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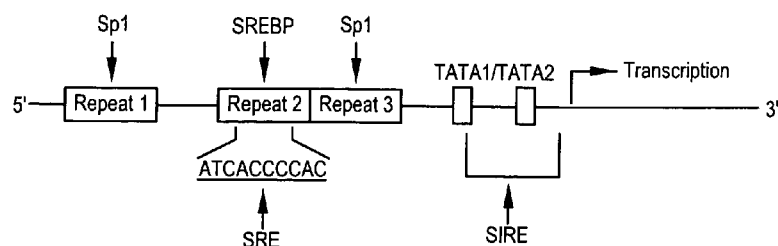
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ORDERS

FIG. 1



(57) Abstract: Methods and compositions containing a berberine related compound are provided for the prevention and treatment of metabolic and cardiovascular disorders including metabolic syndrome, hyperlipidemia, obesity, diabetes, insulin resistance, hyperglycemia, hypertension and elevated cholesterol in mammalian subjects. The methods and compositions of the invention are effective for prevention and treatment of metabolic syndrome, hyperlipidemia, obesity, diabetes, insulin resistance, hyperglycemia, hypertension and elevated cholesterol. Additional compositions and methods are provided which employ a berberine related or derivative compound including demethylated derivatives in combination with a second anti-therapeutic agent to yield more effective treatment tools against metabolic disorders, and/or dual activity therapeutic methods and formulations useful to prevent or reduce hyperlipidemia and/or hyperglycemia and one or more causal or related symptoms or conditions associated with hyperlipidemia and/or hyperglycemia in mammalian subjects.

METHODS AND COMPOSITIONS FOR THE TREATMENT OF METABOLIC AND CARDIOVASCULAR DISORDERS

Cross References to Related Applications

5 [0001] This application claims the priority benefit of United States Provisional patent application number 61/159,423, filed March 11, 2009, United States Provisional patent application number 61/159,427, filed March 11, 2009, and United States Provisional patent application number 61/159,429, filed March 11, 2009, each of which is incorporated herein by reference in its entirety.

Technical Field

10 [0002] The present invention relates to methods and compositions for treating metabolic and cardiovascular disorders such as hyperlipidemia, obesity, diabetes, insulin resistance, glucose intolerance, hyperglycemia, metabolic syndrome and hypertension, as well as conditions or complications associated with these metabolic and cardiovascular disorders in mammals.

Background

20 [0003] Metabolic disorders, particularly glucose and lipid regulatory disorders, are becoming increasingly prevalent as the populations in industrialized nations age and sedentary lifestyles become more common. Such disorders are frequently interrelated and are often predictors or results of each other. For example, diabetes is caused by a combination of insulin resistance and defective secretion of insulin by pancreatic- β cells. Individuals with insulin resistance often have abdominal obesity, dyslipidemia, hypertension, glucose intolerance and a prothrombotic state. This group of symptoms is commonly termed "Metabolic syndrome." Correspondingly, obese individuals as a whole are at higher risk for acquiring insulin resistance. The breakdown of a metabolic pathway thus can trigger myriad disorders such as hyperlipidemia, obesity, diabetes, insulin resistance, glucose intolerance, hyperglycemia, metabolic syndrome and hypertension which may in turn trigger further metabolic dysfunction putting individuals at risk for additional complications and premature morbidity.

30 [0004] Metabolic disorders that effect glucose and lipid metabolism such as hyperlipidemia, obesity, diabetes, insulin resistance, hyperglycemia, glucose intolerance, metabolic syndrome

and hypertension have long term health consequences leading to chronic conditions including cardiovascular disease and premature morbidity. Such metabolic and cardiovascular disorders may be interrelated, aggravating or triggering each other and generating feedback mechanisms that are difficult to interrupt.

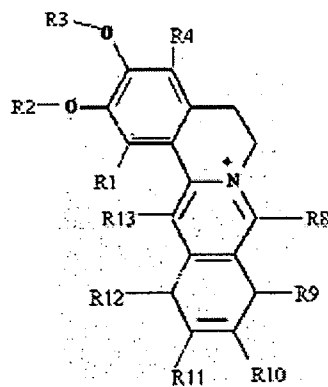
5 [0005] Current pharmaceutical treatments for metabolic and cardiovascular disorders include combinations of lipid-lowering drugs, hypoglycemic drugs, anti-hypertensive agents, diet and exercise. However, complicated therapeutic regimens can cause problems inherent to polypharmacy such as increased side effects, drug-drug interactions, failure of adherence, and increased medication errors. (Grundy, Nat Rev, Drug Discov 5 (4), 295-309 (2006)). There is
10 therefore a compelling, unmet need in the art to identify new compounds, formulations and methods to safely and effectively treat metabolic and cardiovascular disorders and conditions associated with metabolic disorders.

Summary of the Exemplary Embodiments of the Invention

15 [0006] It is therefore an object of the present invention to provide novel and improved compositions and methods for treating and managing metabolic and cardiovascular disorders in mammalian subjects, including humans.

[0007] The invention achieves these objects and satisfies additional objects and advantages by providing novel and surprisingly effective methods and compositions for treating and/or
20 preventing metabolic and cardiovascular disorders including, but not limited to, metabolic syndrome, hyperlipidemia, hypercholesterolemia, obesity, diabetes, insulin resistance, hyperglycemia, glucose intolerance and hypertension in mammalian subjects employing berberine and related compounds, derivatives, metabolites, prodrugs, and proto-berberine compounds and derivatives according to formula I, below.

25



Formula I

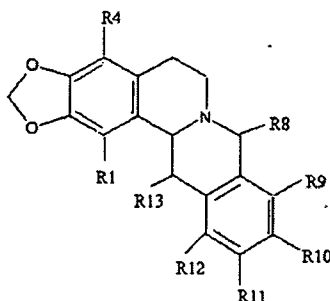
[0028] wherein each of R₁, R₂, R₃, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂ and/or R₁₃ may independently, collectively, or in any combination that yields an active (e.g., anti-dyslipidemic, anti-hyperlipidemic, anti-hyperglycemic, anti-hypertensive, LDL-modulatory, LDLR stability increasing, LDLR-modulatory, AMP-activated protein kinase modulatory or insulin receptor (InsR) modulatory) compound according to this disclosure, be a hydrogen, halogen, hydroxy, alkyl, alkoxy for example methoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, hydroxy, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, methylenedioxy, carbamyl, carbonylamino, alkylsulfonylamino, heterocyclo group, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, or oligosaccharide. For example, in some illustrative

embodiments, R₁, R₄, R₈, R₁₁, R₁₂ and R₁₃ are hydrogen and R₂, R₃, R₉ and R₁₀ are independently selected from hydrogen, hydroxy, methyl or methoxy. In some embodiments, R₂ and R₃ may together form a methylenedioxy group. When more than one R group is present, the R group may be selected from any of the stated groups so as to be the same or different. In other

certain exemplary embodiments, the following illustrative structural modifications according to Formula I above will be selected to provide useful candidate compounds for treating and/or preventing metabolic and cardiovascular disorders in mammalian subjects, e.g., wherein: additional candidate compounds for use within the compositions and methods will be readily

produced and selected according to the further disclosure provided herein below. Further description is provided in U.S. Patent Application No. 11/784,294 filed April 4, 2006 which claims priority to U.S. Patent Application No. 11/229,339 which claims priority to Chinese Patent Application No. 200410095066.X, filed November 23, 2004, and of Chinese Patent Application No. 200410078150.0, filed September 17, 2004, each of which is incorporated by reference herein in their entirety for all purposes. Exemplary candidate compounds in this context include compounds of Formula I, wherein: R₁ is selected from methyl, ethyl, hydroxyl, or methoxy; R₂ is selected from H, methyl, ethyl, methene; R₃ is selected from H, methyl, ethyl, methene; R₄ is selected from methyl, ethyl, hydroxyl, or methoxy; R₈ is selected from straight or branched (C1-C6) alkyl (e.g., substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl); R₉ is selected from methyl, ethyl, hydroxyl, methoxy, Cl, Br; R₁₀ is selected from methyl, ethyl, hydroxyl, Cl, Br, acetyl, tertiarybutylformylacetyl, 3-phenylacryloyl, chloroacetyl, chloroacetylpropanyl, straight or branched (C1-C8) alkyl, (e.g., substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl, tertbutyl formyl and 1-methyl-2ethylpropyl); R₁₁ is selected from methyl, ethyl, hydroxyl, Cl, Br; R₁₂ is selected from methyl, ethyl, hydroxyl, Cl, Br; and R₁₃ is selected from straight or branched (C1-C6) alkyl (e.g., substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl). Additional candidate compounds for use within the compositions and methods will be readily produced and selected according to the further disclosure provided herein below.

[0008] In one embodiment, compositions for use within the invention use the novel compound illustrated by Formula XXVII, below.



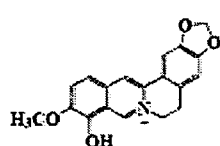
Formula XXVII

wherein each of R₁, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂ and/or R₁₃ may independently, collectively, or in any combination that yields an active (e.g., anti-dyslipidemic, anti-hyperlipidemic, anti-hyperglycemic, anti-cholesterolemic, anti-hypertensive, LDL-modulatory, LDLR-modulatory, LDLR stabilizing, AMP-activated protein kinase modulatory or insulin receptor (InsR) modulatory) compound according to this disclosure, be a hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, acetyl, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, formyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, alkylsulfonylamino, heterocyclo group, or oligosaccharide. When more than one R group is present, the R group may be selected from any of the stated groups so as to be the same or different. In certain exemplary embodiments, R₁, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂ and R₁₃ are each hydrogen.

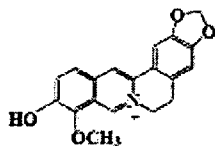
[0009] Useful berberine compounds, berberine-related compounds, berberine salts, berberine derivatives, berberine prodrugs, berberine metabolites, and proto-berberine compounds, salts, prodrugs, metabolites and derivatives, of any of the exemplary Formulae herein, within the formulations and methods of the invention include, but are not limited to, salts of berberine and related or derivative compounds, for example, berberine sulfate, berberine hydrochloride, berberine chloride, palmatine chloride, palmatine, oxyberberine, dihydroberberine, 8-cyanodihydroberberine, (-)-canadine, tetrahydroberberine N-oxide, tetrahydroberberine, N-methyltetrahydroberberinium iodide, 6-protoberberine, 9-ethoxycarbonyl berberine, 9-N,N-dimethylcarbamoyl berberine and 12-bromo berberine, berberine azide, and berberine betaine.

In one embodiment, berberine may be demethylated. In another embodiment, demethylated
beberine may be further reacted to form acetyl, terbutyl formyl, tertiarybutylformylacetyl, 3-
phenylacryloyl, chloracetyl or chloroacetylpropanyl forms of berberine. Other useful forms of
derivatives for use within the invention include other pharmaceutically acceptable active salts of
said compounds, as well as active isomers, enantiomers, polymorphs, glycosylated derivatives,
5 solvates, hydrates, and/or prodrugs of said compounds.

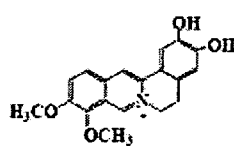
[0010] In alternate embodiments of the invention, compositions for use within the invention use metabolites of
berberine of the formulas VI to IX, below, as well as pharmaceutically acceptable active salts of said
compounds, active isomers, enantiomers, polymorphs, glycosylated derivatives, solvates,
10 hydrates, and/or prodrugs of said compounds.



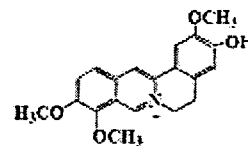
Berberrubine
Formula VI



Thalifendine
Formula VII

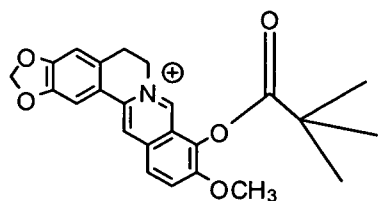


Demethyleneberberine
Formula VIII

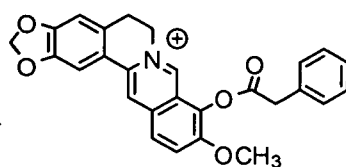


Jatrorrhizine
Formula IX

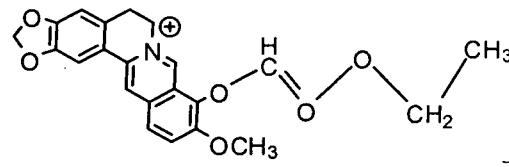
[0011] Exemplary prodrugs of berberrubine are shown in Formulas X-XIII, below.



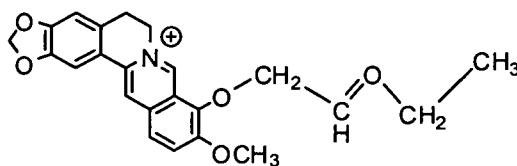
Formula X
713111



Formula XI
713112



Formula XII
713151



Formula XIII
713152

[0012] Useful berberine and related compounds, metabolites, prodrugs, and derivatives within
the formulations and methods of the invention include, but are not limited to, berberrubine,
thalifendine, demethyleneberberine, jatrorrhizine, as well as salts of berberine, other berberine

metabolites, related or derivative compounds, for example, berberine sulfate, berberine hydrochloride, berberine chloride, palmatine chloride, palmatine, oxyberberine, dihydroberberine, 8-cyanodihydroberberine, (-)-canadine, tetrahydroberberine N-oxide, tetrahydroberberine, N-methyltetrahydroberberinium iodide, 6-protoberberine, 9-ethoxycarbonyl
5 berberine, 9-N,N-dimethylcarbamoyl berberine and 12-bromo berberine, berberine azide, and berberine betaine.

[0013] In exemplary embodiments, the compositions and methods of the invention employ a berberine compound or a berberine related or derivative compound of Formula I or Formula XXVII to treat and/or prevent symptoms of metabolic and cardiovascular disorders or another
10 disease or condition associated with metabolic disorders, such as a cardiovascular disease.

[0014] Mammalian subjects amenable for treatment with berberine compounds, berberine-related compounds, berberine salts, berberine derivatives, berberine prodrugs, berberine metabolites, and proto-berberine compounds, salts, prodrugs, metabolites and derivatives, of any of the exemplary Formulae herein (collectively referred to herein as the “active compound”),
15 according to the methods of the invention include, but are not limited to, subjects with hyperlipidemia and subjects with elevated cholesterol and/or elevated triglycerides, including subjects presenting with, or at elevated risk for developing, elevated LDL, elevated cholesterol, and/or elevated triglyceride levels; subjects with hyperglycemia; subjects with elevated blood glucose levels; subjects with diabetes; subjects with insulin resistance; subjects with elevated
20 blood pressure; subjects with obesity; subjects with decreased insulin sensitivity; subjects in a prothrombotic state; subjects in a proinflammatory state.

[0015] These and other subjects are effectively treated, prophylactically and/or therapeutically, by administering to the subject a metabolic correcting effective amount (or, alternatively, an anti-dyslipidemic, anti-hyperlipidemic, anti-cholesterolemic, anti-hyperglycemic, anti-hypertensive,
25 LDL-modulatory, LDLR-modulatory, LDLR stabilizing, insulin receptor (InsR) modulatory, AMP-activated protein kinase modulatory effective amount) of any of the berberine “active compounds”, including any of the herein described berberine compounds, berberine-related compounds, berberine salts, berberine derivatives, berberine prodrugs, berberine metabolites, and proto-berberine compounds, salts, prodrugs, metabolites and derivatives, including but not
30 limited to active compounds of any of the exemplary Formulae herein, sufficient to prevent or reduce metabolic and cardiovascular disorders including metabolic syndrome, hyperlipidemia,

obesity, diabetes, hypercholesterolemia, insulin resistance, hyperglycemia, and hypertension or one or more disease symptoms or conditions associated with metabolic and cardiovascular disorders (or, alternatively, to elicit an anti-dyslipidemic, anti-hyperlipidemic, anti-hyperglycemic, anti-hypertensive, anti-cholesterolemic, anti-metabolic disorder, LDL-modulatory, LDLR-modulatory, LDLR stabilizing, AMP-activated protein kinase modulatory or InsR modulatory response) in the subject. The therapeutically useful methods and formulations of the invention will effectively use a subject compound as noted above, including any active, pharmaceutically acceptable salt of said compounds, as well as active isomers, metabolites, enantiomers, polymorphs, solvates, hydrates, prodrugs, and/or combinations thereof. Berberine is employed as an illustrative embodiment of the invention within the examples herein below.

[0016] In additional embodiments of the invention, mammalian subjects are effectively treated, prophylactically and/or therapeutically, by administering to the subject a cholesterol-controlling effective amount of any of the berberine compounds, berberine-related compounds, berberine salts, berberine derivatives, berberine prodrugs, berberine metabolites, and proto-berberine compounds, salts, prodrugs, metabolites and derivatives, including a compound of any of the exemplary Formulae herein, sufficient to prevent or reduce elevated cholesterol, or one or more associated symptoms or condition(s), in the subject. These therapeutically useful methods and formulations of the invention may likewise employ berberine, a berberine related compound, metabolite, prodrug, or derivative compound, i.e., any of the herein described “active compounds” (including any of these compounds’ pharmaceutically acceptable salts, isomers, enantiomers, polymorphs, solvates, hydrates, prodrugs, and/or combinations thereof).

[0017] Within additional aspects of the invention, combinatorial formulations and methods are provided which employ an effective amount of any of the active berberine compounds (i.e., any of the subject berberine compounds, berberine-related compounds, berberine salts, berberine derivatives, berberine prodrugs, berberine metabolites, and proto-berberine compounds, salts, prodrugs, metabolites and derivatives, including a compound of any active compound of any of the exemplary Formulae described herein) in combination with one or more secondary or adjunctive active agent(s) that is/are combinatorially formulated or coordinately administered with the subject compound to yield lipid lowering and/or glucose lowering effective response (or, alternatively, an anti-dyslipidemic, anti-hyperlipidemic, anti-hypercholesterolemic, anti-hyperglycemic, anti-metabolic syndrome, insulin sensitivity increasing, insulin resistance

decreasing, anti-diabetic, anti-obesity, anti-hypertensive, anti-metabolic disorder, LDL-modulatory, LDLR-modulatory, LDLR stabilizing, AMP-activated protein kinase modulatory or InsR modulatory response) in the subject. Exemplary combinatorial formulations and coordinate treatment methods in this context employ the subject compound in combination with one or more additional, lipid and/or glucose lowering agent(s) or other indicated, secondary or adjunctive therapeutic agents. The secondary or adjunctive therapeutic agents used in combination with, e.g., berberine in these embodiments may possess direct or indirect lipid and/or glucose lowering activity and/or hypertension decreasing activity, including cholesterol lowering activity, insulin resistance decreasing activity, insulin sensitivity increasing activity or glucose regulating activity, alone or in combination with, e.g., berberine, or may exhibit other useful adjunctive therapeutic activity in combination with, e.g., berberine.

[0018] Useful adjunctive therapeutic agents in these combinatorial formulations and coordinate treatment methods include, for example, anti-hyperlipidemic agents; anti-dyslipidemic agents; plasma HDL-raising agents; anti-hypercholesterolemic agents, including, but not limited to, cholesterol-uptake inhibitors; cholesterol biosynthesis inhibitors, e.g., HMG-CoA reductase inhibitors (also referred to as statins, such as lovastatin, simvastatin, pravastatin, fluvastatin, rosuvastatin, pitavastatin, and atorvastatin); HMG-CoA synthase inhibitors; squalene epoxidase inhibitors or squalene synthetase inhibitors (also known as squalene synthase inhibitors); acyl-coenzyme A cholesterol acyltransferase (ACAT) inhibitors, including, but not limited to, melinamide; probucol; nicotinic acid and the salts thereof; niacinamide; cholesterol absorption inhibitors, including, but not limited to, β -sitosterol or ezetimibe; bile acid sequestrant anion exchange resins, including, but not limited to cholestyramine, colestipol, colesevelam or dialkylaminoalkyl derivatives of a cross-linked dextran; LDL receptor inducers; fibrates, including, but not limited to, clofibrate, bezafibrate, fenofibrate and gemfibrozil; vitamin B6 (also known as pyridoxine) and the pharmaceutically acceptable salts thereof, such as the HCl salt; vitamin B12 (also known as cyanocobalamin); vitamin B3 (also known as nicotinic acid and niacinamide, supra); anti-oxidant vitamins, including, but not limited to, vitamin C and E and betacarotene; angiotensin II receptor (AT₁) antagonist, renin inhibitors; platelet aggregation inhibitors, including, but not limited to, fibrinogen receptor antagonists, i.e., glycoprotein IIb/IIIa fibrinogen receptor antagonists; hormones, including but not limited to, estrogen; insulin; ion exchange resins; omega-3 oils; benfluorex; ethyl icosapentate; and amlodipine; appetite-

suppressing agents or anti-obesity agents including, but not limited to, insulin sensitizers, protein tyrosine phosphatase-1B (PTP-1B) inhibitors, dipeptidyl peptidase IV (DP-IV) inhibitors, insulin or insulin mimetics, sequestrants, nicotinic alcohol, nicotinic acid, PPAR α agonists, PPAR γ agonists including, but not limited to glitazones, PPAR α / γ dual agonists, inhibitors of
5 cholesterol absorption, acyl CoA:cholesterol acyltransferase inhibitors, anti-oxidants, anti-obesity compounds, neuropeptide Y5 inhibitors, β_3 adrenergic receptor agonists, ileal bile acid transporter inhibitors, anti-inflammatories and cyclo-oxygenase 2 selective inhibitors; insulin; sulfonylureas, including but not limited to chlorpropamide, glipizide, glyburide, and glimepiride; DPP-4 blockers; biguanides, including but not limited to metformin; thiazolidinediones including
10 but not limited to rosiglitazone, troglitazone and pioglitazone; alpha-glucosidase inhibitors, including, but not limited to, acarbose and meglitol; cannabinoid antagonists, including, but not limited to rimonabant; camptothecin and camptothecin derivatives, D-phenylalanine derivatives; meglitinides; diuretics including, but not limited to, methyclothiazide, hydroflumethiazide, metolazone, chlorothiazide, methyclothiazide, hydrochlorothiazide, quinethazone,
15 chlorthalidone, trichlormethiazide, bendroflumethiazide, polythiazide, hydroflumethiazide, spironolactone, triamterene, amiloride, bumetanide, torsemide, ethacrynic acid, furosemide; beta-blockers including, but not limited to acebutolol, atenolol, betaxolol, bisoprolol, carteolol, metoprolol, nadolol, pindolol, propranolol, and timolol; angiotensin-converting enzyme (ACE) inhibitors including, but not limited to, benazepril, captopril; enalapril, fosinopril, lisinopril,
20 moexipril, perindopril, quinapril, ramipril, andtrandolapril; calcium channel blockers including, but not limited to, amlodipine, diltiazem, felodipine, isradipine, nicardipine sr, nifedipine er, nisoldipine, and verapamil; vasodilators including, but not limited to, nitric oxide, hydralazine, and prostacyclin; angiotensin II receptor blockers including, but not limited to, andesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan; alpha blockers including,
25 but not limited to, doxazosin, prazosin and terazosin; alpha 2 agonists including, but not limited to clonidine and guanfacine. Such agents may be referred to in whole or in part as metabolic disorder therapeutics, metabolic syndrome therapeutics, anti-obesity therapeutics, anti-hypercholesterolemia therapeutics, anti-diabetic therapeutics, insulin resistance therapeutic agents, anti-hyperglycemia agents, anti-hyperlipidemia agents, insulin sensitivity increasing
30 agents, anti-hypertensive agents, and/or blood glucose lowering therapeutic agents. Adjunctive therapies may also be used including, but not limited, physical treatments such as changes in

diet, psychological counseling, behavior modification, exercise and surgery including, but not limited to, gastric partitioning procedures, jejunoileal bypass, stomach stapling, gastric bands, vertical banded gastroplasty, laparoscopic gastric banding, roux-en-Y gastric bypass, biliopancreatic bypass procedures and vagotomy. Some herbal remedies may also be employed effectively in combinatorial formulations and coordinate therapies for treating metabolic disorders, for example curcumin, gugulipid, garlic, vitamin E, soy, soluble fiber, fish oil, green tea, carnitine, chromium, coenzyme Q10, anti-oxidant vitamins, grape seed extract, pantothenic, red yeast rice, and royal jelly.

[0019] The forgoing objects and additional objects, features, aspects and advantages of the instant invention will become apparent from the following detailed description.

Brief Description of the Drawings

[0020] Figure 1 is a drawing of the promoter region of the LDL receptor gene. Three direct repeats and two TATA-like sequences are identified with the promoter region. The cis-acting element of sterols is located on repeat 2, whereas the regulatory element for cytokine OM (SIRE) overlaps the TATA-like sequences.

[0021] Figure 2 is a schematic representation of intracellular regulation of LDL receptor gene expression, including regulation by berberine.

[0022] Figures 3 A and B are quantitative RT-PCR of LDLR mRNA levels in human liver BEL-7402 cells twenty-four hours after being treated with berberine (A) or berberine sulfate (B).

[0023] Figure 4 is a measurement using flow cytometry of the concentration of the protein level of LDLR expressed on the cell surface of BEL-7402 cells twenty-four hours after treatment with 15µg/ml of berberine (BBR).

[0024] Figures 5 A-C are charts of the decrease in serum cholesterol (A) and LDL (B) in hamsters after treatment with varying concentrations of berberine (BBR) and the decrease of LDL as a function of time (C).

[0025] Figure 6 is a depiction of the concentration of total LDLR mRNA and protein extracts as measured by quantitative real time RT-PCR (A) and Western blot (B) in hamsters sacrificed four hours after the last treatment with berberine.

[0026] Figure 7 is a Western Blot showing the concentration of the precursor (P) and mature (M) forms of SREBP2 using a monoclonal antibody to SREBP2 in HepG2 cells.

[0027] Figure 8 is (A) a northern blot showing LDLR expression in HepG2 cells treated with either lovastatin (Lov) alone or in combination with berberine (BBR) for 24 hours and (B) a chart of real-time RT-PCR of the same cells.

[0028] Figure 9 is a chart showing the increase in LDLR promoter activity in the presence of Berberine (BBR), GW707 (GW), and oncostatin M (OM).

[0029] Figure 10 is (A) a northern blot showing concentrations of LDLR mRNA in HepG2 cells treated with berberine (BBR) in the presence of different lengths of time of actinomycin D treatment and (B) a plot of normalized LDLR mRNA signals as a percentage of LDLR mRNA remaining.

[0030] Figure 11 is a schematic representation of the *LDLR* mRNA 3' UTR and the chimeric Luc-LDLR 3' UTR constructs.

[0031] Figure 12 is a northern blot of analysis of Luc-LDLR fusion mRNA in (A) control cells and cells treated with (B) berberine or dimethylsulfoxide (C) as a control.

[0032] Figure 13 is a schematic representation of the constructs containing the deletions of ARE and UCAU motifs (B) and a chart illustrating the responses of the wt pLuc/UTR-2 and deletion constructs to berberine treatment as determined by real-time RT-PCR analysis.

[0033] Figure 14 is a western blot of cellular proteins harvested from (A) Bel-7402 cells or (B) HepG2 cells that were untreated or treated with berberine (BBR) at a dose of 5 µg/ml for different lengths of time as indicated and (C) a western blot of HepG2 cells treated for 1 hour at the indicated concentrations.

[0034] Figure 15 (A) is a chart depicting a dose dependent increase in the expression of InsR mRNA in human hepatoma cells treated with berberine as measured using real time PCR and (B) confirmed by slot blot.

[0035] Figure 16 (A) is a chart depicting the time-dependent effect of berberine on InsR mRNA expression in human hepatoma cells over 24 hours as confirmed by (B) slot blot.

[0036] Figure 17 (A-F) are graphs depicting increased cell surface InsR expression in Caucasian liver cell line HepG2 when treated with (A) IgG, (B) 0 µg/ml of berberine, (C) 2.5 µg/ml of berberine, (D) 5 µg/ml of berberine, (E) 10 µg/ml of berberine, and (F) 15 µg/ml of berberine.

[0037] Figure 18 (A-F) are graphs depicting increased cell surface InsR expression in Asian liver cell line Bel-7402 when treated with (A) IgG, (B) 0 µg/ml of berberine, (C) 2.5 µg/ml of berberine, (D) 5 µg/ml of berberine, (E) 10 µg/ml of berberine, and (F) 15 µg/ml of berberine.

[0038] Figure 19 (A-B) are charts showing that (A) berberine increases glucose consumption in the presence of InsR expression and insulin and that (B) silencing InsR expression abolishes the glucose consumption effect.

[0039] Figure 20 (A-D) are charts showing that treatment of human liver cells with 7.5 µg/ml of berberine increases the surface expression of both InsR and LDLR over time.

[0040] Figure 21 (A-B) are (A) a slot blot of the amount of InsR mRNA in HepG2 cells untreated (column C) or treated with berberine (column BBR) and then treated with actinomycin and normalized with ACTB and (B) a chart of the data plotted as a the percentage of the InsR mRNA remaining.

[0041] Figure 22 is a chart showing the dose dependent increase of Luc mRNA in pGL3-1.5kIRP transfected cells incubated with varying concentrations of berberine (BBR) for eight hours.

[0042] Figure 23 is a chart showing RT-PCR measurements of the amount of InsR and LDLR mRNA in HepG2 cells treated with calphostin (Cal), berberine (BBR) or a combination of calphostin and berberine.

[0043] Figure 24 is a chart showing the relative amounts of InsR and LDLR mRNA as measured by RT-PCR in HepG2 cells treated with U0126 (U), berberine (BBR) or a combination of U0126 and berberine.

[0044] Figure 25 (A) is a picture of a gel of phosphorylated and nonphosphorylated substrates in cell lysates of HepG2 cells treated with berberine (BBR) for 0, 0.25, 1, 2, and 4 hours and (B) a chart of the quantification of protein kinase C (PKC) activity using densitometry and expressed as the number of picomoles of phosphate transferred to the substrate per minute per milligram of sample protein.

[0045] Figure 26 is a chart showing luciferase activity representing normalized InsR promoter activity in pGL3-1.5kIRP transfected HepG2 cells treated with calphostin (Cal), berberine (Ber), phorbol 12-myristate 13-acetate (PMA) or combinations as shown.

[0046] Figure 27 is a graph of the decline in the fasting blood glucose of hyperglycemic rats treated with berberine (BBR).

[0047] Figure 28 is a chart of liver InsR and LDLR mRNA of rats treated with berberine (BBR) as calculated by RT-PCR.

[0048] Figure 29 is a chart of dose-dependent induction of InsR mRNA expression in HepG2 cells incubated with berberine for eight hours as measured by RT-PCR with the amount of InsR

mRNA in untreated cells defined as “1” and the amounts of InsR mRNA from berberine (BBR) treated cells plotted relative to that value.

[0049] Figure 30 (A) is a picture of a gel showing the phosphorylated and nonphosphorylated substrates in cell lysates of liver samples of rats treated with berberine (BBR) and (B) a chart of the quantification of PKC activity using densitometry and expressed as the number of picomoles of phosphate transferred to the substrate per minute per milligram of sample protein.

[0050] Figure 31 is a chart showing the decrease in the level of fasting serum insulin in hyperglycemic rats on a high fat and high cholesterol (HFHC) diet when they were treated with berberine (BBR).

[0051] Figure 32 is a chart of the increase in insulin sensitivity index (ISI) in hyperglycemic rats on a four week HFHC diet when treated with berberine (BBR).

[0052] Figure 33 is a chart of the decrease in serum lipid levels in hyperlipidemic rats treated with varying concentrations of berberine (BBR).

[0053] Figure 34 is a schematic of InsR and LDLR expression and their upregulation by berberine (BBR).

[0054] Figure 35 is a chart of serum insulin levels in hyperglycemic patients as measured before and after two months of therapy with berberine.

[0055] Figure 36 is a chart of InsR expression on the surface of peripheral blood lymphocytes (PBL) of hyperglycemic patients as measured before and after two months of therapy with berberine.

[0056] Figure 37 (A-H) are charts showing the negative correlation between InsR expression on the surface of peripheral blood lymphocytes and fasting blood glucose levels in eight patients 0, 15 and 60 days after treatment with berberine.

[0057] Figure 38 is a diagram of cholesterol synthesis by the body.

[0058] Figure 39 is a chart depicting the effect of various amounts of berberine (BBR) and demethylberberine (L101) on LDLR mRNA levels in cells from the human hepatoma cell line HepG2.

[0059] Figure 40 is a chart depicting LDL changes in LDL-R mRNA levels in human hep G2 cells treated with berberine and berberine metabolites.

[0060] Figure 41 is a chart depicting an increase in insulin receptor activity in human hepG2 cells treated with berberine and berberine metabolites.

[0061] Figure 42 is a chart depicting the increase in the production of LDL receptors and INS receptors in cells treated with berberine and berberine metabolites.

5 Detailed Description of Exemplary Embodiments of the Invention

[0062] The instant invention provides novel methods and compositions for preventing and/or treating metabolic and cardiovascular disorders including but not limited to metabolic syndrome, hyperlipidemia, hypercholesterolemia, obesity, diabetes, insulin resistance, hyperglycemia, hypertension and elevated cholesterol in mammalian subjects, including individuals and *in vitro*,
10 *ex vivo*, and *in vivo* mammalian cells, tissues, and organs. In various embodiments, the methods and compositions are effective to prevent or treat diseases caused by metabolic and cardiovascular disorders including cardiovascular disease.

[0063] As used herein, the term “cardiovascular disease” is intended to include a range of symptoms, conditions, and/or diseases including atherosclerosis, coronary artery disease,
15 pulmonary embolism, diabetic cardiomyopathy, angina pectoris, carotid artery disease, strokes, peripheral vascular disease, cerebral arteriosclerosis, myocardial infarction, high blood pressure, cerebral infarction, restenosis following balloon angioplasty, intermittent claudication, dyslipidemia post-prandial lipidemia and xanthoma, and all conventionally targeted symptoms arising from or associated with the foregoing diseases and conditions.

[0064] Active compounds and formulations of the invention, including anti-metabolic disorder
20 compounds and formulations, employ any of the “active compounds” described herein, selected from berberine compounds, berberine-related compounds, berberine salts, berberine derivatives, berberine prodrugs, berberine metabolites, and proto-berberine compounds, salts, prodrugs, metabolites and derivatives, of any of the exemplary Formulae herein, including glycosylated
25 derivatives, demethylated derivatives, and all active pharmaceutically acceptable salts, solvates, isomers, enantiomers, polymorphs, metabolites and prodrugs of these compounds and combinations thereof.

[0065] In exemplary embodiments, “active compounds” for use within any of the herein-described aspects, examples or embodiments of the invention may be selected from any of the
30 active compounds represented within any of the distinct exemplary classes of compounds

described by Formulae I-XIII, XXVI-XXVIII, or XXXII-XXXVI, including any of the species within these distinct classes of active compounds.

[0066] Active compounds of the invention can be employed as novel glucose or lipid lowering agents. Lipid lowering formulations and methods provided herein, including cholesterol

5 lowering formulations and methods and triglyceride lowering formulations, employ berberine, a berberine related compound, berberine metabolite, berberine prodrug, or berberine derivative compound of any of the Formulae herein, such as Formula I or Formula II, including but not limited to, metabolites of berberine of any of formulae VI-IX, active compounds of Formulae I-V, XXVI-XXVIII, or XXXII-XXXVI, including any of the species within these distinct classes
10 of active compounds above, including glycosylated derivatives, and demethylated derivatives, all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, derivatives including glycosylated derivatives, salts, solvates, isomers, enantiomers, polymorphs, metabolites and prodrugs of these compounds, and combinations thereof, as novel lipid lowering agents.

15 **[0067]** Glucose lowering formulations and methods provided herein employ berberine, a berberine related compound, berberine metabolite, berberine prodrug, or berberine derivative compound of any of the Formulae herein, such as Formula I or Formula II, any active compound of formulae VI-IX, any active compound of Formulae I-V, XXVI-XXVIII, or XXXII-XXXVI, including any of the species within these classes of active compounds (encompassing all
20 complexes, salts, solvates, isomers, enantiomers, polymorphs, metabolites and prodrugs of these compounds and combinations thereof) as novel glucose lowering agents.

[0068] Insulin sensitivity increasing formulations and methods provided herein employ berberine, a berberine related compound, berberine metabolite, berberine prodrug, or berberine derivative compound of any of the Formulae herein, such as Formula I or Formula II, any active
25 compound of formulae VI-IX, any active compound of Formulae I-V, XXVI-XXVIII, or XXXII-XXXVI, including any of the species within these classes of active compounds, and active combinations thereof, as novel insulin sensitivity increasing agents.

[0069] Insulin resistance decreasing formulations and methods provided herein employ berberine, a berberine related compound, berberine metabolite, berberine prodrug, or berberine
30 derivative compound of any of the Formulae herein, such as Formula I or Formula II, any active compound of formulae VI-IX, any active compound of Formulae I-V, XXVI-XXVIII, or

XXXII-XXXVI, including any of the species within these classes of active compounds, and combinations thereof, as novel insulin resistance decreasing agents.

[0070] Anti-obesity formulations and methods provided herein employ berberine, a berberine related compound, berberine metabolite, berberine prodrug, or berberine derivative compound of any of the Formulae herein, such as Formula I or Formula II, any active compound of formulae VI-IX, any active compound of Formulae I-V, XXVI-XXVIII, or XXXII-XXXVI, including any of the species within these classes of active compounds, and active combinations thereof, as novel anti-obesity agents.

[0071] Anti-hypertensive formulations and methods provided herein employ berberine, a berberine related compound, berberine metabolite, berberine prodrug, or berberine derivative compound of any of the Formulae herein, such as Formula I or Formula II, any active compound of formulae VI-IX, any active compound of Formulae I-V, XXVI-XXVIII, or XXXII-XXXVI, including any of the species within these classes of active compounds, and active combinations thereof, as novel hypertension lowering agents.

[0072] Metabolic syndrome treating formulations and methods provided herein employ berberine, a berberine related compound, berberine metabolite, berberine prodrug, or berberine derivative compound of any of the Formulae herein, such as Formula I or Formula II, any active compound of formulae VI-IX, any active compound of Formulae I-V, XXVI-XXVIII, or XXXII-XXXVI, including any of the species within these classes of active compounds, and active combinations thereof, as novel metabolic syndrome treating agents.

[0073] Within the formulations and methods, berberine, a berberine related compound, berberine metabolite, berberine prodrug, or berberine derivative compound of any of the Formulae herein, such as Formula I or Formula II, any active compound of formulae VI-IX, any active compound of Formulae I-V, XXVI-XXVIII, or XXXII-XXXVI, including any of the species within these classes of active compounds, and active combinations thereof, as disclosed herein is effectively used to treat metabolic and cardiovascular disorders in mammalian subjects suffering metabolic and cardiovascular disorders and conditions associated with metabolic and cardiovascular disorders including but not limited to, fatty liver, reproductive abnormalities, growth abnormalities, arterial plaque accumulation, osteoarthritis, gout, joint pain, respiratory problems, skin conditions, sleep apnea, idiopathic intracranial hypertension, lower extremity venous stasis disease, gastro-esophageal reflux, urinary stress incontinence, kidney damage, cardiovascular

diseases such as atherosclerosis, coronary artery disease, peripheral vascular disease, enlarged heart, diabetic cardiomyopathy, pulmonary embolism, angina pectoris, carotid artery disease, stroke, cerebral arteriosclerosis, myocardial infarction, cerebral infarction, restenosis following balloon angioplasty, intermittent claudication, dyslipidemia post-prandial lipidemia, high blood pressure and xanthoma.

[0074] A broad range of mammalian subjects, including human subjects, are amenable to treatment using the formulations and methods of the invention. These subjects include, but are not limited to, human and other mammalian subjects presenting with metabolic and cardiovascular disorders or diseases aggravated or triggered by metabolic and cardiovascular disorders such as fatty liver, reproductive abnormalities, growth abnormalities, arterial plaque accumulation, osteoarthritis, gout, joint pain, respiratory problems, liver dysfunction, skin conditions, sleep apnea, idiopathic intracranial hypertension, lower extremity venous stasis disease, gastro-esophageal reflux, urinary stress incontinence, kidney damage, cardiovascular diseases such as atherosclerosis, coronary artery disease, enlarged heart, peripheral vascular disease, diabetic cardiomyopathy, pulmonary embolism, angina pectoris, carotid artery disease, stroke, cerebral arteriosclerosis, myocardial infarction, cerebral infarction, restenosis following balloon angioplasty, intermittent claudication, dyslipidemia post-prandial lipidemia, high blood pressure and xanthoma. Human and mammalian subjects amenable to treatment using the formulations and methods of the invention further include those displaying symptoms of metabolic and cardiovascular diseases including, but not limited to, weight gain, elevated glucose levels, elevated lipid levels, frequent urination, increased thirst, dehydration, weight loss, blurred vision, fatigue, coma, fatty liver, reproductive abnormalities, growth abnormalities, arterial plaque accumulation, osteoarthritis, gout, joint pain, respiratory problems, skin conditions, sleep apnea, idiopathic intracranial hypertension, gastro-esophageal reflux, urinary stress incontinence, kidney damage, shortness of breath, chest pain, leg pain, tiredness, vision changes, blood in urine, nosebleeds, irregular heartbeat, loss of balance or coordination, weakness, or vertigo.

[0075] Within the methods and compositions of the invention, berberine, a berberine related compound, berberine metabolite, berberine prodrug, or berberine derivative compound of any of the Formulae herein, such as Formula I or Formula II, any active compound of formulae VI-IX, any active compound of Formulae I-V, XXVI-XXVIII, or XXXII-XXXVI, including any of the

species within these classes of active compounds, and active combinations thereof, as disclosed herein is/are effectively formulated or administered as an anti-hyperlipidemia or cholesterol lowering agent effective for treating hyperlipidemia and/or related disorders. In exemplary embodiments, berberine chloride is demonstrated for illustrative purposes to be an anti-

5 hyperlipidemia effective agent in pharmaceutical formulations and therapeutic methods, alone or in combination with one or more adjunctive therapeutic agent(s). The present disclosure further provides additional, pharmaceutically acceptable berberine related and derivative compounds in the form of a native or synthetic compound, including complexes, derivatives, including glycosylated derivatives, salts, solvates, isomers, enantiomers, polymorphs, metabolites and
10 prodrugs of the compounds disclosed herein, and combinations thereof, which are effective as lipid lowering therapeutic agents within the methods and compositions of the invention.

[0076] In healthy adults, a relatively constant level of cholesterol in the body (150 - 200 mg/dL) is maintained primarily by controlling the level of de novo synthesis which is regulated in part by the dietary intake of cholesterol. Slightly less than half of the cholesterol in the body is
15 synthesized de novo with about 20–25% of total daily production occurring in the liver. Other sites of synthesis include the intestines, adrenal glands and reproductive organs. Cholesterol synthesis occurs in the cytoplasm and microsomes through the conversion of acetyl CoA.

[0077] As diagramed in Figure 38, in order to produce cholesterol, the body converts acetyl-CoA to 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) which is then converted to mevalonate.
20 Mevalonate is converted to isopentenyl pyrophosphate (IPP) which is converted to squalene. Squalene is then converted to cholesterol. The acetyl-CoA utilized for cholesterol biosynthesis is derived from either an oxidation reaction (e.g., fatty acids or pyruvate) in the mitochondria and is transported to the cytoplasm, or derived from cytoplasmic oxidation of ethanol by acetyl-CoA synthetase.

25 [0078] Normal healthy adults synthesize cholesterol at a rate of approximately 1g/day and consume approximately 0.3g/day. Cholesterol levels are also maintained through regulation of HMG-CoA Reductase (HMGR) activity and levels, regulation of excess intracellular free cholesterol through the activity of acyl-CoA:cholesterol acyltransferase (ACAT) and regulation of plasma cholesterol levels via LDL receptor-mediated uptake and HDL-mediated reverse
30 transport.

[0079] Hyperlipidemia is an abnormal increase in serum lipids in the bloodstream. It is generally classified as primary hyperlipidemia, which is caused by genetic defects; or secondary hyperlipidemia, which is caused by various disease states, drugs and/or dietary factors.

Hyperlipidemia may also result from a combination of primary and secondary causes of

5 hyperlipidemia. Deficiencies or failures of LDL regulatory mechanisms can result in hyperlipidemia. Hyperlipidemia is a known causal factor for development of atherosclerosis and other cardiovascular and peripheral vascular diseases. Primary hyperlipidemia is generally caused by genetic defects, and secondary hyperlipidemia generally caused by secondary factors such as disease, drugs and/or dietary factors. Hyperlipidemia can also result from a combination
10 of primary and secondary causes.

[0080] Primary hyperlipidemias include familial hyperchylomicronemia, familial hypercholesterolemia, familial combined hyperlipidemia, familial dysbetalipoproteinemia, familial hypertriglyceridemia, and familial defective apolipoprotein B-100. Familial

hyperchylomicronemia is a genetic disorder which results in a deficiency in an enzyme, LP

15 lipase, that breaks down fat molecules. The LP lipase deficiency can cause the accumulation of large quantities of fat or lipoproteins in the blood. Familial hypercholesterolemia is caused by one or more mutations in the LDL receptor gene that result(s) in a malfunctioning LDL receptor or even complete absence of the LDL receptor. These genetic defects are associated with reduced or ineffective clearance of LDL, leading to elevated LDL and total cholesterol levels in

20 the plasma. Familial combined hyperlipidemia, also known as multiple lipoprotein-type hyperlipidemia, can result in periodic elevation of cholesterol and triglyceride levels and a decrease in HDL levels. Familial defective apolipoprotein B-100 is an autosomal dominant genetic abnormality caused by a single nucleotide mutation that substitutes glutamine for arginine. This mutation leads to a reduced affinity of LDL particles for the LDL receptor,

25 increasing plasma levels of LDL and total cholesterol. Familial dysbetalipoproteinemia, also referred to as Type III hyperlipoproteinemia, results in moderate to severe elevations of serum triglyceride and cholesterol levels with abnormal apolipoprotein E function. In familial hypertriglyceridemia, the concentration of plasma VLDL is elevated. This can cause mild to moderately elevated triglyceride levels (and usually not elevated cholesterol levels) and can often
30 be associated with low plasma HDL levels.

[0081] Secondary hyperlipidemia can be triggered by diseases such as uncontrolled diabetes mellitus (insulin-dependent diabetes mellitus and non-insulin-dependent diabetes mellitus) (Bianchi, R., *et al.*, Diab. Nutr. Metabl. 7:43-51 (1994); Welborn, T. A., Aust. NZ J. Med. 24:61-64 (1994)), hypothyroidism, uremia, nephrotic syndrome, acromegaly, obstructive liver disease, and dysproteinemia (multiple myeloma, lupus erythematosus) (Harrison's Principles of Internal Medicine, Ed. Braunwald, E., *et al.*, 11th Edition, McGraw-Hill 1016-1024 (1988)). A number of drugs can also produce secondary hyperlipidemia, including oral contraceptives, glucocorticoids and antihypertensives. Dietary factors such as increased caloric intake, recent weight gain, consumption of foods high in saturated fats and cholesterol, and alcohol intake, can additionally contribute to the development of secondary hyperlipidemia. Elevated lipoprotein levels, regardless of cause, are associated with a number of disease states, including atherosclerosis, coronary artery disease, angina pectoris, carotid artery disease, stroke, cerebral arteriosclerosis, myocardial infarction, cerebral infarction, restenosis following balloon angioplasty, high blood pressure, intermittent claudication, dyslipidemia, post-prandial lipidemia and xanthoma.

[0082] Elevated lipoprotein and glucose levels are frequently found in obese individuals. Obesity is defined as having a body weight that is 20 to 25 percent over the recommended body weight, taking into account a person's particular age, height, and sex. Obesity is a well-established risk factor for a number of potentially life-threatening diseases such as coronary heart disease, osteoarthritis, gout, atherosclerosis, joint pain, sexual and fertility problems, respiratory problems, skin conditions, hypertension, diabetes, stroke, pulmonary embolism, sleep apnea, idiopathic intracranial hypertension, lower extremity venous stasis disease, gastro-esophageal reflux, urinary stress incontinence, and cancer. It also complicates numerous chronic conditions such as respiratory disease, osteoarthritis, osteoporosis, gall bladder disease, and dyslipidemias. The compositions and methods of the present invention are effective in the treatment of all types of hyperlipidemia, regardless of cause.

[0083] One cause of hyperlipidemia is liver dysfunction. In normal humans, when dietary cholesterol is increased, de novo synthesis of cholesterol decreases. However in cases of liver dysfunction, this mechanism fails and cholesterol synthesis continues, increasing cholesterol levels in the body and leading to hyperlipidemia. Liver dysfunction can result from genetic conditions, inflammatory disorders, toxins such as drugs and alcohol, diseases such as hepatitis,

immunological disorders, vascular disorders or metabolic conditions. Regardless of the cause, liver damage can have a systemic effect on the function of metabolic processes and the regulation of blood glucose and serum lipid levels, exacerbating chronic disease states and leading to increased risks for further disease and morbidity.

5 [0084] Certain types of adverse diets also interfere with hepatic control of cholesterol synthesis. For example, an increase in the consumption of saturated fats leads to increased levels of plasma cholesterol, particularly increased LDL and VLDL levels. While not wishing to be bound, current theory suggests that saturated triglycerides suppress hepatic LDL receptors leading to elevated LDL levels in plasma. (Ohtani et al. J. of Lipid Res 31 (8): 1413. (1990))

10 [0085] LDL concentrations in plasma are regulated in part by the LDL receptor which captures LDL particles from the bloodstream and draws them inside the cell, clearing them from the bloodstream when there is too much and releasing them when more LDL is needed.

Transcriptional regulation of the LDL receptor gene is controlled through the sterol regulatory element-binding protein pathway (SREBP). Bile acid sequestrants, cholesterol biosynthesis
15 inhibitors, and cholesterol absorption inhibitors all influence the SREBP pathway and subsequently upregulate LDL receptor expression. The statins competitively inhibit 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA reductase) and block cholesterol biosynthesis in the liver. Hormones, cytokines, growth factors and second messengers also regulate transcription of the LDL receptor gene as outlined in Table 1, below. Post-transcriptional control
20 of the LDL receptor gene is also a target for pharmaceutical intervention. It has been determined in the present invention that berberine is capable of upregulating LDL receptor expression through a post-transcriptional and sterol independent mechanism in hepatocytes (Figure 2).

