women with acanthosis nigricans (which is a marker for insulin resistance), oophorectomy lowers testosterone levels but does not alter insulin resistance. Further, long-acting GnRH agonist treatment in PCOS women decreases plasma testosterone and androstenedione levels into the normal female range, but does not alter glucose tolerance, insulin levels, or insulin action. Thus, although certain synthetic androgens may have a modest effect on insulin sensitivity, natural androgens do not produce insulin resistance of the magnitude found in PCOS.

In contrast, there are several lines of evidence that support the alternative hypothesis that hyperinsulinemia produces hyperandrogenism. First, extreme insulin resistance of a variety of etiologies, ranging from insulin receptor mutations to autoimmune insulin resistance, is associated with ovarian hyperandrogenism. Second, insulin can directly stimulate ovarian androgen secretion in vitro and in vivo in PCOS women. Finally, decreasing insulin levels for 10 days with diazoxide results in a significant decrease in testosterone levels in PCOS women. Insulin does not alter gonado-
tropin release but rather appears to act directly on the ovary. However, these actions of insulin are not observed in normal ovulatory women, suggesting that polycystic ovarian changes are necessary for such insulin effects to be manifested.

[0009] Insulin resistance in PCOS is secondary to a marked decrease in insulin receptor-mediated signal transduction and a modest, but significant, decrease in adipocyte GLUT4 content. In many PCOS women, the decrease in insulin receptor signaling is the result of intrinsic abnormalities in insulin receptor phosphorylation. The magnitude of insulin resistance in PCOS is similar to that in NIDDM and in obesity. However, the cellular mechanisms of insulin resistance appear to differ in PCOS compared to these other common insulin-resistant states. The shift to the right in the insulin dose-response curve for adipocyte glucose uptake is much more striking in PCOS than in obesity. Further, decreases in adipocyte insulin sensitivity and responsiveness are significantly correlated with hyperinsulinemia, glycemia, and/or obesity in individuals with NIDDM or obesity, whereas insulin resistance is independent of these parameters in PCOS. Finally, no persistent abnormalities in insulin receptor autophosphorylation have been identified in NIDDM or obesity.

[0010] Failure to treat NIDDM can result in mortality due to cardiovascular disease and in other diabetic complications including retinopathy, nephropathy, and peripheral neuropathy. For many years treatment of NIDDM has involved a program aimed at lowering blood sugar with a combination of diet and exercise. Alternatively, treatment of NIDDM involved oral hypoglycemic agents, such as sulfonylureas alone or in combination with insulin injections. Recently, alpha-glucosidase inhibitors, such as a carboys, have been shown to be effective in reducing the postprandial rise in blood glucose (Lefevre, et al., Drugs 1992;44: 29-38). In Europe and Canada another treatment used primarily in obese diabetics is metformin, a biguanide.

[0011] In any event, what is required is a method of treating at risk populations such as those with PCOS in order to prevent or delay the onset of NIDDM thereby bringing relief of symptoms, improving the quality of life, preventing acute and long-term complications, reducing mortality and treating accompanying disorders of the populations at risk for NIDDM. The methods of using the disclosed compounds for treating at risk populations with conditions such as PCOS to prevent or delay the onset of NIDDM as taught herein meet these objectives.

[0012] The compounds of the present invention, and methods of making the compounds, are known and some of these are disclosed in U.S. Patents 5,223,522 issued June 29, 1993; 5,132,317 issued July 12, 1992; 5,120,754 issued June 9, 1992; 5,061,717 issued October 29, 1991; 4,897,405 issued January 30, 1990; 4,873,255 issued October 10, 1989; 4,687,777 issued August 18, 1987; 4,572,912 issued February 25, 1986; 4,287,200 issued September 1, 1981. The compounds disclosed in these issued patents are useful as therapeutic agents for the treatment of diabetes, hyperglycemia, hypercholesterolemia, and hyperlipidemia.

[0013] Regarding prevention of NIDDM, there has been one disclosure of this concept using a sulfonylurea as a treatment, but this concept is not highly regarded in the scientific community because prolonged treatment with sulfonylureas can reduce insulin secretion by destroying the pancreatic beta cells. Moreover, sulfonylureas can cause clinically severe hypoglycemia. The concept of using a biguanide, such as metformin, has also been disclosed.

[0014] There is no disclosure in the above-identified references to suggest the use of the compounds identified in this present application in the treatment of at risk populations such as those with PCOS in order to prevent or delay the onset of NIDDM and complications resulting therefrom.

SUMMARY OF THE INVENTION

[0015] In one embodiment of this invention, a method is disclosed for the treatment of PCOS in order to prevent or delay the onset of NIDDM. Improvement in insulin sensitivity by treatment with the compounds of the following formulas will reduce fasting insulin levels, thereby resulting in decreased androgen production and biologic availability in PCOS women. Decreasing androgen levels will improve the clinical symptoms of androgen excess and the anovulation commonly found in PCOS women.

[0016] As agents having the aforementioned effects, the compounds of the following formulas are useful in treating individuals to prevent or delay the onset of NIDDM.

[0017] Treatment of the above populations with the compounds of the following formulas will prevent or delay the onset of NIDDM. Accordingly, the present invention is the use of compounds of Formula I
herein R₁ and R₂ are the same or different and each represents a hydrogen atom or a C₁-C₅ alkyl group; 
R³ represents a hydrogen atom, a C₁-C₆ aliphatic acyl group, an alicyclic acyl group, an aromatic acyl group, a heterocyclic acyl group, an araliphatic acyl group, a (C₁-C₆ alkoxy)carbonyl group, or an aralkyloxy carbonyl group; 
R⁴ and R⁵ are the same or different and each represents a hydrogen atom, a C₁-C₅ alkyl group or a C₁-C₅ alkoxy group, or R⁴ and R⁵ together represent a C₁-C₄ alkylenedioxy group; 
n is 1, 2, or 3; 
W represents the -CH₂-, >CO, or CH-OR⁶ group (in which R⁶ represents any one of the atoms or groups defined for R³ and may be the same as or different from R³); and 
Y and Z are the same or different and each represents an oxygen atom or an imino (=NH) group; 
and pharmaceutically acceptable salts thereof for the manufacture of pharmaceutical compositions for the treatment of polycystic ovary syndrome. The present invention is also the above defined use of compounds of the Formula II

wherein R₁₁ is substituted or unsubstituted alkyl, alkoxy, cycloalkyl, phenylalkyl, phenyl, aromatic acyl group, a 5- or 6-membered heterocyclic group including 1 or 2 heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, or a group of the formula

wherein R₁₃ and R₁₄ are the same or different and each is lower alkyl or R₁₃ and R₁₄ are combined to each other either directly or as interrupted by a heteroatom selected from the group consisting of nitrogen, oxygen, and sulfur to form a 5- or 6-membered ring; wherein R₁₁₂ means a bond or a lower alkylene group; and wherein L₁ and L₂ are the same or different and each is hydrogen or lower alkyl or L₁ and L₂ are combined to form an alkylene group; or a pharmaceutically acceptable salt thereof.
The present invention is also the above defined use of compounds of the Formula III

wherein R₁₅ and R₁₆ are independently hydrogen, lower alkyl containing 1 to 6 carbon atoms, alkoxy containing 1 to 6 carbon atoms, halogen, ethynyl, nitrile, methythio, trifluoromethyl, vinyl, nitro, or halogen substituted benzyloxy; n is 0 to 4 and the pharmaceutically acceptable salts thereof.

The present invention is also directed to the above defined use of compounds of the Formula IV

wherein the dotted line represents a bond or no bond;
V is -CH = CH-, -N = CH-, -CH = N- or S;
D is CH₂, CHOH, CO, C = NOR₁₇ or CH = CH;
X is S, O, NR₁₈ -CH = N or -N = CH;
Y is CH or N;
Z is hydrogen, (C₁-C₇) alkyl, (C₃-C₇)cycloalkyl, phenyl, naphthyl, pyridyl, furyl, thieryl, or phenyl mono- or disubstituted with the same or different groups which are (C₁-C₃)alkyl, trifluoromethyl, (C₁-C₃) alkoxy, fluoro, chloro, or bromo;
Z₁ is hydrogen or (C₁-C₃)alkyl;
R₁₇ and R₁₈ are each independently hydrogen or methyl;
and n is 1, 2, or 3;
the pharmaceutically acceptable cationic salts thereof; and the pharmaceutically acceptable acid addition salts thereof when the compound contains a basic nitrogen.

The present invention is also directed to the above defined use of compounds of the Formula V
wherein the dotted line represents a bond or no bond;
A and B are each independently CH or N, with the proviso that when A or B is N, the other is CH;
X₁ is S, SO, SO₂, CH₂, CHOH, or CO;
n is 0 or 1;
Y₁ is CHR₂₀ or R₂¹, with the proviso that when n is 1 and Y₁ is NR₂¹, X₁ is SO₂ or CO;
Z₂ is CHR₂², CH₃CH₂, CH=CH;
OCH₂, SCH₂, SOCH₂ or SO₂CH₂;
R₁₉, R₂₀, R₂¹, and R₂² are each independently hydrogen or methyl; and
X₂ and X₃ are each independently hydrogen, methyl, trifluoromethyl, phenyl, benzyl, hydroxy, methoxy, phenoxy, benzoyloxy, bromo, chloro, or fluoro;
a pharmaceutically acceptable cationic salt thereof; or
a pharmaceutically acceptable acid addition salt thereof when A or B is N.

