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(54) NOVEL ANTICHOLESTEROL COMPOSITIONS AND METHOD FOR USING SAME

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(57) **ABSTRACT**

Compositions, methods, combinations, and kits for treating a disorder related to elevated serum cholesterol concentration, for example, atherosclerosis, elevated LDL plasma levels, low HDL plasma levels, hypertriglyceridemia, hyperlipidemia, hypertension, hypercholesterolemia, cholesterol gallstones, lipid storage diseases, obesity, and diabetes. The compositions, methods, combinations, and kits of the present invention are pharmaceutical compositions comprising at least two of an LXR receptor modulator, a therapeutically effective amount of a catechin, and/or a therapeutically effective amount of a lipid regulating agent, such as a HMG-CoA reductase inhibitor, a fibric acid derivative, niacin, a bile-acid sequestrant, an absorption inhibitor, probucol, raloxifene and its derivatives, an azetidinone compound, and an unsaturated omega-3 fatty acid.

NOVEL ANTICHOLESTEROL COMPOSITIONS AND METHOD FOR USING SAME

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] Pursuant to 35 U.S.C. §§ 119(e) and 120, this application claims the benefit of U.S. application Ser. No. 09/530,433, filed Apr. 28, 2000, which is the National Stage filing of PCT/US98/23041, filed Oct. 30, 1998, which claims priority to prior U.S. provisional application No. 60/063,770, filed Oct. 31, 1997; U.S. application Ser. No. 09/560,236, filed Apr. 28, 2000, which claims priority to prior U.S. provisional application No. 60/131,728, filed Apr. 30, 1999; U.S. application Ser. No. 10/072,128 filed on Feb. 8, 2002, which claims priority to U.S. provisional application No. 60/267,493, filed Feb. 8, 2001; U.S. application Ser. No. 10/137,695 filed May 2, 2002, which claims priority to U.S. provisional application No. 60/288,643, filed May 3, 2001; and prior U.S. provisional application No. 60/348,020, filed Nov. 8, 2001, the disclosure of which are incorporated herein by reference.

TECHNICAL FIELD OF THE INVENTION

[0002] The present invention relates generally to compositions and methods for treating a disorder related to elevated serum cholesterol concentration.

BACKGROUND OF THE INVENTION

[0003] It has been well known that high cholesterol concentration is related to vascular disorders such as coronary heart disease or atherosclerosis. See, e.g., *Essays of an Information Scientist,* 1986, 9, 282-292; and "Cholesterol", Microsoft® Encarta® Encyclopedia 2000. It has also been found that some neurodegenerative diseases such as elevated senile cognitive impairment or dementia (e.g., Alzheimer's disease) can be attributed to an elevated concentration of cholesterol, as well. See, e.g., Sparks, D. L. et al., *Microsc. Res. Tech.,* 2000, 50, 287-290.

[0004] The average American consumes about 450 mg of cholesterol each day and produces an additional 500 to 1,000 mg in the liver and other tissues. Another source of cholesterol is the 500 to 1,000 mg of biliary cholesterol that is secreted into the intestine daily; about 50 percent is reabsorbed (enterohepatic circulation). Excess accumulation of cholesterol in the arterial walls can result in atherosclerosis, which is characterized by plaque formation. The plaque inhibits blood flow, promotes clot formation and can ultimately cause heart attacks, stroke and claudication.

[0005] Most of the cholesterol in plasma and in atherosclerotic lesions is normally in low-density lipoprotein (LDL) cholesterol. High plasma concentrations of LDL are associated with an increased risk of atherosclerotic cardiovascular disease. A low plasma concentration of high-density lipoprotein (HDL) cholesterol, on the other hand, is a strong risk factor for coronary heart disease, even when LDL and total plasma cholesterol are normal.

[0006] Development of therapeutic agents for the treatment of atherosclerosis and other diseases associated with cholesterol metabolism has been focused on achieving a more complete understanding of the biochemical pathways involved. Most recently, liver X receptors (LXRs) were identified as key components in cholesterol homeostasis.