Table 1. Upregulation of LDL receptor gene expression by different agents

25

Agent(s)	Sites of action	Sterol-dependence	Cis-acting element(s)	Trans-acting Factors	Signaling pathway
Statins	Transcription	Dependent	SRE	SREBPs (activated by proteolytic cleavage)	-

Estrogens	Transcription	Independent	Repeat 3	Estrogen receptor- α and Sp1	-
Insulin/ growth factors	Transcription	Independent	SRE/SRE + repeat 1 and 3	SREBPs (activated by phosphorylation)/SR EBPs + Sp1	ERK*
TNF- α / IL-1] OM	Transcription	Dependent	Unidentified	Unidentified	ERK
PMA	Transcription	Independent	SIRE	Egr1 and c/EBP β	ERK
	Transcription/ post- transcription	Independent	Unidentified/ 3' sequence of LDL receptor 3'UTR	Unidentified	PKC
Berberine	Post-transcription	Independent	5' sequence of LDL receptor 3'UTR	Unidentified	ERK

*c/EBP: CCAAT/enhancer binding protein; Egr1: early growth response gene 1; ERK: extracellular signal-regulated kinase; IL: interleukin; LDL: low density lipoprotein; OM: oncostatin M; PKC: protein kinase C; PMA: phorbol-12-myristate-13-acetate; SIRE: sterol-independent regulatory element; SRE: sterol regulatory element; SREBP: sterol regulatory element-binding protein; TNF: tumor necrosis factor; UTR: untranslated region.

[0086] Those skilled in the art will appreciate that each of the forgoing agents identified in Table 1 that possess activity for regulating LDL receptor expression are useful in combination with the berberine, berberine related compound, berberine metabolite, berberine prodrug, or berberine derivative compound of any of the Formulae herein, such as Formula I or Formula II, any active compound of formulae VI-IX, any active compound of Formulae I-V, XXVI-XXVIII, or XXXII-XXXVI, including any of the species within these classes of active compounds, and active combinations thereof, in various combinatorial formulations and coordinate administration methods as described in detail below.

[0087] As shown in the examples below, active compounds of the invention exercise post-transcriptional control of the LDL receptor as illustrated in Figure 2. The active compound simultaneously elevates InsR expression through the PKC system as illustrated in Figure 34.

[0088] Within the methods and compositions of the invention, one or more of the "active compound(s) (i.e., berberine, a berberine related compound, berberine metabolite, berberine prodrug, or berberine derivative compound of any of the Formulae herein, such as Formula I or Formula II, any active compound of formulae VI-IX, any active compound of Formulae I-V, XXVI-XXVIII, or XXXII-XXXVI, including any of the species within these classes of active

compounds, and active combinations thereof) is/are additionally effectively formulated or administered as a glucose lowering, insulin resistance decreasing and/or insulin sensitivity increasing compound effective for treating hyperglycemia and/or related disorders. In exemplary embodiments, berberine chloride is demonstrated for illustrative purposes to be a glucose lowering effective agent in pharmaceutical formulations and therapeutic methods, alone or in combination with one or more adjunctive therapeutic agent(s). The present disclosure further provides additional, berberine related and derivative compounds, in the form of a native or synthetic compound, including complexes, derivatives, including glycosylated derivatives, salts, solvates, isomers, enantiomers, polymorphs, and prodrugs of the compounds disclosed herein, and combinations thereof, which are effective as glucose lowering therapeutic agents within the methods and compositions of the invention.

[0089] In the examples below, it was determined that increased expression of InsR by berberine is operated through a PKC-dependent mechanism separate from berberine's action on LDLR. Berberine upregulates InsR expression through activation of the promoter of InsR gene (transcriptional mechanism) but upregulates LDLR expression by stabilizing LDLR mRNA through an action on the LDLR mRNA 3'UTR region (post-transcriptional mechanism). The berberine caused increase in InsR expression was observed in muscle tissue and lymphocytes as well as liver cells.

[0090] PKC is a family of phospholipid-dependent serine/threonine kinases that transduce a wide range of biological signals including those related to the insulin pathway. Atypical PKCs (ζ and λ) are downstream events of insulin stimulation (Farese, Am J Physiol Endocrinol Metab 283 (1), E1-11 (2002). In the examples below, PKC inhibitor calphostin C eliminated the stimulating effect of berberine on the promoter of the InsR gene and InsR mRNA transcription, indicating that PKC is required for the effect of berberine on InsR gene transcription. The examples further demonstrate that PKC is a part of the activation mechanism for the InsR gene promoter.

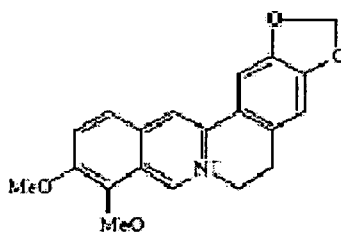
[0091] The elevated expression of InsR on the cell surface served as the primary mechanism of berberine for the restoration of insulin sensitivity *in vivo*. The upregulatory effect of berberine on InsR expression was clearly observed in liver tissue of hyperglycemic rats, and correlated with the reduction of blood glucose. Additionally, increased InsR expression directly translated to enhanced InsR sensitivity in target cells increasing glucose consumption on human hepatic cells treated with insulin. (Figure 19)

[0092] In the clinical study conducted in patients with type II diabetes, a reduction of blood glucose of 26% and HbA_{1c} of 18% was achieved after two months of treatment with berberine. In addition, the 18% reduction of serum triglyceride in these patients reflects at least partially an improved glycogen synthesis from the glucose pool. Since berberine also lowers serum lipids that influence sugar metabolism, the reduction of glucose and triglycerides in the circulation represents a synergistic effect of berberine on the activation of both InsR and LDLR expression. As illustrated in figure 34, berberine increases the LDLR expression through activation of ERK pathway in liver cells, and also elevates InsR expression through the PKC system. The two signal pathways closely collaborate in producing a full cellular response against lipid/glucose related metabolic disorders. In the study described in the examples below, 50% of the type II diabetes patients in the berberine treatment group also had hyperlipidemia. Treatment with berberine not only reduced the blood glucose, but also reduced serum cholesterol by 24%. Additionally, as shown in figure 36, the percentage of lymphocytes expressing InsR on the surface significantly increased after treatment with berberine.

[0093] Essential hypertension is the clinical expression of a disordered interaction between the genetic, physiological, and biochemical systems that usually maintain cardiovascular homeostasis. The multifactorial nature of essential hypertension has made it difficult to completely isolate the action of any one of these systems from the actions of the others. The relation between insulin metabolism/resistance and essential hypertension has the potential to provide insight into the mechanisms that operate this complex interaction. (DeFronzo, Diabetes Care 14: 173-194 (1991). Insulin increases renal sodium retention while increasing free water clearance. Insulin resistance is associated with increased sympathetic nervous system activity and stimulation of vascular smooth muscle growth. Additionally, insulin levels have been found to be significantly higher in adult patients with essential hypertension and borderline hypertension than in normotensive control patients. This is true regardless of the technique used to measure insulin and glucose level and independent of age, sex, and ethnic group. Numerous studies have confirmed the association between weight gain, percent body fat, and insulin resistance. However, there has also been found to be an interaction between insulin and hypertension that is independent of obesity. (Steinberger, Circulation. 107:1448 (2003). Treatment with berberine and berberine related and derivative compounds of Formula XXVII of the present invention is effective in reducing hypertension, regardless of the cause.

[0094] Metabolic syndrome, also known as syndrome X, dysmetabolic syndrome, obesity syndrome, insulin resistance syndrome and Reaven's syndrome, is a collection of risk factors estimated to effect over 50 million Americans. While there are no well-accepted criteria for diagnosing metabolic syndrome, it is generally characterized by abdominal obesity, atherogenic
5 dislipidemia, elevated blood pressure, insulin resistance or glucose intolerance, prothrombotic state and a proinflammatory state. People with metabolic syndrome are at increased risk of coronary heart disease, stroke, peripheral vascular diseases, fatty liver, skin lesions, reproductive abnormalities, growth abnormalities, type II diabetes, and accelerated atherosclerosis as well as other diseases related to the buildup of arterial plaques formed by lipoproteins. Treatment with
10 berberine and berberine related and derivative compounds of Formula XXVII of the present invention is effective in treating metabolic syndrome, regardless of cause.

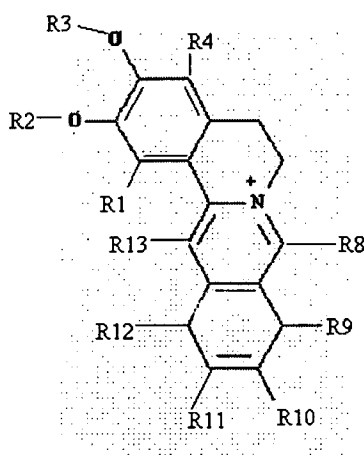
[0095] Berberine is a quaternary alkaloid widely distributed in nine plant families of the structure of the compound of the following Formula II.



Formula II

[0096] Berberine can be found in *Hydrastis canadensis* (goldenseal), *Coptis chinensis* (Coptis, goldenthread, also known as the Chinese herb Huanglian), *Berberis aquifolium* (Oregon grape), *Berberis vulgaris* (barberry), *Berberis aristata* (tree turmeric), *Chinese Isatis*, *Mahonia swaseyi*,
20 *Yerba mansa* (*Anemopsis californica*), and *Phellodendron amurense*. Products from these and other berberine-containing herbal sources, including any preparation or extract therefrom, are contemplated as useful compositions comprising berberine (or berberine analogs, related compounds, proto-berberine compounds and/or derivatives) for use within the invention. Useful
25 berberine compounds, berberine related, proto-berberine and derivative compounds for use within the invention will typically have a structure as illustrated in Formula I or Formula XXVII,

although functionally equivalent analogs, complexes, conjugates, and derivatives of such compounds will also be appreciated by those skilled in the art as within the scope of at least certain aspects of this invention.



Formula I

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Useful berberine compounds, berberine related compounds, berberine metabolites, berberine prodrugs, proto-berberine and derivative compounds for use within the invention according to Formula I will also typically have a structure wherein R₁, R₂, R₃, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂ and/or R₁₃ is selected (each independently, and in any combination yielding an active compound as described) from a hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, oligosaccharide or heterocyclo group.

[0097] In more detailed embodiments, illustrative structural modifications according to Formula I above or Formula XXVII, below will be selected to provide useful candidate compounds for treating and/or preventing metabolic and cardiovascular disorders in mammalian subjects wherein: R₁ is selected from methyl, ethyl, hydroxyl, or methoxy; R₂ is selected from H, methyl, ethyl, methene; R₃ is selected from H, methyl, ethyl, methene; R₄ is selected from a hydrogen atom, methyl, ethyl, hydroxyl, or methoxy, an alkyl group having 1 to 8 carbons, or an alkenyl group having 3 to 8 carbons; R₈ is selected from straight or branched (C1-C6) alkyl (e.g.,

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substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl); R₉ is selected from methyl, ethyl, hydroxyl, methoxy, Cl, Br; R₁₀ is selected from methyl, ethyl, hydroxyl, Cl, Br, hydroxy or an alkoxy group having 1 to 4 carbons, acetyl, tertiarybutylformylacetyl, 3-phenylacryloyl, chloracetyl, chloroacetylpropanyl, straight or branched (C1-C8) alkyl, (e.g., substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl, tertbutyl formyl and 1-methyl-2ethylpropyl); R₁₁ is selected from methyl, ethyl, hydroxyl, Cl, Br; R₁₂ is selected from methyl, ethyl, hydroxyl, Cl, Br; and R₁₃ is selected from straight or branched (C1-C8) alkyl (e.g., substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl, tertbutyl formyl and 1-methyl-2ethylpropyl), hydrogen atom, an alkenyl group having 3 to 8 carbon atoms, a cycloalkylalkyl group having 1 to 7 carbon atoms, a haloalkyl group having 1 to 4 carbon atoms, an ethoxycarbonyl group, an ethoxycarbonylmethyl group, a hydroxycarbonylmethyl group, 1-ethoxycarbonyl ethyl group, or 2-valerolactonyl group.

In some embodiments, R₂ and R₃ may together form a methylenedioxy group. Additional candidate compounds for use within the compositions and methods will be readily produced and selected according to the further disclosure provided herein below. Further description is provided in U.S. Patent Application No. 11/784,294 filed April 4, 2006. Yet additional candidate compounds for use within the compositions and methods of the invention are provided wherein each of the R₁, R₂, R₃, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂, and/or R₁₃ groups indicated in Formula I or the R₁, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂ and/or R₁₃ in Formula XXVII can be optionally (independently, collectively, or in any combination yielding an active compound as described) substituted as described and defined in the following passages.

[0098] In additional detailed embodiments, illustrative structural modifications according to Formula I above will be selected to provide useful candidate compounds for treating and/or

preventing hyperglycemia, insulin resistance, hypercholesterolemia, hyperlipidemia, obesity, diabetes, metabolic syndrome and hypertension in mammalian subjects wherein: R_1 is selected from methyl, ethyl, hydroxyl, or methoxy; R_2 is selected from H, methyl, ethyl, methene; R_3 is selected from H, methyl, ethyl, methene; R_4 is selected from methyl, ethyl, hydroxyl, or methoxy; R_8 is selected from straight or branched (C1-C6) alkyl (e.g., substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl); R_9 is selected from methyl, ethyl, hydroxyl, methoxy, Cl, Br; R_{10} is selected from methyl, ethyl, hydroxyl, Cl, Br; R_{11} is selected from methyl, ethyl, hydroxyl, Cl, Br; R_{12} is selected from methyl, ethyl, hydroxyl, Cl, Br; and R_{13} is selected from straight or branched (C1-C6) alkyl (e.g., substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl). For example, in some illustrative embodiments, R_1 , R_4 , R_8 , R_{11} , R_{12} and R_{13} are hydrogen and R_2 , R_3 , R_9 and R_{10} are independently selected from hydrogen, hydroxy, methyl or methoxy. In some embodiments, R_2 and R_3 may together form a methylenedioxy group. Additional candidate compounds for use within the compositions and methods will be readily produced and according to the further disclosure provided herein below and in U.S. Patent Application No. 11/784,294 filed April 4, 2006 and U.S. Patent Application No. 11/229,339, each of which is incorporated by reference herein in their entirety. Yet additional candidate compounds for use within the compositions and methods of the invention are provided wherein each of the R_1 , R_2 , R_3 , R_4 , R_8 , R_9 , R_{10} , R_{11} , and/or R_{12} groups indicated in the formulas herein can be optionally (independently, collectively, or in any combination yielding an active compound as described) substituted as described and defined in the following passages.

[0099] The term "halogen" as used herein refers to bromine, chlorine, fluorine or iodine. In one embodiment, the halogen is fluorine. In another embodiment, R_9 , R_{10} , R_{11} , R_{12} and/or R_{13} may independently be chlorine or bromine.

[00100] The term "hydroxy" as used herein refers to $-OH$ or $-O^-$.

[00101] The term "acetyl" as used herein refers to $-CH_3CO$.

[00102] The term "methene" as used herein refers to the group $R-CH=R'$

[00103] The term "alkene" as used herein refers to unsaturated hydrocarbons that contain carbon-carbon double bonds. Examples of such alkene groups include ethylene, propene, and the like. In one embodiment, R_2 and/or R_3 may independently be methene.

5 [00104] The term "alkyl" as used herein refers to straight- or branched-chain aliphatic groups containing 1-20 carbon atoms, preferably 1-7 carbon atoms and most preferably 1-6 carbon atoms. This definition applies as well to the alkyl portion of alkoxy, alkanoyl and aralkyl groups. In one embodiment, R_1 , R_2 , R_3 , R_4 , R_8 and/or R_{13} may independently be methyl or ethyl groups. In another embodiment R_8 and/or R_{13} may independently be n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 10 2-methylpropyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 3-methylbutyl, m-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1-2-dimethylbutyl, 1,3-dimethyl or 1-methyl-2ethylpropyl.

[00105] The term "alkoxy" includes substituted and unsubstituted alkyl, alkenyl, and alkynyl groups covalently linked to an oxygen atom. In one embodiment, the alkoxy group 15 contains 1 to 6 carbon atoms. Embodiments of alkoxy groups include, but are not limited to, methoxy, ethoxy, isopropoxy, propoxy, butoxy, and pentoxy groups. In a further embodiment, R_9 , R_{10} , R_{11} , and/or R_{12} may independently be methoxy or ethoxy groups. In another embodiment, R_1 is a methoxy group. Embodiments of substituted alkoxy groups include 20 halogenated alkoxy groups. In a further embodiment, the alkoxy groups can be substituted with groups such as alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonate, phosphinate, cyano, amino (including alkylamino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including 25 alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonate, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties. Exemplary halogen substituted alkoxy groups include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy, and 30 trichloromethoxy. In one embodiment, R_1 , R_4 , R_9 , R_{10} , R_{11} and/or R_{12} may independently be an hydroxyl group.

[00106] The term "nitro," as used herein alone or in combination refers to a --NO₂ group.

[00107] The term "amino" as used herein refers to the group --NRR', where R and R' may independently be hydrogen, alkyl, aryl, alkoxy, or heteroaryl. The term "aminoalkyl" as used herein represents a more detailed selection as compared to "amino" and refers to the group --
5 NRR', where R and R' may independently be hydrogen or (C₁-C₄)alkyl.

[00108] The term "trifluoromethyl" as used herein refers to --CF₃.

[00109] The term "trifluoromethoxy" as used herein refers to --OCF₃.

[00110] The term formyl as used herein refers to HCO-.

[00111] The term "cycloalkyl" as used herein refers to a saturated cyclic hydrocarbon ring
10 system containing from 3 to 7 carbon atoms that may be optionally substituted. Exemplary
embodiments include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In
certain embodiments, the cycloalkyl group is cyclopropyl. In another embodiment, the
(cycloalkyl)alkyl groups contain from 3 to 7 carbon atoms in the cyclic portion and 1 to 4 carbon
atoms in the alkyl portion. In certain embodiments, the (cycloalkyl)alkyl group is cyclopropylmethyl.
15 The alkyl groups are optionally substituted with from one to three substituents selected from the
group consisting of halogen, hydroxy and amino.

[00112] The terms "alkanoyl" and "alkanoyloxy" as used herein refer, respectively, to --C(O)-
alkyl groups and --O-C(O)-alkyl groups, each optionally containing 2-5 carbon atoms. Specific
embodiments of alkanoyl and alkanoyloxy groups are acetyl and acetoxyl, respectively.

20 [00113] The term "aryl" as used herein refers to monocyclic or bicyclic aromatic hydrocarbon
groups having from 6 to 12 carbon atoms in the ring portion, for example, phenyl, naphthyl, biphenyl
and diphenyl groups, each of which may be substituted with, for example, one to four substituents
such as alkyl; substituted alkyl as defined above, halogen, trifluoromethyl, trifluoromethoxy,
hydroxy, alkoxy, cycloalkyloxy, alkanoyl, alkanoyloxy, amino, alkylamino, dialkylamino, nitro,
25 cyano, carboxy, carboxyalkyl, carbamyl, carbamoyl and aryloxy. Specific embodiments of aryl
groups in accordance with the present invention include phenyl, substituted phenyl, naphthyl,
biphenyl, and diphenyl.

[00114] The term "aroyl," as used alone or in combination herein, refers to an aryl radical
derived from an aromatic carboxylic acid, such as optionally substituted benzoic or naphthoic
30 acids.

[00115] The term "nitrile" or "cyano" as used herein refers to the group --CN.

[00116] The term “dialkylamino” refers to an amino group having two attached alkyl groups that can be the same or different.

[00117] The term “alkenyl” refers to a straight or branched alkenyl group of 2 to 10 carbon atoms having 1 to 3 double bonds. Preferred embodiments include ethenyl, 1-propenyl, 2-propenyl, 1-methylethenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-2-propenyl, 1-pentenyl, 2-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 2-hexenyl, 1-heptenyl, 2-heptenyl, 1-octenyl, 2-octenyl, 1,3-octadienyl, 2-nonenyl, 1,3-nonadienyl, 2-decenyl, etc.

[00118] The term “alkynyl” as used herein refers to a straight or branched alkynyl group of 2 to 10 carbon atoms having 1 to 3 triple bonds. Exemplary alkynyls include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 3-butyne, 1-pentyne, 2-pentyne, 4-pentyne, 1-octynyl, 6-methyl-1-heptyne, and 2-decynyl.

[00119] The term “hydroxyalkyl” alone or in combination, refers to an alkyl group as previously defined, wherein one or several hydrogen atoms, preferably one hydrogen atom has been replaced by a hydroxyl group. Examples include hydroxymethyl, hydroxyethyl and 2-hydroxyethyl.

[00120] The term “aminoalkyl” as used herein refers to the group --NRR', where R and R' may independently be hydrogen or (C₁-C₆)alkyl.

[00121] The term “alkylaminoalkyl” refers to an alkylamino group linked via an alkyl group (i.e., a group having the general structure --alkyl-NH-alkyl or --alkyl-N(alkyl)(alkyl)). Such groups include, but are not limited to, mono- and di-(C₁-C₈ alkyl)aminoC₁-C₈ alkyl, in which each alkyl may be the same or different.

[00122] The term “dialkylaminoalkyl” refers to alkylamino groups attached to an alkyl group. Examples include, but are not limited to, N,N-dimethylaminomethyl, N,N-dimethylaminoethyl, N,N-dimethylaminopropyl, and the like. The term dialkylaminoalkyl also includes groups where the bridging alkyl moiety is optionally substituted.

[00123] The term “haloalkyl” refers to an alkyl group substituted with one or more halo groups, for example chloromethyl, 2-bromoethyl, 3-iodopropyl, trifluoromethyl, perfluoropropyl, 8-chlorononyl and the like.

[00124] The term “carboxyalkyl” as used herein refers to the substituent --R'--COOH wherein R' is alkylene; and carbalkoxyalkyl refers to --R'--COOR wherein R' and R are alkylene and alkyl respectively. In certain embodiments, alkyl refers to a saturated straight- or branched-

chain hydrocarbonyl radical of 1-6 carbon atoms such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, 2-methylpentyl, n-hexyl, and so forth. Alkylene is the same as alkyl except that the group is divalent.

[00125] The term "alkoxyalkyl" refers to an alkylene group substituted with an alkoxy group. For example, methoxyethyl [$\text{CH}_3\text{OCH}_2\text{CH}_2\text{--}$] and ethoxymethyl ($\text{CH}_3\text{CH}_2\text{OCH}_2\text{--}$) are both C_3 alkoxyalkyl groups.

[00126] The term "carboxy", as used herein, represents a group of the formula --COOH .

[00127] The term "alkanoylamino" refers to alkyl, alkenyl or alkynyl groups containing the group --C(O)-- followed by --N(H)-- , for example acetylamino, propanoylamino and butanoylamino and the like.

[00128] The term "carbonylamino" refers to the group $\text{--NR--CO--CH}_2\text{--R'}$, where R and R' may be independently selected from hydrogen or $(\text{C}_1\text{--C}_4)\text{alkyl}$.

[00129] The term "carbamoyl" as used herein refers to --O--C(O)NH_2 .

[00130] The term "carbamyl" as used herein refers to a functional group in which a nitrogen atom is directly bonded to a carbonyl, i.e., as in --NRC(=O)R' or --C(=O)NRR' , wherein R and R' can be hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, cycloalkyl, aryl, heterocyclo, or heteroaryl.

[00131] The term "alkylsulfonylamino" refers to refers to the group $\text{--NHS(O)}_2\text{R}_a$ wherein R_a is an alkyl as defined above.

[00132] The term "heterocyclo" refers to an optionally substituted, unsaturated, partially saturated, or fully saturated, aromatic or nonaromatic cyclic group that is a 4 to 7 membered monocyclic, or 7 to 11 membered bicyclic ring system that has at least one heteroatom in at least one carbon atom-containing ring. The substituents on the heterocyclo rings may be selected from those given above for the aryl groups. Each ring of the heterocyclo group containing a heteroatom may have 1, 2 or 3 heteroatoms selected from nitrogen atoms, oxygen atoms and sulfur atoms. Plural heteroatoms in a given heterocyclo ring may be the same or different.

[00133] The term "furyl" refers to a heterocyclic group, having the formula $\text{C}_4\text{H}_3\text{O}$, which may be either the alpha or beta isomer

[00134] As used herein, the term "benzotriazolyl" refers to a monovalent group having a benzene group fused to a triazolyl group. The formula for a benzotriazolyl group is $\text{C}_6\text{H}_4\text{N}_3\text{--}$.

[00135] The term "benzyloxy" refers to an $\text{O--CH}_2\text{Ph}$ substituent, wherein Ph is phenyl or a

substituted phenyl.

[00136] The term “methylenedioxy” refers to a -O-CH₂-O- group.

[00137] The term “methene” refers to a R-CH=R' group.

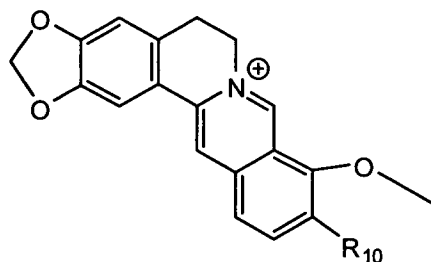
[00138] The term “vinyl” refers to the group CH₂CH.

5 [00139] The term “glycosylate,” “glycosylation” or “glycosylated means the attachment of an oligosaccharide group, preferably, though not limited to, attachment to an nitrogen or oxygen.

[00140] The term “oligosaccharide” as used herein is defined as encompassing 1 to 20 saccharides. Mono-, di-, and trisaccharides are specifically included in the definition of oligosaccharides.

10 [00141] All value ranges expressed herein, are inclusive over the indicated range. Thus, a range of R between 0 to 4 will be understood to include the values of 1, 2, 3, and 4.

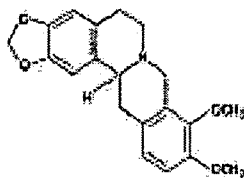
[00142] In some embodiments of the invention, derivative forms of the berberine compound of formula II may be formed through demethylation. In some embodiments, derivatives of berberine may be demethylated as shown in formula XXXII, below:



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Formula XXXII

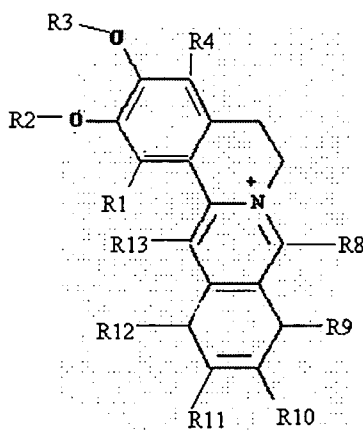
wherein R₁₀ may be a hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, 20 carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, heterocyclo group, methylenedioxy, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropyl, alkylacetyl, or oligosaccharide.

[00143] In other embodiments, the berberine compound of formula XXXII may be hydrogenated, in further embodiments, the berberine compound of formula XXXII may be demethylated and hydrogenated such that it forms compounds such as or derived from canadine of 25 the structure shown below.



Canadine

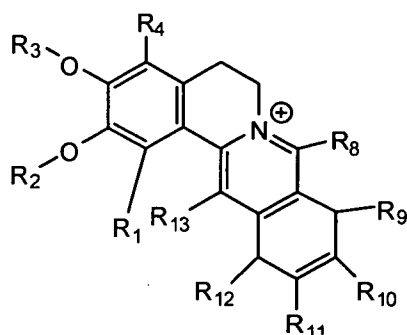
[00144] Useful berberine compounds, berberine related, proto-berberine and derivative compounds for use within the invention will in certain embodiments have structure as illustrated below in Formula XXXIII, although functionally equivalent analogs, complexes, conjugates, and derivatives of such compounds will also be appreciated by those skilled in the art as within the scope of at least certain aspects of this invention.



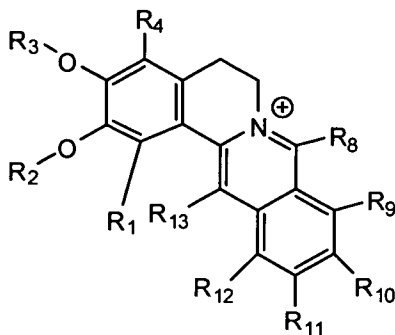
Formula XXXIII

Additional berberine compounds, berberine related, proto-berberine and derivative compounds for use within the invention according to Formula XXXIII or derivatives of Formula XXXIII as shown in Formulas XXXIV, XXXV and XXXVI below will typically have a structure wherein R_1 , R_2 , R_3 , R_4 , R_8 , R_9 , R_{10} , R_{11} , R_{12} and/or R_{13} is selected (each independently, and in any combination yielding an active compound as described) from a hydrogen, halogen, hydroxy, hydroxyalkyl, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl,

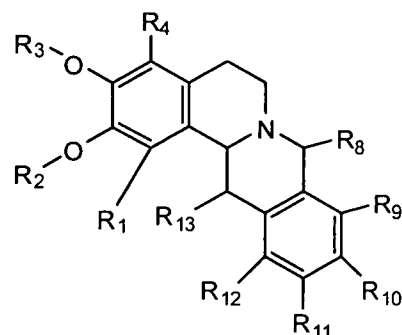
carbamyl, carbonylamino, alkylsulfonylamino, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropenyl, alkylacetyl, oligosaccharide or heterocyclo group.



Formula XXXIV



Formula XXXV



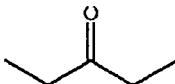
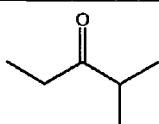
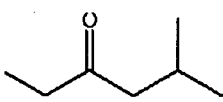
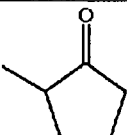
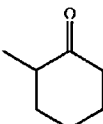
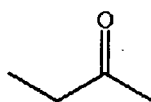
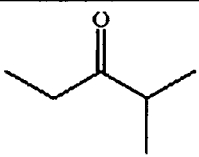
Formula XXXVI

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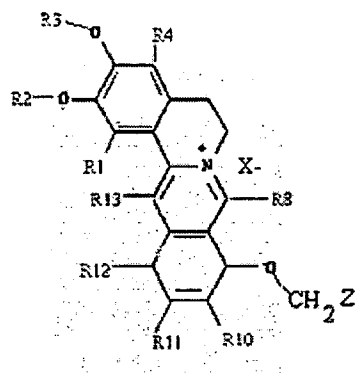
[00145] Exemplary forms of berberine compounds and derivatives of formula I may be found in table 2 below.

Table 2: Exemplary forms of berberine compounds and derivatives of formula I

Composition No.	R ¹	R ²	R ³	R ⁴	R ⁸	R ⁹	R ¹⁰	R ¹¹	R ¹²	R ¹³
1	H		-CH ₂ -	H		CH ₃ O	CH ₃ O	H	H	H
2	H		-CH ₂ -	H	CH ₃	CH ₃ O	CH ₃ O	H	H	H
3	H		-CH ₂ -	H	C ₂ H ₅	CH ₃ O	CH ₃ O	H	H	H
4	H		-CH ₂ -	H	n-Pr	CH ₃ O	CH ₃ O	H	H	H
5	H		-CH ₂ -	H	n-Bu	CH ₃ O	CH ₃ O	H	H	H
6	H		-CH ₂ -	H		CH ₃ O	CH ₃ O	H	H	H
7	H		-CH ₂ -	H	i-Pr	CH ₃ O	CH ₃ O	H	H	H
8	H	CH ₃	CH ₃	H	CH ₃	CH ₃ O	CH ₃ O	H	H	H
9	H	CH ₃	CH ₃	H	C ₂ H ₅	CH ₃ O	CH ₃ O	H	H	H
10	H		-CH ₂ -	H	noctyl	CH ₃ O	CH ₃ O	H	H	H
11	H		-CH ₂ -	H		CH ₃ O	CH ₃ O	H	H	H
12	H	CH ₃	CH ₃	H		CH ₃ O	CH ₃ O	H	H	C ₂ H ₅

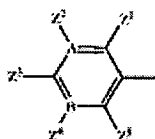
13	H	CH ₃	CH ₃	H		CH ₃ O	CH ₃ O	H	H	C ₂ H ₅
14	H	CH ₃	CH ₃	H		CH ₃ O	CH ₃ O	H	H	C ₂ H ₅
15	H	CH ₃	CH ₃	H		CH ₃ O	CH ₃ O	H	H	C ₂ H ₅
16	H	CH ₃	CH ₃	H		CH ₃ O	CH ₃ O	H	H	C ₂ H ₅
17	H	CH ₃	CH ₃	H		CH ₃ O	CH ₃ O	H	H	C ₂ H ₅
18	H	CH ₃	CH ₃	H		CH ₃ O	CH ₃ O	H	H	C ₂ H ₅
19	H	C ₂ H ₅	C ₂ H ₅	H		C ₂ H ₅ O	C ₂ H ₅ O	H	H	C ₂ H ₅
20	H	C ₂ H ₅	C ₂ H ₅	H		C ₂ H ₅ O	C ₂ H ₅ O	H	H	C ₂ H ₅
21	H	CH ₃	CH ₃	H	H	CH ₃ O	CH ₃ O	H	H	C ₂ H ₅
22	H	C ₂ H ₅	C ₂ H ₅	H	H	C ₂ H ₅ O	C ₂ H ₅ O	H	H	C ₂ H ₅
23	H	CH ₃	CH ₃	H	CH ₃	CH ₃ O	CH ₃ O	H	H	C ₂ H ₅
24	H	CH ₃	CH ₃	H	C ₂ H ₅	CH ₃ O	CH ₃ O	H	H	C ₂ H ₅
25	H	CH ₃	CH ₃	H	n-Bu	CH ₃ O	CH ₃ O	H	H	C ₂ H ₅

[00146] Additional exemplary forms of berberine compounds and derivatives contemplated for use within the methods and compositions of the invention may additionally have the structure of formula IV, below.



Formula IV

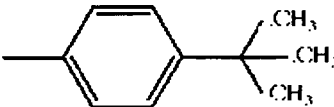
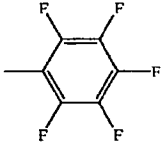
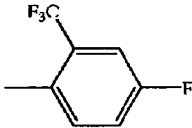
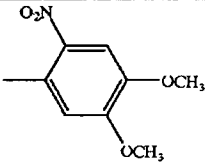
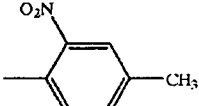
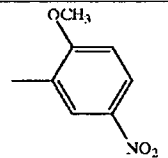
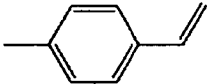
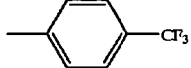
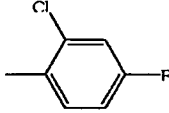
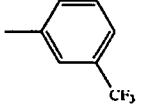
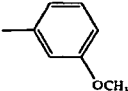
Wherein X represents an inorganic acid ion, organic acid ion, or halide, more particularly, nitrate, sulfate, acetate, tartrate, maleate, succinate, citrate, fumarate, aspartate, salicylate, glycerate, ascorbate, fluoride, chloride, iodide or bromide. Z represents an alkyl group having 5 to 12 carbons, or an alkenyl group having 4 to 6 carbons, a N-benzotriazolyl group, a quinolinyl group, a furyl group, a substituted furyl group, or a radical represented by the formula:

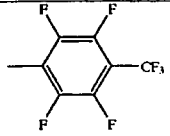
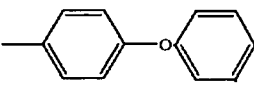
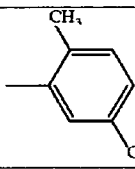
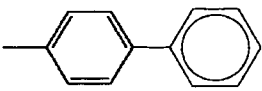
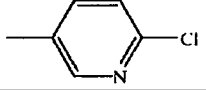
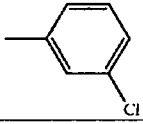
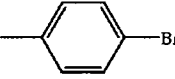
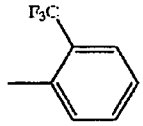
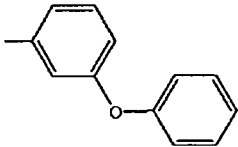
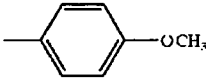
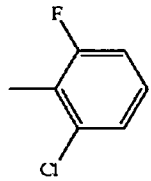
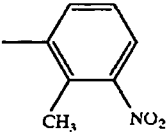
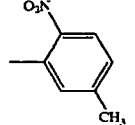


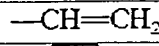
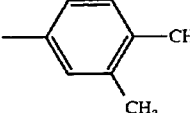
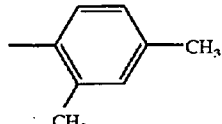
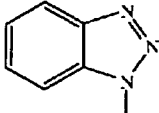
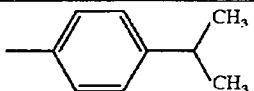
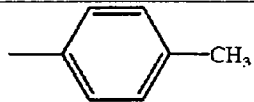
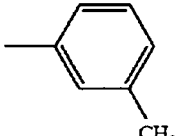
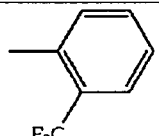
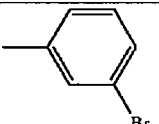
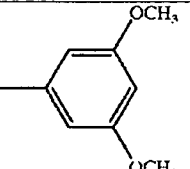
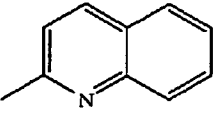
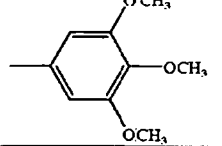
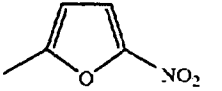
wherein Z^1 , Z^2 , Z^3 , Z^4 and Z^5 which may be the same or different from each other, represent a hydrogen atom, halogen, an alkyl group having 1 to 5 carbons, a trifluoromethyl group, a phenyl group, a substituted phenyl group, a nitro group, an alkoxy group having 1 to 4 carbons, a methylenedioxy group, a trifluoro-methoxy group, a hydroxy group, a benzyloxy group, a phenoxy group, a vinyl group, a benzenesulfonylmethyl group or a methoxycarbonyl group; and A and B which may also be the same or different from each other, represent carbon or nitrogen.

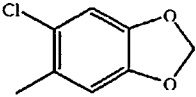
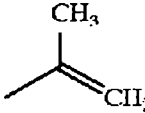
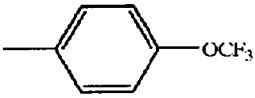
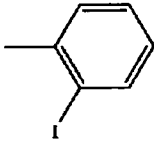
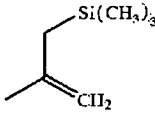
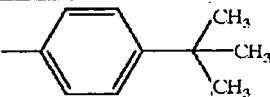
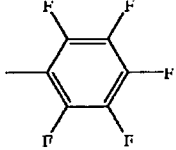
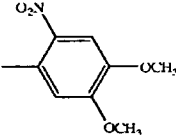
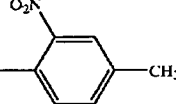
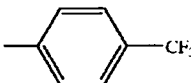
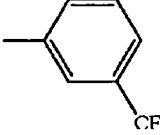
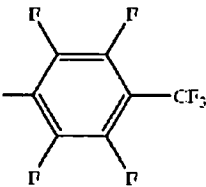
Berberine compounds and derivatives of Formula IV are exemplified by the compounds in the table 3 below.

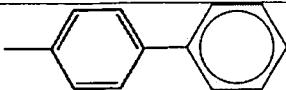
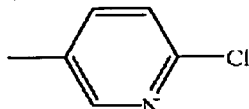
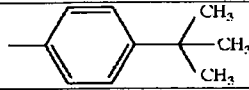
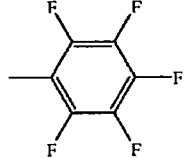
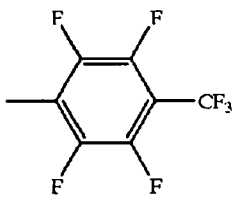
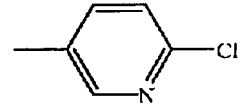
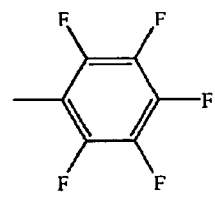
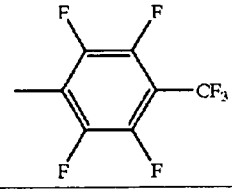
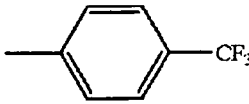
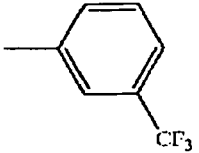
Table 3: Exemplary compositions of berberine compounds and derivatives of formula IV.

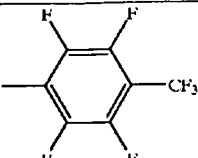
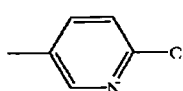
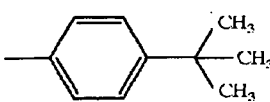
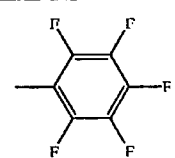
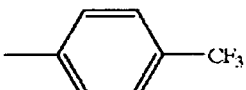
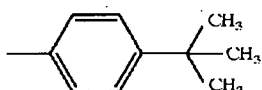
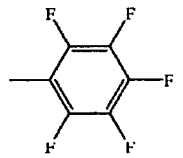
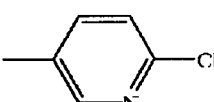
Composition No.	R ¹	R ²	R ³	R ⁴	R ⁸	R ¹⁰	R ¹¹	R ¹²	R ¹³	Z	X
26	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅	CH ₃ (CH ₂) ₁₀ CH ₃	Cl
27	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
28	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
29	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
30	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
31	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
32	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
33	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
34	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
35	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
36	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
37	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl

38	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
39	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
40	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
41	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
42	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
43	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
44	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
45	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
46	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
47	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
48	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
49	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
50	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl

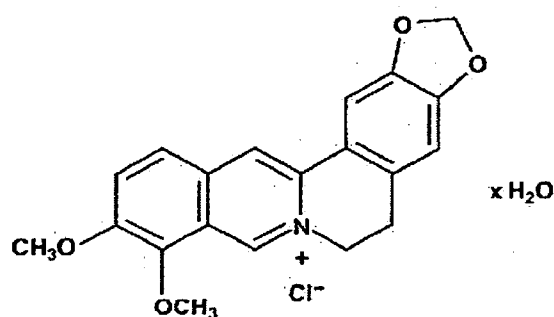
51	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
52	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
53	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
54	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
55	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
56	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
57	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
58	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
59	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
60	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
61	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
62	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
63	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl

64	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
65	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
66	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
67	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
68	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
69	H	-CH ₂ -		H	H	OCH ₃	H	H	C ₂ H ₅	-CH ₂ (CH ₂) ₁₀ CH ₃	I
70	H	-CH ₂ -		H	H	OCH ₃	H	H	C ₂ H ₅		I
71	H	-CH ₂ -		H	H	OCH ₃	H	H	C ₂ H ₅		I
72	H	-CH ₂ -		H	H	OCH ₃	H	H	C ₂ H ₅		I
73	H	-CH ₂ -		H	H	OCH ₃	H	H	C ₂ H ₅		I
74	H	-CH ₂ -		H	H	OCH ₃	H	H	C ₂ H ₅		I
75	H	-CH ₂ -		H	H	OCH ₃	H	H	C ₂ H ₅		I
76	H	-CH ₂ -		H	H	OCH ₃	H	H	C ₂ H ₅		I

77	H	-CH ₂ -	H	H	OCH ₃	H	H	C ₂ H ₅		I	
78	H	-CH ₂ -	H	H	OCH ₃	H	H	C ₂ H ₅		I	
79	H	C ₂ H ₅	C ₂ H ₅	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
80	H	C ₂ H ₅	C ₂ H ₅	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
81	H	C ₂ H ₅	C ₂ H ₅	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
82	H	C ₂ H ₅	C ₂ H ₅	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
83	H	H	H	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
84	H	H	H	H	H	OCH ₃	H	H	C ₂ H ₅		Cl
85	H	C ₂ H ₅	C ₂ H ₅	H	H	OC ₂ H ₅	H	H	C ₂ H ₅	-CH ₂ (CH ₂) ₁₀ CH ₃	Cl
86	H	C ₂ H ₅	C ₂ H ₅	H	H	OC ₂ H ₅	H	H	C ₂ H ₅		Cl
87	H	C ₂ H ₅	C ₂ H ₅	H	H	OC ₂ H ₅	H	H	C ₂ H ₅		Cl

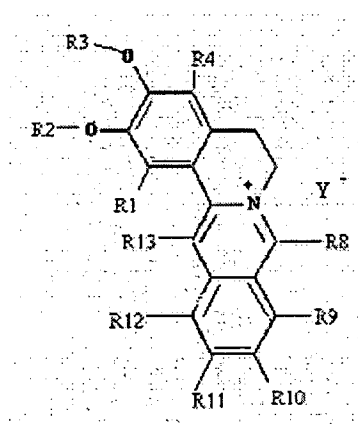
88	H	C ₂ H ₅	C ₂ H ₅	H	H	OC ₂ H ₅	H	H	C ₂ H ₅		Cl
89	H	C ₂ H ₅	C ₂ H ₅	H	H	OC ₂ H ₅	H	H	C ₂ H ₅		Cl
90	H	C ₃ H ₇	C ₃ H ₇	H	H	OC ₃ H ₇	H	H	C ₂ H ₅		Cl
91	H	C ₃ H ₇	C ₃ H ₇	H	H	OC ₃ H ₇	H	H	C ₂ H ₅		Cl
92	H	C ₃ H ₇	C ₃ H ₇	H	H	OC ₃ H ₇	H	H	C ₂ H ₅		Cl
93	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		HSO ₄ ⁻
94	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		CH ₃ CO ₂ ⁻
95	H	CH ₃	CH ₃	H	H	OCH ₃	H	H	C ₂ H ₅		NO ₃ ⁻

[00147] Ionized forms of berberine, such as berberine chloride, are also contemplated for use within the methods and compositions of the invention. Berberine chloride exemplifies this type of compound having the structure of formula XXV below.



Formula V

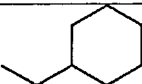
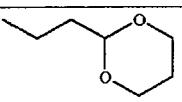
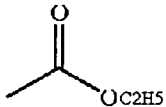
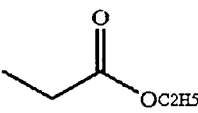
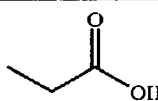
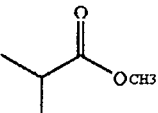
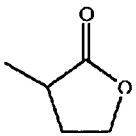
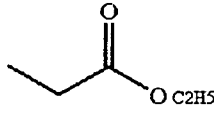
[00148] Additional ionized forms, including protoberberine forms and derivatives are generalized by the structure of formula XXVI wherein Y is a halide and exemplified in table 4 below.



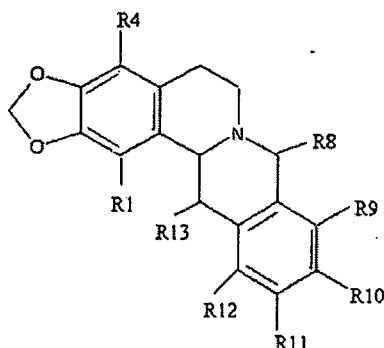
Formula XXVI

Table 4: Exemplary forms of protoberberine compounds and derivatives of formula XXVI.

Composition No.	R ¹	R ²	R ³	R ⁴	R ⁸	R ⁹	R ¹⁰	R ¹¹	R ¹²	R ¹³	Y
96	H	-CH ₂ -		H	H	CH ₃ O	CH ₃ O	H	H	CH ₃	I
97	H	H	H	H	H	CH ₃ O	CH ₃ O	H	H	CH ₃	Cl
98	H	H	H	H	H	OH	OH	H	H	H	Cl

99	H	H	H	H	H	OH	OH	H	H	CH ₃	Cl
100	H	C ₂ H ₅	C ₂ H ₅	H	H	C ₂ H ₅ O	C ₂ H ₅ O	H	H	C ₂ H ₅	Cl
101	H	-CH ₂ -		H	H	CH ₃ O	CH ₃ O	H	H	C ₂ H ₅	I
102	H	H	H	H	H	OH	OH	H	H	C ₂ H ₅	Cl
103	H	CH ₃	CH ₃	H	H	CH ₃ O	CH ₃ O	H	H	C ₂ H ₅	Cl
104	H	-CH ₂ -		H	H	CH ₃ O	CH ₃ O	H	H	Allyl	I
105	H	H	H	H	H	OH	OH	H	H	Allyl	Cl
106	H	CH ₃	CH ₃	H	H	CH ₃ O	CH ₃ O	H	H	n-propyl	I
107	H	CH ₃	CH ₃	H	H	CH ₃ O	CH ₃ O	H	H	n-Bu	I
108	H	CH ₃	CH ₃	H	H	CH ₃ O	CH ₃ O	H	H		I
109	H	CH ₃	CH ₃	H	H	CH ₃ O	CH ₃ O	H	H	n-Octyl	I
110	H	CH ₃	CH ₃	H	H	CH ₃ O	CH ₃ O	H	H		I
111	H	CH ₃	CH ₃	H	H	CH ₃ O	CH ₃ O	H	H		I
112	H	n-Bu	n-Bu	H	H	n-Bu	n-Bu	H	H	H	Cl
113	H	CH ₃	CH ₃	H	H	CH ₃ O	CH ₃ O	H	H		Cl
114	H	CH ₃	CH ₃	H	H	CH ₃ O	CH ₃ O	H	H		Cl
115	H	CH ₃	CH ₃	H	H	CH ₃ O	CH ₃ O	H	H		Cl
116	H	CH ₃	CH ₃	H	H	CH ₃ O	CH ₃ O	H	H		Cl
117	H	-CH ₂ -		H	H	CH ₃ O	CH ₃ O	H	H		Br
118	H	-CH ₂ -		H	H	CH ₃ O	CH ₃ O	H	H		Br
119	H	-CH ₂ -		H	H	CH ₃ O	CH ₃ O	H	H		Br
120	H	CH ₃	CH ₃	H	H	 CH ₃ O	CH ₃ O	H	H	C ₂ H ₅	Cl

[00149] An additional derivative or related form of berberine for use within the embodiments of the present invention is depicted in formula XXVII, below.

