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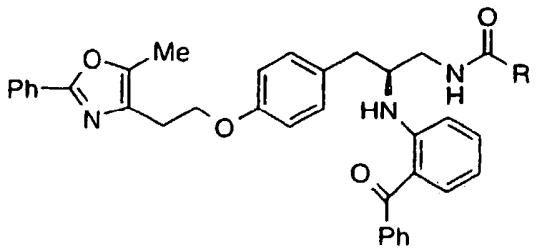
(54) Title: PPAR-GAMMA MODULATORES



(I)

(57) Abstract: The present invention relates to modulators of PPAR-gamma of formula (I), and to processes for the preparation and use of the same. Such PPAR-gamma modulators are useful in the treatment of metabolic diseases and disorders.

WO 2006/044961 A1

PPAR-GAMMA MODULATORES

FIELD OF THE INVENTION

The present invention relates to modulators of PPAR-gamma, and to processes for the preparation and use of the same. Such PPAR-gamma modulators are useful in the treatment of metabolic diseases and disorders.

BACKGROUND OF THE INVENTION

Peroxisome proliferator activated receptors (PPARs) are orphan receptors belonging to the steroid/retinoid receptor superfamily of ligand-activated transcription factors. See, for example, Willson, T. M. et al., J. Med. Chem., (2000), Vol. 43, pp. 527-550. The biological role of the PPARs in the regulation of lipid metabolism and storage is reviewed in, for example, Spiegelman, B. M., Diabetes, (1998), Vol. 47, pp 507-514, Schoonjans, K. et al., Curr. Opin. Lipidol., (1997), Vol. 8, pp 159-166, and Brun, R. P. et al., Curr. Opin. Lipidol., (1997), Vol. 8, pp 212-218.

There are therapeutic uses for PPAR-gamma ligands in the treatment of diseases of lipid metabolism and energy balance, yet it is possible that there will be side effects of these drugs. For example, PPAR-gamma ligands that promote adipocyte differentiation in vivo could lead to increased fat accumulation and weight gain. This side effect might offset the beneficial effects of a PPAR-gamma ligand in the treatment of diabetes or other diseases where obesity is a risk factor. See, for example, the Spiegelman and Brun articles cited above.

There is precedent among other members of the steroid/retinoid receptor superfamily that synthetic ligands can be identified which mimic many of the beneficial effects but inhibit some of the detrimental side effects of the natural ligands. See, for example, McDonnell, D. P., Biochem. Soc. Trans., (1998), Vol. 26, pp 54-60. These synthetic ligands have been given various labels, including antagonists, inverse agonists, anti-hormones, partial agonists, selective receptor modulators, tissue selective ligands, and others. See, for example, Katzenellenbogen, J. A. et al., Mol. Endocrinol., (1996), Vol. 10, pp 119-131.

Molecules that inhibit the adipogenic effects of endogenous PPAR-gamma ligands may be useful in the treatment of diseases caused by increased fat accumulation or lipid storage. See, for example, Tontonoz et al., Curr. Opin. Genet. Dev., (1995), Vol. 5, pp 571-576; Paulik, M. A. and Lenhard, J. M., Cell Tissue Res., (1997), Vol. 290, pp 79-87; Rosenfield, R. L. et al. Dermatology, (1998), Vol. 196, pp 43-46. Thus, molecules that block adipogenesis in adipocytes, pre-adipocytes, bone marrow, or sebocytes may have beneficial effects in the treatment of obesity, osteoporosis, or acne.

PPAR-gamma has been found in tissues other than adipose, and it is believed that synthetic PPAR-gamma ligands and natural PPAR-gamma ligands may have beneficial effects in many other diseases including cardiovascular disease, inflammation, and cancer. See, for example, the Schoonjans article cited above, Ricote, M. et al., Nature, (1998), Vol. 391, pp 79-82, and Mueller, E. et al., Mol. Cell, (1998), Vol. 1, pp 465-470.

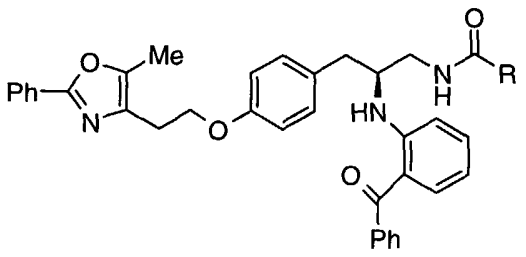
PPAR agonists such as thiazolidinediones, fibrates, and fatty acids share a common binding mode to their receptors. Despite differences in the chemical structure of these agonists, specific hydrogen bond formation between the acidic headgroups of these agonist ligands and a tyrosine residue in the AF2 helix and/or a histidine or tyrosine residue in helix-5, is a critical step in the activation of the receptor by an agonist ligand, see Xu et al., Mol. Cell (1999), Vol. 3, pp. 397-403 and Oberfield et al., PNAS (1999), Vol. 96, pp. 6102-6106.

Many synthetic PPAR-gamma agonists, including thiazolidinediones (see for example U.S. Pat. Nos. 5,089,514, 4,342,771, 4,367,234, 4,340,605, and 5,306,726) and non-thiazolidinediones (see for example U.S. Pat. No. 6,294,580) have been shown to modulate blood glucose levels in mammals. The agonist activity of these molecules is believed to be due to the specific hydrogen bond formation between the molecule and the AF2 helix of PPAR-gamma. Compounds that are structurally similar to these agonists, yet are designed to interact differently with the AF2 region, could have different activities.

The present inventors have discovered that specific alterations in the headgroup responsible for this hydrogen bonding in the AF2 domain can result in a molecule with PPAR-gamma antagonist activity.

SUMMARY OF THE INVENTION

One aspect of the present invention is a compound of formula (I)



(I)

or a salt or solvate thereof, wherein R is CH_3, cyclopropyl, $CH_2CH(CH_3)C(O)OH$, $(CH_2)_2$-4-$C_6H_4SC(CH_3)_2C(O)OH$, CH_2O-3-$C_6H_4NH_2$, or 3-$C_6H_4(CH_2)_2N(CH_3)_2$.

Another aspect of the present invention is a pharmaceutical composition comprising a compound of the present invention.

Another aspect of the present invention is the administration of a compound of the present invention in a method for the treatment of PPARγ mediated conditions or disorders.

Another aspect of the present invention is the administration of a compound of the present invention in a method for the treatment of diabetes, obesity, aging, cancer, acne, osteoporosis, inflammation, metabolic syndrome, impaired glucose tolerance, syndrome X, dyslipidemia or cardiovascular disease.

Another aspect of the present invention includes a compound of the present invention for use in the treatment of PPARγ mediated conditions or disorders.

Another aspect of the present invention includes a compound of the present invention for use in the treatment of diabetes, obesity, aging, cancer, acne, osteoporosis, inflammation, metabolic syndrome, impaired glucose tolerance, syndrome X, dyslipidemia or cardiovascular disease.

Another aspect of the present invention includes using a compound according to the present invention in the manufacture of a medicament for use in the treatment of PPARγ mediated conditions or disorders.

Another aspect of the present invention includes using a compound according to the present invention in the manufacture of a medicament for use in the treatment of diabetes, obesity, aging, cancer, acne, osteoporosis, inflammation, metabolic syndrome, impaired glucose tolerance, syndrome X, dyslipidemia or cardiovascular disease.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a representative experiment demonstrating the effect of the compounds of Examples 4 and 5 on serum glucose levels in ob/ob mice. The figure is a graphical representation of the data contained in Table 2.

Figure 2 is a representative experiment demonstrating the effect of the compounds of Examples 4 and 5 on circulating insulin levels in ob/ob mice. The figure is a graphical representation of the data contained in Table 3.

