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(54) **Title:** PPAR-SPARING THIAZOLIDINEDIONES FOR THE TREATMENT OF KIDNEY RELATED DISEASES

(57) **Abstract:** The present invention relates to thiazolidinedione analogues and pharmaceutical compositions that are useful for treating and/or preventing PKD.



WO 2012/149083 A1

**PPAR-SPARING THIAZOLIDINEDIONES FOR THE TREATMENT OF KIDNEY
RELATED DISEASES**

CROSS REFERENCE TO RELATED APPLICATION

[0001] The present application claims the benefit of U.S. provisional application serial no. 61/480,076, which was filed on April 28, 2011. This provisional application is incorporated herein by reference in its entirety.

TECHNICAL FIELD OF THE INVENTION

[0002] The present invention provides thiazolidinedione analogs and pharmaceutical composition containing thiazolidinedione analogs for use in treating and/or preventing kidney diseases (e.g., polycystic kidney disease).

BACKGROUND OF THE INVENTION

[0003] Polycystic kidney disease ("PKD") is a genetic disorder characterized by the growth of numerous cysts in the kidneys. The kidneys are two organs, each about the size of a fist, located in the upper part of a person's abdomen, toward the back. The kidneys filter wastes and extra fluid from the blood to form urine. They also regulate amounts of certain vital substances in the body. When cysts form in the kidneys, they are filled with fluid. PKD cysts can profoundly enlarge the kidneys while replacing much of the normal structure, resulting in reduced kidney function and leading to kidney failure.

[0004] When PKD causes kidneys to fail, which usually happens after many years, the patient requires dialysis or kidney transplantation. About one-half of people with the most common type of PKD progress to kidney failure, also called end-stage renal disease ("ESRD").

[0005] In the United States, about 600,000 people have PKD, and cystic disease is the fourth leading cause of kidney failure. Grantham JJ, Nair V, Winklhofer F. Cystic diseases of the kidney. In: Brenner BM, ed. Brenner & Rector's The Kidney. Vol. 2. 6th ed. Philadelphia: WB Saunders Company; 2000: 1699–1730.

[0006] Two major inherited forms of PKD exist. Autosomal dominant PKD is the most common inherited disorder of the kidneys. The phrase "autosomal dominant" refers to the probability that if one parent has the disease, there is a 50 percent chance that the disease gene will pass to a child. In some cases, perhaps 10 percent, autosomal dominant PKD occurs spontaneously in patients. In these cases, neither of the parents carries a copy of the disease gene.

[0007] The cysts grow out of nephrons, the tiny filtering units inside the kidneys. The cysts eventually separate from the nephrons and continue to enlarge. The kidneys enlarge along

with the cysts, which can number in the thousands, while roughly retaining their kidney shape. In fully developed autosomal dominant PKD, a cyst-filled kidney can weigh as much as 20 to 30 pounds. High blood pressure is common and develops in most patients by age 20 or 30. The most common symptoms are pain in the back and the sides, between the ribs and hips, and headaches. The pain can be temporary or persistent, mild or severe. People with autosomal dominant PKD also can experience complications including urinary tract infections, hematuria, liver and pancreatic cysts, abnormal heart valves, high blood pressure, kidney stones, aneurysms, and diverticulosis.

[0008] An autosomal recessive form of polycystic kidney disease also exists and appears in infancy or childhood. Autosomal recessive PKD is caused by a mutation in the autosomal recessive PKD gene, called PKHD1. Other genes for the disease might exist but have not yet been discovered by scientists.

[0009] Historical treatments for PKD generally target complications, such as those described above. Pain, hypertension and other complications may be managed with drugs or dialysis, and cysts may be drained or excised surgically.

[0010] The development of therapeutic thiazolidinediones, such as pioglitazone and rosiglitazone, was based on a commonly held understanding that PPAR γ is the generally accepted site of action for insulin sensitizing thiazolidinedione compounds.

[0011] Peroxisome Proliferator Activated Receptors (PPARs) are members of the nuclear hormone receptor super family, which are ligand-activated transcription factors regulating gene expression. PPARs have been implicated in autoimmune diseases and other diseases, i.e. diabetes mellitus, cardiovascular and gastrointestinal disease, and Alzheimer's disease.

[0012] PPAR γ is a key regulator of adipocyte differentiation and lipid metabolism. PPAR γ is also found in other cell types including fibroblasts, myocytes, breast cells, human bone-marrow precursors, and macrophages/monocytes. In addition, PPAR γ has been shown in macrophage foam cells in atherosclerotic plaques.

[0013] Thiazolidinediones, developed originally for the treatment of type-2 diabetes, generally exhibit high-affinity as PPAR γ ligands. The finding that thiazolidinediones might mediate their therapeutic effects through direct interactions with PPAR γ helped to establish the concept that PPAR γ is a key regulator of glucose and lipid homeostasis. However, compounds that involve the activation of PPAR γ also trigger sodium reabsorption and other unpleasant side effects.

[0014] Many thiazolidinediones evaluated for clinical development were shown to activate PPAR γ , which ultimately resulted in the transcription of genes favoring sodium reabsorption,

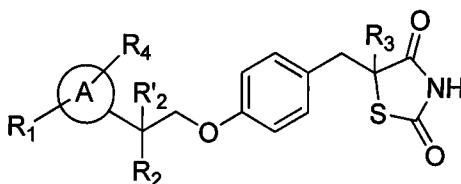
fluid retention, and weight gain in patients. Guan, Y. et al., Nat. Med. (2005) 11:861-866. It is generally believed that this PPAR γ agonism is also responsible for the biological activity of these compounds. Petrovic et al., Am. J. Physiol. Endocrinol. Meta. (2008) 295: E287-E296.

SUMMARY OF THE INVENTION

[0015] The present invention relates to compounds that have reduced binding and/or activation of the nuclear transcription factor PPAR γ . Contrary to the teachings of the literature, PPAR γ sparing compounds of the present invention are able to stimulate the differentiation of BAT and increase the amount of UCP1 protein. These PPAR γ sparing compounds are also useful for the treatment of PKD.

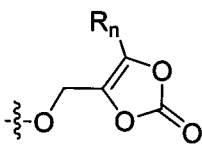
[0016] The compounds of this invention have reduced binding and/or activation of the nuclear transcription factor PPAR γ , do not augment sodium re-absorption, and are useful in treating or PKD. Advantageously, the compounds having lower PPAR γ activity exhibit fewer side effects than compounds having higher levels of PPAR γ activity.

[0017] In one aspect, the present invention provides a method of treating or delaying the onset of PKD comprising administering to a patient a compound of Formula I:



I

or a pharmaceutically acceptable salt (e.g., an alkali earth metal salt) thereof, wherein each of R₁ and R₄ is independently selected from H, halo, aliphatic, and alkoxy, wherein the aliphatic or alkoxy is optionally substituted with 1-3 of halo; R'₂ is H; R₂ is H, halo, hydroxy, or optionally substituted aliphatic, -O-acyl, -O-aroyl, -O-heteroaroyl, -O(SO₂)NH₂,

-O-CH(R_m)OC(O)R_n, -O-CH(R_m)OP(O)(OR_n)₂, -O-P(O)(OR_n)₂, or , wherein each R_m is independently an optionally substituted C₁₋₆ alkyl, each R_n is independently C₁₋₁₂ alkyl, C₃₋₈ cycloalkyl, or phenyl, each of which is optionally substituted, or R₂ and R'₂ together form oxo; R₃ is H or optionally substituted C₁₋₃ alkyl; and ring A is a phenyl, pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl, each of which is substituted with an R₁ group and an R₄ group.

[0018] In some embodiments, R₃ is H. In other embodiments, R₃ is -CH₃.

[0019] In some embodiments, R_4 is H, methyl, methoxy, ethoxy, -O-isopropyl, -CF₃, -OCHF₂ or -OCF₃. For example, R_4 is H.

[0020] In some embodiments, R_1 is H, alkyl, halo or alkoxy. For example, R_1 is H. In other examples, R_1 is halo (e.g., Cl, F, or Br). In other examples, R_1 is C₁₋₃ alkyl (e.g., methyl, ethyl, propyl, or isopropyl). And, in some examples, R_1 is C₁₋₃ alkoxy (e.g., methoxy, ethoxy, propoxy, or -O-isopropyl).

[0021] In some embodiments, ring A is phenyl that is substituted with R_1 and R_4 groups at any chemically feasible position on ring A. For example, ring A is phenyl, and one of R_1 or R_4 is attached to the para or meta position of ring A. In some instances, ring A is phenyl, and one of R_1 or R_4 is attached to the meta position of ring A. In some examples, R_1 is attached to the para or meta position of ring A. For instance, R_1 is attached to the para or meta position of ring A, and R_1 is F or Cl. In other instances, R_1 is attached to the para or meta position of ring A, and R_1 is alkoxy. For example, R_1 is methoxy, ethoxy, propoxy, -O-isopropyl, butoxy, or -O-tertbutyl that is attached to the para or meta position of ring A. In some examples, ring A is phenyl, and R_1 is attached to the meta or ortho position of the phenyl ring. For instance, ring A is phenyl, and R_1 is attached to the ortho position of the phenyl ring. In other instances, ring A is phenyl, and R_1 is methoxy, ethoxy, or -O-isopropyl, wherein any of these groups are attached to the ortho position of ring A. In other examples, R_1 is -CF₃, -OCH₃, -OCHF₂ or -OCF₃, wherein any of these groups are attached to the ortho position of ring A.

[0022] In some embodiments, ring A is pyridin-2-yl or pyridin-3-yl, either of which is substituted with R_1 and R_4 groups at any chemically feasible position on ring A. For example, ring A is pyridin-2-yl, and one of R_1 or R_4 is attached to the 5 position of the ring. In other examples, ring A is pyridin-3-yl, and one of R_1 or R_4 is attached to the 6 position of the ring. In some examples, ring A is pyridin-2-yl, and R_1 is attached to the 5 position of the ring. For instance, R_1 is alkyl or alkoxy, wherein either moiety is attached to the 5 position of ring A. In some instances, R_1 is methyl, ethyl, propyl, isopropyl, butyl, or tertbutyl, wherein any of these moieties is attached to the 5 position of ring A.

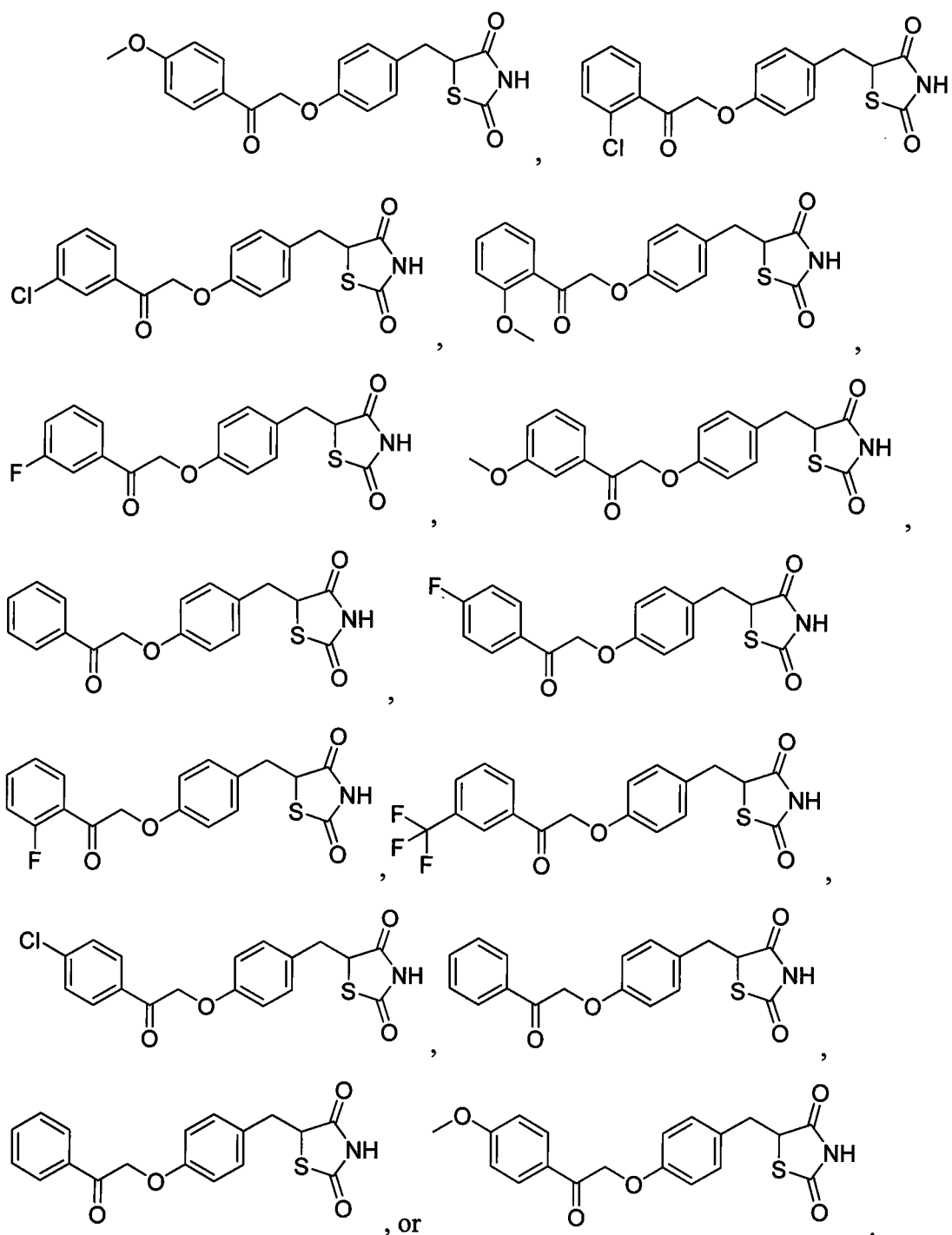
[0023] In some embodiments, R'_2 is H.

[0024] In some embodiments, R_2 is hydroxy.

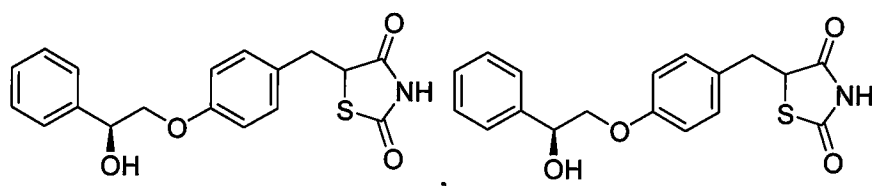
[0025] In some embodiments, R_2 is -O-acyl, -O-aroyl, or -O-heteroaroyl.

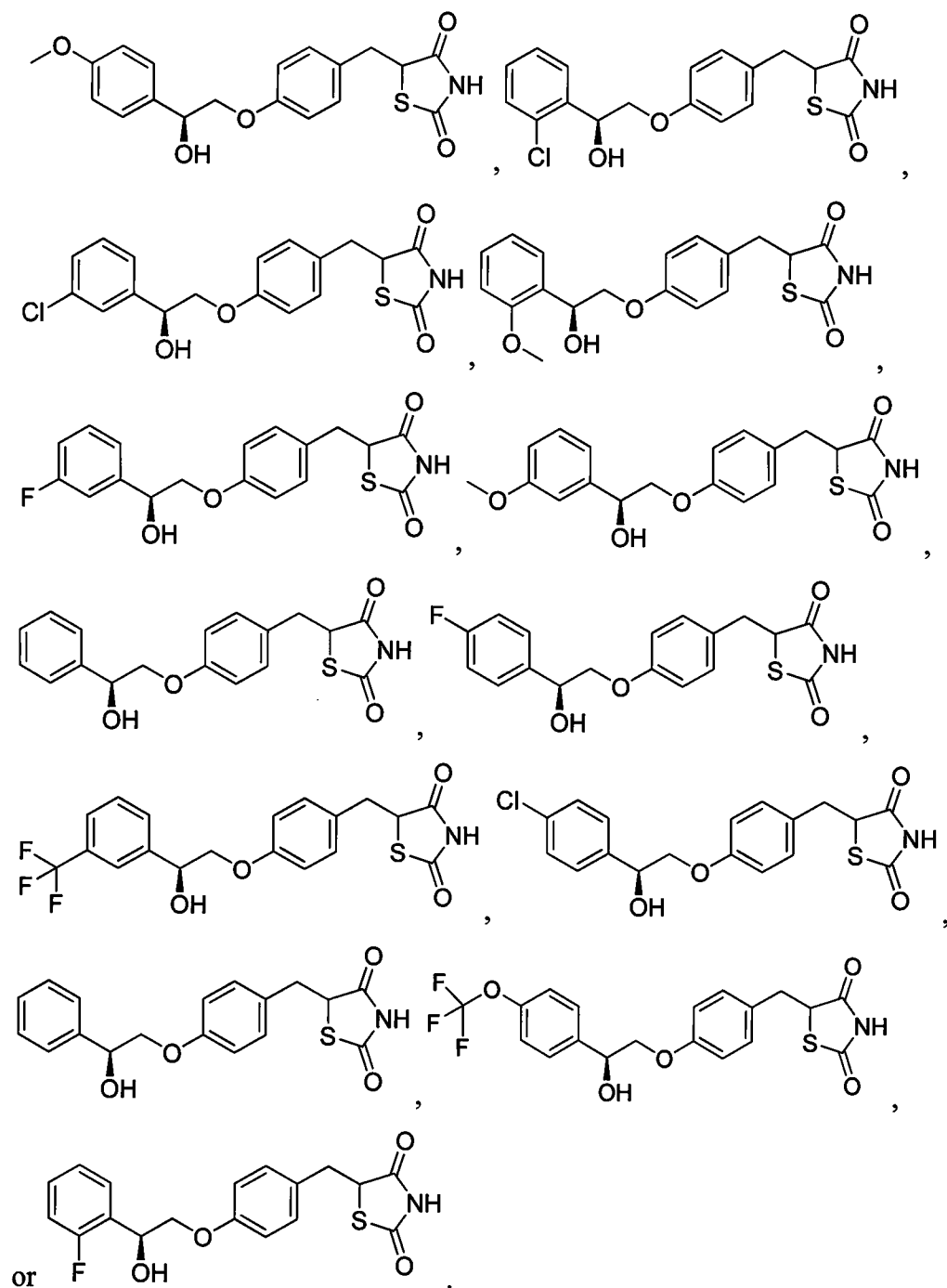
[0026] In some embodiments, R_2 and R'_2 together form oxo.

[0027] In some embodiments, the compound of Formula I is selected from:

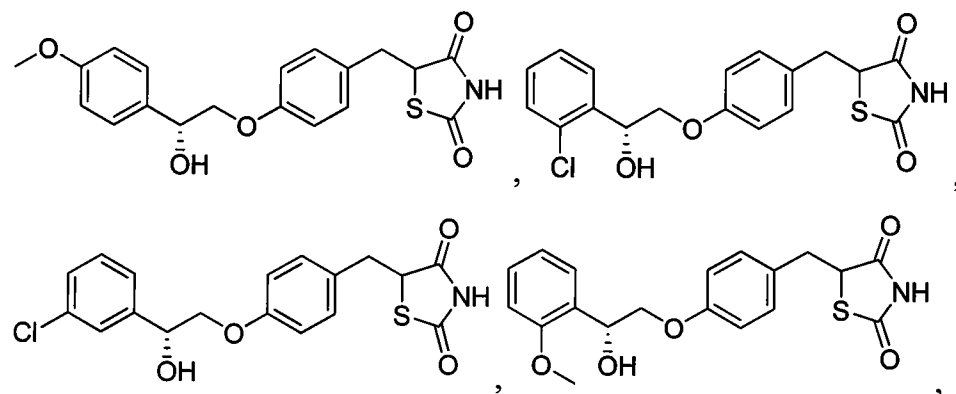


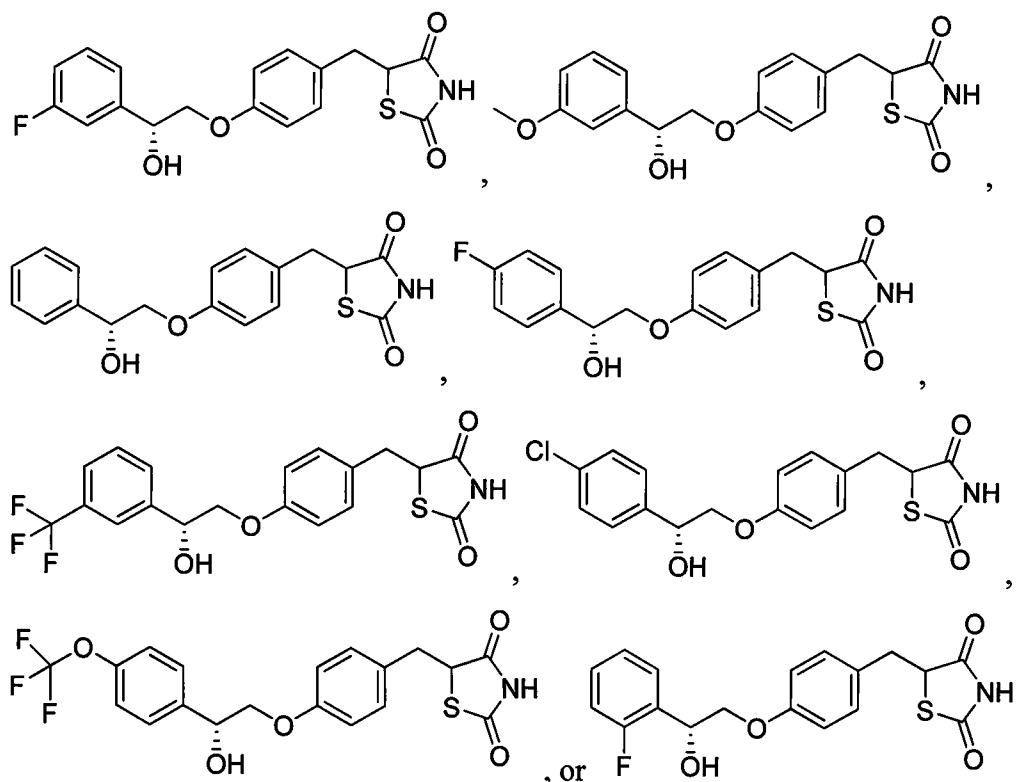
[0028] In some embodiments, the compound of Formula I is selected from:



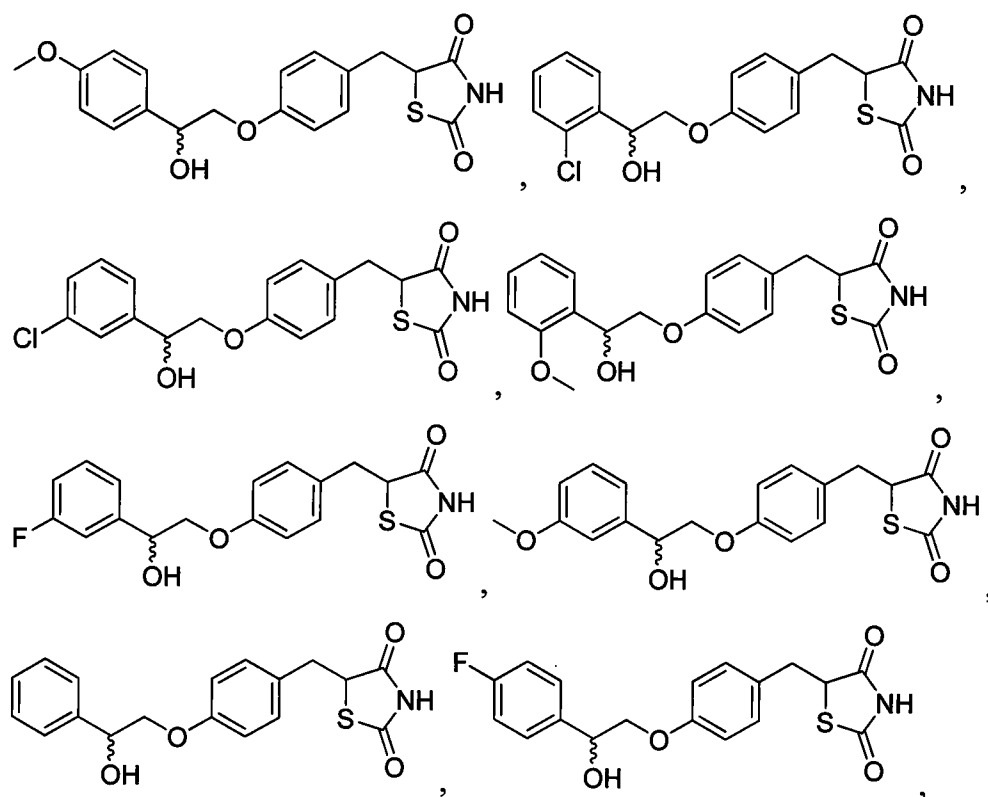


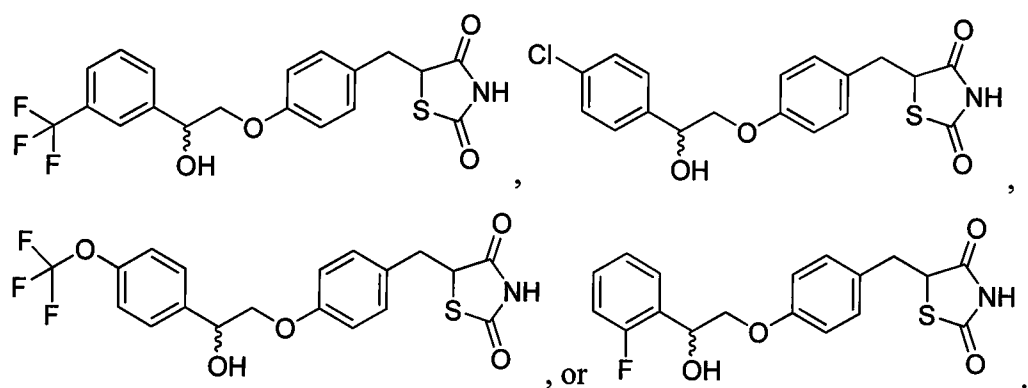
[0029] In some embodiments, the compound of Formula I is selected from:



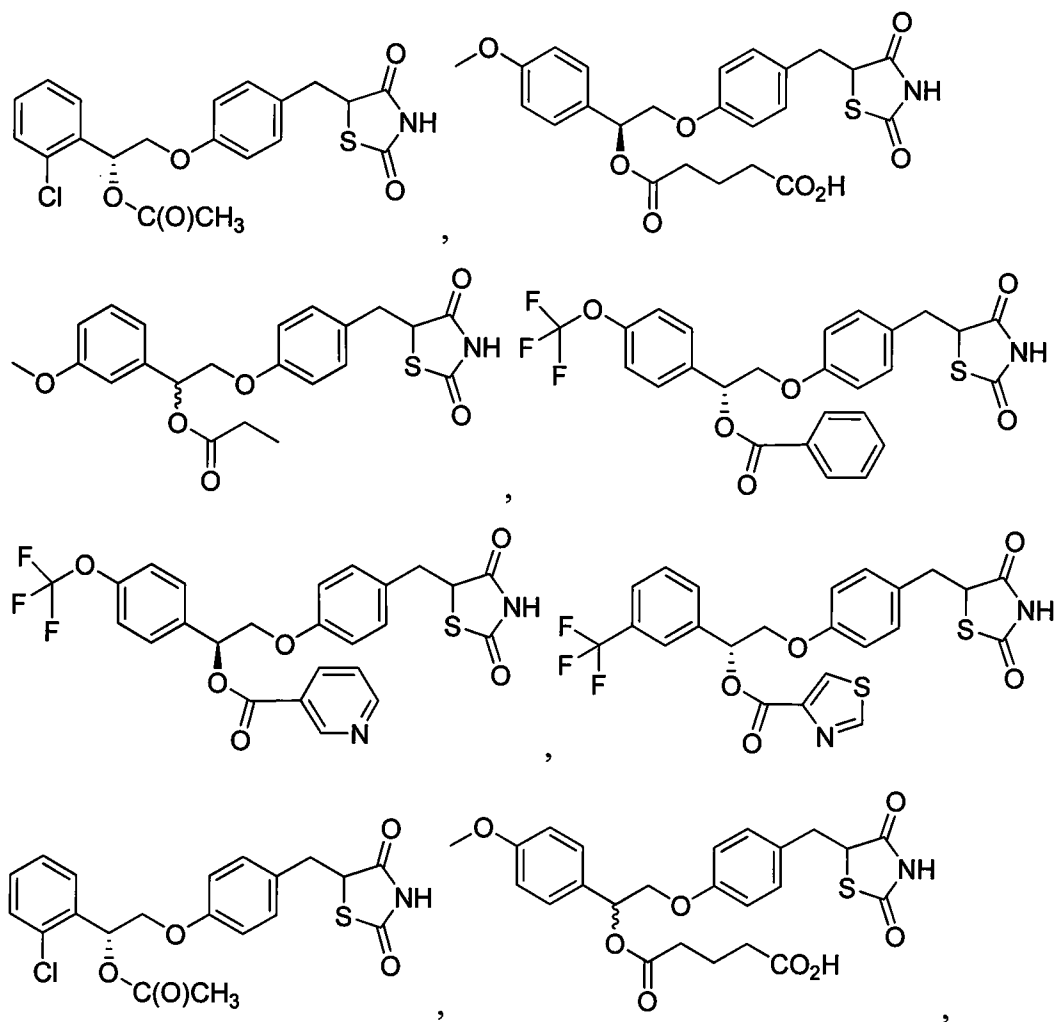


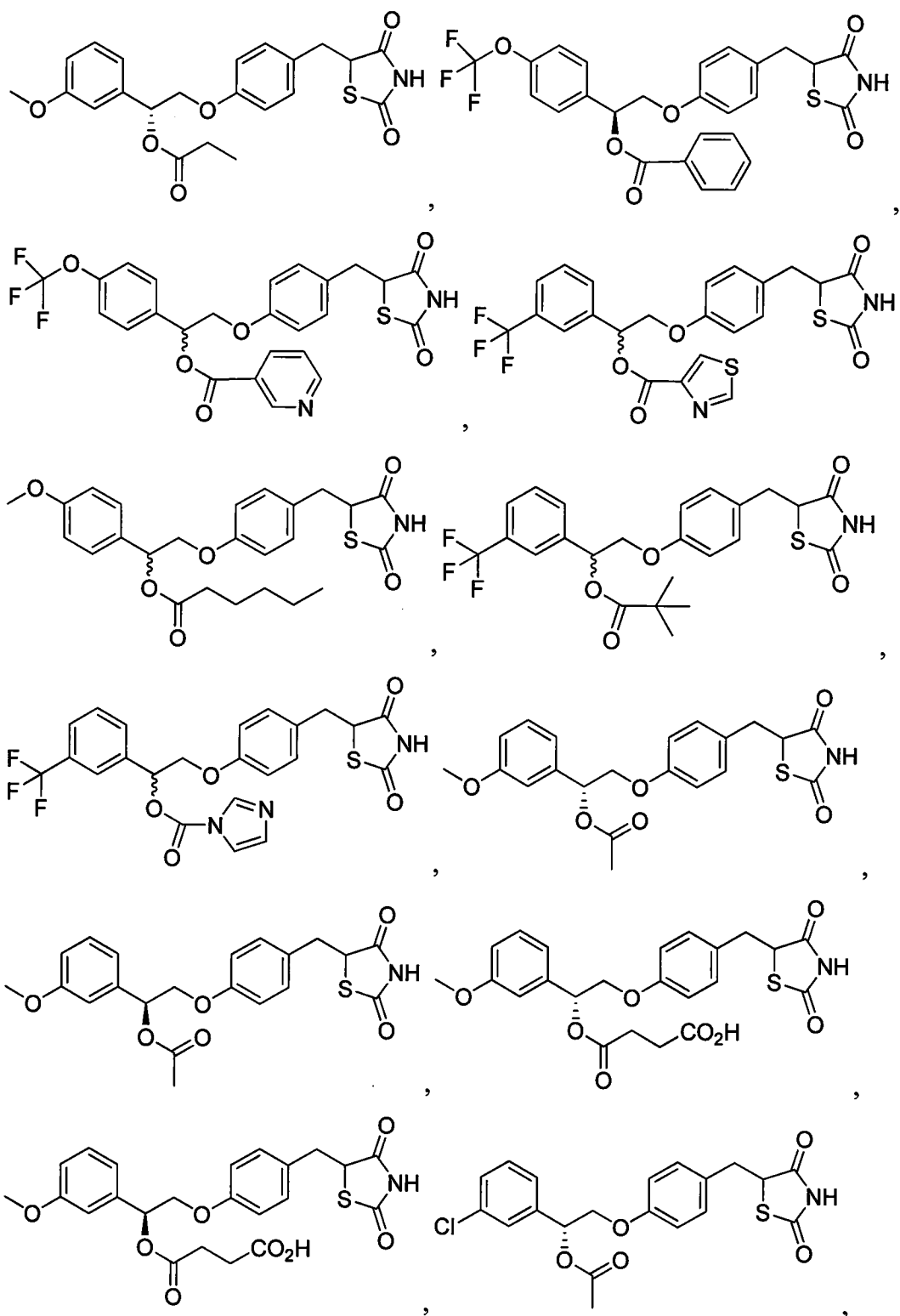
[0030] In some embodiments, the compound of Formula I is selected from:

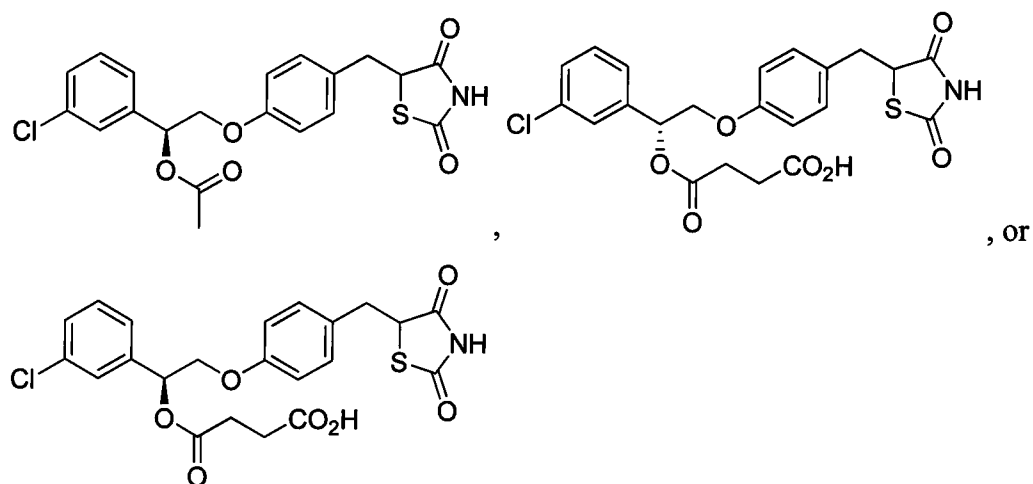




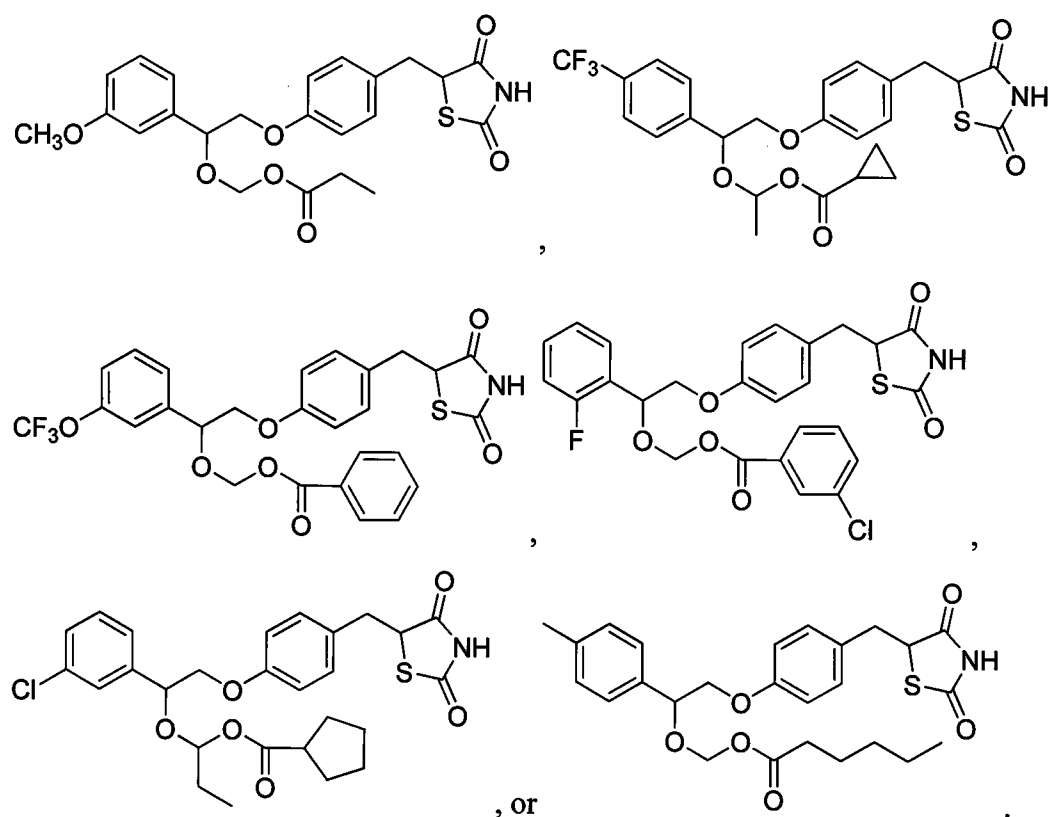
[0031] In some embodiments, the compound of Formula I is selected from:



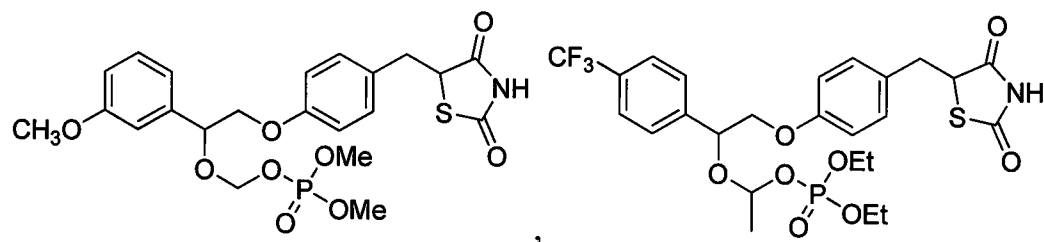


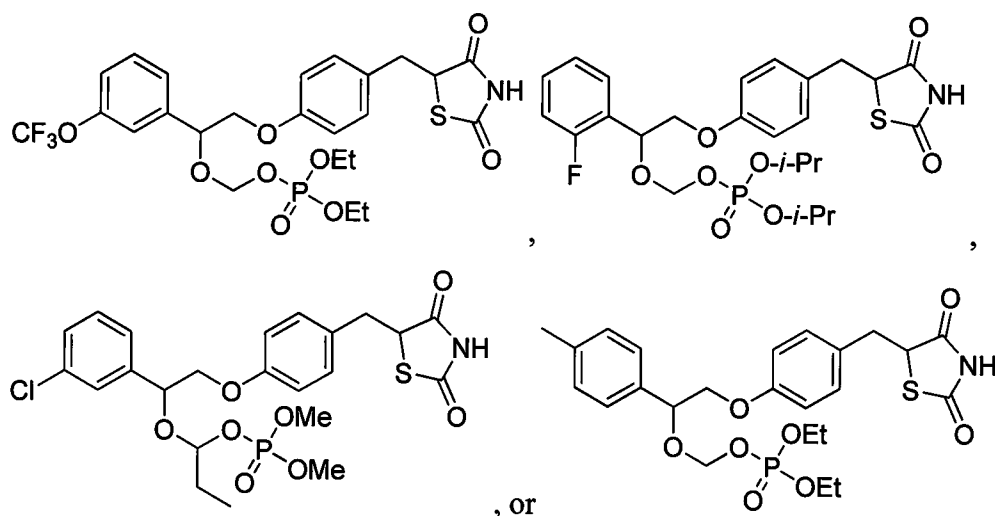


[0032] In some embodiments, the compound of Formula I is selected from:

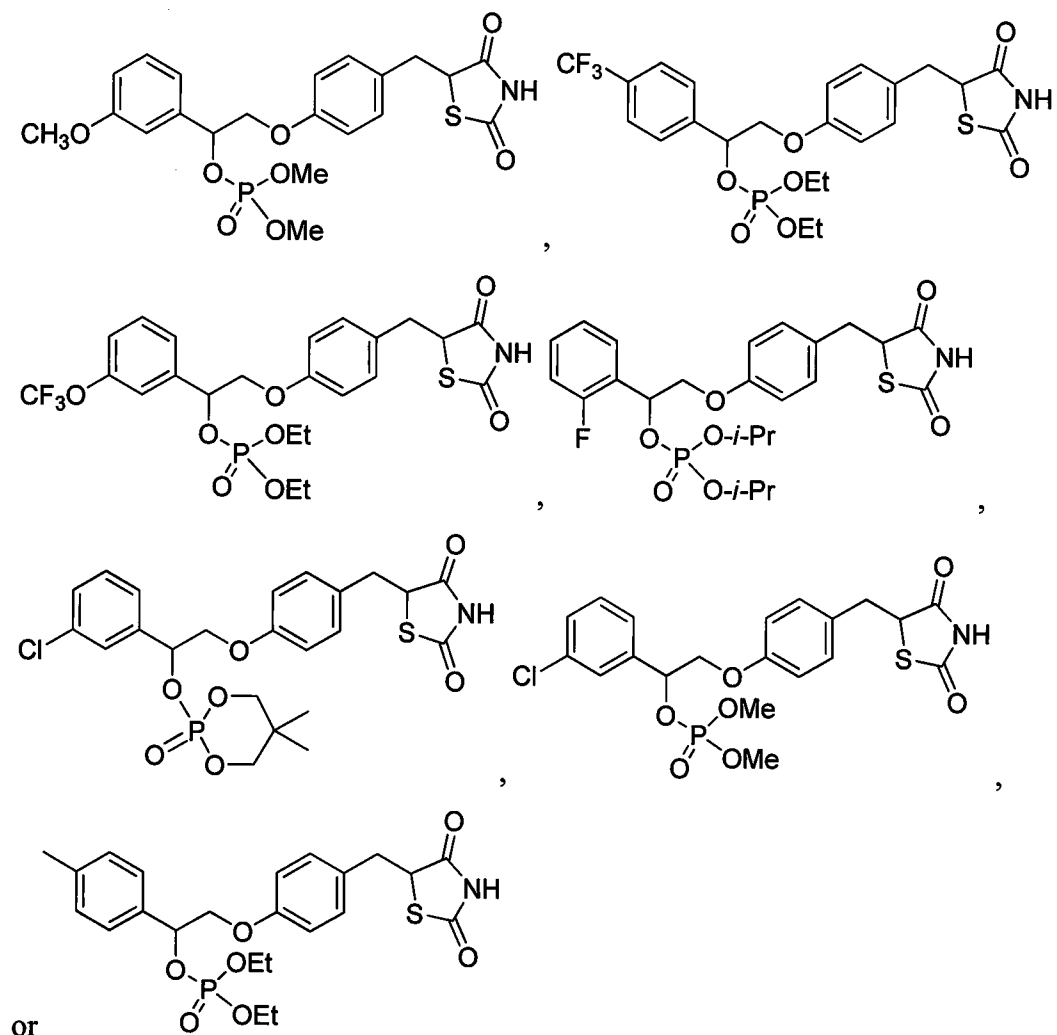


[0033] In some embodiments, the compound of Formula I is selected from:

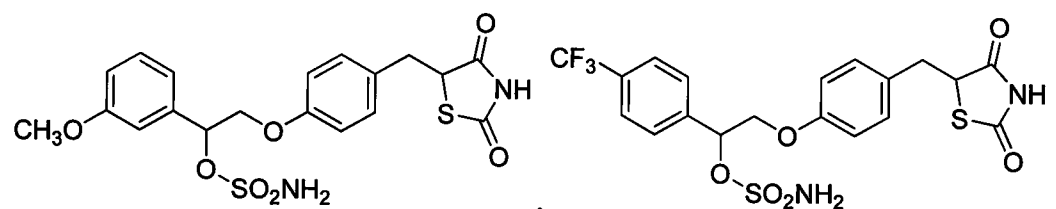


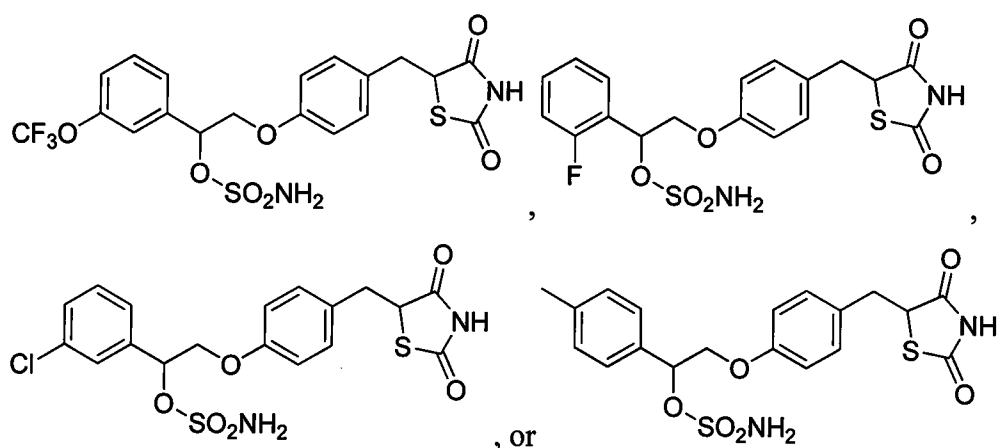


[0034] In some embodiments, the compound of Formula I is selected from:

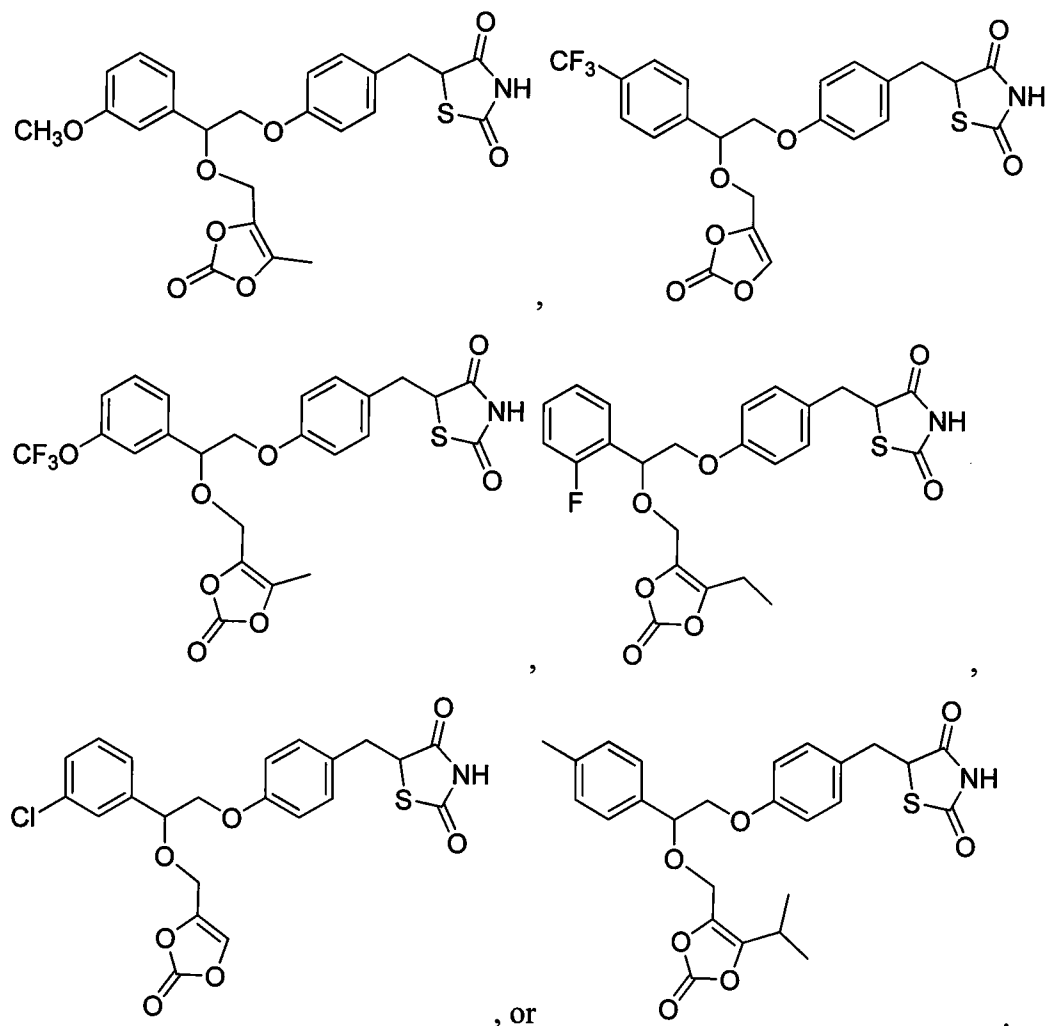


[0035] In some embodiments, the compound of Formula I is selected from:

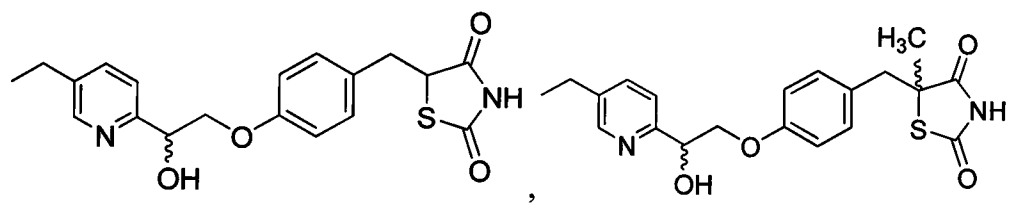


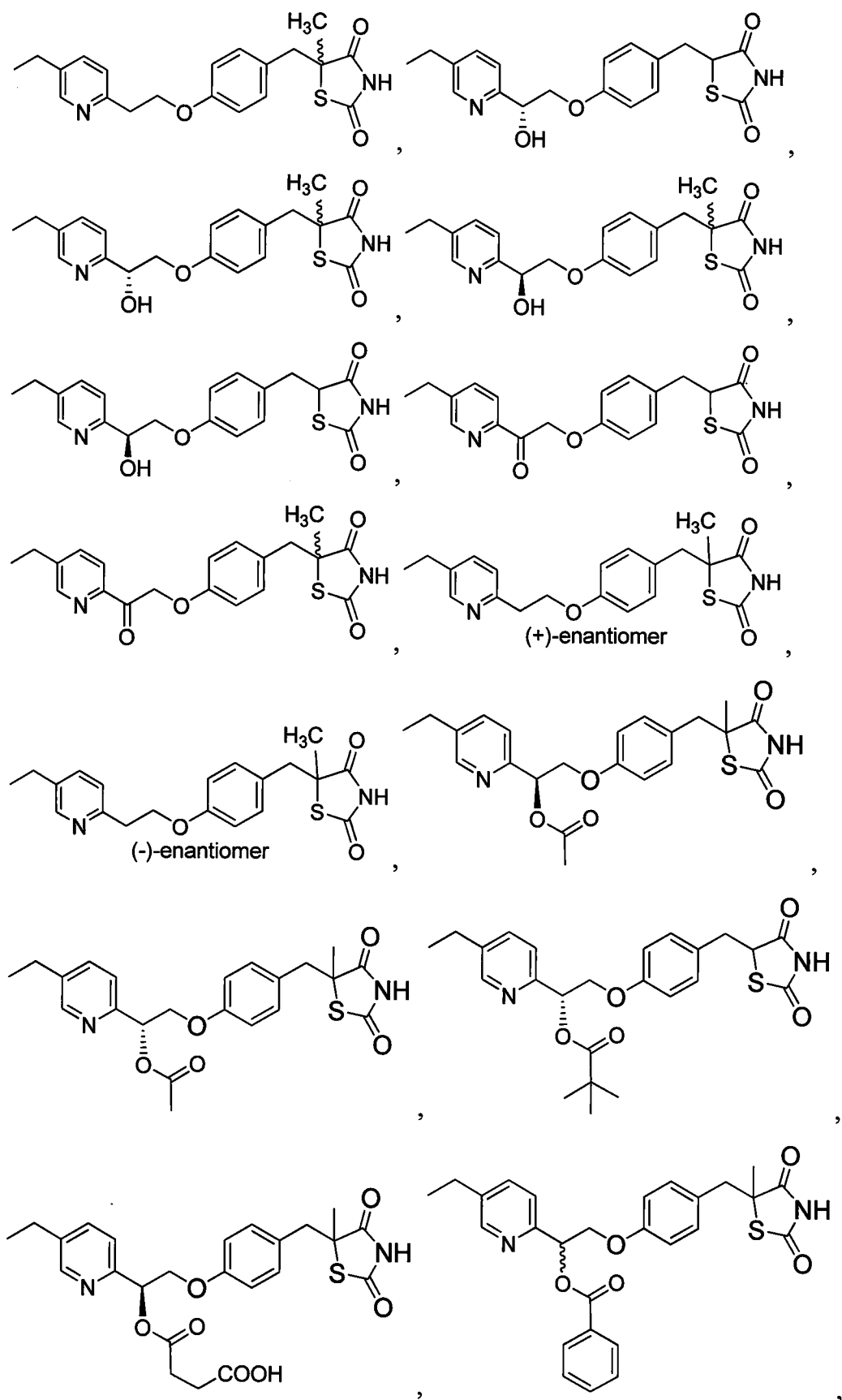


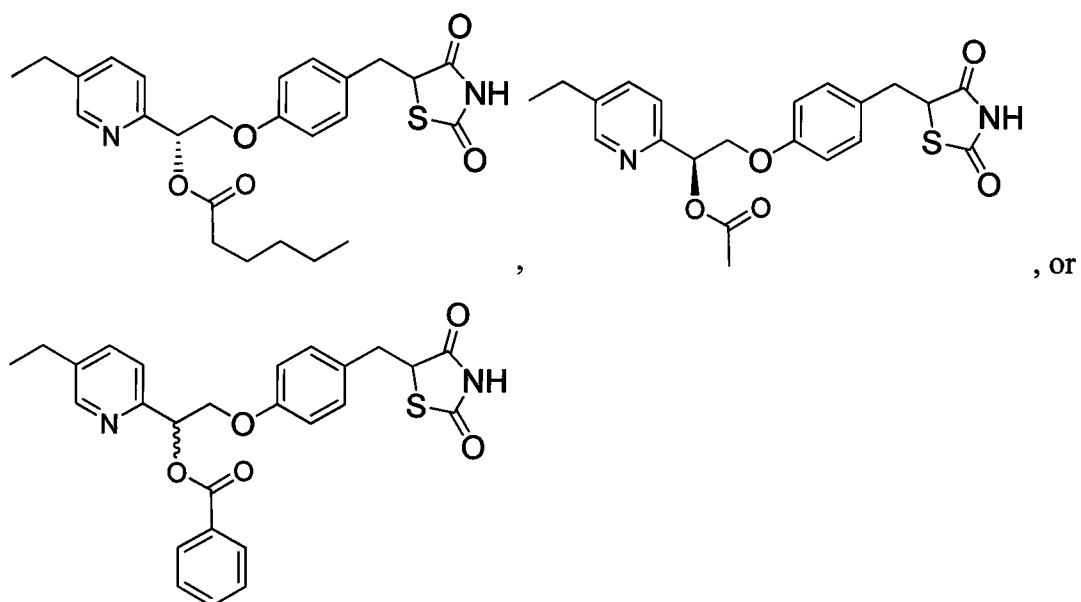
[0036] In some embodiments, the compound of Formula I is selected from:



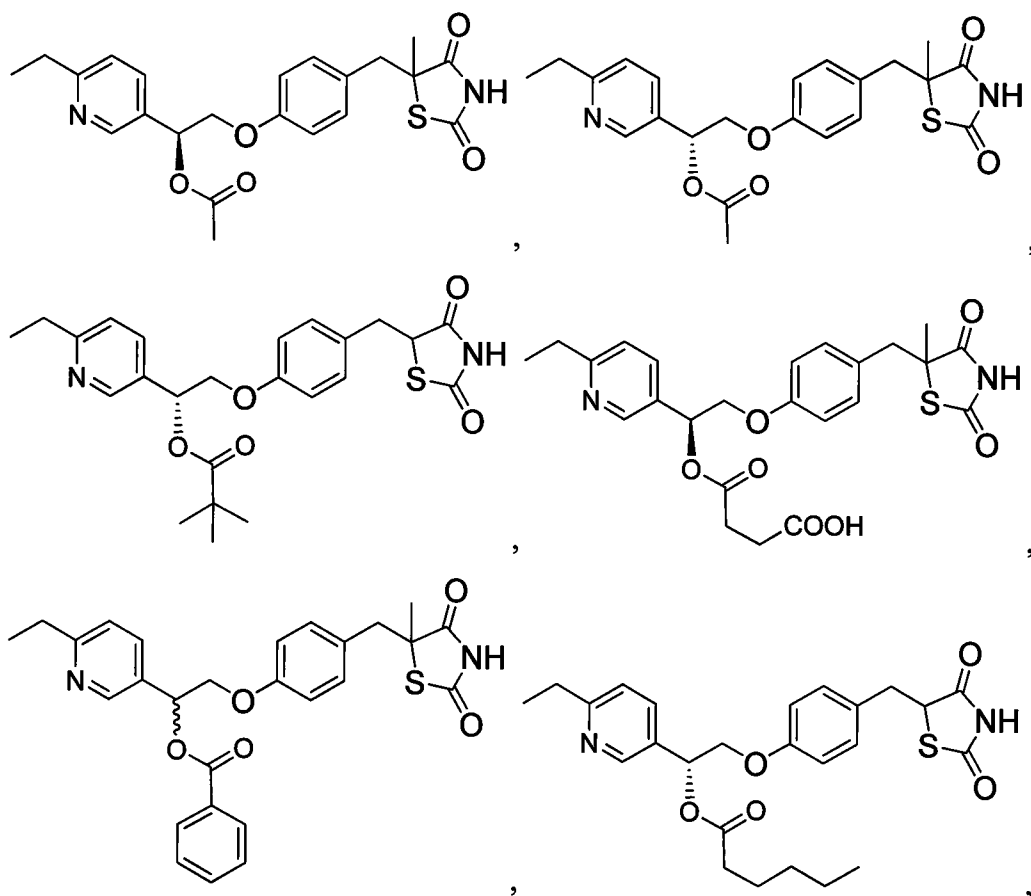
[0037] In some embodiments, the compound of Formula I is selected from:

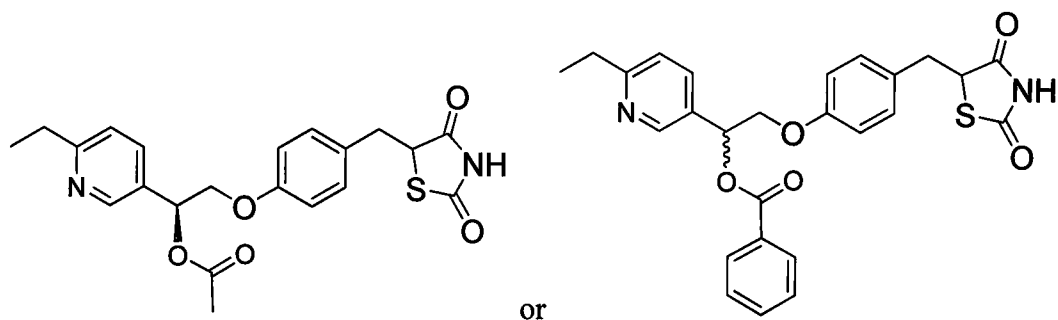




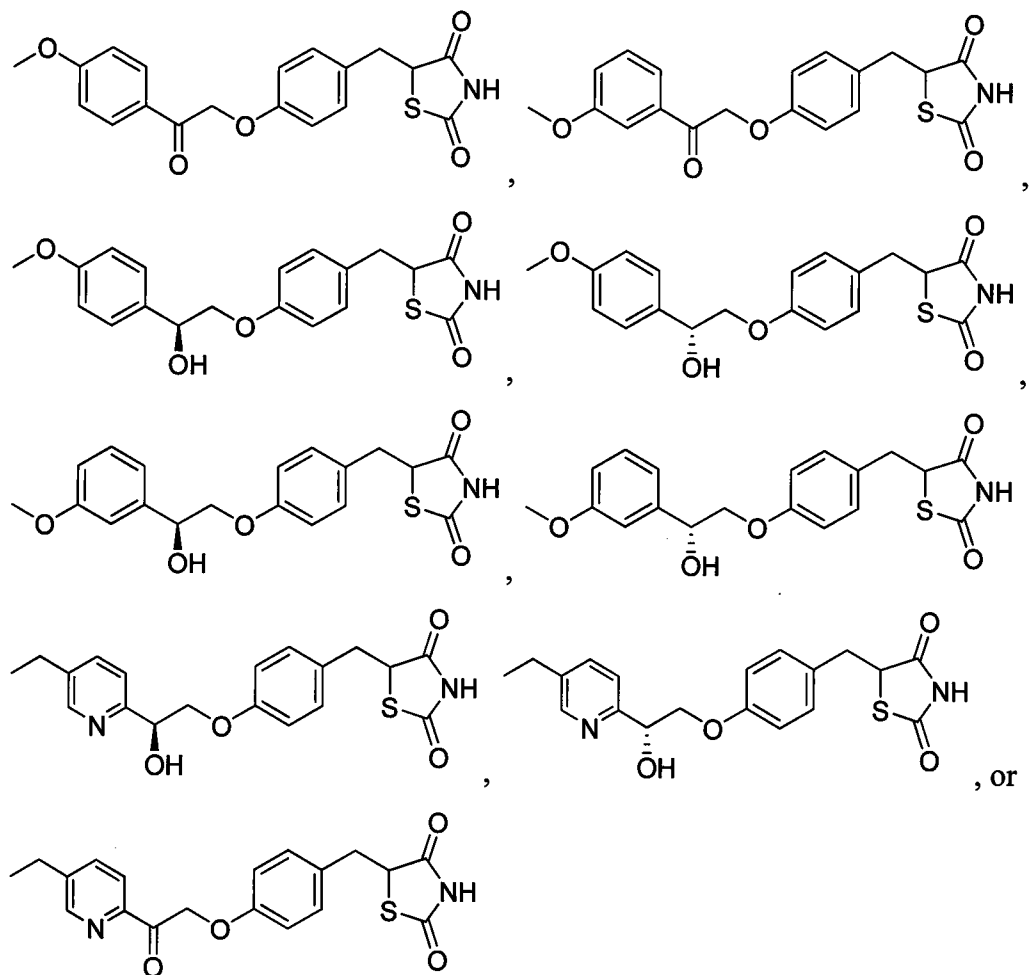


[0038] In some embodiments, the compound of Formula I is selected from:

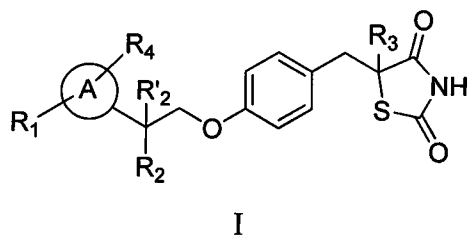




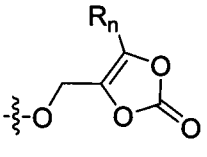
[0039] In some embodiments, the compound of Formula I is selected from:



[0040] Another aspect of the present invention provides a method of treating or delaying the onset of PKD comprising administering to a patient an alkali earth metal salt of a compound of Formula I:



wherein each of R_1 and R_4 is independently selected from H, halo, aliphatic, and alkoxy, wherein the aliphatic or alkoxy is optionally substituted with 1-3 of halo; R'_2 is H; R_2 is H, halo, hydroxy, or optionally substituted aliphatic, -O-acyl, -O-aryl, -O-heteroaryl, -O(SO₂)NH₂, -O-CH(R_m)OC(O) R_n , -O-CH(R_m)OP(O)(OR_n)₂,

-O-P(O)(OR_n)₂, or , wherein each R_m is independently an optionally substituted C₁₋₆ alkyl, each R_n is independently C₁₋₁₂ alkyl, C₃₋₈ cycloalkyl, or phenyl, each of which is optionally substituted, or R_2 and R'_2 together form oxo; R_3 is H or optionally substituted C₁₋₃ alkyl; and ring A is a phenyl, pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl, each of which is substituted with an R_1 group and an R_4 group.

[0041] In some embodiments, the alkali earth metal comprises sodium.

[0042] In other embodiments, the alkali earth metal comprises potassium.

[0043] In some embodiments, R_3 is H.

[0044] In some embodiments, R_4 is H, methyl, methoxy, ethyl, ethoxy, -O-isopropyl, -CF₃, -OCHF₂ or -OCF₃. For example, R_4 is H.

[0045] In some embodiments, R_1 is H, alkyl, halo or alkoxy. For example, R_1 is H. In other examples, R_1 is halo. In some examples, R_1 is C₁₋₃ alkyl.

[0046] In some embodiments, ring A is phenyl that is substituted with R_1 and R_4 groups at any chemically feasible position on ring A. For example, ring A is phenyl, and one of R_1 or R_4 is attached to the para or meta position of ring A. In some instances, ring A is phenyl, and one of R_1 or R_4 is attached to the meta position of ring A. In some examples, R_1 is attached to the para or meta position of ring A. For instance, R_1 is attached to the para or meta position of ring A, and R_1 is F or Cl. In other instances, R_1 is attached to the para or meta position of ring A, and R_1 is alkoxy. For example, R_1 is methoxy, ethoxy, propoxy, -O-isopropyl, butoxy, or -O-tertbutyl that is attached to the para or meta position of ring A. In some examples, ring A is phenyl, and R_1 is attached to the meta or ortho position of the phenyl ring. For instance, ring A is phenyl, and R_1 is attached to the ortho position of the phenyl ring. In other instances, ring A is phenyl, and R_1 is methoxy, ethoxy, or -O-isopropyl, wherein any of these groups are attached to the ortho position of ring A. In other examples, R_1 is -CF₃, -OCH₃, -OCHF₂ or -OCF₃, wherein any of these groups are attached to the ortho position of ring A.

[0047] In some embodiments, ring A is pyridin-2-yl or pyridin-3-yl, either of which is substituted with R_1 and R_4 groups at any chemically feasible position on ring A. For

example, ring A is pyridin-2-yl, and one of R₁ or R₄ is attached to the 5 position of the ring. In other examples, ring A is pyridin-3-yl, and one of R₁ or R₄ is attached to the 6 position of the ring. In some examples, ring A is pyridin-2-yl, and R₁ is attached to the 5 position of the ring. For instance, R₁ is alkyl or alkoxy, wherein either moiety is attached to the 5 position of ring A. In some instances, R₁ is methyl, ethyl, propyl, isopropyl, butyl, or tertbutyl, wherein any of these moieties is attached to the 5 position of ring A.

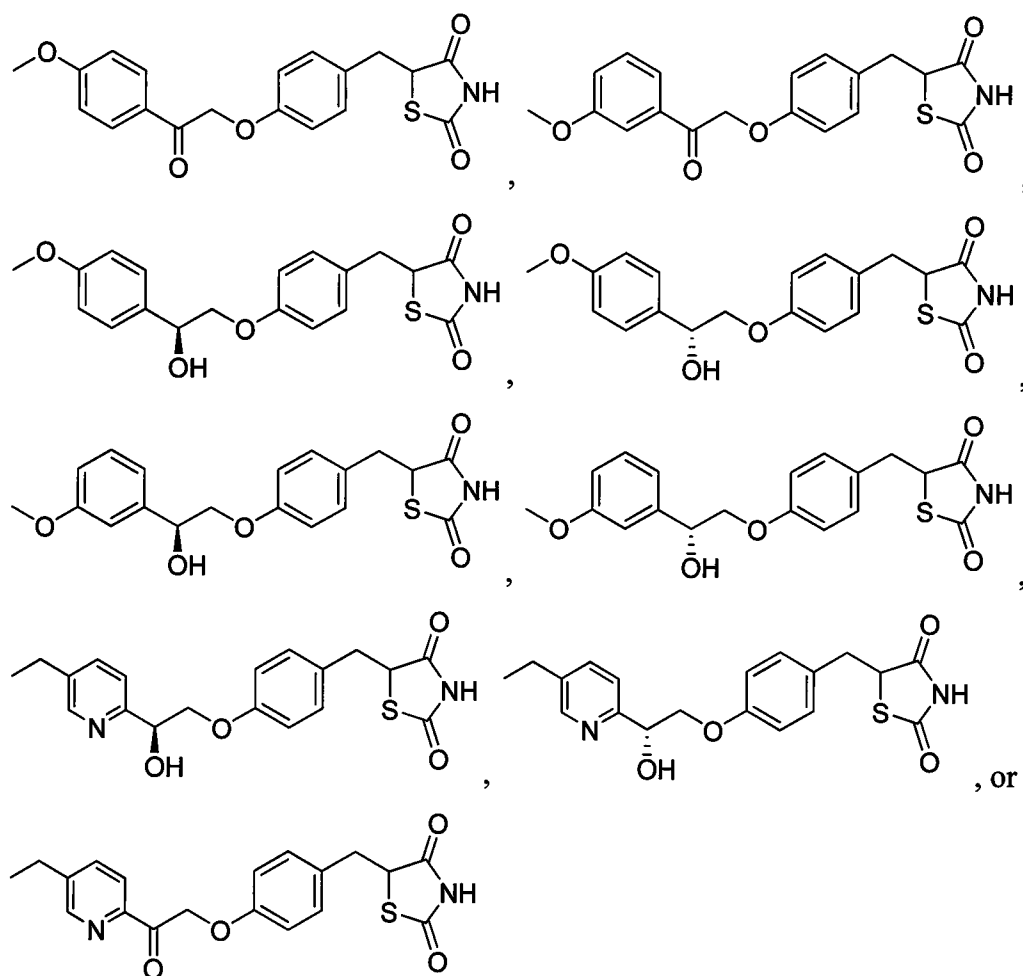
[0048] In some embodiments, R'₂ is H.

[0049] In some embodiments, R₂ is hydroxy.

[0050] In some embodiments, R₂ is -O-acyl, -O-aroyl, or -O-heteroaroyl.

[0051] In some embodiments, R₂ and R'₂ together form oxo.

[0052] In some embodiments, the compound of Formula I is selected from:



[0053] In one implementation of the method, the PKD being treated or delayed is autosomal dominant PKD.

[0054] In another implementation of the method, the PKD being treated or delayed is autosomal recessive PKD.

[0055] Some embodiments further comprise administering to a patient a second pharmaceutical agent having an activity that increases cAMP in the patient.

[0056] In some embodiments, the second pharmaceutical agent further comprises a beta-adrenergic agonist. For example, the beta-adrenergic agonist comprises a beta-1- adrenergic agonist, a beta-2-adrenergic agonist, a beta-3-adrenergic agonist, or any combination thereof. In other examples, the beta-adrenergic agonist comprises noradrenaline, isoprenaline, dobutamine, salbutamol, levosalbutamol, terbutaline, pirbuterol, procaterol, metaproterenol, fenoterol, bitolterol mesylate, salmeterol, formoterol, bambuterol, clenbuterol, indacaterol, L-796568, amibegron, solabegron, isoproterenol, albuterol, metaproterenol, arbutamine, befunolol, bromoacetylalprenololmenthane, broxaterol, cimaterol, cirazoline, denopamine, dopexamine, epinephrine, etilefrine, hexoprenaline, higenamine, isoetharine, isoxsuprine, mabuterol, methoxyphenamine, nylidrin, oxyfedrine, prenalterol, ractopamine, reproterol, rimiterol, ritodrine, tretoquinol, tulobuterol, xamoterol, zilpaterol, zinterol, or any combination thereof.

BRIEF DESCRIPTION OF THE FIGURES

[0057] FIG. 1 presents a bar graph comparing bioavailability of Compound A and its metabolite to sodium salts thereof.

[0058] FIG. 2 presents a bar graph of the area under the curve (AUC) of Compound B and its metal salts.

[0059] FIG. 3 presents a graph of glucose concentration as a function of dosage of Compound A or a sodium salt thereof.

[0060] FIG. 4 presents a bar graph representing mean weight gain for each population of test subjects involved in the drug test described in Example 14.

[0061] FIG. 5 presents a bar graph representing mean cumulative feed intake for each population of test subjects involved in the drug test described in Example 14.

[0062] FIG. 6 presents a bar graph representing the mean kidney weight per unit of body weight for each population of test subjects involved in the drug test described in Example 14.

[0063] FIG. 7 presents a bar graph representing the mean liver weight per unit of body weight for each population of test subjects involved in the drug test described in Example 14.

[0064] FIG. 8 presents a bar graph representing mean renal cyst volume for each population of test subjects involved in the drug test described in Example 14.

[0065] FIG. 9 presents bar graphs representing Fibrosis Scores for renal cortex and renal medulla for each population of test subjects involved in the drug test described in Example 14.

[0066] FIG. 10 presents a bar graph representing mean hepatic cyst volume for each population of test subjects involved in the drug test described in Example 14.

DETAILED DESCRIPTION OF THE INVENTION

[0067] The present invention provides methods of treating and/or delaying the onset of PKD in a patient and pharmaceutical compositions useful for treating and/or delaying the onset of PKD in a patient.

[0068] PPAR γ -sparing thiazolidinediones of the present invention are useful for treating PKD and other metabolic diseases such as diabetes.

[0069] I. DEFINITIONS

[0070] For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0071] As described herein, "protecting group" refers to a moiety or functionality that is introduced into a molecule by chemical modification of a functional group in order to obtain chemoselectivity in a subsequent chemical reaction. Standard protecting groups are provided in Wuts and Greene: "Greene's Protective Groups in Organic Synthesis" 4th Ed, Wuts, P.G.M. and Greene, T.W., Wiley-Interscience, New York:2006.

[0072] As described herein, compounds of the invention may optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the invention.

[0073] As used herein, the term "hydroxyl" or "hydroxy" refers to an -OH moiety.

[0074] As used herein the term "aliphatic" encompasses the terms alkyl, alkenyl, alkynyl, each of which being optionally substituted as set forth below.

[0075] As used herein, an "alkyl" group refers to a saturated aliphatic hydrocarbon group containing 1-12 (e.g., 1-8, 1-6, or 1-4) carbon atoms. An alkyl group can be straight or branched. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-heptyl, or 2-ethylhexyl. An alkyl group can be substituted (i.e., optionally substituted) with one or more substituents such as halo, phospho, cycloaliphatic [e.g., cycloalkyl or cycloalkenyl], heterocycloaliphatic [e.g., heterocycloalkyl or heterocycloalkenyl], aryl, heteroaryl, alkoxy, aroyl, heteroaroyl, acyl [e.g., (aliphatic)carbonyl, (cycloaliphatic)carbonyl, or (heterocycloaliphatic)carbonyl], nitro,

cyano, amido [e.g., (cycloalkylalkyl)carbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkylalkyl)carbonylamino, heteroarylcarbonylamino, heteroaralkylcarbonylamino alkylaminocarbonyl, cycloalkylaminocarbonyl, heterocycloalkylaminocarbonyl, arylaminocarbonyl, or heteroarylaminocarbonyl], amino [e.g., aliphaticamino, cycloaliphaticamino, or heterocycloaliphaticamino], sulfonyl [e.g., aliphatic-SO₂-], sulfinyl, sulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, carboxy, carbamoyl, cycloaliphaticoxy, heterocycloaliphaticoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroarylalkoxy, alkoxycarbonyl, alkylcarbonyloxy, or hydroxy. Without limitation, some examples of substituted alkyls include carboxyalkyl (such as HOOC-alkyl, alkoxycarbonylalkyl, and alkylcarbonyloxyalkyl), cyanoalkyl, hydroxyalkyl, alkoxyalkyl, acylalkyl, aralkyl, (alkoxyaryl)alkyl, (sulfonylamino)alkyl (such as (alkyl-SO₂-amino)alkyl), aminoalkyl, amidoalkyl, (cycloaliphatic)alkyl, or haloalkyl.

[0076] As used herein, an "alkenyl" group refers to an aliphatic carbon group that contains 2-8 (e.g., 2-12, 2-6, or 2-4) carbon atoms and at least one double bond. Like an alkyl group, an alkenyl group can be straight or branched. Examples of an alkenyl group include, but are not limited to allyl, 1- or 2-isopropenyl, 2-butenyl, and 2-hexenyl. An alkenyl group can be optionally substituted with one or more substituents such as halo, phospho, cycloaliphatic [e.g., cycloalkyl or cycloalkenyl], heterocycloaliphatic [e.g., heterocycloalkyl or heterocycloalkenyl], aryl, heteroaryl, alkoxy, aroyl, heteroaroyl, acyl [e.g., (aliphatic)carbonyl, (cycloaliphatic)carbonyl, or (heterocycloaliphatic)carbonyl], nitro, cyano, amido [e.g., (cycloalkylalkyl)carbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkylalkyl)carbonylamino, heteroarylcarbonylamino, heteroaralkylcarbonylamino alkylaminocarbonyl, cycloalkylaminocarbonyl, heterocycloalkylaminocarbonyl, arylaminocarbonyl, or heteroarylaminocarbonyl], amino [e.g., aliphaticamino, cycloaliphaticamino, heterocycloaliphaticamino, or aliphaticsulfonylamino], sulfonyl [e.g., alkyl-SO₂-, cycloaliphatic-SO₂-, or aryl-SO₂-], sulfinyl, sulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, carboxy, carbamoyl, cycloaliphaticoxy, heterocycloaliphaticoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkoxy, alkoxycarbonyl, alkylcarbonyloxy, or hydroxy. Without limitation, some examples of substituted alkenyls include cyanoalkenyl, alkoxyalkenyl, acylalkenyl, hydroxyalkenyl, aralkenyl, (alkoxyaryl)alkenyl, (sulfonylamino)alkenyl (such as (alkyl-SO₂-amino)alkenyl), aminoalkenyl, amidoalkenyl, (cycloaliphatic)alkenyl, or haloalkenyl.

[0077] As used herein, an "alkynyl" group refers to an aliphatic carbon group that contains 2-8 (e.g., 2-12, 2-6, or 2-4) carbon atoms and has at least one triple bond. An alkynyl group can be straight or branched. Examples of an alkynyl group include, but are not limited to, propargyl and butynyl. An alkynyl group can be optionally substituted with one or more substituents such as aroyl, heteroaroyl, alkoxy, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, nitro, carboxy, cyano, halo, hydroxy, sulfo, mercapto, sulfanyl [e.g., aliphaticsulfanyl or cycloaliphaticsulfanyl], sulfinyl [e.g., aliphaticsulfinyl or cycloaliphaticsulfinyl], sulfonyl [e.g., aliphatic-SO₂-, aliphaticamino-SO₂-, or cycloaliphatic-SO₂-], amido [e.g., aminocarbonyl, alkylaminocarbonyl, alkylcarbonylamino, cycloalkylaminocarbonyl, heterocycloalkylaminocarbonyl, cycloalkylcarbonylamino, arylaminocarbonyl, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (cycloalkylalkyl)carbonylamino, heteroaralkylcarbonylamino, heteroarylcarbonylamino or heteroarylaminocarbonyl], urea, thiourea, sulfamoyl, sulfamide, alkoxycarbonyl, alkylcarbonyloxy, cycloaliphatic, heterocycloaliphatic, aryl, heteroaryl, acyl [e.g., (cycloaliphatic)carbonyl or (heterocycloaliphatic)carbonyl], amino [e.g., aliphaticamino], sulfoxy, oxo, carboxy, carbamoyl, (cycloaliphatic)oxy, (heterocycloaliphatic)oxy, or (heteroaryl)alkoxy.

[0078] As used herein, an "amido" encompasses both "aminocarbonyl" and "carbonylamino". These terms when used alone or in connection with another group refer to an amido group such as -N(R^X)-C(O)-R^Y or -C(O)-N(R^X)₂, when used terminally, and -C(O)-N(R^X)- or -N(R^X)-C(O)- when used internally, wherein R^X and R^Y can be aliphatic, cycloaliphatic, aryl, araliphatic, heterocycloaliphatic, heteroaryl or heteroaraliphatic. Examples of amido groups include alkylamido (such as alkylcarbonylamino or alkylaminocarbonyl), (heterocycloaliphatic)amido, (heteroaralkyl)amido, (heteroaryl)amido, (heterocycloalkyl)alkylamido, arylamido, aralkylamido, (cycloalkyl)alkylamido, or cycloalkylamido.

[0079] As used herein, an "amino" group refers to -NR^XR^Y wherein each of R^X and R^Y is independently hydrogen, aliphatic, cycloaliphatic, (cycloaliphatic)aliphatic, aryl, araliphatic, heterocycloaliphatic, (heterocycloaliphatic)aliphatic, heteroaryl, carboxy, sulfanyl, sulfinyl, sulfonyl, (aliphatic)carbonyl, (cycloaliphatic)carbonyl, ((cycloaliphatic)aliphatic)carbonyl, arylcarbonyl, (araliphatic)carbonyl, (heterocycloaliphatic)carbonyl, ((heterocycloaliphatic)aliphatic)carbonyl, (heteroaryl)carbonyl, or (heteroaraliphatic)carbonyl, each of which being defined herein and being optionally substituted. Examples of amino groups include alkylamino, dialkylamino, or arylamino.

When the term "amino" is not the terminal group (e.g., alkylcarbonylamino), it is represented by -NR^{X} , where R^{X} has the same meaning as defined above.

[0080] As used herein, an "aryl" group used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl" refers to monocyclic (e.g., phenyl); bicyclic (e.g., indenyl, naphthalenyl, tetrahydronaphthyl, tetrahydroindenyl); and tricyclic (e.g., fluorenyl, tetrahydrofluorenyl, or tetrahydroanthracenyl, anthracenyl) ring systems in which the monocyclic ring system is aromatic or at least one of the rings in a bicyclic or tricyclic ring system is aromatic. The bicyclic and tricyclic groups include benzofused 2-3 membered carbocyclic rings. For example, a benzofused group includes phenyl fused with two or more C_{4-8} carbocyclic moieties. An aryl is optionally substituted with one or more substituents including aliphatic [e.g., alkyl, alkenyl, or alkynyl]; cycloaliphatic; (cycloaliphatic)aliphatic; heterocycloaliphatic; (heterocycloaliphatic)aliphatic; aryl; heteroaryl; alkoxy; (cycloaliphatic)oxy; (heterocycloaliphatic)oxy; aryloxy; heteroaryloxy; (araliphatic)oxy; (heteroaraliphatic)oxy; aroyl; heteroaroyl; amino; oxo (on a non-aromatic carbocyclic ring of a benzofused bicyclic or tricyclic aryl); nitro; carboxy; amido; acyl [e.g., (aliphatic)carbonyl; (cycloaliphatic)carbonyl; ((cycloaliphatic)aliphatic)carbonyl; (araliphatic)carbonyl; (heterocycloaliphatic)carbonyl; ((heterocycloaliphatic)aliphatic)carbonyl; or (heteroaraliphatic)carbonyl]; sulfonyl [e.g., aliphatic- SO_2 - or amino- SO_2 -]; sulfinyl [e.g., aliphatic-S(O)- or cycloaliphatic-S(O)-]; sulfanyl [e.g., aliphatic-S-]; cyano; halo; hydroxy; mercapto; sulfoxy; urea; thiourea; sulfamoyl; sulfamide; or carbamoyl. Alternatively, an aryl can be unsubstituted.

[0081] Non-limiting examples of substituted aryls include haloaryl [e.g., mono-, di (such as *p,m*-dihaloaryl), and (trihalo)aryl]; (carboxy)aryl [e.g., (alkoxycarbonyl)aryl, ((aralkyl)carbonyloxy)aryl, and (alkoxycarbonyl)aryl]; (amido)aryl [e.g., (aminocarbonyl)aryl, (((alkylamino)alkyl)aminocarbonyl)aryl, (alkylcarbonyl)aminoaryl, (arylaminocarbonyl)aryl, and (((heteroaryl)amino)carbonyl)aryl]; aminoaryl [e.g., ((alkylsulfonyl)amino)aryl or ((dialkyl)amino)aryl]; (cyanoalkyl)aryl; (alkoxy)aryl; (sulfamoyl)aryl [e.g., (aminosulfonyl)aryl]; (alkylsulfonyl)aryl; (cyano)aryl; (hydroxyalkyl)aryl; ((alkoxy)alkyl)aryl; (hydroxy)aryl, ((carboxy)alkyl)aryl; (((dialkyl)amino)alkyl)aryl; (nitroalkyl)aryl; (((alkylsulfonyl)amino)alkyl)aryl; ((heterocycloaliphatic)carbonyl)aryl; ((alkylsulfonyl)alkyl)aryl; (cyanoalkyl)aryl; (hydroxyalkyl)aryl; (alkylcarbonyl)aryl; alkylaryl; (trihaloalkyl)aryl; *p*-amino-*m*-alkoxycarbonylaryl; *p*-amino-*m*-cyanoaryl; *p*-halo-*m*-aminoaryl; or *m*-(heterocycloaliphatic)-*o*-(alkyl)aryl.

[0082] As used herein, an "araliphatic" such as an "aralkyl" group refers to an aliphatic group (e.g., a C₁₋₄ alkyl group) that is substituted with an aryl group. "Aliphatic," "alkyl," and "aryl" are defined herein. An example of an araliphatic such as an aralkyl group is benzyl.

[0083] As used herein, an "aralkyl" group refers to an alkyl group (e.g., a C₁₋₄ alkyl group) that is substituted with an aryl group. Both "alkyl" and "aryl" have been defined above. An example of an aralkyl group is benzyl. An aralkyl is optionally substituted with one or more substituents such as aliphatic [e.g., alkyl, alkenyl, or alkynyl, including carboxyalkyl, hydroxyalkyl, or haloalkyl such as trifluoromethyl], cycloaliphatic [e.g., cycloalkyl or cycloalkenyl], (cycloalkyl)alkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, aryl, heteroaryl, alkoxy, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aroyl, heteroaroyl, nitro, carboxy, alkoxycarbonyl, alkylcarbonyloxy, amido [e.g., aminocarbonyl, alkylcarbonylamino, cycloalkylcarbonylamino, (cycloalkylalkyl)carbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkylalkyl)carbonylamino, heteroarylcarbonylamino, or heteroaralkylcarbonylamino], cyano, halo, hydroxy, acyl, mercapto, alkylsulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl.

[0084] As used herein, a "bicyclic ring system" includes 6-12 (e.g., 8-12 or 9, 10, or 11) membered structures that form two rings, wherein the two rings have at least one atom in common (e.g., 2 atoms in common). Bicyclic ring systems include bicycloaliphatics (e.g., bicycloalkyl or bicycloalkenyl), bicycloheteroaliphatics, bicyclic aryls, and bicyclic heteroaryls.

[0085] As used herein, a "cycloaliphatic" group encompasses a "cycloalkyl" group and a "cycloalkenyl" group, each of which being optionally substituted as set forth below.

[0086] As used herein, a "cycloalkyl" group refers to a saturated carbocyclic mono- or bicyclic (fused or bridged) ring of 3-10 (e.g., 5-10) carbon atoms. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, norbornyl, cubyl, octahydro-indenyl, decahydro-naphthyl, bicyclo[3.2.1]octyl, bicyclo[2.2.2]octyl, bicyclo[3.3.1]nonyl, bicyclo[3.3.2]decyl, bicyclo[2.2.2]octyl, adamantyl, or ((aminocarbonyl)cycloalkyl)cycloalkyl.

[0087] A "cycloalkenyl" group, as used herein, refers to a non-aromatic carbocyclic ring of 3-10 (e.g., 4-8) carbon atoms having one or more double bonds. Examples of cycloalkenyl groups include cyclopentenyl, 1,4-cyclohexa-di-enyl, cycloheptenyl, cyclooctenyl,

hexahydro-indenyl, octahydro-naphthyl, cyclohexenyl, bicyclo[2.2.2]octenyl, or bicyclo[3.3.1]nonenyl.

[0088] A cycloalkyl or cycloalkenyl group can be optionally substituted with one or more substituents such as phospho, aliphatic [e.g., alkyl, alkenyl, or alkynyl], cycloaliphatic, (cycloaliphatic) aliphatic, heterocycloaliphatic, (heterocycloaliphatic) aliphatic, aryl, heteroaryl, alkoxy, (cycloaliphatic)oxy, (heterocycloaliphatic)oxy, aryloxy, heteroaryloxy, (araliphatic)oxy, (heteroaraliphatic)oxy, aroyl, heteroaroyl, amino, amido [e.g., (aliphatic)carbonylamino, (cycloaliphatic)carbonylamino, ((cycloaliphatic)aliphatic)carbonylamino, (aryl)carbonylamino, (araliphatic)carbonylamino, (heterocycloaliphatic)carbonylamino, ((heterocycloaliphatic)aliphatic)carbonylamino, (heteroaryl)carbonylamino, or (heteroaraliphatic)carbonylamino], nitro, carboxy [e.g., HOOC-, alkoxycarbonyl, or alkylcarbonyloxy], acyl [e.g., (cycloaliphatic)carbonyl, ((cycloaliphatic) aliphatic)carbonyl, (araliphatic)carbonyl, (heterocycloaliphatic)carbonyl, ((heterocycloaliphatic)aliphatic)carbonyl, or (heteroaraliphatic)carbonyl], cyano, halo, hydroxy, mercapto, sulfonyl [e.g., alkyl-SO₂- and aryl-SO₂-], sulfinyl [e.g., alkyl-S(O)-], sulfanyl [e.g., alkyl-S-], sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl.

[0089] As used herein, the term "heterocycloaliphatic" encompasses heterocycloalkyl groups and heterocycloalkenyl groups, each of which being optionally substituted as set forth below.

[0090] As used herein, a "heterocycloalkyl" group refers to a 3-10 membered mono- or bicyclic (fused or bridged) (e.g., 5- to 10-membered mono- or bicyclic) saturated ring structure, in which one or more of the ring atoms is a heteroatom (e.g., N, O, S, or combinations thereof). Examples of a heterocycloalkyl group include piperidyl, piperazyl, tetrahydropyranyl, tetrahydrofuryl, 1,4-dioxolanyl, 1,4-dithianyl, 1,3-dioxolanyl, oxazolidyl, isoxazolidyl, morpholinyl, thiomorpholyl, octahydrobenzofuryl, octahydrochromenyl, octahydrothiochromenyl, octahydroindolyl, octahydropyrindinyl, decahydroquinolinyl, octahydrobenzo[*b*]thiophenyl, 2-oxa-bicyclo[2.2.2]octyl, 1-aza-bicyclo[2.2.2]octyl, 3-aza-bicyclo[3.2.1]octyl, and 2,6-dioxa-tricyclo[3.3.1.0^{3,7}]nonyl. A monocyclic heterocycloalkyl group can be fused with a phenyl moiety to form structures, such as tetrahydroisoquinoline, which would be categorized as heteroaryls.

[0091] A "heterocycloalkenyl" group, as used herein, refers to a mono- or bicyclic (e.g., 5- to 10-membered mono- or bicyclic) non-aromatic ring structure having one or more double bonds, and wherein one or more of the ring atoms is a heteroatom (e.g., N, O, or S).

Monocyclic and bicyclic heterocycloaliphatics are numbered according to standard chemical nomenclature.

[0092] A heterocycloalkyl or heterocycloalkenyl group can be optionally substituted with one or more substituents such as phospho, aliphatic [e.g., alkyl, alkenyl, or alkynyl], cycloaliphatic, (cycloaliphatic)aliphatic, heterocycloaliphatic, (heterocycloaliphatic)aliphatic, aryl, heteroaryl, alkoxy, (cycloaliphatic)oxy, (heterocycloaliphatic)oxy, aryloxy, heteroaryloxy, (araliphatic)oxy, (heteroaraliphatic)oxy, aroyl, heteroaroyl, amino, amido [e.g., (aliphatic)carbonylamino, (cycloaliphatic)carbonylamino, ((cycloaliphatic) aliphatic)carbonylamino, (aryl)carbonylamino, (araliphatic)carbonylamino, (heterocycloaliphatic)carbonylamino, ((heterocycloaliphatic) aliphatic)carbonylamino, (heteroaryl)carbonylamino, or (heteroaraliphatic)carbonylamino], nitro, carboxy [e.g., HOOC-, alkoxycarbonyl, or alkylcarbonyloxy], acyl [e.g., (cycloaliphatic)carbonyl, ((cycloaliphatic) aliphatic)carbonyl, (araliphatic)carbonyl, (heterocycloaliphatic)carbonyl, ((heterocycloaliphatic)aliphatic)carbonyl, or (heteroaraliphatic)carbonyl], nitro, cyano, halo, hydroxy, mercapto, sulfonyl [e.g., alkylsulfonyl or arylsulfonyl], sulfinyl [e.g., alkylsulfinyl], sulfanyl [e.g., alkylsulfanyl], sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl.

[0093] A "heteroaryl" group, as used herein, refers to a monocyclic, bicyclic, or tricyclic ring system having 4 to 15 ring atoms wherein one or more of the ring atoms is a heteroatom (e.g., N, O, S, or combinations thereof) and in which the monocyclic ring system is aromatic or at least one of the rings in the bicyclic or tricyclic ring systems is aromatic. A heteroaryl group includes a benzofused ring system having 2 to 3 rings. For example, a benzofused group includes benzo fused with one or two 4 to 8 membered heterocycloaliphatic moieties (e.g., indolizyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furyl, benzo[b]thiophene-yl, quinolinyl, or isoquinolinyl). Some examples of heteroaryl are azetidiny, pyridyl, 1H-indazolyl, furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl, tetrazolyl, benzofuryl, isoquinolinyl, benzthiazolyl, xanthene, thioxanthene, phenothiazine, dihydroindole, benzo[1,3]dioxole, benzo[b]furyl, benzo[b]thiophenyl, indazolyl, benzimidazolyl, benzthiazolyl, puryl, cinnolyl, quinolyl, quinazolyl, cinnolyl, phthalazyl, quinazolyl, quinoxalyl, isoquinolyl, 4H-quinolizyl, benzo-1,2,5-thiadiazolyl, or 1,8-naphthyridyl.

[0094] Without limitation, monocyclic heteroaryls include furyl, thiophene-yl, 2H-pyrrolyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,3,4-thiadiazolyl,

2H-pyranyl, 4-H-pranyl, pyridyl, pyridazyl, pyrimidyl, pyrazolyl, pyrazyl, or 1,3,5-triazyl.

Monocyclic heteroaryls are numbered according to standard chemical nomenclature.

[0095] Without limitation, bicyclic heteroaryls include indolizyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[*b*]furyl, benzo[*b*]thiophenyl, quinoliny, isoquinoliny, indolizyl, isoindolyl, indolyl, benzo[*b*]furyl, bexo[*b*]thiophenyl, indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizyl, quinolyl, isoquinolyl, cinnolyl, phthalazolyl, quinazolyl, quinoxalyl, 1,8-naphthyridyl, or pteridyl. Bicyclic heteroaryls are numbered according to standard chemical nomenclature.

[0096] A heteroaryl is optionally substituted with one or more substituents such as aliphatic [e.g., alkyl, alkenyl, or alkynyl]; cycloaliphatic; (cycloaliphatic)aliphatic; heterocycloaliphatic; (heterocycloaliphatic)aliphatic; aryl; heteroaryl; alkoxy; (cycloaliphatic)oxy; (heterocycloaliphatic)oxy; aryloxy; heteroaryloxy; (araliphatic)oxy; (heteroaraliphatic)oxy; aroyl; heteroaroyl; amino; oxo (on a non-aromatic carbocyclic or heterocyclic ring of a bicyclic or tricyclic heteroaryl); carboxy; amido; acyl [e.g., aliphaticcarbonyl; (cycloaliphatic)carbonyl; ((cycloaliphatic)aliphatic)carbonyl; (araliphatic)carbonyl; (heterocycloaliphatic)carbonyl; ((heterocycloaliphatic)aliphatic)carbonyl; or (heteroaraliphatic)carbonyl]; sulfonyl [e.g., aliphaticsulfonyl or aminosulfonyl]; sulfinyl [e.g., aliphaticsulfinyl]; sulfanyl [e.g., aliphaticulfanyl]; nitro; cyano; halo; hydroxy; mercapto; sulfoxy; urea; thiourea; sulfamoyl; sulfamide; or carbamoyl. Alternatively, a heteroaryl can be unsubstituted.

[0097] Non-limiting examples of substituted heteroaryls include (halo)heteroaryl [e.g., mono- and di-(halo)heteroaryl]; (carboxy)heteroaryl [e.g., (alkoxycarbonyl)heteroaryl]; cyanoheteroaryl; aminoheteroaryl [e.g., ((alkylsulfonyl)amino)heteroaryl and ((dialkyl)amino)heteroaryl]; (amido)heteroaryl [e.g., aminocarbonylheteroaryl, ((alkylcarbonyl)amino)heteroaryl, (((alkyl)amino)alkyl)aminocarbonylheteroaryl, (((heteroaryl)amino)carbonyl)heteroaryl, ((heterocycloaliphatic)carbonyl)heteroaryl, and ((alkylcarbonyl)amino)heteroaryl]; (cyanoalkyl)heteroaryl; (alkoxy)heteroaryl; (sulfamoyl)heteroaryl [e.g., (aminosulfonyl)heteroaryl]; (sulfonyl)heteroaryl [e.g., (alkylsulfonyl)heteroaryl]; (hydroxyalkyl)heteroaryl; (alkoxyalkyl)heteroaryl; (hydroxy)heteroaryl; ((carboxy)alkyl)heteroaryl; (((dialkyl)amino)alkyl)heteroaryl; (heterocycloaliphatic)heteroaryl; (cycloaliphatic)heteroaryl; (nitroalkyl)heteroaryl; (((alkylsulfonyl)amino)alkyl)heteroaryl; ((alkylsulfonyl)alkyl)heteroaryl; (cyanoalkyl)heteroaryl; (acyl)heteroaryl [e.g., (alkylcarbonyl)heteroaryl]; (alkyl)heteroaryl; or (haloalkyl)heteroaryl [e.g., trihaloalkylheteroaryl].

[0098] A "heteroaraliphatic (such as a heteroaralkyl group) as used herein, refers to an aliphatic group (e.g., a C₁₋₄ alkyl group) that is substituted with a heteroaryl group.

"Aliphatic," "alkyl," and "heteroaryl" have been defined above.

[0099] A "heteroaralkyl" group, as used herein, refers to an alkyl group (e.g., a C₁₋₄ alkyl group) that is substituted with a heteroaryl group. Both "alkyl" and "heteroaryl" have been defined above. A heteroaralkyl is optionally substituted with one or more substituents such as alkyl (including carboxyalkyl, hydroxyalkyl, and haloalkyl such as trifluoromethyl), alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, aryl, heteroaryl, alkoxy, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aroyl, heteroaroyl, nitro, carboxy, alkoxycarbonyl, alkylcarbonyloxy, aminocarbonyl, alkylcarbonylamino, cycloalkylcarbonylamino, (cycloalkylalkyl)carbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkylalkyl)carbonylamino, heteroarylcarbonylamino, heteroaralkylcarbonylamino, cyano, halo, hydroxy, acyl, mercapto, alkylsulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl.

[0100] As used herein, "cyclic moiety" and "cyclic group" refer to mono-, bi-, and tri-cyclic ring systems including cycloaliphatic, heterocycloaliphatic, aryl, or heteroaryl, each of which has been previously defined.

[0101] As used herein, a "bridged bicyclic ring system" refers to a bicyclic heterocyclicalipahitic ring system or bicyclic cycloaliphatic ring system in which the rings are bridged. Examples of bridged bicyclic ring systems include, but are not limited to, adamantanyl, norbornanyl, bicyclo[3.2.1]octyl, bicyclo[2.2.2]octyl, bicyclo[3.3.1]nonyl, bicyclo[3.3.2]decyl, 2-oxabicyclo[2.2.2]octyl, 1-azabicyclo[2.2.2]octyl, 3-azabicyclo[3.2.1]octyl, and 2,6-dioxa-tricyclo[3.3.1.0^{3,7}]nonyl. A bridged bicyclic ring system can be optionally substituted with one or more substituents such as alkyl (including carboxyalkyl, hydroxyalkyl, and haloalkyl such as trifluoromethyl), alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, aryl, heteroaryl, alkoxy, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aroyl, heteroaroyl, nitro, carboxy, alkoxycarbonyl, alkylcarbonyloxy, aminocarbonyl, alkylcarbonylamino, cycloalkylcarbonylamino, (cycloalkylalkyl)carbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkylalkyl)carbonylamino, heteroarylcarbonylamino, heteroaralkylcarbonylamino, cyano, halo, hydroxy, acyl, mercapto, alkylsulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl.

[0102] As used herein, an "acyl" group refers to a formyl group or $R^X-C(O)-$ (such as alkyl- $C(O)-$, also referred to as "alkylcarbonyl") where R^X and "alkyl" have been defined previously. Acetyl and pivaloyl are examples of acyl groups.

[0103] As used herein, an "aroyl" or "heteroaroyl" refers to an aryl- $C(O)-$ or a heteroaryl- $C(O)-$. The aryl and heteroaryl portion of the aroyl or heteroaroyl is optionally substituted as previously defined.

[0104] As used herein, an "alkoxy" group refers to an alkyl-O- group where "alkyl" has been defined previously.

[0105] As used herein, a "carbamoyl" group refers to a group having the structure $-O-CO-NR^X R^Y$ or $-NR^X-CO-O-R^Z$, wherein R^X and R^Y have been defined above and R^Z can be aliphatic, aryl, araliphatic, heterocycloaliphatic, heteroaryl, or heteroaraliphatic.

[0106] As used herein, a "carboxy" group refers to $-COOH$, $-COOR^X$, $-OC(O)H$, $-OC(O)R^X$, when used as a terminal group; or $-OC(O)-$ or $-C(O)O-$ when used as an internal group.

[0107] As used herein, a "haloaliphatic" group refers to an aliphatic group substituted with 1-3 halogen. For instance, the term haloalkyl includes the group $-CF_3$.

[0108] As used herein, a "mercapto" group refers to $-SH$.

[0109] As used herein, a "sulfo" group refers to $-SO_3H$ or $-SO_3R^X$ when used terminally or $-S(O)_3-$ when used internally.

[0110] As used herein, a "sulfamide" group refers to the structure $-NR^X-S(O)_2-NR^Y R^Z$ when used terminally and $-NR^X-S(O)_2-NR^Y-$ when used internally, wherein R^X , R^Y , and R^Z have been defined above.

[0111] As used herein, a "sulfamoyl" group refers to the structure $-O-S(O)_2-NR^Y R^Z$ wherein R^Y and R^Z have been defined above.

[0112] As used herein, a "sulfonamide" group refers to the structure $-S(O)_2-NR^X R^Y$ or $-NR^X-S(O)_2-R^Z$ when used terminally; or $-S(O)_2-NR^X-$ or $-NR^X-S(O)_2-$ when used internally, wherein R^X , R^Y , and R^Z are defined above.

[0113] As used herein a "sulfanyl" group refers to $-S-R^X$ when used terminally and $-S-$ when used internally, wherein R^X has been defined above. Examples of sulfanyls include aliphatic-S-, cycloaliphatic-S-, aryl-S-, or the like.

[0114] As used herein a "sulfinyl" group refers to $-S(O)-R^X$ when used terminally and $-S(O)-$ when used internally, wherein R^X has been defined above. Exemplary sulfinyl groups include aliphatic-S(O)-, aryl-S(O)-, (cycloaliphatic(aliphatic))-S(O)-, cycloalkyl-S(O)-, heterocycloaliphatic-S(O)-, heteroaryl-S(O)-, or the like.

[0115] As used herein, a "sulfonyl" group refers to $-S(O)_2-R^X$ when used terminally and $-S(O)_2-$ when used internally, wherein R^X has been defined above. Exemplary sulfonyl groups include aliphatic- $S(O)_2-$, aryl- $S(O)_2-$, (cycloaliphatic(aliphatic))- $S(O)_2-$, cycloaliphatic- $S(O)_2-$, heterocycloaliphatic- $S(O)_2-$, heteroaryl- $S(O)_2-$, (cycloaliphatic(amido(aliphatic)))- $S(O)_2-$ or the like.

[0116] As used herein, a "sulfoxy" group refers to $-O-S(O)-R^X$ or $-S(O)-O-R^X$, when used terminally and $-O-S(O)-$ or $-S(O)-O-$ when used internally, where R^X has been defined above.

[0117] As used herein, a "halogen" or "halo" group refers to fluorine, chlorine, bromine or iodine.

[0118] As used herein, an "alkoxycarbonyl", which is encompassed by the term carboxy, used alone or in connection with another group refers to a group such as alkyl-O-C(O)-.

[0119] As used herein, an "alkoxyalkyl" refers to an alkyl group such as alkyl-O-alkyl-, wherein alkyl has been defined above.

[0120] As used herein, a "carbonyl" refer to $-C(O)-$.

[0121] As used herein, an "oxo" refers to $=O$.

[0122] As used herein, the term "phospho" refers to phosphinates and phosphonates. Examples of phosphinates and phosphonates include $-P(O)(R^P)_2$, wherein R^P is aliphatic, alkoxy, aryloxy, heteroaryloxy, (cycloaliphatic)oxy, (heterocycloaliphatic)oxy aryl, heteroaryl, cycloaliphatic or amino.

[0123] As used herein, an "aminoalkyl" refers to the structure $(R^X)_2N$ -alkyl-.

[0124] As used herein, a "cyanoalkyl" refers to the structure (NC) -alkyl-.

[0125] As used herein, a "urea" group refers to the structure $-NR^X-CO-NR^YR^Z$ and a "thiourea" group refers to the structure $-NR^X-CS-NR^YR^Z$ when used terminally and $-NR^X-CO-NR^Y-$ or $-NR^X-CS-NR^Y-$ when used internally, wherein R^X , R^Y , and R^Z have been defined above.

[0126] As used herein, a "guanidine" group refers to the structure $-N=C(N(R^XR^Y))N(R^XR^Y)$ or $-NR^X-C(=NR^X)NR^XR^Y$ wherein R^X and R^Y have been defined above.

[0127] As used herein, the term "amidino" group refers to the structure $-C(=NR^X)N(R^XR^Y)$ wherein R^X and R^Y have been defined above.

[0128] In general, the term "vicinal" refers to the placement of substituents on a group that includes two or more carbon atoms, wherein the substituents are attached to adjacent carbon atoms.

[0129] In general, the term "geminal" refers to the placement of substituents on a group that includes two or more carbon atoms, wherein the substituents are attached to the same carbon atom.

[0130] The terms "terminally" and "internally" refer to the location of a group within a substituent. A group is terminal when the group is present at the end of the substituent not further bonded to the rest of the chemical structure. Carboxyalkyl, i.e., $R^XO(O)C$ -alkyl is an example of a carboxy group used terminally. A group is internal when the group is present in the middle of a substituent of the chemical structure. Alkylcarboxy (e.g., alkyl- $C(O)O$ - or alkyl- $OC(O)$ -) and alkylcarboxyaryl (e.g., alkyl- $C(O)O$ -aryl- or alkyl- $O(CO)$ -aryl-) are examples of carboxy groups used internally.

[0131] As used herein, an "aliphatic chain" refers to a branched or straight aliphatic group (e.g., alkyl groups, alkenyl groups, or alkynyl groups). A straight aliphatic chain has the structure $-[CH_2]_v-$, where v is 1-12. A branched aliphatic chain is a straight aliphatic chain that is substituted with one or more aliphatic groups. A branched aliphatic chain has the structure $-[CQQ]_v-$ where Q is independently a hydrogen or an aliphatic group; however, Q shall be an aliphatic group in at least one instance. The term aliphatic chain includes alkyl chains, alkenyl chains, and alkynyl chains, where alkyl, alkenyl, and alkynyl are defined above.

[0132] The phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted." As described herein, compounds of the invention can optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the invention. As described herein, the variables R_1 , R_2 , R'_2 , R_3 , and R_4 , and other variables contained in Formula I, described herein, encompass specific groups, such as alkyl and aryl. Unless otherwise noted, each of the specific groups for the variables R_1 , R_2 , R'_2 , R_3 , and R_4 , and other variables contained therein can be optionally substituted with one or more substituents described herein. Each substituent of a specific group is further optionally substituted with one to three of halo, cyano, oxo, alkoxy, hydroxy, amino, nitro, aryl, cycloaliphatic, heterocycloaliphatic, heteroaryl, haloalkyl, and alkyl. For instance, an alkyl group can be substituted with alkylsulfanyl and the alkylsulfanyl can be optionally substituted with one to three of halo, cyano, oxo, alkoxy, hydroxy, amino, nitro, aryl, haloalkyl, and alkyl. As an additional example, the cycloalkyl portion of a (cycloalkyl)carbonylamino can be optionally substituted with one to three of halo, cyano, alkoxy, hydroxy, nitro, haloalkyl, and alkyl.

