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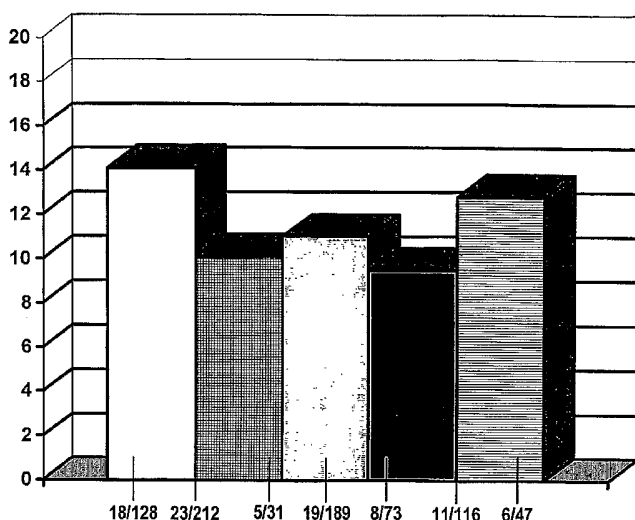
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(54) Title: METHODS FOR AVOIDING EDEMA IN THE TREATMENT OF METABOLIC, INFLAMMATORY, AND CAR-
DIOVASCULAR DISORDERS**Combined Incidence of Edema in First and Second
Phase 2 Studies**

- ☐ Combined Placebo Groups
☒ All Doses Groups Combined
☐ 200 mg Dose Group
☒ 400+600 mg Dose Group Combined
☒ 600 mg Dose Group

(57) Abstract: Compounds, compositions, and methods of treating or preventing edema, inflammatory disorders, pro-inflammatory states, or lowering CRP levels in subjects using edema-sparing PPAR γ modulators or phenoxyacetic acid derivatives are provided. The methods find use as well in treating subjects having elevated markers (CRP, IL-6) for pro-inflammatory states.



Declaration under Rule 4.17:

— of inventorship (Rule 4.17(iv))

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METHODS FOR AVOIDING EDEMA IN THE TREATMENT OF METABOLIC, INFLAMMATORY, AND CARDIOVASCULAR DISORDERS

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER
FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[0001] NOT APPLICABLE

REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER
PROGRAM LISTING APPENDIX SUBMITTED ON A COMPACT DISK.

[0002] This application claims benefit under 35 U.S.C. §112(e) of U.S. Provisional Application Serial No. 60/663,977, filed March 21, 2005, and of U.S. Provisional Application Serial No. 60/664,515 filed March 22, 2005, the disclosure of each of which is incorporated herein in its entirety for all purposes to the extent not inconsistent with the present disclosure. This application is related in subject matter to a PCT application of the same inventorship and assignment as the present application, entitled "Methods for Avoiding Edema in the Treatment or Prevention of PPAR γ -Responsive Diseases, including Cancer," filed March 21, 2006 (Attorney-Client Matter No. 016325-020210PC), which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0003] Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptor superfamily of transcription factors, a large and diverse group of proteins that mediate ligand-dependent transcriptional activation and repression. They play a role in controlling expression of proteins that regulate lipid metabolism. Furthermore, the PPARs are activated by fatty acids and fatty acid metabolites. Three PPAR subtypes have been isolated: PPAR α , PPAR β (also referred to as δ or NUC1), and PPAR γ . Each receptor shows a different pattern of gene expression by binding to DNA sequence elements, termed PPAR response elements (PPRE). In addition, each receptor shows a difference in activation by structurally diverse compounds. To date, PPREs have been identified in the enhancers of a number of genes encoding proteins that regulate lipid metabolism suggesting that PPARs

[0004] PPAR α is found in the liver, heart, kidney, muscle, brown adipose tissue and gut and is involved in stimulating β -oxidation of fatty acids. PPAR α is also involved in the control of cholesterol levels in rodents and in humans. Fibrates are weak PPAR α agonists that are effective in the treatment of lipid disorders. In humans, they have been shown to lower plasma triglycerides and LDL cholesterol. In addition, PPAR α agonists have also been reported to prevent diabetes and to improve insulin sensitivity and reduce adiposity in obese and diabetic rodents (*see Koh, E. H. et al. Diabetes 52:2331-2337 (2003); and Guerre-Millo, M. et al. J. Biol. Chem. 275: 16638-16642 (2000)*).

[0005] PPAR β is ubiquitously expressed. Activation of PPAR β increases HDL levels in rodents and monkeys (*see Oliver, W.R. et al. PNAS 98:5306-5311 (2001); and Leibowitz, M.D. et al. FEBS Letters 473:333-336 (2000)*). Moreover, PPAR β has been recently shown to be a key regulator of lipid catabolism and energy uncoupling in skeletal muscle cells (Dressel, U. *et al. Mol Endocrinol. 17: 2477-2493 (2003)*). In rodents, activation of PPAR β induces fatty β -oxidation in skeletal muscle and adipose tissue, leading to protection against diet-induced obesity and diabetes (*see Wang, Y. X. et al. Cell 113:159-170 (2003); and Tanaka et al. PNAS 100:15924-15929 (2003)*). In human macrophages, PPAR β activation also increases the reverse cholesterol transporter ATP-binding cassette A1 and induces apolipoprotein A1-specific cholesterol efflux (*see Oliver, W.R. et al. PNAS 98:5306-5311 (2001)*).

[0006] PPAR γ is expressed most abundantly in adipose tissue and induces adipocyte differentiation. Drugs of the thiazolidinedione (TZD) class namely troglitazone, pioglitazone, and rosiglitazone are potent and selective activators of PPAR γ . In humans, these drugs increase insulin action, reduce serum glucose, induce the differentiation of preadipocytes to adipocytes, and have small but significant effects on reducing serum triglyceride levels in patients with type 2 diabetes. Unfortunately, such PPAR γ -based therapies have been associated with unwanted weight gain and edema. These agents have also been implicated in the regulation of triglyceride and cholesterol levels in humans or animal models (*See, e.g., U.S. Pat. No. 5,859,501, and PCT publications WO 97/28149 and 99/04815*). The role of PPARs in the regulation of metabolism has been the subject of a number of reviews (*see, Spiegelman, Diabetes, , Vol. 47, pp. 507-514 (1998); Schoonjans, et al., Curr. Opin. Lipidol. 8, 159-166(1997); Brun, et al., Curr. Opin. Lipidol. 8: 212-218 (1997)*).

[0007] The PPAR γ receptor is found in many other tissues than adipose tissue. PPAR γ modulators can have beneficial effects in many other diseases including cardiovascular disease, inflammation, and cancer (Schoonjans et al., *Curr. Opin. Lipidol.* 8, 159-166 (1997); Ricote, et al., *Nature* 391: 79-82 (1998); Mueller, et al., *Mol. Cell* 1: 465-470 (1998)). However, compounds that activate PPAR γ may have, in a number of instances, been associated with adverse side effects such as fluid retention, weight gain, peripheral edema, pulmonary edema, and congestive heart failure. U.S. Patent Application Publication No. 20050020654 describes compounds which antagonize the angiotensin II type 1 receptor and also activate PPAR γ as being of use in avoiding these side effects which can otherwise limit their clinical use.

[0008] More recently, the (-) isomers of halofenic acid and derivatives thereof which are particularly useful in the treatment of insulin resistance, Type 2 diabetes, obesity, and hyperuricemia (See, U.S. Patent Nos. 6,646,004; 6,624,194; 6,613,802; and 6,262,118, each to Luskey et al. and also U.S. Patent Application Publication No. 20040029933 to Zhao et al.) have also been reported to be selective, partial PPAR γ agonists with unexpectedly advantageous properties over their (+) isomers with respect to COX-1 inhibition, glucose lowering, and inhibition of Cytochrome P450 2C9. It has now been surprisingly found that these compounds do not cause edema and also that they reduce inflammation, and so are useful in treating and preventing inflammation and untoward cardiovascular outcomes in patients with edema or those who would experience an adverse health effects of edema.

BRIEF SUMMARY OF THE INVENTION

[0009] In one aspect, the invention relates to the finding that 3-trihalomethylphenoxy 4-halophenyl acetic acids (e.g., (-) halofenic acid or (-) (3-trifluoromethylphenoxy) (4-chlorophenyl) acetic acid (e.g., (-) halofenic acid)), their derivatives, analogs, and prodrugs thereof, while useful as partial agonists of PPAR γ do not cause edema. In particular, the invention provides compounds of formula I, II, III, IVa, IVb, V, VI, and VII for use as edema-sparing PPAR γ modulators. These compounds are particularly useful in treating conditions or subjects for which other PPAR γ modulators are contra-indicated due to their potential to cause edema. Accordingly, the invention provides pharmaceutical compositions and methods of treatment based upon the use of these edema-sparing PPAR γ modulators (*i.e.*, the compounds of formula I, II, III, IVa, IVb, V, VI, and VII) in treating subjects or conditions whose conditions are rendered unsuitable for treatment with other PPAR γ modulators (e.g., troglitazone, pioglitazone, rosiglitazone) due to the ability of these other

PPAR γ modulators to cause edema. For instance, the edema-sparing PPAR γ modulators of the present invention find use in chronically treating pro-inflammatory states associated with elevated C-reactive protein levels. Subjects with elevated C-reactive protein levels are at an increased risk of cerebrovascular and cardiovascular events thromboembolism, myocardial infarction (MI) and cerebrovascular accident (CVA). The use of PPAR γ modulators that cause edema is contra-indicated in subjects with an elevated C-reactive protein level as the drug-induced edema can exacerbate the very condition to be treated. Such conditions would include any condition, including heart or cardiovascular diseases co-incident with, or exacerbated by, edema. Accordingly, in some embodiments, the condition can be coronary arterial disease, cardiac insufficiency, hypertension, myocardial infarction, heart failure, and congestive heart failure. In additional embodiments, the condition can be venous congestion, angina, coronary vasospasm, cardiac ischemia, liver cirrhosis, hyponatremia, renal vasospasm, renal failure, diabetic nephropathy, cerebral edema, cerebral ischemia, stroke, and thrombosis.

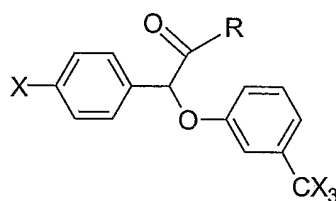
[0010] In some embodiments, the method provides a method of reducing inflammation or lowering C-reactive protein levels in a subject in need thereof by administering an edema-sparing PPAR γ modulator according to the invention. In other embodiments, the invention treats a subject having elevated C-reactive protein levels by administering an edema-sparing PPAR γ modulator. Accordingly, in some embodiments, the invention provides a method of treating a subject in a pro-inflammatory state associated with an increased risk of cardio- or cerebro-vascular events by testing the subject for elevated C-reactive protein levels, or for elevated levels of another marker for a pro-inflammatory state (e.g., soluble adhesion molecules such as E-selectin, P-selectin, intracellular adhesion molecule-1, vascular cell adhesion molecule-1; cytokines such as interleukin-1 β , -6, -8, and -10 and tumor necrosis factor- α ; and fibrinogen), and then administering a subject having an elevated C-reactive protein or marker level, an edema-sparing PPAR γ modulator. In addition, the invention provides methods of treating conditions or subjects for which therapy with a PPAR γ modulator has resulted in edema and the edema-sparing PPAR γ modulators are administered as an alternative therapy.

[0011] In some aspects, the invention also provides compositions and methods for treating a patient having edema, or at increased risk of edema, and a metabolic or cardiovascular disorder by administering to the patient an effective amount of an edema-sparing PPAR γ modulatory compound having formula I, II, III, IVa, IVb, V, VI, or VII. In some

embodiments, the cardiovascular condition is selected from the group consisting of hypertension, stroke, infarct of the heart or brain, coronary arterial disease, myocardial infarction, peripheral vascular atherosclerosis, and congestive heart failure. The subject may have peripheral edema or pulmonary edema. The metabolic disorder can be insulin resistance, metabolic syndrome, Syndrome X, impaired fasting glucose, impaired glucose tolerance, polycystic ovary disease, or "pre-diabetes", or any condition characterized by insulin resistance of any degree. The edema may be secondary to a kidney disease. The subject has or has had left-sided or right-sided heart failure. The edema may be caused by administration of a second therapeutic agent. The risk of edema may be evidenced by a prior history of edema or by co-administration of a drug which is capable of causing edema. In other embodiments, the method may comprise the steps of evaluating whether the patient has edema, and administering a compound of formula I, II, III, IVa, IVb, V, VI, or VII. in the case where the subject has edema.

[0012] In other aspects the invention provides a method of treating a patient who has experienced weight gain or edema when treated with a first PPAR γ modulator, the method comprising stopping administration of the first PPAR γ modulator and administering a second PPAR γ modulator which is a compound of formula I, II, III, IVa, IVb, V, VI, or VII. In some embodiments, the first PPAR γ modulator is troglitazone, pioglitazone, or rosiglitazone.

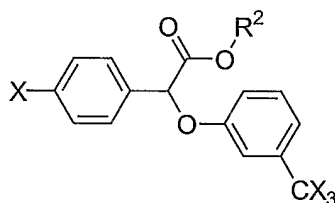
[0013] The invention relates to the surprising finding that 3-trihalomethylphenoxy 4-halophenyl acetic acids (e.g., (-) halofenic acid or (-) (3-trifluoromethylphenoxy) (4-chlorophenyl) acetic acid (e.g., (-) halofenic acid),), their derivatives and prodrugs thereof, while useful as partial agonists of PPAR γ , are also useful as anti-edema agents or edema-sparing PPAR γ modulators. Accordingly, in a first aspect, the invention provides methods of reducing cardiovascular and cerebrovascular risk in patients with concomitant inflammation while avoiding edema, including the adverse effects of edema on health, by administering to a subject in need thereof a phenoxy acetic acid compound analog or a prodrug thereof. In one embodiment, the phenoxy acetic acid compound is a (-) isomer of a compound of Formula I:



(I)

wherein R is a member selected from the group consisting of a hydroxy, alkoxy (*e.g.*, OCH_2CH_3), heteroalkoxy (*e.g.*, $\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$), aryloxy (*e.g.*, OC_6H_5), heteroaryloxy (*e.g.*, $\text{OC}_5\text{H}_4\text{N}$), lower aralkoxy, di-lower alkylamino-lower alkoxy, lower alkanamido lower alkoxy, benzamido-lower alkoxy, ureido-lower alkoxy, N' -lower alkyl-ureido-lower alkoxy, carbamoyl-lower alkoxy, halophenoxy substituted lower alkoxy, carbamoyl substituted phenoxy, carbonyl-lower alkylamino, N,N -di-lower alkylamino-lower alkylamino, halo substituted lower alkylamino, hydroxy substituted lower alkylamino, lower alkanolyloxy substituted lower alkylamino, ureido, arylsulfonamido (*e.g.*, NHTs), alkylsulfonamido (*e.g.*, NHMs) and lower alkoxycarbonylamino; and each X is independently a halogen; or a pharmaceutically acceptable salt thereof. Particularly preferred compounds of the above formula are set forth in U.S. Patent Nos. 6,646,004; 6,624,194; 6,613,802; and 6,262,118 which are incorporated by reference herein with respect to such compound subject matter. Particularly preferred are prodrugs of (-) halofenic acid which therefore release (-) halofenic acid when administered to a subject.

[0014] In another embodiment, the phenoxy acetic acid compound is the (-) isomer of a compound of Formula II:

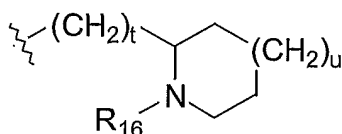
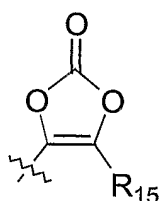


(II)

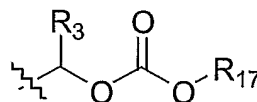
wherein R^2 is a member selected from the group consisting of alkyl, heteroalkyl, aryl, heteroaryl, phenyl-lower alkyl, lower alkanamido-lower alkyl, benzamido-lower alkyl, di-lower alkylamino-lower alkyl, ureido-lower alkyl, N' -lower alkyl-ureido-lower alkyl, carbamoyl-lower alkyl, halophenoxy substituted lower alkyl and carbamoyl substituted phenyl. Particularly preferred R^2 are those which readily undergo hydrolysis *in vivo* or when administered to a subject.

[0015] R^2 groups can also include, without limitation, the following: C_1 - C_5 alkyl, C_1 - C_8 -cyclic alkyl, C_2 - C_5 alkenyl, and C_2 - C_5 alkynyl, wherein the groups are optionally substituted with one or more halogen atoms; phenyl, naphthyl and pyridyl, wherein the groups are optionally substituted with one or more substituents selected from the group consisting of halo, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, $-\text{NO}_2$, $-\text{S}(\text{O})_m(\text{C}_1\text{-C}_5\text{alkyl})$, $-\text{OH}$, $-\text{NR}^3\text{R}^4$, $-\text{CO}_2\text{R}^5$,

$-\text{CONR}^3\text{R}^4$, $-\text{NR}^3\text{COR}^4$, $-\text{NR}^3\text{CONR}^3\text{R}^4$ and $-\text{C}_v\text{F}_w$; $-(\text{CHR}^3)\text{R}^4$; $-\text{R}^7\text{OR}^3$;
 $-\text{R}^7\text{O}_2\text{CR}^8\text{NR}^3\text{R}^4$, $-(\text{CH}_2)_o\text{CH}(\text{R}^3)(\text{CH}_2)_q\text{O}_2\text{CR}^9$; $-(\text{CH}_2)_o\text{CH}(\text{R}^3)(\text{CH}_2)_q\text{NR}^4\text{COR}^9$;
 $-(\text{CH}_2)_o\text{CH}(\text{R}^3)(\text{CH}_2)_q\text{NR}^4\text{CONR}^3\text{R}^4$; $-(\text{CH}_2)_o\text{CH}(\text{R}^3)(\text{CH}_2)_q\text{NR}^4\text{COOR}^{10}$;
 $-(\text{CH}_2)_o\text{CH}(\text{R}^3)(\text{CH}_2)_q\text{NR}^4\text{SO}_2\text{R}^{11}$; $-(\text{CHR}^3)_p\text{CO}_2\text{R}^{12}$; $-(\text{CHR}^3)_p\text{NR}^3\text{R}^4$; $-(\text{CHR}^3)_s\text{CONR}^{13}\text{R}^{14}$

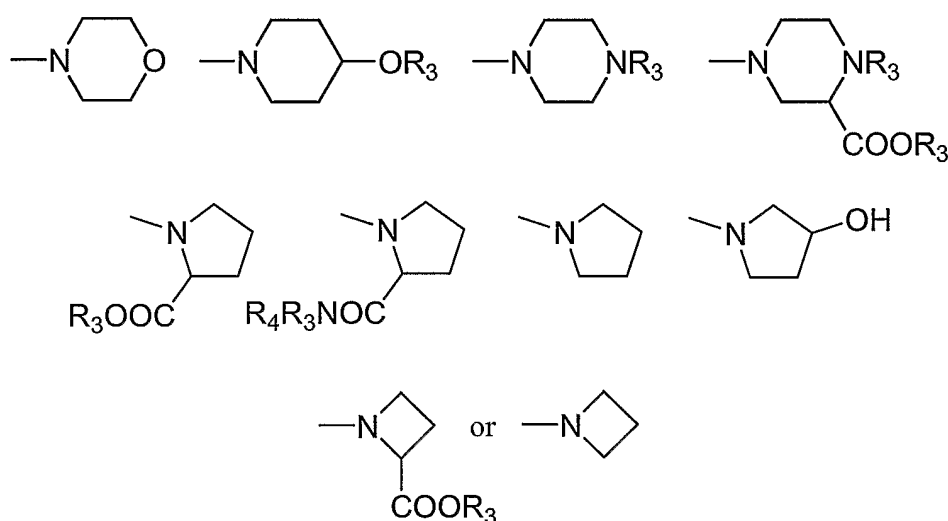


and



Subscripts m, o, q, s, t, u, v and w are integers as follows: m is 0 to 2; o and q are 0 to 5; p is 1 to 5; s is 1 to 3; t is 1 to 5; u is 0 to 1; v is 1 to 3; and w is 1 to $(2v + 1)$. R^3 and R^4 are independently H, $\text{C}_1\text{-C}_5$ alkyl, phenyl or benzyl. R^5 is H, $\text{C}_1\text{-C}_5$ alkyl or NR^3R^4 . R^6 is phenyl, naphthyl, pyridyl, imidazolyl, indoxyl, indolizynyl, oxazolyl, thiazolyl, pyrimidyl, or 1-pyrazolyl optionally substituted with one or more substituents selected from the group consisting of halo, $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_4$ alkoxy, $-\text{NO}_2$, $-\text{S}(\text{O})_m(\text{C}_1\text{-C}_5\text{alkyl})$, $-\text{OH}$, $-\text{NR}^3\text{R}^4$, $-\text{CO}_2\text{R}^5$, $-\text{CONR}^3\text{R}^4$, $-\text{NR}^3\text{COR}^4$, $-\text{NR}^3\text{CONR}^3\text{R}^4$ and $-\text{C}_v\text{F}_w$. R^7 is a $\text{C}_1\text{-C}_8$ saturated or unsaturated, straight-chain, branched or cyclic alkylene or alkylidene group optionally substituted with one or more groups selected from halo, hydroxyl, thiol, amino, monoalkyl amino, dialkyl amino, acylamino, carboxyl, alkylcarboxyl, acyl, aryl, aroyl, aralkyl, cyano, nitro, alkoxy, alkenyloxy, alkylcarbonyloxy and arylcarbonyloxy. R^8 is a $\text{C}_1\text{-C}_8$ straight-chain or branched alkylene or alkylidene optionally substituted with one or more groups selected from amino, monoalkyl amino, dialkyl amino, acylamino, hydroxyl, thiol, methylthiol, carboxyl and phenyl. R^9 and R^{10} are independently H, $\text{C}_1\text{-C}_5$ alkyl, optionally substituted with one or more groups consisting of $\text{C}_1\text{-C}_5$ alkoxy aryl and heteroaryl, wherein the aryl is phenyl or naphthyl optionally substituted with one or more substituents selected from the group consisting of halo, $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_4$ alkoxy, $-\text{NO}_2$, $-\text{S}(\text{O})_m(\text{C}_1\text{-C}_5\text{alkyl})$, $-\text{OH}$, $-\text{NR}^3\text{R}^4$, $-\text{CO}_2\text{R}^5$, $-\text{CONR}^3\text{R}^4$, $-\text{NR}^3\text{COR}^4$, $-\text{NR}^3\text{CONR}^3\text{R}^4$ and $-\text{C}_v\text{F}_w$, and wherein the heteroaryl is pyridyl optionally substituted with one or more substituents selected from the group consisting of halo, $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_4$ alkoxy, $-\text{NO}_2$, $-\text{S}(\text{O})_m(\text{C}_1\text{-C}_5\text{alkyl})$, $-\text{OH}$, $-\text{NR}^3\text{R}^4$, $-\text{CO}_2\text{R}^5$, $-\text{CONR}^3\text{R}^4$, $-\text{NR}^3\text{COR}^4$, $-\text{NR}^3\text{CONR}^3\text{R}^4$ and $-\text{C}_v\text{F}_w$. R^{11} is methyl or phenyl, wherein the phenyl is optionally substituted with methyl and/or $-\text{NO}_2$. R^{12} is H, $\text{C}_1\text{-C}_5$ alkyl, phenyl, benzyl, naphthyl or pyridyl, wherein the $\text{C}_1\text{-C}_5$ alkyl, phenyl, naphthyl,

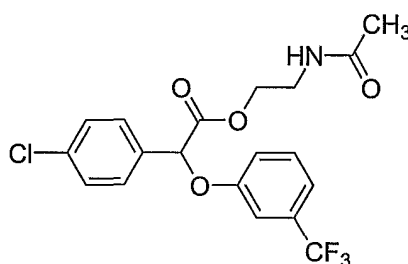
benzyl and pyridyl are optionally substituted with one or more substituents selected from the group consisting of halo, C₁-C₄ alkyl, C₁-C₄ alkoxy, -NO₂, -S(O)_m(C₁-C₅alkyl), -OH, -NR³R⁴, -CO₂R⁵, -CONR³R⁴, -NR³COR⁴, -NR³CONR³R⁴ and -C_vF_w. R¹³ and R¹⁴ are independently the following: alkyl, alkenyl, aryl, aralkyl or cycloalkyl, wherein the groups are optionally substituted with one or more substituents selected from the group consisting of halo, C₁-C₄ alkyl, C₁-C₄ alkoxy, -NO₂, -S(O)_m(C₁-C₅alkyl), -OH, -NR³R⁴, -CO₂R⁵, -CONR³R⁴, -NR³COR⁴, -NR³CONR³R⁴, -CH₂NR³R⁴, OOCR¹⁸ and -C_vF_w; and wherein R¹³ and R¹⁴ are included as -(CHR₃)CONR¹³R¹⁴, NR¹³R¹⁴ is



R¹⁵ is C_vF_w or C₁-C₅ alkyl, wherein C₁-C₅ alkyl is optionally substituted with the following substituents: C₁-C₅ alkoxy; phenyl, optionally substituted with one or more substituents selected from the group consisting of halo, C₁-C₄ alkyl, C₁-C₄ alkoxy, -NO₂, -S(O)_m(C₁-C₅alkyl), -OH, -NR³R⁴, -CO₂R⁵, -CONR³R⁴, -NR³COR⁴, -NR³CONR³R⁴ and -C_vF_w; benzyl, optionally substituted with one or more substituents selected from the group consisting of halo, C₁-C₄ alkyl, C₁-C₄ alkoxy, -NO₂, -S(O)_m(C₁-C₅alkyl), -OH, -NR³R⁴, -CO₂R⁵, -CONR³R⁴, -NR³COR⁴, -NR³CONR³R⁴ and -C_vF_w. R¹⁶ is H, C₁-C₅ alkyl or benzyl. R¹⁷ is C₁-C₅ alkyl, C₃-C₈ cyclic alkyl, phenyl or benzyl. R¹⁸ is H, alkyl, aryl, aralkyl or cycloalkyl, where the group is optionally substituted with one or more substituents selected from the group consisting of halo, C₁-C₄ alkyl, C₁-C₄ alkoxy, -NO₂, -S(O)_m(C₁-C₅alkyl), -OH, -NR³R⁴, -CO₂R⁵, -CONR³R⁴, -NR³COR⁴, -NR³CONR³R⁴ and -C_vF_w. Particularly preferred compounds of the above formula and methods for making such compounds are

taught in U.S. Patent Application Publication No. 20030220399 which is incorporated herein by reference and in particularity with respect to such subject matter.

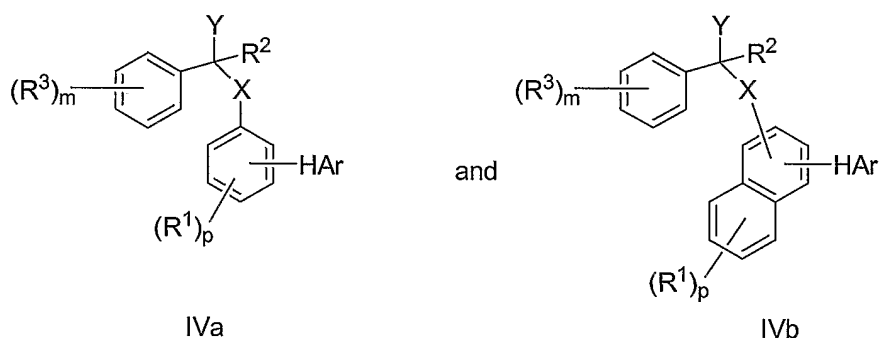
[0016] In an exemplary embodiment, the compound to be administered according to the invention is (-) 2-acetamidoethyl 4-chlorophenyl-(3-trifluoromethylphenoxy) acetate (i.e., (-) halofenate)), a compound of Formula III:



(III)

In some embodiments, the compound of Formula III is administered in the form of a composition which contains the (-) stereoisomer of halofenate and which is substantially free of its (+) stereoisomer.

[0017] In yet other embodiments, the edema-sparing compound is a compound of formula IV:



in which the letter X is selected from O, S, SO, SO₂ and NR, wherein R is H, (C₁-C₈)alkyl, COR^a, COOR^a and CONR^aR^b wherein R^a and R^b are each independently selected from H and (C₁-C₈)alkyl; the letter Y represents CH₂OR^c, CO₂R^c, CHO, CONR^cR^m, CH(=NR^c), CH(=NOR^c) or a carboxylic acid surrogate, wherein R^c is selected from H, (C₁-C₈)alkyl, (C₃-C₈)alkenyl, (C₃-C₈)alkynyl, (C₃-C₇)cycloalkyl, (C₄-C₈)cycloalkyl-alkyl, aryl, aryl(C₁-C₈)alkyl and (C₁-C₈)alkylene-Z, wherein Z is selected from COR^d, COOR^d, NR^dR^e, NR^dCONR^eR^f, NR^dCOR^e, NR^dCOOR^e and CONR^dR^e wherein R^d, R^e and R^f are each independently selected from H, (C₁-C₈)alkyl and phenyl, or optionally two of R^d, R^e and R^f when attached to the same nitrogen atom are combined to form a five- or six-membered ring; and wherein R^m is

selected from H, (C₁-C₈)alkyl, aryl, OH and SO₂Rⁿ, wherein Rⁿ is selected from (C₁-C₈)alkyl, (C₁-C₈)haloalkyl, (C₁-C₈)aralkyl, (C₂-C₈)heteroalkyl, aryl, heteroaryl, (C₁-C₈)alkoxy, aryloxy, alkylamino, dialkylamino, arylamino, diarylamino, haloalkylamino and di(haloalkyl)amino, and R^m and R^c are optionally combined with the nitrogen atom to which each is attached to form a five- or six-membered ring.

[0018] HAr represents a heteroaryl moiety, optionally substituted with from one to three substituents independently selected from halogen, hydroxy, (C₁-C₈)alkyl, aryl(C₁-C₈)alkyl, (C₁-C₈)alkoxy, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)cycloalkyl, (C₄-C₈)cycloalkyl-alkyl, (C₁-C₈)heteroalkyl, (C₂-C₅)heterocyclyl, aryl, aryloxy, heterosubstituted(C₃-C₇)cycloalkyl, heteroalkyl substituted (C₃-C₇)cycloalkyl, (C₁-C₈)haloalkyl, O(C₁-C₈)haloalkyl, nitro, cyano, CO₂R^g, COR^g, NR^gR^h, S(O)_qR^g, SO₂NR^gR^h, NR^gCONR^hRⁱ, NR^gCOR^h, NR^gCOOR^h and CONR^gR^h, wherein R^g, R^h and Rⁱ are each independently selected from H and (C₁-C₈)alkyl, or optionally two of R^g, R^h and Rⁱ when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript q is an integer of from 0 to 2.

[0019] A variety of heteroaryl groups provide compounds having the desired activity. In particular, the heteroaryl groups can be monocyclic or fused bicyclic heteroaryl groups. More particularly, one group of suitable monocyclic heteroaryl groups is provided in Figure 1A. In this Figure, the line extending from the ring indicates the point of attachment to the remainder of the compound and can be made through any available valence on the ring. Other examples of heteroaryl groups are provided in Figure 1B, which illustrates preferred fused-bicyclic heteroaryl groups, wherein attachment to the remainder of the compound can take place through an available valence on either ring.

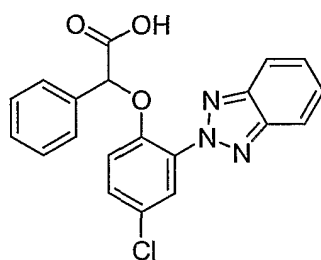
[0020] Returning to formulae IVa and IVb, the subscripts m and p indicate the presence of substituents on their respective rings, wherein each substituent present can be the same or different from any other substituent. More particularly, the subscript m is an integer of from 0 to 4, and the subscript p is an integer of from 0 to 3. More preferably the subscript m is an integer of from 0 to 3, and the subscript p is an integer of from 0 to 3. Still more preferably, the subscript m is an integer of from 0 to 2, and the subscript p is an integer of from 0 to 2. Most preferably, the subscript m is 0, 1 or 2 and the subscript p is 1 or 2.

[0021] Each R¹ and R³ represents a substituent independently selected from halogen, hydroxy, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₁-C₈)alkoxy, (C₃-C₇)cycloalkyl, (C₄-C₈)cycloalkyl-alkyl, (C₁-C₈)haloalkyl, (C₁-C₈)heteroalkyl, (C₂-C₅)heterocyclyl,

heterosubstituted(C₃-C₇)cycloalkyl, heteroalkyl substituted (C₃-C₇)cycloalkyl, O(C₁-C₈)haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl, S(O)_r-phenyl, COR^j, COOR^j, NR^jR^k, S(O)_rR^j, SO₂NR^jR^k, NR^jCONR^kR^l, NR^jCOR^k, NR^jCOOR^k and CONR^jR^k wherein the phenyl ring is optionally substituted and R^j, R^k and R^l are each independently selected from H, (C₁-C₈)alkyl and (C₁-C₈)haloalkyl, or optionally two of R^j, R^k and R^l when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript r is an integer of from 0 to 2. The subscript m is an integer of from 0 to 4 and the subscript p is an integer of from 0 to 3.

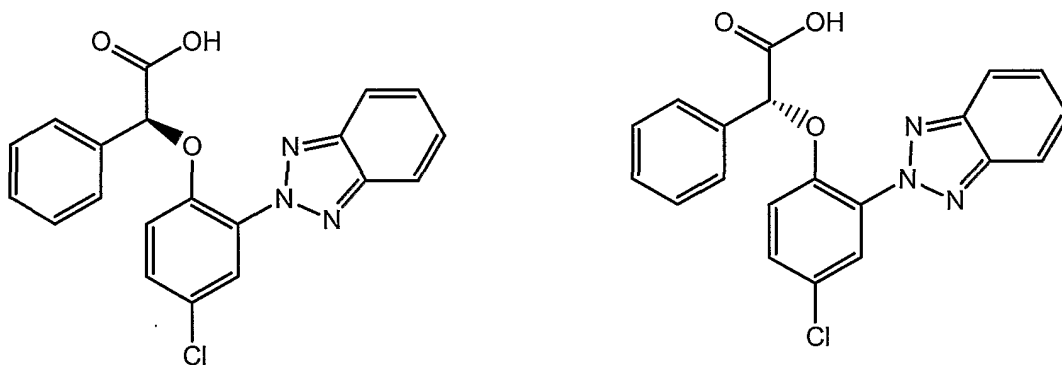
[0022] The symbol R² represents a member selected from H, (C₁-C₈)alkyl, (C₁-C₈)haloalkyl, (C₁-C₈)aralkyl and (C₁-C₄)alkylene-Z, wherein Z is as defined above.

[0023] In one embodiment, the compound is a compound of formula V:

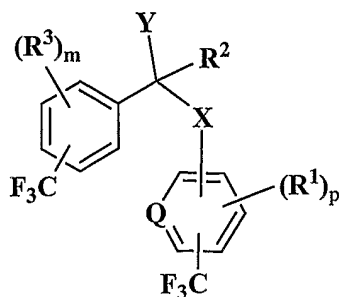


Formula V

which includes the racemate or a substantially purified composition of either isomer thereof:



[0024] In another set of embodiments, the edema-sparing PPAR γ modulator for use according to the invention is a compound of formula VI:



1

Formula VI

or a pharmaceutically acceptable salt thereof, wherein the letter X represents a member selected from the group consisting of O, S, SO, SO₂, CHR and NR, wherein R is H, (C₁-C₈)alkyl, COR^a, COOR^a and CONR^aR^b wherein R^a and R^b are each independently selected from the group consisting of H and (C₁-C₈)alkyl; the letter Y represents a member selected from the group consisting of CH₂OR^c, CO₂R^c, tetrazole, CHO, CONR^cR^m, CH(=NR^c) and CH(=NOR^c), wherein R^c is a member selected from the group consisting of H, (C₁-C₈)alkyl, (C₃-C₈)alkenyl, (C₃-C₈)alkynyl, (C₃-C₇)cycloalkyl, (C₄-C₈)cycloalkyl-alkyl, aryl, aryl(C₁-C₈)alkyl and (C₁-C₈)alkylene-Z, wherein Z is selected from the group consisting of COR^d, COOR^d, NR^dR^e, NR^dCONR^eR^f, NR^dCOR^e, NR^dCOOR^e and CONR^dR^e wherein R^d, R^e and R^f are each independently selected from the group consisting of H, (C₁-C₈)alkyl and phenyl, or optionally two of R^d, R^e and R^f when attached to the same nitrogen atom are combined to form a five- or six-membered ring; and wherein R^m is selected from the group consisting of H, (C₁-C₈)alkyl, aryl and OH, and R^m and R^c are optionally combined with the nitrogen atom to which each is attached to form a five or six membered ring; each of the symbols R¹ and R³ represents a member independently selected from the group consisting of halogen, hydroxy, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₁-C₈)alkoxy, (C₃-C₇)cycloalkyl, (C₄-C₈)cycloalkyl-alkyl, (C₁-C₈)haloalkyl, (C₁-C₈)heteroalkyl, (C₂-C₅)heterocyclyl, heterosubstituted(C₃-C₇)cycloalkyl, heteroalkyl substituted (C₃-C₇)cycloalkyl, O(C₁-C₈)haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl, S(O)_r-phenyl, COR^j, COOR^j, NR^jR^k, S(O)_rR^j, SO₂NR^jR^k, NR^jCONR^kR^l, NR^jCOR^k, NR^jCOOR^k and CONR^jR^k wherein the phenyl ring is optionally substituted and R^j, R^k and R^l are each independently selected from the group consisting of H and (C₁-C₈)alkyl, including (C₁-C₈)haloalkyl, or optionally two of R^j, R^k and R^l when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript r is an integer of from 0 to 2; the symbol R² represents a member selected from the group consisting of H and (C₁-C₈)alkyl; the letter Q represents CH

or N; the subscript m is an integer of from 0 to 3; and the subscript p is an integer of from 0 to 2.

[0025] Turning first to the linkage provided in formula 1 as X, preferred groups are O, S and NR. In one group of embodiments, X is O. In another group of embodiments, X is NR, preferably wherein R is H or (C₁-C₄)alkyl.

[0026] Preferred groups for Y include CH₂OR^c, CO₂R^c, tetrazole, CHO and CONR^cR^m; with CH₂OR^c, CO₂R^c and tetrazole being further preferred. The most preferred embodiments are those in which Y is CH₂OR^c or CO₂R^c.

[0027] Preferred groups for R¹ and R³ are halogen, (C₁-C₈)alkyl, (C₁-C₈)alkoxy, (C₃-C₇)cycloalkyl, (C₄-C₈)cycloalkyl-alkyl, (C₁-C₈)haloalkyl, O(C₁-C₈)haloalkyl, nitro, phenyl, O-phenyl, NR^j-phenyl, NR^jCOR^k, S(O)_r-phenyl and S(O)_rR^j. Particularly preferred groups for R¹ and R³ are halogen, (C₁-C₈)alkyl, (C₁-C₈)haloalkyl, nitro, O-phenyl, NR^jCOR^k and S(O)_rR^j. Still further preferred groups for R¹ and R³ are F, Cl, (C₁-C₄)alkyl, CF₃, NHCOCF₃, NO₂, SCH₃ and OC₆H₄ CF₃.

[0028] The substituent R² is preferably H or (C₁-C₄)alkyl, more preferably H or CH₃. In the most preferred embodiments, R² is H.

[0029] The letter Q is preferably CH.

[0030] The subscript m is preferably 0 to 2. In one group of embodiments, m is 0. In another group of embodiments, m is 1. In yet another group of embodiments, m is 2.

[0031] The subscript p is 0 to 2. In one group of embodiments, p is 0. In another group of embodiments, p is 1. In yet another group of embodiments, p is 2.

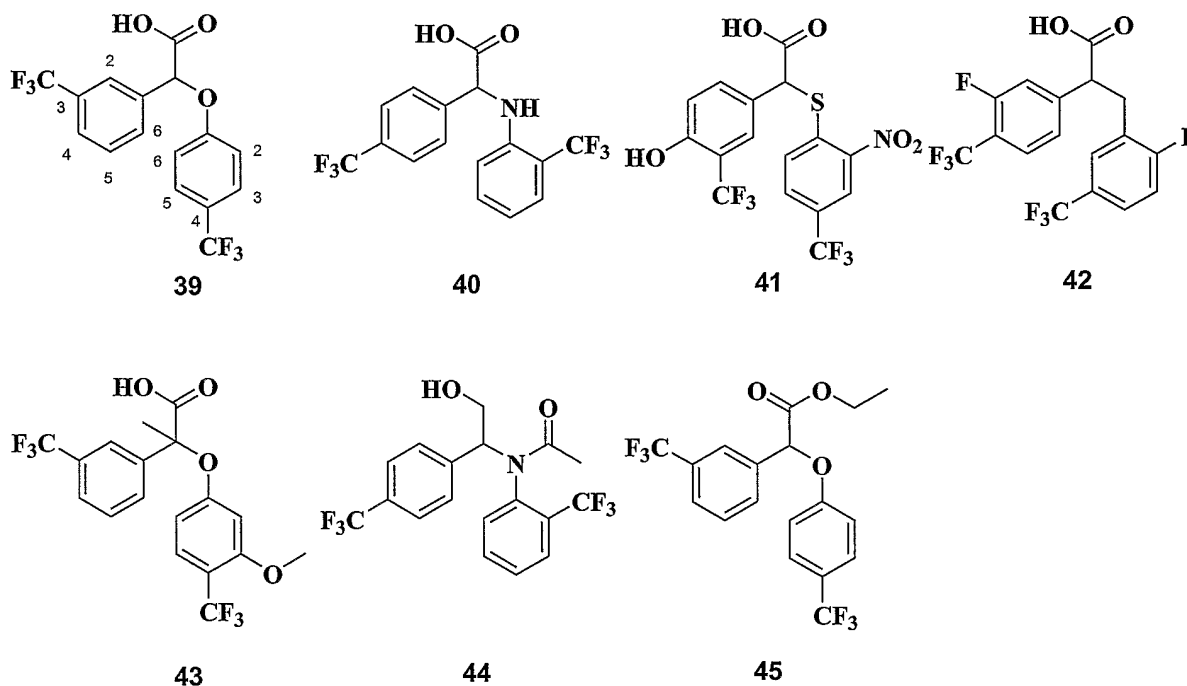
[0032] Within the above groups of embodiments, certain combinations are also preferred. Turning first to the embodiments in which Q is CH, X is preferably O, S or NR. Still further preferred are those embodiments in which Y is CO₂R^c. Even further preferred are those embodiments in which m is 0 to 2 and p is 0 to 1. Within the group of embodiments in which Q is CH, X is O, S or NR, Y is CO₂R^c, m is 0 to 2 and p is 0 to 1, the symbol R¹ will preferably represent halogen, nitro, (C₁-C₈)alkyl, (C₁-C₈)alkoxy, or (C₁-C₈)haloalkyl. Returning to the group of embodiments in which Q is CH, X is O, S or NR, Y is CO₂R^c, m is 0 to 2 and p is 0 to 1, the symbol R³ will preferably represent halogen, nitro, (C₁-C₈)alkyl, (C₁-C₈)alkoxy, or (C₁-C₈)haloalkyl. For those embodiments in which two R³ groups are present, it is understood that each R³ group is independently selected from the provided list.

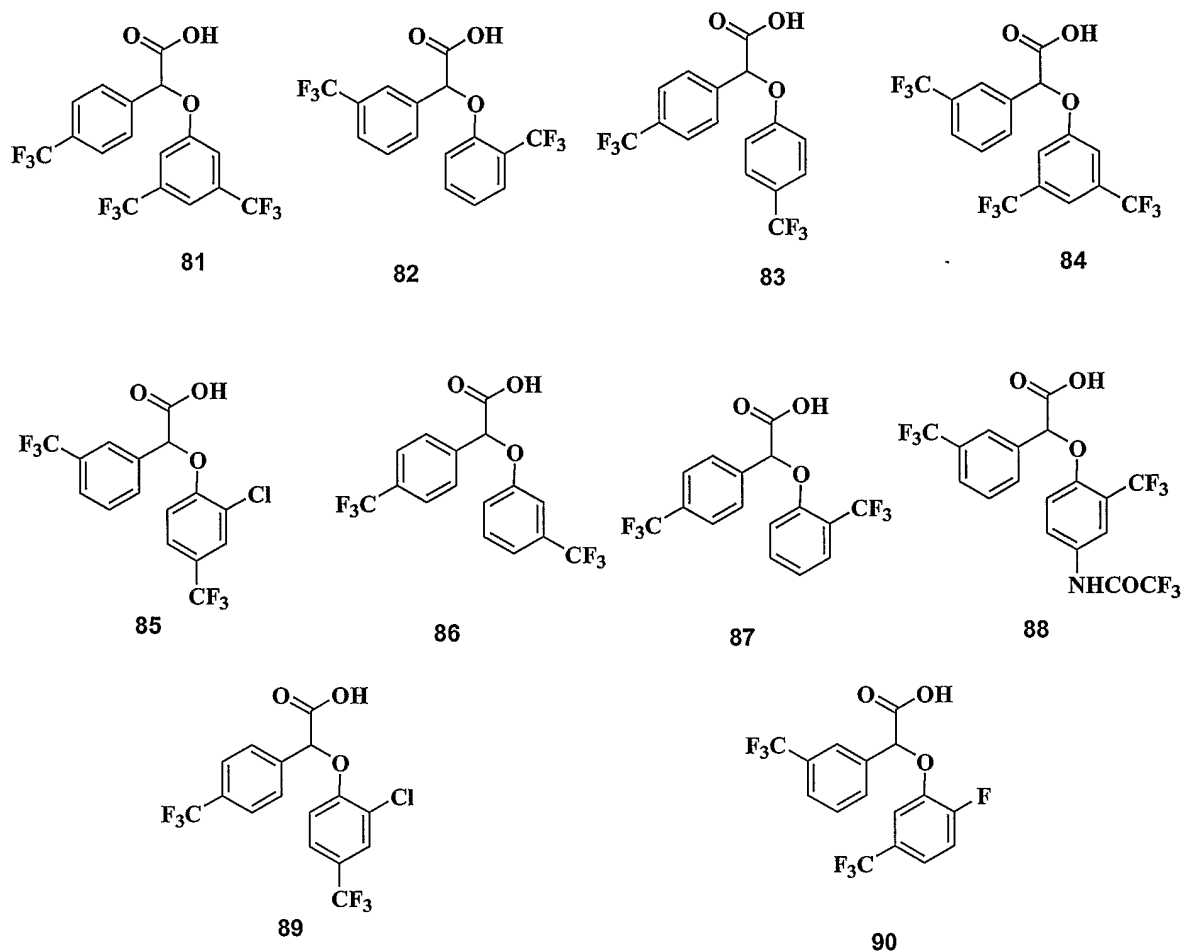
For each of these groups of embodiments, including those in which R^1 and R^3 are provided with their full scope according to formula I above, the symbol R^c is preferably H, (C₁-C₈)alkyl or (C₁-C₈)alkylene Z. Further preferred are those embodiments in which R^2 is H or CH₃.