Figure 3 is a representative experiment demonstrating the effect of the compounds of Examples 4 and 5 on serum triglyceride levels in ob/ob mice. The figure is a graphical representation of the data contained in Table 4.

Figure 4 is a representative experiment demonstrating the effect of the compounds of Examples 4 and 5 on HDL-C levels in ob/ob mice. The figure is a graphical representation of the data contained in Table 5.

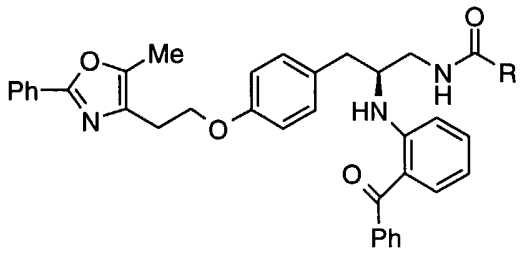
DETAILED DESCRIPTION OF THE INVENTION

Terms are used within their accepted meanings. The following definitions are meant to clarify, but not limit, the terms defined.

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula I or a salt thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include water, ethanol and acetic acid. Most preferably the solvent used is water.

Typically, the salts of the present invention are pharmaceutically acceptable salts. Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention. Salts of the compounds of the present invention may comprise acid addition salts derived from a nitrogen on a substituent in a compound of the present invention. Representative salts include the following salts: acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, monopotassium maleate, mucate, napsylate, nitrate, N-methylglucamine, oxalate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, potassium, salicylate, sodium, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, trimethylammonium and valerate. Other salts, which are not pharmaceutically acceptable, may be useful in the preparation of compounds of this invention and these form a further aspect of the invention.

One embodiment of the present invention is a compound of formula (I)



(I)

or a salt or solvate thereof, wherein R is CH_3, cyclopropyl, $CH_2CH(CH_3)C(O)OH$, $(CH_2)_2$-4-$C_6H_4SC(CH_3)_2C(O)OH$, CH_2O-3-$C_6H_4NH_2$, or 3-$C_6H_4(CH_2)_2N(CH_3)_2$. A preferred embodiment is wherein R is $(CH_2)_2$-4-$C_6H_4SC(CH_3)_2C(O)OH$.

Specific compounds of formula (I) include but are not limited to those compounds described in the Example section that follows. Some particular compounds of formula (I) include:

(S)-{{2-[1-(2-Benzoylphenyl)amino]-2-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propyl}}-acetamide;

(S)-{{2-[1-(2-Benzoylphenyl)amino]-2-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propyl}}cyclopropanecarboxamide;

(S)-{{2-[1-(2-Benzoylphenyl)amino]-2-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propyl}}-aminocarbonyl-(2-methyl)-propionic acid;

(S)-{{2-[1-(2-Benzoylphenyl)amino]-2-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propyl}}-aminocarbonyl-ethyl-4-phenylthio-2',2'-dimethylacetic acid;

(S)-{{2-[1-(2-Benzoylphenyl)amino]-2-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propyl}}-aminocarbonyl-methyloxy-3-aniline; and

N,N-Dimethyl-(S)-{{2-[1-(2-benzoylphenyl)amino]-2-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propyl}}-aminocarbonyl-3-phenethylamine.

While it is possible that, for use in the treatment of metabolic diseases or disorders of the present invention, a compound of formula (I) as well as salts or solvates thereof, may be administered as the raw chemical, it is possible to present the active ingredient as a pharmaceutical composition. Accordingly, the invention further provides pharmaceutical compositions, which may be administered in the methods of treating metabolic diseases or disorders of the present invention. The pharmaceutical compositions include a compound of formula (I) or salt or solvate thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients. The carrier(s), diluent(s) or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Such a unit may contain, for example, 0.5mg to 1g, preferably 1mg to 700mg, more preferably 5mg to 100mg of a compound of formula (I), depending on the

condition being treated, the route of administration and the age, weight and condition of the patient, or pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Furthermore, such pharmaceutical formulations may be prepared by any of the methods well known in the pharmacy art.

The compound of formula (I) may be administered by any appropriate route. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal, and parenteral (including subcutaneous, intramuscular, intraveneous, intradermal, intrathecal, and epidural). It will be appreciated that the preferred route may vary with, for example, the condition of the recipient.

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing and coloring agent can also be present.

Capsules can be made by preparing a powder mixture as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of

the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or natural sweeteners or saccharin or other artificial sweeteners, and the like can also be added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax or the like.

The agents for use according to the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Agents for use according to the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by

iontophoresis as generally described in Pharmaceutical Research, 3(6), 318 (1986).

Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils.

For treatments of the eye or other external tissues, for example mouth and skin, the formulations are preferably applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical formulations adapted for topical administrations to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

Pharmaceutical formulations adapted for topical administration in the mouth include lozenges, pastilles and mouth washes.

Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as enemas.

Pharmaceutical formulations adapted for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists that may be generated by means of various types of metered dose pressurised aerosols, nebulizers or insufflators.

Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

The present invention provides methods for the treatment of several conditions or diseases, all of which comprise the step of administering a compound of formula (I). As used herein, the term "treatment" refers to alleviating the specified condition, eliminating or reducing the symptoms of the condition, slowing or eliminating the progression of the condition and preventing or delaying the initial occurrence of the condition in a subject, or reoccurrance of the condition in a previously afflicted subject.

Moreover, it will be appreciated that the amount of a compound of formula (I) required for use in treatment will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. Typically, the compound of formula (I) will be given in the range of 0.1 to 700 mg/kg body weight of recipient (mammal) per day and more usually in the range of 1 to 100mg/kg body weight per day. The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

The present invention provides a method for treating a condition mediated by PPAR-gamma in an animal such as a mammal (e.g., a human), which method comprises administering to the animal a compound of formula (I). Conditions which are mediated by PPAR-gamma are known in the art and include but are not limited to metabolic diseases and disorders and conditions characterized by inappropriate lipid metabolism. Also, the compounds of the present invention are believed useful, either alone or in combination with other agents, in the treatment of diabetes, obesity, aging, cancer, acne, osteoporosis, inflammation, metabolic syndrome, impaired glucose tolerance, syndrome X, dyslipidemia or cardiovascular disease.

As used herein, a "PPAR-gamma ligand" is a compound that binds to human PPAR-gamma with a pKi of greater than 5.0 when tested in the binding assay described below. As used herein a "PPAR-gamma antagonist" is a PPAR-gamma ligand that gives greater than 50% inhibition of PPAR agoinist induced lipogenesis or transactivation when tested in the adipocyte differentiation or cell-based reporter assay, respectively, as described below.

The following examples are intended for illustration only and are not intended to limit the scope of the invention in any way.

EXAMPLES

As used herein the symbols and conventions used in these processes, schemes and examples are consistent with those used in the contemporary scientific literature, for example, the *Journal of the American Chemical Society* or the *Journal of Biological Chemistry*. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Specifically, the following abbreviations may be used in the examples and throughout the specification:

g (grams);	mg (milligrams);
L (liters);	mL (milliliters);
µL (microliters);	psi (pounds per square inch);
M (molar);	mM (millimolar);
N (Normal);	Kg (kilogram);

Hz (Hertz);	MHz (megahertz);
mol (moles);	mmol (millimoles);
RT (room temperature);	min (minutes);
h (hours);	mp (melting point);
T_r (retention time);	RP (reverse phase);
DCM (dichloromethane);	DCE (dichloroethane);
DMF (*N*,*N*-dimethylformamide);	HOAc (acetic acid);
TMSE (2-(trimethylsilyl)ethyl);	TMS (trimethylsilyl);
TIPS (triisopropylsilyl);	TBS (*t*-butyldimethylsilyl);
THF (tetrahydrofuran);	DMSO (dimethylsulfoxide);
EtOAc (ethyl acetate);	DME (1,2-dimethoxyethane);
TFA (trifluoroacetic acid);	TLC (thin layer chromatography);

HPLC (high pressure liquid chromatography);

HRMS (high resolution mass spectrum)

EDTA (ethylenediaminetetraacetic acid);

D-MEM/F-12 (Dulbeccos's modified Eagle's medium/ Ham's F-12 medium);

SPAP (secreted placental alkaline phosphatase)

Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade). All reactions were conducted under an inert atmosphere at room temperature unless otherwise noted.