[0007] Cholesterol concentration-can be down-regulated by liver X receptors (LXRs) such as LXRa and LXRb (also called UR). LXRs regulate the cholesterol efflux, in part, through the coordinate regulation of genes, e.g., apolipoprotein E (apoE) and ATP-binding cassette transporters A1 (ABCA1), G1 (ABCG1), and G5/G8 (ABCG5/G8) which are involved in lipid metabolism. In addition, LXRs up regulate the gene responsible for bile acid synthesis (i.e., CYP7A1)—the primary excretory means for cholesterol removal from the body. See, e.g., Laffitte, B. A. et al., Proc. Natl. Acad. Sci. USA, 2001, 98 (2), 507-512; Cole, G. M. et al., Micro. Res. Tech., 2000, 50, 316-324; Lu, T. T. et al., Journal Biol. Chem., 2001, 276, 37735-37738 andand Oram J. F. et al., Journal of Lipid Research, 2001, 42, 1173-1179. Thus, modulators of LXR receptors are potential drug candidates for treating a disorder related to high cholesterol concentration.

[0008] Recent studies on the LXRs indicate that they are activated by certain naturally occurring, oxidized derivatives of cholesterol, including 22(R)-hydroxycholesterol, 24(S)-'hydroxycholesterol and 24,25(S)-epoxycholesterol (see Lehmann, et al., J. Biol. Chem. 272(6):3137-3140 (1997)). The expression pattern of LXRs and their oxysterol ligands provided the first hint that these receptors may play a role in cholesterol metabolism (see Janowski, et al., Nature 383:728-731 (1996)). Accordingly, modulation of the LXRs (e.g., use of LXR agonist or antagonists) could provide treatment for a variety of lipid disorders including obesity and diabetes.

[0009] Other drugs are known to lower serum concentrations of LDL cholesterol and may help prevent formation, slow progression, and cause regression of atherosclerotic lesions. Further, trials of these lipid-regulating drugs have shown an association between increases in HDL cholesterol and reduction in clinical coronary events. For example, HMG-CoA reductase inhibitors, otherwise known as "statins," inhibit the enzyme that catalyzes the rate-limiting step in cholesterol syntesis. Statins are more effective than other drugs in lowering plasma concentrations of LDL cholesterol, increasing HDL cholesterol by up to about 15% with high doses, and reducing levels of triglyceride. Statins lower LDL cholesterol levels in the bloodstream by indirectly increasing the number of LDL receptors on the surface of cells. Despite the success of statins, there is a significant patient population, particularly those individuals having substantially elevated blood cholesterol levels, for which these drugs alone are insufficient to achieve the desired efficacy. Moreover, because statins are not able to mobilize cholesterol sequestered in tissue and/or cells (e.g., foam cells in atherosclerotic plaques), this class of compounds, alone, cannot prevent the development of atherosclerosis.

[0010] Bile acid sequestrants are another lipid regulating drug that may lower LDL-cholesterol by about 10 to 20 percent. Cholestyramine, colestipol, and colesevelam are the three main bile acid sequestrants currently available. Small doses of sequestrants can produce useful reductions in LDL-cholesterol. These drugs also tend to increase HDL cholesterol and, in patients with hypertriglyceridemia, cholestyramine, colestipol and, to a lesser extent, colesevelam raise plasma triglycerides. When these drugs are combined, their effects are added together to lower LDL-cholesterol by over 40 percent.

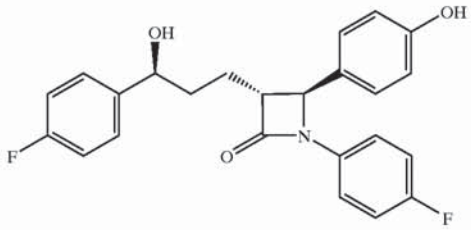
[0011] Fibric acid derivatives ("fibrates"), including gemfibrozil, fenofibrate, bezafibrate (not available in the USA) and clofibrate are used mainly to lower triglycerides and to increase HDL cholesterol. They may lower LDL cholesterol, but when they decrease elevated triglycerides, LDL cholesterol may increase in some patients. Fibrates shift the size distribution of LDL to larger, more buoyant particles which may be less atherogenic than smaller, denser forms. While drugs that mainly lower LDL (statins and bile-acid sequenstrants) show a linear relationship between the degree of cholesterol lowering and the reduction in clinical coronary events, fibrates show a much greater reduction in clinical events than predicted from the degree of cholesterol lowering. This suggests that the effect of fibrates on coronary disease is mediated by a different mechanism, possibly associated with their effects in triglycerides and HDL cholesterol (G. R. Thompson and P. J. Barter, Curr Opin Lipidol 1999; 10:521).

