(19) DANMARK

(10) DK/EP 1940815 T3

(12) Oversættelse af europæisk patentskrift

Patent- og Varemærkestyrelsen

(51) Int.Cl.: *C 07 D 295/22 (2006.01)* *A 61 K 31/496 (2006.01)* *A 61 P 3/10 (2006.01)*

(45) Oversættelsen bekendtgjort den: **2018-11-05**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2018-08-15**

(86) Europæisk ansøgning nr.: **06839511.0**

(86) Europæisk indleveringsdag: **2006-10-23**

(87) Den europæiske ansøgnings publiceringsdag: **2008-07-09**

(86) International ansøgning nr.: **US2006060172**

(87) Internationalt publikationsnr.: **WO2007051095**

(30) Prioritet: **2005-10-25 US 730249 P**

(84) Designerede stater: **AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC NL PL PT RO SE SI SK TR**

(73) Patenthaver: **Kalypsys, Inc., 10420 Wateridge Circle, San Diego, CA 92121, USA**

(72) Opfinder: **PARENT, Stephan, D., 2120 Cumulus Court, West Lafayette, IN 47906, USA**
JONAITIS, David, T., 225 Perrin Avenue, Lafayette, IN 47901, USA
BENNETT, Dennis, A., Apartment 208, 2 Hogan Circle, Mail Box 14, Eureka, MO 63025, USA

(74) Fuldmægtig i Danmark: **Plougmann Vingtoft A/S, Rued Langgaards Vej 8, 2300 København S, Danmark**

(54) Benævnelse: **SALTE AF MODULATORER AF PPAR OG FREMGANGSMÅDER TIL BEHANDLING AF STOFSKIFTESYGDOMME**

(56) Fremdragne publikationer:
EP-A1- 0 107 622
EP-A1- 1 236 719
EP-A2- 0 158 596
EP-A2- 0 173 899
WO-A-2004/092117
WO-A-2005/016881
WO-A-2006/055187
US-A- 4 237 130

DESCRIPTION

FIELD OF THE INVENTION

[0001] The present invention relates to salts the salts for use in treating various diseases by modulation of nuclear receptor mediated processes using these salts, and in particular processes mediated by peroxisome proliferator activated receptors (PPARs).

BACKGROUND OF THE INVENTION

[0002] Peroxisome proliferators are a structurally diverse group of compounds which, when administered to mammals, elicit dramatic increases in the size and number of hepatic and renal peroxisomes, as well as concomitant increases in the capacity of peroxisomes to metabolize fatty acids via increased expression of the enzymes required for the β-oxidation cycle (Lazarow and Fujiki, Ann. Rev. Cell Biol. 1:489-530 (1985); Vamecq and Draye, Essays Biochem. 24:1115-225 (1989); and Nelali et al., Cancer Res. 48:5316-5324 (1988)). Compounds that activate or otherwise interact with one or more of the PPARs have been implicated in the regulation of triglycexide and cholesterol levels in animal models. Compounds included in this group are the fibrate class of hypolipidemic drugs, herbicides, and phthalate plasticizers (Reddy and Lalwani, Crit. Rev. Toxicol. 12:1-58 (1983)). Peroxisome proliferation can also be elicited by dietary or physiological factors such as a high-fat diet and cold acclimatization.

[0003] Biological processes modulated by PPAR are those modulated by receptors, or receptor combinations, which are responsive to the PPAR receptor ligands. These processes include, for example, plasma lipid transport and fatty acid catabolism, regulation of insulin sensitivity and blood glucose levels, which are involved in hypoglycemia/hyperinsulinemia (resulting from, for example, abnormal pancreatic beta cell function, insulin secreting tumors and/or autoimmune hypoglycemia due to autoantibodies to insulin, the insulin receptor, or autoantibodies that are stimulatory to pancreatic beta cells), macrophage differentiation which lead to the formation of atherosclerotic plaques, inflammatory response, carcinogenesis, hyperplasia, and adipocyte differentiation.

[0004] Subtypes of PPAR include PPAR-alpha, PPAR-delta (also known as NUC1, PPAR-beta, and FAAR) and two subtypes of PPAR-gamma. These PPARs can regulate expression of target genes by binding to DNA sequence elements, termed PPAR response elements (PPRE). To date, PPRE's have been identified in the enhancers of a number of genes encoding proteins that regulate lipid metabolism suggesting that PPARs play a pivotal role in the adipogenic signaling cascade and lipid homeostasis (H. Keller and W. Wahli, Trends Endoodn. Met. 291-296, 4 (1993)).

[0005] Insight into the mechanism whereby peroxisome proliferators exert their pleiotropic effects was provided by the identification of a member of the nuclear hormone receptor superfamily activated by these chemicals (Isseman and Green, Nature 347-645-650 (1990)). The receptor, termed PPAR-alpha (or alternatively, PPARα), was subsequently shown to be activated by a variety of medium and long-chain fatty acids and to stimulate expression of the genes encoding rat acyl-CoA oxidase and hydratase-dehydrogenase (enzymes required for peroxisomal β-oxidation), as well as rabbit cytochrome P450 4A6, a fatty acid ω-hydroxylase (Gottlicher et al., Proc. Natl. Acad. Sci. USA 89:4653-4657 (1992); Tugwood et al., EMBO J 11:433-439 (1992); Bardot et al., Biochem. Biophys. Res. Comm. 192:37-45 (1993); Muerhoff et al., J Biol. Chem. 267:19051-19053 (1992); and Marcus et al., Proc. Natl. Acad Sci. USA 90(12):5723-5727 (1993).

[0006] Activators of the nuclear receptor PPAR-gamma (or alternatively, PPAKγ), for example troglitazone, have been clinically shown to enhance insulin-action, to reduce serum glucose and to have small but significant effects on reducing serum triglyceride levels in patients with Type 2 diabetes. See, for example, D. E. Kelly et al., Curr. Opin. Endocrinol. Diabetes, 90-96, 5 (2), (1998); M. D. Johnson et al., Ann. Pharmacother., 337-348, 32 (3), (1997); and M. Leutenegger et al., Curr. Ther. Res., 403-416, 58 (7), (1997).

[0007] The third subtype of PPARs, PPARδ (PPARδ, NUC1), is broadly expressed in the body and has been shown to be a valuable molecular target for treatment of dyslipidemia and other diseases. For example, in a recent study in insulin-resistant obese rhesus monkeys, a potent and selective PPAPδ compound was shown to decrease VLDL and increase HDL in a dose response manner (Oliver et al., Proc. Natl. Acad. Sci. U. S. A.98: 5305, 2001). Also, in a recent study in wild-type and HDL-lacking, $ABCA1^{-/-}$ mice, a different potent and selective PPAKδ compound was shown to reduce fractional cholesterol absorption in the intestine, and coincidently reduce expression of the cholesterol-absorption protein NPC1L1 (van der Veen et al., J. Lipid Res. 2005 46: 526-534).

[0008] Because there are three subtypes of PPAR. and all of them have been shown to play important roles in energy homeostasis and other important biological processes in human body and have been shown to be important molecular targets for treatment of metabolic and other diseases (see Willson, et al. J. Med. Chem. 43: 527-550 (2000)), it is desired in the art to identify compounds which are capable of selectively interacting with only one of the PPAR subtypes or compounds which are capable of interacting with multiple PPAR subtypes. Such compounds would find a wide variety of uses, such as, for example, in the treatment or prevention of obesity, for the treatment or prevention of diabetes, dyslipidemia, metabolic syndrome X and other uses.

[0009] WO2005/016881 relates to bicyclic indoline sulphonamide derivatives, methods for the production thereof and the use thereof in medicament especially as potent PPAR delta aganists for preventing and/or treating cardiovascular diseases, particularly dyslipidemia, arteriosclerosis, and culinary heart disease. WO2004/092117 describes para-sulphonyl substituted phenyl compounds as modulators of PPARs.

SUMMARY OF THE INVENTION

[0010] The present invention provides novel salt forms of PPAR modulators which are useful in the treatment or prevention of conditions and disorders including but not limited to those associated with energy homeostasis, lipid metabolism, adipocyte differentiation, inflammation and diabetic conditions, such as, for example, hyperglycemia and hyperinsulinemia. The invention also provides pharmaceutical use of said salts for the treatment of, for example, conditions and disorders associated with energy homeostasis, lipid metabolism, adipocyte differentiation, inflammation and diabetic conditions, including, but not limited to, hyperglycemia and hyperinsulinemia.

[0011] In particular, the present invention relates to a salt of a compound chosen from 4-[cis-2,6-dimethyl-4-(4-trifluoromethoxy-phenyl)-piperazine-1-sulfonyl]-indan-2-carboxylic acid and (S)-4-(cis-2,6-Dimethyl-4-(4-trifluoromethoxy-benzyl)-piperazine-1-sulfonyl)-indan-2-carboxylic acid, wherein the salt is chosen from sulfate, sodium, potassium, magnesium, calcium, hydrochloride, phosphate, and tosylate.

[0012] The present invention also provides pharmaceutical compositions comprising one or more salts of the invention and one or more pharmaceutically acceptable diluents, excipients or carriers.

[0013] The present invention also provides the salt of the above the aspect for use in the treatment of disease, in particular a PPAR-Medicated disease.

[0014] The novel salt forms of the invention are particularly useful as active pharmaceutical ingredients for the preparation of formulations for use in animals or humans. Thus, the present invention encompasses the use of these solid forms as final drug products. The salts and final drug products of the invention are useful, for example, for the treatment or prevention of conditions and disorders associated with energy homeostasis, lipid metabolism, adipocyte differentiation and inflammation.

