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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO  
DIVISION DE NUEVAS CREACIONES

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S.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-089738-00003-0000

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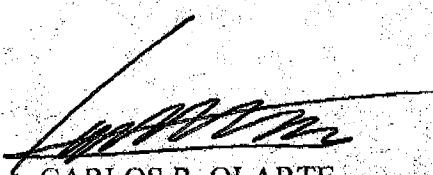
Solicitante: MERCK & CO. INC.

Nuestra Ref.: P2007/000138

**SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN**  
**EL ARTÍCULO 44 DE LA DECISION 486, GACETA No. 597**

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado tal como aparece al pie de mi firma, en mi condición de apoderado, respetuosamente me permito solicitar que se examine si la invención reúne los requisitos de patentabilidad previstos en la misma, dando cumplimiento a lo establecido en el artículo 44 de la Decisión 486 de la comisión de la Comunidad Andina. Adjunto recibo por el monto de \$420.000 pesos para cubrir la tasa correspondiente, según la Resolución 44372 del año 2007.

Atentamente,

  
CARLOS R. OLARTE  
C.C. 79.782.747 de Bogotá  
T.P. 74.295

Anexo: Recibo por \$420.000 pesos

**DIVISIÓN DE NUEVAS CREACIONES**

**RADICACIÓN EXPEDIENTE No. 07-89738**

**EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION**

**FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 597 DE**

**FECHA 31 DE OCTUBRE DE 2008 EL TÉRMINO HÁBIL SEÑALADO POR LA**

**LEY EXPIRA EL 02 DE FEBRERO DE 2009**

**NOTA:** Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

**SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.**

**SI** \_\_\_\_\_

**NO** \_\_\_\_\_ **X** \_\_\_\_\_

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WO 01/60807 A1

(54) Title: ARYLOXYACETIC ACIDS FOR DIABETES AND LIPID DISORDERS

(57) Abstract: A class of aryloxyacetic acids comprises compounds that are potent agonists of PPAR alpha and/or gamma, and are therefore useful in the treatment, control or prevention of non-insulin dependent diabetes mellitus (NIDDM), hyperglycemia, dyslipidemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, atherosclerosis, obesity, vascular restenosis, inflammation, and other PPAR alpha and/or gamma mediated diseases, disorders and conditions.

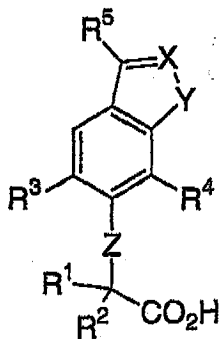
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levels. PPAR $\gamma$  agonists should improve insulin sensitivity, reducing the need for insulin injections in patients with NIDDM. The role of PPAR $\delta$  is less well defined.

#### SUMMARY OF THE INVENTION

- 5           The class of compounds described herein is a new class of PPAR agonists that do not contain a 1,3-thiazolidinedione moiety and therefore are not glitazones. The class of compounds includes compounds that are primarily PPAR $\alpha$  agonists and compounds that are mixed PPAR $\alpha/\gamma$  agonists. These compounds are useful in the treatment, control and/or prevention of diabetes, hyperglycemia, mixed  
10 or diabetic dyslipidemia, and other lipid disorders (including isolated hypercholesterolemia as manifested by elevations in LDL-C and/or non-HDL-C and/or hyperapoproteinemia, hypertriglyceridemia and/or increase in triglyceride-rich-lipoproteins, or low HDL cholesterol concentrations), atherosclerosis, obesity, vascular restenosis, inflammatory conditions, neoplastic conditions, and other PPAR $\alpha$   
15 and/or  $\gamma$  mediated diseases, disorders and conditions.