[0012] No fibrate trial, however, has ever shown significant reduction in total mortality. For example, in a large placebo-controlled trial in patients with stable angina or a previous myocardial infarction who had average plasma lipid concentrations, bezafibrate did not reduce the incidence of myocardial infarction and death significantly after six years. (The BIP Study—Group, Circulation 2000; 102:21). Other fibrates have their disadvantages as well. Gemfibrozil is known to cause gastrointestinal symptoms, and both cholecystectomies and appendectomies are more frequent in gemfibrozil-treated patients (M. H. Frick et al, N. Engl. J. Med. 1987; 317:1237). Clofibrate has a high mortality rate due to malignant and gastrointestinal disease in some early studies.

[0013] Niacin, or nicotinic acid, is another lipid-regulating agent that inhibits production of very-low-density (VLDL) particles in the liver, and increases HDL cholesterol more than any other drug. It also decreases triglycerides, remnant lipoproteins, lipoprotein(a), and total plasma and LDL cholesterol, changing LDL particles from small and dense to large and buoyant forms (J. R. Guyton, et al., Arch. Intern. Med. 2000; 160:1177). Lower doses (1500 to 2000 mg/day) can affect triglycerides and HDL cholesterol markedly; higher doses may be required for substantial reductions of LDL cholesterol.

[0014] Long chain, highly unsaturated omega-3 fatty acids (present in cold-water fish and commercially available in capsules) can decrease triglycerides and may lower lipoprotein (a) after long-term intake (S M Marcovina et al., Arterioscler Thromb Vasc Biol 1999; 19:1250). They have little effect on LDL cholesterol, but may increase HDL. (GISSI-Prevenzione Investigators, Lancet 1999; 354:447).

[0015] Cholesterol absorption inhibitors typically lower LDL cholesterol by 10-20%. Examples of agents that inhibit cholesterol absorption include acyl-coenzyme A: cholesterol acyltransferase (ACAT) inhibitors such as C1-976 (Krause, B. R. et al., Clin. Biochem., 25, 371-377, 1992), 58-035 (Heiden, J. G. et al., J. Up. Res., 24,1127-1134, 1983), and melinamide, stigmastanyl phosphorylcholine and analogs disclosed in EP-430,078A; β-lactam cholesterol absorption inhibitors including but not limited to those disclosed in U.S. Pat. No. 5,661,145, WO 93/02048, and EP 524,595A; sulfated polysaccharides including but not limited to those disclosed in U.S. Pat. No. 5,063,210; and other compounds such as neomycin and naturally occurring plant saponins. In addition, steroidal glycosides described in WO 93/07167-A1 and U.S. Pat. Nos. 4,602,003 and 4,602,005 have been proposed as useful for the control of hypercholesterolemia. Pfizer, Inc. discloses other steroidal glycosides having superior hypocholesterolemic activity in U.S. Pat. No. 5,807,834, WO 93/11150, WO 94/00480, WO 95/18143 and WO 95/18144. Steroidal glycosides inhibit cholesterol absorption thereby decreasing plasma cholesterol levels. Schering-Plough Corp. has disclosed substituted azetidinone compounds as hypocholesterolemic agents, including ezetimide, or SCH58235, and similar compounds in WO 94/17038, WO 95/08532 and WO 93/02048. Ezetimibe has been shown to lower LDL cholesterol by approximately 18% following a once-daily 10 mg dose, either as monotherapy or as combination therapy. (Meittinen, T., Int J Clin Pract. December 2001; 55(10):710-6). Ezetimibe is characterized by the following structure:



[0016] Ezetimibe, and other compounds containing the azetidinone moiety, may be useful in the management of patients who respond poorly to or are unable to tolerate statins, or in patients with hereditary or drug-induced phytosterolaemia. Other cholesterol absorption inhibitors can be identified by their ability to inhibit cholesterol absorption in experimental animals such as the hamster (Harwood et al., J. Lip. Res. 1993; 34:377-95) and will be readily apparent to those skilled in the art.

[0017] Drinking green tea may also contribute to prevent cardiovascular disease by increasing plasma antioxidant capacity in humans. For example, green tea catechins, (−)-epigallocatechin-3-gallate (EGCG) and (−)-epigallocatechin (EGC), have been reported to suppress oxidation of plasma low density lipoprotein (LDL) in vitro (Nakagawa K, et al. Biosci Biotechnol Biochem. December 1997; 61(12):1981-5). Commonly owned U.S. application Ser. No. 09/530,443, discloses that EGCG and related compounds may interact and interfere with a receptor macromolecule (probably containing a protein) that modulates specific lipid synthesis and accumulation.