When two alkoxy groups are bound to the same atom or adjacent atoms, the two alkoxy groups can form a ring together with the atom(s) to which they are bound.

[0133] In general, the term "substituted," whether preceded by the term "optionally" or not, refers to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. Specific substituents are described above in the definitions and below in the description of compounds and examples thereof. Unless otherwise indicated, an optionally substituted group can have a substituent at each substitutable position of the group, and when more than one position in any given structure can be substituted with more than one substituent selected from a specified group, the substituent can be either the same or different at every position. A ring substituent, such as a heterocycloalkyl, can be bound to another ring, such as a cycloalkyl, to form a spiro-bicyclic ring system, e.g., both rings share one common atom. As one of ordinary skill in the art will recognize, combinations of substituents envisioned by this invention are those combinations that result in the formation of stable or chemically feasible compounds.

[0134] The phrase "stable or chemically feasible," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and preferably their recovery, purification, and use for one or more of the purposes disclosed herein. In some embodiments, a stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

[0135] As used herein, an "effective amount" is defined as the amount required to confer a therapeutic effect on the treated patient, and is typically determined based on age, surface area, weight, and condition of the patient. The interrelationship of dosages for animals and humans (based on milligrams per meter squared of body surface) is described by Freireich et al., *Cancer Chemother. Rep.*, 50: 219 (1966). Body surface area may be approximately determined from height and weight of the patient. See, e.g., *Scientific Tables*, Geigy Pharmaceuticals, Ardsley, New York, 537 (1970). As used herein, "patient" refers to a mammal, including a human.

[0136] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention.

Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C - or ^{14}C - enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools or probes in biological assays, or as therapeutic agents.

[0137] As used herein, an "adrenergic agonist" refers to any compound having agonistic activity toward any adrenergic receptor (e.g., β_1 , β_2 , β_3). Note that the terms "beta-adrenergic" and " β -adrenergic" are used interchangeably. This usage also applies to sub-types of beta agonists, (e.g., 'beta-1-adrenergic agonist' is used interchangeable with ' β_1 -adrenergic agonist' and/or ' β_1 -adrenergic agonist').

[0138] As used herein, the term "delaying the onset" of a disease (e.g., PKD) refers to a delay of symptoms of a disease, wherein the delay caused by the administration of a therapeutic agent (e.g., compound, co-crystal, or pharmaceutical composition). The delay of symptoms need not last for the duration of the patient's life, although the delay may last for this duration.

[0139] As used herein, the term "co-crystal" refers to a substantially crystalline material having two or more distinct molecular components (e.g., a compound of formula I or a salt thereof and a phosphodiesterase inhibitor) within its crystal lattice.

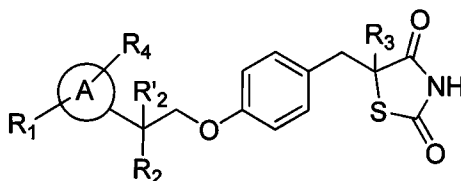
[0140] Chemical structures and nomenclature are derived from ChemDraw, version 11.0.1, Cambridge, MA.

[0141] II. PHARMACEUTICAL COMPOSITIONS

[0142] Thiazolidinedione compounds of the present invention are uniquely effective in treating or preventing PKD in a patient and possess a reduced interaction with $\text{PPAR}\gamma$. Accordingly, these compounds demonstrate reduced side effects related to $\text{PPAR}\gamma$ interaction than $\text{PPAR}\gamma$ activating compounds such as rosiglitazone.

[0143] A. Compounds of Formula I

[0144] The present invention provides pharmaceutical compositions and methods that are useful for treating or preventing PKD in a patient comprising a compound of Formula I:

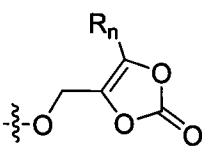


I

or a pharmaceutically acceptable salt thereof, wherein:

Each of R_1 and R_4 is independently selected from H, halo, aliphatic, and alkoxy, wherein the aliphatic or alkoxy is optionally substituted with 1-3 of halo;

R'_2 is H, and R_2 is H, halo, hydroxy, or optionally substituted aliphatic, -O-acyl, -O-aroyl, -O-heteroaroyl, -O(SO₂)NH₂, -O-CH(R_m)OC(O) R_n , -O-CH(R_m)OP(O)(OR_n)₂,

-O-P(O)(OR_n)₂, or , wherein each R_m is independently C₁₋₆ alkyl, each R_n is independently C₁₋₁₂ alkyl, C₃₋₈ cycloalkyl, or phenyl, each of which is optionally substituted; or R_2 and R'_2 together may form oxo;

R_3 is H or C₁₋₃ alkyl; and

Ring A is a phenyl, pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl, each of which is substituted with an R_1 group and an R_4 group.

[0145] In several embodiments, R_1 is H. In some embodiments, R_1 is halo (e.g., F, Cl, or Br). In some embodiments, R_1 is an aliphatic optionally substituted with 1-3 halo. For instance, R_1 is trifluoromethyl (-CF₃). In some embodiments, R_1 is alkoxy. For instance, R_1 is methoxy, ethoxy, propoxy, -O-isopropyl, butoxy, or -O-tertbutyl. In still other embodiments, R_1 is alkoxy substituted with 1-3 halo. For instance, R_1 is -OCHF₂ or -OCF₃. In each of the foregoing embodiments, R_1 can be attached to the ortho, meta, or para position of ring A, when ring A is phenyl. In certain embodiments, R_1 is substituted at the para or meta position of ring A, when ring A is phenyl.

[0146] In some embodiments, ring A is phenyl that is substituted with R_1 and R_4 groups at any chemically feasible position on ring A. For example, ring A is phenyl, and one of R_1 or R_4 is attached to the para or meta position of ring A. In some instances, ring A is phenyl, and one of R_1 or R_4 is attached to the meta position of ring A. In some examples, R_1 is attached to the para or meta position of ring A. For instance, R_1 is attached to the para or meta position of ring A, and R_1 is F or Cl. In other instances, R_1 is attached to the para or meta position of ring A, and R_1 is alkoxy. For example, R_1 is methoxy, ethoxy, propoxy, -O-isopropyl, butoxy, or -O-tertbutyl that is attached to the para or meta position of ring A. In some examples, ring A is phenyl, and R_1 is attached to the meta or ortho position of the

phenyl ring. For instance, ring A is phenyl, and R₁ is attached to the ortho position of the phenyl ring. In other instances, ring A is phenyl, and R₁ is methoxy, ethoxy, or -O-isopropyl, wherein any of these groups are attached to the ortho position of ring A. In other examples, R₁ is -CF₃, -OCH₃, -OCHF₂ or -OCF₃, wherein any of these groups are attached to the ortho position of ring A.

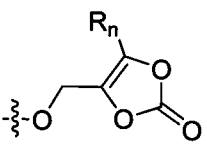
[0147] In some embodiments, ring A is pyridin-2-yl or pyridin-3-yl, either of which is substituted with R₁ and R₄ groups at any chemically feasible position on ring A. For example, ring A is pyridin-2-yl, and one of R₁ or R₄ is attached to the 5 position of the ring. In other examples, ring A is pyridin-3-yl, and one of R₁ or R₄ is attached to the 6 position of the ring. In some examples, ring A is pyridin-2-yl, and R₁ is attached to the 5 position of the ring. For instance, R₁ is alkyl or alkoxy, wherein either moiety is attached to the 5 position of ring A. In some instances, R₁ is methyl, ethyl, propyl, isopropyl, butyl, or tertbutyl, wherein any of these moieties is attached to the 5 position of ring A.

[0148] In several embodiments, R₄ is H. In some embodiments, R₄ is halo, such as F or Cl. In some embodiments, R₄ is an aliphatic optionally substituted with 1-3 halo. For instance, R₄ is trifluoromethyl. In some embodiments R₄ is alkoxy. For instance, R₄ is methoxy, ethoxy, or -O-isopropyl. In still other embodiments, R₄ is alkoxy substituted with 1-3 halo. For instance, R₄ is -OCHF₂ or -OCF₃. In each of the foregoing embodiments, R₄ can be substituted at the ortho, meta, or para position of ring A, when ring A is phenyl. In certain embodiments, R₄ is substituted at the para or meta position of ring A. In some embodiments, R₁ and R₄ are different substituents. In still other embodiments, R₁ and R₄ are the same substituent. In some embodiments when R₁ is aliphatic, R₄ is other than H.

[0149] In several embodiments, each of R₁ and R₄ is independently selected from H, halo, aliphatic, and alkoxy, wherein the aliphatic and alkoxy are optionally substituted with 1-3 of halo.

[0150] In several embodiments, each of R₁ and R₄ is independently selected from H, halo, aliphatic, and alkoxy, wherein the aliphatic and alkoxy are optionally substituted with 1-3 of halo.

[0151] In several embodiments, R₂ is halo, hydroxy, aliphatic, -O-acyl, -O-aroyl, -O-heteroaroyl, -O(SO₂)NH₂, -O-CH(R_m)OC(O)R_n, -O-CH(R_m)OP(O)(OR_n)₂,

-O-P(O)(OR_n)₂, or , wherein each R_m is C₁₋₆ alkyl, R_n is C₁₋₁₂ alkyl, C₃₋₈ cycloalkyl, or phenyl and each substituent R_m or R_n is optionally substituted.

[0152] In some embodiments, R₂ is H.

[0153] In some embodiments, R₂ is hydroxy.

[0154] In some embodiments, R₂ is an optionally substituted straight or branched C₁₋₆ alkyl, an optionally substituted straight or branched C₂₋₆ alkenyl, or an optionally substituted straight or branched C₂₋₆ alkynyl. In other embodiments, R₂ is a C₁₋₆ aliphatic optionally substituted with 1-2 hydroxy, carboxy or halo. In other embodiments, R₂ is a C₁₋₆ alkyl optionally substituted with hydroxy. In further embodiments, R₂ is a C₁₋₆ alkyl optionally substituted with -O-acyl, -O-aryl, -O-heteroaryl. In several other embodiments, R₂ is a methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl, or hexyl, each of which is optionally substituted with hydroxy. In several additional embodiments, R₂ is methyl or ethyl, each of which is substituted with hydroxy.

[0155] In certain embodiments, R₂ is -O-acyl, -O-aryl, or -O-heteroaryl.

[0156] In other embodiments, R₂ is -O-acetyl, -O-hexanoyl, -O-benzoyl, -O-pivaloyl, -O-imidazolyl, -O-succinoyl, -O-thiazoloyl or -O-pyridinoyl, each optionally substituted.

[0157] In some embodiments, R₂ is -O-C(O)-imidazol-1-yl.

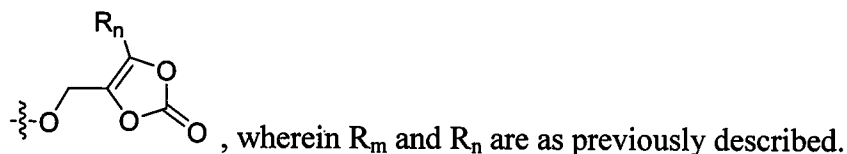
[0158] In certain embodiments, R₂ is -O-CH(R_m)-O-C(O)-R_n.

[0159] In some embodiments, R₂ is -O-CH(R_m)OP(O)(OR_n)₂.

[0160] In some embodiments, R₂ is -O-P(O)(OR_n)₂.

[0161] In other embodiments, R₂ is -O-S(O₂)NH₂.

[0162] In some further embodiments, R₂ is a 1,3-dioxolan-2-one of the Formula



[0163] In several embodiments, R'₂ is H.

[0164] In some embodiments, R₂ and R'₂ together form oxo.

[0165] In some embodiments, R'₂ is H and R₂ has an R configuration.

[0166] In some embodiments, R'₂ is H and R₂ has an S configuration.

[0167] In some embodiments, R'₂ is H and R₂ is racemic.

[0168] In further embodiments, ring A is phenyl or pyridinyl.

[0169] In some embodiments, ring A is pyridin-2-yl.

[0170] In some embodiments, ring A is pyridin-3-yl.

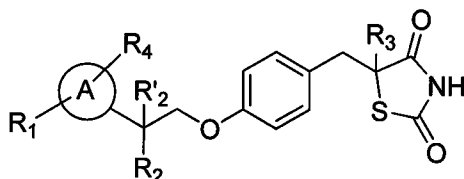
[0171] In some embodiments, ring A is pyridin-4-yl.

[0172] In other embodiments, R₃ is H or optionally substituted C₁₋₃ alkyl.

[0173] In some embodiments, R₃ is H.

[0174] In some embodiments, R_3 is CH_3 .

[0175] Some compositions of the present invention comprise a compound of Formula II:



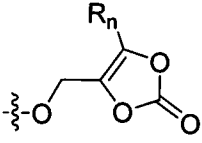
II

or a pharmaceutically acceptable salt thereof, wherein:

Each of R_1 and R_4 is independently selected from H, halo, aliphatic, and alkoxy, wherein the aliphatic or alkoxy is optionally substituted with 1-3 of halo;

R'_2 is H;

R_2 is H, halo, hydroxy, or optionally substituted aliphatic, -O-acyl, -O-aryl, -O-heteroaryl, -O(SO₂)NH₂, -O-CH(R_m)OC(O) R_n , -O-CH(R_m)OP(O)(OR_n)₂,

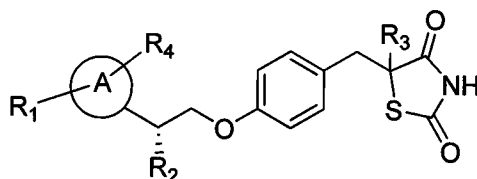
-O-P(O)(OR_n)₂, or , wherein each R_m is independently an optionally substituted C₁₋₆ alkyl, each R_n is independently C₁₋₁₂ alkyl, C₃₋₈ cycloalkyl, or phenyl, each of which is optionally substituted, or

R_2 and R'_2 together form oxo;

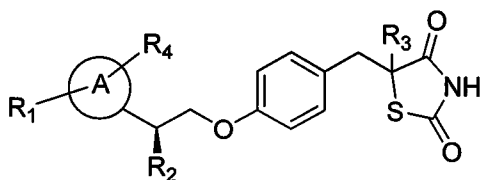
R_3 is H; and

Ring A is a phenyl, pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl, each of which is substituted with an R_1 group and an R_4 group.

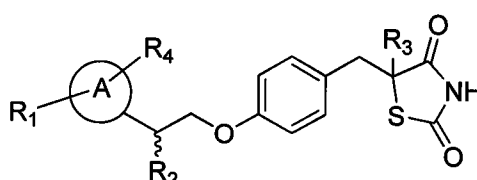
[0176] In some compositions, the compound of Formula I is a compound of Formula IIA, IIB, or IIC:



IIA



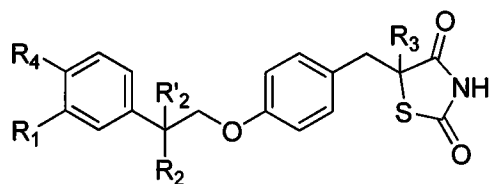
IIB



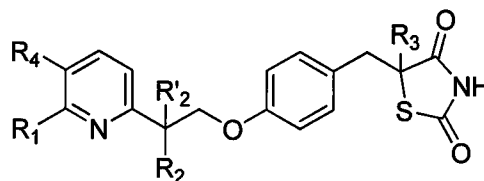
IIC

or a pharmaceutically acceptable salt thereof, wherein R'_2 is H, and R_1 , R_3 , R_4 and ring A are defined above in Formula I.

[0177] In some methods and compositions, the compound of Formula I is a compound of Formula IIIA or IIIB:



IIIA



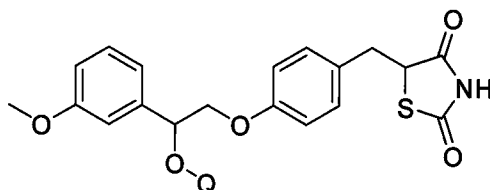
IIIB

or a pharmaceutically acceptable salt thereof, wherein each of R_1 , R_2 , R'_2 , R_3 , and R_4 are defined above in Formula I. In some embodiments, R_2 and R'_2 together form oxo; and R_3 is hydrogen.

[0178] In some instances, in the compound of Formula IIIA, one of R_1 and R_4 is an alkyl or alkoxy and the other is hydrogen. For instance, one of R_1 and R_4 is methyl, ethyl, or propyl, and the other is hydrogen. In other instances, one of R_1 and R_4 is methoxy or ethoxy.

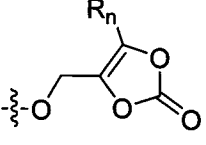
[0179] In some instances, in the compound of Formula IIIB, one of R_1 and R_4 is an alkyl or alkoxy and the other is hydrogen. For instance, one of R_1 and R_4 is methyl, ethyl, or propyl, and the other is hydrogen. In other instances, one of R_1 and R_4 is methoxy or ethoxy.

[0180] Some methods and compositions comprise a compound of Formula IV:



IV

wherein Q is acyl, aroyl, heteroaroyl, $-\text{SO}_2\text{NH}_2$, $-\text{CH}(\text{R}_m)\text{OC}(\text{O})\text{R}_n$, $-\text{CH}(\text{R}_m)\text{OP}(\text{O})(\text{OR}_n)_2$,

$-\text{P}(\text{O})(\text{OR}_n)_2$, or , wherein each R_m is C_{1-6} alkyl, R_n is C_{1-12} alkyl, C_{3-8} cycloalkyl, or phenyl, wherein each substituent is optionally substituted.

[0181] In some embodiments, Q in Formula IV is acyl.

[0182] In some embodiments, Q in Formula IV is -acetyl, -hexanoyl, -benzoyl, -pivaloyl, -succinoyl, each optionally substituted.

[0183] In certain embodiments, Q in Formula IV is acetyl.

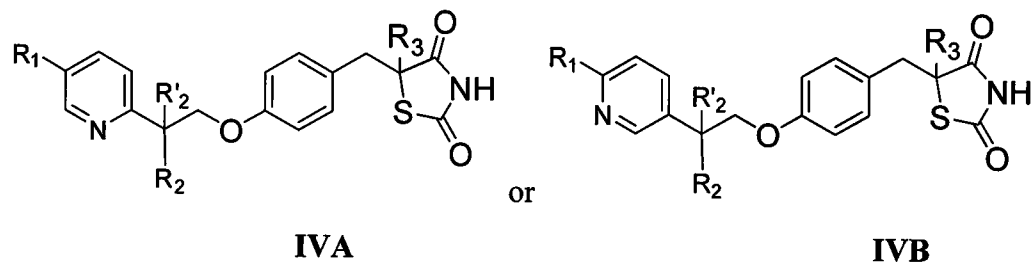
[0184] In certain embodiments, Q in Formula IV is hexanoyl.

[0185] In certain embodiments, Q in Formula IV is benzoyl.

[0186] In certain embodiments, Q in Formula IV is pivaloyl.

[0187] In certain embodiments, Q in Formula IV is succinoyl.

[0188] Some compositions comprise a compound of Formula IVA or IVB:



wherein R₂' is H; R₂ is H, -OH, -O-acyl, -O-aroyl or -O-heteroaryoyl; or R₂ and R₂' together form oxo; R₃ is H; and R₁ is as defined above in Formula I.

[0189] In further embodiments, Q in Formula IVA or IVB is H, -O-acetyl, -O-hexanoyl, -O-benzoyl, -O-pivaloyl, -O-succinoyl, each optionally substituted.

[0190] In some embodiments, Q in Formula IVA or IVB is H.

[0191] In certain embodiments, Q in Formula IVA or IVB is -O-acetyl.

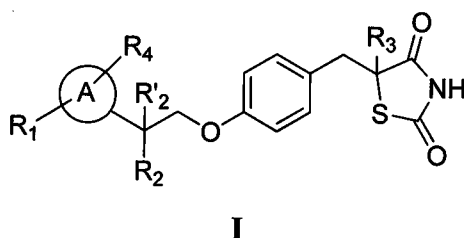
[0192] In certain embodiments, Q in Formula IVA or IVB is -O-hexanoyl.

[0193] In certain embodiments, Q in Formula IVA or IVB is -O-benzoyl.

[0194] In certain embodiments, Q in Formula IVA or IVB is -O-pivaloyl.

[0195] In certain embodiments, Q in Formula IVA or IVB is -O-succinoyl.

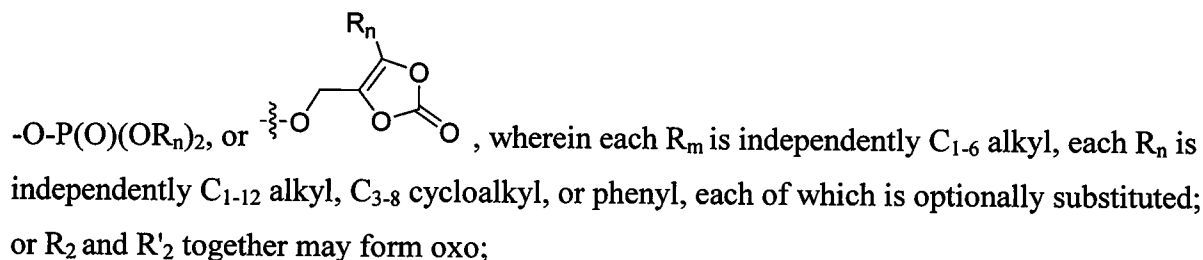
[0196] Some compositions comprise an alkali earth metal salt of a compound of Formula I:



wherein:

Each of R₁ and R₄ is independently selected from H, halo, aliphatic, and alkoxy, wherein the aliphatic or alkoxy is optionally substituted with 1-3 of halo:

R'₂ is H, and R₂ is H, halo, hydroxy, or optionally substituted aliphatic, -O-acyl, -O-aroyl, -O-heteroaroyl, -O(SO₂)NH₂, -O-CH(R_m)OC(O)R_n, -O-CH(R_m)OP(O)(OR_n)₂,



R₃ is H or C₁₋₃ alkyl; and

Ring A is a phenyl, pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl, each of which is substituted with an R₁ group and an R₄ group.

[0197] In some salts, the alkali earth metal is sodium. In other salts, the alkali earth metal is potassium.

[0198] In several salts, R₁ is H. In some embodiments, R₁ is halo (e.g., F, Cl, or Br). In some embodiments, R₁ is an aliphatic optionally substituted with 1-3 halo. For instance, R₁ is trifluoromethyl (-CF₃). In some embodiments, R₁ is alkoxy. For instance, R₁ is methoxy, ethoxy, propoxy, -O-isopropyl, butoxy, or -O-tertbutyl. In still other embodiments, R₁ is alkoxy substituted with 1-3 halo. For instance, R₁ is -OCHF₂ or -OCF₃. In each of the foregoing embodiments, R₁ can be attached to the ortho, meta, or para position of ring A, when ring A is phenyl. In certain embodiments, R₁ is substituted at the para or meta position of ring A, when ring A is phenyl.

[0199] In several salts, ring A is phenyl that is substituted with R₁ and R₄ groups at any chemically feasible position on ring A. For example, ring A is phenyl, and one of R₁ or R₄ is attached to the para or meta position of ring A. In some instances, ring A is phenyl, and one of R₁ or R₄ is attached to the meta position of ring A. In some examples, R₁ is attached to the para or meta position of ring A. For instance, R₁ is attached to the para or meta position of ring A, and R₁ is F or Cl. In other instances, R₁ is attached to the para or meta position of ring A, and R₁ is alkoxy. For example, R₁ is methoxy, ethoxy, propoxy, -O-isopropyl, butoxy, or -O-tertbutyl that is attached to the para or meta position of ring A. In some examples, ring A is phenyl, and R₁ is attached to the meta or ortho position of the phenyl ring. For instance, ring A is phenyl, and R₁ is attached to the ortho position of the phenyl ring. In other instances, ring A is phenyl, and R₁ is methoxy, ethoxy, or -O-isopropyl, wherein any of these groups are attached to the ortho position of ring A. In other examples, R₁ is -CF₃, -OCH₃, -OCHF₂ or -OCF₃, wherein any of these groups are attached to the ortho position of ring A.

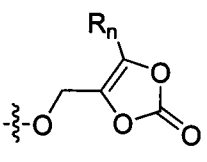
[0200] In several salts, ring A is pyridin-2-yl or pyridin-3-yl, either of which is substituted with R₁ and R₄ groups at any chemically feasible position on ring A. For example, ring A is pyridin-2-yl, and one of R₁ or R₄ is attached to the 5 position of the ring. In other examples, ring A is pyridin-3-yl, and one of R₁ or R₄ is attached to the 6 position of the ring. In some examples, ring A is pyridin-2-yl, and R₁ is attached to the 5 position of the ring. For instance, R₁ is alkyl or alkoxy, wherein either moiety is attached to the 5 position of ring A. In some instances, R₁ is methyl, ethyl, propyl, isopropyl, butyl, or tertbutyl, wherein any of these moieties is attached to the 5 position of ring A.

[0201] In several salts, R_4 is H. In some embodiments, R_4 is halo, such as F or Cl. In several salts, R_4 is an aliphatic optionally substituted with 1-3 halo. For instance, R_4 is trifluoromethyl. In several salts R_4 is alkoxy. For instance, R_4 is methoxy, ethoxy, or -O-isopropyl. In several salts, R_4 is alkoxy substituted with 1-3 halo. For instance, R_4 is -OCHF₂ or -OCF₃. In each of the foregoing salts, R_4 can be substituted at the ortho, meta, or para position of ring A, when ring A is phenyl. In several salts, R_4 is substituted at the para or meta position of ring A. In several salts, R_1 and R_4 are different substituents. In several salts, R_1 and R_4 are the same substituent. In several salts, when R_1 is aliphatic, R_4 is other than H.

[0202] In several salts, each of R_1 and R_4 is independently selected from H, halo, aliphatic, and alkoxy, wherein the aliphatic and alkoxy are optionally substituted with 1-3 of halo.

[0203] In several salts, each of R_1 and R_4 is independently selected from H, halo, aliphatic, and alkoxy, wherein the aliphatic and alkoxy are optionally substituted with 1-3 of halo.

[0204] In several salts, R_2 is halo, hydroxy, aliphatic, -O-acyl, -O-aryl, -O-heteroaryl, -O(SO₂)NH₂, -O-CH(R_m)OC(O) R_n , -O-CH(R_m)OP(O)(OR_n)₂, -O-P(O)(OR_n)₂,

or , wherein each R_m is C₁₋₆ alkyl, R_n is C₁₋₁₂ alkyl, C₃₋₈ cycloalkyl, or phenyl and each substituent R_m or R_n is optionally substituted.

[0205] In several salts, R_2 is H.

[0206] In several salts, R_2 is hydroxy.

[0207] In several salts, R_2 is an optionally substituted straight or branched C₁₋₆ alkyl, an optionally substituted straight or branched C₂₋₆ alkenyl, or an optionally substituted straight or branched C₂₋₆ alkynyl. In several salts, R_2 is a C₁₋₆ aliphatic optionally substituted with 1-2 hydroxy, carboxy or halo. In several salts, R_2 is a C₁₋₆ alkyl optionally substituted with hydroxy. In several salts, R_2 is a C₁₋₆ alkyl optionally substituted with -O-acyl, -O-aryl, -O-heteroaryl. In several salts, R_2 is a methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl, or hexyl, each of which is optionally substituted with hydroxy. In several salts, R_2 is methyl or ethyl, each of which is substituted with hydroxy.

[0208] In several salts, R_2 is -O-acyl, -O-aryl, or -O-heteroaryl.

[0209] In several salts, R_2 is -O-acetyl, -O-hexanoyl, -O-benzoyl, -O-pivaloyl, -O-imidazolyl, -O-succinoyl, -O-thiazoloyl or -O-pyridinoyl, each optionally substituted.

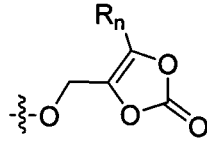
[0210] In several salts, R_2 is -O-C(O)-imidazol-1-yl.

[0211] In several salts, R_2 is -O-CH(R_m)-O-C(O)- R_n .

[0212] In several salts, R_2 is $-O-CH(R_m)OP(O)(OR_n)_2$.

[0213] In several salts, R_2 is $-O-P(O)(OR_n)_2$.

[0214] In several salts, R_2 is $-O-S(O_2)NH_2$.

[0215] In several salts, R_2 is a 1,3-dioxolan-2-one of the Formula , wherein R_m and R_n are as previously described.

[0216] In several salts, R'_2 is H.

[0217] In several salts, R_2 and R'_2 together form oxo.

[0218] In several salts, R'_2 is H and R_2 has an R configuration.

[0219] In several salts, R'_2 is H and R_2 has an S configuration.

[0220] In several salts, R'_2 is H and R_2 is racemic.

[0221] In several salts, ring A is phenyl or pyridinyl.

[0222] In several salts, ring A is pyridin-2-yl.

[0223] In several salts, ring A is pyridin-3-yl.

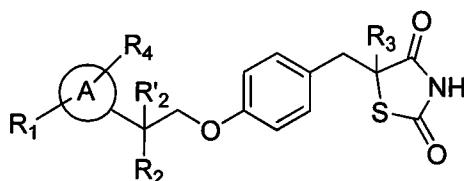
[0224] In several salts, ring A is pyridin-4-yl.

[0225] In several salts, R_3 is H or optionally substituted C_{1-3} alkyl.

[0226] In several salts, R_3 is H.

[0227] In several salts, R_3 is CH_3 .

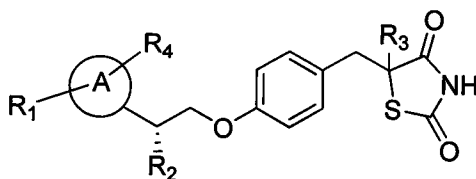
[0228] Some methods and compositions of the present invention comprise an alkali earth metal salt of a compound of Formula II:



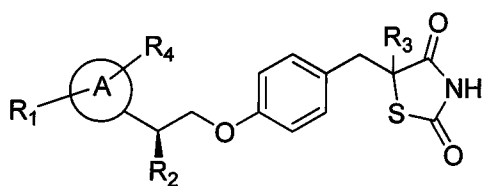
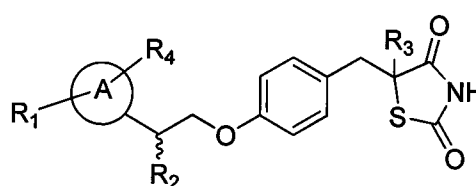
II

[0229] Some alkali earth metal salts of this compound comprise sodium or potassium salts of the compound of Formula II.

[0230] Other alkali earth metal salts useful in methods and compositions of the present invention include sodium or potassium salts of the compound of Formula II, IIA, or IIB:

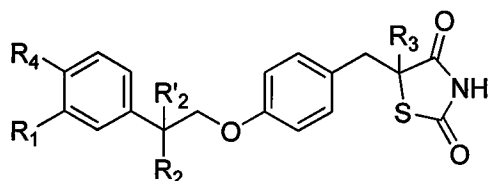
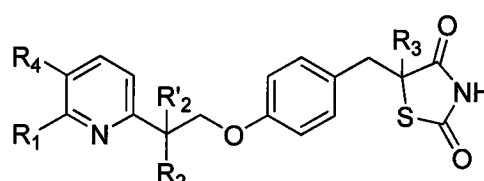


IIA

**IIB****IIC**

wherein R'_2 is H, and R_1 , R_3 , R_4 and ring A are defined above in Formula I.

[0231] In some alkali earth metal salts, the compound of Formula I is a compound of Formula IIIA or IIIB:

**IIIA****IIIB**

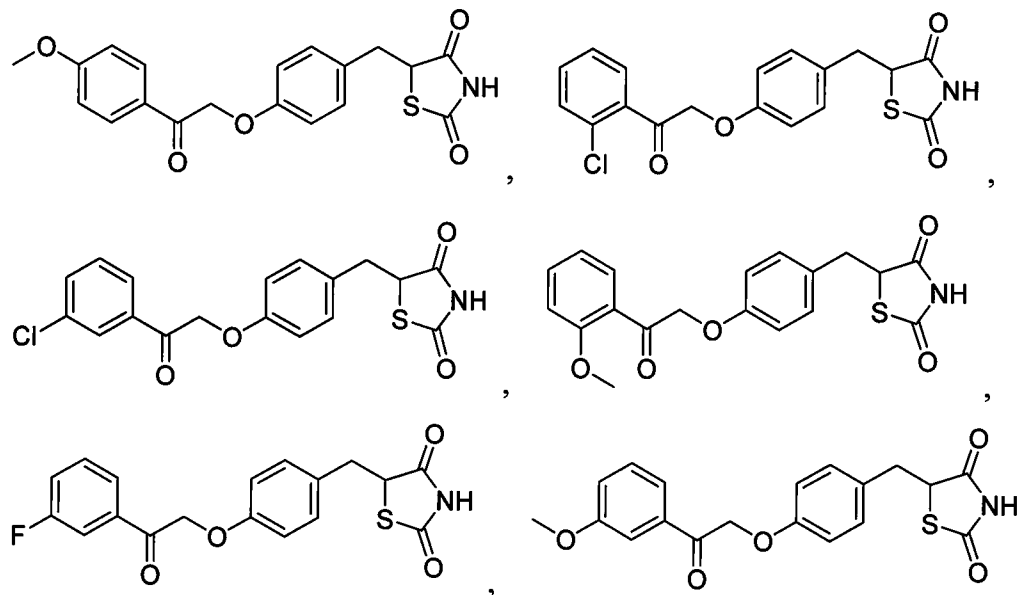
wherein each of R_1 , R_2 , R'_2 , R_3 , and R_4 are defined above in Formula I. In some embodiments, R_2 and R'_2 together form oxo; and R_3 is hydrogen.

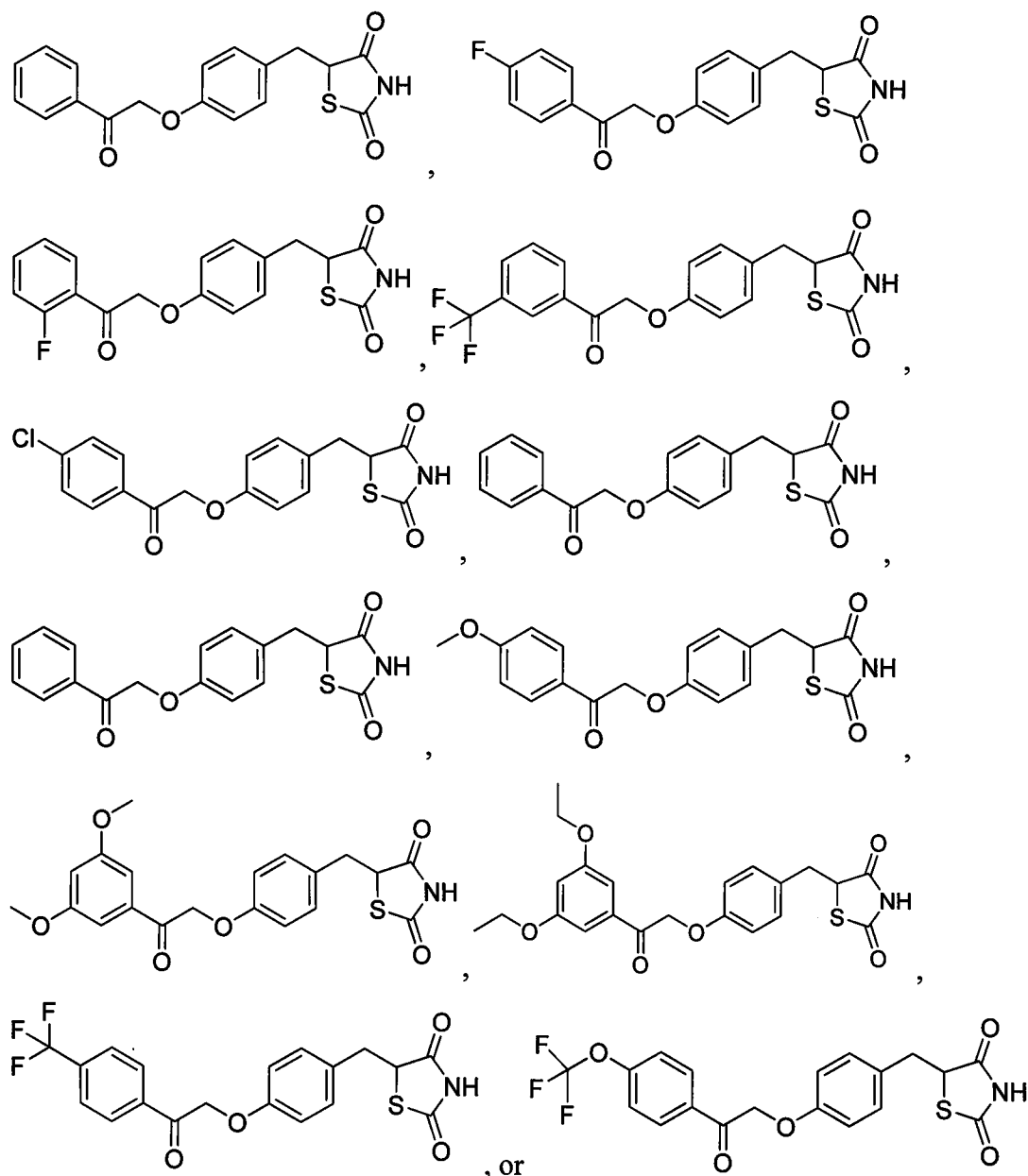
[0232] In some instances, in the compound of Formula IIIA, one of R_1 and R_4 is an alkyl or alkoxy and the other is hydrogen. For instance, one of R_1 and R_4 is methyl, ethyl, or propyl, and the other is hydrogen. In other instances, one of R_1 and R_4 is methoxy or ethoxy.

[0233] In some instances, in the compound of Formula IIIB, one of R_1 and R_4 is an alkyl or alkoxy and the other is hydrogen. For instance, one of R_1 and R_4 is methyl, ethyl, or propyl, and the other is hydrogen. In other instances, one of R_1 and R_4 is methoxy or ethoxy.

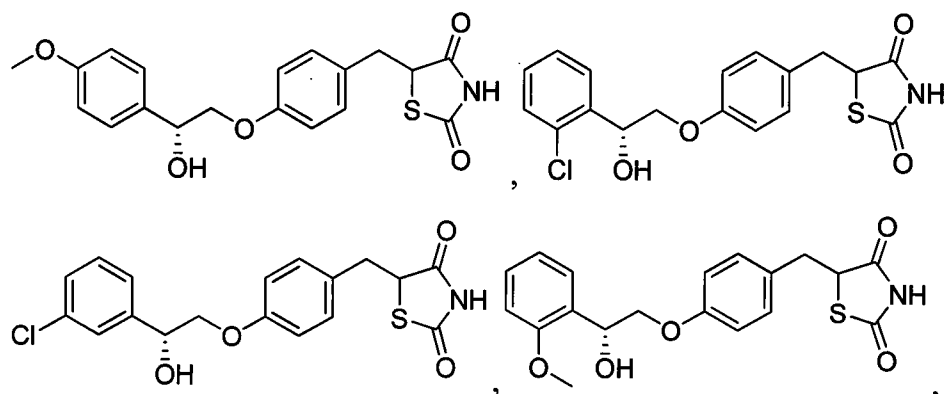
[0234] Several exemplary compounds of Formula I are provided below in Tables A-L, below.

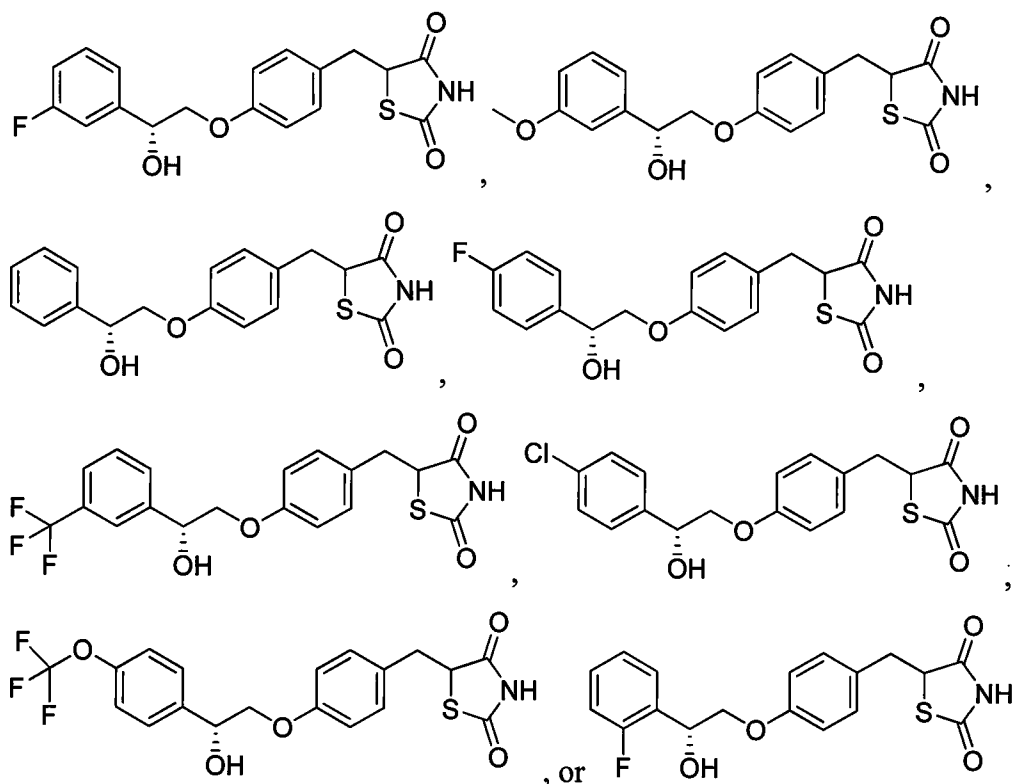
[0235] Table A: Exemplary compounds wherein R_2 and R'_2 form oxo.



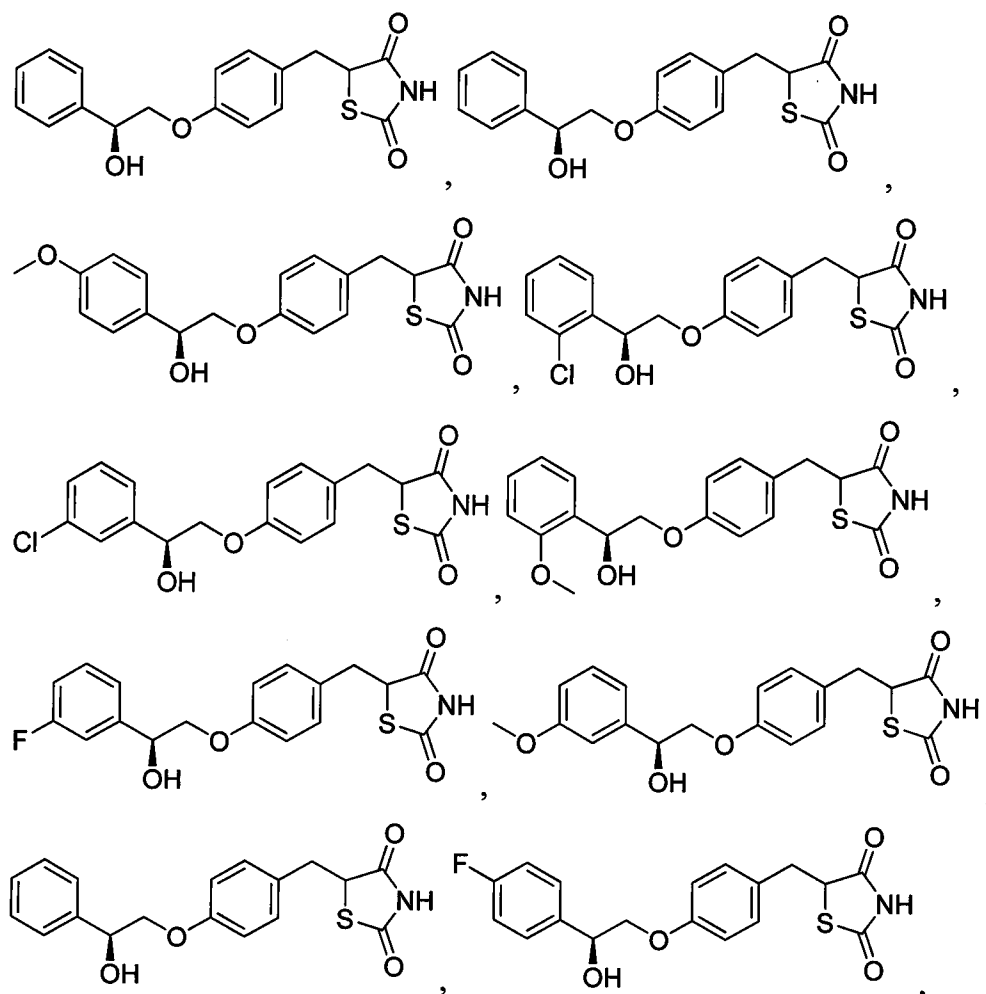


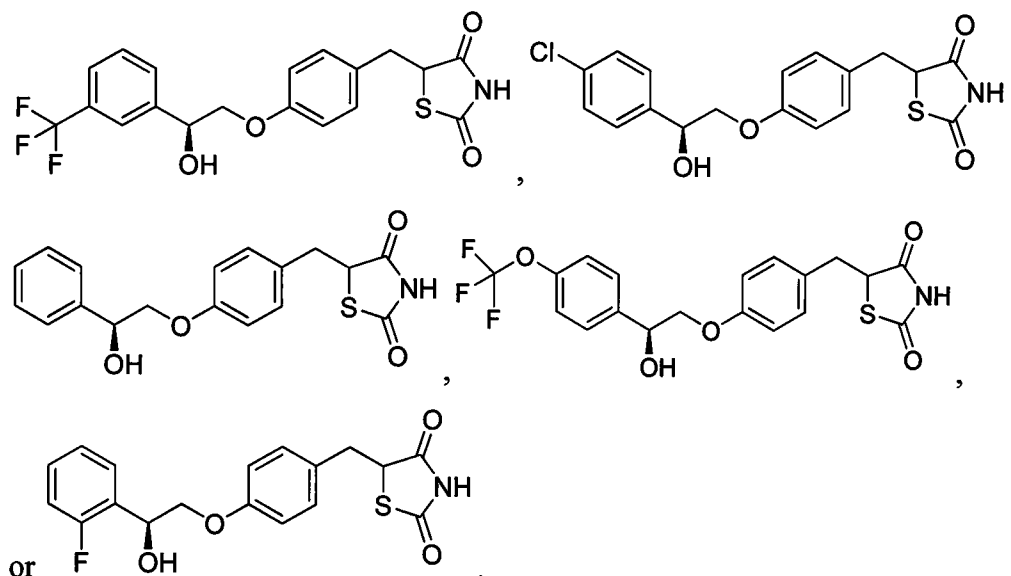
[0236] Table B: Exemplary compounds wherein and ring A is phenyl, R_2 is -OH having an (R) configuration and R'_2 is H.



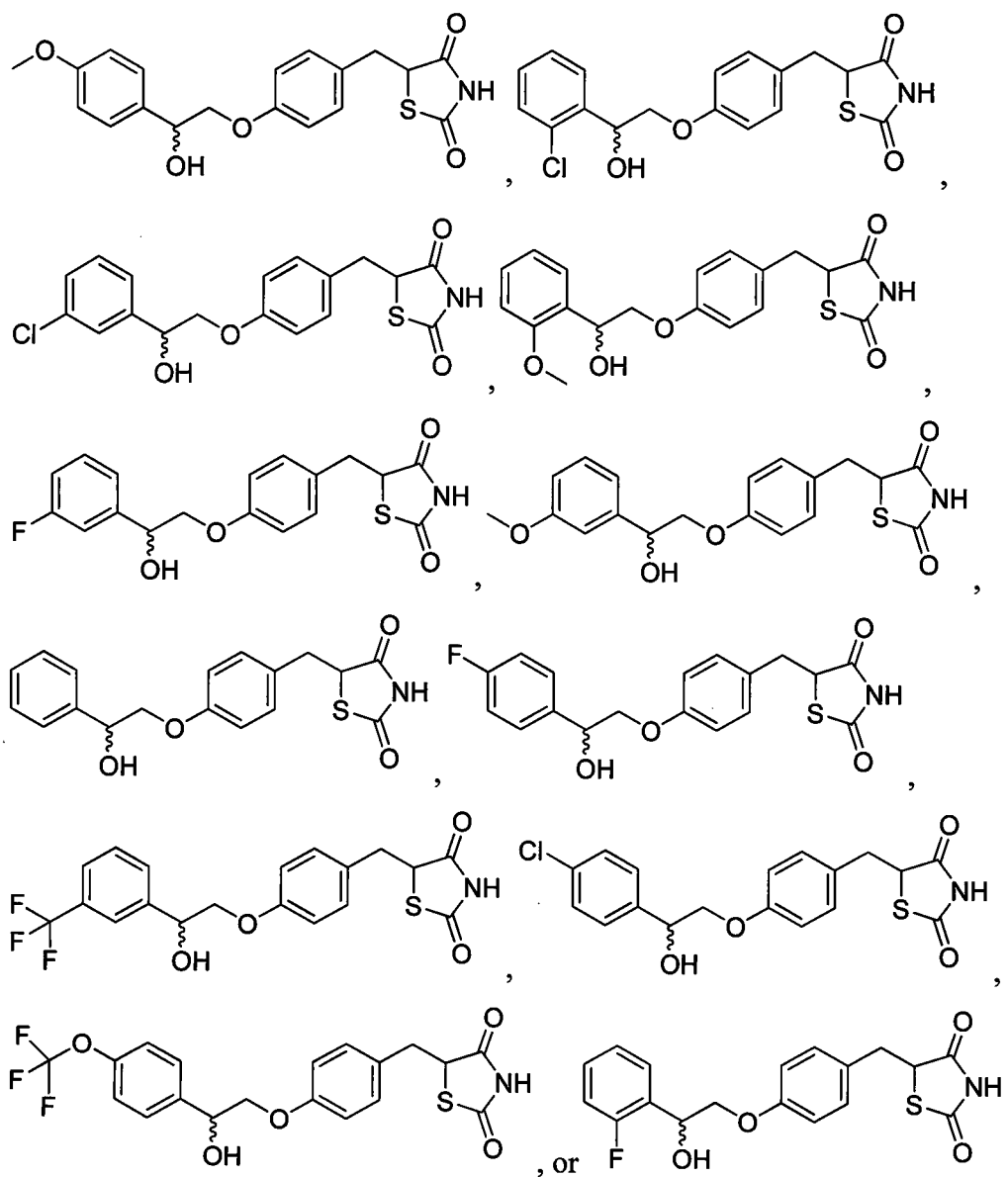


[0237] Table C: Exemplary compounds wherein R₂ is OH having an (S) configuration and R'₂ is H.