DETAILED DESCRIPTION OF THE INVENTION

[0015] The claimed salt forms modulate at least one peroxisome proliferator-activated receptor (PPAR) function. The compound described herein may be activating both PPARδ and PPARγ or PPARα and PPARδ, or all three PPAR subtypes, or selectively activating-predominantly PPARγ, PPARα or PPARδ. Thus, the salts are useful in methods of modulating PPAR comprising contacting said PPAR with a salt of the invention. In certain preferred embodiments, said modulation is selective for PPARδ over PPARα and PPARγ. In certain more preferred embodiments, said modulation of PPARδ is 100-fold selective or greater over said

other subtypes. Most-preferably, said modulation is 200- to 500-fold selective over said other subtypes.

[0016] The salt of the present invention is useful in a method of modulating at least one peroxisome proliferator-activated receptor (PPAR) function comprising the step of contacting the PPAR with a salt of a compound of Formula I, as described herein. The change in cell phenotype, cell proliferation, activity of the PPAR, expression of the PPAR or binding of the PPAR with a natural binding partner may be monitored. Such methods may be modes of treatment of disease, biological assays, cellular assays, biochemical assays, or the like.

[0017] The salt of the present invention may be used in methods of treating disease, comprising administering a therapeutically effective amount of the salt to a patient. Thus, the salts may be used in methods for raising HDL, lowering LDLc, shifting LDL particle size from small dense to normal LDL, or inhibiting cholesterol absorption in a subject; for decreasing insulin resistance or lowering blood pressure in a subject; for treating obesity, diabetes, especially Type 2 diabetes, hyperinsulinemia, metabolic syndrome X, dyslipidemia, and hypercholesterolemia; for treating cardiovascular diseases including vascular disease, atherosclerosis, coronary heart disease, cerebrovascular disease, heart failure and peripheral vessel disease in a subject; for treating cancers including colon, skin, and lung cancers in a subject; for treating inflammatory diseases, including rheumatoid arthritis, asthma, osteoarthritis, disorders associated with oxidative stress, inflammatory response to tissue injury, and autoimmune disease in a subject; and for treating polycystic ovary syndrome, climacteric, pathogenesis of emphysema, ischemia-associated organ injury, doxorubicin-induced cardiac injury, drug-induced hepatotoxicity, hypertoxic lung injury, scarring, wound healing, anorexia nervosa and bulimia nervosa in a subject, all comprising the administration of a therapeutic amount of the salt Preferably, the PPAR may be selected from the group consisting of PPARα, PPARδ, and PPARy. More preferably, the PPAR is PPAPδ.

[0018] As used in the present specification the following terms have the meanings indicated:

[0019] It should be understood that where appropriate the invention encompasses all stereochemical isomeric forms, including diastereomeric, enantiomeric, and epimeric forms, as well as d-isomers and 1-isomers, and mixtures thereof. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centers or by preparation of mixtures of enantiomeric products followed by separation such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, direct separation of enantiomers on chiral chromatographic columns, or any other appropriate method known in the art. Starting compounds of particular stereochemistry are either commercially available or can be made and resolved by techniques known in the art. Additionally, the compounds of the present invention may exist as geometric isomers. The present invention includes all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof. Additionally, compounds may exist as tautomers; all tautomeric isomers are provided by this invention. Additionally, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically

acceptable solvents such as water or ethanol. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

[0020] As used herein, "diabetes" refers to type I diabetes mellitus (juvenile diabetes) or type II diabetes mellitus (non- insulin-dependent diabetes mellitus or NIDDM), preferably, type II diabetes mellitus.

[0021] As used herein, the term "PPAR-mediated condition or disorder" or "PPAR-mediated condition or disease" refers to a condition, disorder, or disease characterized by inappropriate, e.g. less than or greater than normal, PPAR. activity. Inappropriate PPAR activity might arise as the result of PPAR expression in cells which normally do not express PPAR, increased PPAR expression (leading to, e.g. certain energy homeostasis, lipid metabolism, adipocyte differentiation and inflammatory disorders and diseases), or, decreased PPAR expression (leading to, e.g. certain energy homeostasis, lipid metabolism, adipocyte differentiation and inflammatory disorders and diseases). A PPAR mediated condition or disorder may be completely or partially mediated by inappropriate PPAR activity. However, a PPAR-mediated condition or disorder is one in which modulation of PPAR results in some effect on the underlying condition or disease (e.g. a PPAR modulator results in some improvement in patient well-being in at least some patients). Exemplary PPAR-mediated conditions and disorders include, but are not limited to, metabolic disorders, e.g., diabetes, type II diabetes, obesity, hyperglycemia, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia and dyslipidemia, and inflammatory conditions, e.g. rheumatoid arthritis and atherosclerosis.

[0022] The term "modulate," in its various forms, refers to the ability of a compound to increase or decrease the function or activity associated with a particular peroxisome proliferator-activated receptor, preferably the PPARδ receptor. Modulation, as described herein, includes the inhibition or activation of PPAR, either directly or indirectly. Inhibitors are compounds that, e.g., bind to, partially or totally block stimulation, decrease, prevent, delay activation, inactivate, desensitize, or down regulate signal transduction, e.g., antagonists. Activators are compounds that, e.g., bind to, stimulate, increase, open, activate, facilitate, enhance activation, sensitize or up regulate signal transduction, e.g., agonists.
Further, modulation of PPAR. receptor activity is intended to encompass antagonism, agonism, partial antagonism and/or partial agonism of the activity associated with the PPAR receptor.

[0023] The term "composition" as used herein is intended to encompass a product comprising the specified ingredients (and in the specified amounts, if indicated), as well as any product which results, directly or indirectly, from combination of "the specified ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant the diluent, excipient or carrier must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[0024] The term "therapeutically effective amount" refers to the amount of the subject salt that will elicit the biological or medical response of a tissue, system, animal or human that is being

sought by the researcher, veterinarian, medical doctor or other clinician or that is sufficient to prevent development of or alleviate to some extent one or more of the symptoms of the disease being treated. In reference to the treatment of diabetes or dyslipidemia a therapeutically effective amount may refer to that amount which has the effect of (1) reducing the blood glucose levels; (2) normalizing lipids, e.g. triglycerides, low-density lipoprotein; (3) relieving to some extent (or, preferably, eliminating) one or more symptoms associated with the disease, condition or disorder to be treated; and/or (4) raising HDL.

[0025] The term "subject" is defined herein to include animals such as mammals, including, but not limited to, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, and mice. In preferred embodiments, the subject is a human.

[0026] The terms "enhance" or "enhancing" means to increase or prolong either in potency or duration a desired effect. Thus, in regard to enhancing the effect of therapeutic agents, the term "enhancing" refers to the ability to increase or prolong, either in potency or duration, the effect of other therapeutic agents on a system. An "enhancing-effective amount," as used herein, refers to an amount adequate to enhance the effect of another therapeutic agent in a desired system. When used in a patient, amounts effective for this use will depend on the severity and course of the disease, disorder or condition (including, but not limited to, metabolic disorders), previous therapy, the patient's health status and response to the drugs, and the judgment of the treating physician. It is considered well within the skill of the art for one to determine such enhancing-effective amounts by routine experimentation.

[0027] The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

[0028] Particular salts described below include "tosylate salts" or "p-toluenesulfonate salts"

[0029] A tosylate or p-toluenesulfonate salt is an acid addition salt formed from p-toluenesulfonic acid.

[0030] The terms, "polymorphs" and "polymorphic forms" and related terms herein refer to crystal forms of the same molecule, and different polymorphs may have different physical properties such as, for example, melting temperatures, heats of fusion, solubilities, dissolution rates and/or vibrational spectra as a result of the arrangement or conformation of the molecules in the crystal lattice. The differences in physical properties exhibited by polymorphs affect pharmaceutical parameters such as storage stability, compressibility and density (important in formulation and product manufacturing), and dissolution rates (an important factor in bioavailability). Differences in stability can result from changes in chemical reactivity (e.g.. differential oxidation, such that a dosage form discolors more rapidly when comprised of one polymorph than when comprised of another polymorph) or mechanical changes (e.g.

tablets crumble on storage as a kinetically favored polymorph converts to thermodynamically more stable polymorph) or both (e.g., tablets of one polymorph are more susceptible to breakdown at high humidity). As a result of solubility/dissolution differences, in the extreme case, some polymorphic transitions may result in lack of potency or, at the other extreme, toxicity. In addition, the physical properties of the crystal may be important in processing, for example, one polymorph might be more likely to form solvates or might be difficult to filter and wash free of impurities (i.e., particle shape and size distribution might be different between polymorphs).

[0031] Polymorphs of a molecule can be obtained by a number of methods, as known in the art. Such methods include, but are not limited to, melt recrystallization, melt cooling, solvent recrystallization, desolvation, rapid evaporation, rapid cooling, slow cooling, vapor diffusion and sublimation.

[0032] Techniques for characterizing polymorphs include, but are not limited to, differential scanning calorimetry (DSC), X-ray powder diffractometry (XRPD), single crystal X-ray diffractometry, vibrational spectroscopy, e.g. IR and Raman spectroscopy, solid state NMR, hot stage optical microscopy, scanning electron microscopy (SEM), electron crystallography and quantitative analysis, particle size analysis (PSA), surface area analysis, solubility studies and dissolution studies.

[0033] The term, "solvate," as used herein, refers to a crystal form of a substance which contains solvent.