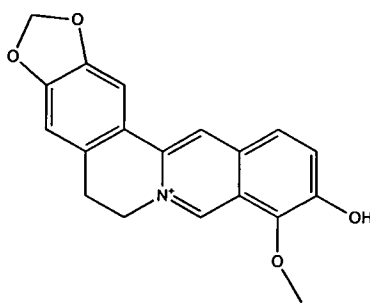


Formula XXVII

5 [00150] In additional detailed embodiments, illustrative structural modifications according to Formula XXVII above will be selected to provide useful candidate compounds for treating and/or preventing hyperglycemia, hyperlipidemia, hypercholesterolemia, insulin resistance, obesity, diabetes, metabolic syndrome and hypertension in mammalian subjects wherein: R₁ is
 10 selected from methyl, ethyl, hydroxyl, or methoxy; R₄ is selected from methyl, ethyl, hydroxyl, or methoxy; R₈ is selected from straight or branched (C1-C6) alkyl (e.g., substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-
 15 dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl); R₉ is selected from methyl, ethyl, hydroxyl, methoxy, Cl, Br; R₁₀ is selected from methyl, ethyl, hydroxyl, Cl, Br, acetyl, tertiarybutylformylacetyl, 3-phenylacryloyl, chloracetyl, chloroacetylpropanyl, straight or branched (C1-C8) alkyl, (e.g., substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-
 20 dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl, terbutyl formyl and 1-methyl-2ethylpropyl); R₁₁ is selected from methyl, ethyl, hydroxyl, Cl, Br; R₁₂ is selected from methyl, ethyl, hydroxyl, Cl, Br; and R₁₃ is selected from straight or branched (C1-C6) alkyl (e.g., substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-

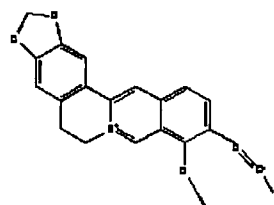
methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl). Yet additional candidate compounds for use within the compositions and methods of the invention are provided wherein each of the R₁, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂, and/or R₁₃ groups indicated in the formulas herein can be optionally (independently, collectively, or in any combination yielding an active compound as described) substituted as described above. In one embodiment, R₁, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂ and R₁₃ are hydrogen.

[00151] In another embodiment, berberine may be demethylated to form the structure of formula XXVIII.

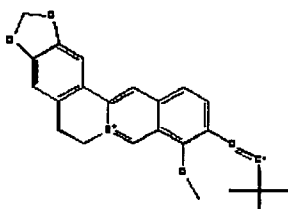


Formula XXVIII

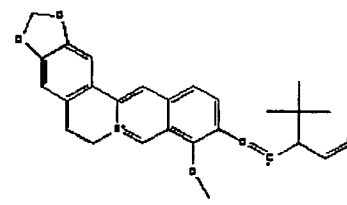
The demethylated form of berberine as shown in Formula XXVIII may be further reacted to form additional structures as represented by:



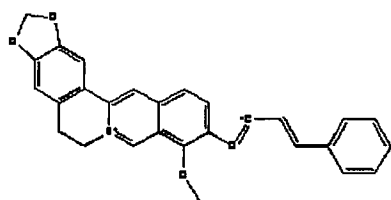
Acetyl
Formula IX



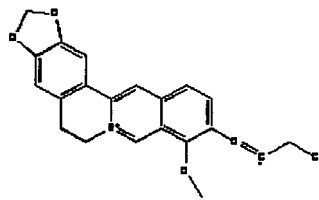
Tertbutyl formyl
Formula X



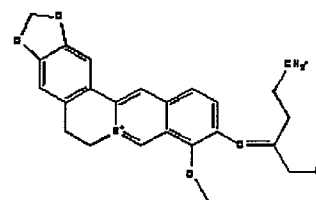
Tertiarybutylformylacetyl
Formula XI



3-Phenylacryloyl
Formula XII

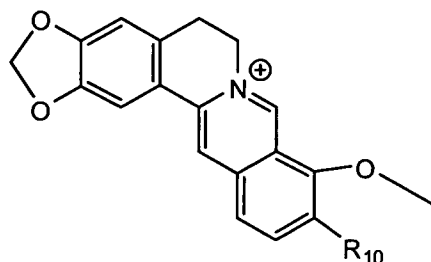


Chloroacetyl
Formula XIII



Chloroacetylpropanyl
Formula XIV

In some embodiments, derivatives of berberine may be demethylated as shown in formula XXXII, below:



Formula XXXII

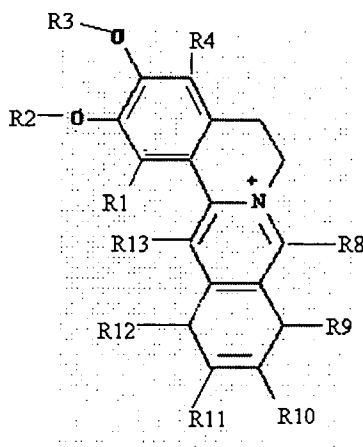
5

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wherein R_{10} may be a hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, heterocyclo group, methylenedioxy, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, or oligosaccharide.

[00152] In other embodiments, berberine and related compounds, derivatives, and proto-berberine compounds and derivatives may additionally be derived from the compound of formula XXXIII

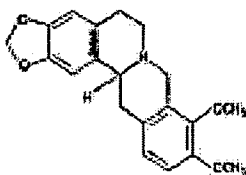
[00153]



Formula XXXIII

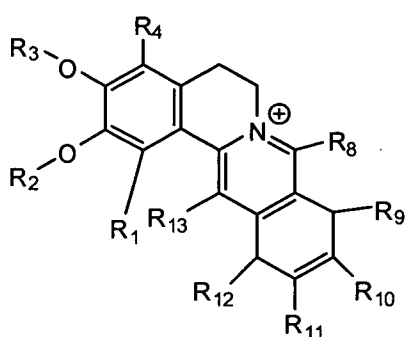
wherein each of R_1 , R_2 , R_3 , R_4 , R_8 , R_9 , R_{10} , R_{11} , R_{12} and/or R_{13} may independently, collectively, or in any combination that yields an active (e.g., anti-dyslipidemic, anti-hyperlipidemic, anti-hyperglycemic, anti-hypertensive, LDL-modulatory, LDLR stability increasing, LDLR-modulatory, AMP-activated protein kinase modulatory or insulin receptor (InsR) modulatory) compound according to this disclosure, be a hydrogen, halogen, hydroxy, hydroxyalkyl, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, heterocyclo group, methylenedioxy, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylproparyl, alkylacetyl, or oligosaccharide. When more than one R group is present, the R group may be selected from any of the stated groups so as to be the same or different. In additional embodiments, two or more R groups may be joined together, for example, R_2 and R_3 may be combined to form a methylenedioxy group. In certain exemplary embodiments, the following illustrative structural modifications according to Formula

XXXIII above will be selected to provide useful candidate compounds for treating and/or preventing metabolic and cardiovascular disorders in mammalian subjects, e.g., wherein: R_1 is selected from hydrogen, methyl, ethyl, hydroxyl, or methoxy; R_4 is selected from hydrogen, methyl, ethyl, hydroxyl, or methoxy; R_8 is selected from hydrogen, straight or branched (C1-C6) alkyl (e.g., substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl); R_9 is selected from hydrogen, methyl, ethyl, hydroxy, methoxy, Cl, Br; R_{10} is selected from hydrogen, methyl, ethyl, hydroxy, Cl, Br, acetyl, tertiarybutylformylacetyl, 3-phenylacryloyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, chloracetyl, chloroacetylpropanyl, straight or branched (C1-C8) alkyl, (e.g., substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl, tertbutyl formyl and 1-methyl-2ethylpropyl); straight or branched (C1-C8) alkoxy; R_{11} is selected from hydrogen, methyl, ethyl, hydroxyl, hydroxyalkyl, Cl, Br; R_{12} is selected from hydrogen, methyl, ethyl, hydroxyl, Cl, Br; and R_{13} is selected from hydrogen, straight or branched (C1-C6) alkyl (e.g., substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl). In some embodiments, R_2 and R_3 may together form a methylenedioxy. Additional candidate compounds for use within the compositions and methods of the invention are provided wherein each of the R_1 , R_4 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , and/or R_{13} groups indicated in the formulas herein can be optionally (independently, collectively, or in any combination yielding an active compound as described) substituted as described above. In one embodiment, R_1 , R_4 , R_8 , R_9 , R_{10} , R_{11} , R_{12} and R_{13} are hydrogen. Additional candidate compounds for use within the compositions and methods will be readily produced and selected according to the further disclosure provided herein below. An exemplary embodiment of Formula XXXIII is canadine shown below as Formula XXXIV or derivatives thereof.

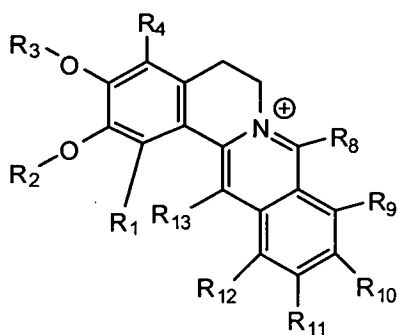


Formula XXXIV

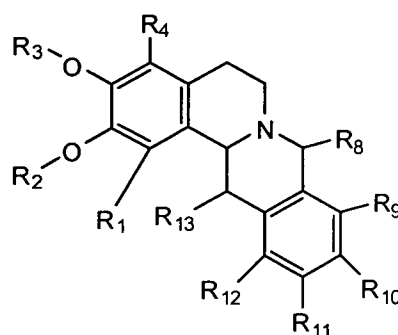
[00154] In some embodiments, compounds of Formula XXXIII may have the structure illustrated by Formulas XXXIV, XXXV, or XXXVI, below.



Formula XXXIV



Formula XXXV



Formula XXXVI

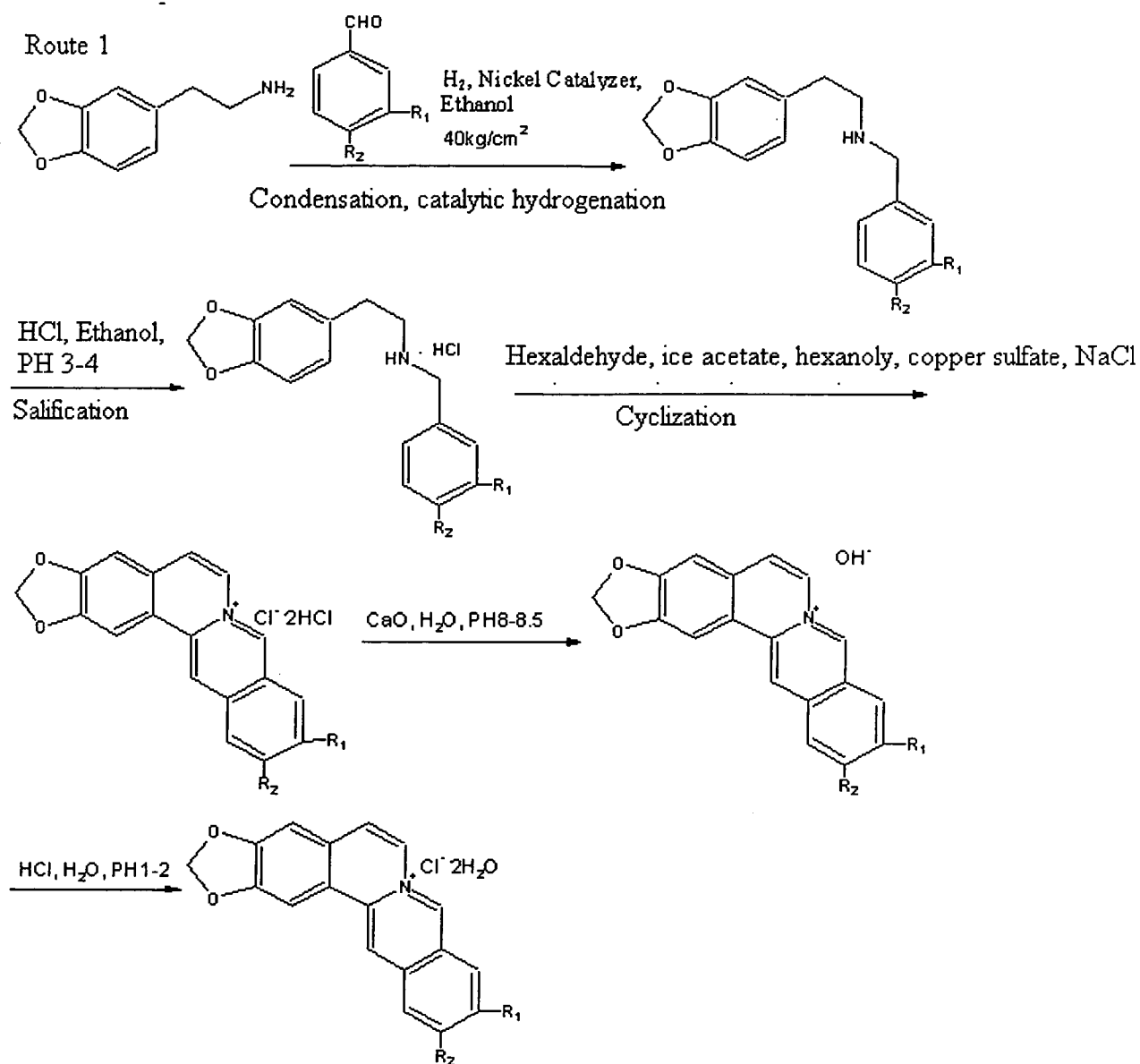
wherein each of R_1 , R_4 , R_8 , R_9 , R_{10} , R_{11} , R_{12} and/or R_{13} may independently, collectively, or in any combination that yields an active (e.g., anti-dyslipidemic, anti-hyperlipidemic, anti-hyperglycemic, anti-cholesterolemic, anti-hypertensive, LDL-modulatory, LDLR-modulatory, LDLR stabilizing, AMP-activated protein kinase modulatory or insulin receptor (InsR) modulatory) compound according to this disclosure, be hydrogen, halogen, hydroxy, hydroxyalkyl, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, heterocyclo group, methylenedioxy, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropenyl, alkylacetyl, or oligosaccharide. When more than one R group is present, the R group may be selected from any of the stated groups so as to be the same or different. In other embodiments, the two or more R groups may be linked, for example, R_2 and R_3 may be combined to form a methylenedioxy group. In certain exemplary embodiments, R_1 , R_4 , R_8 , R_9 , R_{10} , R_{11} , R_{12} and R_{13} are each hydrogen.

[00155] Useful berberine and related compounds and derivatives and proto-berberine

compounds and derivatives within the formulations and methods of the invention include those forms delineated above, including, but not not limited to, salts of berberine and related or derivative compounds, for example, berberine sulfate, berberine hydrochloride, berberine chloride, palmatine chloride, palmatine, oxyberberine, dihydroberberine, 8-

5 cyanodihydroberberine, (-)-canadine, tetrahydroberberine N-oxide, tetrahydroberberine, N-methyltetrahydroberberinium iodide, 6-protoberberine, 9-ethoxycarbonyl berberine, 9-N,N-dimethylcarbamoyl berberine and 12-bromo berberine, berberine azide, and berberine betaine. In one embodiment, berberine may be demethylated. In another embodiment, demethylated beberine may be further reacted for form acetyl, terbutyl formyl, tertiarybutylformylacetyl, 3-
10 phenylacryloyl, chloracetyl or chloroacetylpropanyl forms of berberine. Other useful forms of derivatives for use within the invention include other pharmaceutically acceptable active salts of said compounds, as well as active isomers, enantiomers, polymorphs, glycosylated derivatives, solvates, hydrates, and/or prodrugs of said compounds.

[00156] While berberine, related berberine and proto-berberine compounds and derivative
15 compounds may be generated by any methods known to those skilled in the art, exemplary compounds for use within the invention may also be generated, for example, according to Routes 1, 2, 3, and 4 described herein, below. These reaction and synthetic schemes are provided for illustrative purposes only, and it is understood that abbreviated, alternate, and modified schemes, e.g., encompassing essential elements of these schemes, or their equivalents, are also
20 contemplated within the scope of the invention.

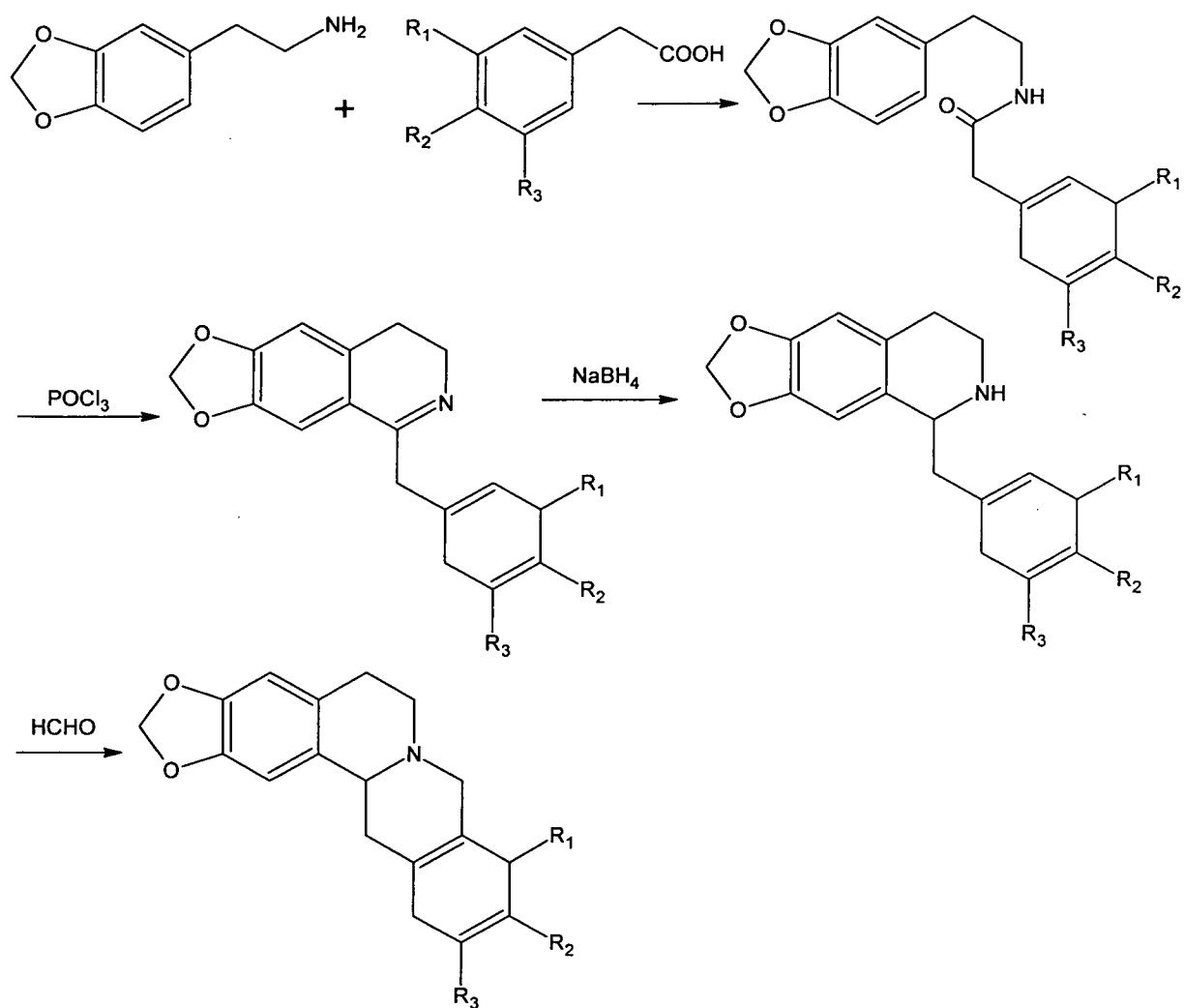


compound 1: $\text{R}_1=\text{H}, \text{R}_2=\text{F}$

compound 2: $\text{R}_1=\text{H}, \text{R}_2=\text{OH}$

compound 3: $\text{R}_1=\text{OH}, \text{R}_2=\text{OCH}_3$

Route 2:

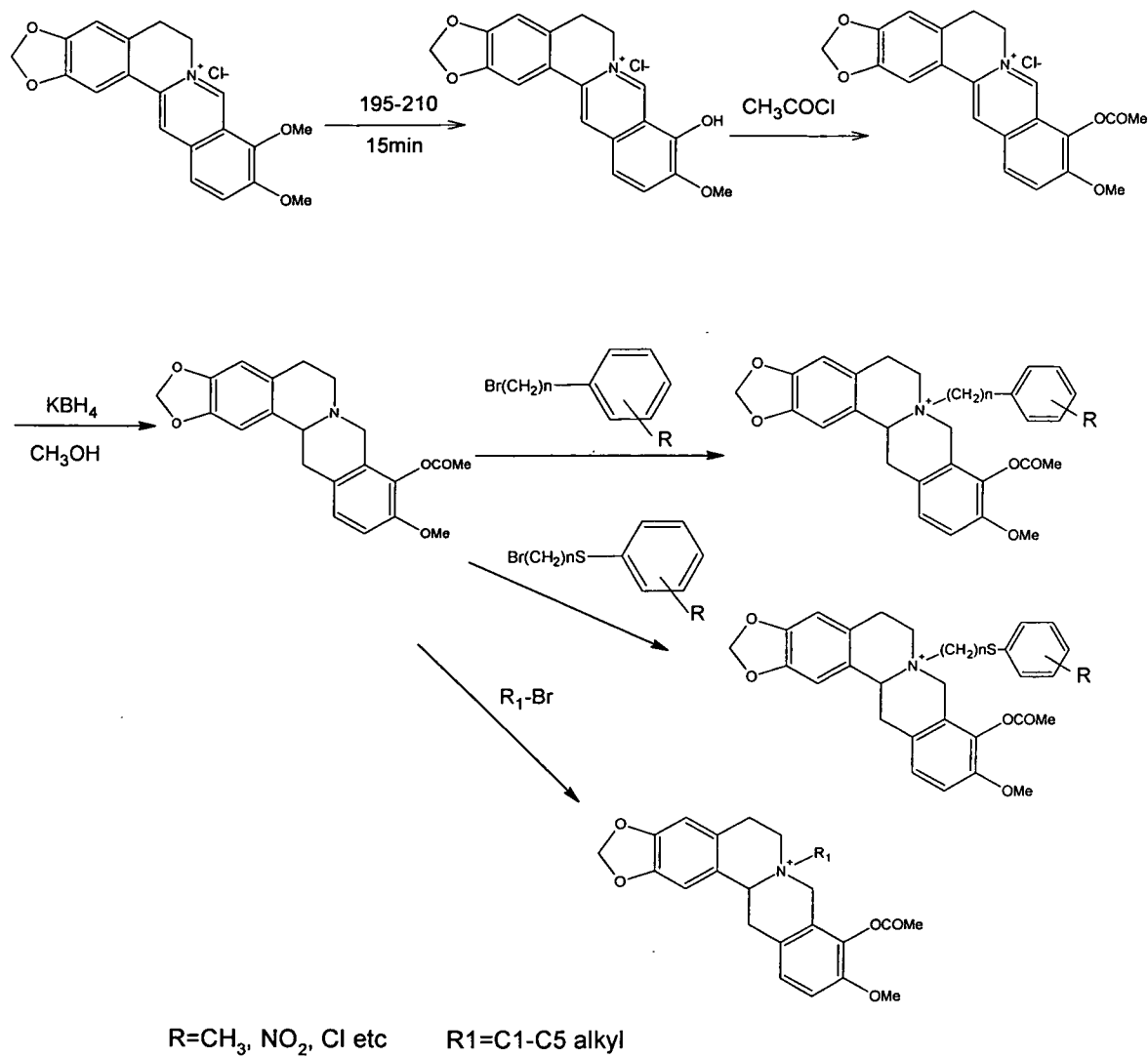


compound 1: $R_1=\text{CH}_3$, $R_2=\text{H}$, $R_3=\text{CH}_3$

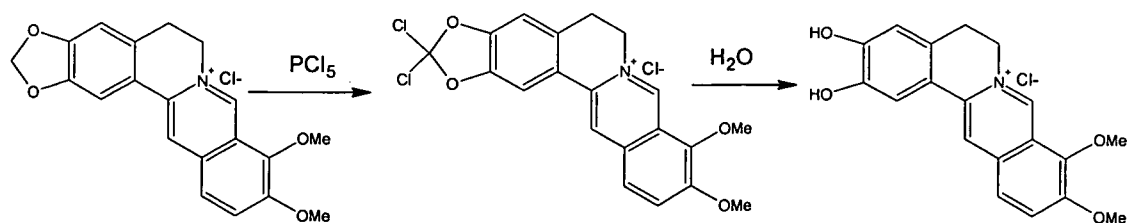
compound 2: $R_1=\text{OH}$, $R_2=\text{OCH}_3$, $R_3=\text{H}$

compound 3: $R_1=\text{H}$, $R_2=\text{OCH}_3$, $R_3=\text{H}$

Route 3:



5 Route 4:



[00157] Lipid lowering compositions comprise an active compound as described herein (including berberine, a berberine related compound, berberine metabolite, berberine prodrug, or berberine derivative compound of any of the Formulae herein, such as Formula I or Formula II, any active compound of formulae VI-IX, any active compound of Formulae I-V, XXVI-XXVIII, or XXXII-XXXVI, including any of the species within these classes of active compounds, and active combinations thereof) in a lipid lowering effective amount for prophylaxis and/or treatment of hyperlipidemia, hypercholesterolemia and elevated triglycerides in a mammalian subject. Typically, a lipid lowering effective amount will comprise an amount of the active compound which is therapeutically effective, in a single or multiple unit dosage form, over a specified period of therapeutic intervention, to measurably alleviate one or more symptoms of hyperlipidemia or elevated cholesterol in the subject, and/or to alleviate one or more symptom(s) of a cardiovascular disease or condition in the subject. Within exemplary embodiments, these compositions are effective within *in vivo* treatment methods to alleviate hyperlipidemia.

[00158] Lipid lowering compositions of the invention typically comprise a lipid lowering effective amount or unit dosage of the active compound, which may be formulated with one or more pharmaceutically acceptable carriers, excipients, vehicles, emulsifiers, stabilizers, preservatives, buffers, and/or other additives that may enhance stability, delivery, absorption, half-life, efficacy, pharmacokinetics, and/or pharmacodynamics, reduce adverse side effects, or provide other advantages for pharmaceutical use. Lipid lowering effective amounts including cholesterol lowering effective amounts and/or triglyceride lowering effective amounts of the active compound will be readily determined by those of ordinary skill in the art, depending on clinical and patient-specific factors. Suitable effective unit dosage amounts of the active compounds for administration to mammalian subjects, including humans, may range from 10 to 1500 mg, 20 to 1000 mg, 25 to 750 mg, 50 to 500 mg, 150 to 500 mg, 100 to 200mg, 200 to 400mg, or 400 to 600 mg. In certain embodiments, the anti-hyperlipidemia or hypolipidemia effective dosage of a berberine derivative compound of Formula XXVII may be selected within narrower ranges of, for example, 10 to 25 mg, 30-50 mg, 75 to 100 mg, 100 to 250 mg, or 250 to 500 mg. These and other effective unit dosage amounts may be administered in a single dose, or in the form of multiple daily, weekly or monthly doses, for example in a dosing regimen

comprising from 1 to 5, or 2-3, doses administered per day, per week, or per month. In one exemplary embodiment, dosages of 10 to 25 mg, 30-50 mg, 75 to 100 mg, 100 to 250 mg, or 250 to 500 mg, are administered one, two, three, four, or five times per day. In more detailed embodiments, dosages of 50-75 mg, 100-200 mg, 250-400 mg, or 400-600 mg are administered once or twice daily. In alternate embodiments, dosages are calculated based on body weight, and may be administered, for example, in amounts from about 0.5mg/kg to about 100mg/kg per day, 1mg/kg to about 75mg/kg per day, 1mg/kg to about 50mg/kg per day, 2mg/kg to about 50mg/kg per day, 2mg/kg to about 30mg/kg per day or 3mg/kg to about 30mg/kg per day.

[00159] Glucose lowering compositions comprise an active compound as described above, or pharmaceutical formulations comprising the active compound in a glucose lowering effective amount effective for prophylaxis and/or treatment of hyperglycemia in a mammalian subject. Typically, a glucose lowering effective amount will comprise an amount of the active compound which is therapeutically effective, in a single or multiple unit dosage form, over a specified period of therapeutic intervention, to measurably alleviate one or more symptoms of hyperglycemia in the subject, and/or to alleviate one or more symptom(s) of a cardiovascular disease or condition in the subject. Within exemplary embodiments, these compositions are effective within *in vivo* treatment methods to alleviate hyperglycemia.

[00160] Insulin sensitivity increasing and insulin resistance decreasing compositions comprising an active compound or pharmaceutical formulation thereof in an insulin sensitivity increasing and/or insulin resistance decreasing effective amount, which is effective for prophylaxis and/or treatment of insulin resistance in a mammalian subject. Typically, a insulin sensitivity increasing and/or insulin resistance decreasing effective amount will comprise an amount of the active compound which is therapeutically effective, in a single or multiple unit dosage form, over a specified period of therapeutic intervention, to measurably alleviate one or more symptoms of insulin resistance in the subject, and/or to alleviate one or more symptom(s) of a cardiovascular disease or condition in the subject. Within exemplary embodiments, these compositions are effective within *in vivo* treatment methods to alleviate insulin resistance.

[00161] Glucose lowering or insulin sensitivity increasing/insulin resistance decreasing compositions of the invention typically comprise a glucose lowering effective amount or unit dosage of the active compound, which may be formulated with one or more pharmaceutically acceptable carriers, excipients, vehicles, emulsifiers, stabilizers, preservatives, buffers, and/or

other additives that may enhance stability, delivery, absorption, half-life, efficacy, pharmacokinetics, and/or pharmacodynamics, reduce adverse side effects, or provide other advantages for pharmaceutical use. Glucose lowering effective amounts of the active compound will be readily determined by those of ordinary skill in the art, depending on clinical and patient-specific factors. Suitable effective unit dosage amounts of the active compounds for administration to mammalian subjects, including humans, may range from 10 to 1500 mg, 20 to 1000 mg, 25 to 750 mg, 50 to 500 mg, or 150 to 500 mg. In certain embodiments, the anti-hyperglycemic effective dosage of the active compound may be selected within narrower ranges of, for example, 10 to 25 mg, 30-50 mg, 75 to 100 mg, 100 to 250 mg, or 250 to 500 mg. These and other effective unit dosage amounts may be administered in a single dose, or in the form of multiple daily, weekly or monthly doses, for example in a dosing regimen comprising from 1 to 5, or 2-3, doses administered per day, per week, or per month. In one exemplary embodiment, dosages of 10 to 25 mg, 30-50 mg, 75 to 100 mg, 100 to 250 mg, or 250 to 500 mg, are administered one, two, three, four, or five times per day. In more detailed embodiments, dosages of 50-75 mg, 100-200 mg, 250-400 mg, or 400-600 mg are administered once or twice daily. In alternate embodiments, dosages are calculated based on body weight, and may be administered, for example, in amounts from about 0.5mg/kg to about 100mg/kg per day, 1mg/kg to about 75mg/kg per day, 1mg/kg to about 50mg/kg per day, 2mg/kg to about 50mg/kg per day, 2mg/kg to about 30mg/kg per day or 3mg/kg to about 30mg/kg per day.

[00162] The amount, timing and mode of delivery of compositions of the invention comprising an anti-hyperlipidemia and/or anti-hyperglycemic effective amount of an active compound as described will be routinely adjusted on an individual basis, depending on such factors as weight, age, gender, and condition of the individual, the acuteness of the hyperlipidemia and/or related symptoms, whether the administration is prophylactic or therapeutic, and on the basis of other factors known to effect drug delivery, absorption, pharmacokinetics, including half-life, and efficacy.

[00163] An effective dose or multi-dose treatment regimen for the instant lipid lowering formulations will ordinarily be selected to approximate a minimal dosing regimen that is necessary and sufficient to substantially prevent or alleviate hyperlipidemia and cardiovascular diseases in the subject, and/or to substantially prevent or alleviate one or more symptoms associated with hyperlipidemia in the subject. A dosage and administration protocol will often

include repeated dosing therapy over a course of several days or even one or more weeks or years. An effective treatment regime may also involve prophylactic dosage administered on a day or multi-dose per day basis lasting over the course of days, weeks, months or even years.

[00164] An effective dose or multi-dose treatment regimen for the instant glucose

5 lowering formulations will ordinarily be selected to approximate a minimal dosing regimen that is necessary and sufficient to substantially prevent or alleviate hyperglycemia in the subject, and/or to substantially prevent or alleviate one or more symptoms associated with hyperglycemia in the subject. A dosage and administration protocol will often include repeated dosing therapy over a course of several days or even one or more weeks or years. An effective treatment regime
10 may also involve prophylactic dosage administered on a day or multi-dose per day basis lasting over the course of days, weeks, months or even years.

[00165] Various assays and model systems can be readily employed to determine the therapeutic effectiveness of anti-hyperlipidemia treatment according to the invention. For example, blood tests to measure total cholesterol as well as triglycerides, LDL and HDL levels
15 are routinely given. Individuals with a total cholesterol level of greater than 200 mg/dL are considered borderline high risk for cardiovascular disease. Those with a total cholesterol level greater than 239 mg/dL are considered to be at high risk. An LDL level of less than 100 mg/dL is considered optimal. LDL levels between 130 to 159mg/dL are borderline high risk. LDL levels between 160 to 189 mg/dL are at high risk for cardiovascular disease and those individuals
20 with an LDL greater than 190 mg/dL are considered to be at very high risk for cardiovascular disease. Triglyceride levels of less than 150 mg/dL are considered normal. Levels between 150–199 mg/dL are borderline high and levels above 200 are considered to put the individual at high risk for cardiovascular disease. Lipid levels can be determined by standard blood lipid profile tests. Effective amounts of the compositions of the invention will lower elevated lipid
25 levels by at least 10%, 20%, 30%, 50% or greater reduction, up to a 75-90%, or 95% or greater. Effective amounts will also move the lipid profile of an individual towards the optimal category for each lipid, i.e., decrease LDL levels from 190mg/dl to within 130 to 159mg/dL or even further to below 100 mg/dL. Effective amounts may further decrease LDL or triglyceride levels by about 10 to about 70 mg/dL, by about 20 to about 50 mg/dL, by about 20 to about 30 mg/dL,
30 or by about 10 to about 20 mg/dL.

[00166] Individuals may also be evaluated using a hs-CRP (high-sensitivity C-reactive protein) blood test. Those with a hs-CRP result of less than 1.0 mg/L are at low risk for cardiovascular disease. Individuals with a hs-CRP result between about 1.0 to 3.0 mg/L are at average risk for cardiovascular disease. Those with a hs-CRP result greater than 3.0 mg/L are at high risk of cardiovascular disease. Effective amounts of the compositions of the present invention will lower hs-CRP results below 3.0mg/L. Effective amounts of the compositions of the present invention can lower hs-CRP results by about 0.5 to about 3.0mg/L, and further by about 0.5 to about 2.0mg/L. An effective amount of a berberine related or derivative compound of Formula XXVII of the present invention will lower the hs-CRP level from over 3.0 mg/L to between 1.0 and 3.0 mg/l, more preferably to about 1.0 mg/L to about 0.6 mg/L.

[00167] Therapeutic effectiveness may be determined, for example, through a change in body fat as determined by body fat measurements. Body fat measurements may be determined by a variety of means including, but not limited to, determinations of skinfold thickness, bioelectrical impedance, air displacement plethysmography, underwater weighing, DEXA scans, measurement on a scale or calculation of body mass index (BMI).

[00168] Percentages of weight due to body fat for normal men are between 10-20%. In athletes, the normal range is between 6-10%. In women, the normal range is between 15-25% and in athletic women it is between 10-15%. Effective amounts of the compounds of the present invention will decrease body fat percentages from above 20-25%. Effective amounts may also decrease body fat percentages to within the normal ranges for that individual. Effectiveness may also be demonstrated by a 2-50%, 10-40%, 15-30%, 20-25% decrease in body fat.

[00169] Skinfold measurements measure subcutaneous fat located directly beneath the skin by grasping a fold of skin and subcutaneous fat between the thumb and forefinger and pulling it away from the underlying muscle tissue. The thickness of the double layer of skin and subcutaneous tissue is then read with a caliper. The five most frequently measured sites are the upper arm, below the scapula, above the hip bone, the abdomen, and the thigh. Skinfold measurements are used to determine relative fatness, changes in physical conditioning programs, and the percentage of body fat in desirable body weight. Effective amounts of berberine related or derivative compound of Formula XXVII will decrease body fat percentages by 2-50%, 10-40%, 15-30%, 20-25%, 30-40% or more.

[00170] Body fat percentages can also be determined by body impedance measurements. Body impedance is measured when a small electrical signal is passed through the body carried by water and fluids. Impedance is greatest in fat tissue, which contains only 10-20% water, while fat-free mass, which contains 70-75% water, allows the signal to pass much more easily.

5 By using the impedance measurements along with a person's height, weight, and body type (gender, age, fitness level), it is possible to calculate the percentage of body fat, fat-free mass, hydration level, and other body composition values. Effective amounts of the active compound will decrease body fat percentages by 2-50%, 10-40%, 15-30%, 20-25%, 30-40% or more.

[00171] Hydrostatic or underwater weighing is another method for determining lean
10 muscle mass and body fat percentages. It is based upon the application of the Archimedes principle, and requires weighing the subject on land, repeated weighing under water, and an estimation of air present in the lungs of the subject using gas dilution techniques. To perform the analysis, an individual is weighed as normal. The subject, in minimal clothing, then sits on a special seat, expels all air from the lungs and is lowered into a tank until all body parts are
15 emerged. Underwater weight is then determined. Body density is then determined using the following calculation: $\text{Body density} = W_a / (((W_a - W_w) / D_w) - (RV + 100\text{cc}))$, where W_a =body weight in air (kg), W_w =body weight in water (kg), D_w =density of water, RV =residual lung volume, and 100cc is the correction for air trapped in the gastrointestinal tract.

[00172] DEXA, or dual energy x-ray absorptiometry scans determine whole body as well
20 as regional measurements of bone mass, lean mass, and fat mass. Total fat mass is expressed in kg and as a percentage of body mass. These are calculated by integrating the measurements for the whole body and different automatic default regions such as arms, trunk, and legs.

[00173] Body fat percentages may further be determined by air displacement
25 plethysmography. Air displacement plethysmography determines the volume of a subject to be measured by measuring the volume of air displaced by the subject in an enclosed chamber. The volume of air in the chamber is calculated through application of Boyle's Law and/or Poisson's Law to conditions within the chamber. More particularly, in the most prevalent method of air displacement plethysmography used for measuring human body composition (such as disclosed in U.S. Pat. No. 4,369,652, issued to Gundlach, and U.S. Pat. No. 5,105,825, issued to
30 Dempster), volume perturbations of a fixed frequency of oscillation are induced within a measurement chamber, which perturbations lead to pressure fluctuations within the chamber.

The amplitude of the pressure fluctuations is determined and used to calculate the volume of air within the chamber using Boyle's Law (defining the relationship of pressure and volume under isothermal conditions) or Poisson's law (defining the relationship of pressure and volume under adiabatic conditions). Body volume is then calculated indirectly by subtracting the volume of air remaining inside the chamber when the subject is inside from the volume of air in the chamber when it is empty. Once the volume of the subject is known, body composition can be calculated based on the measured subject volume, weight of the subject, and subject surface area (which, for human subjects, is a function of subject weight and subject height), using known formulas defining the relationship between density and human fat mass.

[00174] Therapeutic effectiveness of treatment with an active compound of the invention may further be demonstrated, for example, through a change in body mass index. Body Mass Index (BMI) has been recognized by the U.S. Department of Health as a reference relationship between a person's height and weight and can be used to determine when extra weight above an average or normal weight range for a person of a given height can translate into and signal increased probability for additional health risks for that person. While BMI does not directly measure percent of body fat, higher BMIs are usually associated with an increase in body fat, and thus excess weight. A desired BMI range is from about 18 kg/m² to about 24 kg/m², wherein a person is considered to have a healthful weight for the person's height and is neither overweight nor underweight. A person with a BMI above 24 kg/m², such as from about 25 kg/m² to about 30 kg/m², is considered to be overweight, and a person with a BMI above about 30 kg/m² is considered to be obese. A person with a BMI above about 40 kg/m² is considered to be morbidly obese. In another aspect, an individual who has a BMI in the range of about 25 kg/m² to about 35 kg/m², and has a waist size of over 40 inches for a man and over 35 inches for a woman, is considered to be at especially high risk for health problems. Effectiveness of berberine related or derivative compound of Formula XXVII may be demonstrated by a reduction in the body mass index from a range between 40 kg/m² to about 30 kg/m² to 25 kg/m² to about 24 kg/m². A compound of the present invention may also reduce BMI from a range above 30 kg/m² to a range between 30 kg/m² to 25 kg/m² and more preferably to about 24 kg/m². Effectiveness may further be demonstrated by a decrease in body weight from 1-25%, 3-15%, 2-50%, 10-40%, 15-30%, 20-25%. Effectiveness may additionally be demonstrated by a decrease in BMI by 2-50%, 10-

40%, 15-30%, 20-25%, 30-40% or more. Effective amounts of the active compound will lower an individual's BMI to within about 18 kg/m² to about 24 kg/m².

[00175] Therapeutic effectiveness of active compounds of the invention may also be determined by changes in the waist/hip ratio. The waist/hip ratio is determined by dividing the circumference of the waist by the circumference of the hip. Women should have a waist/hip ratio of 0.8 or less and men should have a waist/hip ratio of 0.95 or less. Effective amounts of the active compound will lower the waist/hip ratio by about 2-50%, 10-40%, 15-30%, 20-25% or more. The waist/hip ratio of a female subject may be lowered to 0.8 or less and the ratio of a male subject to a ratio of 0.95 or less. In alternative embodiments, effective amounts of active compounds will decrease weight by about 2-50%, 10-40%, 15-30%, 20-25% or more, or will yield a waist circumference decrease of a similar percentage, e.g., to decrease waist circumference by about 2-50%, 10-40%, 15-30%, 20-25% or more.

[00176] Therapeutic effectiveness may also be demonstrated with a decrease in fasting glucose. A fasting glucose test measures blood glucose after an overnight fast. Fasting glucose levels of 100 to 125 mg/dL are above normal. Effective amounts of active compounds of the invention will decrease fasting glucose levels by about 2-50%, 10-40%, 15-30%, 20-25% or more, or will lower the fasting glucose level from above 125 mg/dL to a range between 70 to 99 mg/dL. An effective amount of a composition of the present invention may further lower fasting glucose levels by about 1 to about 5 mg/dL, by about 1 to about 10 mg/dL, by about 5 to about 20 mg/dL, by about 5 to about 30 mg/dL, by about 20 to about 60 mg/dL or more.

[00177] Therapeutic effectiveness may further be demonstrated by a glucose tolerance test. A glucose tolerance test is taken after an overnight fast and 2 hours after consumption of a glucose solution. An effective amount of an active compound of the invention will lower glucose levels by about 2-50%, 10-40%, 15-30%, 20-25% or more, or from above 200 mg/dL to a range between 140 to 200 mg/dL, and more preferably to below 140 mg/dL. An effective amount of an active compound may alternatively lower glucose levels by about 1 to about 5 mg/dL, by about 1 to about 10 mg/dL, by about 5 to about 20 mg/dL, by about 5 to about 30 mg/dL, by about 20 to about 60 mg/dL or more.

[00178] Therapeutic effectiveness may additionally be demonstrated by a hyperinsulinemic euglycemic clamp study. In a hyperinsulinemic euglycemic clamp study, insulin and glucose are infused intravenously at several different doses to determine what levels

of insulin control different levels of glucose. Through a peripheral vein, insulin is infused at 0.06 units per kg body weight per minute. In order to compensate for the insulin infusion, glucose 20% is infused to maintain blood sugar levels between 5 and 5.5 mmol/l. The rate of glucose infusion is determined by checking the blood sugar levels every 5 minutes. The rate of glucose infusion during the last 30 minutes of the test determines insulin sensitivity. If high levels (7.5 mg/min or higher) are required, the patient is insulin-sensitive. Very low levels (4.0 mg/min or lower) indicate that the body is resistant to insulin action. Levels between 4.0 and 7.5 mg/min are not definitive and suggest "impaired glucose tolerance," an early sign of insulin resistance. Effective amounts of active compounds of the present invention will increase the amount of glucose consumed from below 4.0 mg/min to about 7.5 mg/min or more, or will increase glucose clearance by 2-50%, 10-40%, 15-30%, 20-25% or more.

[00179] Therapeutic effectiveness may further be determined by a glycohemoglobin test. A glycohemoglobin test is a blood test that measures the amount of glucose bound to hemoglobin. The results reflect the amount of glycohemoglobin divided by the total amount of hemoglobin multiplied by 100 (to produce a percentage). An effective amount of an active compound of the invention will decrease the hemoglobin A1c % to less than 14%, preferably to between 8 and 10%, more preferably to between 5 and 8%, more preferably to between 6 and 8% and most preferably to between 4 to 6%, or may decrease the hemoglobin A1c% by about 2-50%, 10-40%, 15-30%, 20-25% or more.

[00180] Therapeutic effectiveness may also be calculated through an insulin suppression test. During this test, subjects receive a continuous infusion of a fixed combination of glucose and insulin, while endogenous insulin secretion is blocked by somatostatin or octreotide. After around 150 min, a steady-state of glucose and insulin levels is achieved, at which time, the steady-state glucose and insulin levels are measured and their quotient calculated as a measure of insulin sensitivity. An effective amount of active compounds of the present invention will increase insulin sensitivity by about 2-50%, 10-40%, 15-30%, 20-25% or more.

[00181] Therapeutic effectiveness may additionally be determined by the C13 glucose breath test in which glucose labeled with non-radioactive C13, is ingested and the byproduct of its metabolism $^{13}\text{CO}_2$ is detected in expired air. In insulin resistant states glucose uptake would be impaired and the production of $^{13}\text{CO}_2$ would therefore also be impaired. An effective amount

of an active compound of the present invention will increase $^{13}\text{CO}_2$ by about 2-50%, 10-40%, 15-30%, 20-25% or more.

[00182] Therapeutic effectiveness may further be determined by a random plasma glucose test. An effective amount of active compound will decrease blood glucose from above
5 200mg/dL to a range between 140 to 200 mg/dL, and more preferably to below 140 mg/dL.

[00183] In another aspect of the invention, therapeutic effectiveness may be determined by a CIGMA test in which $180 \text{ mg/min}^{-1}/\text{m}^{-2}$ of glucose is infused for 120 min at a rate of 5 mg/kg with blood samples are taken at 110, 115 and 120 minutes. An effective amount of an active compound will increase glucose clearance by 2-50%, 10-40%, 15-30%, 20-25% or more.

10 [00184] In a further aspect of the invention, therapeutic effectiveness may be determined by a FSIVGTT test in which an intravenous glucose bolus (0.3g/kg) is administered followed by a 5 minute insulin infusion 20 minutes later. Blood samples are tested for glucose every two minutes for the first 20 minutes and samples are tested for glucose and insulin levels at 22, 24, 26, 28, 30, 33, 36, 40, 50, 60, 70, 80, 100, 120, 140, 160 and 180 minutes. An effective amount
15 of active compound will increase glucose clearance by 2-50%, 10-40%, 15-30%, 20-25% or more.

[00185] Effectiveness may further be determined by blood pressure testing. Effective amounts of active compounds of the present invention will lower blood pressure from above
20 150/100 mm Hg to less than 120/80 mm Hg, preferably to between about 139/89 mm to about 120/80mm Hg, most preferably to less than 120/80mm Hg. Preferably the methods and compositions of the present invention will lower blood pressure to between 110/60 mm Hg to about 120/70 mmHg.

[00186] Therapeutic effectiveness may also be determined by a D-dimer test. An effective amount of an active compound will decrease the amount of d-dimer in a sample to about 0-300
25 ng/ml, or may decrease the d-dimer level in a sample by about 2-50%, 10-40%, 15-30%, 20-25% or more.

[00187] Within additional aspects of the invention, effectiveness of the compositions and methods of the invention may also be demonstrated by a significant decrease or improvement in the complications or symptoms of metabolic and cardiovascular disorders including fatty liver,
30 reproductive abnormalities, growth abnormalities, arterial plaque accumulation, osteoarthritis, gout, joint pain, respiratory problems, skin conditions, sleep apnea, idiopathic intracranial

hypertension, lower extremity venous stasis disease, gastro-esophageal reflux, urinary stress incontinence, kidney damage, cardiovascular diseases such as atherosclerosis, coronary artery disease, enlarged heart, diabetic cardiomyopathy, angina pectoris, carotid artery disease, peripheral vascular disease, stroke, cerebral arteriosclerosis, myocardial infarction, cerebral
5 infarction, restenosis following balloon angioplasty, intermittent claudication, dyslipidemia post-prandial lipidemia, high blood pressure and xanthoma.

[00188] Effectiveness of the compositions and methods of the invention may also be demonstrated by a decrease in the symptoms of cardiovascular disease including shortness of breath, chest pain, leg pain, tiredness, confusion vision changes, blood in urine, nosebleeds,
10 irregular heartbeat, loss of balance or coordination, weakness, or vertigo.

[00189] For each of the indicated conditions described herein, test subjects administered the active compound will exhibit a 5%, 10%, 20%, 30%, 50% or greater reduction, up to a 75-90%, or 95% or greater, reduction, in one or more symptom(s) caused by, or associated with, hyperlipidemia, hyperglycemia, elevated cholesterol, hypertension, metabolic syndrome, obesity,
15 diabetes, elevated glucose and/or a targeted cardiovascular disease or condition in the subject, compared to placebo-treated or other suitable control subjects.

[00190] Within additional aspects of the invention, combinatorial lipid lowering formulations and coordinate administration methods are provided which employ an effective amount of an active compound as described herein in combination with one or more secondary
20 or adjunctive agent(s) that is/are combinatorially formulated or coordinately administered with the active compound to yield a combined, multi-active agent anti-hyperlipidemia composition or coordinate treatment method. Exemplary combinatorial formulations and coordinate treatment methods in this context employ the berberine related or derivative compound in combination with the one or more secondary anti-hyperlipidemia agent(s), or with one or more adjunctive
25 therapeutic agent(s) that is/are useful for treatment or prophylaxis of the targeted (or associated) disease, condition and/or symptom(s) in the selected combinatorial formulation or coordinate treatment regimen.

[00191] Within additional aspects of the invention, combinatorial glucose lowering formulations and coordinate administration methods are provided which employ an effective
30 amount of the active compound and one or more secondary or adjunctive agent(s) that is/are combinatorially formulated or coordinately administered with the active compound to yield a

combined, multi-active agent anti-hyperglycemic composition or coordinate treatment method. Exemplary combinatorial formulations and coordinate treatment methods in this context employ the active compound in combination with the one or more secondary anti-hyperglycemic agent(s), or with one or more adjunctive therapeutic agent(s) that is/are useful for treatment or prophylaxis of the targeted (or associated) disease, condition and/or symptom(s) in the selected combinatorial formulation or coordinate treatment regimen.