The ^{1}H NMR spectra were recorded on a Varian VXR-300, a Varian Unity-300, or a Varian Unity-400 instrument. Chemical shifts are expressed in parts per million (ppm, δ units). Coupling constants are in units of hertz (Hz). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; hept, heptuplet.

Low-resolution mass spectra (MS) were recorded on a JOEL JMS-AX505HA, JOEL SX-102 or a SCIEX-APIiii spectrometers. All mass spectra were taken under electrospray ionization (ES, either in the positive ion mode or negative ion mode), atmospheric pressure chemical ionization (APCI), or by fast atom bombardment (FAB) methods. Infrared (IR) spectra were

obtained on a Nicolet 510 FT-IR spectrometer using a 1-mm NaCl cell. All reactions were monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates (60F-254), visualized with UV light, iodine staining, or 7% ethanolic phosphomolybdic acid or p-anisldehyde solutions. Flash column chromatography was performed on silica gel (230-400 mesh, Merck).

Analytical purity was assessed on a Hewlett Packard series 1050 or 1100 system equipped with a diode array spectrometer. The stationary phase was either a Dynamax C8 column (25 cm x 4.1 mm), a Dynamax 60A C18 column (25 cm x 4.6 mm), a Vydac C18 column (5m, 4.6 mm X 250 mm), a Supelco C18 column (5m, 4.6 mm X 150 mm), or a Rainin C18 column (5m, 4.6 mm X 250 mm). The flow rate was 1.0 to 1.5 mL/min. (t0 = 2.8 or 3.0 min.) and the solvent systems were as described below. Enantiomeric purity was assessed using either a Chiralpak AD column (25 cm x 4.6 mm) or a Chiralpak OD column (25cm x 4.6 mm) on either a Hewlet Packard series 1050 HPLC system equipped with a diode array spectrometer or on a Supercritical Fluid (SFC) system using CO_2 / methanol as the mobile phase.

Method of Design

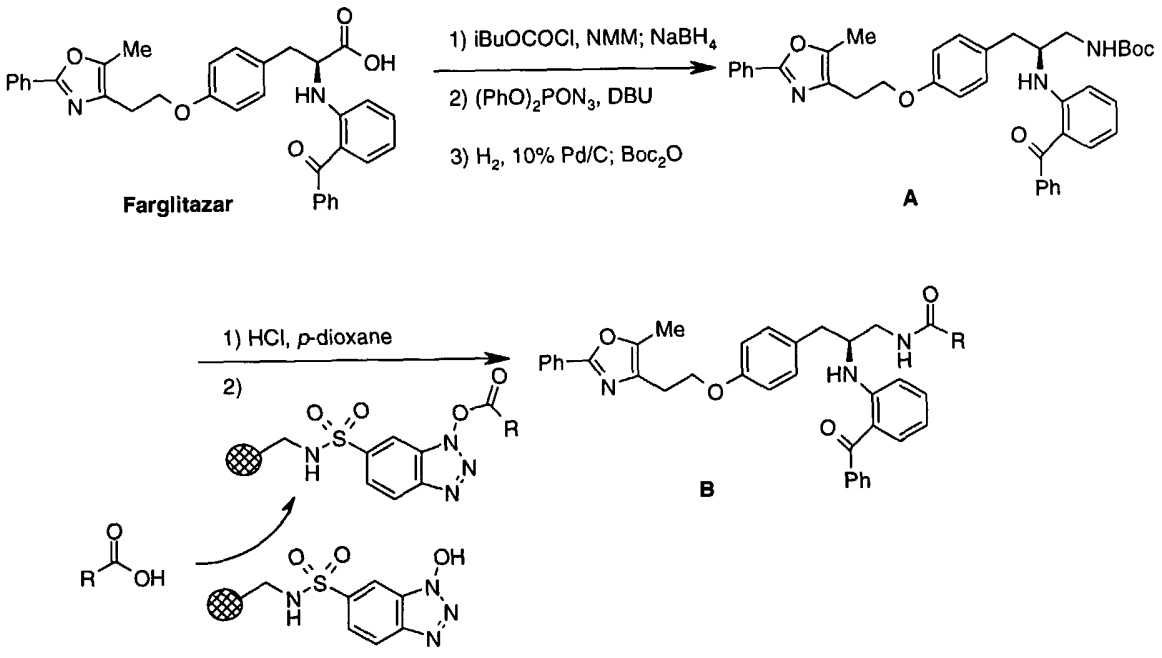
Compounds were designed to replace the acidic group of a PPAR-gamma agonist by an arrangement of atoms that were a) no longer capable of forming a strong hydrogen bond with AF2-contained tyrosine-473 of the ligand binding domain, and/or b) displaced tyrosine-473 or of the ligand binding domain from their agonist-bound positions. Farglitazar, compound **20** described in Henke, B. R. et al., J. Med. Chem., (1998), Vol. 41, 5020-5036, is a PPAR gamma agonist and contains a carboxylic acid group that is capable of forming a hydrogen bond with tyrosine-473 and histidine-323 of the PPAR gamma ligand binding domain. In the following examples, the acid group was replaced by amides and no other modifications were made to the structure of farglitazar.

Method of Synthesis

Compounds of the present invention were prepared from farglitazar (see for example Compound **20** in Henke, B. R. et al., J. Med. Chem., (1998),

Vol. 41, 5020-5036) as shown in Scheme 1 below. Optically pure farglitazar was converted to its corresponding activated ester with isobutyl chloroformate and reduced to the alcohol with sodium borohydride. This alcohol was treated with diphenylphosphoryl azide and subsequently reduced to its corresponding amine by hydrogen over 10% palladium-on-carbon; the amine was protected *in situ* using di-*t*-butyl-dicarbonate to afford **A**. Boc-protected amine **A** was treated with hydrochloric acid and then rapidly acylated with a variety of polystyrene bound HOBT esters to furnish an array of farglitazar inverse amide products **B**. Final products containing terminal carboxylic acid groups were protected as *t*-butyl esters in this acylation step.

Scheme 1



Example 1:

(S)-{{2-[1-(2-Benzoylphenyl)amino]-2-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propyl}}-acetamide

To a stirred, cooled (-15°C) solution of (2S)-[(2-benzoylphenyl)amino]-3-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic acid [compound **20** described in Henke, B.R. et al., J. Med. Chem., (1998), Vol.