[0034] The term "hydrate" refers to a solvate wherein the solvent is water.

[0035] The term, "desolvated solvate," as used herein, refers to a crystal form of a substance which can only be made by removing the solvent from a solvate.

[0036] The term, "amorphous form," as used herein, refers to a noncrystalline form of a substance.

[0037] The salts of the invention are useful in the treatment of a disease or condition ameliorated by the modulation of a PPAR-delta. Specific diseases and conditions modulated by PPAR-delta and for which the compounds and compositions are useful include but are not limited to dyslipidemia, syndrome X, heart failure, hypercholesteremia, cardiovascular disease, type II diabetes mellitus, type 1 diabetes, insulin resistance hyperlipidemia, obesity, anorexia bulimia, inflammation and anorexia nervosa. Other indications include reduction of scarring and wound healing.

[0038] The salts of the invention may also be used (a) for raising HDL in a subject; (b) for treating Type 2 diabetes, decreasing insulin resistance, treating obesity, or lowering blood pressure in a subject; (c) for decreasing LDLc in a subject; (d) for shifting LDL particle size from small dense to normal dense LDL in a subject; (c) for reducing cholesterol absorption or

increasing cholesterol excretion in a subject; (f) for reducing the expression of NPC1L1 in a subject; (g) for treating atherosclerotic diseases including vascular disease, coronary heart disease, cerebrovascular disease and peripheral vessel disease in a subject; or (h) for treating inflammatory diseases, including asthma, rheumatoid arthritis, osteoarthritis, disorders associated with oxidative stress, inflammatory response to tissue injury, psoriasis, ulcerative colitis, dermatitis, and autoimmune disease in a subject.

[0039] The salts of the invention may also be used for treating, ameliorating, or preventing a disease or condition selected from the group consisting of obesity, diabetes, hyperinsulinemia, metabolic syndrome X, polycystic ovary syndrome, climacteric, disorders associated with oxidative stress, inflammatory response to tissue injury, pathogenesis of emphysema, ischemia-associated organ injury, doxorubicin-induced cardiac injury, drug-induced hepatotoxicity, atherosclerosis, and hypertoxic lung injury.

[0040] The compositions containing the salts described herein can be administered for prophylactic and/or therapeutic treatments. In therapeutic applications, the compositions comprising these salts are administered to a patient already suffering from a disease, condition or disorder mediated, modulated or involving the PPARs, including but not limited to metabolic diseases, conditions, or disorders, as described above, in an amount sufficient to cure or at least partially arrest the symptoms of the disease, disorder or condition. Amounts effective for this use will depend on the severity and course of the disease, disorder or condition, previous therapy, the patient's health status and response to the drugs, and the judgment of the treating physician. It is considered well within the skill of the art for one to determine such therapeutically effective amounts by routine experimentation (e.g., a dose escalation clinical trial).

[0041] In prophylactic applications, compositions containing the salts described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, disorder or condition mediated, modulated or involving the PPARs, including but not limited to metabolic diseases, conditions, or disorders, as described above. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's state of health, weight, and the like. It is considered well within the skill of the art for one to determine such prophylactically effective amounts by routine experimentation (e.g., a dose escalation clinical trial).

[0042] Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, the dosage or the frequency of administration, or both, can be reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. When the symptoms have been alleviated to the desired level, treatment can cease. Patients can, however, require intermittent treatment on a long-term basis upon any recurrence of symptoms.

[0043] The amount of a given agent that will correspond to such an amount will vary depending upon factors such as the particular compound, disease condition and its severity,

the identity (e.g., weight) of the subject or host in need of treatment, but can nevertheless be routinely determined in a manner known in the art according to the particular circumstances surrounding the case, including, e.g., the specific agent being administered, the route of administration, the condition being treated, and the subject or host being treated. In general, however, doses employed for adult human treatment will typically be in the range of 0.02-5000 mg per day, preferably 1-1500 mg 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.

[0044] In certain instances, it may be appropriate to administer at least one of the salts described herein in combination with another therapeutic agent. By way of example only, if one of the side effects experienced by a patient upon receiving one of the compounds herein is hypertension, then it may be appropriate to administer an anti-hypertensive agent in combination with the initial therapeutic agent. Or, by way of example only, the therapeutic effectiveness of one of the compounds described herein may be enhanced by administration of an adjuvant (i.e., by itself the adjuvant may only have minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the patient is enhanced). Or, by way of example only, the benefit of experienced by a patient may be increased by administering one of the compounds described herein with another therapeutic agent (which also includes a therapeutic regimen) that also has therapeutic benefit. By way of example only, in a treatment for diabetes involving administration of one of the salts described herein, increased therapeutic benefit may result by also providing the patient with another therapeutic agent for diabetes. In any case, regardless of the disease, disorder or condition being treated, the overall benefit experienced by the patient may simply be additive of the two therapeutic agents or the patient may experience a synergistic benefit.

[0045] Specific, non-limiting examples of possible combination therapies include use of the salts of the compound of formula (I) with: (a) statin and/or other lipid lowering drugs for example MTP inhibitors and LDLR upregulators; (b) antidiabetic agents, e.g. metformin, sulfonylureas, or PPAR-gamma, PPAR-alpha and PPAR-alpha/gamma modulators (for example thiazolidinediones such as e.g. Pioglitazone and Rosiglitazone); and (c) antihypertensive agents such as angiotensin antagonists, e.g., telmisartan, calcium channel antagonists, e.g. lacidipine and ACE inhibitors, e.g., enalapril.

[0046] In any case, the multiple therapeutic agents (one of which is one of the compounds described herein) may be administered in any order or even simultaneously. If simultaneously, the multiple therapeutic agents may be provided in a single, unified form, or in multiple forms (by way of example only, either as a single pill or as two separate pills). One of the therapeutic agents may be given in multiple doses, or both may be given as multiple doses. If not simultaneous, the timing between the multiple doses may vary from more than zero weeks to less than four weeks.

[0047] Suitable routes of administration may, for example, include oral, rectal, transmucosal, pulmonary, ophthalmic or intestinal administration; parenteral delivery, including intramuscular,

subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intranasal, or intraocular injections.

[0048] Alternately, one may administer a salt of the present invention in a local rather than systemic manner, for example, via injection of the compound directly into an organ, often in a depot or sustained release formulation. Furthermore, one may administer the drug in a targeted drug delivery system, for example, in a liposome coated with organ-specific antibody. The liposomes will be targeted to and taken up selectively by the organ.

[0049] The pharmaceutical compositions of the salts of the present invention may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

[0050] Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the salts into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art; *e.g.,* in Remington's Pharmaceutical Sciences, above.

[0051] For intravenous injections, the agents of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art. For other parenteral injections, the agents of the invention may be formulated in aqueous or nonaqueous solutions, preferably with physiologically compatible buffers or excipients. Such excipients are generally known in the art.

[0052] For oral administration, the compositions can be formulated readily by combining the salts with pharmaceutically acceptable carriers or excipients well known in the art. Such carriers enable the salts of the invention to be formulated as tablets, powders, pills, dragees, capsules, liquids, gels, syrups, elixirs, slurries, and suspensions, and for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by mixing one or more solid excipient with one or more salt of the invention, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as: for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium carboxymethyl cellulose; or others such as: polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. If desired, disintegrating agents may be added, such as the cross-linked croscarmellose sodium, polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as

sodium alginate.

[0053] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0054] Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, scaled capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration.

[0055] For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, or gels formulated in conventional manner.

[0056] For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, *e.g.,* dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, *e.g.*, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0057] The compounds may be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, *e.g.,* in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

[0058] Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which

increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

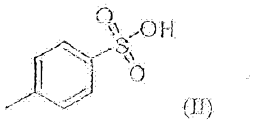
[0059] Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, *e.g.,* sterile pyrogen-free water, before use.

[0060] The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

[0061] In addition to the formulations described previously, the salts may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the salts may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0062] Many delivery systems for hydrophobic pharmaceutical salts may be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as N-methylpyrrolidone also may be employed, although usually at the cost of greater toxicity. Additionally, the salts may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the salts for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

[0063] In the p-toluenesulfonate salt forms of the compounds of Formula I, p-toluenenesulfonic acid is according to Formula (II):



(II)

The salt can be prepared by any suitable method for example, the compounds can be contacted with p-toluenesulfonic acid to yield the p-toluenesulfonate (tosylate) salt form of the invention. The compounds their racemates, and racemic mixtures thereof, prepared by any method can be contacted with a reagent selected from the group consisting of calcium acetate, hydrochloric acid, phosphoric acid, sulfuric acid, sodium hydroxide, potassium hydroxide, magnesium acetate, and p-toluenesulfonic acid, preferably in a 1:1 ratio, in a suitable solvent. Such solvents include but are not limited to diisopropyl ether, toluene, dichloromethane, and acetonitrile. Any technique known in the art can be used to vary conditions to induce precipitation or crystallization, including, without limitation: stirring for varying lengths of time at varying ambient conditions, the addition of hexanes or diethyl ether, evaporation, and reduction of temperature. In particular, 4-[cis-2,6-dimethyl-4-(4-trifluoromethoxy-phenyl)-

piperazine-1-sulfonyl]-indan-2-carboxylic acid can be contacted with p-toluenesulfonic acid to yield 4-[cis-2,6-dimethyl-4-(4-trifluoromethoxy-phenyl)-piperazine-1-sulfonyl]-indan-2-carboxylic acid tosylate. The present invention provides for salts of each racemate of compounds including (S)-4-[cis-2,6-dimethyl-4-(4-trifluoromethoxy-phenyl)-piperazine-1-sulfonyl]-indan-2-carboxylic acid tosylate (Compound 1 tosylate).