[0018] Combination therapies of lipid lowering agents have been described previously as having a synergistic hypolipidemic effect. Nevertheless, in practice, many combinations of existing lipid regulating agents are contraindicated, limiting the options of prescribing physicians for patients requiring greater reductions of plasma LDL-cholesterol levels and greater elevations in HDL cholesterol levels. Thus, although there are a variety of hypercholesterolemia therapies, there is a continuing need and a continuing search in this field of art for alternative therapies.

BRIEF SUMMARY OF THE INVENTION

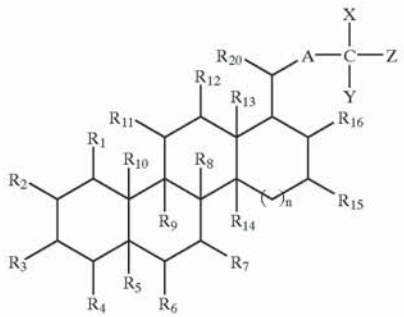
[0019] When tolerable doses of a single drug do not lower blood lipids sufficiently, two or more drugs can be used together, such as an LXR receptor modulator combined with a catechin or a lipid-regulating agent. For example, concurrent use of an oxysterol with a statin or catechin, or with both, may effectively lower LDL cholesterol and raise HDL cholesterol.

[0020] The present invention is directed to compositions, methods, combinations, and kits for treating a disorder related to elevated serum cholesterol concentration, for example, atherosclerosis, elevated LDL plasma levels, low HDL plasma levels, hypertriglyceridemia, hyperlipidemia, hypertension, hypercholesterolemia, cholesterol gallstones, lipid storage diseases, obesity, and diabetes. The compositions, methods, combinations, and kits of the present invention include pharmaceutical compositions comprising an LXR receptor modulator in combination with a therapeutically effective amount of a catechin and/or a therapeutically effective amount of a lipid regulating agent, such as a HMG-CoA reductase inhibitor, a fibric acid derivative, niacin, a bile-acid sequestrant, an absorption inhibitor, probucol, raloxifene and its derivatives, and an unsaturated omega-3 fatty acid.

DETAIL DESCRIPTION OF THE INVENTION

[0021] One aspect of this invention relates to a method of treating a disorder related to high cholesterol concentration, comprising administering an LXR receptor modulator in combination with at least one of a catechin or a lipid regulating agent to a subject in need thereof. In one embodiment, the LXR receptor modulator may be an oxysterol of formula (I):

(I)

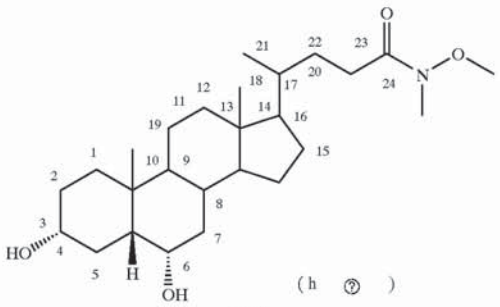


[0022] In formula (I), each of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_{11}, R_{12}, R_{15}, R_{16}, and R_{20}, independently, is hydrogen, halo, alkyl, haloalkyl, hydroxy, amino, carboxyl, oxo, sulfonic acid, or alkyl that is optionally inserted with —NH—, —N(alkyl)-, —O—, —S—, —SO—, —SO_2—, —O—SO_2—, —SO_2—O—, —SO_3—O—, —CO—, —CO—O—, —O—CO—, —CO—NR'—, or —NR'—CO—; each of R_8, R_9, R_{10}, R_{13}, and R_{14}, independently, is hydrogen, halo, alkyl, haloalkyl, hydroxyalkyl, alkoxy, hydroxy, or amino; n is 0, 1, or 2; A is alkylene, alkenylene, or alkynylene; and each of X, Y, and Z, independently, is alkyl, haloalkyl, —OR', —SR', —NR'R", —N(OR')R", or —N(SR')R"; or X and Y together are =O, =S, or =NR'; wherein each of R' and R", independently, is hydrogen, alkyl, or haloalkyl. Note that the carbon atoms shown in formula (I) are saturated with hydrogen unless otherwise indicated.