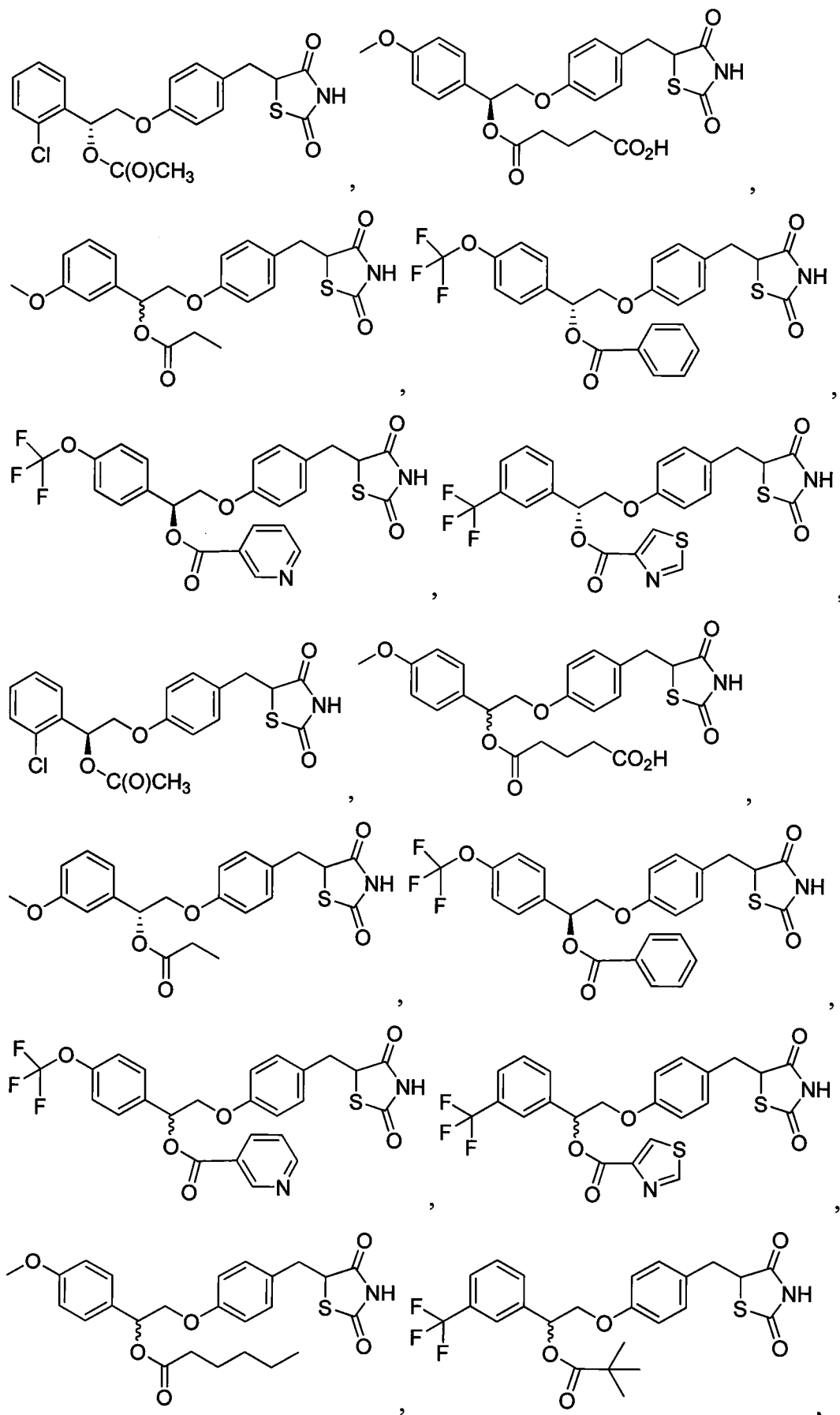


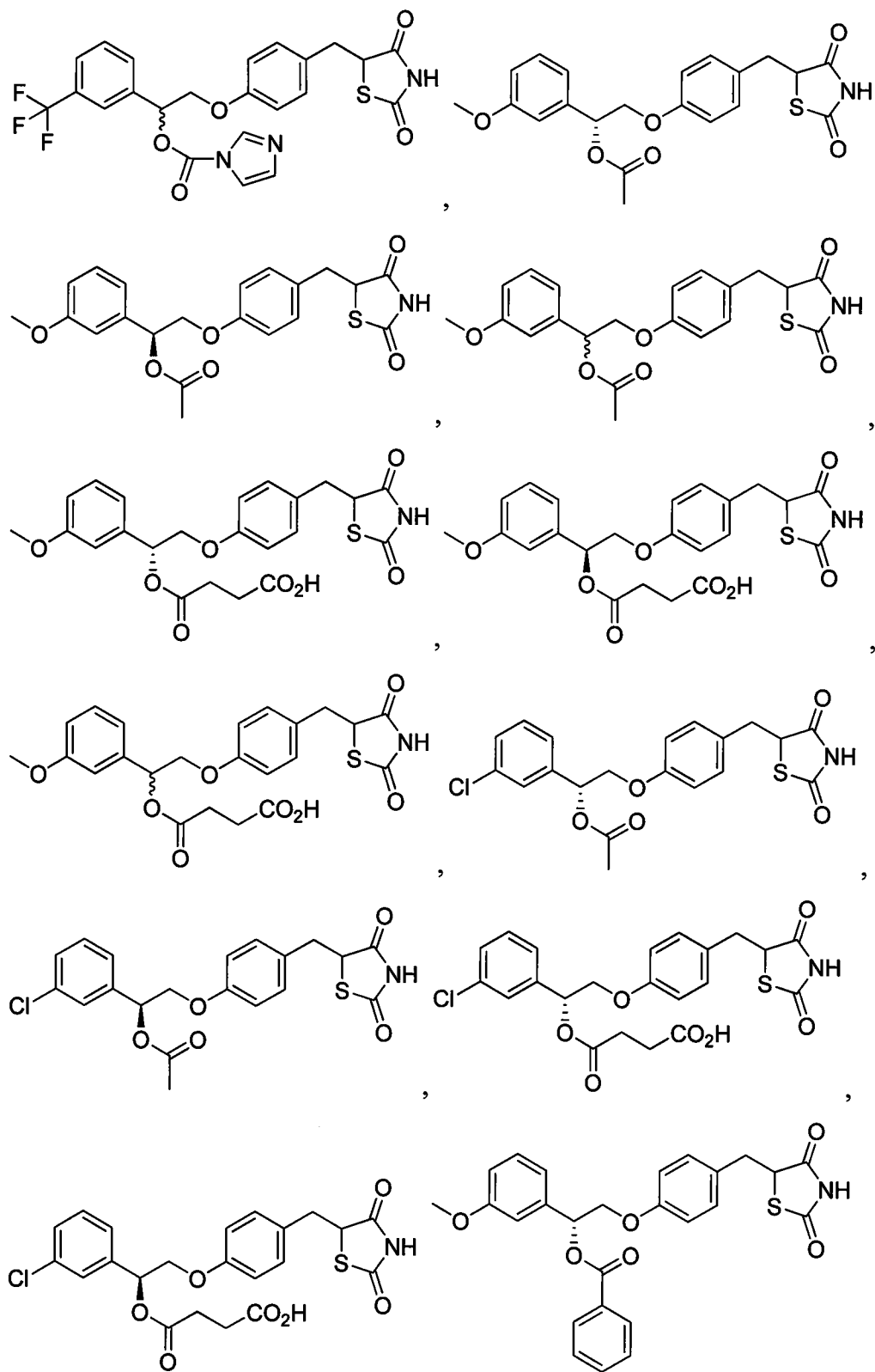


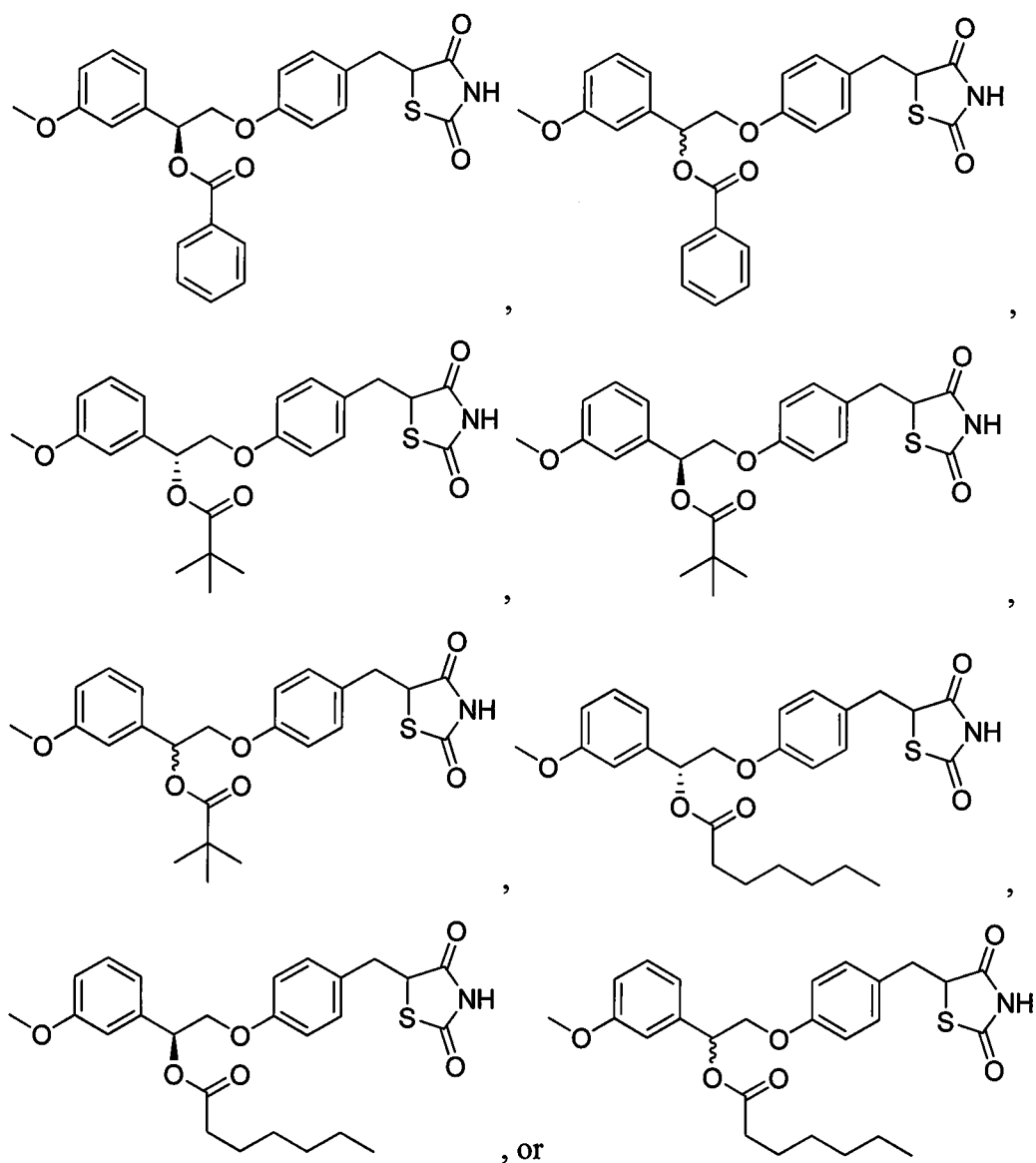
[0238] Table D: Exemplary compounds wherein R_2 is racemic -OH and R'_2 is H.



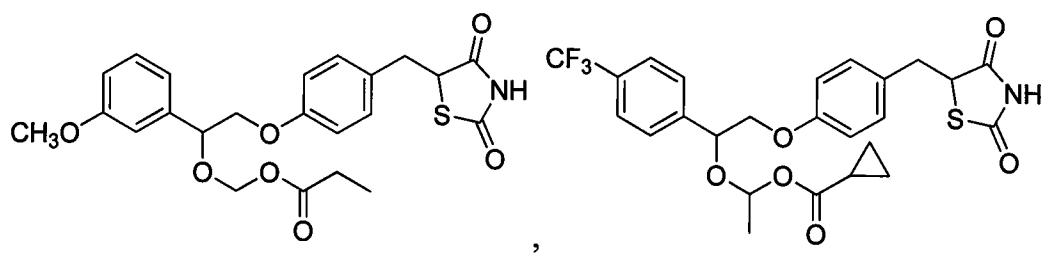
[0239] Table E: Exemplary compounds wherein R₂ is -O-Acyl, -O-Aroyl, or -O-heteroyl, and R'₂ is H.

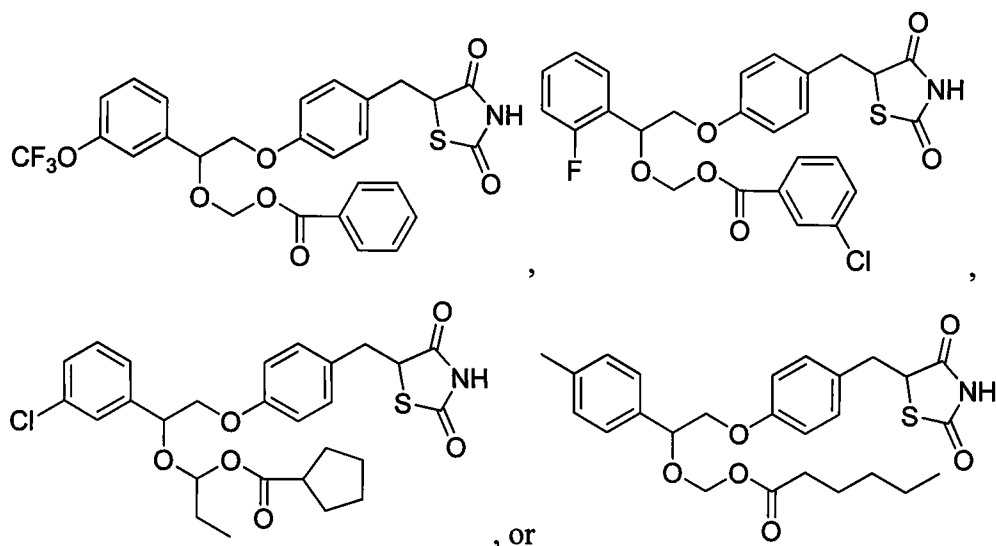




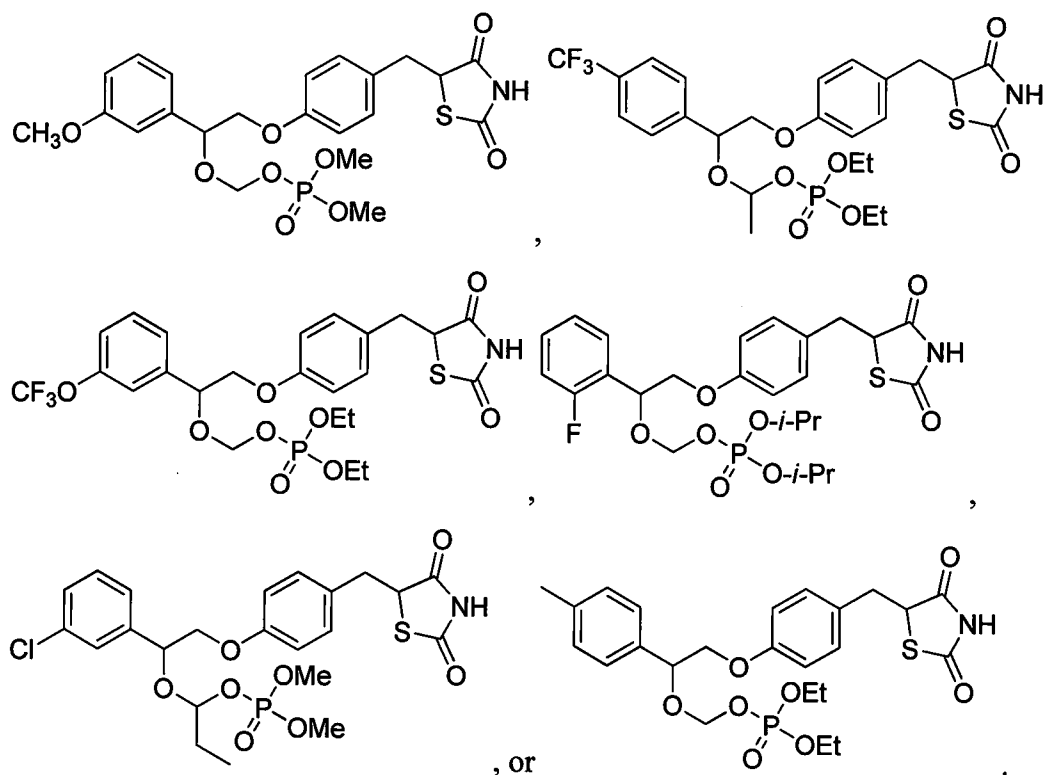


[0240] Table F: Exemplary compounds wherein R_2 is $-O-CH(R_m)-O-C(O)R_n$ and R'_2 is H.

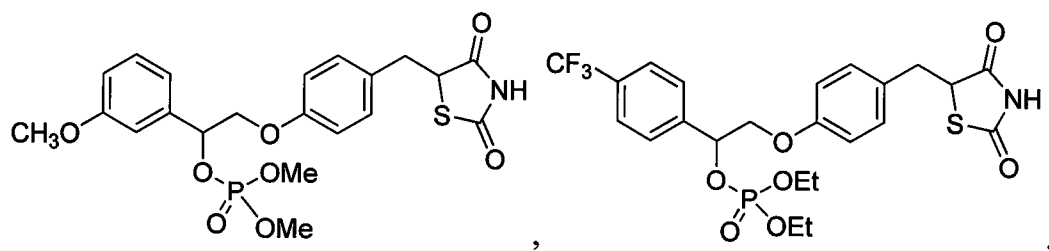


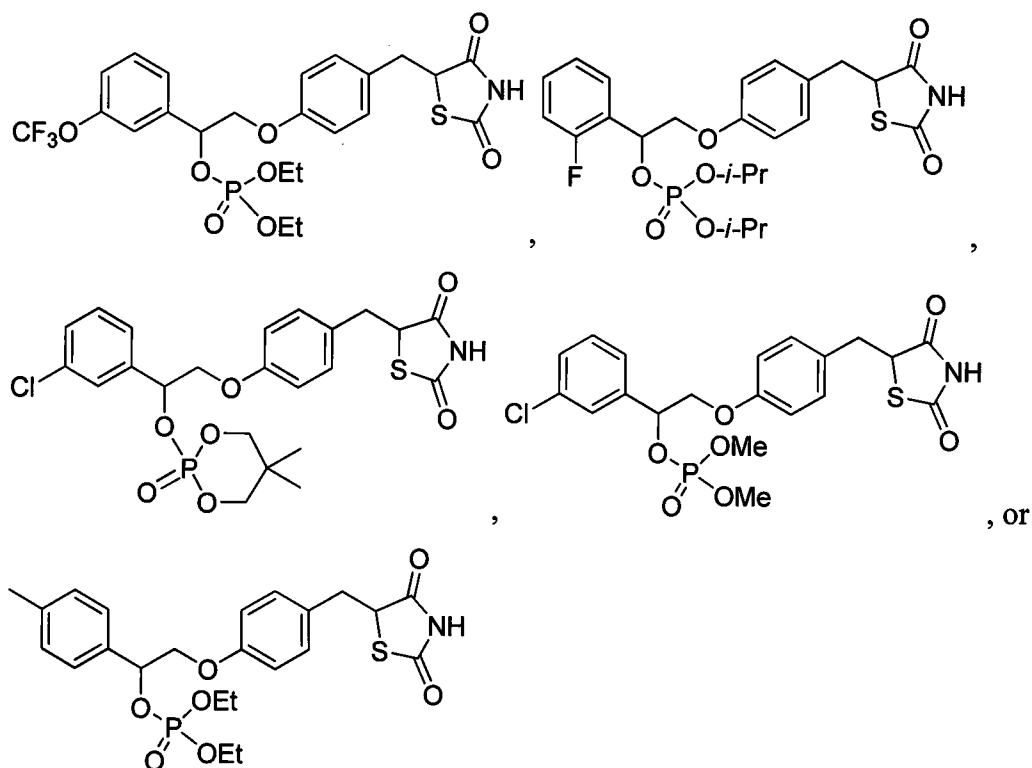


[0241] Table G: Exemplary compounds wherein R₂ is -O-CH(R_m)OP(O)(OR_n)₂ and R'₂ is H.

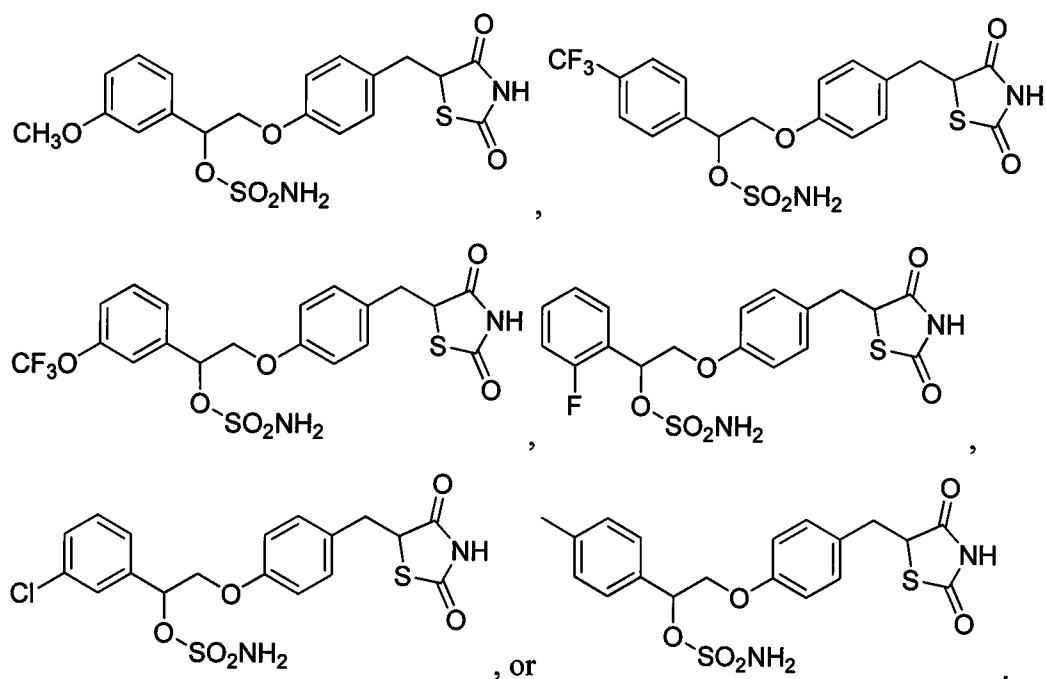


[0242] Table H: Exemplary compounds wherein R₂ is -O-P(O)(OR_n)₂ and R'₂ is H.

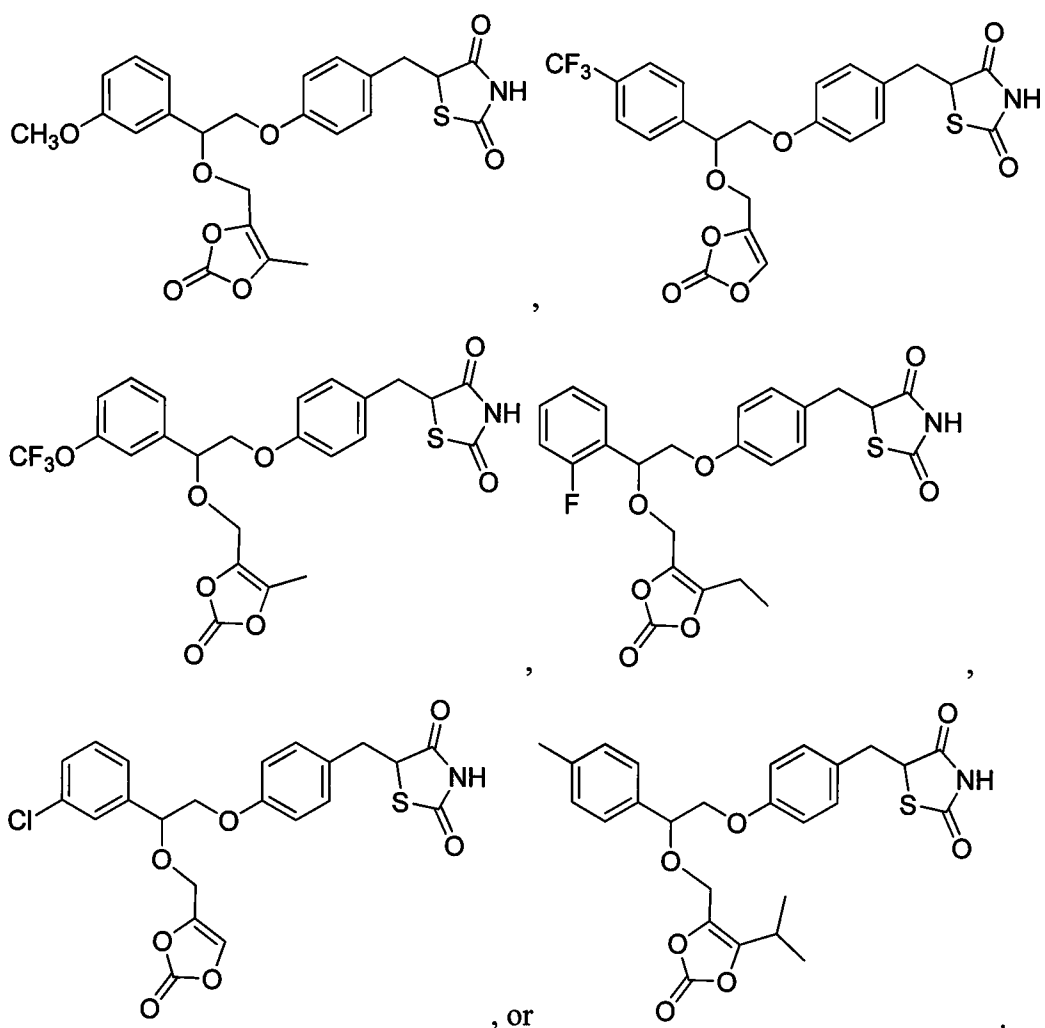




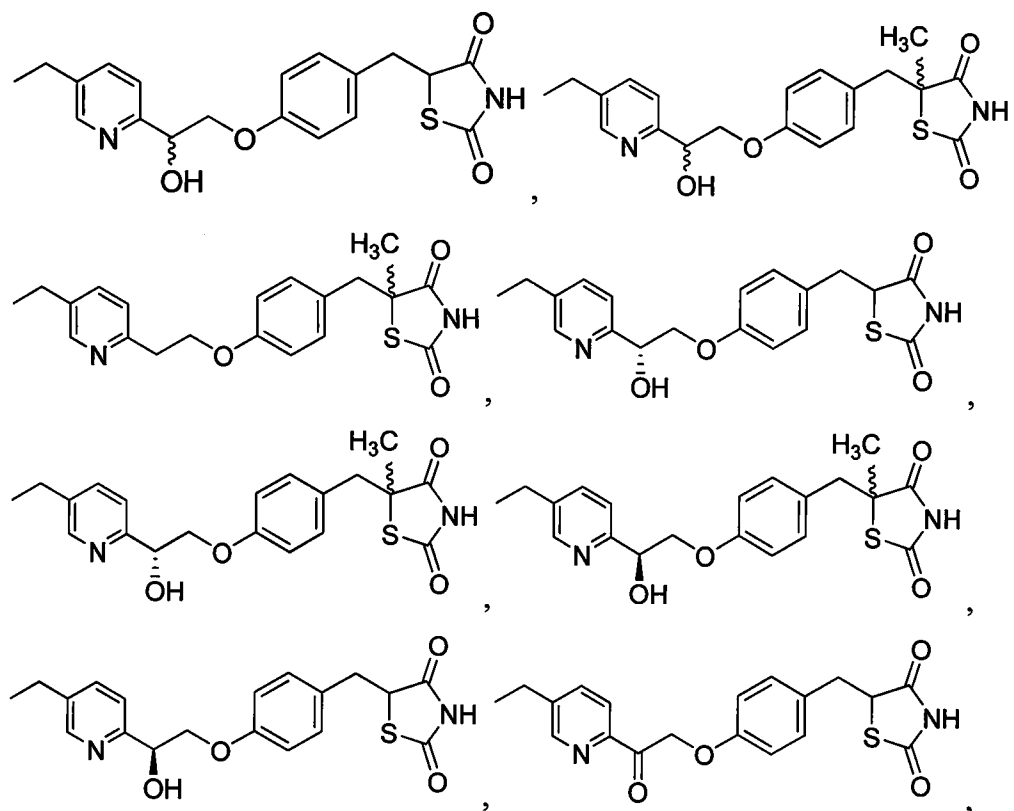
[0243] Table I: Exemplary compounds wherein R_2 is $-O-SO_2NH_2$ and R'_2 is H.

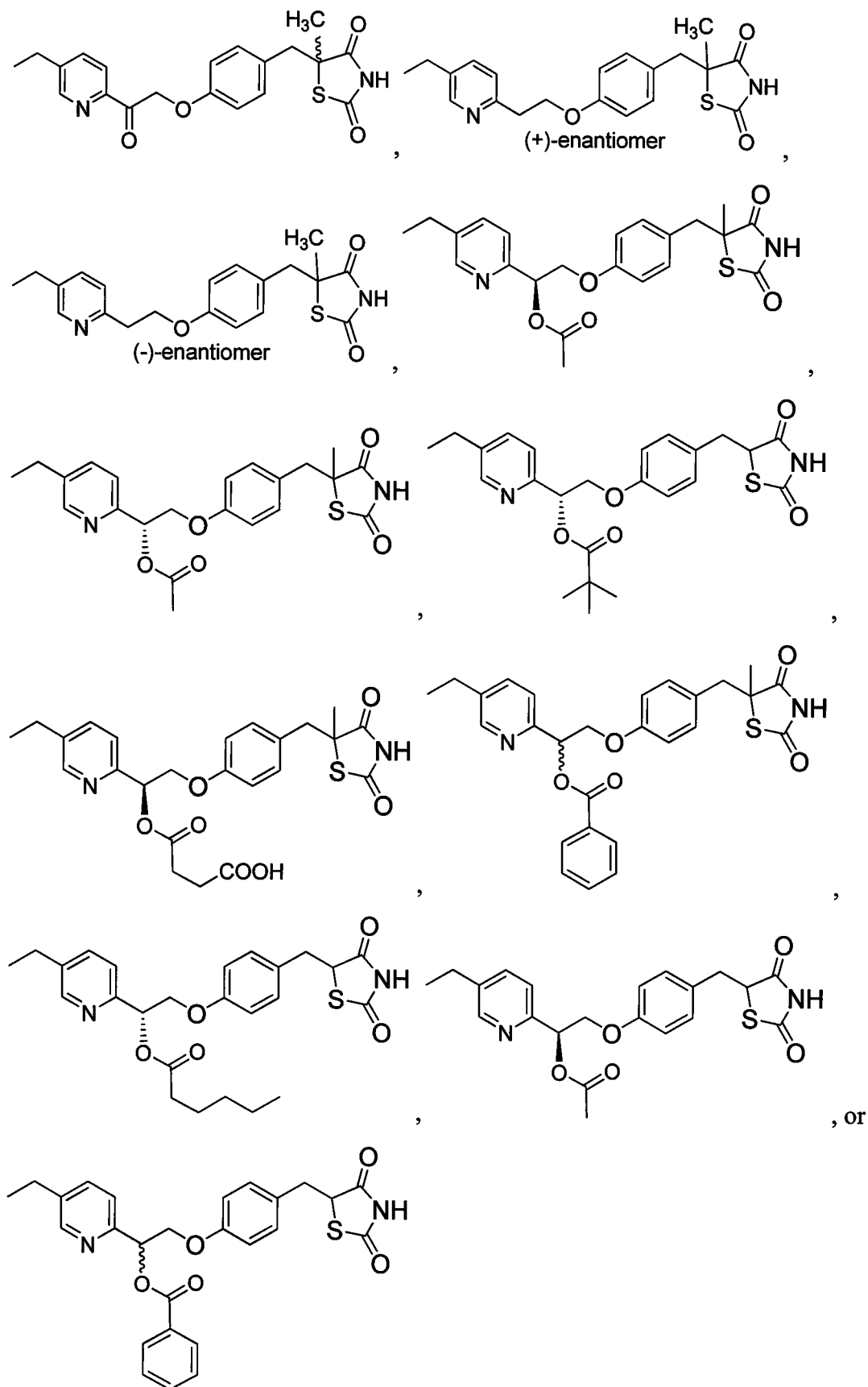


[0244] Table J: Exemplary compounds wherein R_2 is $\begin{matrix} R_n \\ \diagup \quad \diagdown \\ O \quad O \\ \diagdown \quad \diagup \\ O \end{matrix}$ and R'_2 is H.

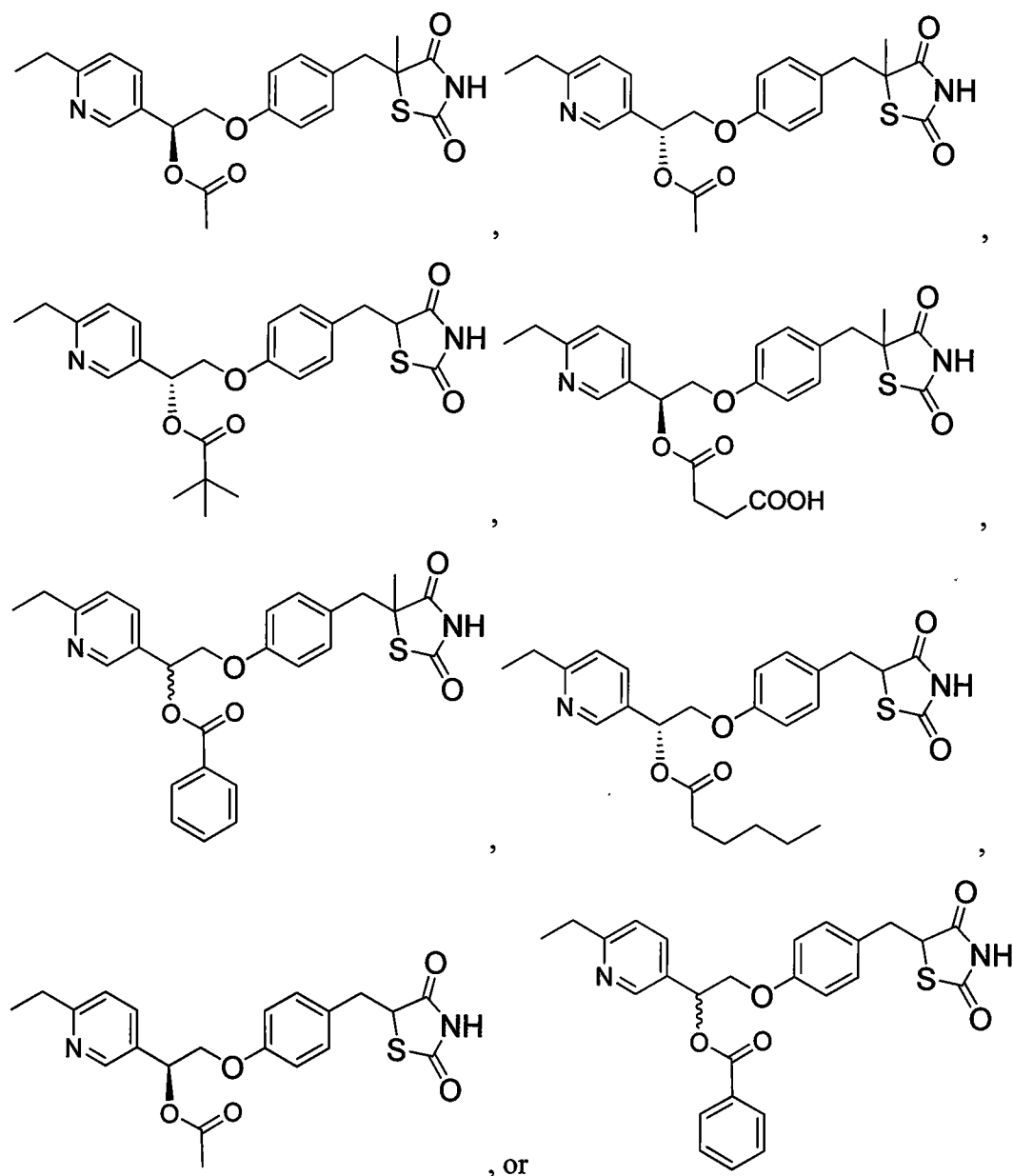


[0245] Table K: Pyridin-2-yl Compounds.





[0246] Table L: Pyridin-3-yl Compounds.



[0247] Exemplary pharmaceutical compositions according to the present invention include a single unit dosage form having about 1 mg to about 200 mg of a compound of Formula I, II, IIA, IIB, IIC, IIIA, IIIB, IV, IVA or IVB, e.g., between about 10 mg to about 120 mg, between about 10 mg to about 100 mg, or about 15 mg to about 60 mg.

[0248] Another aspect of the present invention provides a pharmaceutical composition comprising a compound of Formula I, II, IIA, IIB, IIC, IIIA, IIIB, IV, IVA or IVB, wherein the compound has a PPAR γ activity of 50% or less relative to the activity of rosiglitazone when dosed to produce circulating levels greater than 3 μ M or having a PPAR γ activity of 10 times less than pioglitazone at the same dosage.

[0249] Another aspect of the present invention provides a pharmaceutical composition comprising a compound of Formula I and a pharmaceutically acceptable carrier.

[0250] B. Co-Crystals of a Compound of Formula I

[0251] In another aspect, the present invention provides a method for treating or delaying the onset of PKD comprising administering a co-crystal comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, as described above, and a phosphodiesterase inhibitor. In several embodiments, the phosphodiesterase inhibitor is a selective inhibitor or a non-selective inhibitor.

[0252] For example, the phosphodiesterase inhibitor is a non-selective inhibitor. In several instances, the non-selective phosphodiesterase inhibitor includes caffeine (1,3,7-trimethylxanthine), theobromine (3,7-dimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione), theophylline (1,3-dimethyl-7H-purine-2,6-dione), combinations thereof, or the like.

[0253] In another example, the phosphodiesterase inhibitor is a selective inhibitor. For instance, the selective phosphodiesterase inhibitor includes Milrinone (2-methyl-6-oxo-1,6-dihydro-3,4'-bipyridine-5-carbonitrile), Cilostazol (6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1H)-quinolinone), Cilomilast (4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid), Rolipram (4-(3-cyclopentyloxy-4-methoxyphenyl)pyrrolidin-2-one), Roflumilast (3-(cyclopropylmethoxy)-N-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)benzamide), combinations thereof, or the like.

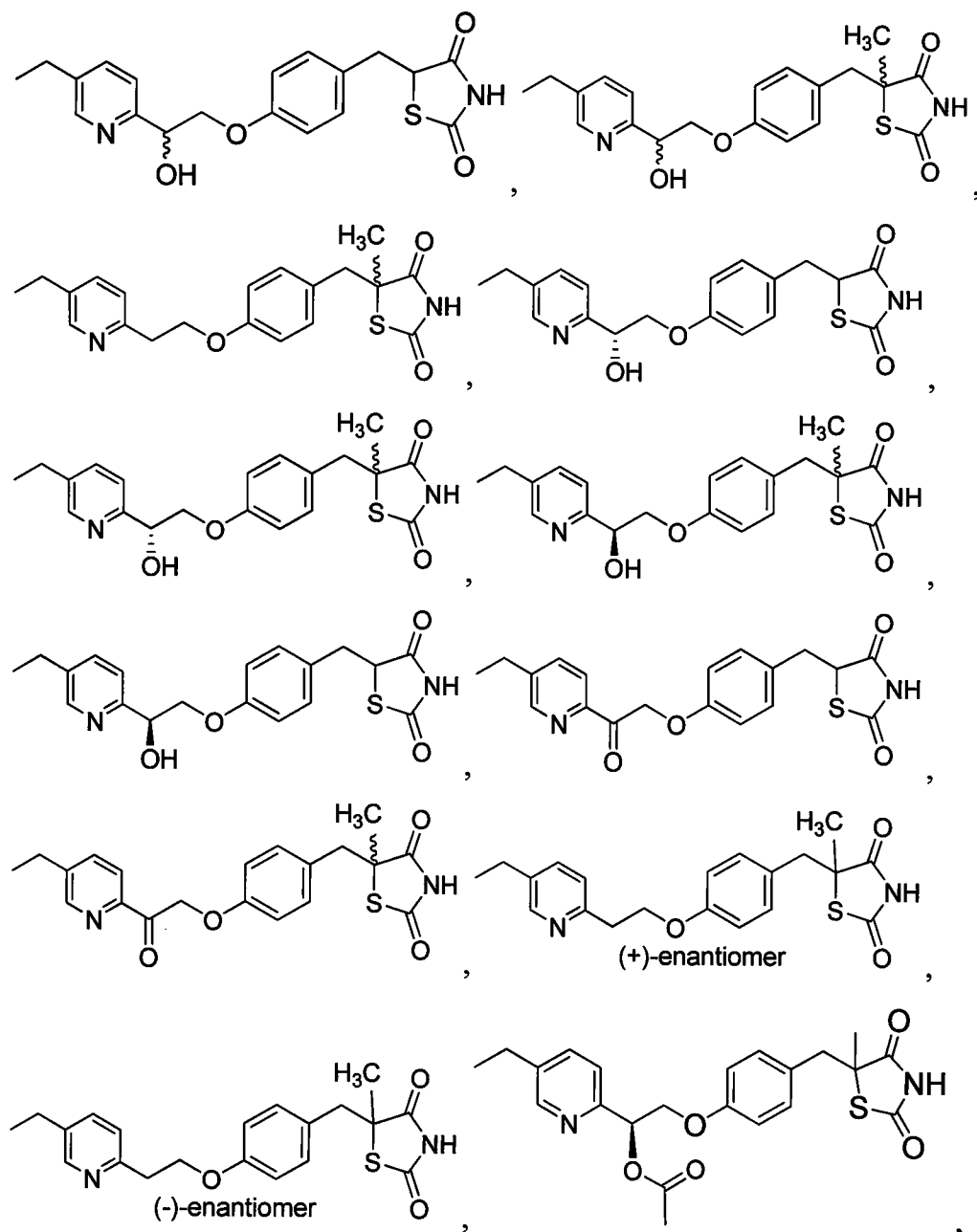
[0254] In several embodiments, the phosphodiesterase inhibitor is present in the co-crystal according to the ratio from about 1:1 to about 1:5 (e.g., 1:1, 1:2, 1:3, or 1:4) wherein the ratio represents the amount of phosphodiesterase inhibitor relative to the amount of compound of Formula I, i.e., amount of phosphodiesterase inhibitor : amount of compound of Formula I. Note that in some embodiments, the co-crystal also comprises method artifacts such as weak acids that are used to facilitate crystal formation.

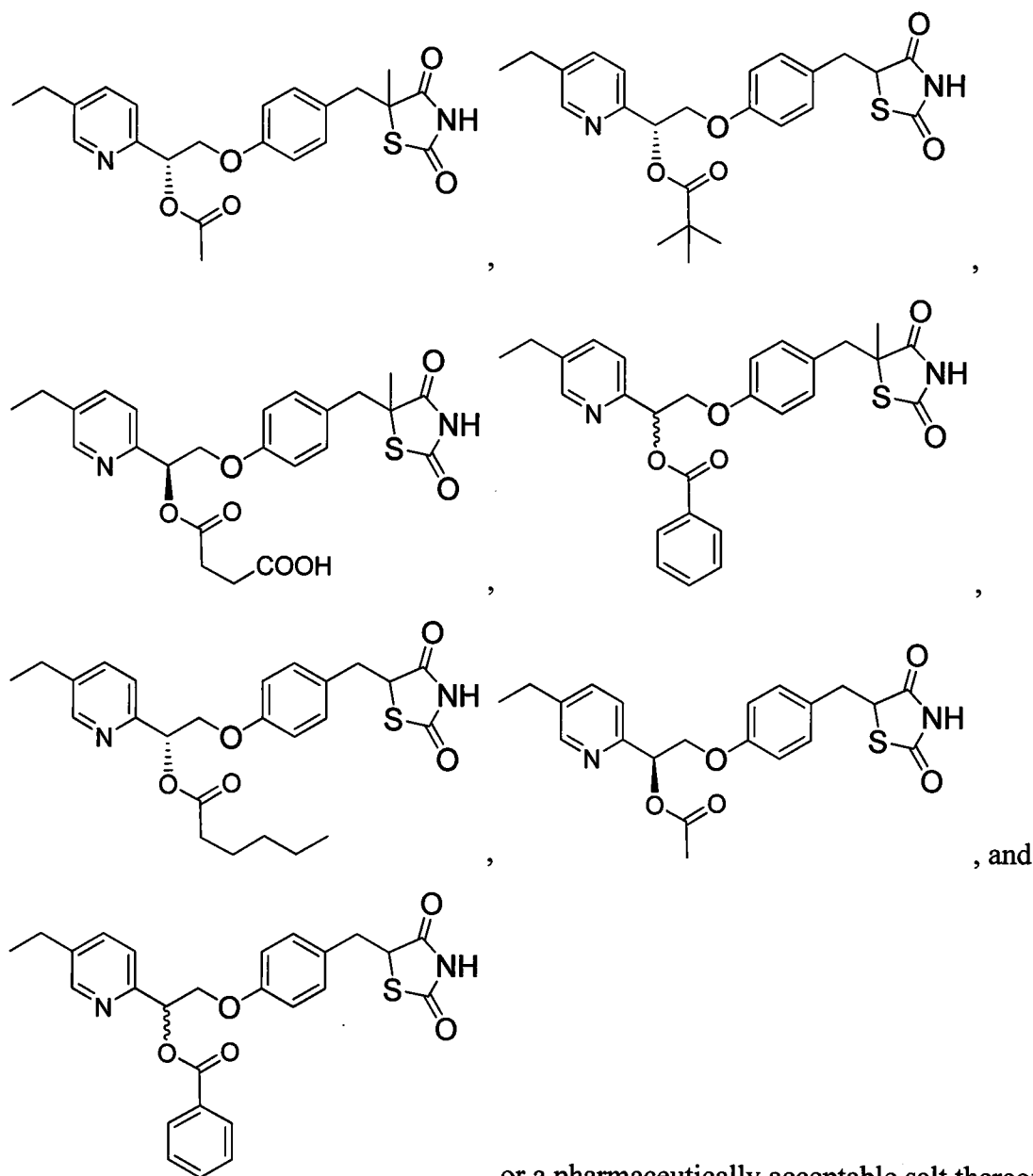
[0255] In some embodiments, the co-crystal comprises caffeine and a compound of Formula I, wherein the caffeine is present according to a ratio of from about 1:1.25 to about 1:1.75, wherein the ratio represents the amount of phosphodiesterase inhibitor relative to the amount of compound of Formula I. In some examples, the co-crystal comprises caffeine and a compound of Formula I, wherein caffeine is present in according to the ratio 1:1.5 relative to the compound of Formula I. In another example, the co-crystal comprises 5-(4-(2-(5-ethylpyridin-2-yl)-2-oxoethoxy)benzyl)-1,3-thiazolidine-2,4-dione and caffeine, wherein the caffeine is present according to the ratio from about 1:1.25 to about 1:1.75 (e.g., about 1:1.5) relative to 5-(4-(2-(5-ethylpyridin-2-yl)-2-oxoethoxy)benzyl)-1,3-thiazolidine-2,4-dione. In another example, the co-crystal comprises 5-(4-(2-(3-methoxyphenyl)-2-oxoethoxy)benzyl)thiazolidine-2,4-dione and caffeine, wherein

the caffeine is present according to the ratio from about 1:1.25 to about 1:1.75 (e.g., about 1:1.5) relative to 5-(4-(2-(3-methoxyphenyl)-2-oxoethoxy)benzyl)thiazolidine-2,4-dione.

[0256] In other embodiments, the present invention provides a co-crystal comprising a compound of Formula I, II, IIA, IIB, IIC, IIIA, IIIB, IV, IVA or IVB, or a pharmaceutically acceptable salt thereof, and a phosphodiesterase inhibitor.

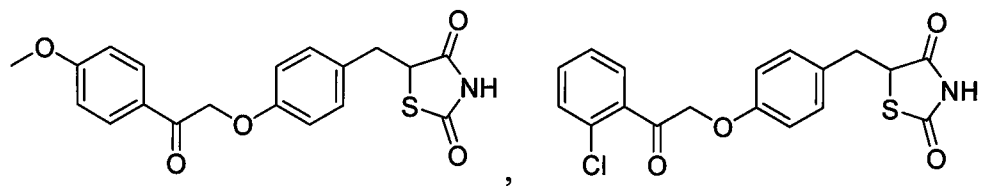
[0257] One embodiment of the present invention provides a co-crystal comprising a compound selected from:

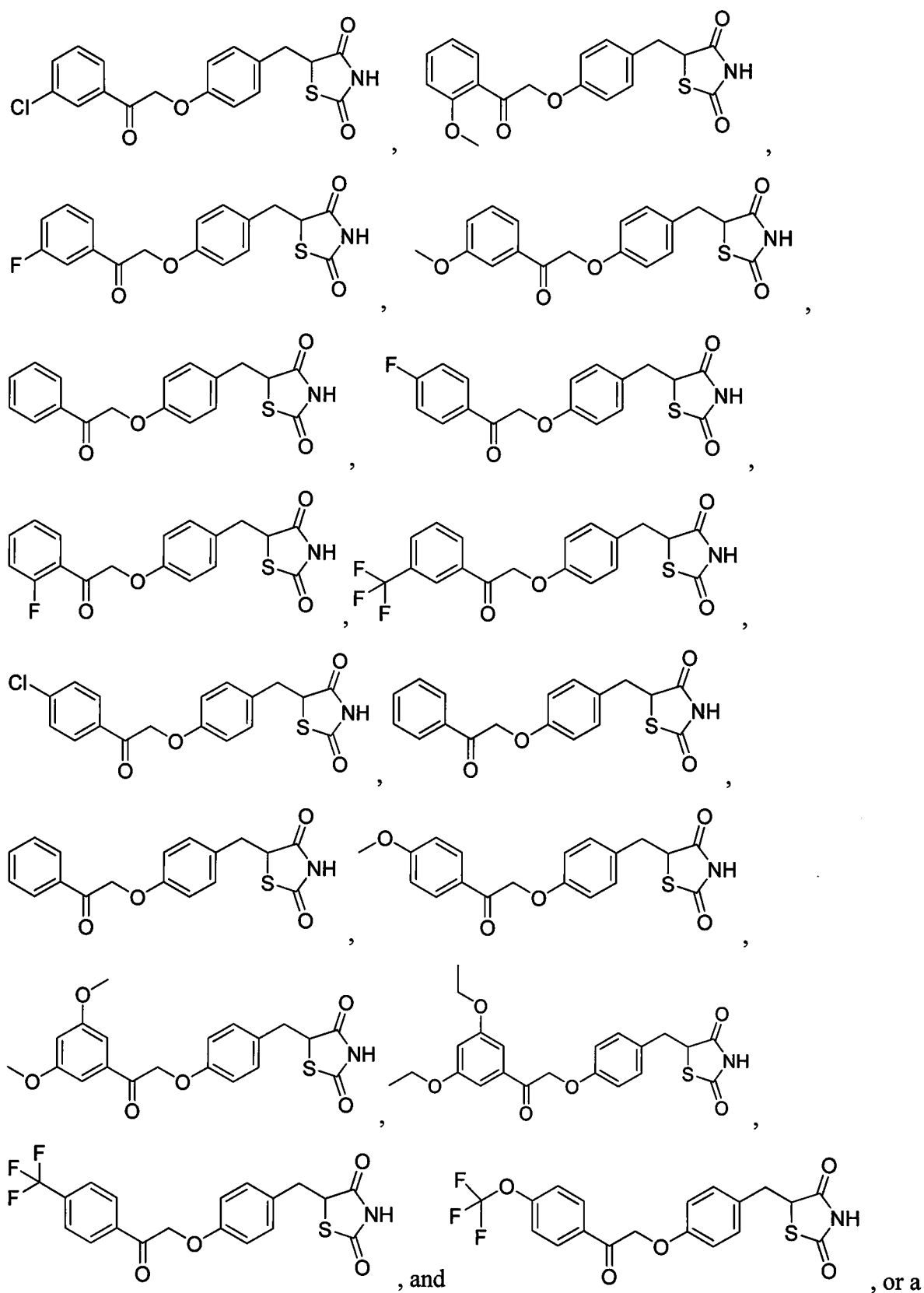




phosphodiesterase inhibitor.

[0258] One embodiment of the present invention provides a co-crystal comprising a compound selected from:





pharmaceutically acceptable salt thereof, and a phosphodiesterase inhibitor.

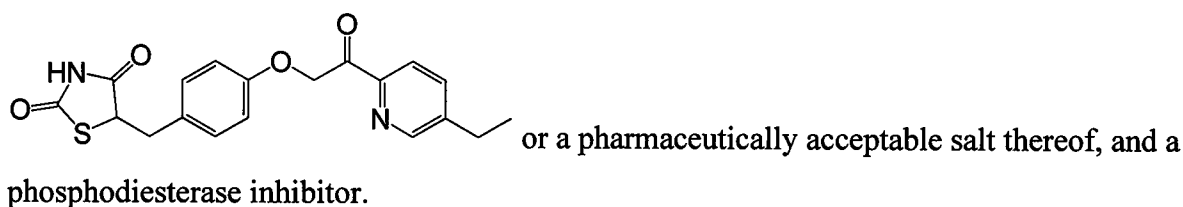
[0259] In several embodiments, the phosphodiesterase inhibitor is a selective inhibitor or a non-selective inhibitor.

[0260] For example, the phosphodiesterase inhibitor is a non-selective inhibitor. In several instances, the non-selective phosphodiesterase inhibitor includes caffeine

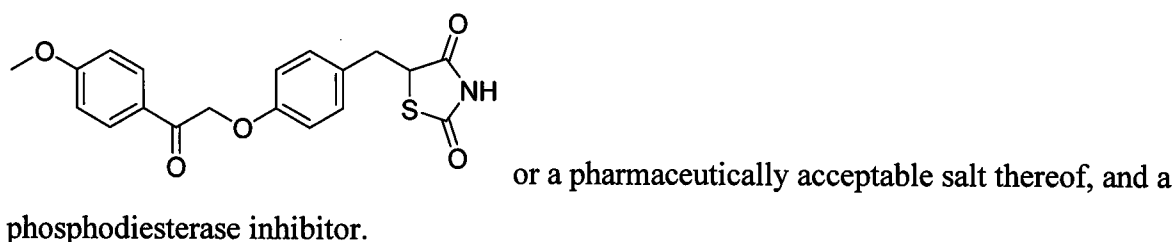
(1,3,7-trimethylxanthine), theobromine (3,7-dimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione), theophylline (1,3-dimethyl-7H-purine-2,6-dione), combinations thereof, and the like.

[0261] In another example, the phosphodiesterase inhibitor is a selective inhibitor. For instance, the selective phosphodiesterase inhibitor includes Milrinone (2-methyl-6-oxo-1,6-dihydro-3,4'-bipyridine-5-carbonitrile), Cilostazol (6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1H)-quinolinone), Cilomilast (4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid), Rolipram (4-(3-cyclopentyloxy-4-methoxyphenyl)pyrrolidin-2-one), Roflumilast (3-(cyclopropylmethoxy)-N-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)benzamide), combinations thereof, and the like.

[0262] In other examples, the co-crystal comprises the compound



[0263] In other examples, the co-crystal comprises the compound

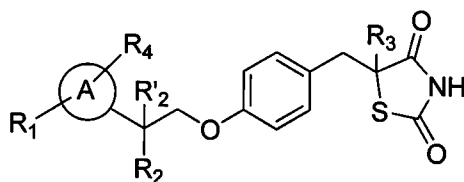


[0264] In other aspects, the present invention provides a pharmaceutical composition comprising a co-crystal, as described above, a second agent that increases the cyclic nucleotide in a patient, and a pharmaceutically acceptable carrier.

[0265] C. Other Pharmaceutical Compositions

[0266] Another aspect of the present invention provides a pharmaceutical composition comprising a compound of Formula I, a pharmaceutically acceptable salt thereof, or a co-crystal thereof; and an agent that affects (e.g., increases) cellular cyclic nucleotide levels (e.g., increases cAMP) in a patient. Agents that increase cAMP in a patient include, without limitation, β -adrenergic agonists, hormones (e.g., GLP1), any combination thereof, or the like.

[0267] In some embodiments, the pharmaceutical composition comprises a compound of Formula I

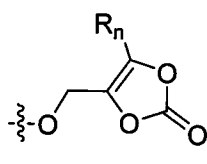


I

or a pharmaceutically acceptable salt thereof, wherein:

Each of R_1 and R_4 is independently selected from H, halo, aliphatic, and alkoxy, wherein the aliphatic or alkoxy is optionally substituted with 1-3 of halo;

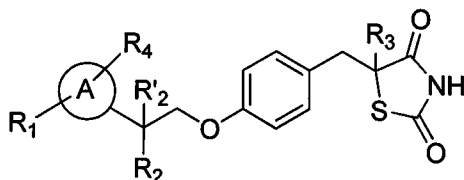
R'_2 is H, and R_2 is H, halo, hydroxy, or optionally substituted aliphatic, -O-acyl, -O-aroyl, -O-heteroaroyl, -O(SO₂)NH₂, -O-CH(R_m)OC(O) R_n , -O-CH(R_m)OP(O)(OR_n)₂,

-O-P(O)(OR_n)₂, or , wherein each R_m is independently C₁₋₆ alkyl, each R_n is independently C₁₋₁₂ alkyl, C₃₋₈ cycloalkyl, or phenyl, each of which is optionally substituted; or R_2 and R'_2 together may form oxo;

R_3 is H or C₁₋₃ alkyl; and

Ring A is a phenyl, pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl, each of which is substituted with an R_1 group and an R_4 group, and a β -adrenergic agonist.