The present invention provides compounds having the structure of Formula I, including pharmaceutically acceptable salts and prodrugs of these compounds:



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I

In the compounds of Formula I:

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R<sup>1</sup> and R<sup>2</sup> are each independently selected from the group consisting of H, F, C<sub>1-5</sub> alkyl, C<sub>2-5</sub> alkenyl, and C<sub>2-5</sub> alkynyl, wherein said alkyl, alkenyl, and alkynyl may be linear or branched and are optionally substituted with 1-3 halogen atoms; or optionally R<sup>1</sup> and R<sup>2</sup> together form a C<sub>3-6</sub> cycloalkyl;

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R<sup>3</sup> and R<sup>4</sup> are each independently selected from the group consisting of C<sub>1-5</sub> alkyl, C<sub>2-5</sub> alkenyl, C<sub>2-5</sub> alkynyl, and chlorine, provided that R<sup>3</sup> and R<sup>4</sup> are not both chlorine, wherein said alkyl, alkenyl, and alkynyl groups may be linear or branched and are optionally substituted with 1-5 fluorine atoms;

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X is N or CR;

Y is O, S, or NR;

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Z is O or S;

Each R group is selected from the group consisting of H, C<sub>1-5</sub> alkyl, C<sub>2-5</sub> alkenyl, and C<sub>2-5</sub> alkynyl, wherein said alkyl, alkenyl, and alkynyl may be linear or branched and are optionally substituted with 1-5 fluorine atoms and/or one -OC<sub>1-3</sub> alkyl, said -OC<sub>1-3</sub> alkyl being optionally substituted with 1-7 fluorine atoms; and

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R<sup>5</sup> is selected from the group consisting of H, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>6-10</sub> Aryl, -OC<sub>1-6</sub> alkyl, -OC<sub>2-6</sub> alkenyl, -OC<sub>2-6</sub> alkynyl, -OC<sub>6-10</sub> Aryl, C<sub>3-6</sub> Cycloalkyl, 5-6-membered Heterocyclyl, 5-6-membered Heteroaryl, -OC<sub>3-6</sub> Cycloalkyl, -O 5-6-membered Heterocyclyl, -O 5-6 membered Heteroaryl, and a C<sub>1-4</sub> alkyl group which comprises at a position interrupting the chain or at the end of the chain a group selected from C<sub>6-10</sub> Aryl, C<sub>3-6</sub> Cycloalkyl, 5-6-membered Heterocyclyl, and 5-6-membered Heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, -Oalkyl, -Oalkenyl, and -Oalkynyl is linear or branched and is optionally substituted with 1-5 fluorine atoms and/or one -OCH<sub>3</sub> or -OCF<sub>3</sub> group, and each of said Aryl, Cycloalkyl, Heteroaryl, Heterocyclyl, -OAryl, -OCycloalkyl, -OHeteroaryl, and -OHeterocyclyl groups is optionally substituted with 1-7 halogen atoms and/or one -OCH<sub>3</sub> or -OCF<sub>3</sub> group.

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These compounds are effective in lowering glucose, lipids, and insulin in diabetic animals. The compounds are expected to be efficacious in the treatment, control and/or prevention of non-insulin dependent diabetes mellitus (NIDDM) in humans and in the treatment, control, and/or prevention of conditions associated with

5 NIDDM, including hyperlipidemia, dyslipidemia, obesity, hypercholesterolemia, hypertriglyceridemia, atherosclerosis, vascular restenosis, inflammatory conditions, neoplastic conditions, and other PPAR $\alpha$  and/or  $\gamma$  mediated diseases, disorders and conditions.

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#### DETAILED DESCRIPTION OF THE INVENTION

The invention has numerous embodiments. Several subsets of compounds having different heterocyclic rings are included, as follows:

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Compounds of Formula I, in which X is N and Y is O;

Compounds of Formula I, in which X is N and Y is S;

Compounds of Formula I, in which X is N and Y is NR;

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Compounds of Formula I, in which X is CR and Y is O;

Compounds of Formula I, in which X is CR and Y is S; and

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Compounds of Formula I, in which X is CR and Y is NR.