[0023] Each of the term "alkyl," the prefix "alk" (as in alkoxy), and the suffix "-alkyl" (as in hydroxyalkyl) refers to a C_{1-8} hydrocarbon chain, linear (e.g., butyl) or branched (e.g., iso-butyl). Alkylene, alkenylene, and alkynylene refer to divalent C_{1-8} alkyl (e.g., ethylene), alkene, and alkyne radicals, respectively. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skills in the art to which this invention belongs.

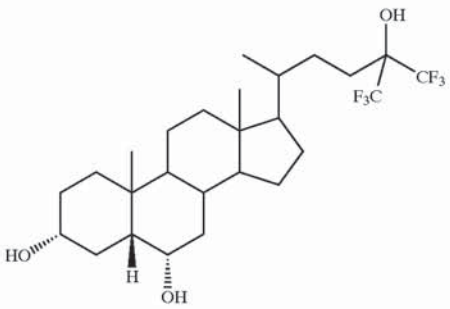
[0024] Referring to formula (I), subsets of the compounds that can be used to practice the method of this invention include those wherein each of R_1, R_2, R_4, R_7, R_8, R_9, R_{11}, R_{12}, R_{14}, R_{15}, R_{16}, independently, is hydrogen; each of R_{10}, R_{13}, and R_{20}, independently, is an alkyl (e.g., methyl, ethyl, butyl, or iso-butyl); n is 0; and A is alkylene; those wherein R_5 is hydrogen (e.g., β hydrogen), and each of R_3 and R_6, independently, is hydroxy (e.g., α hydroxy); those wherein each of X, Y, and Z, independently, is alkyl (e.g., methyl, propyl, or hexyl), haloalkyl (e.g., trifluoromethyl, or 3-chloropropyl), —OR' (e.g., hydroxy or methyocy), or —SR'; and those wherein X and Y together are =O or =S; and Z is —OR', —SR', —NR'R" (e.g., ethylmethylamino), —N(OR')R" (e.g., methoxymethylamino), or —N(SR')R".

[0025] Shown below are hypocholamide (with carbon atoms numbered) and hypocholaride, two of the oxysterol compounds described above that can be used to practice the method of this invention:



(h ⑦)

and



(h ⑦)

⑦ indicates text missing or illegible when filed

[0026] The compounds described above also include their salts and prodrugs, if applicable. Such salts, for example, can be formed between a positively charged substituent in a compound (e.g., amino) and an anion. Suitable anions include, but are not limited to, chloride, bromide, iodide, sulfate, nitrate, phosphate, citrate, methanesulfonate, trifluoroacetate, and acetate. Likewise, a negatively charged substituent in a compound (e.g., carboxylate) can form a salt with a cation. Suitable cations include, but are not limited to, sodium ion, potassium ion, magnesium ion, calcium ion, and an ammonium cation such as tetramethylammonium ion. Examples of prodrugs include esters and other pharmaceutically acceptable derivatives, which, upon administration to a subject, are capable of providing piperazinedione compounds described above.

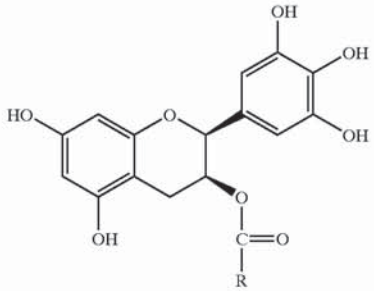
[0027] Compounds that can be used to practice the method of this invention can be synthesized according to methods well known in the art by using a suitable steroid as a starting material. Preparation of these compounds is further detailed in U.S. provisional application No. 60/xxx,xxx filed Nov. 8, 2001.