[0033] In one group are particularly preferred embodiments, Q is CH; X is selected from the group consisting of O and NR; Y is selected from the group consisting of CH₂OR^c and CO₂R^c; the subscript m is 0 to 2 and the subscript p is 0 to 1; each R^1 is selected from the group consisting of halogen, nitro, (C₁-C₈) alkyl and (C₁-C₈) alkoxy; each R^3 is selected from the group consisting of halogen, nitro, (C₁-C₈) alkyl and (C₁-C₈) alkoxy; and R^2 is H or CH₃. Selected groups of embodiments within the above are those in which (i) X is O and Y is CO₂R^c; (ii) X is O and Y is CH₂OR^c; (iii) X is NH and Y is CO₂R^c; (iv) X is NH and Y is CH₂OR^c. Still further preferred embodiments for each of these group are those in which R^1 and R^3 are selected from F, Cl, (C₁-C₄)alkyl, CF₃, NHCOCF₃, NO₂, SCH₃ and OC₆H₄.CF₃.

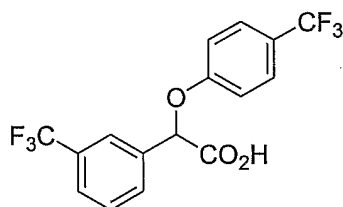
[0034] The compounds of formula VI correspond to those disclosed in PCT Application Publication No. WO/2005/080340 and U.S. Patent Application Publication No. 20050222213 which are each incorporated herein by reference in its entirety, with particular regard to the PPAR γ modulators disclosed therein and methods of making and using same.

[0035] Compounds of formula VI include the following compounds:





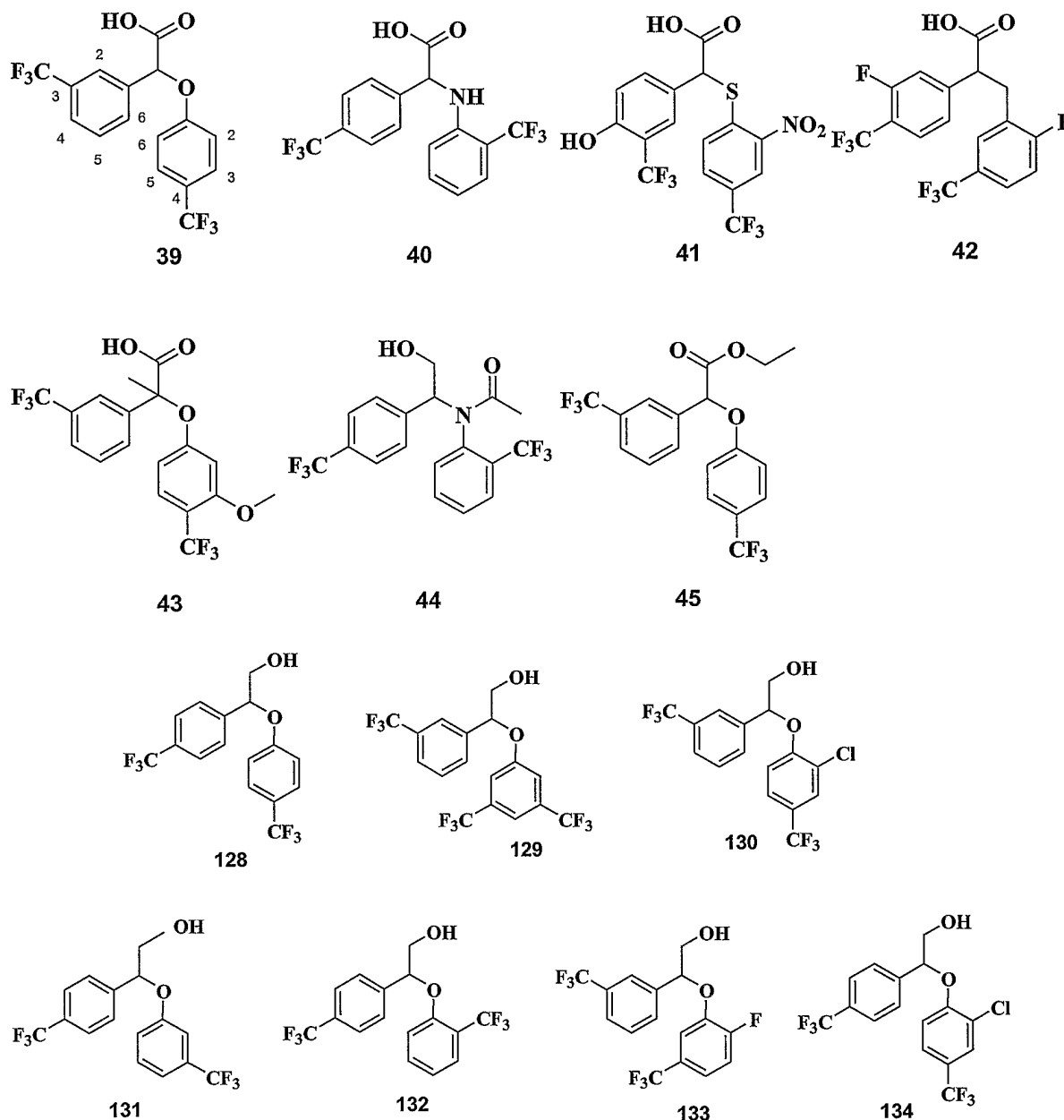
[0036] In one embodiment, the compound is a compound of formula VII, including the pharmaceutically acceptable salts and prodrugs thereof, including, particularly, ester prodrugs thereof which readily hydrolyze in vivo to release a compound of formula VII:



The compound of formula VII may be used as the racemate or either enantiomer which is in a composition that is substantially free of the opposite enantiomer thereof.

[0037] The compounds of formula I, II, III, IVa or IVb, V, VI, and VII are compounds to be administered according to the invention. These compounds include all salts and

polymorphs and solvates and stereoisomers thereof, and particularly, pharmaceutically acceptable salts thereof. Still further, the invention includes compounds that are single isomers of the above formula (e.g., single enantiomers of compounds having a single chiral center), as well as prodrug forms thereof. Exemplary compounds of Figure VI include



[0038] The above compounds have many therapeutic applications in treating inflammation and increased cardiovascular and cerebrovascular risk so as to avoid edema and other edematous diseases. In some embodiments, for instance, the invention provides a method for

treating one or more conditions selected from insulin resistance, metabolic syndrome, type 2 diabetes, coronary artery disease, cerebrovascular disease with or without excess fluid retention, peripheral edema, and pulmonary edema by administering to a subject in need thereof a compound of any one of Formula I, II, III, IVa, IVb, V, VI, or VII. In some embodiments, the invention provides a method for treating or preventing one or more conditions which would be exacerbated by edema (e.g., congestive heart failure, hypertension, angina, cardiac insufficiency, coronary vasospasm, cardiac ischemia, liver cirrhosis, hyponatremia, renal vasospasm, renal failure, diabetic nephropathy, cerebral edema, cerebral ischemia, stroke, and thrombosis) by administering to a subject in need thereof a compound of any one of Formula I, II, III, IVa, IVb, V, VI, or VII. In some further embodiments, the subject has or has had edema.

[0039] In some embodiments, the invention provides a method for treating one or more conditions selected from hypertension, venous congestion, angina, congestive heart failure, cardiac insufficiency, coronary vasospasm, cardiac ischemia, liver cirrhosis, hyponatremia, renal vasospasm, renal failure, diabetic nephropathy, cerebral edema, cerebral ischemia, stroke, and thrombosis by administering to a subject in need thereof a compound of any one of Formula I, II, III, IVa, IVb, V, VI, or VII. In still further embodiments, the subject has or has had edema. In one embodiment, the subject has or has had left-sided heart failure. In another embodiment, the subject has or has had right-sided heart failure.

[0040] In some embodiments, the invention provides a method for treating nephrotic syndrome, a chronic renal disease, or renal insufficiency by administering to a subject in need thereof a compound of any one of formula I, II, III, IVa, IVb, V, VI, or VII. In still further embodiments the subject may have a renal toxicity secondary to exposure to a toxin (e.g, environmental contaminant, heavy metals) or secondary to a side-effect of treatment with a therapeutic drug other than a drug administered according to the invention).

[0041] In yet another embodiment, the invention provides a method for preventing peripheral edema, ascites, cardiac enlargement, excess body fluid retention, or pulmonary edema in a subject having a metabolic or cardiovascular disorder by administering to a subject in need thereof a compound of any one of Formula I, II, III, IVa, IVb, V, VI, or VII. In a further embodiment, the edema was not caused or exacerbated by administration of insulin or an insulin sensitizer or another anti-diabetic agent to the subject. In another

embodiment, the edema was caused or exacerbated by administration of an insulin or an insulin sensitizer or another anti-diabetic agent to the subject.

[0042] In another aspect, the invention provides methods for treating or reducing the risk of a cardiovascular condition in a subject having edema or an elevated CRP level or a pro-inflammatory state, comprising administering to the subject an effective amount of a compound of any one of Formula I, II, III, IVa, IVb, V, VI, or VII. In a further embodiment, the cardiovascular condition is selected from the group consisting of hypertension, stroke, coronary arterial disease, myocardial infarction, peripheral vascular atherosclerosis, and heart failure, particularly, congestive heart failure. In some other further embodiments, the subject has or has had peripheral edema or pulmonary edema. In additional embodiments of the above, the subject is obese or overweight. In yet other further embodiments, the subject has or has had hypertension or a myocardial infarction. In other embodiments, the subject has had an infarction of the central nervous system or brain. In further embodiments of the above, the subject may be obese and hypertensive and over 50 years of age.

[0043] In still another aspect, the invention provides a method for preventing or treating insulin resistance, metabolic syndrome, Syndrome X, impaired fasting glucose, impaired glucose tolerance, polycystic ovary disease, or "pre-diabetes" by administering to a subject having edema and in need thereof a compound of any one of Formula I, II, III, IVa, IVb, V, VI, or VII. In one embodiment, the subject also has ascites or has excess fluid retention and would particularly benefit from use of an edema-sparing PPAR γ modulator.

[0044] In still another aspect, the invention provides a method for treating a subject having an elevated CRP protein level or a pro-inflammatory state and of preventing or treating insulin resistance, metabolic syndrome, Syndrome X, impaired fasting glucose, impaired glucose tolerance, polycystic ovary disease, or "pre-diabetes" in the subject by administering to a subject in need thereof a compound of any one of Formula I, II, III, IVa, IVb, V, VI, or VII. In one embodiment, the subject also has ascites or has excess fluid retention and would particularly benefit from use of an anti-edemic insulin sensitizer.

[0045] In each of the above embodiments and aspects, the compound can be any stereoisomer of a compound of Formulae I, II, III, IVa, IVb, and V, VI, or VII.

[0046] In another aspect, the invention provides modulators of PPAR γ which are useful in treating patient having edema and one or more of the above conditions. In some embodiments, the compound for use according to the invention is a partial agonist of PPAR γ .

In related embodiments, the compound is a compound which is a PPAR γ partial agonist and is of the formulae I, II, III, IVa, IVb, V, VI, or VII. In further embodiments, the compound is a partial PPAR γ agonist which has less than 50%, 25%, or 10% of the agonist activity as a full PPAR γ agonists or which can antagonize up to 50%, 75% or 90% of the agonist activity of a full PPAR γ agonist.

[0047] In another aspect, without intending to be bound by theory, the invention provides methods of identifying a compound for use according to the invention by first screening the compound for PPAR γ modulatory activity and selecting compounds behaving as partial agonists of PPAR γ for further testing for their anti-edema or lack of edema-causing activity in a suitable animal model or clinical trial. In related embodiments, the compound is a compound which is a PPAR γ partial agonist and is of the formulae I, II, III, IVa, IVb, V, VI, or VII. In additional embodiments, the compound is a partial PPAR γ agonist which has less than 50%, 25% , or 10% of the agonist activity as a full PPAR γ agonists or which can antagonize up to 50%, 75% or 90% of the agonist activity of a full PPAR γ agonist. Both halofenac acid and the compound of Formula V are partial PPAR γ agonists. In other embodiments, the compound can be directly screened for anti-edema activity in a suitable animal or clinical model.

[0048] In another aspect, the invention provides methods of providing a beneficial hemodynamic effect. In some embodiments, the invention provides a method of lowering systolic and diastolic blood pressure and to reduce cardiac afterload. In addition, the invention provides methods of reducing intravascular volume and the cardiac preload. In other embodiments, the invention provides a means of increasing cardiac output and/or increasing renal blood flow without an increase in heart rate. In addition, the invention provides a method of reducing cardiovascular mortality by improving hemodynamics. These effects can be accomplished by administering therapeutic amounts of PPAR γ partial agonists and compounds of formulae I, II, III, IVa, IVb, V, VI, or VII.

[0049] In other aspects, the invention relates to the discovery that the compounds of formula I, II, III, IVa, IVb, V, VI, or VII do not cause weight gain, an increase in fat mass, fluid retention, or heart weight. In this aspect the invention provides PPAR γ partial agonists of formula I, II, III, IVa, IVb, V, VI, or VII for the treatment of any of the above conditions, including metabolic disorders, wherein the metabolic condition would be exacerbated by weight gain, an increase in fat mass, or fluid retention, or an increase in heart weight.

[0050] In some embodiments, the invention provides a method for treating or preventing inflammation in a subject, said method comprising administering to the subject a therapeutically effective amount of a compound of formula I, II, III, IVa, IVb, V, VI, or VII. In these embodiments, the subject may have a condition which contra-indicates the administration of an agent which causes edema or excess fluid retention. The condition may be cardiac insufficiency; and the administration may be chronic. The subject may be first identified as having an indication for which an edema causing agent is contra-indicated.

[0051] In additional embodiments, the invention provides a method of treating or preventing a pro-inflammatory state in a human subject having an elevated CRP level by identifying the pro-inflammatory state and then administering to the subject a therapeutically effective amount of a compound of formula I, II, III, IVa, IVb, V, VI, or VII. The subject may have edema or excess fluid retention. The administration may be chronic.

[0052] In yet another embodiment, the invention provides a method of treating or preventing a metabolic or cardiovascular disorder in a human subject, by obtaining a blood or plasma sample from the patient and determining the level of a marker for a pro-inflammatory state therein, and administering a therapeutically effective amount of a compound of Formula I, II, III, IVa, IVb, V, VI, or VII. The marker can be hsCRP or IL-6 or other inflammatory markers (e.g, soluble adhesion molecules such as E-selectin, P-selectin, intracellular adhesion molecule-1, or vascular cell adhesion molecule-1; cytokines such as interleukin-1 β , -6, -8, and -10 and tumor necrosis factor- α); or acute-phase reactants such as fibrinogen). The subject may have edema. The administering and or disorder can be chronic. The metabolic disorder can be hyperglycemia, insulin resistance or type 2 diabetes, Syndrome X, or hyperuricemia. The cardiovascular disorder can be hypertension, stroke, coronary arterial disease, myocardial infarction, pulmonary embolism, cerebral infarct, peripheral vascular atherosclerosis, or congestive heart failure.

[0053] In another embodiment still, the invention provides a method of lowering a hsCRP level in a subject by obtaining a tissue sample from the subject and determining the hsCRP level therein, and administering a therapeutically effective amount of a compound of Formula I, II, III, IVa, IVb, V, VI, or VII. The subject can be obese and hypertensive and over 50 years of age.

[0054] In some embodiments of any of the above, especially with respect to those related to adverse cerebrovascular or cardiovascular events, a HMG-CoA reductase inhibitor,

commonly referred to as a statin is also administered to the subject. Suitable statins include atorvastatin (Lipitor), simvastatin (Zocor), pravastatin (Pravachol), lovastatin (Mevacor), fluvastatin (Lescol), and rosuvastatin (Crestor). These statins may be administered separately or together with an edema-sparing PPAR γ modulator for use according to the invention. The agents may be co-formulated or individually formulated.

BRIEF DESCRIPTION OF THE DRAWINGS

[0055] **Figure 1** illustrates a variety of heteroaryl groups (HAr) useful in compounds of formula I. Figure 1A provides selected monocyclic heteroaryl groups while Figure 1B provides selected fused bicyclic heteroaryl groups. Each of the groups is optionally substituted with R⁴ substituents that can be the same or different.

[0056] **Figure 2** illustrates a family of preferred sub-generic formulae for compounds of the invention wherein HAr is benzoxazol-2-yl; benzothiazol-2-yl and benzimidazol-2-yl.

[0057] **Figure 3** illustrates another family of preferred sub-generic formulae for compounds of the invention, wherein HAr is a fused bicyclic heteroaryl group.

[0058] **Figure 4** illustrates yet another family of preferred sub-generic formulae for compounds of the invention wherein HAr is benzoxazol-2-yl, benzothiazol-2-yl and benzotriazol-2-yl (see Figure 4A). Figure 4B illustrates other preferred compounds having carboxylic acid surrogates in place of CO₂R^c.

[0059] **Figures 5** illustrates yet another family of preferred sub-generic formulae for compounds of the invention wherein HAr is a monocyclic heteroaryl group selected from oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl and triazolyl (see Figures 5A and 5B). Figure 5C illustrates other preferred compounds having carboxylic acid surrogates in place of CO₂R^c.

[0060] **Figure 6** illustrates the activity of (-) halofenic acid or of a (-) halofenate composition which is substantially free of the (+) isomer (MBX-102) and can be hydrolyzed to release (-)halofenic acid to act as a partial agonist of the PPAR γ receptor.

[0061] **Figure 7** shows the tested compound at doses of 200- and 400 mg lowered fasting plasma glucose levels in the experimental groups as compared to the placebo group.

[0062] **Figure 8** shows the tested compound at doses of 200- and 400 mg lowered plasma glucose levels as judged by HbA1c levels in the experimental groups as compared to the placebo group.

[0063] **Figure 9** shows that the test compound at doses of 200 and 400 mg prevented edema formation in the experimental group as compared to the placebo groups.

[0064] **Figure 10** shows that the test compound at doses of 200 and 400 mg did not induce weight gain in the experimental group as compared to the placebo group.

[0065] **Figure 11** shows the tested compound at a dose of 600 mg lowered fasting plasma glucose levels in the experimental group as compared to the placebo group.

[0066] **Figure 12** shows the tested compound at a dose of 600 mg lowered plasma glucose levels as judged by HbA1c levels in the experimental group substantially from baseline, but that the placebo group demonstrated a comparable response. It was determined that two of the 10 clinical sites in this study (sites 60 & 70), who enrolled 43% of the patients, had substantially violated the protocol by placing all of their patients on a sliding scale of short-acting insulin in addition to their baseline doses of intermediate-acting insulin. This explains why HbA1c declined in the placebo group but FPG did not. The most statistically rigorous and conservative approach was to remove both of these violating sites from the analysis, which resulted in improved separation between treatment groups for both HbA1c and FPG, as shown below.

[0067] **Figure 13** shows the tested compound at a dose of 600 mg lowered plasma glucose levels as judged by HbA1c levels in the experimental group as compared to the placebo group in the analysis removing sites 60 and 70.

[0068] **Figure 14** shows that when sites 60 and 70 were removed, the tested compound at a dose of 600 mg lowered fasting plasma glucose levels in the experimental group as compared to the placebo group to an even greater extent than the 400 mg dose in the first study.

[0069] **Figure 15** shows that when sites 60 and 70 were removed from the analysis of the first study, the placebo response is attenuated and the tested compound at doses of 200- and 400 mg lowered plasma glucose levels as judged by HbA1c levels in the experimental groups as compared to the placebo group to an even greater extent than in the original analysis (Figure 8).

[0070] **Figure 16** shows that when sites 60 and 70 were removed from the analysis of the first study, the placebo response is attenuated and the tested compound at doses of 200- and 400 mg lowered fasting plasma glucose levels in the experimental groups as compared to the placebo group to an even greater extent than in the original analysis (Figure 7).

[0071] **Figure 17** shows that the test compound did not increase the incidence of edema formation across the dose range of 200 to 600 mg in the experimental groups as compared to the combined placebo groups from both studies. These results were not changed when sites 60 and 70 were removed.

[0072] **Figure 18** shows that the test compound at a dose of 600 mg did not induce weight gain in the experimental group as compared to the placebo group. This result was not changed when sites 60 and 70 were removed.

[0073] **Figure 19** shows the effect of the test compound Metaglidasen (a composition of (-) halofenate which is substantially free of the (+) isomer) after 14 days of treatment on fasting plasma glucose levels in human subjects also receiving glyburide. The results are contrasted to the work of others for pioglitazone (Actos) at 30 mg after 14 days of treatment.

[0074] **Figure 20** shows the dose dependent effect of Metaglidasen on hsCRP in human patients after 14 days of treatment. The data for pioglitazone (Actos) is taken from Goldberg RB *et al.*, *Diabetes Care* 28(7):1547-54 (2005), which is incorporated herein by reference.

DETAILED DESCRIPTION OF THE INVENTION

[0075] The invention relates to the surprising finding that compounds of Formulae I, II, III, IVa, IVb, V, VI, and VII have edemic properties which makes them therapeutically useful in avoiding or preventing edema. These compounds can be PPAR γ partial agonists, and without intending to be bound by theory, it is believed their anti-edema properties may derive from their particular PPAR γ modulatory activity. Thus, the invention provides compounds, compositions, and methods for reducing cardiovascular and cerebrovascular risk in patients with edema, or patients without edema but whose underlying disease would be exacerbated by edema. The above compounds are taught to be useful in treating insulin resistance, Syndrome X, NIDDM, atherosclerosis, and hyperuricemia. These findings further suggest that a particularly useful subpopulation for therapy with these agents according to the invention are subjects with insulin resistance, Syndrome X, NIDDM, atherosclerosis, hyperlipidemia, hypertriglyceridemia, and/or hyperuricemia who also suffer from edema or

in whom the induction of edema should be avoided. In other distinct embodiments, the invention provides for the treatment of subpopulations in which the subject has edema but does not have one or more of insulin resistance, Syndrome X, NIDDM, atherosclerosis, hyperlipidemia, hypertriglyceridemia, and/or hyperuricemia.

Abbreviations and Definitions

[0076] The abbreviations used herein are conventional, unless otherwise defined.

[0077] The practice of the present invention will employ, unless otherwise indicated, conventional methods of chemistry, biochemistry, molecular biology, cell biology, genetics, immunology and pharmacology, within the skill of the art. Such techniques are explained fully in the literature. See, e.g., Gennaro, A. R., ed. (1990) Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing Co.; Hardman, J. G., Limbird, L. E., and Gilman, A. G., eds. (2001) The Pharmacological Basis of Therapeutics, 10th ed., McGraw-Hill Co.; Colowick, S. et al., eds., Methods In Enzymology, Academic Press, Inc.; Weir, D. M., and Blackwell, C. C., eds. (1986) Handbook of Experimental Immunology, Vols. I-IV, Blackwell Scientific Publications; Maniatis, T. et al., eds. (1989) Molecular Cloning: A Laboratory Manual, 2nd edition, Vols. I-III, Cold Spring Harbor Laboratory Press; Ausubel, F. M. et al., eds. (1999) Short Protocols in Molecular Biology, 4th edition, John Wiley & Sons; Ream et al., eds. (1998) Molecular Biology Techniques: An Intensive Laboratory Course, Academic Press; Newton, C. R., and Graham, A., eds. (1997) PCR (Introduction to Biotechniques Series), 2nd ed., Springer Verlag.

[0078] Unless otherwise stated, the following terms used in the specification and claims have the meanings given below.

[0079] It is noted here that as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise.

[0080] The term "edema" refers to an increase in the interstitial fluid volume. Typically, an increase of several liters may occur before the abnormality is evident. Thus, a weight gain of several kilograms may be apparent. The term edema includes anasarca or gross generalized edema, ascites, and hydrothorax. The term includes both pulmonary edema and peripheral edema and is associated with a harmful renal retention of salt and water. The edema may be caused by a primary heart disease (e.g., right- or left-sided heart failure), renal disease, or be a side-effect of a drug therapy. Edema can also be due to obesity, fluid overload states,

electrolyte imbalances, liver disease, burns, infections, immune reactions, and sepsis.

Symptoms of edema can include weight gain from the retained fluid, congestive heart failure, hypertension, localized ischemia, hypoalbuminemia, hyponatremia, local venous stasis, and local lymphatic stasis. Edema includes lower limb edema and can occur along with venous congestion and/or lymphedema. Swollen lower limbs can be a sign of edema. Edema is often noted clinically by a persistent indentation of the skin "pitting" following pressure.

[0081] The term "edema sparing PPAR γ modulator" or "edema sparing PPAR γ modulator according to the invention" interchangeably refer to the compounds of formula I, II, III, IVa, IVb, V, VI, and VII which are partial agonists of PPAR γ and which do not cause clinically significant edema when administered at therapeutically effective doses.

[0082] C-reactive protein (CRP) is a well known marker for systemic inflammation. CRP was previously known as a highly sensitive but non-specific marker for acute inflammation. CRP is produced in the liver and can rise to very high levels within several hours after acute trauma or surgery and infection. Levels as high as 1000 mg/L may result from severe trauma. It is now known thought that CRP is also a marker for unstable atherosclerotic plaque. Much lower levels of CRP are predictive of the coronary infarct, stroke, and other arterial thrombosis. For instance, studies have shown that circulating levels of inflammatory markers, such as C-reactive protein (CRP), rise in individuals at risk for cardiovascular events. (*see*, Ridker, P. Ann. Intern. Med. 130:933-937 (1999) and AHA/CDC Scientific Statement: Markers of Inflammation and Cardiovascular Disease, *Circulation* 107: 499 511 (2003). In fact, several large-scale prospective epidemiological studies have shown that plasma levels of CRP are a strong independent predictor of risk of myocardial infarction, stroke, peripheral arterial disease, and vascular death among individuals without known cardiovascular disease.

[0083] The term "elevated levels of C-reactive protein" refers to blood or plasma C-reactive protein levels which are indicative of pro-inflammatory state associated with an increased risk of coronary thrombosis. An elevated level of C-reactive protein is typically one which exceeds the normal range and can be 3, 4, 6, 8, or 10 mg/l of blood or plasma. Levels from 2 to 10 mg/l and above have been associated with increased risk of death from cardiovascular events such as myocardial infarction. Although epidemiological studies demonstrate association between low-grade inflammation and vascular risk, the utility of CRP testing appears to be dependent on dividing the CRP values into risk groups. *See*, Ridker, P. *Circulation*. 103:1813-1818 (2001) and AHA/CDC Scientific Statement: Markers of

Inflammation and Cardiovascular Disease, *Circulation* 107: 499 511 (2003). In one embodiment, accordingly, the elevated levels of C-reactive protein refer to levels found for upper second, third or fourth quartile of CRP levels in the general adult population. In another embodiment, the elevated risk is defined by the upper tertile, quartile, or quintile of the reference CRP levels in the general or a reference adult population (e.g., matched for race, age, or sex).

[0084] High sensitivity immunoassays are denoted hsCRP assays. These assays measure CRP levels below 10 mg/L. At these levels, measurement of conditions indicative of chronic, low grade inflammation are now possible. Using such methods, the CDC (Centers for Disease Control and Prevention) has determined 0.08-3.1 mg/L as a normal reference range for healthy persons. The American Heart Association and the Centers for Disease Control have defined three such risk groups: Low Risk <1.0 Average Risk 1.0 to 3.0 and high risk >3.0 mg/l. (See, AHA/CDC Scientific Statement: Markers of Inflammation and Cardiovascular Disease, *Circulation* 107: 499 511 (2003). Accordingly, in one embodiment, "elevated CRP levels" refers to blood levels in excess of 3 mg/l, 4 mg/l, or 6 mg/l as determined using high sensitivity immunoassays or else refers to equivalent levels as measured by any alternative methodology.

[0085] Methods of measuring CRP are well known in the art (see, U.S. Patent No. 6,040,147 which is incorporated herein by reference with particular reference to the methods of measuring CRP levels and their clinical significance.) Preferably, the CRP levels are measured twice, about two weeks apart to insure a stable baseline value has been determined. Typically, values over 10 mg/l are suggestive of an acute trauma or infection and are discarded and the values retaken after two weeks.

[0086] Methods of measuring CRP are known to one of ordinary skill in the art. See, Shapiro D et al., *Clin Chim Acta* 180(3):285-92 (1989) and Price CP et al., *Clin Chem Lab Med* 37(2):109-13 (1999).

[0087] When used with respect to a health condition, the term "chronic" indicates means a long-lasting condition which may be life-long or persist of indefinite length, usually lasting for one or months. When used with respect to the administration of a pharmaceutical agent, the terms "chronic," "chronically" and the like refer to an administration which is for an indefinite period, usually lasting for a period of at least one or more months and which may be for an indefinite period.

[0088] In another aspect, the invention is directed to a method for treating a subject having, or susceptible to having inflammation, an immune disorder, a type I hypersensitivity, asthma or allergy, comprising administering to said subject a therapeutically effective amount of an edema sparing modulator of PPAR γ . In one embodiment, the subject has one or more symptoms selected from the group consisting of an increase in T_{H2} type cytokines, lung airway inflammation, eosinophil infiltration, mucous production in the lung, airway hyperreactivity (AHR) and elevated serum IgE levels. In each of the above embodiments, the phenoxyacetic acid PPAR γ modulator can be a compound of any one of formula I, II, III, IVa, IVb, V, VI, and VII. In some embodiments, the compound is a compound of Formula III or V. In some further embodiments, the compound is a (-) isomer of the phenoxy acetic acid compound of Formula II. In any of the above embodiments, the subject can be one who has edema, at increased risk of developing edema, or one who is being administered an agent which causes edema, or has a condition which would be exacerbated by edema.

[0089] The term "cardiovascular disease" includes heart failure, hypertension, atherosclerosis, arteriosclerosis, myocardial infarction, stroke, and thrombosis. "Heart failure" includes congestive heart failure, heart failure with diastolic dysfunction, heart failure with systolic dysfunction, heart failure associated with cardiac hypertrophy, and heart failure that develops as a result of chemically induced cardiomyopathy, congenital cardiomyopathy, and cardiomyopathy associated with ischemic heart disease or myocardial infarction. In another aspect the invention provides a method for treating or reducing the risk of a cardiovascular condition in a subject, comprising administering to a subject an effective amount of a compound selected from the group consisting of formula I, II, III, IVa, IVb, V, VI, or VII. In one embodiment, the cardiovascular condition can be hypertension, stroke, coronary arterial disease, myocardial infarction, peripheral vascular atherosclerosis, or congestive heart failure. In additional embodiments, the subject is obese. In other embodiments, the subject has or has had hypertension. In still other embodiments, the subject has had an infarction of the central nervous system or brain or a myocardial infarction. In still other embodiments, the subject has or has had peripheral edema or pulmonary edema or ascites or hyothorax. In some embodiments, the subject is obese and hypertensive and over 50 years of age. In other embodiments still, the subject has insulin resistance, metabolic syndrome, Syndrome X, impaired fasting glucose, impaired glucose tolerance, polycystic ovary disease, or "pre-diabetes", or any condition characterized by insulin resistance of any degree.

[0090] The term "hypertension" generally includes borderline hypertension (blood pressures between 120/80 and 140/90) and mild hypertension (blood pressures which are greater than a systolic/diastolic reading of 140-159/90-99) as well as the more severe forms of hypertension with higher diastolic values (e.g., greater than 160) or higher systolic values (e.g., greater than 100 or 120) (as measured in mmHg).

[0091] "Alkyl" refers to a linear saturated monovalent hydrocarbon radical or a branched saturated monovalent hydrocarbon radical having the number of carbon atoms indicated in the prefix. For example, (C₁-C₆)alkyl is meant to include methyl, ethyl, *n*-propyl, 2-propyl, *tert*-butyl, pentyl, and the like. For each of the definitions herein (e.g., alkyl, alkenyl, alkoxy, aralkyloxy), when a prefix is not included to indicate the number of main chain carbon atoms in an alkyl portion, the radical or portion thereof will have six or fewer main chain carbon atoms.

[0092] "Alkylene" refers to a linear saturated divalent hydrocarbon radical or a branched saturated divalent hydrocarbon radical having the number of carbon atoms indicated in the prefix. For example, (C₁-C₆)alkylene is meant to include methylene, ethylene, propylene, 2-methylpropylene, pentylene, and the like.

[0093] "Alkenyl" refers to a linear monovalent hydrocarbon radical or a branched monovalent hydrocarbon radical having the number of carbon atoms indicated in the prefix and containing at least one double bond, but no more than three double bonds. For example, (C₂-C₆)alkenyl is meant to include, ethenyl, propenyl, 1,3-butadienyl and the like.

[0094] "Alkynyl" means a linear monovalent hydrocarbon radical or a branched monovalent hydrocarbon radical containing at least one triple bond and having the number of carbon atoms indicated in the prefix. The term "alkynyl" is also meant to include those alkyl groups having one triple bond and one double bond. For example, (C₂-C₆)alkynyl is meant to include ethynyl, propynyl, and the like.

[0095] "Alkoxy", "aryloxy" or "aralkyloxy" refers to a radical -OR wherein R is an alkyl, aryl or arylalkyl, respectively, as defined herein, e.g., methoxy, phenoxy, benzyloxy, and the like.

[0096] "Heteroaralkyloxy" refers to a radical -OR wherein R is a heteroaralkyl as defined herein, e.g., pyridin-2-ylmethyloxy, and the like.

[0097] "Aryl" refers to a monovalent monocyclic or bicyclic aromatic hydrocarbon radical of 6 to 10 ring atoms which is substituted independently with one to four substituents, preferably one, two, or three substituents selected from alkyl, cycloalkyl, cycloalkyl-alkyl, halo, nitro, cyano, hydroxy, alkoxy, amino, acylamino, mono-alkylamino, di-alkylamino, haloalkyl, haloalkoxy, heteroalkyl, COR (where R is hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, phenyl or phenylalkyl), $-(CR'R'')_n-COOR$ (where n is an integer from 0 to 5, R' and R'' are independently hydrogen or alkyl, and R is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, phenyl or phenylalkyl) or $-(CR'R'')_n-CONR^xR^y$ (where n is an integer from 0 to 5, R' and R'' are independently hydrogen or alkyl, and R^x and R^y are independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, phenyl or phenylalkyl). More specifically the term aryl includes, but is not limited to, phenyl, biphenyl, 1-naphthyl, and 2-naphthyl, and the substituted forms thereof.

[0098] "Aralkyl" or "Aryl(C₁-C_x)alkyl" refers to the radical $-R^xR^y$ where R^x is an alkylene group (having eight or fewer main chain carbon atoms) and R^y is an aryl group as defined above. Thus, "aralkyl" refers to groups such as, for example, benzyl, phenylethyl, 3-(4-nitrophenyl)-2-methylbutyl, and the like. Similarly, "Aralkenyl" means a radical $-R^xR^y$ where R^x is an alkenylene group (an alkylene group having one or two double bonds) and R^y is an aryl group as defined above, *e.g.*, styryl, 3-phenyl-2-propenyl, and the like.

[0099] "Arylheteroalkyl" means a radical $-R^xR^y$ where R^x is an heteroalkylene group and R^y is an aryl group as defined herein, *e.g.*, 2-hydroxy-2-phenyl-ethyl, 2-hydroxy-1-hydroxymethyl-2-phenyl-ethyl, and the like.

[0100] "Cycloalkyl" refers to a monovalent cyclic hydrocarbon radical of three to seven ring carbons. The cycloalkyl group may have one double bond and may also be optionally substituted independently with one, two, or three substituents selected from alkyl, optionally substituted phenyl, or $-C(O)R^z$ (where R^z is hydrogen, alkyl, haloalkyl, amino, mono-alkylamino, di-alkylamino, hydroxy, alkoxy, or optionally substituted phenyl). More specifically, the term cycloalkyl includes, for example, cyclopropyl, cyclohexyl, cyclohexenyl, phenylcyclohexyl, 4-carboxycyclohexyl, 2-carboxamidocyclohexenyl, 2-dimethylaminocarbonyl-cyclohexyl, and the like.

[0101] "Cycloalkyl-alkyl" means a radical $-R^xR^y$ wherein R^x is an alkylene group and R^y is a cycloalkyl group as defined herein, *e.g.*, cyclopropylmethyl, cyclohexenylpropyl, 3-

cyclohexyl-2-methylpropyl, and the like. The prefix indicating the number of carbon atoms (*e.g.*, C₄-C₁₀) refers to the total number of carbon atoms from both the cycloalkyl portion and the alkyl portion.

[0102] "Haloalkyl" refers to an alkyl group which is substituted with one or more same or different halo atoms, *e.g.*, -CH₂Cl, -CF₃, -CH₂CF₃, -CH₂CCl₃, and the like, and further includes those alkyl groups such as perfluoroalkyl in which all hydrogen atoms are replaced by fluorine atoms. The prefix "halo" and the term "halogen" when used to describe a substituent, refer to -F, -Cl, -Br and -I.

[0103] "Heteroalkyl" means an alkyl radical as defined herein with one, two or three substituents independently selected from cyano, -OR^w, -NR^xR^y, and -S(O)_nR^z (where n is an integer from 0 to 2), with the understanding that the point of attachment of the heteroalkyl radical is through a carbon atom of the heteroalkyl radical. R^w is hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, aryl, aralkyl, alkoxycarbonyl, aryloxycarbonyl, carboxamido, or mono- or di-alkylcarbonyl. R^x is hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, aryl or aralkyl. R^y is hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, aryl, aralkyl, alkoxycarbonyl, aryloxycarbonyl, carboxamido, mono- or di-alkylcarbonyl or alkylsulfonyl. R^z is hydrogen (provided that n is 0), alkyl, cycloalkyl, cycloalkyl-alkyl, aryl, aralkyl, amino, mono-alkylamino, di-alkylamino, or hydroxyalkyl. Representative examples include, for example, 2-hydroxyethyl, 2,3-dihydroxypropyl, 2-methoxyethyl, benzyloxymethyl, 2-cyanoethyl, and 2-methylsulfonyl-ethyl. For each of the above, R^w, R^x, R^y, and R^z can be further substituted by amino, fluorine, alkylamino, di-alkylamino, OH or alkoxy. Additionally, the prefix indicating the number of carbon atoms (*e.g.*, C₁-C₁₀) refers to the total number of carbon atoms in the portion of the heteroalkyl group exclusive of the cyano, -OR^w, -NR^xR^y, or -S(O)_nR^z portions.

[0104] "Heteroaryl" means a monovalent monocyclic or bicyclic radical of 5 to 12 ring atoms having at least one aromatic ring containing one, two, or three ring heteroatoms selected from N, O, or S, the remaining ring atoms being C, with the understanding that the attachment point of the heteroaryl radical will be on an aromatic ring. The heteroaryl ring is optionally substituted independently with one to four substituents, preferably one or two substituents, selected from alkyl, cycloalkyl, cycloalkyl-alkyl, halo, nitro, cyano, hydroxy, alkoxy, amino, acylamino, mono-alkylamino, di-alkylamino, haloalkyl, haloalkoxy, heteroalkyl, -COR (where R is hydrogen, alkyl, phenyl or phenylalkyl, -(CR'R'')_n-COOR (where n is an integer from 0 to 5, R' and R'' are independently hydrogen or alkyl, and R is

hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, phenyl or phenylalkyl), or $-(CR'R'')_n-$ $CONR^xR^y$ (where n is an integer from 0 to 5, R' and R'' are independently hydrogen or alkyl, and R^x and R^y are, independently of each other, hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, phenyl or phenylalkyl). More specifically the term heteroaryl includes, but is not limited to, pyridyl, furanyl, thienyl, thiazolyl, isothiazolyl, triazolyl, imidazolyl, isoxazolyl, pyrrolyl, pyrazolyl, pyridazinyl, pyrimidinyl, benzofuranyl, tetrahydrobenzofuranyl, isobenzofuranyl, benzothiazolyl, benzoisothiazolyl, benzotriazolyl, indolyl, isoindolyl, benzoxazolyl, quinolyl, tetrahydroquinolyl, isoquinolyl, benzimidazolyl, benzisoxazolyl or benzothienyl, and the derivatives thereof.

[0105] "Heteroaralkyl" means a radical $-R^xR^y$ where R^x is an alkylene group and R^y is a heteroaryl group as defined herein, *e.g.*, pyridin-3-ylmethyl, 3-(benzofuran-2-yl)propyl, and the like.

[0106] "Heteroaralkenyl" means a radical $-R^xR^y$ where R^x is an alkenylene group and R^y is a heteroaryl group as defined herein, *e.g.*, 3-(pyridin-3-yl)propen-2-yl, and the like.

[0107] "Heterocyclyl" or "cycloheteroalkyl" means a saturated or unsaturated non-aromatic cyclic radical of 3 to 8 ring atoms in which one or two ring atoms are heteroatoms selected from O, NR (where R is independently hydrogen or alkyl) or S(O)_n (where n is an integer from 0 to 2), the remaining ring atoms being C, where one or two C atoms may optionally be replaced by a carbonyl group. The heterocyclyl ring may be optionally substituted independently with one, two, or three substituents selected from alkyl, cycloalkyl, cycloalkyl-alkyl, halo, nitro, cyano, hydroxy, alkoxy, amino, mono-alkylamino, di-alkylamino, haloalkyl, haloalkoxy, -COR (where R is hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, phenyl or phenylalkyl), $-(CR'R'')_n-COOR$ (n is an integer from 0 to 5, R' and R'' are independently hydrogen or alkyl, and R is hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, phenyl or phenylalkyl), or $-(CR'R'')_n-CONR^xR^y$ (where n is an integer from 0 to 5, R' and R'' are independently hydrogen or alkyl, R^x and R^y are, independently of each other, hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, phenyl or phenylalkyl). More specifically the term heterocyclyl includes, but is not limited to, tetrahydropyranyl, piperidino, N-methylpiperidin-3-yl, piperazino, N-methylpyrrolidin-3-yl, 3-pyrrolidino, 2-pyrrolidon-1-yl, morpholino, thiomorpholino, thiomorpholino-1-oxide, thiomorpholino-1,1-dioxide, pyrrolidinyl, and the derivatives thereof. The prefix indicating the number of carbon atoms (*e.g.*, C₃-C₁₀) refers to

the total number of carbon atoms in the portion of the cycloheteroalkyl or heterocyclyl group exclusive of the number of heteroatoms.

[0108] "Heterocyclylalkyl" or "Cycloheteroalkyl-alkyl" means a radical $-R^xR^y$ where R^x is an alkylene group and R^y is a heterocyclyl group as defined herein, *e.g.*, tetrahydropyran-2-ylmethyl, 4-methylpiperazin-1-ylethyl, 3-piperidinylmethyl, and the like.

[0109] "Heterosubstituted cycloalkyl" means a cycloalkyl group wherein one, two, or three hydrogen atoms are replaced by substituents independently selected from the group consisting of cyano, hydroxy, alkoxy, amino, acylamino, mono-alkylamino, di-alkylamino, or $-SO_nR$ (where n is an integer from 0 to 2 and when n is 0, R is hydrogen or alkyl and when n is 1 or 2, R is alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, amino, acylamino, mono-alkylamino, di-alkylamino, or hydroxyalkyl). Examples include 4-hydroxycyclohexyl, 2-aminocyclohexyl *etc.*

[0110] "Heteroalkylene" refers to a linear saturated divalent hydrocarbon radical of one to six carbons or a branched saturated hydrocarbon radical of three to six carbon atoms with one, two or three substituents independently selected from $-OR^w$, $-NR^xR^y$, and $-S(O)_nR^z$ (where n is an integer from 0 to 2) where, R^w , R^x , R^y , and R^z are as defined herein for a heteroalkyl radical. Examples include, 2-hydroxyethan-1,2-diyl, 2-hydroxypropan-1,3-diyl and the like.

[0111] "Heteroalkyl substituted cycloalkyl" means a cycloalkyl group wherein one, two, or three hydrogen atoms are replaced independently by heteroalkyl groups, with the understanding that the heteroalkyl group is attached to the cycloalkyl group *via* a carbon-carbon bond. Examples include 1-hydroxymethyl-cyclopent-1-yl, 2-hydroxymethyl-cyclohex-2-yl and the like.

[0112] "Heteroalkyl substituted heterocyclyl" means a heterocyclyl group wherein one, two, or three hydrogen atoms are replaced independently by heteroalkyl groups, with the understanding that the heteroalkyl group is attached to the heterocyclyl group *via* a carbon-carbon bond. Examples include 4-hydroxymethyl-piperidin-1-yl, and the like.