In further subsets of the compounds of Formula I described above, in which the compounds of Formula I have different heterocycles fused to the aromatic ring (i.e. different values of X and Y), R<sup>5</sup> is selected from the group consisting of H,

30 C<sub>1-5</sub> alkyl, C<sub>2-5</sub> alkenyl, C<sub>2-5</sub> alkynyl, OC<sub>1-5</sub> alkyl, OC<sub>2-5</sub> alkenyl, OC<sub>2-5</sub> alkynyl, and phenyl; in these compounds, the alkyl, alkenyl, alkynyl, -Oalkyl, -Oalkenyl, and -Oalkynyl are optionally substituted with 1-5 fluorine atoms, and phenyl is optionally substituted with 1-5 halogens. In a preferred subset, R<sup>5</sup> is selected from the group consisting of H, C<sub>1-5</sub> alkyl, C<sub>2-5</sub> alkenyl, C<sub>2-5</sub> alkynyl, OC<sub>1-5</sub> alkyl, OC<sub>2-5</sub> alkenyl,

208  
208

and OC<sub>2-5</sub> alkynyl, where alkyl, alkenyl, alkynyl, -Oalkyl, -Oalkenyl, and -Oalkynyl are optionally substituted with 1-5 fluorine atoms.

In preferred compounds, R<sup>1</sup> and R<sup>2</sup> are each H or C<sub>1-3</sub> alkyl, and the  
5 number of carbon atoms in R<sup>1</sup> and R<sup>2</sup> together is 0-5.

In preferred embodiments, R<sup>3</sup> and R<sup>4</sup> are each independently C<sub>1-5</sub> alkyl. In additional preferred embodiments, one of R<sup>3</sup> and R<sup>4</sup> is C<sub>2-5</sub> alkyl, and the other of R<sup>3</sup> and R<sup>4</sup> is C<sub>1-5</sub> alkyl. In another preferred embodiment, both R<sup>3</sup> and R<sup>4</sup>  
10 are C<sub>2-5</sub> alkyl. In other preferred compounds, one of R<sup>3</sup> and R<sup>4</sup> is Cl or C<sub>1-5</sub> alkyl, and the other of R<sup>3</sup> and R<sup>4</sup> is C<sub>2-5</sub> alkyl. In general, the alkyl groups are linear or branched. In the most preferred compounds R<sup>3</sup> and R<sup>4</sup> are linear when they are alkyl.

In preferred compounds, R<sup>5</sup> is selected from C<sub>1-5</sub> alkyl and -OC<sub>1-5</sub>  
15 alkyl, where the alkyl and -Oalkyl are optionally substituted with 1-5 fluorine atoms.

In preferred embodiments, Z is O.

In preferred embodiments, X is N and Y is O, so that the compounds  
20 are benzisoxazoles.

In highly preferred embodiments of the groups of compounds above, R<sub>5</sub> is C<sub>1-3</sub> alkyl, -OC<sub>1-3</sub> alkyl, CF<sub>3</sub>, C<sub>2</sub>F<sub>5</sub>, -OCF<sub>3</sub> or -OC<sub>2</sub>F<sub>5</sub>; and R<sup>3</sup> and R<sup>4</sup> are each n-propyl.  
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Specific examples of compounds of this invention are provided as  
Examples 1-29.

The invention further includes pharmaceutical compositions  
30 comprising any of the compounds described above and a pharmaceutically acceptable carrier.

209

Salts

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts in the solid form may exist in more than one crystal structure, and may also be in the form of hydrates. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pantoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

Metabolites - Prodrugs

Metabolites of the compounds of this invention that are therapeutically active also are within the scope of the claimed parent compound. Prodrugs, which are compounds that are converted to the claimed compounds as they are being administered to a patient or after they have been administered to a patient, are also

210

present invention are administered at a daily dosage of from about 0.1 milligram to about 100 milligram per kilogram of animal body weight, preferably given as a single daily dose or in divided doses two to six times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 1.0 milligrams to about 1000 milligrams, preferably from about 1 milligrams to about 50 milligrams. In the case of a 70 kg adult human, the total daily dose will generally be from about 7 milligrams to about 350 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

#### 10 Pharmaceutical Compositions

Another aspect of the present invention provides pharmaceutical compositions which comprise a compound of Formula I and a pharmaceutically acceptable carrier. The pharmaceutical compositions of the present invention comprise a compound of Formula I or a pharmaceutically acceptable salt or prodrug thereof as an active ingredient, as well as a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic bases or acids and organic bases or acids.