[0268] In some embodiments, the pharmaceutical composition comprises a compound of Formula I

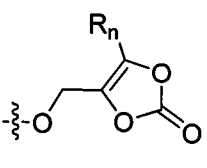


I

or a pharmaceutically acceptable salt thereof, wherein:

Each of R_1 and R_4 is independently selected from H, halo, aliphatic, and alkoxy, wherein the aliphatic or alkoxy is optionally substituted with 1-3 of halo;

R'_2 is H, and R_2 is H, halo, hydroxy, or optionally substituted aliphatic, -O-acyl, -O-aroyl, -O-heteroaroyl, -O(SO₂)NH₂, -O-CH(R_m)OC(O) R_n , -O-CH(R_m)OP(O)(OR_n)₂,

-O-P(O)(OR_n)₂, or , wherein each R_m is independently C₁₋₆ alkyl, each R_n is independently C₁₋₁₂ alkyl, C₃₋₈ cycloalkyl, or phenyl, each of which is optionally substituted; or R_2 and R'_2 together may form oxo;

R₃ is H or C₁₋₃ alkyl; and

Ring A is a phenyl, pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl, each of which is substituted with an R₁ group and an R₄ group, and GLP1.

[0269] In several embodiments, R₁ is H. In some embodiments, R₁ is halo (e.g., F, Cl, or Br). In some embodiments, R₁ is an aliphatic optionally substituted with 1-3 halo. For instance, R₁ is trifluoromethyl (-CF₃). In some embodiments, R₁ is alkoxy. For instance, R₁ is methoxy, ethoxy, propoxy, -O-isopropyl, butoxy, or -O-tertbutyl. In still other embodiments, R₁ is alkoxy substituted with 1-3 halo. For instance, R₁ is -OCHF₂ or -OCF₃. In each of the foregoing embodiments, R₁ can be attached to the ortho, meta, or para position of ring A, when ring A is phenyl. In certain embodiments, R₁ is substituted at the para or meta position of ring A, when ring A is phenyl.

[0270] In some embodiments, ring A is phenyl that is substituted with R₁ and R₄ groups at any chemically feasible position on ring A. For example, ring A is phenyl, and one of R₁ or R₄ is attached to the para or meta position of ring A. In some instances, ring A is phenyl, and one of R₁ or R₄ is attached to the meta position of ring A. In some examples, R₁ is attached to the para or meta position of ring A. For instance, R₁ is attached to the para or meta position of ring A, and R₁ is F or Cl. In other instances, R₁ is attached to the para or meta position of ring A, and R₁ is alkoxy. For example, R₁ is methoxy, ethoxy, propoxy, -O-isopropyl, butoxy, or -O-tertbutyl that is attached to the para or meta position of ring A. In some examples, ring A is phenyl, and R₁ is attached to the meta or ortho position of the phenyl ring. For instance, ring A is phenyl, and R₁ is attached to the ortho position of the phenyl ring. In other instances, ring A is phenyl, and R₁ is methoxy, ethoxy, or -O-isopropyl, wherein any of these groups are attached to the ortho position of ring A. In other examples, R₁ is -CF₃, -OCH₃, -OCHF₂ or -OCF₃, wherein any of these groups are attached to the ortho position of ring A.

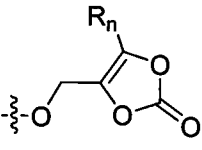
[0271] In some embodiments, ring A is pyridin-2-yl or pyridin-3-yl, either of which is substituted with R₁ and R₄ groups at any chemically feasible position on ring A. For example, ring A is pyridin-2-yl, and one of R₁ or R₄ is attached to the 5 position of the ring. In other examples, ring A is pyridin-3-yl, and one of R₁ or R₄ is attached to the 6 position of the ring. In some examples, ring A is pyridin-2-yl, and R₁ is attached to the 5 position of the ring. For instance, R₁ is alkyl or alkoxy, wherein either moiety is attached to the 5 position of ring A. In some instances, R₁ is methyl, ethyl, propyl, isopropyl, butyl, or tertbutyl, wherein any of these moieties is attached to the 5 position of ring A.

[0272] In several embodiments, R_4 is H. In some embodiments, R_4 is halo, such as F or Cl. In some embodiments, R_4 is an aliphatic optionally substituted with 1-3 halo. For instance, R_4 is trifluoromethyl. In some embodiments R_4 is alkoxy. For instance, R_4 is methoxy, ethoxy, or -O-isopropyl. In still other embodiments, R_4 is alkoxy substituted with 1-3 halo. For instance, R_4 is -OCHF₂ or -OCF₃. In each of the foregoing embodiments, R_4 can be substituted at the ortho, meta, or para position of ring A, when ring A is phenyl. In certain embodiments, R_4 is substituted at the para or meta position of ring A. In some embodiments, R_1 and R_4 are different substituents. In still other embodiments, R_1 and R_4 are the same substituent. In some embodiments when R_1 is aliphatic, R_4 is other than H.

[0273] In several embodiments, each of R_1 and R_4 is independently selected from H, halo, aliphatic, and alkoxy, wherein the aliphatic and alkoxy are optionally substituted with 1-3 of halo.

[0274] In several embodiments, each of R_1 and R_4 is independently selected from H, halo, aliphatic, and alkoxy, wherein the aliphatic and alkoxy are optionally substituted with 1-3 of halo.

[0275] In several embodiments, R_2 is halo, hydroxy, aliphatic, -O-acyl, -O-aroyl, -O-heteroaroyl, -O(SO₂)NH₂, -O-CH(R_m)OC(O) R_n , -O-CH(R_m)OP(O)(OR_n)₂,

-O-P(O)(OR_n)₂, or , wherein each R_m is C₁₋₆ alkyl, R_n is C₁₋₁₂ alkyl, C₃₋₈ cycloalkyl, or phenyl and each substituent R_m or R_n is optionally substituted.

[0276] In some embodiments, R_2 is H.

[0277] In some embodiments, R_2 is hydroxy.

[0278] In some embodiments, R_2 is an optionally substituted straight or branched C₁₋₆ alkyl, an optionally substituted straight or branched C₂₋₆ alkenyl, or an optionally substituted straight or branched C₂₋₆ alkynyl. In other embodiments, R_2 is a C₁₋₆ aliphatic optionally substituted with 1-2 hydroxy, carboxy or halo. In other embodiments, R_2 is a C₁₋₆ alkyl optionally substituted with hydroxy. In further embodiments, R_2 is a C₁₋₆ alkyl optionally substituted with -O-acyl, -O-aroyl, -O-heteroaroyl. In several other embodiments, R_2 is a methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl, or hexyl, each of which is optionally substituted with hydroxy. In several additional embodiments, R_2 is methyl or ethyl, each of which is substituted with hydroxy.

[0279] In certain embodiments, R_2 is -O-acyl, -O-aroyl, or -O-heteroaroyl.

[0280] In other embodiments, R_2 is -O-acetyl, -O-hexanoyl, -O-benzoyl, -O-pivaloyl, -O-imidazolyl, -O-succinoyl, -O-thiazoloyl or -O-pyridinoyl, each optionally substituted.

[0281] In some embodiments, R_2 is -O-C(O)-imidazol-1-yl.

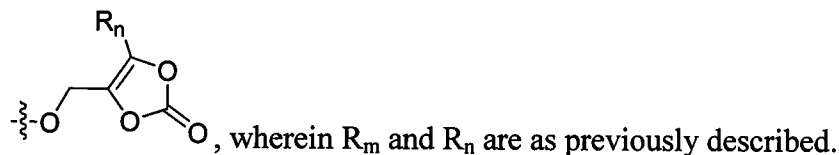
[0282] In certain embodiments, R_2 is -O-CH(R_m)-O-C(O)- R_n .

[0283] In some embodiments, R_2 is -O-CH(R_m)OP(O)(OR $_n$) $_2$.

[0284] In some embodiments, R_2 is -O-P(O)(OR $_n$) $_2$.

[0285] In other embodiments, R_2 is -O-S(O $_2$)NH $_2$.

[0286] In some further embodiments, R_2 is a 1,3-dioxolan-2-one of the Formula



[0287] In several embodiments, R'_2 is H.

[0288] In some embodiments, R_2 and R'_2 together form oxo.

[0289] In some embodiments, R'_2 is H and R_2 has an R configuration.

[0290] In some embodiments, R'_2 is H and R_2 has an S configuration.

[0291] In some embodiments, R'_2 is H and R_2 is racemic.

[0292] In further embodiments, ring A is phenyl or pyridinyl.

[0293] In some embodiments, ring A is pyridin-2-yl.

[0294] In some embodiments, ring A is pyridin-3-yl.

[0295] In some embodiments, ring A is pyridin-4-yl.

[0296] In other embodiments, R_3 is H or optionally substituted C $_{1-3}$ alkyl.

[0297] In some embodiments, R_3 is H.

[0298] In some embodiments, R_3 is CH $_3$.

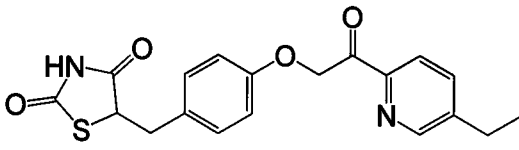
[0299] In some embodiments, the pharmaceutical composition comprises an alkali earth metal salt of a compound of Formula I, as described above. In some instances, the alkali earth metal is sodium. In other instances, the alkali earth metal is potassium.

[0300] In some embodiments, the present invention provides a pharmaceutical composition comprising a compound of Formula I, a salt thereof (e.g., a sodium or potassium salt), or a co-crystal thereof, and a β -adrenergic agonist (e.g., a β_1 -adrenergic agonist, a β_2 -adrenergic agonist, a β_3 -adrenergic agonist, or any combination thereof). Non-limiting examples of β -adrenergic agonists include noradrenaline, isoprenaline, dobutamine, salbutamol, levosalbutamol, terbutaline, pirbuterol, procaterol, metaproterenol, fenoterol, bitolterol mesylate, salmeterol, formoterol, bambuterol, clenbuterol, indacaterol, L-796568, amibegron, solabegron, isoproterenol, albuterol, metaproterenol, arbutamine, befunolol,

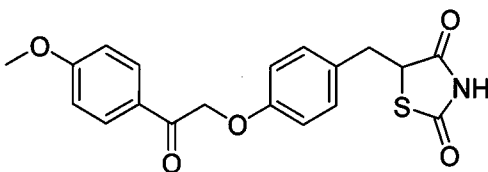
bromoacetylalprenololmenthane, broxaterol, cimaterol, cirazoline, denopamine, dopexamine, epinephrine, etilefrine, hexoprenaline, higenamine, isoetharine, isoxsuprine, mabuterol, methoxyphenamine, nylidrin, oxyfedrine, prenalterol, ractopamine, reproterol, rimiterol, ritodrine, tretoquinol, tulobuterol, xamoterol, zilpaterol, zinterol, or any combination thereof.

[0301] In other embodiments, the pharmaceutical composition of the present invention comprises a co-crystal comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, and a phosphodiesterase inhibitor; and an agent that increases cAMP levels in a patient (e.g., β -adrenergic agonist or GLP1). For instance, the composition comprises a co-crystal comprising a compound of Formula I, II, IIA, IIB, IIC, IIIA, IIIB, IV, IVA or IVB, or a pharmaceutically acceptable salt thereof, and a phosphodiesterase inhibitor; and a β -adrenergic agonist. Any of the phosphodiesterase inhibitors or combinations thereof are suitable for use in co-crystals used to formulate pharmaceutical compositions of the present invention that also include one or more agents that increase cyclic nucleotide (e.g., cAMP) levels in a patient (e.g., a β -adrenergic agonist).

[0302] In one particular example, the pharmaceutical composition comprises a co-crystal

comprising the compound  or a pharmaceutically acceptable salt thereof, and a phosphodiesterase inhibitor; and a β -adrenergic agonist.

[0303] In one particular example, the pharmaceutical composition comprises a co-crystal

comprising the compound  or a pharmaceutically acceptable salt thereof, and a phosphodiesterase inhibitor; and a β -adrenergic agonist.

[0304] One aspect of the present invention provides a pharmaceutical composition comprising a compound of Formula I, II, IIA, IIB, IIC, IIIA, IIIB, IV, IVA or IVB, in combination with a beta-adrenergic agonist and at least one additional weight loss drug. Non-limiting examples of other weight loss drugs include appetite suppressants (e.g., Meridia, or the like), fat absorption inhibitors (e.g., Xenical, or the like), or compounds that augment sympathomimetic activity such as ephedrine or its various salts.

[0305] Another aspect provides a pharmaceutical composition comprising a co-crystal comprising a compound of Formula I, II, IIA, IIB, IIC, IIIA, IIIB, IV, IVA or IVB, or a pharmaceutically acceptable salt thereof, and a phosphodiesterase inhibitor in combination with a beta-adrenergic agonist and at least one additional weight loss drug. Non-limiting

examples of other weight loss drugs include appetite suppressants (e.g., Meridia, or the like), fat absorption inhibitors (e.g., Xenical, or the like), or compounds that augment sympathomimetic activity such as ephedrine or its various salts.

[0306] III. METHODS

[0307] Another aspect of the present invention provides a method of treating or preventing PKD in a patient comprising administering a pharmaceutical composition comprising a compound of Formula I, II, IIA, IIB, IIC, IIIA, IIIB, IV, IVA or IVB.

[0308] Several embodiments comprise the step of administering to a patient a compound of Formula I and an agent that increases a cyclic nucleotide level (e.g., increases cellular cAMP levels) in a patient. The administration of these ingredients can be sequential (e.g., the compound of Formula I is administered first in time, and the agent is administered second in time) or simultaneous, i.e., both ingredients are administered at substantially the same time.

[0309] Several embodiments comprise the step of administering to a patient a pharmaceutical composition comprising a co-crystal comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, and a phosphodiesterase inhibitor; and an agent that increases a cyclic nucleotide level in a patient (e.g., a β -adrenergic agonist).

[0310] Another aspect of the present invention provides a method of treating or preventing diabetes in a patient comprising administering a pharmaceutical composition comprising a compound of Formula I, II, IIA, IIB, IIC, IIIA, IIIB, IV, IVA or IVB, or a pharmaceutically acceptable salt thereof.

[0311] Several methods comprise the step of administering to a patient a compound of Formula I and an agent that increases a cyclic nucleotide level in a patient.

[0312] Several methods comprise the step of administering to a patient a pharmaceutical composition comprising a co-crystal comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, and a phosphodiesterase inhibitor; and an agent that increases a cyclic nucleotide level in a patient (e.g., a β -adrenergic agonist).

[0313] In one embodiment, the method of treating or preventing diabetes further comprises administering a co-therapy such as a third pharmaceutical agent, a restricted diet, increase the duration and/or exertion of a patient's physical activity, or any combination thereof.

[0314] Another aspect of the present invention provides a method of treating and/or preventing diabetes comprising administering a pharmaceutical composition comprising a compound of Formula I, II, IIA, IIB, IIC, IIIA, IIIB, IV, IVA or IVB, wherein said compound has a purity of about 70 e.e.% or more. For example, the method treating PKD comprises administering a pharmaceutical composition comprising a compound of Formula I wherein

the compound has a purity of about 80% e.e. or more (e.g., 90% e.e. or more, 95% e.e. or more, 97% e.e. or more, or 99% e.e. or more).

[0315] According to yet another embodiment, the present invention provides a method of treating or reducing the severity of PKD.

[0316] Another aspect of the present invention provides a method of treating or preventing PKD in a patient comprising administering a pharmaceutical composition comprising a compound of Formula I, II, IIA, IIB, IIC, IIIA, IIIB, IV, IVA or IVB.

[0317] Several methods comprise the step of administering to a patient a compound of Formula I and an agent that increases a cyclic nucleotide level (e.g., increases cellular cAMP levels) in a patient. The administration of these ingredients can be sequential (e.g., the compound of Formula I is administered first in time, and the agent is administered second in time) or simultaneous, i.e., both ingredients are administered at substantially the same time.

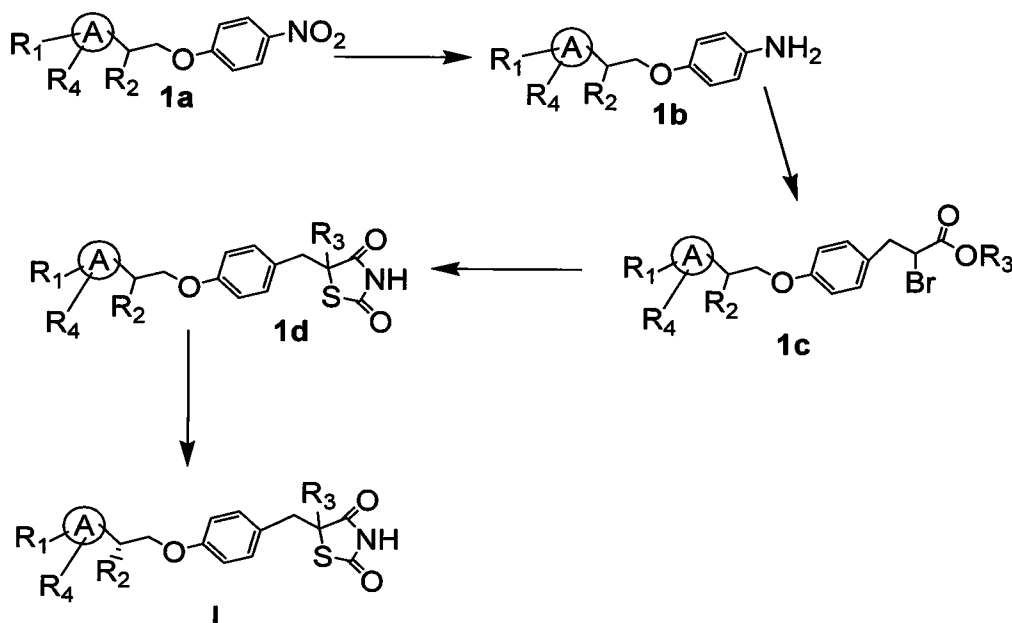
[0318] Several methods comprise the step of administering to a patient a co-crystal comprising a compound of Formula I and a phosphodiesterase inhibitor; and an agent that increases a cyclic nucleotide level in a patient.

[0319] In one embodiment, the method of treating PKD further comprises administering a co-therapy such as a third pharmaceutical agent (e.g., diuretic or the like).

[0320] IV. GENERAL SYNTHETIC SCHEMES

[0321] The compounds of Formula I and II may be readily synthesized from commercially available or known starting materials by known methods. Exemplary synthetic routes to produce compounds of Formula I, II, IIA, IIB, IIC, IIIA, IIIB, IV, IVA or IVB are provided in Scheme 1 below.

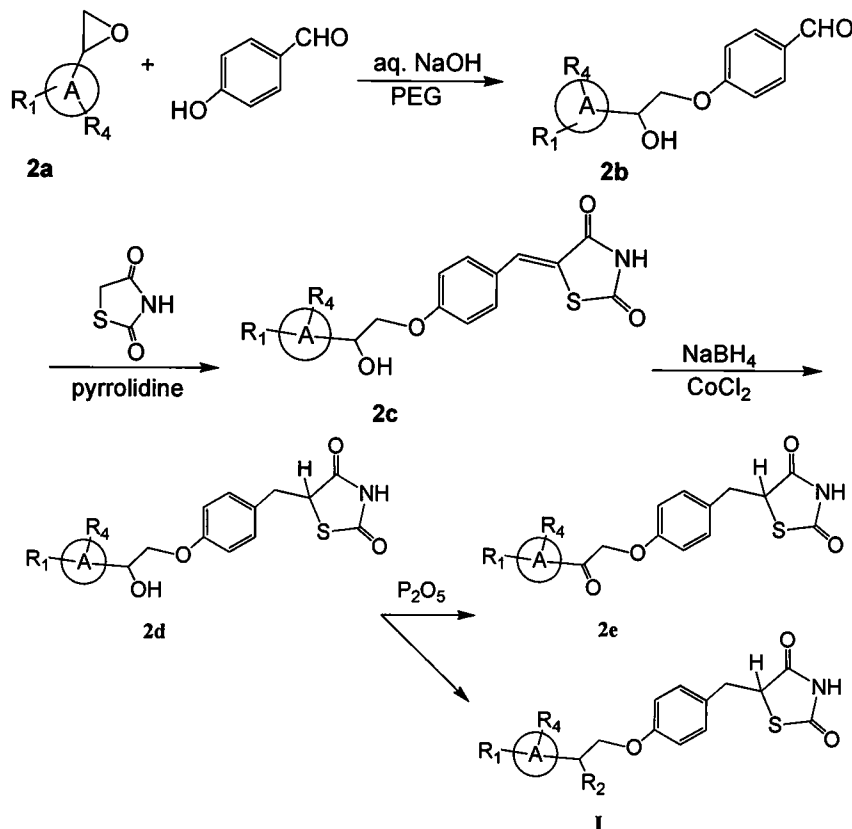
[0322] Scheme 1:



[0323] Referring to Scheme 1, the starting material **1a** is reduced to form the aniline **1b**. The aniline **1b** is diazotized in the presence of hydrobromic acid, acrylic acid ester, and a catalyst such as cuprous oxide to produce the alpha-bromo acid ester **1c**. The alpha-bromo acid ester **1c** is cyclized with thiourea to produce racemic thiazolidinedione **1d**. Compounds of Formula II can be separated from the racemic mixture using any suitable process such as HPLC.

[0324] In Scheme 2 below, R_2 and R'_2 form an oxo group or -O-Q and R_3 is hydrogen.

[0325] **Scheme 2:**



[0326] Referring to Scheme 2, the starting material **2a** is reacted with 4-hydroxybenzaldehyde under basic conditions (e.g., aq. NaOH) to give a mixture of regioisomeric alcohols **2b** that were separated by chromatography. The regioisomeric alcohols **2b** is reacted with 2,4-thiazolidinedione using pyrrolidine as base to give compound **2c**. Cobalt catalyzed reduction with sodium borohydride affords compound **2d**, which is oxidized, for example, with phosphorus pentoxide in the presence of dimethyl sulfoxide, to give the ketone **2e**. Alternatively, compounds of Formula I wherein R_2 is -O-Q, may be prepared from the hydroxy compound **2d** using known methods of alkylation, acylation, sulfonation or phosphorylation.

[0327] V. USES, FORMULATIONS, AND ADMINISTRATION

[0328] As discussed above, the present invention provides compounds that are useful as treatments for PKD.

[0329] Accordingly, in another aspect of the present invention, pharmaceutically acceptable compositions are provided, wherein these compositions comprise any of the compounds as described herein, and optionally comprise a pharmaceutically acceptable carrier, adjuvant or vehicle. In certain embodiments, these compositions optionally further comprise one or more additional therapeutic agents.

[0330] It will also be appreciated that certain of the compounds of present invention can exist in free form for treatment, or where appropriate, as a pharmaceutically acceptable derivative or a prodrug thereof. According to the present invention, a pharmaceutically acceptable derivative or a prodrug includes, but is not limited to, pharmaceutically acceptable salts, esters, salts of such esters, or any other adduct or derivative which upon administration to a patient in need is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof.

[0331] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A "pharmaceutically acceptable salt" means any non-toxic salt or salt of an ester of a compound of this invention that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof.

[0332] Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, et al. describes pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate,

lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate and aryl sulfonate.

[0333] As described above, the pharmaceutically acceptable compositions of the present invention additionally comprise a pharmaceutically acceptable carrier, adjuvant, or vehicle, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of the invention, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this invention. Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl

cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[0334] According to the invention an "effective amount" of the compound or pharmaceutically acceptable composition is that amount effective for treating, preventing, or lessening the severity of a disease such as PKD.

[0335] The pharmaceutical compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of PKD related diseases.

[0336] The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the particular agent, its mode of administration, and the like. The compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors known in the medical arts. The term "patient", as used herein, means an animal, for example, a mammal, and more specifically a human.

[0337] The pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally,

intraperitoneally, topically (as by powders, ointments, or drops), buccally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect. Alternatively, the compounds of the invention may be administered orally or parenterally at dosage levels of between 10 mg/kg and about 120 mg/kg.

[0338] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[0339] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[0340] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[0341] In order to prolong the effect of a compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsulated matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[0342] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[0343] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[0344] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets,

dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[0345] The active compounds can also be in microencapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[0346] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, eardrops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms are prepared by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[0347] As described generally above, the compounds of the invention are useful as treatments for metabolic diseases.

[0348] The activity, or more importantly, reduced PPAR γ activity of a compound utilized in this invention as a treatment of PKD may be assayed according to methods described generally in the art and in the examples provided herein.

[0349] It will also be appreciated that the compounds and pharmaceutically acceptable compositions of the present invention can be employed in combination therapies, that is, the compounds and pharmaceutically acceptable compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an inventive compound may be administered concurrently with another agent used to treat the same disorder), or they may achieve different effects (e.g., control of any adverse effects). As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated".

[0350] The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[0351] The compounds of this invention or pharmaceutically acceptable compositions thereof may also be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents and catheters.

Accordingly, the present invention, in another aspect, includes a composition for coating an implantable device comprising a compound of the present invention as described generally above, and in classes and subclasses herein, and a carrier suitable for coating said implantable device. In still another aspect, the present invention includes an implantable device coated with a composition comprising a compound of the present invention as described generally above, and in classes and subclasses herein, and a carrier suitable for coating said implantable device. Suitable coatings and the general preparation of coated implantable devices are described in US Patents 6,099,562; 5,886,026; and 5,304,121, each of which is incorporated by reference. The coatings are typically biocompatible polymeric materials such as a

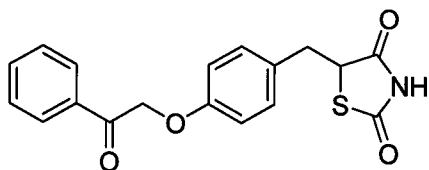
hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccharides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition.

[0352] Another aspect of the invention relates to treating metabolic diseases in a biological sample or a patient (e.g., in vitro or in vivo), which method comprises administering to the patient, or contacting said biological sample with a pharmaceutical composition comprising a compound of Formula I, II, IIA, IIB, IIC, IIIA, IIIB, IV, IVA or IVB. The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[0353] In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

[0354] VI. EXAMPLES

[0355] **Example 1: 5-[4-(2-oxo-2-phenylethoxy)benzyl]-1,3-thiazolidine-2,4-dione.**



[0356] **Step 1: Preparation of 4-(2-hydroxy-2-phenylethoxy)benzaldehyde.**

[0357] To 2-(4-fluorophenyl)oxirane (6.50 g, 54.0 mmol) was added toluene (85 mL), 4-hydroxybenzaldehyde (9.89 g, 81.0 mmol), PEG4000 (polyethylene glycol, 1.15 g) and 1M NaOH (85 mL) and the stirring mixture was heated at 78°C overnight. After cooling to RT the reaction mixture was extracted with EtOAc, and the organic phase was washed with brine, dried (Na₂SO₄), filtered and evaporated in vacuo. The resulting yellow oil was chromatographed on a medium silica gel column eluting with 0-10% EtOAc/DCM. Fractions containing predominantly the higher R_f spot were combined and evaporated in vacuo to give 1.85g (14%) of the title compound as a yellow oil. Fractions containing predominantly the lower R_f spot were combined and evaporated in vacuo to give 0.64g of the regioisomer as a colorless, viscous oil. Mixed fractions were combined and rechromatographed eluting with 30% EtOAc/hexanes. Fractions containing the higher R_f material were combined and evaporated in vacuo to give an additional 2.64 g (20%) of the title compound as a colorless

oil. Fractions containing the lower R_f material were combined and evaporated in vacuo to give an additional 1.82 g of the regioisomer as a colorless viscous oil.

[0358] Step 2: Preparation of 5-[4-(2-hydroxy-2-phenylethoxy)benzylidene]-1,3-thiazolidine-2,4-dione.

[0359] To a stirring solution of 4-[(2S)-2-hydroxy-2-phenylethoxy]benzaldehyde (2.63 g, 10.8 mmol) in absolute EtOH (75 mL) was added 2,4-thiazolidinedione (1.27 g, 10.8 mmol) and piperidine (0.54 mL, 5.4 mmol), and the resulting solution was heated to reflux. The reaction was refluxed overnight. The reaction mixture was allowed to cool to RT. No precipitate formed. The pH of reaction mixture was ca. 5. Acetic acid (20 drops) was added, and the reaction was evaporated in vacuo. The material was adsorbed onto silica gel and chromatographed eluting with 30-40% EtOAc/hexanes. Fractions containing product were combined and evaporated in vacuo to give 3.18g (86%) of the title compound as a light yellow solid. MS (ESI-) for $C_{18}H_{15}NO_4S$ m/z 340.1 (M-H)⁻.

[0360] Step 3: Preparation of 5-[4-(2-hydroxy-2-phenylethoxy)benzyl]-1,3-thiazolidine-2,4-dione.

[0361] To a mixture of 5-[4-(2-hydroxy-2-phenylethoxy)benzylidene]-1,3-thiazolidine-2,4-dione (1.50 g, 4.39 mmol) in THF (20 mL) was added H₂O (20 mL), 1M NaOH (3 mL), cobalt (II) chloride hexahydrate (0.60 mg, 0.003 mmol) and dimethylglyoxime (15 mg, 0.13 mmol). A solution of sodium tetrahydroborate (240 mg, 6.33 mmol) in 0.2M NaOH (3.6 mL) was added. The reaction mixture immediately turned dark but very soon assumed a clear yellow appearance. Acetic acid was added dropwise until the solution turned dark (3 drops). After ca. one hour, the reaction lightened. Additional NaBH₄, CoCl₂ and HOAc were added to produce a deep blue-purple color. When that color faded, more NaBH₄ was added. When HPLC analysis indicated that the reaction was complete, it was partitioned between H₂O and EtOAc, and the organic phase was washed with brine, dried (Na₂SO₄), filtered and evaporated in vacuo. The resulting foamy solid was chromatographed, eluting with 50% EtOAc/hexanes. Fractions containing product were combined and evaporated in vacuo to give 1.15 g (76%) of the title compound as a white solid. MS (ESI-) for $C_{18}H_{17}NO_4S$ m/z 342.1 (M-H)⁻.

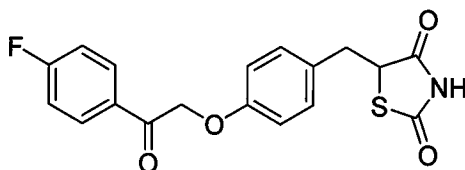
[0362] Step 4: Preparation of 5-[4-(2-oxo-2-phenylethoxy)benzyl]-1,3-thiazolidine-2,4-dione.

[0363] To a stirring solution of 5-[4-(2-hydroxy-2-phenylethoxy)benzyl]-1,3-thiazolidine-2,4-dione (1.00 g, 2.91 mmol) in DCM (35 mL) was added DMSO (2 mL) and the solution was cooled to 0 °C. Phosphorus pentoxide (0.83 g, 2.91 mmol) was added followed by

triethylamine (1.8 mL, 13.1 mmol). The reaction was allowed to slowly warm to RT. After 2 hours, the reaction mixture was partitioned between DCM and water and the organic phase was washed with brine, dried (Na_2SO_4), filtered and evaporated in vacuo. The resulting yellow oil was chromatographed on silica gel eluting with 25-35% EtOAc/hexanes.

Fractions containing product were combined and evaporated in vacuo to give 0.40 g (40%) of the title compound as a white solid. Trituration with ether afforded 245 mg of clean product. MS (ESI-) for $\text{C}_{18}\text{H}_{15}\text{NO}_4\text{S}$ m/z 340.1 (M-H) $^-$.

[0364] Example 2: Preparation of 5-{4-[2-(4-fluorophenyl)-2-oxoethoxy]benzyl}-1,3-thiazolidine-2,4-dione.



[0365] Step 1: Preparation of 4-[2-(fluorophenyl)-2-hydroxyethoxy]benzaldehyde.

[0366] To a stirring solution of 2-(4-fluorophenyl)oxirane (5.60 g, 40.0 mmol) in toluene (65 mL) was added 4-hydroxybenzaldehyde (7.40 g, 61.0 mmol), 1M NaOH (65 mL) and PEG4000 (polyethylene glycol, 0.85 g) and the reaction was heated at 78 °C overnight. After cooling to RT, the reaction was extracted with EtOAc (2 × 150 mL) and the combined extracts were washed with brine, dried (Na_2SO_4), filtered and evaporated in vacuo. The resulting light brown oil was chromatographed on silica gel eluting with 30-40% EtOAc/hexanes. Fractions containing the higher R_f spot were combined and evaporated in vacuo to give 2.38 g of the regioisomer of the product as a white solid. Fractions containing the lower R_f spot were combined and evaporated in vacuo to give 1.54g (22%) of the title compound as a colorless viscous oil.

[0367] Step 2: Preparation of 5-{4-[2-(4-fluorophenyl)-2-hydroxyethoxy]benzylidene}-1,3-thiazolidine-2, 4-dione.

[0368] To a stirring solution of the aldehyde (2.36 g, 10.8 mmol) in absolute EtOH (75 mL) was added 2,4-thiazolidinedione (1.06 g, 9.07 mmol) and piperidine (0.45 mL, 4.50 mmol), and the resulting solution was heated to reflux. After refluxing overnight, the reaction was allowed to cool to RT, and then evaporated in vacuo. The residue was adsorbed onto silica gel and chromatographed, eluting with 30-40% EtOAc/hexanes. Fractions containing product were combined and evaporated in vacuo to give 0.88 g (27%) of the title compound as a yellow solid. MS (ESI-) for $\text{C}_{18}\text{H}_{14}\text{FNO}_4\text{S}$ m/z 358.1 (M-H) $^-$.

[0369] Step 3: Preparation of 5-{4-[2-(4-fluorophenyl)-2-hydroxyethoxy]benzyl}-1,3-thiazolidine-2,4-dione.

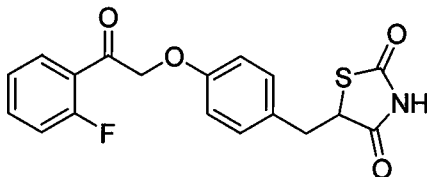
[0370] To a stirring mixture of 5-{4-[2-(4-fluorophenyl)-2-hydroxyethoxy]benzylidene}-1,3-thiazolidine-2,4-dione (0.87 g, 2.40 mmol) in THF/H₂O (1:1, 20 mL) was added 1M NaOH (2 mL), cobalt (II) chloride hexahydrate (0.30 g, 0.001 mmol), dimethylglyoxime (8.4 mg, 0.073 mmol), and finally sodium tetrahydroborate (0.13 g, 3.53 mmol). The reaction turned a deep blue/purple color. After a short time, the dark color began to fade and HOAc was added dropwise to regenerate the darker color. When the color faded and addition of HOAc failed to regenerate it, NaBH₄ was added to regenerate the darker color. The reaction was left to stir at RT overnight. The reaction was partitioned between water and EtOAc. The organic phase was washed with brine, dried (Na₂SO₄), filtered and evaporated in vacuo. The resulting light brown oil was chromatographed, eluting with 35% EtOAc/hexanes. Fractions containing compound were combined and evaporated in vacuo to give 0.77 g (88%) of a light yellow solid. The yellow solid was dissolved in THF (8 mL) and H₂O (8 mL), and the resulting solution was treated with CoCl₂ (a small crystal), and 2,2'-dipyridyl (5 mg). Finally, NaBH₄ was added in small portions until the deep blue color persisted. The reaction mixture was partitioned between EtOAc and H₂O, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried (Na₂SO₄), filtered and evaporated in vacuo. The resulting slightly tinted oil was chromatographed on a small silica gel column eluting with 25-35% EtOAc/hexanes. Fractions containing product were combined and evaporated in vacuo to afford 527 mg (60%) of the title compound as a white solid. MS (ESI-) for C₁₈H₁₆FNO₄S m/z 360.1 (M-H)⁻.

[0371] Step 4: Preparation of 5-{4-[2-(4-fluorophenyl)-2-oxoethoxy]benzyl}-1,3-thiazolidine-2,4-dione.

[0372] To a stirring solution of 5-{4-[2-(4-fluorophenyl)-2-hydroxyethoxy]benzyl}-1,3-thiazolidine-2,4-dione (0.52 g, 1.40 mmol) in DCM (15 mL) was added DMSO (0.5 mL) and the solution was cooled to 0°C. Phosphorus pentoxide (0.41 g, 1.44 mmol) was added followed by triethylamine (0.90 mL, 6.48 mmol). The reaction was allowed to slowly warm to RT and then stirred for 5 hours. The reaction mixture was partitioned between DCM and H₂O, and the aqueous phase was extracted with DCM. The combined organic phases were washed with brine, dried (Na₂SO₄), filtered and evaporated in vacuo. The resulting white solid was chromatographed on a small silica gel column eluting with 10% EtOAc/DCM. Fractions containing product were combined and evaporated in vacuo to give 0.25 g (48%) of

the title compound as a white solid. MS (ESI+) for $C_{18}H_{14}FNO_4S$ m/z 359.9 (M+H)⁺. MS (ESI-) for $C_{18}H_{14}FNO_4S$ m/z 358.0 (M-H)⁻.

[0373] Example 3: Preparation of 5-{4-[2-(2-fluorophenyl)-2-oxoethoxy]benzyl}-1,3-thiazolidine-2,4-dione.



[0374] Step 1: Preparation of 2-(2-fluorophenyl)oxirane.

[0375] To a solution of o-fluorostyrene (5.0 g, 41.0 mmol) and acetic acid (2.33 mL, 40.9 mmol) in dioxane (33 mL) and H₂O (78 mL) at 0 °C was added N-bromosuccinimide (8.02 g, 45.0 mol) in three portions. The reaction was allowed to warm to RT and stirred overnight. Sodium carbonate (8.68 g, 81.9 mmol) was added in portions and then 1M NaOH (ca. 10 mL) was added and the reaction was stirred at RT overnight. The reaction mixture was partitioned between water and EtOAc, and the aqueous phase was extracted with EtOAc. The combined organic phases washed with brine, dried (Na₂SO₄), filtered and evaporated in vacuo to give 5.31 g (94%) of the title compound as a slightly tinted oil which was used without further purification. MS (ESI+) for C_8H_7FO m/z 138.1 (M+H)⁺.

[0376] Step 2: Preparation of 4-[2-(2-fluorophenyl)-2-hydroxyethoxy]benzaldehyde.

[0377] To a stirring solution of 2-(2-fluorophenyl)oxirane (5.30 g, 38.4 mmol) in toluene (65 mL) was added 4-hydroxybenzaldehyde (7.0 g, 58.0 mmol), 1M NaOH (65 mL) and PEG4000 (polyethylene glycol, 0.85 g) and the stirring mixture was heated at 78 °C overnight. The reaction was allowed to cool to RT and then extracted with EtOAc (2 x 150 mL). The combined extracts were washed with brine, dried (Na₂SO₄), filtered and evaporated in vacuo. The resulting light brown oil was adsorbed onto silica gel and chromatographed, eluting with 30-40% EtOAc/hexanes to give 2 major spots. Fractions containing the higher R_f spot were combined and evaporated in vacuo to give 1.10g (11%) of the title compound as a colorless oil. Fractions containing the lower R_f spot were combined and evaporated in vacuo to give 0.67g (7%) of the regioisomer as a colorless oil.

[0378] Step 3: Preparation of 5-{4-[2-(2-fluorophenyl)-2-hydroxyethoxy]benzylidene}-1,3-thiazolidine-2,4-dione.

[0379] To a stirring solution of the aldehyde (2.36 g, 10.8 mmol) in absolute EtOH (40 mL) was added 2,4-thiazolidinedione (0.495 g, 4.23 mmol) and piperidine (0.21 mL, 2.10 mmol), and the resulting solution was heated to reflux. After refluxing overnight, the reaction mixture was cooled to RT and then evaporated in vacuo. The residue was dissolved in

EtOAc and this solution was washed with dilute aqueous HOAc, brine, dried (Na₂SO₄), filtered and evaporated in vacuo. The resulting yellow solid was washed with DCM and acetone and the filtrate was evaporated in vacuo. This material was adsorbed onto silica gel and chromatographed using 10-25% EtOAc/DCM. Fractions containing compound were combined and evaporated in vacuo to give 0.51 g of the title compound as a yellow solid. MS (ESI-) for C₁₈H₁₄FNO₄S m/z 358.0 (M-H)⁻.

[0380] Step 4: Preparation of 5-{4-[2-(2-fluorophenyl)-2-hydroxyethoxy]benzyl}-1,3-thiazolidine-2,4-dione.

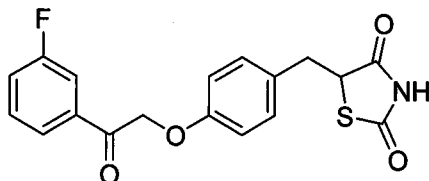
[0381] To a stirring mixture of 5-{4-[2-(2-fluorophenyl)-2-hydroxyethoxy]benzylidene}-1,3-thiazolidine-2,4-dione (0.52 g, 1.40 mmol) in THF/H₂O (1:1, 16 mL) was added 1M NaOH (2 mL), cobalt (II) chloride hexahydrate (0.2 mg, 0.0009 mmol), 2,2'-bipyridine (50.8 mg, 0.33 mmol), and finally sodium tetrahydroborate (0.11 g, 2.90 mmol). The reaction turned a deep blue/purple color. After a short time, the dark color began to fade and HOAc was added dropwise to regenerate the darker color. When the color faded and addition of HOAc failed to regenerate it, NaBH₄ was added to regenerate the darker color. Added small portions of NaBH₄ and HOAc dropwise until deep blue color persisted. After repeating this several times, HPLC indicated that the reaction was complete despite the fact that the deep blue color has given way to a light brown solution. The reaction was partitioned between water and EtOAc. The organic phase was washed with brine, dried (Na₂SO₄), filtered and evaporated in vacuo. The resulting light brown oil was chromatographed, eluting with 35% EtOAc/hexanes. Fractions containing compound were combined and evaporated in vacuo to give 0.32 g of the title compound as a white solid. MS (ESI-) for C₁₈H₁₆FNO₄S m/z 360.1 (M-H)⁻.

[0382] Step 5: Preparation of 5-{4-[2-(2-fluorophenyl)-2-oxoethoxy]benzyl}-1,3-thiazolidine-2,4-dione.

[0383] To a stirring solution of 5-{4-[2-(2-fluorophenyl)-2-hydroxyethoxy]benzyl}-1,3-thiazolidine-2,4-dione (0.29 g, 0.80 mmol) in DCM (15 mL) was added DMSO (0.5 mL) and the solution was cooled to 0 °C. Phosphorus pentoxide (0.23 g, 0.80 mmol) was added, followed by triethylamine (0.50 mL, 3.6 mmol). The reaction was allowed to slowly warm to RT. After 3 hours, water was added and the phases were separated. The pH of the aqueous phase was adjusted to ca. 7 and the aqueous phase was extracted with DCM. The combined organic phases were washed with brine, dried (Na₂SO₄), filtered and evaporated in vacuo. The resulting white solid was chromatographed on a small silica gel column eluting with 10% EtOAc/DCM. Fractions containing product were combined and evaporated in vacuo to give

0.19 g (66%) of the title compound as a white solid. MS (ESI-) for $C_{18}H_{14}FNO_4S$ m/z 358.0 (M-H)⁻.

[0384] Example 4: Preparation of 5-{4-[2-(3-fluorophenyl)-2-oxoethoxy]benzyl}-1,3-thiazolidine-2,4-dione.



[0385] Step 1: Preparation of 2-(3-fluorophenyl)oxirane.

[0386] To a solution of m-fluorostyrene (5.00 g, 41.0 mmol) and acetic acid (2.33 mL, 40.9 mmol) in dioxane (33 mL) and H₂O (78 mL) at 0 °C was added N-bromosuccinimide (8.02 g, 45.0 mmol) in three portions. The reaction was allowed to warm to RT. After 4 hours, 2N NaOH (60 mL) was added and the reaction was left to stir at RT overnight. The reaction mixture was partitioned between water and EtOAc, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried (Na₂SO₄), filtered and evaporated in vacuo to give 6.30 g of the title compound as a slightly tinted oil which was used without further purification.

[0387] Step 2: Preparation of 4-[2-(3-fluorophenyl)-2-hydroxyethoxy]benzaldehyde.

[0388] To a stirring solution of 2-(3-fluorophenyl)oxirane (5.60 g, 40.5 mmol) in toluene (65 mL) was added 4-hydroxybenzaldehyde (7.40 g, 61.0 mmol), 1M NaOH (65 mL) and PEG4000 (polyethylene glycol, 0.85 g) and the stirring mixture was heated at 78 °C overnight. The reaction mixture was allowed to cool to RT and then extracted with EtOAc (2 x 150 mL). The combined extracts were washed with brine, dried (Na₂SO₄), filtered and evaporated in vacuo. The resulting light brown oil was chromatographed eluting with 30-40% EtOAc/hexanes to give 2 major spots. Fractions containing the higher R_f spot were combined and evaporated in vacuo to give 1.78 g (17%) of the title compound as a white solid. Fractions containing the lower R_f spot were combined and evaporated in vacuo to give 0.90 g (9%) of the regioisomer as a nearly colorless oil.

[0389] Step 3: Preparation of 5-{4-[2-(3-fluorophenyl)-2-hydroxyethoxy]benzylidene}-1,3-thiazolidine-2,4-dione.

[0390] To a stirring solution of the aldehyde (2.36 g, 10.8 mmol) in absolute EtOH (40 mL) was added 2,4-thiazolidinedione (0.90 g, 7.69 mmol) and piperidine (0.76 mL, 7.7 mmol), and the resulting solution was heated to reflux. After 6 hours, the reaction mixture was allowed to cool to RT. The mixture was evaporated in vacuo and the residue was dissolved in EtOAc. This solution was washed with a dilute aqueous HOAc, brine, dried (Na₂SO₄),

filtered and evaporated in vacuo. The resulting yellow solid was dissolved in MeOH/DCM adsorbed onto silica gel and chromatographed eluting with 30% EtOAc/DCM. Fractions containing compound were combined and evaporated in vacuo to afford 2.17 g (86%) of the title compound as a yellow solid. MS (ESI-) for $C_{18}H_{14}FNO_4S$ m/z 358.1 (M-H)⁻.

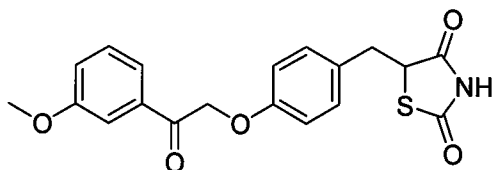
[0391] Step 4: Preparation of 5-{4-[2-(3-fluorophenyl)-2-hydroxyethoxy]benzyl}-1,3-thiazolidine-2,4-dione.

[0392] 5-{4-[2-(3-fluorophenyl)-2-hydroxyethoxy]benzylidene}-1,3-thiazolidine-2,4-dione (1.00 g, 2.78 mmol) was suspended in THF (15 mL) and H₂O (10 mL). To this solution was added a small crystal of cobalt chloride followed by 2,2'-bipyridine (98 mg, 0.63 mmol). NaBH₄ was added in portions until blue color persisted. The color gradually faded and was regenerated repeatedly by small additions of borohydride and HOAc. When HPLC analysis indicated that the reaction was complete, the reaction mixture was partitioned between EtOAc and H₂O. HOAc was added until the pH of the aqueous phase was ca. 6. The aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried (Na₂SO₄), filtered and evaporated in vacuo. The residue was chromatographed on a small silica gel column eluting with 20% EtOAc/DCM. Fractions containing product were combined and evaporated in vacuo to give 0.72 g (72%) of the title compound as a white solid. This material was rechromatographed on a small silica column eluting with 10-20% EtOAc/DCM. MS (ESI-) for $C_{18}H_{16}FNO_4S$ m/z 360.1 (M-H)⁻.

[0393] Step 5: Preparation of 5-{4-[2-(3-fluorophenyl)-2-oxoethoxy]benzyl}-1,3-thiazolidine-2,4-dione.

[0394] To a stirring solution of 5-{4-[2-(3-fluorophenyl)-2-hydroxyethoxy]benzyl}-1,3-thiazolidine-2,4-dione (0.62 g, 1.70 mmol) in DCM (15 mL) was added DMSO (0.5 mL) and the solution was cooled to 0 °C. Added phosphorus pentoxide (0.49 g, 1.72 mmol) followed by triethylamine (1.1 mL, 7.72 mmol). The reaction mixture was allowed to slowly warm to RT. After 2 hours, HPLC shows that the reaction was complete. Added water and separated phases. The pH of the aqueous phase was adjusted to ca. 7 with 2M NaOH and the aqueous phase was then extracted with EtOAc. The combined extracts were washed with brine, dried (Na₂SO₄), filtered and evaporated in vacuo. The resulting white solid was chromatographed on a small silica gel column eluting with 10% EtOAc/DCM. Fractions containing product were combined and evaporated in vacuo to give 0.25g (40%) of the title compound as a white solid. MS (ESI-) for $C_{18}H_{14}FNO_4S$ m/z 358.0 (M-H)⁻.

[0395] Example 5: Preparation of 5-{4-[2-(3-methoxyphenyl)-2-oxoethoxy]benzyl}-1,3-thiazolidine-2,4-dione.



[0396] *Step 1: 2-(3-methoxyphenyl)oxirane.*

[0397] To a solution of 3-vinylanisole (5.0 g, 37.0 mmol) and acetic acid (2.1 mL, 37.0 mmol) in dioxane (33 mL) and H₂O (78 mL) at 0 °C was added N-bromosuccinimide (7.30 g, 41.0 mmol) in three portions. The reaction was allowed to warm to RT and then 2M NaOH (50 mL) was added. The reaction was left to stir at RT overnight. The reaction mixture was then partitioned between water and EtOAc, and the aqueous phase was extracted with EtOAc. The combined organic phases washed with brine, dried (Na₂SO₄), filtered and evaporated in vacuo to give 5.60 g (100%) of the title compound as a slightly tinted oil.

[0398] *Step 2: 4-[2-hydroxy-2-(3-methoxyphenyl)ethoxy]benzaldehyde.*

[0399] To a stirring solution of 2-(3-methoxyphenyl)oxirane (5.60 g, 37.0 mmol) in toluene (65 mL) was added 4-hydroxybenzaldehyde (6.80 g, 5.60 mmol), 1M NaOH (65 mL) and PEG4000 (polyethylene glycol, 0.85 g) and the stirring mixture was heated at 78 °C overnight. The reaction mixture was allowed to cool to RT and extracted with EtOAc (2 x 150 mL). The combined extracts were washed with brine, dried (Na₂SO₄), filtered and evaporated in vacuo. The resulting light brown oil was chromatographed, eluting with 30-40% EtOAc/hexanes. Fractions containing the higher R_f spot were combined and evaporated in vacuo to give 1.86 g (18%) of the title compound as a clear colorless oil. Fractions containing the lower R_f spot were combined and evaporated in vacuo to give 0.90 g (9%) the regioisomer as a nearly colorless oil.

[0400] *Step 3: 5-{4-[2-hydroxy-2-(3-methoxyphenyl)ethoxy]benzylidene}-1,3-thiazolidine-2,4-dione.*

[0401] To a stirring solution of 4-[2-hydroxy-2-(3-methoxyphenyl)ethoxy]benzaldehyde (1.76 g, 6.46 mmol) in absolute EtOH (50 mL) was added 2,4-thiazolidinedione (0.83 g, 7.11 mmol) and piperidine (0.70 mL, 7.11 mmol), and the resulting solution was heated to reflux. The reaction was refluxed overnight and then evaporated in vacuo. The residue was dissolved in EtOAc and this solution was washed with water (pH adjusted to ca. 5-6 with HOAc), brine, dried (Na₂SO₄), filtered and adsorbed onto silica gel. After chromatography with 20-30% EtOAc/DCM, the fractions containing compound were combined and evaporated in vacuo to give 1.38 g (58%) of the title compound as a yellow solid. MS (ESI-) for C₁₉H₁₇NO₅S m/z 370.1 (M-H)⁻.

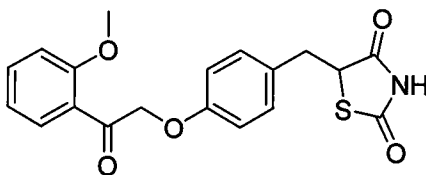
[0402] Step 4: 5-{4-[2-hydroxy-2-(3-methoxyphenyl)ethoxy]benzyl} -1,3-thiazolidine-2,4-dione.

[0403] 5-{4-[2-hydroxy-2-(3-methoxyphenyl)ethoxy]benzylidene}-1,3-thiazolidine-2,4-dione (1.15 g, 3.10 mmol) was dissolved in THF (15 mL). Added H₂O (15 mL) and sufficient THF to give a clear solution. A small crystal of cobalt chloride was added, followed by 2,2'-bipyridine (109 mg, 0.70 mmol). NaBH₄ was added in portions until the blue color persisted. The color gradually faded, but was regenerated repeatedly by small additions of borohydride and HOAc. When HPLC indicated that the reaction was complete the reaction mixture was partitioned between EtOAc and H₂O. HOAc was added until the pH of the aqueous phase was ca. 6, and then the aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried (Na₂SO₄), filtered and evaporated in vacuo. The residue was chromatographed on a small silica gel column eluting with 20% EtOAc/DCM. Fractions containing product were combined and evaporated in vacuo to give 0.82 g (74%) of the title compound as a white solid. MS (ESI-) for C₁₉H₁₉NO₅S m/z 372.0 (M-H)⁻.

[0404] Step 5: Preparation of 5-{4-[2-(3-methoxyphenyl)-2-oxoethoxy]benzyl}-1,3-thiazolidine-2,4-dione.