41, 5020-5036] (5.00 g, 9.15 mmol) in DME (50 mL) was added *N*-methylmorpholine (0.92 g, 9.15 mmol) followed by isobutyl chloroformate (1.26 g, 9.25 mmol). The resulting suspension was stirred for 5 min and then filtered and cooled (-15°C). To this solution was added a solution of sodium borohydride (0.35 g, 9.30 mmol) in water (5 mL). After 5 min the reaction was diluted with water (250 mL) and warmed to RT. The mixture was poured into HCl (1 *N*, 250 mL) and extracted with DCM. The organic layer was washed with brine and dried over $MgSO_4$. Removal of solvent under reduced pressure and recrystallization of the resulant solid from EtOAc/hexane (1:1, 250 mL) provided the desired primary alcohol as a yellow solid (3.88 g, 80% yield). To a stirred solution of the yellow solid (500 mg, 0.94 mmol) and diphenylphosphoryl azide (1.28 g, 4.64 mmol) in DMF was added DBU (764 mg, 5.02 mmol). The mixture was heated at 90°C for 18 h, cooled to RT, and the DMF removed *in vacuo*. The residue was partitioned between EtOAc and HCl (1 *N*), and the separated organic layer washed with water, sat'd sodium bicarbonate, and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give a solid. This crude material was purified by silica gel chromatography eluting with 1:4 ethyl acetate/hexanes to give the azide as a yellow solid (475 mg, 91% yield). The azide (389 mg, 0.70 mol) was dissolved in THF (10 mL). Under an atmosphere of nitrogen, di-*tert*-butyl-dicarbonate (463 mg, 2.12 mmol) and 10% Pd/C (70 mg) were added. The solution was stirred under one atmosphere of hydrogen for 18 h. The solution was filtered (celite) and concentrated under reduced pressure to an oil. The crude material was purified by silica gel chromatography eluting with 2:1 ethyl acetate/hexanes to give intermediate **A** as a yellow solid (219 mg, 50% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.59 (d, J = 8.5 Hz, 1H), 8.00 (m, 2H), 7.59 (m, 2H), 7.5 – 7.2 (m, 8H), 7.15 (m, 2H), 6.85 (m, 1H), 6.78 (m, 2 H), 6.52 (t, J = 7.4, 1H), 4.83 (br s, 1H), 4.22 (t, J = 6.6, 2 H), 3.97 (m, 1H), 3.49 (m, 1H), 3.26 (m, 1H), 2.95 (t, J = 6.6, 2H), 2.83 (m, 2H), 2.39 (s, 3 H), 1.43 (s, 9H). MS (APCI) *m/z* 632 (M+1). Intermediate **A** (223 mg, 0.35 mmol) was dissovled in HCl/dioxane (4 *M*, 4.0 mL). The solution was stirred for 1 h and concentrated under reduced pressure to give a yellow solid (200 mg, 99%

yield). Polystyrene bound hydroxybenzotriazole (PS-HOBT, 29 mg, 0.030 mmol) was suspended in DMF (1 mL). Acetic acid (2.7 mg, 0.045 mmol), 4-dimethylaminopyridine (DMAP, 2.2 mg, 0.018 mmol), and diisoproylcarbodiimide (DIC, 17 mg, 0.135 mmol) were added, and the resulting suspension was shaken for 2 h. The resin was filtered, washed with DCM, and suspended in DCM (1 mL). The yellow, deprotected HCl salt of intermediate **A** (12 mg, 0.021 mmol) and polystyrene bound *N*-methylmorpholine (22 mg, 0.09 mmol) were added to the suspension. After 2 h of rotation, the organic solution was collected by filtration and concentrated under reduced pressure to give a crude oil that was purified by silica gel chromatography to give Example 1 as a yellow solid (9 mg, 75% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm 1.2 (m, 1 H), 1.8 (m, 2 H), 1.9 (s, 3 H), 2.0 (s, 1 H), 2.4 (s, 3 H), 2.8 (m, 1 H), 3.0 (d, *J*=5.8, 2 H), 4.2 (t, *J*=6.1, 2 H), 6.7 (d, *J*=8.6, 2 H), 6.8 (d, *J*=8.6, 1 H), 7.0 (m, 2 H), 7.2 (s, 3 H), 7.3 (m, 1 H), 7.4 (m, 6 H), 7.5 (m, 2 H), 8.1 (d, *J*=6.1, 2 H). MS (APCI) *m/z* 574 (M+1).

Example 2:

(S)-{{2-[1-(2-Benzoylphenyl)amino]-2-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propyl}}-cyclopropanecarboxamide

Example **2** was prepared from intermediate **A** and cyclopropanecarboxylic acid as described for Example **1** (11 mg, 88% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.7 (d, *J*=7.7, 2 H) 0.9 (m, 2 H) 1.3 (m, 1 H) 2.2 (s, 1 H) 2.4 (s, 3 H) 2.9 (m, 4 H) 3.4 (d, *J*=6.6, 1 H) 3.6 (d, *J*=6.3, 1 H) 4.0 (m, 1 H) 4.2 (t, *J*=6.6, 2 H) 5.9 (d, *J*=5.5, 1 H) 6.5 (t, *J*=7.5, 1 H) 6.8 (d, *J*=8.3, 2 H) 6.9 (d, *J*=8.6, 1 H) 7.1 (d, *J*=8.6, 2 H) 7.4 (m, 9 H) 8.0 (dd, *J*=7.3, 2.1, 2 H) 8.6 (s, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 7.5, 10.5, 15.0, 26.5, 38.9, 43.6, 53.9, 66.8, 112.7, 114.6, 114.8, 117.9, 121.6, 126.2, 127.9, 128.3, 128.9, 129.3, 129.9, 130.1, 130.5, 131.2, 132.8, 135.3, 135.8, 140.6, 145.3, 151.6, 157.7, 174.2, 199.8; HRMS (ES) *m/z* calcd for $C_{38}H_{38}N_3O_4$ (MH+) 600.2862, found 600.2863.

Example 3:

(S)-{{2-[1-(2-Benzoylphenyl)amino]-2-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propyl}}-aminocarbonyl-(2-methyl)-propionic acid

Example **3** was prepared as a mixture of diastereomers from intermediate **A** and racemic 2-methylsuccinic anhydride as described for Example **1** (DIC and PS-HOBT omitted). (13 mg, 94% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.1 (m, 3 H), 2.2 (m, 2 H), 2.4 (m, 3 H), 2.4 (m, 2 H), 2.6 (m, 2 H), 2.8 (m, 2 H), 2.9 (m, 2 H), 3.4 (m, 2 H), 4.1 (m, 2 H), 6.5 (m, 2 H), 6.9 (m, 4 H), 7.1 (m, 2 H), 7.4 (m, 8 H), 8.0 (m, 2 H), 8.5 (s, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 10.45, 17.12, 17.37, 17.74, 17.89, 26.39, 36.22, 26.39, 36.98, 37.05, 38.12, 38.38, 38.84, 39.28, 39.50, 43.21, 43.29, 53.51, 53.63, 53.75, 66.76, 66.81, 112.57, 112.65, 112.70, 114.54, 114.64, 114.71, 114.80, 114.85, 117.63, 117.73, 117.84, 126.21, 127.63, 127.69, 128.30, 128.94, 129.24, 129.28, 129.69, 129.80, 130.00, 130.18, 130.47, 131.18, 132.62, 132.69, 135.49, 135.53, 135.59, 135.84, 135.95, 140.39, 140.45, 145.40, 151.40, 151.46, 151.54, 157.65, 157.70, 172.62, 175.19, 176.49, 199.88, 200.01; HRMS (ES) *m/z* calcd for $C_{39}H_{40}N_3O_6$ (MH+) 646.2917, found 646.2928.

Example 4:

(S)-{{2-[1-(2-Benzoylphenyl)amino]-2-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propyl}}-aminocarbonyl-ethyl-4-phenylthio-2',2'-dimethylacetic acid

Example **4** was prepared from intermediate **A** and 4-(1-*t*-butylcarboxy-1-methylethylthio)-phenylpropionic acid as described for Example **1**. The purified product was treated with 95% TFA in DCM to deprotect the acid functionality. Concentration under reduced pressure gave a yellow solid (4 mg, 22% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.43 (s, 6 H), 2.50 (s, 3 H), 2.53 (m, 2 H), 2.7-2.8 (m, 4 H), 3.13 (m, 2 H), 3.25 (m, 1 H), 3.48 (m, 1 H), 3.94 (m, 1 H), 4.17 (m, 2 H), 6.73-6.82 (m, 4 H), 7.00-7.06 (m, 4 H), 7.34 (d, *J* = 7.3, 2 H), 7.45-7.67 (m, 10 H), 8.06 (d, *J* = 7.1, 2 H), 11.3 (br s, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 10.49, 23.98, 25.54, 25.62, 31.51, 37.21,

37.70, 42.61, 55.97, 65.23, 114.79, 115.70, 118.48, 120.30, 121.40, 127.66, 127.92, 128.62, 128.89, 128.99, 129.20, 129.53, 129.68, 129.99, 130.51, 132.44, 134.49, 135.90, 137.30, 138.89, 141.78, 147.91, 149.01, 157.21, 160.68, 175.47, 178.85, 200.19; HRMS (ES) *m/z* calcd for $C_{47}H_{48}N_3O_6S$ (MH+) 782.3264, found 782.3283.