The compositions include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

In practical use, the compounds of Formula I can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in

21

- (e) cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors (lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, itavastatin, ZD-4522 and other statins), (ii) sequestrants (cholestyramine, colestipol, and dialkylaminoalkyl derivatives of a cross-linked dextran), (iii) nicotinic acid or a salt thereof, (iv) PPAR $\alpha$  agonists such as fenofibric acid derivatives (gemfibrozil, clofibrate, fenofibrate and benzaifibrate), (v) PPAR $\alpha$ / $\gamma$  dual agonists, such as KRP-297, (vi) inhibitors of cholesterol absorption, such as for example beta-sitosterol, (vii) acyl CoA:cholesterol acyltransferase inhibitors, such as for example avasimibe, and (viii) anti-oxidants, such as probucol;
- 5 (f) PPAR $\delta$  agonists such as those disclosed in WO97/28149;
- 10 (g) antiobesity compounds such as fenfluramine, dexfenfluramine, phentiramine, sulbitramine, orlistat, neuropeptide Y5 inhibitors, and  $\beta$ 3 adrenergic receptor agonists;
- (h) an ileal bile acid transporter inhibitor; and
- 15 (i) agents intended for use in inflammatory conditions such as aspirin, non-steroidal anti-inflammatory drugs, glucocorticoids, azulfidine, and cyclo-oxygenase 2 selective inhibitors.

The above combinations include combinations of a compound of the present invention not only with one other active compound, but also with two or more other active compounds. Non-limiting examples include combinations of compounds having Formula I with two or more active compounds selected from biguanides, sulfonylureas, HMG-CoA reductase inhibitors, other PPAR agonists, PTP-1B inhibitors, DP-IV inhibitors, and anti-obesity compounds.

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## 25 BIOLOGICAL ASSAYS

### A) PPAR Binding Assays

For preparation of recombinant human PPAR $\gamma$ , PPAR $\delta$ , and PPAR $\alpha$ : Human PPAR $\gamma$ <sub>2</sub>, human PPAR $\delta$  and human PPAR $\alpha$  were expressed as gst-fusion proteins in *E. coli*. The full length human cDNA for PPAR $\gamma$ <sub>2</sub> was subcloned into the pGEX-2T expression vector (Pharmacia). The full length human cDNAs for PPAR $\delta$  and PPAR $\alpha$  were subcloned into the pGEX-KT expression vector (Pharmacia). *E. coli* containing the respective plasmids were propagated, induced, and harvested by centrifugation. The resuspended pellet was broken in a French press and

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212

debris was removed by centrifugation at 12,000 X g. Recombinant human PPAR receptors were purified by affinity chromatography on glutathione sepharose. After application to the column, and one wash, receptor was eluted with glutathione. Glycerol (10%) was added to stabilize the receptor and aliquots were stored at -80°C.

- 5 For binding to PPAR $\gamma$ , an aliquot of receptor was incubated in TEGM (10 mM Tris, pH 7.2, 1 mM EDTA, 10% glycerol, 7  $\mu$ L/100 mL  $\beta$ -mercaptoethanol, 10 mM Na molybdate, 1 mM dithiothreitol, 5  $\mu$ g/mL aprotinin, 2  $\mu$ g/mL leupeptin, 2  $\mu$ g/mL benzamidine and 0.5 mM PMSF) containing 0.1% non-fat dry milk and 10 nM [ $^3$ H $_2$ ] AD5075, (21 Ci/mmol),  $\pm$  test compound as described in
- 10 Berger et al (Novel peroxisome proliferator-activated receptor (PPAR $\gamma$ ) and PPAR $\delta$  ligands produce distinct biological effects. J. Biol. Chem. (1999), 274: 6718-6725. Assays were incubated for ~16 hr at 4°C in a final volume of 150  $\mu$ L. Unbound ligand was removed by incubation with 100  $\mu$ L dextran/gelatin-coated charcoal, on ice, for ~10 min. After centrifugation at
- 15 3000 rpm for 10 min at 4°C, 50  $\mu$ L of the supernatant fraction was counted in a Topcount.