[0405] To a stirring solution of 5-{4-[2-hydroxy-2-(3-methoxyphenyl)ethoxy]benzyl}-1,3-thiazolidine-2,4-dione (0.62 g, 1.7 mmol) in DCM (15 mL) was added DMSO (0.5 mL) and the solution was cooled to 0 °C. Added phosphorus pentoxide (0.52 g, 1.8 mmol) followed by triethylamine (1.2 mL, 8.3 mmol). The reaction was allowed to slowly warm to RT. After 2 hours water was added and the phases were separated. The pH of the aqueous phase was adjusted to ca. 7 with 2M NaOH. The aqueous phase was extracted with EtOAc. The combined extracts were washed with brine, dried (Na₂SO₄), filtered and evaporated in vacuo. The resulting white solid was chromatographed on a small silica gel column eluting with 10% EtOAc/DCM. Fractions containing product were combined and evaporated in vacuo to give 0.33 g (54%) of the title compound as a white solid. MS (ESI+) for C₁₉H₁₇NO₅S m/z 372.0 (M+H)⁺. MS (ESI-) for C₁₉H₁₇NO₅S m/z 370.1 (M-H)⁻.

[0406] Example 6: Preparation of 5-{4-[2-(2-methoxyphenyl)-2-oxoethoxy]benzyl}-1,3-thiazolidine-2,4-dione.



[0407] Step 1: Preparation of 2-(2-methoxyphenyl)oxirane.

[0408] To a solution of 2-vinyl anisole (5.0 g, 0.037 mol) and acetic acid (2.1 mL, 37 mmol) in dioxane (33 mL) and H₂O (78 mL) at 0°C was added N-bromosuccinimide (7.30 g, 40.1 mmol) in three portions. The reaction was allowed to warm to RT and after 1 hour, 2M NaOH (50 mL) was added. The reaction was left to stir at RT overnight. The reaction mixture was partitioned between water and EtOAc, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried (Na₂SO₄), filtered and evaporated in vacuo to give 7.56 g slightly tinted oil. This was dissolved in dioxane, 2N NaOH was added and the reaction was stirred at RT overnight. Repeated aqueous work-up gave 5.60 g of the title compound as a nearly colorless oil.

[0409] Step 2: Preparation of 4-[2-hydroxy-2-(2-methoxyphenyl)ethoxy]benzaldehyde.

[0410] To a stirring solution of 2-(2-methoxyphenyl)oxirane (5.60 g, 37.3 mmol) in toluene (65 mL) was added 4-hydroxybenzaldehyde (6.80 g, 56.0 mmol), 1M NaOH (65 mL) and PEG4000 (polyethylene glycol, 0.85 g) and the stirring mixture was heated at 78°C overnight. The reaction was allowed to cool to RT and it was then extracted with EtOAc (2 x 150 mL). The combined extracts were washed with brine, dried (Na₂SO₄), filtered and evaporated in vacuo. The resulting light oil was adsorbed onto silica gel and chromatographed eluting with 30-40% EtOAc/hexanes to give 2 major spots. Fractions containing the higher R_f spot were combined and evaporated in vacuo to give 1.71 g (17%) the regioisomer as a brown oil. Fractions containing the lower R_f spot were combined and evaporated in vacuo to give 2.05 g (20%) of the title compound as a yellow solid.

[0411] Step 3: Preparation of (5Z)-5-{4-[2-hydroxy-2-(2-methoxyphenyl)ethoxy]benzylidene}-1,3-thiazolidine-2,4-dione.

[0412] To a stirring solution of 4-[2-hydroxy-2-(2-methoxyphenyl)ethoxy]benzaldehyde (1.71 g, 6.28 mmol) in absolute EtOH (50 mL) was added 2,4-thiazolidinedione (0.81g, 6.91 mmol) and piperidine (0.68 mL, 6.9 mmol), and the resulting solution was heated to reflux. The reaction was refluxed overnight and then evaporated in vacuo. The residue was dissolved in EtOAc and this solution was washed with aqueous HOAc (pH 5-6), brine, dried (Na₂SO₄), filtered and evaporated in vacuo. The residue was adsorbed onto silica gel and chromatographed on silica gel eluting with 20-40% EtOAc/DCM. Fractions containing product were combined and evaporated in vacuo to give 1.87 g (80%) of the title compound as a light yellow solid. MS (ESI-) for C₁₉H₁₇NO₅S m/z 370.1 (M-H)⁻.

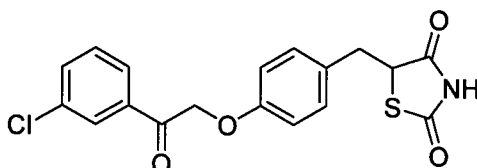
[0413] Step 4: 5-{4-[2-hydroxy-2-(2-methoxyphenyl)ethoxy]benzyl} -1,3-thiazolidine-2,4-dione.

[0414] (5Z)-5-{4-[2-hydroxy-2-(2-methoxyphenyl)ethoxy]benzylidene}-1,3-thiazolidine-2,4-dione (1.00 g, 2.69 mmol) was dissolved in THF (20 mL). Water (20 mL) was added and then sufficient additional THF was added to give a clear solution. A small crystal of cobalt chloride was added followed by 2,2'-bipyridine (95 mg, 0.61 mmol). The reaction mixture was cooled to 0 °C. NaBH₄ was added in portions until the blue color persisted. The color gradually faded and was regenerated repeatedly by small additions of borohydride and HOAc. When HPLC indicated that the reaction was complete the reaction mixture was partitioned between EtOAc and H₂O. HOAc was added until the pH of the aqueous phase was ca. 6, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried (Na₂SO₄), filtered and evaporated in vacuo. The residue was chromatographed on a small silica gel column eluting with 20% EtOAc/DCM. Fractions containing product were combined and evaporated in vacuo to give 0.63 g (63%) of the title compound as a white solid. MS (ESI-) for C₁₉H₁₉NO₅S m/z 372.1 (M-H)⁻.

[0415] Step 5: Preparation of 5-{4-[2-(2-methoxyphenyl)-2-oxoethoxy]benzyl}-1,3-thiazolidine-2,4-dione.

[0416] To a stirring solution of phosphorus pentoxide (0.30 g, 1.10 mmol) in DCM (8 mL) at 0°C was added a solution of 5-{4-[2-hydroxy-2-(2-methoxyphenyl)ethoxy]benzyl}-1,3-thiazolidine-2,4-dione (0.20 g, 0.54 mmol) in DCM (8 mL) followed by dimethyl sulfoxide (0.20 mL, 2.80 mmol). After stirring for 15 minutes, N,N-diisopropylethylamine (0.28 mL, 1.60 mmol) was added. After 45 minutes, the reaction mixture was cast into cold saturated NaHCO₃ and extracted with EtOAc (×2). The combined extracts were washed with brine, dried (Na₂SO₄), filtered and evaporated in vacuo. The residue was chromatographed on a small silica gel column eluting with 0-10% EtOAc/DCM. Fractions containing product were combined and evaporated in vacuo to give 175 mg (88%) of the title compound as a light yellow solid. MS (ESI-) for C₁₉H₁₇NO₅S m/z 370.1 (M-H)⁻.

[0417] Example 7: Preparation of 5-{4-[2-(3-chlorophenyl)-2-oxoethoxy]benzyl}-1,3-thiazolidine-2,4-dione.



[0418] Step 1: 2-(3-chlorophenyl)oxirane.

[0419] To a solution of m-chlorostyrene (5.70 g, 41.0 mmol) and acetic acid (2.33 mL, 40.9 mmol) in dioxane (33 mL) and H₂O (78 mL) at 0°C was added N-bromosuccinimide (8.02 g,

45.0 mmol) in three portions. The reaction was allowed to warm to RT. After 4 hours, 2N NaOH (60 mL) was added and the reaction was allowed to stir at RT overnight. The reaction mixture was partitioned between water and EtOAc, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried (Na₂SO₄), filtered and evaporated in vacuo to give 6.20 g of a slightly tinted oil which was used without further purification.

[0420] *Step 2: 4-[2-(3-chlorophenyl)-2-hydroxyethoxy]benzaldehyde.*

[0421] To a stirring solution of 2-(3-chlorophenyl)oxirane (6.20 g, 40.0 mmol) in toluene (65 mL) was added 4-hydroxybenzaldehyde (7.30 g, 60.0 mmol), 1M NaOH (65 mL) and PEG4000 (polyethylene glycol, 0.85 g) and the stirring mixture was heated at 78°C for three hours. The reaction was allowed to cool to RT and then extracted with EtOAc (2 × 150 mL). The combined extracts were washed with brine, dried (Na₂SO₄), filtered and evaporated in vacuo. The resulting light brown oil was adsorbed onto silica gel and chromatographed eluting with 25-40% EtOAc/hexanes. There are 2 major spots. Fractions containing the higher R_f spot were combined and evaporated in vacuo to give 1.08 g (10%) of the desired product as a colorless oil. Fractions containing the lower R_f spot were combined and evaporated in vacuo to give 0.95 g (8%) of the regioisomer as a colorless oil, 44B. Some starting epoxide (2.85 g) was also recovered.

[0422] *Step 3: 5-{4-[2-(3-chlorophenyl)-2-hydroxyethoxy]benzylidene}-1,3-thiazolidine-2,4-dione.*

[0423] To a stirring solution of 4-[2-(3-chlorophenyl)-2-hydroxyethoxy]benzaldehyde (1.08 g, 3.90 mmol) in absolute EtOH (50 mL) was added 2,4-thiazolidinedione (0.50 g, 4.29 mmol) and piperidine (0.42 mL, 4.3 mmol), and the resulting solution was heated to reflux and then stirred overnight at room temperature. The reaction mixture was evaporated in vacuo and the residue was dissolved in EtOAc. This solution was washed with aqueous HOAc (pH 5-6), brine, dried (Na₂SO₄), filtered and evaporated in vacuo. The residue was adsorbed onto silica gel and chromatographed eluting with 10-20% EtOAc/DCM. Fractions containing product were combined and evaporated in vacuo to give 1.31 g (89%) of the product as a light yellow solid. MS (ESI+) for C₁₈H₁₄ClNO₄S m/z 375.0 (M+H)⁺. MS (ESI-) for C₁₈H₁₄ClNO₄S m/z 374.1 (M-H)⁻.

[0424] *Step 4: 5-{4-[2-(3-chlorophenyl)-2-hydroxyethoxy]benzyl}-1,3-thiazolidine-2,4-dione.*

[0425] 5-{4-[2-(3-chlorophenyl)-2-hydroxyethoxy]benzylidene}-1,3-thiazolidine-2,4-dione (0.74 g, 2.00 mmol) was dissolved in THF (20 mL). Water (20 mL) was added and then

more THF was added until all solids dissolved. A small crystal of cobalt chloride was added, followed by 2,2'-bipyridine (69 mg, 0.44 mmol). The reaction mixture was cooled to 0°C. NaBH₄ was added in portions until the blue color persisted. The color gradually faded and was regenerated repeatedly by small additions of borohydride and HOAc. When HPLC indicated that the reaction was complete, the reaction mixture was partitioned between EtOAc and H₂O. HOAc was added until the pH of the aqueous phase was ca. 6, and then the aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried (Na₂SO₄), filtered and evaporated in vacuo. The residue was chromatographed on a small silica gel column eluting with 0-10% EtOAc/DCM. Fractions containing product were combined and evaporated in vacuo to give 0.44 g (59%) of a sticky yellow solid. MS (ESI-) for C₁₈H₁₆ClNO₄S m/z 376.1 (M-H)⁻.

[0426] Step 5: Preparation of 5-{4-[2-(3-chlorophenyl)-2-oxoethoxy]benzyl}-1,3-thiazolidine-2,4-dione.

[0427] To a stirring solution of phosphorus pentoxide (0.38 g, 1.30 mmol) in DCM (8 mL) at 0°C was added a solution of 5-{4-[2-(3-chlorophenyl)-2-hydroxyethoxy]benzyl}-1,3-thiazolidine-2,4-dione (0.25 g, 0.66 mmol) in DCM (8 mL) followed by dimethyl sulfoxide (0.23 mL, 3.30 mL). After stirring for 15 minutes N,N-diisopropylethylamine (0.34 mL, 2.00 mmol) was added. After 45 minutes the reaction was poured into cold saturated NaHCO₃ and the mixture was extracted with EtOAc (×2). The combined extracts were washed with brine, dried (Na₂SO₄), filtered and evaporated in vacuo. The residue was chromatographed on a small silica gel column eluting with 0-15% EtOAc/DCM. Fractions containing product were combined and evaporated in vacuo to give 117 mg (47%) of a white solid. MS (ESI-) for C₁₈H₁₄ClNO₄S m/z 374.1 (M-H)⁻.

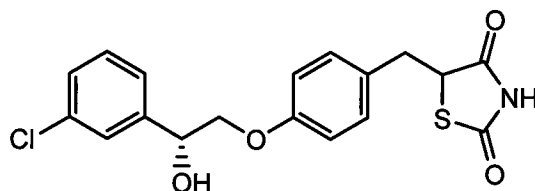
[0428] Example 8: Preparation of 5-{4-[2-(2-chlorophenyl)-2-oxoethoxy]benzyl}-1,3-thiazolidine-2,4-dione.

[0429] The title compound can be prepared as described in Example 7 using appropriate starting materials, such as 2-(2-chlorophenyl)oxirane.

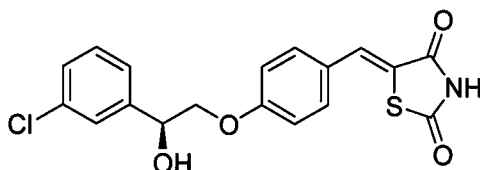
[0430] Example 9: Preparation of 5-{4-[2-(4-methoxyphenyl)-2-oxoethoxy]benzyl}-1,3-thiazolidine-2,4-dione.

[0431] The title compound was prepared as described in Examples 5 and 6 using appropriate starting materials, such as 2-(4-methoxyphenyl)oxirane. MS (ESI-) for C₁₉H₁₇NO₅S 370.2 m/z (M-1).

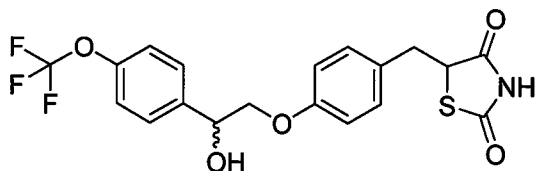
[0432] Physical Data for Representative Compounds

[0433] ¹H-NMR Data (400mHz)

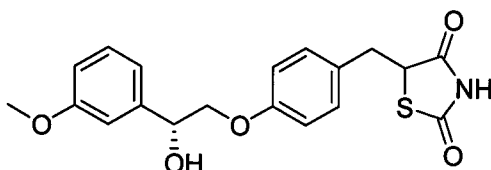
¹H-NMR (DMSO-*d*₆) δ: 12.00 (s, 1H), 7.50 (s, 1H), 7.42-7.32 (m, 3H), 7.13 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.77 (d, *J* = 5.0 Hz, 1H), 4.92 (d, *J* = 6.2 Hz, 1H), 4.86 (dd, *J* = 8.9, 4.3 Hz, 1H), 4.00 (m, 2H), 3.29 (dd, *J* = 14.3, 4.3 Hz, 1H), 3.05 (dd, *J* = 14.2, 9.0 Hz, 1H).



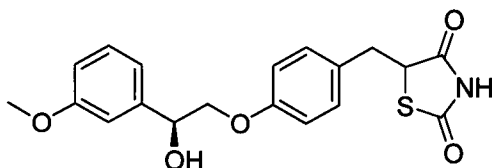
¹H-NMR (DMSO-*d*₆) δ: 12.52 (s, 1H), 7.75 (s, 1H), 7.54 (m, 3H), 7.44-7.33 (m, 3H), 7.11 (d, *J* = 8.91 Hz, 2H), 5.84 (d, *J* = 4.77 Hz, 1H), 4.97 (m, 1H), 4.12 (m, 2H).



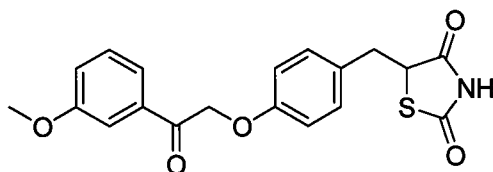
¹H-NMR (CDCl₃) δ: 8.32 (brs, 1H), 7.50 (d, *J* = 8.50 Hz, 2H), 7.26 (m, 2H), 7.17 (m, 2H), 6.88 (m, 2H), 5.15 (dd, *J* = 8.71, 3.11 Hz, 1H), 4.51 (dd, *J* = 9.23, 4.04 Hz, 1H), 4.09 (dd, *J* = 9.64, 3.21 Hz, 1H), 3.45 (dd, *J* = 14.1, 3.94 Hz, 1H), 3.13 (dd, *J* = 14.2, 9.23 Hz, 1H), 2.87 (brs, 1H).



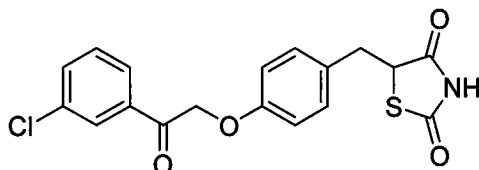
¹H-NMR (CDCl₃) δ: 8.35 (brs, 1H), 7.23 (t, *J* = 8.09, 1H), 7.07 (d, *J* = 8.71 Hz, 2H), 6.94 (m, 2H), 6.81 (m, 3H), 5.03 (dd, *J* = 8.60, 2.80 Hz, 1H), 4.42 (dd, *J* = 9.33, 3.94 Hz, 1H), 4.02 (m, 1H), 3.93 (t, *J* = 9.23 Hz, 1H), 3.76 (s, 3H), 3.36 (dd, *J* = 14.20, 3.84 Hz, 1H), 3.04 (dd, *J* = 14.10, 9.33 Hz, 1H), 2.75 (brs, 1H).



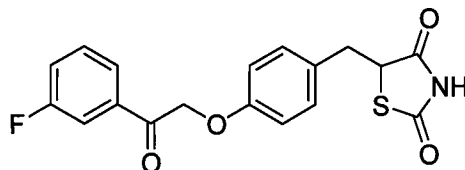
¹H-NMR (CDCl₃) δ: 8.42 (brs, 1H), 7.23 (t, *J* = 7.98 Hz, 1H), 7.07 (d, *J* = 8.71 Hz, 2H), 6.94 (m, 2H), 6.82-6.78 (m, 3H), 5.03 (dd, *J* = 8.71, 2.90 Hz, 1H), 4.41 (dd, *J* = 9.33, 3.94 Hz, 1H), 4.02 (m, 1H), 3.93 (t, *J* = 9.12 Hz, 1H), 3.76 (s, 3H), 3.36 (dd, *J* = 14.10, 3.94 Hz, 1H), 3.03 (dd, *J* = 14.31, 9.33 Hz, 1H), 2.77 (brs, 1H).



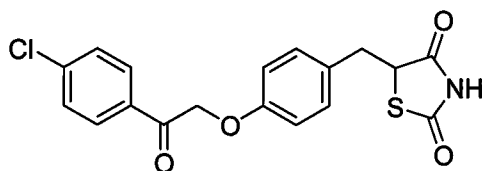
$^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 12.03 (brs, 1H), 7.62 (d, $J = 7.67$ Hz, 1H), 7.49 (m, 2H), 7.27 (dd, $J = 8.19, 2.38$ Hz, 1H), 7.16 (d, $J = 8.50$ Hz, 2H), 6.91 (d, $J = 8.50$ Hz, 2H), 5.55 (s, 2H), 4.88 (dd, $J = 9.12, 4.35$ Hz, 1H), 3.84 (s, 3H), 3.33-3.29 (m, 1H), 3.05 (dd, $J = 14.31, 9.12$ Hz, 1H).



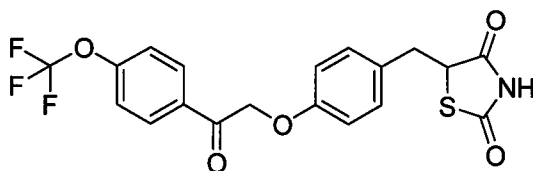
$^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 12.02 (brs, 1H), 8.05 (t, $J = 1.66$ Hz, 1H), 7.96 (d, $J = 7.88$ Hz, 1H), 7.77 (m, 1H), 7.61 (t, $J = 7.88$ Hz, 1H), 7.16 (d, $J = 8.71$ Hz, 2H), 6.93 (d, $J = 8.71$ Hz, 2H), 5.57 (s, 2H), 4.88 (dd, $J = 9.12, 4.35$ Hz, 1H), 3.31 (m, 1H), 3.06 (dd, $J = 14.20, 9.23$ Hz, 1H).



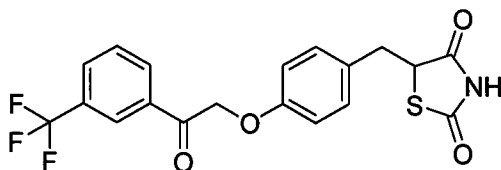
$^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 12.02 (brs, 1H), 7.83 (m, 2H), 7.59 (m, 2H), 7.16 (d, $J = 8.71$ Hz, 2H), 6.93 (d, $J = 8.71$ Hz, 2H), 5.56 (s, 2H), 4.88 (dd, $J = 9.12, 4.35$ Hz, 1H), 3.33-3.29 (m, 1H), 3.06 (dd, $J = 14.10, 9.12$ Hz, 1H).



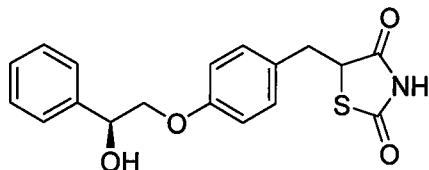
$^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 12.02 (s, 1H), 8.03 (d, $J = 8.71$ Hz, 2H), 7.65 (d, $J = 8.50$ Hz, 2H), 7.15 (d, $J = 8.50$ Hz, 2H), 6.92 (d, $J = 8.71$ Hz, 2H), 5.54 (s, 2H), 4.88 (dd, $J = 9.12, 4.35$ Hz, 1H), 3.33-3.29 (m, 1H), 3.05 (dd, $J = 14.10, 9.12$ Hz, 1H).



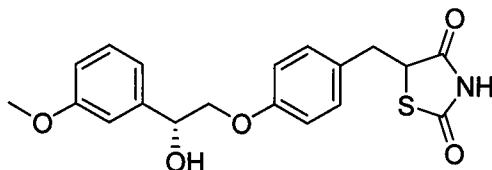
$^1\text{H-NMR}$ (CDCl_3) δ : 8.08 (m, 3H), 7.34 (d, $J = 8.09$ Hz, 2H), 7.17 (d, $J = 8.71$ Hz, 2H), 6.90 (d, $J = 8.71$ Hz, 2H), 5.23 (s, 2H), 4.51 (dd, $J = 9.43, 3.84$ Hz, 1H), 3.46 (dd, $J = 14.10, 3.94$ Hz, 1H), 3.13 (dd, $J = 14.20, 9.43$ Hz, 1H), 1.60 (brs, 1H).



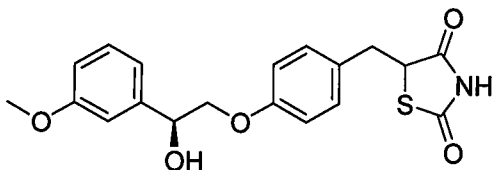
$^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 12.20 (s, 1H), 8.30 (m, 2H), 8.07 (d, $J = 7.88$ Hz, 1H), 7.82 (t, $J = 7.88$ Hz, 1H), 7.16 (d, $J = 8.71$ Hz, 2H), 6.95 (d, $J = 8.71$ Hz, 2H), 5.64 (s, 2H), 4.88 (dd, $J = 9.33, 4.35$ Hz, 1H), 3.34-3.29 (m, 1H), 3.06 (dd, $J = 14.10, 9.12$ Hz, 1H).



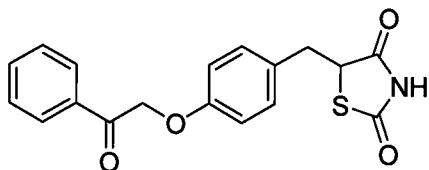
$^1\text{H-NMR}$ (CDCl_3) δ : 8.42 (brs, 1H), 7.38 (m, 5H), 7.15 (d, $J = 8.50$ Hz, 2H), 6.88 (d, $J = 8.50$ Hz, 2H), 5.14 (dd, $J = 8.81, 3.01$ Hz, 1H), 4.50 (dd, $J = 9.33, 3.94$ Hz, 1H), 4.11 (m, 1H), 4.01 (t, $J = 9.23$ Hz, 1H), 3.45 (dd, $J = 14.20, 3.84$ Hz, 1H), 3.12 (dd, $J = 14.20, 9.43$ Hz, 1H), 2.84 (brs, 1H).



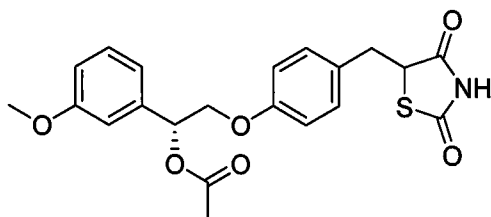
$^1\text{H-NMR}$ (CDCl_3) δ : 8.35 (brs, 1H), 7.23 (t, $J = 8.09$, 1H), 7.07 (d, $J = 8.71$ Hz, 2H), 6.94 (m, 2H), 6.81 (m, 3H), 5.03 (dd, $J = 8.60, 2.80$ Hz, 1H), 4.42 (dd, $J = 9.33, 3.94$ Hz, 1H), 4.02 (m, 1H), 3.93 (t, $J = 9.23$ Hz, 1H), 3.76 (s, 3H), 3.36 (dd, $J = 14.20, 3.84$ Hz, 1H), 3.04 (dd, $J = 14.10, 9.33$ Hz, 1H), 2.75 (brs, 1H).



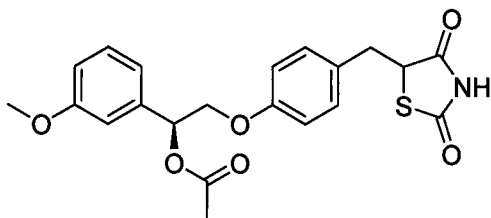
$^1\text{H-NMR}$ (CDCl_3) δ : 8.42 (brs, 1H), 7.23 (t, $J = 7.98$ Hz, 1H), 7.07 (d, $J = 8.71$ Hz, 2H), 6.94 (m, 2H), 6.82-6.78 (m, 3H), 5.03 (dd, $J = 8.71, 2.90$ Hz, 1H), 4.41 (dd, $J = 9.33, 3.94$ Hz, 1H), 4.02 (m, 1H), 3.93 (t, $J = 9.12$ Hz, 1H), 3.76 (s, 3H), 3.36 (dd, $J = 14.10, 3.94$ Hz, 1H), 3.03 (dd, $J = 14.31, 9.33$ Hz, 1H), 2.77 (brs, 1H).



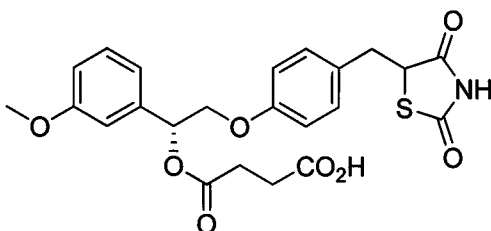
$^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 12.03 (brs, 1H), 8.02 (m, 2H), 7.69 (t, $J = 7.36$ Hz, 1H), 7.57 (t, $J = 7.67$ Hz, 2H), 7.15 (d, $J = 8.50$ Hz, 2H), 6.91 (d, $J = 8.50$ Hz, 2H), 5.56 (s, 2H), 4.88 (dd, $J = 9.23, 4.25$ Hz, 1H), 3.31 (m, 2H), 3.05 (dd, $J = 14.02, 9.23$ Hz, 1H).



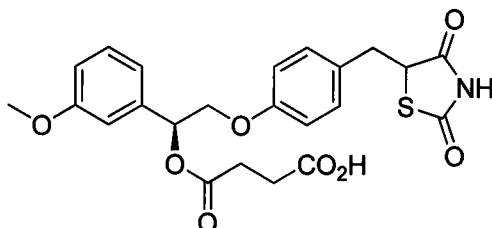
$^1\text{H-NMR}$ (CDCl_3): δ = 8.57(brs, 1H), 7.28(m, 1H), 7.16(m, 1H), 6.99(m, 2H), 6.87(m, 3H), 6.12(dd, J =7.8, 3.6Hz, 1H), 4.49(dd, J =9.3, 3.9Hz, 1H), 4.25(m, 1H), 4.13(dd, J =10.5, 3.6Hz, 1H), 3.83(s, 3H), 3.45(dd, J =14.2, 3.8Hz, 1H), 3.10(dd, J =14.0, 9.6Hz, 1H), 2.14(s, 3H).



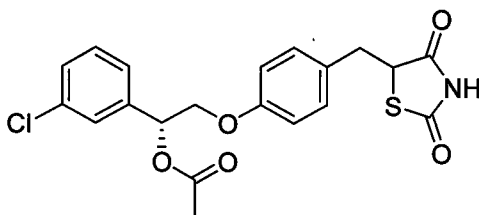
$^1\text{H-NMR}$ (CDCl_3): δ = 8.31(brs, 1H), 7.29(m, 1H), 7.17(m, 1H), 6.99(m, 2H), 6.88(m, 3H), 6.12(dd, J =7.8, 3.4Hz, 1H), 4.50(dd, J =9.4, 3.8Hz, 1H), 4.25(m, 1H), 4.13(dd, J =10.4, 3.7Hz, 1H), 3.83(s, 3H), 3.45(dd, J =14.2, 3.8Hz, 1H), 3.11(dd, J =14.1, 9.3Hz, 1H), 2.14(s, 3H).



$^1\text{H-NMR}$ (CDCl_3): δ = 8.65(m, 1H), 7.29(m, 1H), 7.13(m, 1H), 6.97(m, 2H), 6.86(m, 3H), 6.13(m, 1H), 4.49(dd, J =9.1, 3.9Hz, 1H), 4.24(m, 1H), 4.14(m, 1H), 3.82(s, 3H), 3.40(m, 1H), 3.12(dd, J =14.2, 9.0Hz, 1H), 2.69(m, 4H).

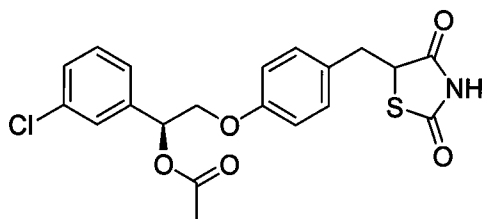


$^1\text{H-NMR}$ (CDCl_3): δ = 8.78(brs, 1H), 7.29(m, 1H), 7.13(m, 1H), 6.97(m, 2H), 6.85(m, 3H), 6.12(m, 1H), 4.47(dd, J =8.8, 3.8Hz, 1H), 4.20(m, 2H), 3.81(s, 3H), 3.36(m, 1H), 3.13(m, 1H), 2.68(m, 4H).

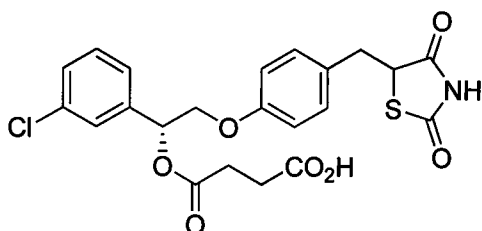


$^1\text{H-NMR}$ (CDCl_3): δ = 8.74(brs, 1H), 7.42(s, 1H), 7.31(m, 2H), 7.15(d, J =8.7Hz, 2H), 6.85(d, J =8.7Hz, 2H), 6.10((dd, J =7.4, 4.0Hz, 1H), 4.50(dd, J =9.3, 3.9Hz, 1H), 4.24(M, 1H),

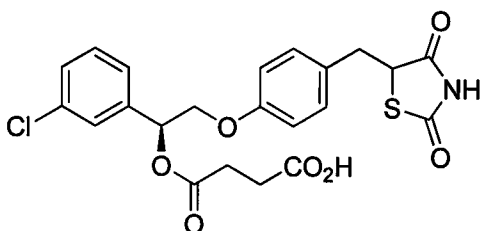
4.13(dd, J=10.4, 4.2Hz, 1H), 3.45(dd, J=14.1, 3.7Hz, 1H), 3.10(dd, J=14.0, 9.4Hz, 1H), 2.15(s, 3H).



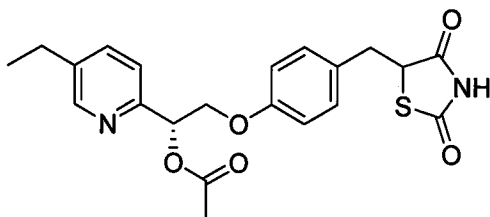
¹H-NMR (CDCl₃): δ = 8.67(brs, 1H), 7.42(s, 1H), 7.30(m, 2H), 7.15(d, J=7.2Hz, 2H), 6.85(d, J=8.5Hz, 2H), 6.10(dd, J=7.4, 4.0Hz, 1H), 4.50(dd, J=9.3, 3.9Hz, 1H), 4.24(m, 1H), 4.13(dd, J=10.4, 4.2Hz, 1H), 3.45(dd, J=14.2, 3.8Hz, 1H), 3.11(dd, J=14.2, 9.4Hz, 1H), 2.15(s, 3H).



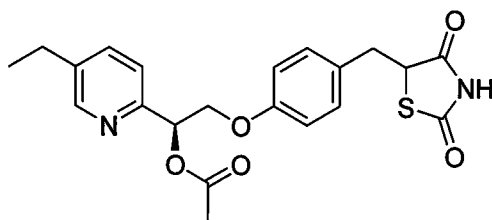
¹H-NMR (CDCl₃): δ = 8.94(d, J=4.8Hz, 1H), 7.40(s, 1H), 7.30(m, 3H), 7.14(d, J=8.5Hz, 2H), 6.84(d, J=8.5Hz, 2H), 6.11(m, 1H), 4.49(dd, J=9.0, 3.8Hz, 1H), 4.23(m, 1H), 4.13(m, 1H), 3.40(dd, J=14.1, 3.5Hz, 1H), 3.13(dd, J=14.1, 9.1Hz, 1H), 2.71(m, 4H).



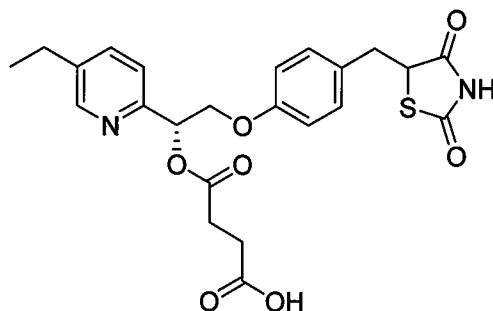
¹H-NMR (CDCl₃): δ = 8.88(d, J=6.4Hz, 1H), 7.40(s, 1H), 7.30(m, 3H), 7.14(d, J=8.5Hz, 2H), 6.84(d, J=7.7Hz, 2H), 6.11(m, 1H), 4.49(dd, J=9.1, 3.9Hz, 1H), 4.24(m, 1H), 4.14(m, 1H), 3.40(dd, J=14.3, 3.7Hz, 1H), 3.13(dd, J=14.2, 9.0Hz, 1H), 2.70(m, 4H).



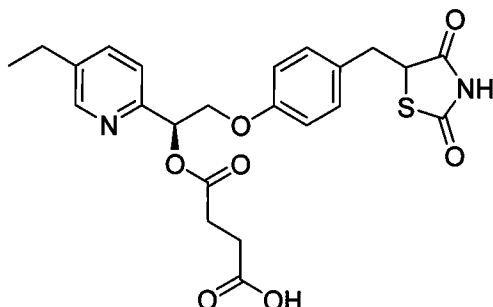
¹H-NMR (CDCl₃): δ = 9.34(brs, 1H), 8.46, s, 1H), 7.56(dd, J=8.0, 2.0Hz, 1H), 7.36(d, J=8.0, 1H), 7.13(d, J=7.1Hz, 2H), 6.86(dd, J=8.6, 1.8Hz, 2H), 6.18(dd, J=6.4, 4.1Hz, 1H), 4.48(m, 1H), 4.41(m, 1H), 3.44(m, 1H), 3.09(m, 1H), 2.67(q, J=7.6Hz, 2H), 2.15(s, 3H), 1.26(t, J=7.6Hz, 3H).



$^1\text{H-NMR}$ (CDCl_3): δ = 8.85(brs, 1H), 8.46(d, J =1.7Hz, 1H), 7.56(dd, J =8.0, 2.0Hz, 1H), 7.37(d, J =8.1Hz, 1H), 7.13(d, J =8.7Hz, 2H), 6.86(d, J =7.1Hz, 2H), 6.19(dd, J =6.4, 4.2Hz, 1H), 4.49(dd, J =9.1, 3.5Hz, 1H), 4.41(m, 2H), 3.44(m, 1H), 3.10(m, 1H), 2.67(q, J =7.5Hz, 2H), 2.16(s, 3H), 1.26(t, 3H).



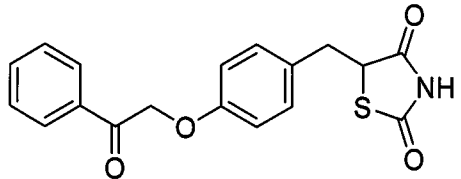
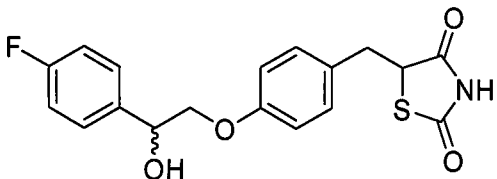
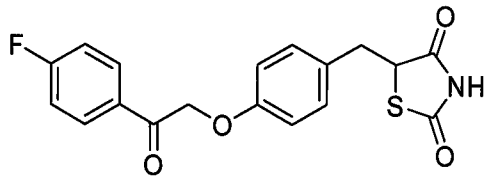
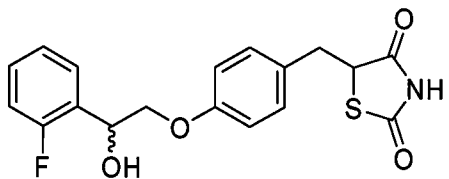
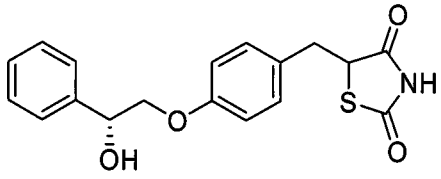
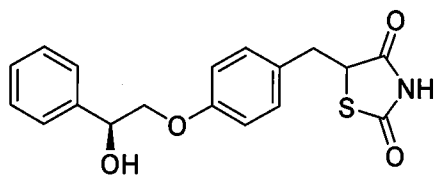
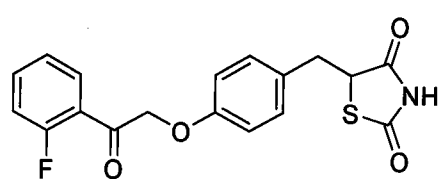
$^1\text{H-NMR}$ (CDCl_3): δ = 8.63(brs, 1H), 8.45(s, 1H), 7.77(t, J =7.6Hz, 1H), 7.56(dd, J =7.9, 1.9Hz, 1H), 7.10(d, J =8.3Hz, 2H), 6.83(d, J =8.5Hz, 2H), 6.19(t, J =5.1Hz, 1H), 4.46(dd, J =9.0, 3.8Hz, 1H), 4.39(m, 2H), 3.38(dd, J =14.2, 3.8Hz, 1H), 3.10(dd, J =14.2, 9.2Hz, 1H), 2.68(m, 6H), 1.24(t, J =7.6Hz, 3H).

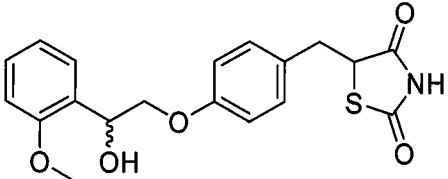
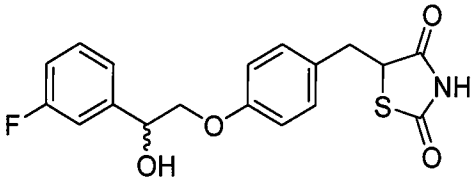
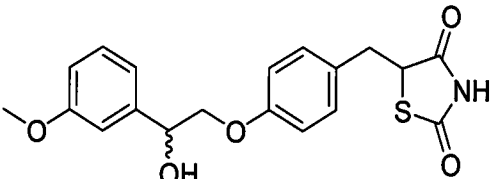
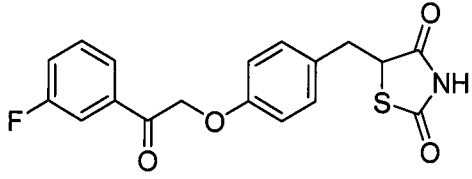
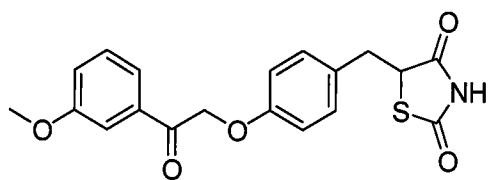
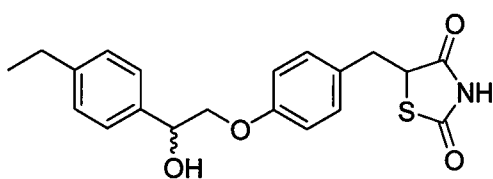
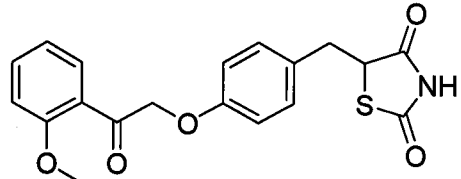


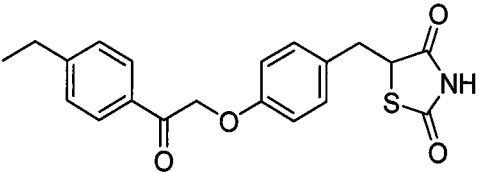
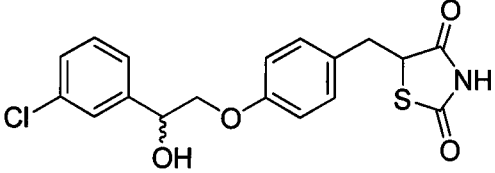
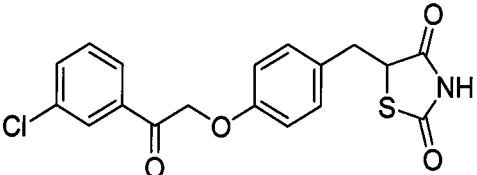
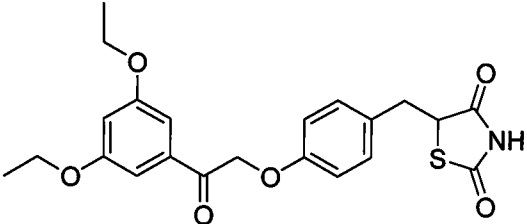
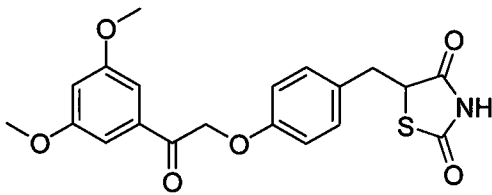
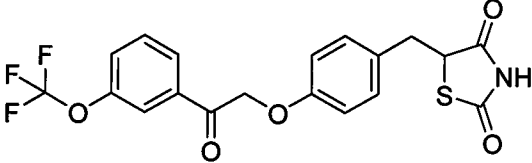
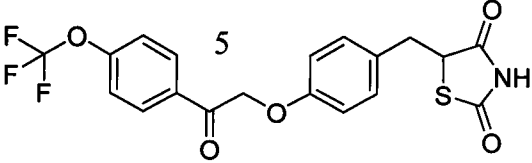
$^1\text{H-NMR}$ (CDCl_3): δ = 9.20(brs, 1H), 8.48(s, 1H), 7.60(d, J =1.7Hz, 1H), 7.40(d, J =8.1Hz, 1H), 7.12(dd, J =8.5, 1.7Hz, 2H), 6.84(dd, J =8.7, 2.7Hz, 2H), 6.20(m, 1H), 4.49(dd, J =8.3, 4.2Hz, 1H), 4.40(m, 2H), 3.33(m, 1H), 3.18(m, 1H), 2.71(m, 6H), 1.25(t, J =7.6Hz, 3H).

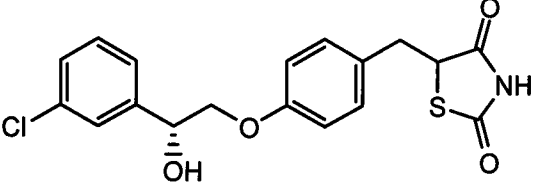
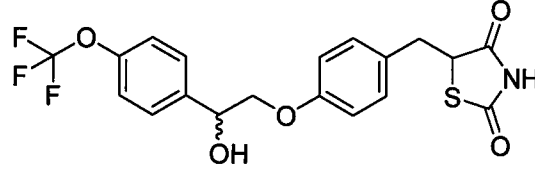
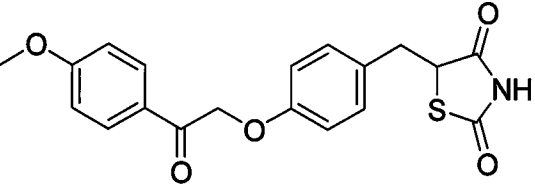
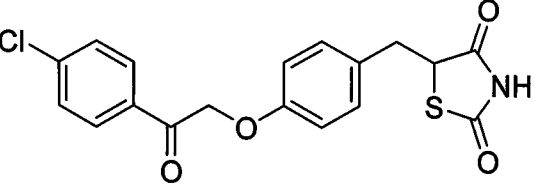
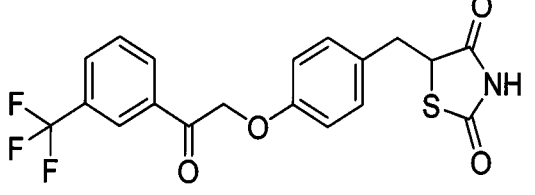
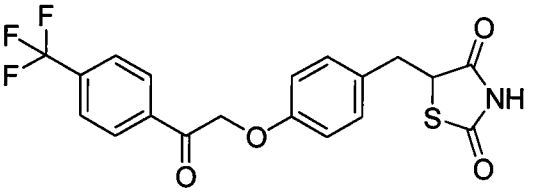
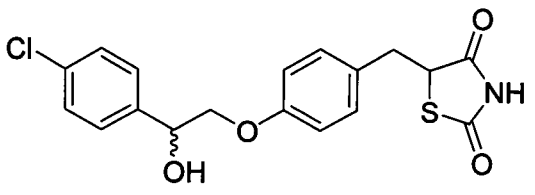
[0434] Mass Spectra

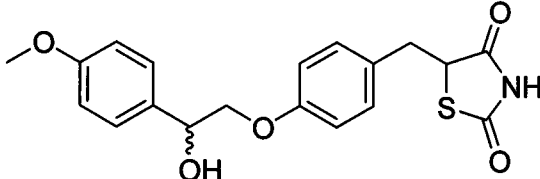
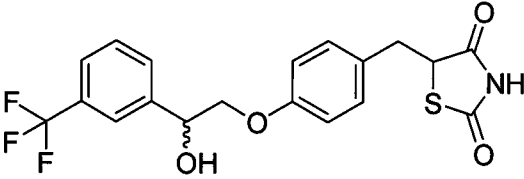
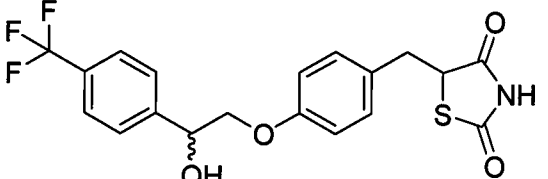
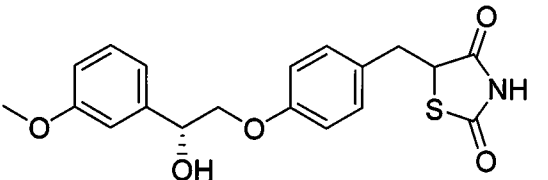
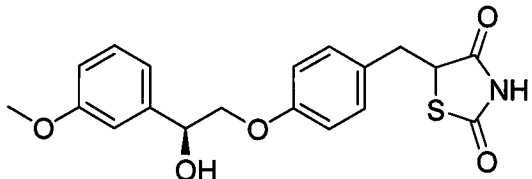
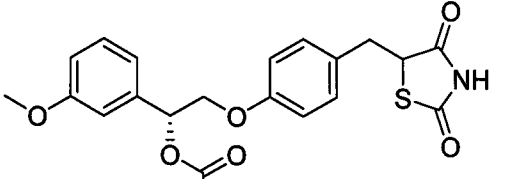
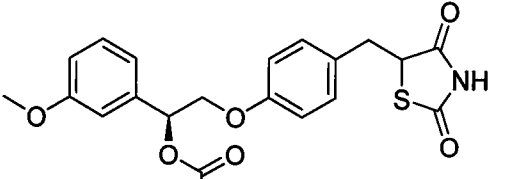
Structure	Calc. MW	Found MW
	343.4	ES+ 366.0 (M+Na) ES- 342.1 (M-1)

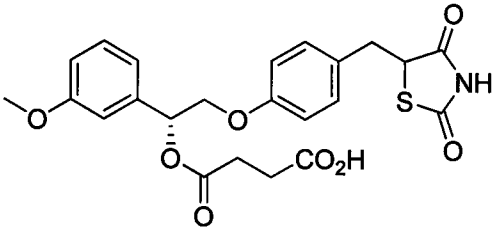
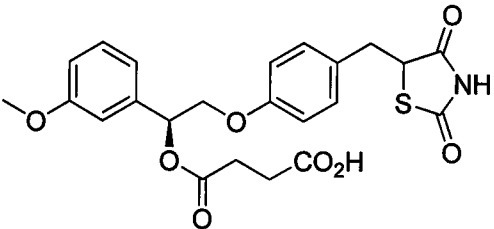
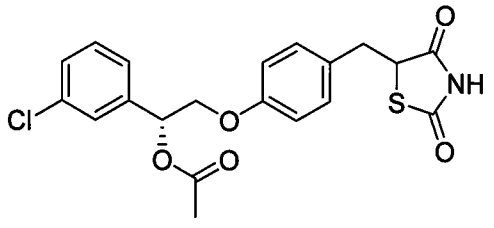
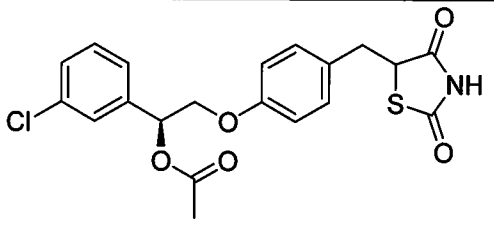
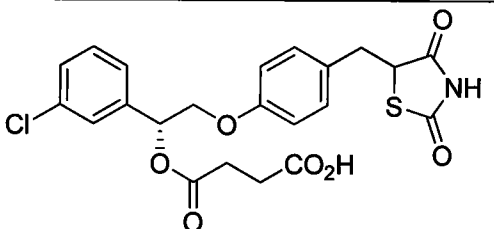
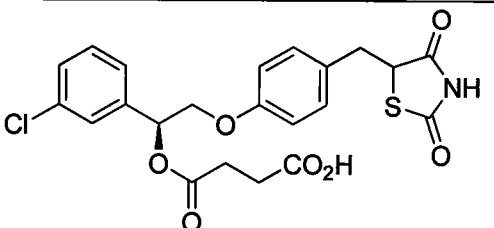
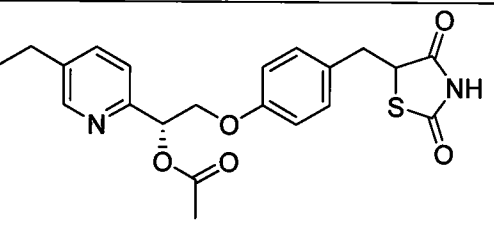
Structure	Calc. MW	Found MW
	341.38	ES+ 363.9 (M+Na) ES- 340.0 (M-1)
	361.39	ES- 360.1 (M-1)
	359.37	ES+ 360.2 (M+1) ES- 358.2 (M-1)
	361.39	ES- 360.1 (M-1)
	343.4	ES- 342.2 (M-1)
	343.4	ES- 342.1 (M-1)
	359.37	ES- 358.0 (M-1)

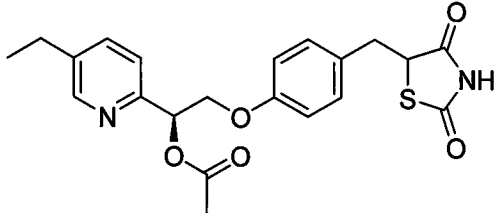
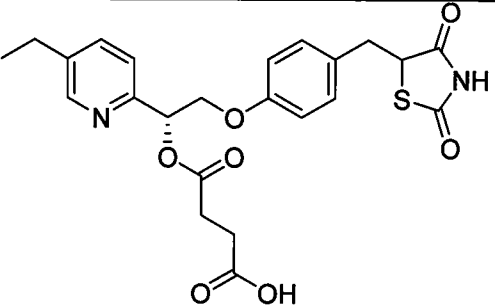
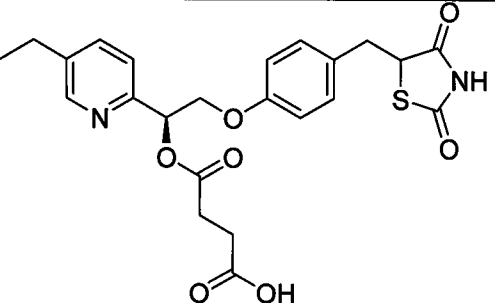
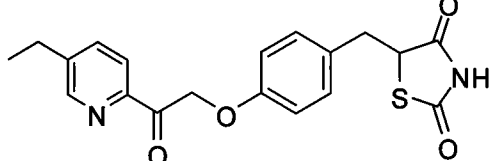
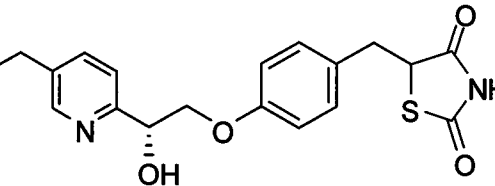
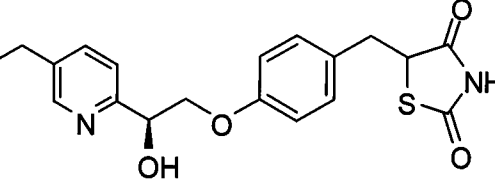
Structure	Calc. MW	Found MW
	373.42	ES- 372.1 (M-1)
	361.39	ES+ 384.0 (M+Na) ES- 360.1 (M-1)
	373.42	ES- 372.0 (M-1)
	359.37	ES- 358.2 (M-1)
	371.41	ES+ 372.0 (M+1) ES- 370.1 (M-1)
	371.45	ES- 370.2 (M-1)
	371.41	ES- 370.1 (M-1)

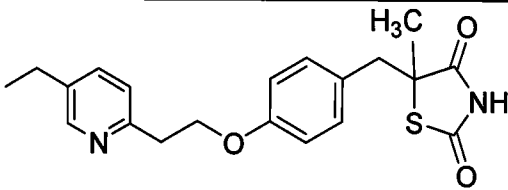
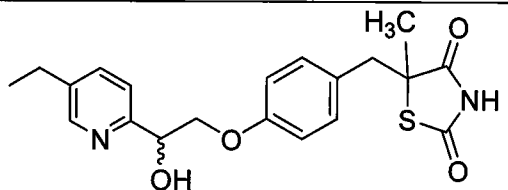
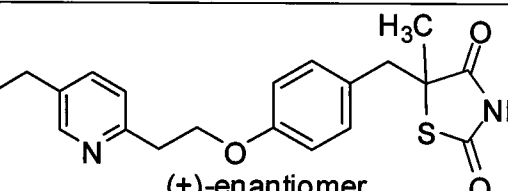
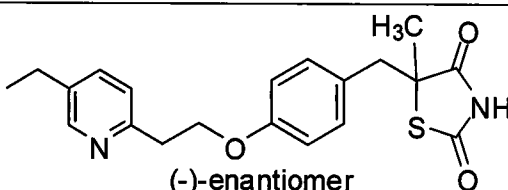
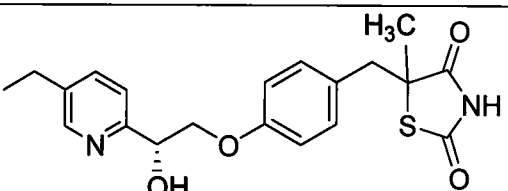
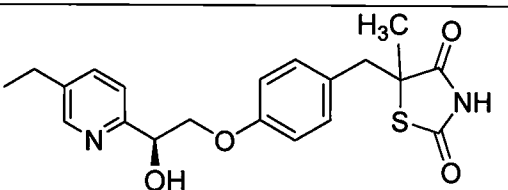
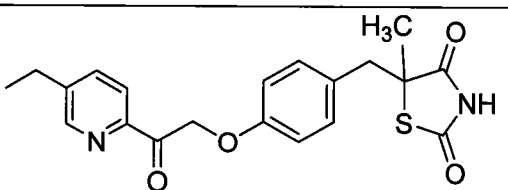
Structure	Calc. MW	Found MW
	369.43	ES+ 370.0 (M+1) ES- 368.1 (M-1)
	377.84	ES- 376.0 (M-1)
	375.83	ES- 374.0 (M-1)
	429.49	ES+ 430.1 (M+1) ES- 428.2 (M-1)
	401.43	ES+ 402.1 (M+1) ES- 400.2 (M-1)
	425.38	ES+ 426.0 (M+1) ES- 424.1 (M-1)
	425.38	ES+ 425.9 (M+1) ES- 424.2 (M-1)

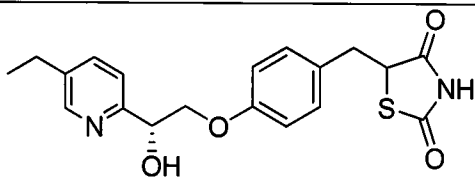
Structure	Calc. MW	Found MW
	377.84	ES- 376.2 (M+1)
	427.39	ES- 426.3 (M+)
	371.41	ES- 370.2 (M-1)
	375.83	ES+ 376.2 (M+1)
	409.38	ES- 408.3 (M-1)
	409.38	ES- 408.1 (M-1)
	377.84	ES- 376.1 (M-1)

Structure	Calc. MW	Found MW
	373.42	ES- 372.1 (M-1)
	411.39	ES- 410.2 (M-1)
	411.39	ES- 410.2 (M-1)
	373.42	ES- 372.1 (M-1)
	373.42	ES- 372.1 (M-1)
	415.46	ES- 414.10 (M-1)
	415.46	ES- 414.1 m/z (M-1)

Structure	Calc. MW	Found MW
	473.5	ES- 472.0 m/z (M-1)
	473.5	ES- 472.0 m/z (M-1)
	419.88	ES- 418.0 m/z (M-1)
	419.88	ES- 418 m/z (M-1)
	477.19	ES- 476.0 m/z (M-1)
	477.19	ES- 476.0 m/z (M-1)
	414.47	ES+ 415.0 m/z (M+1); ES- 413.0 m/z (M-1)

Structure	Calc. MW	Found MW
	414.47	ES+ 415.0 m/z (M-1); ES- 413.0 m/z (M-1)
	472.51	ES+ 473.0 m/z (M+1); ES- 471.0 m/z (M-1)
	472.51	ES+ 472.9 m/z (M+1) ES- 471.0 m/z (M-1)
	370.42	ES +371.1 m/z (M+1) ES - 369.1 (M-1)
	372.11	ES +373.1 m/z (M+1) ES - 371.1 (M-1)
	372.11	ES +373.0 m/z (M+1) ES - 371.1 (M-1)

Structure	Calc. MW	Found MW
	370.47	ES+ 371.2 m/z (M+1) ES- 369.2 (M-1)
	386.46	ES +387.3 m/z (M+1) ES - 385.3 (M-1)
 (+)-enantiomer	370.47	ES +371.2 m/z (M+1) ES - 369.2 (M-1)
 (-)-enantiomer	370.47	ES +371.2 m/z (M+1) ES - 369.2 (M-1)
	386.46	ES +387.3 m/z (M+1) ES - 385.3 (M-1)
	386.46	ES +387.2 m/z (M+1) ES - 385.2 (M-1)
	384.45	ES +385.1 m/z (M+1) ES - 383.1 (M-1)

Structure	Calc. MW	Found MW
	386.46	ES+ 373.2 (M+1) ES- 371.2 (M-1)

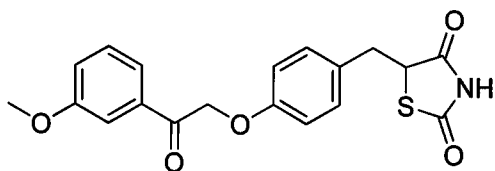
[0435] Example 10: Preparation of Co-Crystals.