[0064] In particular, the present invention provides for salts of 4-[cis-2,6-Dimethyl-4-(4-trifluoromethoxy-benzyl)-piperazine-1-sulfonyl]-indan-2-carboxylic acid and each of its isolated racemates.

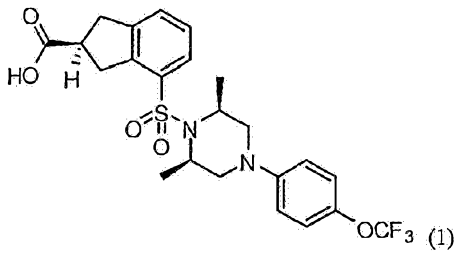
[0065] As shown in detail in the examples below, the tosylate salt displays excellent crystallization properties.

[0066] In another aspect, the present invention provides pharmaceutical compositions for modulating PPARδ activity in humans and animals.

EXAMPLE 1

Synthesis of Compound 1

[0067]

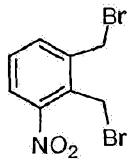


(1)

(S)-4-[cis-2,6-Dimethyl-4-(4-trifluoromethoxy-phenyl)-piperazine-1-sulfonyl]-indan-2-carboxylic acid

Step 1

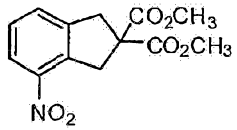
[0068]



[0069] 1,2-Bis(bromomethyl)-3-nitrobenzene: A 5 liter flask was charged with 20g 1,2-dimethyl-3-nitrobenzene (0.13 mol), 50 g N-bromosuccinimide (0.28 mol), 5 g azobis(isobutyronitrile) (3.0 mmol), and 200 mL of dichloromethane. This was irradiated with a 120 watt floodlamp to effect gentle relux under nitrogen for 18 hours. The mixture was then cooled and precipitated succinimide was removed by filtration. The filtrate was concentrated and the residue was purified by chromatography on silica (5%-50% CH_2Cl_2 in hexanes) to give 2.6 g white solid (64%).

Step 2

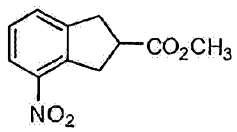
[0070]



[0071] Dimethyl-4-nitroindane-2,2-dicarboxylate: To a solution stirred under nitrogen at room temperature of 5.0 mL methanol in 15.0 mL ether was added 0.84 g 60% sodium hydride (0.021 mol) in small portions (sodium hydride was used because metallic sodium was not available). After the addition was complete, the nearly clear and colorless solution was stirred for 5 minutes. To it was then added 1.3g dimethyl malonate, giving a slightly cloudy colorless solution. To this was rapidly added a suspension of 3.1 g 1,2-bis(bromomethyl)3-nitrobenzene, which immediate gave a precipitate suspended in a dark green solution. This was removed by filtation and the filtrate was concentrated. The residue was purified on silica (20%-100% CH_2Cl_2 in hexanes) to give 1.93 g off-white solid (67%).

Step 3

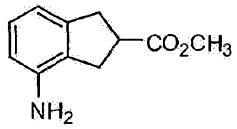
[0072]



[0073] Methyl-4-nitroindane-2-carboxylate: A mixture of 4.84 g dimethyl-4-nitroindane-2,2-dicarboxylate (.0167 mol), 0.84 g lithium chloride (0.0198 mol), 1.1 mL water, and 18 mL dimethylsulfoxide was heated to 160 C under nitrogen for two hours. It was then allowed to cool and the dimethylsulfoxide was removed under high vacuum. The residue was purified on silica (10%-100% CH_2Cl_2 in hexanes) to give 2.5 g white solid (65 %).

Step 4

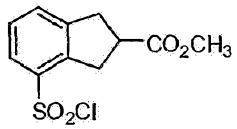
[0074]



[0075] Methyl-4-aminoindane-2-carboxylate: A mixture of 2.4 g methyl-4-nitroindane-2-carboxylate (0.11 mol), 1.1 g 10% palladium on carbon (0.01 mol), and 15 mL ethyl acetate was shaken under 55 PSI hydrogen for 1 hour. It was then filtered and the filtrate was concentrated to give 2.07 g white solid (100%).

Step 5

[0076]

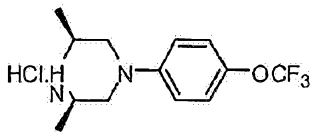


[0077] Methyl-4-chlorosulfonyl-2-carboxylate: A mixture of 2.5 g methyl-4-aminoindane-2-carboxylate (0.013 mol), 12.5 mL acetonitrile, and 12.5 mL H_2O was cooled to -5 C in an ice-salt bath. To this was added 2.6 mL concentrated HCl (0.014 mol). To this was added dropwise over 20 minutes a solution of 1.0 g sodium nitrite (0.021 mol) in 5 mL water. After the addition was complete the solution was stirred for 20 minutes. It was then transferred to a jacketed addition funnel cooled with ice water. The solution was added dropwise to a solution stirred under nitrogen at 55 C of 4.2 g potassium thioxanthate (0.026 mol) in 20 mL H_2O. As the addition took place, a dark layer rose to the top of the diazonium ion solution which was **not added.** After the addition was complete the mixture was stirred at 55 C for 30 minutes, then was allowed to cool and was extracted with 40 mL ethyl acetate. The organic layer was dried ($MgSO_4$) and concentrated. The residue was loaded on 80 mL silica gel which was slurry-packed in hexanes. This was eluted with 100 mL hexanes, then 1%-50% CH_2Cl_2 in hexanes in 50 mL fractions to give 1.3g amber oil (33 %).

[0078] A mixture of 3.6 g of the above compound in 30 mL CCl_4 and 10 mL H_2O was vigorously stirred and cooled to 3 C. Chlorine gas was bubbled through at such a rate that the temperature stayed below 10 C. After conversion was complete, the phases were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated to give 4.0g yellow oil (>100%).

Step 6

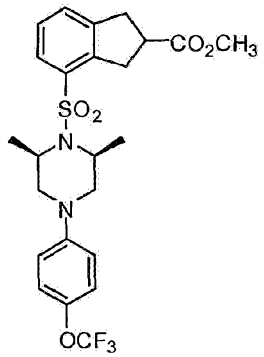
[0079]



[0080] 4-[cis-2,6-Dimethyl-4-(4-trifluoromethoxy-phenyl)-piperazine hydrochloride: A mixture of 200g cis-2,6-dimethylpiperazine (1.75 mol), 421g 1-bromo-4-trifluoromethoxybezene (1.74 mol), 200g sodium-t-butoxide (2.08 mol), 10g tris(dibenzylideneacetone)dipalladium (.011 mol), 20g 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (.047 mol), and 4 L toluene was degassed through 5 vacuum-nitrogen cycles (Firestone valve) and heated to 100 C under nitrogen for 2 hours. The reaction was allowed to cool and was filtered through celite. The filtrate was concentrated under vacuum and the residue was diluted with hexanes (2L). The mixture was filtered and the filtrate diluted with diethyl ether (2L). To this was added concentrated HCl (150ml, 1.8 mol) and the resulting mixture agitated briefly resulting in precipitation of the product which was collected by filtration and dried under vacuum (2mm Hg, 14 hr) to give 467g tan solid (86%).

Step 7

[0081]



[0082] 4-[cis-2,6-Dimethyl-4-(4-trifluoromethoxy-phenyl)-piperazine-1-sulfonyl]-indan-2-methyl ester: A mixture of 2.13g methyl-4-chlorosulfonyl-2-carboxylate (0.0078 mol), 3.0g 4-[cis-2,6-dimethyl-4-(4-trifluoromethoxy-phenyl)-piperazine hydrochloride (0.0109 mol), 20 mL acetonitrile, and 3.0 g K_2CO_3 (0.0217 mol) was heated to 60 C under nitrogen with stirring for 20 hours. It was then filtered and the filtrate was concentrated. The residue was purified by chromatography on silica (5%-50% EtOAc in hexanes) to give 2.64g viscous yellow oil (66%).

Step 8

[0083] 4-[cis-2,6-Dimethyl-4-(4-trifluoromethoxy-phenyl)-piperazine-1-sulfonyl]-indan-2-carboxylic acid: To a solution stirred at room temperature of 2.64g 4-[cis-2,6-dimethyl-4-(4-trifluoromethoxy-phenyl)-piperazine-1-sulfonyl]-indan-2-methyl ester (0.0052 mol) in the minimum amount of THF (ca 15 mL) was added a solution of 0.14 g LiOH (0.0057 mol) in the minimum amount of water (ca 2.5 mL). This was capped and stirred at room temperature for 12 hours. Examination by HPLC showed the reaction was 85% complete so an additional 0.020g LiOH (0.125 eq total) was added and stirring was continued for 3 hours. It was then concentrated to remove THF and partitioned between EtOAc and water. The aqueous layer was treated with 0.54 mL conc. HCl. It was then extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and concentrated to give 2.38g yellow amorphous solid (93%).