The present invention also relates to the above defined use of compounds of the Formula VI

or a pharmaceutically acceptable salt thereof wherein R₂³ is alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, phenyl or mono- or di-substituted phenyl wherein said substituents are independently alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 3 carbon atoms, halogen, or trifluoromethyl.

The present invention also provides the above defined use of a compound of Formula VII
or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically accept-
able solvate thereof, wherein:
A₂ represents an alkyl group, a substituted or unsubstituted aryl group, or an aralkyl group wherein the alkylene or
the aryl moiety may be substituted or unsubstituted;
A₃ represents a benzene ring having in total up to 3 optional substituents;
R₂₄ represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group wherein the alkyl or the aryl moiety
may be substituted or unsubstituted, or a substituted or unsubstituted aryl group; or A₂ together with R₂₄ represents
substituted or unsubstituted C₂-₃ polymethylene group, optional substituents for the polymethylene group being
selected from alkyl or aryl or adjacent substituents together with the methylene carbon atoms to which they are
attached form a substituted or unsubstituted phenylene group;
R₂₅ and R₂₆ each represent hydrogen, or R₂₅ and R₂₆ together represent a bond;
X₄ represents O or S; and
n represents an integer in the range of from 2 to 6.

The present invention also provides the above defined use of a compound of Formula VIII

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically accept-
able solvate thereof, wherein:
R₂₇ and R₂₈ each independently represent an alkyl group, a substituted or unsubstituted aryl group, or an aralkyl
group being substituted or unsubstituted in the aryl or alkyl moiety; or R₂₇ together with R₂₈ represents a linking
group, the linking group consisting of an optionally substituted methylene group and either a further optionally sub-
stituted methylene group or an O or S atom, optional substituents for the said methylene groups being selected
from alkyl-, aryl, or aralkyl, or substituents of adjacent methylene groups together with the carbon atoms to which
they are attached form a substituted or unsubstituted phenylene group;
R₂₉ and R₃₀ each represent hydrogen, or R₂₉ and R₃₀ together represent a bond;
A₄ represents a benzene ring having in total up to 3 optional substituents;
X₅ represents O or S; and
n represents an integer in the range of from 2 to 6.

The present invention also provides the above defined use of a compound of Formula IX
or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically accept-
able solvate thereof, wherein:
A₅ represents a substituted or unsubstituted aromatic heterocyclyl group;
A₆ represents a benzene ring having in total up to 5 substituents:
X₆ represents O, S, or NR₃₂ wherein R₃₂ represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl
group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;
Y₂ represents O or S;
R₃₁ represents an alkyl, aralkyl, or aryl group; and
n represents an integer in the range of from 2 to 6.

Suitable aromatic heterocyclyl groups include substituted or unsubstituted, single or fused ring aromatic heterocyclyl groups comprising up to 4 hetero atoms in each ring selected from oxygen, sulphur, or nitrogen.

Favored aromatic heterocyclyl groups include substituted or unsubstituted single ring aromatic heterocyclyl groups having 4 to 7 ring atoms, preferably 5 or 6 ring atoms.

In particular, the aromatic heterocyclyl group comprises 1, 2, or 3 heteroatoms, especially 1 or 2, selected from oxygen, sulphur, or nitrogen.

Suitable values for A₅ when it represents a 5-membered aromatic heterocyclyl group include thiazolyl and
oxazoyl, especially oxazoyl.

Suitable values for A₅ when it represents a 6-membered aromatic heterocyclyl group include pyridyl or pyrimidinyl.

Suitable R₃₁ represents an alkyl group, in particular a C₁₋₆ alkyl group, for example a methyl group. Prefer-
ably, A₅ represents a moiety of formula (a), (b), or (c):

wherein:
R₃₃ and R₃₄ each independently represents a hydrogen atom, an alkyl group, or a substituted or unsubstituted aryl
group or when R₃₃ and R₃₄ are each attached to adjacent carbon atoms, then R₃₃ and R₃₄ together with the carbon
atoms to which they are attached form a benzene ring wherein each carbon atom represented by R₃₃ and R₃₄
together may be substituted or unsubstituted; and in the moiety of Formula (a), X₇ represents oxygen or sulphur.

In one favored aspect R₃₃ and R₃₄ together represent a moiety of Formula (d):
wherein $R_{35}$ and $R_{36}$ each independently represent hydrogen, halogen, substituted or unsubstituted alkyl, or alkoxy.

The present invention also provides for the above defined use of compounds for Formula X

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:

- $A_7$ represents a substituted or unsubstituted aryl group;
- $A_8$ represents a benzene ring having in total up to 5 substituents;
- $X_8$ represents O, S, or NR$_{39}$ wherein R$_{39}$ represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;
- $Y_3$ represents O or S;
- $R_{37}$ represents hydrogen;
- $R_{38}$ represents hydrogen or an alkyl, aralkyl, or aryl group or $R_{37}$ together with $R_{38}$ represents a bond; and
- $n$ represents an integer in the range of from 2 to 6.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The compounds used in the treatment methods of the invention, which are 5-[4-(chromoanalkoxy)benzyl]-thiazolidene derivatives, may be represented by the Formulas (Ia), (Ib), and (Ic)
(in which \(R^1, R^2, R^3, R^4, R^5, n, y,\) and \(Z\) are as defined above) and include pharmaceutically acceptable salts thereof.

[0034] In the compounds of the invention, where \(R^1\) or \(R^2\) represents an alkyl group, this may be a straight or branched chain alkyl group having from 1 to 5 carbon atoms and is preferably a primary or secondary alkyl group, for example the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, or isopentyl group.

[0035] Where \(R^3, R^6,\) or \(R^6'\) represents an aliphatic acyl group, this preferably has from 1 to 6 carbon atoms and may include one or more carbon-carbon double or triple bonds. Examples of such groups include the formyl, acetyl, propionyl, butyryl, isobutyryl, hexanoyl, acryloyl, methacyroyl, and crotonyl groups.

[0036] Where \(R^3, R^6,\) or \(R^6'\) represents an alicyclic acyl group, it is preferably a cyclopentanecarbonyl, cyclohexanecarbonyl, or cycloheptanecarbonyl group.

[0037] Where \(R^3, R^6,\) or \(R^6'\) represents an aromatic acyl group, the aromatic moiety thereof may optionally have one or more substituents (for example, nitro, amino, alkylamino, dialkylamino, alkoxy, halo, alkyl, or hydroxy substituents); examples of such aromatic acyl groups included the benzoyl, p-nitrobenzoyl, m-fluorobenzoyl, o-chlorobenzoyl, p-aminobenzoyl, m-(dimethylamino)benzoyl, o-methoxybenzoyl, 3,4-dichlorobenzoyl, 3,5-di-t-butyl-4-hydroxybenzoyl, and 1-naphthoyl groups.

[0038] Where \(R^3, R^6,\) or \(R^6'\) represents a heterocyclic acyl group, the heterocyclic moiety thereof preferably has one or more, preferably one, oxygen, sulfur, or nitrogen hetero atoms and has from 4 to 7 ring atoms; examples of such heterocyclic acyl groups include the 2-furoyl, 3-thienyl, 3-pyridinecarbonyl (nicotinoyl), and 4-pyridinecarbonyl groups.

[0039] Where \(R^3, R^6,\) or \(R^6'\) represents an araliphatic acyl group, the aliphatic moiety thereof may optionally have one or more carbon-carbon double or triple bonds and the aryl moiety thereof may optionally have one or more substituents (for example, nitro, amino, alkylamino, dialkylamino, alkoxy, halo, alkyl, or hydroxy substituents); examples of such araliphatic acyl groups include the phenylacetyl, p-chlorophenylacetyl, phenylpropionyl, and cinnamoyl groups.

[0040] Where \(R^3, R^6,\) or \(R^6'\) represents a (C\(_1-C_6\)) alkoxy)carbonyl group, the alkoxy moiety thereof may be any one of those included within the araliphatic acyl group represented by \(R^3, R^6,\) or \(R^6'\), but is preferably a methyl or ethyl group, and the alkoxy carbonyl group represented by \(R^3, R^6,\) or \(R^6'\) is therefore preferably a methoxycarbonyl or ethoxycarbonyl group.

[0041] Where \(R^3, R^6,\) or \(R^6'\) represents an aralkyloxycarbonyl group, the aralkyl moiety thereof may be any one of those included within the araliphatic acyl group represented by \(R^3, R^6,\) or \(R^6'\), but is preferably a benzyloxycarbonyl
group.

[0042] Where R⁴ and R⁵ represent alkyl groups, they may be the same or different and may be straight or branched chain alkyl groups. They preferably have from 1 to 5 carbon atoms and examples include the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, and isopentyl groups.

[0043] Where R⁴ and R⁵ represent alkoxy groups, these may be the same or different and may be straight or branched chain groups, preferably having from 1 to 4 carbon atoms. Examples include the methoxy, ethoxy, propoxy, isopropoxy, and butoxy groups. Alternatively, R⁴ and R⁵ may together represent a C₁-C₄ alkylenedioxy group, more preferably a methylenedioxy or ethylenedioxy group.