[0113] "Optionally substituted phenyl" means a phenyl ring which is optionally substituted independently with one to four substituents, preferably one or two substituents selected from alkyl, cycloalkyl, cycloalkyl-alkyl, halo, nitro, cyano, hydroxy, alkoxy, amino, acylamino, mono-alkylamino, di-alkylamino, haloalkyl, haloalkoxy, heteroalkyl, $-COR$ (where R is

hydrogen, alkyl, phenyl or phenylalkyl, $-(CR'R'')_n-COOR$ (where n is an integer from 0 to 5, R' and R'' are independently hydrogen or alkyl, and R is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, phenyl or phenylalkyl), or $-(CR'R'')_n-CONR^xR^y$ (where n is an integer from 0 to 5, R' and R'' are independently hydrogen or alkyl, and R^x and R^y are, independently of each other, hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, phenyl or phenylalkyl).

[0114] For each of the definitions above, the term "di-alkylamino" refers to an amino moiety bearing two alkyl groups that can be the same, or different.

[0115] As used herein, the term "carboxylic acid surrogate" refers to those moieties that are used as surrogates for a carboxylic acid moiety. Such groups are generally known to one of skill in the art (see, for example, THE PRACTICE OF MEDICINAL CHEMISTRY; Wermuth, C.G., ed., Academic Press, New York, 1996, page 203). Suitable isosteres or surrogates include $-C(O)NHSO_2R$ wherein R can be alkyl, haloalkyl, heteroalkyl, aralkyl, aryl, heteroaryl, heterocyclyl, alkoxy, haloalkoxy, aryloxy, alkylamino, haloalkylamino, dialkylamino, dihaloalkylamino, arylamino, diarylamino, arakylamino, diaralkylamino or other groups to provide an overall acidic character to the moiety; sulfonic acids; sulfinic acids; phosphonic acids; phosphinic acids; activated sulfonamides (e.g., $-SO_2NHX$ wherein X is an electron withdrawing group relative to an alkyl group, such as an acyl group or aryl group; activated carboxamides (e.g., $-C(O)NHCN$); hydroxamic acids ($-C(O)NHOH$); acidic heterocycles or substituted heterocycles (e.g., tetrazoles, triazoles, hydroxypyrazoles, hydroxyoxazoles, hydroxythiadiazoles); and acidic alcohols (e.g., $-C(CF_3)_2OH$ or $-CH(CF_3)OH$).

[0116] Compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers". Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers". When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the *R*- and *S*-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (*i.e.*, as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer

or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture".

[0117] The compounds of this invention may exist in stereoisomeric form if they possess one or more asymmetric centers or a double bond with asymmetric substitution and, therefore, can be produced as individual stereoisomers or as mixtures. Unless otherwise indicated, the compounds of the invention are intended to include all individual stereoisomers as well as mixtures. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see discussion in Chapter 4 of ADVANCED ORGANIC CHEMISTRY, 4th edition J. March, John Wiley and Sons, New York, 1992).

[0118] "Pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include:

(1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynapthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or

(2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, trimethylamine, *N*-methylglucamine, and the like.

[0119] "Prodrugs" means any compound which releases an active parent drug.

[0120] "Protecting group" refers to a grouping of atoms that when attached to a reactive group in a molecule masks, reduces or prevents that reactivity. Examples of protecting groups can be found in T.W. Greene and P.G. Wuts, PROTECTIVE GROUPS IN ORGANIC

CHEMISTRY, (Wiley, 2nd ed. 1991) and Harrison and Harrison *et al.*, COMPENDIUM OF SYNTHETIC ORGANIC METHODS, Vols. 1-8 (John Wiley and Sons. 1971-1996).

Representative amino protecting groups include formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl (CBZ), *tert*-butoxycarbonyl (Boc), trimethyl silyl (TMS), 2-trimethylsilyl-ethanesulfonyl (SES), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl (FMOC), nitro-veratryloxycarbonyl (NVOC) and the like. Representative hydroxy protecting groups include those where the hydroxy group is either acylated or alkylated such as benzyl and trityl ethers as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers and allyl ethers.

[0121] Turning next to the compositions of the invention, the term "pharmaceutically acceptable carrier or excipient" means a carrier or excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes a carrier or excipient that is acceptable for veterinary use as well as human pharmaceutical use. A "pharmaceutically acceptable carrier or excipient" as used in the specification and claims includes both one and more than one such carrier or excipient.

[0122] With reference to the methods of the present invention, the following terms are used with the noted meanings:

[0123] The terms "treating" or "treatment" of a disease includes:

- (1) preventing the disease, *i.e.*, causing the clinical symptoms of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease,
- (2) inhibiting the disease, *i.e.*, arresting or reducing the development of the disease or its clinical symptoms, or
- (3) relieving the disease, *i.e.*, causing regression of the disease or its clinical symptoms.

[0124] The term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician. "A therapeutically effective amount" includes the amount of a compound that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the

disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, *etc.*, of the mammal to be treated.

[0125] The term "mammal" includes, without limitation, humans, domestic animals (*e.g.*, dogs or cats), farm animals (cows, horses, or pigs), monkeys, rabbits, mice, and laboratory animals.

[0126] The term "insulin resistance" can be defined generally as a disorder of glucose metabolism. More specifically, insulin resistance can be defined as the diminished ability of insulin to exert its biological action across a broad range of concentrations producing less than the expected biologic effect. (*see, e.g.*, Reaven, G. M., *J. Basic & Clin. Phys. & Pharm.* (1998) 9: 387-406 and Flier, J. *Ann Rev. Med.* (1983) 34: 145-60). Insulin resistant persons have a diminished ability to properly metabolize glucose and respond poorly, if at all, to insulin therapy. Manifestations of insulin resistance include insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in liver. Insulin resistance can cause or contribute to polycystic ovarian syndrome, Impaired Glucose Tolerance (IGT), gestational diabetes, hypertension, obesity, atherosclerosis and a variety of other disorders. Eventually, the insulin resistant individuals can progress to a point where a diabetic state is reached. The association of insulin resistance with glucose intolerance, an increase in plasma triglyceride and a decrease in high-density lipoprotein cholesterol concentrations, high blood pressure, hyperuricemia, smaller denser low-density lipoprotein particles, and higher circulating levels of plasminogen activator inhibitor-1), has been referred to as "Syndrome X" (*see, e.g.*, Reaven, G. M., *Physiol. Rev.* (1995) 75: 473-486) or more recently, "metabolic syndrome."

[0127] The term "diabetes mellitus" or "diabetes" means a disease or condition that is generally characterized by metabolic defects in production and utilization of glucose which result in the failure to maintain appropriate blood sugar levels in the body. The result of these defects is elevated blood glucose, referred to as "hyperglycemia." Two major forms of diabetes are Type 1 diabetes and Type 2 diabetes. As described above, Type 1 diabetes is generally the result of an absolute deficiency of insulin, the hormone which regulates glucose utilization. Type 2 diabetes often occurs in the face of normal, or even elevated levels of insulin and can result from the inability of tissues to respond appropriately to insulin. Most Type 2 diabetic patients are insulin resistant and have a relative deficiency of insulin, in that

insulin secretion can not compensate for the resistance of peripheral tissues to respond to insulin. In addition, many Type 2 diabetics are obese. Other types of disorders of glucose homeostasis include Impaired Glucose Tolerance, which is a metabolic stage intermediate between normal glucose homeostasis and diabetes, and Gestational Diabetes Mellitus, which is glucose intolerance in pregnancy in women with no previous history of Type 1 or Type 2 diabetes.

[0128] The term “atherosclerosis” encompasses vascular diseases and conditions that are recognized and understood by physicians practicing in the relevant fields of medicine. Atherosclerotic cardiovascular disease, coronary heart disease (also known as coronary artery disease or ischemic heart disease), cerebrovascular disease and peripheral vessel disease are all clinical manifestations of atherosclerosis and are therefore encompassed by the terms “atherosclerosis” and “atherosclerotic disease”.

[0129] The term “modulate” refers to the treating, prevention, suppression, enhancement or induction of a function or condition.

[0130] The terms “obese” and “obesity” refers to, according to the World Health Organization, a Body Mass Index (BMI) greater than 27.8 kg/m² for men and 27.3 kg/m² for women (BMI equals weight (kg)/height (m²). Obesity is linked to a variety of medical conditions including diabetes and hyperlipidemia. Obesity is also a known risk factor for the development of Type 2 diabetes (*See, e.g., Barrett-Conner, E., Epidemiol. Rev. (1989) 11: 172-181; and Knowler, et al., Am. J. Clin. Nutr. (1991) 53:1543-1551*).

[0131] The term “substantially free” with respect to the enantiomeric purity of a compound means that the compound or composition contains a substantially greater proportion of a specified isomer of the compound in relation to its other isomer. In a preferred embodiments, the compound or composition has at least 90% by weight the specified isomer and 10% by weight or less of the other isomer. In a more preferred embodiment, the compound or composition has at least 99% by weight of the specified isomer and 1% by weight or less of the other isomer. In the most preferred embodiments, the compound or composition contains greater than 99%, 99.5% or 99.9% by weight of a specified isomer. These percentages are based upon the total amount of halofenate in the composition.

[0132] For instance, a composition of the (-) isomer which is “substantially free” of the (+) isomer” indicates the composition has a substantially greater proportion of the (-) isomer of the compound in relation to the (+) isomer. In a preferred embodiments, the compound

composition is at least 90% by weight the (–) isomer and 10% by weight or less the (+) isomer. In a more preferred embodiment, the (–) compound is at least 99% by weight the (–) isomer and 1% by weight or less the (+) isomer. In the most preferred embodiment, the (–) isomer is greater than 99%, 99.5% or 99.9% by weight the (–) isomer as compared to the (+) isomer. These percentages are accordingly based upon the total amount of the compound in the composition. With regard to the compounds of formula I to III, the (–) enantiomer is preferred although both are active as PPAR γ partial agonists.

[0133] Changes in drug metabolism mediated by inhibition of cytochrome P450 enzymes has a very high potential to precipitate significant adverse effects in patients. Such effects were previously noted in patients treated with racemic halofenate. Recently, racemic halofenic acid was found to inhibit cytochrome P450 2C9, an enzyme known to play a significant role in the metabolism of specific drugs. This inhibition can lead to significant problems with drug interactions with anticoagulants, anti-inflammatory agents and other drugs metabolized by this enzyme. However, quite surprisingly, a substantial difference was observed between the enantiomers of halofenic acid in their inability to inhibit cytochrome P450 2C9, the (–) enantiomer being about twenty-fold less active whereas the (+) enantiomer was quite potent. Thus, use of the (–) enantiomer of halofenic acid and its derivatives can avoid the inhibition of this enzyme and the adverse effects on drug metabolism previously observed with racemic mixtures of halofenic acid or its derivatives. In addition, the (–) isomers of halofenic acid and its derivatives of formula I, II, or III have a superior properties with respect to inhibition of cyclooxygenase 1 (COX-1) which reduce their potential to cause stomach upset as compared to the (+) isomers of halofenic acids and its derivatives. These properties also extend to halofenate and serve to make the (–) isomer of halofenate preferred to the (+) isomer of halofenate in the instant invention.

[0134] The term “enantiomeric excess” or “ee” is related to the term “optical purity” in that both are measures of the same phenomenon. The value of ee will be a number from 0 to 100, 0 being racemic and 100 being pure, single enantiomer. A compound that is referred to as 98% optically pure can be described as 96% ee. In some embodiments, the (–) halofenate as an ee of at least 90%, 95%, 98%, 99%, 99.5% or 99.9%. Methods for achieving such levels of optical purity are disclosed in the examples.

[0135] “PPAR γ ” is a member of the peroxisome proliferator-activated receptor family. PPAR γ encompasses variants of the receptor such as PPAR γ 1 and PPAR γ 2. These two

isoforms have different N-terminal amino acid sequence reflecting alternate splicing of a primary RNA transcript (*see*, Tontonoz, P. et al., *Genes & Dev.* 8:1224-34 (1994); Zhu et al. *J. Biol. Chem.* 268: 26817-20 (1993)).

[0136] A "PPAR γ agonist" is an agent that binds to PPAR γ to activate or enhance the transcriptional activity of a PPAR γ receptor. In certain embodiments, an agonist may induce activation of transcription by PPAR γ transcriptional complexes by mimicking a natural ligand for the receptor.

[0137] A "PPAR γ partial agonist" is an agent that binds to PPAR γ to activate or enhance the transcriptional activity of a PPAR γ receptor. However, a "partial agonist" also has some antagonist activity and can antagonize the agonist activity of a full PPAR γ agonist. Partial agonists are characterized by dose-response curves which, even at the upper end, provide less than the full activation of the PPAR γ receptor than that which can be achieved with a full PPAR γ agonist such as rosiglitazone or pioglitazone. In preferred embodiments, the compounds for use according to the invention are selective, partial PPAR γ agonists.

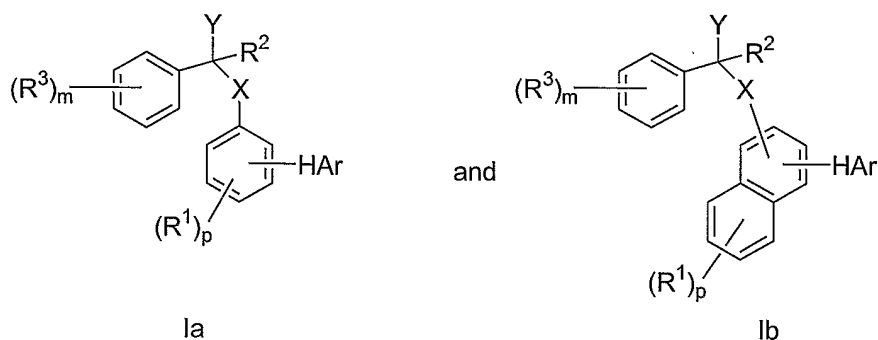
[0138] A "selective" or "specific" PPAR γ ligand, modulator, agonist, or partial agonist is one that interacts preferentially with PPAR γ as compared to PPAR α , PPAR β , and PPAR δ (e.g., can activate, bind to, or inhibit the PPAR γ receptor at concentration levels which do not appreciably activate, bind to, or inhibit these of other PPAR receptors).

Compounds For Use According to the Invention

[0139] Compounds for use according to the invention include those of formulae I, II, III, IVa, IVb, V, VI, and VI as set forth above.

[0140] There are a number of exemplary embodiments.

[0141] Embodiment 1. A compound having a formula selected from the group consisting of:



wherein

X is a member selected from the group consisting of O, S, SO, SO₂ and NR, wherein R is H, (C₁-C₈)alkyl, COR^a, COOR^a and CONR^aR^b wherein R^a and R^b are each independently selected from the group consisting of H and (C₁-C₈)alkyl;

Y is a member selected from the group consisting of CH₂OR^c, CO₂R^c, CHO, CONR^cR^m, CH(=NR^c), CH(=NOR^c) and carboxylic acid surrogates, wherein R^c is a member selected from the group consisting of H, (C₁-C₈)alkyl, (C₃-C₈)alkenyl, (C₃-C₈)alkynyl, (C₃-C₇)cycloalkyl, (C₄-C₈)cycloalkyl-alkyl, aryl, aryl(C₁-C₈)alkyl and (C₁-C₈)alkylene-Z, wherein Z is selected from the group consisting of COR^d, COOR^d, NR^dR^e, NR^dCONR^eR^f, NR^dCOR^e, NR^dCOOR^e and CONR^dR^e wherein R^d, R^e and R^f are each independently selected from the group consisting of H, (C₁-C₈)alkyl and phenyl, or optionally two of R^d, R^e and R^f when attached to the same nitrogen atom are combined to form a five- or six-membered ring; and wherein R^m is selected from the group consisting of H, (C₁-C₈)alkyl, aryl, OH and SO₂Rⁿ, wherein Rⁿ is selected from the group consisting of (C₁-C₈)alkyl, (C₁-C₈)haloalkyl, aryl(C₁-C₈)alkyl, (C₁-C₈)heteroalkyl, aryl, heteroaryl, (C₁-C₈)alkoxy, aryloxy, alkylamino, dialkylamino, arylamino, diarylamino, haloalkylamino and di(haloalkyl)amino, and R^m and R^c are optionally combined with the nitrogen atom to which each is attached to form a five- or six-membered ring;

HAr is heteroaryl moiety, optionally substituted with from one to three substituents independently selected from the group consisting of halogen, hydroxy, (C₁-C₈)alkyl, aryl(C₁-C₈)alkyl, (C₁-C₈)alkoxy, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)cycloalkyl, (C₄-C₈)cycloalkyl-alkyl, (C₁-C₈)heteroalkyl, (C₂-C₅)heterocyclyl, aryl, aryloxy, heterosubstituted(C₃-C₇)cycloalkyl, heteroalkyl substituted (C₃-C₇)cycloalkyl, (C₁-C₈)haloalkyl, O(C₁-C₈)haloalkyl, nitro, cyano, CO₂R^g, COR^g, NR^gR^h, S(O)_qR^g, SO₂NR^gR^h, NR^gCONR^hRⁱ, NR^gCOR^h, NR^gCOOR^h and CONR^gR^h, wherein R^g, R^h and Rⁱ are each independently selected from the group consisting of H and (C₁-C₈)alkyl, or optionally two of R^g, R^h and Rⁱ when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript q is an integer of from 0 to 2;

each R¹ and R³ is a member independently selected from the group consisting of halogen, hydroxy, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₁-C₈)alkoxy, (C₃-C₇)cycloalkyl, (C₄-C₈)cycloalkyl-alkyl, (C₁-C₈)haloalkyl, (C₁-

C₈)heteroalkyl, (C₂-C₅)heterocyclyl, heterosubstituted(C₃-C₇)cycloalkyl, heteroalkyl substituted (C₃-C₇)cycloalkyl, O(C₁-C₈)haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl, S(O)_r-phenyl, COR^j, COOR^j, NR^jR^k, S(O)_rR^j, SO₂NR^jR^k, NR^jCONR^kR^l, NR^jCOR^k, NR^jCOOR^k and CONR^jR^k wherein the phenyl ring is optionally substituted and R^j, R^k and R^l are each independently selected from the group consisting of H, (C₁-C₈)alkyl and (C₁-C₈)haloalkyl, or optionally two of R^j, R^k and R^l when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript r is an integer of from 0 to 2;

R² is a member selected from the group consisting of H, (C₁-C₈)alkyl, (C₁-C₈)haloalkyl, aryl(C₁-C₈)alkyl and (C₁-C₄)alkylene-Z, wherein Z is as defined above;

the subscript m is an integer of from 0 to 4;

the subscript p is an integer of from 0 to 3; and

pharmaceutically acceptable salts thereof.

[0142] Embodiment 2. A compound of embodiment 1, wherein Y is selected from the group consisting of CH₂OR^c, CO₂R^c, tetrazol-5-yl, CONHSO₂Rⁿ and CHO.

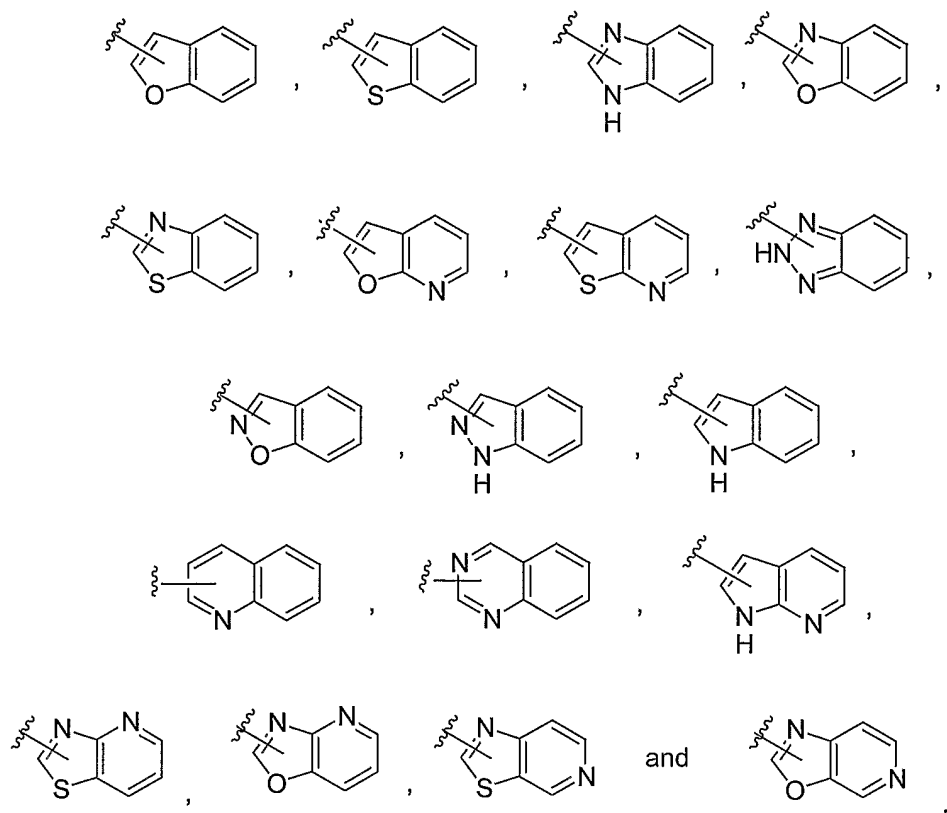
[0143] Embodiment 3. A compound of embodiment 1, wherein Y is selected from the group consisting of CH₂OR^c, tetrazol-5-yl, CONHSO₂Rⁿ and CO₂R^c

[0144] Embodiment 4. A compound of embodiment 3, wherein HAr is a fused bicyclic heteroaryl moiety, wherein each of said HAr groups is optionally substituted with from one to three substituents independently selected from the group consisting of halogen, (C₁-C₄)alkyl, aryl, aryloxy, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, O(C₁-C₄)haloalkyl, nitro, cyano, CO₂R^g, COR^g and CONR^gR^h.

[0145] Embodiment 5. A compound of embodiment 4, wherein X is selected from the group consisting of O, S and NH

[0146] Embodiment 6. A compound of embodiment 5, wherein R² is selected from the group consisting of H, CH₃ and CF₃.

[0147] Embodiment 7. A compound of embodiment 6, wherein HAr is attached to the 2- or 3-position of the ring bearing X and is selected from the group consisting of:



wherein each of said HAr groups is optionally substituted with from one to three substituents independently selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, O(C₁-C₄)haloalkyl, nitro, cyano, CO₂R^g, COR^g and CONR^gR^h, and wherein the wavy line indicates the point of attached to the ring bearing X through attachment to any available ring member in either ring of HAr.

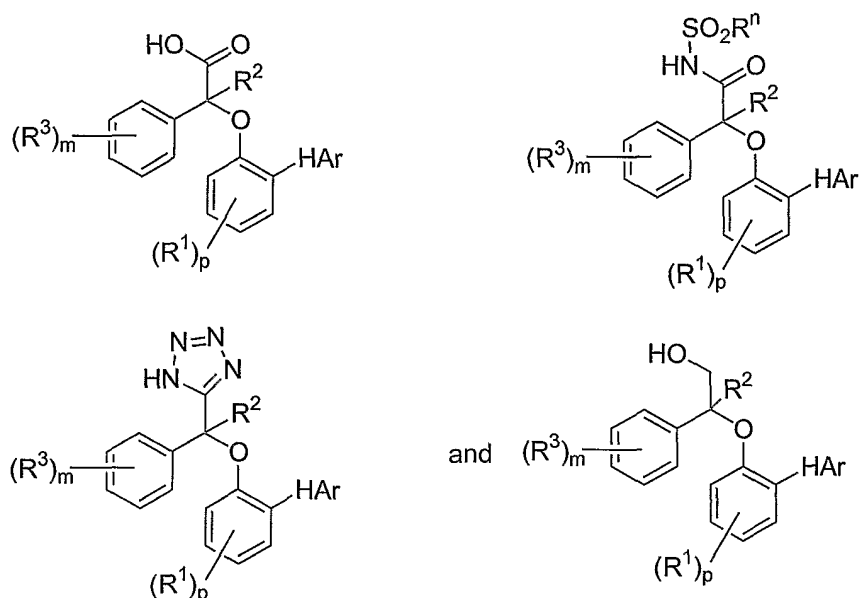
[0148] Embodiment 8. A compound of embodiment 7, wherein the subscript m is 0 to 2 and each R³ when present is independently selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, O(C₁-C₄)haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl and S(O)_r-phenyl.

[0149] Embodiment 9. A compound of embodiment 8, wherein p is an integer of from 0 to 2 and each R¹ when present is independently selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, O(C₁-C₄)haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl and S(O)_r-phenyl.

[0150] Embodiment 10. A compound of embodiment 9, wherein m is an integer of from 0 to 2; each R³ when present is independently selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, O(C₁-C₄)haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl and S(O)_r-phenyl; p is an integer of from 0 to 2; and each R¹ is

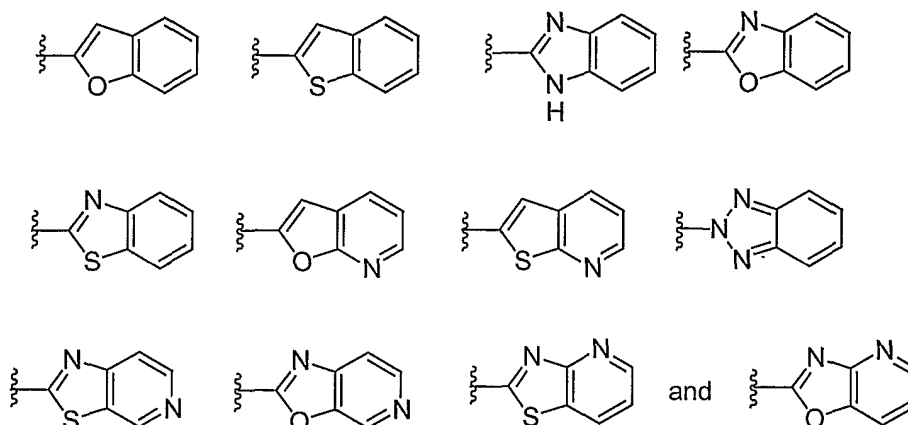
independently selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, O(C₁-C₄)haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl and S(O)_r-phenyl.

[0151] Embodiment 11. A compound of embodiment 7, having a formula selected from the group consisting of:



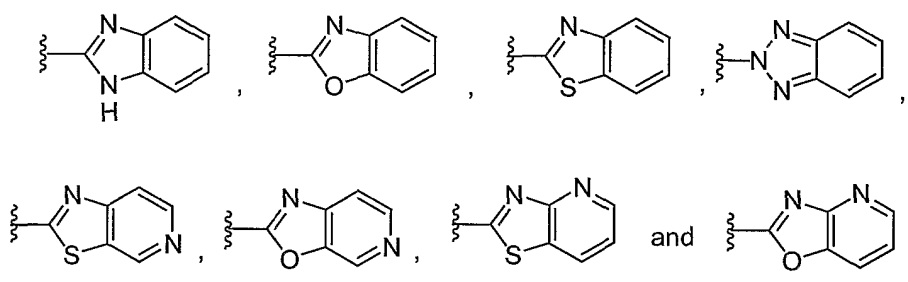
wherein the subscript *m* is an integer of from 0 to 2, the subscript *p* is an integer of from 0 to 2, and R¹ and R³ are each independently selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, O(C₁-C₄)haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl and S(O)_r-phenyl; and Rⁿ is selected from the group consisting of (C₁-C₈)alkyl, (C₁-C₈)haloalkyl, aryl(C₁-C₈)alkyl, (C₁-C₈)heteroalkyl, aryl, heteroaryl, (C₁-C₈)alkoxy, aryloxy, alkylamino, dialkylamino, arylamino, diarylamino, haloalkylamino and di(haloalkyl)amino.

[0152] Embodiment 12. A compound of embodiment 11, wherein HAr is selected from the group consisting of



wherein each of said HAr groups is optionally substituted with from one to three substituents independently selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, O(C₁-C₄)haloalkyl, nitro, cyano, CO₂R^g, COR^g and CONR^gR^h.

[0153] Embodiment 13. A compound of embodiment 12, wherein HAr is selected from the group consisting of



wherein each of said HAr groups is optionally substituted with from one to three substituents independently selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, O(C₁-C₄)haloalkyl, nitro, cyano, CO₂R^c, COR^c and CONR^cR^d.

[0154] Embodiment 14. A compound of embodiment 13, wherein HAr is 2-benzoxazolyl; R² is H or CH₃; the subscript m is 0 or 1, and p is 1 or 2; and R¹ and R³ are each independently selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, O(C₁-C₄)haloalkyl, nitro, cyano, CO₂R^g, COR^g and CONR^gR^h.

[0155] Embodiment 15. A compound of embodiment 13, wherein HAr is 2-benzothiazolyl; R² is H or CH₃; the subscript m is 0 or 1, and p is 1 or 2; and R¹ and R³ are each independently selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, O(C₁-C₄)haloalkyl, nitro, cyano, CO₂R^g, COR^g and CONR^gR^h.

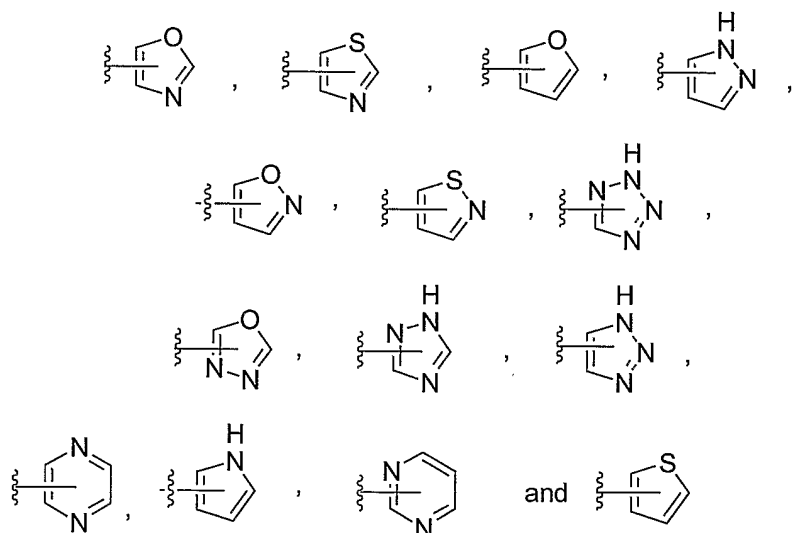
[0156] Embodiment 16. A compound of embodiment 13, wherein HAr is 2-benzotriazolyl; R^2 is H or CH_3 ; the subscript m is 0 or 1, and p is 1 or 2; and R^1 and R^3 are each independently selected from the group consisting of halogen, (C_1-C_4) alkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkyl, $O(C_1-C_4)$ haloalkyl, nitro, cyano, CO_2R^g , COR^g and $CONR^gR^h$.

[0157] Embodiment 17. A compound of embodiment 3, wherein HAr is a monocyclic heteroaryl moiety, wherein each of said HAr groups is optionally substituted with from one to three substituents independently selected from the group consisting of halogen, (C_1-C_4) alkyl, (C_1-C_8) heteroalkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkyl, $O(C_1-C_4)$ haloalkyl, aryl (C_1-C_4) alkyl, aryl, heteroaryl, nitro, cyano, CO_2R^g , COR^g and $CONR^gR^h$.

[0158] Embodiment 18. A compound of embodiment 17, wherein X is selected from the group consisting of O, S and NH.

[0159] Embodiment 19. A compound of embodiment 18, wherein R^2 is selected from the group consisting of H, CH_3 and CF_3 .

[0160] Embodiment 20. A compound of embodiment 19, wherein HAr is attached to the 2- or 3-position of the phenyl ring bearing X and is selected from the group consisting of



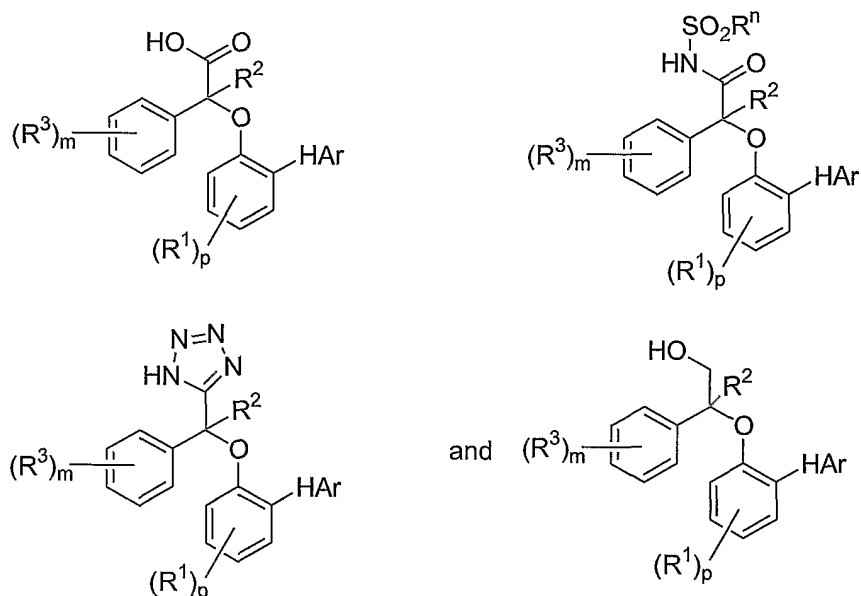
wherein each of said HAr groups is optionally substituted with from one to three substituents independently selected from the group consisting of halogen, (C_1-C_4) alkyl, (C_1-C_8) heteroalkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkyl, $O(C_1-C_4)$ haloalkyl, aryl (C_1-C_4) alkyl, aryl, heteroaryl, nitro, cyano, CO_2R^g , COR^g and $CONR^gR^h$, and the wavy line indicates the attachment to the ring bearing X.

[0161] Embodiment 21. A compound of claim 20, wherein m is 0 to 2 and each R^3 when present is independently selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, O(C₁-C₄)haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl and S(O)_r-phenyl.

[0162] Embodiment 22. A compound of embodiment 21, wherein p is 0 to 2 and each R^1 when present is independently selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, O(C₁-C₄)haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl and S(O)_r-phenyl.

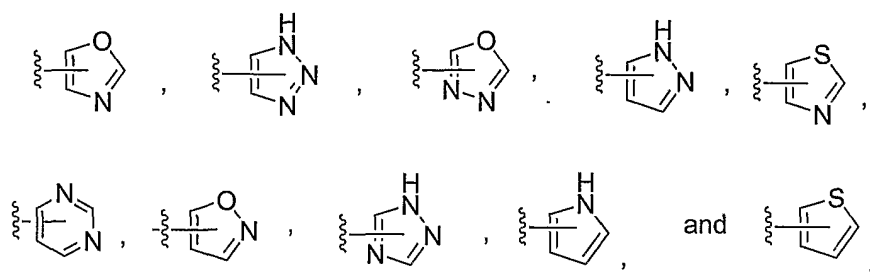
[0163] Embodiment 23. A compound of embodiment 22, wherein m is an integer of from 0 to 2; each R^3 is independently selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, O(C₁-C₄)haloalkyl, nitro and cyano; p is an integer of from 0 to 2; and each R^1 is independently selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, O(C₁-C₄)haloalkyl, nitro and cyano.

[0164] Embodiment 24. A compound of embodiment 20, having a formula selected from the group consisting of:



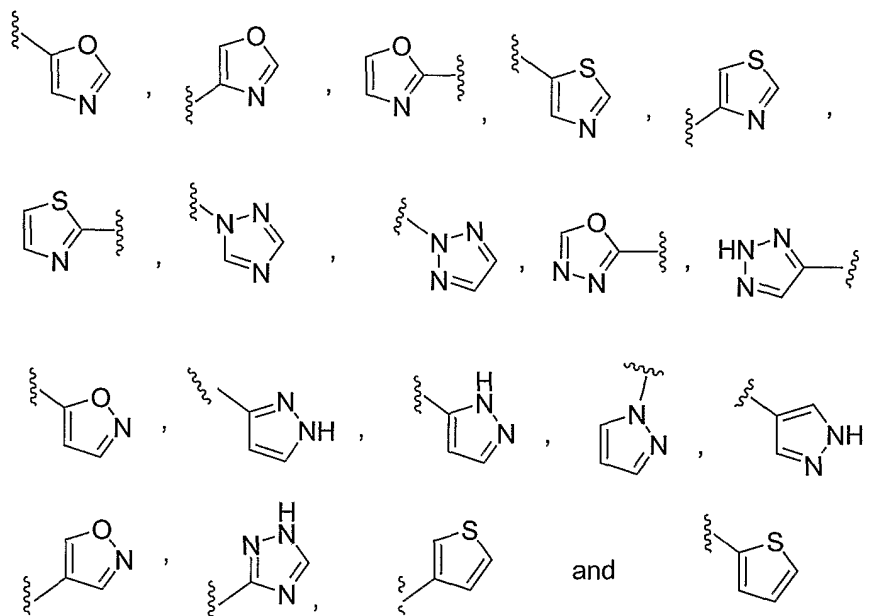
wherein m is an integer of from 0 to 2, p is an integer of from 0 to 2, and R^1 and R^3 are each independently selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, O(C₁-C₄)haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl and S(O)_r-phenyl; and R^n is selected from the group consisting of (C₁-C₈)alkyl, (C₁-C₈)haloalkyl, aryl(C₁-C₈)alkyl, (C₁-C₈)heteroalkyl, aryl, heteroaryl, (C₁-C₈)alkoxy, aryloxy, alkylamino, dialkylamino, arylamino, diarylamino, haloalkylamino and di(haloalkyl)amino.

[0165] Embodiment 25. A compound of embodiment 24, wherein HAr is selected from the group consisting of



wherein each of said HAr groups is optionally substituted with from one to three substituents independently selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₈)heteroalkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, O(C₁-C₄)haloalkyl, aryl(C₁-C₄)alkyl, aryl, heteroaryl, nitro, cyano, CO₂R^g, COR^g and CONR^gR^h.

[0166] Embodiment 26. A compound of embodiment 24, wherein HAr is selected from the group consisting of



wherein each of said HAr groups is optionally substituted with from one to two substituents independently selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₈)heteroalkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, O(C₁-C₄)haloalkyl, aryl(C₁-C₄)alkyl, aryl, heteroaryl, nitro, cyano, CO₂R^g, COR^g and CONR^gR^h.

[0167] Embodiment 27. A compound of embodiment 26, wherein m is an integer of from 0 to 2, p is an integer of from 0 to 2, R¹ and R³ are each independently selected from

the group consisting of F, Cl, Br, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, O(C₁-C₄)haloalkyl, CN, NO₂ and phenyl.

[0168] Embodiment 28. A compound of embodiment 27, wherein HAr is optionally substituted 2-, 4- or 5-thiazolyl wherein the thiazolyl is optionally substituted with from one to two substituents selected from the group consisting of F, Cl, Br, (C₁-C₄)alkyl, aryl(C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, O(C₁-C₄)haloalkyl, CN and phenyl; R² is H or CH₃; the subscript m is 0 or 1 and p is 1 or 2; and R¹ and R³ are each independently selected from the group consisting of F, Cl, Br, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, O(C₁-C₄)haloalkyl, CN, NO₂ and phenyl.

[0169] Embodiment 29. A compound of embodiment 27, wherein HAr is selected from the group consisting of optionally substituted 1, 3, 4 or 5-pyrazolyl wherein the pyrazolyl is optionally substituted with from one to two substituents selected from the group consisting of F, Cl, Br, (C₁-C₄)alkyl, aryl(C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, O(C₁-C₄)haloalkyl, CN and phenyl; R² is H or CH₃; the subscript m is 0 or 1 and p is 1 or 2; and R¹ and R³ are each independently selected from the group consisting of F, Cl, Br, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, O(C₁-C₄)haloalkyl, CN, NO₂ and phenyl.

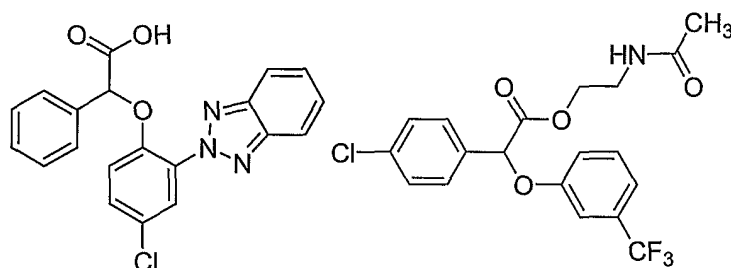
[0170] Embodiment 30. A compound of embodiment 27, wherein HAr is optionally substituted 2-, 4- or 5-oxazolyl wherein the oxazolyl is optionally substituted with from one to two substituents selected from the group consisting of F, Cl, Br, (C₁-C₄)alkyl, aryl(C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, O(C₁-C₄)haloalkyl, CN and phenyl; R² is H or CH₃; the subscript m is 0 or 1 and p is 1 or 2; and R¹ and R³ are each independently selected from the group consisting of F, Cl, Br, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, O(C₁-C₄)haloalkyl, CN, NO₂ and phenyl.

[0171] Embodiment 31. A compound of embodiment 27, wherein HAr is optionally substituted 1,2,3-triazol-2-yl wherein the 1,2,3-triazol-2-yl is optionally substituted with from one to two substituents selected from the group consisting of F, Cl, Br, (C₁-C₄)alkyl, aryl(C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, O(C₁-C₄)haloalkyl, CN and phenyl; R² is H or CH₃; the subscript m is 0 or 1 and p is 1 or 2; and R¹ and R³ are each independently selected from the group consisting of F, Cl, Br, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, O(C₁-C₄)haloalkyl, CN, NO₂ and phenyl.

[0172] Methods of making the above compounds is taught in U.S. Patent Application Publication No. 20040029933, assigned to the same assignee as the present application and

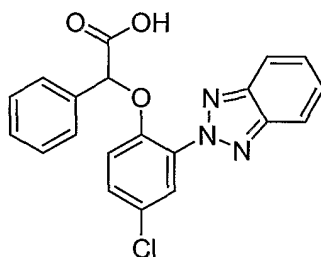
which is incorporated by reference in its entirety. This reference also presents *in vivo* biological data on the activity of representative compounds of Formula V. See also PCT Application Publication No. WO03/080545, which is incorporated herein by reference.

[0173] In some embodiments the compound is of one of the following formula:



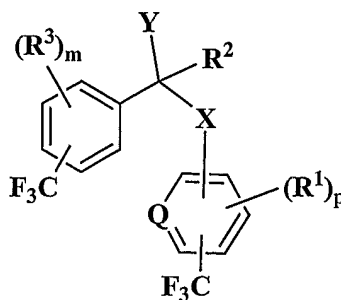
or a pharmaceutically acceptable salt or solvate thereof. Preferably, the compound according to formula I, II, III is the (-) isomer. Methods for making such compounds are taught in U.S. Patent Application Publication No. 20030220399 which is incorporated herein by reference. Methods of resolving alpha-(phenoxy)phenylacetic acid derivatives are taught in U.S. Patent Application Publication No. 20050033084 which is incorporated herein by reference in its entirety.

[0174] In another embodiment, the compound is a prodrug of any of the above compounds which is hydrolysable *in vivo* to yield a therapeutically effective amount of a the corresponding compound or acid or a compound of the formula:



In some embodiments, more than 80%, 90%, 95%, or 99% of the prodrug is converted to the acid by hydrolysis *in vivo*.

[0175] In other embodiments, the compound is a compound of the formula



1

including all pharmaceutically acceptable salts and prodrugs thereof, in which X is a member selected from the group consisting of O, S, SO, SO₂, CHR and NR, and R is H, (C₁-C₈)alkyl, COR^a, COOR^a and CONR^aR^b and in which R^a and R^b are each independently selected from the group consisting of H and (C₁-C₈)alkyl; and Y is a member selected from the group consisting of CH₂OR^c, CO₂R^c, tetrazole, CHO, CONR^cR^m, CH(=NR^c) and CH(=NOR^c), in which R^c is a member selected from the group consisting of H, (C₁-C₈)alkyl, (C₃-C₈)alkenyl, (C₃-C₈)alkynyl, (C₃-C₇)cycloalkyl, (C₄-C₈)cycloalkyl-alkyl, aryl, aryl(C₁-C₈)alkyl and (C₁-C₈)alkylene-Z, in which Z is selected from the group consisting of COR^d, COOR^d, NR^dR^e, NR^dCONR^eR^f, NR^dCOR^e, NR^dCOOR^e and CONR^dR^e in which R^d, R^e and R^f are each independently selected from the group consisting of H, (C₁-C₈)alkyl and phenyl, or optionally two of R^d, R^e and R^f when attached to the same nitrogen atom are combined to form a five- or six-membered ring; and in which R^m is selected from the group consisting of H, (C₁-C₈)alkyl, aryl and OH, and R^m and R^c are optionally combined with the nitrogen atom to which each is attached to form a five or six-membered ring; each R¹ and R³ is a member independently selected from the group consisting of halogen, hydroxy, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₁-C₈)alkoxy, (C₃-C₇)cycloalkyl, (C₄-C₈)cycloalkyl-alkyl, (C₁-C₈)haloalkyl, (C₁-C₈)heteroalkyl, (C₂-C₅)heterocyclyl, heterosubstituted(C₃-C₇)cycloalkyl, heteroalkyl substituted (C₃-C₇)cycloalkyl, O(C₁-C₈)haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl, S(O)_r-phenyl, COR^j, COOR^j, NR^jR^k, S(O)_rR^j, SO₂NR^jR^k, NR^jCONR^kR^l, NR^jCOR^k, NR^jCOOR^k and CONR^jR^k in which the phenyl ring is optionally substituted and R^j, R^k and R^l are each independently selected from the group consisting of H and (C₁-C₈)alkyl, or optionally two of R^j, R^k and R^l when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript r is an integer of from 0 to 2; and R² is a member selected from the group consisting of H and (C₁-C₈)alkyl; Q is CH or N; and the subscript m is an integer of from 0 to 3; and the subscript p is an integer of from 0 to 2.