[00192] Within further aspects of the invention, combinatorial hypertension lowering formulations and coordinate administration methods are provided which employ an effective amount of active compound and one or more secondary or adjunctive agent(s) that is/are combinatorially formulated or coordinately administered with the active compound to yield a combined, multi-active agent anti-hypertensive composition or coordinate treatment method. Exemplary combinatorial formulations and coordinate treatment methods in this context employ active compound in combination with the one or more secondary anti-hypertensive agent(s), or with one or more adjunctive therapeutic agent(s) that is/are useful for treatment or prophylaxis of the targeted (or associated) disease, condition and/or symptom(s) in the selected combinatorial formulation or coordinate treatment regimen

[00193] For most combinatorial formulations and coordinate treatment methods of the invention, active compound is formulated, or coordinately administered, in combination with one or more secondary or adjunctive therapeutic agent(s), to yield a combined formulation or coordinate treatment method that is combinatorially effective or coordinately useful to treat hyperlipidemia, hyperglycemia, hypertension, metabolic syndrome, diabetes, obesity, insulin resistance and/or one or more symptom(s) of a metabolic disorder or condition in the subject. Exemplary combinatorial formulations and coordinate treatment methods in this context employ active compound in combination with one or more secondary or adjunctive therapeutic agents selected from, e.g., The secondary or adjunctive therapeutic agents used in combination with, e.g., berberine in these embodiments may possess direct or indirect lipid and/or glucose lowering activity and/or hypertension decreasing activity, including cholesterol lowering activity, insulin resistance decreasing activity, insulin sensitivity increasing activity or glucose regulating activity, alone or in combination with, e.g., berberine, or may exhibit other useful adjunctive therapeutic activity in combination with, e.g., berberine. Useful adjunctive therapeutic agents in these combinatorial formulations and coordinate treatment methods include, for example, anti-

hyperlipidemic agents; anti-dyslipidemic agents; plasma HDL-raising agents; anti-hypercholesterolemic agents, including, but not limited to, cholesterol-uptake inhibitors; cholesterol biosynthesis inhibitors, e.g., HMG-CoA reductase inhibitors (also referred to as statins, such as lovastatin, simvastatin, pravastatin, fluvastatin, rosuvastatin, pitavastatin, and atorvastatin); HMG-CoA synthase inhibitors; squalene epoxidase inhibitors or squalene synthetase inhibitors (also known as squalene synthase inhibitors); acyl-coenzyme A cholesterol acyltransferase (ACAT) inhibitors, including, but not limited to, melinamide; probucol; nicotinic acid and the salts thereof; niacinamide; cholesterol absorption inhibitors, including, but not limited to, β -sitosterol or ezetimibe; bile acid sequestrant anion exchange resins, including, but not limited to cholestyramine, colestipol, colesevelam or dialkylaminoalkyl derivatives of a cross-linked dextran; LDL receptor inducers; fibrates, including, but not limited to, clofibrate, bezafibrate, fenofibrate and gemfibrozil; vitamin B6 (also known as pyridoxine) and the pharmaceutically acceptable salts thereof, such as the HCl salt; vitamin B12 (also known as cyanocobalamin); vitamin B3 (also known as nicotinic acid and niacinamide, supra); anti-oxidant vitamins, including, but not limited to, vitamin C and E and betacarotene; angiotensin II receptor (AT_1) antagonist; renin inhibitors; platelet aggregation inhibitors, including, but not limited to, fibrinogen receptor antagonists, i.e., glycoprotein IIb/IIIa fibrinogen receptor antagonists; hormones, including but not limited to, estrogen; insulin; ion exchange resins; omega-3 oils; benfluorex; ethyl icosapentate; and amlodipine; appetite-suppressing agents or anti-obesity agents including, but not limited to, insulin sensitizers, protein tyrosine phosphatase-1B (PTP-1B) inhibitors, dipeptidyl peptidase IV (DP-IV) inhibitors, insulin or insulin mimetics, sequestrants, nicotiny alcohol, nicotinic acid, PPAR α agonists, PPAR γ agonists including glitazones, PPAR α / γ dual agonists, inhibitors of cholesterol absorption, acyl CoA:cholesterol acyltransferase inhibitors, anti-oxidants, anti-obesity compounds, neuropeptide Y5 inhibitors, β_3 adrenergic receptor agonists, ileal bile acid transporter inhibitors, anti-inflammatories and cyclooxygenase 2 selective inhibitors; insulin; sulfonylureas, including but not limited to chlorpropamide, glipizide, glyburide, and glimepiride; cannabinoid antagonists including, but not limited to, rimonabant; camptothecin and camptothecin derivatives, DPP-4 blockers; biguanides, including but not limited to metformin and phenformin; thiazolidinediones including but not limited to rosiglitazone, troglitazone and pioglitazone; alpha-glucosidase inhibitors, including, but not limited to, acarbose and meglitol; D-phenylalanine derivatives; meglitinides; diuretics

including, but not limited to, methyclothiazide, hydroflumethiazide, metolazone, chlorothiazide, methyclothiazide, hydrochlorothiazide, quinethazone, chlorthalidone, trichlormethiazide, bendroflumethiazide, polythiazide, hydroflumethiazide, spironolactone, triamterene, amiloride, bumetanide, torsemide, ethacrynic acid, furosemide; beta-blockers including, but not limited to
5 acebutolol, atenolol, betaxolol, bisoprolol, carteolol, metoprolol, nadolol, pindolol, propranolol, and timolol.; angiotensin-converting enzyme (ACE) inhibitors including, but not limited to, benazepril, captopril; enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril; calcium channel blockers including, but not limited to, amlodipine, diltiazem, felodipine, isradipine, nicardipine sr, nifedipine er, nisoldipine, and verapamil; vasodilators
10 including, but not limited to, nitric oxide, hydralazine, and prostacyclin; angiotensin II receptor blockers including, but not limited to, andesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan; alpha blockers including, but not limited to, doxazosin, prazosin and terazosin; alpha 2 agonists including, but not limited to clonidine and guanfacine. Such agents may be referred to in whole or in part as metabolic disorder therapeutics, metabolic syndrome
15 therapeutics, anti-obesity therapeutics, anti-hypercholesterolemia therapeutics, anti-diabetic therapeutics, insulin resistance therapeutic agents, anti-hyperglycemia agents, insulin sensitivity increasing agents, anti-hypertensive agents, and/or blood glucose lowering therapeutic agents. Adjunctive therapies may also be used including, but not limited, physical treatments such as changes in diet, psychological counseling, behavior modification, exercise and surgery including,
20 but not limited to, gastric partitioning procedures, jejunoileal bypass, stomach stapling, gastric bands, vertical banded gastroplasty, laparoscopic gastric banding, roux-en-Y gastric bypass, biliopancreatic bypass procedures and vagotomy. Some herbal remedies may also be employed effectively in combinatorial formulations and coordinate therapies for treating metabolic disorders, for example curcumin, gugulipid, garlic, vitamin E, soy, soluble fiber, fish oil, green
25 tea, carnitine, chromium, coenzyme Q10, anti-oxidant vitamins, grape seed extract, pantothenic acid, red yeast rice, and royal jelly.

[00194] To practice coordinate administration methods of the invention, the active compound may be administered, simultaneously or sequentially, in a coordinate treatment protocol with one or more of the secondary or adjunctive therapeutic agents contemplated herein.
30 Thus, in certain embodiments active compound is administered coordinately with a non-berberine lipid lowering agent; a non-berberine glucose lowering agent; a non-berberine insulin

sensitivity increasing agent; a non-berberine anti-diabetic agent; a non-berberine cholesterol lowering agent; a non-berberine triglyceride lowering agent, a non-berberine insulin resistance lowering agent; a non-berberine anti-hypertensive agent; or a non-berberine anti-obesity agent, or any other secondary or adjunctive therapeutic agent contemplated herein, using separate
5 formulations or a combinatorial formulation as described above (i.e., comprising both active compound and a non-berberine therapeutic agent). This coordinate administration may be done simultaneously or sequentially in either order, and there may be a time period while only one or both (or all) active therapeutic agents individually and/or collectively exert their biological activities. A distinguishing aspect of all such coordinate treatment methods is that the active
10 compound exerts at least some lipid lowering activity, some glucose lowering activity, and/or some hypertension lowering activity which yields a favorable clinical response in conjunction with a complementary agent, or distinct, clinical response provided by the secondary or adjunctive therapeutic agent. Often, the coordinate administration of the active compound with the secondary or adjunctive therapeutic agent will yield improved therapeutic or prophylactic
15 results in the subject beyond a therapeutic effect elicited by the active compound or the secondary or adjunctive therapeutic agent administered alone. This qualification contemplates both direct effects, as well as indirect effects. Within exemplary embodiments, the active compound will be coordinately administered (simultaneously or sequentially, in combined or separate formulation(s)), with one or more secondary therapeutic agents as described above.

20 **[00195]** The pharmaceutical compositions of the present invention may be administered by any means that achieve their intended therapeutic or prophylactic purpose. Suitable routes of administration for the compositions of the invention include, but are not limited to, oral, buccal, nasal, aerosol, topical, transdermal, mucosal, injectable, slow release, controlled release, iontophoresis, sonophoresis, and including all other conventional delivery routes, devices and
25 methods. Injectable methods include, but are not limited to, intravenous, intramuscular, intraperitoneal, intraspinal, intrathecal, intracerebroventricular, intraarterial, subcutaneous and intranasal routes.

[00196] The compositions of the present invention may further include a pharmaceutically acceptable carrier appropriate for the particular mode of administration being
30 employed. Dosage forms of the compositions of the present invention include excipients recognized in the art of pharmaceutical compounding as being suitable for the preparation of

dosage units as discussed above. Such excipients include, without intended limitation, binders, fillers, lubricants, emulsifiers, suspending agents, sweeteners, flavorings, preservatives, buffers, wetting agents, disintegrants, effervescent agents and other conventional excipients and additives.

5 **[00197]** If desired, the compositions of the invention can be administered in a controlled release form by use of a slow release carrier, such as a hydrophilic, slow release polymer. Exemplary controlled release agents in this context include, but are not limited to, hydroxypropyl methyl cellulose, having a viscosity in the range of about 100 cps to about 100,000 cps or other biocompatible matrices such as cholesterol.

10 **[00198]** Compositions of the invention will often be formulated and administered in an oral dosage form, optionally in combination with a carrier or other additive(s). Suitable carriers common to pharmaceutical formulation technology include, but are not limited to, microcrystalline cellulose, lactose, sucrose, fructose, glucose, dextrose, or other sugars, di-basic calcium phosphate, calcium sulfate, cellulose, methylcellulose, cellulose derivatives, kaolin,
15 mannitol, lactitol, maltitol, xylitol, sorbitol, or other sugar alcohols, dry starch, dextrin, maltodextrin or other polysaccharides, inositol, or mixtures thereof. Exemplary unit oral dosage forms for use in this invention include tablets, which may be prepared by any conventional method of preparing pharmaceutical oral unit dosage forms can be utilized in preparing oral unit dosage forms. Oral unit dosage forms, such as tablets, may contain one or more conventional
20 additional formulation ingredients, including, but not limited to, release modifying agents, glidants, compression aides, disintegrants, lubricants, binders, flavors, flavor enhancers, sweeteners and/or preservatives. Suitable lubricants include stearic acid, magnesium stearate, talc, calcium stearate, hydrogenated vegetable oils, sodium benzoate, leucine carbowax, magnesium lauryl sulfate, colloidal silicon dioxide and glyceryl monostearate. Suitable glidants
25 include colloidal silica, fumed silicon dioxide, silica, talc, fumed silica, gypsum, and glyceryl monostearate. Substances which may be used for coating include hydroxypropyl cellulose, titanium oxide, talc, sweeteners and colorants.

30 **[00199]** Additional compositions of the invention can be prepared and administered in any of a variety of inhalation or nasal delivery forms known in the art. Devices capable of depositing aerosolized purified berberine related or derivative compounds of Formula XXVII formulations in the sinus cavity or pulmonary alveoli of a patient include metered dose inhalers,

nebulizers, dry powder generators, sprayers, and the like. Methods and compositions suitable for pulmonary delivery of drugs for systemic effect are well known in the art. Additional possible methods of delivery include deep lung delivery by inhalation. Suitable formulations, wherein the carrier is a liquid, for administration, as for example, a nasal spray or as nasal drops, may include aqueous or oily solutions of berberine related or derivative compounds of Formula XXVII and any additional active or inactive ingredient(s).

[00200] Further compositions and methods of the invention are provided for topical administration of an active compound of the invention. Topical compositions may comprise the active compound along with one or more additional active or inactive component(s) incorporated in a dermatological or mucosal acceptable carrier, including in the form of aerosol sprays, powders, dermal patches, sticks, granules, creams, pastes, gels, lotions, syrups, ointments, impregnated sponges, cotton applicators, or as a solution or suspension in an aqueous liquid, non-aqueous liquid, oil-in-water emulsion, or water-in-oil liquid emulsion. These topical compositions may comprise the active compound dissolved or dispersed in a portion of water or other solvent or liquid to be incorporated in the topical composition or delivery device. It can be readily appreciated that the transdermal route of administration may be enhanced by the use of a dermal penetration enhancer known to those skilled in the art. Formulations suitable for such dosage forms incorporate excipients commonly utilized therein, particularly means, e.g. structure or matrix, for sustaining the absorption of the drug over an extended period of time, for example, 24 hours. Transdermal delivery may also be enhanced through techniques such as sonophoresis.

[00201] Yet additional compositions of are designed for parenteral administration of the active compound(s), e.g. to be administered intravenously, intramuscularly, subcutaneously or intraperitoneally, including aqueous and non-aqueous sterile injectable solutions which, like many other contemplated compositions of the invention, may optionally contain anti-oxidants, buffers, bacteriostats and/or solutes which render the formulation isotonic with the blood of the mammalian subject; and aqueous and non-aqueous sterile suspensions which may include suspending agents and/or thickening agents. The formulations may be presented in unit-dose or multi-dose containers. Additional compositions and formulations of the invention may include polymers for extended release following parenteral administration. The parenteral preparations may be solutions, dispersions or emulsions suitable for such administration. The subject agents may also be formulated into polymers for extended release following parenteral administration.

Pharmaceutically acceptable formulations and ingredients will typically be sterile or readily sterilizable, biologically inert, and easily administered. Such polymeric materials are well known to those of ordinary skill in the pharmaceutical compounding arts. Parenteral preparations typically contain buffering agents and preservatives, and injectable fluids that are pharmaceutically and physiologically acceptable such as water, physiological saline, balanced salt solutions, aqueous dextrose, glycerol or the like. Extemporaneous injection solutions, emulsions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit, daily sub-dose, as described herein above, or an appropriate fraction thereof, of the active ingredient(s).

[00202] In more detailed embodiments, compositions of the invention may comprise an active compound encapsulated for delivery in microcapsules, microparticles, or microspheres, prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly(methylmethacrylate) microcapsules, respectively; in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules); or within macroemulsions.

[00203] As noted above, in certain embodiments the methods and compositions of the invention may employ pharmaceutically acceptable salts, e.g., acid addition or base salts of the above-described active compounds. Suitable acid addition salts are formed from acids which form non-toxic salts, for example, hydrochloride, hydrobromide, hydroiodide, sulphate, hydrogen sulphate, nitrate, phosphate, and hydrogen phosphate salts. Additional pharmaceutically acceptable salts include, but are not limited to, metal salts such as sodium salts, potassium salts, cesium salts and the like; alkaline earth metals such as calcium salts, magnesium salts and the like; organic amine salts such as triethylamine salts, pyridine salts, picoline salts, ethanolamine salts, triethanolamine salts, dicyclohexylamine salts, N,N'-dibenzylethylenediamine salts and the like; organic acid salts such as acetate, citrate, lactate, succinate, tartrate, maleate, fumarate, mandelate, acetate, dichloroacetate, trifluoroacetate, oxalate, and formate salts; sulfonates such as methanesulfonate, benzenesulfonate, and p-toluenesulfonate salts; and amino acid salts such as arginate, asparagine, glutamate, tartrate, and gluconate salts. Suitable base salts are formed from bases that form non-toxic salts, for example aluminum, calcium, lithium, magnesium, potassium, sodium, zinc and diethanolamine salts.

[00204] To illustrate the range of useful salt forms of active compounds of the invention, an exemplary assemblage of salt forms of berberine were produced and tested for their solubility (Table 5). The novel berberine salts thus provided embody yet additional aspects of the invention and exemplify the broad assemblage of useful berberine and related compounds herein.

Table 5. Exemplary Berberine Salts

Sample Code	Solvent	Amount of Solute (mg)	Amount of Solvent	Solubility Ranking
1. Citrate	Distill			
	Water	10	7.5	Slightly Soluble
2. Cysteine	Distill			
	Water	10	8.8	Slightly Soluble
3. Acetate	Distill			
	Water	10	9.0	Slightly Soluble
4. Lactate	Distill			
	Water	10	6.0	Slightly Soluble
5. Nitrate	Distill			
	Water	10	8.0	Slightly Soluble
6. Methanesulfonate	Distill			
	Water	10	1.5	Slightly Soluble
7. Hydrosulfate*	Distill			
	Water	10	1.5	Slightly Soluble
8. Sulfate*	Distill			
	Water	10	0.5	Slightly Soluble
9. Salicylate	Distill			
	Water	10	6.5	Slightly Soluble
10. Oxalate	Distill			
	Water	10	6.0	Slightly Soluble
11. Phosphate	Distill			
	Water	10	8.0	Slightly Soluble
12. Formate	Distill			
	Water	10	8.5	Slightly Soluble
13. Benzoate	Distill			
	Water	10	7.0	Slightly Soluble
14. Tartrate	Distill			
	Water	10	7.0	Slightly Soluble
15. Toluenesulfonate	Distill			
	Water	10	11.0	Extremely Slightly Soluble
16. Trifluoroacetate	Distill			
	Water	10	7.5	Slightly Soluble
17. Control:	Distill			
Hydrochloric	Water	10	10.0	Extremely Slightly Soluble

[00205] In other detailed embodiments, the methods and compositions of the invention employ prodrugs of berberine related or derivative compounds of any of the Formulae described herein. Prodrugs are considered to be any covalently bonded carriers which release the active parent drug in vivo. Examples of prodrugs useful within the invention include esters or amides

with hydroxyalkyl or aminoalkyl as a substituent, and these may be prepared by reacting such compounds as described above with anhydrides such as succinic anhydride.

[00206] The invention disclosed herein will also be understood to encompass methods and compositions comprising related or derivative compounds of any of the Formulae described herein using in vivo metabolic products of the said compounds (either generated *in vivo* after administration of the subject precursor compound, or directly administered in the form of the metabolic product itself). Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification, glycosylation and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes methods and compositions of the invention employing compounds produced by a process comprising contacting any active compound as described herein with a mammalian subject for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled compound of the invention, administering it parenterally in a detectable dose to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur and isolating its conversion products from the urine, blood or other biological samples.

[00207] The invention disclosed herein will also be understood to encompass diagnostic compositions for diagnosing the risk level, presence, severity, or treatment indicia of, or otherwise managing a hyperlipidemia and/or cardiovascular disease or condition in a mammalian subject, comprising contacting a labeled (e.g., isotopically labeled, fluorescent labeled or otherwise labeled to permit detection of the labeled compound using conventional methods) active compound as described herein to a mammalian subject (e.g., to a cell, tissue, organ, or individual) at risk or presenting with one or more symptom(s) of hyperlipidemia and/or cardiovascular disease, and thereafter detecting the presence, location, metabolism, and/or binding state (e.g., detecting binding to an unlabeled binding partner involved in LDL receptor physiology/metabolism) of the labeled active compound using any of a broad array of known assays and labeling/detection methods.

[00208] The invention disclosed herein will also be understood to encompass diagnostic compositions for diagnosing the risk level, presence, severity, or treatment indicia of, or otherwise managing a metabolic disorder disease or condition in a mammalian subject, comprising contacting a labeled (e.g., isotopically labeled, fluorescent labeled or otherwise

labeled to permit detection of the labeled compound using conventional methods) active compound to a mammalian subject (e.g., to a cell, tissue, organ, or individual) at risk or presenting with one or more symptom(s) of metabolic disorders, and thereafter detecting the presence, location, metabolism, and/or binding state (e.g., detecting binding to an unlabeled binding partner involved in InsR receptor physiology/metabolism) of the labeled compound using any of a broad array of known assays and labeling/detection methods.

[00209] The invention disclosed herein will further be understood to encompass diagnostic compositions for diagnosing the risk level, presence, severity, or treatment indicia of, or otherwise managing a hyperglycemic disease or condition in a mammalian subject, comprising contacting a labeled (e.g., isotopically labeled, fluorescent labeled or otherwise labeled to permit detection of the labeled compound using conventional methods) active compound to a mammalian subject (e.g., to a cell, tissue, organ, or individual) at risk or presenting with one or more symptom(s) of hyperglycemia, and thereafter detecting the presence, location, metabolism, and/or binding state (e.g., detecting binding to an unlabeled binding partner involved in InsR receptor physiology/metabolism) of the labeled compound using any of a broad array of known assays and labeling/detection methods.

[00210] The invention disclosed herein will additionally be understood to encompass diagnostic compositions for diagnosing the risk level, presence, severity, or treatment indicia of, or otherwise managing insulin resistance in a mammalian subject, comprising contacting a labeled (e.g., isotopically labeled, fluorescent labeled or otherwise labeled to permit detection of the labeled compound using conventional methods) active compound to a mammalian subject (e.g., to a cell, tissue, organ, or individual) at risk or presenting with one or more symptom(s) of insulin resistance, and thereafter detecting the presence, location, metabolism, and/or binding state (e.g., detecting binding to an unlabeled binding partner involved in InsR receptor physiology/metabolism) of the labeled compound using any of a broad array of known assays and labeling/detection methods.

[00211] The invention disclosed herein will also be understood to encompass diagnostic compositions for diagnosing the risk level, presence, severity, or treatment indicia of, or otherwise managing a hypertensive disease or condition in a mammalian subject, comprising contacting a labeled (e.g., isotopically labeled, fluorescent labeled or otherwise labeled to permit detection of the labeled compound using conventional methods) active compound to a

mammalian subject (e.g., to a cell, tissue, organ, or individual) at risk or presenting with one or more symptom(s) of hypertension, and thereafter detecting the presence, location, metabolism, and/or binding state (e.g., detecting binding to an unlabeled binding partner involved in InsR receptor physiology/metabolism) of the labeled compound using any of a broad array of known assays and labeling/detection methods.

[00212] The invention disclosed herein will further be understood to encompass diagnostic compositions for diagnosing the risk level, presence, severity, or treatment indicia of, or otherwise managing diabetes in a mammalian subject, comprising contacting a labeled (e.g., isotopically labeled, fluorescent labeled or otherwise labeled to permit detection of the labeled compound using conventional methods) active compound to a mammalian subject (e.g., to a cell, tissue, organ, or individual) at risk or presenting with one or more symptom(s) of diabetes, and thereafter detecting the presence, location, metabolism, and/or binding state (e.g., detecting binding to an unlabeled binding partner involved in InsR receptor physiology/metabolism) of the labeled compound using any of a broad array of known assays and labeling/detection methods.

[00213] The invention disclosed herein will also be understood to encompass diagnostic compositions for diagnosing the risk level, presence, severity, or treatment indicia of, or otherwise managing a metabolic syndrome disease or condition in a mammalian subject, comprising contacting a labeled (e.g., isotopically labeled, fluorescent labeled or otherwise labeled to permit detection of the labeled compound using conventional methods) active compound to a mammalian subject (e.g., to a cell, tissue, organ, or individual) at risk or presenting with one or more symptom(s) of metabolic syndrome, and thereafter detecting the presence, location, metabolism, and/or binding state (e.g., detecting binding to an unlabeled binding partner involved in InsR receptor physiology/metabolism) of the labeled compound using any of a broad array of known assays and labeling/detection methods.

Examples

[00214] The experiments described below demonstrate novel and powerful uses for berberine compounds and berberine related and derivative compounds including compounds of Formula XXVII as cholesterol lowering drugs that can effectively lowers serum cholesterol, triglycerides and LDL through a mechanism other than that used by current hypolipidemic drugs,

such as statins. In exemplary experiments, cells from a human hepatoma-derived cell line, HepG2, were treated for 24 hours with 700 compounds isolated from Chinese herbs. RNA was then isolated from the cells and analysis of LDLR mRNA was determined using semi-quantitative RT-PCR assays. Of the compounds tested, berberine demonstrated the greatest increase in LDLR expression. Treating HepG2 cells cultured in medium containing 0.5% lipoprotein-depleted fetal bovine serum or serum supplemented with sterols and berberine caused time dependent increases in the expression of LDLR mRNA.

[00215] The experiments further demonstrate the novel and powerful uses for berberine compounds and berberine related and derivative compounds in decreasing insulin resistance, increasing glucose consumption, and decreasing serum insulin. These experiments further demonstrate that berberine acts on the insulin receptor (InsR) through a second pathway that differs from the pathway that leads to an increase in LDLR expression. In exemplary experiments, HepG2 cells treated with berberine had an increased expression of InsR. Additionally, both hyperglycemic rats and humans treated with berberine had decreased levels of blood glucose and increased levels of InsR. These and additional findings are further expanded and elucidated within the following examples.

Example I

Effects of Berberine on the levels of cholesterol, triglycerides and LDL protein in a hyperlipidemia Chinese Hamster

[00216] Two weeks prior to treatment, female Chinese hamsters purchased from the National Institute of Vaccine and Serum research (Beijing, China) were switched to a high fat and cholesterol diet (10% lard, 10% egg yolk powder and 1% cholesterol). After two weeks, groups of 14 hamsters were given either 10 mg/kg/day of berberine through intraperitoneal injection, 20 mg/kg/day of berberine through intraperitoneal injection, 50 mg/kg/day, 100 mg/kg/day of berberine orally or saline for ten days. Serum cholesterol, triglyceride and LDL levels were measured after 4 h fasting before, during and after the course of the treatment. Four hours after the course of the treatment, the animals were sacrificed and their livers removed for analysis.

[00217] As can be seen in Table 6, berberine decreased the levels of cholesterol, triglycerides and LDL protein in all of the treated animals. After the 10 day treatment, a dose of

50/mg/kg/day of berberine reduced LDL by 26% and a dose of 100 mg/kg/day reduced LDL by 42%. Reductions in serum LDL were observed by day 5 and became significant by day 7 at both doses (Figure 5).

Table 6: Lipid lowering effects of berberine in hyperlipidemia Chinese hamster

Treatment		n	Cholesterol	Triglycerides	LDL Protein
Saline	(control group)	14	6.4 $\pm$ 1.0	3.6 $\pm$ 0.4	2.8 $\pm$ 0.9
Berberine	10mg/kg/day (intraperitoneal injection)	14	4.1 $\pm$ 0.7**	2.6 $\pm$ 0.3	1.6 $\pm$ 0.3**
	20mg/kg/day (intraperitoneal injection)	14	3.2 $\pm$ 0.5***	1.7 $\pm$ 0.5*	0.9 $\pm$ 0.1***
	50mg/kg/day	8	3.5 $\pm$ 0.5		2.07 $\pm$ 0.9
	100mg/kg/day (oral)	14	3.8 $\pm$ 0.7**	1.9 $\pm$ 0.4*	1.2 $\pm$ 0.2**

*P<0.05; **P<0.01; ***P<0.001 (compared to the control group)

[00218] At the end of treatment, three animals from each group were killed and liver LDLR mRNA and protein expressions were examined by quantitative real-time RT-PCR and western blot analysis. For the real-time RT-PCR, reverse transcription with random primers using Superscript II at 42°C for 30 minutes with 1 μ g of total RNA was performed using the ABI Prism 7900-HT Sequence Detection System and Universal MasterMix (Applied Biosystems, Foster City, CA). LDLR and GAPD mRNA expression levels were determined using the human LDLR and GAPD Pre-developed TaqMan Assay Reagents (Applied Biosystems). As can be seen in Figure 6, LDLR mRNA and protein levels were elevated in all berberine treated hamsters in a dose dependent manner. There was a 3.5 fold increase in mRNA and a 2.6 fold increase in protein in hamster livers treated with 100 mg/kg/day of berberine.

Example II

Effects of berberine in humans with hyperlipidemia

[00219] Human patients with hyperlipidemia (52 males and 39 females) were randomly divided into two groups and treated with either 0.5g of berberine hydrochloride twice a day (n=63) or a placebo (n=28) for three months. After three months, fasting serum concentrations of cholesterol, triglycerides, HDL and LDL were measured using standard blood lipid tests. Liver and kidney functions were also measured. Those treated with berberine had statistically significant lower cholesterol, triglycerides and LDL protein levels than those treated with the placebo, with berberine hydrochloride lowering serum levels of cholesterol by 18% ($P<0.001$), triglycerides by 28% ($P<0.001$) and LDL by 20% ($P<0.001$). Because some participants were taking other medications that could have influenced the results, the results were reanalyzed using only the data from those participants who were neither on drugs nor special diets before or during berberine therapy. As can be seen in Table 7, the results of those who were only taking berberine hydrochloride were even more significant with serum levels of cholesterol decreasing by 29% ($P<0.0001$), triglycerides by 35% ($P<0.0001$) and LDL by 25% ($P<0.0001$). Berberine was well tolerated by all subjects and no side effects were observed with the exception of one patient having mild constipation during treatment, which was relieved after reducing the dose to 0.25 g twice per day. BBR did not change kidney functions (as determined by measurements of creatine, blood urea nitrogen, and total bilirubin in treated and placebo subjects), but substantially improved liver function—reducing levels of alanine aminotransaminase, aspartate aminotransaminase, and gama glutamyl transpeptidase, by approximately 48%, 36%, and 41%, respectively. The placebo group showed no significant changes in these parameters.

Table 7: Lipid lowering effects of berberine in hyperlipidemia patients

	Berberine treatment (3 months)	Berberine Group ^a (n=32)	Placebo Group (n=11)
Serum level of cholesterol		>5/2 mmol/L	>5.2 mmol/L
Cholesterol (mmol/L)	Before	5.9± 0.7	6.0 ± 0.8
	After	4.2±0.9*	5.8 ± 0.6
Triglycerides (mmol/L)	Before	2.3±1.8	2.2 ± 0.7
	After	1.5±0.9*	2.0 ± 1.0
LDL Protein (mmol/L)	Before	3.2±0.7	3.7 ± 0.7
	After	2.4±0.6***	3.7± 0.8
HDL Protein	Before	1.1 ± 0.3	1.2 ± 0.5
	After	1.1 ± 0.3	1.2 ± 0.4

^aStatistical analysis of the baselines of cholesterol, triglyceride, HDL-c, and LDL-c showed that there were no significant differences between the berberine and placebo groups before therapy ($p>0.05$). *** $P<0.0001$ as compared to baselines of before treatment group (matched t test)

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Example III

The effect of berberine on LDLR expression

- [00220] Bel-7402 cells were treated with 0, 0.5, 1, 2.5, 5, $\mu\text{g/ml}$ of berberine or 2.5, 7.5 and 15 $\mu\text{g/ml}$ of berberine sulfate. The cells were then centrifuged and washed and LDLR mRNA was extracted. LDLR mRNA levels were then measured using scan quantitative RT-PCR, (Figure 3 A and B). As can be seen in Figure 3 A and B, treatment with berberine and berberine sulfate increased LDLR mRNA expression in a dose dependent fashion with 5 $\mu\text{g/ml}$ berberine increasing LDLR mRNA expression 2.3 fold. Berberine also increased LDLR protein expression on the surface of BEL-7402 cells.
- 15 [00221] Bel-7402 cells treated with 5 $\mu\text{g/ml}$ of berberine were detached with cell removal buffer containing EDTA, washed and resuspended in FACS solution (PBS with 0.5% BSA and 0.02% sodium azide) at a density of 1×10^6 cells/ml. Cells were then incubated with monoclonal antibody to LDLR (Santa Cruz Biotechnology, Inc., Santa Cruz, CA) at a final dilution of 1:50 and left at room temperature for 1 hour. The cells were then reacted with isotope
- 20 matched, nonspecific mouse IgG as a control for nonspecific staining. The cells were then washed and stained with FITC conjugated goat antibody to mouse IgG (Santa Cruz

Biotechnology, Inc., Santa Cruz, CA, 1:100 dilution) and the fluorescence intensity was analyzed by FACS (FACSort, Becton Dickinson, Franklin Lakes, NJ). As can be seen in Figure 4, berberine increased cell surface LDLR protein expression 4 times.

[00222] The above studies demonstrate that berberine's serum lipid lowering effect is mediated through an increase in LDLR expression.

Example IV

Use of berberine and simvastatin in combination to lower serum lipid levels in rats

[00223] Rats were fed a high fat high cholesterol (HFHC) diet for 10 days, and then divided into groups of seven. The rats were then administered berberine or simvastatin, or a combination of berberine and simvastatin orally for 25 days. After 25 days, serum cholesterol, triglyceride and LDL-c levels were measured. As can be seen in Table 8, treatment with berberine significantly decreased the cholesterol, triglycerides and LDL-c levels in the rats and was more effective than simvastatin in lowering triglyceride and LDL-c levels. The combination of simvastatin, and berberine lowered the cholesterol, triglyceride and LDL-c levels further than either alone.

Table 8: Combination treatment with berberine and simvastatin in rats

Experiment Group	N	Daily dose (oral, mg/kg)	Total Cholesterol (mmol/L)	Triglyceride (mmol/L)	LDL-c (mmol/L)
Normal Control Group	7	no	2.6±0.4	1.9±0.6	1.4±0.3
Untreated hyper-lipidemia Group	7	no	6.4±0.6	3.2±0.3	2.4±0.3
Berberine Treatment Group	7	100	3.8±0.5	2.1±0.3	1.2±0.2
Simvastatin Treatment Group	7	25	3.6±0.4	2.5±0.3	1.4±0.1
Berberine+Simvastatin Group	7	100+25	2.5±0.4	1.6±0.2	1.1±0.2

After 25 days, blood total cholesterol, triglyceride and LDL-c levels were examined. The results in tables are average $\pm$ standard error.

Example V

Use of berberine to increase LDLR mRNA stability

[00224] HepG2 cells were cultured with either berberine hydrochloride or GW707 as a positive control for 8 hours. Total cell lysates from untreated cells or cells treated with either berberine or GW707 were then harvested and analyzed by Western blot. As can be seen in Figure 7, GW707 substantially increased the amount of the mature form of SREB-2, whereas berberine had no effect. These data indicate that berberine effectively increases LDLR expression by a mechanism distinct from that used by statins, thereby further evincing that this novel drug and its related and derivative compounds will provide useful anti-hyperlipidemic formulations and methods with minimal side effects attributed to other known anti-hyperlipidemic drugs.

Example VI

Function of berberine in the presence of statins

[00225] HepG2 cells were cultured in LPDS medium and were then untreated, treated with lovastatin at 0.5 and 1 μ M concentrations with or without berberine for 24 hours, or were treated with berberine alone. As can be seen in Figure 8, berberine and lovastatin had additive stimulation effects on LDLR mRNA expression, which data evince general utility of the novel, combinatorial formulations and coordinate treatment methods describe herein above.

Example VII

Analysis of LDLR promoter activity

[00226] HepG2 cells were transfected with the reporter construct pLDLR234Luc, which contains the SRE-1 motif and the sterol-independent regulatory element that mediates the cytokine oncostatin M-induced transcription of the LDLR gene. After transfection, cells were cultured in 0.5% lipoprotein depleted fetal bovine serum (LPDS) or LPDS and cholesterol medium followed by an 8 hour treatment with berberine (10 μ g), GW707 (2 μ g) or oncostatin M (50 ng/ml). As can be seen in Figure 9, LDLR promoter activity was strongly elevated by

GW707 and oncostatin M under both culturing conditions. Berberine had no effect, further evincing that this compound operates via a different mechanism of LDLR regulation compared to other known drugs possessing anti-hyperlipidemic activity.

Example VIII

Stabilization of LDLR mRNA by berberine

[00227] HepG2 cells were cultured and then left alone or treated with berberine for 15 hours. After 15 hours, actinomycin D (5µg/ml) was added to cells at 0, 20, 40, 60, 90, 120, or 150 minutes. Total mRNA was isolated and analyzed by Northern blot for the amount of LDLR mRNA. As can be seen in Figure 10, berberine prolonged the turnover rate of LDLR transcript by approximately threefold. In contrast, the mRNA stability of HMG-CoA reductase was not altered by berberine.

Example IX

Transfection of HepG2 cells

[00228] Three consecutive fragments of LDLR 3'UTR were inserted into a cytomegalovirus promoter driven *Luc* plasmid (pLuc) at the 3' end of the *Luc* coding sequence before the SV40 polyadenylation signal. The wild-type *Luc* reporter plasmid pLuc was constructed by insertion of the *Luc* cDNA into the *Hind*III and *Xba* sites of pcDNA3.1/Zeo(+). Addition of the *LDLR* 3'UTR was accomplished by PCR amplifying different regions of the 2.5kb 3'UTR of *LDLR* mRNA using *Xba*I-tailed primers and pLDLR3 as the template. The wild type pLuc and the chimeric plasmids pLuc-UTR-2, UTR-3 and UTR-4 were transfected into HepG2 cells (Figure 11). Cells seeded in culture dishes were transiently transfected with the chimeric plasmids. Twenty-four hours after transfection, cells were trypsinized and reseeded equally into two dishes for each plasmid transfection. After overnight incubation, one dish was treated with dimethylsulfoxide as the solvent control and another was treated with berberine for eight hours. To detect the presence of *Luc-LDLR* fusion transcripts, a PCR reaction was performed to amplify a 550 base pair fragment of *Luc* coding region with 5' primer *Luc-2up* (5'-GCTGGAGAGCAACTGCARAAGGC-3') (SEQ ID NO:1) and the 3' primer *Luc-2lo* (5'-GCAGACCAGTAGATCCAGAGG-3') (SEQ ID NO:2) using pGL3-basic as the template. The PCR fragment was labeled with ³²P and used in the northern blot analysis to measure expression

of *Luc* mRNA and *Luc*-LDLR 3'UTR chimeric fusion. As can be seen in figure 12, inclusion of UTR-2 and UTR-3 sequences reduced expression levels of *Luc* mRNA by approximately 3-4 fold, indicating the presence of destabilization determinants within these groups whereas the *Luc* mRNA levels were only moderately reduced by fusing with UTR-4. Berberine increased the level of *Luc*-UTR-2 mRNA by 2.5 fold without affecting expressions of *Luc*UTR-3 and *Luc*-UTR-4 or the wild type. This demonstrates that berberine affected the mRNA stability of the heterologous *Luc*-LDLR transcript and that the stabilization is mediated through regulatory sequences present in the 5' proximal region of the LDLR 3'UTR (nt 2677-3582).

Example X

Determination of the Role of ARE and UCAU motif in

Berberine mediated LDLR mRNA stabilization

[00229] To create ARE deletion constructs, an Apa site at nt 3,384 was generated for deleting ARE3, and an Apa1 site at nt 3,334 for deleting ARE2 by site-directed mutagenesis using pLuc/UTR-2 as the template. Mutated plasmids were cut with Apa1 to remove the ARE-containing region and then the remaining vector was religated with the 5' proximal region of UTR-2. To create the UCAU motif deletion, two SacII sites for internal deletion of nt 3,062-3,324 were generated using UTR-2 as the template. All constructs were sequenced and the correct clones were further propagated to isolate plasmid DNA. These constructs and the berberine responsive wild-type construct were transfected into HepG2 cells. The effects of berberine on the chimeric *Luc* transcripts were determined by measuring *Luc* mRNA using a quantitative real-time RT-PCR assay. Deletion of the ARE3 region resulted in a partial loss of berberine stimulation and deletion of both the ARE3 and ARE2 rendered the construct unresponsive to berberine. The stabilizing effect of berberine on the *Luc* transcript was also abolished by deleting the UCAU motifs. (Figure 13).

Example XI

Activation of the MEK1-ERK pathway by berberine

[00230] HepG2 or Bel-7402 cells were treated with berberine for 0.25, 0.5, 0.75, 1, 2, 8, and 24 hours respectively and tested for levels of activated ERK by western blotting using antibodies that only recognize the activated (phosphorylated) ERK. In both hepatoma cell lines,

berberine rapidly activated ERK and the kinetics of ERK activation preceded the upregulation of LDLR expression by berberine (Figure 14A and B). The activation of berberine is also dose dependent (Figure 14C). These data indicate that activation of ERK pathway is a prerequisite event in the berberine mediated stabilization of the LDLR transcript.

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Example XII
Pharmacokinetics of Berberine

[00231] Healthy human volunteers were given 300 mg of berberine orally. Blood samples were taken 0.5, 1, 2, 3, 4, 5, 7, 12 and 24 hours after administration and evaluated for berberine concentration by HPLC. The blood concentration curve was analyzed by 3P87 Pharmacokinetics Software program (Chinese Pharmacological Association, China). Using a one compartment model, the median pharmacokinetic parameter estimates (ranges) were as follows: Peak Time: Tpeaking: 2.37 hr, peak concentration: Cmax: 394.7ng/ml, vanishing half life: T1/2: 2.91 h, the area under the curve AUC: 2799.0μg/L h, clear rate CL: 130.5L/h. The average drug retention time was 32.63 hours.

[00232] In parallel animal model studies, four canine (beagle) subjects were given 45 mg/kg of berberine orally. Serum concentrations of the drug were determined by HPLC at 2 and 3 hours after administration. There was no obvious spectrum peak detected suggesting that the concentration was below the minimum detection limit of 10 ng/ml. One dog receiving 280mg/kg of berberine had a berberine peak showing a concentration of 31.4 ng/ml after two hours and 22.6 ng three hours after administration. After the berberine had cleared the system, the same dog was then administered 700 mg/kg of berberine and blood samples were taken 2, 3, 5, 7, 9 and 24 hours after administration resulting in concentrations of 21.51, 44.89, 49.54, 36.35, 27.83, and 16.01ng/ml respectively.

[00233] Four beagles were injected intravenously with 100 mg/kg of berberine. Using a two compartment model, the pharmacokinetic parameter estimates were as follows: Vanishing half life T1/2B is 12.59±8.83h. Area under the curve AUC is 1979.31±1140.31μg/h.L; blood clearance rate: CL is 60.70±24.38L/h.

[00234] In additional, parallel animal model studies, 3H-berberine was administered intravenously to 5 rabbits (25MBq/kg) and through intravenous drip to four rabbits (46.25Mbq/kg). 0.1ml of blood was removed at various times and radiation emissions were

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measured. The pharmacokinetic parameter estimates for both groups were as follows: $T_{1/2\alpha}$ respectively: 1.41 ± 0.16 h, 1.03 ± 0.11 h, and $T_{1/2\beta}$ respectively: 35.3 ± 1.3 h, 35.8 ± 2.0 h, V_d respectively 20 ± 3 L/kg and 22.1 ± 1.7 L/kg.

[00235] 50mg/kg of berberine was administered through stomach infusion to six rabbits.

5 Serum samples were taken at various points after administration and RP-HPLC was used to measure the drug concentration. The blood drug concentration-time data was analyzed using the 3P87 pharmacokinetics software program (Chinese Pharmacological Association, China). Using automated fitting, the rabbit berberine pharmacokinetics model was found to match with the One Compartment Open model. The main pharmacokinetics parameters were as follows: peak time
10 T_{peak} : 0.63 ± 0.25 h, peak concentration C_{max} : 92.72 ± 50.89 ng/ml, vanishing half life: $T_{1/2\beta}$: 3.11 ± 0.58 h, the area under the curve, AUC: 491.7 ± 295.5 μg h/L. The results indicate that berberine can be absorbed rapidly to reach the effective concentration.

[00236] The rabbit blood protein binding rate was measured by *in vitro* dialysis at a rate of $38 \pm 3\%$ ($XD \pm S$, $n=6$).

15 [00237] In yet additional animal models studies, mice were injected in the tail vein with 3H-berberine ($135\text{LBq}/10\text{g}$). Tissue radiation emission was measured 5 minutes to 2 hours after administration with the distribution of the berberine concentrations from highest to lowest being: lung>liver>kidney>spleen> heart>intestine>stomach>brain.

[00238] In a final series of animal model studies, rats were orally administered 3H-berberine. Forty-eight hours after administration, excretions were tested for the presence of
20 berberine. 2.7% of the oral dose was measured in the urine and 86% of the oral dose was measured in the fecal matter.

[00239] Rats received intravenous berberine ($9.25\text{MBq}/\text{kg}$). Six days accumulation of rat urine and fecal secretions were measured for the presence of berberine. 73% of the intravenous
25 dose of the berberine was found in the accumulated urine in both metabolized and unmetabolized forms. 10.9% of the intravenous dose was found in the fecal matter.

[00240] Three rats were given berberine ($9.25\text{MBq}/\text{kg}$) intravenously. After 24 hours, gall bladder secretions were collected and evaluated for the presence of berberine. There was $10.1 \pm 0.9\%$ ($\bar{x} \pm \text{SD}$, $n=3$) of berberine in the gall bladder secretions.

Example XIII

Toxicity analysis of berberine

[00241] Rats and mice were administered berberine through a variety of techniques, including orally, through subcutaneous injection, intraperitoneal injection and intravenous injection.

[00242] In rats, toxicity was achieved with an oral dose of $LD_{50} > 15000$ mg/kg. Toxicity through subcutaneous injection was LD_{50} 7970-10690 mg/kg. Toxicity through intraperitoneal injection was LD_{50} 138.1-146.2 mg/kg and LD_{50} 46.2-63.3 mg/kg when the berberine was administered through intravenous injection.

[00243] In mice, toxicity was achieved with an oral dose of $LD_{50} > 29586$ -4500 mg/kg. Toxicity through subcutaneous injection was LD_{50} 13.9-20 mg/kg. Toxicity through intraperitoneal injection was LD_{50} 30-32.2 mg/kg and LD_{50} 7.6-10.2 mg/kg with intravenous injection.

[00244] For long term toxicity determination, rats were administered 300 mg/kg of berberine orally for 182 days. No abnormalities were found in blood tests, blood biochemistry, urine analysis or histopathology

[00245] To assess teratologic potential, pregnant mice were orally administered a daily dose of between 30-480 mg/kg of berberine beginning on day 7 of the pregnancy and continuing for seven days. Rats were administered berberine beginning on day 9 of their pregnancy for seven days. No birth defects were evident.

Example XIV

Exemplary Combinatorial Therapy Employing Berberine and Lovastatin

[00246] In accordance with the above teachings, combinatorial drug therapy employing a berberine compound or berberine related or derivative compound of Formula I, in combination with an exemplary, secondary anti-hyperlipidemia agent, was demonstrated using berberine and an exemplary statin, lovastatin, in rat model subjects. The procedures for this study accord with those of the foregoing example, and the results are provided in Table 9, below.

Table 9. Combinatorial anti-hyperlipidemia efficacy of berberine and lovastatin in a coordinate treatment regimen

Cholesterol and LDL concentration in mmol/L

Treatment	Cholesterol Day 0	Cholesterol Day 15	LDL Day 0	LDL Day 15	Number of rats	P value
Normal diet	1.35	1.30	0.8	0.85	5	
High fat diet	3.6	3.5	2.2	2.1	9	
High fat diet and Berberine (80mg/kg/day)	3.65	2.75	2.25	1.7	9	<0.05
High fat diet and Lovastatin (10mg/kg/day)	3.6	2.7	2.15	1.62	9	<0.05
High fat diet and Berberine+lovastatin	3.8	2.6	2.3	1.55	11	<0.01

Day 0 represents: untreated rats

Day 15 represents: rats treated for 15 days

- 5 [00247] The foregoing data evince effectiveness of an exemplary berberine compound employed in a coordinate treatment protocol with a secondary anti-hyperlipidemia agent, in accordance with the teachings herein above.

Example XV

10 Effects of Berberine on blood glucose in rats

[00248] Nineteen Wistar rats (Male, 250 g, the Institute of Experiment Animal Sciences, Chinese Academy of Medical Sciences, Beijing) were fed high fat and high cholesterol (HFHC) diet containing 25% lard, 20% sucrose and 5% yolk powder (Institute of Experiment Animal Sciences) for 4 weeks to induce insulin resistance status. Then, after fasting for 24 hours, 20
15 mg/kg of streptozotocin (Sigma) dissolved in 0.01 M citric acid buffer (pH 4.3) was injected via the tail vein. A week later, rats with blood glucose concentrations over 11.1 mmol/L were considered hyperglycemic and divided into two groups of 7 and one group of 5 as the control.

[00249] The rats in the two groups of 7 were treated with berberine orally twice a day for 14 days, at 8:00 am and 5:00 pm, with a total dose of berberine at 75 mg/kg/day or 150
20 mg/kg/day, respectively. Blood samples were taken by tail snip after 4 hours fasting on indicating days of treatment, and blood glucose was measured. On the last day of the experiment, all of the rats fasted overnight and were then sacrificed.

[00250] The livers were dissected and stored in liquid nitrogen for RNA extraction, real-time RT-PCR and PKC activity assay. Total blood samples were also collected to assay fasting

blood glucose and serum insulin levels. The insulin levels were analyzed using radio-immunoassay (Linco Research, St Charles, MO). The insulin sensitivity indexes (ISI) were calculated according to the formula: $10^4 / (\text{fasting serum insulin} \times \text{fasting blood glucose})$ (Hanson, Am. J. Epidemiol. 151(2), 190-198 (2000)). The insulin level and ISI of normal rats were also determined for comparison. As can be seen in Figure 32, the HFHC diet significantly reduced insulin sensitivity ($p < 0.001$). It also elevated the fasting blood glucose from 7 to 12.8 mmol/L ($P < 0.001$). Treatment for 14 days with berberine resulted in dose-dependent declines in fasting blood glucose with a dose of 75 mg/kg/day reducing glucose by 22% ($p < 0.01$), and 150 mg/kg/day lowering glucose by 33% as compared to untreated rats on the same HFHC diet (Figure 27).

[00251] The time-dependent effect of berberine was also observed (Figure 27), with decreases in blood glucose observed by day 5 and statistically significant by day 9 at both 75 mg/kg/day and 150 mg/kg/day ($p < 0.05$, < 0.01).

[00252] Liver mRNA extracts were used for quantitative real time RT-PCR assay. Total cellular RNA was reverse-transcribed into cDNA using the Reverse Transcription System (Promega, Madison, WI). Quantitative real-time PCR were performed with these cDNA using the Applied Biosystems 7500 Real-Time PCR System and TaqMan® Universal PCR Master Mix (Applied Biosystems, Foster City, CA). All of the 20 X TaqMan® Gene Expression Assay reagents containing gene-specific primers and TaqMan® probes for human or rat InsR, ACTB and LDLR were purchased from Applied Biosystems. 2.5 µl of cDNA sample, 12.5 µl of Universal PCR Master Mix, and 1.25 µl of TaqMan® Gene Expression Assay reagent were mixed in a 25 µl reaction system, and the comparative C_T method was used in relative gene quantification using the TaqMan® SDS analysis software. As can be seen in Figures 28 and 29, InsR mRNA was elevated in all berberine treated rats in a dose-dependent manner with a 1.8- and 2.3-fold increase in InsR mRNA in the livers of rats treated with 75 and 150 mg/kg/day respectively ($p < 0.01$, < 0.001). (Results represent the mean $\pm$ sd of liver InsR mRNA and LDLR mRNA of each group.)