- For binding to PPAR $\delta$ , an aliquot of receptor was incubated in TEGM (10 mM Tris, pH 7.2, 1 mM EDTA, 10% glycerol, 7  $\mu$ L/100 mL  $\beta$ -mercaptoethanol, 10 mM Na molybdate, 1 mM dithiothreitol, 5  $\mu$ g/mL aprotinin, 2  $\mu$ g/mL leupeptin, 2
- 20  $\mu$ g/mL benzamide and 0.5 mM PMSF) containing 0.1% non-fat dry milk and 2.5 nM [ $^3$ H $_2$ ]-Comp'd A, (17 Ci/mmol),  $\pm$  test compound as described in Berger et al (Novel peroxisome proliferator-activated receptor (PPAR $\gamma$ ) and PPAR $\delta$  ligands produce distinct biological effects. 1999 J Biol Chem 274: 6718-6725). (Comp'd A is 3-chloro-4-(3-(7-propyl-3-trifluoromethyl-6-benz-[4,5]-
- 25 isoxazoloxy)propylthio)phenylacetic acid, Ex. 20 in WO 97/28137). Assays were incubated for ~16 hr at 4°C in a final volume of 150  $\mu$ L. Unbound ligand was removed by incubation with 100  $\mu$ L dextran/gelatin-coated charcoal, on ice, for ~10 min. After centrifugation at 3000 rpm for 10 min at 4°C, 50  $\mu$ L of the supernatant fraction was counted in a Topcount.

213

For binding to PPAR $\alpha$ , an aliquot of receptor was incubated in TEGM (10 mM Tris, pH 7.2, 1 mM EDTA, 10% glycerol, 7  $\mu$ L/100 mL  $\beta$ -mercaptoethanol, 10 mM Na molybdate, 1 mM dithiothreitol, 5  $\mu$ g/mL aprotinin, 2  $\mu$ g/mL leupeptin, 2  $\mu$ g/mL benzamide and 0.5 mM PMSF) containing 0.1% non-fat dry milk and 5.0 nM [3H2]-Comp'd B, (34 Ci/mmol),  $\pm$  test compound. (Comp'd B is (3-(4-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)butyloxy))phenylacetic acid, Ex.62 in WO 97/28137). Assays were incubated for ~16 hr at 4°C in a final volume of 150  $\mu$ L. Unbound ligand was removed by incubation with 100  $\mu$ L dextran/gelatin-coated charcoal, on ice, for ~10 min. After centrifugation at 3000 rpm for 10 min at 4°C, 50  $\mu$ L of the supernatant fraction was counted in a Topcount.

#### B). Gal-4 hPPAR Transactivation Assays

The chimeric receptor expression constructs, pcDNA3-hPPAR $\gamma$ /GAL4, pcDNA3-hPPAR $\delta$ /GAL4, pcDNA3-hPPAR $\alpha$ /GAL4 were prepared by inserting the yeast GAL4 transcription factor DBD adjacent to the ligand binding domains (LBDs) of hPPAR $\gamma$ , hPPAR $\delta$ , hPPAR $\alpha$ , respectively. The reporter construct, pUAS(5X)-tk-luc was generated by inserting 5 copies of the GAL4 response element upstream of the herpes virus minimal thymidine kinase promoter and the luciferase reporter gene. pCMV-lacZ contains the galactosidase Z gene under the regulation of the cytomegalovirus promoter. COS-1 cells were seeded at  $12 \times 10^3$  cells/well in 96 well cell culture plates in high glucose Dulbecco's modified Eagle medium (DMEM) containing 10% charcoal stripped fetal calf serum (Gemini Bio-Products, Calabasas, CA), nonessential amino acids, 100 units/ml Penicillin G and 100 mg/ml Streptomycin sulfate at 37 °C in a humidified atmosphere of 10% CO<sub>2</sub>. After 24 h, transfections were performed with Lipofectamine (GIBCO BRL, Gaithersburg, MD) according to the instructions of the manufacturer. Briefly, transfection mixes for each well contained 0.48  $\mu$ L of Lipofectamine, 0.00075  $\mu$ g of pcDNA3-PPAR/GAL4 expression vector, 0.045  $\mu$ g of pUAS(5X)-tk-luc reporter vector and 0.0002  $\mu$ g of pCMV-lacZ as an internal control for transactivation efficiency. Cells were incubated