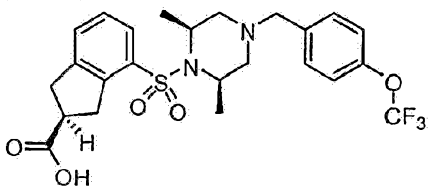
Step 9

[0084] (S)-4-[cis-2,6-Dimethyl-4-(4-trifluoromethoxy-phenyl)-piperazine-1-sulfonyl]-indan-2-carboxylic acid: The compound (S)-4-[cis-2,6-dimethyl-4-(4-trifluoromethoxy-phenyl)-piperazine-1-sulfonyl]-indan-2-carboxylic acid was obtained by chiral HPLC (chiralpak ASH 0.46 x 15 cm Hex/IPA 94:6 (v/v) with 0.1 % TFA, flow rate 1 ml/min) separation from the racemate. LCMS 497.1 $(M-1)^-$.

EXAMPLE 2

Synthesis of Compound 2

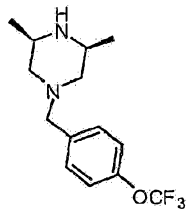
[0085]



(S)-4-[cis-2,6-Dimethyl-4-(4-trifluoromethoxy-benzyl)-piperazine-1-sulfonyl]-indan-2-carboxylic acid

Step 1

[0086]



[0087] cis-3,5-Dimethyl-1-(4-trifluoromethoxy-benzyl)-piperazine: To a solution of 4-(trifluoromethoxy)-benzaldehyde (776 uL, 4.38 mmol) in methylene chloride (30 mL) was added cis-2,6-dimethyl piperazine (1.0 g, 8.77 mmol). After 1 hour sodium triacetoxy borohydride (2.45 g, 8.77 mmol) was added to the mixture. The solution was stirred at room temperature for an additional 4 hours. The reaction was concentrated *in vacuo,* diluted with ethyl acetate and extracted with 1N HCl (2 X 50 mL). The aqueous layer was then neutralized with NaOH and extracted with ethyl acetate (3 X 50 mL). The organic layer was dried (Na_2SO_4) and concentrated to provide cis-3,5-dimethyl-1-(4-trifluoromethoxy-benzyl)-piperazine (1.01 g, 80 %). ^1H NMR (400 MHz, CD_3OD) δ 7.42 (d, 2H), 7.23 (d, 2H), 3.54 (s, 2H), 2.98-2.88 (m, 2H), 2.82-2.74 (m, 2H), 1.69 (t, 2H), 1.05 (d, 6H); LCMS 289.5 $(M+1)^+$.

Step 2

[0088] 4-[cis-2,6-Dimethyl-4-(4-trifluoromethoxy-benzyl)-piperazine-1-sulfonyl]-indan-2-carboxylic acid: The compound 4-[cis-2,6-dimethyl-4-(4-trifluoromethoxyl-benzyl)-piperazine-1-sulfonyl]-indan-2-carboxylic acid was synthesized according to the procedure in Example 1 using cis-3,5-dimethyl-1-(4-trifluoromethoxy-benzyl)-piperazine. ^1H NMR (400 MHz, CD_3OD) δ 7.74-7.64 (m, 4H), 7.47 (d, 1H), 7.39-7.28 (m, 2H), 4.42 (s, 2H), 4.21-2.18 (m, 2H), 3.50-3.34 (m, 5H), 3.33-3.19 (m, 4H), 1.56 (d, 6H); LCMS 497.5 $(M+1)^+$.

Step 3

[0089] (S)-4-[cis-2,6-Dimethyl-4-(4-trifluoromethoxy-benzyl)-piperazine-1-sulfonyl]-indan-2-carboxylic acid: A single enantiomer of Example 2 was obtained with the following protocol. The product from example 2 Step 1 and the product from Example 1 Step 5 were reacted using the conditions outlined in Example 9 Step 6 to yield the racemic methyl ester. Chiral separation using OJ-H, 25 % methanol in CO_2 (100 bar), 5 mL/min followed by hydrolysis using conditions outlined in Example 1 Step 7 provided (S)-4-(cis-2,6-dimethyl-4-(3-trifluorometlaoxy)benzyl)piperazin-1-ylsulfonyl)-2,3-dihydro-1H-indene-2-carboxylic acid. ^1H NMR (400 MHz, CD_3OD) δ 7.66 (d, 1H), 7.46 (d, 1H), 7.41 (d, 2H), 7.36-7.30 (m, 1H), 7.19 (d,

2H), 4.08-3.99 (m, 1H), 3.94-3.8 (m, 1H), 3.56-3.49 (m, 2H), 3.43 (s, 2H), 3.40-3.22 (m, 3H), 2.57 (t, 2H), 2.09-1.92 (m, 2H), 1.56 (d, 6H); LCMS 513.5

EXAMPLE 3

Preparation of salts of Compound 1

Calcium:

[0090] Compound 1 and base ($Ca(OAc)_2$) were combined in 1:1 molar ratio in methanol solvent. No precipitation occurred, so the solution was allowed to evaporate. White solids and broken glass formed upon drying. Ether solvent was added; most of the solid dissolved, so the solution was placed in a freezer for 1 day, resulting in a clear solution with few solids. This solution was left to evaporate under ambient conditions, yielding solids with areas of birefringence.

Hydrochloride:

[0091] Compound 1 and hydrochloric acid were combined in 1:1 molar ratio in methanol. No precipitation occurred, so the solution was allowed to evaporate yielding a clear oil upon drying. This oil was dissolved in DCM and hexanes were added, yielding a white solution which was then capped and left under ambient conditions for one day. A clear solution resulted which was placed in a freezer.

Phosphate:

[0092] Compound 1 and phosphoric acid were combined in 1:1 molar ratio in acetonitrile (ACN) solvent. No precipitation occurred. Tetrahydrofuran (THF) antisolvent was added, still resulting in no precipitation. The solution was allowed to evaporate under ambient conditions, yielding an opaque film. This was placed in an ambient vacuum oven for 1 day. White solids were recovered.

Sulfate:

[0093] Compound 1 and sulfuric acid were combined in a 1:1 molar ratio in methanol solvent. No precipitation occurred, so the solution was allowed to evaporate, yielding a clear film. This

was placed in an ambient vacuum oven for 3 days, resulting in a clear film with brown streaks throughout.

Potassium:

[0094] Compound 1 and KOH base were combined in a 1:1 molar ratio in ethanol solvent. Hexanes were added. No precipitation occurred, so the solution was allowed to evaporate, resulting in a light yellow film. This was redissolved in EtOH, and an attempt was made at precipitation by adding hexanes, resulting in a foggy solution, which was subsequently filtered. No solid was recovered upon filtration; the filtrate was allowed to evaporate, yielding a clear film. This was dissolved in ACN and left to evaporate to half volume in order to concentrate the solution. Ethyl ether was added, resulting in no precipitation. The solution was allowed to evaporate, yielding a clear film. This was left to evaporate under ambient conditions for three days, yielding light yellow solids.

Magnesium:

[0095] Compound 1 and magnesium acetate were combined in a 1:1 molar ratio in methanol solvent. No precipitation occurred, so the solution was allowed to evaporate, resulting in a clear oil with a milky film. Ethyl ether was added, and the clear oil dissolved while the milky film coagulated at bottom of the reaction vessel into small drops. The solution was placed in a freezer for one day, yielding a clear solution with immiscible oil drops. This was left to evaporate under ambient conditions, leaving a clear film. This was placed in an ambient vacuum oven for one day, yielding off white solids.

Sodium:

[0096] Compound 1 and sodium hydroxide were combined in a 1:1 molar ratio in ethanol solvent. Hexanes were added; no precipitation occurred, so the solution was allowed to evaporate, resulting in a light yellow film. This was dissolved in McOH, and an attempt at precipitation was made by adding ethyl ether. No precipitation occurred, so the solution was allowed to evaporate, yielding a clear film. This was dissolved in dichloromethane (DCM) and left to evaporate to half volume in order to concentrate the solution. The addition of hexanes resulted in a white precipitate which was placed on an ambient slurry wheel for four days, resulting in a clear, immiscible oil in solution. This was stirred under ambient conditions with a magnetic stirbar for two days, resulting in a clear oil at the base of the solution. This was left to evaporate under ambient conditions, yielding a clear film. This was placed in an ambient vacuum oven for one day, yielding off white solids.

P-Toluenesulfonate:

[0097] Compound 1 and p-toluenesulfonic acid were combined in a 1:1 molar ratio in tetrahydrofuran (THF) solvent. No precipitation occurred. The clear solution was chilled in an ice water bath and allowed to evaporate under a dry nitrogen purge, yielding off-white solids.

EXAMPLE 4

Alternate direct preparation of the tosylate salt of Compound 1

Step 1

[0098] 32% HCl is added to a solution of sodium nitrite in water and acetonitrile at 0 °C. The solution is cooled to -5 °C and a solution of (R,S)-4-amino-indan-2-carboxylic acid methyl ester hydrochloride in water, acetonitrile, and 32% HCl is added, keeping the temperature between -7 and -10 °C. The resulting cold diazonium solution is added to a solution of potassium ethyixanthogenate, in water and acetonitrile, at 60 °C. After heating at 60 °C, the mixture is cooled to room temperature and extracted from dichioromethane. The organic solution is charged into the reactor and concentrated under reduced pressure. Dichloromethane and water are added, the mixture cooled to 5 °C, and chlorine gas passed through the mixture. The organic solution is separated and the aqueous solution is extracted from dichioromethane. The combined organic solution is dried over magnesium sulfate and concentrated under reduced pressure to afford (R,S)-4-chlorosulfonyl-indan-2-carboxylic acid. HPLC may be used to monitor the reaction.