[0044] Preferred classes of compounds of Formula I are as follows:

1. Compounds in which R³ represents a hydrogen atom, a C₁-C₆ aliphatic acyl group, an aromatic acyl group, or a heterocyclic acyl group.
2. Compounds in which Y represents an oxygen atom; R¹ and R² are the same or different and each represents a hydrogen atom or a C₁-C₆ aliphatic acyl group, an aromatic acyl group, or a pyridinecarbonyl group; and R⁴ and R⁵ are the same or different and each represents a hydrogen atom, a C₁-C₆ alkyl group, or a C₁ or C₂ alkoxy group.
3. Compounds as defined in (2) above, in which: R¹, R², R⁴, and R⁵ are the same or different and each represents a hydrogen atom or a C₁-C₆ alkyl group; n is 1 or 2; and W represents the -CH₂- or >CO group.
4. Compounds as defined in (3) above, in which R⁵ represents a hydrogen atom, a C₁-C₆ aliphatic acyl group, a benzoyl group, or a nitro group.
5. Compounds as defined in (4) above, in which: R¹ and R⁴ are the same or different and each represents a C₁-C₆ alkyl group; R² and R⁵ are the same or different and each represents the hydrogen atom or the methyl group; and R³ represents a hydrogen atom or a C₁-C₆ aliphatic acyl group.
6. Compounds in which: W represents the -CH₂- or >CO group; Y and Z both represent oxygen atoms; n is 1 or 2; R¹ and R² are the same or different and each represents a C₁-C₄ alkyl group; R² and R³ are the same or different and each represents the hydrogen atom or the methyl group; and R⁴ represents a hydrogen atom or a C₁-C₄ aliphatic acyl group.
7. Compounds as defined in (6) above, in which n is 1.
8. Compounds as defined in (6) or (7) above, in which W represents the -CH₂- group.

[0045] Preferred compounds among the compounds of Formula I are those wherein:

- R¹ is a C₁-C₄ alkyl group, more preferably a methyl or isobutyl group, most preferably a methyl group;
- R² is a hydrogen atom or a C₁-C₄ alkyl group, preferably a hydrogen atom, or a methyl or isopropyl group, more preferably a hydrogen atom or a methyl group, most preferably a methyl group;
- R³ is a hydrogen atom, a C₁-C₆ aliphatic acyl group, an aromatic acyl group or a pyridinecarbonyl group, preferably a hydrogen atom, or an acetyl, butyryl, benzoyl, or nicotinyl group, more preferably a hydrogen atom or an acetyl, butyryl or benzoyl group, most preferably a hydrogen atom or an acetyl group;
- R⁴ is a hydrogen atom, a C₁-C₄ alkyl group or a C₁ or C₂ alkoxy group, preferably a methyl, isopropyl, t-butyl, or methoxy group, more preferably a methyl or t-butyl group, most preferably a methyl group;
- R⁵ is a hydrogen atom, a C₁-C₄ alkyl group or a C₁ or C₂ alkoxy group, preferably a hydrogen atom, or a methyl or methoxy group, more preferably a hydrogen atom or a methyl group, and most preferably a methyl group;
- n is 1 or 2, preferably 1;
- Y is an oxygen atom;
- Z is an oxygen atom or an imino group, most preferably an oxygen atom; and
- W is a -CH₂- or >C=O group, preferably a -CH₂- group.

[0046] Referring to the general Formula II, the substituents may be any from 1 to 3 selected from nitro, amino, alkylamino, dialkylamino, alkoxy, halo, alkyl, or hydroxy, the aromatic acyl group may be benzoyl and naphthoyl. The alkyl group R₁₁ may be a straight chain or branched alkyl of 1 to 10 carbon atoms, such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, i-butyl, t-butyl, n-pentyl, i-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, and n-decyl; the cycloalkyl group R₁₁ may be a cycloalkyl group of 3 to 7 carbon atoms, such as cyclopropyl, cyclopentyl, cyclohexyl, and cycloheptyl; and the phenylalkyl group R₁₁ may be a phenylalkyl group of 7 to 11 carbon atoms such as benzyl and phenethyl. As examples of the heterocyclic group R₁₁ may be mentioned 5- or 6-membered groups each including 1 or 2 hetero-atoms selected from among nitrogen, oxygen, and sulfur, such as pyridyl, thienyl, furyl, thiazolyl, etc. When R₁₁ is
the lower alkyls R<sub>13</sub> and R<sub>14</sub> may each be a lower alkyl of 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl, and n-butyl. When R<sub>13</sub> and R<sub>14</sub> are combined to each other to form a 5- or 6-membered heterocyclic group as taken together with the adjacent N atom, i.e., in the form of

this heterocyclic group may further include a heteroatom selected from among nitrogen, oxygen, and sulfur as exemplified by piperidino, morpholino, pyrrolidino, and piperazino. The lower alkylene group R<sub>12</sub> may contain 1 to 3 carbon atoms and thus may be, for example, methylene, ethylene, or trimethylene. The bond R<sub>12</sub> is equivalent to the symbol "-", ",", or the like which is used in chemical structural formulas, and when R<sub>12</sub> represents such a bond, the compound of general Formula II is represented by the following general Formula II(a)

Thus, when R<sub>12</sub> is a bond, the atoms adjacent thereto on both sides are directly combined together. As examples of the lower alkyls L<sub>1</sub> and L<sub>2</sub>, there may be mentioned lower alkyl groups of 1 to 3 carbon atoms, such as methyl and ethyl. The alkylene group formed as L<sub>1</sub> and L<sub>2</sub> are joined together is a group of the formula -(CH<sub>2</sub>)<sub>n</sub> [where n is an integer of 2 to 6]. The cycloalkyl, phenylalkyl, phenyl, and heterocyclic groups mentioned above, as well as said heterocyclic group may have 1 to 3 substituents in optional positions on the respective rings. As examples of such substituents may be mentioned lower alkyls (e.g., methyl, ethyl, etc.), lower alkoxy groups (e.g., methoxy, ethoxy, etc.), halogens (e.g., chlorine, bromine, etc.), and hydroxyl. The case also falls within the scope of the general Formula II that an alkylendioxy
group of the formula \(-O-(\text{CH}_2)_m-O-\) is an integer of 1 to 3, such as methylenedioxy, is attached to the two adjacent carbon atoms on the ring to form an additional ring.

[0047] The preferred compounds of Formula III are those wherein \(R_{15}\) and \(R_{16}\) are independently hydrogen, lower alkyl containing 1 to 6 carbon atoms, alkoxy containing 1 to 6 carbon atoms, halogen, ethynyl, nitrile, trifluoromethyl, vinyl, or nitro; \(n\) is 1 or 2 and the pharmaceutically acceptable salts thereof.

[0048] Preferred in Formula IV are compounds wherein the dotted line represents no bond, particularly wherein \(D\) is CO or CHOH. More preferred are compounds wherein \(V\) is \(-\text{CH} = \text{CH}-\), \(-\text{CH} = \text{N}-\), or \(-\text{S}-\) and \(n\) is 2, particularly those compounds wherein \(X\) is O and \(Y\) is N, X is S and \(Y\) is CH or \(X\) is \(-\text{CH} = \text{N}-\) and \(Y\) is CH. In the most preferred compounds \(X\) is O or S and \(Y\) is N forming an oxazol-4-yl, oxazol-5-yl, thiazol-4-yl, or thiazol-5-yl group; most particularly a 2-[(2-thienyl), (2-furyl), phenyl, or substituted phenyl]-5-methyl-4-oxazolyl group.

[0049] The preferred compounds in Formula V are:

- those wherein the dotted line represents no bond, \(A\) and \(B\) are each CH, \(X_1\) is CO, \(n\) is 0, \(R_{19}\) is hydrogen, \(Z_2\) is \(\text{CH}_2\text{CH}_2\) or \(\text{CH} = \text{CH}\) and \(X_3\) is hydrogen, particularly when \(X_2\) is hydrogen, 2-methoxy, 4-benzyloxy, or 4-phenyl;
- those wherein \(A\) and \(B\) are each CH, \(X_1\) is S or SO\(_2\), \(n\) is 0, \(R_{19}\) is hydrogen, \(Z_2\) is \(\text{CH}_2\text{CH}_2\) and \(X_3\) is hydrogen, particularly when \(X_2\) is hydrogen or 4-chloro.

[0050] A preferred group of compounds is that of Formula VI wherein \(R_{23}\) is (C\(_1\)-C\(_6\))alkyl, (C\(_3\)-C\(_7\))cycloalkyl, phenyl, halophenyl, or (C\(_1\)-C\(_6\))alkylphenyl. Especially preferred within this group are the compounds where \(R_{23}\) is phenyl, methylphenyl, fluoroalkyl, chloroalkyl, or cyclohexyl.

[0051] When used herein with regard to Formulas VII through X, the term "aryl" includes phenyl and naphthyl, suitably phenyl, optionally substituted with up to 5, preferably up to 3, groups selected from halogen, alkyl, phenyl, alkoxy, haloalkyl, hydroxy, amino, nitro, carboxy, alkoxy carbonyl, alkoxy carbonyl alkyl, alkyl carboxyloxy, or alkyl carboxyl groups.

[0052] The term "halogen" refers to fluorine, chlorine, bromine, and iodine; preferably chlorine.

[0053] The terms "alkyl" and "alkoxy" relate to groups having straight or branched carbon chains, containing up to 12 carbon atoms.

[0054] Suitable alkyl groups are C\(_{1-12}\) alkyl groups, especially C\(_{1-6}\) alkyl groups, e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, or tert-butyl groups.

[0055] Suitable substituents for any alkyl group include those indicated above in relation to the term "aryl".

[0056] Suitable substituents for any heterocyclyl group include up to 4 substituents selected from the group consisting of alkyl, aryl, and halogen or any 2 substituents on adjacent carbon atoms, together with the carbon atoms to which they are attached, may form an aryl group, preferably a benzene ring, and wherein the carbon atoms of the aryl group represented by the said 2 substituents may themselves be substituted or unsubstituted.