214  
214

in the transfection mixture for 5 h at 37° C in an atmosphere of 10% CO<sub>2</sub>. The cells were then incubated for ~48 h in fresh high glucose DMEM containing 5% charcoal stripped fetal calf serum, nonessential amino acids, 100 units/ml Penicillin G and 100 mg/ml Streptomycin sulfate ± increasing concentrations of test compound. Since the compounds were solubilized in DMSO, control cells were incubated with equivalent concentrations of DMSO; final DMSO concentrations were ≤ 0.1%, a concentration which was shown not to effect transactivation activity. Cell lysates were produced using Reporter Lysis Buffer (Promega, Madison, WI) according to the manufacturer's instructions. Luciferase activity in cell extracts was determined using Luciferase Assay Buffer (Promega, Madison, WI) in an ML3000 luminometer (Dynatech Laboratories, Chantilly, VA). β-galactosidase activity was determined using β-D-galactopyranoside (Calbiochem, San Diego, CA).

#### C. *In Vivo* Studies

Male db/db mice (10-11 week old C57Bl/KFJ, Jackson Labs, Bar Harbor, ME) were housed 5/cage and allowed *ad lib.* access to ground Purina rodent chow and water. The animals, and their food, were weighed every 2 days and were dosed daily by gavage with vehicle (0.5% carboxymethylcellulose) ± test compound at the indicated dose. Drug suspensions were prepared daily. Plasma glucose, and triglyceride concentrations were determined from blood obtained by tail bleeds at 3-5 day intervals during the study period. Glucose, and triglyceride, determinations were performed on a Boehringer Mannheim Hitachi 911 automatic analyzer (Boehringer Mannheim, Indianapolis, IN) using heparinized plasma diluted 1:6 (v/v) with normal saline. Lean animals were age-matched heterozygous mice maintained in the same manner.

#### EXAMPLES

215 72

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO  
DIRECCIÓN DE NUEVAS CREACIONES

2020  
Bogotá, D.C.,

Abogado  
CARLOS OLARTE

ASUNTO

Radicación 07 89738  
Trámite 011  
Evento 379  
Actuación 519  
Oficio  
Folios 017

U 587.1

Patente de Invención ☒ Patente de Modelo de Utilidad ☐  
Vía Nacional ☐  
Vía PCT (Fase Nacional) ☒ Cap. I ☐ Cap. II ☒  
No. Solicitud Internacional PCT/US2006/ 007740  
Fecha de Presentación Internacional 03/Marzo/2006

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

1. Documentos estudiados

Descripción: Folios 76 a 153 como se radicó inicialmente.  
Reivindicaciones: Folios 154 a 171 como se radicó inicialmente  
Prioridad: US 60 658.661 de Marzo 04 de 2005.

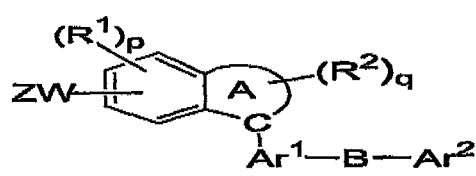
2. Objeto de la invención

Objeto: La presente invención se refiere a compuestos aromáticos condensados que tienen uno o más grupos funcionales, incluyendo sus sales farmacéuticamente aceptables, que son útiles como compuestos terapéuticos en el tratamiento de diabetes mellitus tipo 2 y estados patológicos asociados con esta enfermedad, incluyendo la obesidad y trastornos lipídicos.