Step 2:

[0099] Potassium carbonate is added to a mixture of *cis*-3,5-dimethyl-1-(4-trifluoromethoxy-phenyl)-piperazine hydrochloride in dichioromethane and water. After stirring at room temperature, the organic phase is collected and the aqueous layer extracted from dichioromethane. The combined organic solution is charged into the reactor and concentrated under reduced pressure, followed by the addition of acetonitrile and potassium carbonate. A solution of (R,S)-4-chlorosulfonyl-indan-2-carboxylic acid, in acetonitrile, is added to the reaction mixture. After heating at 50 °C, the reaction mixture is cooled to 20 °C. The mixture is transferred into a 200 L movable agitation feed tank, which is charged with Celite, and the suspension is stirred. The suspension is filtered, filter cake washed with acetonitrile, and the filtrate is concentrated under reduced pressure, cooled to 0-5 °C, and 32% HCl added. Following further concentration and filtration, the filtrate is concentrated to give an oil which is purified by silica gel chromatography and recrystallized from isopropanol to give the product

(R,S)-4-[cis-2,6-dimethyl-4-(4-trifluoromethoxy-phenyl)-piperazine-1-sulfonyl]-indan-2-carboxylic acid methyl ester (>95% by HPLC).

Step 3:

[0100] Simulated moving bed (SMB) chromatography was used to separate the S- and R-enantiomers of (R,S)-4-[cis-2,6-dimethyl-4-(4-trifluoromethoxy-phenyl)-piperazine-1-sulfonyl] -indan-2-carboxylic acid methyl ester. The SMB method uses a Chiralpak AS column and nheptane/isopropanol (1:1 v/v) to yield the S-enantiomer, (S)-4-[cis-2,6-dimethyl-4-(4-trifluoromethoxy-phenyl)-piperazine-1-sulfonyl]-indan-2-carboxylic acid methyl ester (>99.0% by chiral HPLC).

Step 4:

[0101] To a solution of (S)-4-[cis-2,6-dimethyl-4-(4-trifluoromethoxy-phenyl)-piperazine-1-sulfonyl]-indan-2-carboxylic acid methyl ester, in THF, is added a solution of lithium hydroxide in water, which is stirred at 20 °C and concentrated under reduced pressure. The reaction mixture is cooled to 9 °C, neutralized with 32% HCl, and extracted from toluene. Water is removed from the organic solution by azeotropic distillation. Following distillation, the organic solution is cooled to ambient temperature and transferred to a feeding vessel. The reactor is charged with p-toluenesulfonic acid in toluene and water is removed by azeotropic distillation. The solution is cooled to 60 °C, followed by the addition of the organic solution from the feeding vessel. The mixture is stirred at 83 °C, then cooled to 10 °C to induce crystallization. The product suspension is filtered, the filter cake rinsed with heptane, and dried on a rotovap, at 40 °C, to afford (S)-4-[cis-2,6-dimethyl-4-(4-trifluoromethoxy-phenyl)-piperazine-1-sulfonyl]-indan-2-carboxylic acid tosylate. ^{1}HNMR δ 1.60(d), 1.62(d), 2.33(s), 3.23(m), 3.49(m), 3.39(m), 4.05(m), 4.49(m), 3.40(dd), 3.23(dd), 7.14(d), 7.14(d), 7.09(d), 7.09(d), 7.59(d), 7.59(d), 7.71(d), 7.26,dd, 7.57(d), 7.57(d), 7.40(d).

XRPD characterization of the tosylate salt of Compound 1

[0102] The methyl ester precursor of (S)-4-[cis-2,6-dimethyl-4-(4-trifluoromethoxy-phenyl)-piperazine-1-sulfonyl]-indan-2-carboxylic acid tosylate (hereinafter optionally referred to as "Compound 1 tosylate") was used for this experiment instead of Compound 1 tosylate due to the unsuitability of the Compound 1 tosylate crystals for X-ray structure determination. Compound 1 tosylate methyl ester was prepared via an esterification of Compound 1 tosylate followed by recrystallization from isopropanol. Other experiments have established that the stereochemistry is retained in converting the methyl ester to Compound 1 tosylate.

[0103] The sample submitted for analysis contained numerous large, well formed rectangular

blocks. One such block was trimmed to the dimensions 0.4 x 0.3 x 0.3 mm3, coated with mineral oil, picked up on a Nylon loop and chilled to 100 K on the goniometer stage of a Bruker three-axis platform diffractometer equipped with an APEX detector and a KryoCool low-temperature device. All software used in the subsequent data collection, processing and refinement is contained in libraries maintained by Bruker-AXS, Madison, WI.

[0104] From sixty randomly chosen exposures taken in three sequences of twenty exposures at 0.3 deg intervals, it was possible to uniquely assign the crystal to the orthorhombic crystal system with the reported unit cell dimensions. From systematic absences in the diffraction data, it was determined that the particular orthorhombic space group was $P2_12_12$, and, from the volume of the unit cell, that it contained eight molecules. A full hemisphere of data were collected at 100 K yielding 40547 reflections, of which 10238 were crystallographically independent under orthorhombic symmetry providing up to a four-fold redundancy in coverage and a very low merging R factor. The data were first processed by SAINT, a program that integrated the 1,800 individual exposures and prepares a list of reflections and intensities. Corrections were made for absorption, polarization and Lorenzian distortion using SADABS. The structure was solved using direct methods (TREF) and subsequent difference maps were used to locate all non- hydrogen atoms. Refinement using SHELXTL routines for a model incorporating anisotropic thermal parameters for all non-hydrogen atoms and hydrogen atoms as idealized isotropic contributions resulted in a final structure with very low residuals and esd's for bond parameters. Table 1 presents the crystal data and structure refinement for Compound 1 tosylate. Table 2 presents the atomic coordinates and equivalent isotropic displacement parameters for Compound 1 tosylate. Table 3 presents the bond lengths for Compound 1 tosylate. Table 4 presents the bond angles for Compound 1 tosylate.

Table 1.

Identification code	**Compound 1 Tosylate**
Empirical formula	C24 H27 F3 N2 O5 S
Formula weight	512.54
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal System	Orthorhombic
Space Group	P2(1)2(1)2
Unit Cell Dimensions	a = 17.322(3) Å α = 900
	b = 25.036(4) Å β = 90°
	c = 10.8883(18) Å γ = 90°
Volume	472 1.9(13) $Å^3$
Z	8
Density (calculated)	1.442 g/cm^3
Absorption Coefficient	0.200 mm^{-1}
F(000)	2144

Identification code	**Compound 1 Tosylate**
Crystal Size	0.40 x 0.30 x 0.30 mm^3
Theta range for data collection	1.43 to 27.61°
Index Ranges	-21≤h≤21, -31≤k≤31, -13≤l≤13
Reflections Collected	40547
Independent Reflections	10238 [R(int) = 0.0318]
Completeness to theta = 27.61°	95.70%
Absorption correction	0.200 mm^{-1}
Max. and min. transmission	0.9424 and 0.9242
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	10238 / 0 / 631
Goodness-of-fit on F2	1.026
Final R indices [1>2sigma(I)]°	R1 = 0.0344, wR2 = 0.0914
R indices (all data)	R1 = 0.0373, wR2 = 0.0930
Absolute structure parameter	0.03(4)

Table 2

	x	**y**	**z**	**U(eq)**
S(1)	8077(1)	3662(1)	3670(1)	17(1)
S(1')	2973(1)	3589(1)	-8615(1)	19(1)
F(1)	12175(1)	4789(1)	-4796(1)	37(1)
F(1')	6004(1)	4999(1)	-582(1)	52(1)
F(2')	7218(1)	4842(1)	-411(1)	38(1)
F(2)	11782(1)	5189(1)	-3162(1)	38(1)
F(3')	6773(1)	5256(1)	-1993(1)	43(1)
F(3)	10979(1)	4991(1)	-4587(1)	38(1)
O(1)	6577(1)	4385(1)	-1742(1)	27(1)
O(1')	11507(1)	4332(1)	-3503(1)	28(1)
O(2)	7363(1)	3950(1)	3590(1)	22(1)
O(2')	2239(1)	3841(1)	-8433(1)	24(1)
O(3')	3307(1)	3584(1)	-9822(1)	27(1)
O(3)	8472(1)	3642(1)	4827(1)	23(1)
O(4)	6185(1)	3206(1)	-901(1)	47(1)
O(4')	199(1)	2692(1)	-5704(1)	32(1)
O(5)	5166(1)	2750(1)	-220(1)	30(1)
O(5')	700(1)	2883(1)	-3860(1)	25(1)