Example 5:

(S)-{{2-[1-(2-Benzoylphenyl)amino]-2-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propyl}}-aminocarbonyl-methyloxy-3-aniline

Example **5** was prepared from intermediate **A** and *N*-Boc-3-aminophenyloxyacetic acid as described for Example **1**. The purified product was treated with 95% TFA in DCM (5 mL) to deprotect the amine functionality. Concentration under reduced pressure gave a yellow solid (1 mg, 8% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.48 (s, 3 H), 2.75 (m, 2 H), 3.06 (m, 2 H), 3.51 (br s, 2 H), 4.02 (t, *J* = 6.0, 1 H), 4.08 (m, 2 H), 4.41 (s, 2 H), 6.60 (t, *J* = 7.5, 1 H), 6.72 (d, *J* = 8.6, 2 H), 6.78 (m, 1 H), 6.91-7.03 (m, 4 H), 7.14-7.26 (m, 2 H), 7.35-7.63 (m, 10 H), 8.04 (d, *J* = 7.5, 2 H), 11.62 (br s, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 10.35, 23.85, 37.94, 42.31, 54.26, 66.82, 110.12, 113.63, 114.18, 114.75, 115.49, 116.34, 116.84, 118.52, 121.29, 127.63, 127.78, 128.49, 129.23, 129.73, 129.95, 130.37, 131.34, 131.72, 131.81, 134.50, 136.01, 136.20, 139.61, 148.98, 149.92, 157.14, 157.85, 170.35, 200.61; HRMS (ES) *m/z* calcd for $C_{42}H_{41}N_4O_5$ (MH+) 681.3077, found 681.3094.

Example 6:

N,N-Dimethyl-(S)-{{2-[1-(2-benzoylphenyl)amino]-2-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propyl}}-aminocarbonyl-3-phenethylamine

Example **6** was prepared from intermediate **A** and *N,N*-dimethyl 3-(2-aminoethyl)benzoic acid as described for Example **1** (2 mg, 16% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.4 (s, 3 H), 2.9 (m, 6 H), 3.0 (t, *J*=6.4, 2 H), 3.4 (s, 2 H), 3.6 (t, *J*=5.7, 2 H), 4.1 (m, 3 H), 4.3 (s, 2 H), 6.5 (t, *J*=7.4, 1 H), 6.8 (d, *J*=8.4, 2 H), 7.0 (dd, *J*=14.9, 8.1, 2 H), 7.2 (d, *J*=8.4, 2 H), 7.2 (m, 3 H), 7.3 (m, 2 H), 7.4 (m, 5 H), 7.5 (d, *J*=7.3, 1 H), 7.5 (m, 2 H), 8.0 (m, 2 H); ^{13}C

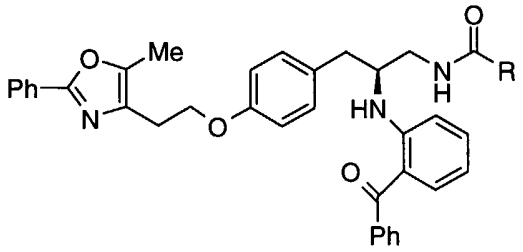
NMR (101 MHz, $CDCl_3$) δ ppm 10.48, 26.05, 39.01, 43.75, 43.57, 53.57, 56.51, 62.74, 66.60, 112.82, 113.23, 114.72, 114.83, 117.95, 118.40, 120.59, 126.42, 126.89, 128.33, 129.09, 129.25, 129.99, 130.18, 130.52, 130.73, 131.20, 132.17, 135.49, 135.82, 136.12, 140.55, 145.96, 151.42, 157.44, 157.60, 159.90, 167.71, 199.85; HRMS (ES) *m/z* calcd for $C_{45}H_{47}N_4O_5$ (MH+) 723.3546, found 723.3555.

Biological Data

Binding Assay

Test compounds were assayed for binding to the human PPAR-gamma receptor ligand binding domain as described in Nichols, J. S. et al., Anal. Biochem., (1998), Vol. 257, pp 112-119. Each of the above examples exhibited a $pK_i > 6$ in the binding assay. pKi values shown in Table 1 are representative values derived from one or more experiments.

Table 1



Cmpd	R	Binding PPARγ pK_i	CV-1 Cell PPARγ pEC_{50}
1	CH_3	6.9	6.0
2	cyclopropyl	7.2	6.2
3	$CH_2CH(CH_3)C(O)OH$	6.4	<5.0
4	$(CH_2)_2$-4-$C_6H_4SC(CH_3)_2C(O)OH$	6.6	<5.0
5	CH_2O-3-$C_6H_4NH_2$	6.7	<5.0
6	3-$C_6H_4(CH_2)_2N(CH_3)_2$	7.0	<5.0

Compounds of the invention were also run in representative binding assays of PPAR-alpha and PPAR-delta as described in Xu et al, Mol. Cell (1999) , Vol. 3, pp 397-403. Select compounds of the invention exhibited PPAR-alpha and PPAR-delta binding pKi's of 5.0-6.0.

Cell-based Reporter Assay

CV-1 cells were maintained in DME high glucose medium (Irvine Scientific) supplemented with 10% fetal bovine serum and 2 mM glutamine. Cells were split into D-MEM/F-12 medium (Gibco) supplemented with 10 % charcoal stripped fetal bovine serum for 3 d before harvesting. Cells were harvested into D-MEM/F-12 medium (Gibco) supplemented with 10 % charcoal stripped fetal bovine serum and counted. Cells were seeded at a density of 24,000 cells per well into 96-well plates and incubated overnight at 5% CO_2 and 37 °C. Cells were transfected for 6 to 20 hours based on the lipofectamine protocol (Gibco) with the following amounts of DNA per well: 2 ng PSG5 GAL4-human PPAR-gamma, 8 ng UAS-tk-SPAP, 25 ng beta-gal, 45 ng pBluescript. See Lehmann, J. M. et al., J. Biol. Chem., (1995), Vol. 270, pp 12953-12956 and Brown, P. J. et al., Chem. Biol., (1997), Vol. 4, pp 909-918. Cells were incubated overnight at 5 % CO_2 and 37 °C. Test compounds were solublized to 10 mM in DMSO. Test compounds were then serially diluted from 1e-5 M to 1e-10 M into D-MEM/ F-12 (Gibco) medium supplemented with 10% delipidated and charcoal stripped calf serum (Sigma) heat inactivated at 60 °C for 30 minutes, 2 mM glutamine, and Pen-Strep. This medium into which the test compounds were diluted also contained 100 nM rosiglitazone. These test compound dilutions were added 100 microliters/well to the transfected cell plates after the transfection media were aspirated. DMSO controls and 1 micromolar rosiglitazone controls were added to each cell plate. Cells were incubated overnight at 5 % CO_2 and 37 °C. Cells were lysed with 25 microliters 0.5 % Triton X-100. Two daughter plates were made from each mother plate. One daughter received 200 microliters/well SPAP substrate (Sigma 104) and the other daughter received 200 microliters/well beta-gal substrate (Sigma N-1127). Once developed, cell plates were read at 405 nM. SPAP data were normalized to beta-gal, and % maximum inhibition of transactivation was calculated relative to the 1 micromolar rosiglitazone positive control. The above examples exhibited > 50 % inhibition of transactivation at 10 μM induced by rosiglitazone in this reporter assay. The pEC50 was also determined for the compounds of the present invention employing the above described assay except that the

medium into which the test compounds were diluted did not contain 100 nM rosiglitazone. The calculated pEC50 values as shown in Table 1 are representative values derived from one or more experiments.