[0057] Specific examples of compounds of the present invention are given in the following list:

\[\text{(+)-5-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]-phenyl][methyl]-2,4-thiazolidinedione};\]
\[4-(2-naphthylmethyl)-1,2,3,5-oxathiazolidone-2-oxide;\]
\[5-[4-[2-[N-(benzoxazol-2-yl)-N-methylamino]-ethoxy][benzyl]-5-methylthiazolidine-2,4-dione;\]
\[5-[4-[2-[4-dioxo-5-phenylthiazolidine-3-yl]-ethoxy][benzyl]thiazolidine-2,4-dione;\]
\[5-[4-[2-N-methyl-N-(phenoxycarbonyl)amino]-ethoxy][benzyl]thiazolidine-2,4-dione;\]
\[5-[4-[2-phenoxycarbonyl]thiazolidine-2,4-dione;\]
\[5-[4-[3-(5-methyl-2-phenyloxazol-4-yl)propionyl]-benzyl]thiazolidine-2,4-dione;\]
\[5-[4-[2-(4-chlorophenyl)sulfonyl][benzyl]thiazolidine-2,4-dione;\]
\[5-[4-[3-(5-methyl-2-phenyloxazol-4-yl)propionyl]-benzyl]thiazolidine-2,4-dione.\]

[0058] As defined herein, "complications of NIDDM" is referred to as cardiovascular complications or several of the metabolic and circulatory disturbances that are associated with hyperglycemia, e.g., insulin resistance, hyperinsulinemia and/or hyperproinsulinemia, delayed insulin release, dyslipidemia, retinopathy, peripheral neuropathy, nephropathy, and hypertension.

[0059] The compounds of Formulas I through X are capable of further forming pharmaceutically acceptable base salts.

[0060] The compounds of Formulas I through X are capable of further forming both pharmaceutically acceptable acid addition and/or base salts. All of these forms are within the scope of the present invention.

[0061] Pharmaceutically acceptable acid addition salts of the compounds of Formulas I through X include salts derived from nontoxic inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, hydrofluoric, phosphorous, and the like, as well as the salts derived from nontoxic organic acids, such as alphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic
acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginine and the like and gluconate, galacturonate, n-methylglucamine (see, for example, Berge S.M., et al., "Pharmaceutical Salts," Journal of Pharmaceutical Science 1977;66:1-19).

The acid addition salts of said basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. The free base form may be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner or as above. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base for purposes of the present invention.

Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine (see, for example, Berge S.M., et al., "Pharmaceutical Salts," Journal of Pharmaceutical Science 1977;66:1-19).

The base addition salts of said acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. The free acid form may be regenerated by contacting the salt form with an acid and isolating the free acid in the conventional manner or as above. The free acid forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid for purposes of the present invention.

Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

Certain of the compounds of the present invention possess one or more chiral centers and each center may exist in different configurations. The compounds can, therefore, form stereoisomers. Although these are all represented herein by a limited number of molecular formulas, the present invention includes the use of both the individual, isolated isomers and mixtures, including racemates, thereof. Where stereospecific synthesis techniques are employed or optically active compounds are employed as starting materials in the preparation of the compounds, individual isomers may be prepared directly; on the other hand, if a mixture of isomers is prepared, the individual isomers may be obtained by conventional resolution techniques, or the mixture may be used as it is, without resolution.

Furthermore, the thiazolidene part of the compound of Formulas I through X can exist in the form of tautomeric isomers. All of the tautomers are represented by Formulas I through X, and are intended to be a part of the present invention.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For parenteral injection liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents as desired.
Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsules, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 100 mg preferably 0.5 mg to 100 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

In therapeutic use in the treatment of at risk populations such as those with impaired glucose tolerance, to prevent or delay the onset of NIDDM and complications arising therefrom, the compounds utilized in the pharmaceutical methods of this invention are administered along with a pharmaceutically acceptable carrier at the initial dosage of about 0.01 mg to about 20 mg per kilogram daily. A daily dose range of about 0.01 mg to about 10 mg per kilogram is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

The following nonlimiting examples illustrate the inventors' preferred methods for preparing the compounds of the invention.

The compounds of Formulas I through X are valuable agents in returning an individual to a state of glucose tolerance and therefore preventing or delaying the onset of NIDDM. Tests were conducted which showed that compounds of Formulas I through X possess the disclosed activity. The tests employed on the compounds of Formulas I through X were performed by the following study.

EXAMPLE 1

A study will be performed to determine the effect of troglitazone \((\pm)-5-[(4-[3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-ylmethoxy]-phenyl)methyl]-2,4-thiazolidinedione\) on insulin resistance and androgen levels in PCOS women. Since hyperandrogenism results in chronic anovulation and hirsutism, decreasing androgen levels may improve hirsutism and even restore normal ovulatory menstrual function in PCOS women. The specific aim of the study will be to determine the effects of improved insulin sensitivity and decreased insulin levels secondary to troglitazone treatment on circulating androgen and gonadotropin levels in PCOS women.

I. SUBJECTS

A. General Selection Criteria. A total of 30 women will be studied. All subjects will be in excellent health, between the ages of 18-45 years, and euthyroid. There will be no history of cardiorespiratory, hepatic, or renal dysfunction. No subject will be taking any medications known to affect reproductive hormone levels or carbohydrate metabolism for at least 1 month prior to study, with the exception of oral contraceptives, which will be discontinued 3 months prior to study. Obesity will be defined as body mass index (BMI: wt (kg)/hr\(^2\)(m) of \(\geq\)27 kg/m\(^2\), non-obese patients will have a BMI of \(\leq\)25 kg/m\(^2\).

B. Selection criteria for PCOS. The diagnosis of PCOS will require biochemically documented hyperandrogenism (serum levels of testosterone, biologically available testosterone, and/or androstenedione two standard deviations or more above the control mean), chronic anovulation (<6 menses/year or dysfunctional uterine bleeding), and polycystic ovaries present on vaginal ovarian ultrasound. These are the least controversial criteria for diagnosis for PCOS. The LH:FSH ratio and hirsutism will not be used as selection criteria. Androgen secreting tumors, Cushing's Syndrome, and late-onset congenital adrenal hyperplasia will be excluded by appropriate tests in all women.
Women with hyperprolactinemia will be excluded because of the possible effect of hyperprolacticemia on insulin sensitivity.

C. Disqualification Criteria

1. Pregnancy
2. Intercurrent medical illness
3. Hepatic or renal dysfunction
4. Hemoglobin<11 gm/dL
5. Weight <50 kg.

II. STUDY PROTOCOL

[0084]

A. Subject Preparation for All Studies. All testing will be performed during a period of documented anovulation by plasma progesterone levels in PCOS women. Subjects will consume a 55% carbohydrate, 30% fat, 15% protein weight maintaining diet for 3 days prior to testing and all testing will be done in the post-absorptive state after 10-12 hours fast.

B. Protocol

1. Visit 1 - Day 1. A complete history and physical examination will be performed and blood for a complete blood count, electrolytes, thyroid function (thyroid profile with TSH level), renal chemistries and liver function will be obtained. Blood for testosterone (T), biologically available T (uT), LH, FSH, dehydroepiandrosterone sulfate (DHEAS), androstenedione (A), sex hormone binding globulin (SHBG), estrone (E1), estradiol (E2), insulin, and C-peptide levels will be obtained. A 75 g glucose load will be ingested in the morning after a 10-12 hr fast, and glucose and insulin levels will be obtained every 30 minutes for 2 hours. All PCOS women will have fasting insulin levels $\geq 15 \mu U/mL$ and may have impaired glucose tolerance by WHO criteria. No subject, however, will have diabetes mellitus.

2. Visit 1 - Day 2. A frequently sampled intravenous glucose tolerance test (FSIGT) will be performed. Basal blood samples will be collected at -15, -10, -5, and -1 minute. Glucose (300 mg/kg) will be injected as an IV bolus at time 0 minute and tolbutamide (500 mg) will be injected at 20 minutes. Blood samples will be taken at 2, 3, 4, 5, 8, 10, 12, 14, 16, 19, 22, 23, 24, 25, 27, 30, 40, 50, 60, 70, 90, 100 minutes, and every 20 minutes thereafter until 240 minutes for glucose and insulin levels.

3. Troglitazone therapy. Troglitazone will be started after Visit 1, Day 2, when a urine pregnancy test will be documented to be negative. Troglitazone will be administered in a double-blind randomized trial of two dose levels: 200 mg/day and 400 mg/day. Subjects will be randomly assigned to one of the two daily doses of troglitazone. All women will take two pills: either two 200 mg pills or a 200 mg pill and a placebo pill. There will be 15 subjects in each of the two treatment groups. Troglitazone will be administered as a single daily dose with breakfast.

4. Visits 2 and 3. Subjects will return monthly. Blood will be obtained every 10 minutes x 3 and the plasma pooled for assay of T, uT, A, DHEAS, SHBG, E2, E1, LH, and FSH levels. Insulin and glucose levels basally and 2 hours after 75 g glucose will be determined.

5. Visit 4. The studies performed at Visit 1 will be repeated. Subjects will be instructed to return all unused supplies or empty bottles at the time of each visit to ensure compliance. Details related to patient dosage and compliance will be recorded on the case report form.
III. STATISTICAL ANALYSIS

Each subject will serve as her own control, and the data will be analyzed by paired t-test. Differences in treatment vs baseline hormone levels and parameters of insulin action will be compared between the two dose groups by unpaired t-tests. Repeated measures of analysis of variance will be performed to determine changes over time. Log transformation of the data will be performed when necessary to achieve homogeneity of variance. This is a pilot study and 15 PCOS women each will be examined at two dose levels of troglitazone.