[00253] These results were concurrent with the increased activity of PKC in the livers of berberine treated rats (Figure 30). PKC activity was analyzed using the PepTag® Assay for Non-Radioactive Detection of Protein Kinase-C or cAMP-Dependent Protein Kinase kit (Promega) according to the protocol. Briefly, after homogenization and partial purification, 10

5 μ l of sample protein was mixed with 5 μ l of PepTag® Cl peptide (specific substrate of PKC), 5 μ l of reaction buffer and 5 μ l of PKC activator solution in a 25 μ l reaction system. The reactions were performed at 30°C for 30 minutes. Then, the samples were loaded onto a 0.8% agarose gel. After electrophoresis, the phosphorylated and nonphosphorylated PepTag® Cl peptide were separated, with the phosphorylated ones negatively charged. The gels were photographed under an UV light. The bands containing the phosphorylated substrate were then excised and melted. They were transferred to a 96-well plate and quantified using densitometry according to the supplier's protocol. The catalytic activity of total PKC of a specific sample was expressed as pmol/min/mg, representing the number of picomoles of phosphate transferred to the substrate per minute per milligram of proteins of the sample.

[00254] Additionally, the fasting serum insulin in the rats was measured. As shown in figures 31 and 32 (**p<0.01 and ***p<0.001), untreated rats fed a HFHC diet for 4 weeks demonstrated a significant increase of fasting serum insulin and a decrease of the insulin sensitivity index (ISI) in comparison to the normal controls, indicating insulin resistance in the animals. As can be seen in figure 31, treatment of the animals with berberine significantly reduced the serum insulin levels in the insulin resistant rats as well as improved the ISI (Figure 32), suggesting a restoration of the impaired insulin sensitivity and a reduction of insulin resistance.

[00255] The lipid profile of the rats was also measured after the 14 day treatment with berberine. As can be seen in figure 33, 150 mg/kg/day of berberine reduced cholesterol by 25%, LDL-c by 33% and triglyceride by 24% (p <0.01, **0.01 and *0.05 respectively), as compared to the control animals administered the same HFHC diet. The therapeutic efficacy observed in this animal model reflects a synergistic effect of berberine on InsR and LDLR, which antagonizes insulin resistance and significantly improves sugar- and lipid- metabolism *in vivo*.

Example XVI

Effects of Berberine on Metabolic Syndrome

[00256] Twenty-eight patients 28 (male/female, 17/11; age, 57±8y) were diagnosed as having metabolic syndrome if they met three or more of the following criteria: fasting blood glucose >7 mmol/L, serum triglyceride > 1.7 mmol/L, fasting blood insulin > 13 mmcU/mL, blood pressure >135/85 and/or BMI > 23. (Eckel, Lancet 365 (9468), 1415-28 (2005); Executive

Summary, JAMA 285, 2486-2497 (2001); Balkau, Diabet. Med. 16, 442-443 (1999)) The patients were enrolled in this study at the Nanjing First Hospital, Nanjing, China. The patients were requested to end previous medications or therapies for at least two weeks prior to the beginning of the study.

5 [00257] The patients were then given 1 gram of berberine per day, orally for two months. Blood samples were taken both before and after two months of berberine treatment. Fasting blood levels of glucose, LDL-c, cholesterol, HDL-c, triglyceride and blood insulin were measured using standard methods routinely applied in hospitals. Liver and kidney functions were also monitored in the patients.

10 [00258] As can be seen in Table 10, treatment with berberine reduced fasting blood glucose from 10.7 ± 0.56 to 8.0 ± 0.45 mmol/L (Mean $\pm$ SE, $p < 0.001$), blood insulin from 17 ± 2.15 to 12.1 ± 1.35 mmol/L ($p < 0.05$), triglyceride from 2.0 ± 0.22 to 1.47 ± 0.14 mmol/L ($p < 0.001$), cholesterol from 6.1 ± 0.11 to 4.7 ± 0.16 mmol/L ($p < 0.0001$), blood pressure from 156/86 to 133/79 ($p < 0.01$ for both) and body-mass-index (BMI) from 23.8 ± 0.63 to 23.1 ± 0.6 ($p < 0.01$).

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Table 10

Therapeutic effect of berberine in patients with metabolic syndrome

Clinical measurement*	Patients with metabolic syndrome [#] (n=28)		
	Before BBR treatment	After BBR treatment	P
FBG (<7.0, mmol/L)	10.7±0.56	8.0±0.45	0.00027
Blood Insulin (2.5-13.0, mIU/L)	17±2.15	12.1±1.35	0.028
Blood Triglyceride (<1.7, mmol/L)	2.0±0.22	1.47±0.14	0.001
Blood Cholesterol <5.2, (mmol/L)	6.1±0.11	4.7±0.16	0.0001
BMI**	23.8±0.63	23.1±0.6	0.007
Blood Pressure	156/86	133/79	0.01(for both)

FBG: Fasting blood glucose.

[#]: BBR treatment, 1g/day, Bid, 2 months; Values are means ± SEs.

*: Normal range and units.

** : Asians at BMI of 23-24 has equivalent risk of metabolic syndrome as a BMI of 25-29.9 in white people.

BMI: Body-Mass-Index.

Example XVII

Effect of berberine on InsR expression in human hepatoma cell lines

5 [00259] Cells from the human hepatoma cell line HepG2 were incubated with 0, 1, 2.5, 5, 10 or 15 µg/ml of berberine respectively for eight hours. Total cellular RNA was isolated using the Ultraspec RNA lysis solution (Biotecx Laboratories, Houston, TX) following the vendor's protocols. 10pg of the RNA sample was transferred to nitrocellulose membrane via a slot-blot apparatus (Schleicher & Schuell, Keene, NH). The blots were fixed by baking at 80°C for 2h, 10 followed by hybridization to a 0.89-kb long, 32P-labelled human InsR cDNA probe. The same membranes were then stripped and re-hybridized to a human ACTB probe as internal control. Quantitative real time RT-PCR assays were also done. For the RT-PCR assay, total cellular RNA was reverse-transcribed into cDNA using the Reverse Transcription System (Promega, Madison, WI). Quantitative real-time PCR were performed with these cDNA using the Applied Biosystems 7500 Real-Time PCR System and TaqMan® Universal PCR Master Mix (Applied Biosystems, Foster City, CA). All of the 20 X TaqMan® Gene Expression Assay reagents 15 containing gene-specific primers and TaqMan® probes for human or rat InsR, ACTB and LDLR

were purchased from Applied Biosystems. 2.5 µl of cDNA sample, 12.5 µl of Universal PCR Master Mix, and 1.25 µl of TaqMan® Gene Expression Assay reagent were mixed in a 25 µl reaction system, and the comparative C_T method was used in relative gene quantification using the TaqMan® SDS analysis software. InsR mRNA levels were corrected by measuring ACTB mRNA levels.

[00260] As can be seen in figure 15, berberine showed a dose dependent increase in the expression of InsR mRNA. Using the abundance of InsR mRNA in untreated cells as a baseline of 1 and plotting the amount of InsR mRNA from berberine treated cells relative to that value, quantitative real time RT-PCR showed a 40% increase of InsR mRNA in cells treated with 2.5 µg/ml of berberine for 8 hours and a maximal increase of 3.2-fold of the control was seen with a concentration of 15 µg/ml (Figure 15A). A similar magnitude of increase in InsR mRNA level was confirmed by the slot blot (Figure 15B).

[00261] The effect of berberine was also time-dependent. HepG2 cells were treated with 7.5 µg/ml for 0, 2, 4, 6, 8 or 24 hours and total RNA was isolated as described above for slot blot and RT-PCR assays of InsR mRNA and ACTB mRNA expression. The level of InsR mRNA increased 4 h after exposure of cells to berberine and reached the peak level of 2.5-fold of the control at 8 h; the expression of InsR mRNA remained high for at least 24 h (Figure 16).

HepG2 cells cultured with 0, 2.5, 5, 10 or 15 µg/ml of berberine or normal mouse IgG (Figure 17) for eight hours then detached, washed and resuspended in FACS solution (PBS with 0.5% BSA and 0.02% sodium azide) at a density of 1×10^6 cells/ml. Cells were then incubated with a monoclonal antibody to *InsR* (NeoMarkers, Fremont, CA) at a final dilution of 1:100 (room temperature, 0.5 h). An isotype-matched, nonspecific mouse IgG was used as a control for nonspecific staining. Then, cells were washed and stained with FITC conjugated goat-anti-mouse IgG (Santa Cruz Biotech, 1:200 dilution). The fluorescent intensity was examined by flow cytometry (FAC Sort, Becton Dickinson, CA). As can be seen in Figure 17, berberine increased cell surface expression in Caucasian liver cell line HepG2.

[00262] The effect of berberine on InsR was further confirmed in another hepatoma cell line, Bel-7402 of Chinese origin (Figure 18). The results showed an identical upregulating effect of berberine on InsR expression in cells with either Asian (Bel-7402) or Caucasian (HepG2) genetic background. The expression of PPAR- α mRNA in liver cells was not changed by berberine (data not shown).

[00263] The increased InsR expression directly translated into an enhanced InsR sensitivity in target cells. Glucose consumption of human hepatic cells treated with insulin was significantly increased by berberine (** $p < 0.01$, $n = 4$; Figure 19A). In order to determine the role of InsR in this effect, siRNA was used to silence InsR gene decreasing the level of InsR mRNA expression and decreasing the effectiveness of berberine on increasing InsR mRNA levels. (Figure 19B)

[00264] Human InsR siRNA duplex, non-specific control siRNA, siRNA transfection reagent and siRNA transfection medium were obtained from Santa Cruz Biotechnology, Inc. (Santa Cruz, CA) and the vendor's siRNA transfection procedure was followed. Briefly, HepG2 cells were seeded onto six-well plates in antibiotic-free RPMI-1640 medium containing 10% fetal bovine serum (FBS). After 60 - 80% confluence of monolayer, FBS containing medium was discarded and cells were washed with siRNA transfection medium (2 mL/well). 0.8 mL of siRNA transfection medium containing 6 μ L of human InsR siRNA duplex (or control siRNA) and 6 μ L of siRNA transfection reagent were well mixed at room temperature for 30 min, followed by loading onto washed HepG2 cells. After an 8 hr incubation, the transfection mixture was removed and fresh RPMI-1640 medium supplied with 10% FBS was added. The cells were then incubated for 24 hr. Then, the culture medium was replaced with fresh medium and incubated for an additional 24 hr. At the end of incubation, FBS containing medium was removed and replaced with serum-free fresh RPMI-1640 medium. 7.5 μ g/mL of berberine and/or 0.5 nM of insulin were added to the InsR siRNA transfected or untransfected cells. After 12 hr incubation, the amount of glucose in the sample medium was determined. The glucose consumption was calculated according to the following formula: glucose level of the fresh RPMI-1640 minus glucose level of the used RPMI-1640. Inhibition of InsR mRNA and protein expression by InsR siRNA was confirmed by either real-time RT-PCR or Western-Blot analysis.

[00265] As can be seen in figure 19, silencing InsR with siRNA in the liver cells strongly inhibited InsR mRNA expression and completely abolished its effect on insulin-related glucose consumption (Figure 19 A). The results indicate that the presence of InsR on the cell surface and insulin in the circulation are both essential for berberine to increase the cellular consumption of glucose. Therefore, berberine antagonizes insulin resistance and improves cellular response to insulin through upregulating the expression of InsR on the cell surface. This effect on InsR

together with the action on LDLR renders berberine useful in the treatment of sugar- and lipid-metabolic disorders.

[00266] To view the simultaneous increase of the expression of LDLR and InsR by berberine, double-immune staining was conducted. HepG2 cells were treated with 7.5 µg/ml of berberine for 0, 4, 8 or 12 hours, then detached and fixed in 4% paraformaldehyde solution. Cells were then washed and treated with PBA (PBS with 5% BSA) on ice for 15 min. After discarding the supernatant, cells were resuspended in PBA and incubated simultaneously with a monoclonal antibody against InsR (Santa Cruz Biotech. Inc., Santa Cruz, CA, 1 :40) and a rabbit-polyclonal antibody against LDLR (Santa Cruz, 1 :20) on ice for 1 hr. Normal mouse IgG and rabbit IgG were used as controls. After incubation, cells were washed with PBA followed by staining with a FITC-conjugated goat-anti-mouse IgG (Santa Cruz, 1:100), as well as a TRITC-conjugated goat-anti-rabbit IgG (Santa Cruz, 1 :50) on ice for 40 min. After incubation with secondary antibodies, cells were washed twice with PBA and suspended in 4% paraformaldehyde. The fluorescence intensities of FITC/TRITC on cell surface were analyzed by flow cytometry. As seen in figure 20, the results demonstrated a remarkable upregulation of both LDLR and InsR in a similar magnitude on the surface of human hepatocytes treated with berberine, suggesting the dual-target bioactivity of berberine for metabolic syndrome.

Example XVIII

Effect of berberine on InsR mRNA stability

[00267] HepG2 cells were treated or untreated with 7.5 µg/ml of berberine for 8h. Then, 5 µg/ml of actinomycin D was added to block the transcription. Total cellular RNA was harvested at 0, 2, 4, 6, or 8 hours after actinomycin D treatment, and slot-blotted to nitrocellulose membranes as described above. The membranes were respectively hybridized with InsR and ACTB specific probes as described above, and bands were quantitated through densitometry. The InsR mRNA levels were normalized to ACTB, and their remaining percentages are plotted against time and the decaying rate or half-life of InsR mRNA was calculated (Figure 21B).

[00268] As shown in Figure 21, unlike that of LDLR mRNA, berberine treatment did not prolong the turnover rate of InsR transcript with respect to the untreated cells (4.7 hr vs. 4.4 hr), suggesting that enhanced InsR gene expression by berberine occurs in the transcriptional rather than the post-transcriptional stage.

Example XIX

Analysis of InsR promoter activity

[00269] The InsR gene promoter contains a 1.8 kb long segment (Mitchell, Science 245,
5 371-378 (1989); Araki J. Biol. Chem. 262, 16186-16191 (1987)). The InsR promoter luciferase
gene fusion plasmid (pGL3-1.5kIRP) was kindly provided by Dr. Araki E of the Graduate
School of Medical Sciences, Kumamoto University, Honjo, Kumamoto, Japan. In this fusion
construct, 1.5 kb fragment of the human insulin receptor gene promoter was inserted into the
Hind III site of pGL3-basic vector forming pGL3-1.SkIRP fusion plasmid (Nakamaru, Biochem
10 Biophys Res Commun. 328 (2) 449-454 (2005)).

[00270] HepG2 cells (2 X 10⁵) were transfected with 1 µg of the pGL3-1.SkIRP using the
FuGENE 6 Transfection Reagent (Roche Applied Science, Indianapolis, IN). After overnight
incubation, the cells were treated with DMSO as the solvent control or with 0, 1, 2.5, 5, 7.5 and
10 µg/ml berberine for 8 h. Cell lysates were prepared and luciferase activities were measured
15 using the Luciferase Reporter Gene Assay (Roche Applied Science). The experiment was
repeated 4 times. As shown in figure 22, berberine increased the level of Luc mRNA in the
pGL3-1.5kIRP transfected cells at a dose-dependent manner, and at a concentration of 10 µg/ml,
berberine elevated Luc mRNA level in the cells by 2.5-fold. The expression of the Luc mRNA
in the cells transfected with pGL3 was not affected by berberine (data not shown). The results
20 demonstrate the stimulating effect of berberine on the InsR gene promoter.

Example XX

Determination of the pathway for berberine-induced InsR gene transcription

[00271] To explore the pathway responsible for the berberine-induced InsR gene
25 transcription, different kinase inhibitors were used, including the MEK1-ERK inhibitor U0126,
the p38 kinase inhibitor SB203580, the c-Jun N-terminal kinase inhibitor curcumin, the PI-3
kinase inhibitor wortmannin, and the PKC inhibitor calphostin C.

[00272] HepG2 cells were pretreated with each of the inhibitors 1 hour prior to treatment
with 7.5 µg of berberine for 8 hours. Total RNA was then isolated and the relative amount of
30 InsR and LDLR mRNA was measured by quantitative RT-PCR as described in Example XVII.

It was determined that the activity of berberine on InsR gene transcription was most sensitive to the PKC inhibitor calphostin C.

[00273] Calphostin C at 0.2 μ M completely eliminated the activity of berberine on InsR gene transcription, but did not change the level of LDLR mRNA (Figure 23). In contrast, inhibition of ERK pathway by U0126 did not effect the activity of berberine on InsR transcription, but completely abolished the increase of LDLR mRNA (Figure 24). These results indicate that the berberine pathway on InsR gene expression is separate from its effect on LDLR.

Example XXI

Activation of the PKC pathway by berberine

[00274] To determine whether berberine directly activates PKC, pGL3-1.5kIRP transfected HepG2 cells were either not treated, treated with 0.2 μ M of calphostin C, 5 μ g/ml of berberine or 0.5 μ M of PKC activator phorbol-12-myristate-13-acetate (PMA) (Gandino, Oncogene, 5 (%), 721-725 (1990) or combinations thereof for eight hours. The activity of total PKC in the control and berberine treated cells was assessed by PKC activity assay.

[00275] Cellular PKC activity was analyzed using the PepTag® Assay for Non-Radioactive Detection of Protein Kinase-C or cAMP-Dependent Protein Kinase kit (Promega) according to the protocol. Briefly, after homogenization and partial purification, 10 μ l of sample protein was mixed with 5 μ l of PepTag® Cl peptide (specific substrate of PKC), 5 μ l of reaction buffer and 5 μ l of PKC activator solution in a 25 μ l reaction system. The reactions were performed at 30°C for 30 minutes. Then, the samples were loaded onto a 0.8% agarose gel. After electrophoresis, the phosphorylated and nonphosphorylated PepTag® Cl peptide were separated, with the phosphorylated ones negatively charged. The gels were photographed under an UV light. The bands containing the phosphorylated substrate were then excised and melted. They were transferred to a 96-well plate and quantified using densitometry according to the supplier's protocol. The catalytic activity of total PKC of a specific sample was expressed as pmol/min/mg, representing the number of picomoles of phosphate transferred to the substrate per minute per milligram of proteins of the sample.

[00276] As shown in figure 25, PKC activity was increased in liver cells treated with berberine in a time-dependent fashion; the elevation of PKC activity was first observed at 0.5 hr (after berberine treatment) and went up with time. The kinetics of PKC activation preceded the

upregulation of InsR expression by berberine. Pre-treatment of the cells with PKC inhibitor Calphostin C diminished the ability of berberine to stimulate the InsR gene promoter (Figure 26). The PKC activator PMA exhibited the same results confirming that the PKC pathway is a part of the mechanism for the activation of the InsR gene promoter. This result supports the data in Figure 23, and indicates that activation of PKC pathway is essential for the berberine-mediated upregulation of InsR expression.

Example XXII

Effect of berberine on blood glucose in hyperglycemic patients with type II diabetes

[00277] Ninety-seven hyperglycemic patients (54 males and 43 females) with fasting blood glucose >7 mmol/L and post-prandial blood glucose >11.1 mmol/L were enrolled in a study at the Nanjing First Hospital in Nanjing, China. The patients were asked to end any current treatments for hyperglycemia at least 2 weeks prior to commencement of the study.

[00278] Fifty of the patients (male/female, 27/23; age 57 ± 8 y) were randomly assigned to be given 0.5 gram twice a day (1g/day total) of berberine (Nanjing Second Pharmaceuticals, Inc., Nanjing, China), orally for 2 months. Out of these 50 patients, 25 had hyperlipidemia, 9 had hypertension and 2 had cardiovascular disease. Twenty-six patients (male/female, 15/11; age 56 ± 11 y) were given 1.5 grams of metformin (Double-Crane Pharmaceutical, Inc., Beijing, China) per day, orally for two months. Of these twenty-six patients, 11 had hyperlipidemia, and four had hypertension. The remaining twenty-one patients (male/female, 11/10, age 49 ± 10 y) were given 4 mg per day of rosiglitazone (GlaxoWellcome, UK), orally for two months. Of these 21 patients, ten had hyperlipidemia and four had hypertension. Metformin and rosiglitazone served as reference controls as they are standard treatments for type II diabetes. Statistical analysis of the baselines of fasting blood glucose, HbA1c and triglycerides showed no significant differences among the groups prior to treatment ($p>0.05$).

[00279] Blood samples were taken prior to the commencement of therapy and after completion of the therapy. As can be seen in Table 11, berberine significantly lowered the fasting blood levels of glucose by 26% ($p<0.0001$), hemoglobin A1c (HbA1c) by 18% ($p<0.0001$) and triglycerides by 18% ($p<0.002$).

Table 11

Effects of Berberine on Fasting Blood Glucose, HbA1c,
and Triglycerides in Patients with Type II Diabetes.

Measurement (normal range)	Treatment (2 months)	BBR Type 2 diabetes (>7.0 mmol/L, n=50)	Metformin Type 2 diabetes (>7.0 mmol/L, n=26)	Rosiglitazone Type 2 diabetes (>7.0 mmol/L, n=21)
Fasting blood glucose (FBG)				
FBG	Before	10.4 $\pm$ 0.4	10.9 $\pm$ 0.5	9.1 $\pm$ 0.8
(<7.0mmol/L)	After	7.7 $\pm$ 0.3***	7.6 $\pm$ 0.3***	7.5 $\pm$ 0.6**
HbA1c	Before	8.3 $\pm$ 0.3	9.4 $\pm$ 0.5	8.3 $\pm$ 0.4
(4.0-6.0%)	After	6.8 $\pm$ 0.2***	7.2 $\pm$ 0.3***	6.8 $\pm$ 0.3**
Triglyceride	Before	1.7 $\pm$ 0.1	1.7 $\pm$ 0.2	1.9 $\pm$ 0.3
(<1.7mmol/l)	After	1.4 $\pm$ 0.1**	1.6 $\pm$ 0.1	1.6 $\pm$ 0.1

Results are presented as Mean $\pm$ SE.

p<0.01; *p<0.001 as compared to the baseline of "before treatment".

[00280] Additionally as seen in figure 35, serum insulin levels decreased into the normal range (2.5-13mIU/L) after treatment with berberine. Although liver enzymes were within normal range before and after berberine treatment, the levels declined with statistical significance in ALT (31 $\pm$ 19 vs 23 $\pm$ 16, p<0.002) and r-GT (47 $\pm$ 26 vs 31 $\pm$ 23, p<0.002); kidney function remained stable and in normal range after berberine treatment (BUN, 5.8 $\pm$ 1.0 vs 5.7 $\pm$ 1.2; Cr, 70 $\pm$ 13 vs 71 $\pm$ 14).

Example XXIII

Determination of an increase in InsR expression in patients treated with berberine

[00281] Peripheral blood lymphocytes (PBL) were collected for InsR expression analysis. InsR protein expressed on the surface of peripheral blood lymphocytes were stained with monoclonal antibody against human insulin receptor (Pharmagen, San Diego, CA) and analyzed in a flow cytometer (BD and Company, San Jose, CA)

[00282] As shown in figure 36, the % of PBL expressing InsR on the surface significantly increased after treatment with berberine (p<0.002). Eight patients returned for further testing two weeks after the treatment with berberine ended. As shown in figure 37, all of the eight returning patients demonstrated a negative correlation between fasting blood glucose and insulin receptor expression, and the increase of InsR expression on the surface of lymphocytes

accompanied a reduction of blood glucose. This is in agreement with the results in the animal experiments in Example XV.

Example XXIV

Effect of demethylberberine on HepG2 cells

[00283] Cells from the human hepatoma cell line HepG2 were incubated with 0, 2.5, 5, and 10 µg/ml of berberine or demethylberberine (L101) respectively for eight hours. Total cellular RNA was isolated using the Ultraspec RNA lysis solution (Biotecx Laboratories, Houston, TX) following the vendor's protocols. 10pg of the RNA sample was transferred to nitrocellulose membrane via a slot-blot apparatus (Schleicher & Schuell, Keene, NH). The blots were fixed by baking at 80°C for 2h, followed by hybridization to a 0.89-kb long, 32P-labelled human InsR cDNA probe. The same membranes were then stripped and re-hybridized to a human ACTB probe as internal control. Quantitative real time RT-PCR assays were also done. For the RT-PCR assay, total cellular RNA was reverse-transcribed into cDNA using the Reverse Transcription System (Promega, Madison, WI). Quantitative real-time PCR were performed with these cDNA using the Applied Biosystems 7500 Real-Time PCR System and TaqMan® Universal PCR Master Mix (Applied Biosystems, Foster City, CA). All of the 20 X TaqMan® Gene Expression Assay reagents containing gene-specific primers and TaqMan® probes for human or rat InsR, ACTB and LDLR were purchased from Applied Biosystems (Foster City, CA). 2.5 µl of cDNA sample, 12.5 µl of Universal PCR Master Mix, and 1.25 µl of TaqMan® Gene Expression Assay reagent were mixed in a 25 µl reaction system, and the comparative C_T method was used in relative gene quantification using the TaqMan® SDS analysis software. InsR mRNA levels were corrected by measuring ACTB mRNA levels.

[00284] As can be seen in Figure 39, both berberine and demethylberberine increased LDLR mRNA expression in a dose dependent manner.

Example XXV

Synthesis of berberrubine

[00285] 50mg of berberine chloride was irradiated for 5 minutes in a flask placed in an alumina bath. This is then combined with 50ml of water and the mixture was extracted 8 to 10 times with 150ml of chloroform. The combined organic layer was evaporated *in vacuo* to yield a

32 mg residue. This residue was eluted with CHCl_3 :MeOH (9:1) through a silica gel column (2 x 40cm) to separate berberrubine chloride (yield 67%). (Das *et al.*, *Synthetic Communications* 32:3027-3029 (2002)).

Example XXVI

Synthesis of demethyleneberberine

5

[00286] 100mg of berberine chloride and 100mg of phloroglucin were mixed with 100ml 60% H_2SO_4 and stirred at 100 °C in an oil bath for 20 minutes. The mixture was then cooled, concentrated and resuspended in H_2O -acetone (1:1) and then purified by silica gel chromatography (column 2 x 40cm) with CHCl_3 :MeOH (20:1→9:1) to yield demethyleneberberine (42%). (Pan *et al.*, *Faming Zhuanli Shenqing Gongkai Shoumingshu* CN 1314347, September 26, 2001).

Example XXVII

Isolation of thalifendine and jatrorrhizine

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[00287] Commercial berberine chloride (95% pure) contained two impurities with peaks at m/z 338 and 332. 500 mg of berberine chloride was dissolved in 1% NH_4OH (10ml) and eluted through a polyamide C-100 column (4 x 100cm) with 300ml of 1% NH_4OH . Fractions containing compounds with quasi molecular ions at m/z 338 and 322 were combined, concentrated, and eluted through a column of silica gel (1 x 40cm), with CHCl_3 :MeOH (100:1→20:1→to yield thalifendine and jatrorrhizine. (Otsuka H., *et al.* *Makino Yakugaku Zasshi* 101:883-890 (1981)).

Example XXVIII

Effect of Berberine and Berberine Metabolites on

25

LDLR mRNA and INSrRNA levels on human HepG2 cells

[00288] Cells from the human hepatoma cell line HepG2 were incubated with 10 μg of berberine, berberrubine, thalifendine, demethyleneberberine, or jatrorrhizine for 8 hours at 37°C. Total cellular RNA was isolated using the Ultraspec RNA lysis solution (Biotecxs Laboratory, Houston, TX) following the vender's protocols. 10pg of the RNA sample was transferred to

nitrocellulose membrane via a slot-blot apparatus (Schleicher & Schuell, Keene, NH). The blots were fixed by baking at 80°C for 2h, followed by hybridization to a 0.89-kb long, 32P-labelled human InsR cDNA probe. The same membranes were then stripped and re-hybridized to a human ACTB probe as internal control. Quantitative real time RT-PCR assays were also done. For the RT-PCR assay, total cellular RNA was reverse-transcribed into cDNA using the Reverse Transcription System (Promega, Madison, WI). Quantitative real-time PCR were performed with these cDNA using the Applied Biosystems 7500 Real-Time PCR System and TaqMan® Universal PCR Master Mix (Applied Biosystems, Foster City, CA). All of the 20 X TaqMan® Gene Expression Assay reagents containing gene-specific primers and TaqMan® probes for human or rat InsR, ACTB and LDLR were purchased from Applied Biosystems. 2.5 µl of cDNA sample, 12.5 µl of Universal PCR Master Mix, and 1.25 µl of TaqMan® Gene Expression Assay reagent were mixed in a 25 µl reaction system, and the comparative C_T method was used in relative gene quantification using the TaqMan® SDS analysis software.

[00289] As can be seen in Table 12 and Figure 40, berrubine upregulated liver cell LDLR expression with about 50% greater activity than berberine and jatrorrhizine had nearly double the activity of berberine whereas thalifendine and demthyleneberberine had much less of an effect than berberine.

Table 12

LDLR mRNA levels of Berberine and Four metabolites.

Compound	Mean (fold of control)	SD
Control	1.0	0.0
Berberine 10 ug/ml	1.95	0.12
Berberrubine 10 ug/ml	3.01	0.23
Thalifendine 10 ug/ml	1.03	0.09
Demethyleneberberine 10 ug/ml	1.12	0.10
Jatrorrhizine 10 ug/ml	3.96	0.29

[00290] InsR expression was also increased by treatment with the berberine metabolites though they were less effective than berberine itself. As shown in Figure 41 and Table 13, each of the berberine metabolites increased InsR expression at least 50% more than the control.

Table 13

Ins Receptor upregulation by Berberine and four metabolites.

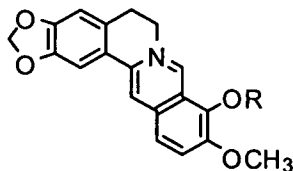
INS Receptor Upregulation	x times control	% upregulation
IgG		4.8%
Control	1	38.1%
Berberine	2.3	86.6%
Berberrubine	1.5	56.7%
Thalifendine	1.5	56.4%
Demethyleneberberine	1.5	58.1%
Jatrorrhizine	1.6	61.2%

Example XXIX

Measurement of plasma concentration of Berberine and Berberrubine following administration of prodrugs of Berberrubine.

5 [00291] In order to determine whether prodrugs of berberrubine are absorbed and adequately cleaved in-vivo to achieve serum levels of berberrubine, 18 Wistar rats (180-200 gm each) were divided into six groups. Each group received a single oral dose (300mg/kg) of either berberine, berrubine, or a berrubine prodrug. Blood samples were taken 1 hour and 3 hours after administration of the dose. 400 μ l of acetonitrile was added to the samples taken 1 hour after administration of the respective compounds and 600 μ l of acetonitrile was added to the samples taken 3 hours after the administration of the respective compounds. The samples were vortexed and centrifuged at 15,000rpm for 10 minutes. The supernatant was then removed and dried in a centrifugal vacuum concentrator at 60°C. The dried extract was redissolved in 70 μ l MeOH-NaAC buffer (50:50, v/v), centrifuged at 15000rpm for 7 minutes and a 50 μ l sample of supernatant was injected into a Nova-Pak C18 column (Waters, Milford, MA) for HPLC analysis. The results were detected using UV at 345nm.

[00292] The four ester prodrugs of berberrubine used in the experiment had the following structures



- 20 XIN 713111 wherein R= COC(CH₃)₃
 XIN 713112 wherein R= COCH=CHPh
 XIN 713151 wherein R= CH₂COOCH₂CH₃

XIN 713152 wherein R= COOCH₂CH₃

[00293] All four ester prodrugs were absorbed from the gut. As can be seen in Table 14, all four ester prodrugs were cleaved by blood esterases, resulting in serum levels of berberrubine. Additionally, administration of berberrubine ester prodrugs resulted in higher serum levels of
5 berberrubine than administration of berberine.

Table 14

Comparison of availability of ester prodrugs of beruberrine

Test Compound	Avg. BBR area by HPLC		Avg. Berruberrine area by HPLC	
	1 hr	3 hr	1 hr	3 hr
Berberine	9356	6868	4235	4783
Berruberrine	0	0	281026	100168
XIN 713111	0	0	60084	53115
XIN 713112	0	0	15519	18232
XIN 713151	0	0	99619	36574
XIN 713152	0	0	282722	266982

[00294] Although the foregoing invention has been described in detail by way of example
10 for purposes of clarity of understanding, it will be apparent to the artisan that certain changes and modifications may be practiced within the scope of the appended claims which are presented by way of illustration not limitation. In this context, various publications and other references have been cited within the foregoing disclosure for economy of description. Each of these references is incorporated herein by reference in its entirety for all purposes. It is noted, however, that the
15 various publications discussed herein are incorporated solely for their disclosure prior to the filing date of the present application, and the inventors reserve the right to antedate such disclosure by virtue of prior invention.

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Each of the following publications is incorporated herein by reference for economy and ease of description, for all purposes including description of additional aspects, embodiments, modifications and uses of the invention.

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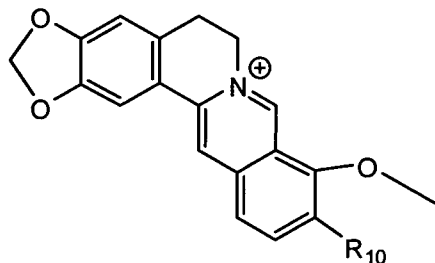
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We claim:

1. A method for preventing or treating metabolic disorders in a mammalian subject comprising administering an anti-metabolic disorder effective amount of a compound of Formula XXXII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph
5 or prodrug thereof, to said subject,



Formula XXXII

wherein R₁₀ is selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, heterocyclo group, methylenedioxy, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, and oligosaccharide groups.

2. The method of claim 1, wherein the metabolic disorder is hyperlipidemia, obesity, diabetes, insulin resistance, glucose intolerance, hyperglycemia, metabolic syndrome or hypertension.

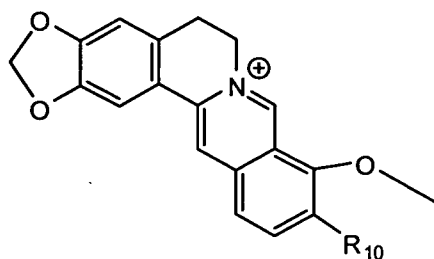
3. The method of claim 1, further comprising administering a secondary metabolic disorder therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said compound of Formula XXXII or other adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said compound of Formula XXXII to treat or prevent metabolic disorder or a related symptom or condition thereof in said subject.

4. The method of claim 3, wherein the secondary metabolic disorder therapeutic or adjunctive therapeutic agent is administered to said subject in a coordinate administration

protocol, simultaneously with, prior to, or after, administration of said compound of Formula XXXII to the subject.

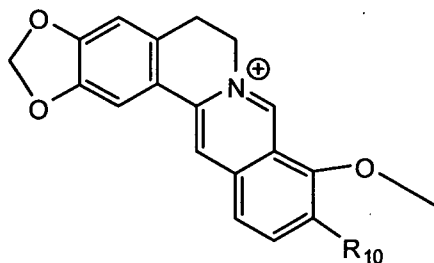
5. The method of claim 3, wherein the secondary metabolic disorder therapeutic or adjunctive therapeutic agent is selected from anti-hyperlipidemic agents, anti-dyslipidemic agents, plasma HDL-raising agents, cholesterol-uptake inhibitors, cholesterol biosynthesis inhibitors, HMG-CoA reductase inhibitors, HMG-CoA synthase inhibitors, squalene epoxidase inhibitors, squalene synthetase inhibitors, acyl-coenzyme A cholesterol acyltransferase (ACAT) inhibitors, nicotinic acid and the salts thereof, niacinamide, cholesterol absorption inhibitors, bile acid sequestrant anion exchange resins, LDL receptor inducers, fibrates, vitamin B6, vitamin B12, vitamin B3, anti-oxidant vitamins, angiotensin II receptor (AT₁) antagonist, renin inhibitors, platelet aggregation inhibitors, hormones, insulin, ion exchange resins, omega-3 oils, benfluorex, ethyl icosapentate, amlodipine, insulin sensitizers, protein tyrosine phosphatase-1B (PTP-1B) inhibitors, dipeptidyl peptidase IV (DP-IV) inhibitors, insulin mimetics, sequestrants, nicotinyl alcohol, nicotinic acid, PPAR α agonists, PPAR α / γ dual agonists, neuropeptide Y5 inhibitors, β_3 adrenergic receptor agonists, ileal bile acid transporter inhibitors, anti-inflammatories, cyclo-oxygenase 2 selective inhibitors, sulfonyleureas, DPP-4 blockers, biguanides, alpha-glucosidase inhibitors, D-phenylalanine derivatives, meglitinides, diuretics, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, vasodilators, angiotensin II receptor blockers, and alpha blockers.
6. The method of claim 3, wherein the secondary metabolic disorder therapeutic or adjunctive therapeutic agent is a statin or HMG-CoA reductase inhibitor.
7. The method of claim 6, wherein the statin or HMG-CoA reductase inhibitor is lovastatin, simvastatin, pravastatin, fluvastatin, rosuvastatin, pitavastatin, or atorvastatin.
8. The method of claim 3, wherein the secondary metabolic disorder therapeutic or adjunctive therapeutic agent is a cholesterol-uptake inhibitor or a cholesterol biosynthesis inhibitor.
9. The method of claim 1, further comprising advising or engaging the subject to undertake an additional therapeutic treatment selected from the group consisting of exercise, diet modification, or surgery.
10. The method of claim 3, wherein the secondary metabolic disorder or adjunctive therapeutic agent is an herbal-derived product or extract.

11. The method of claim 10, wherein the herbal-derived product or extract is curcumin, gugulipid, garlic, vitamin E, soy, soluble fiber, fish oil, green tea, carnitine, chromium, coenzyme Q10, anti-oxidant vitamins, grape seed extract, pantothenic acid, red yeast rice, or royal jelly.
- 5 12. The method of claim 1, wherein the administration of said effective amount of the compound of Formula XXXII is anti-metabolic disorder effective to decrease total cholesterol in said subject to about 200mg/dL.
13. The method of claim 1, wherein the administration of said compound of Formula XXXII is anti-metabolic disorder effective to decrease LDL levels in said subject to about 130 mg/dL.
- 10 14. The method of claim 1, wherein the administration of said effective amount of the compound of Formula XXXII is anti-metabolic disorder effective to decrease triglycerides in said subject to about 150 mg/dL.
- 15 15. The method of claim 1, wherein the administration of said effective amount of the compound of Formula XXXII is anti-metabolic disorder effective to decrease hs-CRP in said subject to about 2.0 mg/L.
16. The method of claim 1, wherein the administration of said effective amount of the compound of Formula XXXII is anti-metabolic disorder effective to decrease fasting glucose by about 5 to about 30 mg/dL.
- 20 17. The method of claim 1, wherein the administration of said compound of Formula XXXII is anti-metabolic disorder effective to decrease hemoglobin A1c% to less than 14%.
18. The method of claim 1, wherein the administration of said compound of Formula XXXII is anti-metabolic disorder effective to increase $^{13}\text{CO}_2$ consumption by about 15% to about 30%.
19. The method of claim 1, wherein the administration of said effective amount of the compound of Formula XXXII is anti-metabolic disorder effective to lower blood pressure from about 150/100 mmHg to about 120/80 mm Hg.
- 25 20. A composition for preventing, treating or alleviating metabolic disorder in a mammalian subject comprising an anti-metabolic disorder effective amount of a compound of Formula XXXII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug



wherein R_{10} is selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, heterocyclo group, methylenedioxy, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylproparyl, alkylacetyl, and oligosaccharide groups.

21. A method for treating one or more conditions associated with metabolic disorders comprising administering to a mammalian subject an effective amount of a compound of Formula XXXII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject

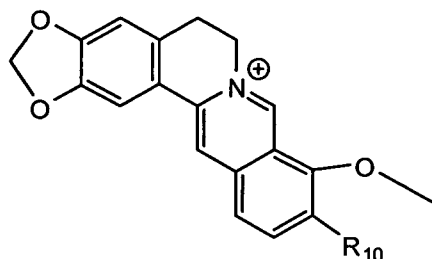


Formula XXXII

wherein R_{10} is selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, heterocyclo group, methylenedioxy, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylproparyl, alkylacetyl, and oligosaccharide groups.

22. A method for preventing or treating metabolic syndrome in a mammalian subject comprising administering an anti-metabolic syndrome effective amount of a compound of

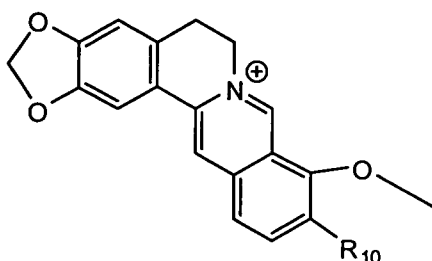
Formula XXXII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject



Formula XXXII,

- 5 wherein R₁₀, is selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, heterocyclo group, methylenedioxy, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropenyl, alkylacetyl, and oligosaccharide groups.

23. A composition for preventing, treating or alleviating metabolic syndrome in a mammalian subject comprising an anti-metabolic syndrome effective amount of a compound of Formula XXXII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof

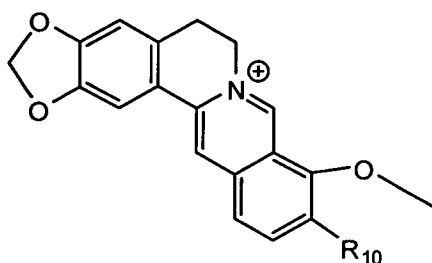


Formula XXXII,

- 15 wherein R₁₀ is selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, heterocyclo group, methylenedioxy, acetyl, formyl,

phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, and oligosaccharide groups; and a secondary metabolic syndrome therapeutic agent or other adjunctive therapeutic agent useful in the treatment of a metabolic syndrome.

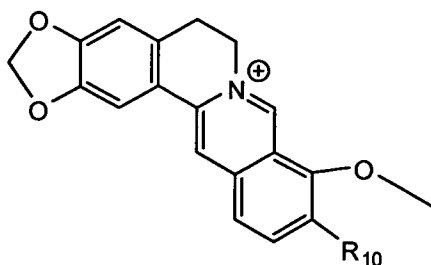
24. A method for preventing or treating obesity in a mammalian subject comprising
 5 administering an anti-obesity effective amount of a compound of Formula XXXII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject



Formula XXXII,

10 wherein R₁₀ is selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, heterocyclo group, methylenedioxy, acetyl, formyl,
 15 phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, and oligosaccharide groups

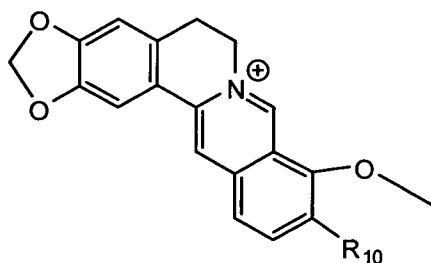
25. A composition for preventing, alleviating or treating obesity or complications associated with obesity in a mammalian subject comprising an anti-obesity effective amount of a compound of Formula XXXII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof



Formula XXXII,

wherein R₁₀, is selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, heterocyclo group, methylenedioxy, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, and oligosaccharide groups.

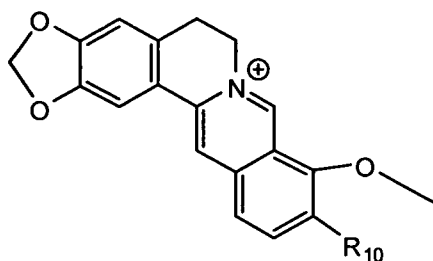
26. A method for preventing or treating diabetes in a mammalian subject comprising administering an anti-diabetic effective amount of a compound of Formula XXXII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject



Formula XXXII,

wherein R₁₀, is selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, heterocyclo group, methylenedioxy, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, and oligosaccharide groups.

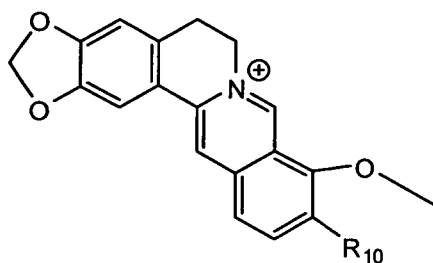
27. A composition for preventing, treating or alleviating diabetes in a mammalian subject comprising an anti-diabetic effective amount of a compound of Formula XXXII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof



Formula XXXII,

wherein R₁₀ is selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, heterocyclo group, methylenedioxy, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, and oligosaccharide groups.

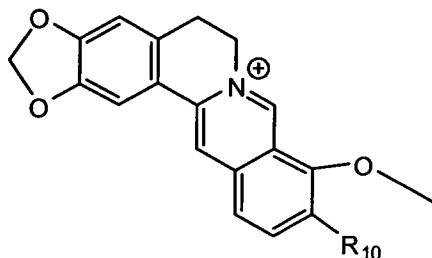
28. A method for preventing or treating insulin resistance in a mammalian subject comprising administering an anti-insulin resistance effective amount of a compound of Formula XXXII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject



Formula XXXII,

wherein R₁₀ is selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, heterocyclo group, methylenedioxy, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, and oligosaccharide groups.

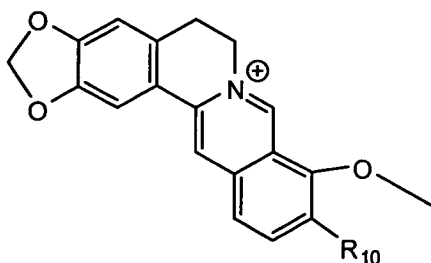
29. A composition for preventing, treating or alleviating insulin resistance in a mammalian subject comprising an anti-insulin resistance effective amount of a compound of Formula XXXII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof



Formula XXXII,

wherein R_{10} is selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, heterocyclo group, methylenedioxy, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, and oligosaccharide groups.

30. A method for preventing or treating hyperglycemia in a mammalian subject comprising administering an anti-hyperglycemic effective amount of a compound of Formula XXXII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject

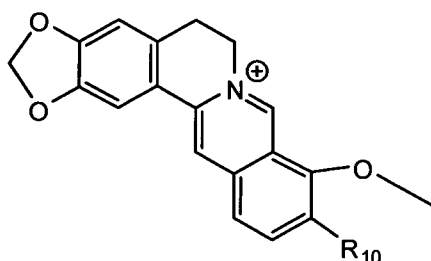


Formula XXXII,

wherein R_{10} is selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl,

haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, heterocyclo group, methylenedioxy, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, and oligosaccharide groups.

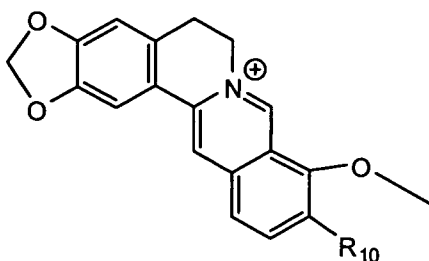
31. A composition for preventing, treating or alleviating hyperglycemia in a mammalian
 5 subject comprising an anti-hyperglycemic effective amount of a compound of Formula XXXII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof



Formula XXXII,

10 wherein R₁₀ is selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, heterocyclo group, methylenedioxy, acetyl, formyl,
 15 phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, and oligosaccharide groups.

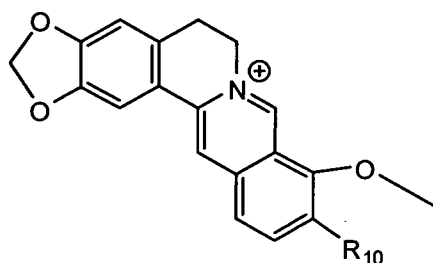
32. A method for increasing insulin sensitivity in a mammalian subject comprising administering an effective amount of a compound of Formula XXXII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject



Formula XXXII,

wherein R₁₀ is selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, heterocyclo group, methylenedioxy, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, and oligosaccharide groups.

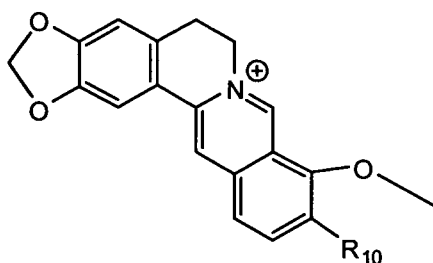
33. A composition for increasing insulin sensitivity in a mammalian subject comprising a insulin sensitivity increasing effective amount of a compound of Formula XXXII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof



Formula XXXII,

wherein R₁₀ is selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, heterocyclo group, methylenedioxy, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, and oligosaccharide groups.

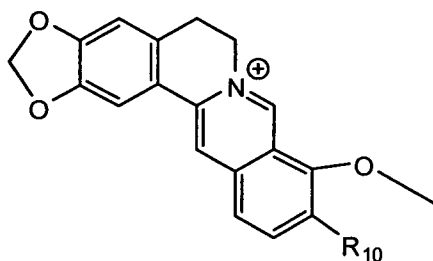
34. A method for preventing or treating hypertension in a mammalian subject comprising administering an anti-hypertensive effective amount of a compound of Formula XXXII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject



Formula XXXII,

wherein R₁₀ is selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, heterocyclo group, methylenedioxy, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, and oligosaccharide groups.

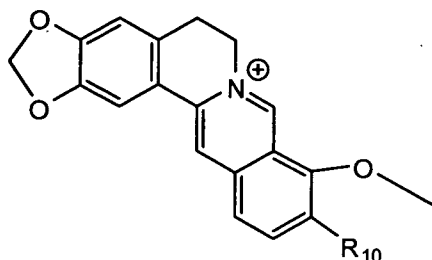
35. A composition for preventing, treating or alleviating hypertension in a mammalian subject comprising an anti-hypertensive effective amount of a compound of Formula XXXII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof



Formula XXXII,

wherein R₁₀ is selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, heterocyclo group, methylenedioxy, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, and oligosaccharide groups.

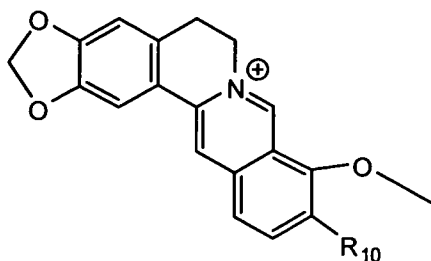
36. A method of modulating InsR expression in a mammalian subject comprising administering to said subject an effective amount of a compound of Formula XXXII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof



Formula XXXII,

wherein R₁₀ is selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, heterocyclo group, methylenedioxy, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, and oligosaccharide groups; and a secondary anti-hyperglycemic agent or other adjunctive therapeutic agent useful in the treatment of hyperglycemia.