Adipocyte Differentiation Assay

C3H10T1/2 clone 8 murine fibroblasts (American Type Culture Collection) below passage 22 were maintained in Dulbecco's modified Eagle's medium (Life Technologies, Inc.) supplemented with 10 % fetal calf serum and 100 units/mL penicillin G and 100 microgram/mL streptomycin. One day after passage into 96-well microtiter plates (12.5 x 103 cells/cm^2), the cells were treated with 150 nM rosiglitazone plus 1 micromolar insulin and 1 micromolar 9-cis-retinoic acid (Sigma, St. Louis, Mo). Vehicle or test compounds, which had been solublized to 10 mM in DMSO and then serially diluted from 1e-5 M to 1e-10 M into medium, were added. After 7 days, cells were lysed in 0.01% Digitonin (Sigma, St. Louis, Mo) and the lipogenic activity determined by measuring total triglycerides using a Glycerol-Triglyceride (GPO-Trinder) kit (337-B,Sigma, St. Louis, Mo). The mixture was incubated at 37 °C for 2 h and the absorbance read at 550 nm. The % maximum inhibition of lipogenesis was calculated relative to the vehicle treated cells. The above examples exhibited > 50 % inhibition of lipogenesis at 50 μM induced by rosiglitazone (150 nM) in this adipocyte differentiation assay.

Mouse Model of Diabetes

Forty (40), age-matched male ob/ob mice were obtained from The Jackson Laboratory (Bar Harbor, Maine) and allowed to acclimate in the facilities for 7 days. At 8.5 weeks of age, the animals were sorted into four groups such that the mean body weight of each group was not different. The animals were then dosed for 7 days with either vehicle (0.5% hydroxy-propyl-methylcellulose + 0.1% Tween 80), a PPAR-gamma agonist (GW7845X, 3 mg/kg bid) or test compounds (Examples 4 and 5, 30 mg/kg bid). A terminal blood sample was taken at the end of dosing to determine changes in serum glucose, insulin, triglyceride, and HDL-c levels. The PPAR-gamma agonist GW7845 is (*S*)-2-(1-carboxy-2-{4-[2-(5-methyl-2-phenyloxazol-4-

yl)ethoxy]phenyl}ethylamino)benzoic acid methyl ester, and was used as the positive control (compound 63, Cobb et al., *J. Med. Chem.* **1998,** *41,* 5055-5069). Results are as shown in Tables 2-5, and corresponding Figures 1-4.

Table 2 summarizes serum glucose levels in mg/dL for each study animal, and the mean, first and second standard deviations, and standard error of the mean, for each treatment group. Figure 1 is the graphical representation of the data contained in Table 2.

Table 2

Serum Glucose mg/dL					
Animal #	**Baseline**	**Vehicle**	**GW7845**	**Ex. 5**	**Ex. 4**
1	449	489	209	423	225
2	319	591	237	593	351
3	478	686	313	502	353
4	474	621	182	559	231
5	464	683	217	587	316
6	586	520	254	450	394
MEAN	**461.67**	**598.33**	**235.33**	**519.00**	**311.67**
1 S.D.	85.32	81.87	45.29	72.06	69.38
2 S.D.	170.64	163.73	90.59	144.13	138.77
SEM	38.16	36.61	20.26	32.23	31.03

Table 3 summarizes circulating insulin levels in ng/mL for each study animal, and the mean, first and second standard deviations, and standard error of the mean, for each treatment group. Figure 2 is the graphical representation of the data contained in Table 3.

Table 3

Circulating Insulin ng/mL					
Animal #	**Baseline**	**Vehicle**	**GW7845**	**Ex. 5**	**Ex. 4**
1	7.016	23.607	6.857	8.426	8.662

2	22.692	17.171	2.082	8.206	8.363
3	14.860	10.416	4.378	13.736	15.093
4	7.689	25.962	4.229	7.271	3.818
5	22.686	6.357	2.183	8.986	6.246
6	48.8	31.937	2.573	5.108	9.116
MEAN	**20.6245**	**19.2416**	**3.7168**	**8.6222**	**8.5498**
1 S.D.	15.417	1 S.D.	1.838	1 S.D.	3.765
2 S.D.	30.834	2 S.D.	3.676	2 S.D.	7.530
SEM	6.895	SEM	0.822	SEM	1.684

Table 4 summarizes serum triglyceride levels in mg/dL for each study animal, and the mean, first and second standard deviations, and standard error of the mean, for each treatment group. Figure 3 is the graphical representation of the data contained in Table 4.

Table 4

Serum Triglycerides mg/dL					
Animal #	**Baseline**	**Vehicle**	**GW7845**	**Ex. 5**	**Ex. 4**
1	106.0	173.0	48.0	129.0	47.0
2	154.0	166.0	62.0	134.0	51.0
3	170.0	268.0	62.0	156.0	59.0
4	187.0	179.0	102.0	217.0	52.0
5	193.0	197.0	48.0	126.0	61.0
6	253.0	185.0	37.0	170.0	63.0
MEAN	**177.17**	**194.67**	**59.83**	**155.33**	**55.50**
1 S.D.	48.48	37.45	22.75	34.72	6.38
2 S.D.	96.96	74.90	45.51	69.44	12.76
SEM	21.68	16.75	10.18	15.53	2.85

Table 5 summarizes HDL-C levels in mg/dL for each study animal, and the mean, first and second standard deviations, and standard error of the

mean, for each treatment group. Figure 4 is the graphical representation of the data contained in Table 5.

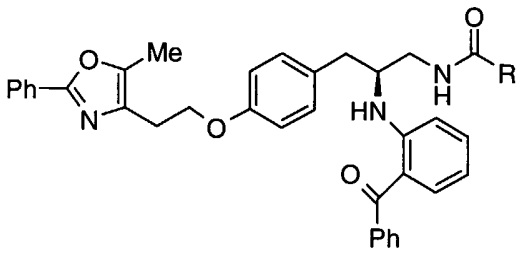
Table 5

Serum Cholesterol mg/dL					
Animal #	**Baseline**	**Vehicle**	**GW7845**	**Cmpd 5**	**Cmpd 4**
1	147	122	195	223	211
2	128	118	221	209	220
3	135	149	225	213	245
4	140	112	222	195	209
5	132	139	213	208	179
6	156	126	260	207	204
MEAN	**139.67**	**127.67**	**222.67**	**209.17**	**211.33**
1 S.D.	10.37	13.84	21.27	9.09	21.51
2 S.D.	20.73	27.67	42.53	18.17	43.02
SEM	4.64	6.19	9.51	4.06	9.62

CLAIMS

What is claimed is:

1. A compound of formula (I)



(I)

or salt or solvate thereof, wherein;

R is CH_3, cyclopropyl, $CH_2CH(CH_3)C(O)OH$, $(CH_2)_2$-4-$C_6H_4SC(CH_3)_2C(O)OH$, CH_2O-3-$C_6H_4NH_2$, or 3-$C_6H_4(CH_2)_2N(CH_3)_2$.