IV. HUMAN SUBJECTS

A. Risks

1. Blood Withdrawal. All subjects will have normal a complete blood count and hemoglobin levels >11 mg/dL. No subject will have >500 mL blood drawn in 24-hour period and >1000 mL blood drawn over 12-week period.

2. FSIGT. There is a small risk of hypoglycemia during FSIGT, and the test will be terminated immediately by administration of 50% dextrose if signs or symptoms of severe hypoglycemia develop. There is a small risk of allergy to tolbutamide; the drug will not be given to any subject with a history of allergy to sulfa drugs or sulfonylureas.

3. Troglitazone. The major side effects of troglitazone are nausea, peripheral edema, and abnormal liver function. Other reported adverse events include dyspnea, headache, thirst, gastrointestinal distress, insomnia, dizziness, incoordination, confusion, fatigue, pruritus, rash, alterations in blood cell counts, changes in serum lipids, acute renal insufficiency, and dryness of the mouth. Additional symptoms that have been reported, for which the relationship to troglitazone is unknown, include palpitations, sensations of hot and cold, swelling of body parts, skin eruption, stroke, and hyperglycemia.

4. Disqualification Criteria. Subjects will be disqualified if they will develop one or more of the following: HB <11 gm/dL, wt <50 kg, abnormal hepatic or renal chemistries, hypertension, pregnancy, significant illnesses, or excessive bleeding.

### Table:

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<th>Visit 1 - Day 1</th>
<th>History Physical</th>
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<th>Pregnancy Test</th>
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<th>Hormones&lt;sup&gt;b&lt;/sup&gt;</th>
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<td>X</td>
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<td>X</td>
<td>3 months</td>
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</table>

<sup>a</sup> Chemistry - Complete blood count with differential, electrolytes, liver function, renal function, thyroid profile with TSH level

<sup>b</sup> Hormones - T, µT, LH, FSH, DHEAS, SHBG, P, A, E<sub>2</sub>, E<sub>1</sub>, insulin, C-peptide levels

Claims

1. Use of a compound of Formula I
wherein R₁ and R₂ are the same or different and each represents a hydrogen atom or a C₁-C₅ alkyl group; R³ represents a hydrogen atom, an aliphatic acyl group, an alicyclic acyl group, an aromatic acyl group, a heterocyclic acyl group, an araliphatic acyl group, a (C₁-C₅ alkoxy)carbonyl group, or an aralkyloxy carbonyl group; R⁴ and R⁵ are the same or different and each represents a hydrogen atom, a C₁-C₅ alkyl group or a C₁-C₅ alkoxy group, or R⁴ and R⁵ together represent a C₁-C₄ alkylenedioxy group; n is 1, 2, or 3; W represents the -CH₂-, >CO, or CO-OR⁶ group (in which R⁶ represents any 1 of the atoms or groups defined for R³ and may be the same as or different from R³); and Y and Z are the same or different and each represents an oxygen atom or an imino (=NH) group; and pharmaceutically acceptable salts thereof, for the manufacture of pharmaceutical compositions for the treatment of polycystic ovary syndrome.

2. Use of a compound of Formula I according to claim 1 wherein Y and Z are oxygen.

3. Use of a compound of Formula I according to claim 1 wherein W is -CH₂⁻.

4. Use of a compound of Formula I according to claim 1 wherein n is 1.

5. Use of a compound of Formula I according to claim 1 wherein R¹, R², R⁴, and R⁵ are lower alkyl and R³ is H.

6. Use of a compound of Formula I according to claim 1 wherein Z and Y are oxygen, n is 1, and W is -CH₂⁻.

7. Use of a compound of Formula I according to claim 1 which is (+)-5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl][methyl]-2,4-thiazolidinedione.

8. Use of a compound of Formula II

wherein R₁₁ is substituted or unsubstituted alkyl, alkoxy, cycloalkyl, phenylalkyl, phenyl, aromatic acyl group, a 5- or 6-membered heterocyclic group including 1 or 2 heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, or a group of the formula
In each of claims 9, 11 and 12, wherein R₁₃ and R₁₄ are the same or different and each is lower alkyl or R₁₃ and R₁₄ are combined to each other either directly or as interrupted by a heteroatom selected from the group consisting of nitrogen, oxygen, and sulfur to form a 5- or 6-membered ring;
wherein R₁₂ means a bond or a lower alkylene group; and
wherein L₁ and L₂ are the same or different and each is hydrogen or lower alkyl or L₁ and L₂ are combined to form an alkylene group, or a pharmaceutically acceptable salt thereof,
for the manufacture of pharmaceutical compositions for the treatment of polycystic ovary syndrome.

9. Use of a compound of Formula II according to claim 8, wherein the compound is selected from pioglitazone or ciglitazone.

10. Use of a compound of Formula III

wherein R₁₅ and R₁₆ are independently hydrogen, lower alkyl containing 1 to 6 carbon atoms, alkoxy containing 1 to 6 carbon atoms, halogen, ethynyl, nitrile, methylthio, trifluoromethyl, vinyl, nitro, or halogen substituted benzyloxy; n is 0 to 4 and the pharmaceutically acceptable salts thereof,
for the manufacture of pharmaceutical compositions for the treatment of polycystic ovary syndrome.

11. Use of a compound of Formula IV

wherein the dotted line represents a bond or no bond;
V is -CH=CH-, -N=CH-, -CH=N- or S;
D is CH₂, CHOH, CO, C=NOR₁₇ or CH=CH
X is S, O, NR₁₈, -CH=N- or -N=CH-;
Y is CH or N;
Z is hydrogen, (C₁-C₇) alkyl, (C₃-C₇) cycloalkyl, phenyl, naphthyl, pyridyl, furyl, thienyl, or phenyl mono- or disubstituted with the same or different groups which are (C₁-C₃) alkyl, trifluoromethyl, (C₁-C₃) alkoxy, fluoro, chloro, or bromo;
Z' is hydrogen or (C₁-C₃)alkyl;
R₁₇ and R₁₈ are each independently hydrogen or methyl; and n is 1, 2, or 3; or
the pharmaceutically acceptable cationic salts thereof;
and the pharmaceutically acceptable acid addition salts thereof when the compound contains a basic nitrogen, for the manufacture of pharmaceutical compositions for the treatment of polycystic ovary syndrome.

12. Use of a compound of Formula V

wherein the dotted line represents a bond or no bond;
A and B are each independently CH or N, with the proviso that when A or B is N, the other is CH;
X₁ is S, SO, SO₂, CH₂, CHOH, or CO;
n is 0 or 1;
Y₁ is CHR₂₀ or NR₂₁, with the proviso that when n is 1 and Y₁ is NR₂₁, X₁ is SO₂ or CO;
Z₂ is CHR₂₂, CH₂CH₂, CH=CH,

OCH₂, SCH₂, SOCH₂ or SO₂CH₂;
R₁₉, R₂₀, R₂₁ and R₂₂ are each independently hydrogen or methyl; and
X₂ and X₃ are each independently hydrogen, methyl, trifluoromethyl, phenyl, benzyl, hydroxy, methoxy, phe-noxy, benzyloxy, bromo, chloro, or fluoro, or a pharmaceutically acceptable cationic salt thereof; or
a pharmaceutically acceptable acid addition salt thereof when A or B is N,
for the manufacture of pharmaceutical compositions for the treatment of polycystic ovary syndrome.

13. Use of a compound of Formula VI
or a pharmaceutically acceptable salt thereof
wherein $R_{23}$ is alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, phenyl, or mono- or disubstituted phenyl wherein said substituents are independently alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 3 carbon atoms, halogen, or trifluoromethyl, for the manufacture of pharmaceutical compositions for the treatment of polycystic ovary syndrome.

14. Use of a compound of Formula VII

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:

$A_2$ represents an alkyl group, a substituted or unsubstituted aryl group, or an aralkyl group wherein the alkylene or the aryl moiety may be substituted or unsubstituted;

$A_3$ represents a benzene ring having in total up to 3 optional substituents;

$R_{24}$ represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group wherein the alkyl, or the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group; or $A_2$ together with $R_{24}$ represents substituted or unsubstituted $C_{2-3}$ polymethylene group, optional substituents for the polymethylene group being selected from alkyl or aryl or adjacent substituents together with the methylene carbon atoms to which they are attached form a substituted or unsubstituted phenylene group;

$R_{25}$ and $R_{26}$ each represent hydrogen, or $R_{25}$ and $R_{26}$ together represent a bond;

$X_4$ represents O or S; and

$n$ represents an integer in the range of from 2 to 6,

for the manufacture of pharmaceutical compositions for the treatment of polycystic ovary syndrome.

15. Use of a compound of Formula VIII
or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:

R27 and R28 each independently represent an alkyl group, a substituted or unsubstituted aryl group, or an aralkyl group being substituted or unsubstituted in the aryl or alkyl moiety; or R27 together with R28 represents a linking group, the linking group consisting of an optionally substituted methylene group and either a further optionally substituted methylene group or an O or S atom, optional substituents for the said methylene groups being selected from alkyl, aryl, or aralkyl, or substituents of adjacent methylene groups together with the carbon atoms to which they are attached form a substituted or unsubstituted phenylene group; 

R29 and R30 each represent hydrogen; or R29 and R30 together represent a bond;

A4 represents a benzene ring having in total up to 3 optional substituents;

X5 represents O or S; and 
n represents an integer in the range of from 2 to 6,

for the manufacture of pharmaceutical compositions for the treatment of polycystic ovary syndrome.