[0176] In particular embodiments of the above, Q is CH. In others, X is selected from the group consisting of O, S and NR. In still others, Y is CO₂R^c. In some embodiments of the

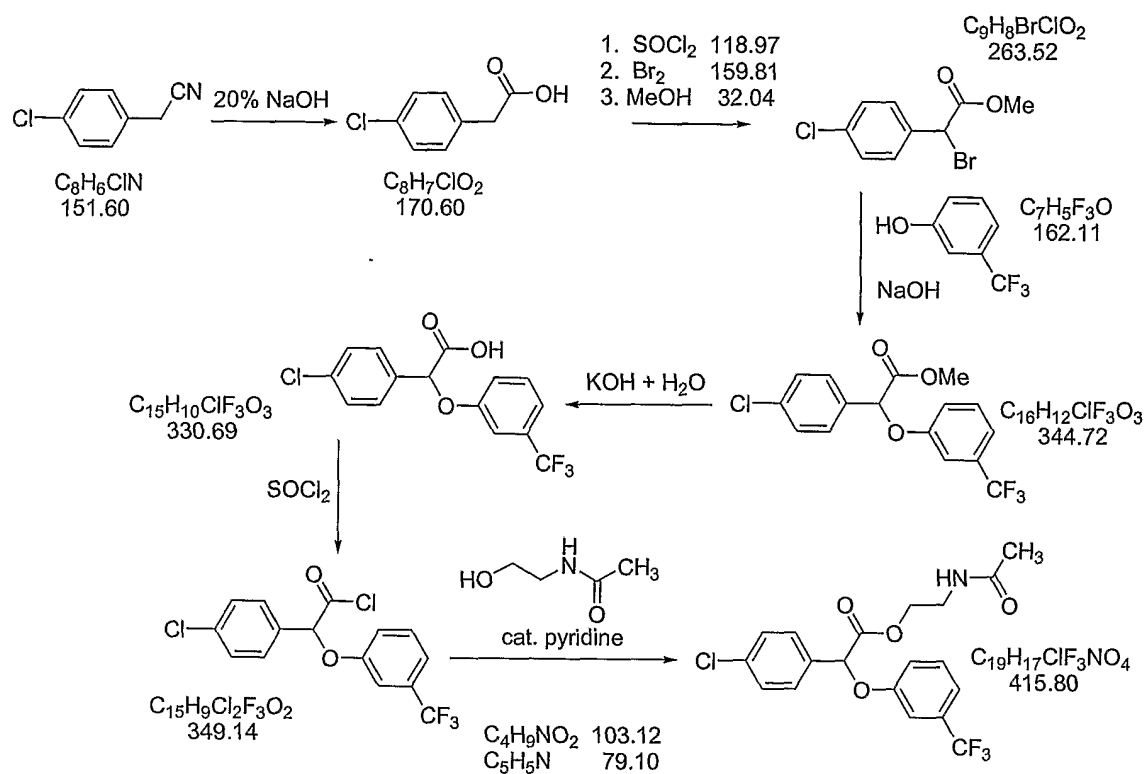
above, m is 0 to 2 and the subscript p is 0 to 1 and, optionally, further, each R^3 is selected from the group consisting of halogen, nitro, (C_1-C_8) alkyl, (C_1-C_8) haloalkyl, (C_1-C_8) alkoxy and (C_1-C_8) haloalkoxy. In other embodiments of any of the above, R^1 is selected from the group consisting of halogen, nitro, (C_1-C_8) alkyl, (C_1-C_8) haloalkyl, (C_1-C_8) alkoxy and (C_1-C_8) haloalkoxy. In yet other embodiments of any of the above, R^c is selected from the group consisting of H, (C_1-C_8) alkyl and (C_1-C_8) alkylene-Z, and optionally further, R^2 is H or CH_3 .

[0177] In yet another embodiment of the above formula, Q is CH; X is selected from the group consisting of O and NR; Y is selected from the group consisting of CH_2OR^c and CO_2R^c ; the subscript m is 0 to 2 and the subscript p is 0 to 1; each R^1 is selected from the group consisting of halogen, nitro, (C_1-C_8) alkyl and (C_1-C_8) alkoxy; each R^3 is selected from the group consisting of halogen, nitro, (C_1-C_8) alkyl and (C_1-C_8) alkoxy; and R^2 is H or CH_3 . In still further embodiments, X is O and Y is CO_2R^c . In yet other embodiments, X is O and Y is CH_2OR^c . In still another embodiment, X is NH and Y is CO_2R^c . In another embodiment, X is NH and Y is CH_2OR^c .

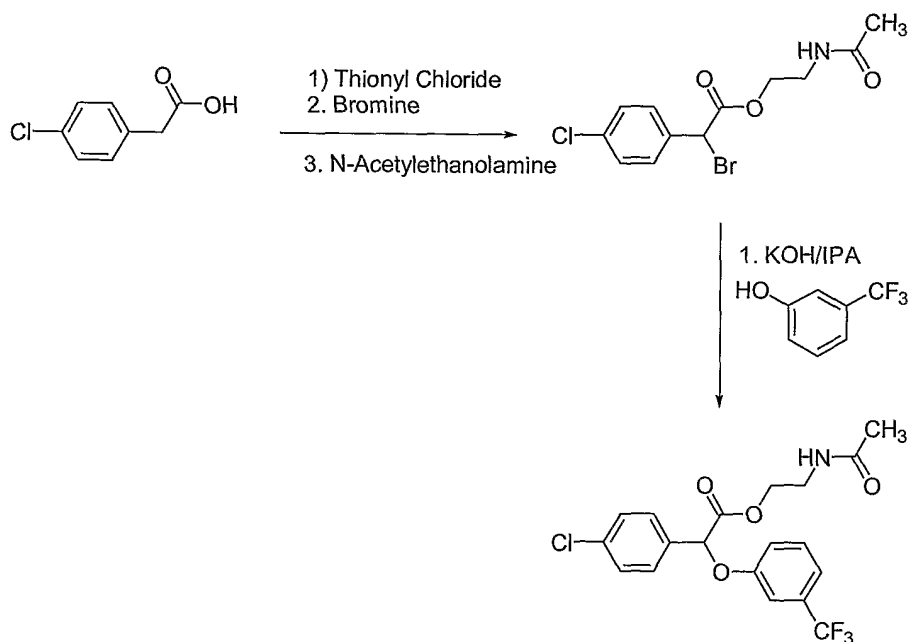
Methods of Making Halofenate

[0178] Exemplary processes for making the compounds of the present invention are generally depicted in Schemes 1 and 2:

Scheme 1:



Scheme 2:



[0179] According to Scheme 1, a substituted phenyl acetonitrile is converted to a substituted phenyl acetic acid. The substituted phenyl acetic acid is converted to an activated acid derivative (e.g., acid chloride), followed by halogenation at the alpha-carbon and esterification with an alcohol. The halogenated ester is treated with a substituted phenol (e.g., 3-trifluoromethylphenol), yielding an aryl ether, which is hydrolyzed to form a carboxylic acid derivative. The acid derivative is converted to an activated acid derivative and subsequently treated with a nucleophile (e.g., N-acetyethanolamine) to afford the desired product.

[0180] According to Scheme 2, a substituted phenyl acetic acid is converted to an activated acid derivative (e.g., acid chloride) followed by halogenation at the alpha-carbon. The activated acid portion of the molecule is reacted with a nucleophile (e.g., N-acetyethanolamine) to provide a protected acid. The halogenated, protected acid is treated with a substituted phenol (e.g., 3-trifluoromethylphenol), yielding the desired product.

[0181] The stereoisomers of the compounds of the present invention can be prepared by using reactants or reagents or catalysts in their single enantiomeric form in the process wherever possible or by resolving the mixture of stereoisomers by conventional methods, discussed *supra* and in the Examples. Some of the preferred methods include use of microbial resolution, resolving the diastereomeric salts formed with chiral acids or chiral bases and chromatography using chiral supports. *See, also* U.S. Patent Application Publication No. 20050033084 published February 10, 2005, which is incorporated herein by reference in its entirety and particularly with respect to methods of making and resolving such compounds including halofenate. *See, also*, U.S. Patent Nos. 6,646,004; 6,624,194; 6,613,802; and 6,262,118, each to Luskey et al. and which are incorporated herein by reference in their entirety. The synthesis of the compounds of the present invention is further described in the Examples.

[0182] The chemical synthesis of racemic mixtures of (3-trihalomethylphenoxy) (4-halophenyl) acetic acid derivatives can also be performed by the methods described in U.S. Patent No. 3,517,050, the teaching of which are incorporated herein by reference. The individual enantiomers can be obtained by resolution of the racemic mixture of enantiomers using conventional means known to and used by those of skill in the art. *See, e.g.*, Jaques, J., *et al.*, in ENANTIOMERS, RACEMATES, AND RESOLUTIONS, John Wiley and Sons, New York (1981). Other standard methods of resolution known to those skilled in the art, including but

not limited to, simple crystallization and chromatographic resolution, can also be used (*see, e.g.*, STEREOCHEMISTRY OF CARBON COMPOUNDS (1962) E. L. Eliel, McGraw Hill; Lochmuller, J. *Chromatography* (1975) 113, 283-302). Additionally, the compounds of the present invention, *i.e.*, the optically pure isomers, can be prepared from the racemic mixture by enzymatic biocatalytic resolution. Enzymatic biocatalytic resolution has been generally described previously (*see, e.g.*, U.S. Patent Nos. 5,057,427 and 5,077,217, the disclosures of which are incorporated herein by reference). Other generic methods of obtaining enantiomers include stereospecific synthesis (*see, e.g.*, Li, A. J. *et al.*, *Pharm. Sci.* (1997) 86: 1073-1077).

Methods for Screening anti-Edema Activity.

[0183] Methods for assessing anti-edemic activity or the lack of edema-causing activity are known to one of ordinary skill in the art. Edema can be assessed according to the number of subjects developing the edema or by the severity of the edema. Improvements in edema can be assessed by comparing subjects administered the test compound to a placebo group. Edema can be assessed by measuring interstitial fluid volumes by use of tracers or MRI imaging. Edema can be indirectly monitored by assessing fluid balance, including urinary output. Given the density and volume of water involved, edema can be assessed by following body weight changes. Clinically, edema may be monitored indirectly by assessing blood pressure or the circumference of extremities (*e.g.*, degree of swelling and proportional area of swelling) or the severity and extent of "pitting" upon application of pressure to the skin. Pulmonary edema can be assessed by patient reports of dyspnea and discomfort or by listening to the chest for the tell-tale signs of fluid accumulation and swelling in the lungs.

[0184] Similarly, methods for assessing renal function, heart function, hypertension and the like are well known to one of ordinary skill in the arts.

Methods of Screening for Anti-lipidemic, Anti-glycemic, and Anti-Uricemic Activity of the Compounds to be used according to the invention.

[0185] Methods for screening compounds for the above-recited activities on blood lipids, glucose, and uric acid are well known to one of ordinary skill in the art. Methods of monitoring blood lipids, glucose levels, and uric acid levels are commonly used in medicine and the veterinary arts. U.S. Patent Application Publications No. 20030220399 and 20040029933, and U.S. Patents Nos. 6,646,004; 6,624,194; 6,613,802; and 6,262,118 which are each incorporated herein by reference illustrate the application of such methods to

phenoxyacetic acids. These assays may also be useful in screening for pharmacologically acceptable compounds for use according to the invention.

Methods for Screening for PPAR γ Partial Agonism.

[0186] Optionally, agents for possible use according to the invention, can be first screened according to their ability to bind to PPAR γ . Such first identification of compounds that specifically bind PPAR γ can be accomplished by any means known in the art, such as, for example, electrophoretic mobility shift assays and competitive binding assays. One of ordinary skill in the art is readily aware of how to screen compounds for PPAR γ activity, including partial agonism. For instance, see European Patent Application Publications Nos. EP1469071, EP1288303, EP1267171, European Patent No. EP1016714, United States Patent Application Publications Nos. 20040077659, 20040010119, 20020119499, 20020031539, and 20030039980; and United States Patents Nos. 6815168, 6200802, 6689574, 6365361, and 6365361 which are each incorporated herein by reference with respect to such methodologies. Mammalian PPAR subtypes (e.g., rat, mouse, hamster, rabbit, primate, guinea pig) are preferably used. More preferably, human PPAR subtypes are used.

[0187] Electrophoretic mobility shift assays can be used to determine whether test compounds bind to PPAR γ and affect its electrophoretic mobility (Forman, et al. (1997) PNAS 94:4312 and Kliewer, et al. (1994) PNAS 91:7355). Electrophoretic mobility shift assays involve incubating a PPAR-RXR with a test compound in the presence of a labeled nucleotide sequence. Labels are known to those of skill in the art and include, for example, radioactive isotopes and non-radioactive labels such as fluorescent labels or chemiluminescent labels. Fluorescent molecules which can be used to label nucleic acid molecules include, for example, fluorescein isothiocyanate and pentafluorophenyl esters. Fluorescent labels and chemical methods of DNA and RNA fluorescent labeling have been reviewed recently (Proudnikov et al., 1996, Nucleic Acids Res. 24:4535-42).

[0188] Monoclonal antibodies specific for PPAR subtypes can be used to identify PPAR γ specific binding compounds in modified electrophoretic mobility shift assays. Purified PPAR β , PPAR α or PPAR γ can be incubated with an appropriate amount of a test compound in the presence of RXR. For these assays, the test compound need not be labeled. PPAR subtype specific monoclonal antibodies can be incubated with the PPAR-RXR-test compound mixture. For instance, test compounds that bind PPAR induce supershifting of the PPAR-

RXR complex on a gel (Forman, et al. (1997), PNAS 94:4312) which can be detected by anti-PPAR monoclonal antibodies using a Western blot (immunoblot).

[0189] In addition to electrophoretic mobility shift assays, competitive binding assays can be used to identify PPAR γ specific binding compounds. In competitive assays, the binding of test compounds to PPAR γ can be determined by measuring the amount of ligand that they displaced (competed away) from PPAR γ . Purified PPAR subtype receptors can be incubated with varying amounts of a test compound in the presence of labeled ligands specific for each PPAR subtype. For example, GW 2433 and L-783483 can be used in conjunction with PPAR β ; GW 2331 can be used in conjunction with PPAR α ; and rosiglitazone, AD-5075, and SB-236636 can be used in conjunction with PPAR γ . Specificity of the test compound for each PPAR subtype can be determined by detection of the amount of labeled ligand that remains bound to each PPAR after incubation with the test compound. Labels are discussed above.

[0190] The ability of a compound to activate PPAR γ can be measured using any means known in the art. PPAR γ activators are thought to act by inducing PPAR γ -RXR heterodimer formation. The PPAR γ -RXR heterodimer then binds to DNA sequences containing the corresponding binding motif and activates PPAR target genes. Preferably PPAR γ activators activate PPAR γ by at least 5-10 fold, more preferably 10-100 fold, more preferably 100-500 fold, more preferably 500-1000 fold, most preferably greater than 1000 fold above base level. PPAR γ can be transfected into cells. The transfected cells can be then exposed to candidate compounds. Any means known in the art can be used to determine whether PPAR γ is activated by the candidate compound, such as for example, by measuring levels of reporter gene expression and cell proliferation.

[0191] Any of the well-known procedures for introducing foreign nucleotide sequences into host cells may be used to transfect PPAR γ into cells. Methods of transfection have also been described in U.S. Pat. Nos. 5,616,745, 5,792,6512, 5,965,404, and 6,051,429 and in Current Protocols in Molecular Biology, Ausubel, et al., ed. (2001). It is only necessary that the particular genetic engineering procedure used be capable of successfully introducing at least one gene into the host cell capable of expressing PPAR γ . After the expression vector is introduced into the cells, the transfected cells can be cultured under conditions favoring expression of PPAR γ .

[0192] Expression of reporter genes in response to compounds identified as binders of

PPAR γ may also be used to measure PPAR γ activation. PPAR γ may be co-transfected with reporter genes known in the art such as, for example, luciferase, β -galactosidase, alkaline phosphatase, fluorescent green protein, or chloramphenicol acetyltransferase. The transfected cells can be exposed to appropriate concentrations of candidate compounds with rosiglitazone as a positive control. Reporter gene expression will be induced by compounds that bind and activate PPAR γ . Thus, compounds that induce reporter gene expression can be identified as activators of PPAR γ (Forman, et al. (1997) PNAS 94:4312). Preferably the compounds induce reporter gene expression at levels at least 5-10 fold, more preferably 10-100 fold, more preferably 100-500 fold, more preferably 500-1000 fold, most preferably greater than 1000 fold greater than the negative control.

Pharmaceutical Compositions and Methods of Treating Diseases and Conditions

[0193] In accordance with the present invention, a therapeutically effective amount of a compound of Formula I, II, III, IVa, IVb, V, VI, or VII can be used for the preparation of a pharmaceutical composition useful for treating or preventing edema and the various other conditions and diseases set forth above.

[0194] The compositions of the invention can include compounds of Formula I, II, III, IVa, IVb, V, VI, or VII, pharmaceutically acceptable salts thereof, or a hydrolyzable precursor thereof. In general, the compound is mixed with suitable carriers or excipient(s) in a therapeutically effective amount. By a "therapeutically effective dose", "therapeutically effective amount", or, interchangeably, "pharmacologically acceptable dose" or "pharmacologically acceptable amount", it is meant that a sufficient amount of the compound of the present invention and a pharmaceutically acceptable carrier, will be present in order to achieve a desired result, *e.g.*, alleviating a symptom or complication of edema.

[0195] The compounds of Formula I, II, III, IVa, IVb, V, VI, or VII that are used in the methods of the present invention can be incorporated into a variety of formulations for therapeutic administration. More particularly, the compounds of Formula I, II, III, IVa, IVb, V, VI, or VII can be formulated into pharmaceutical compositions by combination with appropriate, pharmaceutically acceptable carriers or diluents, and can be formulated into preparations in solid, semi-solid, liquid or gaseous forms, such as tablets, capsules, pills, powders, granules, dragees, gels, slurries, ointments, solutions, suppositories, injections, inhalants and aerosols. As such, administration of the compounds can be achieved in various ways, including oral, buccal, rectal, parenteral, intraperitoneal, intradermal, transdermal,

intratracheal administration. Moreover, the compound can be administered in a local rather than systemic manner, in a depot or sustained release formulation. In addition, the compounds can be administered in a liposome.

[0196] The compounds of Formula I, II, III, IVa, IVb, V, VI, or VII can be formulated with common excipients, diluents or carriers, and compressed into tablets, or formulated as elixirs or solutions for convenient oral administration, or administered by the intramuscular or intravenous routes. The compounds can be administered transdermally, and can be formulated as sustained release dosage forms and the like. Compounds of Formula I, II, III, IVa, IVb, V, VI, or VII can be administered alone, in combination with each other, or they can be used in combination with other known compounds useful in the treatment of a subject's particular condition. In some embodiments, the compounds are co-administered to a subject being treated with an agent known to cause or causally associated with edema in treated subjects.

[0197] Suitable formulations for use in the present invention are found in *Remington's Pharmaceutical Sciences* (Mack Publishing Company (1985) Philadelphia, PA, 17th ed.), which is incorporated herein by reference. Moreover, for a brief review of methods for drug delivery, see, Langer, *Science* (1990) 249:1527-1533, which is incorporated herein by reference. The pharmaceutical compositions described herein can be manufactured in a manner that is known to those of skill in the art, *i.e.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes. The following methods and excipients are merely exemplary and are in no way limiting.

[0198] For injection, the compounds can be formulated into preparations by dissolving, suspending or emulsifying them in an aqueous or nonaqueous solvent, such as vegetable or other similar oils, synthetic aliphatic acid glycerides, esters of higher aliphatic acids or propylene glycol; and if desired, with conventional additives such as solubilizers, isotonic agents, suspending agents, emulsifying agents, stabilizers and preservatives. Preferably, the compounds of the present invention can be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

[0199] For oral administration, the compounds of Formula I, II, III, IVa, IVb, V, VI, or VII can be formulated readily by combining with pharmaceutically acceptable carriers that are well known in the art. Such carriers enable the compounds to be formulated as tablets, pills, dragees, capsules, emulsions, lipophilic and hydrophilic suspensions, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by mixing the compounds with a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents can be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[0200] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions can be used, which can optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments can be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0201] Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds can be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers can be added. All formulations for oral administration should be in dosages suitable for such administration. For instance, these doses is from 100 to 800 mg per day by the oral route, or from about 200 mg to about 400 mg by the oral route.

[0202] For buccal administration, the compositions can take the form of tablets or lozenges formulated in conventional manner.

[0203] For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas, or from propellant-free, dry-powder inhalers. In the case of a pressurized aerosol the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, *e.g.*, gelatin for use in an inhaler or insufflator can be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0204] The compounds can be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection can be presented in unit dosage form, *e.g.*, in ampules or in multidose containers, with an added preservative. The compositions can take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and can contain formulator agents such as suspending, stabilizing and/or dispersing agents.

[0205] Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds can be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions can contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension can also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, the active ingredient can be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

[0206] The compounds can also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter, carbowaxes, polyethylene glycols or other glycerides, all of which melt at body temperature, yet are solidified at room temperature.

[0207] In addition to the formulations described previously, the compounds can also be formulated as a depot preparation. Such long acting formulations can be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection.

Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0208] Alternatively, other delivery systems for hydrophobic pharmaceutical compounds can be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. In a presently preferred embodiment, long-circulating, *i.e.*, stealth liposomes can be employed. Such liposomes are generally described in Woodle, *et al.*, U.S. Patent No. 5,013,556. The compounds of the present invention can also be administered by controlled release means and/or delivery devices such as those described in U.S. Pat. Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719.

[0209] Certain organic solvents such as dimethylsulfoxide (DMSO) also can be employed, although usually at the cost of greater toxicity. Additionally, the compounds can be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various types of sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules can, depending on their chemical nature, release the compounds for a few hours up to over 100 days.

[0210] The pharmaceutical compositions also can comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

[0211] Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in a therapeutically effective amount. The amount of composition administered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration and the judgment of the prescribing physician. Determination of an effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

[0212] For any compound used in the method of the present invention, a therapeutically effective dose can be estimated initially from cell culture assays or animal models.

[0213] Moreover, toxicity and therapeutic efficacy of the compounds described herein can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, by determining the LD₅₀, (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effect is the therapeutic index and can be expressed as the ratio between LD₅₀ and ED₅₀. Compounds which exhibit high therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a dosage range that is not toxic for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED₅₀ with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (*See, e.g., Fingl et al. 1975 In: The Pharmacological Basis of Therapeutics, Ch. 1*).

[0214] The amount of active compound that can be combined with a carrier material to produce a single dosage form will vary depending upon the disease treated, the mammalian species, and the particular mode of administration. However, as a general guide, suitable unit doses for the compounds of the present invention can, for example, preferably contain between 100 mg to about 3000 mg of the active compound. A preferred unit dose is between 100 mg to about 1000 mg. A more preferred unit dose is between 100 to about 600 mg. Such unit doses can be administered more than once a day, for example 2, 3, 4, 5 or 6 times a day, but preferably 1 or 2 times per day, so that the total daily dosage for a 70 kg adult is in the range of 0.1 to about 250 mg per kg weight of subject per administration. A preferred dosage is 5 to about 250 mg per kg weight of subject per administration, and such therapy can extend for a number of weeks or months, and in some cases, years. A more preferred dosage is from 2 mg/kg to about 10 mg/kg. It will be understood, however, that the specific dose level for any particular patient will depend on a variety of factors including the activity of the specific compound employed; the age, body weight, general health, sex and diet of the individual being treated; the time and route of administration; the rate of excretion; other drugs which have previously been administered; and the severity of the particular disease undergoing therapy, as is well understood by those of skill in the area.

[0215] A typical dosage can be one 10 to about 1500 mg tablet taken once a day, or, multiple times per day, or one time-release capsule or tablet taken once a day and containing a proportionally higher content of active ingredient. In some embodiments, the dosage can be

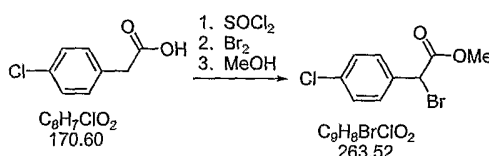
a 50 to 800 mg or a 200 to 600 mg tablet taken once a day, or, multiple times per day, or one time-release capsule or tablet taken once a day and containing a proportionally higher content of active ingredient. The time-release effect can be obtained by capsule materials that dissolve at different pH values, by capsules that release slowly by osmotic pressure, or by any other known means of controlled release.

[0216] It can be necessary to use dosages outside these ranges in some cases as will be apparent to those skilled in the art. Further, it is noted that the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with individual patient response.

[0217] For the compositions provided above, one of skill in the art will understand that preferred compounds for use in each are those compounds that are preferred above and particularly those compounds provided in formulae IIa through IIat, and IIIa through IIIt in Figures 2, 3, 4A, 4B, 5A, 5B and 5C. Still further preferred compounds for the compositions, methods and kits are those compounds provided in the Examples below.

EXAMPLE 1

[0218] This example relates to the preparation of Methyl Bromo-(4-chlorophenyl)-acetate:



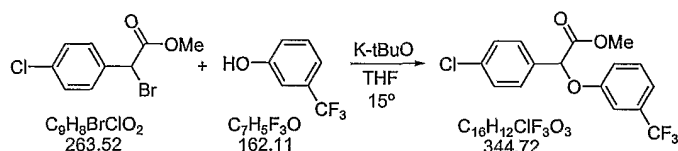
[0219] The initial compound listed in Scheme 1, *i.e.*, 4-chlorophenylacetic acid, is readily available from several commercial sources (*e.g.*, Aldrich and Fluka).

[0220] A 5-L Morton reactor equipped with a magnetic stirrer, a pot temperature control, and addition funnel was vented through a gas scrubber and charged with p-chlorophenylacetic acid (720 gm, 4.2 moles) and SOCl_2 (390 ml, 630 gm, 5.3 moles). The reaction was stirred, heated and held at $55^\circ \pm 5^\circ \text{C}$ for 1 hour. Bromine (220 ml., 670 gm, 5.3 moles) was then added over 20 min. and stirred at $55^\circ \pm 5^\circ \text{C}$ for 16 hours. The temperature was raised to 80°C for 7 hours and then cooled to 9°C in an ice-water bath. Methanol (2.0 L, 1.6 kg, 49.4 moles) was then carefully added. The solvent was stripped to obtain 2 liquids weighing 1.28kg. These were dissolved in a mixture of 0.84 L water and 2.1 L ether and separated. The organic phase was washed once with 0.78 L 25% (w:w) aqueous NaCl and dried over 0.13 kg MgSO_4 . This was filtered through Whatman #1 filter paper and stripped

of solvent to obtain 0.985 kg of orange liquid. The proton NMR showed this to be 80% product and 19% non-brominated ester. The HPLC showed 82% product and 18% non-brominated ester. HPLC was run on a Zorbax SB-C8 column at 30° C measuring 250 X 4.6 mm and 5 μ particle size. The mobile phase was 60:40 (v:v) acetonitrile: 0.1% H₃PO₄ at 1.5 ml/min. Detection was at 210 nm. The injected sample of 1 μ l was dissolved in acetonitrile at a concentration of 10 mg/ml. The product had a retention time of 5.0 min. and that of the non-brominated ester was 3.8 min. This crude product was purified by vacuum distillation to obtain 96% pure product with an 84% yield. The product proton NMR (CDCl₃, 300 MHz) showed shifts at 3.79 (s, 3H), 5.32 (s, 1H) and 7.20-7.55 (m, 4H) ppm.

EXAMPLE 2

[0221] This example relates to the preparation of Methyl 4-Chlorophenyl-(3-trifluoromethylphenoxy)-acetate:

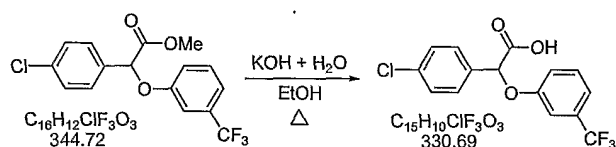


[0222] This step was similar to the same step in U.S. 3,517,050 with one exception; potassium t-butoxide was used in place of sodium methoxide to prevent generation of the corresponding methyl ether. A 5-L Morton reactor equipped with an overhead stirrer, a pot temperature detector, and addition funnel and under a nitrogen atmosphere was charged with methyl bromo-(4-chlorophenyl)-acetate (830 gm, 3.0 moles) and THF (600 ml). The reactor was cooled to 14° ± 3° C in an ice-water bath and then a similarly cooled solution of trifluoromethyl-m-cresol (530 gm, 3.3 moles) in 1.0 M potassium t-butoxide in THF (3.1 L, 3.1 moles) was added. The reaction proceeded exothermically with a typical temperature rise exceeding 25° C and the addition was controlled to maintain a temperature of 15° ± 2° C and stirred at ambient temperature for 2 hours. HPLC was run on a Zorbax SB-C8 column at 30° C measuring 250 x 4.6 mm and 5 μ particle size. The mobile phase was 60:40 (v:v) acetonitrile: 0.1% H₃PO₄ at 1.5 ml/min. Detection was at 210 nm. The injected sample of 1 μ l was dissolved in acetonitrile at a concentration of 10 mg/ml. The product had a retention time of 9.6 min., the starting ester eluted at 5.0 min., the phenol at 3.0 and the non-brominated ester at 3.8 min. The solvent was stripped using a rotary evaporator to obtain a yellow slush that was dissolved in a mixture of 4.0 L water and 12.0 L ether. The mixture

was separated and the organic phase was washed once with 1.6 L 5% (w:w) aqueous NaOH followed by 1.6 L water and finally 1.6 L 25% (w:w) aqueous NaCl. The organic phase was dried over 0.32 kg MgSO₄ and filtered through Whatman #1 filter paper. The solvent was stripped to obtain 1.0 kg of damp, off-white crystals. This was recrystallized on the rotary evaporator by dissolving in 1.0 L methylcyclohexane at 75° C and then cooling to 20° C. The crystals were filtered through Whatman #1 filter paper and washed with three 0.25 L portions of cool (15° C) methylcyclohexane. The wet product (0.97 kg) was dried overnight to obtain 0.81 kg of 98% pure product that corresponds to a 79% yield. The product proton NMR (CDCl₃, 300 MHz) shows shifts at 3.75 (s, 3H), 5.63 (s, 1H) and 7.05-7.55 (m, 8H).

EXAMPLE 3

[0223] This example relates to the preparation of 4-Chlorophenyl-(3-trifluoromethylphenoxy)-acetic Acid:

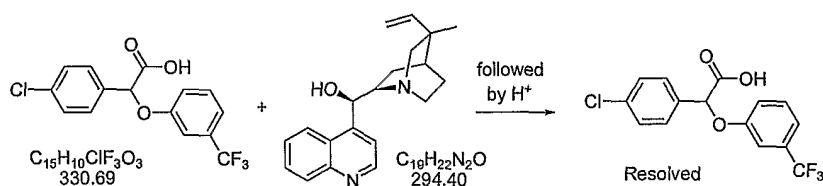


[0224] A 12-L Morton reactor with magnetic stirrer, pot temperature controller, a reflux condenser and under a nitrogen atmosphere was charged with methyl 4-chlorophenyl-(3-trifluoromethylphenoxy)-acetate (810 gm, 2.3 moles) and absolute ethanol (5.8 L) and heated with stirring to 57° C to dissolve the solid. A solution of KOH (520 gm, 9.3 moles) in 0.98 L water was added. The solution was refluxed for 30 min. and solvent was stripped by a rotary evaporator to obtain 2.03 kg of a mixture of two nearly colorless liquids. These were dissolved in water (16 L) and treated with 16 gm neutral Norit, then filtered through a pad of infusorial earth retained on Whatman #1 filter paper. The pH of the filtrate was lowered from an initial range of 13 to a range of 1 to 2 by adding a total of 2.75 L of 3 M HCl (8.25 moles). A very sticky solid formed after the addition of the first 2.30 L of acid and ether (7 L) was added at this point. The two layers were separated and the organic layer was dried over MgSO₄ (230 gm) and filtered through Whatman #1 filter paper. The solvent was then stripped to obtain 0.85 kg water-white syrup. The material was then recrystallized on the rotary evaporator by adding methylcyclohexane (800 ml) and cooling to 18° C with slow rotation. The temperature was then dropped to 5° C, the crystals were filtered, and washed 5 times with 0.10 L portions of cold (0° C) methylcyclohexane to obtain 0.59 kg wet crystals.

The wet crystals were dried to obtain 0.48 kg (62% yield) product with no p-chlorophenylacetic acid detectable in the proton NMR. The product proton NMR (CDCl_3 , 300 MHz) shows shifts at 5.65 (s, 1H), 7.02-7.58 (m, 8H) and 10.6 (s, 1H).

EXAMPLE 4

[0225] This example relates to the preparation of resolved enantiomers of 4-Chlorophenyl-(3-trifluoromethylphenoxy)-acetic Acid:



[0226] A 12-L open-top Morton reactor with an overhead stirrer was charged with 4-chlorophenyl-(3-trifluoromethyl-phenoxy)-acetic acid (350 gm, 1.06 moles) and isopropanol (4.0 L) and heated to 65°±3° C. A slurry of (–) cinchonidine (300 gm, 1.02 moles) in isopropanol (2.0 L) was added, rinsing all solid into the reactor with an additional 0.8 L of isopropanol. The temperature dropped from 65° to 56° C and a transparent, orange solution ultimately formed and the mixture was held at 55°±5° C for 2 hours. Fine crystals were collected by filtration through Whatman #1 filter paper, washing once with 0.7 L hot (55° C) isopropanol. The crystals were dried for 16 hours at ambient temperature in a 12.6-L vacuum oven under a 5 LPM nitrogen flow. The dry solid weighed 0.37 kg and had an 80% enantiomeric excess (ee) of the (+) enantiomer. The enantiomeric excess was determined by HPLC using a 250 x 4.6 mm R,R-WhelkO-1 column at ambient temperature. Injected samples were 20 µl of 2 mg/ml solutions of the samples in ethanol. The column was eluted with 95:5:0.4, hexane:isopropanol:acetic acid at a flow of 1 ml/min. Detection was at 210 nm. The (+) enantiomer eluted at 7 to 8 min. and the (–) enantiomer at 11 to 13 min. The mother liquor dropped a second crop almost immediately that was filtered, washed, and dried to afford 0.06 kg salt that has a 90% ee of the (–)-enantiomer. Similarly third, fourth and fifth crops weighing 0.03 kg, 0.03 kg and 0.7 kg, respectively, were obtained; with (–) enantiomer excesses of 88%, 89% and 92%, respectively.

[0227] The crude (+) salt (320 gm) was recrystallized from a mixture of ethanol (5.9 L) methanol (1.2 L). The mixture was heated with overhead stirring to dissolve, cooled at ambient temperature for 16 hours, filtered and washed twice with 0.20 L of 5:1 (v:v)

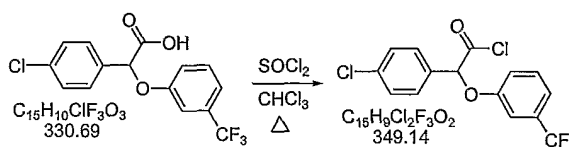
ethanol:methanol. The crystals were dried to obtain 0.24 kg of the (+) enantiomer that had an ee of 97%. This corresponded to an 80% recovery of this isomer. The resolved salt was suspended in a mixture of ether (6.5 L) and water (4.0 L) with overhead stirring. The pH was lowered to 0-1 as measured by pH indicating strips with a solution of concentrated H₂SO₄ (0.13 L) in water (2.5 L). The phases were separated and the organic phase and washed twice with 6.5 L portions of water. Ether (1.9 L) was added and the organic layer washed once more with 6.5 L water. After the final separation, 0.1 L of 25% (w:w) aqueous NaCl was added clean up any slight emulsion. The product was dried over 0.19 kg MgSO₄, filtered and solvent removed solvent to obtain 0.13 kg of water-white syrup that solidifies on cooling. This corresponded to a 97% recovery of product that had a 95% ee of the (+) enantiomer. $[\alpha]_D +5.814^\circ$ (c.=0.069 in methyl alcohol).

[0228] The combined, crude (–) salt (200 gm) was recrystallized from isopropanol (3.1 L). The mixture was heated to dissolve almost all of the solid and fast-filtered to remove insoluble solids. The mixture was then cooled with stirring at ambient temperature for 16 hours, filtered, washed, and dried to obtain 0.16 kg of the (–) enantiomer that has an ee of 97%. This corresponds to a 49% recovery of this isomer. The (–) enantiomer of the acid was isolated in the same manner as described above for the (+) acid. The resolved salt was suspended in ether and water, the pH lowered with concentrated H₂SO₄, and the product extracted in the organic phase.

EXAMPLE 5

[0229] This example relates to the making of either isomer of halofenate;

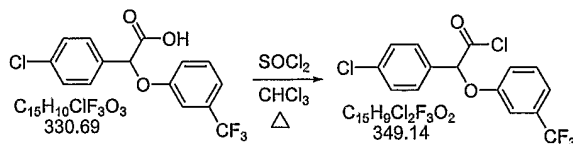
[0230] A. Preparation of (–) 4-Chlorophenyl-(3-trifluoromethylphenoxy)-acetyl Chloride:



[0231] A 2-L evaporation flask with magnetic stirrer, Claissen adapter, pot thermometer and a reflux condenser routed to a gas scrubber was charged with (–) 4-chlorophenyl-(3-trifluoromethylphenoxy)-acetic acid (143 g, 0.42 mole based on 97% purity) and CHCl₃ (170 ml) and heated to boiling in order to dissolve. SOCl₂ (38 ml, 62.1 gm, 0.52 mole) was added. The mixture was heated to reflux (68° C final) for 4.5 hours and then stripped of volatiles to

obtain 151 g yellow, turbid liquid (103% apparent yield). The material was used in the next step without further purification.

[0232] B. Preparation of (+) 4-Chlorophenyl-(3-trifluoromethylphenoxy)-acetyl Chloride:

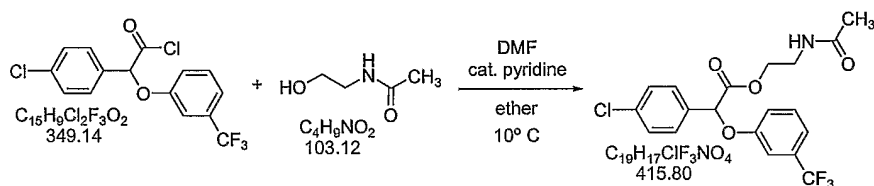


[0233] A 3-L evaporation flask with magnetic stirrer, Claissen adapter, pot thermometer and a reflux condenser routed to a gas scrubber was charged with (+) 4-chlorophenyl-(3-trifluoromethylphenoxy)-acetic acid (131 g, 0.37 mole) and CHCl_3 (152 ml) and heated to boiling in order to dissolve. SOCl_2 (35 ml, 56.5 g, 0.48 mole) was added. The mixture was heated to reflux (70° C final) for 4 hours and then stripped of volatiles to obtain 139 g liquid. The material was used in the next step without further purification.

EXAMPLE 6

[0234] This example further illustrates making the (+) and (-) isomers of halofenate.

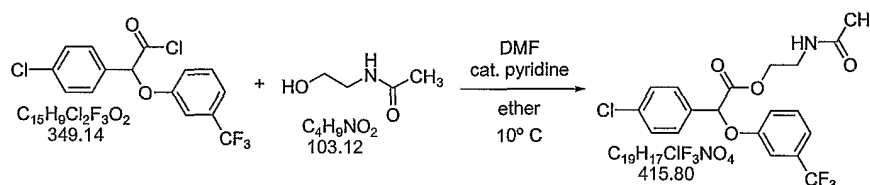
[0235] A. Preparation of (-) 2-Acetamidoethyl 4-Chlorophenyl-(3-trifluoromethylphenoxy)-acetate:



[0236] A 3-L round-bottom flask with magnetic stirrer, pot thermometer, under a nitrogen atmosphere and in an ice-water bath was charged with DMF (420 ml), pyridine (37 ml, 36 g, 0.46 mole) and N-acetoethanolamine (39 ml, 43 g, 0.42 mole). The mixture was cooled to 0° to 5° C and a solution of crude (-) 4-chlorophenyl-(3-trifluoromethylphenoxy)-acetyl chloride (151 gm, 0.42 mole based on 100% yield of previous step) in ether (170 ml) was added over a 40 min. period so as to maintain the pot temperature below 13° C. The mixture was stirred at ambient temperature for 16 hours and dissolved by adding water (960 ml) followed by ethyl acetate (630 ml). The water addition proceeded exothermically raising the temperature from 24° to 34° C. Ethyl acetate addition caused a temperature drop to 30° C.

The layers were separated and the aqueous phase extracted once with ethyl acetate (125 ml). The combined organic layers were extracted once with 7% (w:w) aqueous NaHCO₃ (125 ml) and five times with 60 ml portions of water and then twice with 60 ml portions of 25% (w:w) aqueous NaCl. The product was dried over MgSO₄ (42 g) and filtered through Whatman #1 filter paper. Solvent was stripped using a rotary evaporator to obtain 160 g of a yellow syrup corresponding to an 80% yield based on the proton NMR that shows 87% product, 8% EtOAc, 4% non-brominated amide, and 1% DMF. This syrup was dissolved in MTBE (225 ml) at ambient temperature and chilled (-15° C) 85% hexanes (400 ml) was added with stirring. Two liquids formed, then crystals, then the mixture formed a solid. The solid mass was scraped onto a Buchner funnel fitted with Whatman #1, packed down and washed three times with 100 ml portions of 1:1 (v:v) MTBE:hexanes to obtain 312 g wet product which dries to 127 gm, corresponding to a 73% yield.

[0237] B. Preparation of (+) 2-Acetamidoethyl 4-Chlorophenyl-(3-trifluoromethylphenoxy)-acetate

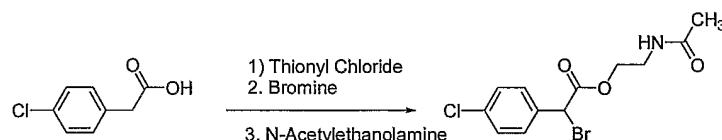


[0238] A 3-L round-bottom flask with magnetic stirrer, pot thermometer, under a nitrogen atmosphere and in an ice-water bath was charged with DMF (365 ml), pyridine (33 ml, 32.3 g, 0.41 mole) and N-acetoethanolamine (34 ml, 38.1 g, 0.37 mole). The mixture was cooled to 0° to 5° C and a solution of crude (+) 4-chlorophenyl-(3-trifluoromethylphenoxy)-acetyl chloride (139 gm, 0.37 mole based on 100% yield of previous step) in ether (155 ml) was added over a 25 min. period so as to maintain the pot temperature below 13° C. The mixture was stirred at ambient temperature 40 hours and dissolved by adding water (850 ml) followed by ethyl acetate (550 ml). The water addition proceeded exothermically raising the temperature from 24° to 34° C. Ethyl acetate addition caused a temperature drop to 30° C. The layers were separated and the aqueous phase extracted once with ethyl acetate (110 ml). The combined organic layers were washed twice with 55 ml portions of water and then five times with 55 ml portions of 25% (w:w) aqueous NaCl and dried over 30 g MgSO₄ and filtered through Whatman #1 filter paper. Solvent was stripped using a rotary evaporator to obtain 168 g yellow liquid corresponding to an 86% yield based on the proton NMR that

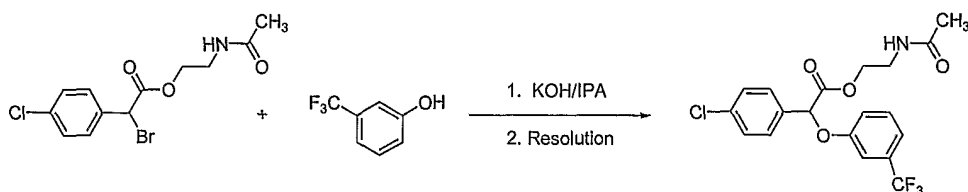
shows 79% product, 9% EtOAc, 8% non-brominated amide, and 4% DMF. The product was crystallized in an 800-ml beaker by dissolving in MTBE (200 ml) at ambient temperature, cooling at -15° for 1.4 hours, adding 200 ml 85% hexanes and then chilling 1 hour. The solid mass was scraped out onto a Buchner funnel fitted with Whatman #1, packed down and washed once with 1:1 (v:v) MTBE:hexanes (100 ml) to obtain 201 gm wet product. The product was dried under nitrogen flow and triturated with 85% hexanes (700 ml) using an overhead stirrer. The material was filtered and dried to obtain 87 gm product. $[\alpha]_D +2.769^{\circ}$ (c.=0.048 in methyl alcohol). $[\alpha]_D -2.716^{\circ}$ (c.=0.049 in methyl alcohol). The (+) and (–) enantiomers were also analyzed by HPLC using a 250 x 4.6 mm R,R-WhelkO-1 column at ambient temperature. Injected samples were 20 μ l of 2 mg/ml solutions of the samples in ethanol. The column was eluted with 60:40, isopropanol:hexane at a flow of 1 ml/min. Detection was at 220 nm. The (+) enantiomer eluted at 5.0 to 5.2 min. and the (–) enantiomer at 5.7 to 5.9 min.

EXAMPLE 7

[0239] This example describes the preparation of (–) 2-Acetamidoethyl 4-Chlorophenyl-(3-trifluoro methylphenoxy)-acetate ((–) halofenate).