2. A compound of claim 1, wherein said compound is selected from the group consisting of:

(S)-{{2-[1-(2-Benzoylphenyl)amino]-2-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propyl}}-acetamide;

(S)-{{2-[1-(2-Benzoylphenyl)amino]-2-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propyl}}cyclopropanecarboxamide;

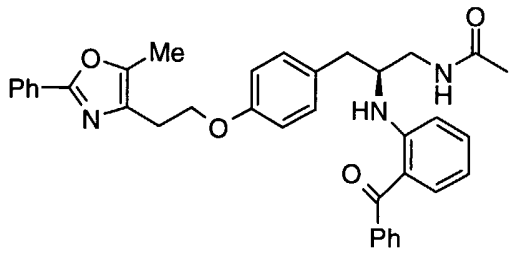
(S)-{{2-[1-(2-Benzoylphenyl)amino]-2-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propyl}}-aminocarbonyl-(2-methyl)-propionic acid;

(S)-{{2-[1-(2-Benzoylphenyl)amino]-2-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propyl}}-aminocarbonyl-ethyl-4-phenylthio-2',2'-dimethylacetic acid;

(S)-{{2-[1-(2-Benzoylphenyl)amino]-2-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propyl}}-aminocarbonyl-methyloxy-3-aniline; and

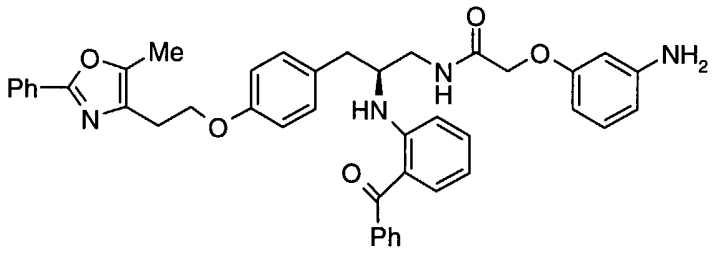
N,N-Dimethyl-(S)-{{2-[1-(2-benzoylphenyl)amino]-2-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propyl}}-aminocarbonyl-3-phenethylamine.

3. A compound of claim 1, wherein said compound is



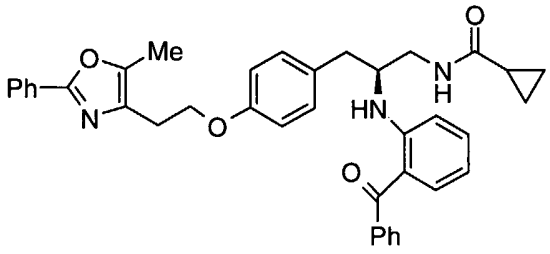
or a salt or solvate thereof.

4. A compound of claim 1, wherein said compound is



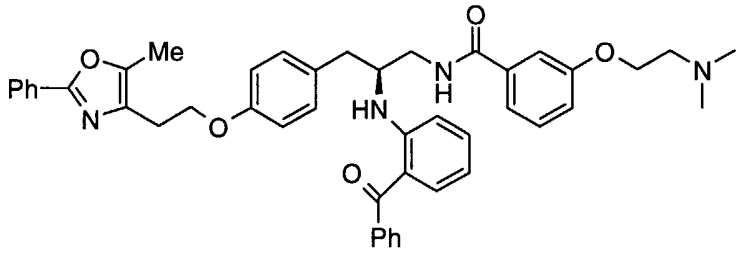
or a salt or solvate thereof.

5. A compound of claim 1, wherein said compound is



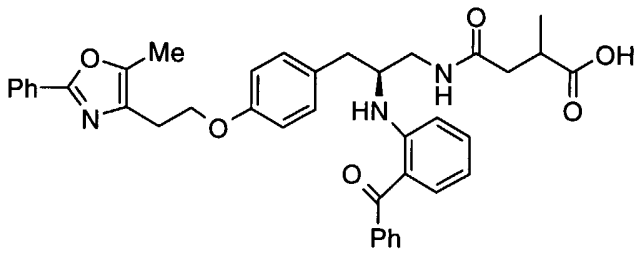
or a salt or solvate thereof.

6. A compound of claim 1, wherein said compound is



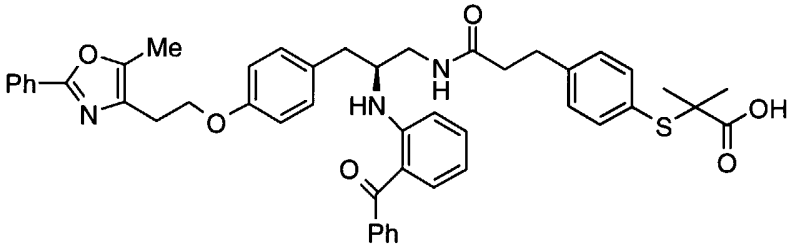
or a salt or solvate thereof.

7. A compound of claim 1, wherein said compound is



or a salt or solvate thereof.

8. A compound of claim 1, wherein said compound is



or a salt or solvate thereof.

9. A compound of claim 1, wherein said compound is a PPAR-gamma antagonist.

10. A pharmaceutical composition comprising a compound according to claims 1 to 8, and a pharmaceutically acceptable carrier.

11. A method of treatment of a PPARγ mediated condition or disorder comprising the administration of a compound according to claims 1 to 8.

12. A method of treatment of diabetes, obesity, aging, cancer, acne, osteoporosis, inflammation, metabolic syndrome, impaired glucose tolerance, syndrome X, dyslipidemia or cardiovascular disease comprising the administration of a compound according to claims 1 to 8.

13. A compound according to claims 1 to 8 for use in the treatment of PPARγ mediated conditions or disorders.

14. A compound according to claims 1 to 8 for use in the treatment of diabetes, obesity, aging, cancer, acne, osteoporosis, inflammation, metabolic syndrome, impaired glucose tolerance, syndrome X, dyslipidemia or cardiovascular disease.

15. Use of a compound according to claims 1 to 8 in the manufacture of a medicament for use in the treatment of PPARγ mediated conditions or disorders.

16 Use of a compound according to claims 1 to 8 in the manufacture of a medicament for use in the treatment of diabetes, obesity, aging, cancer, acne, osteoporosis, inflammation, metabolic syndrome, impaired glucose tolerance, syndrome X, dyslipidemia or cardiovascular disease.

Figure 1

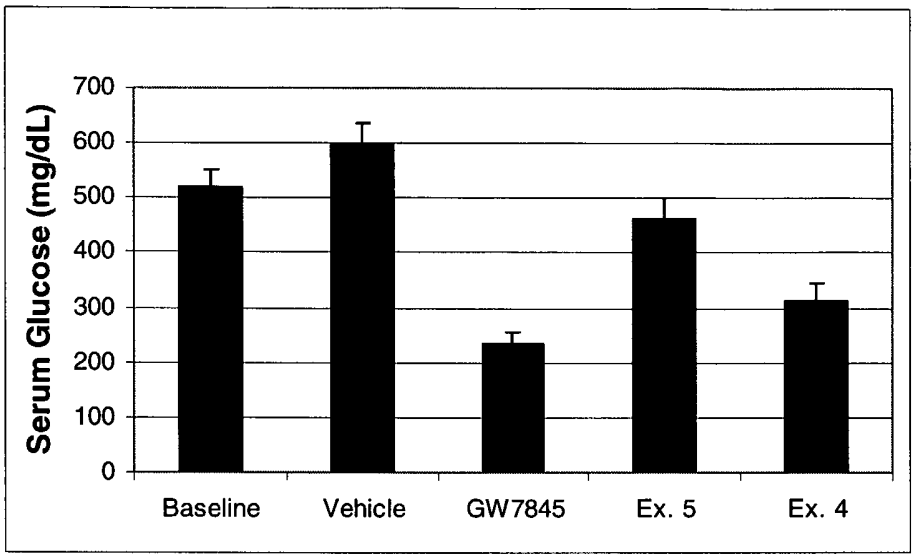

Serum Glucose (mg/dL)
700
600
500
400
300
200
100
0
Baseline
Vehicle
GW7845
Ex. 5
Ex. 4