Título de la solicitud: "Compuestos aromáticos condensados con actividad antidiabética"

El problema planteado en esta solicitud es la necesidad de proporcionar una nueva clase de compuestos agonistas y agonistas parciales de PPAR-gamma, útiles en el tratamiento y control de hiperglucemia y resistencia a la insulina.

Para resolver este problema técnico la solicitud en estudio proporciona un compuesto de la fórmula (I) y composiciones que lo contienen.



El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A61K31/416, 31/423, 31/4439,31/513, A61P3/10, C07D261/20,307/80,413/04,403/04,239/34.

### 3. Excepción a la Patentabilidad (Art 20 D 486 literal (d))

El objeto de las reivindicaciones 16 – 17 no es patentable, porque se refiere a un método de tratamiento.

### 4. Reivindicaciones relativas a un uso o a un segundo uso (Art 14 y 21 D 486)

El objeto de las reivindicaciones 15 no es patentable, porque se refiere a un uso.

### 5. De la Solicitud de Patente

#### Reivindicaciones (Art 30 D 486, Art 22 PCT)

La reivindicación 1 no es concisa, porque presenta una excesiva complejidad, lo cual dificulta determinar la extensión del objeto que se busca proteger.

En concordancia con lo anterior, se observa que existen ejemplos de compuestos para cuando el anillo A fusionado al benceno forman el Benzofurilo, naftaleno, Benzoisoxazolilo, Indazolilo y además, que en los ejemplos Ar1 puede ser fenilo sustituido por alquilo; Ar2 puede ser fenilo sustituido por alquilo, halógeno y triflurometoxi y B puede ser O y C=O; por lo tanto se debe precisar dentro de la reivindicación el anillo A, el condensado, cicloalquilo.

Por lo tanto es necesario, que los sustituyentes de cada variable sean definidos de forma específica, acorde con los compuestos ejemplificados, que resuelvan el problema planteado con la actividad biológica que se les atribuye (moduladores de APPR); o sea que se haga una generalización razonable de la materia reclamada. La anterior restricción también aplica para las reivindicaciones dependientes.

La reivindicación 18, no es concisa cuando menciona las expresiones tales como: "agentes que mejoran el perfil lipídico de un paciente " y los términos listados en la presente reivindicación, como biguanidas, sulfonilureas etc, ya que estos se refieren a una categoría farmacológica de compuestos, muy general, que presentan esta actividad y n o definen un compuesto específico por su estructura o nombre químico, como se mencionó antes.

Se requiere al Solicitante hacer las aclaraciones necesarias.

### 6. Unidad de invención (Art 25 D 486)

La reivindicación 18, no presenta unidad de invención porque las diversas composiciones que se pueden obtener, que incluyen el compuesto de formula (I) y el otro u otros compuestos (de diferentes estructuras químicas, p. ej. biguanidas, sulfonilureas, entre otros) darían lugar a muchos grupos inventivos.

7. Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la Fecha de Presentación de la Solicitud de Prioridad: Marzo 04 de 2005

y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

| Item | Documento | Título                                               | Fecha de Publicación* |
|------|-----------|------------------------------------------------------|-----------------------|
| D1   | WO0160807 | Aryloxyacetic Acids For Diabetes And Lipid Disorders | Agosto 223 de 2001    |

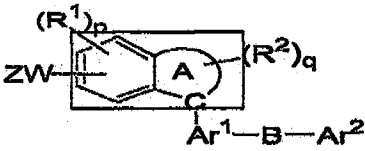
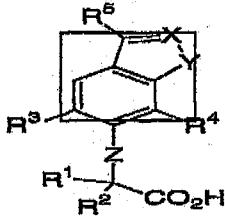
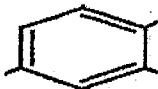
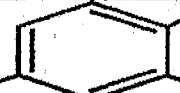
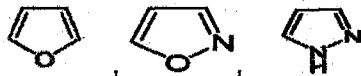
D1 divulga (páginas 6-9, 13, 17, 20-23, folios 204-214) un compuesto de la fórmula (I) y las composiciones que lo contienen.