[0240] 4-Chlorophenylacetic acid was combined with 1,2-dichloroethane and the resulting solution was heated to 45°C . Thionyl chloride was added to the reaction mixture, which was heated at 60°C for 18 hours. The reaction was allowed to cool to room temperature and was then added slowly to a solution of N-acetyethanolamine in dichloromethane. After stirring 30 min., the reaction was quenched with aqueous potassium carbonate and sodium thiosulfate. The organic layer was washed with water, dried over magnesium sulfate and filtered. Removal of the solvent by rotary evaporation provided N-acetylaminoethyl 2-bromo-2-(4-chlorophenyl)acetate as an oil.



[0241] 3-Hydroxybenzotrifluoride was added to a solution of potassium hydroxide in isopropanol. N-acetylaminoethyl 2-bromo-2-(4-chlorophenyl)acetate in isopropanol was added to the isopropanol/phenoxide solution and stirred at room temperature for 4 hours. The isopropanol was removed by vacuum distillation, and the resulting slush was dissolved in ethyl acetate and washed twice with water and once with brine. After drying over magnesium sulfate and filtration, the solvent was removed to give crude product as an oil. The crude product was dissolved in hot toluene/hexanes (1:1 v/v) and cooled to between 0 and 10 °C to crystallize the product. The filter cake was washed with hexanes/toluene (1:1 v/v) and then dried under vacuum at 50 °C. The isolated solid was dissolved in hot 1:6 (v/v) isopropanol in hexanes. After cooling, the pure racemic 2-Acetamidoethyl 4-Chlorophenyl-(3-trifluoro methylphenoxy)-acetate formed as a crystalline solid. The solid was collected by filtration, the filter cake washed with 1:6 (v/v) isopropanol in hexanes and dried under vacuum at 50 °C.

[0242] The racemic compound was dissolved in a solution of 20% isopropanol (IPA) and 80% hexane at 2.5% (wt/wt). The resulting solution was passed over a Whelk-O R,R Chiral Stationary Phase (CSP) in continuous fashion until >98% ee extract could be removed. The solvent was evaporated from the extract under reduced pressure to provide (-) 2-Acetamidoethyl 4-Chlorophenyl-(3-trifluoro methylphenoxy)-acetate. (The Simulated Moving Bed resolution was conducted by Universal Pharm Technologies LLC of 70 Flagship Drive, North Andover, MA 01845.)

Example 8

[0243] Example 8 illustrates the partial agonism of the (-) isomer of either halofenic acid or halofenate on PPAR γ (see, Figure 6). The test compound displayed an ability to induce PPAR γ expression a few fold while significantly antagonizing the agonist activity of rosiglitazone.

Example 9

[0244] Example 9 presents the results of two randomized, double-blind, placebo-controlled, multi-centre studies on type 2 diabetics with inadequate control on insulin. The first study included 217 patients, randomized to dose groups of Placebo, 200 and 400 mg of a composition of (-) halofenate which was substantially free of the (+) isomer. The second study followed a substantially identical overall design, and included 100 patients randomized to dose groups of placebo and 600 mg of a composition of (-) halofenate which was substantially free of the (+) isomer. Both studies were about 4 months long, with a stabilization/run in period for 2 to 4 weeks and a 3 month treatment period. Endpoints included fasting plasma glucose (FPG), HbA1c, weight, and the incidence of edema.

[0245] As indicated below, the various experimental and placebo groups in the first study had similar demographics and base line characteristics.

	Pbo (n = 75)	200 mg (n = 73)	400 mg (n = 69)	Total (n = 217)	p-value
Age $\pm$ SD	54.3 $\pm$ 10.9	53.1 $\pm$ 10.1	53.1 $\pm$ 10.4	53.5 $\pm$ 10.5	0.720
Female (%)	74.7	56.2	69.6	66.8	0.048
Weight (kg $\pm$ SD)	81.6 $\pm$ 18.0	80.0 $\pm$ 17.6	79.6 $\pm$ 19.8	80.4 $\pm$ 18.4	0.791
BMI (kg/m ² $\pm$ SD)	31.6 $\pm$ 4.6	30.3 $\pm$ 5.2	30.2 $\pm$ 5.5	30.7 $\pm$ 5.1	0.189
HbA1c (% $\pm$ SD)	9.1 $\pm$ 1.03	9.0 $\pm$ 0.92	9.1 $\pm$ 1.05	9.1 $\pm$ 1.00	0.539
% HbA1c > 9%	58.7	56.2	59.4	58.1	NS
FPG (mg/dL $\pm$ SD)	170.0 $\pm$ 50.2	173.3 $\pm$ 48.9	184.0 $\pm$ 58.1	174.1 $\pm$ 52.4	NS
Duration of T2DM (yrs)	13.9 $\pm$ 7.8	14.2 $\pm$ 7.6	13.2 $\pm$ 6.5	13.8 $\pm$ 7.3	0.695

[0246] As indicated below, the experimental and placebo groups in the second study also had similar demographics and base line characteristics.

Age $\pm$ SD	53.1 $\pm$ 10.8	53.7 $\pm$ 10.6	53.4 $\pm$ 10.6	0.799
Female (%)	71.7	68.1	70.0	0.694
Weight (kg $\pm$ SD)	75.9 $\pm$ 16.7	79.2 $\pm$ 17.7	77.5 $\pm$ 17.2	0.330

BMI (kg/m ² ± SD)	29.9 ± 4.4	30.7 ± 4.9	30.3 ± 4.6	0.411
HbA1c (% ± SD)	9.6 ± 1.12	9.4 ± 1.14	9.5 ± 1.13	0.520
% HbA1c > 9%	73.6	74.5	74.0	NS
FPG (mg/dL ± SD)	171.8 ± 58.3	160.3 ± 50.7	166.5 ± 54.9	NS
Duration of T2DM (yrs)	13.9 ± 8.1	13.6 ± 6.9	13.7 ± 7.5	0.851

[0247] As shown below, the experimental and placebo groups in the first study had similar dispositions over the course of the study.

	Pbo	200 mg	400 mg	Total
Started Treatment	75	74	69	217
Discontinued Study Drug	4 (5.3%)	5 (6.8%)	8 (11.6%)	17 (7.8%)
Completed ≥ 67 Days	71 (94.7%)	68 (91.9%)	61 (88.4%)	200 (92.2%)
Discontinued due to AE	2 (2.7%)	3 (4.1%)	3 (4.3%)	8 (3.7%)
Discontinued for Other Reasons	2 (2.7%)	2 (2.7%)	5 (7.2%)	9 (4.1%)

[0248] As shown below, the experimental and placebo groups in the second study also had similar dispositions over the course of the study.

Started Treatment	53	47	100
Discontinued Study Drug	4 (7.3%)	1 (2.0%)	5 (4.7%)
Completed ≥ 63 Days	49 (89.1%)	46 (90.2%)	95 (89.6%)
Discontinued due to AE	0 (0%)	0 (0%)	0 (0%)
Discontinued for Other	4 (7.3%)	1 (2.0%)	5 (4.7%)

Reasons

[0249] Figure 7 shows the tested compound at doses of 200- and 400 mg lowered fasting plasma glucose levels in the experimental groups as compared to the placebo group.

[0250] Figure 8 shows the tested compound at doses of 200- and 400 mg lowered plasma glucose levels as judged by HbA1c levels in the experimental groups as compared to the placebo group.

[0251] Figure 9 shows that the test compound at doses of 200- and 400 mg prevented edema formation in the experimental group as compared to the placebo groups.

[0252] Figure 10 shows that the test compound at doses of 200- and 400 mg did not induce weight gain in the experimental group as compared to the placebo group.

[0253] Figure 11 shows the tested compound at a dose of 600 mg lowered fasting plasma glucose levels in the experimental group as compared to the placebo group.

[0254] Figure 12 shows the tested compound at a dose of 600 mg lowered plasma glucose levels as judged by HbA1c levels in the experimental group substantially from baseline, but that the placebo group demonstrated a comparable response. It was determined that two of the 10 clinical sites in this study (sites 60 & 70), who enrolled 43% of the patients, had substantially violated the protocol by placing all of their patients on a sliding scale of short-acting insulin in addition to their baseline doses of intermediate-acting insulin. This explains why HbA1c declined in the placebo group but FPG did not. The most statistically rigorous and conservative approach was to remove both of these violating sites from the analysis, which resulted in improved separation between treatment groups for both HbA1c and FPG, as shown below. Hence, these analyses address the impact of sites 60 and 70 on data presented in the priority provisional application.

[0255] Figure 13 shows the tested compound at a dose of 600 mg lowered plasma glucose levels as judged by HbA1c levels in the experimental group as compared to the placebo group in the analysis removing sites 60 and 70. Hence, these analyses address the impact of sites 60 and 70 on data presented in the priority provisional application.

[0256] Figure 14 shows that when sites 60 and 70 were removed, the tested compound at a dose of 600 mg lowered fasting plasma glucose levels in the experimental group as compared

to the placebo group to an even greater extent than the 400 mg dose in the first study. Hence, these analyses address the impact of sites 60 and 70 on data presented in the priority provisional application.

[0257] Figure 15 shows that when sites 60 and 70 were removed from the analysis of the first study, the placebo response is attenuated and the tested compound at doses of 200- and 400 mg lowered plasma glucose levels as judged by HbA1c levels in the experimental groups as compared to the placebo group to an even greater extent than in the original analysis (Figure 8).

[0258] Figure 16 shows that when sites 60 and 70 were removed from the analysis of the first study, the placebo response is attenuated and the tested compound at doses of 200- and 400 mg lowered fasting plasma glucose levels in the experimental groups as compared to the placebo group to an even greater extent than in the original analysis (Figure 7).

[0259] Figure 17 shows that the test compound did not increase the incidence of edema formation across the dose range of 200- to 600 mg in the experimental groups as compared to the combined placebo groups from both studies. These results were not changed when sites 60 and 70 were removed.

[0260] Figure 18 shows that the test compound at a dose of 600 mg did not induce weight gain in the experimental group as compared to the placebo group. This result was not changed when sites 60 and 70 were removed.

[0261] Additional analyses indicated that metaglisasen had a neutral effect on the HDL/cholesterol profile and was not associated with an excess of adverse effects on selected parameters with respect to the upper GI tract, the liver, the blood, or kidney (data not shown).

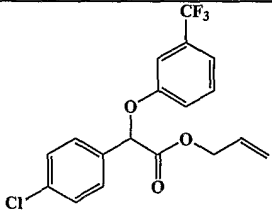
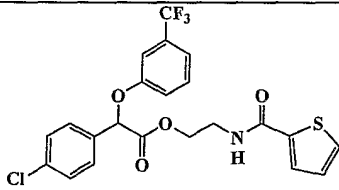
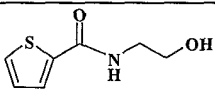
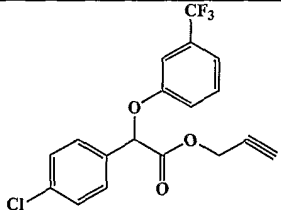
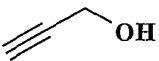
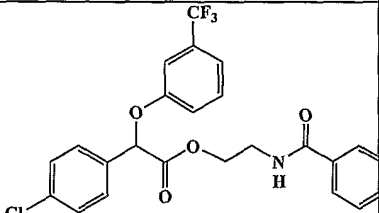
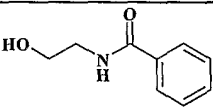
[0262] Other analyses indicated that metaglidasen could substantially lower blood glucose levels in patients also receiving glyburide (see Figure 19). In addition, metaglidasen could also lower hsCRP levels (see Figure 20). Additional results showed that metaglidasen lowered serum triglycerides substantially (data not shown).

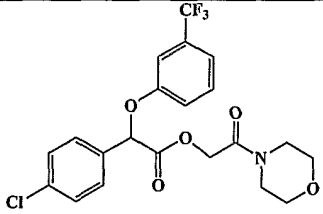
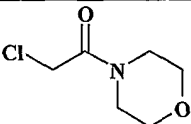
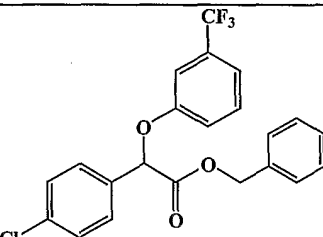
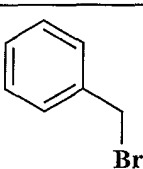
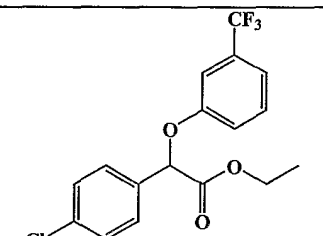
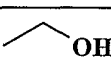
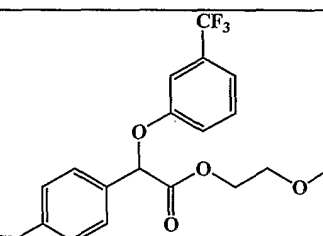
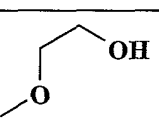
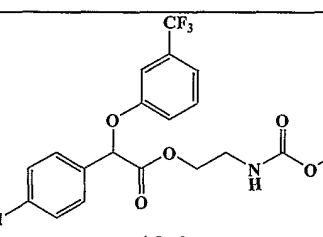
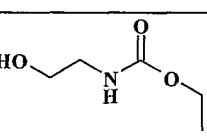
[0263] The results of separate animal studies (e.g., monkeys and rats) has found that metaglidasen did not cause increases at therapeutically relevant doses in heart weight or fluid accumulation (data not shown).

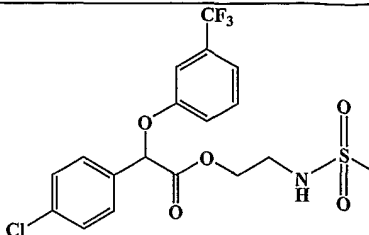
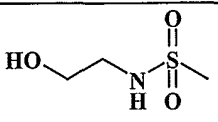
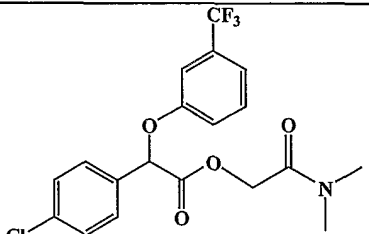
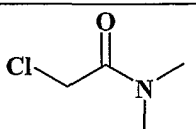
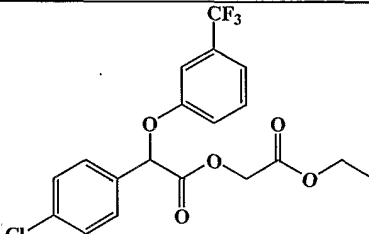
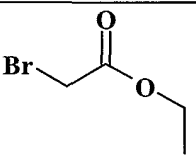
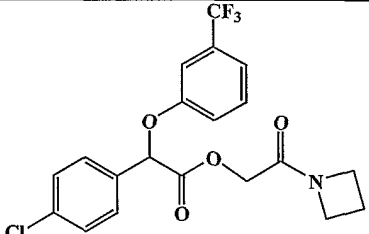
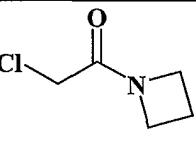
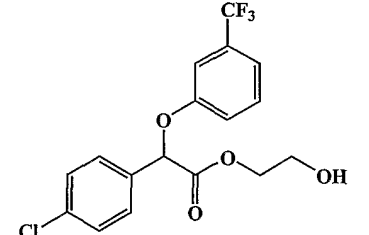
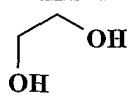
EXAMPLE 10

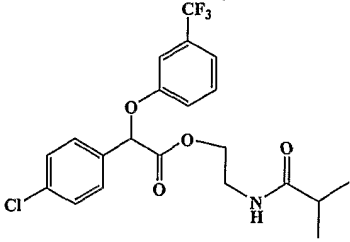
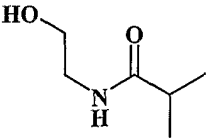
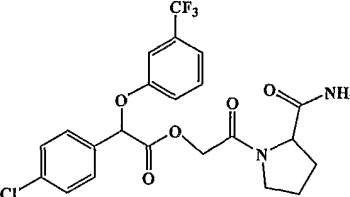
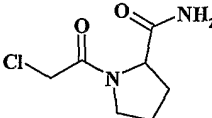
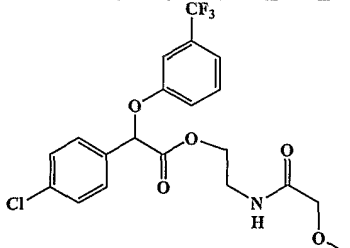
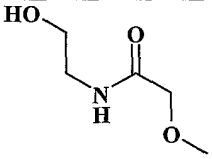
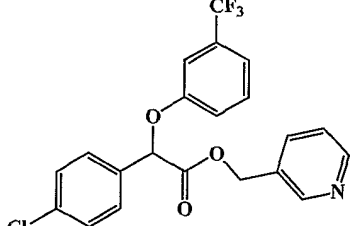
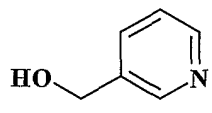
[0264] This Example provides structures of additional prodrug compounds, along with characterization data and reference to the methods employed for preparation the source of starting materials. Methods of making such compounds are known to one of ordinary skill in the art by methods set forth in PCT Patent Application Publication No.: WO/2002/044113.

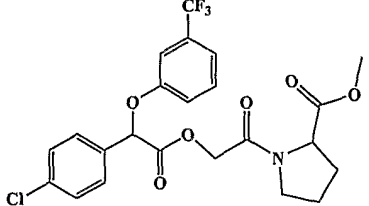
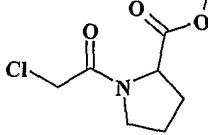
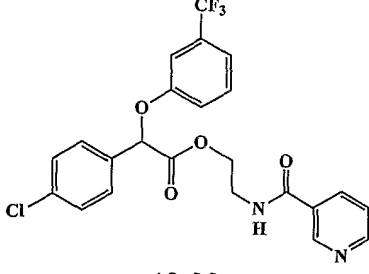
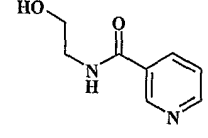
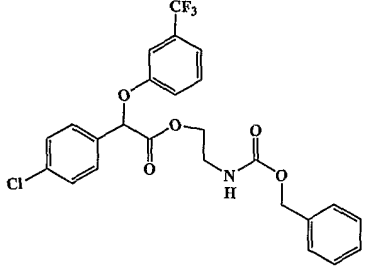
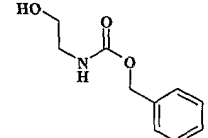
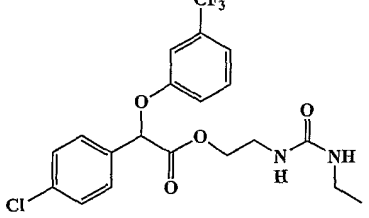
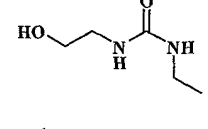
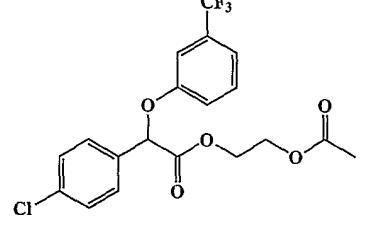
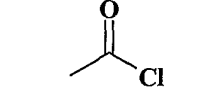
Illustrative compounds, source of reagents and coupling methods

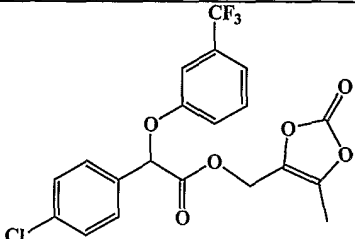
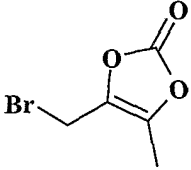
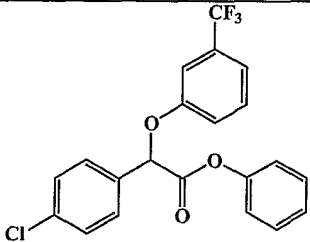
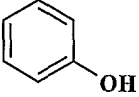
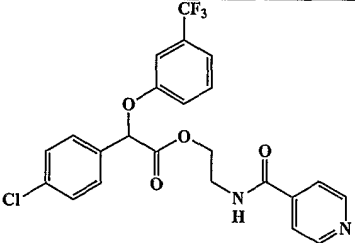
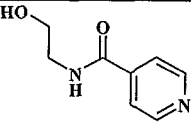
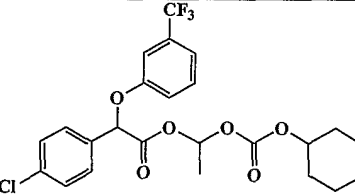
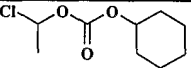
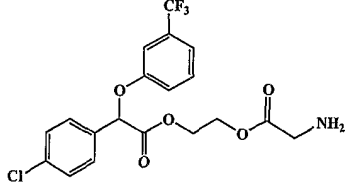
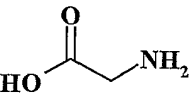
Compound and number	Reagent and Source Reference:	Structural elucidation
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 19.2	 U.S. Patent No. 5,506,224	$[\alpha]^{24}_D$ - 27.16 (c 6.99, CHCl ₃) ¹ HNMR (400MHz, CHCl ₃): δ7.0-7.5 (11H, m), 5.9 (1H, m), 4.3 (2H, m), 3.6(2H, m). LCMS, 482, 99% 98%ee
 19.3	 Aldrich	$[\alpha]^{24}_D$ - 44.46 (c 5.90, CHCl ₃) ¹ HNMR (400MHz, CHCl ₃): δ7.0-7.5 (13H, m), 5.6 (1H, s), 4.7 (2H, dd), 2.4(1H, s). LCMS, 368, 99% 98%ee
 19.4	 Aldrich	$[\alpha]^{24}_D$ - 35.40 (c 12.6, CHCl ₃) ¹ HNMR (400MHz, CHCl ₃): δ7.0-7.5 (13H, m), 6.0 (1H, m), 5.6 (1H, s), 4.3 (2H, m), 3.6 (2H, m). LCMS, 477, 99% 97.4%ee

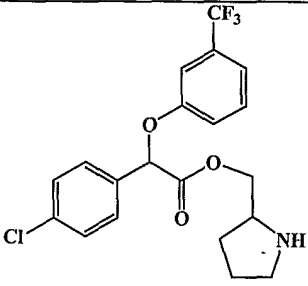
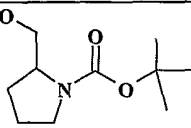
 19.5	 Maybridge	$[\alpha]^{24}_D$- 57.39 (c 10.3, CHCl₃) ¹HNMR (400MHz, CHCl₃): δ 7.1-7.5 (8H, m), 5.7 (1H, s), 4.9 (1H, d), 4.6 (1H, d), 3.6 (8H, m). LCMS, 457, 99% 97.4%ee
 19.6	 Aldrich	$[\alpha]^{24}_D$- 35.38 (c 7.36, CHCl₃) ¹HNMR (400MHz, CHCl₃): δ 7.0-7.5 (13H, m), 5.6 (1H, s), 5.1 (2H, dd). LCMS, 421, 99% 98%ee
 19.7	 Aldrich	$[\alpha]^{24}_D$- 56.34 (c 5.32, CHCl₃) ¹HNMR (400MHz, CHCl₃): δ 7.0-7.5 (8H, m), 5.6 (1H, s), 4.2 (2H, m), 1.1 (3H, t). LCMS, 358, 98% 98%ee
 19.8	 Aldrich	$[\alpha]^{24}_D$- 54.13 (c 8.40, CHCl₃) ¹HNMR (400MHz, CHCl₃): δ 7.0-7.5 (8H, m), 5.6 (1H, s), 4.4 (1H, m), 4.2 (1H, m), 3.5 (2H, m), 3.3 (3H, s). LCMS, 445, 97% 97.7%ee
 19.9	 U.S. Patent No. 5,506,224	$[\alpha]^{24}_D$- 43.30 (c 6.61, CHCl₃) ¹HNMR (400MHz, CHCl₃): δ 7.0-7.5 (8H, m), 5.6 (1H, s), 4.5 (1H, m), 4.2 (2H, m), 4.0 (2H, m), 3.3 (2H, m), 1.1 (3H, m). LCMS, 445, 97% 96.8%ee

 19.10	 U.S. Patent No. 5,506,224	$[\alpha]^{24}_D$- 42.33 (c 7.30, CHCl_3) ^1HNMR (400MHz, CHCl_3): δ7.0-7.5 (8H, m), 5.6 (1H, s), 4.3 (2H, m), 4.1 (1H, m), 3.3 (2H, m), 2.8 (3H, s). LCMS, 451, 97% 96.5%ee
 19.11	 Aldrich	$[\alpha]^{24}_D$- 57.87 (c 2.57, CHCl_3) ^1HNMR (400MHz, CHCl_3): δ7.0-7.5 (8H, m), 5.6 (1H, s), 4.9 (1H, d), 4.6(1H, d), 2.9 (3H, s), 2.8 (3H, s). LCMS, 415, 98% 97.1%ee
 19.12	 Aldrich	$[\alpha]^{24}_D$- 62.27 (c 5.35, CHCl_3) ^1HNMR (400MHz, CHCl_3): δ7.0-7.5 (8H, m), 5.6 (1H, s), 4.2 (2H, m), 1.1 (3H, t). LCMS, 416, 99% 98%ee
 19.13	 U.S. Patent No. 3,998,808	$[\alpha]^{24}_D$- 49.85 (c 11.3, CHCl_3) ^1HNMR (400MHz, CHCl_3): δ7.0-7.5 (8H, m), 5.7 (1H, s), 4.6 (2H, d), 4.4 (2H, d), 4.0 (4H, m), 2.3 (2H, m). LCMS, 427, 96% 96.1%ee
 19.14	 Aldrich	$[\alpha]^{24}_D$- 51.17 (c 6.76, CHCl_3) ^1HNMR (400MHz, CHCl_3): δ7.0-7.5 (8H, m), 5.6 (1H, s), 5.3 (1H, s), 4.3 (2H, m), 3.7 (2H, m). LCMS, 374, 98% 95.9%ee

 19.15	 U.S. Patent No. 5,506,224	$[\alpha]^{24}_D$- 40.97 (c 8.18, CHCl_3) $^1\text{HNMR}$ (400MHz, CHCl_3): δ 7.0-7.5 (8H, m), 5.6 (1H, s), 5.3 (1H, m), 4.1 (2H, m), 3.4 (2H, m), 2.1 (1H, m), 1.0 (3H, d) LCMS, 443, 99% 97.1%ee
 19.16	 Synthesis (1991) 571	$[\alpha]^{24}_D$- 111.2 (c 10.8, CHCl_3) $^1\text{HNMR}$ (400MHz, CHCl_3): δ 7.0-7.5 (8H, m), 6.7 (1H, m), 5.6 (1H, s), 5.3 (1H, m), 4.9 (1H, d), 4.4 (1H, m), 4.4 (1H, d), 3.4 (1H, m), 3.3 (1H, m), 2.4 (1H, m), 2.2 (1H, m), 2.0 (1H, m), 1.8 (1H, m). LCMS, 484, 99% 96%ee
 19.17	 US Pat 5,506,224	$[\alpha]^{24}_D$- 36.72 (c 8.90, CHCl_3) $^1\text{HNMR}$ (400MHz, CHCl_3): δ 6.8-7.5 (8H, m), 6.5 (1H, m), 5.6 (1H, s), 4.3 (2H, m), 3.8 (2H, s), 3.5 (2H, m), 3.4 (3H, s). LCMS, 445, 99% 98%ee
 19.18	 Aldrich	$[\alpha]^{24}_D$-21.23 (c 13.2, CHCl_3) $^1\text{HNMR}$ (400MHz, CHCl_3): δ 8.6 (1H, σ), 7.8 (1H, δ), 7.0-7.6 (10H, m), 5.6 (1H, s), 5.2 (2H, s). LCMS, 421, 99% 97%ee

 19.19	 J.Med.Chem (1997) 3594	$[\alpha]^{24}_D$- 108.3 (c 9.36, CHCl₃) ¹HNMR (400MHz, CHCl₃): 87.0-7.5 (8H, m), 5.8 (1H, s), 5.0 (2H, d), 4.5 (1H, m), 4.5 (2H, d), 3.7 (3H, s), 3.4-3.7 (2H, m), 1.8-2.3 (4H, m) . LCMS, 499, 99% 98.3%ee
 19.20	 U.S. Patent No. 5,506,224	$[\alpha]^{24}_D$- 32.05 (c 6.00, CHCl₃) ¹HNMR (400MHz, CHCl₃): δ 9.4 (1H, br. s), 8.7 (1H, br. s), 8.4 (1H, br. s), 7.7 (1H, br.s), 7.0-7.5 (8H, m), 5.8 (1H, s), 4.4(2H, m), 3.7 (2H, m). LCMS, 479, 99% 97.6%ee
 19.21	 Aldrich	$[\alpha]^{24}_D$- 28.19 (c 14.3, CHCl₃) ¹HNMR (400MHz, CHCl₃): 87.0-7.5 (13H, m), 5.6 (1H, s), 5.1 (2H, s), 4.6 (1H, m), 4.2 (2H, m), 3.4 (2H, m). LCMS, 507, 99% 98%ee
 19.22	 Chem.Soc.Rev (1975) 231	$[\alpha]^{24}_D$- 39.80 (c 5.90, CHCl₃) ¹HNMR (400MHz, CHCl₃): 87.0-7.5 (8H, m), 5.6 (1H, s), 4.2 (2H, m), 4.0 (1H, m), 3.4 (2H, m), 3.0 (2H, m), 1.0 (3H, t). LCMS, 444, 99% 98%ee
 19.23	 Aldrich	$[\alpha]^{24}_D$- 44.75 (c 7.60, CHCl₃) ¹HNMR (400MHz, CHCl₃): 87.0-7.5 (8H, m), 5.6 (1H, s), 4.1-4.4 (4H, m), 1.9 (3H, s). LCMS, 416, 99% 98.36%ee

 19.24	 U.S. Patent No. 5,466,811	$[\alpha]^{24}_D$- 35.63 (c 5.30, CHCl_3) $^1\text{HNMR}$ (400MHz, CHCl_3): δ 7.0-7.5 (8H, m), 5.6 (1H, s), 4.9 (2H, dd), 2.1 (3H, s). LCMS, 442, 99% 98.3%ee
 19.25	 Aldrich	$[\alpha]^{24}_D$- 38.42 (c 8.78, CHCl_3) $^1\text{HNMR}$ (400MHz, CHCl_3): δ 6.9-7.7 (13H, m), 5.8 (1H, s). LCMS, 406, 99% 99%ee
 19.26	 Aldrich	$[\alpha]^{24}_D$- 28.50 (c 8.40, CHCl_3) $^1\text{HNMR}$ (400MHz, CHCl_3): δ 8.8 (2H, d), 7.5 (2H, d), 7.0-7.4 (8H, m), 6.3 (1H, s), 5.6 (1H, s), 4.4 (2H, br. s), 3.8 (2H, br. s). LCMS, 478, 99% 97%ee
 19.27	 Syn. (1986) 627	$[\alpha]^{24}_D$- 31.48 (c 5.00, CHCl_3) $^1\text{HNMR}$ (400MHz, CHCl_3): δ 7.0-7.5 (8H, m), 6.8 (1H, m), 5.6 (1H, s), 4.5 (1H, m), 1.2-2.0 (13H, m). LCMS, 500, 99% 99%ee
 19.28	 Sigma	$[\alpha]^{24}_D$- 29.52 (c 2.04, CHCl_3) $^1\text{HNMR}$ (400MHz, CHCl_3): δ 7.0-7.5 (8H, m), 5.6 (1H, s), 4.2-4.5 (4H, m), 3.7 (2H, m). LCMS, 431, 99% 96.4%ee

 19.29	 Sigma	$[\alpha]^{24}_D$ -20.83 (c 5.42, CHCl₃) ¹HNMR (400MHz, CHCl₃): δ 7.0-7.5 (8H, m), 5.6 (1H, s), 4.4 (1H, m), 3.2-4.0 (2H, m), 1.6-2.2 (4H, m). LCMS, 413, 98% 75%ee
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EXAMPLE 11

[0265] This example illustrates methodology and conditions for the chiral analysis of prodrug esters of (-)-CPTA.

[0266] Since the chiral center of the prodrug esters is adjacent to the carbonyl of the acid, the esters were analyzed to confirm that the optical center had not racemized during the coupling. Both MBX102 and the MBX102 acid have been resolved on a normal phase chiral column, but confirmation of the relative retentions of the enantiomeric esters on such a column would require standards of both enantiomers for all the compounds involved. Alternatively, the esters could be hydrolyzed to the known acids and the ratio of the enantiomeric acids could be analyzed, but some degree of racemization is likely under these conditions. Reverse phase chiral columns offer the ability to be interfaced with an LC-MS system, so that the enantiomers could be positively identified without separate standards. Under negative ion, selected ion monitoring (SIM) conditions, an LC-MS would be expected to be an order of magnitude more sensitive than UV detection as well as being much more specific. The application of chiral-column-LC-MS has proven to be an excellent method for characterizing the optical purity of this series of compounds. The quantitation limit has been shown to be well below the 2.5% limit set for the alternate optical isomer, and the extremely low level of detection gives more flexibility in the separation of the series, as well as establishing the relative retentions of the enantiomeric pairs in most cases without the need to produce racemized material.

[0267] The enantiomers of the prodrug esters synthesized were well separated using one of the columns and solvent systems listed below. Most of the enantiomers were separated using the reverse phase ES-OVM column with the mass spectrometer as a detector. Since this gives the added confirmation of the molecular species and isotope ratio, this was the preferred technique. For enantiomeric pairs which were not separated on the reverse phase

column, a normal phase system was used and some of the sample was partly racemized to establish the retention time of the enantiomers.

Description of Analytical Conditions:

[0268] Reversed Phase separation:

Column: Shinwa Chemicals Ultron ES-OVM 4.6 x 150mm with matching pre column (part # 712111630). Available from Mac Mod Analytical.

Solvents: "A" Acetonitrile, Ethanol or Methanol. "B" Water containing 20milli molar $\text{NH}_4\text{OCOCH}_3$ (Ammonium Acetate) adjusted to pH 4.6 with acetic acid.

Solvent Flow: 1 milliliter per minute Isocratic as indicated.

Detector: UV for method development at 220 or 270 nm or as specified. LC-MS using negative ion electrospray, monitoring two ions, M-H^- and the chlorine 37 isotope ($\text{M}+1^-$)

Mass Spectrometer: Waters / Micromass ZMD Bench top LC-MS with Electrospray source.

HPLC: Agilent 1050 or Shimadzu LC-10 as indicated.

Software: HP 3396 integrator for method development and Micromass MassLynx V3.4 for quantitation.

Methods Development:

[0269] Most prodrug esters separated using between 10 and 40% acetonitrile in water with an ammonium acetate buffer at pH 4.6. The free acid was a contaminant in the crude or racemized samples. The retention times of the acids were pH dependant, but the chromatography of the esters was in general not sensitive to pH. Retention and peak shape were affected by the concentration and injection solvent, and the samples were injected using a minimum concentration and the column solvent mixture for best results. The desired enantiomer was retained less and with a retention time of approximately 5 minutes, the second enantiomer eluted from 1 to 3 minutes later with complete separation in most cases. There was some peak tailing from the main enantiomer in some cases. The amount of acetonitrile was adjusted to give a retention time of about 5 minutes for the main component or best peak separation with maximum peak sharpness. Peaks retained more than 10 minutes tended to be too broad to accurately quantify the second enantiomer at levels under 2%.

Detection Limit:

[0270] Sample 1061-18-05 (the benzyl ester, MW 420) was mixed with racemized material to give an expected concentration of 2.47% of the unwanted enantiomer. The sample was analyzed repeatedly by LC-MS (monitoring ions at 419 and 421) giving an average of 2.6% recovery of the second enantiomer with a 10.9% RSD. See Figure 18.

[0271] Normal Phase Separation:

Column: Analytical Column: Regis (S,S) WHELK-0 4.6 x 250mm with Peek Scientific Cyano pre column (part # DC5-CN). Preparative Column Regis (S,S) WHELK-0 20 x 250mm with Cyano pre column.

Solvents: "A" 10% of Solvent B in Hexane.

"B" Isopropanol (IPA), Ethanol or Ethyl Acetate buffered with ammonium acetate or triethylamine when indicated.

Solvent Flow: 1.2, 1.5 or 25 milliliter per minute Isocratic as indicated.

Detector: UV for method development at 270 nm or as specified.

HPLC: Agilent 1050, Gilson 321 or Shimadzu LC-10 as indicated.

Software: Gilson Unipoint, HP 3396 Integrator or Micromass MassLynx V 3.4 as indicated.

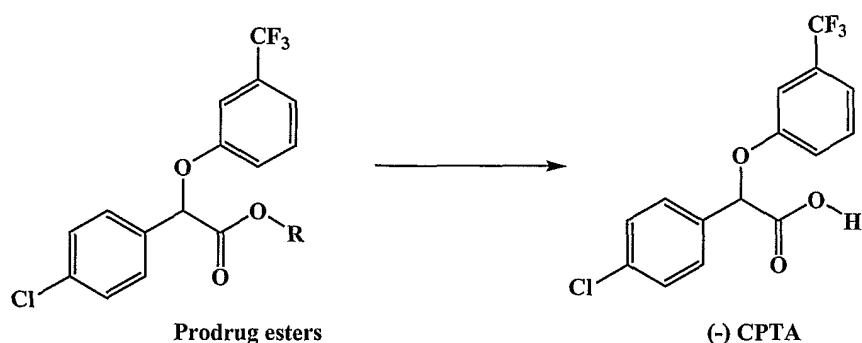
Methods Development:

[0272] Most prodrug esters separated using between 10 and 40% alcohol in Hexane without a modifier. The desired enantiomer was retained less. With a retention time of approximately 5 minutes for the first enantiomer, the second enantiomer eluted from 1 to 3 minutes later with complete separation. The compounds with a basic amine group required ammonium acetate (0.2%) as a modifier to sharpen the peak shape. Triethyl amine was tried but was not effective as a modifier. IPA was normally the first solvent tried, if the separations were not complete, ethanol or ethylacetate were used. The enantiomeric excess for each compound was measured using reverse phase chromatography when possible, but in several cases, separation was only possible using normal phase. In these cases, the data were collected and integrated using the MicroMass MassLynx software to be consistent with the other analyses (Figure 19).

EXAMPLE 12

[0273] This example illustrates the plasma hydrolysis of various prodrug esters of the (S)-enantiomer of CPTA at physiological conditions. Hydrolysis was monitored and analyzed by

HPLC. The hydrolytic product was identified by comparison to authentic (-) CPTA and the hydrolytic rates were calculated.



[0274] Human plasma (heparinized, pooled) was obtained from Golden West Biololgicals Inc., USA; Plasma incubation was carried out in a Water Bath Shaker (New Brunswick Scientific, Inc.); Sample analyses were carried out on Agilent HPLC 1100 system.

General hydrolytic procedure:

[0275] Prepare 31.25 or 62.5 mM prodrug stock solutions in 100% DMSO. Add 4 μ L of 31.25 or 62.5 mM prodrug stock solutions to 1.0 mL of plasma in a microcentrifuge tube to make plasma concentration at 125 or 250 μ M, mix gently. Aliquots of 50 μ L are transferred to 15 microcentrifuge vials. Three samples are immediately removed to a freezer at about -80°C (0 time point), the remaining samples are incubated in a bath shaker at 37°C. Three samples are removed at 30 min, 2, 7 and 24 hr, and stored at -80°C until analysis. The relative concentrations of MBX-compounds are determined by HPLC methods. If there are enough data points, the hydrolytic rate can be calculated using WinNonlin software. Table 10 provides a summary of plasma half-lives of some pro-drug esters and Figures 20A-20G illustrate the hydrolytic curves of those prodrug esters.

HPLC: Agilent 1100 HPLC System

Column: Phenomenex Luna C18(2) 5u 150 x 2 mm lot #105554-2
 Phenomenex Luna C18(2) 5u 250 x 4.6 mm lot #103992-8

Solvent Flow Rate: 0.25 or 1 ml / minute

Injection Volume: 20 or 40 μ L

Run Time: 7 to 15 min

Solvent Composition: 45 to 76%ACN/0.1% TFA in Water (V/V)

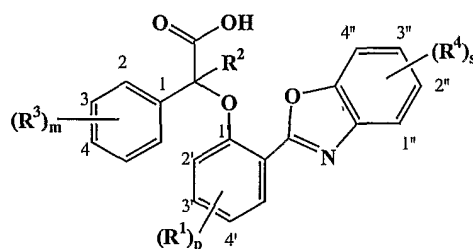
Detection: Diode Array UV-Visible Detector at 220 mn

Table 10
Plasma Half-Life of (-) CPTA Prodrugs

Compound number	Plasma T_{1/2} (hours)
19.1	5.5
19.2	< 1
19.3	< 1
19.4	< 1
19.5	< 0.5
19.6	6.3
19.7	< 7
19.8	< 2
19.9	< 1
19.10	< 1
19.11	< 0.5
19.12	< 0.5
19.13	< 0.5
19.14	< 2
19.15	< 1
19.16	< 0.5
19.17	< 1
19.18	< 1
19.19	< 0.5
19.20	< 0.5
19.21	< 2
19.22	< 1
19.23	< 1
19.24	< 0.5
19.25	< 0.5
19.26	< 1
19.27	< 1
19.28	< 0.5

EXAMPLE 13

[0276] This example sets forth exemplary benzooxazole analogs for use according to their invention and their activity in vivo.

Table 1: 2- Benzooxazole analogs**Compound I-X and Ia-X**

Compound	R ²	(R ³) _m	(R ¹) _p	(R ⁴) _s	Configuration
I-1	H	4-Cl	H	H	R/S
I-3	H	3-CF ₃	H	H	R/S
I-89	H	3-CF ₃	4'-CF ₃	H	R/S
I-92	H	H	4'-CF ₃	H	R/S
I-190	H	4-Cl	4'-Cl	H	R/S
I-191	H	3- CF ₃	4'-Cl	H	R/S
I-193	H	4-OMe	4'-Cl	H	R/S
I-194	H	3-Cl	4'-Cl	H	R/S
I-369	H	H	4'-CF ₃	H	S
I-372	H	4-Cl	4'-CF ₃	H	(+)
Ia-365	Me	H	4'-CF ₃	H	S
Ia-366	Me	H	4'-CF ₃	H	R

In vivo Activities

[0277] The anti-diabetic activities of the compounds were evaluated in the C57BL/6j ob/ob Mice model.

[0278] Male, 7-9 weeks old, C57BL/6J ob/ob mice were purchased from The Jackson Laboratory (Bar Harbor, ME, USA). Animals were housed (4-5 mice/cage) under standard

laboratory conditions at $22 \pm 3^{\circ}\text{C}$ temperature and $50 \pm 20\%$ relative humidity, and were maintained on a diet of Purina rodent chow and water *ad libitum*. Prior to treatment, blood was collected from the tail vein of each animal. Mice that had non-fasting plasma glucose levels between 250 and 500 mg/dl were used. Each treatment group consisted of 8-10 mice that were distributed so that the mean glucose levels were equivalent in each group at the start of the study. Mice were dosed orally by gavage once a day for 1-4 days with vehicle and one or more dose of test compound at a dose ranging from 5 to 125 mg/kg. Compounds were delivered in a liquid formulation containing 5% (v/v) dimethyl sulfoxide (DMSO), 1% (v/v) Tween 80® and 0.9% (w/v) methylcellulose. The gavage volume was 10 ml/kg. Blood samples were taken at 6 hours after the each dose and analyzed for plasma glucose. Food intake and body weight were measured daily. Plasma glucose concentrations were determined colorimetrically using a commercial glucose oxidase method (Sigma Chemical Co, St. Louis, MO, USA). Significant difference between groups (comparing drug-treated to vehicle-treated) was evaluated using the Student unpaired t-test.

[0279] The following table summarizes the anti-diabetic effects of selected compounds of the present invention and provides their relative potency. Compounds that are effective for glucose lowering at the dose of ≥ 125 mg/kg are assigned a potency of +; compounds that are effective for glucose lowering at a dose of >25 mg/kg but <125 mg/kg are assigned a potency of ++; compounds that are effective for glucose lowering at a dose of ≤ 25 mg/kg are assigned a potency of ++++. For example, a compound at 25 mg/kg that lowered the animal glucose level from 400 mg/dL (vehicle group value) to 250 mg/dL, is assigned the potency of +++.

Potency of Selected Compounds

Number	Compound #	Potency	Insulin Level compared with vehicle
1	I-1	++	Lower
2	I-3	+	Lower
3	I-89	+++	Lower
4	I-92	+++	Lower

5	I-190	+++	Lower
6	I-191	+++	Lower
7	I-193	+++	Lower
8	I-194	+++	Lower
9	I-369	+++	Lower
10	I-372	+++	Lower
11	Ia-365	+++	Lower
12	Ia-366	+++	Lower

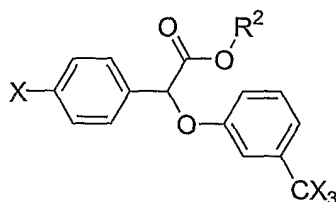
EXAMPLE 14

[0280] This example relates to the glucose lowering activity of ($\pm$) halofenate analogs and (–) halofenate analogs.