Figure 2

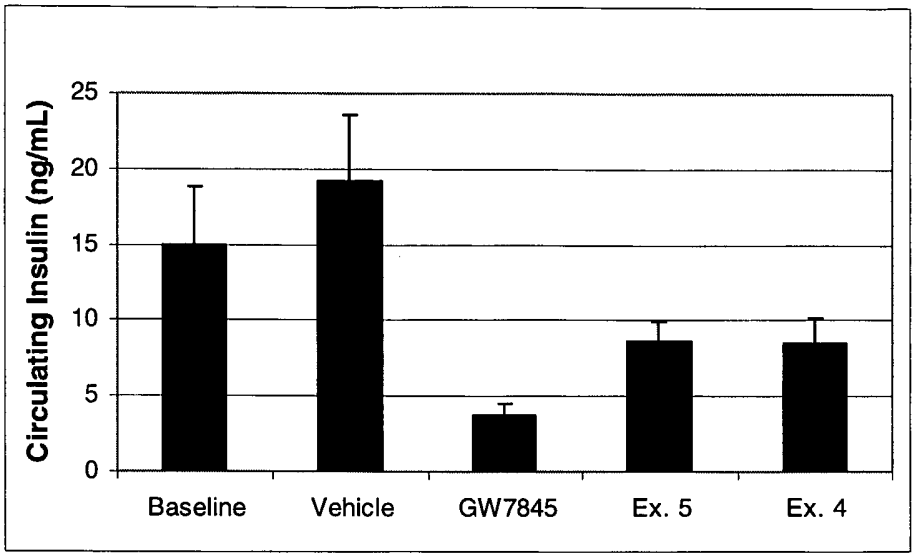

Circulating Insulin (ng/mL)
25
20
15
10
5
0
Baseline
Vehicle
GW7845
Ex. 5
Ex. 4

Figure 3

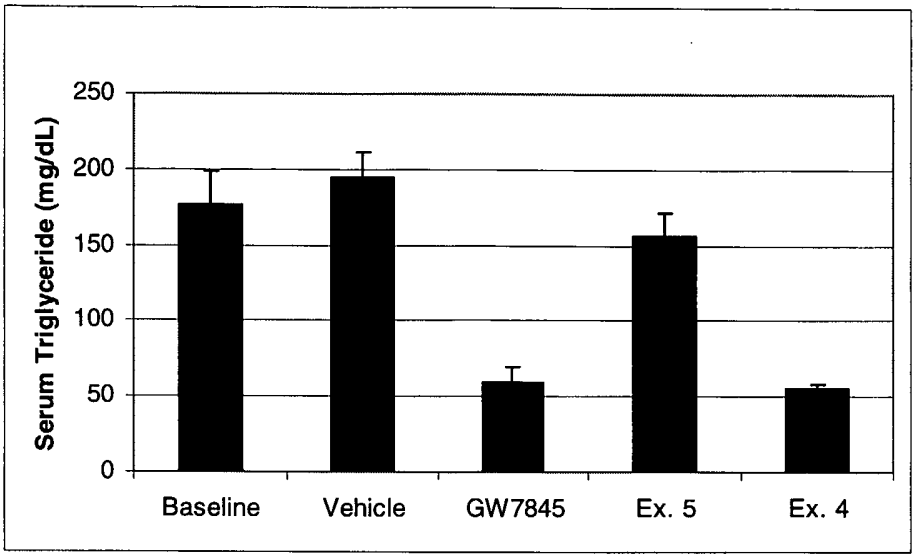
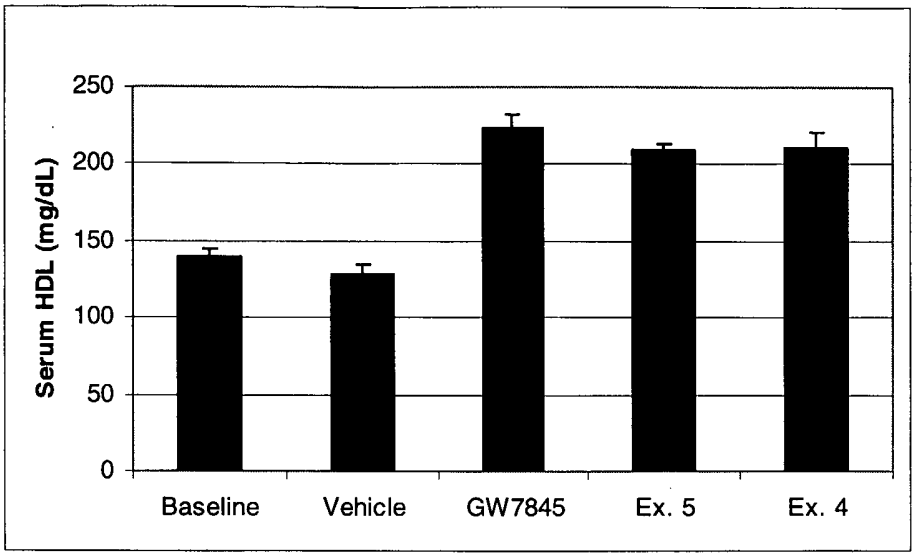

Serum Triglyceride (mg/dL)
250
200
150
100
50
0
Baseline
Vehicle
GW7845
Ex. 5
Ex. 4

Figure 4


Serum HDL (mg/dL)
250
200
150
100
50
0
Baseline
Vehicle
GW7845
Ex. 5
Ex. 4

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/037580

A. CLASSIFICATION OF SUBJECT MATTER
C07D263/32 A61K31/421 A61P3/04 A61P3/10 A61P9/00
A61P19/10 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, INSPEC, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	COBB J E ET AL: "N-(2-Benzoylphenyl)-L-tyrosine PPAR gamma agonists. 3. Structure-activity relationship and optimization of the N-aryl substituent" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 41, no. 25, 3 December 1998 (1998-12-03), pages 5055-5069, XP002156427 ISSN: 0022-2623 cited in the application the whole document in particular figures 4-7; tables 4,5 and Conclusion in page 5061 -/--	1-16

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 March 2006	29/03/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Papathoma, S

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/037580

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	COLLINS J L ET AL: "n-(2-BENZOYLPHENYL)-L-TYROSINE PPAR-GAMMA AGONISTS. 2. STRUCTURE-ACTIVITY RELATIONSHIP AND OPTIMIZATION OF THE PHENYL ALKYL ETHER MOIETY" JOURNAL OF MEDICINAL AND PHARMACEUTICAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 41, 1998, pages 5037-5054, XP002211273 the whole document in particular tables 1-5 and Conclusion in pages 5044, 5047and 5048	1-16
A	COOPER, JOEL P. ET AL: "Synthesis and identification of a novel 6,5,6 -tricyclic lactam" HETEROCYCLES , 60(3), 607-613 CODEN: HTCYAM; ISSN: 0385-5414, 2003, XP001246724 page 608; figure 1	1-16
A	WO 01/17994 A (GLAXO GROUP LIMITED; COBB, JEFFREY, EDMOND; LAMBERT, MILLARD, HURST, I) 15 March 2001 (2001-03-15) the whole document	1-16
A	WO 2004/046091 A (GALDERMA RESEARCH & DEVELOPMENT, S.N.C; CLARY, LAURENCE; BOUIX-PETER,) 3 June 2004 (2004-06-03) abstract; claims 1-22; example 10 page 1 - page 3	1-16
A	US 2003/069275 A1 (CHENG PETER T ET AL) 10 April 2003 (2003-04-10) the whole document	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2005/037580

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