[0028] U.S. application Ser. No. 09/560,236, U.S. provisional application No. 60/267,493, and U.S. provisional application No. 60/288,643, disclose other compounds that may modulate LXR receptors. Other oxysterols that may regulate LXR receptors include 25-hydroxycholesterol; 24-(S), 25-epoxycholesterol; 24 (S)-hydroxycholesterol; 22-(R)-hydroxycholesterol; 24 (R), 25-epoxycholesterol; 22 (R)-hydroxy-24 (S), 25-epoxycholesterol; 22 (S)-hydroxy-24 (R), 25-epoxycholesterol; 24 (R)-hydroxycholesterol; 22 (S)-hydroxycholesterol; 22 (R), 24 (S)-dihydroxycholesterol; 25-hydroxycholesterol; 22 (R)-hydroxycholesterol; 22 (S)-hydroxycholesterol; 24 (S), 25-dihydroxycholesterol; 24 (R), 25-dihydroxycholesterol; 24,25-dehydrocholesterol; 25-epoxy-22 (R)-hydroxycholesterol; 20 (S)-hydroxycholesterol; 7a-hydroxy-24 (S), 25-epoxycholesterol; 7p-hydroxy-24 (S), 25-epoxycholesterol; 7-oxo-24 (S), 25-expoxycholesterol; and 7a-hydroxycholesterol. Other LXR receptor modulators may included 24-(S), 25-iminocholesterol; methyl-38-hydroxycholonate; N,N-dimethyl-3p-hydroxycholonamide; (20R, 22R)-cholest-5-ene-3p, 20,22-triol; 4,4-dimethyl-5-a-cholesta-8,14,24-trien-3-ss-ol; 7-oxocholesterol; desmosterol; and those disclosed in WO 01/15676 to the University of British Columbia. Still other LXR receptor modulators may include androstans, such as androstenol, androstenol-3-acetate, 5α-androstan-3a-ol, disclosed in WO 96/36230 to the Salk Institute; aromatic substituted compounds disclosed in U.S. Pat. No. 6,316,503, WO 01/03705, and WO 01/82917, all assigned to Tularik; 5-(tetradecyloxy)-2-furan-carboxylic acid ("TOFA") disclosed in U.S. Pat. No. 5,939,322 and compounds disclosed in WO 01/41704, both assigned to Merck; and GlaxoSmith-Kine's synthetic LXR agonists T1317 and GW3965.

[0029] An in vitro assay can be conducted to preliminarily screen other compounds for efficacy in modulating LXRs, thereby decreasing the cholesterol level and treating a disorder related to a high cholesterol concentration. For instance, kidney cells are transfected with a luciferase reporter gene (which includes a human c-fos minimal promoter) and an LXR. After incubating the transfected cells with a compound to be tested, the activity of luciferase is measured to determine the transactivation extent of the reporter gene. Compounds that show efficacy in the preliminary in vitro assay can be further evaluated in an animal study by a method also well known in the art. For example, a compound can be orally administered to mice. The efficacy of the compound can be determined by comparing cholesterol levels in various tissues of the treated mice with those in non-treated mice.

[0030] The pharmaceutical composition of the present invention may include an LXR receptor modulator as described above in combination with a natural and synthetic flavanoids, catechols, curcumin-related substances, quinones, catechins, particularly epigallocatechin derivatives, and fatty acids and their analogues or derivatives. Catechins that are structurally similar to epicatechin gallate (ECG) and epigallocatechin gallate (EGCG) have been found to be particularly useful as disclosed in co-pending U.S. Ser. No. 09/530,443. EGCG has an additional hydroxyl group on the epicatechin gallate molecule, which has been found to be surprisingly active in modulating several 5α-reductase mediated processes. EGCG derivatives having such an additional OH group on the altering ECG molecule may interact and interfere with a receptor macromolecule (probably containing a protein) that modulates specific lipid synthesis and accumulation. Lipids can modulate gene expression, cell development and differentiation, and organ growth. Specific interference of lipid metabolism in the cells and organs may control the growth of the organs, in particular, prostate, sebaceous, preputial and other secretory organs. In certain applications, it is expected that benign or abnormal growth or cancer of these organs may be treated or even prevented by administration of catechin related compounds.

[0031] Epigallocatechin derivatives have the formula:



[0032] wherein R is a chain with 2 to 20 atoms selected from the group consisting of carbon, oxygen, sulfur, and nitrogen. These atoms may be in a straight chain or branched form, or in the form of aromatic ring structures, which may have a substitution of one to three carbon, alkyl, or halogenated alkyl, nitro, amino, methylated amino, carboxyl, or hydroxy groups or halogen atoms.

[0033] The LXR receptor modulators may also be advantageously combined and/or used in combination with other lipid-regulating agents, different from the subject compounds. In many instances, administration in combination with the disclosed LXR receptor modulator enhances the efficacy of such modulators. Lipid-regulating agents may include, but are not limited to, statins, otherwise known as HMG-CoA reductase inhibitors, such as mevastatin, pravastatin, atorvastatin, rosuvastatin, cerivastatin, fluvastatin, lovastatin, and simvastatin; bile acid sequestrants such as

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