[0281] Male, 8-9 weeks old, C57BL/6J ob/ob mice were purchased from The Jackson Laboratory (Bar Harbor, ME, USA). Animals were housed (4-5 mice/cage) under standard laboratory conditions at $22 \pm 3^{\circ}\text{C}$ temperature and $50 \pm 20\%$ relative humidity, and were maintained on a diet of Purina rodent chow and water *ad libitum*. Prior to treatment, blood was collected from the tail vein of each animal. Mice that had non-fasting plasma glucose levels between 250 and 500 mg/dl were used. Each treatment group consisted of 8-10 mice that were distributed so that the mean glucose levels were equivalent in each group at the start of the study. Mice were dosed orally by gavage once a day for 1-3 days with either vehicle, (–) halofenic acid, ($\pm$) analog 14, 29, 33, 34, 35, 36, 37, or 38 at 125 mg/kg or (–) analog 29, 36, 37 or 38 at 150 mg/kg. Compounds were delivered in a liquid formulation containing 5% (v/v) dimethyl sulfoxide (DMSO), 1% (v/v) tween 80 and 0.9% (w/v) methylcellulose. The gavage volume was 10 ml/kg. Blood samples were taken at 6 hours after the each dose and analyzed for plasma glucose. Food intake and body weight were measured daily. Plasma glucose concentrations were determined colorimetrically using glucose oxidase method

(Sigma Chemical Co, St. Louis, MO, USA). Significant difference between groups (comparing drug-treated to vehicle-treated) was evaluated using the Student unpaired t-test.

[0282] As illustrated in the following table, compounds were evaluated in 5 different experiments. Single dose (–) halofenic acid significantly reduced plasma glucose concentrations at 6 hours. Analog 14 significantly lowered plasma glucose concentrations at 6, 30 and 54 hours. Analog 33 significantly lowered plasma glucose concentrations at 6 and 54 hours. Analog 29 and 38 significantly lowered plasma glucose concentrations at 6, 30 and 54 hours. Analog 35 and 36 significantly lowered plasma glucose concentrations at 30 and 54 hours. Analog 37 significantly lowered plasma glucose concentrations at 54 hours. Single dose (–) analogs 29, 36, 37 and 38 significantly reduced plasma glucose concentrations at 6 hours. Compound treatments did not affect the animal's food intake and body weight.



Formula II

Table 1: (±) and (–) Halofenate analogs. Compounds described in reference to Formula II.

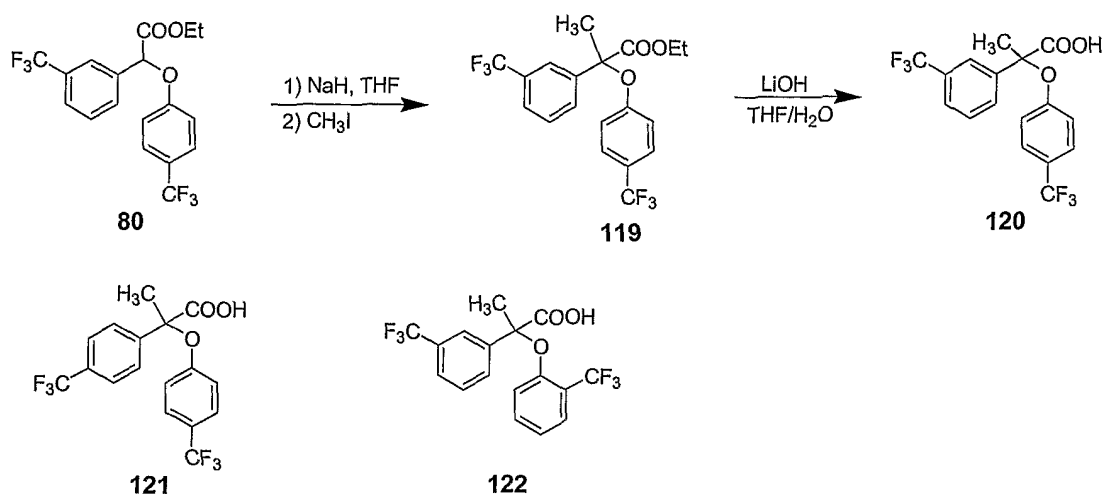
Cmpd No.	X	CX ₃	R ²
halofenic acid	Cl	CF ₃	H
14	F	CF ₃	(CH ₂) ₂ NHAc
29	Br	CF ₃	(CH ₂) ₂ NHAc
33	Cl	CF ₃	(CH ₂) ₃ CH ₃
35	Cl	CF ₃	(CH ₂) ₂ N(CH ₃) ₂
36	Cl	CF ₃	(CH ₂) ₂ NHCOPh
37	Cl	CF ₃	CH ₂ CONH ₂
38	Cl	CF ₃	CH ₂ CON(CH ₃) ₂

Table 2 Glucose-lowering Activities of (±)Halofenate and (-)Halofenate Analogs

	Predose Glucose (mg/dl)	6 hours		30 hours		54 hours	
		Glucose (mg/dl)	P	Glucose (mg/dl)	P	Glucose (mg/dl)	P
			VALUE vs. veh		VALUE vs. veh		VALUE vs. veh
Vehicle	313±18	303±19.8		NA		NA	
(-)halofenic acid	312.9±17.7	163.8±11.8	0.0011	NA		NA	
Vehicle	360.2±27.8	405.8±25.8		356.0±27.6		386.1±20.6	
(±)Analog 14	361.0±17.1	328.9±34.1	0.0444	267.0±21.3	0.0099	293.0±29.4	0.0092
Vehicle	291.6±18.5	363.0±25.1		340.8±30.0		351.5±23.8	
(±)Analog 33	292.0±19.1	227.5±13.2	0.0001	298.0±15.3	0.1119	286.6±9.9	0.0125
Vehicle	387.1±14.3	371.5±24.2		326.2±22.5		374.0±37.9	
(±)Analog 29	387.1±16.0	299.7±24.5	0.0259	237.4±14.9	0.0020	293.3±9.7	0.0268
(±)Analog 35	387.0±18.0	319.6±26.7	0.0834	276.8±17.6	0.0504	286.2±31.5	0.0458
(±)Analog 37	387.4±18.8	345.4±19.7	NS	312.5±21.7	NS	285.1±14.7	0.0210
Vehicle	329.6±16.1	361.8±23.2		346.5±24.6		379.2±24.4	
(±)Analog 36	329.7±17.6	300.5±27.3	0.0522	249.7±8.6	0.0008	272.2±18.4	0.0013
(±)Analog 38	329.4±18.9	303.2±18.2	0.0312	245.6±15.6	0.0014	243.1±10.6	0.0000
Vehicle	373.0±13.6	405.8±33.7		NA		NA	
(-)Analog 36	373.2±15.5	281.1±18.2	0.0019	NA		NA	
(-)Analog 37	373.4±16.1	271.7±22.5	0.0018	NA		NA	
(-)Analog 38	373.4±16.1	251.2±23.6	0.0007	NA		NA	
(-)Analog 29	372.2±17.1	333.5±16.1	0.0353	NA		NA	

Example 15

Preparation of 2-(4-trifluoromethyl-phenoxy)-2-(3-trifluoromethyl-phenyl)-propionic acid

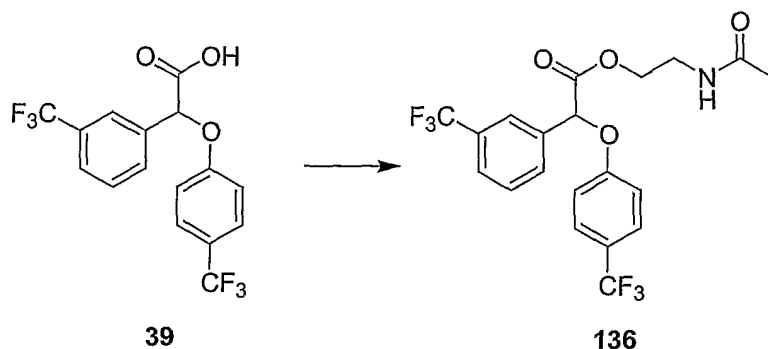


[0283] To a solution of ester **80** (3.01 g, 7.69 mmol) in anhydrous THF (30 mL) was added NaH (60% in oil, 0.80 g, 0.020 mol). After the resulting solution was stirred at rt for 2 h, iodomethane (2.5 mL, 0.040 mol) was added. The resulting mixture was stirred at rt overnight. The reaction was quenched with sat. NH₄Cl, diluted with EtOAc, washed with diluted aqueous HCl and brine, dried over Na₂SO₄, concentrated *in vacuo*, and purified by flash chromatography on silica gel (5 : 95 EtOAc / hexanes) to afford ester **119** (3.18 g, 87%) as a colorless liquid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.91 (1H, s), 7.88 (1H, d), 7.7 (1H, d), 7.69 (1H, d), 7.65 (2H, d), 7.02 (1H, d), 4.16 (2H, q), 2.48 (3H, s), 1.03 (3H, t) ppm. To a solution of ester **119** (1.03 g, 2.17 mmol) in THF / H₂O (15 mL / 5 mL) at rt was added lithium hydroxide monohydrate (0.95 g, 0.022 mol). The resulting solution was refluxed at rt for 1 h, cooled to rt, quenched with 1N aqueous HCl and extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated *in vacuo* to afford acid **120** (0.93 g, 96%) as a pale-yellow liquid.

[0284] Using the above procedures, but substituting the appropriate α-phenoxy phenyl acetic esters for **80**, there were obtained the following compounds: 2-(4-Trifluoromethyl-phenoxy)-2-(4-trifluoromethyl-phenyl)-propionic acid, **121**; 2-(2-Trifluoromethyl-phenoxy)-2-(3-trifluoromethyl-phenyl)-propionic acid, **122**, ¹H NMR (d-DMSO, 400 MHz) δ 13.85 (s, 1H), 8.04 (s, 1H), 7.86 (d, 1H), 7.74 (d, 1H), 7.70-7.66 (m, 3H), 7.56 (m, 1H), 7.15 (m, 1H), 6.89 (d, 1H), 1.89 (s, 3H).

EXAMPLE 16

Preparation of (4-trifluoromethyl-phenoxy)-(3-trifluoromethyl-phenyl)-acetic acid 2-acetylamino-ethyl ester, **136**.

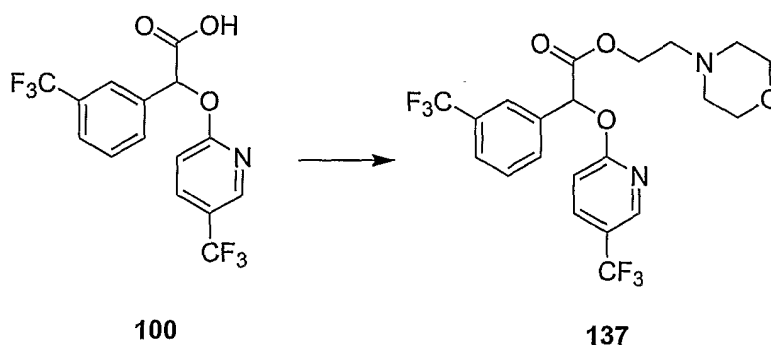


[0285] To a slurry of acid **39** (25.8 g, 0.071 mol) in anhydrous 1,2-dichloroethane (380 mL) was added thionyl chloride (16.0 mL, 0.21 mol), and then the resulting mixture was refluxed for 2 h. The mixture was cooled to rt, diluted with dry THF (150 mL) until the cloudy mixture turned clear, and then N-acetyethanolamine (39.12 g, 0.38 mol) was added. The resulting solution was stirred at rt overnight. The reaction was quenched with sat. NaHCO₃ carefully, diluted with EtOAc, and washed with water. The organic layer was washed with brine, dried over Na₂SO₄, concentrated *in vacuo*, and the residue was recrystallized from *i*PrOH / hexanes (11 mL / 31.5 mL) to afford pure product **136** (22.78 g, 71%) as a off-white solid. ¹H NMR (400 MHz, CDCl₃): δ 7.89 (1H, s), 7.80 (1H, d), 7.69 (1H, d), 7.57-7.61 (3H, t), 7.06 (2H, t), 5.78 (1H, s), 5.27 (1H, br), 4.24 (2H, m), 3.45 (2H, dd), 1.81 (3H, s) ppm.

[0286] Using the above procedure, but employing different carboxylic acids and/or different alcohols, the corresponding esters analogous to **136** are obtained.

EXAMPLE 17

Preparation of (3-trifluoromethyl-phenyl)-(6-trifluoromethyl-pyridin-3-yloxy)-acetic acid 2-morpholin-4-yl-ethyl ester, **137**.

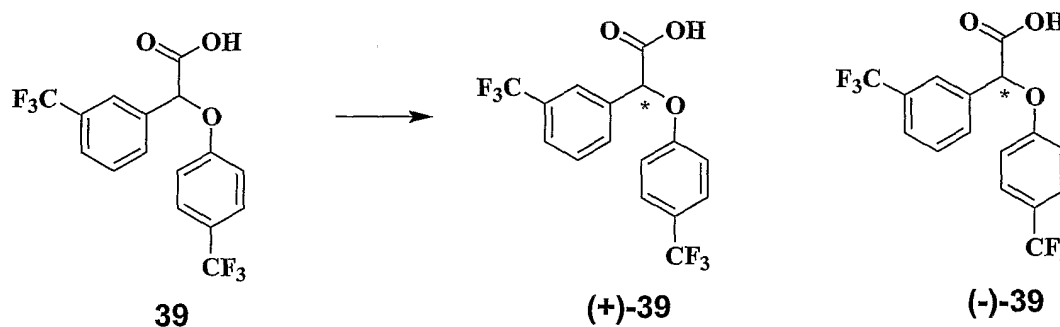


[0287] (3-Trifluoromethyl-phenyl)-(5-trifluoromethyl-pyridin-2-yloxy)-acetic acid, **100**, prepared as described in Example 4, (0.05 mol) was converted into the acid chloride, using the procedure of Example 6. The acid chloride (0.01 mol) was dissolved in tetrahydrofuran (25 mL) and N,N-dimethylaniline (2 mL) and morpholinoethanol (2 mL) were added. The progress of the reaction was monitored by TLC. When the reaction was complete, water and ether were added. The organic phase was washed with dilute hydrochloric acid, dried and concentrated. The residue was chromatographed to afford the title compound **137**.

[0288] Using the above procedure, but employing different carboxylic acids and/or different alcohols, the corresponding esters analogous to **137** can be obtained.

EXAMPLE 18

Preparation of Enantiomers of (4-trifluoromethyl-phenoxy)-(3-trifluoromethyl-phenyl)-acetic acid, **39**

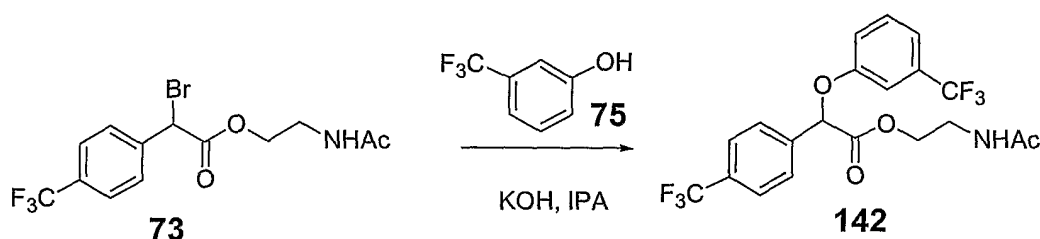


[0289] Optically pure (-)-**39** salt was obtained *via* classical resolution by serial recrystallization of the salt of the racemic acid **39** with (1R,2R)-(-)-2-amino-1-(4-nitrophenyl)-1,3-propanediol (0.55 eq.) in EtOAc / hexanes at 75 °C to rt. The first crystal collected afforded (-)-**39** salt. Serial recrystallization of the remaining mother liquid afforded another optically pure (+)-**39** salt. After acidification of both salts with 1N HCl in EtOAc, optically pure (-)-**39** and (+)-**39** were obtained as white solids respectively. (+)-**39**, $[\alpha]^{25}_D = +$

74.6 ($c = 0.55$, CH₃OH), and (-)-**39** [α]_D²⁵ $\lambda = -74.8$ ($c = 0.89$, CH₃OH). Chiral HPLC analysis of enantiomers was carried out at $\lambda = 220$ nm by injecting 10 μ L of an approximately a 0.5 mg/mL solution of the sample dissolved in mobile phase onto a 25 cm x 4.6 mm Regis Technologies (R,R) Whelk-O 15 μ m column with a 1.5 mL/min flow of (1.5/98.5/0.05) *i*PrOH/hexanes/TFA. Under these conditions, (+)-enantiomer eluted at 6.6 min, (-) enantiomer at 8.8 min (approximate retention times).

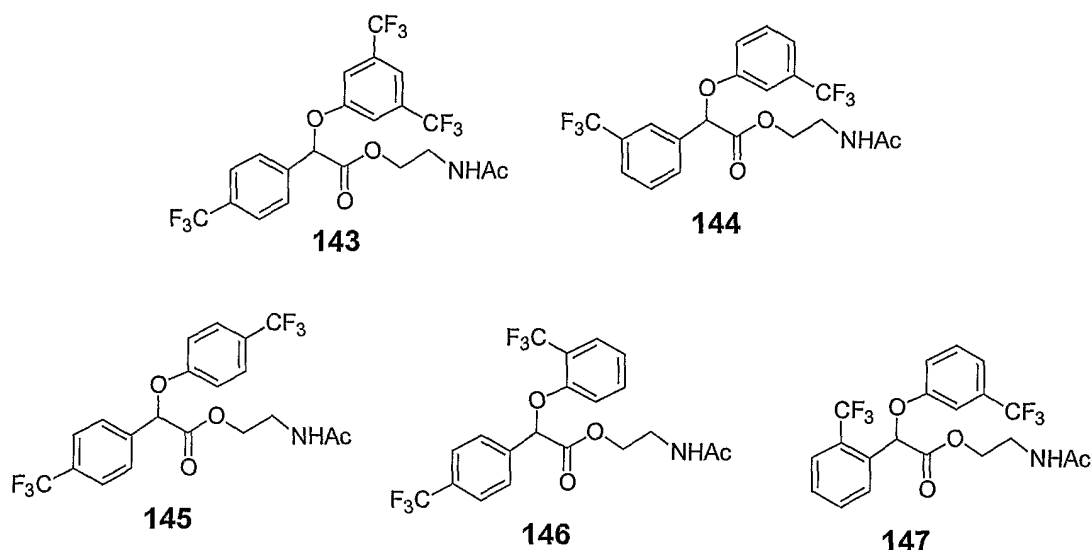
EXAMPLE 19

Preparation of Esterified Compounds



[0290] Potassium hydroxide (2.6 g, 0.046 mole) was dissolved in isopropanol (40 mL) under argon by heating to 50-60 °C. The solution was cooled to 0-10 °C in an ice bath. To this was added 3-trifluoromethylphenol (6.5 mL (8.7 g), 0.053 mole), which raised the internal temperature to 10-20°C. (2-Acetamidoethyl)-4-trifluoromethylphenylbromoacetate **73** (16.2 g, 0.044 mole) was dissolved in 12 mL isopropanol and cooled to 0-10°C. The phenoxide solution was then added to the bromoester, which raised the internal temperature to 5-15°C. The resulting mixture was stirred for 4 h in the cold bath. Citric acid (1.6 g, 0.0084 mole) was added in 12 mL water. The mixture was filtered to remove white potassium bromide and the cake washed with isopropanol (20 mL). The isopropanol was rotary evaporated and the residue dissolved in ethyl acetate (72 mL) and extracted with water (24 mL). The ethyl acetate phase was dried over sodium sulfate and filtered and the filter cake washed with ethyl acetate. After rotary evaporation, crude product were obtained. This was dissolved in ethyl ether: hexane (1:1) and diluted with hexane, whereupon some material oiled out. The mixture was cooled in an ice bath to 2-5°C a white solid formed at once and was filtered and washed with ethyl ether: hexane (1:1) to afford **142**, after drying under vacuum.

Using the above procedures, but substituting the appropriate phenols and bromoesters for 73, the following compounds were obtained: 143-147.



EXAMPLE 20

In vivo Activities

[0291] The anti-diabetic activities of the compounds were evaluated in the C57BL/6j ob/ob Mice model.

A. Materials and methods

[0292] Male, 7-9 weeks old, C57BL/6J ob/ob mice were purchased from The Jackson Laboratory (Bar Harbor, ME, USA). Animals were housed (4-5 mice/cage) under standard laboratory conditions at $22 \pm 3^{\circ}\text{C}$ temperature and $50 \pm 20\%$ relative humidity, and were maintained on a diet of Purina rodent chow and water *ad libitum*. Prior to treatment, blood was collected from the tail vein of each animal. Mice that had non-fasting plasma glucose levels between 250 and 500 mg/dl were used. Each treatment group consisted of 8-10 mice that were distributed so that the mean glucose levels were equivalent in each group at the start of the study. Mice were dosed orally by gavage once a day for 1-4 days with vehicle and one or more dose of test compound at a dose ranging from 5 to 125 mg/kg. Compounds were delivered in a liquid formulation containing 5% (v/v) dimethyl sulfoxide (DMSO), 1% (v/v) Tween 80® and 0.9% (w/v) methylcellulose. The gavage volume was 10 ml/kg. Blood samples were taken at 6 hours after the each dose and analyzed for plasma glucose. Food intake and body weight were measured daily. Plasma glucose concentrations were

determined colorimetrically using a commercial glucose oxidase method (Sigma Chemical Co, St. Louis, MO, USA). Significant difference between groups (comparing drug-treated to vehicle-treated) was evaluated using the Student unpaired t-test.

B. Results

[0293] **Table 1** provides the relative potency of some selected compounds of the invention. Compounds that are effective for glucose lowering at the dose of ≤ 125 mg/kg are assigned a potency of ++; compounds that are less effective for glucose lowering, typically exhibiting activity at a multiple dose or elevated dose of >125 mg/kg is assigned the potency of +.

Table 1. Potency of Invention Compounds

Number	Compound #	Potency	Insulin Level compared with vehicle
1	39	++	Lower
2	81	++	Lower
3	83	++	Lower
4	85	++	Lower
5	86	++	Lower
6	89	++	Lower
7	100	++	Lower
8	120	++	Lower
9	121	++	Lower
10	128	++	Lower
11	136	++	Lower
12	(-)-39	++	Lower

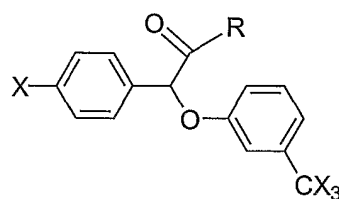
Number	Compound #	Potency	Insulin Level compared with vehicle
13	(+)-39	++	Lower
14	142	++	Lower
15	143	++	Lower
16	144	++	Lower
17	145	++	Lower
18	146	+	Lower
19	147	+	Lower

[0294] Each publication, patent application, patent, and other reference cited herein is incorporated by reference in its entirety to the extent that it is not inconsistent with the present disclosure. In particular, all publications cited herein are incorporated herein by reference in their entirety for the purpose of describing and disclosing the methodologies, reagents, and tools reported in the publications that might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

[0295] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

WHAT IS CLAIMED IS:

1. A method for treating or preventing inflammation in a subject, the method comprising administering to the subject a therapeutically effective amount of an edema-sparing PPAR γ modulator.
2. The method of claim 1, wherein the subject has a condition which contra-indicates the administration of a PPAR γ modulator which causes edema.
3. The method of claim 1, wherein the subject has edema or excess fluid retention.
4. The method of claim 1, wherein the subject has cardiac insufficiency.
5. The method of claim 1, wherein the administration is chronic.
6. The method of claim 1, wherein the subject is human.
7. A method of claim 1, comprising the step of first identifying the subject as having an indication for which an edema causing agent is contra-indicated.
8. A method of claim 1, wherein the modulator is a compound of formula I:

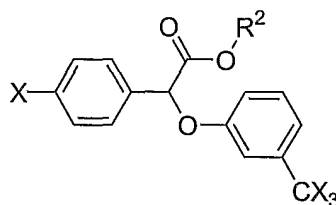


Formula I

wherein R is a member selected from the group consisting of a hydroxy, alkoxy, heteroalkoxy, aryloxy, heteroaryloxy, lower aralkoxy, di-lower alkylamino-lower alkoxy, lower alkanamido lower alkoxy, benzamido-lower alkoxy, ureido-lower alkoxy, N'-lower alkyl-ureido-lower alkoxy, carbamoyl-lower alkoxy, halophenoxy substituted lower alkoxy, carbamoyl substituted phenoxy, carbonyl-lower alkylamino, N,N-di-lower alkylamino-lower alkylamino, halo substituted lower alkylamino, hydroxy substituted lower alkylamino, lower

alkanolyloxy substituted lower alkylamino, ureido, arylsulfonamido, alkylsulfonamido and lower alkoxycarbonylamino; and each X is independently a halogen; or a pharmaceutically acceptable salt thereof.

9. A method of claim 1, wherein the modulator is a compound of Formula II,

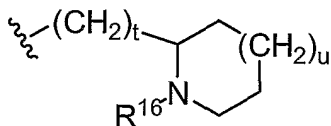
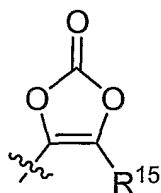


(II)

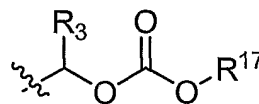
wherein:

each X is independently a halogen and

R^2 is a member selected from the group consisting of: C_1 - C_5 alkyl, C_1 - C_8 -cyclic alkyl, C_2 - C_5 alkenyl, and C_2 - C_5 alkynyl, wherein the groups are optionally substituted with one or more halogen atoms; phenyl, naphthyl and pyridyl, wherein the groups are optionally substituted with one or more substituents selected from the group consisting of halo, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, $-\text{NO}_2$, $-\text{S}(\text{O})_m(\text{C}_1\text{-C}_5\text{alkyl})$, $-\text{OH}$, $-\text{NR}^3\text{R}^4$, $-\text{CO}_2\text{R}^5$, $-\text{CONR}^3\text{R}^4$, $-\text{NR}^3\text{COR}^4$, $-\text{NR}^3\text{CONR}^3\text{R}^4$ and $-\text{C}_v\text{F}_w$; $-(\text{CHR}^3)\text{R}^4$; $-\text{R}^7\text{OR}^3$; $-\text{R}^7\text{O}_2\text{CR}^8\text{NR}^3\text{R}^4$; $-(\text{CH}_2)_o\text{CH}(\text{R}^3)(\text{CH}_2)_q\text{O}_2\text{CR}^9$; $-(\text{CH}_2)_o\text{CH}(\text{R}^3)(\text{CH}_2)_q\text{NR}^4\text{COR}^9$; $-(\text{CH}_2)_o\text{CH}(\text{R}^3)(\text{CH}_2)_q\text{NR}^4\text{CONR}^3\text{R}^4$; $-(\text{CH}_2)_o\text{CH}(\text{R}^3)(\text{CH}_2)_q\text{NR}^4\text{COOR}^{10}$; $-(\text{CH}_2)_o\text{CH}(\text{R}^3)(\text{CH}_2)_q\text{NR}^4\text{SO}_2\text{R}^{11}$; $-(\text{CHR}^3)_p\text{CO}_2\text{R}^{12}$; $-(\text{CHR}^3)_p\text{NR}^3\text{R}^4$; $-(\text{CHR}^3)_s\text{CONR}^{13}\text{R}^{14}$;

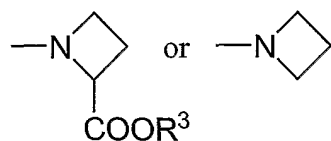


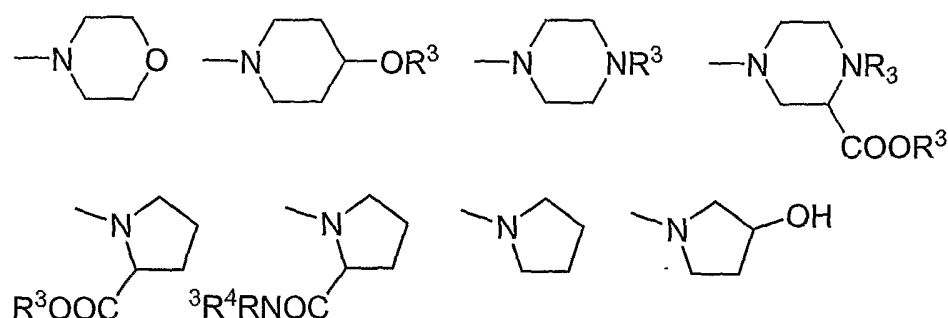
and



wherein m is 0 to 2, o and q are 0 to 5, p is 1 to 5, s is 1 to 3, t is 1 to 5, u is 0 to 1, v is 1 to 3, and w is 1 to $(2v + 1)$; and wherein R^3 and R^4 are independently H, C_1 - C_5 alkyl, phenyl or benzyl; and wherein R^5 is H, C_1 - C_5 alkyl or NR^3R^4 ; and wherein R^6 is phenyl, naphthyl, pyridyl, imidazolyl, indoxyl, indolizynyl, oxazolyl, thiazolyl, pyrimidyl, or 1-pyrazolyl

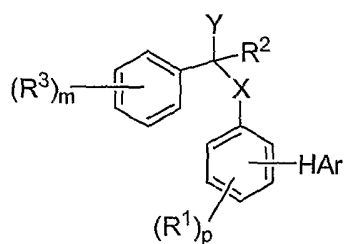
optionally substituted with one or more substituents selected from the group consisting of halo, C₁-C₄ alkyl, C₁-C₄ alkoxy, -NO₂, -S(O)_m(C₁-C₅alkyl), -OH, -NR³R⁴, -CO₂R⁵, -CONR³R⁴, -NR³COR⁴, -NR³CONR³R⁴ and -C_vF_w; and wherein R⁷ is a C₁-C₈ saturated or unsaturated, straight-chain, branched or cyclic alkylene or alkylidene group optionally substituted with one or more groups selected from halo, hydroxyl, thiol, amino, monoalkyl amino, dialkyl amino, acylamino, carboxyl, alkylcarboxyl, acyl, aryl, aroyl, aralkyl, cyano, nitro, alkoxy, alkenyloxy, alkylcarbonyloxy and arylcarbonyloxy; and wherein R⁸ is a C₁-C₈ straight-chain or branched alkylene or alkylidene optionally substituted with one or more groups selected from amino, monoalkyl amino, dialkyl amino, acylamino, hydroxyl, thiol, methylthiol, carboxyl and phenyl; and wherein R⁹ and R¹⁰ are independently H, C₁-C₅ alkyl, optionally substituted with one or more groups consisting of C₁-C₅ alkoxy aryl and heteroaryl, wherein the aryl is phenyl or naphthyl optionally substituted with one or more substituents selected from the group consisting of halo, C₁-C₄ alkyl, C₁-C₄ alkoxy, -NO₂, -S(O)_m(C₁-C₅alkyl), -OH, -NR³R⁴, -CO₂R⁵, -CONR³R⁴, -NR³COR⁴, -NR³CONR³R⁴ and -C_vF_w, and wherein the heteroaryl is pyridyl optionally substituted with one or more substituents selected from the group consisting of halo, C₁-C₄ alkyl, C₁-C₄ alkoxy, -NO₂, -S(O)_m(C₁-C₅alkyl), -OH, -NR³R⁴, -CO₂R⁵, -CONR³R⁴, -NR³COR⁴, -NR³CONR³R⁴ and -C_vF_w; and wherein R¹¹ is methyl or phenyl, wherein the phenyl is optionally substituted with methyl and/or -NO₂; and wherein R¹² is H, C₁-C₅ alkyl, phenyl, benzyl, naphthyl or pyridyl, wherein the C₁-C₅ alkyl, phenyl, naphthyl, benzyl and pyridyl are optionally substituted with one or more substituents selected from the group consisting of halo, C₁-C₄ alkyl, C₁-C₄ alkoxy, -NO₂, -S(O)_m(C₁-C₅alkyl), -OH, -NR³R⁴, -CO₂R⁵, -CONR³R⁴, -NR³COR⁴, -NR³CONR³R⁴ and -C_vF_w; and wherein R¹³ and R¹⁴ are independently the following: alkyl, alkenyl, aryl, aralkyl or cycloalkyl, wherein the groups are optionally substituted with one or more substituents selected from the group consisting of halo, C₁-C₄ alkyl, C₁-C₄ alkoxy, -NO₂, -S(O)_m(C₁-C₅alkyl), -OH, -NR³R⁴, -CO₂R⁵, -CONR³R⁴, -NR³COR⁴, -NR³CONR³R⁴, -CH₂NR³R⁴, OOCR¹⁸ and -C_vF_w; and wherein when R¹³ and R¹⁴ are included as -(CHR₃)CONR¹³R¹⁴, NR¹³R¹⁴ is



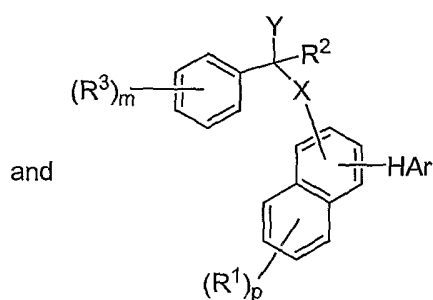


and wherein R^{15} is C_vF_w or C_1 - C_5 alkyl, wherein C_1 - C_5 alkyl is optionally substituted with the following substituents: C_1 - C_5 alkoxy; phenyl, optionally substituted with one or more substituents selected from the group consisting of halo, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, $-\text{NO}_2$, $-\text{S}(\text{O})_m(\text{C}_1\text{-C}_5\text{alkyl})$, $-\text{OH}$, $-\text{NR}^3\text{R}^4$, $-\text{CO}_2\text{R}^5$, $-\text{CONR}^3\text{R}^4$, $-\text{NR}^3\text{COR}^4$, $-\text{NR}^3\text{CONR}^3\text{R}^4$ and $-\text{C}_v\text{F}_w$; benzyl, optionally substituted with one or more substituents selected from the group consisting of halo, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, $-\text{NO}_2$, $-\text{S}(\text{O})_m(\text{C}_1\text{-C}_5\text{alkyl})$, $-\text{OH}$, $-\text{NR}^3\text{R}^4$, $-\text{CO}_2\text{R}^5$, $-\text{CONR}^3\text{R}^4$, $-\text{NR}^3\text{COR}^4$, $-\text{NR}^3\text{CONR}^3\text{R}^4$ and $-\text{C}_v\text{F}_w$; and wherein R^{16} is H, C_1 - C_5 alkyl or benzyl; and wherein R^{17} is C_1 - C_5 alkyl, C_3 - C_8 cyclic alkyl, phenyl or benzyl; and wherein R^{18} is H, alkyl, aryl, aralkyl or cycloalkyl, where the group is optionally substituted with one or more substituents selected from the group consisting of halo, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, $-\text{NO}_2$, $-\text{S}(\text{O})_m(\text{C}_1\text{-C}_5\text{alkyl})$, $-\text{OH}$, $-\text{NR}^3\text{R}^4$, $-\text{CO}_2\text{R}^5$, $-\text{CONR}^3\text{R}^4$, $-\text{NR}^3\text{COR}^4$, $-\text{NR}^3\text{CONR}^3\text{R}^4$ and $-\text{C}_v\text{F}_w$.

10. A method of claim 1, wherein the modulator is a compound having a formula selected from the group consisting of:



Formula IVa



Formula IVb

wherein

X is a member selected from the group consisting of O, S, SO, SO₂ and NR, wherein R is H, (C₁-C₈)alkyl, COR^a, COOR^a and CONR^aR^b wherein R^a and R^b are each independently selected from the group consisting of H and (C₁-C₈)alkyl;

Y is a member selected from the group consisting of CH₂OR^c, CO₂R^c, CHO, CONR^cR^m, CH(=NR^c), CH(=NOR^c) and carboxylic acid surrogates, wherein R^c is a member selected from the group consisting of H, (C₁-C₈)alkyl, (C₃-C₈)alkenyl, (C₃-C₈)alkynyl, (C₃-C₇)cycloalkyl, (C₄-C₈)cycloalkyl-alkyl, aryl, aryl(C₁-C₈)alkyl and (C₁-C₈)alkylene-Z, wherein Z is selected from the group consisting of COR^d, COOR^d, NR^dR^e, NR^dCONR^eR^f, NR^dCOR^e, NR^dCOOR^e and CONR^dR^e wherein R^d, R^e and R^f are each independently selected from the group consisting of H, (C₁-C₈)alkyl and phenyl, or optionally two of R^d, R^e and R^f when attached to the same nitrogen atom are combined to form a five- or six-membered ring; and wherein R^m is selected from the group consisting of H, (C₁-C₈)alkyl, aryl, OH and SO₂Rⁿ, wherein Rⁿ is selected from the group consisting of (C₁-C₈)alkyl, (C₁-C₈)haloalkyl, aryl(C₁-C₈)alkyl, (C₁-C₈)heteroalkyl, aryl, heteroaryl, (C₁-C₈)alkoxy, aryloxy, alkylamino, dialkylamino, arylamino, diarylamino, haloalkylamino and di(haloalkyl)amino, and R^m and R^c are optionally combined with the nitrogen atom to which each is attached to form a five- or six-membered ring;

HAr is heteroaryl moiety, optionally substituted with from one to three substituents independently selected from the group consisting of halogen, hydroxy, (C₁-C₈)alkyl, aryl(C₁-C₈)alkyl, (C₁-C₈)alkoxy, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)cycloalkyl, (C₄-C₈)cycloalkyl-alkyl, (C₁-C₈)heteroalkyl, (C₂-C₅)heterocyclyl, aryl, aryloxy, heterosubstituted(C₃-C₇)cycloalkyl, heteroalkyl substituted (C₃-C₇)cycloalkyl, (C₁-C₈)haloalkyl, O(C₁-C₈)haloalkyl, nitro, cyano, CO₂R^g, COR^g, NR^gR^h, S(O)_qR^g, SO₂NR^gR^h, NR^gCONR^hRⁱ, NR^gCOR^h, NR^gCOOR^h and CONR^gR^h, wherein R^g, R^h and Rⁱ are each independently selected from the group consisting of H and (C₁-C₈)alkyl, or optionally two of R^g, R^h and Rⁱ when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript q is an integer of from 0 to 2;

each R¹ and R³ is a member independently selected from the group consisting of halogen, hydroxy, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₁-C₈)alkoxy, (C₃-C₇)cycloalkyl, (C₄-C₈)cycloalkyl-alkyl, (C₁-C₈)haloalkyl, (C₁-C₈)heteroalkyl, (C₂-C₅)heterocyclyl, heterosubstituted(C₃-C₇)cycloalkyl,

heteroalkyl substituted (C₃-C₇)cycloalkyl, O(C₁-C₈)haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl, S(O)_r-phenyl, COR^j, COOR^j, NR^jR^k, S(O)_rR^j, SO₂NR^jR^k, NR^jCONR^kR^l, NR^jCOR^k, NR^jCOOR^k and CONR^jR^k wherein the phenyl ring is optionally substituted and R^j, R^k and R^l are each independently selected from the group consisting of H, (C₁-C₈)alkyl and (C₁-C₈)haloalkyl, or optionally two of R^j, R^k and R^l when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript r is an integer of from 0 to 2;

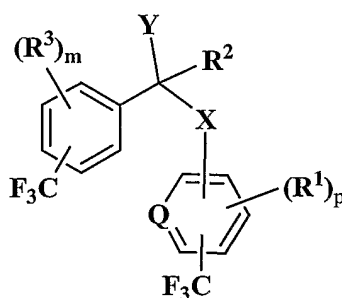
R² is a member selected from the group consisting of H, (C₁-C₈)alkyl, (C₁-C₈)haloalkyl, aryl(C₁-C₈)alkyl and (C₁-C₄)alkylene-Z, wherein Z is as defined above;

the subscript m is an integer of from 0 to 4;

the subscript p is an integer of from 0 to 3; and

pharmaceutically acceptable salts thereof.

11. The method of claim 1, wherein the modulator is a compound having the formula



Formula VI

and all pharmaceutically acceptable salts and prodrugs thereof, wherein

X is a member selected from the group consisting of O, S, SO, SO₂, CHR and NR, wherein R is H, (C₁-C₈)alkyl, COR^a, COOR^a and CONR^aR^b wherein R^a and R^b are each independently selected from the group consisting of H and (C₁-C₈)alkyl;

Y is a member selected from the group consisting of CH₂OR^c, CO₂R^c, tetrazole, CHO, CONR^cR^m, CH(=NR^c) and CH(=NOR^c), wherein R^c is a member selected from the group consisting of H, (C₁-C₈)alkyl, (C₃-C₈)alkenyl, (C₃-C₈)alkynyl, (C₃-C₇)cycloalkyl, (C₄-C₈)cycloalkyl-alkyl, aryl, aryl(C₁-C₈)alkyl and (C₁-C₈)alkylene-Z, wherein Z is

selected from the group consisting of COR^d , COOR^d , NR^dR^e , $\text{NR}^d\text{CONR}^e\text{R}^f$, NR^dCOR^e , NR^dCOOR^e and CONR^dR^e wherein R^d , R^e and R^f are each independently selected from the group consisting of H, $(\text{C}_1\text{-C}_8)\text{alkyl}$ and phenyl, or optionally two of R^d , R^e and R^f when attached to the same nitrogen atom are combined to form a five- or six-membered ring; and wherein R^m is selected from the group consisting of H, $(\text{C}_1\text{-C}_8)\text{alkyl}$, aryl and OH, and R^m and R^c are optionally combined with the nitrogen atom to which each is attached to form a five or six-membered ring;

each R^1 and R^3 is a member independently selected from the group consisting of halogen, hydroxy, $(\text{C}_1\text{-C}_8)\text{alkyl}$, $(\text{C}_2\text{-C}_8)\text{alkenyl}$, $(\text{C}_2\text{-C}_8)\text{alkynyl}$, $(\text{C}_1\text{-C}_8)\text{alkoxy}$, $(\text{C}_3\text{-C}_7)\text{cycloalkyl}$, $(\text{C}_4\text{-C}_8)\text{cycloalkyl-alkyl}$, $(\text{C}_1\text{-C}_8)\text{haloalkyl}$, $(\text{C}_1\text{-C}_8)\text{heteroalkyl}$, $(\text{C}_2\text{-C}_5)\text{heterocyclyl}$, heterosubstituted $(\text{C}_3\text{-C}_7)\text{cycloalkyl}$, heteroalkyl substituted $(\text{C}_3\text{-C}_7)\text{cycloalkyl}$, $\text{O}(\text{C}_1\text{-C}_8)\text{haloalkyl}$, nitro, cyano, phenyl, O-phenyl, $\text{NR}^j\text{-phenyl}$, $\text{S}(\text{O})_r\text{-phenyl}$, COR^j , COOR^j , NR^jR^k , $\text{S}(\text{O})_r\text{R}^j$, $\text{SO}_2\text{NR}^j\text{R}^k$, $\text{NR}^j\text{CONR}^k\text{R}^l$, NR^jCOR^k , NR^jCOOR^k and CONR^jR^k wherein the phenyl ring is optionally substituted and R^j , R^k and R^l are each independently selected from the group consisting of H and $(\text{C}_1\text{-C}_8)\text{alkyl}$, or optionally two of R^j , R^k and R^l when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript r is an integer of from 0 to 2;

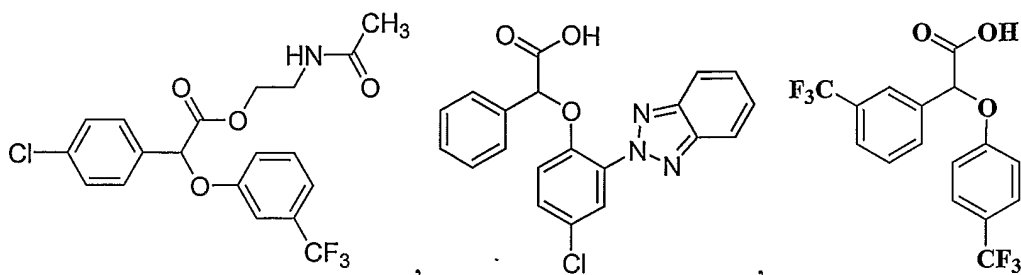
R^2 is a member selected from the group consisting of H and $(\text{C}_1\text{-C}_8)\text{alkyl}$;

Q is CH or N

the subscript m is an integer of from 0 to 3; and

the subscript p is an integer of from 0 to 2.

12 . The method of claim 1, wherein the modulator has the formula selected from the group consisting of:



Formula III

Formula V

Formula VII.

13. A method of treating a human subject known to have an elevated CRP level, comprising administering to the subject a therapeutically effective amount of a compound of formula I, II, III, IVa, IVb, V, VI, or VII.

14. A method of claim 13, wherein the subject has edema or excess fluid retention.

15. The method of claim 13, wherein the elevated CRP level is at least 3 mg/l.

16. The method of claim 13, wherein the administration is chronic.

17. The method of claim 13, wherein the therapeutically effective amount is from 100 to 800 mg per day by the oral route.

18. The method of claim 13, wherein the therapeutically effective amount is about 200 mg to about 600 mg per day by the oral route.

19. A method of treating or preventing a cerebrovascular or cardiovascular disorder in a human patient, the method comprising the steps of:

obtaining a blood sample from the patient and determining the level of a marker for a pro-inflammatory state therein, and

administering a therapeutically effective amount of a compound of Formula I, II, III, IVa, IVb, V, VI, or VII.