	x	y	z	U(eq)
N(1)	9584(1)	4134(1)	625(1)	18(1)
N(1')	4574(1)	4142(1)	-5757(1)	18(1)
N(2)	8649(1)	3903(1)	2633(1)	17(1)
N(2')	3574(1)	3857(1)	-7655(1)	19(1)
C(1')	6049(1)	4342(1)	-2736(2)	21(1)
C(1)	11000(1)	4301(1)	-2471(2)	20(1)
C(2)	11327(1)	4232(1)	-1324(2)	22(1)
C(2')	6348(1)	4293(1)	-3901(2)	21(1)
C(3')	5849(1)	4227(1)	-4885(2)	19(1)
C(3)	10847(1)	4176(1)	-316(2)	20(1)
C(4)	10046(1)	4188(1)	-444(2)	17(1)
C(4')	5052(1)	4204(1)	-4707(2)	17(1)
C(S)	9734(1)	4259(1)	-1616(2)	20(1)
C(S)	4765(1)	4250(1)	-3515(2)	21(1)
C(6')	5264(1)	4316(1)	-2523(2)	24(1)
C(6)	10214(1)	4315(1)	-2637(2)	23(1)
C(7')	4716(1)	3653(1)	-6463(2)	20(1)
C(7)	9732(1)	3651(1)	1352(2)	19(1)
C(8)	9460(1)	3724(1)	2673(2)	18(1)
C(8')	4394(1)	3705(1)	-7762(2)	19(1)
C(9)	8395(1)	4325(1)	1769(2)	16(1)
C(9')	3342(1)	4296(1)	-6820(2)	18(1)
C(10')	3748(1)	4217(1)	-5583(2)	18(1)
C(10)	8759(1)	4223(1)	506(2)	18(1)
C(11)	7916(1)	2991(1)	3218(2)	16(1)
C(11')	2897(1)	2913(1)	-8151(2)	19(1)
C(12')	3378(1)	2540(1)	-8716(2)	22(1)
C(12)	8369(1)	2595(1)	3768(2)	19(1)
C(13')	3345(1)	2007(1)	-8366(2)	25(1)
C(13)	8289(1)	2067(1)	3397(2)	21(1)
C(14)	7749(1)	1923(1)	2519(2)	22(1)
C(14')	2832(1)	1838(1)	-7471(2)	24(1)
C(15)	7291(1)	2317(1)	1996(2)	19(1)
C(15')	2350(1)	2210(1)	-6918(2)	20(1)
C(16)	6669(1)	2255(1)	1039(2)	23(1)

	x	y	z	U(eq)
C(16')	1722(1)	2113(1)	-5992(2)	21(1)
C(17')	1576(1)	2677(1)	-5454(2)	20(1)
C(17)	6235(1)	2801(1)	1106(2)	23(1)
C(18')	1802(1)	3065(1)	-6499(2)	21(1)
C(18)	6845(1)	3198(1)	1557(2)	22(1)
C(19)	7380(1)	2854(1)	2319(2)	18(1)
C(19')	2389(1)	2750(1)	-7231(2)	17(1)
C(20)	11602(1)	4816(1)	-3989(2)	28(1)
C(20')	6631(1)	4857(1)	-1200(2)	30(1)
C(21')	4868(1)	4077(1)	-8577(2)	25(1)
C(21)	9980(1)	4095(1)	3421(2)	23(1)
C(22)	8570(1)	4886(1)	2219(2)	21(1)
C(22')	3488(1)	4849(1)	-7354(2)	22(1)
C(23')	750(1)	2748(1)	-5048(2)	21(1)
C(23)	5875(1)	2947(1)	-108(2)	25(1)
C(24)	4791(1)	2862(1)	-1389(2)	34(1)
C(24')	-75(1)	2959(1)	3404(2)	28(1)

Table 3

Bond	Length, Å	Bond	Length, Å
S(1)-O(2)	1.4327(12)	C(2)-C(3)	1.384(2)
S(1)-O(3)	1.4352(12)	C(2')-C(3')	1.387(2)
S(1)-N(2)	1.6186(14)	C(3')-C(4')	1.395(2)
S(1)-C(11)	1.7737(16)	C(3)-C(4)	1.396(2)
S(1')-O(2')	1.4336(12)	C(4)-C(5)	1.397(2)
S(1')-O(3')	1.4363(13)	C(4')-C(S')	1.395(2)
S(1')-N(2')	1.6206(14)	C(5)-C(6)	1.395(2)
S(1')-C(11')	1.7716(17)	C(5')-C(6')	1.393(2)
F(1)-C(20)	1.328(2)	C(7')-C(8')	1.526(2)
F(1')-C(20')	1.327(2)	C(7)-C(8)	1.525(2)
F(2')-C(20')	1.331(2)	C(8)-C(21)	1.530(2)
F(2)-C(20)	1.333(2)	C(8')-C(21')	1.527(2)
F(3')-C(20')	1.343(2)	C(9)-C(22)	1.519(2)
F(3)-C(20)	1.334(2)	C(9)-C(10)	1.534(2)
O(1')-C(20')	1.325(2)	C(9')-C(22')	1.524(2)

Bond	Length, Å	Bond	Length, Å
O(1')-C(1')	1.4214(19)	C(9')-C(10')	1.532(2)
O(1)-C(20)	1.334(2)	C(11)-C(19)	1.393(2)
O(1)-C(1)	1.4281(19)	C(11)-C(12)	1.399(2)
O(4)-C(23)	1.207(2)	C(11')-C(19')	1.394(2)
O(4)-C(23')	1.200(2)	C(11')-C(12')	1.395(2)
O(5)-C(23)	1.328(2)	C(12')-C(13)	1.389(2)
O(5)-C(24)	1,456(2)	C(12)-C(13)	1.388(2)
O(5')-C(23')	1.340(2)	C(13')-C(14')	1.385(3)
O(5')-C(24')	1.444(2)	C(13)-C(14)	1.385(2)
N(1)-C(4)	1.418(2)	C(14)-C(15)	1.388(2)
N(1)-C(10)	1.453(2)	C(14')-C(15')	1.387(2)
N(1)-C(7)	1.467(2)	C(15)-C(19)	1.400(2)
N(1')-C(4')	1.421(2)	C(15)-C(16)	1.507(2)
N(1')-C(10')	1.456(2)	C(15')-C(19')	1.396(2)
N(1')-C(7')	1.465(2)	C(15')-C(16')	1.503(2)
N(2)-C(8)	1.4757(19)	C(16)-C(17)	1.562(2)
N(2)-C(9)	1.481(2)	C(16')-C(17')	1.550(2)
N(2')-C(8')	1.475(2)	C(17')-C(23')	1.508(2)
N(2')-C(9')	1.482(2)	C(17')-C(18')	1.546(2)
C(1')-C(2')	1.376(2)	C(17)-C(23)	1.506(2)
C(1')-C(6')	1.380(2)	C(17)-C(18)	1.531(2)
C(1)-C(6)	1.374(3)	C(18')-C(19')	1.514(2)
C(1)-C(2)	1.382(3)	C(18)-C(19)	1.511(2)

Table 4

Bond	Angle, °	Bond	Angle, °
O(2)-S(1)-O(3)	118.86(8)	C(22)-C(9)-C(10)	111.24(13)
O(2)-S(1)-N(2)	107.41(7)	N(2')-C(9')-C(22')	113.32(14)
O(3)-S(1)-N(2)	109.45(7)	N(2)-C(9')-C(10')	108.65(12)
O(2)-S(1)-C(11)	108.90(7)	C(22)-C(9')-C(10')	112.10(13)
O(3)-S(1)-C(11)	106.57(7)	N(1')-C(10')-C(9')	110.68(13)
N(2)-S(1)-C(11)	104.80(7)	N(1)-C(10)-C(9)	110.45(13)
O(2)-S(1')-O(3')	119.20(8)	C(19)-C(11)-C(12)	120.04(15)
O(2')-S(1')-N(2)	107.42(7)	C(19)-C(11)-S(1)	122.16(12)
O(3')-S(1')-N(2')	109.51(8)	C(12)-C(11)-S(1)	117.76(13)
O(2')-S(1')-C(11')	108.40(7)	C(19')-C(11')-C(12')	119.80(15)

Bond	Angle, °	Bond	Angle, °
O(3')-S(1')-C(11')	106.44(8)	C(19')-C(11')-S(1')	122.17(12)
N(2')-S(1')-C(11')	104.99(7)	C(12')-C(11')-S(1')	118.02(13)
C(20')-O(1')-C(1')	116.85(13)	C(13')-C(12')-C(11')	119.85(16)
C(20)-O(1)-C(1)	115.87(13)	C(13)-C(12)-C(11)	119.64(16)
C(23)-O(5)-C(24)	114.96(14)	C(12')-C(13')-C(14')	120.85(16)
C(23')-O(5')-C(24')	115.20(14)	C(12)-C(13)-C(14)	121.09(15)
C(4)-N(1)-C(10)	117.82(14)	C(15)-C(14)-C(13)	118.91(15)
C(4)-N(1)-C(7)	115.03(12)	C(15')-C(14')-C(13')	119.14(16)
C(10)-N(1)-C(7)	110.23(13)	C(14)-C(15)-C(19)	121.20(16)
C(4')-N(1')-C(10')	116.99(14)	C(14)-C(15)-C(16)	128.27(15)
C(4')-N(1')-C(7)	114.59(13)	C(19)-C(15)-C(16)	110.53(14)
C(10')-N(1')-C(7')	110.00(13)	C(14')-C(15')-C(19')	120.94(16)
C(8)-N(2)-C(9)	121.21(13)	C(14')-C(15')-C(16')	128.19(16)
C(8)-N(2)-S(1)	116.69(11)	C(19')-C(15')-C(16')	110.82(14)
C(9)-N(2)-S(1)	121.78(11)	C(15)-C(16)-C(17)	102.80(13)
C(8')-N(2')-C(9')	120.03(13)	C(15')-C(16')-C(17')	102.93(13)
C(8')-N(2)-S(1')	117.51(11)	C(23')-C(17')-C(18')	112.40(14)
C(9')-N(2')-S(1')	121.86(11)	C(23')-C(17')-C(16')	111.90(14)
C(2')-C(1')-C(6')	121.47(16)	C(18')-C(17')-C(16')	104.64(13)
C(2')-C(P)-O(1')	117.75(14)	C(23)-C(17)-C(18)	114.25(15)
C(6')-C(1')-O(1')	120.65(16)	C(23)-C(17)-C(16)	111.73(14)
C(6)-C(1)-C(2)	121.86(16)	C(18)-C(17)-C(16)	104.57(14)
C(6)-C(1)-O(1)	120.28(16)	C(19')-C(18')-C(17')	103.31(13)
C(2)-C(1)-O(1)	117.79(15)	C(19)-C(18)-C(17)	103.26(13)
C(1)-C(2)-C(3)	118.90(15)	C(11)-C(19)-C(15)	119.05(15)
C(1)-C(2')-C(3')	119.21(15)	C(11)-C(19)-C(18)	130.90(15)
C(2')-C(3)-C(4')	120.96(16)	C(15)-C(19)-C(18)	110.04(14)
C(2)-C(3)-C(4)	121.05(16)	C(11')-C(19')-C(15')	119.37(15)
C(5)-C(4)-C(3)	118.60(16)	C(11')-C(19')-C(18')	130.45(15)
C(5)-C(4)-N(1)	122.97(15)	C(15')-C(19')-C(18')	110.09(14)
C(3)-C(4)-N(1)	118.43(15)	F(1)-C(20)-F(2)	107.96(15)
C(5)-C(4')-C(3')	118.60(15)	F(1)-C(20)-O(1)	107.93(15)
C(5')-C(4')-N(1')	123.37(15)	F(2)-C(20)-O(1)	113.46(15)
C(3)-C(4')-N(1')	118.02(15)	F(1)-C(20)-F(3)	107.35(14)