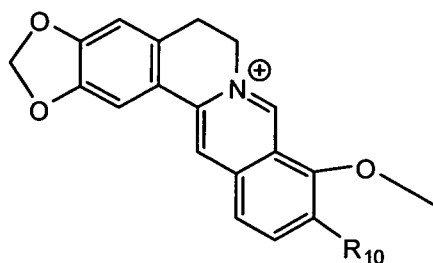
37. A composition for increasing InsR expression in a mammalian cell, tissue, organ, or individual comprising an InsR effective amount of a compound of Formula XXXII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof



Formula XXXII,

wherein R₁₀ is selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, heterocyclo group, methylenedioxy, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, and oligosaccharide groups.

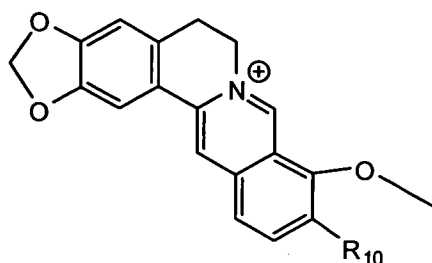
38. A method of modulating PKC activity in a mammalian subject selected from a mammalian cell, tissue, organ, or individual comprising administering to said subject a PKC activity modulatory effective amount of a compound of Formula XXXII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof



Formula XXXII,

wherein R₁₀ is selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, heterocyclo group, methylenedioxy, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, and oligosaccharide groups.

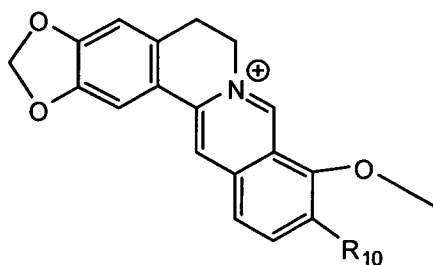
39. A method for increasing LDLR stability in a mammalian cell, tissue, organ or individual comprising administering to a mammalian subject an effective amount of a compound of Formula XXXII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof



Formula XXXII,

wherein R₁₀ is selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, heterocyclo group, methylenedioxy, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, and oligosaccharide groups.

40. A method of modulating ERK activation in a mammalian subject selected from a mammalian cell, tissue, organ, or individual comprising administering to said subject an ERK activation modulatory effective amount of a compound of Formula XXXII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof

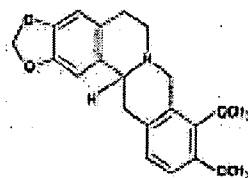


Formula XXXII,

wherein R₁₀ is selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl,

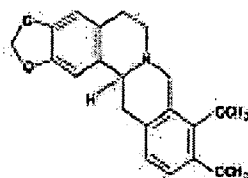
carbonylamino, alkylsulfonylamino, heterocyclo group, methylenedioxy, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, and oligosaccharide groups.

41. A method for preventing or treating metabolic disorders in a mammalian subject comprising administering an anti-metabolic disorder effective amount of a compound of Formula XIV, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject,



Formula XIV

42. A composition for preventing, treating or alleviating metabolic disorder in a mammalian subject comprising an anti-metabolic disorder effective amount of a compound of Formula XIV, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug



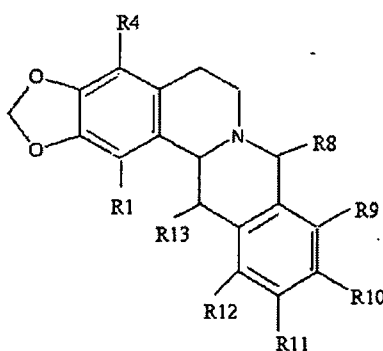
Formula XIV

- and a secondary therapeutic agent.

43. The composition of claim 42, wherein the secondary therapeutic agent is anti-hyperlipidemic agents, anti-dyslipidemic agents, plasma HDL-raising agents, cholesterol-uptake inhibitors, cholesterol biosynthesis inhibitors, HMG-CoA reductase inhibitors, HMG-CoA synthase inhibitors, squalene epoxidase inhibitors, squalene synthetase inhibitors, acyl-coenzyme A cholesterol acyltransferase (ACAT) inhibitors, nicotinic acid and the salts thereof, niacinamide, cholesterol absorption inhibitors, bile acid sequestrant anion exchange resins, LDL receptor inducers, fibrates, vitamin B6, vitamin B12, vitamin B3, anti-oxidant vitamins,

angiotensin II receptor (AT₁) antagonist, renin inhibitors, platelet aggregation inhibitors, hormones, insulin, ion exchange resins, omega-3 oils, benfluorex, ethyl icosapentate, amlodipine, insulin sensitizers, protein tyrosine phosphatase-1B (PTP-1B) inhibitors, dipeptidyl peptidase IV (DP-IV) inhibitors, insulin mimetics, sequestrants, nicotinyl alcohol, nicotinic acid,
 5 PPAR α agonists, PPAR α / γ dual agonists, neuropeptide Y5 inhibitors, β_3 adrenergic receptor agonists, ileal bile acid transporter inhibitors, anti-inflammatories, cyclo-oxygenase 2 selective inhibitors, sulfonylureas, DPP-4 blockers, biguanides, alpha-glucosidase inhibitors, D-phenylalanine derivatives, meglitinides, diuretics, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, vasodilators, angiotensin II receptor blockers, and
 10 alpha blockers.

44. A method for preventing or treating metabolic disorders in a mammalian subject comprising administering an anti-metabolic disorder effective amount of a compound of Formula XXVII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject



Formula XXVII,

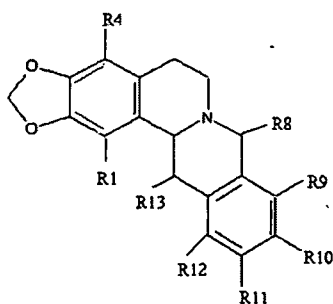
wherein each of R₁, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂ and/or R₁₃ is, independently, collectively, or in any combination, selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile,
 20 dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylproparyl, alkylacetyl, oligosaccharide and heterocyclo groups.

45. The method of claim 44, wherein R₁ is selected from methyl, ethyl, hydroxyl, or methoxy; R₄ is selected from methyl, ethyl, hydroxyl, or methoxy; R₈ is selected from straight or branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl; R₉ is selected from methyl, ethyl, hydroxyl, methoxy, Cl, Br; R₁₀ is selected from methyl, ethyl, hydroxyl, Cl, Br, acetyl, tertiarybutylformylacetyl, 3-phenylacryloyl, chloroacetyl, chloroacetylpropanyl, straight or branched (C1-C8) alkyl, (e.g., substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl, terbutyl formyl and 1-methyl-2ethylpropyl); R₁₁ is selected from methyl, ethyl, hydroxyl, Cl, Br; R₁₂ is selected from methyl, ethyl, hydroxyl, Cl, Br; and R₁₃ is selected from straight or branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl.
46. The method of claim 44, wherein the metabolic disorder is hyperlipidemia, obesity, diabetes, insulin resistance, glucose intolerance, hyperglycemia, metabolic syndrome or hypertension.
47. The method of claim 44, further comprising administering a secondary metabolic disorder therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said compound of Formula XXVII or other adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said compound of Formula XXVII to treat or prevent metabolic disorder or a related symptom or condition thereof in said subject.
48. The method of claim 44, wherein the secondary metabolic disorder therapeutic or adjunctive therapeutic agent is administered to said subject in a coordinate administration

protocol, simultaneously with, prior to, or after, administration of said compound of Formula XXVII to the subject.

49. The method of claim 44, wherein the secondary metabolic disorder therapeutic or adjunctive therapeutic agent is selected from anti-hyperlipidemic agents, anti-dyslipidemic agents, plasma HDL-raising agents, cholesterol-uptake inhibitors, cholesterol biosynthesis inhibitors, HMG-CoA reductase inhibitors, HMG-CoA synthase inhibitors, squalene epoxidase inhibitors, squalene synthetase inhibitors, acyl-coenzyme A cholesterol acyltransferase (ACAT) inhibitors, nicotinic acid and the salts thereof, niacinamide, cholesterol absorption inhibitors, bile acid sequestrant anion exchange resins, LDL receptor inducers, fibrates, vitamin B6, vitamin B12, vitamin B3, anti-oxidant vitamins, angiotensin II receptor (AT₁) antagonist, renin inhibitors, platelet aggregation inhibitors, hormones, insulin, ion exchange resins, omega-3 oils, benfluorex, ethyl icosapentate, amlodipine, insulin sensitizers, protein tyrosine phosphatase-1B (PTP-1B) inhibitors, dipeptidyl peptidase IV (DP-IV) inhibitors, insulin mimetics, sequestrants, nicotinyl alcohol, nicotinic acid, PPAR α agonists, PPAR α / γ dual agonists, neuropeptide Y5 inhibitors, β_3 adrenergic receptor agonists, ileal bile acid transporter inhibitors, anti-inflammatories, cyclo-oxygenase 2 selective inhibitors, sulfonylureas, DPP-4 blockers, biguanides, alpha-glucosidase inhibitors, D-phenylalanine derivatives, meglitinides, diuretics, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, vasodilators, angiotensin II receptor blockers, and alpha blockers.

50. A composition for preventing or alleviating metabolic disorder in a mammalian subject comprising an anti-metabolic disorder effective amount of a compound of Formula XXVII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof

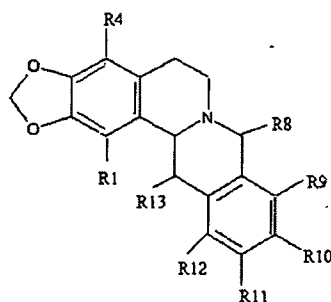


Formula XXVII,

wherein each of R₁, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂ and/or R₁₃ is, independently, collectively, or in any combination, selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, oligosaccharide and heterocyclo groups; and a secondary metabolic disorder therapeutic agent or other adjunctive therapeutic agent useful in the treatment of a metabolic disorder.

51. The composition of claim 50, wherein R₁ is selected from methyl, ethyl, hydroxyl, or methoxy; R₄ is selected from methyl, ethyl, hydroxyl, or methoxy; R₈ is selected from straight or branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl; R₉ is selected from methyl, ethyl, hydroxyl, methoxy, Cl, Br; R₁₀ is selected from methyl, ethyl, hydroxyl, Cl, Br, acetyl, tertiarybutylformylacetyl, 3-phenylacryloyl, chloracetyl, chloroacetylpropanyl, straight or branched (C1-C8) alkyl, (e.g., substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl, tertbutyl formyl and 1-methyl-2ethylpropyl); R₁₁ is selected from methyl, ethyl, hydroxyl, Cl, Br; R₁₂ is selected from methyl, ethyl, hydroxyl, Cl, Br; and R₁₃ is selected from straight or branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl.

52. A composition for treating metabolic disorders in a mammalian subject comprising a metabolic disorder treating effective amount of a compound of Formula XXVII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof



Formula XXVII,

wherein each of R₁, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂ and/or R₁₃ is, independently, collectively, or in any combination, selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, oligosaccharide and heterocyclo groups; and a secondary metabolic disorder therapeutic agent or other adjunctive therapeutic agent useful in the treatment of a metabolic disorder.

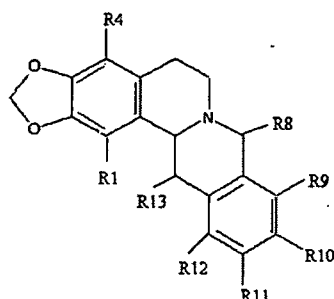
53. The composition of claim 52, wherein R₁ is selected from methyl, ethyl, hydroxyl, or methoxy; R₄ is selected from methyl, ethyl, hydroxyl, or methoxy; R₈ is selected from straight or branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl; R₉ is selected from methyl, ethyl, hydroxyl, methoxy, Cl, Br; R₁₀ is selected from methyl, ethyl, hydroxyl, Cl, Br, acetyl, tertiarybutylformylacetyl, 3-

phenylacryloyl, chloracetyl, chloroacetylpropyl, straight or branched (C1-C8) alkyl, (e.g., substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl, tertbutyl formyl and 1-methyl-2ethylpropyl);
5 R_{11} is selected from methyl, ethyl, hydroxyl, Cl, Br; R_{12} is selected from methyl, ethyl, hydroxyl, Cl, Br; and R_{13} is selected from straight or branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl.
10

54. The composition of claim 52, wherein the secondary metabolic disorder therapeutic or adjunctive therapeutic agent is selected from the group consisting of: anti-hyperlipidemic agents, anti-dyslipidemic agents, plasma HDL-raising agents, cholesterol-uptake inhibitors, cholesterol
15 biosynthesis inhibitors, HMG-CoA reductase inhibitors, HMG-CoA synthase inhibitors, squalene epoxidase inhibitors, squalene synthetase inhibitors, acyl-coenzyme A cholesterol acyltransferase (ACAT) inhibitors, nicotinic acid and the salts thereof, niacinamide, cholesterol absorption inhibitors, bile acid sequestrant anion exchange resins, LDL receptor inducers, fibrates, vitamin B6, vitamin B12, vitamin B3, anti-oxidant vitamins, angiotensin II receptor
20 (AT_1) antagonist, renin inhibitors, platelet aggregation inhibitors, hormones, insulin, ion exchange resins, omega-3 oils, benfluorex, ethyl icosapentate, amlodipine, insulin sensitizers, protein tyrosine phosphatase-1B (PTP-1B) inhibitors, dipeptidyl peptidase IV (DP-IV) inhibitors, insulin mimetics, sequestrants, nicotinyl alcohol, nicotinic acid, camptothecin, camptothecin derivatives, PPAR α agonists, PPAR γ agonists, PPAR α / γ dual agonists, neuropeptide Y5
25 inhibitors, β_3 adrenergic receptor agonists, ileal bile acid transporter inhibitors, anti-inflammatories, cyclo-oxygenase 2 selective inhibitors, sulfonylureas, DPP-4 blockers, biguanides, alpha-glucosidase inhibitors, D-phenylalanine derivatives, meglitinides, diuretics, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, vasodilators, angiotensin II receptor blockers, and alpha blockers.

30 55. A method for treating one or more conditions associated with metabolic disorders comprising administering to a mammalian subject an effective amount of a compound of

Formula XXVII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject



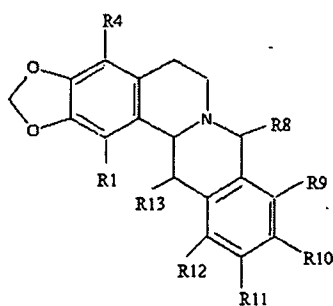
Formula XXVII,

- 5 wherein each of R₁, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂ and/or R₁₃ is, independently, collectively, or in any combination, selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl,
- 10 carbonylamino, alkylsulfonylamino, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, oligosaccharide and heterocyclo groups.
56. The method of claim 55, wherein R₁ is selected from methyl, ethyl, hydroxyl, or methoxy; R₄ is selected from methyl, ethyl, hydroxyl, or methoxy; R₈ is selected from straight or branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-
- 15 methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl; R₉ is selected from methyl, ethyl, hydroxyl, methoxy, Cl, Br; R₁₀ is selected from methyl, ethyl, hydroxyl, Cl, Br, acetyl, tertiarybutylformylacetyl, 3-
- 20 phenylacryloyl, chloracetyl, chloroacetylpropanyl, straight or branched (C1-C8) alkyl, (e.g., substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl, tertbutyl formyl and 1-methyl-2ethylpropyl);

R₁₁ is selected from methyl, ethyl, hydroxyl, Cl, Br; R₁₂ is selected from methyl, ethyl, hydroxyl, Cl, Br; and R₁₃ is selected from straight or branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl.

57. The method of claim 55, wherein said one or more conditions include(s) fatty liver, reproductive abnormalities, growth abnormalities, arterial plaque accumulation, osteoarthritis, gout, joint pain, respiratory problems, skin conditions, sleep apnea, idiopathic intracranial hypertension, lower extremity venous stasis disease, gastro-esophageal reflux, urinary stress incontinence, kidney damage, cardiovascular disease, atherosclerosis, coronary artery disease, enlarged heart, diabetic cardiomyopathy, peripheral vascular disease, pulmonary embolism, angina pectoris, carotid artery disease, stroke, cerebral arteriosclerosis, myocardial infarction, cerebral infarction, restenosis following balloon angioplasty, intermittent claudication, dyslipidemia post-prandial lipidemia, high blood pressure and xanthoma.

58. A method for preventing or treating metabolic syndrome in a mammalian subject comprising administering an anti-metabolic syndrome effective amount of a compound of Formula XXVII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject



Formula XXVII,

wherein each of R₁, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂ and/or R₁₃ is, independently, collectively, or in any combination, selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile,

dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, oligosaccharide and heterocyclo groups.

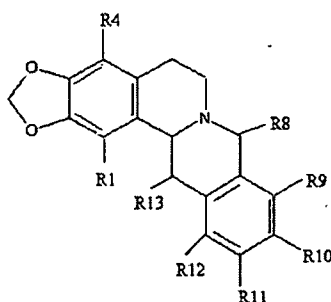
5 59. The method of claim 58, wherein R_1 is selected from methyl, ethyl, hydroxyl, or methoxy; R_4 is selected from methyl, ethyl, hydroxyl, or methoxy; R_8 is selected from straight or branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 10 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl; R_9 is selected from methyl, ethyl, hydroxyl, methoxy, Cl, Br; R_{10} is selected from methyl, ethyl, hydroxyl, Cl, Br, acetyl, tertiarybutylformylacetyl, 3-phenylacryloyl, chloracetyl, chloroacetylpropanyl, straight or branched (C1-C8) alkyl, (e.g., substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 15 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl, tertbutyl formyl and 1-methyl-2ethylpropyl); R_{11} is selected from methyl, ethyl, hydroxyl, Cl, Br; R_{12} is selected from methyl, ethyl, hydroxyl, Cl, Br; and R_{13} is selected from straight or branched (C1-C6) alkyl, including substitution 20 selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl.

60. The method of claim 142, further comprising administering a secondary metabolic 25 syndrome therapeutic agent or adjunctive agent that is effective in a combinatorial formulation or coordinate treatment regimen with said compound of Formula XXVII to treat or prevent metabolic syndrome or a related symptom or condition thereof in said subject.

61. The method of claim 60, wherein the secondary metabolic syndrome therapeutic or adjunctive therapeutic agent is selected from anti-hyperlipidemic agents, anti-dyslipidemic 30 agents, plasma HDL-raising agents, cholesterol-uptake inhibitors, cholesterol biosynthesis inhibitors, HMG-CoA reductase inhibitors, HMG-CoA synthase inhibitors, squalene epoxidase

inhibitors, squalene synthetase inhibitors, acyl-coenzyme A cholesterol acyltransferase (ACAT) inhibitors, nicotinic acid and the salts thereof, niacinamide, cholesterol absorption inhibitors, bile acid sequestrant anion exchange resins, LDL receptor inducers, fibrates, vitamin B6, vitamin B12, vitamin B3, anti-oxidant vitamins, angiotensin II receptor (AT₁) antagonist, renin inhibitors, platelet aggregation inhibitors, hormones, insulin, ion exchange resins, omega-3 oils, benfluorex, ethyl icosapentate, amlodipine, insulin sensitizers, protein tyrosine phosphatase-1B (PTP-1B) inhibitors, dipeptidyl peptidase IV (DP-IV) inhibitors, insulin mimetics, sequestrants, nicotinyl alcohol, nicotinic acid, PPAR α agonists, PPAR γ agonists, PPAR α / γ dual agonists, neuropeptide Y5 inhibitors, β_3 adrenergic receptor agonists, ileal bile acid transporter inhibitors, anti-inflammatories, cyclo-oxygenase 2 selective inhibitors, sulfonylureas, DPP-4 blockers, biguanides, alpha-glucosidase inhibitors, D-phenylalanine derivatives, meglitinides, diuretics, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, vasodilators, angiotensin II receptor blockers, and alpha blockers.

62. A composition for treating metabolic syndrome in a mammalian subject comprising a metabolic syndrome treating effective amount of a compound of Formula XXVII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof



Formula XXVII,

20 wherein each of R₁, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂ and/or R₁₃ is, independently, collectively, or in any combination, selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl,

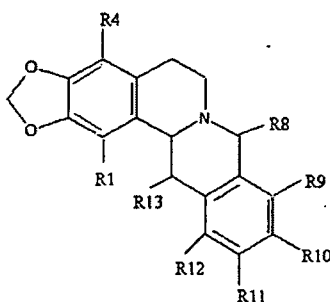
carbonylamino, alkylsulfonylamino, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, oligosaccharide and heterocyclo groups; and a secondary metabolic syndrome therapeutic agent or other adjunctive therapeutic agent useful in the treatment of a metabolic syndrome.

5 63. The composition of claim 63, wherein R₁ is selected from methyl, ethyl, hydroxyl, or methoxy; R₄ is selected from methyl, ethyl, hydroxyl, or methoxy; R₈ is selected from straight or branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 10 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl; R₉ is selected from methyl, ethyl, hydroxyl, methoxy, Cl, Br; R₁₀ is selected from methyl, ethyl, hydroxyl, Cl, Br, acetyl, tertiarybutylformylacetyl, 3-phenylacryloyl, chloracetyl, chloroacetylpropanyl, straight or branched (C1-C8) alkyl, (e.g., substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 15 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl, terbutyl formyl and 1-methyl-2ethylpropyl); R₁₁ is selected from methyl, ethyl, hydroxyl, Cl, Br; R₁₂ is selected from methyl, ethyl, hydroxyl, Cl, Br; and R₁₃ is selected from straight or branched (C1-C6) alkyl, including substitution 20 selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl.

64. The composition of claim 63, wherein the secondary metabolic syndrome therapeutic or 25 adjunctive therapeutic agent is selected from the group consisting of: anti-hyperlipidemic agents, anti-dyslipidemic agents, plasma HDL-raising agents, cholesterol-uptake inhibitors, cholesterol biosynthesis inhibitors, HMG-CoA reductase inhibitors, HMG-CoA synthase inhibitors, squalene epoxidase inhibitors, squalene synthetase inhibitors, acyl-coenzyme A cholesterol acyltransferase (ACAT) inhibitors, nicotinic acid and the salts thereof, niacinamide, cholesterol 30 absorption inhibitors, bile acid sequestrant anion exchange resins, LDL receptor inducers, fibrates, vitamin B6, vitamin B12, vitamin B3, anti-oxidant vitamins, angiotensin II receptor

(AT₁) antagonist, renin inhibitors, platelet aggregation inhibitors, hormones, insulin, ion exchange resins, omega-3 oils, benfluorex, ethyl icosapentate, amlodipine, insulin sensitizers, protein tyrosine phosphatase-1B (PTP-1B) inhibitors, dipeptidyl peptidase IV (DP-IV) inhibitors, insulin mimetics, sequestrants, nicotinyl alcohol, nicotinic acid, PPAR α agonists, PPAR γ agonists, PPAR α / γ dual agonists, cannabinoid antagonists, neuropeptide Y5 inhibitors, β_3 adrenergic receptor agonists, ileal bile acid transporter inhibitors, anti-inflammatories, cyclo-oxygenase 2 selective inhibitors, sulfonylureas, DPP-4 blockers, biguanides, alpha-glucosidase inhibitors, D-phenylalanine derivatives, meglitinides, diuretics, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, vasodilators, angiotensin II receptor blockers, and alpha blockers.

65. A method for preventing or treating obesity in a mammalian subject comprising administering an anti-obesity effective amount of a compound of Formula XXVII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject



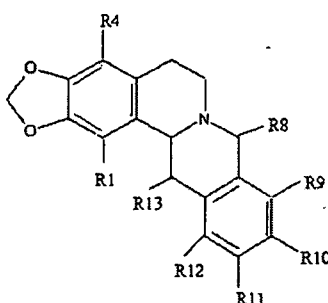
Formula XXVII,

wherein each of R₁, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂ and/or R₁₃ is, independently, collectively, or in any combination, selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, oligosaccharide and heterocyclo groups.

66. The method of claim 65, wherein R₁ is selected from methyl, ethyl, hydroxyl, or methoxy; R₄ is selected from methyl, ethyl, hydroxyl, or methoxy; R₈ is selected from straight or branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl; R₉ is selected from methyl, ethyl, hydroxyl, methoxy, Cl, Br; R₁₀ is selected from methyl, ethyl, hydroxyl, Cl, Br, acetyl, tertiarybutylformylacetyl, 3-phenylacryloyl, chloroacetyl, chloroacetylpropanyl, straight or branched (C1-C8) alkyl, (e.g., substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl, tertbutyl formyl and 1-methyl-2ethylpropyl); R₁₁ is selected from methyl, ethyl, hydroxyl, Cl, Br; R₁₂ is selected from methyl, ethyl, hydroxyl, Cl, Br; and R₁₃ is selected from straight or branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl.
67. The method of claim 65, wherein the obesity is caused by treatment of the mammalian subject with atypical neuroleptics.
68. The method of claim 65, further comprising administering a secondary anti-obesity therapeutic agent or adjunctive agent that is effective in a combinatorial formulation or coordinate treatment regimen with said compound of Formula XXVII to treat or prevent obesity or a related symptom or condition thereof in said subject.
69. The method of claim 68, wherein the secondary anti-obesity therapeutic or adjunctive therapeutic agent is selected from insulin sensitizers, biguanides, protein tyrosine phosphatase-1B (PTP-1B) inhibitors, dipeptidyl peptidase IV (DP-IV) inhibitors, insulin, insulin mimetics, sulfonylureas, α -glucosidase inhibitors, cholesterol lowering agents, sequestrants, nicotinyl alcohol, nicotinic acid or a salt thereof, PPAR α agonists, PPAR γ agonists, PPAR α / γ dual agonists, anti-obesity compounds, cannabinoid antagonists, inhibitors of cholesterol absorption,

acyl CoA:cholesterol acyltransferase inhibitors, anti-oxidants, neuropeptide Y5 inhibitors, β_3 adrenergic receptor agonists, an ileal bile acid transporter inhibitor, a non-steroidal anti-inflammatory drugs, glucocorticoids, azulfidine, or cyclo-oxygenase 2 selective inhibitors.

70. A method of preventing or alleviating complications associated with obesity in a mammalian subject comprising administering an effective amount of a of said compound of Formula XXVII to said subject or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject



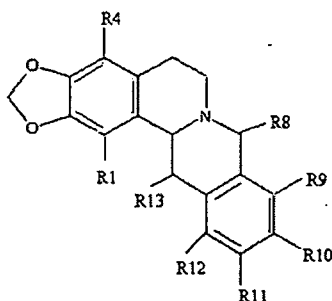
Formula XXVII,

wherein each of R₁, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂ and/or R₁₃ is, independently, collectively, or in any combination, selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, oligosaccharide and heterocyclo groups.

71. The method of claim 70, wherein R₁ is selected from methyl, ethyl, hydroxyl, or methoxy; R₄ is selected from methyl, ethyl, hydroxyl, or methoxy; R₈ is selected from straight or branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl; R₉ is selected from methyl, ethyl, hydroxyl, methoxy, Cl, Br; R₁₀ is selected from methyl, ethyl, hydroxyl, Cl, Br, acetyl, tertiarybutylformylacetyl, 3-

phenylacryloyl, chloracetyl, chloroacetylpropanyl, straight or branched (C1-C8) alkyl, (e.g., substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl, tertbutyl formyl and 1-methyl-2ethylpropyl);
 5 R_{11} is selected from methyl, ethyl, hydroxyl, Cl, Br; R_{12} is selected from methyl, ethyl, hydroxyl, Cl, Br; and R_{13} is selected from straight or branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl.

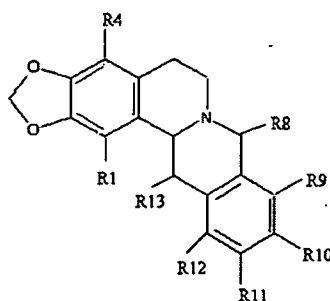
72. A composition for preventing, alleviating or treating obesity or complications associated with obesity in a mammalian subject comprising an anti-obesity effective amount of a compound of Formula XXVII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate,
 15 polymorph or prodrug thereof



Formula XXVII,

wherein each of R_1 , R_4 , R_8 , R_9 , R_{10} , R_{11} , R_{12} and/or R_{13} is, independently, collectively, or in any combination, selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile,
 20 dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, oligosaccharide and heterocyclo groups.

73. The composition of claim 72, wherein R₁ is selected from methyl, ethyl, hydroxyl, or methoxy; R₄ is selected from methyl, ethyl, hydroxyl, or methoxy; R₈ is selected from straight or branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl; R₉ is selected from methyl, ethyl, hydroxyl, methoxy, Cl, Br; R₁₀ is selected from methyl, ethyl, hydroxyl, Cl, Br, acetyl, tertiarybutylformylacetyl, 3-phenylacryloyl, chloracetyl, chloroacetylpropanyl, straight or branched (C1-C8) alkyl, (e.g., substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl, tertbutyl formyl and 1-methyl-2ethylpropyl); R₁₁ is selected from methyl, ethyl, hydroxyl, Cl, Br; R₁₂ is selected from methyl, ethyl, hydroxyl, Cl, Br; and R₁₃ is selected from straight or branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl.
74. A method for preventing or treating diabetes in a mammalian subject comprising administering an anti-diabetic effective amount of a compound of Formula XXVII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject

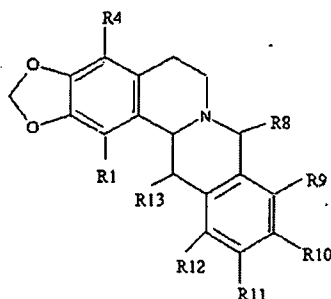


Formula XXVII,

wherein each of R₁, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂ and/or R₁₃ is, independently, collectively, or in any combination, selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, oligosaccharide and heterocyclo groups.

75. The method of claim 74, wherein R₁ is selected from methyl, ethyl, hydroxyl, or methoxy; R₄ is selected from methyl, ethyl, hydroxyl, or methoxy; R₈ is selected from straight or branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl; R₉ is selected from methyl, ethyl, hydroxyl, methoxy, Cl, Br; R₁₀ is selected from methyl, ethyl, hydroxyl, Cl, Br, acetyl, tertiarybutylformylacetyl, 3-phenylacryloyl, chloracetyl, chloroacetylpropanyl, straight or branched (C1-C8) alkyl, (e.g., substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl, *tert*butyl formyl and 1-methyl-2ethylpropyl); R₁₁ is selected from methyl, ethyl, hydroxyl, Cl, Br; R₁₂ is selected from methyl, ethyl, hydroxyl, Cl, Br; and R₁₃ is selected from straight or branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl.

76. A composition for preventing or alleviating diabetes in a mammalian subject comprising an anti-diabetic effective amount of a compound of Formula XXVII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof



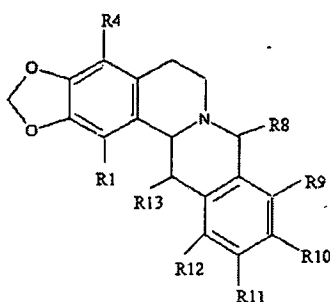
Formula XXVII,

wherein each of R₁, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂ and/or R₁₃ is, independently, collectively, or in any combination, selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, oligosaccharide and heterocyclo groups.

77. The composition of claim 76, wherein R₁ is selected from methyl, ethyl, hydroxyl, or methoxy; R₄ is selected from methyl, ethyl, hydroxyl, or methoxy; R₈ is selected from straight or branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl; R₉ is selected from methyl, ethyl, hydroxyl, methoxy, Cl, Br; R₁₀ is selected from methyl, ethyl, hydroxyl, Cl, Br, acetyl, tertiarybutylformylacetyl, 3-phenylacryloyl, chloracetyl, chloroacetylpropanyl, straight or branched (C1-C8) alkyl, (e.g., substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl, tertbutyl formyl and 1-methyl-2ethylpropyl); R₁₁ is selected from methyl, ethyl, hydroxyl, Cl, Br; R₁₂ is selected from methyl, ethyl, hydroxyl, Cl, Br; and R₁₃ is selected from straight or branched (C1-C6) alkyl, including substitution

selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl.

- 5 78. A method for preventing or treating insulin resistance in a mammalian subject comprising administering an anti-insulin resistance effective amount of a compound of Formula XXVII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject



10 Formula XXVII,

wherein each of R₁, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂ and/or R₁₃ is, independently, collectively, or in any combination, selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, 15 haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, oligosaccharide and heterocyclo groups.

79. The method of claim 78, wherein R₁ is selected from methyl, ethyl, hydroxyl, or methoxy; R₄ is selected from methyl, ethyl, hydroxyl, or methoxy; R₈ is selected from straight or 20 branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl; R₉ is selected from methyl, ethyl, hydroxyl, methoxy, Cl, Br; R₁₀ is

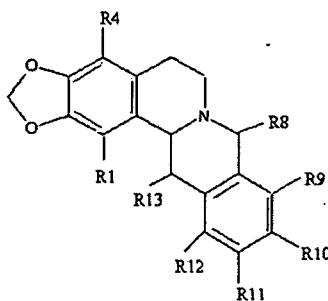
selected from methyl, ethyl, hydroxyl, Cl, Br, acetyl, tertiarybutylformylacetyl, 3-phenylacryloyl, chloracetyl, chloroacetylpropanyl, straight or branched (C1-C8) alkyl, (e.g., substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl, terbutyl formyl and 1-methyl-2ethylpropyl); R₁₁ is selected from methyl, ethyl, hydroxyl, Cl, Br; R₁₂ is selected from methyl, ethyl, hydroxyl, Cl, Br; and R₁₃ is selected from straight or branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl.

80. A composition for preventing or alleviating insulin resistance in a mammalian subject comprising an anti-insulin resistance effective amount of a compound of Formula XXVII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof

Formula XXVII,

wherein each of R₁, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂ and/or R₁₃ is, independently, collectively, or in any combination, selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, oligosaccharide and heterocyclo groups.

81. A method for preventing or treating hyperglycemia in a mammalian subject comprising administering an anti-hyperglycemic effective amount of a compound of Formula XXVII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject



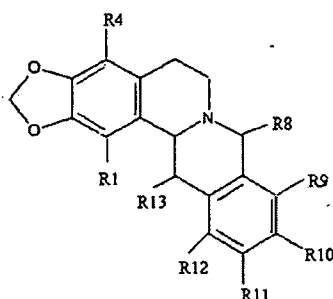
Formula XXVII,

wherein each of R₁, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂ and/or R₁₃ is, independently, collectively, or in any combination, selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, oligosaccharide and heterocyclo groups.

82. The method of claim 81, wherein R₁ is selected from methyl, ethyl, hydroxyl, or methoxy; R₄ is selected from methyl, ethyl, hydroxyl, or methoxy; R₈ is selected from straight or branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl; R₉ is selected from methyl, ethyl, hydroxyl, methoxy, Cl, Br; R₁₀ is selected from methyl, ethyl, hydroxyl, Cl, Br, acetyl, tertiarybutylformylacetyl, 3-phenylacryloyl, chloracetyl, chloroacetylpropanyl, straight or branched (C1-C8) alkyl, (e.g., substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl, tertbutyl formyl and 1-methyl-2ethylpropyl); R₁₁ is selected from methyl, ethyl, hydroxyl, Cl, Br; R₁₂ is selected from methyl, ethyl, hydroxyl, Cl, Br; and R₁₃ is selected from straight or branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl,

1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl.

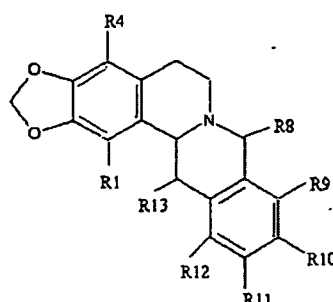
83. A composition for preventing or alleviating hyperglycemia in a mammalian subject comprising an anti-hyperglycemic effective amount of a compound of Formula XXVII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof



Formula XXVII,

wherein each of R₁, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂ and/or R₁₃ is, independently, collectively, or in any combination, selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, oligosaccharide and heterocyclo groups.

84. A method for increasing insulin sensitivity in a mammalian subject comprising administering an effective amount of a compound of Formula XXVII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject

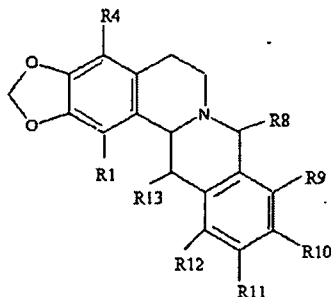


Formula XXVII,

wherein each of R₁, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂ and/or R₁₃ is, independently, collectively, or in any combination, selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, oligosaccharide and heterocyclo groups.

85. The method of claim 84, wherein R₁ is selected from methyl, ethyl, hydroxyl, or methoxy; R₄ is selected from methyl, ethyl, hydroxyl, or methoxy; R₈ is selected from straight or branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl; R₉ is selected from methyl, ethyl, hydroxyl, methoxy, Cl, Br; R₁₀ is selected from methyl, ethyl, hydroxyl, Cl, Br, acetyl, tertiarybutylformylacetyl, 3-phenylacryloyl, chloracetyl, chloroacetylpropanyl, straight or branched (C1-C8) alkyl, (e.g., substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl, tertbutyl formyl and 1-methyl-2ethylpropyl); R₁₁ is selected from methyl, ethyl, hydroxyl, Cl, Br; R₁₂ is selected from methyl, ethyl, hydroxyl, Cl, Br; and R₁₃ is selected from straight or branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl.

86. A method for preventing or treating hypertension in a mammalian subject comprising administering an anti-hypertensive effective amount of a compound of Formula XXVII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject



Formula XXVII,

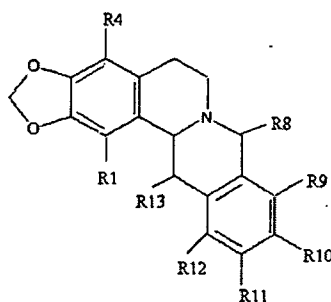
wherein each of R₁, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂ and/or R₁₃ is, independently, collectively, or in any combination, selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino,

trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, oligosaccharide and heterocyclo groups.

87. The method of claim 86, wherein R₁ is selected from methyl, ethyl, hydroxyl, or methoxy; R₄ is selected from methyl, ethyl, hydroxyl, or methoxy; R₈ is selected from straight or branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl; R₉ is selected from methyl, ethyl, hydroxyl, methoxy, Cl, Br; R₁₀ is selected from methyl, ethyl, hydroxyl, Cl, Br, acetyl, tertiarybutylformylacetyl, 3-phenylacryloyl, chloracetyl, chloroacetylpropanyl, straight or branched (C1-C8) alkyl, (e.g., substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl, tertbutyl formyl and 1-methyl-2ethylpropyl); R₁₁ is selected from methyl, ethyl, hydroxyl, Cl, Br; R₁₂ is selected from methyl, ethyl, hydroxyl, Cl, Br; and R₁₃ is selected from straight or branched (C1-C6) alkyl, including substitution

selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl.

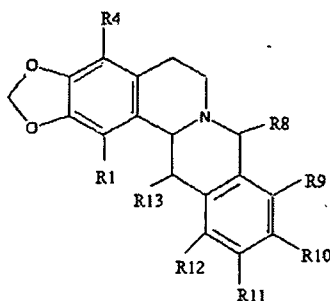
- 5 88. A composition for preventing or alleviating hypertension in a mammalian subject comprising an anti-hypertensive effective amount of a compound of Formula XXVII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof



10 Formula XXVII,

wherein each of R₁, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂ and/or R₁₃ is, independently, collectively, or in any combination, selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylproparyl, alkylacetyl, oligosaccharide and heterocyclo groups.

- 15 89. A method of modulating InsR expression in a mammalian subject comprising
20 administering to said subject an effective amount of a compound of Formula XXVII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof



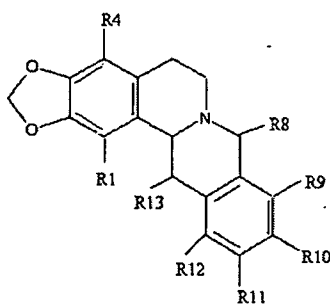
Formula XXVII,

wherein each of R₁, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂ and/or R₁₃ is, independently, collectively, or in any combination, selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, and heterocyclo groups; and a secondary anti-hyperglycemic agent or other adjunctive therapeutic agent useful in the treatment of hyperglycemia.

90. The method of claim 89, wherein R₁ is selected from methyl, ethyl, hydroxyl, or methoxy; R₄ is selected from methyl, ethyl, hydroxyl, or methoxy; R₈ is selected from straight or branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl; R₉ is selected from methyl, ethyl, hydroxyl, methoxy, Cl, Br; R₁₀ is selected from methyl, ethyl, hydroxyl, Cl, Br, acetyl, tertiarybutylformylacetyl, 3-phenylacryloyl, chloracetyl, chloroacetylpropanyl, straight or branched (C1-C8) alkyl, (e.g., substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl, tertbutyl formyl and 1-methyl-2ethylpropyl); R₁₁ is selected from methyl, ethyl, hydroxyl, Cl, Br; R₁₂ is selected from methyl, ethyl, hydroxyl, Cl, Br; and R₁₃ is

selected from straight or branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl.

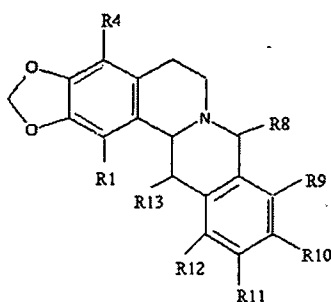
91. A method of modulating PKC activity in a mammalian subject selected from a mammalian cell, tissue, organ, or individual comprising administering to said subject a PKC activity modulatory effective amount of a compound of Formula XXVII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof



Formula XXVII,

wherein each of R₁, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂ and/or R₁₃ is, independently, collectively, or in any combination, selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, oligosaccharide and heterocyclo groups, a berberine analog or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof.

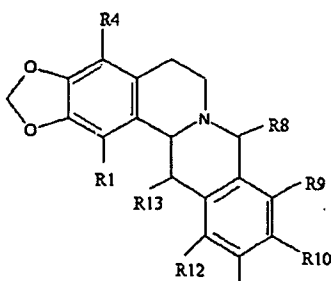
92. A method of lowering blood glucose in a mammalian subject selected from a mammalian cell, tissue, organ, or individual comprising administering to said subject a blood glucose lowering effective amount of a compound of Formula XXVII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof



Formula XXVII,

wherein each of R₁, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂ and/or R₁₃ is, independently, collectively, or in any combination, selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, oligosaccharide and heterocyclo groups, a berberine analog or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof.

93. A method for preventing or treating one or more symptoms of hyperlipidemia or of a cardiovascular disease or condition caused by hyperlipidemia in a mammalian subject comprising administering an anti-hyperlipidemic effective amount of a compound of Formula XXVII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject



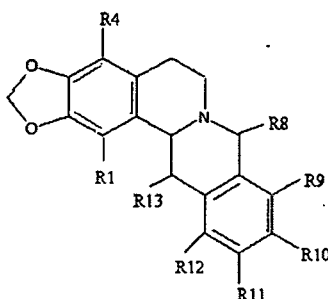
Formula XXVII,

wherein each of R₁, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂ and/or R₁₃ is, independently, collectively, or in any combination, selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, and heterocyclo groups.

94. The method of claim 93, wherein R₁ is selected from methyl, ethyl, hydroxyl, or methoxy; R₄ is selected from methyl, ethyl, hydroxyl, or methoxy; R₈ is selected from straight or branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl; R₉ is selected from methyl, ethyl, hydroxyl, methoxy, Cl, Br; R₁₀ is selected from methyl, ethyl, hydroxyl, Cl, Br, acetyl, tertiarybutylformylacetyl, 3-phenylacryloyl, chloracetyl, chloroacetylpropanyl, straight or branched (C1-C8) alkyl, (e.g., substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl, terbutyl formyl and 1-methyl-2ethylpropyl); R₁₁ is selected from methyl, ethyl, hydroxyl, Cl, Br; R₁₂ is selected from methyl, ethyl, hydroxyl, Cl, Br; and R₁₃ is selected from straight or branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl.

95. A composition for treating or preventing hyperlipidemia in a mammalian subject comprising an anti-hyperlipidemia effective amount of a compound of Formula XXVII, or a

pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof



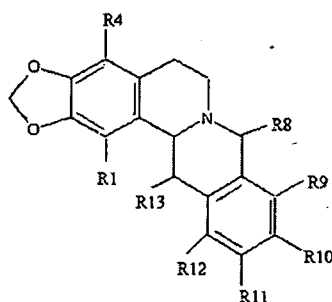
Formula XXVII,

5 wherein each of R₁, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂ and/or R₁₃ is, independently, collectively, or in any combination, selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, and heterocyclo groups.

96. The composition of claim 95, wherein R₁ is selected from methyl, ethyl, hydroxyl, or methoxy; R₄ is selected from methyl, ethyl, hydroxyl, or methoxy; R₈ is selected from straight or branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl; R₉ is selected from methyl, ethyl, hydroxyl, methoxy, Cl, Br; R₁₀ is selected from methyl, ethyl, hydroxyl, Cl, Br, acetyl, tertiarybutylformylacetyl, 3-phenylacryloyl, chloracetyl, chloroacetylpropanyl, straight or branched (C1-C8) alkyl, (e.g., substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl,

3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl, tertbutyl formyl and 1-methyl-2ethylpropyl);
 R₁₁ is selected from methyl, ethyl, hydroxyl, Cl, Br; R₁₂ is selected from methyl, ethyl, hydroxyl,
 Cl, Br; and R₁₃ is selected from straight or branched (C1-C6) alkyl, including substitution
 selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl,
 5 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-
 methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl,
 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl.

97. A method of modulating LDLR expression in a mammalian subject comprising
 administering to said subject an effective amount of a compound of Formula XXVII, or a
 10 pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug
 thereof



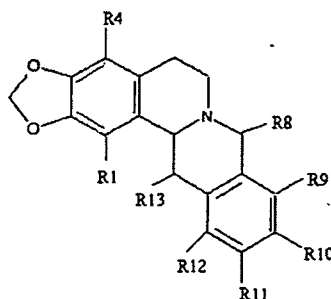
Formula XXVII,

wherein each of R₁, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂ and/or R₁₃ is, independently, collectively, or in any
 15 combination, selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino,
 trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile,
 dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl,
 haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl,
 carbonylamino, alkylsulfonylamino, acetyl, formyl, phenylacryloyl, haloacetyl,
 20 haloacetylpropyl, alkylacetyl, and heterocyclo groups..

98. The method of claim 97, wherein R₁ is selected from methyl, ethyl, hydroxyl, or
 methoxy; R₄ is selected from methyl, ethyl, hydroxyl, or methoxy; R₈ is selected from straight or

branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl; R₉ is selected from methyl, ethyl, hydroxyl, methoxy, Cl, Br; R₁₀ is selected from methyl, ethyl, hydroxyl, Cl, Br, acetyl, tertiarybutylformylacetyl, 3-phenylacryloyl, chloroacetyl, chloroacetylpropanyl, straight or branched (C1-C8) alkyl, (e.g., substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl, tertbutyl formyl and 1-methyl-2ethylpropyl); R₁₁ is selected from methyl, ethyl, hydroxyl, Cl, Br; R₁₂ is selected from methyl, ethyl, hydroxyl, Cl, Br; and R₁₃ is selected from straight or branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl.

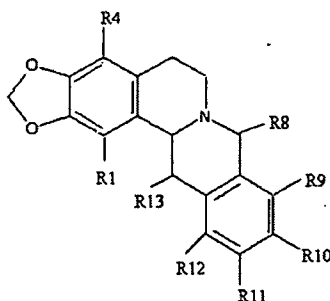
99. A method for increasing LDLR stability in a mammalian cell, tissue, organ or individual comprising administering to a mammalian subject an effective amount of a compound of Formula XXVII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof



Formula XXVII,

wherein each of R₁, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂ and/or R₁₃ is, independently, collectively, or in any combination, selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, and heterocyclo groups, a berberine analog or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof.

100. A method of modulating ERK activation in a mammalian subject selected from a mammalian cell, tissue, organ, or individual comprising administering to said subject an ERK activation modulatory effective amount of a compound of Formula XXVII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof



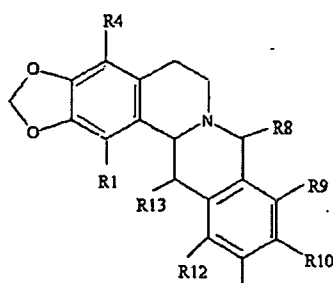
Formula XXVII,

wherein each of R₁, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂ and/or R₁₃ is, independently, collectively, or in any combination, selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, and heterocyclo groups, a berberine analog or a

pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof.

101. The method of claim 100, wherein R₁ is selected from methyl, ethyl, hydroxyl, or methoxy; R₄ is selected from methyl, ethyl, hydroxyl, or methoxy; R₈ is selected from straight or
 5 branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl; R₉ is selected from methyl, ethyl, hydroxyl, methoxy, Cl, Br; R₁₀ is
 10 selected from methyl, ethyl, hydroxyl, Cl, Br, acetyl, tertiarybutylformylacetyl, 3-phenylacryloyl, chloroacetyl, chloroacetylpropanyl, straight or branched (C1-C8) alkyl, (e.g., substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl, tertbutyl formyl and 1-methyl-2ethylpropyl);
 15 R₁₁ is selected from methyl, ethyl, hydroxyl, Cl, Br; R₁₂ is selected from methyl, ethyl, hydroxyl, Cl, Br; and R₁₃ is selected from straight or branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl.

102. A method of inhibiting cholesterol synthesis in a mammalian subject selected from a mammalian cell, tissue, organ, or individual comprising administering to said subject a
 25 cholesterol synthesizing inhibitory effective amount of a compound of Formula XXVII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof

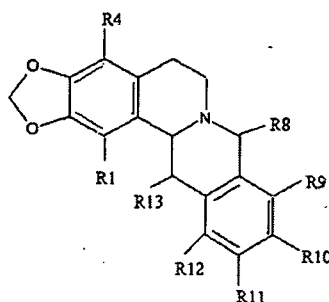


Formula XXVII,

wherein each of R₁, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂ and/or R₁₃ is, independently, collectively, or in any combination, selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, and heterocyclo groups, a berberine analog or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof.

103. The method of claim 102, wherein R₁ is selected from methyl, ethyl, hydroxyl, or methoxy; R₄ is selected from methyl, ethyl, hydroxyl, or methoxy; R₈ is selected from straight or branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl; R₉ is selected from methyl, ethyl, hydroxyl, methoxy, Cl, Br; R₁₀ is selected from methyl, ethyl, hydroxyl, Cl, Br, acetyl, tertiarybutylformylacetyl, 3-phenylacryloyl, chloracetyl, chloroacetylpropanyl, straight or branched (C1-C8) alkyl, (e.g., substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl, tertbutyl formyl and 1-methyl-2ethylpropyl); R₁₁ is selected from methyl, ethyl, hydroxyl, Cl, Br; R₁₂ is selected from methyl, ethyl, hydroxyl, Cl, Br; and R₁₃ is selected from straight or branched (C1-C6) alkyl, including substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2 dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl and 1-methyl-2ethylpropyl.