16. Use of a compound of Formula IX

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:

A5 represents a substituted or unsubstituted aromatic heterocyclyl group;

A6 represents a benzene ring having in total up to 5 substituents;

X6 represents O, S, or NR32 wherein R32 represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;

Y2 represents O or S;

R31 represents an alkyl, aralkyl, or aryl group; and 
n represents an integer in the range of from 2 to 6,

for the manufacture of pharmaceutical compositions for the treatment of polycystic ovary syndrome.

17. Use of a compound of Formula X
or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically
acceptable solvate thereof, wherein:
A7 represents a substituted or unsubstituted aryl group;
A8 represents a benzene ring having in total up to 5 substituents;
X8 represents O, S, or NR₃⁹ wherein R₃⁹ represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl
group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl
group;
Y₃ represents O or S;
R₃⁷ represents hydrogen;
R₃₈ represents hydrogen or an alkyl, aralkyl, or aryl group or R₃⁷ together with R₃₈ represents a bond; and n
represents an integer in the range of from 2 to 6,
for the manufacture of pharmaceutical compositions for the treatment of polycystic ovary syndrome.

Patentansprüche

1. Verwendung einer Verbindung der Formel I

   \[
   \begin{align*}
   &R^1 und R^2 sind gleich oder verschieden und jedes davon steht für ein Wasserstoffatom oder einen C₁⁻C₅⁻Alkyl-
   \end{align*}
   \]

   \[
   \begin{align*}
   &rest; \\
   &R² steht für ein Wasserstoffatom, einen aliphatischen C₁⁻C₆⁻Acyrest, einen alicyclischen Acyrest, einen aroma-
   \end{align*}
   \]

   \[
   \begin{align*}
   &tischen Acyrest, einen heterocyclischen Acyrest, einen araliphatischen Acyrest, einen (C₁⁻C₆⁻Alkoxy)car-
   \end{align*}
   \]

   \[
   \begin{align*}
   &bonyrest oder einen Aralkyloxycarbonyrest; \\
   &R³ und R⁵ sind gleich oder verschieden und jedes davon steht für ein Wasserstoffatom, einen C₁⁻C₅⁻Acyrest \\
   \end{align*}
   \]

   \[
   \begin{align*}
   &oder einen C₁⁻C₆⁻Alkoxyrest, oder R³ und R⁵ stehen zusammen für einen C₁⁻C₄⁻Alkyldioxyrest; \\
   &n ist gleich 1, 2 oder 3; \\
   &W steht für den Rest -CH₂-, >CO oder CO-OR⁶ (in welchem R⁶ für jedwelches der für R³ definierten Atome \\
   \end{align*}
   \]

   \[
   \begin{align*}
   &und Reste steht und gleich wie oder verschieden von R³ sein kann); und \\
   &Y und Z sind gleich oder verschieden und jedes davon steht für ein Sauerstoffatom oder einen Iminorest \\
   \end{align*}
   \]

   \[
   \begin{align*}
   & (=NH); \\
   &sowie pharmazeutisch annehmbarer Salze davon, \\
   \end{align*}
   \]

   zur Herstellung von Arzneimittelzusammensetzungen zur Behandlung des ovarianen polyzystischen Syn-
2. Verwendung einer Verbindung der Formel I nach Anspruch 1, worin Y und Z für Sauerstoff stehen.

3. Verwendung einer Verbindung der Formel I nach Anspruch 1, worin W für -CH₂- steht.

4. Verwendung einer Verbindung der Formel I nach Anspruch 1, worin n gleich 1 ist.

5. Verwendung einer Verbindung der Formel I nach Anspruch 1, worin R₁, R², R⁴ und R⁵ für Niederalkyl stehen und R³ für H steht.

6. Verwendung einer Verbindung der Formel I nach Anspruch 1, worin Y und Z für Sauerstoff stehen, n gleich 1 ist und W für -CH₂- steht.

7. Verwendung einer Verbindung der Formel I nach Anspruch 1, welche (+)-5-[(4-[(3,4-Dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl)methyl]-2,4-thiazolidindion ist.

8. Verwendung einer Verbindung der Formel II

![Chemical Structure Image]

worin gilt:

R₁₁ steht für einen substituierten oder unsubstituierten Rest Alkyl, Alkoxy, Cycloalkyl, Phenylalkyl, Phenyl oder aromatisches Acyl, einen heterocyclischen Rest aus 5 oder 6 Elementen einschließlich 1 oder 2 aus der von Stickstoff, Sauerstoff und Schwefel gebildeten Gruppe ausgewählter Heteroatome, oder für einen Rest der Formel worin gilt:

![Chemical Structure Image]

R₁₃ und R₁₄ sind gleich oder verschieden und jedes davon steht für Niederalkyl, oder R₁₃ und R₁₄ sind miteinander zur Bildung eines aus 5 oder 6 Elementen bestehenden Ringes, entweder unmittelbar oder durch ein aus der von Stickstoff, Sauerstoff und Schwefel gebildeten Gruppe ausgewähltes Heteroatom getrennt, kombiniert;

R₁₂ steht für eine Bindung oder einen Niederalkylenrest; und

L₁ und L₂ sind gleich oder verschieden und jedes davon steht für Wasserstoff oder Niederalkyl, oder L₁ und L₂ sind zur Bildung eines Alkylenrests kombiniert;

sowie pharmazeutisch annehmbarer Salze davon,
zur Herstellung von Arzneimittelzusammensetzungen zur Behandlung des ovarialen polyzystischen Syndroms.

10. Verwendung einer Verbindung der Formel III

![Chemical Structure](image)

worin gilt:

- $R_{15}$ und $R_{16}$ stehen unabhängig voneinander für Wasserstoff, Niederalkyl mit 1 bis 6 Kohlenstoffatomen, Alkoxy mit 1 bis 6 Kohlenstoffatomen, Halogen, Ethynyl, Nitril, Methylthio, Trifluormethyl, Vinyl, Nitro oder mit Halogen substituiertes Benzyloxy;
- $n$ ist gleich 1 bis 4;
- sowie der pharmazeutisch annehmbaren Salze davon,
- zur Herstellung von Arzneimittelzusammensetzungen zur Behandlung des ovarialen polyzystischen Syndroms.

11. Verwendung einer Verbindung der Formel IV

![Chemical Structure](image)

worin gilt:

- die gestrichelte Linie steht für eine oder keine Bindung;
- $V$ steht für -CH=CH-, -N=CH-, -CH=N- oder S;
- $D$ steht für CH₂, CHOH, CO, C=NOR₁₇ oder CH=CH;
- $X$ steht für S, O, NR₁₈, -CH=N- oder -N=CH-;
- $Y$ steht für CH oder N;
- $Z$ steht für Wasserstoff, (C₁-C₇)-Alkyl, (C₃-C₇)-Cycloalkyl, Phenyl, Naphthyl, Pyridyl, Furyl, Thiényl oder mit gleichen oder verschiedenen aus (C₁-C₇)-Alkyl, Trifluormethyl, (C₁-C₃)-Alkoxy, Fluor, Chlor oder Brom bestehenden Resten mono- oder disubstituiertes Phenyl;
- $Z'$ steht für Wasserstoff oder (C₁-C₃)-Alkyl;
- $R_{17}$ und $R_{18}$ stehen unabhängig voneinander für Wasserstoff oder Methyl; und
- $n$ ist gleich 1, 2 oder 3;
- sowie pharmazeutisch annehmbarer cationischer Salze davon,
- sowie der pharmazeutisch annehmbaren Säureadditionssalze davon, wenn die Verbindung ein basisches Stickstoff enthält,
zur Herstellung von Arzneimittelzusammensetzungen zur Behandlung des ovarialen polyzystischen Syndroms.

12. Verwendung einer Verbindung der Formel V

\[ \text{V} \]

worin gilt:

- die gestrichelte Linie steht für eine oder keine Bindung;
- A und B stehen unabhängig voneinander für CH oder N mit der Massgabe, dass, wenn A oder B für N steht, das andere für CH steht;
- \( X_1 \) steht für S, SO, SO₂, CH₂, CHO oder CO;
- \( n \) ist gleich 0 oder 1;
- \( Y_1 \) steht für \( \text{CHR}_{20} \) oder \( \text{NR}_{21} \) mit der Massgabe, dass, wenn \( n \) gleich 1 ist und \( Y_1 \) für \( \text{NR}_{21} \) steht, \( X_1 \) für SO₂ oder CO steht;
- \( Z_2 \) steht für \( \text{CHR}_{22} \), \( \text{CH₂CH₂} \), CH=CH,
- \( \text{OCH₂, SCH₂, SOCH₂ oder SO₂CH₂} \);
- \( R_{19}, R_{20}, R_{21} \) und \( R_{22} \) stehen unabhängig voneinander für Wasserstoff oder Methyl; und
- \( X_2 \) und \( X_3 \) stehen unabhängig voneinander für Wasserstoff, Methyl, Trifluormethyl, Phenyl, Benzyl, Hydroxy, Methoxy, Phenoxy, Benzylxoy, Brom, Chlor oder Fluor;
- sowie eines pharmazeutisch annehmbaren cationischen Salzes davon, oder eines pharmazeutisch annehmbaren Säureadditionssalzes davon, wenn A oder B für N steht,
- zur Herstellung von Arzneimittelzusammensetzungen zur Behandlung des ovarialen polyzystischen Syndroms.