8. Examen de Patentabilidad (Art 14 D486)

Nivel Inventivo (Art18 D486)

La reivindicación 1 consiste en un compuesto de fórmula (I)

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

| Características esenciales                                                                                                                     | D1                                                                                                                                                                          |
|------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                             | estructura formula I<br><br>Folio 205, pg6                                             |
|                                                             | ✓ <br>Folio 205, pg6,                                                                   |
| R1=alquil C1-C5, halógeno y P=2                                                                                                                | ✓ R3 y R4= alquil C1-C5 y Cl, folio 206, pg, 7líneas 6-7                                                                                                                    |
| -WZ= O-C-(R5)(R6)-Z; cuando R5 y R6 son H, halógeno, alquil C1-C5,-alquenil C2-C5,opcionalmente sust. por 1-3 halógenos y Z=-CO2R7 siendo R7=H | ✓ Folios 205 y 206, pg 6 y 7<br>Z-C-(R1)(R2)-CO2H; cuando Z=O, R1 y R2 son H, F, alquil C1-C5,-alquenil C2-C5, opcionalmente sust. por 1-3 halógenos y Z=-CO2R7 siendo R7=H |
| A=heteroaromático 5 miembros con 1-2 hetoátomos seleccionados de O,N                                                                           | ✓ <br>Folios 205-206, pg6 y 7                                                          |
| R2=no existe cuando q=0                                                                                                                        | -                                                                                                                                                                           |
| Ar1= fenilo, naftilo                                                                                                                           | R5= C6-10 Aryl ( fenilo, naftilo)                                                                                                                                           |
| B- Ar2                                                                                                                                         | -                                                                                                                                                                           |

El documento D1, considerado el estado de la técnica más cercano a la invención definida en la reivindicación 1, divulga un compuesto de fórmula (I).

La diferencia entre la invención, definida en la reivindicación 1, y el compuesto de D1 consiste en la Característica B- Ar2.

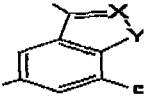
Pero esta diferencia no muestra ningún efecto sorprendente porque los compuestos Expediente 07 897381er Art 45

218 219

de D1 son moduladores de APPR  $\alpha$  y  $\gamma$ , al igual que los reclamados.

Por lo tanto, el Problema Técnico Objetivo que pretende resolver esta invención se puede formular así: "cómo modificar los compuestos de D1, para obtener compuestos útiles como moduladores de APPR  $\alpha$  y  $\gamma$ ".

En consecuencia, el experto en la materia que tenga que resolver el problema de: "cómo modificar los compuestos de D1, para obtener compuestos igualmente moduladores de APPR  $\alpha/\gamma$ , lo lograría, introduciendo sustituyentes adicionales en el

anillo  (ya divulgado en D1), esperando que los nuevos compuestos presenten actividad como moduladores de APPR  $\alpha/\gamma$ .

Conclusión:  
La reivindicación 1 cumple el requisito de novedad (Art. 16), pero no cumple con el requisito de nivel inventivo (Art. 18).

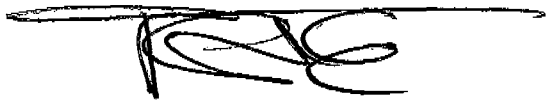
9. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud están afectados así:

| Item | Documento      | Reivindicaciones afectadas | Requisito que afecta |
|------|----------------|----------------------------|----------------------|
| D1   | WO 2004/019869 | 1-14                       | Nivel Inventivo      |

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

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.



JOSÉ LUIS SALAZAR LÓPEZ  
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha 01 ABR. 2011

|                            |                                        |
|----------------------------|----------------------------------------|
| CONCEPTO TÉCNICO<br>No.483 | EXAMINADOR TÉCNICO<br>Código No.202078 |
|----------------------------|----------------------------------------|