[0436] Co-Crystal A:

[0437] To caffeine (0.194g, 1mmol) and 5-(4-(2-(5-ethylpyridin-2-yl)-2-oxoethoxy)benzyl)-1,3-thiazolidine-2,4-dione (0.370g, 1mmol) was added acetonitrile (20mL). The mixture was warmed in a 75 °C oil bath until the solids dissolved. Warming was continued for about 10 minutes, then the solution was filtered and allowed to cool to room temperature. The solvent was allowed to evaporate until crystallization was complete. Co-crystalline solid was isolated by filtration and was dried in vacuo. The melting point of the resulting crystalline material was measure to be from about 123°C to about 131°C. Note that melting point for pure caffeine is reported to be from about 234° C to about 236° C, and the melting point for pure 5-(4-(2-(5-ethylpyridin-2-yl)-2-oxoethoxy)benzyl)-1,3-thiazolidine-2,4-dione was measured to be from about 140°C to about 142° C.

[0438] Co-Crystal B:

[0439] To caffeine (0.194g, 1mmol) and 5-(4-(2-(3-methoxyphenyl)-2-oxoethoxy)benzyl)thiazolidine-2,4-dione having the structure:



(0.371g, 1mmol) is added acetonitrile (20mL). The mixture is warmed in a 75 °C oil bath until the solids dissolve. Warming continues for about 10 minutes, and the solution is filtered and cooled to room temperature. The solvent is evaporated until crystallization is complete. Co-crystalline solid is isolated by filtration and dries in vacuo.

[0440] Example 11: Salts.

[0441] A compound of Formula I may be converted to a salt by dissolving the compound in a solvent in which the alkali earth metal salt of the organic compound is insoluble or is only sparingly soluble; adding one or more molar equivalents of a base, such as NaOH, KOH, or the like, to the solvent containing the dissolved compound of Formula I to form a precipitate

of the organic compound salt; and collecting the precipitate using filtration, decanting or some similar method to produce the salt of the organic compound of Formula I in a pure form.

[0442] Alternatively, a compound of Formula I may be converted to a salt by dissolving the compound in a solvent in which the salt of the organic compound is also soluble; adding one or more molar equivalents of a base with a relatively low boiling point, such as NaOH, KOH, or the like, to the solvent containing the dissolved compound of Formula I; and then evaporating the solvent and any excess base contained in the solution to produce the salt of the organic compound in a pure form.

[0443] **Example 11A: Sodium 5-{4-[2-(5-ethylpyridin-2-yl)-2-oxoethoxy]benzyl}-2,4-dioxo-1,3-thiazolidin-3-ide.**

[0444] 5-{4-[2-(5-ethylpyridin-2-yl)-2-oxoethoxy]benzyl}-1,3-thiazolidine-2,4-dione (Compound A) (100mg, 0.27mmol) was suspended in anhydrous abs. EtOH (3ml) and the mixture was heated with a heat gun until all solids dissolved. Added sodium ethoxide (18mg, 0.27mmol). Stirred for 1 hour. Evaporated in vacuo and dried under high vac. (ca. 50°C) for 2 hours to give a white solid (110mg, 100%).

[0445] Analytical Calc. for C₁₉H₁₇N₂NaO₄S plus 2.38% H₂O: C, 56.77; H, 4.53; N, 6.97. Found: C, 57.08; H, 4.33; N, 6.85.

[0446] **Example 11B: Potassium 5-{4-[2-(5-ethylpyridin-2-yl)-2-oxoethoxy]benzyl}-2,4-dioxo-1,3-thiazolidin-3-ide.**

[0447] 5-{4-[2-(5-ethylpyridin-2-yl)-2-oxoethoxy]benzyl}-1,3-thiazolidine-2,4-dione (Compound A) (100mg, 0.27mmol) in THF (3ml) was added a 1M solution of potassium tert-butoxide in THF (0.27ml, 0.27mmol). Stirred at RT for 2 hours. Evaporated in vacuo. Dried under high vac. (ca. 50°C) for 2 hours to give a salmon-colored solid (110mg, 100%).

[0448] Analytical Calc. for C₁₉H₁₇KN₂O₄S plus 2.88% H₂O and 7.95% KOH: C, 49.74; H, 4.21; N, 6.11. Found: C, 49.98; H, 3.79; N, 5.90.

[0449] **Example 11C: Sodium 5-{4-[2-(3-methoxyphenyl)-2-oxoethoxy]benzyl}-2,4-dioxo-1,3-thiazolidin-3-ide.**

[0450] 5-{4-[2-(3-methoxyphenyl)-2-oxoethoxy]benzyl}-1,3-thiazolidine-2,4-dione (Compound B) (100mg, 0.27mmol) was suspended in THF (3ml) and the mixture was heated with a heat gun until all solids dissolved. Added sodium tert-butoxide (26mg, 0.27mmol). Stirred at RT for 2 hours. Evaporated in vacuo. Dried under high vac. (ca. 50°C) for 2 hours to give an off-white solid (110mg, 100%).

[0451] Analytical Calc. for $C_{19}H_{16}NNaO_5S$ plus 1.60% H_2O : C, 57.08; H, 4.21; N, 3.50.

Found: C, 56.91; H, 4.01; N, 3.30.

[0452] Example 11D: Potassium 5-{4-[2-(3-methoxyphenyl)-2-oxoethoxy]benzyl}-2,4-dioxo-1,3-thiazolidin-3-ide.

[0453] A stirring suspension of 5-{4-[2-(3-methoxyphenyl)-2-oxoethoxy]benzyl}-1,3-thiazolidine-2,4-dione (Compound B) in THF (3ml) was heated with a heat gun until all solids dissolved. Added a 1M solution of potassium tert-butoxide in THF (0.27ml, 0.27mmol). Stirred for 2 hours at RT. Evaporated in vacuo. Dried under high vac (ca. 50 °C) for 2 hours to give a salmon-colored solid (110mg, 100%).

[0454] Analytical Calc. for $C_{19}H_{16}K_1N_1O_5S$ plus 2.50% H_2O and 7.96% KOH: C, 49.84; H, 3.96; N, 3.06. Found: C, 49.65; H, 3.58; N, 3.07.

[0455] Example 11E: Potassium 5-{4-[2-(3-methoxyphenyl)-2-oxoethoxy]benzyl}-2,4-dioxo-1,3-thiazolidin-3-ide.

[0456] A mixture of methanol (1.0 lit) and potassium hydroxide flakes (85% w/w) (35.5 gm, 0.539 mol) is stirred to get a clear solution at 25-30°C. To this solution is added 5-{4-[2-(3-methoxyphenyl)-2-oxoethoxy]benzyl}-1,3-thiazolidine-2,4-dione (200 gm, 0.539 mol) in single lot under stirring along with methanol (200 ml). A clear solution is formed and precipitate begins to form within 10-15 min. Stirred the reaction mixture for 6 hr. Filtered the solid obtained and washed with methanol (200 ml) and dried in oven at 50-55°C to yield potassium salt of 5-{4-[2-(3-methoxyphenyl)-2-oxoethoxy]benzyl}-1,3-thiazolidine-2,4-dione (185 gm).

[0457] Example 12: Biological Properties of Compound Salts.

[0458] Several biological properties of the compound salts were assessed.

[0459] Example 12A: Bioavailability of sodium salt of Compound A.

[0460] Referring to FIG. 1, the bioavailability of the sodium salt of Compound A was evaluated by crossover design in 4 male cynomolgus monkeys having weights ranging from 4.52 to 5.12 kg. The monkeys fasted overnight and were dosed by oral gavage washed down with 10 ml tap water. Blood samples were taken at .25, .5, 1, 2, 3, 4, 6, 9, 12, 24, and 48 hours after a single dosage was administered and assayed for drug related materials with a LCMS assay using an internal standard. 90 mg of drug was put in 00 gelatin capsules containing 90 mg of free base equivalents. This was compared to an iv injection of 2 ml/kg and 45 mg of free base solution in 50% hydroxypropyl β -cyclodextran. The absolute availability versus an iv injection was determined for both parent compound and major

metabolite. It is noted that the sodium salt of Compound A, for both the metabolite and the parent compound, had significantly higher bioavailability than their free base counterparts.

[0461] Example 12B: Bioavailability of potassium and sodium salts of Compound B.

[0462] Referring to FIG. 2, the area under the curve (AUC) of compound related materials was compared following dosing of 250 mg of Compound B as powder in capsules of free acid (PIC), formulated tablets of micronized free acid, or formulated tablets of the Na or K salt of Compound B given at the same free acid equivalents. (N=4 cynomolgus monkeys). The formulated, compressed tablet also contained in each case approximately 40.5% lactose, 16.8% microcrystalline cellulose, 1.9% Croscarmellose sodium, 0.5% colloidal silicon dioxide, and 0.9% magnesium stearate. It is noted that both the sodium and potassium salts of Compound B had significantly higher bioavailability than their free acid counterparts. Also, the salts of the bulk acid showed great advantage over the compressed tablet with micronized free acid.

[0463] Example 12C: Pharmacological activity of sodium salt of Compound A.

[0464] Referring to FIG 3, the Na salt of Compound A demonstrated an excellent dose response for lowering blood glucose in the diabetic KKAY mouse. In these experiments, free base or sodium salt was given to diabetic KKAY mice (N=6) and blood glucose was measured after 4 days of daily treatment at the doses indicated. KKAY mice, 8-12 weeks of age, were given the doses of the compounds according to the dosages on the X axis of FIG. 3. The compounds were given by gavage once daily at 10 mg/kg. On the fifth day (after 4 daily doses at the levels shown) a blood sample was taken to measure plasma glucose.

[0465] Example 13: Assays.

[0466] Assays for Measuring Reduced PPAR γ Receptor Activation

[0467] Whereas activation of the PPAR γ receptor is generally believed to be a selection criteria to select for molecules that may have anti-diabetic and insulin sensitizing pharmacology, this invention finds that activation of this receptor should be a negative selection criterion. Molecules will be chosen from this chemical space because they have reduced, not just selective, activation of PPAR γ . The optimal compounds have at least a 10-fold reduced potency as compared to pioglitazone and less than 50% of the full activation produced by rosiglitazone in assays conducted in vitro for transactivation of the PPAR γ receptor. The assays are conducted by first evaluation of the direct interactions of the molecules with the ligand binding domain of PPAR γ . This can be performed with a commercial interaction kit that measures the direct interaction by fluorescence using rosiglitazone as a positive control.

[0468] PPAR γ binding is measured by a TR-FRET competitive binding assay using Invitrogen LanthaScreenTM TR-FRET PPAR γ Competitive Binding Assay (Invitrogen #4894). This assay uses a terbium-labeled anti-GST antibody to label the GST tagged human PPAR γ ligand binding domain (LBD). A fluorescent small molecule pan-PPAR ligand tracer binds to the LBD causing energy transfer from the antibody to the ligand resulting in a high TR-FRET ratio. Competition binding by PPAR γ ligands displace the tracer from the LBD causing a lower FRET signal between the antibody and tracer. The TR-FRET ratio is determined by reading the fluorescence emission at 490 and 520 nm using a Synergy2 plate reader (BioTek). The ability of several exemplary compounds of the present invention to bind to PPAR γ was also measured using a commercial binding assay (Invitrogen Corporation, Carlsbad, CA) that measures the test compounds ability to bind with PPAR-LBD/Fluormone PPAR Green complex. These assays were performed on three occasions with each assay using four separate wells (quadruplicate) at each concentration of tested compound. The data are mean and SEM of the values obtained from the three experiments. Rosiglitazone was used as the positive control in each experiment. Compounds were added at the concentrations shown, which ranged from 0.1-100 micromolar.

[0469] PPAR γ activation in intact cells may be measured by a cell reporter assay using Invitrogen GeneBLazer PPAR γ Assay (Invitrogen #1419). This reporter assay uses the human PPAR γ ligand binding domain (LBD) fused to the GAL4 DNA binding domain (DBD) stably transfected into HEK 293H cells containing a stably expressed beta-lactamase reporter gene under the control of an upstream activator sequence. When a PPAR γ agonist binds to the LBD of the GAL4/PPAR fusion protein, the protein binds to the upstream activator sequence activating the expression of beta-lactamase. Following a 16 hour incubation with the agonists the cells are loaded with a FRET substrate for 2 hours and fluorescence emission FRET ratios are obtained at 460 and 530 nm in a Synergy2 plate reader (BioTek).

[0470] In addition to showing the reduced activation of the PPAR γ receptor in vitro, the compounds will not produce significant activation of the receptor in animals. Compounds dosed to full effect for insulin sensitizing actions in vivo (see below) will be not increase activation of PPAR γ in the liver as measured by the expression of a P2, a biomarker for ectopic adipogenesis in the liver [Matsusue K, Haluzik M, Lambert G, Yim S-H, Oksana Gavrilova O, Ward JM, Brewer B, Reitman ML, Gonzalez FJ. (2003) Liver-specific disruption of PPAR in leptin-deficient mice improves fatty liver but aggravates diabetic

phenotypes. J. Clin. Invest.; 111: 737] in contrast to pioglitazone and rosiglitazone, which do increase a P2 expression under these conditions.

[0471] Mitochondrial Membrane Competitive Binding Crosslinking Assay

[0472] A photoaffinity crosslinker was synthesized by coupling a carboxylic acid analog of pioglitazone to a p-azido-benzyl group containing ethylamine as in Amer. J. Physiol 256:E252-E260. The crosslinker was iodinated carrier free using a modification of the Iodogen (Pierce) procedure and purified using open column chromatography (PerkinElmer). Specific crosslinking is defined as labeling that is prevented by the presence of competing drug. Competitive binding assays are conducted in 50 mM Tris , pH 8.0. All crosslinking reactions are conducted in triplicate using 8 concentrations of competitor ranging from 0-25 μ M. Each crosslinking reaction tube contains 20 μ g of crude mitochondrial enriched rat liver membranes, 0.1 μ Ci of 125I-MSDC-1101, and $\pm$ competitor drug with a final concentration of 1% DMSO. The binding assay reaction is nutated at room temperature in the dark for 20 minutes and stopped by exposure to 180,000 μ Joules. Following crosslinking, the membranes are pelleted at $20,000 \times g$ for 5 minutes, the pellet is resuspended in Laemmli sample buffer containing 1% BME and run on 10-20% Tricine gels. Following electrophoresis the gels are dried under vacuum and exposed to Kodak BioMax MS film at -80°C. The density of the resulting specifically labeled autoradiography bands are quantitated using ImageJ software (NIH) and IC₅₀ values determined by non-linear analysis using GraphPad Prism™. Selected compounds in this assay demonstrated an IC₅₀ of less than 20 μ M, less than 5 μ M or less than 1 μ M. The crosslinking to this protein band is emblematic of the ability of the PPAR-sparing compounds to bind to the mitochondria, the key organelle responsible for the effectiveness of these compounds for this utility.

[0473] Example 14: Animal Studies.

[0474] Male PCK rats (PCK/CrljCrl-Pkhd1^{pck}, Charles River Labs, n=60) were 3 weeks of age on arrival. Rats were housed individually and maintained on non-irradiated Purina 5002 and reverse osmosis drinking water ad lib during the 7 day facility acclimation period. The light cycle was maintained at 1800-0600 hr throughout study duration. Room temperature was monitored daily and maintained at 22-25°C.

[0475] Four week old PCK rats were randomized based on body weight for assignment to receive *ad lib* Purina 5002 chow (Control, n=20) or Compound A, i.e., 5-(4-(2-(5-ethylpyridin-2-yl)-2-oxoethoxy)benzyl)-1,3-thiazolidine-2,4-dione, admixed with 5002 chow at 300 ppm (LOW, n=19) or 600 ppm (HIGH, n=20) for 14 weeks. Body weight and feed intake were recorded weekly. Animals were anesthetized with CO₂ inhalation and

exsanguinated via cardiac puncture. Whole blood was processed for serum. Fresh serum was analyzed for BUN, creatinine, AST, and ALT using AU480 clinical analyzer. Serum total bilirubin and alkaline phosphatase were assessed at termination. Organ weights (liver, left and right kidney) were recorded. The right kidney (partially sectioned through middle toward pelvis) and one lobe of liver were fixed in 10% formalin for histological examination. The left kidney was quickly frozen in liquid nitrogen and maintained at -70° for future analysis. Compound A, in powder form, was provided for admixture into Purina 5002 rat chow by TestDiets (Richmond, IN).

[0476] Results:

[0477] Referring to FIGS 4-10, all data are represented as group mean $\pm$ SEM. Data were analyzed using JMP (SAS software). All normalizations were calculated using terminal (day 98) body weight. Treatment effects among groups were determined using Dunnett's comparison of group means ($p < 0.05$).

[0478] Body Weight:

[0479] Referring to FIG. 1, body weight in 4 week old PCK rats averaged 116.3 ± 3.1 g and there were no differences among groups at baseline. Cumulative weight gain throughout the 14 week study was significantly higher in PCK rats fed Compound A at the lower level compared to control animals (487.2 ± 9.0 vs. 441.7 ± 6.8 g); however, this increase was not observed in animals fed Compound A at the higher dose when compared to control (457.7 ± 14.9 vs. 441.7 ± 6.8 g).

[0480] Food Consumption:

[0481] Referring to FIG. 2, daily feed consumption remained steady from week to week in all groups. Over the 14 week study, cumulative feed consumption averaged 2579.2 ± 31.5 , 2843.8 ± 39.1 and 2787.6 ± 37.4 g for control, low and high test groups. Cumulative intake was significantly higher (8-10%) in both Compound A treatment groups compared to control. Based on average body weight and feed intake throughout the study, average Compound A delivery was estimated to be 23.7 ± 0.2 and 49.9 ± 0.6 mg/kg/day for the low and high concentrations.

[0482] Kidney Weight:

[0483] Referring to FIG. 3, fourteen week feeding of Compound A at 300 and 600 ppm significantly reduced total kidney weight compared to control animals (7.86 ± 0.33 , 6.47 ± 0.22 and 6.13 ± 0.18 g for control, low and high, respectively). Similarly, kidney weight as a percent of body weight was significantly reduced compared to controls (1.41 ± 0.6 , 1.08 ± 0.05 and 1.08 ± 0.04 % for control, low and high concentrations, respectively). The effect on

kidney size was independent of the concentration of Compound A administered as there were no significant differences between the low dose and high dose response.

[0484] Renal Function:

[0485] Compared to the clinical chemistry reference ranges for rats (Patrick E.Sharp and Marie C.LaRegina), significant impairments in renal function as assessed by clinical chemistry at termination (serum BUN, serum creatinine) were not noted in PCK rats. However, the low concentration of Compound A appeared to significantly reduce BUN ($\approx 13\%$) when compared to control animals (16.87 ± 0.9 vs. 14.7 ± 0.35 mg/dL), as described in Table 1:

[0486] Table 1: Renal function clinical chemistry.

	Control	Compound A 300 ppm	Compound A 600 ppm
Serum BUN (Range 11-23 mg/dL)	16.9 ± 0.9	$14.7 \pm 0.34^*$	15.4 ± 0.35
Serum Creatinine (Range 0.4-1.4 mg/dL)	0.35 ± 0.008	0.35 ± 0.007	0.37 ± 0.005

[0487] Liver Weight:

[0488] Referring to FIG. 4, liver weight was significantly reduced in PCK rats by Compound A treatment (34.6 ± 2.6 , 27.4 ± 1.1 and 23.5 ± 1.1 g for control, low and high test groups, respectively). Similarly, when normalized to body weight, liver weight was significantly reduced (27-32%) following Compound A treatment compared to control (6.26 ± 0.52 , 4.59 ± 0.24 and 4.21 ± 0.32 % for control, low and high test groups, respectively).

[0489] Liver Injury:

[0490] Liver injury was assessed from terminal clinical chemistry (ALP, ALT, AST and total bilirubin). There were no significant differences in AST or total bilirubin among treatment groups compared to control. Compound A administered at 300 or 600 ppm elicited a significant increase in ALP ($\approx 25\%$) compared to control (310.5 ± 8.4 , 388.2 ± 14.9 and 388.5 ± 13.9 IU/L for control, low and high test groups, respectively). Similar significant increases in ALT ($\approx 23\%$ for the low concentration and 16% for the high concentration) were noted after Compound A treatment. Assessment of liver injury is complicated by the observation of significant hepatic inflammation in all samples.

[0491] Table 2: Liver injury.

	Control	Compound A 300 ppm	Compound A 600 ppm
Serum ALT (IU/L)	68.7 ± 2.0	$84.6 \pm 4.0^*$	$79.8 \pm 4.4^*$
Serum AST (IU/L)	138.2 ± 14.3	148.1 ± 14.3	160.3 ± 32.8

	Control	Compound A 300 ppm	Compound A 600 ppm
Serum ALP (IU/L)	310.6±8.4	388.2±14.9*	388.5±14.0*
Serum total bilirubin (mg/dL)	0.42±0.13	0.15±0.01	0.40±0.26

[0492] Histology:**[0493] Renal Cyst Volume:**

[0494] Referring to FIG. 5, Compound A administered at either dose level significantly reduced normalized renal cyst volume from that observed in vehicle treated animals (33.4% at low dose and 41.7% for high dose). Cyst volume as a % of BW was 0.53 ± 0.05 , 0.35 ± 0.03 and 0.31 ± 0.03 %BW for the vehicle, low and high dose study groups, respectively.

[0495] Renal Fibrosis:

[0496] Referring to FIG. 6, renal fibrosis (1-4 scoring scale) was about 40% higher in medullary regions compared to cortical regions of the kidney across all groups. Compound A treatment significantly reduced fibrosis in the cortical region at both dose levels when compared to vehicle treatment (1.6 ± 0.07 , 1.39 ± 0.04 and 1.35 ± 0.04 for vehicle, low and high dose groups, respectively). Medullary fibrosis was significantly reduced compared to vehicle in the high dose group only (2.25 ± 0.07 , 2.03 ± 0.06 and 1.95 ± 0.07 for vehicle, low and high dose groups, respectively).

[0497] Hepatic Cyst Volume:

[0498] Referring to FIG. 7, significant cholangitis was noted in all liver samples independent of treatment group. Normalized cyst volume was significantly reduced by Compound A when administered at either dose (1.92 ± 0.5 , 0.99 ± 0.2 and 0.89 ± 0.2 % BW for the vehicle, low and high dose study groups, respectively).

[0499] Conclusion:

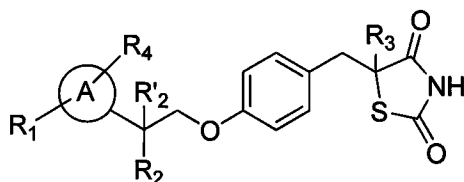
[0500] Compound A administration (25 - 50 mg/kg/day, 14 weeks) significantly reduced cystic disease in PCK rats as evidenced by smaller kidneys, reduced fibrotic change and reduced renal cystic volume. Similarly, hepatic cyst development and liver enlargement was significantly reduced following administration of Compound A.

OTHER EMBODIMENTS

[0501] It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A method of treating or delaying the onset of PKD comprising administering to a patient a compound of Formula I:



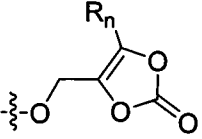
I

or a pharmaceutically acceptable salt thereof, wherein:

Each of R_1 and R_4 is independently selected from H, halo, aliphatic, and alkoxy, wherein the aliphatic or alkoxy is optionally substituted with 1-3 of halo;

R'_2 is H;

R_2 is H, halo, hydroxy, or optionally substituted aliphatic, -O-acyl, -O-aroyl, -O-heteroaroyl, -O(SO₂)NH₂, -O-CH(R_m)OC(O)R_n, -O-CH(R_m)OP(O)(OR_n)₂,

-O-P(O)(OR_n)₂, or , wherein each R_m is independently an optionally substituted C₁₋₆ alkyl, each R_n is independently C₁₋₁₂ alkyl, C₃₋₈ cycloalkyl, or phenyl, each of which is optionally substituted, or

R_2 and R'_2 together form oxo;

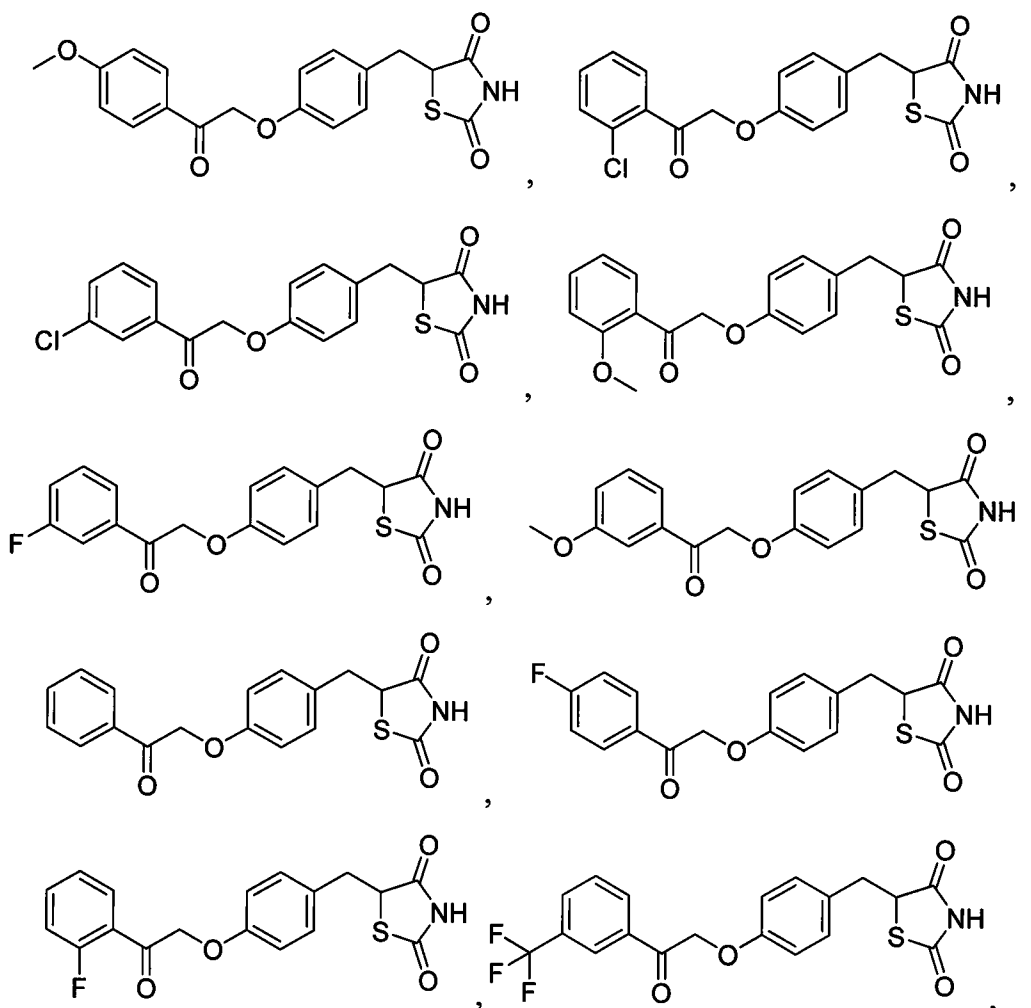
R_3 is H; and

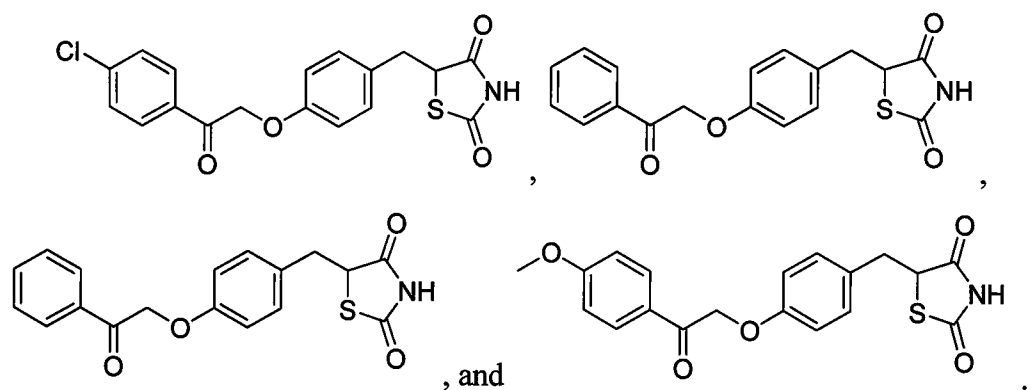
Ring A is a phenyl, pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl, each of which is substituted with an R_1 group and an R_4 group at any chemically feasible position on ring A.

2. The method of claim 1, wherein R_4 is H, methyl, methoxy, ethyl, ethoxy, -O-isopropyl, -CF₃, -OCHF₂ or -OCF₃.
3. The method of either of claims 1 or 2, wherein R_4 is H.
4. The method of any of claims 1-3, wherein R_1 is H, alkyl, halo or alkoxy.
5. The method of any of claims 1-4, wherein R_1 is H.
6. The method of any of claims 1-4, wherein R_1 is halo.
7. The method of any of claims 1-4, wherein R_1 is C₁₋₃ alkyl.

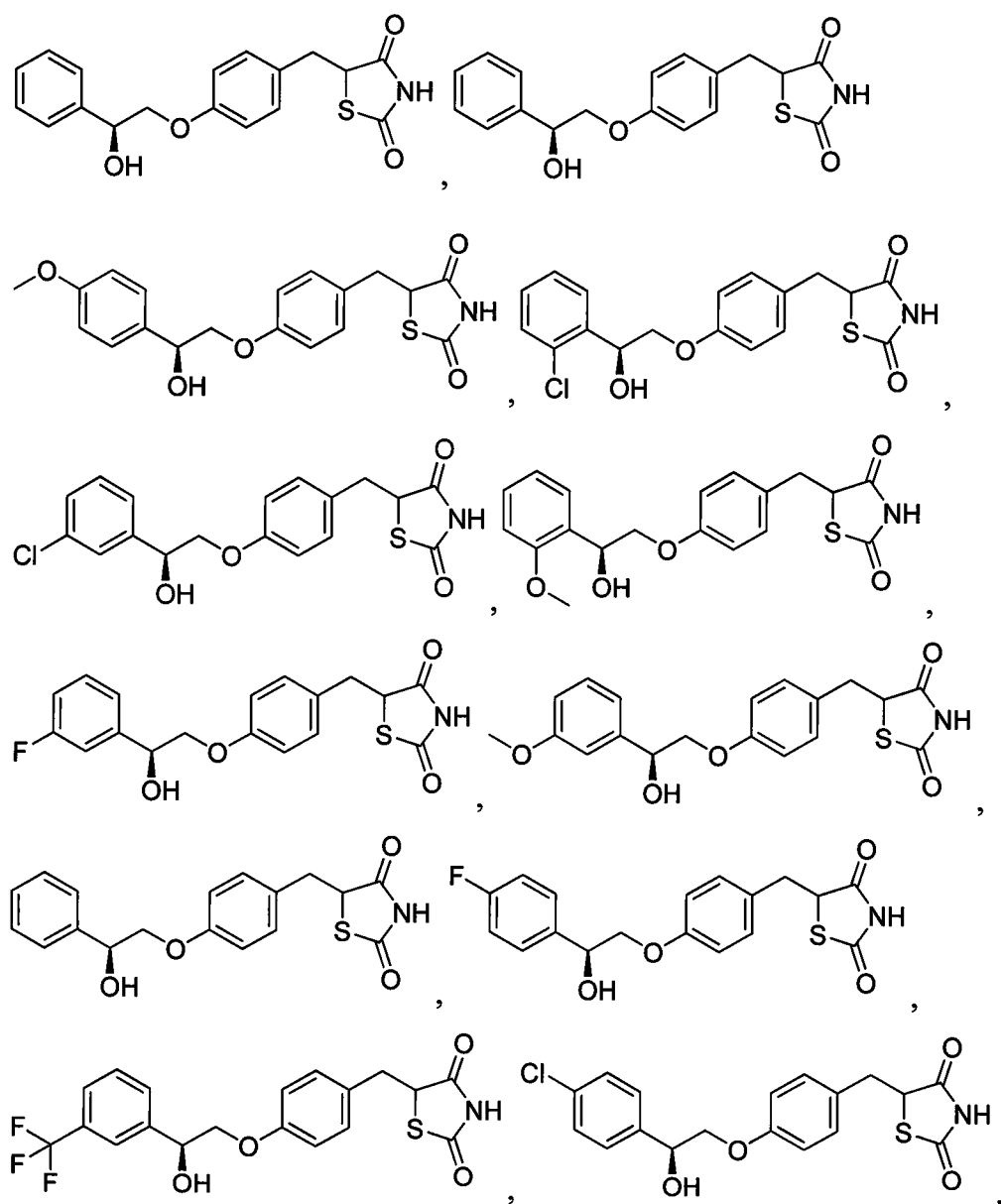
8. The method of any claims 1-7, wherein ring A is phenyl that is substituted with R₁ and R₄ groups at any chemically feasible position on ring A.
9. The method of any of claims 1-7, wherein ring A is pyridin-2-yl or pyridin-3-yl, either of which is substituted with R₁ and R₄ groups at any chemically feasible position on ring A.
10. The method of claim 8, wherein ring A is phenyl, and one of R₁ or R₄ is attached to the para or meta position of ring A.
11. The method of claim 10, wherein ring A is phenyl, and one of R₁ or R₄ is attached to the meta position of ring A.
12. The method of claim 9, wherein ring A is pyridin-2-yl, and one of R₁ or R₄ is attached to the 5 position of the ring.
13. The method of claim 9, wherein ring A is pyridin-3-yl, and one of R₁ or R₄ is attached to the 6 position of the ring.
14. The method of claim 10, wherein R₁ is attached to the para or meta position of ring A.
15. The method of claim 14, wherein R₁ is F or Cl.
16. The method of claim 14, wherein R₁ is alkoxy.
17. The method of claim 16, wherein R₁ is methoxy, ethoxy, propoxy, -O-isopropyl, butoxy, or -O-tertbutyl.
18. The method of claim 8, wherein ring A is phenyl, and R₁ is attached to the meta or ortho position of the phenyl ring.
19. The method of claim 18, wherein ring A is phenyl, and R₁ is attached to the ortho position of the phenyl ring.
20. The method of claim 19, wherein ring A is phenyl, and R₁ is methoxy, ethoxy, or -O-isopropyl.
21. The method of claim 19, wherein R₁ is -CF₃, -OCH₃, -OCHF₂ or -OCF₃.
22. The method of claim 12, wherein ring A is pyridin-2-yl, and R₁ is attached to the 5 position of the ring.

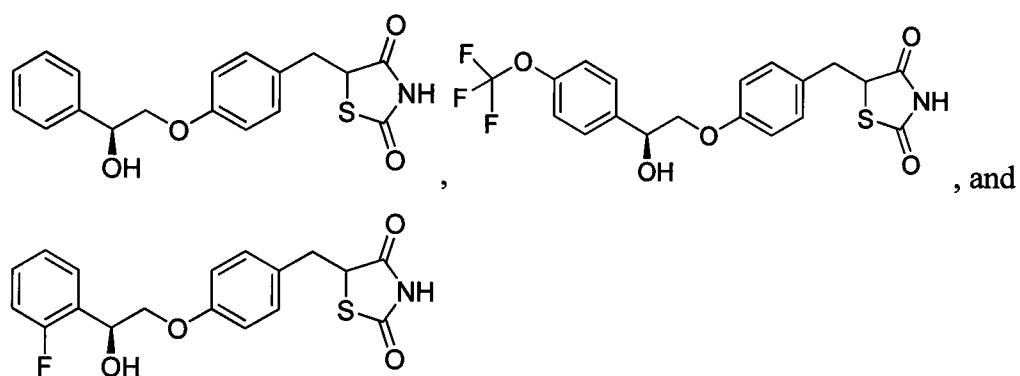
23. The method of claim 22, wherein R_1 is alkyl or alkoxy.
24. The method of claim 23, wherein R_1 is methyl, ethyl, propyl, isopropyl, butyl, or tertbutyl.
25. The method of any of claims 1-24, wherein R'_2 is H.
26. The method of any of claims 1-25, wherein R_2 is hydroxy.
27. The method of any of claims 1-25, wherein R_2 is -O-acyl, -O-aroyl, or -O-heteroaroyl.
28. The method of any of claims 1-24, wherein R_2 and R'_2 together form oxo.
29. The method of claim 1, wherein the compound of Formula I is selected from:



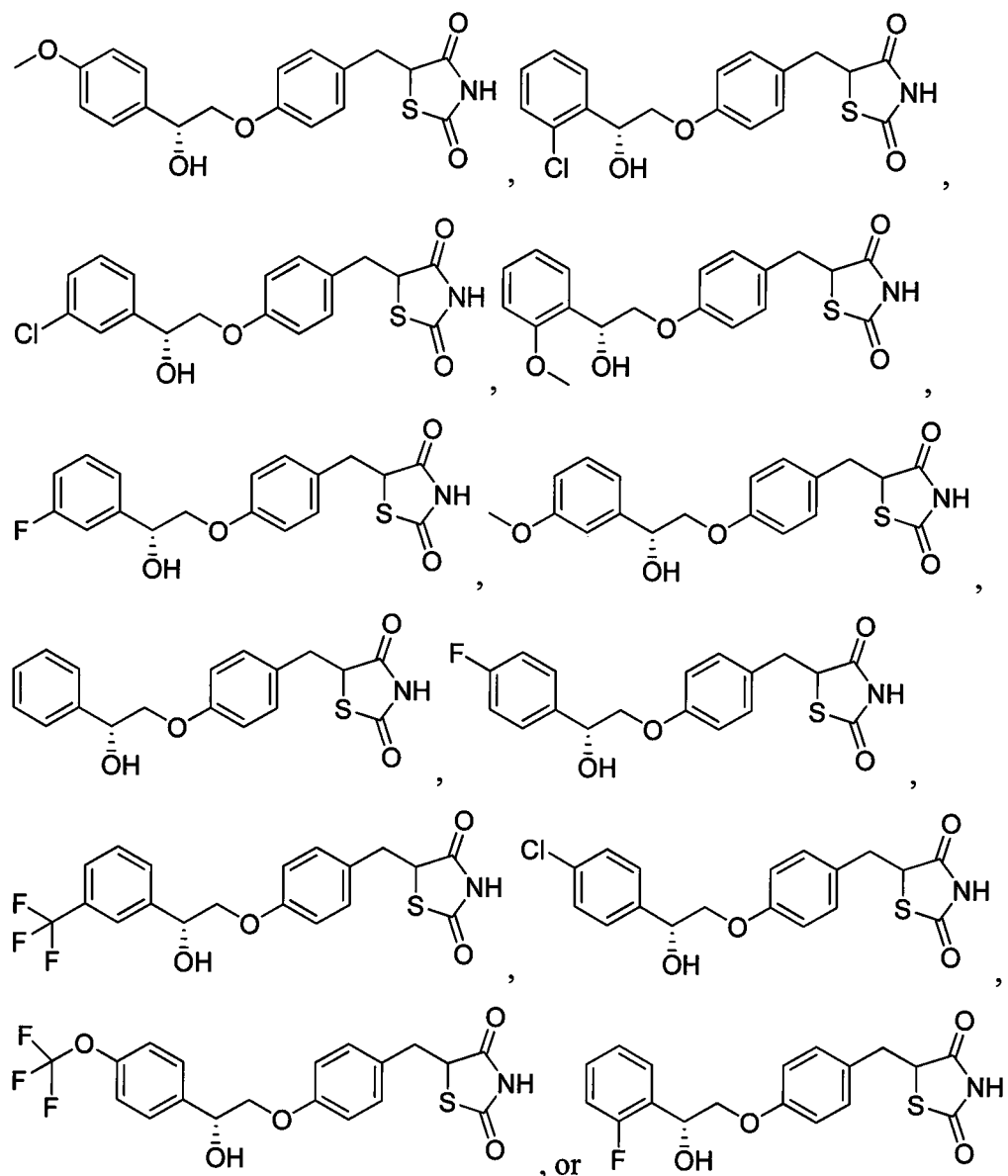


30. The method of claim 1, wherein the compound of Formula I is selected from:

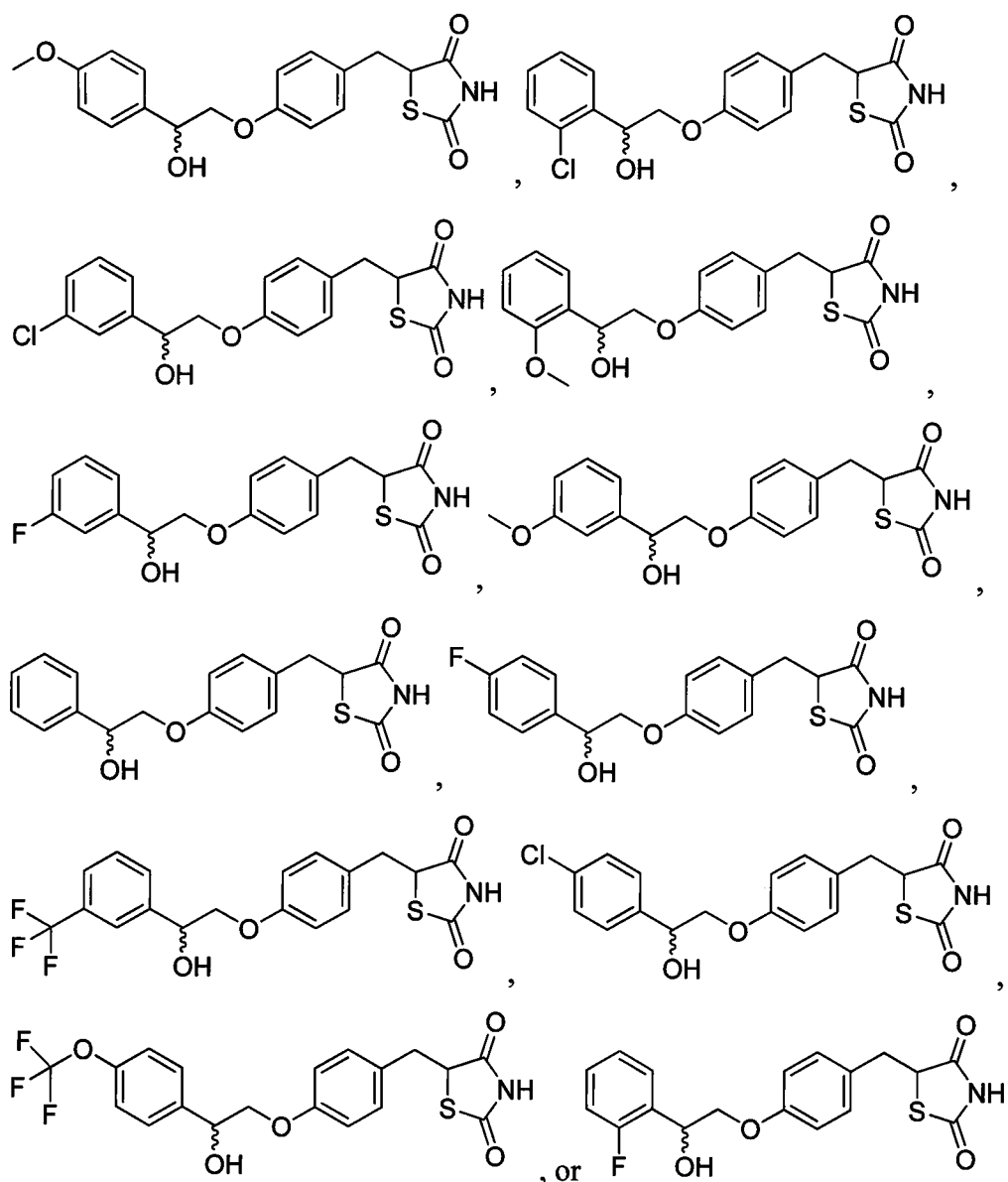




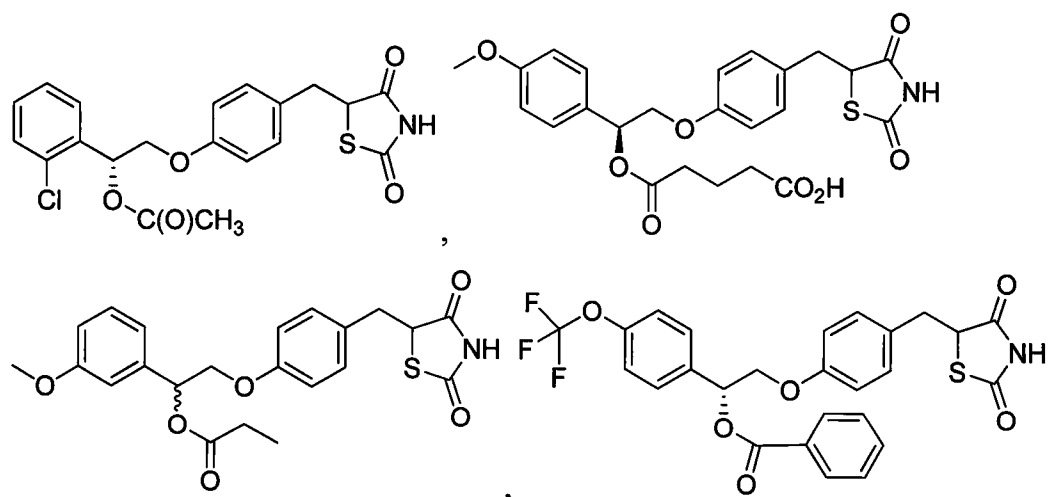
31. The method of claim 1, wherein the compound of Formula I is selected from:

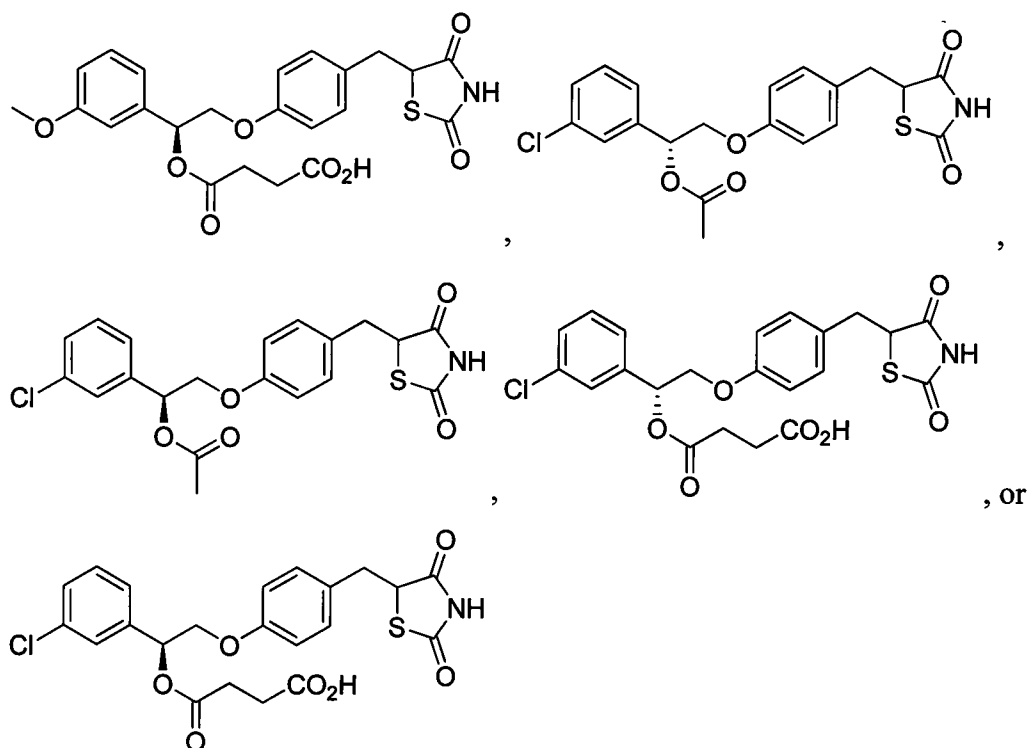


32. The method of claim 1, wherein the compound of Formula I is selected from:

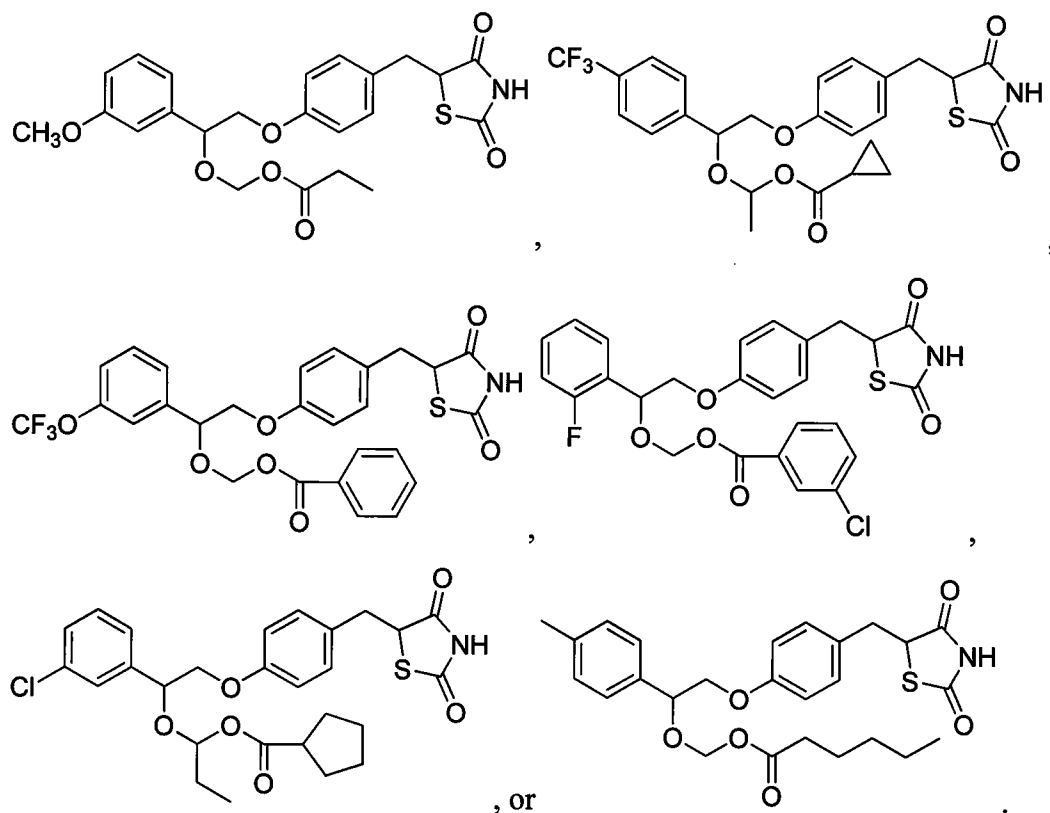


33. The method of claim 1, wherein the compound of Formula I is selected from:

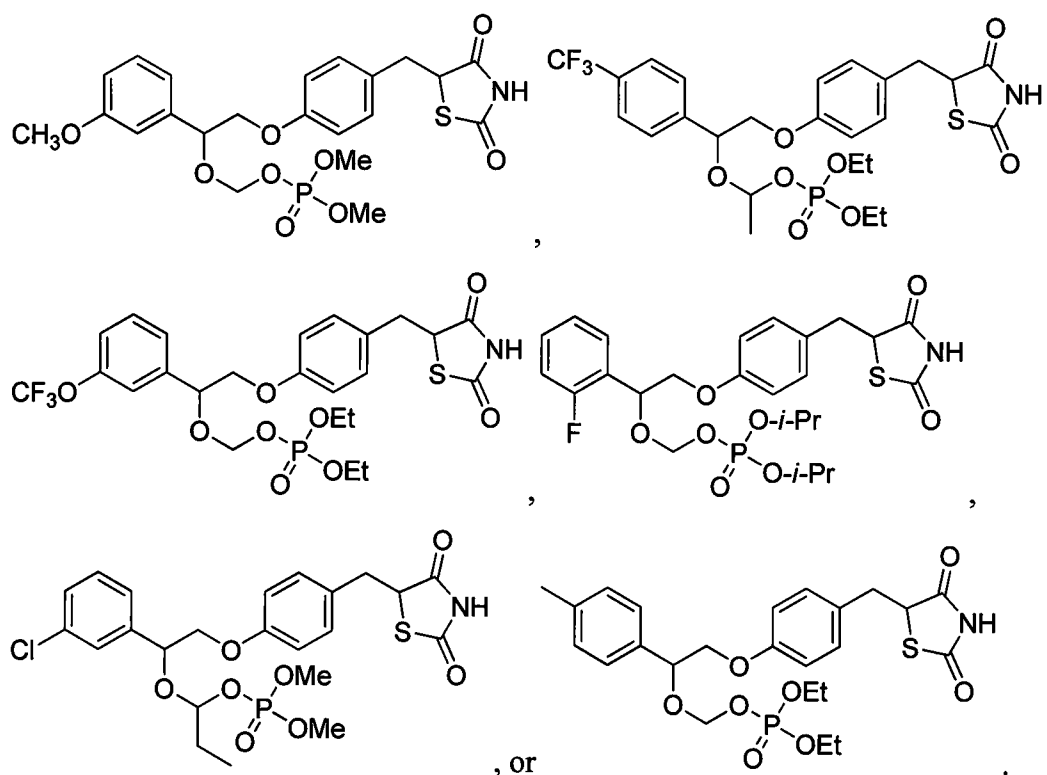




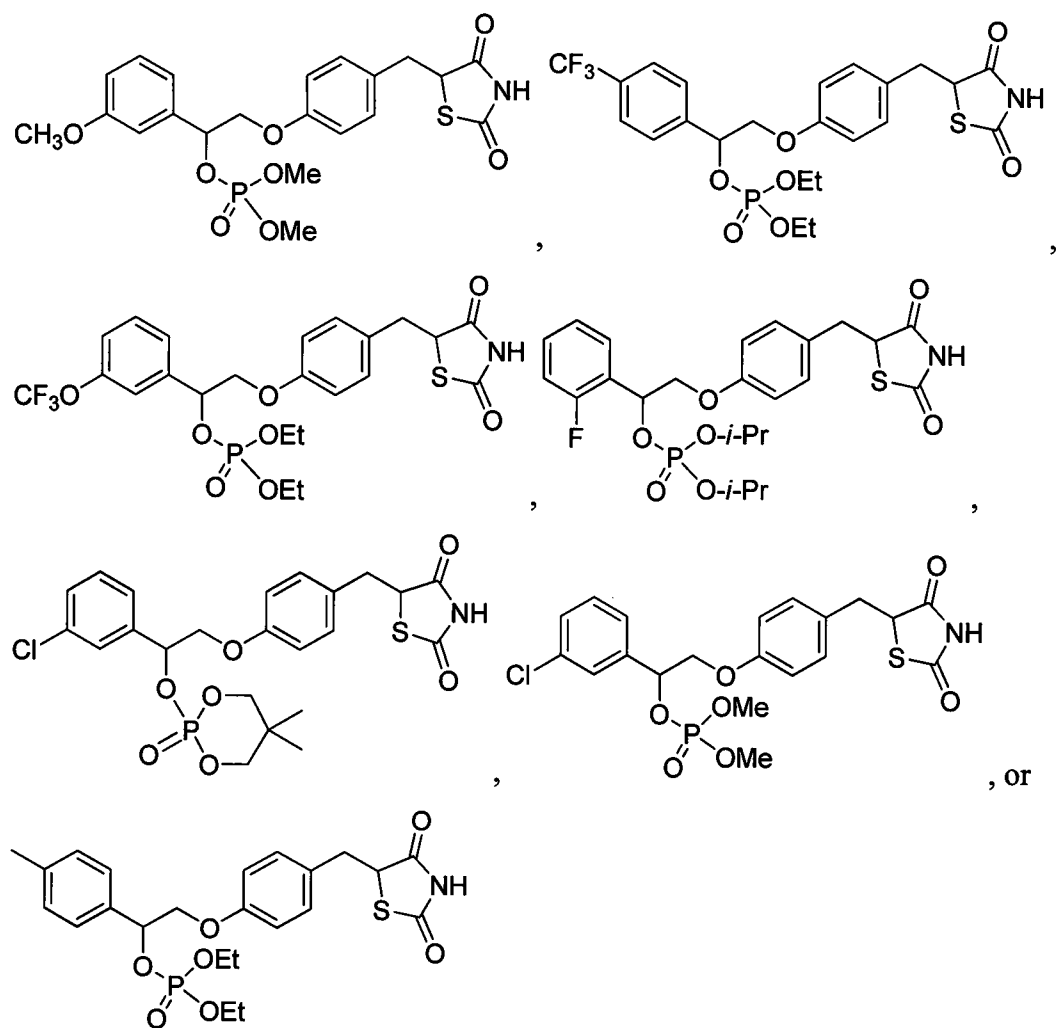
34. The method of claim 1, wherein the compound of Formula I is selected from:



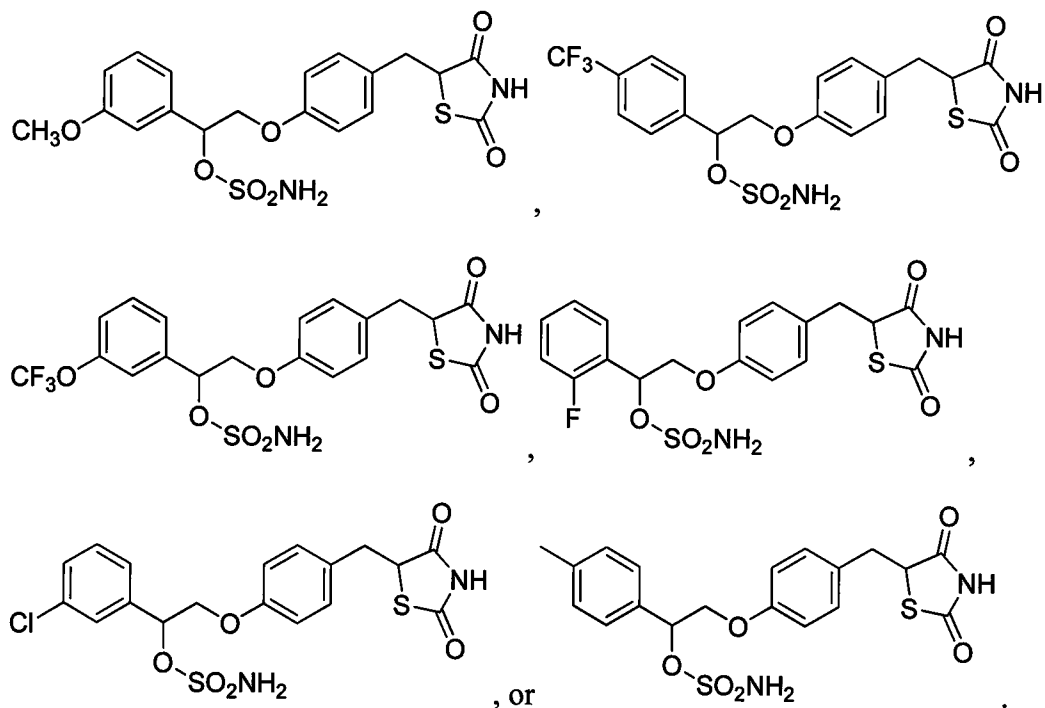
35. The method of claim 1, wherein the compound of Formula I is selected from:



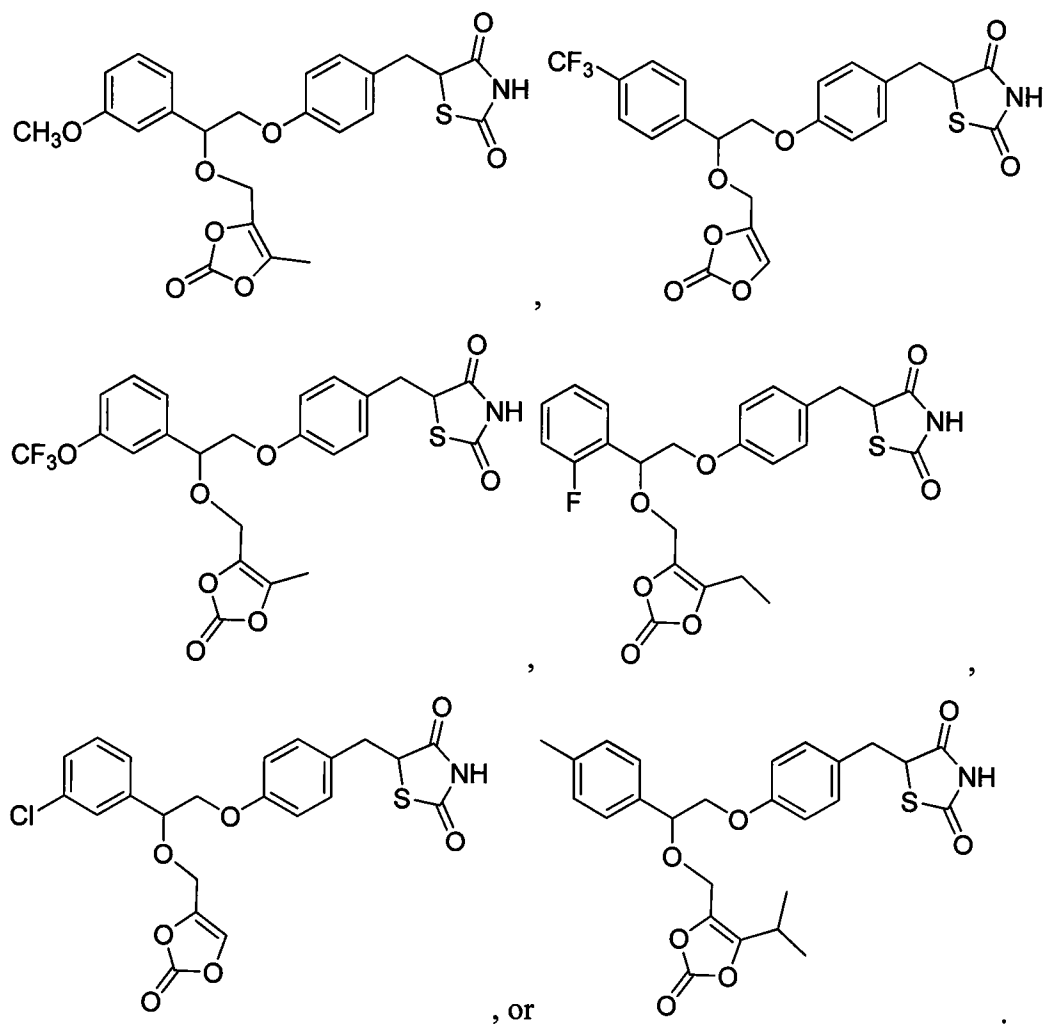
36. The method of claim 1, wherein the compound of Formula I is selected from:

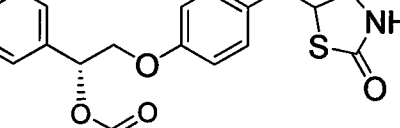
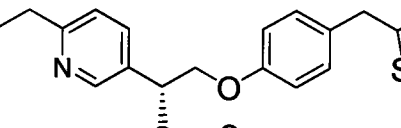


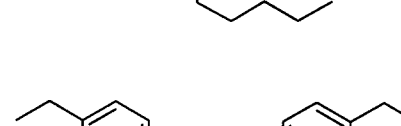
37. The method of claim 1, wherein the compound of Formula I is selected from:



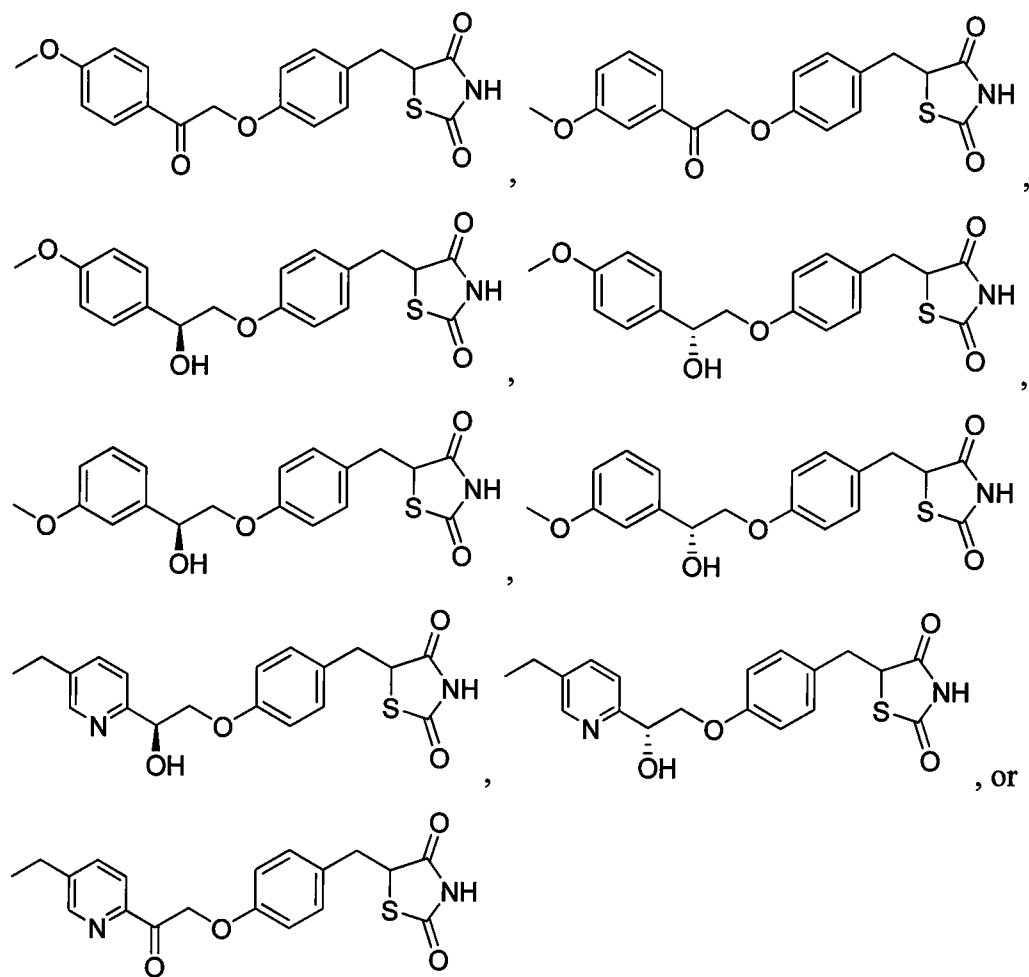
38. The method of claim 1, wherein the compound of Formula I is selected from:



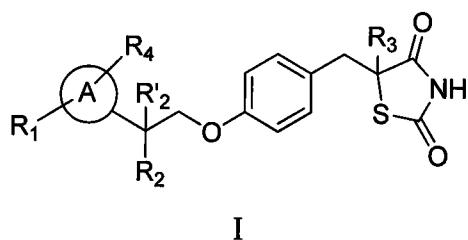



41. The method of claim 1, wherein the compound of Formula I is selected from:



42. A method of treating or delaying the onset of PKD comprising administering to a patient an alkali earth metal salt of a compound of Formula I:

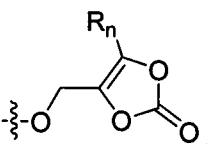


wherein:

Each of R_1 and R_4 is independently selected from H, halo, aliphatic, and alkoxy, wherein the aliphatic or alkoxy is optionally substituted with 1-3 of halo;

R'_2 is H;

R_2 is H, halo, hydroxy, or optionally substituted aliphatic, -O-acyl, -O-aroyl, -O-heteroaroyl, -O(SO₂)NH₂, -O-CH(R_m)OC(O)R_n, -O-CH(R_m)OP(O)(O)(OR_n)₂,

$\text{-O-P(O)(OR}_n\text{)}_2$, or , wherein each R_m is independently an optionally substituted C_{1-6} alkyl, each R_n is independently C_{1-12} alkyl, C_{3-8} cycloalkyl, or phenyl, each of which is optionally substituted, or

R_2 and R'_2 together form oxo;

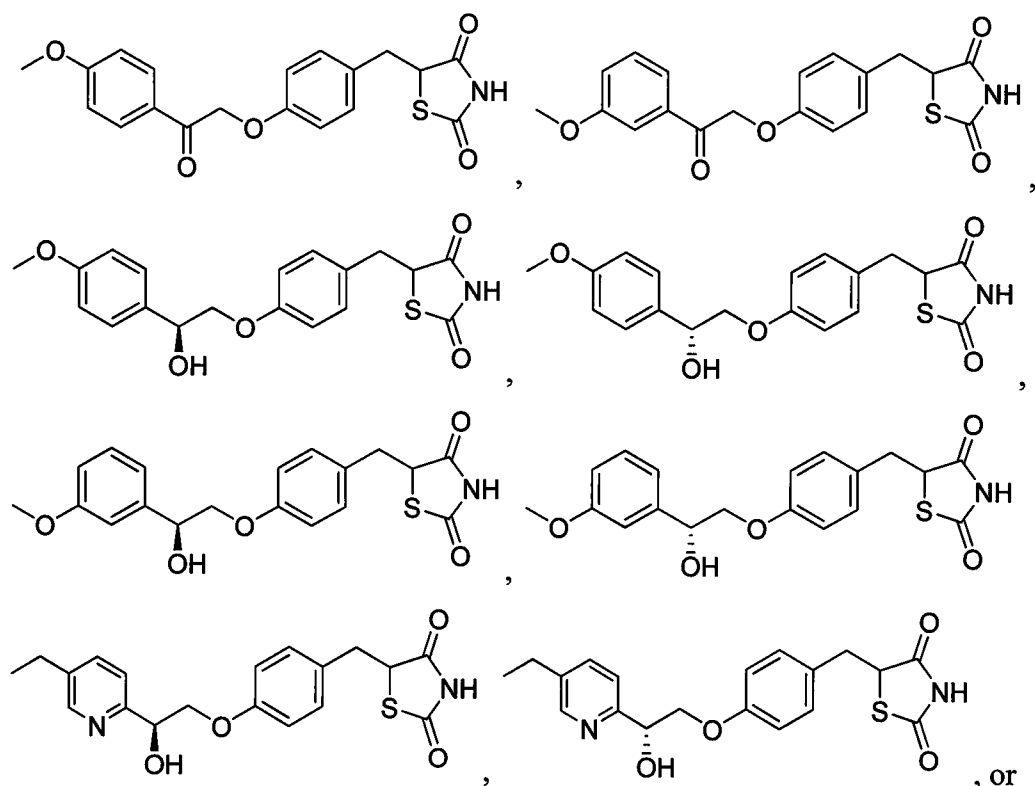
R_3 is H; and

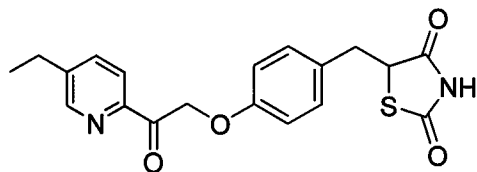
Ring A is a phenyl, pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl, each of which is substituted with an R_1 group and an R_4 group.

43. The method of claim 42, wherein the alkali earth metal comprises sodium.
44. The method of claim 42, wherein the alkali earth metal comprises potassium.
45. The method of any of claims 42-44, wherein R_4 is H, methyl, methoxy, ethyl, ethoxy, -O-isopropyl, -CF₃, -OCHF₂ or -OCF₃.
46. The method of any of claims 42-45, wherein R_4 is H.
47. The method of any of claims 42-46, wherein R_1 is H, alkyl, halo or alkoxy.
48. The method of any of claims 42-47, wherein R_1 is H.
49. The method of any of claims 42-47, wherein R_1 is halo.
50. The method of any of claims 42-47, wherein R_1 is C_{1-3} alkyl.
51. The method of any of claims 42-50, wherein ring A is phenyl that is substituted with R_1 and R_4 groups at any chemically feasible position on ring A.
52. The method of any of claims 42-50, wherein ring A is pyridin-2-yl or pyridin-3-yl, either of which is substituted with R_1 and R_4 groups at any chemically feasible position on ring A.

53. The method of claim 51, wherein ring A is phenyl, and one of R₁ or R₄ is attached to the para or meta position of ring A.
54. The method of claim 53, wherein ring A is phenyl, and one of R₁ or R₄ is attached to the meta position of ring A.
55. The method of claim 52, wherein ring A is pyridin-2-yl, and one of R₁ or R₄ is attached to the 5 position of the ring.
56. The method of claim 52, wherein ring A is pyridin-3-yl, and one of R₁ or R₄ is attached to the 6 position of the ring.
57. The method of claim 53, wherein R₁ is attached to the para or meta position of ring A.
58. The method of claim 57, wherein R₁ is F or Cl.
59. The method of claim 57, wherein R₁ is alkoxy.
60. The method of claim 59, wherein R₁ is methoxy, ethoxy, propoxy, -O-isopropyl, butoxy, or -O-tertbutyl.
61. The method of claim 51, wherein ring A is phenyl, and R₁ is attached to the meta or ortho position of the phenyl ring.
62. The method of claim 61, wherein ring A is phenyl, and R₁ is attached to the ortho position of the phenyl ring.
63. The method of claim 52, wherein ring A is phenyl, and R₁ is methoxy, ethoxy, or -O-isopropyl.
64. The method of claim 52, wherein R₁ is -CF₃, -OCH₃, -OCHF₂ or -OCF₃.
65. The method of claim 55, wherein ring A is pyridin-2-yl, and R₁ is attached to the 5 position of the ring.

66. The method of claim 65, wherein R_1 is alkyl or alkoxy.
67. The method of claim 66, wherein R_1 is methyl, ethyl, propyl, isopropyl, butyl, or tertbutyl.
68. The method of any of claims 42-67, wherein R'_2 is H.
69. The method of any of claims 42-68, wherein R_2 is hydroxy.
70. The method of any of claims 42-68, wherein R_2 is -O-acyl, -O-aroyl, or -O-heteroaroyl.
71. The method of any of claims 42-67, wherein R_2 and R'_2 together form oxo.
72. The method of any of claims 42-44, wherein the compound of Formula I is selected from:





73. The method of either of claims 1 or 42, further comprising administering to a patient a second pharmaceutical agent having an activity that increases cAMP in the patient.

74. The method of claim 73, wherein the second pharmaceutical agent further comprises a beta-adrenergic agonist.

75. The method of claim 74, wherein the beta-adrenergic agonist comprises a beta-1-adrenergic agonist, a beta-2-adrenergic agonist, a beta-3-adrenergic agonist, or any combination thereof.

76. The method of claim 74, wherein the beta-adrenergic agonist comprises noradrenaline, isoprenaline, dobutamine, salbutamol, levosalbutamol, terbutaline, pirbuterol, procaterol, metaproterenol, fenoterol, bitolterol mesylate, salmeterol, formoterol, bambuterol, clenbuterol, indacaterol, L-796568, amibegron, solabegron, isoproterenol, albuterol, metaproterenol, arbutamine, befunolol, bromoacetylalprenololmenthane, broxaterol, cimaterol, cirazoline, denopamine, dopexamine, epinephrine, etilefrine, hexoprenaline, higenamine, isoetharine, isoxsuprine, mabuterol, methoxyphenamine, nylidrin, oxyfedrine, prenalterol, ractopamine, reproterol, rimiterol, ritodrine, tretoquinol, tulobuterol, xamoterol, zilpaterol, zinterol, or any combination thereof.

77. The method of any of claims 1-76, wherein the PKD being treated or delayed is autosomal dominant PKD.

78. The method of any of claims 1-76, wherein the PKD being treated or delayed is autosomal recessive PKD.

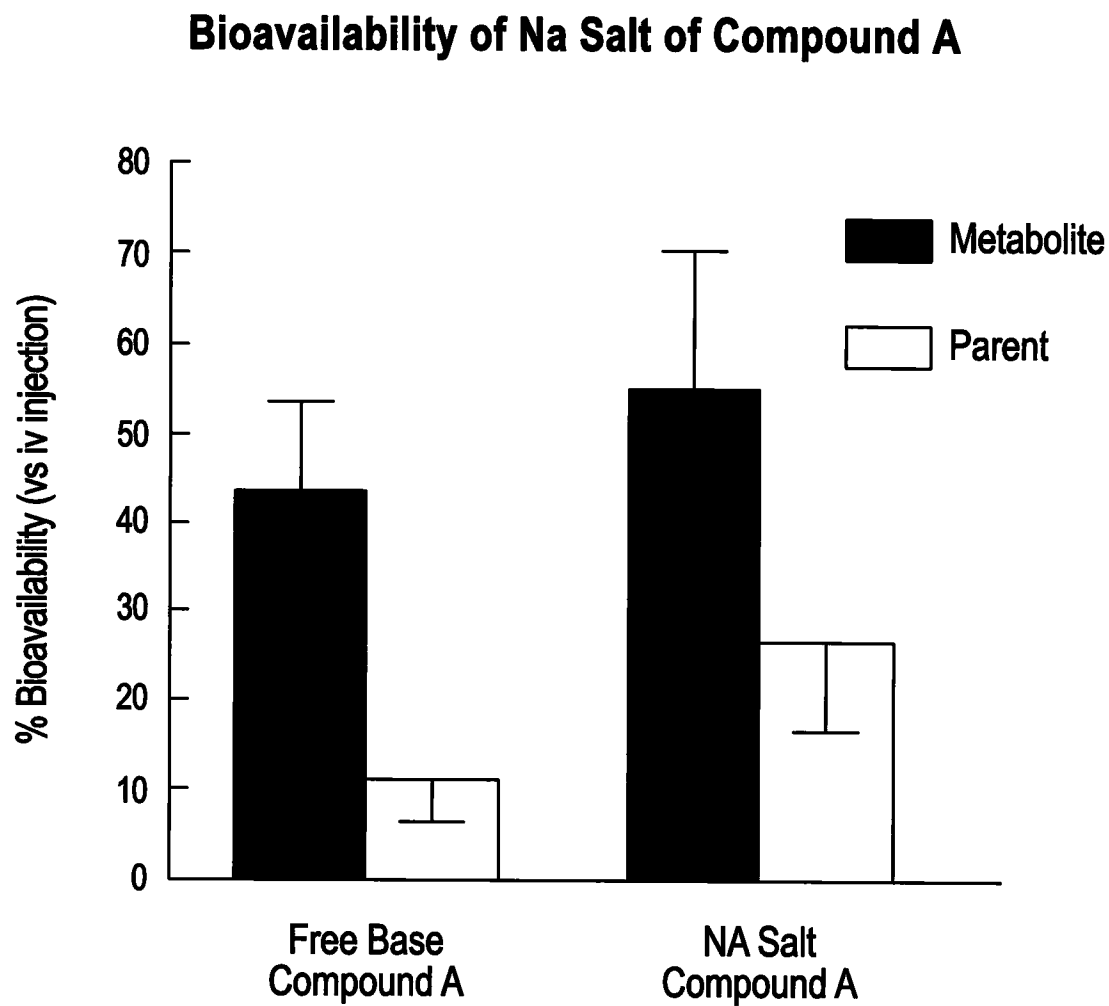


FIG. 1

Increase AUC versus Powder in Capsule (PIC)

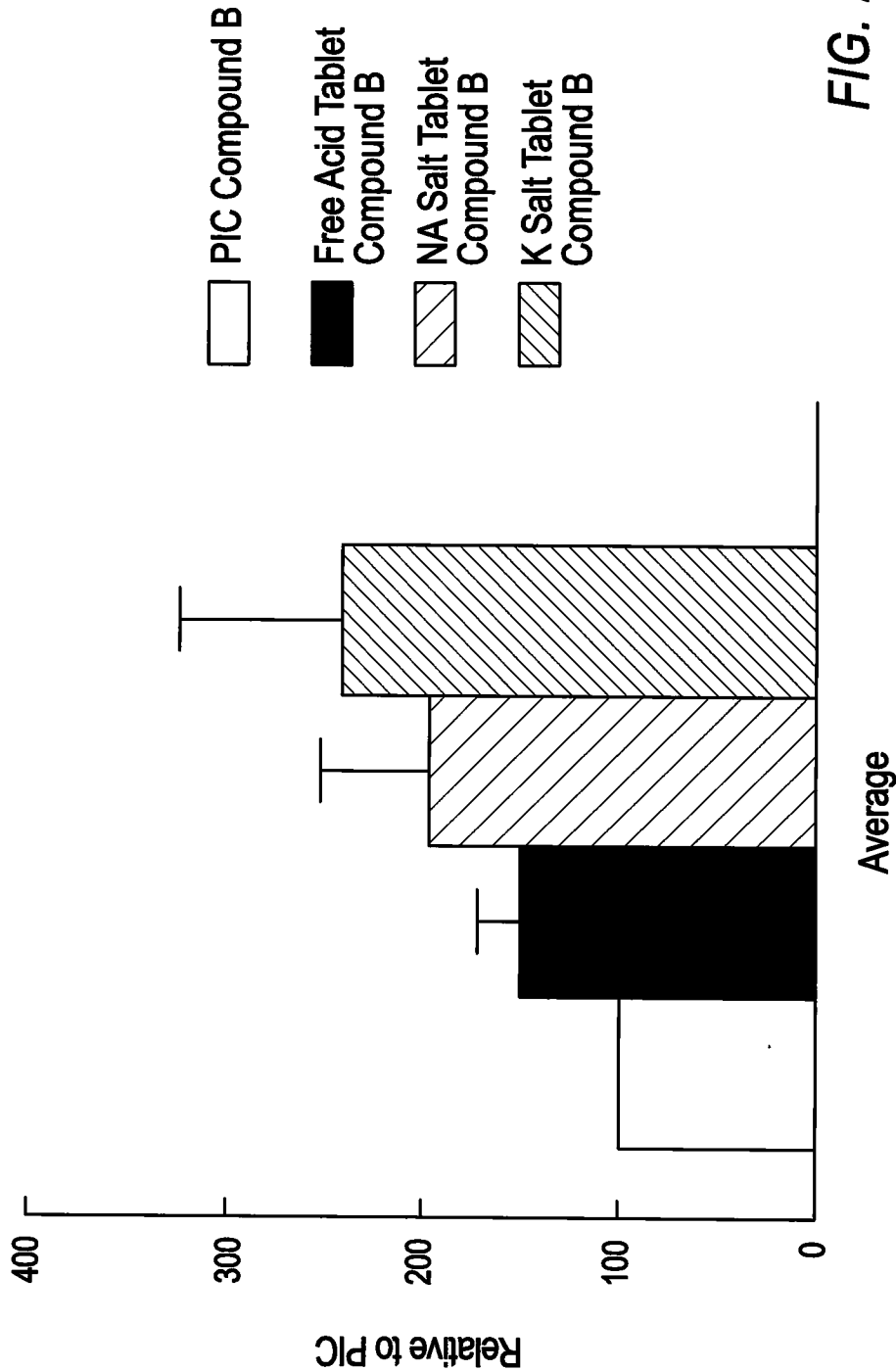


FIG. 2

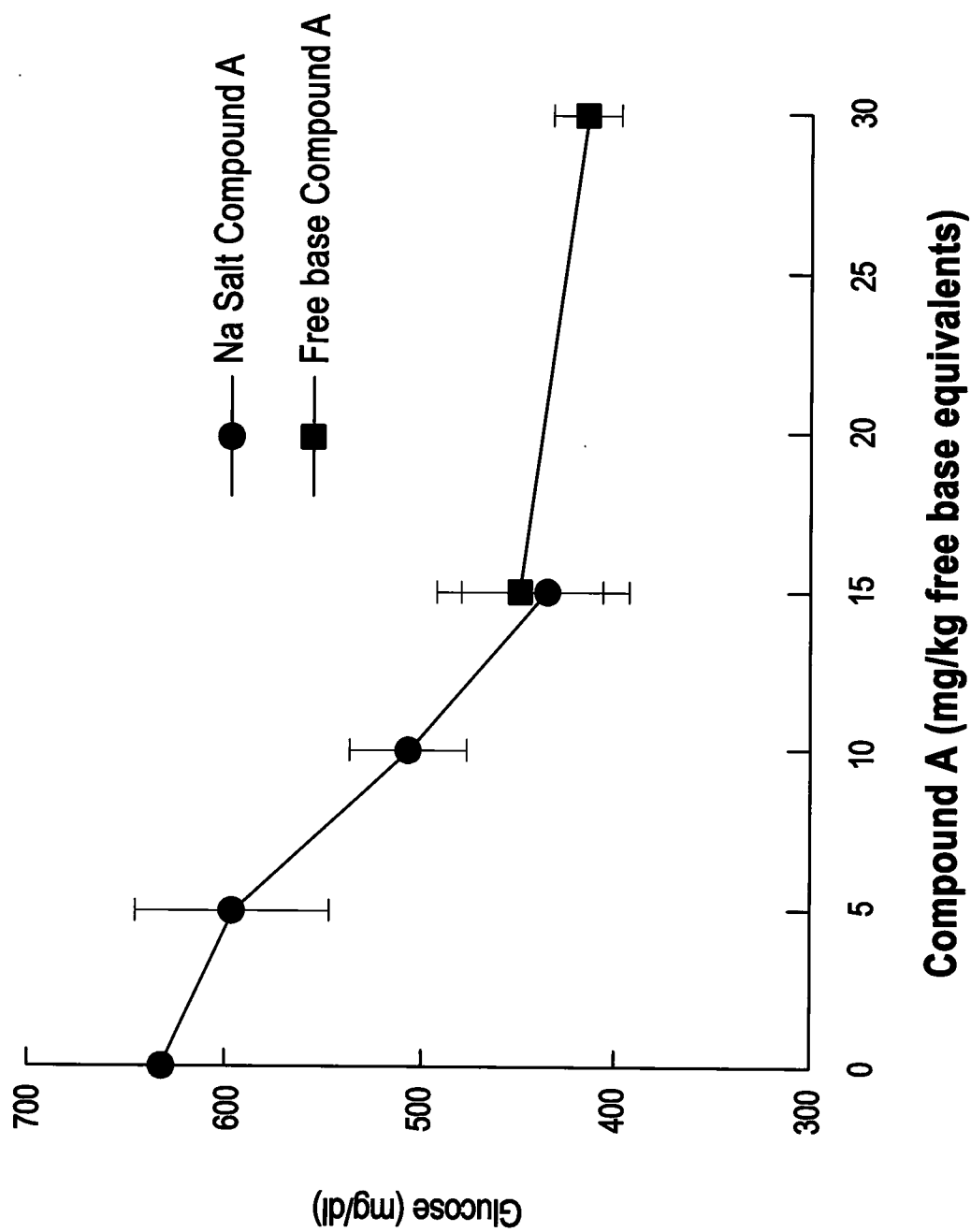
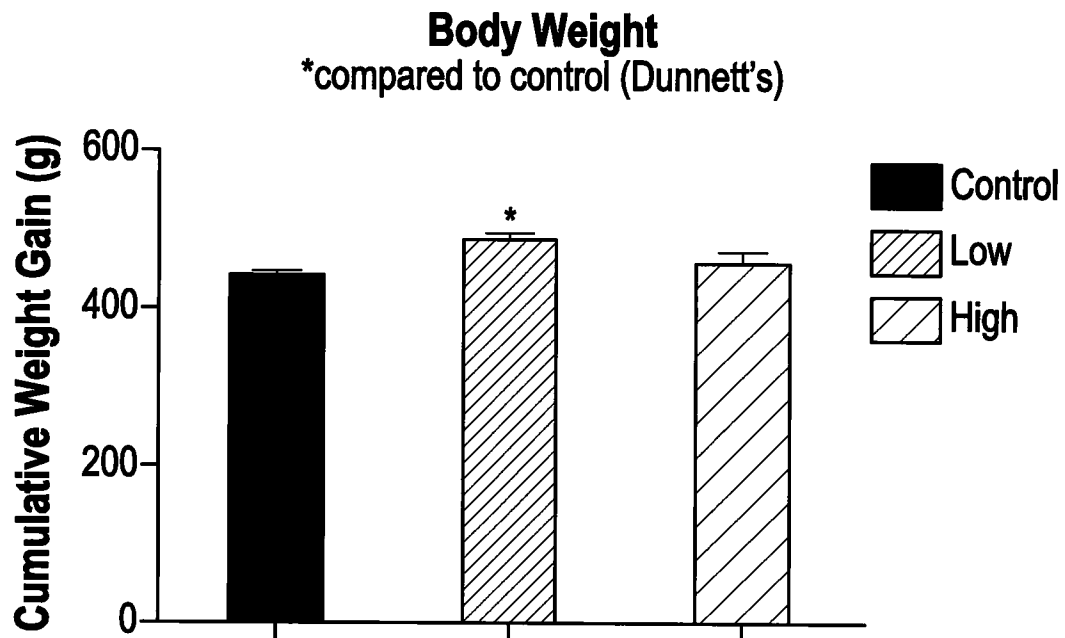
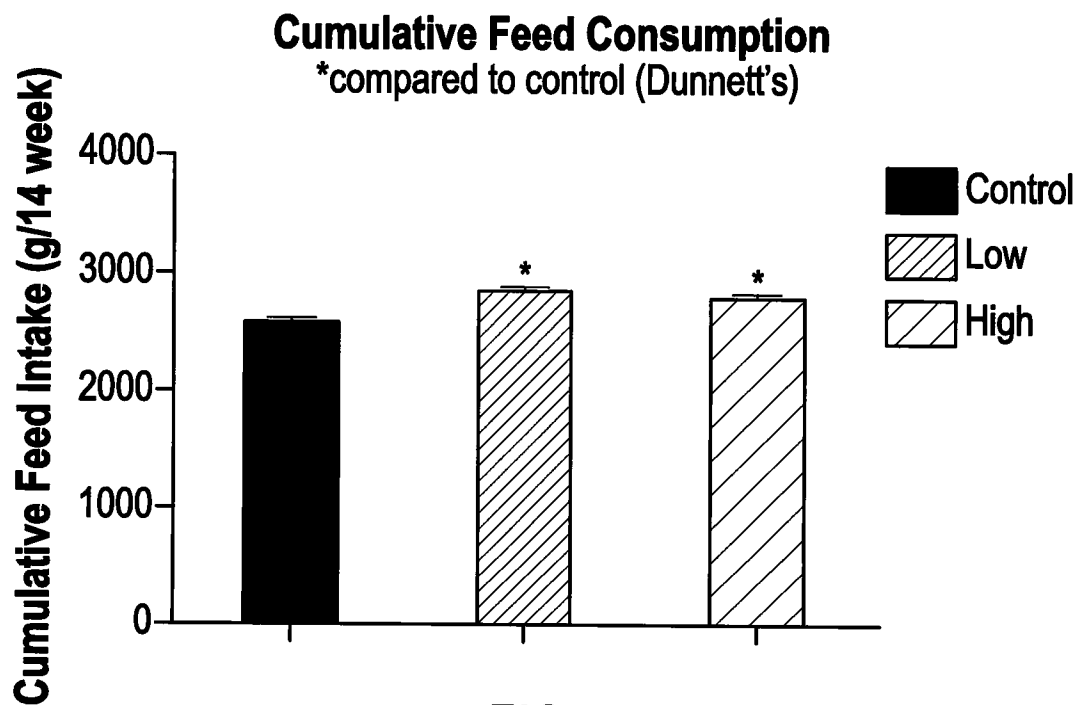


FIG. 3

*FIG. 4**FIG. 5*

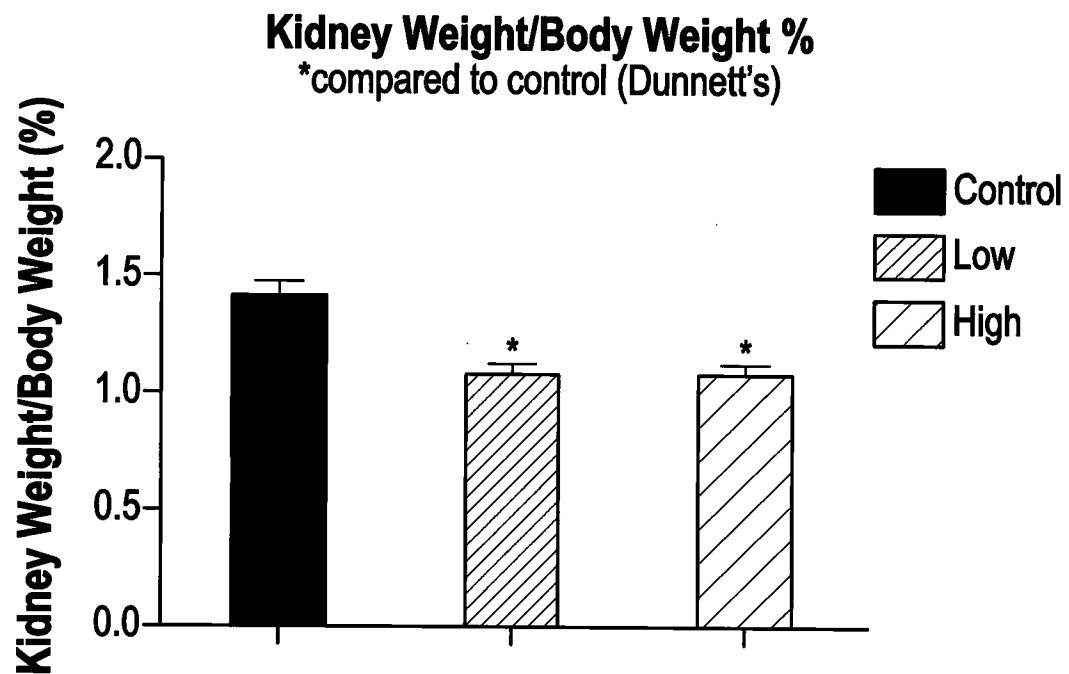


FIG. 6

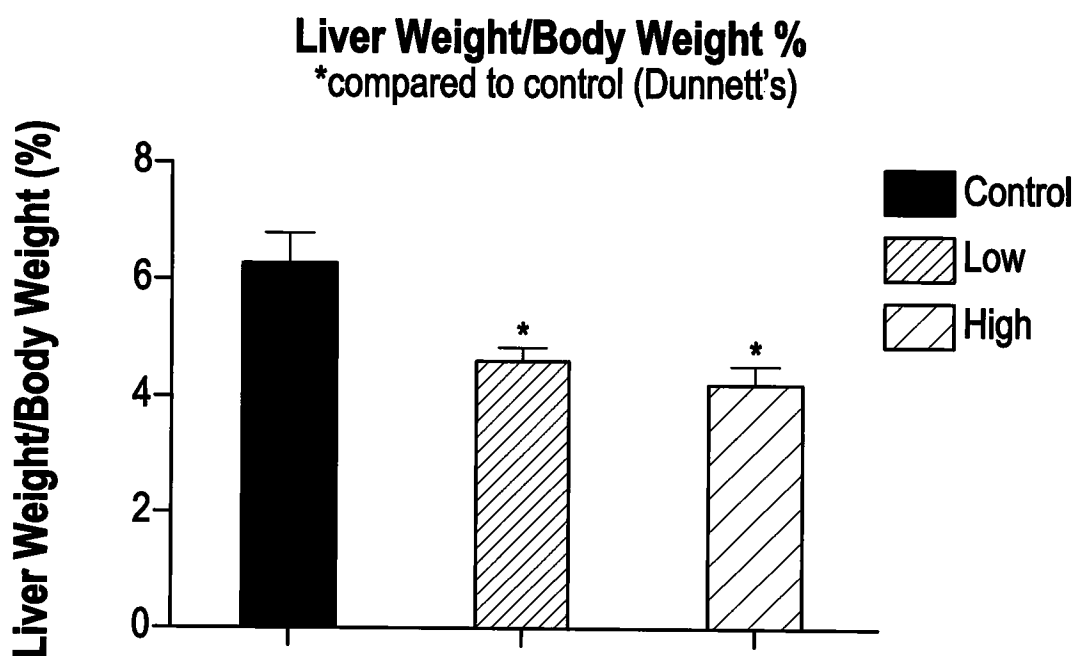
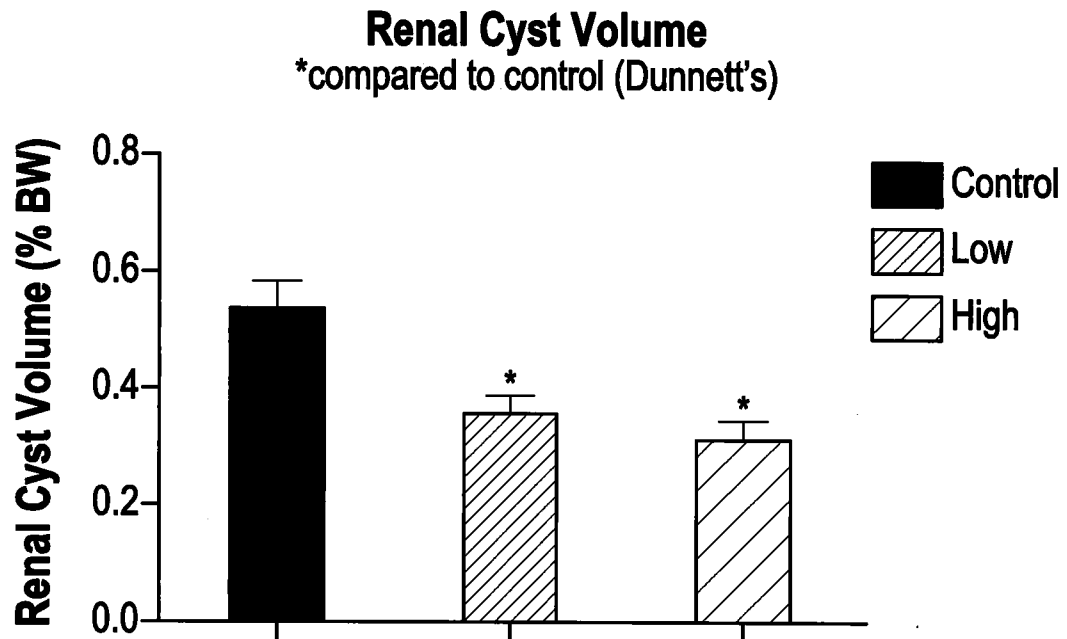
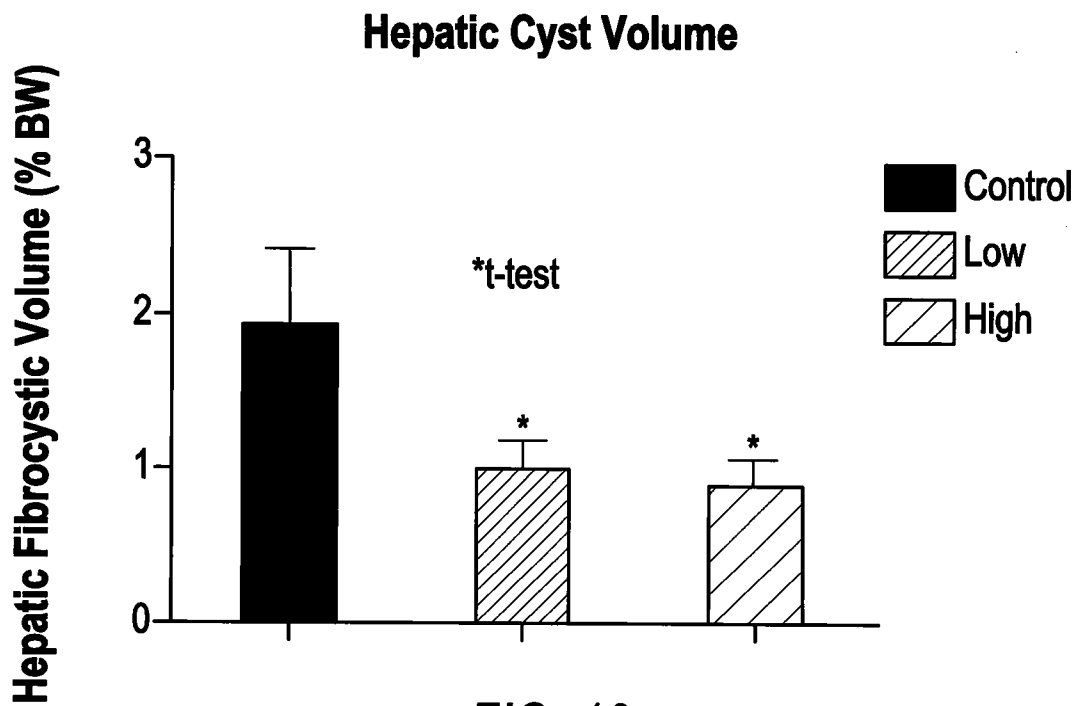


FIG. 7

*FIG. 8**FIG. 10*

Renal Fibrosis



FIG. 9

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/035083

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/426 A61P13/12
ADD.

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)
A61K

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 practicable, search terms used)

EP0-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2008/207711 A1 (LI RONG [US] ET AL) 28 August 2008 (2008-08-28) See claims and paragraphs [0004, 0005, 0006, 0018-0021], examples 1, 2: use of thiazolidinediones ("glitazones", and in particular pioglitazone) for treating polycystic kidney disease ----- -/--	1-5, 7, 9, 10, 12, 14, 26, 42-48, 50, 52, 55, 57, 65, 67, 68

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

30 May 2012

Date of mailing of the international search report

14/06/2012

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Veronese, Andrea

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/035083

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	----- LIU YAWEI ET AL: "Rosiglitazone inhibits cell proliferation by inducing G1 cell cycle arrest and apoptosis in ADPKD cyst-lining epithelia cells.", BASIC & CLINICAL PHARMACOLOGY & TOXICOLOGY JUN 2010 LNKD- PUBMED:20210794, vol. 106, no. 6, June 2010 (2010-06), pages 523-530, XP002676819, ISSN: 1742-7843 See abstract and page 529 last paragraph: PPAR gamma agonists are promising drugs for the treatment of ADPKD	1-5,7,9, 10,12, 14,26, 42-48, 50,52, 55,57, 65,67,68
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Y	See page 26, lines 18-19 and claims 1 and 9: PPAR gamma modulators, e.g. pioglitazone decrease renal cystic enlargement See the alkali metal salts of page 25, paragraph [0135]	1-78
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/035083

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Y	WO 2010/105048 A1 (METABOLIC SOLUTIONS DEV COMPAN [US]; COLCA GERARD R [US]; LARSEN SCOTT) 16 September 2010 (2010-09-16) See the compounds of examples and claims, and their use as PPAR gamma agonists and see paragraph [0007]: reduced side effects compared to other PPAR agonists -----	1-78

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