13. Verwendung einer Verbindung der Formel VI

\[ \text{VI} \]

oder eines pharmazeutisch annehmbaren Salzes davon,
worin gilt:
$R_{23}$ steht für Alkyl mit 1 bis 6 Kohlenstoffatomen, Cycloalkyl mit 3 bis 7 Kohlenstoffatomen, Phenyl oder mono- oder disubstituiertes Phenyl, wobei die Substituenten unabhängig voneinander aus Alkyl mit 1 bis 6 Kohlenstoffatomen, Alkoxy mit 1 bis 3 Kohlenstoffatomen, Halogen oder Trifluormethyl bestehen,
zur Herstellung von Arzneimittelzusammensetzungen zur Behandlung des ovarialen polyzystischen Syndroms.

14. Verwendung einer Verbindung der Formel VII

oder einer tautomeren Form davon und/oder eines pharmazeutisch annehmbaren Salzes davon und/oder eines pharmazeutisch annehmbaren Solvats davon,
worin gilt:
$A_2$ steht für einen Alkylrest, einen substituierten oder unsubstituierten Arylrest oder einen Aralkylrest, bei welchem der Alkyl- oder Aryl-Molekülteil substituiert oder unsubstituiert sein kann;
$A_3$ steht für einen Benzolring mit wahlweise bis zu gesamthaft 3 Substituenten;
$R_{24}$ steht für ein Wasserstoffatom, einen Alkylrest, einen Acylrest, einen Aralkylrest, bei welchem der Alkyl- oder Aryl-Molekülteil substituiert oder unsubstituiert sein kann, oder für einen substituierten oder unsubstituierten Arylrest; oder $A_2$ und $R_{24}$ stehen zusammen für einen substituierten oder unsubstituierten C-2-3-Polyethylenrest, wobei Substituenten des Polyethylenrests unter Alkyl oder Aryl ausgewählt sein können; oder es bilden benachbarte Substituenten zusammen mit den Methylen-Kohlenstoffatomen, mit denen sie verbunden sind, einen substituierten oder unsubstituierten Polyphenylenrest;
$R_{25}$ und $R_{26}$ stehen für je ein Wasserstoffatom, oder $R_{25}$ und $R_{26}$ stehen zusammen für eine Bindung;
$X_4$ steht für O oder S; und
$n$ steht für eine natürliche Zahl im Bereich von 2 bis 6;
zur Herstellung von Arzneimittelzusammensetzungen zur Behandlung des ovarialen polyzystischen Syndroms.

15. Verwendung einer Verbindung der Formel VIII

oder einer tautomeren Form davon und/oder eines pharmazeutisch annehmbaren Salzes davon und/oder eines pharmazeutisch annehmbaren Solvats davon,
worin gilt:
R_{27} und R_{28} stehen unabhängig voneinander für einen Alkylrest, einen substituierten oder unsubstituierten Arylrest oder einen Aralkylrest, bei welchem der Aryl- oder Alkyl-Molekülteil substituiert oder unsubstituiert sein kann; oder R_{27} und R_{28} stehen zusammen für einen Bindungsrest, wobei der Bindungsrest aus einem wahlweise substituierten Methylenrest und entweder einem weiteren wahlweise substituierten Methylenrest oder einem S- oder O-Atom besteht, Substituenten der genannten Methylenreste unter Alkyl, Aryl oder Aralkyl ausgewählt sein können, oder Substituenten von benachbarten Methylenresten zusammen mit den Kohlenstoffatomen, mit denen sie verbunden sind, einen substituierten oder unsubstituierten Phenylenrest bilden; R_{29} und R_{30} stehen für je ein Wasserstoffatom, oder R_{29} und R_{30} stehen zusammen für eine Bindung; A_4 steht für einen Benzolring mit wahlweise bis zu gesamthaft 3 Substituenten;
X_5 steht für O oder S; und
n steht für eine natürliche Zahl im Bereich von 2 bis 6;
zur Herstellung von Arzneimittelzusammensetzungen zur Behandlung des ovarialen polyzystischen Syndroms.

16. Verwendung einer Verbindung der Formel IX

oder einer tautomeren Form davon und/oder eines pharmazeutisch annehmbaren Salzes davon und/oder eines pharmazeutisch annehmbaren Solvats davon, worin gilt:
A_5 steht für einen substituierten oder unsubstituierten aromatischen heterocyclischen Rest;
X_6 steht für O, S oder NR_{32}, wobei R_{32} für ein Wasserstoffatom, einen Alkylrest, einen Acylrest, einen Aralkylrest, bei welchem der Aryl-Molekülteil substituiert oder unsubstituiert sein kann, oder für einen substituierten oder unsubstituierten Arylrest steht;
Y_2 steht für O oder S;
R_{31} steht für einen Alkyl-, Aralkyl- oder Arylrest; und
n steht für eine natürliche Zahl im Bereich von 2 bis 6;
zur Herstellung von Arzneimittelzusammensetzungen zur Behandlung des ovarialen polyzystischen Syndroms.

17. Verwendung einer Verbindung der Formel X
oder einer tautomeren Form davon und/oder eines pharmazeutisch annehmbaren Salzes davon und/oder eines pharmazeutisch annehmbaren Solvats davon, worin gilt:

$A_7$ steht für einen substituierten oder unsubstituierten Arylrest;

$A_8$ steht für einen Benzolring mit wahlweise bis zu gesamthaft 5 Substituenten;

$X_8$ steht für $O$, $S$ oder $NR_3$, wobei $R_3$ für ein Wasserstoffatom, einen Alkylrest, einen Acylrest, einen Aralkylrest, bei welchem der Aryl-Molekülteil substituiert oder unsubstituiert sein kann, oder für einen substituierten oder unsubstituierten Arylrest steht;

$Y_3$ steht für $O$ oder $S$;

$R_{37}$ steht für Wasserstoff;

$R_{38}$ steht für Wasserstoff oder einen Alkyl-, Aralkyl- oder Arylrest, oder $R_{37}$ und $R_{38}$ stehen zusammen für eine Bindung; und

$n$ steht für eine natürliche Zahl im Bereich von 2 bis 6; zur Herstellung von Arzneimittelzusammensetzungen zur Behandlung des ovarialen polyzystischen Syndroms.

**Revendications**

1. L'utilisation d'un composé de formule I

\[
\begin{align*}
\text{Rang} & \quad \text{Description} \\
1 & \quad \text{Rang 1 et Rang 2 sont identiques ou différents et représentent chacun un atome d'hydrogène ou un groupe alkyle en C}_{1}\text{-C}_{5} ; \\
2 & \quad \text{Rang 3 représente un atome d'hydrogène, un groupe acyle aliphatique en C}_{1}\text{-C}_{6}, \text{un groupe acyle alicyclique, un groupe acyle aromatique, un groupe acyle hétérocyclique, un groupe acyle araliphatique, un groupe (C}_{1}\text{-C}_{6} \text{ alcoxy)carbonyle ou un groupe aralkyloxycarbonyle ;} \\
3 & \quad \text{Rang 4 et Rang 5 sont identiques ou différents et représentent chacun un atome d'hydrogène, un groupe alkyle en C}_{1}\text{-C}_{5} \text{ ou un groupe alcoxy en C}_{1}\text{-C}_{5} \text{ ou bien Rang 4 et Rang 5 forment ensemble un groupe alkylénedioxy en C}_{1}\text{-C}_{4} ; n vaut 1, 2 ou 3. W représente un groupe -CH}_{2}\text{-, »CO, ou CO-OR}_{6} ; (où R}_{6} \text{ représente n'importe lequel des atomes ou groupes définis à propos de R}_{3} \text{ et peuvent être identiques ou différents de R}_{3} ; et} \\
4 & \quad \text{Y et Z sont identiques ou différents et représentent chacun un atome d'oxygène ou un groupe imino (=NH) ; ainsi que leurs sels pharmaceutiquement acceptables, pour la fabrication de compositions pharmaceutiques pour le traitement du syndrome de la polykystose ovarienne.}
\end{align*}
\]

2. L'utilisation d'un composé de formule I selon la revendication 1, dans lequel Y et Z sont l'oxygène.

3. L'utilisation d'un composé de formule I selon la revendication 1, dans lequel W est -CH}_{2}-. 

4. L'utilisation d'un composé de formule I selon la revendication 1, dans lequel n vaut 1.

5. L'utilisation d'un composé de formule I selon la revendication 1, dans lequel R}_{1}, R}_{2}, R}_{4} et R}_{5} sont des alkyles inférieurs et R}_{3} est H.

6. L'utilisation d'un composé de formule I selon la revendication 1, dans lequel Z et Y sont de l'oxygène, n vaut 1 et W est -CH}_{2}-. 

7. L'utilisation d'un composé de formule I selon la revendication 1, qui est la (+)-5-[[4-[3,4-dihydro-6-hydroxy-2,5,7,8-tétraméthyl-2H-1-benzopyran-2-y][méthoxy]phényl][méthyl]-2,4-thiazolidinedione.

8. L'utilisation d'un composé de formule II

\[
\begin{align*}
\text{II} & \\
\text{R}_{11} & \\
\text{R}_{12} & \\
\text{R}_{13} & \\
\text{R}_{14} & \\
\text{L}_1 & \\
\text{L}_2 & \\
\end{align*}
\]

dans laquelle \( R_{11} \) est un groupe substitué ou non substitué alkyle, alcoxy, cycloalkyle, phénylalkyle, phényle, aromatique acyle, ou un groupe hétérocyclique à 5 ou 6 éléments comportant 1 ou 2 hétéroatomes choisis dans le groupe consistant en azote, oxygène et soufre, ou un groupe de formule :

\[
\begin{align*}
\text{R}_{13} & \\
\text{R}_{14} & \\
\end{align*}
\]

où \( R_{13} \) et \( R_{14} \) identiques ou différents sont chacun un alkyle inférieur ou bien \( R_{13} \) et \( R_{14} \) se combinent ensemble soit directement soit par l'intermédiaire d'un hétéroatome choisi dans le groupe consistant en azote, oxygène et soufre pour former un cycle à 5 ou 6 éléments ; où \( R_{12} \) représente une liaison ou un groupe alkylène inférieur et ; où \( L_1 \) et \( L_2 \), identiques ou différents, représentent chacun un hydrogène ou un alkyle inférieur ou bien \( L_1 \) et \( L_2 \) se combinent pour former un groupe alkylène, ou bien un de leurs sels pharmaceutiquement acceptables, pour la fabrication de compositions pharmaceutiques pour le traitement du syndrome de la polykystose ovarienne.