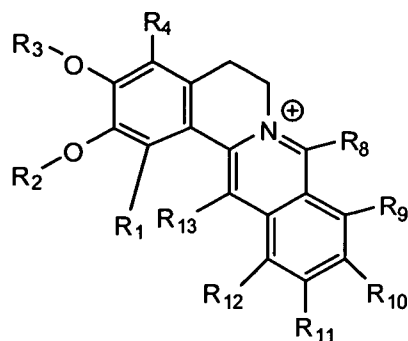
104. A method of inhibiting triglyceride synthesis in a mammalian subject selected from a mammalian cell, tissue, organ, or individual comprising administering to said subject a triglyceride synthesis inhibiting effective amount of a compound of Formula XXVII, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof



Formula XXVII,

wherein each of R₁, R₄, R₈, R₉, R₁₀, R₁₁, R₁₂ and/or R₁₃ is, independently, collectively, or in any combination, selected from hydrogen, halogen, hydroxy, alkyl, alkoxy, nitro, amino, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, alkanoyl, alkanoyloxy, aryl, aroyl, aralkyl, nitrile, dialkylamino, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, carboxyalkyl, alkoxyalkyl, carboxy, alkanoylamino, carbamoyl, carbamyl, carbonylamino, alkylsulfonylamino, acetyl, formyl, phenylacryloyl, haloacetyl, haloacetylpropanyl, alkylacetyl, and heterocyclo groups, a berberine analog or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof.

105. A method for preventing or treating metabolic disorders in a mammalian subject comprising administering an anti-metabolic disorder effective amount of a compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject



Formula I

wherein R₁, R₄, R₈, R₁₁, R₁₂ and R₁₃ are hydrogen and R₂, R₃, R₉ and/or R₁₀ are independently or collectively selected from hydrogen, hydroxy, methyl or methoxy.

106. The method of claim 105 wherein R₂ and R₃ form a methylenedioxy group.

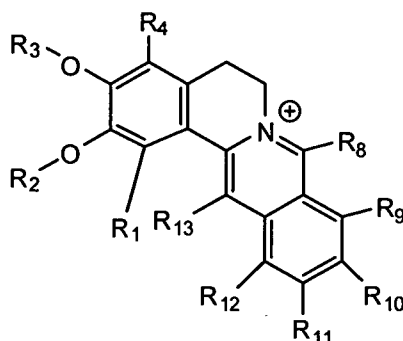
107. The method of claim 105, wherein the metabolic disorder is obesity, diabetes, insulin resistance, glucose intolerance, hyperglycemia, metabolic syndrome, or hypertension.

108. The method of claim 105, further comprising administering a secondary metabolic disorder therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said compound of Formula I or other adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said compound of Formula I to treat or prevent metabolic disorder or a related symptom or condition thereof in said subject.

109. The method of claim 108, wherein the secondary metabolic disorder therapeutic or adjunctive therapeutic agent is selected from anti-hyperlipidemic agents, anti-dyslipidemic agents, plasma HDL-raising agents, cholesterol-uptake inhibitors, cholesterol biosynthesis inhibitors, HMG-CoA reductase inhibitors, HMG-CoA synthase inhibitors, squalene epoxidase inhibitors, squalene synthetase inhibitors, acyl-coenzyme A cholesterol acyltransferase (ACAT) inhibitors, nicotinic acid and the salts thereof, niacinamide, cholesterol absorption inhibitors, bile acid sequestrant anion exchange resins, LDL receptor inducers, fibrates, vitamin B₆, vitamin B₁₂, vitamin B₃, anti-oxidant vitamins, angiotensin II receptor (AT₁) antagonist, renin inhibitors, platelet aggregation inhibitors, hormones, insulin, ion exchange resins, omega-3 oils, benfluorex, ethyl icosapentate, amlodipine, insulin sensitizers, protein tyrosine phosphatase-1B (PTP-1B) inhibitors, dipeptidyl peptidase IV (DP-IV) inhibitors, insulin mimetics, sequestrants, nicotinyl alcohol, nicotinic acid, PPAR α agonists, PPAR α / γ dual agonists, neuropeptide Y5 inhibitors, β_3 adrenergic receptor agonists, ileal bile acid transporter inhibitors, anti-

inflammatories, cyclo-oxygenase 2 selective inhibitors, sulfonylureas, DPP-4 blockers, biguanides, α -glucosidase inhibitors, D-phenylalanine derivatives, meglitinides, diuretics, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, vasodilators, angiotensin II receptor blockers, and alpha blockers.

- 5 110. A composition for treating metabolic disorders in a mammalian subject comprising a metabolic disorder treating effective amount of a compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof

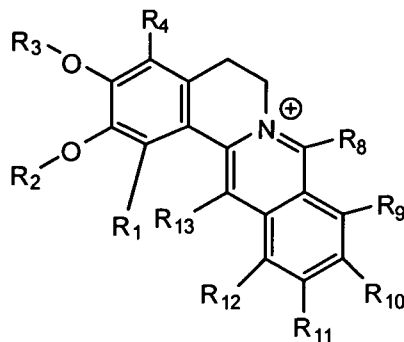


Formula I,

- 10 wherein R_1 , R_4 , R_8 , R_{11} , R_{12} and R_{13} are hydrogen and R_2 , R_3 , R_9 and/or R_{10} are independently or collectively selected from hydrogen, hydroxy, methyl or methoxy.

111. The composition of claim 110 wherein R_2 and R_3 form a methylenedioxy group

112. A method for treating one or more conditions associated with metabolic disorders comprising administering to a mammalian subject an effective amount of a compound of
15 Formula I or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject



Formula I

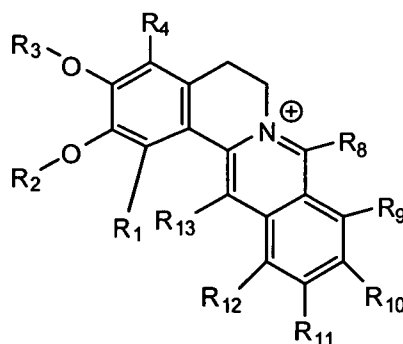
- 20 wherein R_1 , R_4 , R_8 , R_{11} , R_{12} and R_{13} are hydrogen and R_2 , R_3 , R_9 and/or R_{10} are independently or collectively selected from hydrogen, hydroxy, methyl or methoxy.

113. The method of claim 112 wherein R₂ and R₃ form a methylenedioxy group.

114. The method of claim 112, wherein the metabolic disorder is obesity, diabetes, insulin resistance, glucose intolerance, hyperglycemia, metabolic syndrome or hypertension.

115. The method of claim 112, wherein said one or more conditions include(s) fatty liver,
 5 reproductive abnormalities, growth abnormalities, arterial plaque accumulation, osteoarthritis, gout, joint pain, respiratory problems, skin conditions, sleep apnea, idiopathic intracranial hypertension, lower extremity venous stasis disease, gastro-esophageal reflux, urinary stress incontinence, kidney damage, cardiovascular disease, atherosclerosis, coronary artery disease, enlarged heart, diabetic cardiomyopathy, peripheral vascular disease, pulmonary embolism,
 10 angina pectoris, carotid artery disease, stroke, cerebral arteriosclerosis, myocardial infarction, cerebral infarction, restenosis following balloon angioplasty, intermittent claudication, dyslipidemia post-prandial lipidemia, high blood pressure and xanthoma.

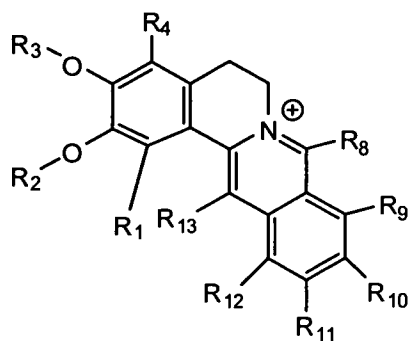
116. A method of modulating InsR expression in a mammalian subject comprising administering to said subject an effective amount of a compound of Formula I, or a
 15 pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject



Formula I

wherein R₁, R₄, R₈, R₁₁, R₁₂ and R₁₃ are hydrogen and R₂, R₃, R₉ and/or R₁₀ are independently or
 20 collectively selected from hydrogen, hydroxy, methyl or methoxy.

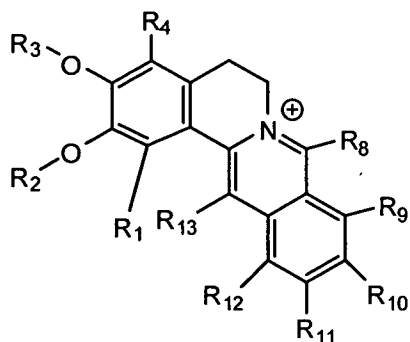
117. A composition for increasing InsR expression in a mammalian cell, tissue, organ, or individual comprising an InsR effective amount of a compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject



Formula I

wherein R_1 , R_4 , R_8 , R_{11} , R_{12} and R_{13} are hydrogen and R_2 , R_3 , R_9 and/or R_{10} are independently or collectively selected from hydrogen, hydroxy, methyl or methoxy.

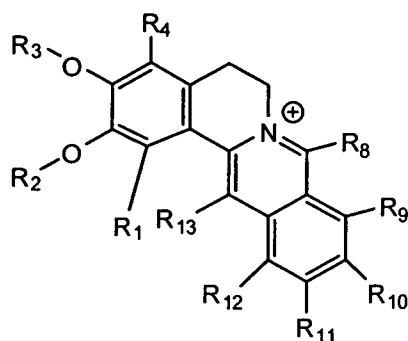
118. A method of modulating PKC activity in a mammalian subject selected from a mammalian cell, tissue, organ, or individual comprising administering to said subject a PKC activity modulatory effective amount of a compound of Formula I or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject.



Formula I

wherein R_1 , R_4 , R_8 , R_{11} , R_{12} and R_{13} are hydrogen and R_2 , R_3 , R_9 and/or R_{10} are independently or collectively selected from hydrogen, hydroxy, methyl or methoxy.

119. A method of lowering blood glucose in a mammalian subject selected from a mammalian cell, tissue, organ, or individual comprising administering to said subject a blood glucose lowering effective amount of a compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject

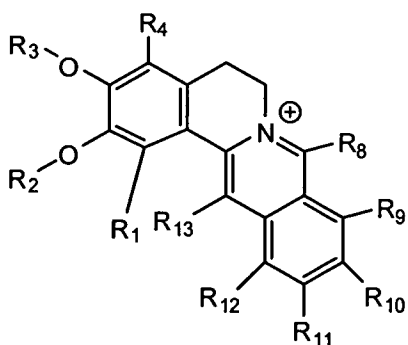


Formula I

wherein R₁, R₄, R₈, R₁₁, R₁₂ and R₁₃ are hydrogen and R₂, R₃, R₉ and/or R₁₀ are independently or collectively selected from hydrogen, hydroxy, methyl or methoxy.

5 120. The method of claim 119, wherein R₂ and R₃ form a methylenedioxy group.

121. A method of modulating LDLR expression in a mammalian subject comprising administering to said subject an effective amount of a compound or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject

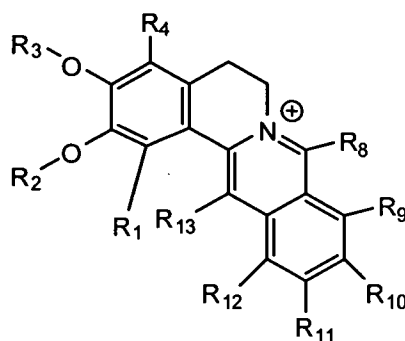


Formula I

wherein R₁, R₄, R₈, R₁₁, R₁₂ and R₁₃ are hydrogen and R₂, R₃, R₉ and/or R₁₀ are independently or collectively selected from hydrogen, hydroxy, methyl or methoxy.

122. The method of claim 121 wherein R₂ and R₃ form a methylenedioxy group.

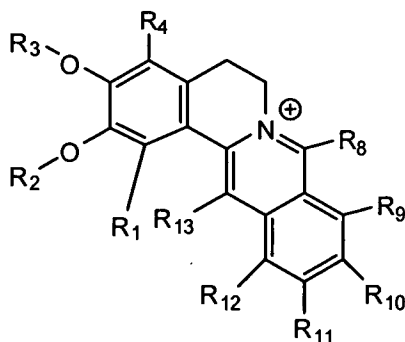
15 123. A method for increasing LDLR stability in a mammalian cell, tissue, organ or individual comprising administering to a mammalian subject an effective amount of a compound of Formula I or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject



Formula I

wherein R₁, R₄, R₈, R₁₁, R₁₂ and R₁₃ are hydrogen and R₂, R₃, R₉ and/or R₁₀ are independently or collectively selected from hydrogen, hydroxy, methyl or methoxy.

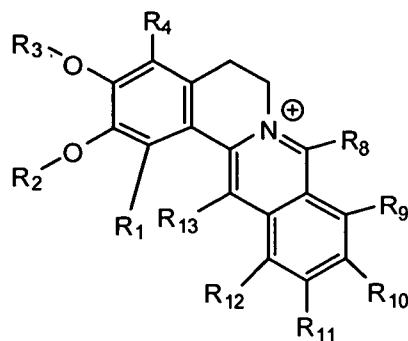
- 5 124. A method of modulating ERK activation in a mammalian subject selected from a mammalian cell, tissue, organ, or individual comprising administering to said subject an ERK activation modulatory effective amount of a compound of Formula or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject



Formula I

wherein R₁, R₄, R₈, R₁₁, R₁₂ and R₁₃ are hydrogen and R₂, R₃, R₉ and/or R₁₀ are independently or collectively selected from hydrogen, hydroxy, methyl or methoxy.

- 10 125. A method of modulating AMP activated protein kinase activation in a mammalian subject selected from a mammalian cell, tissue, organ, or individual comprising administering to said subject an AMP activated protein kinase modulatory effective amount of a compound of Formula or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject

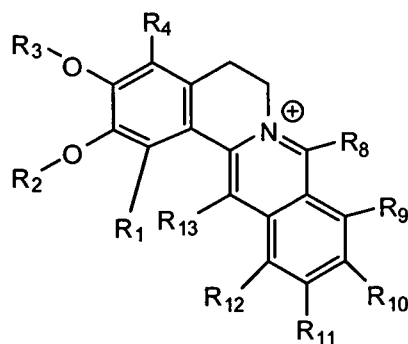


Formula I

wherein R₁, R₄, R₈, R₁₁, R₁₂ and R₁₃ are hydrogen and R₂, R₃, R₉ and/or R₁₀ are independently or collectively selected from hydrogen, hydroxy, methyl or methoxy.

5 126. The method of claim 125 wherein R₂ and R₃ form a methylenedioxy group.

127. A composition for increasing AMP activated protein kinase activation in a mammalian cell, tissue, organ, or individual comprising an AMP activated protein kinase activating effective amount of a compound of Formula I or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject



Formula I

wherein R₁, R₄, R₈, R₁₁, R₁₂ and R₁₃ are hydrogen and R₂, R₃, R₉ and/or R₁₀ are independently or collectively selected from hydrogen, hydroxy, methyl or methoxy.

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FIG. 1

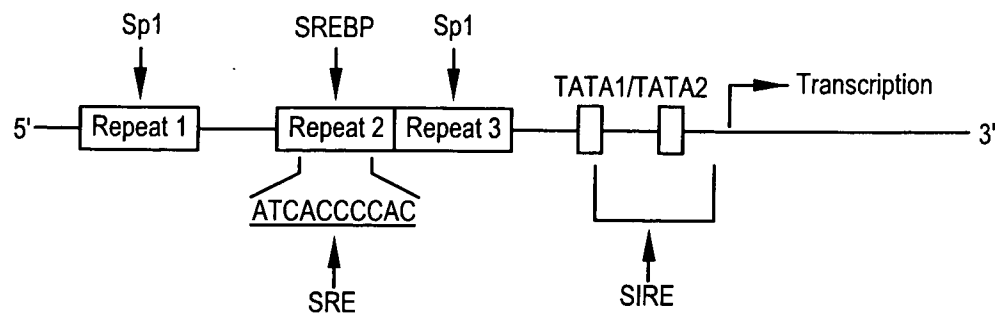
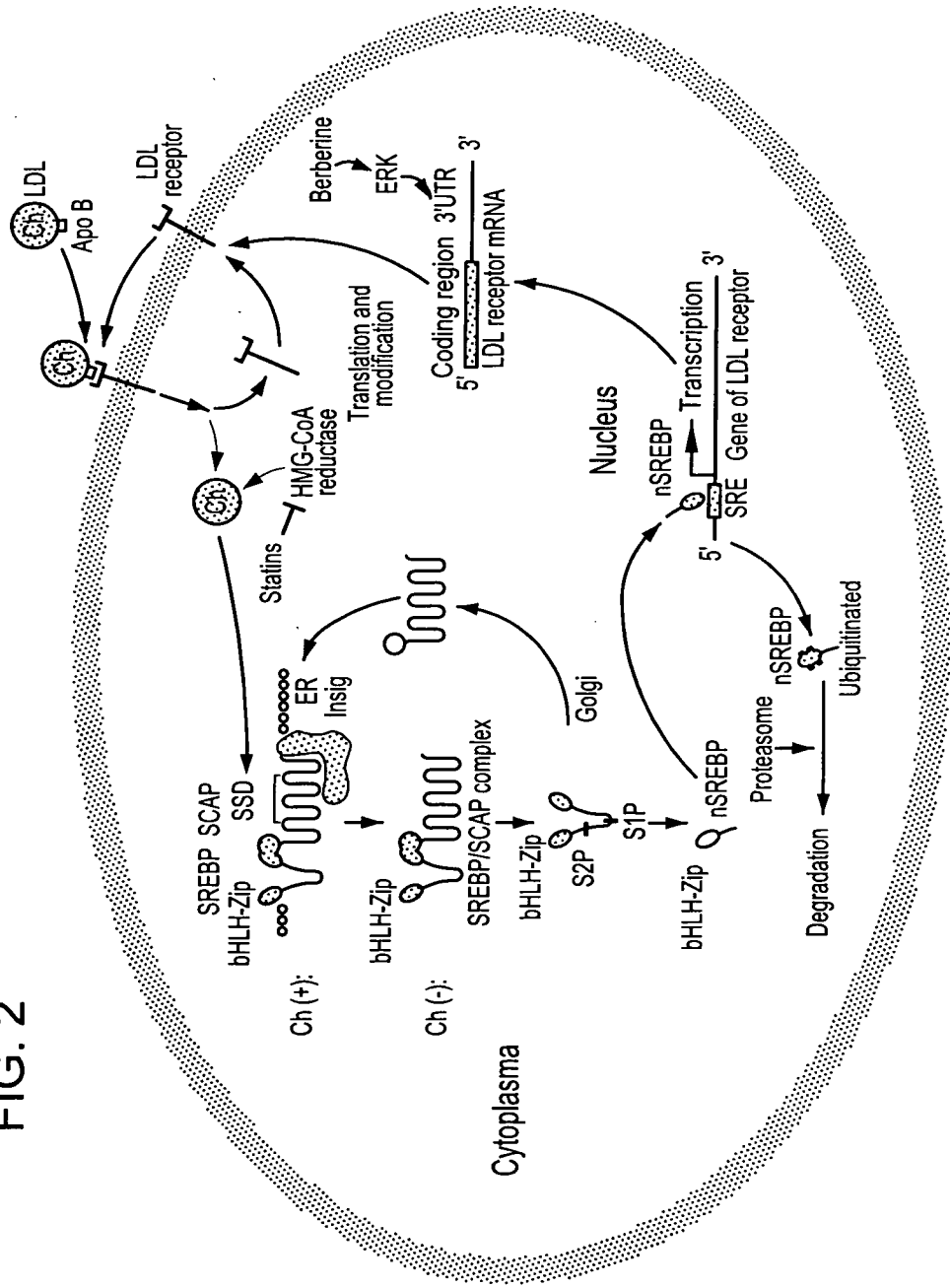


FIG. 2



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FIG. 3

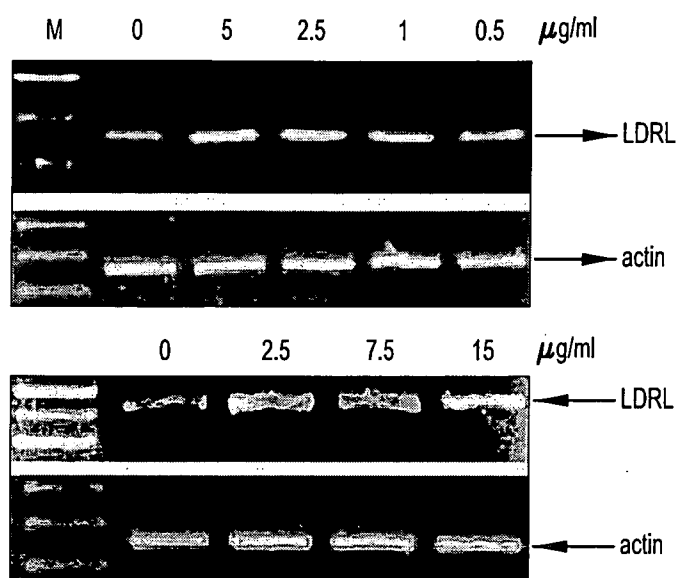
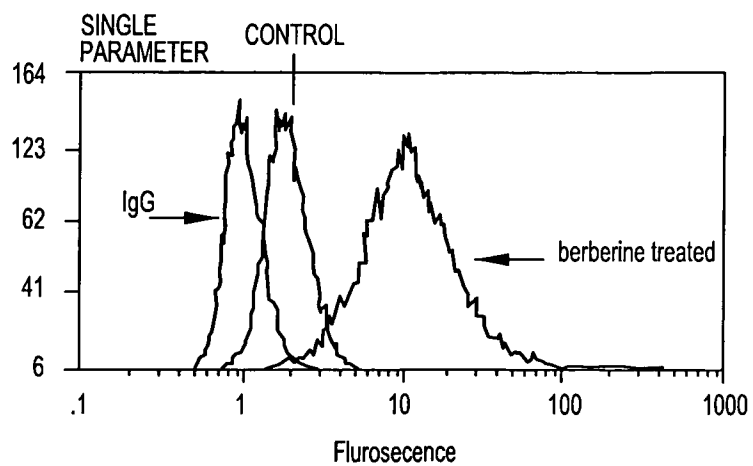
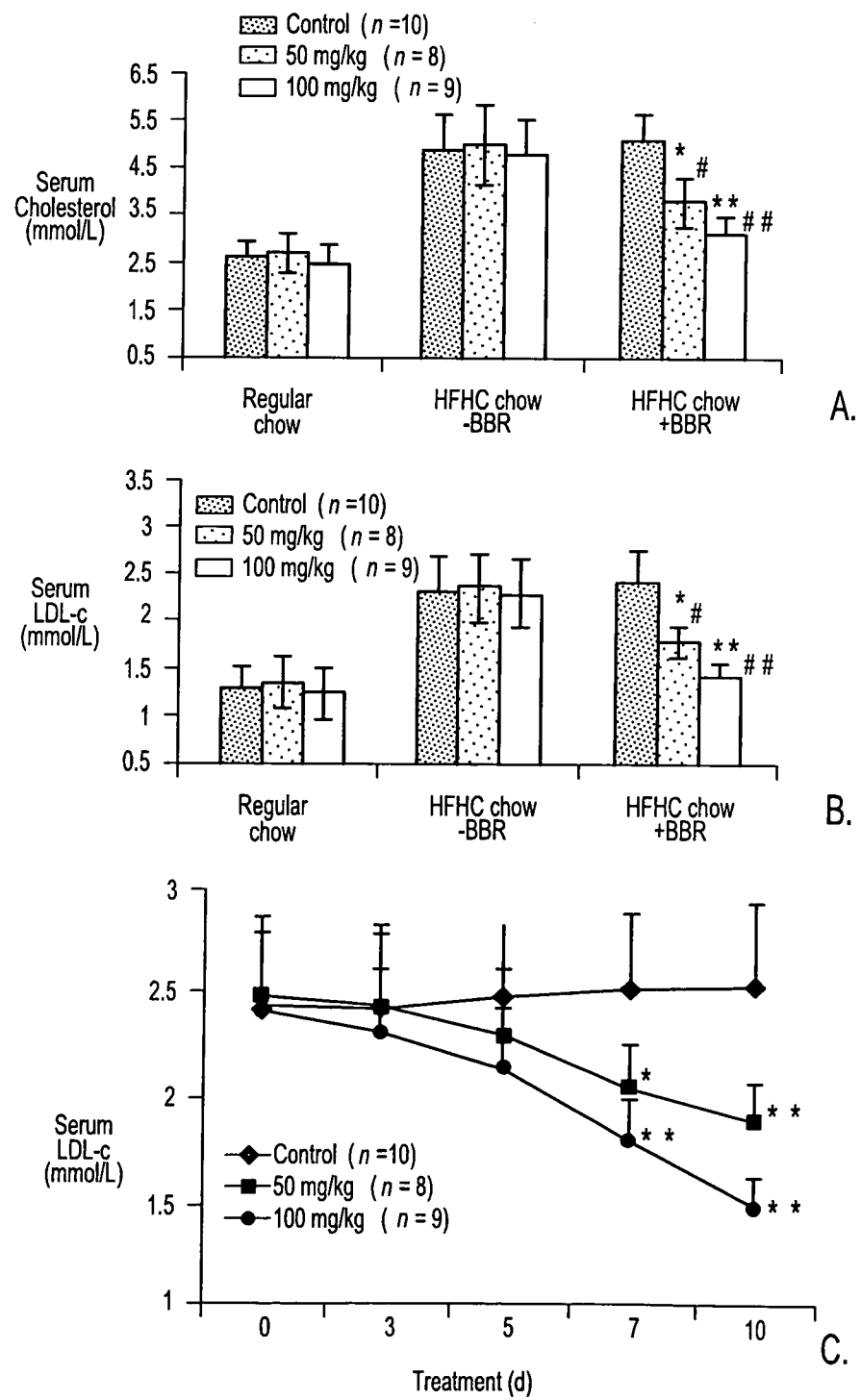


FIG. 4



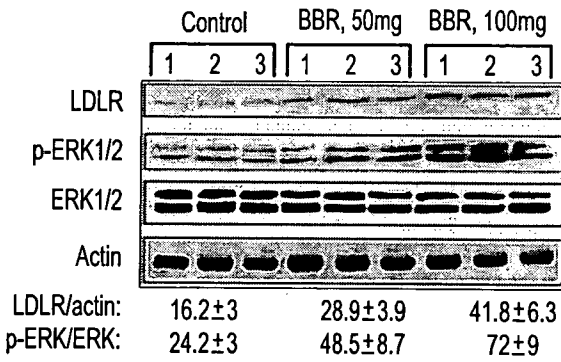
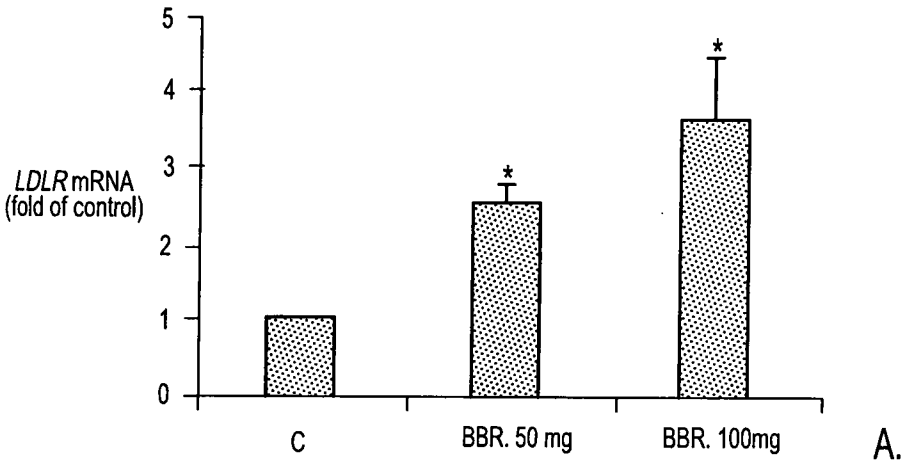
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FIG. 5



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FIG. 6



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FIG. 7

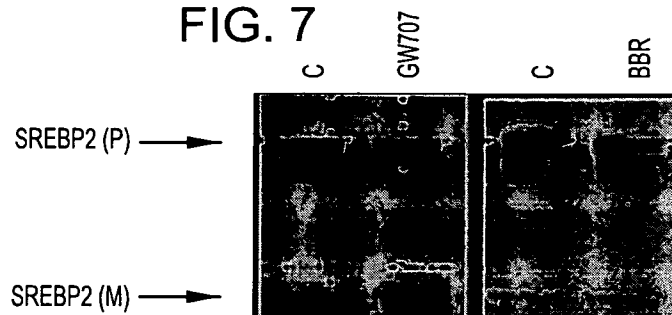
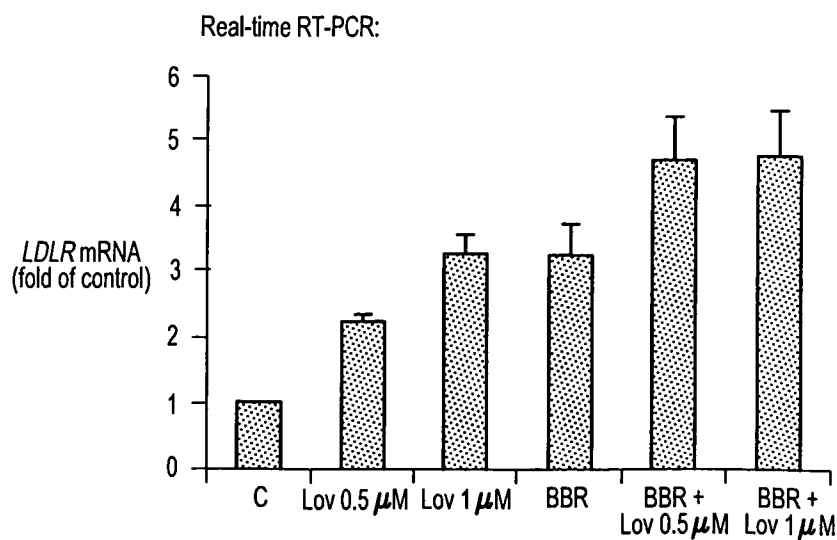
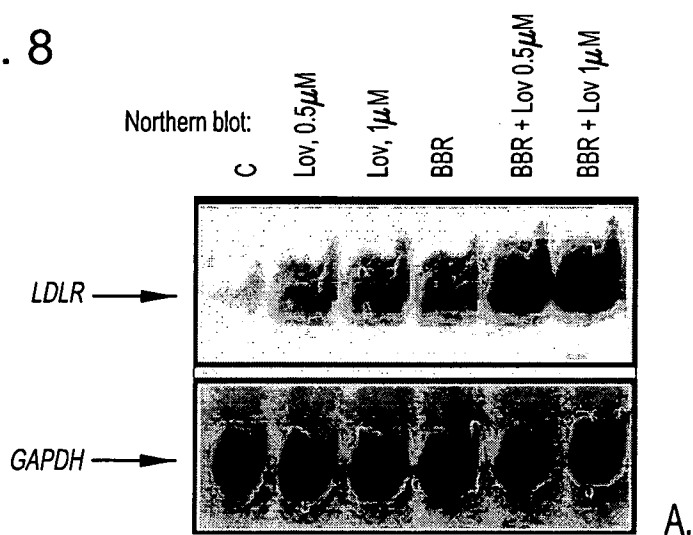
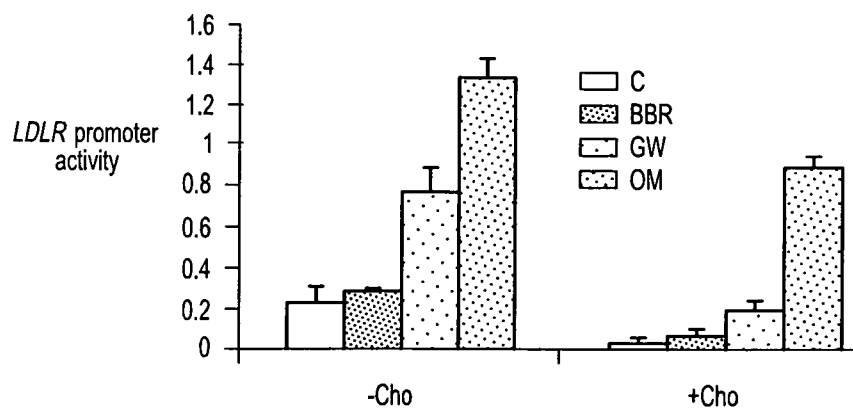
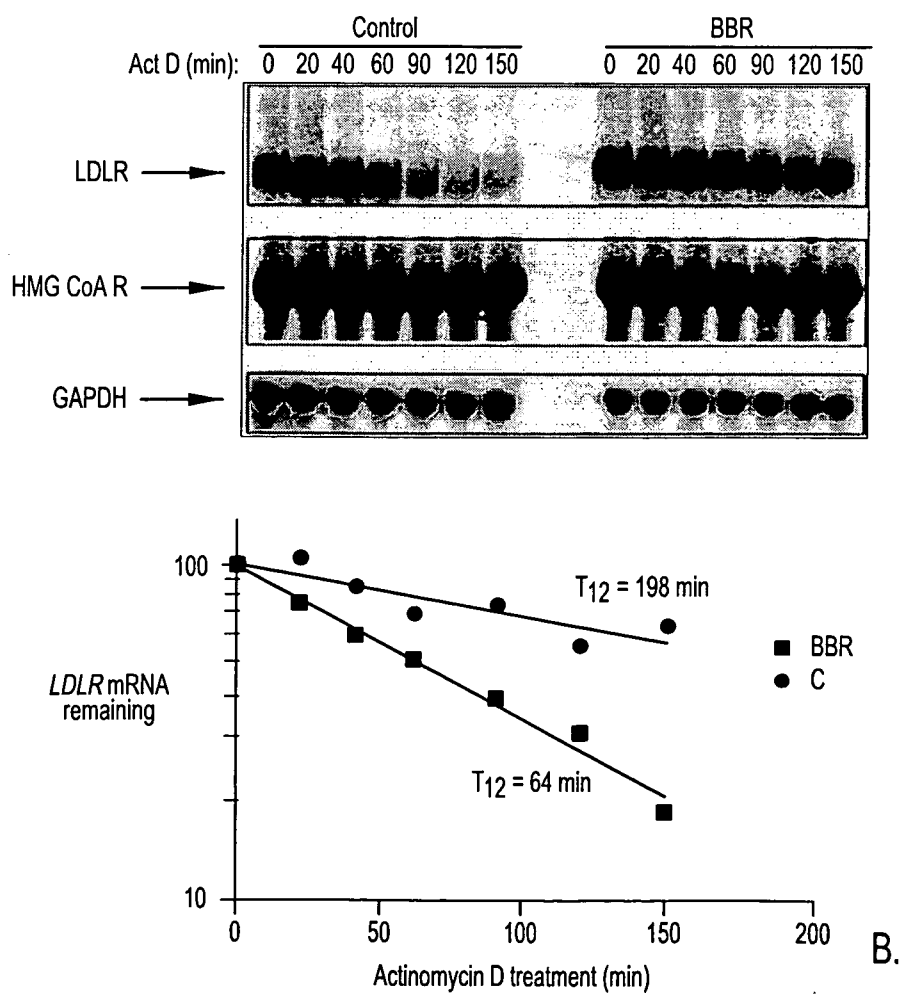


FIG. 8



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FIG. 9**FIG. 10**

B.

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FIG. 11

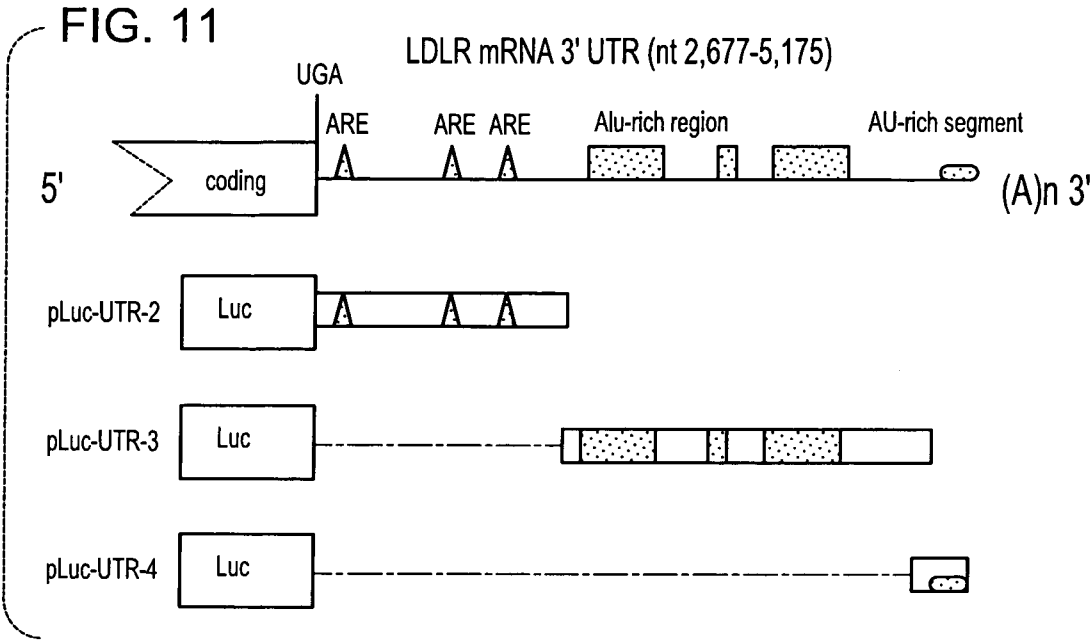
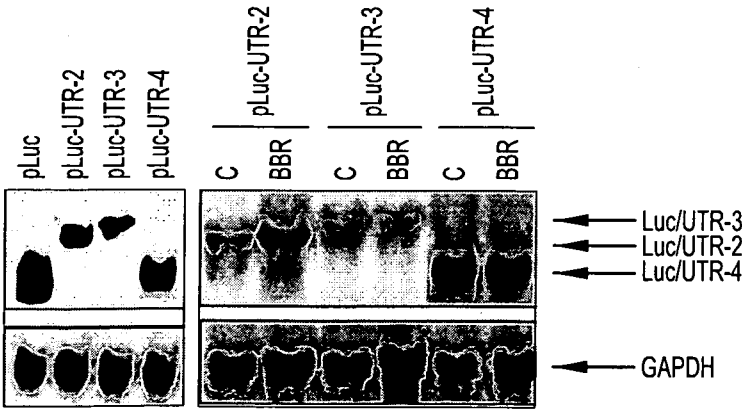
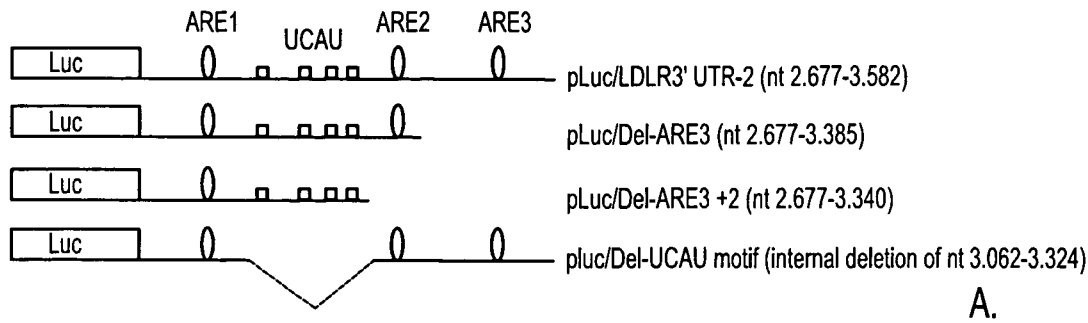


FIG. 12

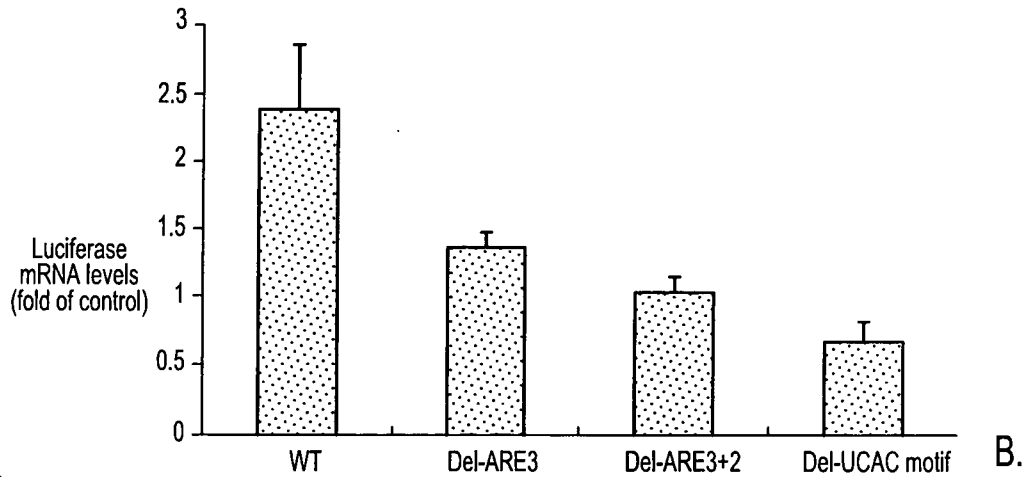


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FIG. 13

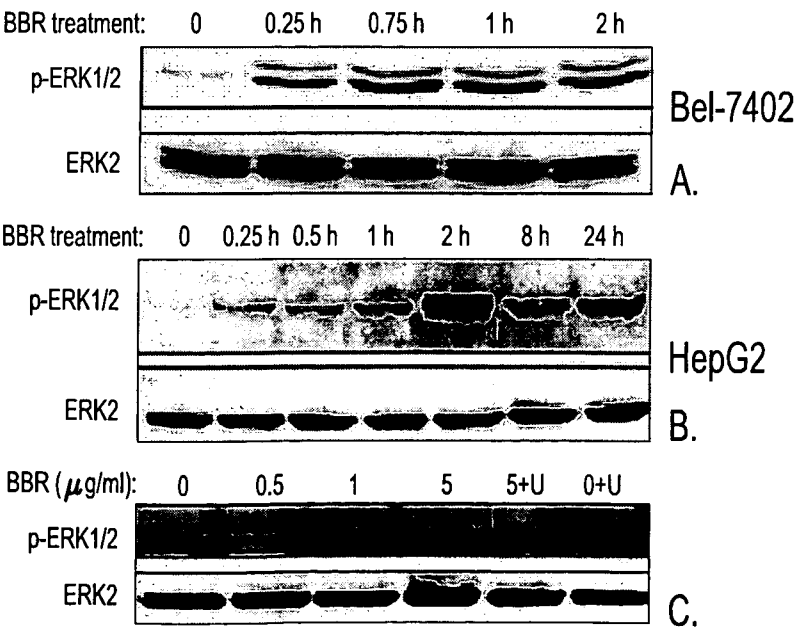


A.



B.