Bond	Angle, °	Bond	Angle, °
C(6)-C(5)-C(4)	120.69(15)	F(2)-C(20)-F(3)	106.83(15)
C(6')-C(5')-C(4')	120.65(15)	O(1)-C(20)-F(3)	113.04(16)
C(1')-C(6')-C(5')	119.10(16)	O(1'')-C(20')-F(1')	114.08(17)
C(1)-C(6)-C(5)	118.90(16)	O(1')-C(20')-F(2')	108.41(15)
N(1')-C(7')-C(8')	110.72(13)	F(1')-C(20')-F(2')	107.79(15)
N(1)-C(7)-C(8)	110.88(13)	O(1')-C(20')-F(3')	112.95(16)
N(2)-C(8)-C(7)	107.60(13)	F(1')-C(20')-F(3')	106.07(16)
N(2)-C(8)-C(21)	113.06(14)	F(2')-C(20')-F(3')	107.22(15)
C(7)-C(8)-C(21)	113.12(14)	O(4')-C(23')-O(5')	123.55(16)
N(2')-C(8')-C(7')	107.50(13)	O(4')-C(23')-C(17')	124.49(16)
N(2')-C(8')-C(21')	113.94(14)	O(5')-C(23')-C(17')	111.97(14)
C(7')-C(8')-C(21')	113.22(14)	O(4)-C(23)-0(5)	122.99(17)
N(2)-C(9)-C(22)	113.35(13)	O(4)-C(23)-C(17)	125.01(17)
N(2)-C(9)-C(10)	109.16(12)	O(5)-C(23)-C(17)	112.01(15)

Biological Activity Assay

[0105] Compounds 1 and 2 were assayed to measure their biological activity with respect to EC_{50} values and efficacy for modulating PPARα, PPARγ, and PPARδ as set forth below. Compounds were screened for functional potency in transient transfection assays in CV-1 cells for their ability to activate the PPAR subtypes (transactivation assay). A previously established chimeric receptor system was utilized to allow comparison of the relative transcriptional activity of the receptor subtypes on the same synthetic response element and to prevent endogenous receptor activation from complicating the interpretation of results. See, for example, Lehmann, J. M.; Moore, L. B.; Smith-Oliver, T. A; Wilkinson, W.O.; Willson, T. M.; Kliewer, S. A., An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor δ (PPARδ), J. Biol. Chem., 1995, 270, 12953-6. The ligand binding domains for murine and human PPARα, PPAPγ, and PPARδ are each fused to the yeast transcription factor GAL4 DNA binding domain. CV-1 cells were transiently transfected with expression vectors for the respective PPAR chimera along with a reporter construct containing four or five copies of the GAL4 DNA binding site driving expression of luciferase. After 8-16 h, the cells are replated into multi-well assay plates and the media is exchanged to phenol-red free DME medium supplemented with 5% delipidated calf serum. 4 hours after replating, cells were treated with either compounds or 1% DMSO for 20-24 hours. Luciferase activity was then assayed with Britelite (Perkin Elmer) following the manufacturer's protocol and measured with either the Perkin Elmer Viewlux or Molecular Devices Acquest (see, for example, Kliewer, S. A., et. al. Cell 1995, 83, 813-819). Rosiglitazone is used as a positive control in the PPARγ assay. Wy-

14643 and GW7647 is used as a positive control in the PPARα assay. GW501516 is used as the positive control in the PPARδ assay. Results are shown in Table 5 below:

Table 5

Compound	PPAR alpha	PPAR delta	PPAR gamma
	A = > 100 μM	**A = > 100 μM**	**A = > 100 μM**
	B = 5-100 μM	**B = 5-100 μM**	**B = 5-100 μM**
	C = < 5 μM	**C = < 5 μM**	**C = < 5 μM**
1	A	C	A
2	A	C	B

[0106] This table is adapted from Table 1 in US2006/0205736, published Sept. 14, 2006.

[0107] From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- WO2005016881A **[0009]**
- WO2004092117A **[0009]**
- US20060205736A **[0106]**

Non-patent literature cited in the description

- **LAZAROWFUJIKI**Ann. Rev. Cell Biol., 1985, vol. 1, 489-530 **[0002]**
- **VAMECQDRAYE**Essays Biochem., 1989, vol. 24, 1115-225 **[0002]**

- **NELALI et al.**Cancer Res., 1988, vol. 48, 5316-5324 [0002]
- **REDDYLALWANI**Crit. Rev. **T**oxicol., 1983, vol. 12, 1-58 [0002]
- **H. KELLERW. WAHLIT**rends Endoodn. Met., 1993, vol. 4, 291-296 [0004]
- **ISSEMANGREEN**Nature, 1990, vol. 347, 645-650 [0005]
- **GOTTLICHER et al.**Proc. Natl. Acad. Sci. USA, 1992, vol. 89, 4653-4657 [0005]
- **TUGWOOD et al.**EMBO J, 1992, vol. 11, 433-439 [0005]
- **BARDOT et al.**Biochem. Biophys. Res. Comm., 1993, vol. 192, 37-45 [0005]
- **MUERHOFF et al.**J Biol. Chem., 1992, vol. 267, 19051-19053 [0005]
- **MARCUS et al.**Proc. Natl. Acad Sci. USA, 1993, vol. 90, 125723-5727 [0005]
- **D. E. KELLY et al.**Curr. Opin. Endocrinol. Diabetes, 1998, vol. 5, 290-96 [0006]
- **M. D. JOHNSON et al.**Ann. Pharmacother., 1997, vol. 32, 3337-348 [0006]
- **M. LEUTENEGGER et al.**Curr. **T**her. Res., 1997, vol. 58, 7403-416 [0006]
- **OLIVER et al.**Proc. Natl. Acad. Sci. U. S. A., 2001, vol. 98, 5305- [0007]
- **VAN DER VEEN et al.**J. Lipid Res., 2005, vol. 46, 526-534 [0007]
- **WILLSON et al.**J. Med. Chem., 2000, vol. 43, 527-550 [0008]
- **LEHMANN, J. M.MOORE, L. B.SMITH-OLIVER, T. AWILKINSON, W.O.WILLSON, T. M.KLIEWER, S. A.**An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor δ (PPARδ)J. Biol. Chem., 1995, vol. 270, 12953-6 [0105]
- **KLIEWER, S. A.**Cell, 1995, vol. 83, 813-819 [0105]

Patentkrav

1. Salt af en forbindelse valgt fra 4-[cis-2,6-dimethyl-4-(4-trifluormethoxy-phenyl)-piperazin-1-sulfonyl]-indan-2-carboxylsyre og (S)-4-[cis-2,6-Dimethyl-4-(4-trifluormethoxy-benzyl)-piperazin-1-sulfonyl]-indan-2-carboxylsyre, hvor saltet er valgt fra sulfat, natrium, kalium, magnesium, calcium, hydrochlorid, phosphat, og tosylat.

2. Saltet ifølge krav 1, hvor saltet er tosylat-saltet.

3. (S)-4-[cis-2,6-Dimethyl-4-(4-trifluormethoxy-benzyl)-piperazin-1-sulfonyl]-indan-2-carboxylsyre-tosylat.

4. (S)-4-[cis-2,6-dimethyl-4-(4-trifluormethoxy-phenyl)-piperazin-1-sulfonyl]-indan-2-carboxylsyre-tosylat.

5. Farmaceutisk sammensætning omfattende et salt ifølge et hvilket som helst af kravene 1, 2, 3, eller 4, sammen med et farmaceutisk acceptabelt fortyndingsmiddel eller bærer.

6. Saltet ifølge et hvilket som helst af kravene 1, 2, 3, eller 4, til anvendelse i behandlingen af sygdom.

7. Saltet ifølge et hvilket som helst af kravene 1, 2, 3, eller 4, til anvendelse i behandlingen af diabetes, type II-diabetes, fedme, hyperglycæmi, insulinresistens, hyperinsulinæmi, hyperkolesterolæmi, hypertension, hyperlipoproteinæmi, hyperlipidæmi, dyslipidæmi, hypertriglylceridæmi, syndrom X, kardiovaskulær sygdom, hjertesvigt, rheumatoid arthritis, aterosklerose type 1-diabetes, insulinresistens, inflammation, sårheling, eller ardannelse.