9. L'utilisation d'un composé de formule II selon la revendication 8, dans lequel le composé est choisi parmi la pioglitazone ou la ciglitazone.

10. L'utilisation d'un composé de formule III

\[
\begin{align*}
\text{III} & \\
\text{R}_{15} & \\
\text{R}_{16} & \\
\end{align*}
\]

dans laquelle \( R_{15} \) et \( R_{16} \) sont indépendamment un hydrogène, un alkyl inférieur comportant 1 à 6 atomes de
carbone, un alcoxy comportant 1 à 6 atomes de carbone, un halogène, un éthynyle, un nitrile, un méthylthio,
un trifluorométhyle, un vinyle, un nitro ou un benzylxoy halogéné ;
n vaut 0 à 4 ainsi que leurs sels pharmaceutiquement acceptables, pour la fabrication de compositions phar-
maceutiques pour le traitement du syndrome de la polykystose ovarienne.

11. L'utilisation d'un composé de formule IV

\[
\text{IV}
\]

dans laquelle le trait en pointillé représente une liaison ou une absence de liaison ;
V est -CH=CH-, -N=CH-, -CH=N- ou S ;
D est CH₂, CHOH, CO, C=NR₁₇ ou CH=CH ;
X est S, O, N₂⁺ ou S⁺-CH=CH⁺ ;
Z est CH ou N ;
Z' est un hydrogène ou un alkyle (en C₁-C₇), un cycloalkyle (en C₃-C₇), phényle, naphthyle, pyridyle, furyle, thié-
nyle, ou phényl, mono ou disubstitué avec des groupes identiques ou différents qui sont des alkyles (en C₃-
C₇), trifluorométhyle, alcoxy (en C₁-C₃), fluoro, chloro ou bromo ;
Z' est un hydrogène ou un alkyle (en C₁-C₃) ;
R₁₇ et R₁₈ sont chacun indépendamment un hydrogène ou un méthyle ; et n vaut 0, 1 ou 3 ; ou bien
leurs sels cationiques pharmaceutiquement acceptables ; ainsi que leurs sels d'addition d'acide pharmaceuti-
quement acceptables lorsque le composé contient un azote basique, pour la fabrication de compositions phar-
maceutiques pour le traitement du syndrome de la polykystose ovarienne.

12. L'utilisation d'un composé de formule V

\[
\text{V}
\]

dans laquelle le trait en pointillé représente une liaison ou une absence de liaison ;
A et B sont chacun indépendamment CH ou N, avec cette condition que si A ou B est N, l'autre est un CH ;
X₁ est S, SO, SO₂, CHO ou CO ; n vaut 0 ou 1 ;
Y₁ est CHR₂₀ ou NR₂₁, avec cette condition que si n vaut 1 et Y₁ est
NR₂₁, X₁ est SO₂ ou CO ;
Z₂ est CHR₂₂, CH₂CH₂, CH=CH,
OCH₂, SCH₂, SOCH₂ ou SO₂CH₂ ;
R₁₉, R₂₀, R₂₁ et R₂₂ sont chacun indépendamment un hydrogène ou un méthyle ; et
X₂ et X₃ sont chacun indépendamment un hydrogène, un méthyle, un trifluorométhyle, un phényle, un benzyle,
un hydroxy, un méthoxy, un phénoxy, un benzyl, un chlore, un fluor ou un de leurs sels cationiques pharmaceutiquement acceptables ou bien un sel d’addition d’acide pharmaceutiquement acceptables
quand A ou B est N,
pour la fabrication d’une composition pharmaceutique pour le traitement du syndrome de la polykystose ovarienne.

13. L’utilisation d’un composé de formule VI

ou d’un de ses sels pharmaceutiquement acceptables où R₂₃ est un alkyle comportant 1 à 6 atomes de carbone, cycloalkyle comportant de 3 à 7 atomes de carbone, phényle, ou phényle mono- ou disubstitué où les-dits substituants sont indépendamment un alkyle de 1 à 6 atomes de carbone, un alcoxy de 1 à 3 atomes de carbone, halogène ou trifluorométhyle, pour la fabrication de compositions pharmaceutiques pour le traitement du syndrome de la polykystose ovarienne.

14. L’utilisation d’un composé selon la formule VII

ou de ses formes tautomères et/ou un de ses sels pharmaceutiquement acceptables, et/ou un de ses produits de solvatation pharmaceutiquement acceptables, dans lesquels :
A₂ représente un groupe alkyle, un groupe aryle substitué ou non substitué, ou un groupe aralkyle, où les résidus alkylène ou aryle peuvent être substitués ou non substitués ;
A₃ représente un cycle benzénique comportant au total jusqu’à 3 substituants éventuels ;
R₂₄ représente un atome d’hydrogène, un groupe alkyle, un groupe acyle, un groupe aralkyle dont le reste alkyle ou le reste aryle peut être substitué ou non substitué, ou bien un groupe aryle substitué ou non substitué ;
ou bien A₂ avec R₂₄ représente un groupe polyméthylène en C₂-3 substitué ou non substitué, les substituants éventuels du groupe polyméthylène étant choisis parmi alkyle ou aryle où les substituants adjacents forment ensemble avec le carbone du méthylène auquel ils sont fixés un groupe phénylène substitué ou non substitué ;
R_{25} et R_{26}, représentent chacun un hydrogène ou bien R_{25} et R_{26} représentent ensemble une liaison ;
X_4 représente O ou S ; et
n représente un entier dans la fourchette de 2 à 6, pour la fabrication de compositions pharmaceutiques pour
le traitement du syndrome de la polykystose ovarienne.

15. L'utilisation d'un composé de formule VIII

![Formule VIII](image)

ou une de ses formes tautomères et/ou un de ses sels pharmaceutiquement acceptables et/ou un de ses pro-
duits de solvation pharmaceutiquement acceptables, dans lesquels :
R_{27} et R_{28} représentent indépendamment chacun un groupe alkyle, un groupe aryle substitué ou non substi-
tué, ou un groupe aralkyle substitué ou non substitué sur le résidu aryle ou alkyle ; ou bien R_{27} associé à R_{28}
représente un groupe de liaison, le groupe de liaison consistant en un groupe méthylène éventuellement substi-
tué et soit un groupe méthylène éventuellement encore substitué ou un atome de O ou de S, les substituants
evolutifs desdits groupes méthylène étant choisis parmi alkyle, aryle ou aralkyle ou bien les substituants de
groupes méthylène adjacents avec les atomes de carbone auxquels ils sont fixés forment un groupe phény-
lène substitué ou non substitué ;
R_{29} et R_{30} représentent chacun un hydrogène ou bien R_{29} et R_{30} représentent ensemble une liaison ;
A_4 représente un cycle benzénique ayant au total jusqu'à 3 substituants éventuels ;
X_5 représente O ou S ; et
n représente un entier dans la fourchette de 2 à 6, pour la fabrication de compositions pharmaceutiques pour
le traitement du syndrome de la polykystose ovarienne.

16. L'utilisation d'un composé de formule IX

![Formule IX](image)

ou une de ses formes tautomères et/ou un de ses sels pharmaceutiquement acceptables, et/ou un de ses pro-
duits de solvation pharmaceutiquement acceptables, dans lesquels :
A_5 représente un groupe aromatique, hétérocyclique substitué ou non substitué ;
A_6 représente un cycle benzénique comportant au total jusqu'à 5 substituants
X_6 représente O, S ou NR_{32}, R_{32} représentant un atome d'hydrogène, un groupe alkyle, un groupe acyle, un
groupe aralkyle dont le reste aryle peut être substitué ou non substitué ou un groupe aryle substitué ou non
substitué ;
Y_2 représente O ou S ;
R_{31} représente un groupe alkyle, aralkyle ou aryle ; et
n représente un entier dans la fourchette de 2 à 6 ; pour la fabrication d'une composition pharmaceutique pour
le traitement du syndrome de la polykystose ovarienne.
17. L'utilisation d'un composé de formule X ;

ou une de ses formes tautomères et/ou un de ses sels pharmaceutiquement acceptables et/ou un de ses produits de solvatation pharmaceutiquement acceptables dans lesquels ;
A7 représente un groupe aryle substitué ou non substitué ;
A8 représente un cycle benzénique ayant au total jusqu'à 5 substituants ;
X8 représente O, S ou NR39 où R39 représente un atome d'hydrogène, un groupe alkyle, un groupe acyle, un groupe aralkyle dont le reste aryle peut être substitué ou non substitué, ou bien un groupe aryle substitué ou non substitué ;
Y3 représente O ou S ;
R37 représente l'hydrogène ;
R38 représente l'hydrogène ou un groupe alkyle, aralkyle ou aryle ou bien R37 avec R38 représente une liaison ; et n représente un nombre entier dans la fourchette de 2 à 6, pour la fabrication d'une composition pharmaceutiquement pour le traitement du syndrome de la polykystose ovarienne.