FIG. 14



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FIG. 15

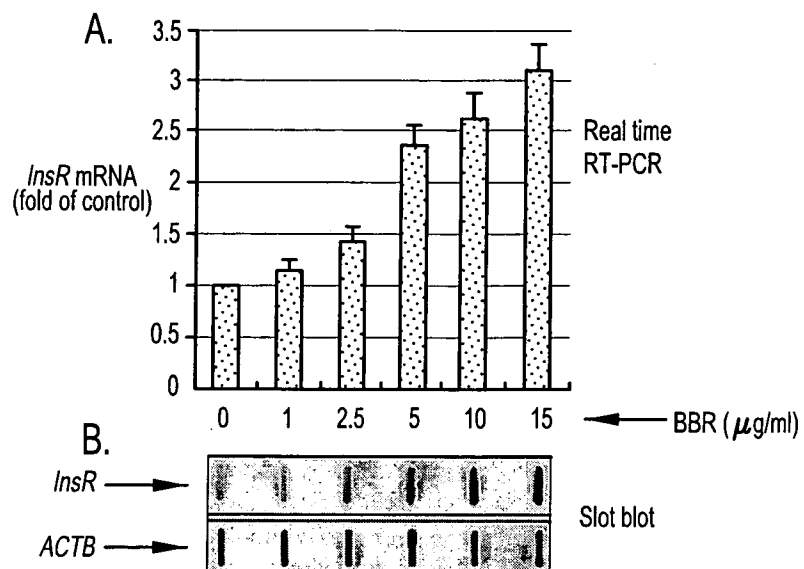
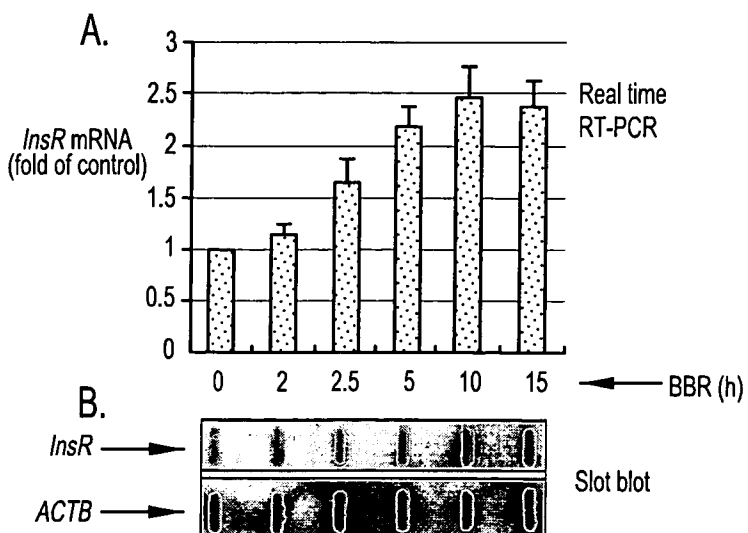


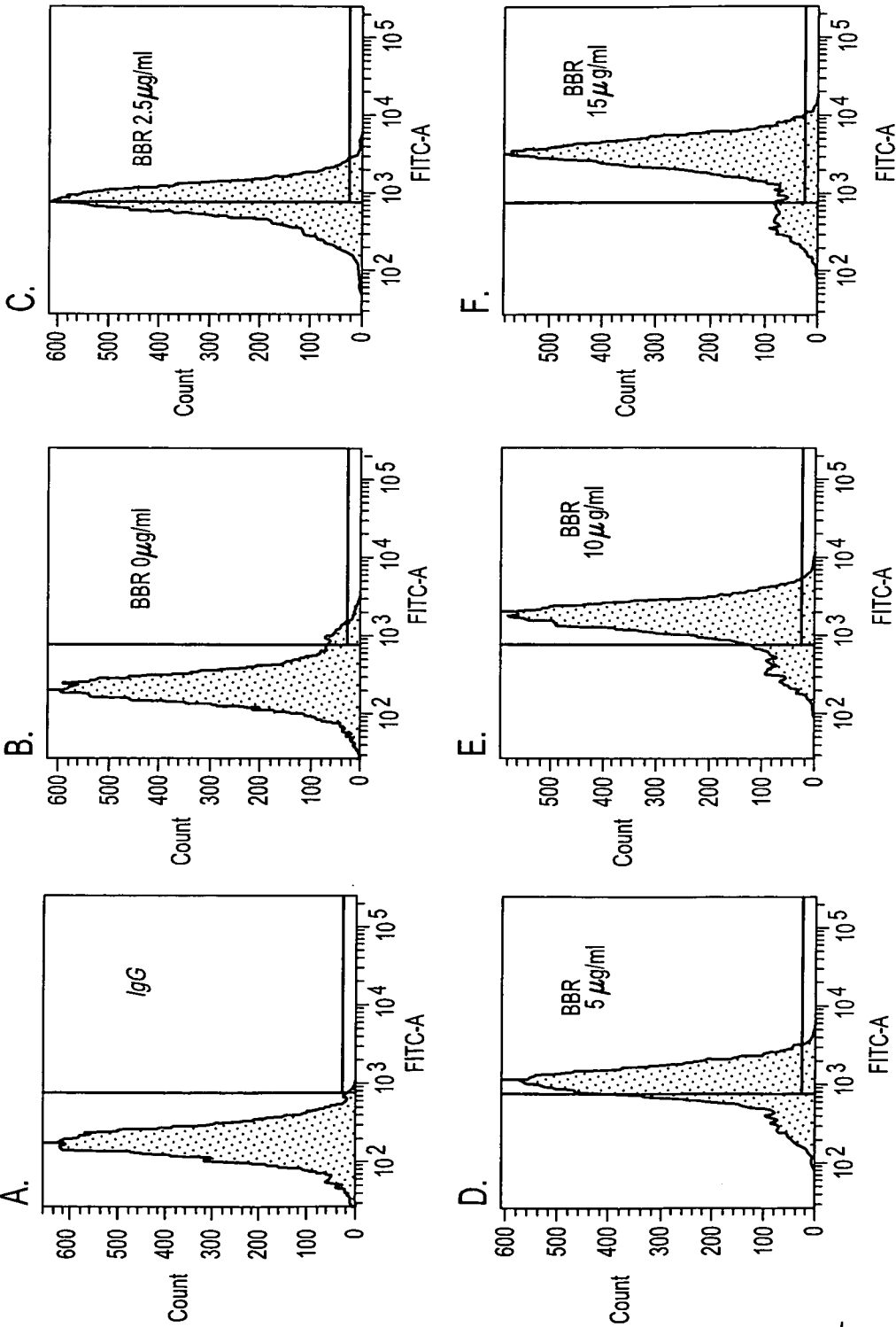
FIG. 16



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FIG. 17

(HepG2, 8h)



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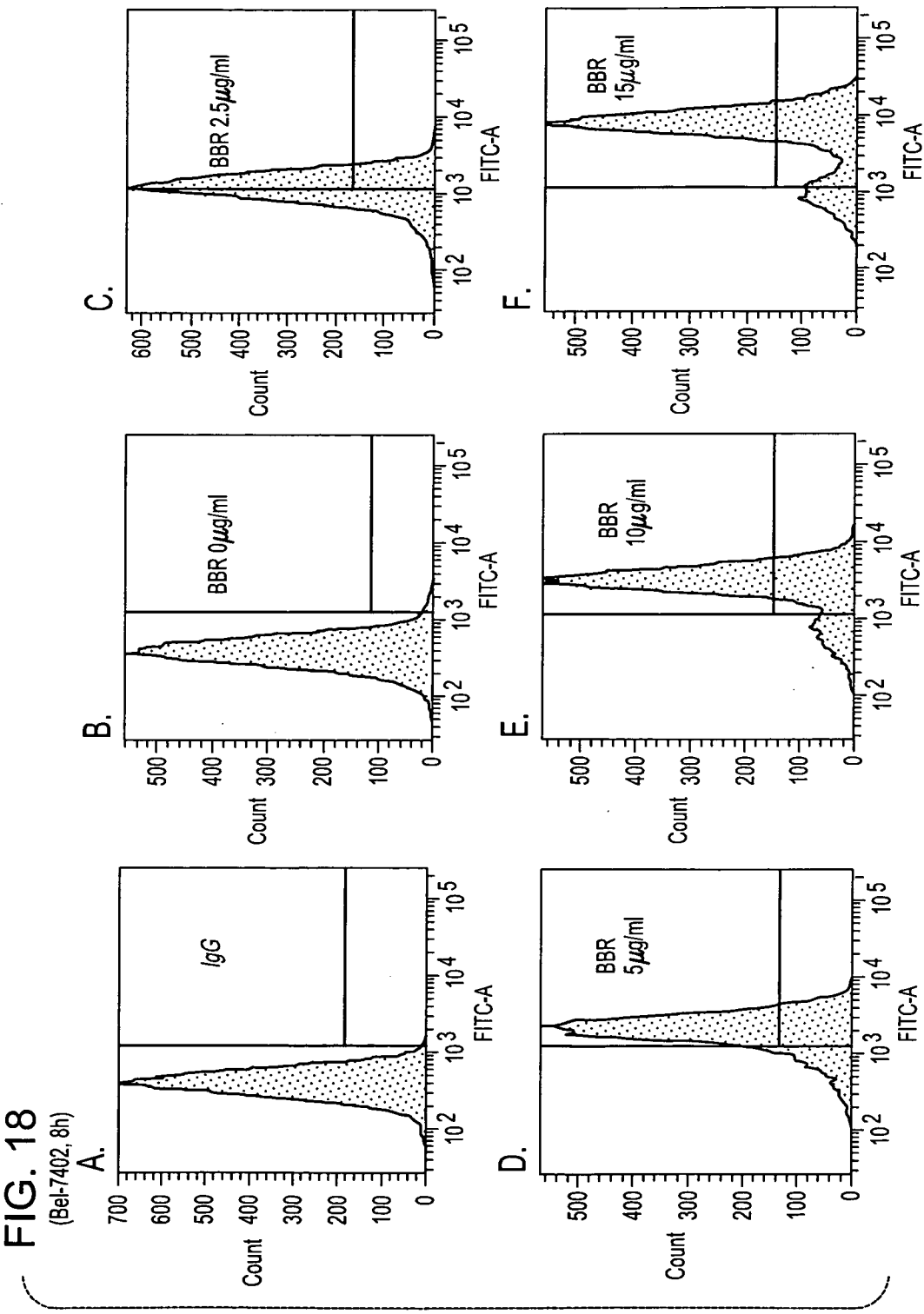
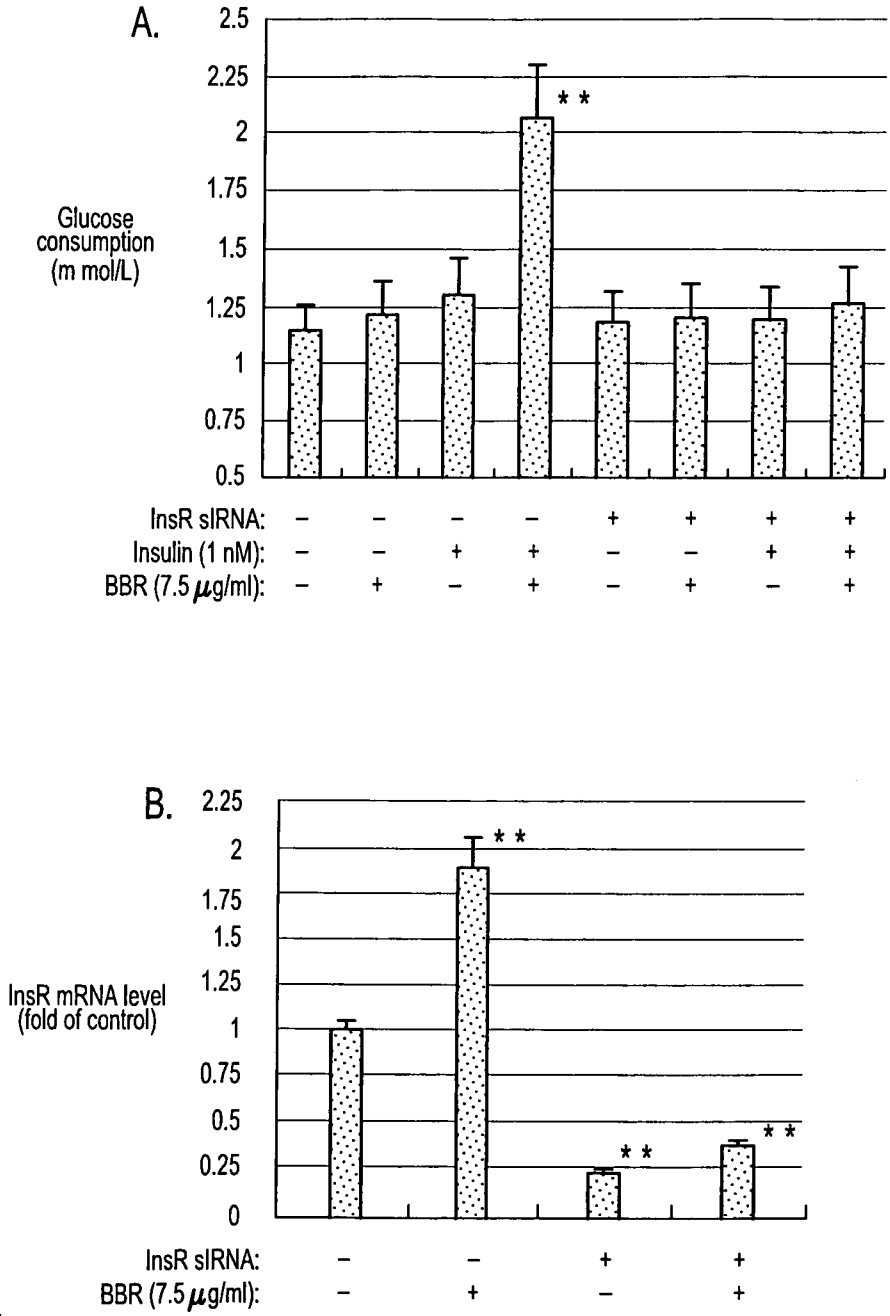
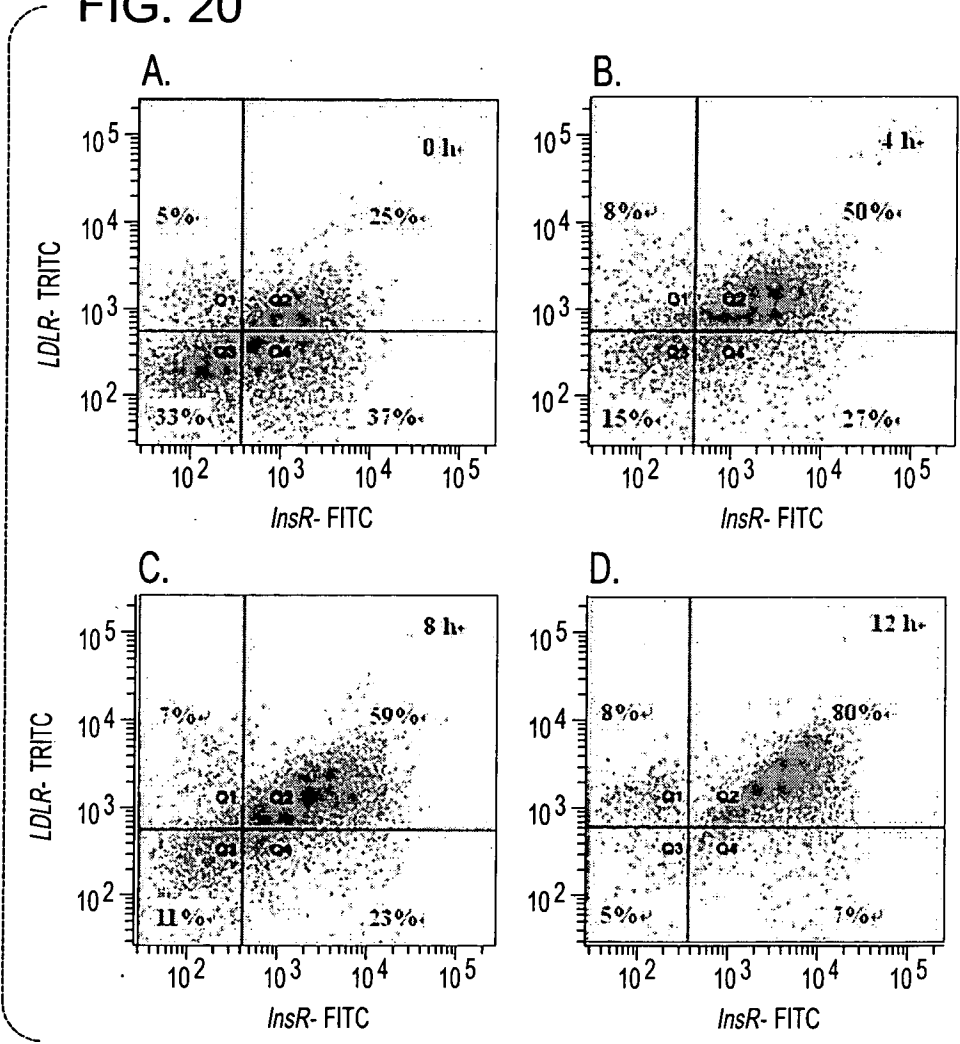


FIG. 19



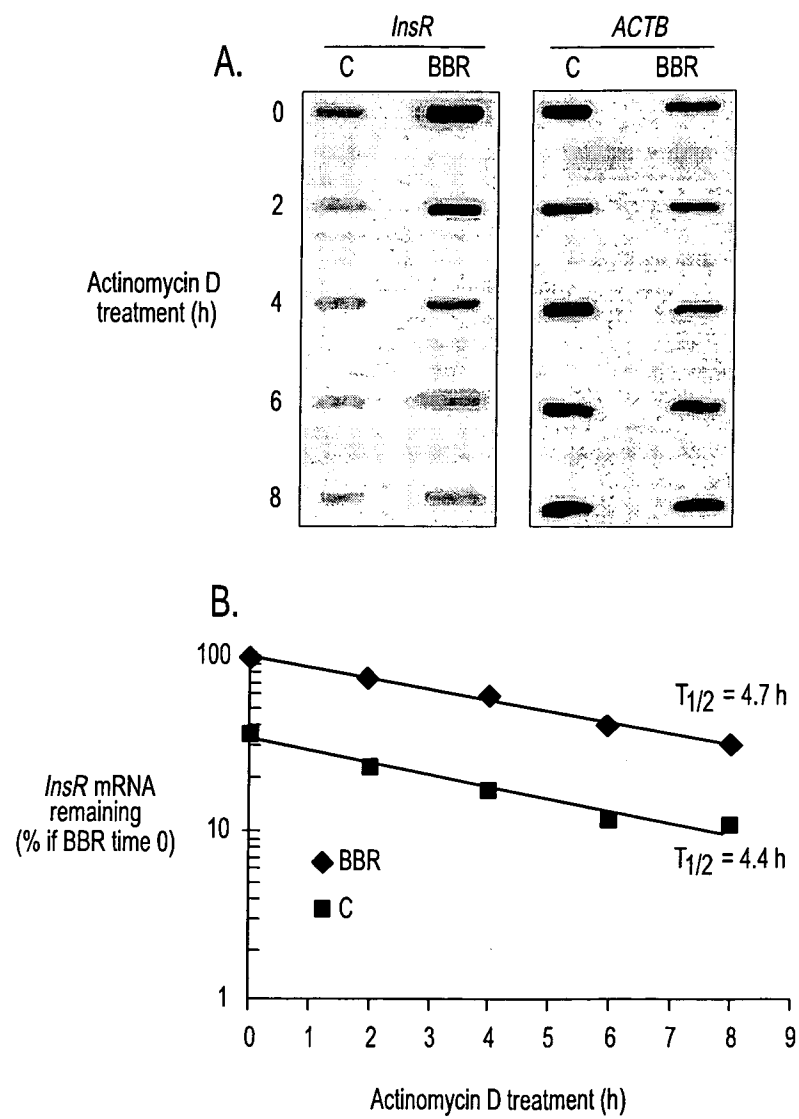
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FIG. 20



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FIG. 21



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FIG. 22

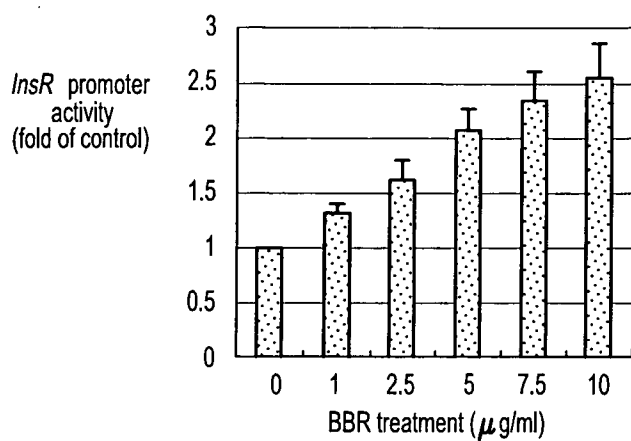


FIG. 23

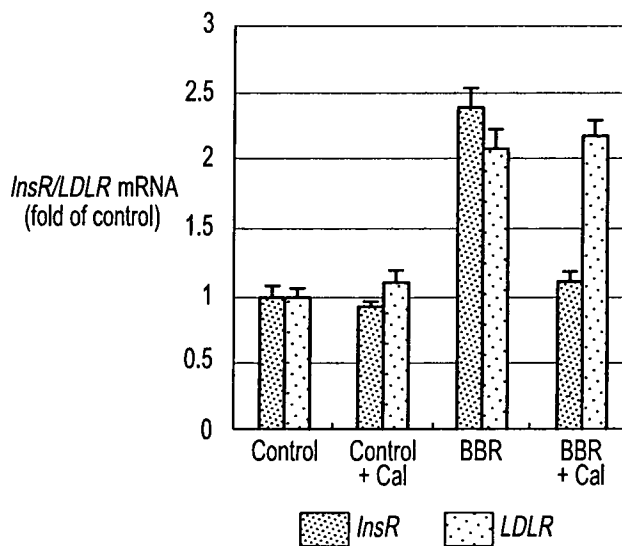


FIG. 24

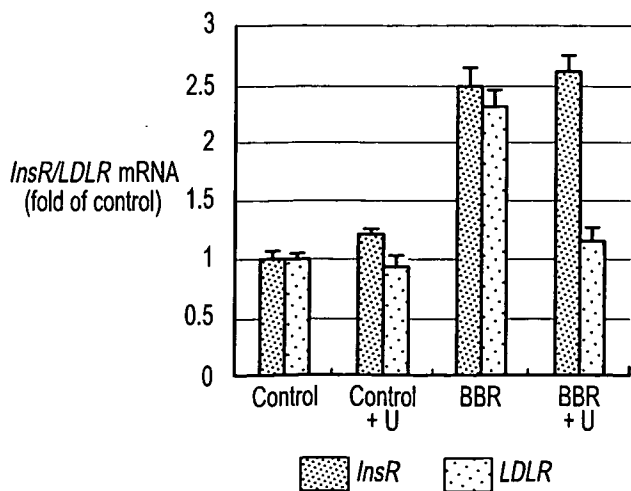
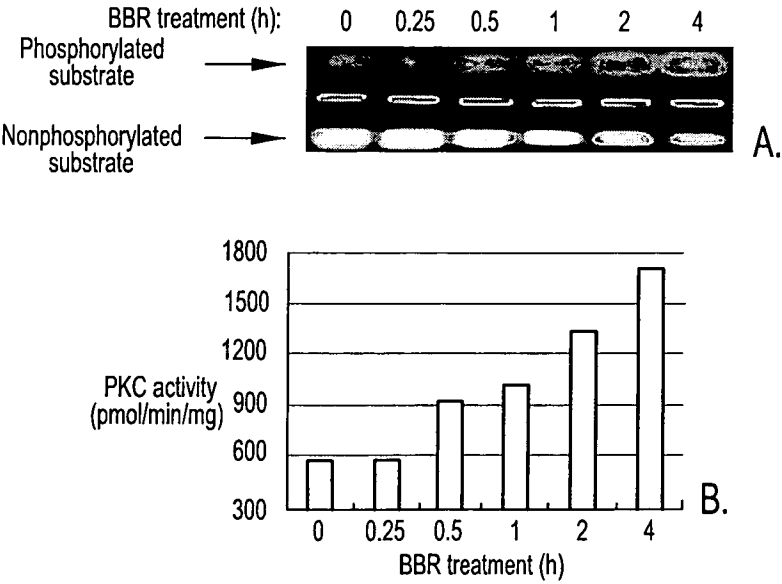


FIG. 25



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FIG. 26

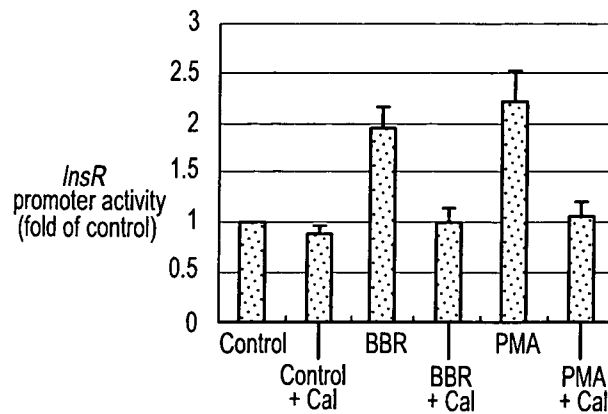


FIG. 27

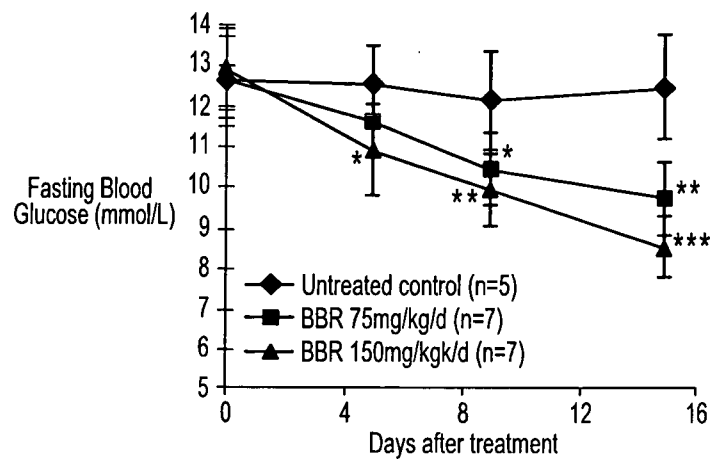
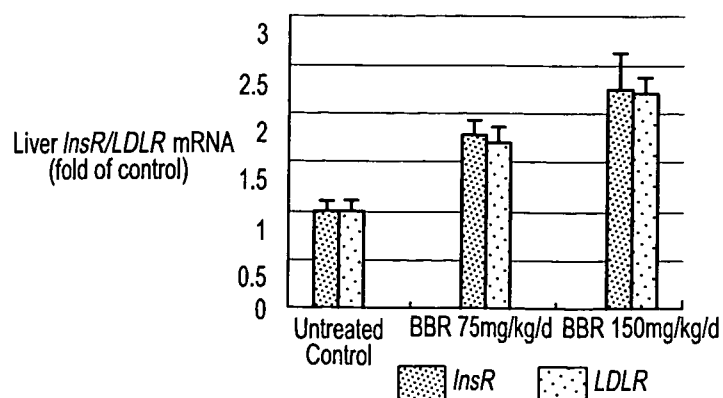


FIG. 28



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FIG. 29

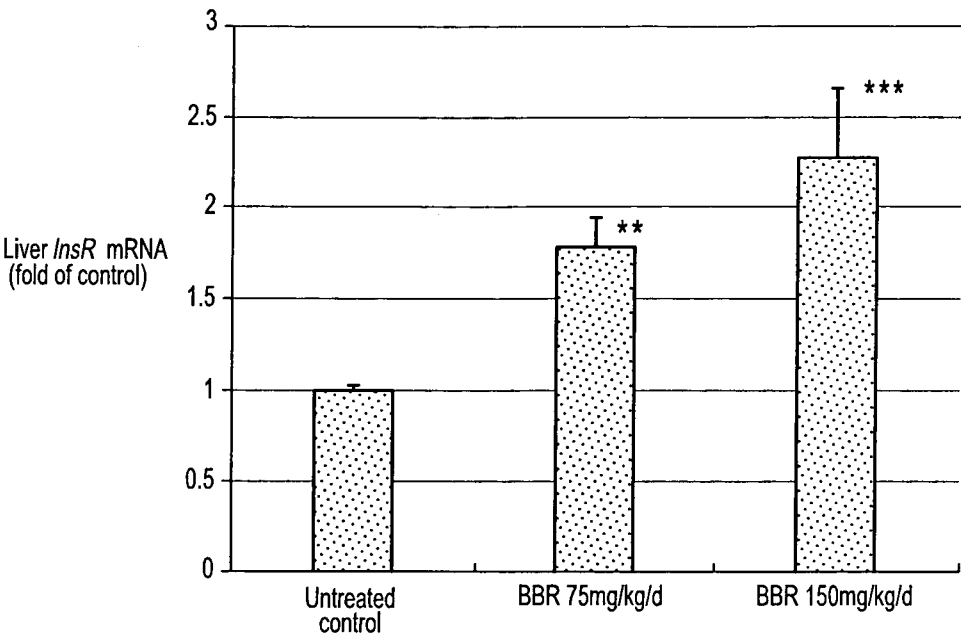
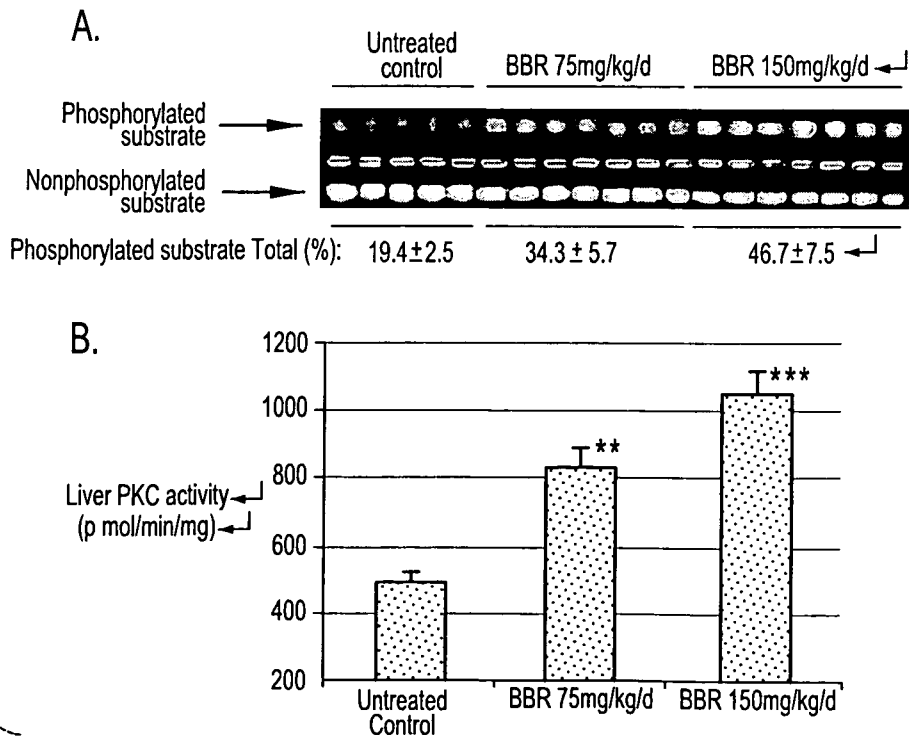


FIG. 30



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FIG. 31

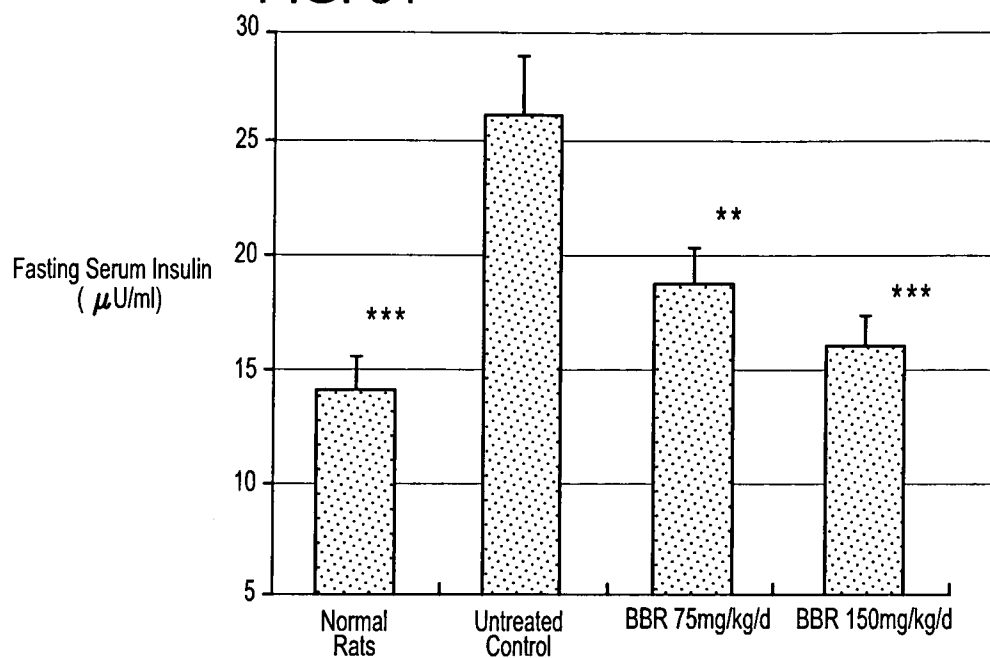


FIG. 32

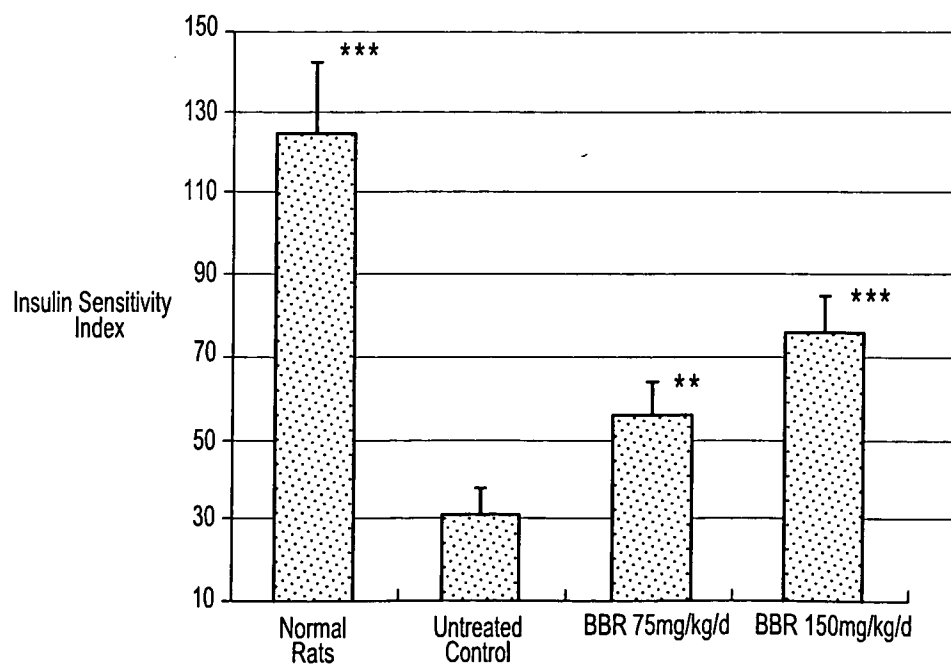


FIG. 33

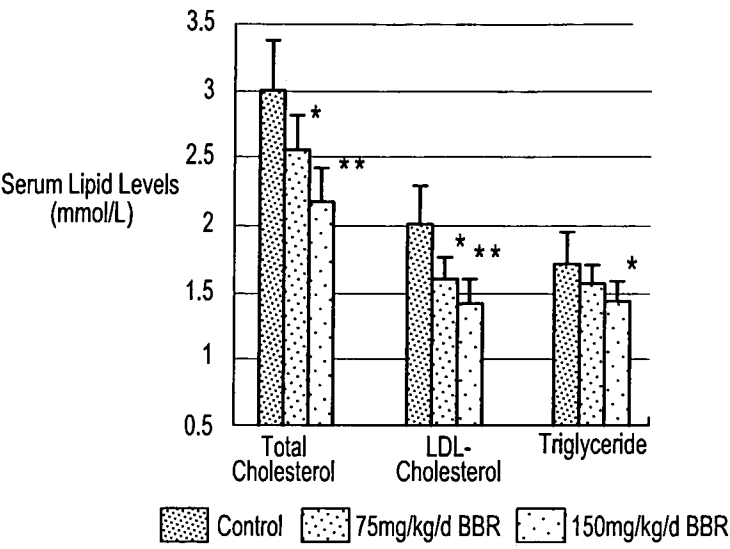
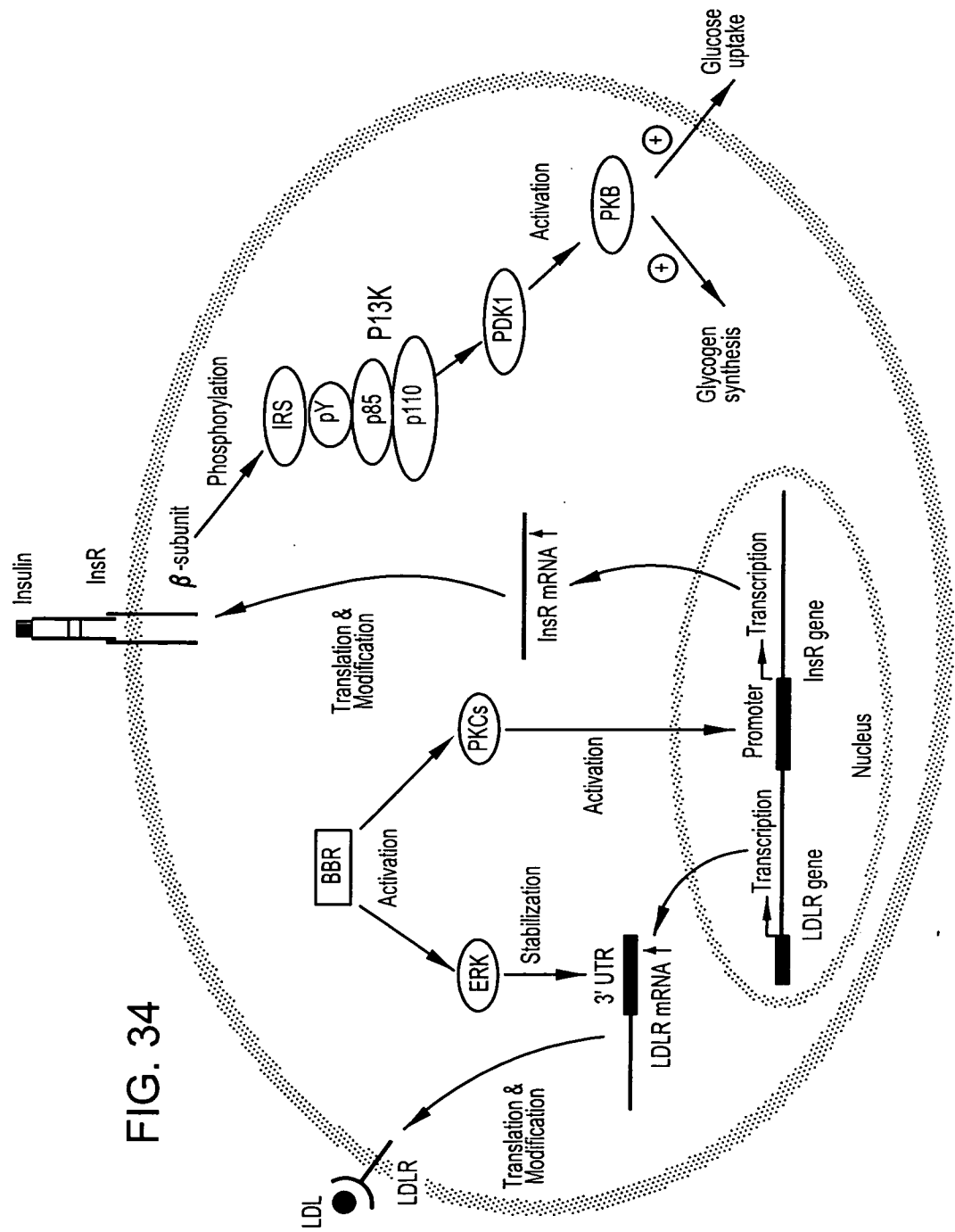


FIG. 34



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FIG. 35

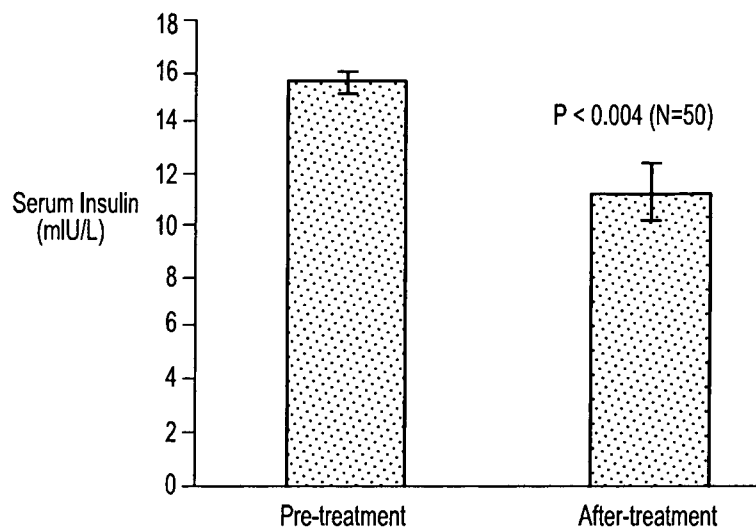


FIG. 36

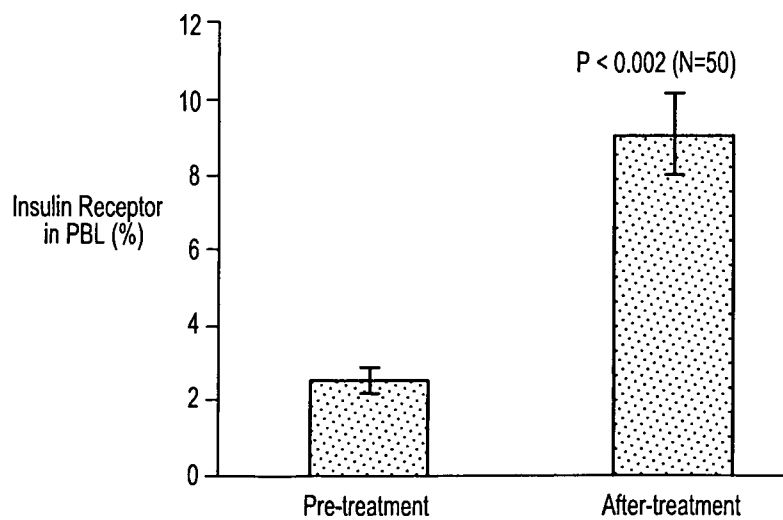
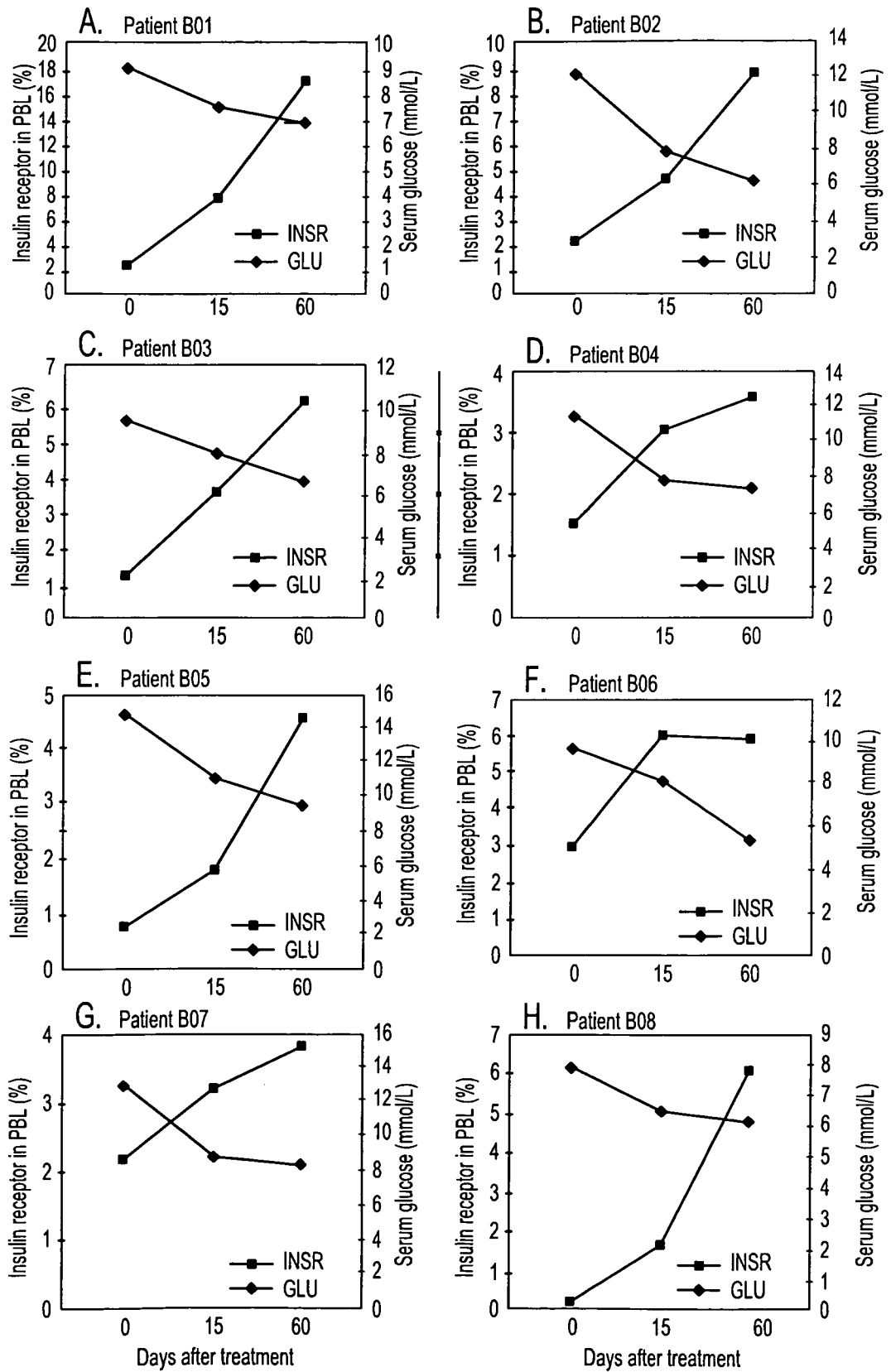


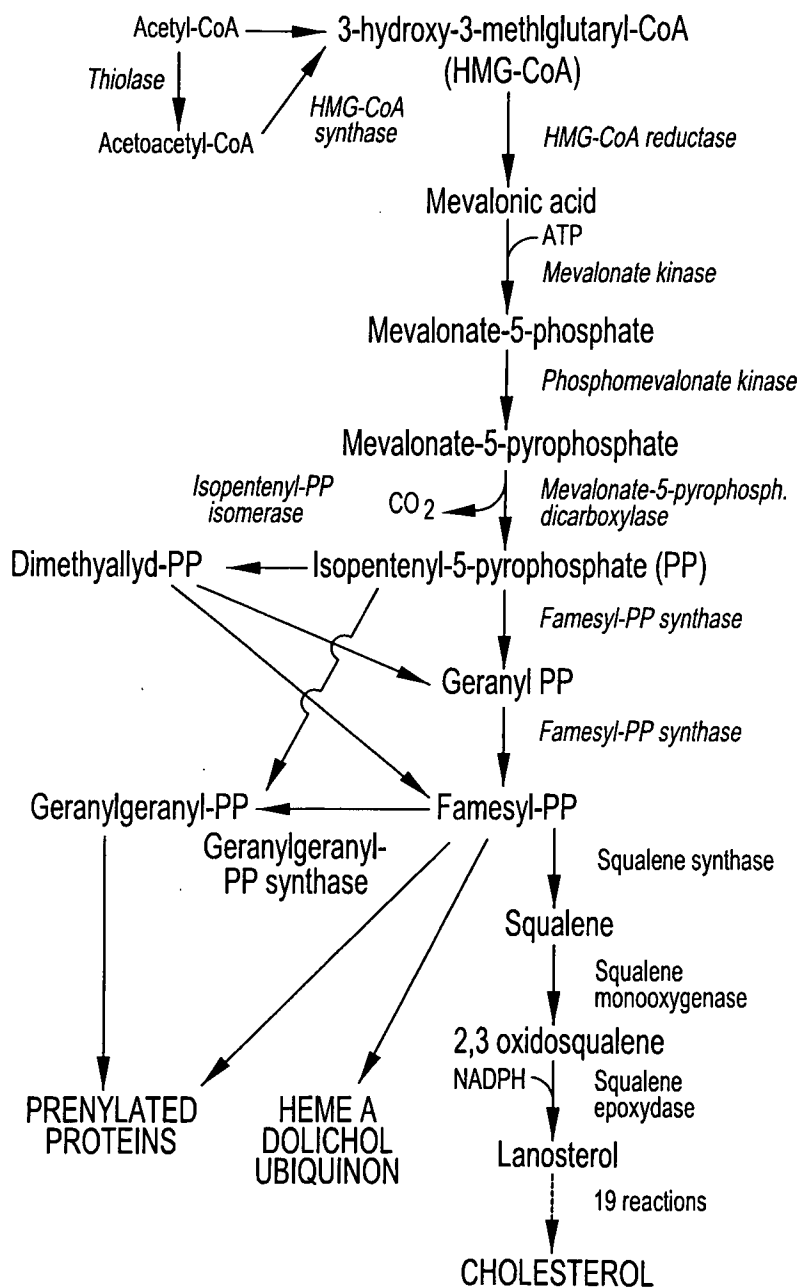
FIG. 37

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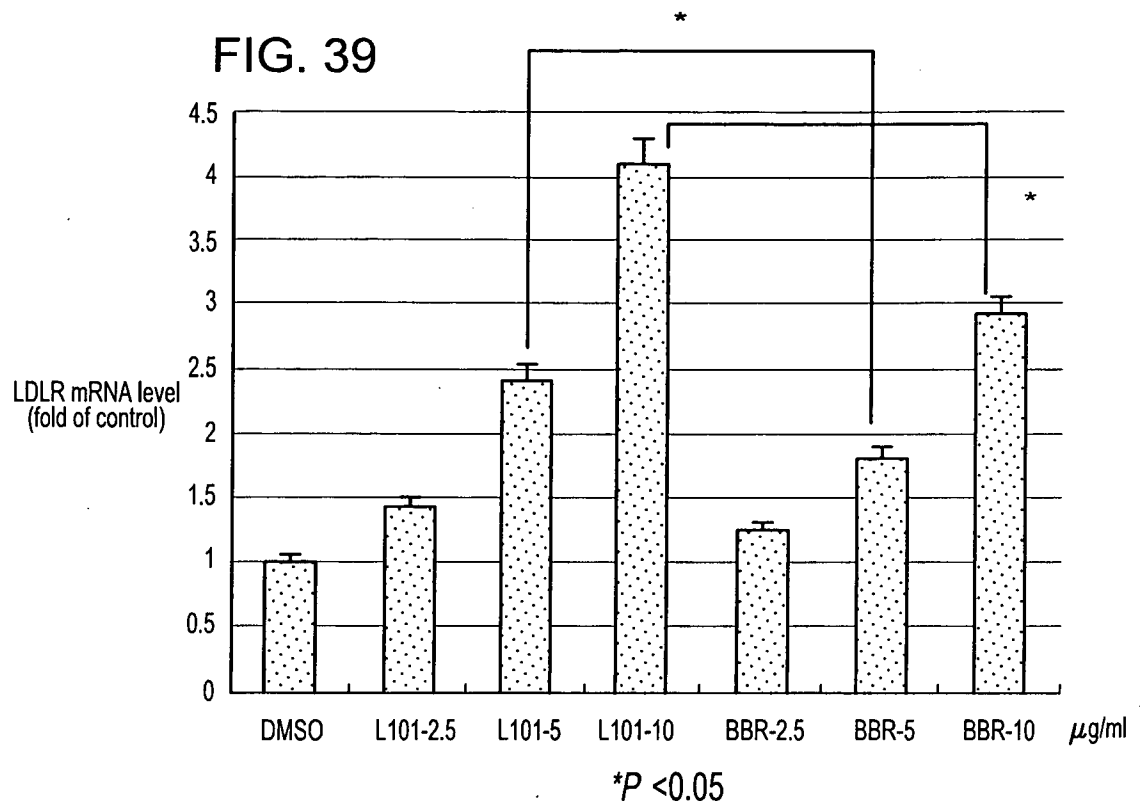


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FIG. 38



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FIG. 40

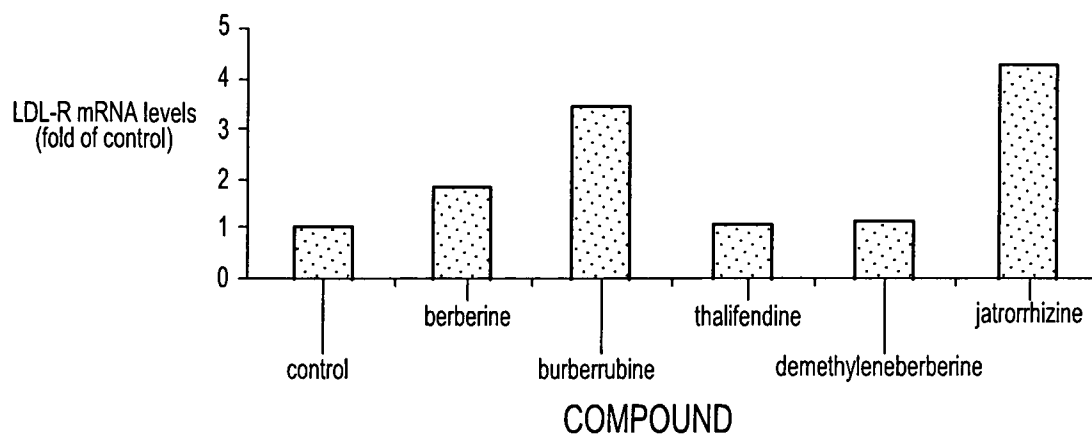


FIG. 41

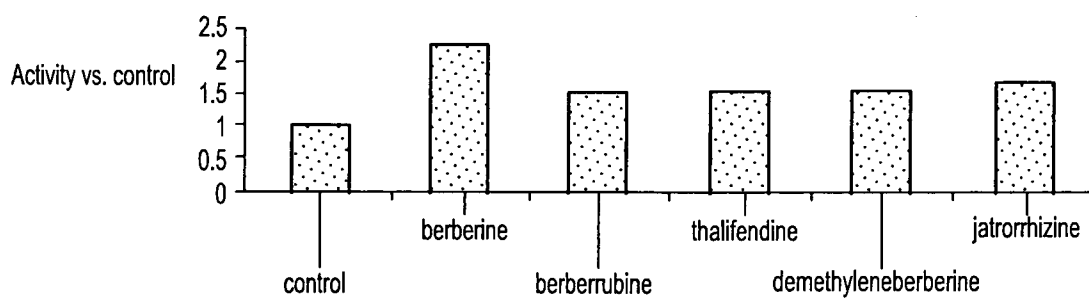
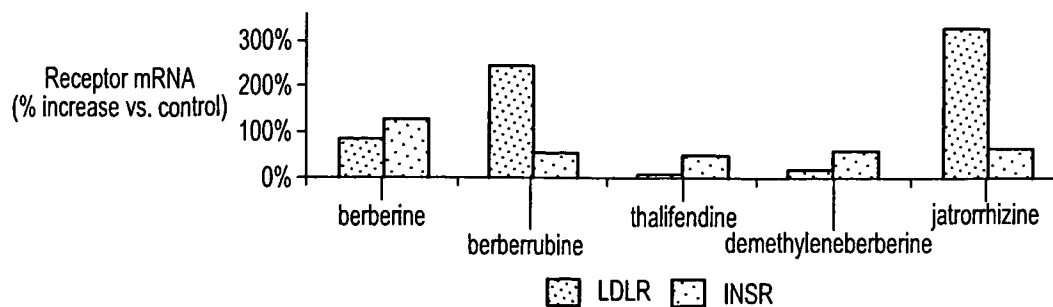


FIG. 42



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 10/00750

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A01N 43/42; A61K 31/44 (2010.01)

USPC - 514/284

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

USPC: 514/284

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/3, 26, 169, 185, 280 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PubWEST (USPT, PGPB, EPAB, JPAB), Google Patents/Scholar

Search Terms Used: berberine derivative, metabolic disorder, diabetes, insulin resistance, hypertension, LDL receptor, hyperlipidemia

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2008/0081781 A1 (Lippa et al.) 03 April 2008 (03.04.2008) para [0013], [0015]-[0016], [0018]-[0025], [0029], [0032]-[0033], [0101], [0108], [0114], [0166]-[0167], [0178]-[0179], [0191], [0194], [0196], [0200], [0207], [0211], [0239], [0243]-[0244]	1-124 ----- 125-127
Y	Brusq et al. Inhibition of lipid synthesis through activation of AMP kinase: an additional mechanism for the hypolipidemic effects of berberine. J Lipid Research, 2006, Vol 47, pg 1281- 1288; abstract	125-127
A	US 2005/0019435 A1 (Young) 27 January 2005 (27.01.2005) entire doc esp. Fig. 1A	1
P/A	US 2010/0113494 A1 (Hu et al.) 06 May 2010 (06.05.2010) entire doc esp. para [0026]	1

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

26 May 2010 (26.05.2010)

Date of mailing of the international search report

09 JUN 2010

Name and mailing address of the ISA/US

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