20. The method of claim 19, wherein the marker is hsCRP or IL-6.

21. The method of claim 20, wherein the marker is hsCRP and the determined level is at least 3 mg/l.

22. The method of claim 19, wherein the patient has edema.
23. The method of claim 19, wherein the administering is chronic.
24. The method of claim 19, wherein the patient further has hyperglycemia or type 2 diabetes.
25. The method of claim 19, wherein the patient further has metabolic syndrome.
26. The method of claim 19, wherein the patient further has insulin resistance.
27. The method of claim 19, wherein the cardiovascular disorder is selected from the group consisting of hypertension, coronary arterial disease, myocardial infarction, peripheral vascular atherosclerosis, and congestive heart failure.
28. The method of claim 19, wherein the therapeutically effective amount is from 100 to 800 mg per day by the oral route.
29. The method of claim 19, wherein the therapeutically effective amount is about 200 mg to about 600 mg per day by the oral route.
30. A method of lowering a CRP level in a subject in need thereof, said method comprising:
 - obtaining a body fluid sample from the subject and determining the CRP level therein, and
 - administering a therapeutically effective amount of an edema-sparing PPAR γ modulator of Formula I, II, III, IVa, IVb, V, VI, or VII;
 - wherein the CRP level is lowered.
31. The method of claim 30, wherein the subject is obese and hypertensive and over 50 years of age.
32. The method of claim 30, wherein the therapeutically effective amount is from 100 to 800 mg per day by the oral route.

33. The method of claim 30, wherein the therapeutically effective amount is from about 200 mg to about 600 mg.

34. The method of claim 30, wherein the body fluid is blood.

35. A method of treating a patient in need of therapy with a PPAR γ modulator, said method comprising the steps of:

evaluating whether the patient has edema, and

administering a compound of formula I, II, III, IVa, IVb, V, VI, or VII.

36. A method for treating a patient having edema or at risk of having edema and a metabolic disorder or edema and a cardiovascular disorder, said method comprising administering to said patient an effective amount of a PPAR γ modulatory compound selected from the group consisting of formula I, II, III, IVa, IVb, V, VI, or VII.

37. The method of claim 36, wherein said cardiovascular disorder is selected from the group consisting of hypertension, stroke, coronary arterial disease, myocardial infarction, peripheral vascular atherosclerosis, and congestive heart failure.

38. The method of claim 36, wherein the metabolic disorder is insulin resistance, metabolic syndrome, impaired fasting glucose, impaired glucose tolerance, polycystic ovary disease, or "pre-diabetes", or any condition characterized by insulin resistance of any degree.

39. A method of treating a patient having edema and in need of therapy with a PPAR γ modulator, said method comprising the steps of:

first evaluating whether the patient has edema, and then

administering a compound of formula I, II, III, IVa, IVb, V, VI, or VII.

40. A method of treating a patient who has experienced weight gain or edema when treated with a first PPAR γ modulator, said method comprising stopping administration of the first PPAR γ modulator and administering a second PPAR γ modulator which is a compound of formula I, II, III, IVa, IVb, V, VI, or VII.

41. The method of claim 40, wherein the first PPAR γ modulator is troglitazone, pioglitazone, or rosiglitazone.

42. A method of treating or preventing a metabolic disorder in a human patient, the method comprising the steps of:

obtaining a blood sample from the patient and determining the level of a marker for a pro-inflammatory state therein, and

administering a therapeutically effective amount of a compound of Formula I, II, III, IVa, IVb, V, VI, or VII.

43. The method of claim 42, wherein the marker is hsCRP or IL-6.

44. The method of claim 43, wherein the marker is hsCRP and the determined level is at least 3 mg/l.

45. The method of claim 42, wherein the patient has edema.

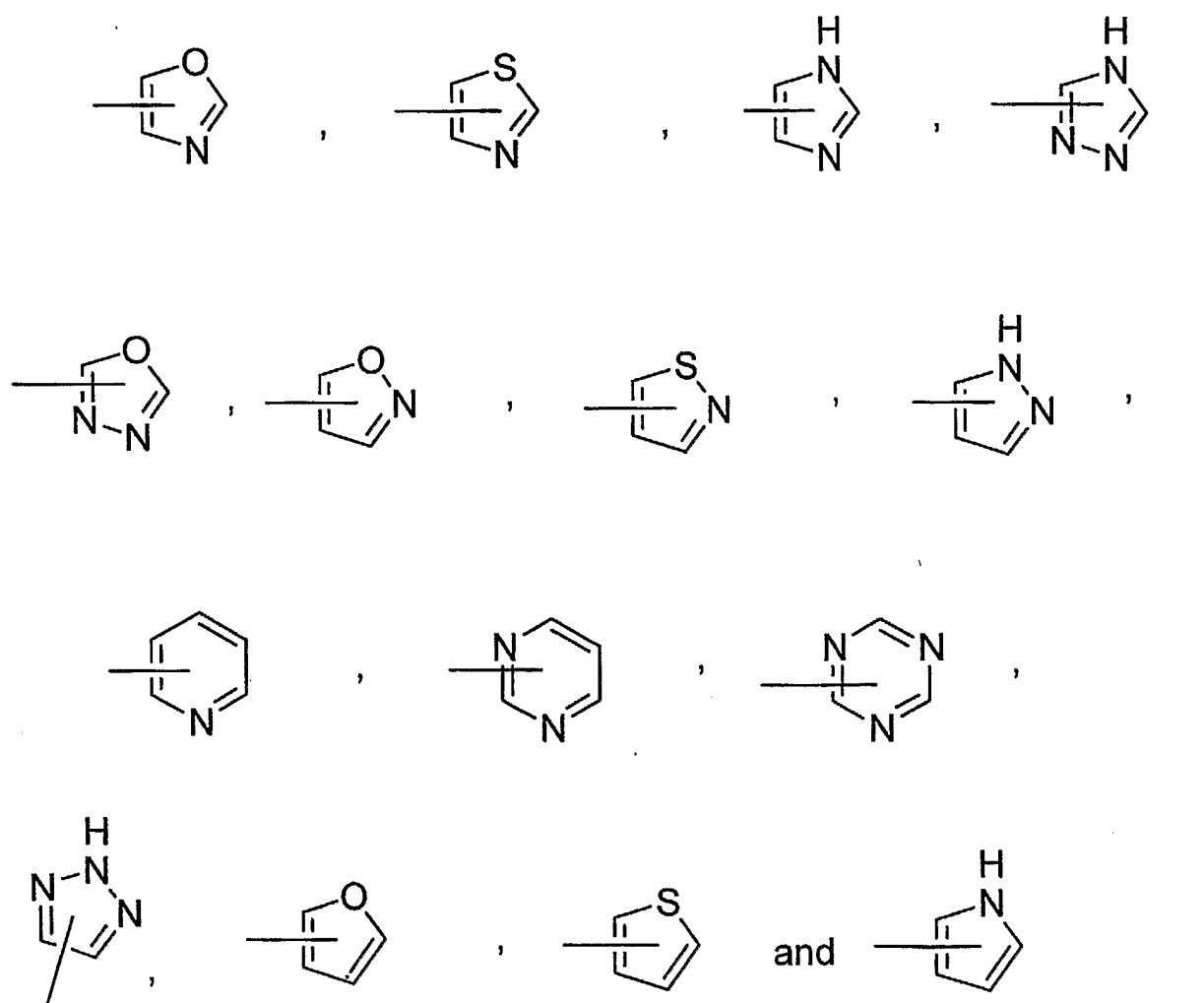
46. The method of claim 42, wherein the administering is chronic.

47. The method of claim 42, wherein the patient has hyperglycemia or type 2 diabetes.

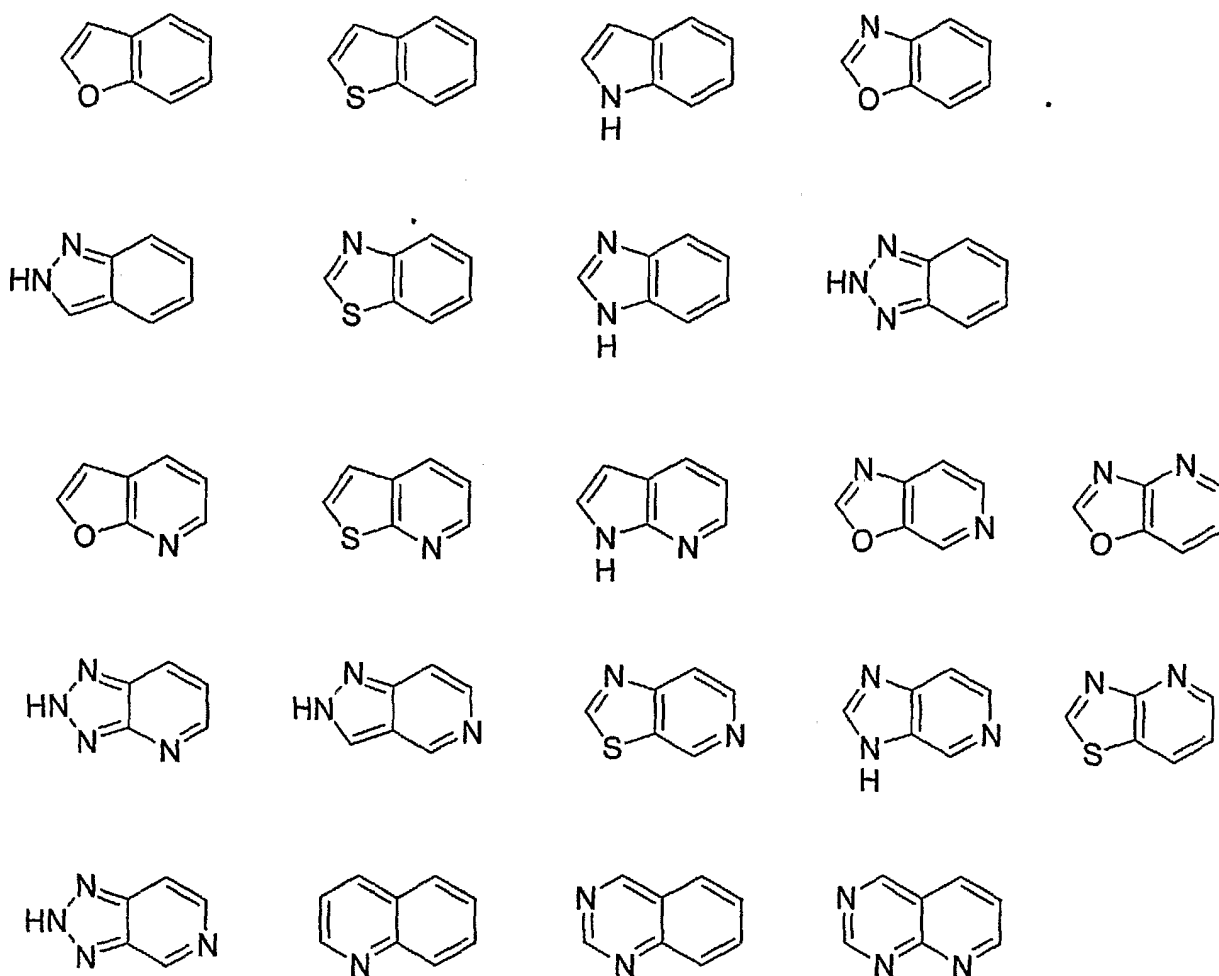
48. The method of claim 42, wherein the subject has metabolic syndrome.

49. The method of claim 42, wherein the subject has insulin resistance.

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**FIG. 1A**

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**FIG. 1B**

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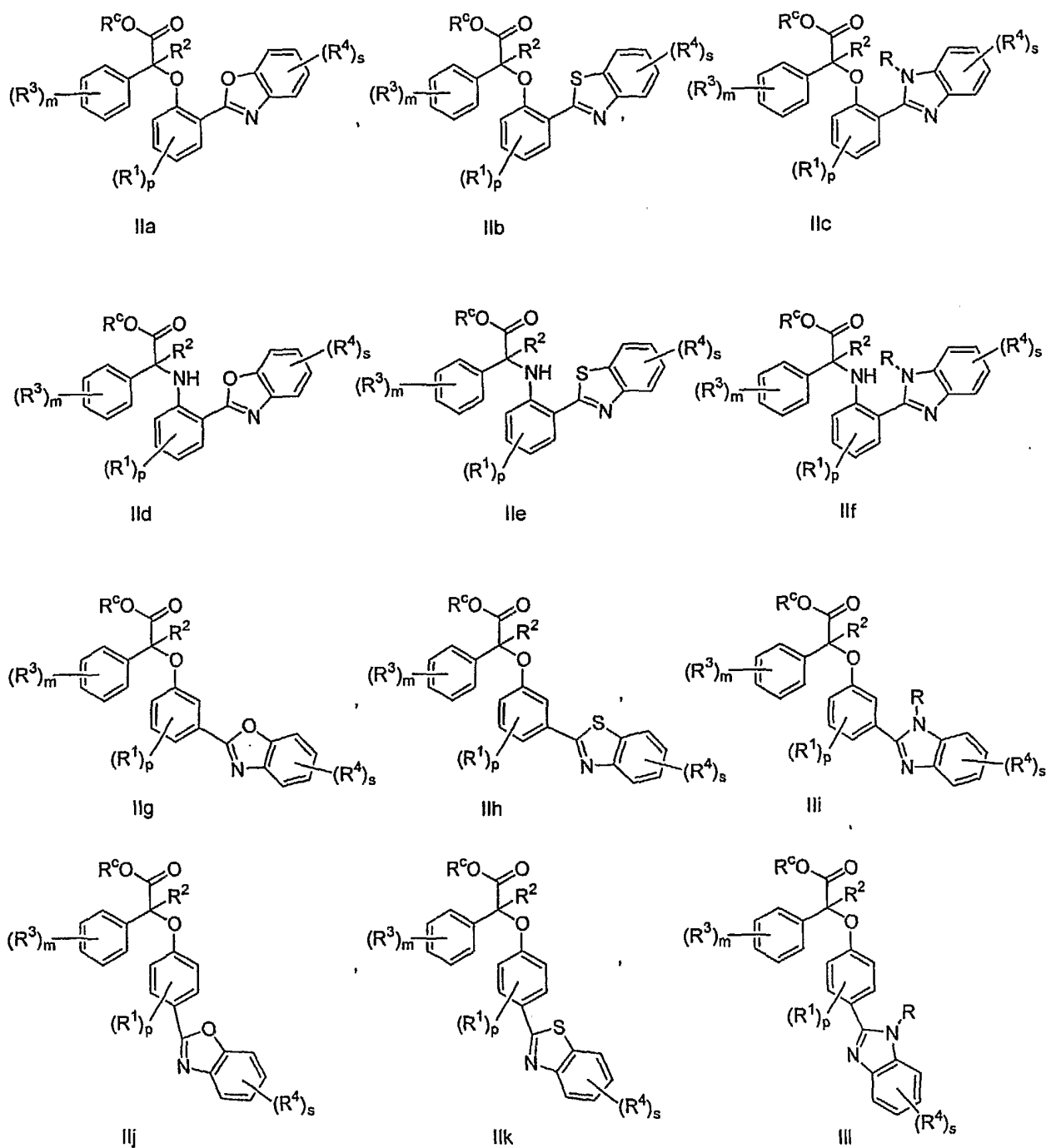
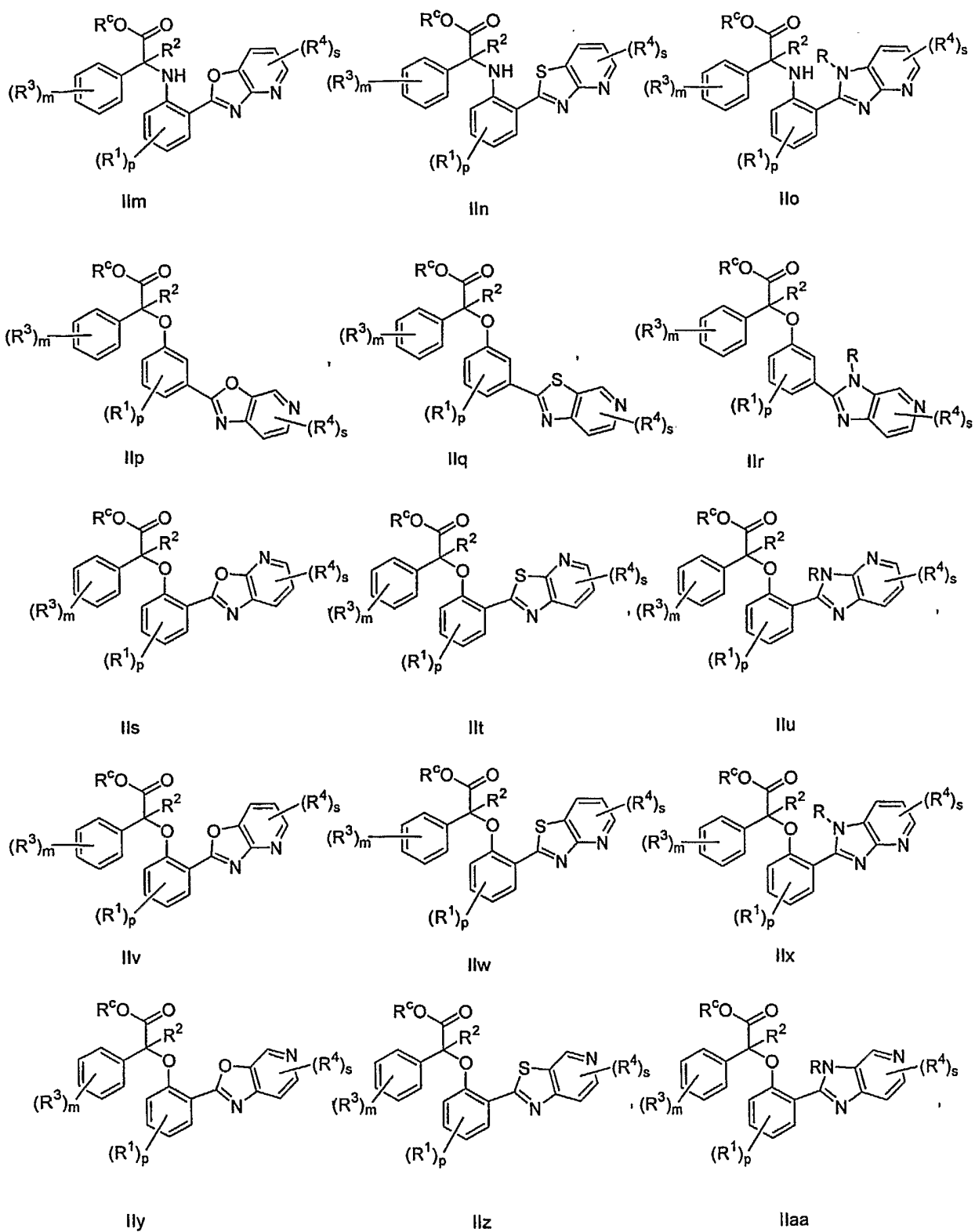


FIG. 2

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**FIG. 3**

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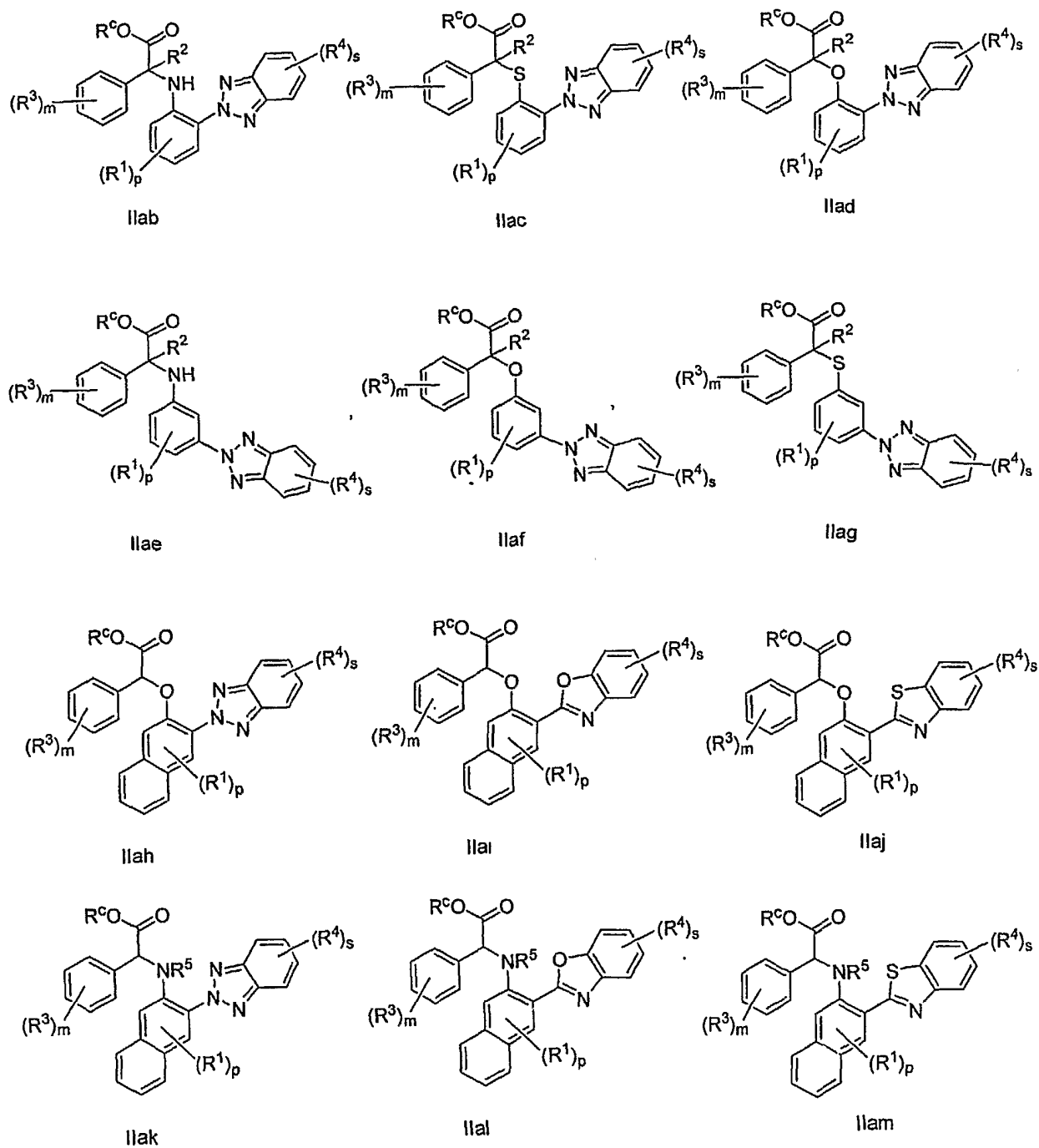
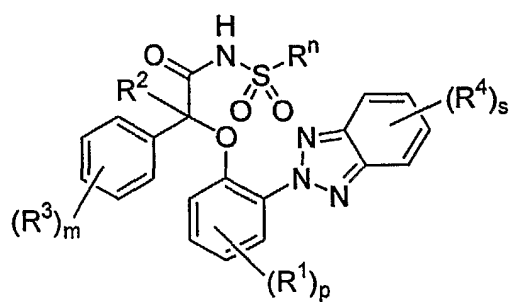
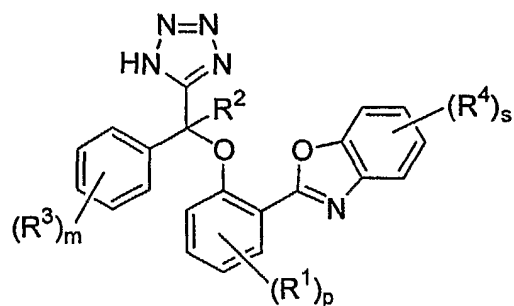


FIG. 4A

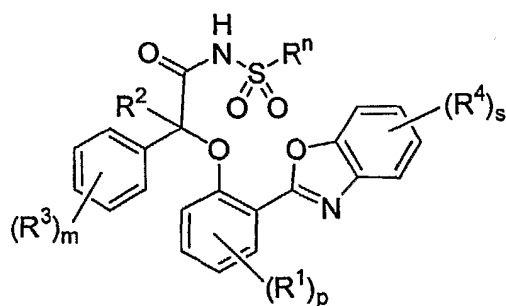
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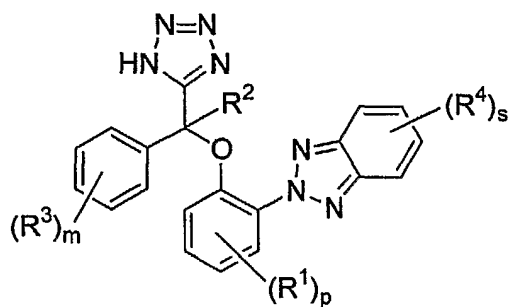
IIan



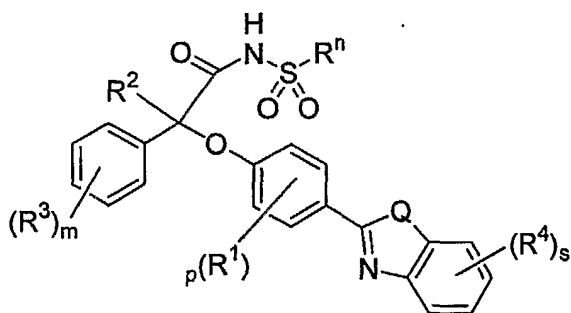
IIao



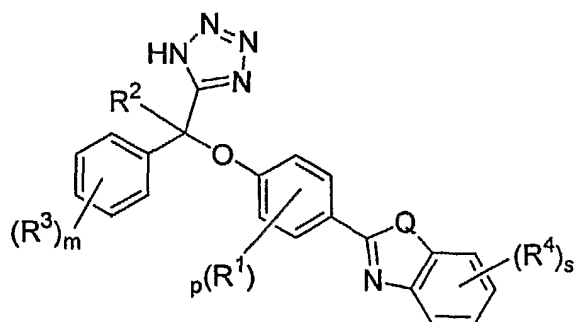
IIap



IIaq



IIar Q = O
 IIas Q = S
 IIat Q = NH or NR



IIax Q = O
 IIay Q = S
 IIaz Q = NH or NR

FIG. 4B

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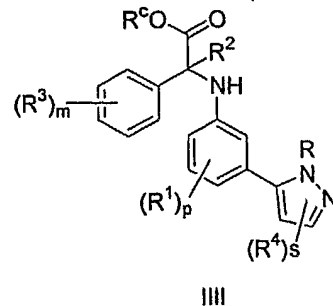
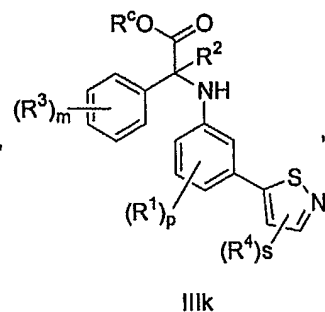
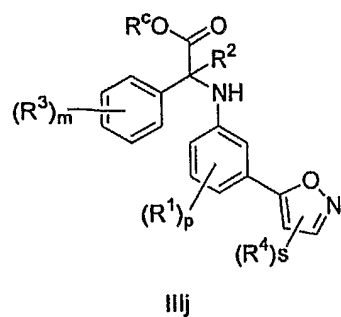
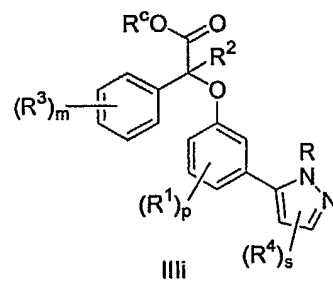
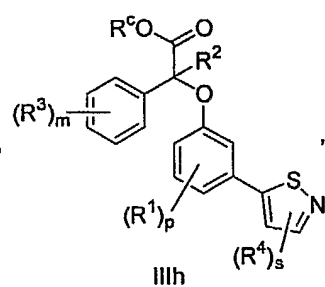
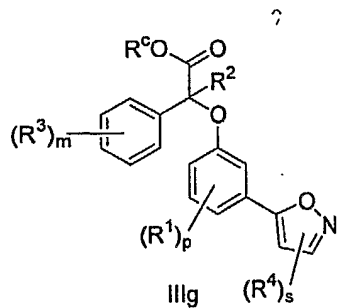
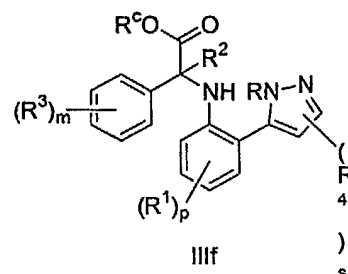
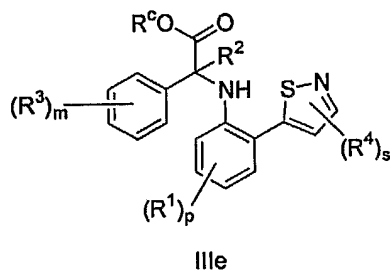
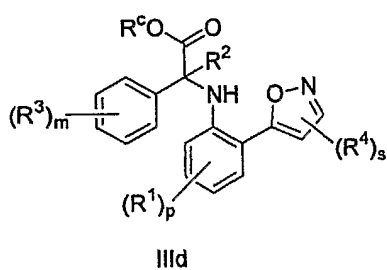
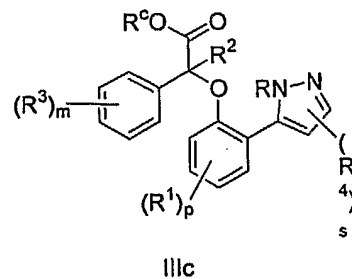
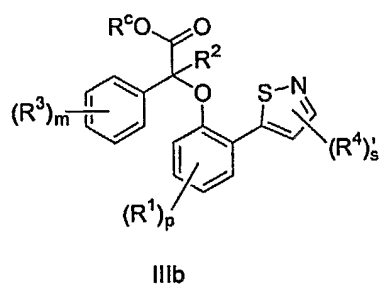
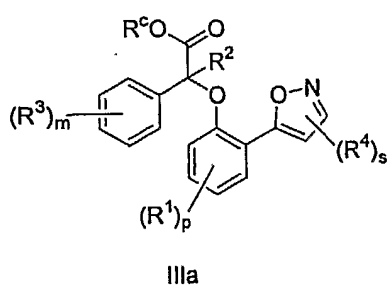
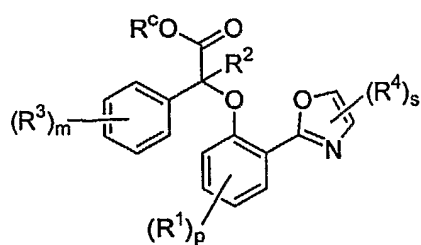
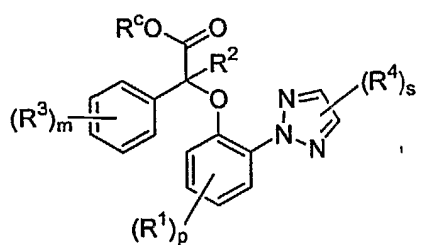


FIG. 5A

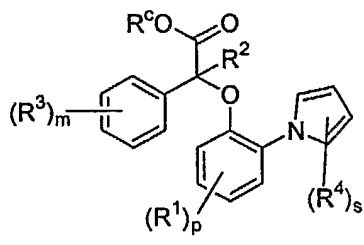
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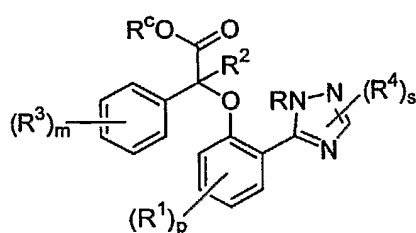
IIIIm



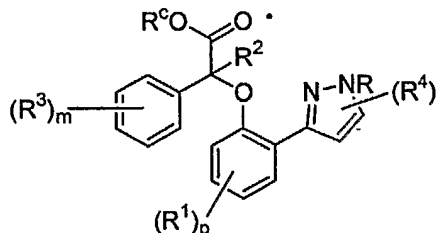
IIIIn



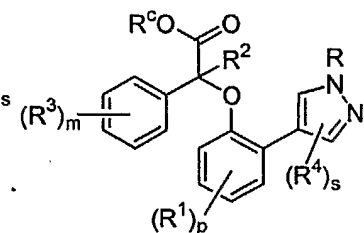
IIIIo



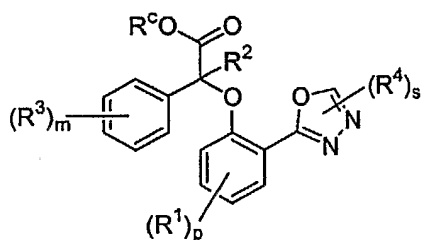
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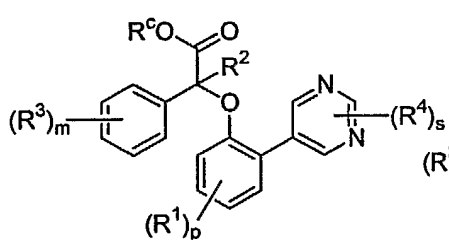
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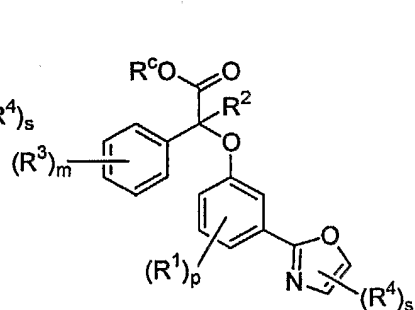
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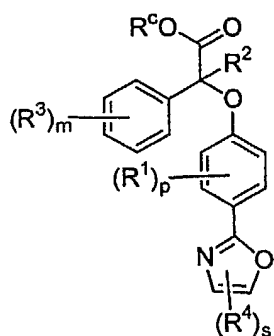
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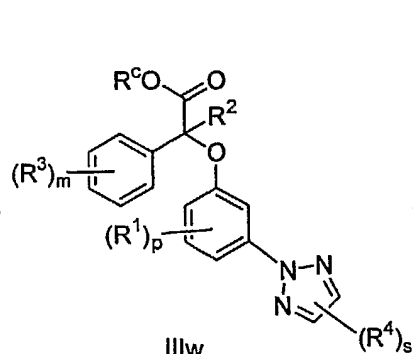
IIIIt



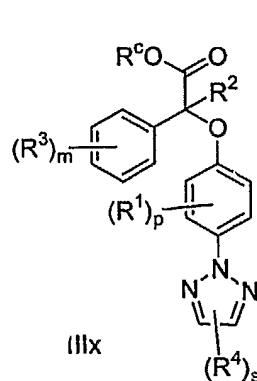
IIIIu



III Iv



III Iw



III Ix

FIG. 5B

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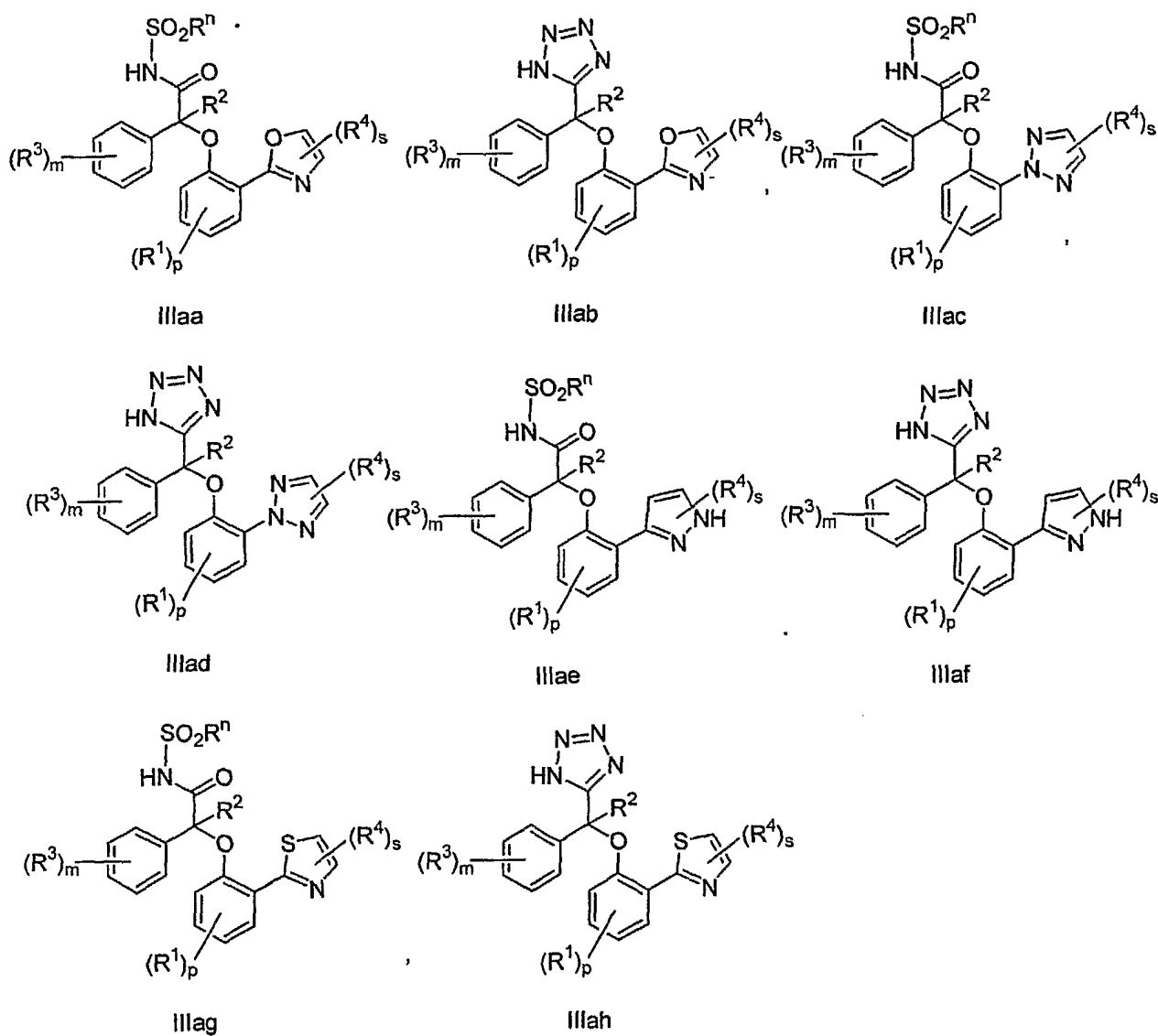
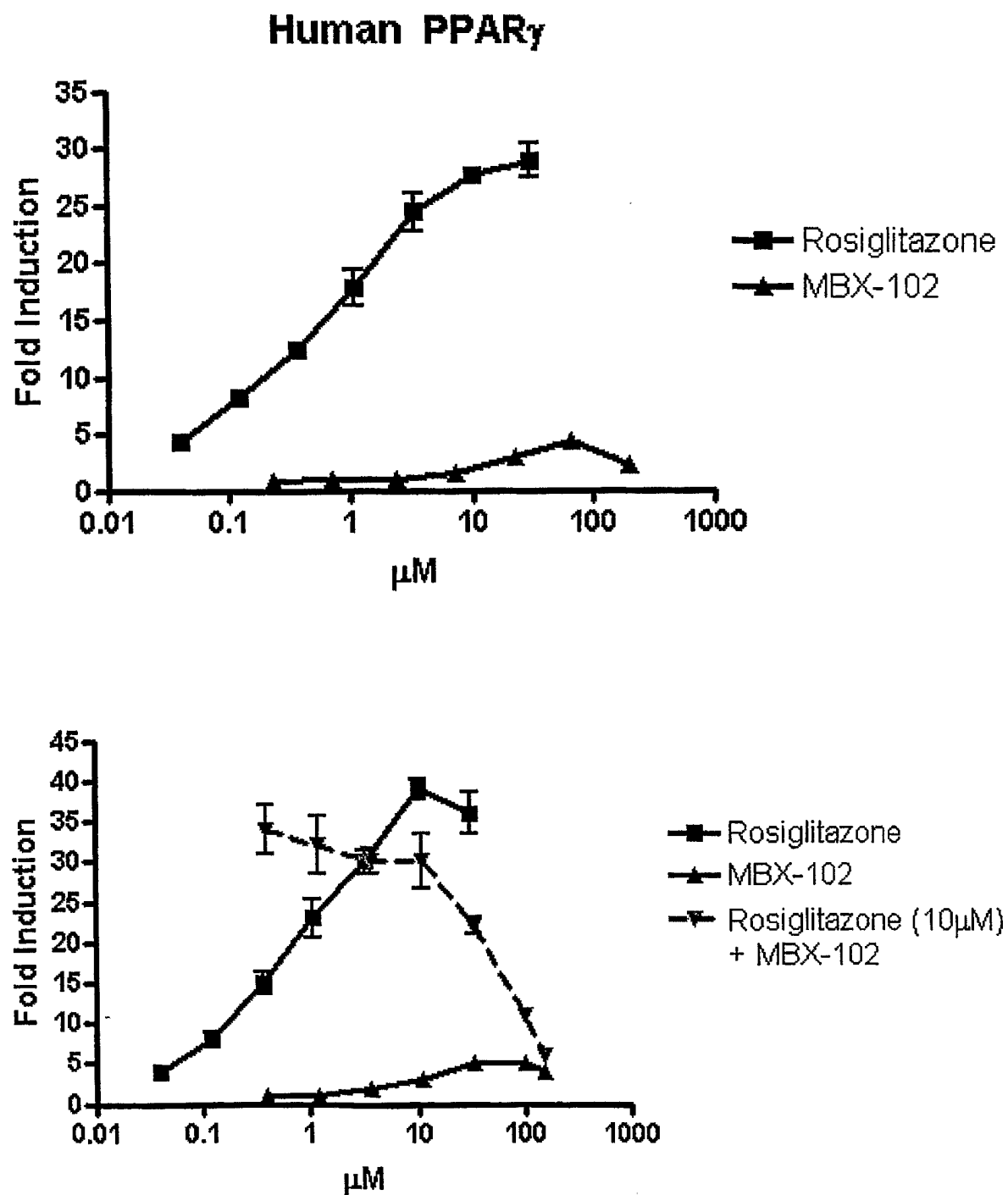


FIG. 5C

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**FIG. 6**

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Absolute Change from Baseline in the First Study

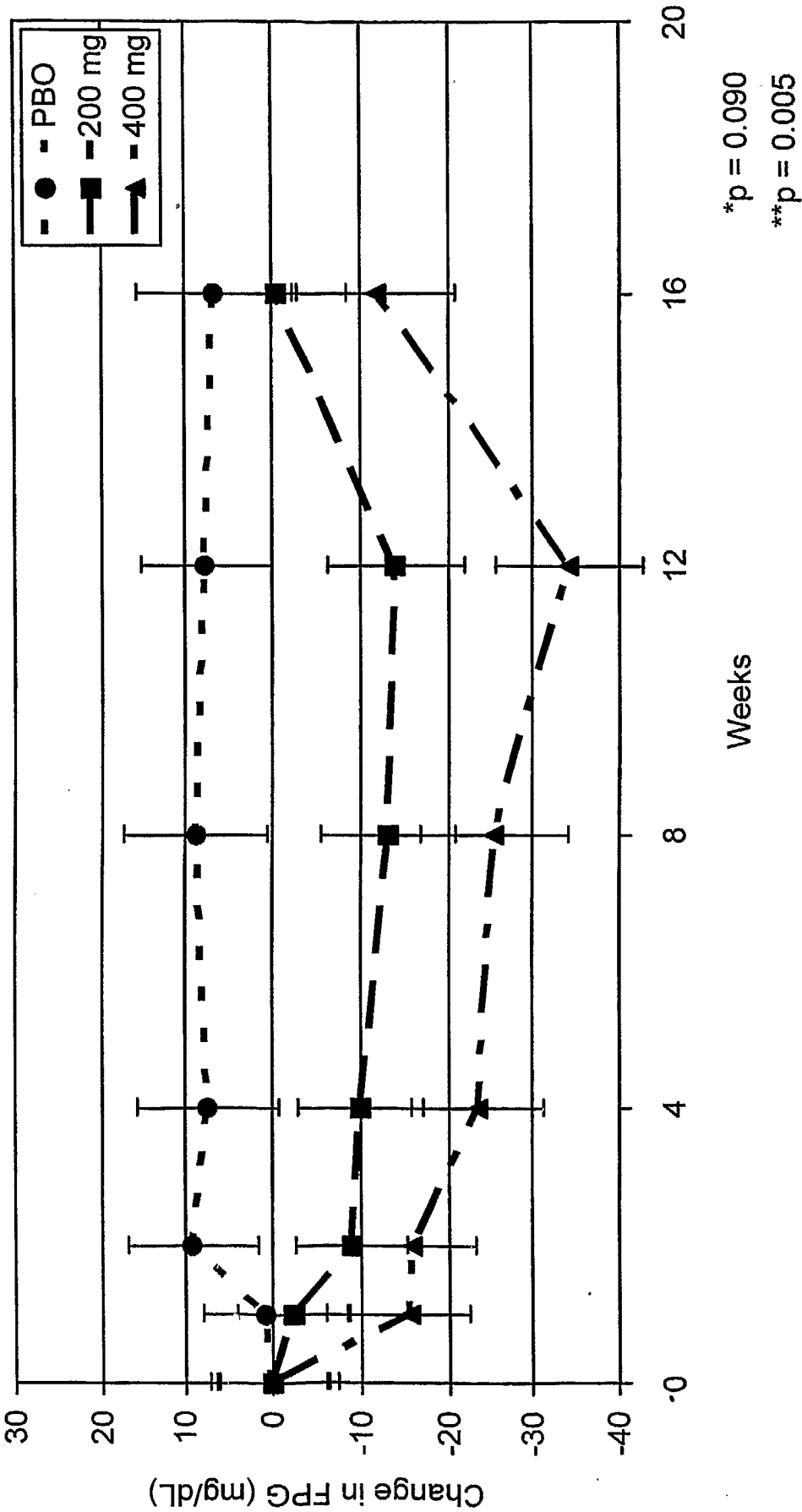


FIG. 7

HbA1c - Absolute Change from Baseline in the First Study

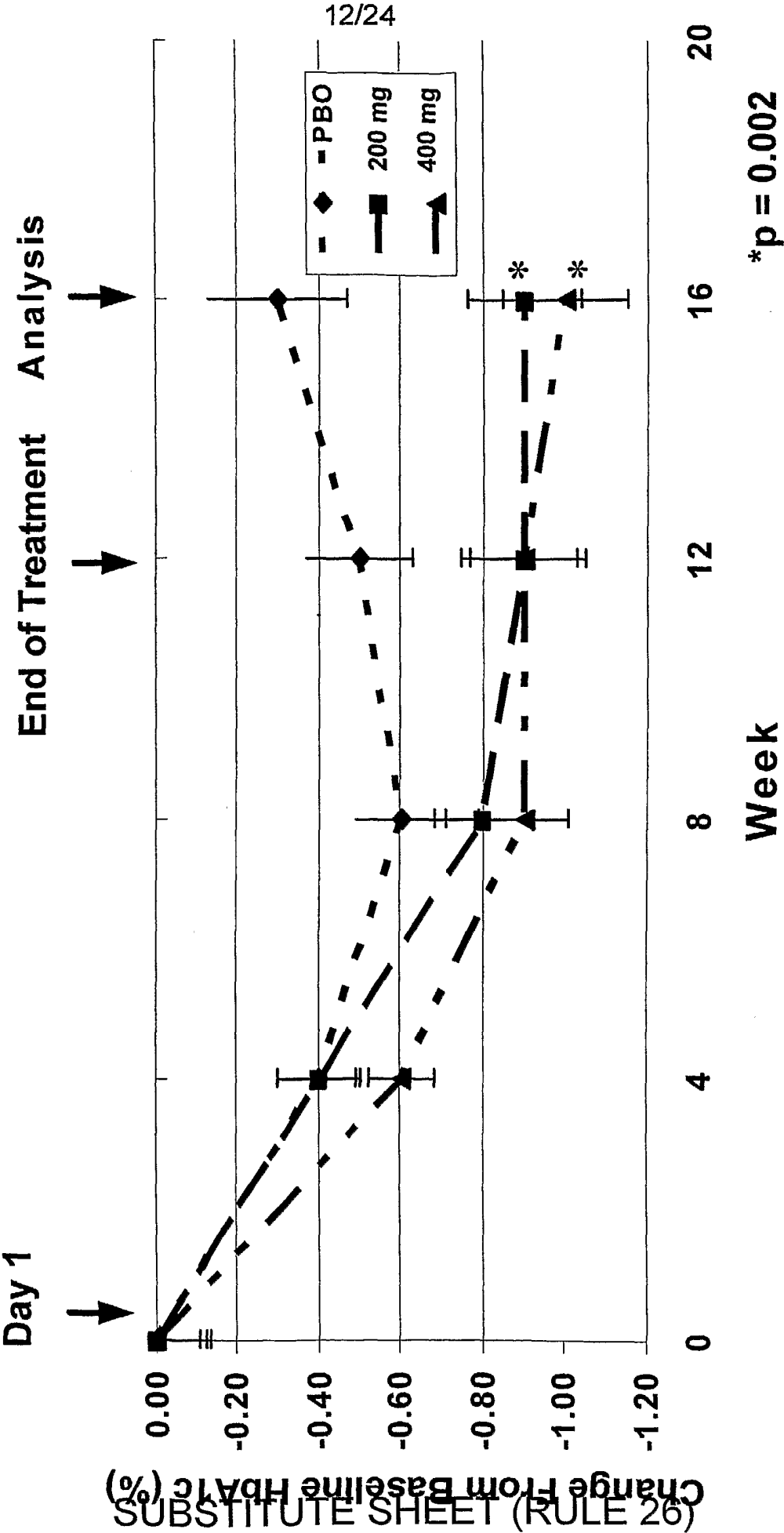


FIG. 8

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Incidence of Edema in the First Study

*** Armitage-Cochran Trend Test**
p = 0.0256 (one-sided)
0.0511 (two-sided)

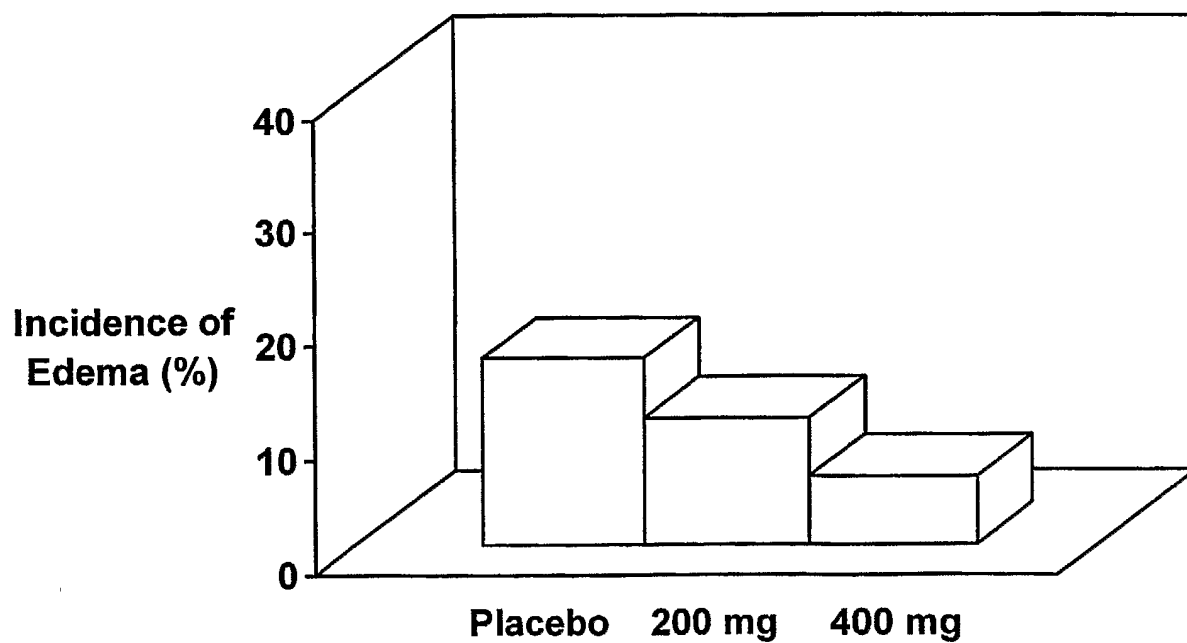
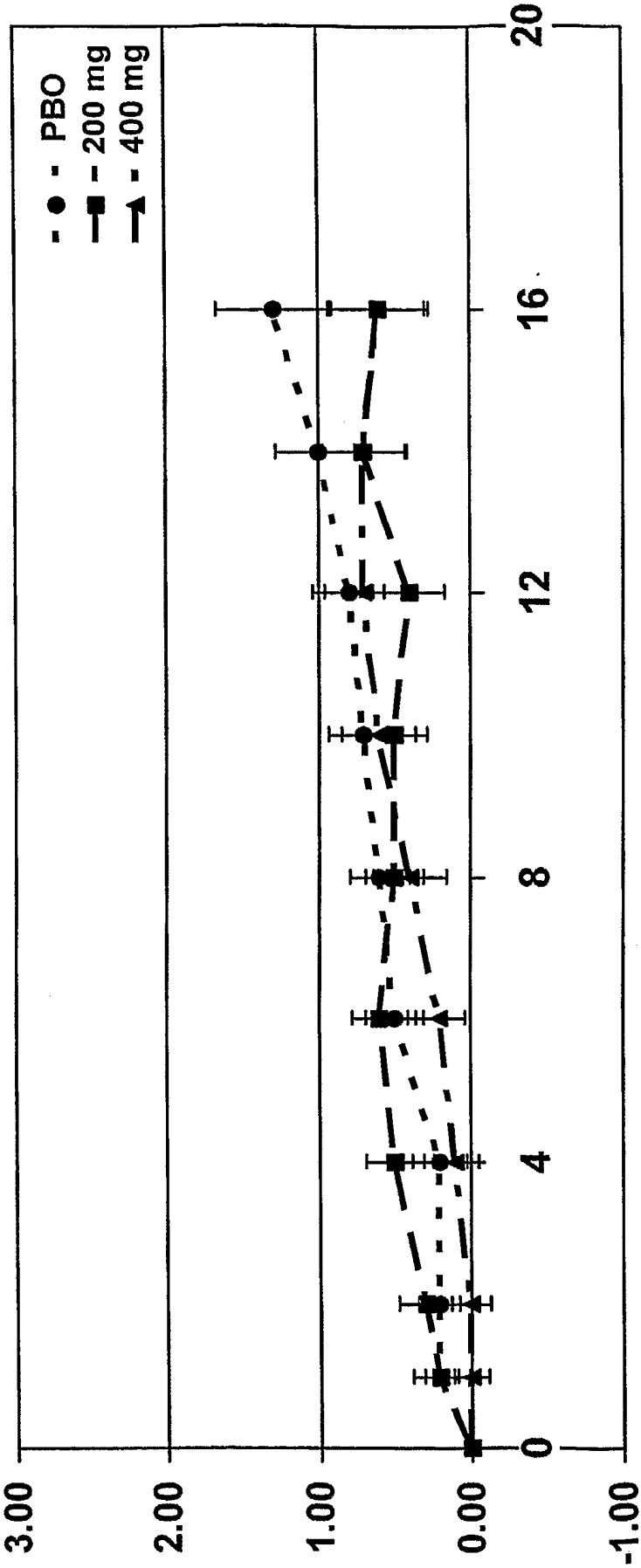


FIG. 9

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Change from Baseline in Weight First Study



Weeks

FIG. 10

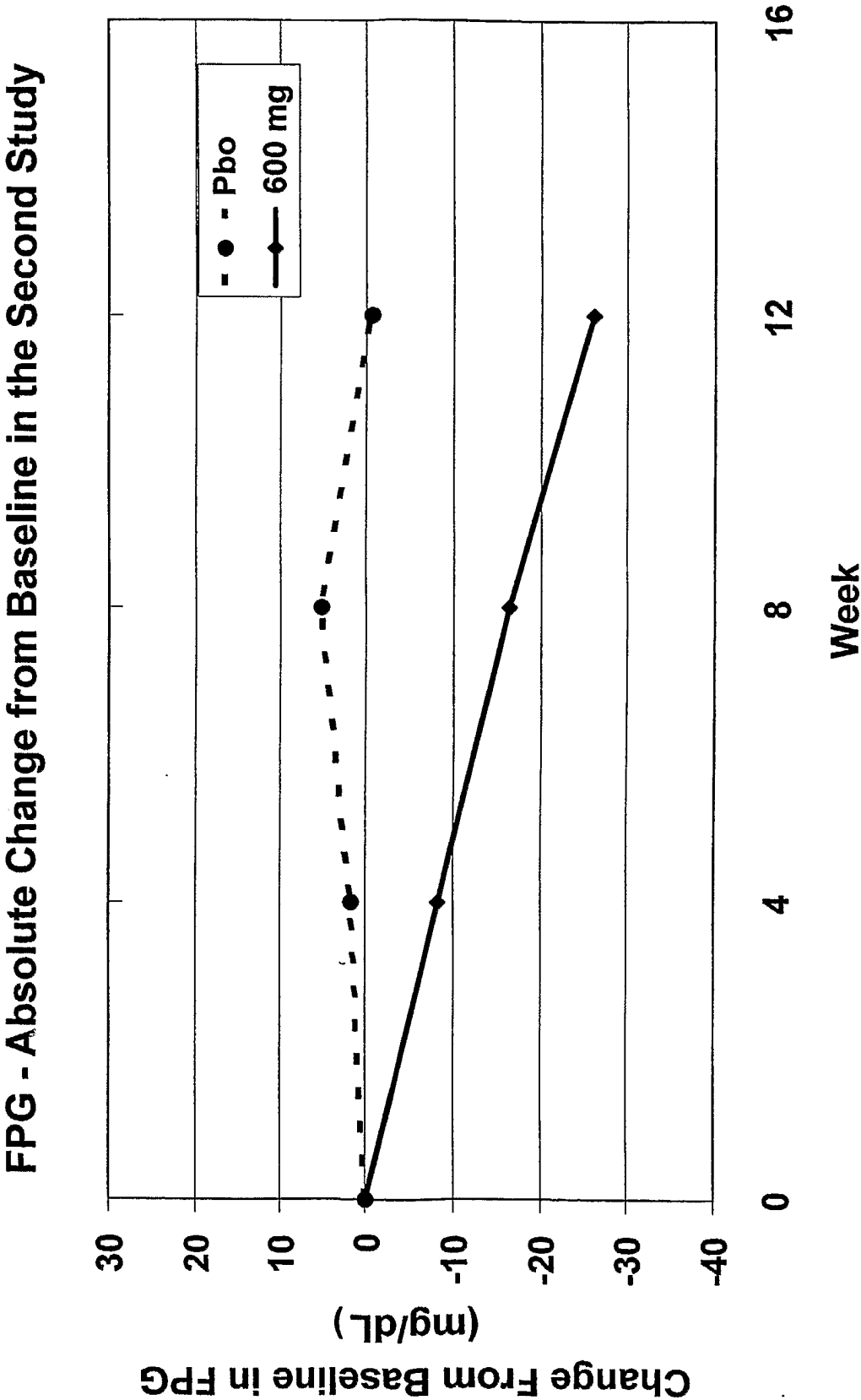


FIG. 11

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HbA1c - Absolute Change from Baseline in the Second Study

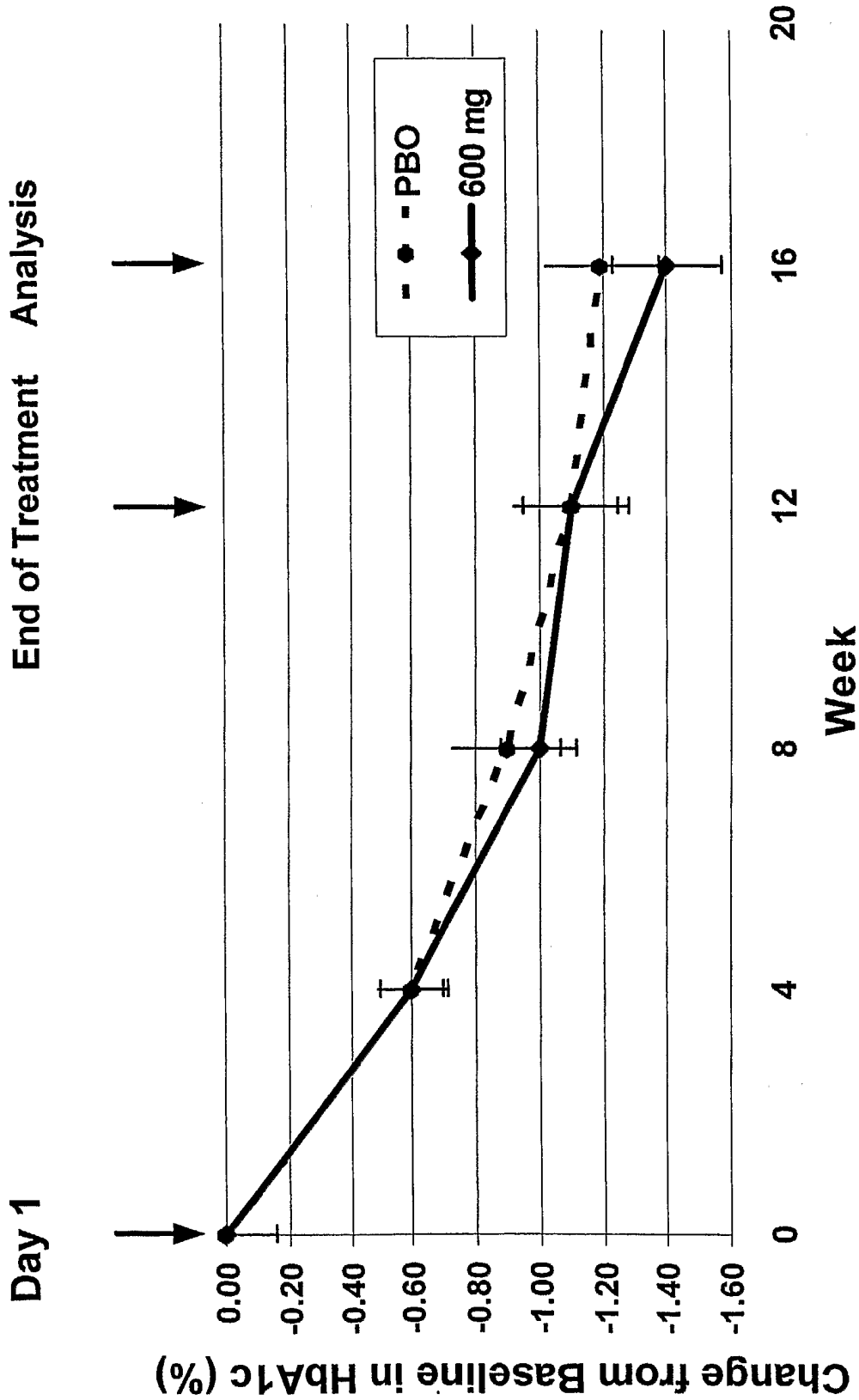


FIG. 12

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**HbA1c - Absolute Change from Baseline in
the Second Study (Minus Sites 60 & 70)**

35% of these patients showed HbA1c drops of $\geq 1.0\%$
(mean = 1.64%, range 1.1-2.7%), highly suggestive of
increased insulin use (protocol violation)

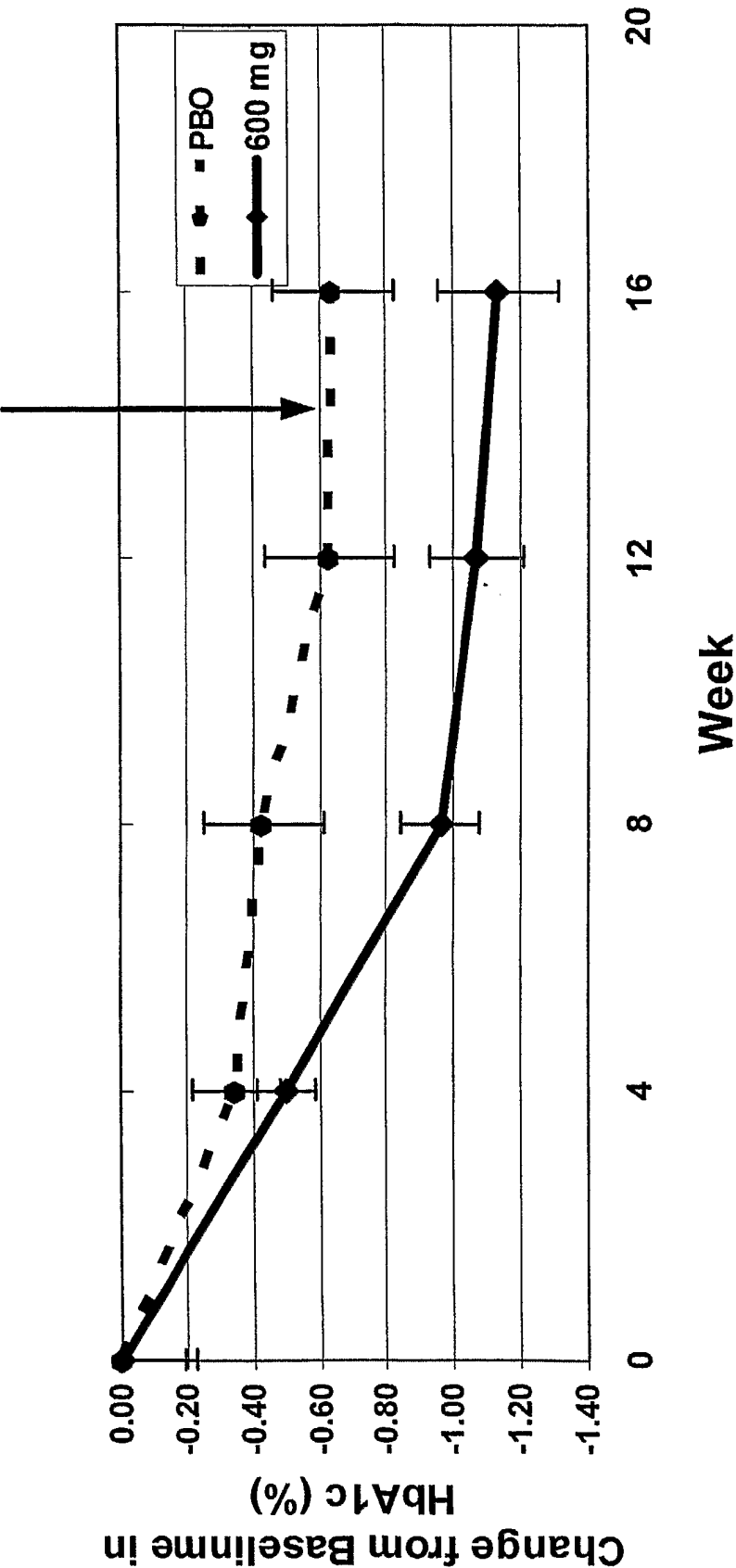


FIG. 13

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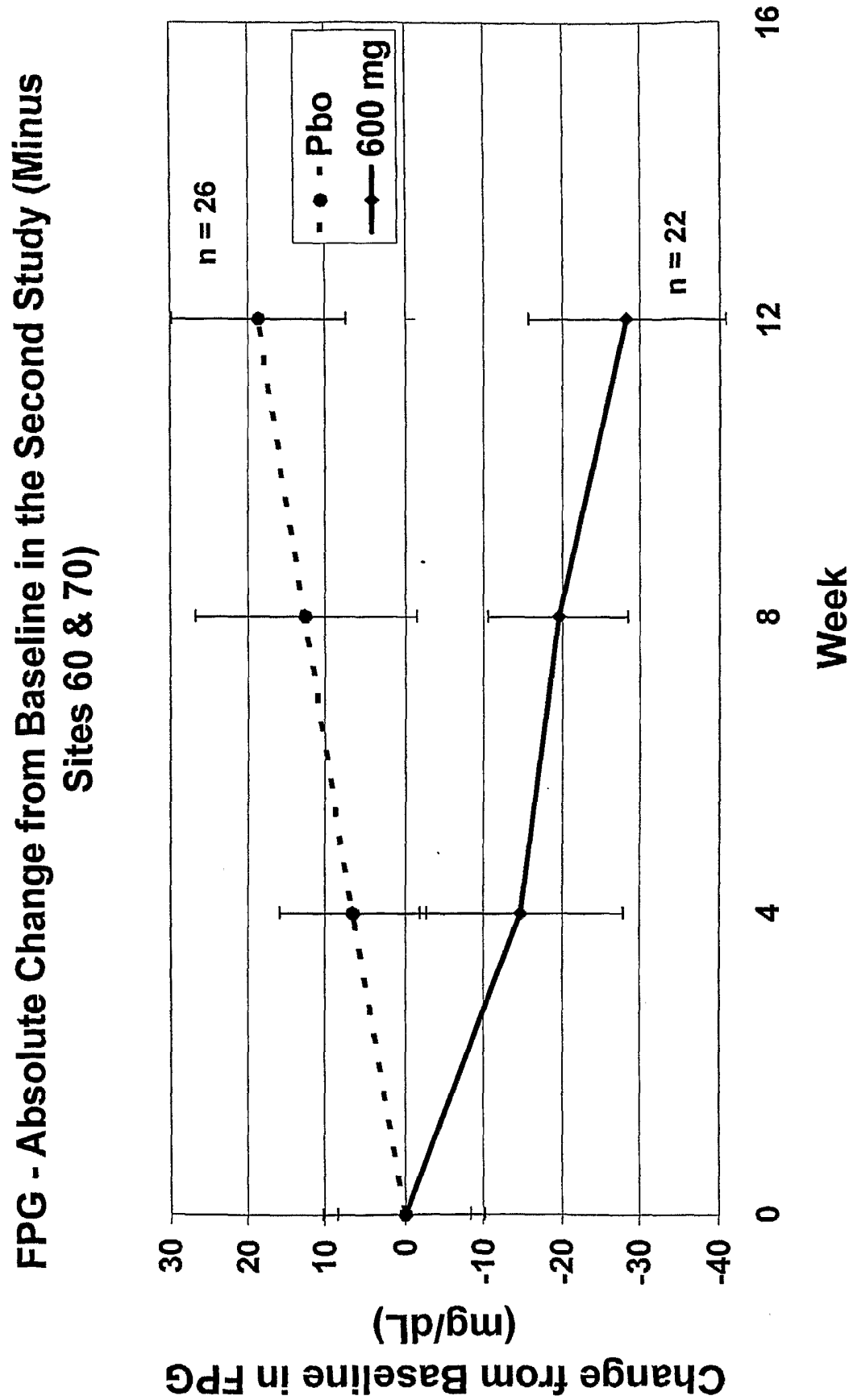


FIG. 14

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HbA1c - Absolute Change from Baseline in the First Study (Minus Sites 60 & 70)

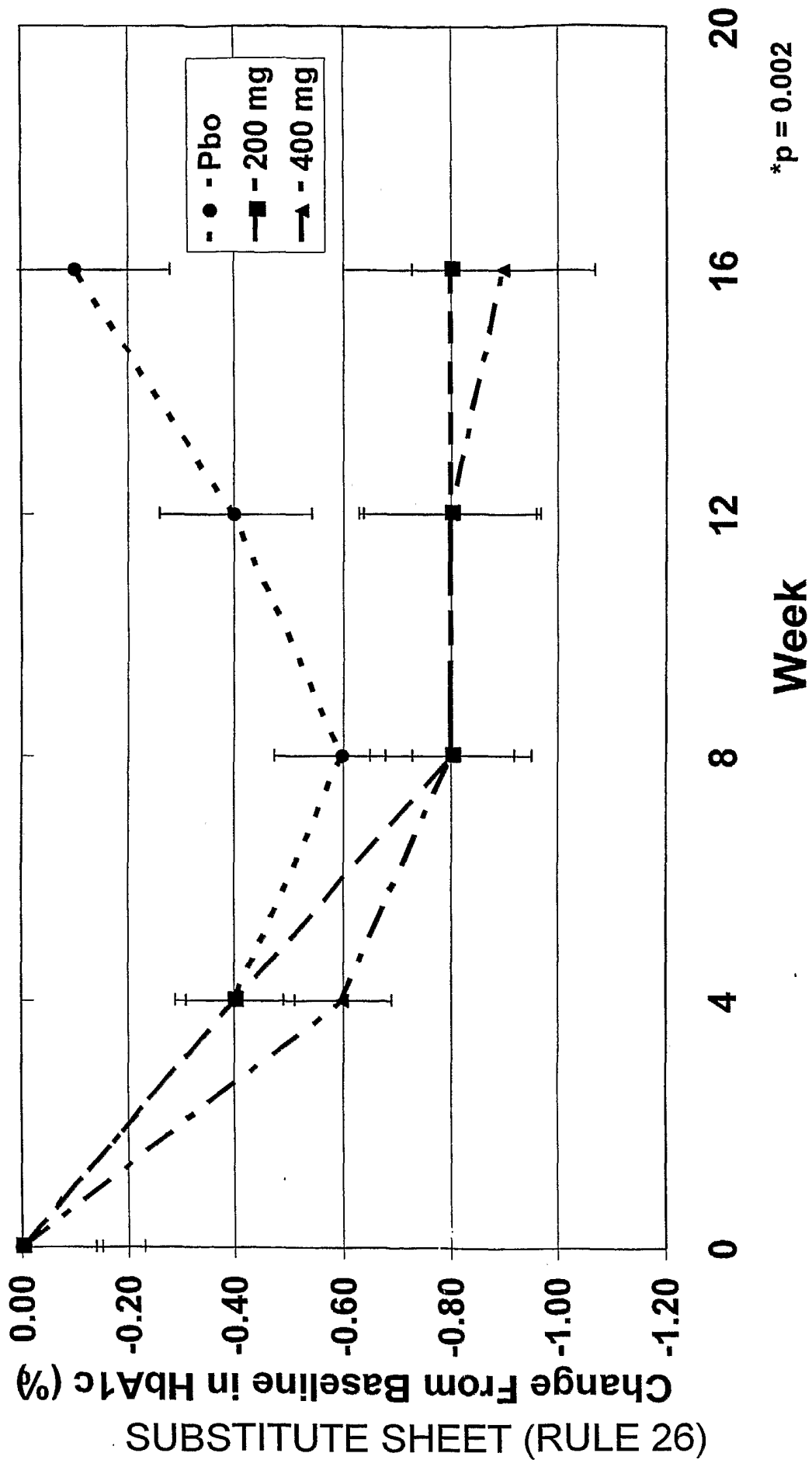
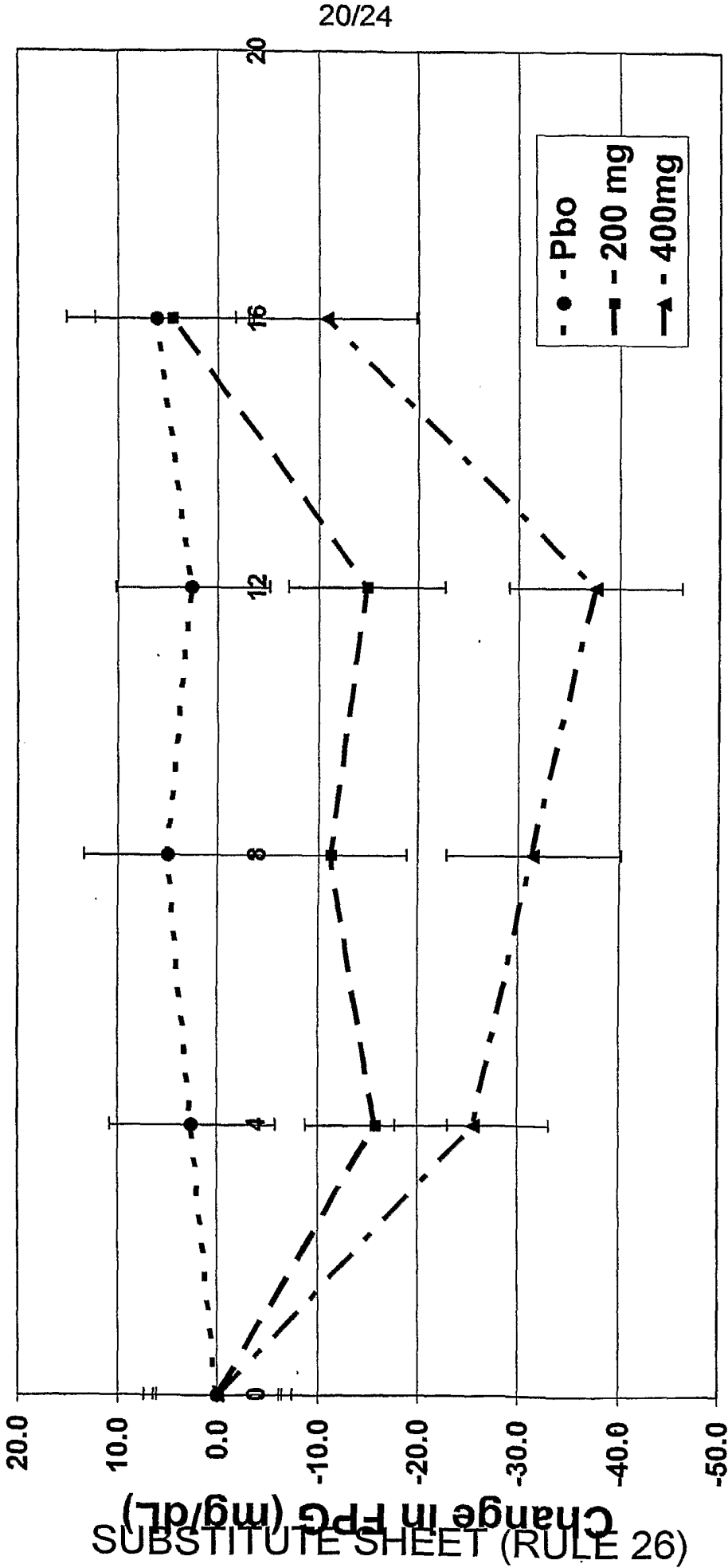


FIG. 15

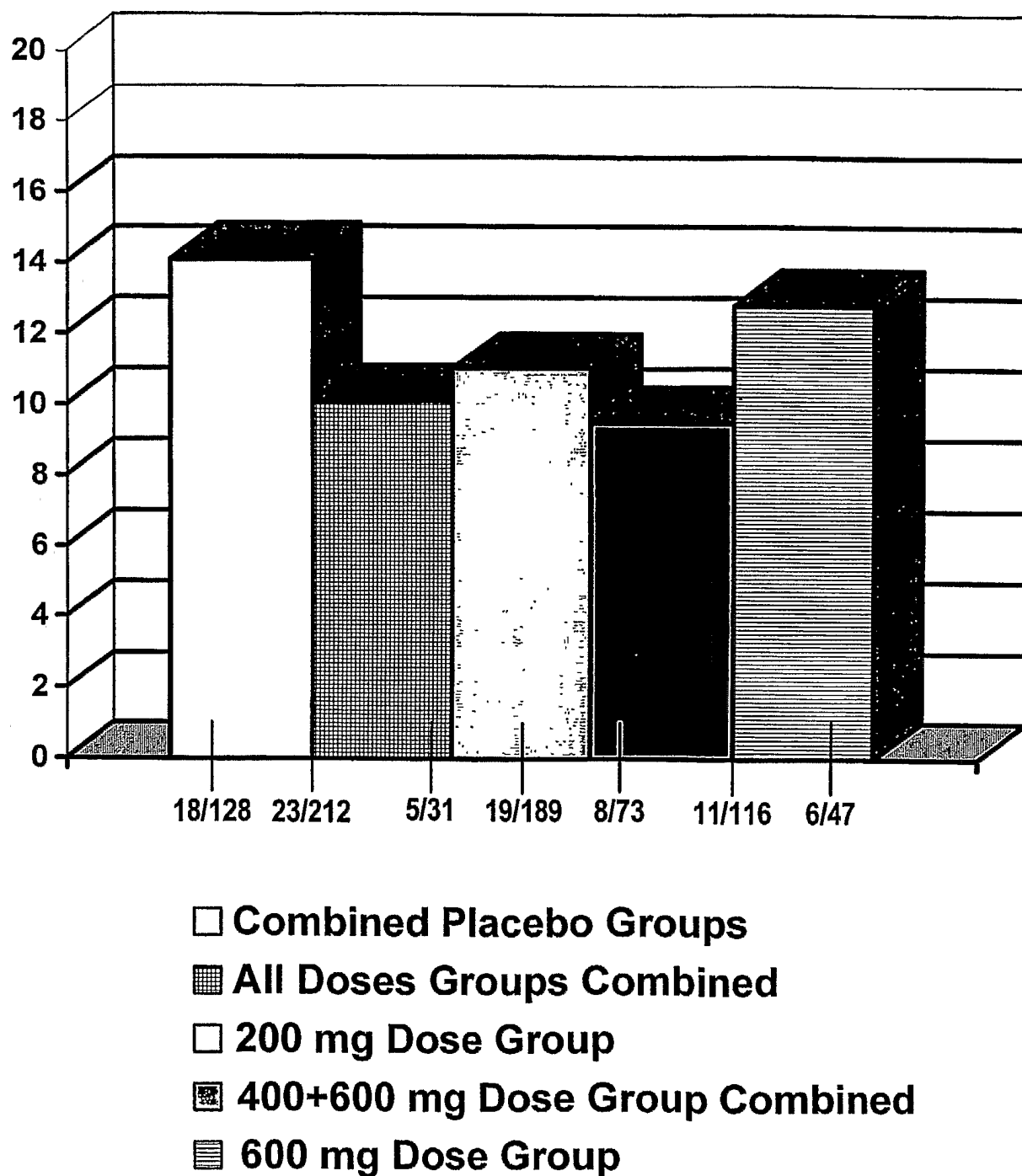
FPG - Absolute Change from Baseline in the First Study (Minus Sites 60 & 70)



Weeks
FIG. 16

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Combined Incidence of Edema in First and Second Phase 2 Studies

**FIG. 17**

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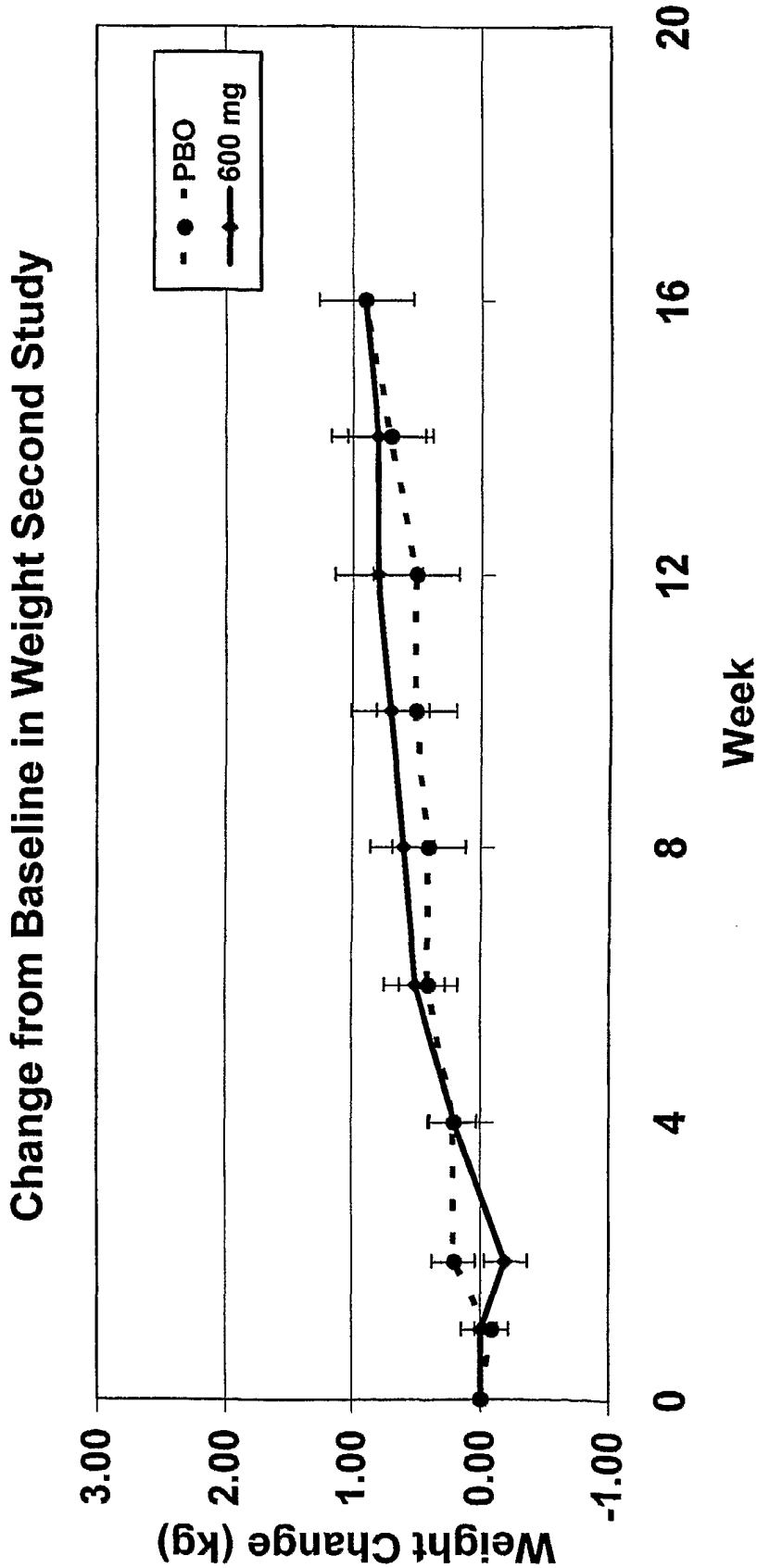
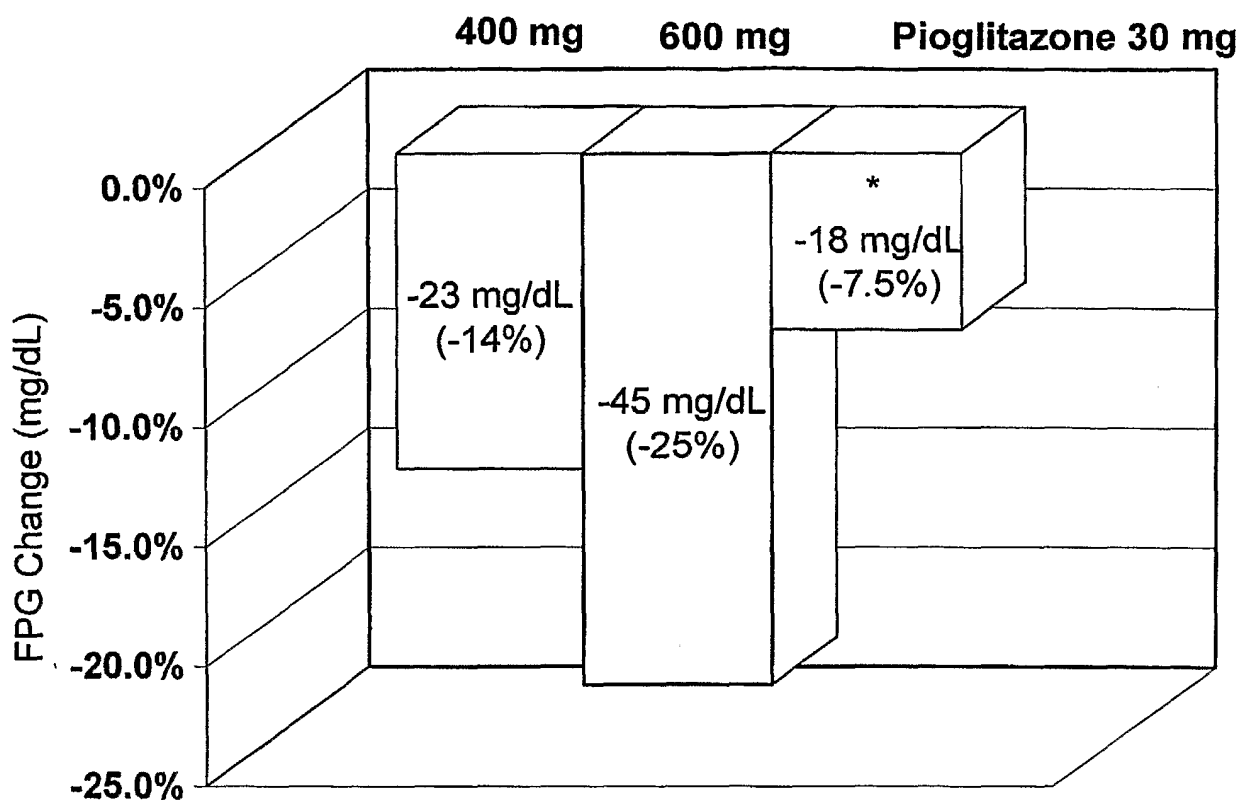


FIG. 18

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**Dose-dependent Decrease in FPG Relative
to Baseline in Glyburide Interaction Study
(14 Day Treatment)**

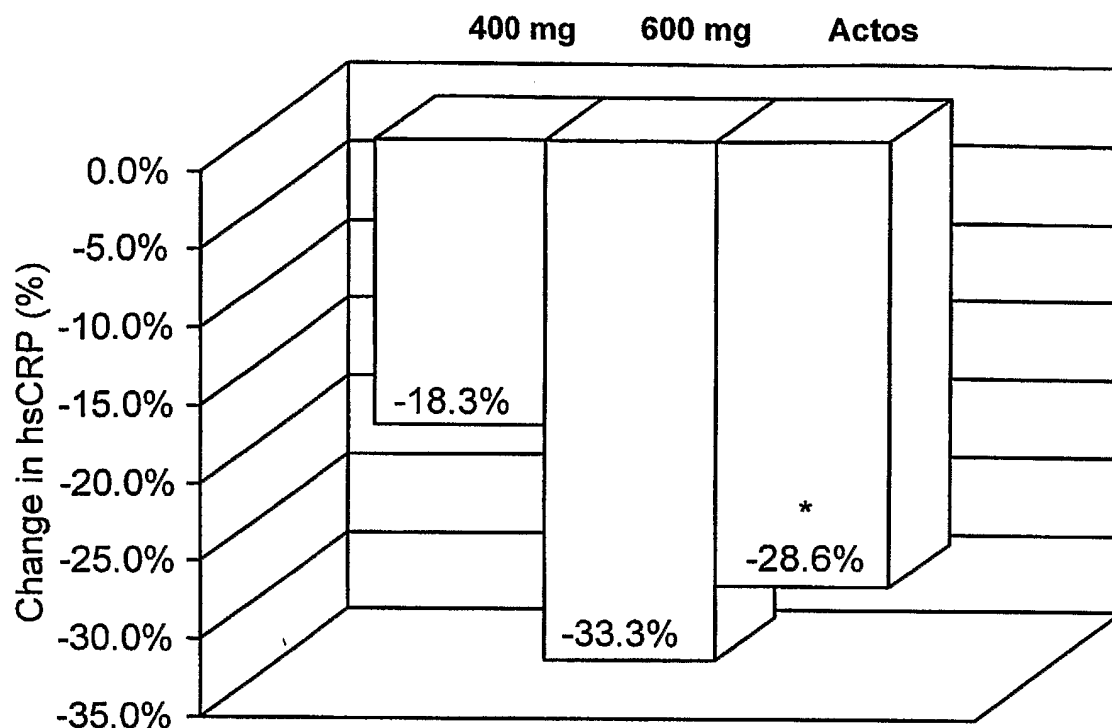


* 2 week data from 16 week study in Summary Basis of Approval

FIG. 19

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Dose-dependent Decrease in hsCRP (14 Day Treatment vs 3-6 months for Actos)



* Goldberg RB, et al. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. Diabetes Care 28(7):1547-54, 2005

FIG. 20